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por el

DR. LUIS RAZETTI

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y del Congreso Venezolano de Ciencias Médicas

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de Caracas

Órgano oficial de la Academia Nacional de Medicina
y del Congreso Venezolano de Ciencias Médicas

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Editor en Jefe
Enrique Santiago López-Loyo

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Muhammad Miftahussurur

37th Continuing Medical Education (PKB XXXVII) in conjunction with 3rd Airlangga Internal Medicine - International Continuing Medical Education (AIM-ICME 3) Committee
October 7-9, 2022
Indonesian Society of Internal Medicine
Surabaya Chapter

Í N D I C E

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Guest Editor
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Varios

Los trabajos enviados deberán cumplir con los requisitos que se describen a continuación.

EDITORIALES

Esta sección estará dedicada al análisis y la reflexión sobre los problemas de salud de la población, los distintos enfoques preventivos y terapéuticos, así como los avances logrados en el campo de la investigación biomédica y otros que considere la Dirección-Redacción.

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Deberán contener en la página frontal, el título conciso e informativo del trabajo; nombre(s) y apellido(s) de cada autor; grados académicos de los autores e institución en la cual se realizó el trabajo; nombre y dirección actual del autor responsable de la correspondencia; un título corto de no más de 40 caracteres (contando espacios y letras) y las palabras clave.

Los trabajos originales, revisiones sistemáticas y metanálisis deben tener un resumen estructurado, como se indica a continuación:

Debe contener un máximo de 250 palabras, y los siguientes segmentos:

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- Objetivo: ¿Cuál es el propósito del estudio?
- Métodos: ¿Cómo se realizó el estudio? (selección de la muestra, métodos analíticos y observacionales).
- Resultados: ¿Cuáles son los aspectos más impor-tantes? (datos concretos y en lo posible su signifi-cancia estadística)
- Conclusión: ¿Cuál es la más importante que responde al objetivo?

Al final se anotarán 3 a 6 palabras clave.

Resumen en inglés

Debe corresponderse con el resumen en español.Se sugiere que este sea revisado por un traductor experimentado, a fin de garantizar la calidad del mismo.

Introducción

Incluir los antecedentes, el planteamiento del problema y el objetivo del estudio en una redacción libre y continua debidamente sustentada por la bibliografía.

Método

Señalar claramente las características de la muestra, el o los métodos empleados con las referencias pertinentes, de forma que se permita a otros investigadores, realizar estudios similares.

Resultados

Incluir los hallazgos importantes del estudio, comparándolos con las figuras estrictamente necesarias y que amplíen la información vertida en el texto.

Discusión

Relacionar los resultados con lo reportado en la literatura y con los objetivos e hipótesis planteados en el trabajo.

Conclusión

Describir lo más relevante que responda al objetivo del estudio.

Agradecimientos

En esta sección se describirán los agradecimientos a personas e instituciones así como los financiamientos.

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Deberán constar de resumen en español e inglés (máximo 100 palabras) en formato libre. Constará de introducción, presentación del caso, discusión, ilustraciones y referencias, con una extensión máxima de 10 cuartillas y apegadas a las instrucciones a los autores.

Historia y filosofía de la medicina

En esta sección se incluirán los artículos relacionados con aspectos históricos, filosóficos, bases conceptuales y éticas de la medicina. Aunque su estructura se dejará a criterio del autor, deberá incluir resúmenes en español e inglés (máximo 100 palabras) en formato libre, referencias bibliográficas citadas en el texto y en listadas al final del

manuscrito, siguiendo los lineamientos citados para los manuscritos de GMC.

Actualidades terapéuticas

Se informará sobre los avances y descubrimientos terapéuticos más recientes aparecidos en la literatura nacional e internacional y su aplicación en nuestro ámbito médico. La extensión máxima será de cuatro cuartillas y con un máximo de cinco referencias bibliográficas. Deberá incluir resúmenes en español en inglés, en formato libre (máximo 100 palabras).

Información epidemiológica

Será una sección de información periódica sobre los registros epidemiológicos nacionales e internacionales, destacando su importancia, su comparación con estudios previos y sus tendencias proyectivas. La extensión máxima será de cuatro cuartillas y deberá incluir resúmenes en español en inglés (máximo 100 palabras), en formato libre.

Comunicaciones breves

Serán considerados en esta sección, los informes preliminares de estudios médicos y tendrán la estructura formal de un resumen como se describió previamente (máximo 150 palabras). Se deberán incluir 10 citas bibliográficas como máximo.

Bioética

Se plantearán los aspectos éticos del ejercicio profesional y aquellos relacionados con los avances de la investigación biomédica y sus aplicaciones preventivas y terapéuticas. Su extensión máxima será de cuatro cuartillas y cuatro referencias bibliográficas, deberá incluir resúmenes en español e ingles (máximo 100 palabras) en formato libre.

El médico y la ley

Esta sección estará dedicada a contribuciones tendientes a informar al médico acerca de las disposi-ciones legales, riesgos y omisiones de la práctica profesional que puedan conducir a enfrentar problemas legales. Su máxima extensión será de cuatro cuartillas y no más de cinco referencias bibliográficas. Deberá incluir resúmenes en español e inglés (máximo 100 palabras).

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3. Resumen corto que integre las conclusiones del informe para un público con orientación clínica.
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Special Issue: Hot Topics in Internal Medicine

Muhammad Miftahussurur MD, PhD

Invited Editor

For the past years, COVID-19 has drawn attention and has become a global burden. It affected almost all countries around the world and has had a catastrophic effect resulting in over 278 million cases and 5.4 million deaths worldwide. Not only does it cause pulmonary complications, but it also affects other organ systems. Within this special issue, a systematic review by Gianto et al. highlighted the need to consider acute kidney injury when managing COVID-19 patients as it contributed and/or correlated with disease severity, prognosis, and mortality. In addition, COVID-19 can also aggravate the severity of concomitant diseases, as presented by Kandinata et al. showing that hypoglycemia in a patient suffering from insulinoma and hydrocephalus was amplified by COVID-19. Many comorbidities are associated with the increase in severity and mortality of COVID-19. Diabetes mellitus is the second most common comorbidity in COVID-19 patients after hypertension. Aminy et al. analyzed the correlation of dynamic D-dimer levels with mortality in COVID-19 patients with type-2 Diabetes Mellitus (T2DM). Their study showed that hypercoagulation characterized by an elevated D-dimer was likely present in patients with COVID-19 and T2DM at an early stage. Hypercoagulation was strongly related to disease progression and mortality outcome. Therefore, the D-dimer levels should be monitored as early as possible to detect hypercoagulation-related complications thereby decreasing the morbidity and mortality of COVID-19 patients, especially of those with T2DM. Another study conducted by Putri et al. described the profile of patients with Autoimmune Rheumatic Diseases (ARD) contracted with COVID-19 at Dr. Soetomo Hospital in 2020-2022. The study inferred that ARD patients with COVID-19 were predominantly female and the most common primary ARD diagnoses were undifferentiated spondylarthritis (SpA), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriatic arthritis.

During the COVID-19 pandemic era, tightness of the chest, coughing, and fever were commonly associated with COVID-19-associated pneumonia. However, it is important to also consider other possible diagnoses, including bacterial pneumonia and masses in the thoracic cavity. For example, Gunawan et al. nicely documented the presence of a (metastatic) pericardial involvement of lung malignancy that was complicated by cardiac tamponade, which shared some similarities in clinical characteristics with pneumonia in general. Meanwhile, as shown by Mudjari et al., in pregnant women, Ovarian Hyperstimulation Syndrome (OHSS) which was exacerbated by the presence of ascites could cause bacterial peritonitis and blood disorders such as thrombocytosis, which in turn can cause thromboembolic events and mortality. Apart from SARS-CoV-2, pregnant women also need to prevent other infections, including *Toxoplasma gondii* which can infect humans through household animals such as cats, or by consuming contaminated vegetables or

fruits, or undercooked meat. Pregnant women can transmit such an infection to their fetuses. Nevertheless, toxoplasmosis can cause sudden blindness in immunocompetent non-pregnant females, as shown by Brimantyo et al.

As time goes by, the world now adapts to living alongside COVID-19. While many aspects have returned to some version of normal, the healthcare system must continue evolving as new challenges approach for which health professionals have to be prepared. In this Research Topic, we present some of the hot topics in Internal Medicine with a selection of the most impactful special issues. Rahardjo et al. presented an open experimental study and showed standard lifestyle intervention plus diet substitution with sorghum rice for 7 days have an effect on fasting blood glucose (FBG) and beta cell function in prediabetic patients but not on insulin resistance (IR). A study conducted by Awalia et al. contributes some evidence that asymptomatic hyperuricemia demonstrated a wide of structural damages in the evaluation of ultrasonography musculoskeletal. Ultrasound seems to be a suitable tool to early detect these structural changes. Syakdiyah et al. confirmed the utilization of The Systemic Immune-inflammation Index (SII) in Ulcerative Colitis (UC) through systematic research. The SII value of UC/active patients was significantly higher than in non-UC/remission UC. It is suggested that SII may be a valuable biomarker to predict the activity of UC. Another study presented characteristics of pregnant women with thyroid disorders (Hidayati et al.). Maternal thyroid dysfunction is associated with an increased risk for early abortion, preterm delivery, neonatal morbidity, and other obstetrical complications. The study result showed most pregnant women were hyperthyroid without previous history of thyroid disease, and the first symptom commonly appeared in the third trimester. It was found that Caesarean section was preferred as the delivery method, with minimal complications and the condition of the fetus was quite good. Hidayati et al. also showed that arterioportal fistula could worsen the GI variceal bleeding complications of hepatic cirrhosis. Interestingly, as documented by Vidyani et al., hepatic cirrhosis could also cause an accumulation of fluid in the pleura (i.e., pleural effusion) without any heart and lung manifestations, so-called hepatic hydrothorax. Meanwhile, Pramesthi et al. displayed that immunocompromised patient, such as patients with psoriatic arthritis, are susceptible to various opportunistic infections, one of which is Norwegian scabies.

In the field of rheumatology, one of the topics that remained interesting to be discussed is SLE. This topic has been a major problem as the patient has grown more in numbers. Primasatya et al. found a unique case of vasculitis as an uncommon manifestation of SLE in an adult male patient, which responded well to methylprednisolone treatment. Another case of autoimmune disease that caught our attention is dermatomyositis. Here, Satyawardhana et al. presented a case of a 38-year-old male with a red-purplish rash around the eyes, an elevation of a serum muscle enzyme, and abnormal electromyography, which was improved by cyclophosphamide, but not corticosteroids.

Whilst, autoimmune diseases of the blood and other hematologic disorders are still of concern. One of the unique cases that we received is immune thrombocytopenic purpura (ITP) in a peritoneal tuberculosis patient treated with anti-tuberculosis drugs. Yulistiawati concluded that although it was rare, ITP could be a manifestation of extra-pulmonary tuberculosis infection that could be treated using Anti-Tuberculosis Treatment and steroids. Another unique case was autoimmune hemolytic anemia (AIHA), amoebic dysenteries, and intracranial hemorrhage as rare manifestations of smoldering multiple myeloma (SMM), presented by Kusumawindani et al., which reminds us to be more aware of the SMM even in the absence of progression to overt Multiple Myeloma (MM).

In the field of oncology, we have a few unique cases that are interesting to discuss. First was the diagnostic problem of facial tumors in the elderly by Taurini et al. and second, was the first reported case of a Huge Frant'z tumor in Southeast Asia by Arianti et al. Taurini et al. concluded that plasmablastic lymphoma was difficult to diagnose because the anatomical pathology picture often overlapped with plasmacytoma in the gold standard IHC CD138 (+), which is aggressive and relapses. Arianti et al. documented a patient who experienced abdominal pain, and when FNAB was performed, a pseudopapillary

neoplasm of the pancreas was found. Later the patient underwent a distal pancreatectomy which successfully improved the patient's condition.

In the field of tropical and infectious diseases, as we know Indonesia has been an endemic area for Leprosy. The third most common form of clinical manifestation of leprosy is arthritis. This manifestation is often underdiagnosed because of its similarity to rheumatoid arthritis (Tumewu et al.). Early diagnosis and prompt treatment are necessary because proper treatments with MDT and steroids could prevent further disability.

This special issue contains 21 articles, 5 original articles, 2 systematic reviews, and 14 case reports covering internal medicine issues. We hope that through these articles, broader insights and advanced innovation can be brought.

Concluding remarks

COVID-19 has caused a significant impact on our health and well-being. In addition to the pulmonary manifestations, COVID-19 has been shown to also affect other organs, facilitating the progression of other concomitant diseases and worsening the prognosis of other comorbidities. At present, we are slowly moving from the COVID-19 pandemic to the post-pandemic era. Unfortunately, we are not yet free from healthcare-associated threats, both infectious and non-infectious diseases. In this special issue, we have compiled several interesting findings from recent studies and case reports, highlighting the complexity of diseases we are currently facing. Only by close collaborative approaches, meticulous observations, and thorough evaluations, we can solve the post-COVID-19 healthcare-related issues ahead.

Edición especial: temas candentes en medicina interna

Muhammad Miftahussurur MD, PhD

Editor Invitado

Durante los últimos años, COVID-19 ha llamado la atención y se ha convertido en una carga global. Afectó a casi todos los países del mundo y ha tenido un efecto catastrófico con más de 278 millones de casos y 5,4 millones de muertes en todo el mundo. No solo causa complicaciones pulmonares, sino que también afecta a otros sistemas de órganos. Dentro de este número especial, una revisión sistemática de Gianto y col. destacó la necesidad de considerar la lesión renal aguda al manejar pacientes con COVID-19, ya que contribuía y/o se correlacionaba con la gravedad, el pronóstico y la mortalidad de la enfermedad. Además, el COVID-19 también puede agravar la gravedad de enfermedades concomitantes, tal como lo presentan Kandinata y col., quienes muestran que la hipoglucemia en un paciente que padecía insulinoma e hidrocefalia fue amplificada por COVID-19. Muchas comorbilidades están asociadas con el aumento de la gravedad y la mortalidad del COVID-19. La diabetes mellitus es la segunda comorbilidad más común en pacientes con COVID-19 después de la hipertensión. Aminy y col. analizaron la correlación de los niveles dinámicos de dímero D con la mortalidad en pacientes con COVID-19 y diabetes mellitus tipo 2 (DM2). Su estudio mostró que la hipercoagulación caracterizada por un dímero D elevado, probablemente estaba presente en pacientes con COVID-19 y DM2 en una etapa temprana. La hipercoagulación estuvo fuertemente relacionada con la progresión de la enfermedad y el resultado de la mortalidad. Por lo tanto, los niveles de dímero D deben monitorearse lo antes posible para detectar complicaciones relacionadas con la hipercoagulación y así disminuir la morbilidad y mortalidad de los pacientes con COVID-19, especialmente de aquellos con DM2. Otro estudio realizado por Putri y col. describió el perfil de pacientes con Enfermedades Reumáticas Autoinmunes (ERA) contraídos con COVID-19 en el Hospital Dr. Soetomo en 2020-2022. El estudio infirió que los pacientes con ARD con COVID-19 eran predominantemente mujeres y los diagnósticos primarios de ARD más comunes fueron la espondiloartritis indiferenciada (SpA), el lupus eritematoso sistémico (LES), la artritis reumatoide (AR) y la artritis psoriásica.

Durante la era de la pandemia de COVID-19, la opresión en el tórax, la tos y la fiebre se asociaron comúnmente con la neumonía asociada a COVID-19. Sin embargo, es importante considerar también otros posibles diagnósticos, como neumonía bacteriana y masas en la cavidad torácica. Por ejemplo, Gunawan y col. documentaron muy bien la presencia de una afectación pericárdica (metastásica) de una neoplasia pulmonar que se complicó con un taponamiento cardíaco, que compartía algunas similitudes en las características clínicas con la neumonía en general. Por su parte, como muestran Mudjari y col., en mujeres embarazadas, el Síndrome de Hiperestimulación Ovárica (SHEO), exacerbado por la presencia de ascitis,

puede causar peritonitis bacteriana y trastornos sanguíneos como la trombocitosis, que a su vez pueden causar eventos tromboembólicos y mortalidad. Además del SARS-CoV-2, las mujeres embarazadas también deben prevenir otras infecciones, incluido el *Toxoplasma gondii*, que puede infectar a los humanos a través de animales domésticos como los gatos, o al consumir verduras o frutas contaminadas, o carne poco cocida. Las mujeres embarazadas pueden transmitir dicha infección a sus fetos. Sin embargo, la toxoplasmosis puede causar ceguera súbita en mujeres no embarazadas inmunocompetentes, como lo demuestran Brimantyo y col.

A medida que pasa el tiempo, el mundo ahora se adapta a vivir junto al COVID-19. Si bien muchos aspectos han vuelto a la versión de la normalidad, el sistema de salud debe continuar evolucionando a medida que se acercan nuevos desafíos para los cuales los profesionales de la salud deben estar preparados. En este título de investigación, presentamos algunos de los temas candentes en medicina interna con una selección de los temas especiales de mayor impacto. Rahardjo y col. presentaron un estudio experimental abierto y mostraron que la intervención estándar en el estilo de vida, más la sustitución de la dieta con arroz de sorgo durante 7 días tiene un efecto sobre la glucosa en sangre en ayunas (FBG) y la función de las células beta en pacientes prediabéticos, pero no sobre la resistencia a la insulina (IR). Un estudio realizado por Awalia y col. aporta evidencia que la hiperuricemia asintomática demostró una amplia gama de daños estructurales en la evaluación de la ecografía musculoesquelética. La ecografía parece ser una herramienta adecuada para detectar precozmente estos cambios estructurales. Syakdiyah y col. confirmaron la utilización del índice de inflamación inmune sistémica (SII) en la colitis ulcerosa (CU) a través de la investigación sistemática. El valor SII de CU/ pacientes activos fue significativamente mayor que en CU no-CU/remisión. Se sugiere que SII puede ser un biomarcador valioso para predecir la actividad de la CU. Otro estudio presentó características de gestantes con trastornos tiroideos (Hidayati y col.). La disfunción tiroidea materna se asocia con un mayor riesgo de aborto temprano, parto prematuro, morbilidad neonatal y otras complicaciones obstétricas. El resultado del estudio mostró que la mayoría de las mujeres embarazadas tenían hipertiroidismo sin antecedentes de enfermedad tiroidea, y el primer síntoma aparecía comúnmente en el tercer trimestre. Se encontró que la cesárea fue preferida como método de parto, con mínimas complicaciones y la condición del feto fue bastante buena. Hidayati y col. también mostraron que la fístula arterioportal podría empeorar las complicaciones hemorrágicas de las várices gastrointestinales de la cirrosis hepática. Curiosamente, como documentaron Vidyani y col., la cirrosis hepática también podría causar una acumulación de líquido en la pleura (es decir, derrame pleural) sin manifestaciones cardíacas ni pulmonares, lo que se conoce como hidrotórax hepático. Por su parte, Pramesthi y col. mostraron que los pacientes inmunocomprometidos, como los pacientes con artritis psoriásica, son susceptibles a diversas infecciones oportunistas, una de las cuales es la sarna noruega.

En el campo de la reumatología, uno de los temas que resultan interesantes para ser discutidos es el LES. Este tema ha sido un problema importante ya que el número de pacientes ha crecido mucho. Primasatya y col. encontraron un caso único de vasculitis como manifestación infrecuente de LES en un paciente masculino adulto, que respondió bien al tratamiento con metilprednisolona. Otro caso de enfermedad autoinmune que llamó nuestra atención es la dermatomiositis. Aquí, Satyawardhana y col. presentaron el caso de un paciente masculino de 38 años con un exantema rojo-morado alrededor de los ojos, elevación de una enzima muscular sérica y electromiografía anormal, que mejoró con ciclofosfamida, pero no con corticoides.

Mientras tanto, las enfermedades autoinmunes de la sangre y otros trastornos hematológicos siguen siendo motivo de preocupación. Uno de los casos singulares que recibimos es la púrpura trombocitopénica inmune (PTI) en un paciente con tuberculosis peritoneal tratado con fármacos antituberculosos. Yulistiawati concluyó que, aunque era raro, la PTI podría ser una manifestación de infección tuberculosa extrapulmonar que podría tratarse con tratamiento antituberculoso y esteroides. Otro caso único fue la anemia hemolítica autoinmune (AIHA), las disenterías amebianas y la hemorragia intracraneal como manifestaciones raras del

mieloma múltiple latente (SMM), presentado por Kusumawindani y col., que nos recuerda que debemos ser más conscientes del SMM incluso en ausencia de progresión a mieloma múltiple (MM) manifiesto.

En el campo de la oncología, tenemos algunos casos únicos que son interesantes para discutir. Primero fue el problema diagnóstico de los tumores faciales en el anciano de Taurini y col. y segundo, fue el primer caso informado de un tumor Huge Frant'z en el sudeste asiático por Arianti y col. Taurini y col. concluyeron que el linfoma plasmablástico era difícil de diagnosticar debido a que el cuadro anatomopatológico a menudo se superponía con el plasmocitoma en el patrón oro IHC CD138 (+), que es agresivo y recidivante. Arianti y col. documentaron un paciente que presentó dolor abdominal, y al realizarle PAAF se encontró una neoplasia pseudopapilar de páncreas. Posteriormente, el paciente se sometió a una pancreatectomía distal que mejoró con éxito la condición del paciente.

En el campo de las enfermedades tropicales e infecciosas, como sabemos, Indonesia ha sido un área endémica para la lepra. La tercera forma más común de manifestación clínica de la lepra es la artritis. Esta manifestación suele estar infradiagnosticada por su similitud con la artritis reumatoide (Tumewu y col.). El diagnóstico temprano y el tratamiento oportuno son necesarios porque los tratamientos adecuados con MDT y esteroides podrían prevenir una mayor discapacidad.

Este número especial contiene 21 artículos, 5 artículos originales, 2 revisiones sistemáticas y 14 informes de casos que cubren temas de medicina interna. Esperamos que, a través de estos artículos, se puedan aportar conocimientos más amplios e innovación avanzada.

Observaciones finales

La COVID-19 ha causado un impacto significativo en nuestra salud y bienestar. Además de las manifestaciones pulmonares, se ha demostrado que la COVID-19 afecta también a otros órganos, facilitando la progresión de otras enfermedades concomitantes y empeorando el pronóstico de otras comorbilidades. En la actualidad, estamos pasando lentamente de la pandemia del COVID-19 a la era pospandémica. Desafortunadamente, todavía no estamos libres de las amenazas asociadas con la atención médica, tanto las enfermedades infecciosas como las no infecciosas. En este número especial, hemos recopilado varios hallazgos interesantes de estudios e informes de casos recientes, que destacan la complejidad de las enfermedades a las que nos enfrentamos actualmente. Solo mediante enfoques de estrecha colaboración, observaciones meticulosas y evaluaciones exhaustivas, podemos resolver los problemas relacionados con la atención médica posteriores a COVID-19 que se avecinan.

ARTÍCULO ORIGINAL

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Characteristics of Pregnant Women with Thyroid Disorders at Wahidin Sudirohusodo Hospital Makassar

Características de las mujeres embarazadas con trastornos de la tiroides en el Hospital Wahidin Sudirohusodo de Makassar

Prema Hapsari Hidayati[1a*], Irmayanti[2a], Masita Fujiko[3a], Mochammad Erwin Rachman[4a], Syafira Ananda Marendengi[5a]

SUMMARY

Backgrounds: *At least 2 %-3 % of pregnant women experience thyroid dysfunction, which affects the health of the mother and baby. There is still little research on pregnant women with thyroid disorders.*
Aim: *Investigating the characteristics of pregnant women with thyroid disorders in Dr. Wahidin Sudirohusodo Hospital Makassar.*
Methods: *A descriptive retrospective study based on medical record data for 2019-2020.* **Results:** *There were 15 of 399 pregnant women (3.76 %) who had thyroid disorders; most of them were hyperthyroid (60 %) without any previous thyroid history (73.3 %). They were aged 20-35 years (86.7 %), Bugis ethnicity (46.7 %), multiparous (60 %), had previous delivery history by cesarean section (56.7 %) and had a normal BMI (73.3 %). Thyroid complaints first appeared in the third trimester (66.7 %) with a high level of FT4 (46.7 %) and normal TSH (60.0 %). The current delivery method was Sectio Caesarea (60.0 %) without any complications (73.3 %), and the Apgar score of the babies was≥8 (53.3 %). Overall, the babies' condition was good in 86.7 % of cases.*
Conclusion*: The most common thyroid disorder suffered by pregnant women at Wahidin Sudirohusodo Hospital in 2019-202 was hyperthyroidism, and most of them gave birth in good condition.*

Keywords: *Pregnant mothers, thyroid disorders, characteristics.*

RESUMEN

Antecedentes: *Al menos el 2 %-3 % de las mujeres embarazadas experimentan disfunción tiroidea, lo que afecta la salud de la madre y el bebé. Todavía hay poca investigación sobre mujeres embarazadas con trastornos de la tiroides.*
Objetivo*: Investigar las características de las mujeres embarazadas con trastornos de la tiroides en el Hospital Dr. Wahidin Sudirohusodo Makassar.*
Métodos: *Estudio retrospectivo descriptivo basado en datos de historias clínicas de 2019-2020.*
Resultados: *Hubo 15 de 399 gestantes (3,76 %) que presentaron trastornos tiroideos; la mayoría eran hipertiroideos (60 %) sin antecedentes tiroideos previos (73,3 %). Tenían entre 20 y 35 años (86,7 %), etnia bugis (46,7 %), multíparas (60 %), antecedentes de parto por cesárea (56,7 %) e IMC normal (73,3 %).*

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Las quejas de tiroides aparecieron por primera vez en el tercer trimestre (66,7 %) con un nivel alto de FT4 (46,7 %) y TSH normal (60,0 %). El método de parto actual fue la cesárea (60,0 %) sin ninguna complicación (73,3 %) y el puntaje de Apgar de los bebés fue ≥8 (53,3 %). En general, el estado de los bebés era bueno en el 86,7 % de los casos.

Conclusión: *El trastorno tiroideo más común que sufrieron las mujeres embarazadas en el Hospital Wahidin Sudirohusodo en 2019-202 fue el hipertiroidismo, y la mayoría dio a luz en buenas condiciones.*

Palabras clave: *Madres embarazadas, trastornos de la tiroides, características.*

INTRODUCTION

The thyroid is the largest endocrine gland in the human body, located at the front of the neck. The thyroid gland produces thyroxine (T4) and triiodothyronine (T3) which are controlled by feedback mechanisms involving Thyroid Stimulating Hormone (TSH). The abnormalities of thyroid function consist of hypothyroidism and hyperthyroidism (1). Disorders of the thyroid gland are the second most common endocrine disorder in the world after diabetes (2). The American Thyroid Association reported that about 20 million Americans experience some form of thyroid disease, and more than 12 % of the US population is estimated to have thyroid dysfunction during their lifetime (3). In Indonesia, based on the 2013 RISKESDAS, there are about 0.4 % of the population experiences hyperthyroidism (4). In 2017, the Indonesian Ministry of Health reported that as many as 17 million Indonesians experienced thyroid disorders, with the highest prevalence in South Sumatra (5).

Normal thyroid function is essential for fetal development. Deficiency or excess of thyroid hormone can occur in pregnancy and cause problems for both mother and baby. At least 2 % - 3 % of pregnant women are affected by thyroid dysfunction. Hyperthyroidism occurs in 0.2 % - 0.4 % of pregnant women and is commonly associated with Grave's disease. The incidence of hypothyroidism in pregnancy is between 0.5 %-3.5 % and is usually caused by Hashimoto's thyroiditis. However, it can also be seen in areas with iodine deficiency (6).

Pregnant women with thyroid dysfunction need to get appropriate therapy and regular monitoring during pregnancy to protect the mother and baby (7). However, screening for thyroid abnormalities in every pregnancy is still not recommended, only performed on high-risk pregnant women. Furthermore, the lack of public knowledge about thyroid disease, limited facilities to check thyroid hormones, and differences in interpretation of typical thyroid function values in pregnant women make the risk of fetal death due to thyroid dysfunction still high, around 79 % (8,9). Therefore, recognizing the signs of thyroid disorders in pregnant women is essential. Unfortunately, now, there are still limited publications regarding this. So, this study aimed to examine the characteristics of pregnant women with thyroid disorders in Indonesia, especially in Makassar.

METHODS

This research is a descriptive study with a retrospective approach using data from the medical records of all pregnant women who perform antenatal care and childbirth at RSUP Dr. Wahidin Sudirohusodo Makassar from January 2019 to December 2020 or 2 years. The inclusion criteria in this study were all pregnant women diagnosed with thyroid disorders during antenatal care until after delivery. Meanwhile, the exclusion criteria are if there are incomplete thyroid function laboratory results.

RESULTS

In this study, we found that 399 pregnant women had their pregnancy checked at Dr. Wahidin Sudirohusodo Makassar from January 2019 to December 2020. Among them, 15 people were diagnosed with thyroid disorders and included in this research. The characteristics of our research sample are presented in Table 1.

Table 1. Characteristics of Pregnant Women with Thyroid Abnormalities at RSUP Dr. Wahidin Sudirohusodo Makassar Year 2019-2020

Characteristics Pregnant Women with Thyroid Disorders	Amount (15 people)	Percentage (%)
Age		
<20 years	0	0
20-35 years old	13	86.7
>35 years old	2	13.3
Mother's Tribe		
Makassar	6	40.0
Bugis	7	46.6
Mandarin	1	6.7
Tolaki	1	6.7
The gestational age of the mother at the time of the first symptom		
First Trimester	0	0
Second Trimester	5	33.3
Third Trimester	10	66.7
Thyroid complaints and history		
Complaints of thyroid disorders in pregnancy	11	73.3
History of thyroid disorders in pregnancy	4	26.7
Mother's nutritional status		
Body Mass Index		
Underweight	0	0
Normal	11	73.3
Overweight	2	13.3
Obesity	2	13.3
Upper arm circumference		
Normal	1	6.7
Not Listed in Medical Records	2	13.3

Based on Table 1, the proportion of pregnant women with thyroid disorders based on age occurred in the age group 20-35 years were 13 people (86.7 %) and aged more than 35 years two people (13.3 %). The highest proportion based on the ethnicity of pregnant women occurred in the Bugis tribe, which was seven people (46.6 %); while the Makassar tribe was six people (40.0 %), the Mandar and Tolaki tribes were one person each (6.7 %). In addition, this study found that symptoms related to thyroid disorders most often first appeared in the third trimester of pregnancy (66.7 %) compared to the second trimester (33.3 %), and there were only 26.7 % of mothers had a history of thyroid disorder before. We also found that 73.3 % of our sample had an average Body Mass Index (BMI), 13.3 % were overweight, and 13.3 % had obese.

Table 2. Diagnosis and Thyroid Function Test Result

Diagnosis and Laboratory Examination of Pregnant Women with Thyroid Disorders	Amount (15 people)	Percent (%)
Thyroid Disorders Diagnosis		
Hypothyroid	1	6.7
Hyperthyroid	9	60.0
Non-toxic goiter	5	13.3
TSH Thyroid Function Test		
Decrease	3	33.3
Normal	9	60.0
Increase	1	6.7
Thyroid Function Test FT4		
Decrease	1	6.7
Normal	7	46.7
Increase	7	46.7

In this study, 60 % of pregnant women were diagnosed with hyperthyroidism, 6.7 % were diagnosed with hypothyroidism, and 33.3 % were diagnosed with non-toxic goiter. From the result of thyroid function tests, we found that 60 % of our sample had within a normal range of TSH, 33.3 % had low TSH, and 6.7 % had high TSH. Meanwhile, from the free T4 result, we found 46.7 % had a high level, 46.7 % had an average level result, and 6.7 % had a low-level result.

Table 3. Characteristics based on pregnancy history and perinatal condition

Characteristics	Amount (15 people)	Percent (%)
Pregnancy History		
Primipara	4	26.7
Multipara	9	60.0
Grande para	2	13.3
Childbirth History Previously		
Only Sectio Cesarean procedure	8	56.7
Just Normal	2	13.3
Never gave birth before	5	30.0
Current Method of Delivery		
Sectio Cesarean procedure	9	60.0
Normal	6	40.0
Experiencing Complications During Labor		
Bleeding Complications	4	26.7
No Complications	11	73.3
Condition of the Baby Born		
Born Healthy	13	86.7
Died	2	13.3
Condition of the Baby Born		
No Resuscitation	13	86,7
Requires Resuscitation	2	13.3
APGAR ScoreBaby		
8	8	53,3
<8	5	33.3
Weight and Length of Babies Born		
Normal	8	53,3
LBW and short	5	33.3

In this study, from pregnancy history, we found that 60 % of pregnant women were multipara, 26.7 % were primipara dan 13.3 % were Grande para. Among those women, 56.7 % had a history of cesarean section for previous labor methods, 13.3 % had a regular procedure, and 30 % never gave birth. Meanwhile, based on the current delivery method, 60 % had a section cesarean procedure, and 40 % had the standard way. However, about 26.7 % of pregnant women experience complications during childbirth, and 73.3 % do not.

In this study, we found 86.7 % of babies were born healthy, but 13.3 % died after some time of intensive therapy. Among those healthy babies, 53.3 % had an APGAR Score of more than eight, and 33.3 % had APGAR Score below eight. In addition, about 53.3 % of babies had average weight and length, while 33.3 % had low birth weight and short size.

DISCUSSION

This study's results align with research conducted by Dülek in 2019, which show that at least 2 % -3 % of pregnant women are affected by thyroid dysfunction. Hyperthyroidism occurs in 0.2 %-0.4 % of pregnant women. Furthermore, hyperthyroidism during pregnancy can cause complications such as stillbirth, abortion, premature birth, preeclampsia, heart failure, and thyroid storm (7).

The highest age group in this study was the age group of 20-35 years. This result is in line with research conducted by Cooper and Laurberg (2013) who found that the highest incidence of hyperthyroidism was found in women aged > 30 years, and the incidence was around 55-80 per 100 000 people per year. Whereas in women aged 20-29 years, the incidence is 35-50 cases per 100 000 per year, and for women younger than 20 years, the risk is much lower (10).

Based on RISKESDAS in 2013, the prevalence of hyperthyroidism in South Sulawesi province was the fourth highest in Indonesia, with a prevalence of around 0.5 %. However, concerning pregnant women, to the best of the author's knowledge, this study is the first to publish the incidence of thyroid disorders in pregnant women in Indonesia, especially in Makassar, South Sulawesi. Our study also found that most pregnant women with thyroid disorders came from the Bugis and Makassar ethnic groups.

Diagnosis and complaints of thyroid disorders in pregnant women in this study were found in the second and third trimesters, similar to research conducted by Gheorghiu et al., 2021. In most cases, thyroid disorders in pregnancy, such as subclinical hyperthyroidism, appear after the sixth week of pregnancy due to increased physiological secretions (11).

In this study, we found that most pregnant women had normal BMI with average TSH levels and increased FT4, which is in line with Kumar et al., in 2017. BMI significantly correlates with TSH levels during the first and second trimesters of normal pregnancy. Higher average TSH values while lower normal range FT4 were found in obese pregnant women compared to average-weight pregnant women. Nevertheless, this correlation was not seen in pregnant women with euthyroid (12).

In this study, most pregnant women with thyroid disorders had a history of multiparous pregnancy. This result is in line with the 2021 Khakurel et al. study, which found that the prevalence of pregnant women with thyroid disorders with a history of primiparas is less than multiparas (13), history and delivery method by cesarean section had the highest proportion in this study. This choice may be due to consideration of the possibility of complications that might worsen the condition of the baby and mother (7).

Complications experienced by pregnant women with thyroid disorders during childbirth in the study were postpartum hemorrhage, which occurs only in 13.3 % of pregnant women. This result was in line with research by Tudosa et al., in 2010; complications of postpartum hemorrhage by 18.3 % occur through uterine hypotony and coagulation disorders (14).

In this study, we found that most of the babies that were born had average weight and length. Meanwhile, Tudosa et al., in 2010 and Dülek in 2019 found that hypothyroidism and hyperthyroidism can cause prematurity, fetal heart complications, low birth weight babies, and increased frequency of cesarean delivery. However, if treated quickly and appropriately, the results will be good (7,14).

Two babies required intensive care due to jaundice, hypothyroidism, and APGAR score under eight. Congenital hypothyroidism can cause mental retardation unless thyroid therapy is given within two weeks of birth, with initial screening TSH and T4 measurements. Meanwhile, resuscitation was carried out based on the neonatal resuscitation algorithm (15).

CONCLUSION

Most pregnant women with thyroid abnormalities in RSUP Wahidin Sudirohusodo Makassar were hyperthyroid without previous history of thyroid disease, and the first symptom commonly appeared in the third trimester. Most of them were aged 20-35, Bugis ethnicity, had normal BMI, normal TSH, and increased FT4. In this study, it was found that section Caesarea was preferred as the delivery method, with minimal complications and the condition of the fetus was quite good.

Conflicts of Interest

The authors declare no conflict of interest.

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ARTÍCULO ORIGINAL

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Ultrasonography Profiles in Patients with Asymptomatic Hyperuricemia

Perfiles de ecografía en pacientes con hiperuricemia asintomática

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SUMMARY

Backgrounds: *Asymptomatic hyperuricemia (AHU) patients mostly do not develop gouty arthritis. The best procedure to investigate whether they have MSU deposition has not been established. We report our preliminary study about ultrasonography on AHU patients.*

Methods*: In this cross-sectional study, we enrolled asymptomatic hyperuricemia patients who matched the gout classification criteria of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) (2015). Six joints were examined per patient by ultrasonography including the first metacarpophalangeal (MCP) joints, first metatarsophalangeal (MTP) joints, and trochlear knees to determine pathological findings which may demonstrate clinically silent urate deposits in asymptomatic hyperuricemia individuals.*

Results*: Average age was 49.27±12.35 years old. The average serum uric acid level was 7.64±1.67 mg/dL. Ultrasonography of the first MCP showed joint effusion in 11 patients (73 %), double contour in 10 patients (66 %), tophus in 1 patient (6 %), snowstorm appearance in 1 patient, hypervascularization in 1 patient, and synovitis in 3 patients (20 %). Four patients revealed normal features. First MTP joints showed 13 joint effusions (86 %), double contours in 13 patients (86 %), 1 bone erosion (6 %), 3 tophi (20 %), and 2 synovitis (13 %). There was no hypervascularization or snowstorm appearance found. Two patients showed normal USG. From trochlear knees, we found 1 joint effusion (6 %), and 1 double contour (6 %), and 14 patients were normal.*

Conclusions*: Abnormal ultrasound findings such as double contour sign and tophi were detected in asymptomatic hyperuricemia. The most frequent joint affected was the first MTP. Whether this result influences our decision to initiate urate-lowering therapy and anti-inflammatory treatment is still to be determined.*

Keywords: *Asymptomatic hyperuricemia, joints, ultrasonography.*

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RESUMEN

Antecedentes: *Los pacientes con hiperuricemia asintomática (AHU) en su mayoría no desarrollan artritis gotosa. No se ha establecido el mejor procedimiento para investigar si tienen depósito de MSU. Presentamos nuestro estudio preliminar sobre ultrasonografía en pacientes de AHU.*

Métodos: *En este estudio transversal, reclutamos pacientes con hiperuricemia asintomática que coincidían con los criterios de clasificación de gota del Colegio Americano de Reumatología (ACR)/Liga Europea Contra el Reumatismo (EULAR) (2015). Se examinaron seis articulaciones por paciente mediante ultrasonografía, incluidas las primeras articulaciones metacarpofalángicas (MCP), las primeras articulaciones metatarsofalángicas (MTP) y las rodillas trocleares para determinar los hallazgos patológicos que pueden demostrar depósitos de urato clínicamente silenciosos en individuos asintomáticos con hiperuricemia.*

Resultados*: La edad promedio fue de 49,27±12,35 años. El nivel medio de ácido úrico sérico fue de 7,64±1,67 mg/dL. La ecografía de la primera MCP mostró derrame articular en 11 pacientes (73 %), doble contorno en 10 pacientes (66 %), tofo en 1 paciente (6 %), aspecto de tormenta de nieve en 1 paciente, hipervascularización en 1 paciente y sinovitis en 3 pacientes (20 %). Cuatro pacientes revelaron características normales. Las primeras articulaciones MTP presentaron 13 derrames articulares (86 %), doble contorno en 13 pacientes (86 %), 1 erosión ósea (6 %), 3 tofos (20 %) y 2 sinovitis (13 %). No se encontró hipervascularización ni apariencia de tormenta de nieve. Dos pacientes mostraron USG normal. De las rodillas trocleares encontramos 1 derrame articular (6 %), 1 doble contorno (6 %) y 14 pacientes eran normales.*

Conclusiones: *En la hiperuricemia asintomática se detectó un hallazgo ecográfico anormal como signo de doble contorno y tofos. La articulación más frecuentemente afectada fue la primera MTP. Queda por determinar si este resultado influye en nuestra decisión de iniciar un tratamiento hipouricemiante y un tratamiento antiinflamatorio.*

Palabras clave: *Hiperuricemia asintomática, articulaciones, ultrasonografía.*

INTRODUCTION

Asymptomatic hyperuricemia is defined as elevated uric acid levels with no clinical symptoms and is commonly viewed as an entity that should not be treated (1,2). Hyperuricemia may result from increased production or decreased excretion of uric acid (3). Many individuals with hyperuricemia are clinically asymptomatic, with 5 %-18.83 % estimated to develop gout later (4). The disease burden of hyperuricemia is increasing, especially in high-income countries and economically developing worlds with urban lifestyles (3,5). The prevalence of hyperuricemia in the United States was 21.4 %, while in China the prevalence was 13.3 % (6,7). Serum uric acid levels are also associated with all-cause and cardiovascular mortality, independent of other cardiovascular risk factors (8).

Advanced imaging and microscopy studies have shown that monosodium urate (MSU) crystals are present in many people with hyperuricemia with no history of flares and no clinical evidence of tophi (9). Monosodium urate deposition on cartilage is an early step in developing gout. This deposition may also lead to direct mechanical damage of the joint, predisposing it to degenerative arthritis. Additionally, occultly deposited MSU may induce low-level inflammation, with systemic consequences (10). A single-center retrospective cohort study of 5 899 Japanese adults with asymptomatic hyperuricemia without comorbidities had a significant risk of developing cardiometabolic conditions (11). The imaging technique, such as joint ultrasonography may demonstrate clinically silent urate deposits in asymptomatic hyperuricemia individuals (12,13). Ultrasound (US) has advantages over other imaging modalities including the lack of ionizing radiation, non-invasive, relatively cost, patient acceptability, and ease of access (14). Pathological findings on ultrasonography like tophi in tendons and synovium, double contour sign in the first metatarsophalangeal joint, and increased vascularity were documented in asymptomatic hyperuricemia patients (15-17).

To date, there is still no consensus approved for urate-lowering therapy indication in asymptomatic hyperuricemia individuals (18). The latest systematic review study has found evidence that asymptomatic hyperuricemia should be treated only under specific circumstances (19). This is different from Japan where asymptomatic hyperuricemia patients are actively treated to prevent coronary events, CKD, and arterial

hypertension (20). In this study, we analyzed the joint ultrasonography results from patients who were diagnosed with asymptomatic hyperuricemia to evaluate MSU crystal deposition and lesions in joints in considering whether to initiate urate-lowering therapy and anti-inflammatory treatment.

METHODS

Study design and participant

This was a descriptive study using a cross-sectional approach. Patients aged 30-70 years old, diagnosed with asymptomatic hyperuricemia in the internal medicine outpatient clinic in Dr. Soetomo Teaching Hospital from February 1st to April 30th, 2015, were eligible for this study. The required inclusion criteria for patients with asymptomatic hyperuricemia matched the gout classification criteria of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) (2015). The exclusion criteria for patients with gout were prior diagnosis of other crystal-related arthropathies, patients with a history of fracture of upper or lower limbs, dislocation, and patients with rheumatoid arthritis and osteomyelitis. Urate levels in fasting serum in asymptomatic hyperuricemia patients were greater than 7 mg/dL for men, and >6 mg/dL for women, and this was confirmed at least twice. All the following data, including demographics (i.e., sex, age, and uric acid level) were collected. The first metacarpophalangeal, first metatarsophalangeal, and trochlear knee were assessed using ultrasonography for each patient, which corresponds to 6 screened joints per patient. Written informed consent was obtained from all patients, and the study protocol was approved by the ethics committee of the Dr. Soetomo Teaching Hospital Surabaya, Indonesia (238/Panke KKE/IV/2015).

US Assessment

The US examination was performed by skilled sonographers who had more than 10 years of experience in the musculoskeletal US in Dr. Soetomo Teaching Hospital. Hitachi Hi Vision Avius diagnostic apparatus (probe frequency 5-10 MHz) was used for the US examination. US gout lesion in asymptomatic hyperuricemia patients was evaluated in first metacarpophalangeal-metatarsophalangeal joints and trochlear knee for double countersign (DCS), tophi, joint effusion, bone erosion, vascularization enhancement on doppler, and snowstorm appearance.

Statistical Analysis

The results of this study were processed on SPSS software version 24 (SPSS Inc., Chicago, IL, USA) and expressed as descriptive data. All continuous data were presented in mean ± standard deviation (SD). Meanwhile, categorical data were presented in numbers and percentages.

RESULTS

Clinical Characteristics of the Study Population

The clinical characteristics of the patients are shown in Table 1. The study included 15 patients who came to the internal medicine outpatient clinic from February 1st to April 30th, 2015. Patient's average age was 49.27 ± 12.35 years old, predominated by those who were 51-60 years old (46.67 %), followed by the 31-40 years old group (26.67 %), and respectively 13.33 % for 41-50- and 61-70-years old group. The number of female patients (60 %) was greater than male patients (40 %). The laboratory findings of uric acid level with an average of 7.64 ± 1.67 mg/dL.

Table 1. Clinical characteristics of asymptomatic hyperuricemia patients

Characteristics	n (%)
Gender	
Male	6 (40)
Female	9(60)
Age, mean ± SD (years old)	49.27 ± 12.35
31-40	4 (26.67)
41-50	2 (13.33)
51-60	7 (46.67)
61-70	2 (13.33)
Laboratory findings	
Uric Acid (mg/dL)	7.64 ± 1.67

US Findings in Patients with Asymptomatic Hyperuricemia

The Ultrasound findings of the first MCP for asymptomatic hyperuricemia patients are shown in Figure 1. Joint effusion (73 %), double contour sign (66 %), and synovitis (20 %) were documented on ultrasound of the first MCP. Power Doppler ultrasound detected increased vascularity in 1 patient (6 %), as well as tophus and snowstorm appearance documented in 1 patient.

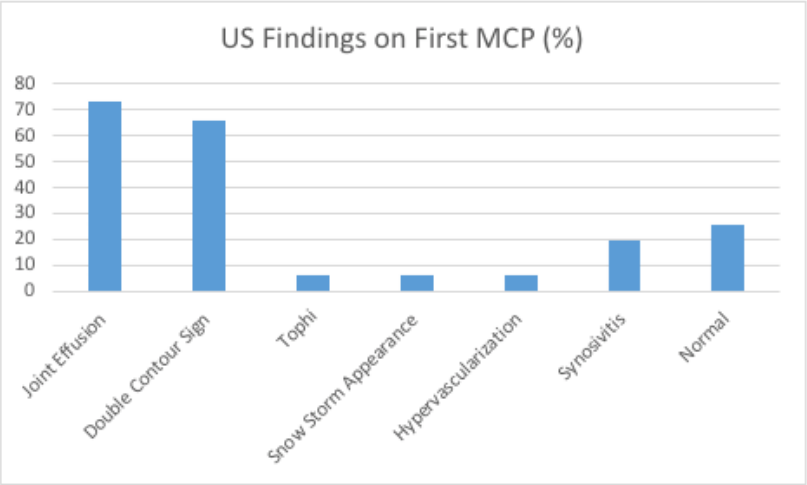

Figure 1. Ultrasound findings on first metacarpophalangeal joints.

Meanwhile, US findings of first MTP joints showed 13 joint effusions (86 %), double contour in 13 patients (86 %), 1 bone erosion (6 %), 3 tophi (20 %), and 2 synovitis (13 %) as shown on Figure 2. There was no hypervascularization nor snowstorm appearance found, and two patients had normal US evaluation of the first MTP.

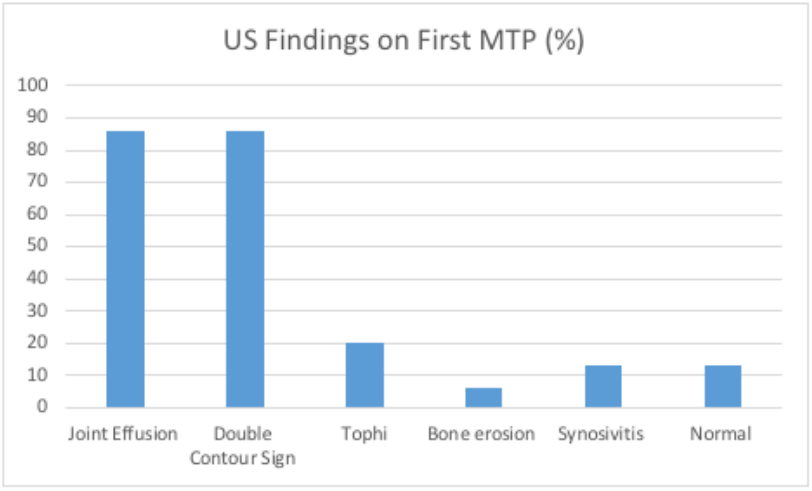

Figure 2. Ultrasound findings on first metatarsophalangeal joints.

From trochlear knees, we found 1 joint effusion (6 %), 1 double countur (6 %), and 14 patients were normal as shown on Figure 3.

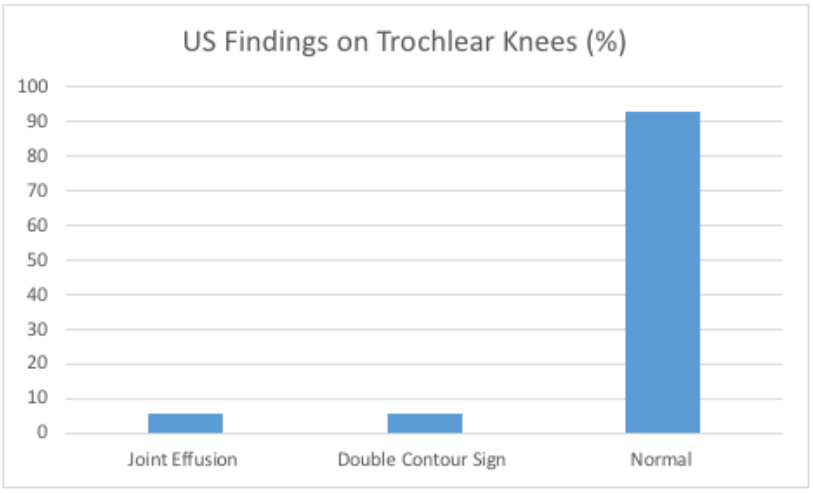

Figure 3. Ultrasound findings on trochlear knees.

DISCUSSION

The demographic of this study shows that the average age of asymptomatic hyperuricemia patients in this study was 49.27 years old, which were correspond to a cross-sectional study of gout and asymptomatic Japanese patients (21). The total sample of our study was limited due to a rare case found in our tertiary hospital, where AHU cases are usually found in first-level referral health facilities. Our study was aimed at demonstrating a wide spectrum of subclinical structural damage in asymptomatic individuals with hyperuricemia. Some structural changes in joints can be seen on ultrasound. Previous studies have confirmed that asymptomatic hyperuricemia and gout may share the same ultrasonic appearance (22-24).

Characteristic US abnormalities of MSU crystal deposits were presented as double contour sign (DCS), hyperechoic aggregates (HAG), and tophi in people with gout and asymptomatic hyperuricemia. Those features of MSU deposition are associated with clinically evident foot-related pain, impairment, and functional disability. Other than those features, soft tissue inflammation (synovial lesions i.e., synovial hypertrophy and synovitis) and bone erosion are also detected in gout and asymptomatic hyperuricemia (13,25). Lower limb joints are more affected in the early stage of gout, especially the first MTP than upper limb joints including hands, wrist, and elbow (13). In this study, we found double contour signs were documented in the ultrasound of the first MCP (66 %) and first MTP (86 %), respectively. It is in line with the study conducted in Mexico, the prevalence of the double contour sign in the first MTP joints was higher in asymptomatic hyperuricemia than in normo-uricemia patients (25 % vs 0 %) (26). Tophi formation was found in the first MCP (6 %) and first MTP (20 %) individuals included in our study, like the study conducted by Pineda et al. (26). Our findings also supported by the systematic review and meta-analysis study showed the most common site scanned was first MTP and the common lesion reported the double contour followed by tophus in asymptomatic hyperuricemia (17).

A study conducted in China showed that HAG is the US sign for early MSU crystal deposition, while DCS and tophi are for chronic gout. DCS and tophi were correlated with bone erosion which made irreversible injuriousness in gout (13). Previous research suggested that MSU deposition in joints is a crucial factor in gouty arthritis attacks. Urate crystal deposits can lead to chronic inflammatory conditions that may trigger a cellular inflammatory response. Asymptomatic hyperuricemia is associated with cardiovascular, renal, and metabolic disease. Evidence suggests that urate-lowering may reduce comorbid risk in patients with asymptomatic hyperuricemia, and timely ULT may also minimize DCS and tophi in gout patients (10,13). Many guidelines for the management of hyperuricemia and gout from various countries show conflicting policies regarding asymptomatic hyperuricemia. According to ACR 2020 and EULAR 2016 guidelines for asymptomatic hyperuricemia patients with no prior gout flares or subcutaneous tophi, they conditionally recommend against initiating any pharmacologic ULT. But Japanese guideline recommends pharmacological treatment using ULT besides lifestyle modification if plasma uric acid level ≥ 9 mg/dL in people without complications such as kidney disease, urolithiasis, hypertension, ischemic heart disease, diabetes mellitus, and metabolic syndrome. Taiwanese guideline also recommends starting ULT treatment if the plasma uric acid level is≥ 9 mg/dL for people with comorbidity and ≥ 10 mg/dL for those without any comorbidity (27-30).

The limitation of our study was no interventional trials to investigate if urate-lowering therapy has positive effects on those patients with asymptomatic hyperuricemia. We did not follow and monitor the clinical condition as well (i.e., development of joint pain/arthritis later on), nor the ultrasound sequence after several months/years.

CONCLUSION

In conclusion, our study contributes some evidence that asymptomatic hyperuricemia demonstrated a wide of structural damages in the evaluation of ultrasonography musculoskeletal. The US seems to be a suitable tool to early detect these structural changes. Our observations might have an impact on further treatment decisions, such as performing musculoskeletal US of predilection joints in patients with asymptomatic hyperuricemia. When to initiate urate-lowering therapy is still a big question, especially in patients with a high risk of pathological specific findings of gout by the US and those with other cardiovascular and metabolic comorbidities.

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ARTÍCULO ORIGINAL

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Effect of White Rice Substitution with Sorghum Rice on Beta Cell Function and Insulin Resistance in Prediabetes

Efecto de la sustitución del arroz blanco por arroz con sorgo sobre la función de las células beta y la resistencia a la insulina en la prediabetes

Teguh Rahardjo[1a], Soebagijo Adi Soelistijo[2b*], Sony Wibisono Mudjanarko[3b]

SUMMARY

Background: *Decrease in the function of beta cells and insulin resistance (IR) is found in prediabetes. Sorghum rice is a staple food substitute for white rice which has low GI and GL, high fiber, rich in polyphenols which can improve IR and beta cell function. This study aims to analyze the effect of sorghum rice on beta cell function and IR in prediabetes.*
Methods: *An open experimental study with a pre-posttest design on prediabetes patients at Bojonegoro Police Polyclinic and Bojonegoro Bhayangkara Hospital. Treatment is standard lifestyle intervention plus the substitution of white rice with sorghum rice for 7 days compared to a standard lifestyle. IR examination using the HOMA-IR formula and beta cell function with HOMA-B.*
Results: *Standard lifestyle intervention plus diet substitution with sorghum rice for 7 days in prediabetes patients resulted in FBG of 7.5 mg/dL (p=0.014) and an increase in HOMA-B of 85.3 % (p= 0.019), while the decrease in HOMA-IR was not significant (p=0.060). When compared with the standard lifestyle, this intervention was better but not statistically significant (p>0.05).*
Conclusion: *Standard lifestyle intervention plus diet substitution with sorghum rice for 7 days influences FBG and beta cell function in prediabetic patients but not on IR.*

Keywords: *Prediabetes, rice sorghum, beta cell function, insulin resistance.*

RESUMEN

Antecedentes: *Disminución de la función de las células beta y resistencia a la insulina (RI) encontrada en la prediabetes. El arroz con sorgo es un alimento básico sustituto del arroz blanco que tiene un IG y un CG bajos, un alto contenido de fibra y es rico en polifenoles que pueden mejorar la función de las células beta y la RI. Este estudio tiene como objetivo analizar el efecto del arroz sorgo sobre la función de las células beta y la IR en la prediabetes.*
Métodos: *Estudio experimental abierto con un diseño de pre-postest en pacientes con prediabetes en el*

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Policlínico de Policía de Bojonegoro y el Hospital Bojonegoro Bhayangkara. El tratamiento es una intervención de estilo de vida estándar más sustitución de arroz blanco con arroz de sorgo durante 7 días en comparación con un estilo de vida estándar. Examen IR utilizando la fórmula HOMA-IR y función de células beta con HOMA-B.

Resultados: *La intervención estándar en el estilo de vida más la sustitución de la dieta con arroz con sorgo durante 7 días en pacientes con prediabetes resultó en FBG de 7,5 mg/dL (p=0,014) y aumento en HOMA-B de 85,3 % (p= 0,019), mientras que la disminución en HOMA-IR no fue significativo (p=0,060). Cuando se comparó con el estilo de vida estándar, esta intervención fue mejor pero no estadísticamente significativa (p>0,05).*

Conclusión*: La intervención estándar en el estilo de vida más la sustitución de la dieta con arroz con sorgo durante 7 días influye en la FBG y la función de las células beta en pacientes prediabéticos, pero no en la RI.*

Palabras clave*: Prediabetes, arroz sorgo, función de las células beta, resistencia a la insulina.*

INTRODUCTION

Prediabetes is a condition where there is an increase in blood sugar or glycated hemoglobin (HbA1c) above normal but does not meet the criteria for diabetes (1). Prediabetes has a risk of 2-10 times becoming diabetes mellitus (DM) and about 1/3 of cases of prediabetes will develop DM. Prediabetes itself is a toxic condition that causes an increase in the occurrence of both macro and microvascular complications (2). The prevalence of prediabetes in Indonesia continues to increase, currently ranking 3rd after China and America at 29.1 million (3). This increase is since health workers and the public, in general, do not know clearly what prediabetes is and how it is managed (4).

Even though prediabetes does not meet the criteria for diabetes, there is a decrease in pancreatic beta cell function by 70 %-80 %, a decrease in beta cell volume by 30 %-40 %, and insulin resistance (IR) that has reached its maximum or is close to maximum (5). The risk of macrovascular complications in the form of cardiovascular disease increases by 13 %, coronary heart disease by 10 %, and stroke by 6 % in prediabetes. The risk of microvascular complications also increases, namely retinopathy by 8 %, microalbuminuria by 15.5 %, and polyneuropathy by 11 %-25 %. 16.6 % of patients with chronic kidney disease are prediabetic (6,7).

Lifestyle modification is the main treatment for prediabetes which includes regulation of dietary intake and activity as well as physical exercise (1,4). One of the characteristics of the Indonesian population is the consumption of white rice as a staple food that has a high glycemic index and glycemic load which is one of the causes of prediabetes (4,8), so it is necessary to replace white rice with other staple foods that has a low glycemic index (GI) and glycemic load (GL).

Sorghum rice is a food substitute for white rice which is processed from the sorghum (Sorghum bicolor) plant which has low GI and GL. Sorghum rice has great potential as nutritional therapy in diabetes and prediabetes because it has a low GI and GL (9,10). Human studies using sorghum bread as a substitute for wheat bread also appear to be effective in lowering post-meal blood sugar and insulin concentrations (9,10). However, existing studies have only investigated blood sugar levels and insulin concentrations after a single meal replacement. In addition, there are no studies that have assessed the replacement of staple foods in the form of white rice with sorghum rice for a longer period. Thus, we investigated the effect of the substitution of white rice with sorghum rice for 7 days on IR and beta cell function in prediabetic patients receiving standard lifestyle interventions. This work attempted to analyze the effect of sorghum rice on beta cell function and IR for prediabetes in Bojonegoro Police Polyclinic and Bojonegoro Bhayangkara Hospital.

MATERIALS AND METHODS

This open experimental study was conducted between March and April 2022. The population was prediabetic patients at Bojonegoro Police Polyclinic and Bojonegoro Bhayangkara Hospital. In this design, there is a control group, namely subjects who get an education on healthy living behavior with a white rice diet, and a treatment group who gets an education on healthy living behavior and a sorghum rice diet for 7 days. Under the supervision of general

practitioners, nutritionists, and health affairs officers at the Bojonegoro Police Polyclinic and Bojonegoro Bhayangkara Hospital, parameters of FBG, HOMA-IR, and HOMA-B were measured before and after treatment (pre and posttest).

The participant had been informed about the goal, procedure, confidentiality guarantee, and the right to refuse to be the subject of research through the form of information for consent. After the participant had agreed to participate in the research, they signed the informed consent form. This research proposal had been certified by the Health Research Ethics Committee in the Faculty of Medicine Airlangga University for ethical clearance (certificate number 52/EC/KEPK/FKUA/2022).

They were recruited using the randomized block technique, by dividing the first three groups, namely normal weight, overweight, and obese. After that, randomization was carried out to be divided into two control and treatment groups. The number of samples required was calculated using a comparative formula with paired numerical data of more than 1 group (11), with the result being 22 participants. Participants included in this study were 18 to 58 years of age, diagnosed with prediabetes in accordance with the PERKENI criteria (12), willing to participate in lifestyle change interventions from polyclinic and hospital, willing to sign informed consent, and have a cellphone with a camera for diet monitoring. Those with pregnant; had malignancy; diabetes; and infection condition, taking blood sugar lowering drugs; steroids; and obesity drugs, had undergone cirrhosis hepatitis Child-Pugh B and C, and had glomerular filtration rate < 60 mL/min/1.73 m^2 were excluded from the study.

The independent variables in this study were sorghum rice and standard lifestyle, while the dependent variables were FBG, HOMA-IR, and HOMA-B. The difference in Fasting glucose, HOMA-IR, and HOMA-B before and after intervention in the treatment group was statistically analyzed using the Wilcoxon Signed Rank test. Measurement of FBG after the participant fasting for 8 hours. HOMA-IR is a mathematical model that estimates the level of insulin resistance based on FBG and basal insulin levels. HOMA-R result is obtained from HOMA-IR = (FBG level in mmol/L x basal insulin level in mIU/mL) / 22.5. HOMA-B is a mathematical model that estimates pancreatic beta cell function based on FBG and basal insulin levels. HOMA-B result is obtained from HOMA-B = (20 × basal insulin level in mIU/mL)/(FBG in mmol/L 3.5 (13).

RESULT

In this study, there were 25 participants involved. Table 1 displays the participants' characteristics. The number of male and female samples was relatively the same where more male samples were given white rice treatment and more female samples were given sorghum rice treatment. The p-value in the sex difference test based on the control and treatment groups obtained a value of 0.158, which indicates that there is no significant differences between sex.

Data on changes in Fasting glucose, insulin, HOMA-IR, and HOMA-B before and after the intervention in the treatment group are shown in Table 2, while data on differences of Fasting glucose, HOMA-IR, HOMA-B before and after intervention in the treatment group using the Wilcoxon signed Rank test (data not normal) is shown in Table 3.

The intervention group of this study showed a significant difference in the value of FBG and HOMA-B pre and post-intervention, while the difference in HOMA-IR was not statistically significant (Table 3).

This study found the FBG delta for the control group with a mean of -2.62 ± 6.89 and a median of -2.00 (-9.00 – 15.00) and a mean intervention group of -7.50 ± 7.19 and a median of -5.00 (-9.00 – 16.00) (Figure 1). Delta of the HOMA-IR control group was -1.41 ± 2.61 and a median of -2.49 (-3.11 – 6.30), while the intervention group with a mean of -1.36 ± 2.40 and median of -2.87 (-3.11 – 4.72) (Figure 2). Delta of the HOMA-B control group was 33.93 ± 85.46 % and a median of 22.19 (-156 – 173.39) %, while the intervention group with a mean of 85.30 ± 118.70 % and median of 40.90 (-72 – 354.76) % (Figure 3).

The results of changes (delta) of FBG and HOMA-B in the control group are better than the

Table 1. Basic Characteristics of Participants of the Study

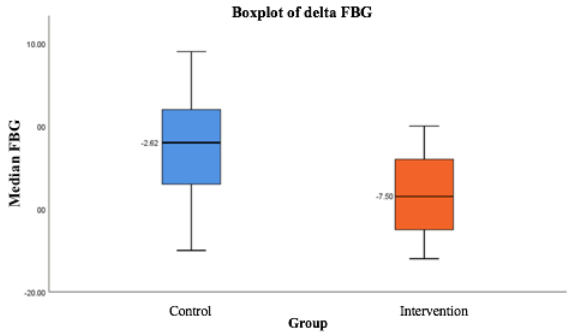
Characteristic	Group		p-value
	Control (White Rice)	Treatment (Sorghum Rice)	
Gender – n (%)			
Male	8 (61.5 %)	4 (33.3 %)	0.158
Female	5 (38.4 %)	8 (61.7 %)	
Age - Mean ± SD	33.83 ± 8.12	39.42 ± 5.68	0.061
Smoking – n (%)			
No	9 (69.2 %)	10 (83.3 %)	0.409
Yes	4 (30.7 %)	2 (16.6 %)	
Hypertension – n (%)			
No	11 (84.6 %)	11 (91.6 %)	0.588
Yes	2 (15.3 %)	1 (8.3 %)	
Systolic Blood Pressure (mmHg)			
Mean ± SD	120.77 ± 14.86	123.17 ± 12.13	0.664
Diastolic Blood Pressure			
(mmHg) Median (Range)	80 (71-106)	82 (70-100)	0.406
Dyslipidaemia – n (%)			
No	5 (38.4 %)	6 (50 %)	0.561
Yes	8 (61.5 %)	6 (0.9 %)	
Body Weight (kilogram)			
Mean ± SD	71.32 ± 12.89	70.60 ± 10.84	0.867
Body Mass Index			
Mean ± SD	27.38 ± 4.03	28.58 ± 4.65	0.500
Abdominal circumference			
(cm) Median (Range)	94 (67-103)	94 (68-101)	0.894
Fasting Blood Glucose			
(mg/dL) Median (Range)	102 (100-125)	104 (100-125)	0.769
Insulin - Mean ± SD	26.46 ± 9.36	27.42 ± 7.67	0.782
HOMA-B			
Median (Range)	180.2 (100.6-288.2)	184.3 (107.6-210.8)	0.247
HOMA-IR Mean ± SD	6.92 ± 2.55	7.20 ± 2.24	0.780
Total Calories	970.71 ± 44.29	961.45 ± 82.24	0.732
Carbohydrate - Median (Range)	132.35 (72.80-139.60)	125.00 (98.00-146.60)	0.574
Protein - Mean ± SD	44.58 ± 6.53	46.37 ± 9.25	0.584
Lipid - Mean ± SD	36.33 ± 5.09	34.41 ± 5.98	0.397
Cholesterol - Median (Range)	68.65 (46-301.80)	103.60 (18.40-556)	0.810
Fiber - Mean ± SD	9.40 ± 2.04	9.48 ± 1.97	0.850

Table 2. Changes in Fasting glucose, insulin, HOMA-IR, and HOMA-B before and after the intervention in the treatment group

Variable	Time	Min-Max	Median	Mean	SD
Fasting glucose	Pre	100 – 125	104	105.67	7.22
	Post	84 – 109	99	98.17	7.27
Insulin	Pre	17.68 – 39.16	29.02	27.42	7.67
	Post	13.40 – 43.30	19.13	23.86	11.01
HOMA-IR	Pre	4.36 – 10.82	7.40	7.20	2.24
	Post	2.90 – 10.47	4.53	5.84	2.75
HOMA-B	Pre	107.56 – 210.76	184.29	162.97	42.07
	Post	107.45 – 470.71	225.19	248.27	122.29

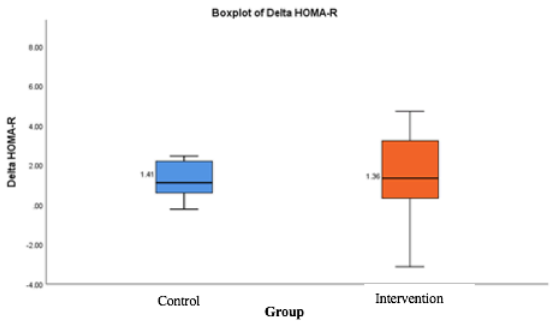
Table 3. The difference in Fasting glucose, HOMA-IR, and HOMA-B before and after intervention in the treatment group

Variable	Time	Median	Mean ± SD	Wilcoxon signed Rank test	
				Delta	p-value
Fasting glucose	Pre	104.00	105.67 ± 7.22	-7.5	0.014*
	Post	99.00	98.17 ± 7.27		
HOMA-IR	Pre	7.40	7.20 ± 2.24	-1.36	0.060
	Post	4.53	5.84 ± 2.75		
HOMA-B	Pre	184.29	162.97 ± 42.07	85.3	0.019*
	Post	225.19	248.27 ± 122.29		



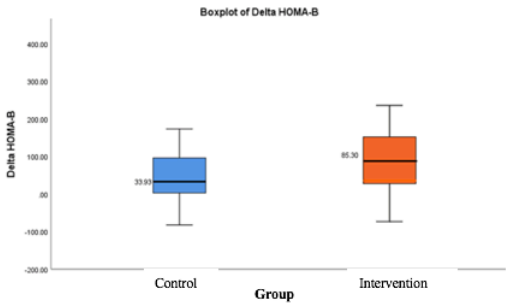
Delta FBG	n	Mean ± SD	Median (Min-Max)	p-value t-test
Control	13	-2.62 ± 6.89	-2.00 (-9.00 – 15.00)	0.096
Intervention	12	-7.50 ± 7.19	-5.00 (-9.00 – 16.00)	

Figure 1. Boxplot diagram of FBG delta comparison before and after intervention between control and treatment groups.



Delta HOMA-R	n	Mean ± SD	Median (Min-Max)	p-value t-test
Control	13	-1.41 ± 2.61	-2.49 (-3.11 – 6.30)	0.961
Intervention	12	-1.36 ± 2.40	-2.87 (-3.11 – 4.72)	

Figure 2. Boxplot diagram of delta HOMA-IR comparison before and after intervention between control and treatment groups.



Delta HOMA-B	n	Mean ± SD	Median (Min-Max)	p-value t-test
Control	13	33.93 ± 85.46	22.19 (-156 – 173.39)	0.224
Intervention	12	85.30 ± 118.70	40.90 (-72 – 354.76)	

Figure 3. Boxplot diagram of delta HOMA-B comparison before and after intervention between control and treatment groups.

intervention group, while the median of HOMA -IR delta is better for the intervention group, but the control group is better on its average. Furthermore, changes in FBG, HOMA-IR, and HOMA-B from the control group were compared with the intervention group. The distribution of changes (delta) of FBG, HOMA-IR, and HOMA-B data was normal, then tested by t-test, the results of which did not give a statistically significant difference for FBG, HOMA-IR, and HOMA-B.

DISCUSSION

The subjects in this study were people with prediabetes in accordance with the PERKENI criteria (12), where the prevalence in Indonesia continued to increase. The proportion of impaired fasting blood glucose by gender is more or less the same, namely 27.3 % for men and 25.3 % for women, while the proportion of impaired glucose tolerance suffered more by women (34.7 %) than men (26.8 %). In this study, the proportion of males compared to females was balanced, that is, of the 25 research subjects, 12 (42 %) were male and 13 were female (48 %), which were not statistically significantly different (p= 0.158) (Table 1) (14).

The prevalence of prediabetes increases with age as beta cell function and insulin sensitivity decrease. The International Diabetes Federation (IDF) in the IDF Atlas 9th Edition reports that the prevalence of impaired glucose tolerance increases with age, and reaches its peak in the 50-54 years age range which reaches around 42 million cases globally; and is predicted to continue to increase in 2030 and 2045, reaching 48 million and 62 million cases, respectively (3). In this study, the mean age of the 25 research subjects was 36.52 ± 7.47 years, while the mean age in the treatment group was 39.42 ± 5.68 years and in the control group 33.85 ± 8.12 years, where they were not statistically different (p=0.061) (Table 1).

Smoking habits can trigger inflammation that results in insulin resistance and increases blood glucose levels. The effect of smoking on prediabetes has been reported in several studies where in the group of active smokers, the risk of developing prediabetes increased 1.8-2.3 times compared to non-smokers. In a young male population, it was found that smoking also increases insulin resistance by decreasing glucose uptake (15). This is found in approximately 10 %-40 % of men who smoke (16,17). In this study, smoking habits in the treatment group (33.3 %) and control (66.7 %) were not significantly different (p=0.409) (Table 1).

Likewise, Systolic Blood Pressure values, the treatment sample had a higher mean of 123.17 mmHg compared to 120.77 mmHg. The Diastolic Blood Pressure values was also higher in the

treatment group where the median value was 82 mmHg compared to 80 mmHg in the control group. P-values for systolic and diastolic blood pressure was 0.664 and 0.406, respectively, which indicates that the distribution of systolic and diastolic values of the research sample is also homogeneous (Table 1). Hypertension and dyslipidemia along with obesity causes insulin resistance and impaired blood glucose levels, increasing the risk of prediabetes and even diabetes. RISKESDAS data found that hypertension contributes to the onset of prediabetes, where the prevalence of prediabetes can be reduced to 56.5 % by preventing the occurrence of hypertension (14). Hypertension also has an important role in causing insulin resistance. Increased activation of the renin-angiotensin-aldosterone system (RAAS) will cause insulin resistance through stimulation of angiotensin II to type 1 receptor, which in turn will increase the production of reactive oxygen species (ROS) in adipocytes, striated muscle, and cardiovascular tissue (18,19). Otherwise, the condition of insulin resistance itself can also increase the risk of hypertension. This occurs through decreased production of endothelium-derived nitrous/nitric oxide. Activation of the sympathetic nerves and increased sodium reabsorption in the kidneys can also increase the incidence of insulin resistance (18). In this study, comorbid hypertension in the treatment group (33.3 %) and control (66.7 %) did not differ statistically (p=0.588) (Table 1).

Likewise, comorbid dyslipidemia in the treatment group (42.9 %) and control (57.1 %) did not differ significantly (p=0.561) (Table 1). Patients with insulin resistance usually show a decreased lipid profile in HDL as well as an increase in VLDL and LDL. Patients with insulin resistance have increased VLDL synthesis which will increase TG. This can occur in obese patients, non-obese, patients with type 2 diabetes mellitus, and even in healthy reported that sorghum supplementation for 90 days significantly reduced total and LDL cholesterol in 15 diabetic subjects, but did not significantly reduce HDL, VLDL, and TG cholesterol (20,21).

Several studies have shown that obesity, especially central obesity, is a strong predictor of the onset of prediabetes. The results of the RISKESDAS data analysis showed that prediabetes was significantly associated with obesity and central obesity; where obesity increases the risk of developing prediabetes by 1.2 times, while central obesity increases the risk of developing prediabetes by 1.5 times (14). In this study, the mean body mass index (BMI) for both the treatment and control groups was included in the WHO category of obesity (BMI > 27.0). The mean BMI of the treatment group was 28.58 ± 4.65 kg/m^2 and the mean BMI of the treatment group was 27.38 ± 4.03 kg/m^2, both of which were not statistically diferent (p=0.50). The weight characteristics of the two groups in this study were also not significantly different (p=0.867), where the mean weight of the treatment group was 70.60 ± 10.84 kg and the control group was 71.32 ± 12.89 kg. The median abdominal circumference measured in this study was found to be the same in both groups, namely 94 cm (Table 1).

In a randomized controlled trial, Anunciacao et al. reported that patients who consumed sorghum experienced significant weight loss, decreased abdominal circumference, hip-to-height ratio, and body fat percentage (22). This study is a clinical dietary intervention study where nutrition in both groups needs to be well controlled. The number of calories received by the treatment group from sorghum rice was 961.45 ± 82.24 kcal/day, while the control group received white rice with total calories of 970.71 ± 44.29 kcal/day, where both were not statistically different (p=0.732). The composition of carbohydrates, protein, fat, cholesterol and fiber from sorghum rice received by the treatment group and white rice received by the control group as a whole did not differ statistically (p=0.574, 0.584, 0.397, 0.810, and 0.850). From this data, it is expected that the treatment bias of the number of calories received between the two groups does not occur (Table 1).

The baseline glycemic profile before treatment in the two groups also did not show a significant difference. The range of FBG levels in the treatment group was 92-125 mg/dL (median = 104) statistically not different from the range of FBG values for the control group of 100-125 mg/dL (median = 102), where the p-value = 0.769. The mean insulin levels of the two groups were also not significantly different (p=0.782), where the mean insulin level in the treatment group was

27.42 ± 7.67 U/mL and the average insulin level in the control group was 26.46 ± 9.36 U/mL. The HOMA-B and HOMA-IR values obtained also did not show a significant difference between the two groups. The range of HOMA-B values for the treatment group was 107.6-210.8 (median = 184.3), while the range of HOMA-B values for the control group was 100.6–288.2 (median = 180.2), where p-value = 0.247. The mean HOMA-R-value for the treatment group was 7.20 ± 2.24, while the mean HOMA-IR-value for the control group was 6.92 ± 2.55, where p-value = 0.780 (Table 1).

Research on the effect of sorghum on FBG, HOMA-IR, and HOMA-B in prediabetes is still very limited. We did not find any research that had the same PICOS (Population, Intervention, Control, Outcome, and type of study). Clinical experimental research that is almost similar to this research is the study by Gu with 15 prediabetic men as research subjects. Gu conducted a sorghum cake intervention compared to a wheat cake control with a washout period of one week. What was measured were post-prandial blood glucose and insulin levels, namely at 15 minutes before (baseline), 0, 15, 30, 45, 60, 75, 90, 120, and 180 minutes after treatment in each group. This study concluded that the sorghum cake had a higher functional fiber content compared to the control; with the benefit of significantly lowering blood glucose and insulin levels at intervals of 45-120 minutes. The mean incremental area under curve (iAUC) blood glucose and insulin levels were significantly reduced by 35 % and 36.7 %, respectively (9).

Research with a longer period is the 2002 DPP in America, within 6 months it was found that there was a significant decrease in FBG and the incidence of DM in the group that underwent lifestyle intervention compared to the placebo group (23). In research conducted by Rachmawati et al. in Indonesia, giving sorghum cake for 28 days to obese subjects reduced FBG from 88.40±7.87 mg/dL to 82.40±4.03 mg/dL which was significant (24).

Most people with prediabetes are not aware that they have prediabetes. Early identification of prediabetes can proactively prevent progression to type 2 diabetes mellitus through diet control, physical activity, and lifestyle changes (25). A large study in China's Da Qing Diabetes Prevention Outcome Study, the Diabetes Prevention Program Research in America, the Japanese Diabetes Prevention Program in Japan, and the Indian Diabetes Program in India showed that lifestyle changes were proven to prevent the occurrence of DM2. Physical exercise and diet both acutely and chronically. combating glucose metabolism and insulin sensitivity (26).

This study compares the standard lifestyle intervention with the standard lifestyle intervention plus the substitution of white rice with sorghum rice. Compared to white rice which has a high GI of 74-82, sorghum rice has a low GI of 32. The glycemic load of sorghum rice (3.15-3.4 for brown sorghum rice and 4.6 for white sorghum rice) is much lower than that of white rice (20.5). The high content of resistant starch (up to 60 %) makes it difficult for rice sorghum to be enzymatically digested by the amylase enzyme during the first 120 minutes (27). This study found a significant difference in fasting blood sugar levels before and after the intervention, but this decrease (-7.50 ± 7.19) did not have a significant difference when compared to the control group (-2.62 ± 6.69; p> 0.05). Research conducted by Rachmawati et al. with a longer study period gave significant results (24). It may take a longer period to show a significant difference between the standard intervention and the standard intervention plus substitution with sorghum rice.

CONCLUSION

Standard lifestyle intervention plus diet substitution with sorghum rice for 7 days influences FBG and beta cell function in prediabetic patients but not on IR. The limitation of this study is that it did not evaluate glycated hemoglobin (HbA1c) and oral glucose tolerance test, and patients' activities, whereas it is also an important point for prediabetes monitoring.

Conflict of interest

The authors declare no conflict of interest.

Sponsor

The authors declare no sponsor is involved.

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Correlation of Dynamic D-dimer Levels with Mortality in COVID-19 Patients with Type 2 Diabetes Mellitus

Correlación de los niveles dinámicos de dímero D con la mortalidad en pacientes con COVID-19 y diabetes mellitus tipo 2

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SUMMARY

Background: *Hypercoagulation characterized by elevated D-dimer has been reported in COVID-19 patients. This condition is aggravated in Type 2 Diabetes Mellitus (T2DM) patients through various mechanisms. This study aimed to analyze the correlation of dynamic D-dimer levels with mortality in COVID-19 patients with T2DM.*
Methods: *This retrospective study was conducted by taking data on adult COVID-19 patients with T2DM. D-dimer levels were checked serially on days 1, 4, 7, 10 and the last examination before patients died or were discharged. Correlation analysis between D-dimer levels and mortality was performed at each examination.*
Results: *Of a total of 224 COVID-19 and T2DM patients, 26.3% were deceased. Median D-dimer days 1, 4, 7, 10, and last examination in survived patients were 870, 960, 930, 885, 770 and deceased patients were 2 640, 2 620, 3 790, 3 440, 3 520, respectively. Patients who died had consistently higher D-dimer levels across all examinations ($p<0.01$). The results from ROC analysis to predict mortality showed that the highest AUCs obtained on day 10 and at the last examination were 0.87 and 0.92, respectively. Similar results were found in correlation analysis with contingency coefficients 0.447 and 0.523, respectively.*
Conclusion: *Dynamic D-dimer correlates with mortality in COVID-19 patients with T2DM.*

Keywords: *COVID-19, Diabetes Mellitus, D-dimer, Mortality*

RESUMEN

Antecedentes: *Se ha reportado hipercoagulación caracterizada por dímero D elevado en pacientes con*

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COVID-19. Esta condición se agrava en pacientes con diabetes mellitus tipo 2 (T2DM) a través de varios mecanismos. Este estudio tuvo como objetivo analizar la correlación de los niveles dinámicos de dímero D con la mortalidad en pacientes con COVID-19 con DM2.
Métodos: *Este estudio retrospectivo se realizó tomando datos de pacientes adultos con COVID-19 con DM2. Los niveles de dímero D se comprobaron en serie los días 1, 4, 7, 10 y el último examen antes de que los pacientes murieran o fueran dados de alta. En cada examen se realizó un análisis de correlación entre los niveles de dímero D y la mortalidad.*
Resultados: *De un total de 224 pacientes con COVID-19 y DM2, el 26,3 % fallecieron. La mediana de los días 1, 4, 7, 10 del dímero D y el último examen en pacientes sobrevivientes fue 870, 960, 930, 885, 770 y los pacientes fallecidos fueron 2 640, 2 620, 3 790, 3 440, 3 520, respectivamente. Los pacientes que fallecieron tenían niveles de dímero D consistentemente más altos en todos los exámenes (p<0,01). Los resultados del análisis ROC para predecir la mortalidad mostraron que las AUC más altas obtenidas el día 10 y en el último examen fueron 0,87 y 0,92, respectivamente. Resultados similares se encontraron en el análisis de correlación con coeficientes de contingencia de 0,447 y 0,523, respectivamente.*
Conclusión: *El dímero D dinámico se correlaciona con la mortalidad en pacientes con COVID-19 con DM2.*

Palabras clave: *COVID-19, diabetes mellitus, dímero D, mortalidad.*

INTRODUCTION

Corona Virus Disease-19 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2). COVID-19 has become a global burden since it was first reported in Wuhan, China, with the number of cases continuing to increase. Various kinds of variants due to mutations have contributed greatly to the increase in COVID-19 cases. Until October 2022, it was reported that the total number of COVID-19 worldwide had reached more than 600 million cases, while in Indonesia more than 6 million cases (1).

Diabetes mellitus is the second most common comorbidity in COVID-19 patients after hypertension, reaching 35.4 %. Diabetes has been known to increase the severity and mortality of COVID-19 (1). A variety of biomarkers are currently used to predict the mortality outcome from COVID-19. D-dimer is a hypercoagulation marker that has long been used in deep vein thrombosis and pulmonary embolism cases and is currently in COVID-19 (2,3). Diabetes mellitus and COVID-19 are closely related to hypercoagulable conditions through overlapping pathophysiological mechanisms (4). The pro-inflammatory conditions in these diseases can induce immunothrombosis. The SARS-CoV-2 virus can directly invade endothelial cells resulting in endothelial dysfunction (5,6), while diabetes also causes endothelial dysfunction due to chronic hyperglycemia and oxidative stress (7). Another mechanism is through the renin-angiotensin system, where ACE2 downregulation in COVID-19 will increase angiotensin-II and decrease angiotensin-1-7 (8), while diabetic patients also have activation of the renin-angiotensin system (9). In the end, pro-inflammatory conditions, endothelial dysfunction, and increased angiotensin-II will lead to a hypercoagulable state.

Inflammatory conditions and coagulopathy in COVID-19 are dynamic processes, where in severe cases, this process can continue and is characterized by an increase in various biomarkers. This study aimed to analyze the correlation between dynamic D-dimer levels and mortality in confirmed COVID-19 patients with diabetes. To our knowledge, this is the first study to analyze this correlation in a population of COVID-19 patients with diabetes.

METHODS

Study Design, Participants, and Data Collection

We conducted a retrospective, analytical study in Dr. Soetomo General Hospital Surabaya, a tertiary referral hospital in Indonesia. A total of 224 patients diagnosed with COVID-19 and type 2 diabetes mellitus (T2DM) from August 1, 2020, to July 31 2021 were enrolled in this study. This study used secondary data taken from medical records.

The diagnosis of COVID-19 was confirmed through a real-time reverse transcriptase-

polymerase chain reaction (RT-PCR), while T2DM was confirmed from past history or HbA1c more than 6.5 at the time of hospitalization. We only included patients hospitalized for at least 7 days, so serial D-dimer data could be obtained. Exclusion criteria included pregnancy, cancer, trauma, history of venous thromboembolism or use of anticoagulants, and incomplete medical record data.

Patients were divided based on the mortality outcome at the end of hospitalization into survived and deceased patients. Data were collected including demographic, symptoms, onset, comorbidities, and laboratory results. Routine laboratory tests such as complete blood count (CBC), liver function tests (LFTs), renal function tests (RFTs), serum electrolytes, C-reactive protein (CRP), procalcitonin, albumin, blood glucose level, and HbA1c were collected on the admission (day 1). D-dimer levels were collected at five-time points: day 1, 4, 7, 10, and the last examination before the patient died or was discharged. We labeled those as DD 1, DD 4, DD 7, DD 10, and DD last. D-dimer was analyzed using Sysmex CS-2500 with units of nanogram/milliliter (ng/mL).

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 for Windows (IBM, Armonk, NY, USA). All data are presented as number (n) and percentage (%) for categorical, median, and range for continuous variables. The normality of data distribution was tested using Kolmogorov-Smirnov. The difference between the two groups was compared using an independent t-test or Mann-Whitney U test as appropriate. The receiver operating curve (ROC) was constructed to evaluate the D-dimer levels in predicting death. The area under the curve (AUC) was calculated, with higher values indicating better discriminatory ability. The correlation between D-dimer level and mortality was assessed by the contingency coefficient, and the odds ratio (OR) was assessed using the optimal cut-off value from the ROC curve. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Demography, clinical characteristics, and laboratory results

A total of 224 patients with COVID-19 and T2DM were included in this study. 165 (73.7 %) patients survived until hospital discharge, while 59 (26.3 %) died. The median age was 54 (25-83) years, male patients were 51.3 %. Most of the patients had a history of diabetes of fewer than 5 years and were first diagnosed during hospitalization. The most common comorbidity was hypertension, followed by chronic kidney disease, coronary artery disease, and others. The median length of hospitalization was 6 days and the length of stay for most patients was more than 14 days. Among survived patients, 53.9 % were severe cases, and all deceased patients were severe cases. Demographic data and clinical characteristics of the patients can be seen in Table 1.

The patient's laboratory results at admission can be seen in Table 2. The blood glucose showed higher results in deceased patients (257 vs. 233), while HbA1c was higher in survived patients (8.6 vs. 9.3). Several inflammatory markers were higher in deceased patients including white blood cells (9.12 vs 8.39), neutrophils (7.56 vs 6.49), NLR (7.6 vs 5.4), CRP (10.7 vs 8), and procalcitonin (0.37 vs 0.2).

Dynamic D-dimer changes based on mortality outcome

In our study, D-dimer values were obtained from all patients on DD 1, DD 4, DD 7, and DD last (survived patients 165 vs. deceased patients 59), but on DD 10 several patients had been discharged or died (survived patients 130 vs. deceased patient 36). The results of our study showed that deceased patients had higher median D-dimer levels than survived patients consistently across all examinations. The difference is statistically significant with p value < 0.001 (Table 3).

Table 1. Clinical characteristics of COVID-19 patients with T2DM on the initial admission

Variable	**All patients (N = 224)**	**Survived (N = 165)**	**Death (N = 59)**
Age (years)			
Median (range)	54 (25-83)	54 (25-82)	56 (32-83)
Sex			
Male	115 (51.3 %)	84 (50.9 %)	31 (52.5 %)
Female	109 (48.7 %)	81 (49.1 %)	28 (47.5 %)
Diabetes onset, years (mean±SD)	3.63±4.65	3.56±4.84	3.81±4.10
First diagnosed	72 (32.1 %)	57 (34.5 %)	15 (25.4 %)
< 5 years	92 (41.1 %)	64 (38.8 %)	28 (47.5 %)
5-10 years	31 (13.8 %)	23 (13.9 %)	8 (13.6 %)
> 10 years	29 (12.9 %)	21 (12.7 %)	8 (13.6 %)
Comorbidity			
Hypertension	89 (39.7 %)	59 (35.8 %)	30 (50.8 %)
CKD	13 (5.8 %)	6 (3.6 %)	7 (11.9 %)
CAD	11 (4.9 %)	7 (4.2 %)	4 (6.8 %)
Stroke	9 (4.0 %)	6 (3.6 %)	3 (5.1 %)
Chronic pulmonary disease	11 (4.9 %)	9 (5.5 %)	2 (3.4 %)
Hepatitis B	10 (4.5 %)	8 (4.8 %)	2 (3.4 %)
Symptom onset, days			
Median (range)	6 (2-14)	6 (2-14)	6 (3-14)
Symptom			
Cough	171 (76.3 %)	125 (75.8 %)	46 (78.0 %)
Shortness of breath	153 (68.3 %)	108 (65.5 %)	45 (76.3 %)
Fever	136 (60.7 %)	98 (59.4 %)	38 (64.4 %)

CAD: coronary artery disease; CKD: chronic kidney disease

Table 2. Laboratory findings of the COVID-19 patients with T2DM on the initial admission

Laboratory Median (range)	All patients (N = 224)	Survived N = 165)	Death (N = 59)
Hemoglobin (g/dL)	13.3 (6.7-16.8)	13.3 (7.1-16.8)	13.1 (6.7-16.7)
White blood cells (x10^9/L)	8.61 (2.72-42.97)	8.39 (2.72-26.09)	9.12 (3.74-42.97)
Neutrophil (x109/L)	6.76 (1.93-41.34)	6.49 (1.93-23.77)	7.56 (2.64-41.34)
Lymphocyte (x10^9/L)	1.11 (0.30-3.39)	1.15 (0.30-3.04)	1.03 (0.51-3.85)
Platelet (x10^9/L)	258 (16-980)	268 (16-712)	232 (95-980)
BUN (mg/dL)	15 (2-110)	14 (2-90)	23 (5-110)
Creatinin (mg/dL)	1.0 (0.4-15.6)	0.9 (0.4-10.8)	1.3 (0.4-15.6)
AST (U/L)	49 (13-233)	46 (13-233)	65 (18-226)
ALT (U/L)	43 (8-368)	40 (8-368)	46 (14-320)
Plasma glucose (mg/dL)	236 (20-624)	233 (20-590)	257 (83-624)
HbA1c (g%)	8.9 (5.5-19.7)	9.3 (5.6-19.7	8.6 (5.5-17.3)
NLR	5.9 (1.1-43.7)	5.4 (1.5-35)	7.6 (1.1-43.7)
CRP (mg/L)	9.0 (0.1-37.9)	8.0 (0.1-37.9)	10.7 (0.9-37)
Prokalsitonin (ng/mL)	0.23 (0.01-100.00)	0.2 (0.01-3.63)	0.37 (0.01-100.00)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio

Table 3. D-dimer results on serial examination during hospitalization

D-dimer, median (ng/mL)	Survived (N = 165)	Death (N = 59)	p-value
DD 1	870	2 640	< 0.001
DD 4	960	2 620	< 0.001
DD 7	930	3 790	< 0.001
DD 10	885	3 440	< 0.001
DD last	770	3 520	< 0.001

Survived patients had relatively stable dynamic D-dimer changes in the range of 500-1 000 ng/dL, while the deceased patient had a sharp increase in D-dimer on day 7, followed by a slight decrease on day 10. On the last examination, D-dimer levels were not much different from day 10 (Figure 1).

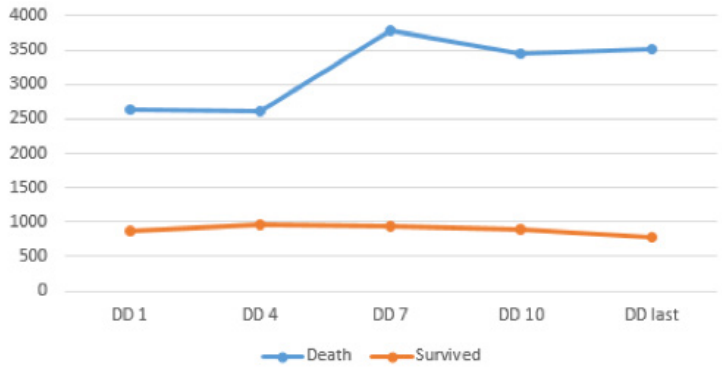

Figure 1. Dynamic D-dimer levels changes (in ng/dL) in COVID-19 patients with T2DM during hospitalization.

Correlation of dynamic D-dimer levels with mortality

The area under the curve of D-dimer levels on DD 1, DD 4, DD 7, DD 10, and DD last is shown in Figure 2 and Table 4. All of them show values more than 0.7, indicating good predictive values for mortality. Apparently, the higher AUCs were obtained with increasing examination time, from 0.759 on DD 1 to 0.865 on DD 10, also the highest AUC was obtained at DD last (0.920). We didn't show the AUC of DD 10 in Figure 2 because of the different numbers of patients.

D-dimer cut-off values as the optimal threshold for predicting mortality in COVID-19 patients with diabetes were shown in Table 4. The correlation of dynamic D-dimer levels with mortality can be seen from the contingency coefficient and odds ratio. In our study, we found a correlation between D-dimer and mortality better

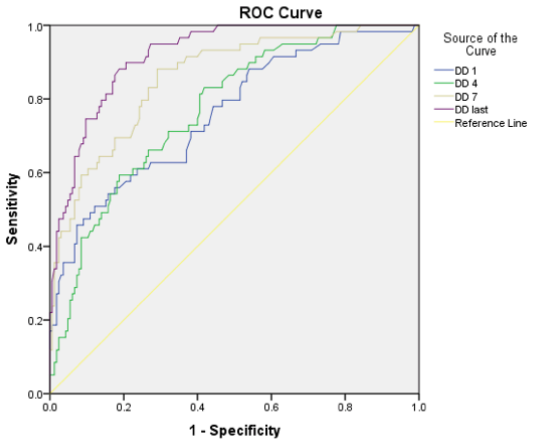

Figure 2. ROC curves of dynamic D-dimer as a predictor of mortality.

on later examinations. Contingency coefficient and OR were obtained respectively on DD 1 0.25 and 3.33 (1.78-6.21), then continued to increase until DD 10 0.45 and 13.35 (5.47-32.6). The highest value was obtained at DD last. All correlation analyses had p< 0.001.

Table 4. AUCs, cut-off values, and correlation analysis between dynamic D-dimer levels with mortality

D-dimer	AUC	Cut off	OR	Contingency coefficient	P value
DD 1	0.759	1 225	3.33 (1.78-6.21)	0.250	< 0.001
DD 4	0.772	1 560	5.22 (2.72-10.01)	0.329	< 0.001
DD 7	0.858	1 770	11.06 (5.43-22.52)	0.438	< 0.001
DD 10	0.865	1 520	13.35 (5.47-32.6)	0.447	< 0.001
DD last	0.920	1 565	23.98 (10.86-52.95)	0.523	< 0.001

Abbreviations: AUC, area under the curve; OR, odds ratio

DISCUSSION

This study was conducted in a referral hospital, so most of the patients were severe cases, thus contributing to the high mortality rate (26.3 %). This result is different from several studies in China which reported about 60 % were non-severe cases (10,11). The median age in this study is consistent with a meta-analysis study (12) but differs from a multicenter study in France (CORONADO study) that showed an older mean age (69.8±13.0 years) (13). Our study also found patients with relatively young age who already had diabetes, with the youngest being 25 years old. Type 2 diabetes mellitus at a young age is currently a burden with an increasing trend and is associated with lifestyle, obesity, and some non-modifiable factors such as genetics.

Most of the patients in our study had a history of diabetes for less than 5 years, followed by a first diagnosed diabetes reaching 32.1 %. A study in China reported slightly different results in first-diagnosed diabetes of 20.8 %, while the CORONADO study reported a mean duration of diabetes of 13.6±10.9 years, with first-diagnosed diabetes only 3.1 % (13). The higher rate of first-diagnosed diabetes compared to other studies is because this condition is more common in developing countries. Indonesia ranks third in the country with the highest number of newly diagnosed diabetes in the world, which is 14.3 million people (14). Another contributing factor is the possibility of COVID-19-induced diabetes, where the invasion of the SARS-CoV-2 on pancreatic beta cells can cause acute disturbances of insulin secretion or even destruction of the beta cells (15). A large number of patients with first-diagnosed diabetes is a burden, especially in developing countries like Indonesia, where new patients are often diagnosed with very high HbA1c levels or various complications. When these patients suffer from COVID-19, they are at a higher risk of experiencing a worse outcome.

The most common comorbidity in our study was hypertension. A meta-analysis reported hypertension reaching 21.4 % in COVID-19 patients (16), Cariou et al. even reported a very high rate of 77.2 % (13). The next most common comorbidities are CKD, CHD, and stroke, with a prevalence of less than 10 %. These three diseases are micro-vascular and macro-vascular complications of T2DM. COVID-19 patients with diabetes have more comorbidities than those without diabetes (17). These conditions also contribute to a higher mortality rate in COVID-19 patients with diabetes due to the higher risk of coagulopathy and organ dysfunction.

We found a high glycemic profile with plasma glucose > 200 and HbA1c > 8.5. A cohort study in the UK showed poor glycemic control before hospital admission and HbA1C levels were associated with higher mortality

in COVID-19 patients (18), however, the CORONADO study reported no association between them (13). The severity of COVID-19 is related to the dysregulated immune response, resulting in a cytokine release syndrome characterized by an increase in pro-inflammatory cytokines, and this condition is exacerbated by hyperglycemia. Patients with COVID-19 with diabetes have decreased lymphocytes and increased neutro-phils, interleukin-6, ferritin, and CRP (19). Finally, diabetes and hyperglycemia in COVID-19 are associated with the worsening condition, Acute respiratory distress syndrome (ARDS), and mortality (20). Glucose-lowering agents, especially insulin, play an important role in the management of COVID-19 with diabetes, especially in hospitalized patients where metabolic stress is generally more severe (19,21). Therefore, it is essential to closely monitor and manage blood glucose levels in COVID-19 patients with diabetes to reduce complications and mortality.

D-dimer levels in our study were consistently higher in deceased patients than in survived patients across all examinations. Long et al. reported similar results to our study, in which D-dimer was examined at baseline, days 3-5, and composite endpoints. D-dimer levels were higher in deceased patients than survived patients, and also higher in later examinations (22). We found that D-dimer levels of survived patients tended to be stable in the range of 500-1000 ng/mL, while deceased patients increased on day 7 and decreased slightly on day 10. Huang et al. reported different results, D-dimer levels on days 1, 3, 7, and 15 continued to increase in deceased patients (23). The clinical course of COVID-19 can be divided into three phases, starting at the beginning of infection (phase 1), then sometimes progressing to pulmonary involvement (phase 2), and less frequently experiencing systemic inflammation (phase 3). Severe COVID-19 occurs in phase 3 which is characterized by cytokine release syndrome, coagulopathy, and ARDS. Phase 2 generally occurs 5-7 days after onset. In the next 5-7 days, a small proportion (about 10 %-15 %) of patients progress to phase 3 which can be fatal, with mortality estimated at 20-30 % (24). In our study, patients presented to the hospital at a median of 6 days of symptom onset. Deceased patients may present in a severe condition (phase 3) so the D-dimer has a high initial value, although some patients may present in phase 2 which progresses to phase 3 and die. By day 7, all patients should be in phase 3 which may explain the increase in D-dimer compared to days 1 and 4.

We performed the ROC analysis to predict mortality in COVID-19 patients with diabetes and determine the cut-off levels on serial D-dimer tests. The cut-off values of the D-dimer can be seen in table 3. The ROC curve analysis showed the AUC at DD 1, DD 4, DD 7, DD 10, and DD last were 0.759, 0.772, 0.858, 0.865, and 0.92, respectively. Our study also shows a significant correlation between dynamic D-dimer and mortality, with contingency coefficients 0.25, 0.329, 0.438, 0.447, 0.523, and odds ratios 3.33, 5.22, 11.06, 13.35, and 23.98, respectively. A meta-analysis reported that patients with high D-dimer levels were at increased risk of mortality with an OR 3.28 (3.00-3.58, $p< 0.001$). The cut-off value of D-dimer in that study varied from 500, 1 000, and 2 000, to more than 2 000 ng/mL (25). Long et al. made ROC curve analysis of D-dimer to predict mortality at days 1, 3-5, and composite endpoint with AUC results from 0.742, 0.818, and 0.851, respectively (22). We can see that D-dimer correlates with mortality better with increasing examination days. The best correlation was found at the last examination before the patient died or was discharged, but it could not be used as a predictor of death because of the uncertainty of the examination time.

The hypercoagulation associated with COVID-19 is a process involving the virus itself, immune response, and ACE2 dysregulation (5,26). The SARS-CoV-2 infection will activate an aggressive inflammatory response, especially in uncontrolled diabetes patients where the immune system is impaired, will trigger uncontrolled production of pro-inflammatory cytokines and even cytokine storms. This hyperinflammatory condition will induce endothelial damage and excessive thrombin formation (19). The longer the history of diabetes, the greater the risk of endothelial dysfunction and micro-vascular or macro-vascular complications, which results in an even greater hypercoagulable condition (27). In addition, organ damage and hypoxemia due to COVID-19 also stimulate thrombosis by

increasing blood viscosity and activating the hypoxia-inducible transcription factor-dependent signaling pathway, leading to decreased blood flow, endothelial dysfunction, and further inflammation (25).

The main causes of death in COVID-19 include ARDS, sepsis with organ failure, and septic shock (28). However, it should be noted that hypercoagulable conditions can contribute to various thrombosis manifestations that can lead to death. The thrombosis manifestations include pulmonary embolism, micro-thrombosis in the lungs or known as pulmonary intravascular coagulopathy, macro-thrombosis, and micro-thrombosis in other organs such as the brain, heart, liver, and even systemic thrombosis (29). In our hospital, most of the COVID-19 patients died from respiratory failure and organ failure due to sepsis. However, we did not find a diagnosis of pulmonary embolism because CT angiography was not performed. We believe that the incidence of a pulmonary embolism due to COVID-19 in our hospital is quite high considering the high number of patients who died from respiratory failure with very high D-dimer levels.

However, this study had several limitations, such as a relatively small sample size, limited available data from the medical record, and a single-center study in one referral hospital. For more accurate and precise results, and wider generalizability of the findings, prospective studies, and a larger sample size are required to confirm the findings further.

CONCLUSION

The results of this study showed that a hypercoagulation characterized by an elevated D-dimer was likely present in patients with COVID-19 and T2DM at the early stage. Hypercoagulation is strongly related to disease progression and mortality outcomes. This can be seen from the higher levels of D-dimer in deceased patients, and the tendency for relatively higher levels on later examination. Correlation analysis also showed a stronger correlation between D-dimer levels and mortality on later examination. Therefore, the D-dimer levels should be monitored as early as possible to detect hypercoagulation-related complications thereby decreasing the morbidity and mortality of COVID-19 patients, especially those with diabetes.

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Conflict of Interest

The authors have no conflict of interest to declare.

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COVID-19 and autoimmune rheumatic diseases

COVID-19 y enfermedades reumáticas autoinmune

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SUMMARY

Background: *Coronavirus disease 2019 (COVID-19) was declared a pandemic since it rapidly spread worldwide. COVID-19 has various manifestations, ranging from asymptomatic to life-threatening conditions. During the pandemic, patients with autoimmune rheumatic diseases (ARD) were included in the population at risk. In addition, the use of immunosuppressants or disease-modifying antirheumatic drugs (DMARDs) was considered to increase the susceptibility to infection. Studies have reported that COVID-19 and ARD have similarities in their clinical findings and immune responses. This study aims to understand the profile of patients with ARD infected with COVID-19 at Dr. Soetomo Hospital in 2020–2022.*
Methods: *An observational cross-sectional study using the medical records of ARD patients was carried out in the rheumatology outpatient clinic at Dr. Soetomo Hospital, Surabaya.*
Results: *This study included 200 patients. Of these, 49 (24.5 %) were infected with COVID-19. The study population was predominantly female (93.9 %), with a mean age of 43±14.3 years old. Methylprednisolone was the most frequent medication used. A total of 63.2 % of the samples had asymptomatic–mild COVID-19 conditions, while the others had moderate–severe COVID-19 conditions. There were 14 cases (28.6 %) that developed ARD post-COVID-19 infection.* **Conclusion:** *The proportion of COVID-19 among ARD patients was 24.5 %.*

Keywords: *Autoimmune rheumatic disease, COVID-19, humans and health.*

RESUMEN

Antecedentes: *La enfermedad por coronavirus 2019 (COVID-19) fue declarada pandemia debido a que se propagó rápidamente por todo el mundo. La COVID-19 tiene varias manifestaciones, que van*

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desde condiciones asintomáticas hasta condiciones que amenazan la vida. Durante la pandemia, los pacientes con enfermedades reumáticas autoinmunes (ERA) se incluyeron en la población de riesgo. Además, se consideró que el uso de inmunosupresores o fármacos antirreumáticos modificadores de la enfermedad (FAME) aumentaba la susceptibilidad a la infección. Los estudios han indicado que COVID-19 y ARD tienen similitudes en sus hallazgos clínicos y respuestas inmunes. El objetivo de este estudio es comprender el perfil de los pacientes con ERA infectados con COVID-19 en el Hospital Dr. Soetomo en 2020-2022. **Métodos:** *Se llevó a cabo un estudio transversal observacional utilizando los registros médicos de pacientes con ERA en la consulta externa de reumatología del Hospital Dr. Soetomo, Surabaya.* **Resultados:** *Este estudio incluyó a 200 pacientes. De estos, 49 (24,5 %) estaban infectados con COVID-19. La población de estudio fue predominantemente femenina (93,9 %), con una edad media de 43±14,3 años. La metilprednisolona fue el medicamento más frecuentemente utilizado. Un total de 63,2 % de las muestras tenían condiciones de COVID-19 asintomático-leve, mientras que el resto tenían condiciones de COVID-19 moderadas-graves. Hubo 14 casos (28,6 %) que desarrollaron ERA post-infección por COVID-19.* **Conclusión:** *La proporción de COVID-19 entre los pacientes con ERA fue del 24,5 %.*

Palabras clave*: Enfermedad reumática autoinmune, COVID-19, humanos y salud.*

INTRODUCTION

The Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-2) was discovered as pneumonia cases in Wuhan City, China, in December 2019. The World Health Organization (WHO) officially named the disease resulting from the infection of SARS-CoV-2 as coronavirus disease 2019 (COVID-19). As the disease rapidly spread worldwide, the WHO then declared COVID-19 a pandemic. In the early days of the pandemic, few studies were conducted related to this disease. However, based on the observations, COVID-19 appeared to have various manifestations, ranging from asymptomatic to life-threatening conditions. Autoimmune rheumatic diseases are characterized by a dysregulation of the immune systems and immune-mediated inflammation against joints, bones, muscles, and connective tissues, predominantly. Patients with ARD were included in the population at risk of COVID-19. ARD patients are dependent on immunosuppressants or DMARDs, which have effects on the immune system to control disease progression. Therefore, an increased risk for worse COVID-19 disease outcomes may be observed in immune-compromised populations (1). It was reported that COVID-19 was twice as common in people with autoimmune diseases compared to the general population (2). Although it seems that the COVID-19 pandemic puts ARD patients at risk, several studies have reported that COVID-19 and ARD have similarities in their clinical findings and immune-mediated injuries, such as cytokine storm and tissue damage (1).

Our study aimed to describe the special interplay between COVID-19 and ARD, which began with data collection of the profile of patients with ARD infected with COVID-19 at Dr. Soetomo Hospital in 2020-2022, including the demographics data, clinical characteristics of ARD patients, their COVID-19 infection, and vaccination history.

METHODS

We conducted a retrospective observational cross-sectional study, including patients with autoimmune rheumatic diseases who were infected with SARS-CoV-2, and who attended the rheumatology outpatient clinic at Dr. Soetomo Hospital, Surabaya.

We obtained the following data from the medical records: demographics, comorbidities, ARD patients' current diagnoses and treatments, and their COVID-19 infection and vaccination history. A diagnosis of SARS-CoV-2 infection was considered if the patients had a positive polymerase chain reaction (PCR) test, a positive antigen test (3), and high suspicions of infection following the clinical symptoms' scoring (4). The COVID-19 severity was determined based on the COVID-19 Treatment Guidelines of the National Institutes of Health (5), which categorized the disease as asymptomatic or presymptomatic infection and mild, moderate, severe, and critical illness.

After collecting the data by total sampling, 49 of 200 patients were eligible for this study. The results of the descriptive analyses are presented in Table 1 using frequencies and percentages for the qualitative variables and median values for continuous variables. The Mann–Whitney test was used to conduct a bivariate analysis of the predictive factors that could determine the severity of the COVID-19 manifestations.

RESULTS

Our study identified 49 patients from a total population of 200, through the inclusion and exclusion criteria. The proportion of ARD patients infected with COVID-19 was 24.5 % (Table 1).

Table 1. COVID-19 History

COVID-19 Infection History	Frequency (n = 200)
History of infection	
Never getting infected	151 (75.5 %)
Infected	49 (24.5 %)

The patients' characteristics are presented in Table 2, including the demographic data, in which females were the majority, and the patients had a mean age of 43±14.3 years. The most common primary ARD diagnoses were undifferentiated spondyloarthritis (SpA), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriatic arthritis, accounting for 44.9 %, 32.7 %, 16.3 %, and 4.1 %, respectively. The frequency of the undifferentiated SpA was higher than the SLE in the sample compared to the population data. There were various ARD-related current medications including methylprednisolone (65.3 %), methotrexate (32.7 %), chloroquine/hydroxychloroquine (26.5 %). The most notable comorbidities among the ARD patients were hypertension (24.5 %), cardiovascular disease (16.3 %), and diabetes mellitus (6.1 %).

Table 2. Characteristics of the ARD Patients Infected with COVID-19

Characteristics of the ARD Patients Infected with COVID-19	Frequency (n = 49)
Sex	
Female	46 (93.9 %)
Male	3 (6.1 %)
Age (years)	43±14.3
≤ 30	13 (27 %)
31 – 40	10 (20 %)
41 – 50	11 (22 %)
51 – 60	8 (16 %)
≥ 61	7 (14 %)
ARD diagnosis	
Undifferentiated spondyloarthritis	22 (44.9 %)
Systemic lupus erythematosus	16 (32.7 %)
Rheumatoid arthritis	8 (16.3 %)
Psoriatic arthritis	2 (4.1 %)
Scleroderma	1 (2.0 %)
ARD current medication	
Not receiving any current medication	2 (4.1 %)
Methylprednisolone	32 (65.3 %)
Methotrexate	16 (32.7 %)
Chloroquine/Hydroxychloroquine	13 (26.5 %)
Sulfasalazine	10 (20.4 %)
NSAIDs	8 (16.3 %)
Mycophenolate sodium	7 (14.3 %)
Azathioprine	4 (8.2 %)
Leflunomide	3 (6.1 %)
Comorbidities	
Hypertension	12 (24.5 %)
Cardiovascular disease	8 (16.3 %)
Diabetes Mellitus	3 (6.1 %)

Table 3 describes the history of COVID-19 infections. More than half of the ARD patients with COVID-19 had asymptomatic–mild COVID-19 clinical conditions (63.2 %), and 36.7 % had moderate–severe clinical conditions. The patients carried out self-isolation (69.4 %) and underwent hospital admission (30.6 %). Only 22.4 % had received the COVID-19 vaccine; two people had been vaccinated once, six people had received two doses, and three people had received three. Despite the infection, 57.1 % of the ARD patients chose to continue their ARD medication, and 14.3 % chose to stop. For those who chose to continue their ARD medication, it was mostly due to the lack of knowledge and information regarding this issue.

Table 3. COVID-19 Infection History

COVID-19 Infection History	Frequency (n = 49)
COVID-19 diagnosis assessment	
PCR swab, positive	35 (71.4 %)
Clinical symptoms	8 (16.3 %)
Antigen swab, positive	6 (12.2 %)
COVID-19 source of infection	
Family	22 (44.9 %)
Public place	15 (30.6 %)
Workplace / School	12 (24.5 %)
Year of COVID-19 Infection	
2021	30 (61.2 %)
2020	10 (20.4 %)
2022	9 (18.4 %)
COVID-19 clinical condition	
Mild	25 (51 %)
Severe	10 (20.4 %)
Moderate	8 (16.3 %)
Asymptomatic	6 (12.2 %)
Management during COVID-19 infection	
Self-isolation	34 (69.4 %)
Hospital admission	15 (30.6 %)
COVID-19 vaccination history	
Unvaccinated	38 (77.6 %)
Vaccinated	11 (22.4 %)
ARD medication status during COVID-19 infection	
Continued	28 (57.1 %)
Not diagnosed with ARD yet	14 (28.6 %)
Stopped	7 (14.3 %)

The data showed that 28.6 % of the sample had a COVID-19 infection before being diagnosed with ARD. The characteristics of the patients diagnosed with ARD post-COVID-19 infection are presented in Table 4.

Table 4. Post-COVID-19 Infection ARD Diagnosis History

Post-COVID-19 Infection ARD Diagnosis	Frecuency (n = 14)
Sex	
Female	12 (85.7 %)
Male	2 (14.3 %)
COVID-19 clinical condition	
Mild	6 (42.9 %)
Moderate	4 (28.6 %)
Severe	3 (21.4 %)
Asymptomatic	1 (7.1 %)
Management taken during COVID-19 infection	
Self-isolation	9 (64.3 %)
Hospital admission	5 (35.7 %)
ARD current diagnosis	
Undifferentiated spondyloarthritis	7 (50 %)
Rheumatoid arthritis	5 (35.7 %)
Systemic lupus erythematosus	2 (14.3 %)

We conducted a bivariate analysis using the Mann–Whitney test to analyze the predictive factors that might determine the severity of COVID-19. In the beginning, we wanted to conduct multivariate analysis with logistic regression, but the potentially predictive factors were not significantly associated with the outcomes, as seen in Table 5.

Table 5. Analysis of the Factors Potentially Predicting the Severity of COVID-19

Potentially Predictive Factors		Severity of COVID-19				p-value
		Asymptomatic	Mild	Moderate	Severe	
Age	≤ 60 years	6	21	8	7	p=0.332 *
	>60 years	0	4	0	3	
Comorbidity	Hypertension or Diabetes or CVD	2	6	6	3	p=0.334 *
	No comorbidity	4	19	2	7	
Continuing DMARDs during COVID-19	Stopped/no medication	2	11	4	4	p=0.810 *
	Continued	4	14	4	6	
Vaccination	Not vaccinated	6	16	6	10	p=0.392 *
	Vaccinated ≥ 1x	0	9	2	0	

* Not significant using the Mann-Whitney test.

DISCUSSION

In this study, 49 of 200 (24.5 %) ARD patients were infected with COVID-19 during 2020-2022. This number was higher than the results of a study conducted by the Indonesian Rheumatology Association (6) in 2020 of 1.93 %. We need to consider that in the early days of the pandemic, the diagnostic tools were not evenly spread, and studies had not been carried out related to the assessment methods for COVID-19. The prevalence and epidemiological characteristics of COVID-19 in Indonesia from March 2020 to February 2021 showed that 15.7 % were confirmed positive for SARS-CoV-2 (7). Another study from Egypt showed relatively the same proportion as our study, at 25.7 % (8).

The female predominance in this study paralleled a previous cohort study conducted by Alhowaish et al. (9). However, the result was contrary to studies that reported that males were more vulnerable to COVID-19 (10). Yet, because our patients were mostly women, conclusions cannot be drawn. Our patients had a mean age of 43±14.3 years. The average number was similar to that of the study of Alhowaish et al. (9) with 48.3±16 years and the study of Bakasis et al. (11) with 46.6±15.4 years in patients with asymptomatic, mild, or moderate disease. Those studies documented the onset of ARD in COVID-19 patients around the fourth decade.

The most common primary ARD diagnoses were undifferentiated SpA, SLE, RA, and psoriatic arthritis. A previous study showed that subjects with SpA were 27 % more likely to develop COVID-19 than the controls, but the increase did not reach statistical significance (12). The results of this study were different from studies conducted in Saudi Arabia, where rheumatoid arthritis (41.8 %) was the most frequent ARD diagnosis in COVID-19-infected patients (9). Theoretically, ARD patients were included in the population at risk during the pandemic due to the underlying immune-mediated disease and their dependence on immunosuppressive or immunomodulatory treatments. As the first-line treatment for SpA, NSAID use was not associated with the severity of COVID-19, worse in-hospital mortality, critical care admission, or ventilation (13). Our study echoed the cohort study conducted in Saudi Arabia (9) with methylprednisolone, methotrexate, and hydroxychloroquine as the three medications most widely used by ARD patients. Corticosteroids play an important role in immunity and inflammation, especially at low doses (14). This study failed to document the dose-related frequency of steroid use, but a study in France reported that corticosteroids were associated with a higher risk of severe COVID-19 (15). However, as the studies on COVID-19 and its treatment have evolved, the use of corticosteroids for COVID-19 therapy has been considered. Most of our patients continued the use of ARD medications during COVID-19. The correlation between the continuation of ARD medications and the COVID-19 clinical outcome needs to be further investigated, and the data regarding the use of systemic corticosteroids in ARD patients during COVID-19 must be interpreted with caution. Aside from methylprednisolone, methotrexate is also widely used by ARD patients. One study in Spain found no difference in the mortality rates between patients admitted for COVID-19 with DMARD use versus no DMARD use (16). Another previous study suggested that the use of methotrexate did not impact the susceptibility to or severity of COVID-19 (12). As stated before, our patients continued their medications despite COVID-19 infection. Advanced study is needed to confirm whether continuing or discontinuing ARD medications during COVID-19 will have a significant impact. In addition, a prospective study of DMARDs' disruption showed that over half of the participants appeared to have a flare of the underlying systemic ARD in the weeks following acute infection (17).

Regardless, there is controversy over the treatments for ARD patients during the COVID-19 course and its associated comorbidities; this study documented asymptomatic–mild symptoms (fever, fatigue, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, and diarrhea) in more than half of the patients. This result was supported by a current observational cohort study, where most patients had a mild course (11). Around 30.6 % of ARD patients were admitted to the hospital during their COVID-19 infection. The result was lower compared to the data from the Global Rheumatology Alliance (18). However,

the ARD patients did not have a significantly high risk of hospitalization (HR: 0.87, 95 % CI: 0.68–1.11) (19).

From the data on whether to continue ARD medication during COVID-19 infection, 28.6 % of the infected participants were not diagnosed with ARD. This finding was in line with a systematic review analyzing the current data of new-onset systemic and rheumatic autoimmune diseases in COVID-19, which identified 99 patients that fulfilled the classification criteria with the common diagnosis of vasculitis and arthritis (20).

In our study, neither age, comorbidities, continuing DMARDs during infection, nor COVID-19 vaccination affected the severity of the COVID-19 manifestations ($p>0.05$). This was different from many studies. This could be due to the small sample size and the fact that we did not differentiate the variants of the SARS-CoV-2 virus.

Our study had some limitations. First, the numbers of participants were limited. Second, since this study used medical records, which provided some of the data based on information provided by the patients, potential biases were inevitable. Third, this descriptive study could not see the strength of the relationship between variables, so further research is needed.

CONCLUSION

Our study emphasized that the ARD patients with COVID-19 at Dr. Soetomo Hospital were predominantly female, with a mean age of 43±14.3 years old. The most common primary ARD diagnoses were undifferentiated SpA, SLE, RA, and psoriatic arthritis. The proportion of COVID-19 among the ARD patients was 24.5 %, with more than half of the sample having an asymptomatic–mild COVID-19 course. Finally, 28.6 % of the ARD cases were diagnosed after COVID-19 infection.

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Conflicts of Interest

The authors declare no conflict of interest.

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Characteristics of COVID-19 Patients who Developed Acute Kidney Injury and Its Association with Mortality: A Systematic Review

Características de los pacientes con COVID-19 que desarrollaron lesión renal aguda y su asociación con la mortalidad: una revisión sistemática

Evan Kurniawan Gianto[1*]

SUMMARY

Introduction: *AKI incidence reported in COVID-19 patients is increasing with contradictory study results about AKI development with increased mortality. This study was conducted to assess a possible correlation between risk factors that led to AKI and increased mortality.*
Methods: *A total of eight articles found through an online database published between 2020 and 2021 were used. A total of 9 455 patients with COVID-19 were divided into AKI and non-AKI.*
Results: *There are 2 754 AKI patients with a mean age of 67, 1 781 (64.7 %) are male, 1 161 (42.1 %) are diabetic, 1 823 (66.2 %) hypertensive, and 1 508 (54.7 %) use mechanical ventilation, with 39.2 % (1 052) mortality rate. In non-AKI patients, there are 6 701 patients with a mean age of 60, 3 595 (53.6 %) are male, 1 759 (26.2 %) are diabetic, 3 133 (46.7 %) hypertensive, and 490 (7.3 %) use mechanical ventilation, with a 7.6 % (508) mortality rate. Several studies suggest various mechanisms of AKI development, including multi-organ dysfunction syndrome, direct kidney infection, acute respiratory distress syndrome, infection-related mitochondrial failure, cytokine storm, SARS-CoV-2 renal tropism, and even mechanical ventilation usage.*
Conclusion: *AKI contributes to and or correlates with severity, prognosis, and mortality in COVID-19 patients. It develops more often in older males with Diabetes and or Hypertension and those with mechanical ventilation compared to non-AKI patients. Mortality in COVID-19 with AKI population is significantly higher than in those without AKI.*

Keywords: *COVID-19, acute kidney injury, diabetes mellitus, hypertension, mechanical ventilation, mortality rate.*

RESUMEN

Introducción: *La incidencia de lesión renal aguda (LRA) en pacientes con COVID-19 está aumentando con resultados de estudios contradictorios sobre el desarrollo de LRA con mayor mortalidad. Este estudio se realizó para obtener una imagen de una posible correlación entre los factores de riesgo que llevaron a la LRA y el aumento de la mortalidad.*

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Métodos: *Se utilizan un total de ocho artículos encontrados a través de una base de datos en línea publicados entre 2020 y 2021. Un total de 9 455 pacientes con COVID-19 se dividieron en LRA y no LRA.*
Resultados: *Hay 2754 pacientes con LRA con una edad media de 67 años, 1 781 (64,7 %) son del sexo masculino, 1 161 (42,1 %) diabéticos, 1 823 (66,2 %) hipertensos y 1 508 (54,7 %) utilizan ventilación mecánica, con una tasa de mortalidad del 39,2 % (1 052). En pacientes sin LRA hay 6 701 pacientes con una edad media de 60 años, 3 595 (53,6 %) son del sexo masculino, 1 759 (26.2 %) diabéticos, 3 133 (46,7 %) hipertensos y 490 (7,3 %) utilizan ventilación mecánica, con una tasa de mortalidad del 7,6 % (508). Varios estudios sugieren varios mecanismos de desarrollo de LRA, incluido el síndrome de disfunción multiorgánica, la infección renal directa, el síndrome de dificultad respiratoria aguda, la falla mitocondrial relacionada con la infección, la tormenta de citoquinas, el tropismo renal por SARS-CoV-2 e incluso el uso de ventilación mecánica.*
Conclusión: *LRA contribuye y se correlaciona con la gravedad, el pronóstico y la mortalidad en pacientes con COVID-19. Se desarrolla con mayor frecuencia en hombres mayores con diabetes o hipertensión y también en aquellos con ventilación mecánica en comparación con pacientes sin LRA. La mortalidad en la población de COVID-19 con LRA es significativamente mayor que en aquellos sin LRA.*

Palabras clave: *COVID-19, daño renal agudo, diabetes mellitus, hipertensión arterial, ventilación mecánica, tasa de mortalidad.*

INTRODUCTION

Coronavirus disease (COVID-19) first emerged in 2019. As this paper was written, the latest WHO Epidemiological Update reported over 278 million cases and 5.4 million deaths worldwide (1,2). Indonesia reported 4 259 644 cases and 143 969 deaths (3). Most infected people developed a mild to moderate respiratory illness and would recover without special treatment or medical attention. Although most patients present with mild symptoms, older people and those with comorbidities are highly prone to develop serious illnesses (1). Some studies focused on pulmonary complications more than other complications, although Acute Kidney Injury (AKI) is common among critically ill patients infected with COVID-19, AKI data are few or they simply report incidence (4-7). AKI is a recognized factor of poor prognosis and is also associated with high mortality rates in ICU (6,8-10). Most patients with AKI are older and have concomitant conditions like Hypertension or Diabetes Mellitus (4,6,11). Therefore, AKI is another notable non-respiratory clinical sign of COVID-19 infection (4). Several studies report variable results for COVID-19-induced AKI, which varies from 3 %-50 % depending on the severity and the setting of the studies, with a mortality rate ranging from 60 %-90 % (6-8,11,12).

Some cells are more vulnerable to SARS-CoV-2 infection, including Artery Smooth Muscle cells, Cardiac Epithelial cells, Gastrointestinal system, Intestinal Epithelial cells, Kidney Tubular Epithelial cells, Liver Endothelial cells, and Pulmonary Alveolar cells type II (10). The kidney is a target for SARS-CoV-2 infection, resulting in virus-induced direct cytotropic effect and cytokine-induced systemic inflammatory response (5,8). Glomerular filtration and urine production may be affected by subsequent stressors such as cytokine storm, hypoxia, drug-associated nephrotoxicity, secondary infection with various viruses, bacteria, and fungi, and the use of high intra-thoracic pressure and PEEP (6,12). Thus, this study was conducted to assess a possible correlation between risk factors that led to AKI and increased mortality.

METHODS

Eligibility Criteria

The following research manuscripts and studies were cited: research papers where the study sample is adults who got infected with COVID-19 that have data on numbers of AKI and non-AKI patients, gender, mean age, comorbidities such as hypertension, and diabetes mellitus, use of mechanical ventilation, and in-hospital mortality rate.

Search Strategies and Study Selection

This study was made in December 2021 by a comprehensive literature search using Google Scholar for articles published between 2020 and

2021, with keywords COVID-19, Acute Kidney Injury, and AKI. A total of 30 articles were collected and screened by the author 5 articles were removed due to duplication, 6 articles were removed after screening the abstract, and 11 articles were excluded due to lack of data of interest. Finally, 8 articles that met all the Inclusion criteria are eligible for use in this study.

Data Extraction

Data extraction was conducted using a standardized extraction table that includes the author's name, location, year, age, sex, hypertension, diabetes mellitus, usage of mechanical ventilation, and mortality rate.

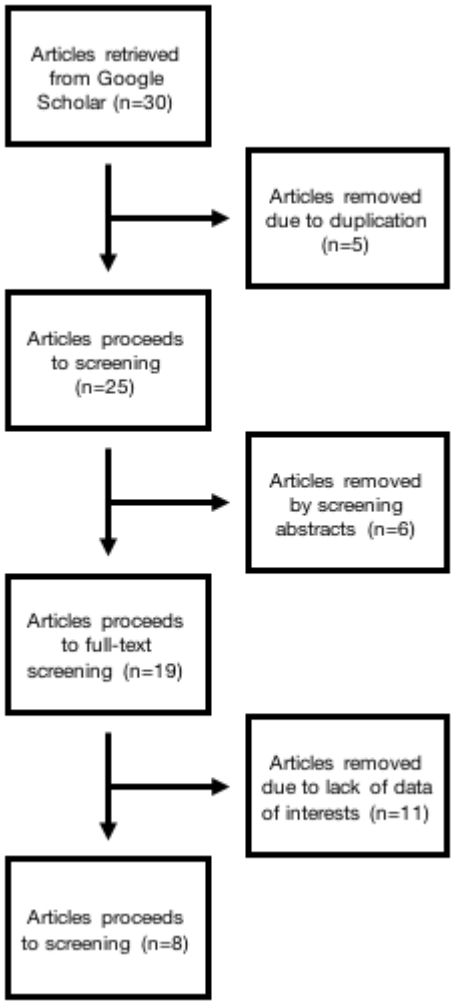

Figure 1. PRISMA flow chart.

RESULTS

Characteristics of the studies

Eight articles used in this systematic review were published between 2020 and 2021. A total of 9 455 patients with COVID-19 from 8 studies were collected. There are 2 754 (29.1 %) patients with COVID-19 who developed AKI and 6 701 (70.9 %) patients who did not develop AKI along the way. All studies report the characteristics of interest such as mean age, gender, diabetes, hypertension, use of mechanical ventilation, and mortality rate.

Characteristics of COVID-19 patients with AKI and without AKI (non-AKI)

Zahid et al. (13) observed 128 patients with AKI, with a mean age of 67, among them 89 (69.5 %) are male, with 67 (52.3 %) diabetic and 97 (75.8 %) hypertensive. 68 (53.1 %) end up with mechanical ventilation and a 52.7 % (109) mortality rate. As for non-AKI patients, there are 341 patients observed with a mean age of 65, among them 179 (52.5 %) are male, with 152 (44.6 %) diabetic and 226 (66.3 %) hypertensives. 32 (9.4 %) ended up with mechanical ventilation and a 28.4 % (97) mortality rate. It was concluded that AKI in COVID-19 is common and carried high mortality.

Hirsch et al. (14) observed 1993 patients with a mean age of 69, among them 1270 (63.7 %) are male, with 830 (41.6 %) diabetic and 1 292 (64.8 %) hypertensive. With 1068 (53.6 %) ending up with mechanical ventilation and a 34.8 % (694) mortality rate. As for non-AKI patients, there are 3 456 patients observed with a mean age of 61, among them 2 047 (59.2 %) are male, with 967 (28 %) diabetic and 1 745 (50.5 %) hypertensive. 122 (3.5 %) ended up with mechanical ventilation and a 5.6 % (194) mortality rate. This study concludes that AKI occurs frequently among COVID-19 patients and is associated with a poor prognosis.

Pelayo et al. (15) observed 110 patients with a mean age of 70, among them 60 (54.5 %) are male, with 58 (53 %) diabetic and 104 (80 %) hypertensive. 37 (34 %) ended up with mechanical

ventilation and a 31 % (34) mortality rate. As for non-AKI patients, there are 113 patients observed with a mean age of 61, among them 55 (48.7 %) are male, with 46 (41 %) diabetic and 76 (64 %) hypertensive. 11 (10 %) ended up with mechanical ventilation and a 9 % (10) mortality rate. It is concluded that there is a high burden of AKI among COVID-19 patients with multiple comorbidities.

Joseph et al. (16) observed 81 patients with a mean age of 60, among them 59 (73 %) are male, with 27 (34 %) diabetic and 48 (60 %) hypertensive. 49 (61 %) ended up with mechanical ventilation and a 28 (35 %) mortality rate. As for non-AKI patients, there are 19 patients observed with a mean age of 54, among them 11 (58 %) are male, with 3 (16 %) diabetic and 8 (42 %) hypertensive. 6 (32 %) ended up with mechanical ventilation and a 5 % (1) mortality rate. This study concludes that the proportion of patients with AKI during severe COVID-19 infection is higher.

Cui et al. (17) observed 21 patients with a mean age of 61, among them 12 (57.1 %) are male, with 2 (9.5 %) diabetic and 9 (42.9 %) hypertensive. 14 (66.7 %) ended up with mechanical ventilation and a 57.1 % (12) mortality rate. As for non-AKI patients, there are 95 patients observed with a mean age of 58, among them 54 (56.8 %) are male, with 26 (27.4 %) diabetic and 29 (30.5 %) hypertensive. 25 (26.3 %) ended up with mechanical ventilation and a 12 (12.6 %) mortality rate. Cui et al. found that patients with AKI had higher in-hospital mortality.

Cheng et al. (18) observed 99 patients with a mean age of 66, among them 67 (67.7 %) are male, with 23 (23.2 %) diabetic and 40 (40.4 %) hypertensive. 80 (80.8 %) ended up with mechanical ventilation and a 71.7 % (71) mortality rate. As for non-AKI patients, there are 1 293 patients observed with a mean age of 63, among them 644 (50 %) are male, with 218 (17 %) diabetic and 459 (35 hypertensives). With 204 (16 %) ending up with mechanical ventilation and a 10 % (129) mortality rate. In contrast with other studies, Cheng et al. found that AKI is uncommon but still carries high in-hospital mortality.

Paek et al. (19) observed 28 patients with a mean age of 74, among them 16 (57 %) are male, with 16 (57 %) diabetic and 22 (78.6 %) hypertensive. 13 (46.4 %) ending up with mechanical ventilation and a 46.4 % (13) mortality rate. As for non-AKI patients, there are 676 patients observed with a mean age of 57, among them 194 (28.7 %) are male, with 107 (15.8 %) diabetic and 204 (30.2 %) hypertensives. With 8 (1.2 %) ending up with mechanical ventilation and a 1.6 % (11) mortality rate. This study concluded that AKI incidence is low, but severe AKI was associated with in-hospital death.

Lee et al. (20) observed 294 patients with a mean age of 69, among them 208 (71 %) are male, with 138 (47 %) diabetic and 211 (72 %) hypertensive. 179 (61 %) ended up with mechanical ventilation and a 40 % (118) mortality rate. As for non-AKI patients, there are 708 patients observed with a mean age of 63, among them 411 (58 %) are male, with 240 (34 %) diabetic and 386 (55 %) hypertensive. 82 (12 %) ended up with mechanical ventilation and an 8 % (54) mortality rate. This study identified a high incidence of AKI in hospitalized patients with COVID-19.

With all studies combined, there are 2 754 AKI patients with a mean age of 67, among them, 1 781 (64.7 %) are male, with 1161 (42.1 %) diabetic patients and 1 823 (66.2 %) hypertensive patients. With 1 508 (54.7 %) ending up with mechanical ventilation and a 39.2 % (1 052) mortality rate. As for non-AKI patients, there are 6 701 patients with a mean age of 60, among them, 3 596 (53.6 %) are male, with 1759 (26.2 %) diabetic patients and 3 133 (46.7 %) hypertensive patients. With 490 (7.3 %) ending up with mechanical ventilation and a 7.6 % (508) mortality rate (13-20).

DISCUSSION

The comparison data of this systematic review showed that patients with AKI present in older patients, an even greater male percentage, a greater percentage of patients with diabetes and hypertension as comorbidities, a significantly higher percentage of mechanical ventilation usage, and a significantly higher mortality rate. Although SARS-CoV-2 mainly targets the respiratory system, as the primary binding site, ACE2 receptor expression determines

Table 1. Study characteristics of AKI patients

Author	Year	Country	Sample	Mean Age	Male, n (%)	Diabetes, n (%)	Hypertension, n (%)	Mechanical Ventilation, n (%)	Mortality, n (%)
Zahid et al.	2020	USA	128	67	89 (69.5)	67 (52.3)	97 (75.8)	68 (53.1)	109 (52.7)
JS Hirsch et al.	2020	USA	1993	69	1270 (63.7)	830 (41.6)	1292 (64.8)	1068 (53.6)	694 (34.8)
Pelayo et al.	2020	USA	110	70	60 (54.5)	58 (53)	104 (80)	37 (34)	34 (31)
Joseph et al.	2020	France	81	60	59 (73)	27 (34)	48 (60)	49 (61)	28 (35)
Cui et al.	2020	China	21	61	12 (57.1)	2 (9.5)	9 (4.9)	14 (66.7)	12 (57.1)
Cheng et al.	2020	China	99	66	67 (67.7)	23 (23.2)	40 (40.4)	80 (80.8)	71 (71.7)
Paek JH et al.	2020	Korea	28	74	16 (57)	16 (57)	22 (78.6)	13 (46.4)	13 (46.4)
Lee et al.	2021	USA	294	69	208 (71)	138 (47)	211 (72)	179 (61)	118 (40)
	Total		2754	67	1781 (64.7)	1161 (42.1)	1823 (66.2)	1508 (54.7)	1052 (39.2)

Table 2. Study characteristics of non-AKI patients

Author	Year	Country	Sample	Mean Age	Male, n (%)	Diabetes, n (%)	Hypertension, n (%)	Mechanical Ventilation, n (%)	Mortality, n (%)
Zahid et al.	2020	USA	341	65	179 (52.5)	152 (44.6)	226 (66.3)	32 (9.4)	97 (28.4)
JS Hirsch et al.	2020	USA	3456	61	2047 (59.2)	967 (28)	1745 (50.5)	122 (3.5)	194 (5.6)
Pelayo et al.	2020	USA	113	61	55 (48.7)	46 (41)	76 (64)	11 (10)	10 (9)
Joseph et al.	2020	France	19	54	11 (58)	3 (16)	8 (42)	6 (32)	1 (5)
Cui et al.	2020	China	95	58	54 (56.8)	26 (27.4)	29 (30.5)	25 (26.3)	12 (12.6)
Cheng et al.	2020	China	1293	63	644 (50)	218 (17)	459 (35)	204 (16)	129 (10)
Paek JH et al.	2020	Korea	676	57	194 (28.7)	107 (15.8)	204 (30.2)	8 (1,2)	11 (1.6)
Lee et al.	2021	USA	708	63	411 (58)	240 (34)	386 (55)	82 (12)	54 (8)
	Total		6701	60	3595 (53.6)	1759 (26.2)	3133 (46.7)	490 (7.3)	508 (7.6)

Table 3. Study characteristics comparison

	AKI (n = 2754)	non-AKI (n = 6701)
Mean Age	67	60
Male, n (%)	1781 (64.7)	3595 (53.6)
Diabetes, n (%)	1161 (42.1)	1759 (26.2)
Hypertension, n (%)	1823 (66.2)	3133 (46.7)
Mechanical Ventilation, n (%)	1508 (54.7)	490 (7.3)
Mortality, n (%)	1052 (39.2)	508 (7.6)

its tropism (5). Several organs that express ACE2 receptors are alveolar type II cells, colon colonocytes, esophagus keratinocytes, ileum, kidney proximal tubules, liver cholangiocytes, rectum, and stomach epithelial cells (12). Men also have a higher ACE2 level compared to women, and to make it worse, SARS-CoV-2 has a selective tropism for the kidneys, this might be due to ACE2 expression in the kidney that is much more than in the lung tissue (5,7,8). In

the kidney specifically, ACE2 is expressed in the brush borders apical membrane of the proximal tubules and podocytes (6,12). As such, SARS-CoV-2 renal tropism is associated with disease severity and finally the development of AKI (21).

Ahmadian et al. found viral components in the urine may be an indicator of renal tubule direct infection (12). A prominent acute proximal tubular injury, peritubular erythrocyte aggregation, glomerular fibrin thrombi, and ischemic collapse due to increased clotting, disseminated intravascular coagulation, and small vessel thrombosis is reported as findings from a kidney biopsy of an AKI patient with COVID-19 (5,12).

Several studies suggest various mechanisms of AKI development, including multi-organ dysfunction syndrome, direct kidney infection, acute respiratory distress syndrome, infection-related mitochondrial failure, and cytokine storm (9). While various mechanisms, including the release of pathogen-associated molecular patterns, COVID-19-associated macrophage activation, hyperferritinemia, cytokine storms, and damage-associated molecular proteins, which can trigger the release of tissue factors and the activation of coagulation factors, can lead to hyper-coagulability (5). Cytokine storm is one of the proposed mechanisms of COVID-19-induced organ damage, therefore, the ideal course of treatment to lower or eliminate inflammatory cytokines would be efficient to avoid cytokine-induced organ damage (12). SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a receptor to facilitate viral entry (11). ACE2 also converts angiotensin II into angiotensin 1-7, which mitigates renin-angiotensin system-related vasoconstriction (6). It is believed that the virus might infiltrate the kidney by invading podocytes and obtaining access to the proximal tubule (5). ACE2 is highly expressed in the kidney's proximal tubule, causing RAAS imbalance (6). In SARS-CoV-2 patients with various characteristics like hypertension, cardiovascular disorders, diabetes, and advanced age, it has been observed that ACE2 deficiency suppresses its protective roles, diminishes anti-inflammatory benefits, and increases the effects of angiotensin II (12). When invasive mechanical ventilation is utilized in combination with a non-protective approach, the inflammatory effects are one mechanism that is being proposed (6).

The proportion of patients developing AKI is significantly higher with severe COVID-19 infection (8). In terms of mortality, Gabarre et al. studied that only AKI stage 2 or above was linked to a higher risk of mortality. This association may reflect the severity of the disease itself or the underlying patient condition (6).

The limitation of this study is that it didn't compare the degree of AKI and also not using data from specific Asian populations which may further elaborate on the correlation between AKI incidence, its severity, and mortality.

CONCLUSION

Acute Kidney Injury needs to be put into consideration when managing COVID-19 patients as it contributes and or correlates with disease severity, prognosis, and mortality of patients. In this systematic review, we found that AKI develops more often in older males, with Diabetes and Hypertension as comorbidities compared to non-AKI patients. The use of mechanical ventilation in AKI patients can translate to current disease severity but also can contribute as aggravating factors for AKI development. With overall mortality in COVID-19 with an AKI population significantly higher than those without AKI, management of COVID-19 that usually focused heavily on the respiratory system needs to put the renal system into consideration.

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Conflict of Interests

The author has no conflicts of interest to declare.

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ARTÍCULO DE REVISIÓN

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Elevated Systemic Immune – Inflammation Index for Predictor of Ulcerative Colitis: A Systematic Review and Meta-analysis

Sistema inmunológico sistémico elevado: índice de inflamación para predecir la colitis ulcerosa: una revisión sistemática y un metaanálisis

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SUMMARY

Introduction: *The Systemic Immune-inflammation Index (SII) is a simple, non-invasive, and low-cost parameter that has been studied to predict ulcerative colitis (UC). However, the result remains inconclusive. Therefore, this study aimed to confirm the utilization of SII in UC.*
Methods: *A systematic search was conducted. The inclusion criteria were articles that investigated the relationship between SII and UC and reported a specific cut-off value, specific sensitivity, specificity, and area under the curve (AUC). The odds ratio (OR) and mean difference (MD) using a 95 % confidence interval (CI) were used.*
Results: *Five studies enrolling 1386 patients were included. SII Index was significantly higher in UC patients (MD: 523.48 (95 % CI 303.89-743.07, P<0.00001). Furthermore, four studies were included in sensitivity, specificity, diagnostic odds ratio, cut-off values, and AUC analyses. The SII Index of 595.47 was the cut-off value for UC, with a sensitivity of 57 % and a specificity of 69 %. The AUC was 0.66 (95 % CI 0.61-0.70).*
Conclusion: *The SII index significantly increased in UC. Patients with SII >595.47 had odds of UC threefold greater than patients with lower SII.*

Keywords: *Ulcerative colitis, systemic immune-inflammation index, meta-analysis.*

RESUMEN

Introducción: *El Índice de Inflamación Inmune Sistémica (SII) es un parámetro simple, no invasivo y de bajo costo que ha sido estudiado para predecir la colitis ulcerosa (CU). Sin embargo, el resultado sigue sin ser concluyente. Por lo tanto, este estudio tuvo como objetivo confirmar la utilización de SII en CU.*
Métodos: *Se realizó una búsqueda sistemática. Los criterios de inclusión fueron artículos que investigaron la relación entre SII y UC e informaron un valor de corte específico, sensibilidad específica, especificidad*

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y área bajo la curva (AUC). Se utilizaron los odds ratio (OR) y la diferencia de medias (DM) utilizando un intervalo de confianza (IC) del 95 %.
Resultados: *Se incluyeron cinco estudios con 1 386 pacientes. El índice SII fue significativamente mayor en pacientes con CU (DM: 523,48 (IC del 95 %: 303,89-743,07, P<0,00001). Además, se incluyeron cuatro estudios en cuanto a sensibilidad, especificidad, razón de probabilidades diagnósticas, valores de corte y análisis de AUC. El índice SII de 595,47 fue el valor de corte para la CU, con una sensibilidad del 57 % y una especificidad del 69 %, el AUC fue de 0,66 (IC 95 % 0,61-0,70).*
Conclusión: *El índice SII aumentó significativamente en la CU. Los pacientes con SII> 595.47 tenían probabilidades de CU tres veces mayores que los pacientes con menor SII.*

Palabras clave: *Colitis ulcerosa, índice de inmuno-inflamación sistémica, metaanálisis.*

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory condition of the mucosal colon, which is associated with genetic predisposition, epithelial barrier defects, dysregulated immune responses, and environmental factors (1). Incidence rates of UC vary considerably depending on the region. In 2017, UC incidence rates ranged from 0.97 to 57.9 per 100 000 in Europe, 8.8 to 23.14 per 100 000 in North America, and 0.15 to 6.5 per 100 000 in Asia and the Middle East (2). Nonetheless, with increasing urbanization and a shift from rural areas to cities, UC incidence in Asia has significantly risen (3).

The diagnosis of ulcerative colitis is made by clinical, endoscopic findings and histological evaluation. Determination of disease activity is essential in determining the patient's treatment (1). Imaging under endoscopy may accurately reflect the current inflammation of the intestines. Endoscopy biopsy is essential in determining a diagnosis, disease severity, treatment response, and recurrence (4). However, it is expensive, invasive, and weakly repeatable, and surgery may aggravate the disease (5). Hence, researchers continued to explore non-invasive measurements to determine the severity of UC and the level of inflammatory burden.

Several biomarkers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fecal calprotectin (FC), and fecal lactoferrin (FL), are currently used for this purpose (6). Although CRP and ESR can help differentiate inflammatory from noninfectious conditions, these are nonspecific markers that can be increased in various other disease states (7,8). ESR is nonspecific and does not change as rapidly as CRP, further limiting its utility (7). While FC and FL levels are affected by bowel movements, different results can be obtained in the following days, and not practical to collect specimens (7,9,10). For these reasons, the search for a reliable, fast, and easy non-invasive method to determine the activity in ulcerative colitis continues.

The systemic immune-inflammation index (SII) is a simple, non-invasive, and low-cost biomarker of the inflammatory status and immune response. SII, combined with neutrophils, lymphocytes, and platelets, was first used in 2014 by Hu to evaluate the prognosis of hepatocellular carcinoma (HCC) (11). It is obtained by multiplying the neutrophil count and platelet count and dividing by the lymphocyte count. A higher SII value indicates a relatively low lymphocyte count and elevated neutrophil and platelet counts, demonstrating a more robust inflammatory response and weaker cell-mediated immunity (12). In recent years, SII has been used as a biomarker for predicting and assessing neuropsychiatric impairment, inflammatory disease, and cancer (13-15). Several studies have investigated the predictive value of SII in diagnosing UC. However, the result remains inconclusive.

This study aimed to determine the diagnostic test value of the SII in patients with clinical suspicion of UC. Our primary objective was to investigate whether SII can predict UC and distinguish between UC/active UC and non-UC/remission UC. Our second objective was to determine cut-off values of SII for UC and non-UC.

METHODS

This systematic review was performed according to an agreed predefined protocol. The study was conducted and presented according to Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) statement standards (16). The protocol for this study is registered in the international prospective register of systematic reviews (PROSPERO registration number CRD42022369714).

Eligibility criteria

This study included all observational studies reporting SII in participants of any age and gender with clinical suspicion or confirmed diagnosis of UC or active UC. Comparisons of UC or active UC versus non-UC or remission UC are considered in this study.

Studies were included if they met the following criteria: (a) the studies investigated the SII value in UC/active UC versus non-UC/remission UC; (b) a specific value of area under the curve (AUC) and a cut-off value divided the patients into high and low groups; (c) a specific diagnostic sensitivity and diagnostic specificity value; and (d) the studies had sufficient data to evaluate the diagnostic odds ratio (DOR).

Furthermore, articles were disqualified if they met the following criteria: (a) non-English study; (b) they were duplicate articles, reviews, conference summaries, and letters; (c) they were basic medical experiments, animal studies, case reports, and editorials; (d) the studies had unavailable data.

Search strategy

A systematic search of several online databases (Pubmed, SAGE Journals, Scopus, Web of Science, and Google Scholar) was performed on September 25, 2022, using the terms "(SII index OR systemic immune-inflammation index) AND ulcerative colitis".

Selection Process

Two authors independently screened the literature and identified relevant studies according to inclusion and exclusion criteria. Any disagreements were resolved by discussion with the third author.

Data Extraction

Two authors independently extracted the data from selected studies using Microsoft Excel. The following data were extracted from included studies: first author's name, year of publication, country, study design, study size and clinical condition of the study participants, sample size, clinical information of the study populations, and outcome data. The third author resolved any disagreements.

Quality assessment

Two authors used the Newcastle-Ottawa Scale to evaluate the quality of non-randomized studies in meta-analysis to determine the risk of bias (17). The quality of included studies was measured using three criteria: 1) selection, 2) comparability, and 3) outcome. The quality of the studies (good, fair, and poor) by awarding stars in each domain following the guidelines. A "good" quality score requires a selection score of 3 or 4 stars, a comparability score of 1 or 2, and an outcome score of 2 or 3. Two stars in the selection, one or two stars in comparability, and two or three stars in the results were necessary for a "fair" quality score. A "poor" quality score corresponded to a selection score of 0 or 1, a comparability score of 0 or 1, or an outcome score of 0 or 1.

Statistical analyses

For the primary objective of this study, we calculated the mean SII for each group in each comparison. Data are presented as mean differences (MD) and standard deviations (SDs). Median, sample size, range, or interquartile range were used to estimate mean and SD (18,19) The Stata 17 software was used for descriptive statistics, and the Review Manager 5.4 software was used for meta-analysis. The individual patient was used as the unit of analysis. Because of the anticipated clinical between-study heterogeneity, we used the random effects model for the analyses, and results were reported in a forest plot with 95 % confidence intervals (CIs).

Heterogeneity among the studies was assessed using the Cochran Q test (χ^2). We quantified inconsistency by calculating I^2 and interpreted it using the following guide: 0 %-50 % may represent low heterogeneity, 50 %-75 % may represent moderate heterogeneity, and 75 %-100 % may represent high heterogeneity. Pooled estimates for sensitivity, specificity, diagnostic odds ratio (DOR), and positive and negative likelihood ratios with the corresponding 95 % confidence interval (CI) were calculated using the Midas command in Stata 17 to measure the effectiveness of a diagnostic test. A summary receiver operating characteristic (SROC) curve was generated, and AUC analyses were used to describe overall accuracy as a potential summary of the SROC curve (20). Youden index statistic was used to identify the best predictive cut-off values (21).

Publication bias assessment

The Egger test assessed publication bias for a small study effect; $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of included study

A total of 75 records were found in our initial article search. After duplicates were excluded, 65 articles were screened, and five studies were assessed for eligibility. Five studies were included in the systematic review and meta-analysis. A flowchart of the included study is shown in Figure 1.

Characteristics of the five prospective single-center studies are presented in Table 1. Five studies enrolling 1 386 patients were included in pooled weight mean difference analysis (22-26), and four studies enrolling 984 patients were included in sensitivity, specificity, DOR, cut-off value, and AUC analyses (23-26). Three studies compared active UC versus remission UC (22-24), and two analyses UC versus non-UC (25,26). The optimal cut-off of SII in predicting UC ranges from 485.95 - 781.5.

Quality assessment

Quality assessment of all included studies was done using the Newcastle–Ottawa Scale. The assessments of studies are shown in Table 2. The overall quality of included studies was fair, but there was a study with poor quality.

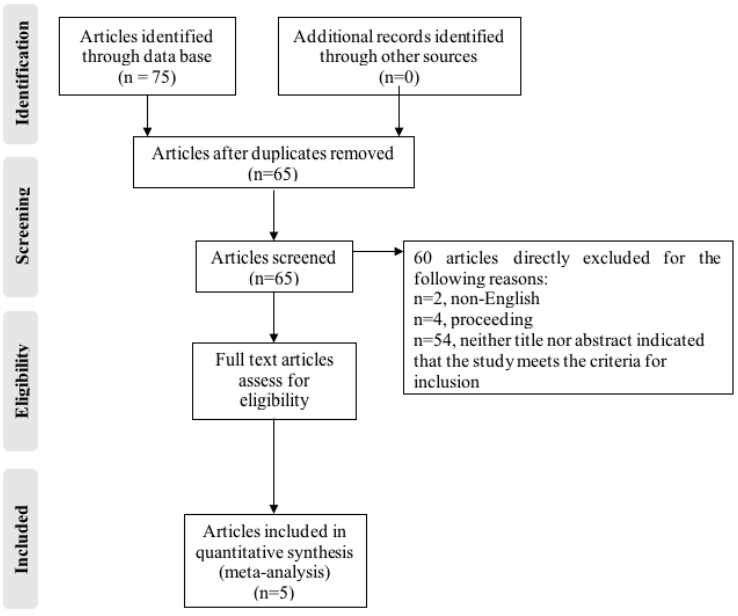

Figure 1. PRISMA flow chart of included studies.

Table 1. Baseline characteristic of included studies

First author	Year	Country	Study design	Study size (n)	Active UC	Control	Mean age	Centers	Optimal cut-off
Güven	2022	Turkey	Retrospective	402	237	165	47.4±13.7	Single	-
Lin	2022	China	Retrospective	187	151	36	47.4 ± 16.3	Single	595.47
Pakoz	2022	Turkey	Retrospective	81	47	34	44.0 ± 15.20 (active UC): 46.9 ± 13.5 (control)	Single	781.5
Xie	2021	China	Retrospective	362	187	185	41.94 ± 13.40 (active UC); 42.37 ± 10.70 (control)	Single	485.95
Zhang	2021	China	Retrospective	344	172	172	48 (35-57) (active UC); 47.50 (37-56) (control) *	Single	562.22

*Median (interquartile range)
Abbreviations: n, sample size; UC, ulcerative colitis

Table 2. Newcastle Ottawa Scale quality assessment

Items	Selection Adequacy of case definition	Representative of the cases	Selection of controls	Definition of controls	Comparability	Exposure Ascertainment of exposure	Same method of ascertainment	Non-Response Rate	Total scores	Quality assessment based on Ottawa scale
Güven (2022)	*	*	-	*	*	*	*	-	6	Fair
Lin (2022)	*	*	-	*	*	*	*	-	6	Fair
Pakoz (2022)	*	*	-	*	**	*	*	-	7	Fair
Xie (2021)	*	*	-	*	**	*	*	-	7	Fair
Zhang (2021)	*	*	-	*	*	*	*	-	6	Fair

Meta-analysis

The forest plot of SII value between patients with active UC/UC and control/remission UC is shown in Figure 2. SII was significantly higher in patients with active UC/UC (MD: 523.48 (95 % CI 303.89-743.07), p<0.00001). However, heterogeneity was significant (p<0.00001; I^2=95 %). The likelihood of publication bias was significantly based on the Egger test (p=0.0107).

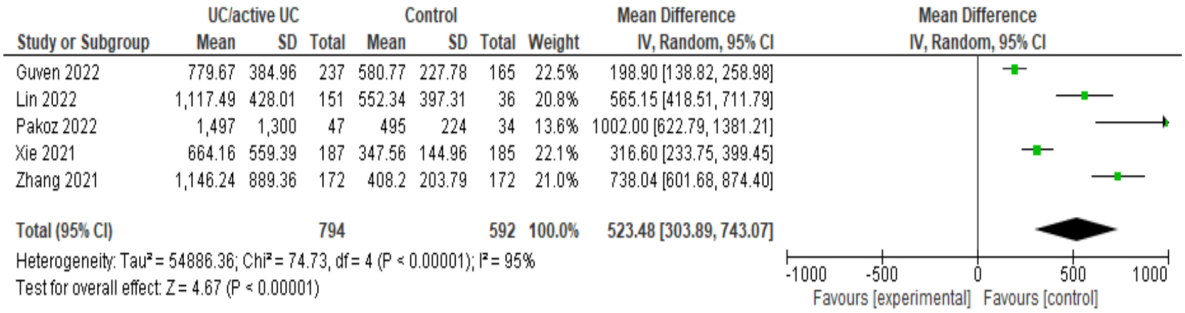

Figure 2. Forest plot of mean difference.

Accuracy of SII in predicting UC

Heterogeneity analysis showed that the sensitivity and specificity I^2 values were high ((92.00 (95 % CI 85.83-98.16), p<0.001) and (91.17 (95 % CI 84.18-98.16) p<0.001), respectively) and both p values were <0.001, indicating significant interstudy heterogeneity. The overall sensitivity and specificity of the SII in predicting UC were 57 % (95 % CI 45 % - 69 %) and 69 % (95 % CI, 49 %-84 %), respectively (Figure 3). The positive likelihood ratio, negative likelihood ratio, and DOR were 1.9 (95 % CI, 0.9-4.0), 0.61(95 % CI, 0.37-1.0), and 3 (95 % CI, 1-11), respectively. The Youden index determined the optimum SII cut-off as > 595.47. SROC analysis plot is shown in Figure 4. The AUC was 0.66 (95 % CI 0.61-0.70), implying that the SII was poor discriminant to predict UC cases.

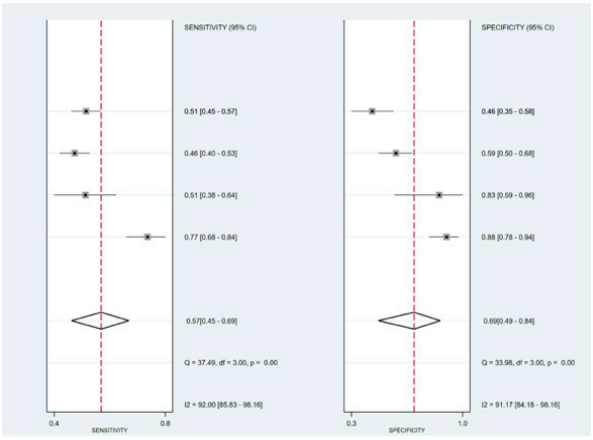

Figure 3. Forest plots for the sensitivity and specificity of the SII in predicting UC.

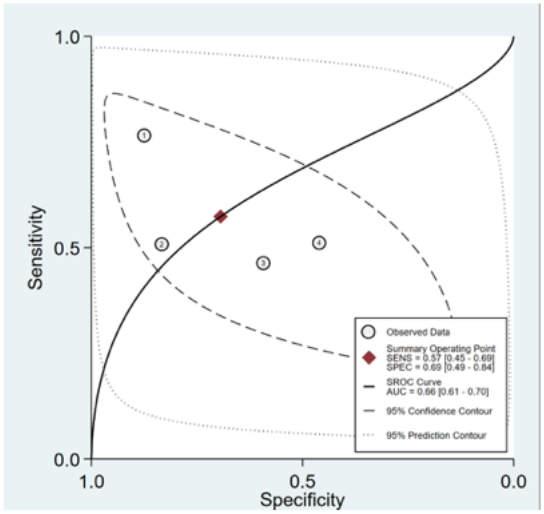

Figure 4. SROC curve of SII in all studies.

DISCUSSION

UC is a chronic inflammatory condition that frequently relapses. Several studies have reported relapse after clinical remission. Fukuda et al. reported a relapse rate of 26 % after two years in patients treated with 5-Aminosalicylic acids (5-ASA) (27). Bello et al. reported that 75 % of patients treated with mesalazine relapsed after 29 months of follow-up (28). Bots et al. reported that 18 of 24 UC patients relapsed in median 18 months follow-up after anti-TNF therapy withdrawal (29). Assessment to diagnosis is important to help the clinician monitor activity and determine therapy.

Truelove and Witts criteria scores are widely used for determining UC clinical remission. Nevertheless, the chief of these limitations are the ambiguous definitions of improvement and worsening and the lack of a severity score that can be tracked over time (30). Presently, colonoscopy and pathology biopsy remains the gold standard for determining the diagnosis and severity of ulcerative colitis (31). However, a severe case of UC is not a candidate for a colonoscopy since it could result in operation-related damage (32). Also, colonoscopy does not help predict disease recurrence in remission patients. Therefore, it is crucial to find a suitable non-invasive measurement.

An appropriate diagnosis and monitoring help the clinician to achieve and maintain the remission stage. Several examinations and biomarkers have already been established to help diagnose and monitor UC's severity. The simplest biomarker to detect the active stage suggested in Truelove – Witts's criteria is ESR and CRP. However, CRP and ESR will also increase quickly when tissue necrosis, infection, and other factors occur. Consequently, using it as a sole index to evaluate activity is insufficient (33). Other indicators should be used in addition to colonoscopy and other testing techniques.

The systemic immune-inflammation index (SII) is a simple, non-invasive, and low-cost biomarker of the inflammatory status and immune response. We performed this study to determine whether SII can predict UC/active UC. Our study showed that SII was significantly higher in patients with UC/active UC compared to those with non-UC/remission UC. Our results suggested that patients with SII value > 595.47 has odds of the UC/active UC happening threefold greater than patients with lower SII value. However, our SROC results show that the AUC is 0.66 (95 % CI 0.61-0.70), which means poor discrimination. This may be because SII may not be specific for UC, and SII values will be elevated in any inflammatory condition. So, focusing on the distribution of the future population with and without risk factors is necessary. This is because this risk distribution ultimately determines the risk distribution of cases/patients and controls/non-patients, which ultimately determines the ROC and AUC curves. A broader population risk distributions result in an enormous AUC of the ROC curve (34).

Other biomarkers extensively studied to predict UC are the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR). Similar to SII, NLR is a simple biomarker derived from hematological parameters. A meta-analysis by Ma et al., which included 11 articles, showed that the NLR of patients with UC was significantly higher than that of the control group (35). Nevertheless, this study did not perform diagnostic test accuracy analysis. Meanwhile, the summary study of PLR utilization in UC does not yet exist, so the results are inconclusive.

The major strengths of our study are the use of a more advanced statistical power approach and resolution to combine the outcomes of different analyses better understand the diagnostic accuracy of SII value for predicting UC. To our knowledge, our study is the first meta-analysis to investigate the predictive value of SII in UC.

There are some inadequacies in our study. First, only five articles were included in the meta-analysis, the number of participants in each study was relatively small, and the research addressed China and Turkey populations, which limits the universality of the population and may affect the conclusion. Second, the heterogeneity of the conclusion is high. Third, there was significant publication bias was observed in the Egger test.

Future studies comparing or combining the SII with other biomarkers such as NLR, PLR, and CRP might be needed to verify the most reliable one to predict relapse or active UC. In addition, a further meta-analysis with more studies in

prospective, multicenter, and large populations is also needed to confirm the diagnosis accuracy of SII.

CONCLUSION

The SII value of UC/active patients was significantly higher than in non-UC/remission UC. It is suggested that SII may be a valuable biomarker to predict the activity of UC. However, there are some inadequacies in our study. Further studies comparing or combining SII with other simple biomarkers such as NLR, PLR, and CRP might be needed to verify the best predictive value to predict UC/active UC. In addition, meta-analysis in prospective studies, multicenter, and large populations are needed to confirm the diagnosis accuracy of SII for predicting UC.

The Academic Collaboration of the Authors

Noer Halimatus Syakdiyah: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft.

Hendy Bhaskara Perdana Putra: Conceptualization, Methodology, Validation, Writing - original draft.

Noer Halimatus Sya'baniyah: Resources, Writing - original draft, Writing- review, and editing

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Conflicts of Interest

The authors declare no conflict of interest.

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A Rare Case of Insulinoma in a Patient with Hydrocephalus and COVID-19

Un caso raro de insulinoma en un paciente con hidrocefalia y COVID-19

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SUMMARY

Insulinoma is a rare entity, in which neuroglycopenia symptoms of recurrent hypoglycemia are often confused with the neuropsychiatric disorder, especially in a patient with hydrocephalus. Hypoglycemia leads to a proinflammatory and procoagulant state, which may worsen the COVID-19 prognosis. We report a case of a 25-year-old woman with an initial presentation of seizure. No previous medical history and drugs were recorded. Intravenous dextrose is administered as low blood sugar was evident but no marked improvement in consciousness was observed. Later head CT scan revealed hydrocephalus and brain atrophy. While intracranial lesion was thought to be the reason, recurrent hypoglycemia was recorded despite meticulous partial parenteral nutrition. Plasma insulin and C-peptide test showed inappropriately high values in the hypoglycemic state (154.5 uIU/mL and 12.1 ng/mL, respectively) and lead to insulinoma, which was in accordance with the MRI result. Thorough non-operative management was commenced, and blood glucose was eventually controlled. Unfortunately, the patient developed pneumonia COVID-19 and died of respiratory failure. Diagnosis of insulinoma in hydrocephalus patients with seizures and altered levels of consciousness is challenging. Non-operative management is difficult in an unconscious patient, let alone in an isolation room. Moreover, the COVID-19 prognosis is proven to be worse in hypoglycemic patients.

Keywords: *COVID-19, hydrocephalus, hypoglycemia, insulinoma, seizures.*

RESUMEN

El insulinoma es una entidad rara, en la que los síntomas de neuroglucopenia de hipoglucemia recurrente a menudo se confunden con un trastorno neuropsiquiátrico, especialmente en un paciente con hidrocefalia. La hipoglucemia conduce a un estado proinflamatorio y procoagulante, lo que puede empeorar el pronóstico de la COVID-19. Presentamos

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el caso de una mujer de 25 años con un cuadro inicial de convulsiones. No se registraron antecedentes médicos ni fármacos. Se administró dextrosa intravenosa ya que era evidente un bajo nivel de azúcar en la sangre, pero no se observó una mejora marcada en la conciencia. Posteriormente, la tomografía computarizada de la cabeza reveló hidrocefalia y atrofia cerebral. Si bien se pensó que la causa era una lesión intracraneal, se registró hipoglucemia recurrente a pesar de una meticulosa nutrición parenteral parcial. Las pruebas de insulina plasmática y péptido C mostraron valores inapropiadamente altos en el estado de hipoglucemia (154,5 uIU/mL y 12,1 ng/mL, respectivamente) y dieron lugar a insulinoma, lo que concordaba con el resultado de la resonancia magnética. Se inició un manejo no quirúrgico minucioso y finalmente se controló la glucosa en sangre. Desafortunadamente, el paciente desarrolló neumonía por COVID-19 y murió por insuficiencia respiratoria. El diagnóstico de insulinoma en pacientes con hidrocefalia con convulsiones y niveles alterados de conciencia es un desafío. El manejo no quirúrgico es difícil en un paciente inconsciente, y mucho menos en una sala de aislamiento. Además, se ha demostrado que el pronóstico de COVID-19 es peor en pacientes con hipoglucemia.

Palabras clave: *COVID-19, hidrocefalia, hipoglucemia, insulinoma, convulsiones.*

INTRODUCTION

Insulinoma is one differential diagnosis of hypoglycemia caused by endogenous hyperinsulinism. It is a rare disease with an incidence of 1 in 250 000. Most insulinoma is benign and occurs sporadically, only less than 10 % is associated with malignancy and multiple endocrine neoplasias (MEN type-1) (1).

Glucose is the main substrate for neuron metabolism, as evident in the neuroglycopenic manifestation of hypoglycemia. Hypoglycemia must be excluded in a patient presenting with seizure and altered level of consciousness (2). However, only a few studies had reported seizures in insulinoma and only two had reported hydrocephalus in chronic hypoglycemia (3.4). According to our studies, this is the first case reporting COVID-19 in a patient with insulinoma. COVID-19 itself was detrimental to the immune system, let alone recurrent hypoglycemia that occurred in insulinoma.

CASE PRESENTATION

A 25-year-old woman was referred to the emergency room with an altered level of consciousness and focal to bilateral tonic-clonic seizure. The seizure happened about 1 minute 4-5 times a day with no recovery of consciousness in between. No previous seizures nor trauma was reported, although the family did report previous multiple syncopes one month before the seizure occurred, especially in the morning. The family denied any use of antidiabetic drugs or any other hypoglycemia-associated drug. No history of eating disorder, autoimmune disorder, diabetes, liver, cardiac, or kidney failure.

During the physical examination, a Glasgow coma scale of 8 and an increased heart rate of 110 bpm with regular rhythm were recorded, while other vital signs were unremarkable. Both pupils were isochor and showed normal light reflex. Motoric examination revealed spasticity within all extremities with no lateralization. No pathological reflex was noted.

An urgent blood glucose test indicated low blood glucose (30 mg/dL) and intravenous dextrose was given accordingly. The seizure ceased momentarily but no improvement of consciousness was observed despite the normalization of blood glucose. A Head CT scan from the previous hospital revealed brain atrophy and hydrocephalus (Figure 1), hence a ventriculoperitoneal (VP) shunt was done before referral to improve CSF flow, yet no improvement was observed. CSF analysis was unremarkable with a negative nucleic acid amplification test (NAAT) for *Mycobacterium tuberculosis*. Moreover, brain magnetic resonance angiography (MRA) showed normal results. Herpes simplex virus (HSV) antibody was negative with a normal ANA test. Electroencephalography had not been done due to the deterioration of the patient's condition. Strangely, routine blood glucose checks kept showing low blood glucose despite meticulous partial parenteral nutrition and careful drug consideration.

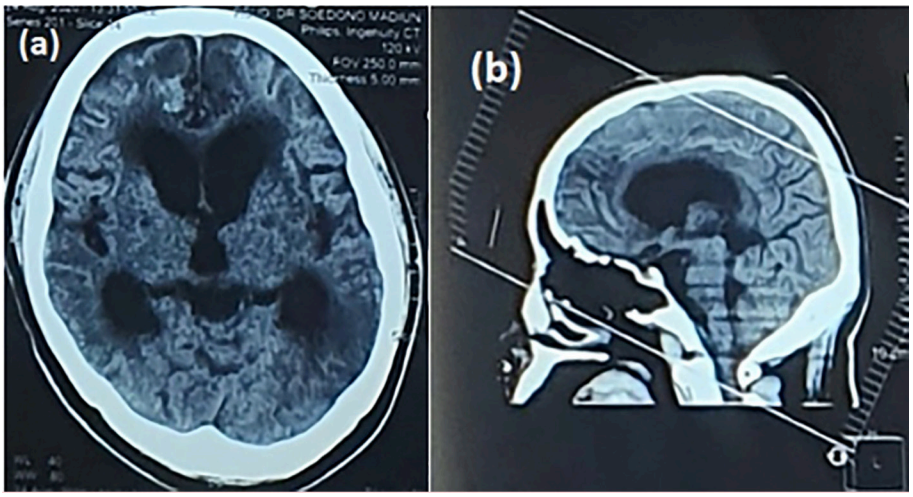

Figure 1. Head CT-scan revealed dilatation of lateral and third ventricle in axial (a) and sagittal view (b).

Insulin plasma and C-peptide levels were ordered in a hypoglycemic state (blood glucose of 45 mg/dL) and they showed inappropriately high levels (154.5 uIU/mL and 12.1 ng/mL, respectively). Later MRI abdomen resulted in a contrast-enhanced mass of 2.9 x 2 cm in the corpus of the pancreas suggestive of insulinoma (Figure 2). Metastasis was not seen in the MRI abdomen and chest CT scan. TSH and cortisol levels were also tested to rule out hormonal deficiencies, with Ca 19-9 to rule out malignancy.

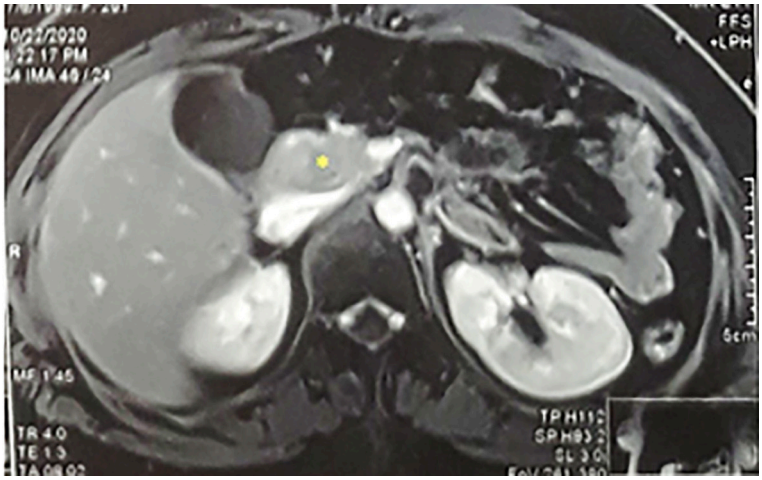

Figure 2. MRI abdomen revealed a hypointense irregular mass (yellow starred) in the pancreatic corpus 2.9x2 cm with contrast enhancement.

The complete results of the laboratory examination are shown in Table 1. An initial diagnosis of insulinoma and epileptic seizures caused by recurrent hypoglycemia was made.

Table 1. Laboratory Findings during Hospitalization

Lab Test	Result	Normal range[1]
Insulin*	154.5 uIU/mL	0.5-300 uIU/mL
C-peptide*	12.1 ng/mL	0.9-7.1 ng/mL
TSH	0.768 uIU/mL	0.55-4.78 uIU/mL
Cortisol	117.2 ng/mL	20.2-131.0 ng/mL
Ca 19-9	17.39 U/mL	<37 U/mL

*Test was done in a hypoglycemic state (BS of 45 mg/dL)
[1] Based on local laboratory references

An initial surgical plan had already been scheduled, but the patient developed respiratory distress with bilateral pulmonary infiltrates and positive PCR COVID-19 result. Therefore, surgery was canceled and the patient was transferred to the isolation room. A careful nutrition plan was arranged along with the administration of steroids, verapamil, and octreotide, in which the last failed to show any effect on the blood glucose level. The dietary plan included frequent enteral feeding of milk, fruit juices, and fructose syrup, which is quite difficult to manage in an isolation room. The parenteral fluid consisting of maltose and dextrose was also given. Three-hourly blood glucose monitoring is shown in Figure 3. Unfortunately, several days later, despite the final follow-up of PCR COVID-19 showed a negative result, and the patient died of respiratory failure.

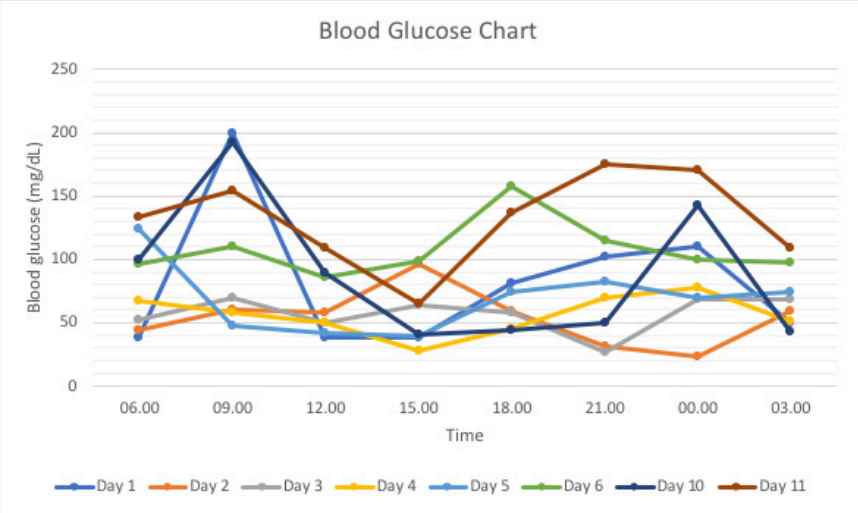

Figure 3. Blood glucose chart throughout different regimens. Day 1 consisted of diet and steroid iv. Day 2-4 subcutaneous octreotide was given in an increased dose. Day 5 octreotide was stopped, and verapamil was given enterally. Day 6 Three-hourly dextrose was administered intravenously. On day 10 patient was transferred to an isolation room. Day 10-11 no changes in glucose management therapy.

DISCUSSION

Insulinoma must be considered in a patient with recurrent hypoglycemia, as this is the prototype of endogenous hyperinsulinism. However, hypoglycemic drug usage, critical illness, and hormonal deficiency must be ruled out first. Based on its pathophysiology, diagnosis is established with failure of decreased insulin level in response to hypoglycemia. Documentation of plasma insulin concentrations of 3 uIU/

mL (18 pmol/L) or higher, plasma C-peptide concentrations of 0.6 ng/mL (0.2 nmol/L) or higher, and plasma proinsulin concentrations of 5.0 pmol/L or higher when hypoglycemic happened (blood glucose less than 55 mg/dL) is required, which was fulfilled in this case (1). CT or MRI localizes 80 % of the tumor, and MRI may be more sensitive. Endoscopic ultrasound and selective pancreatic arterial calcium injection can also be used but to a lesser extent (5).

Insulinoma is typically presented as a history of neuroglycopenia episodes, especially in a fasting state. Seizure and altered mental state are a few of the neuroglycopenic symptoms that had been reported in insulinoma, up to 17 %-23 % and 75 %-80 %, respectively (5-7). Of these reports, the initial diagnosis was neuropsychiatric disorder, which implied a challenge in diagnosing insulinoma. Moreover, Dagett (8) reported up to 7 cases of insulinoma presenting with neuroglycopenia episodes, two of those experienced altered mental consciousness and rigidity despite optimal treatment for hypoglycemia and eventually regained consciousness after the removal of insulinoma. In line with these reports, no improvement of consciousness was observed in our patient, and oddly, seizures still occurred despite blood glucose control, which lead us to false assumption of primary intracranial disorder.

No case of hydrocephalus in insulinoma had been reported, but Iino (3) and Blau (4) had reported hydrocephalus occurred in chronic hypoglycemia. Iino reported hydrocephalus developed as brain atrophy and impairment in CSF flow occurred, which was proven with ventricular reflux evident in RI cisternography. Moreover, this normal pressure hydrocephalus was only established in a repeated coma state of hypoglycemic, in which hypoglycemia brain damage developed. Endogenous neurotoxin aspartate is released and damage to white matter and periventricular reduce its elasticity properties, hence dilating the ventricle under CSF pressure (3).

Blood glucose stabilization is substantial in insulinoma. Surgery remains the first-line treatment, but for those unresectable or unable (in this case due to respiratory distress of COVID-19), diet and pharmacological including diazoxide and octreotide can be tried (1). Frequent feeding through a nasogastric tube is given to this patient, in form of milk and fruit juices. Diazoxide was not available in our hospital, so octreotide was given instead. Octreotide binds to somatostatin receptor-2, which is present in varying degrees in insulinoma (9). Hence, octreotide response is variable, as proven in our case. Glucocorticoid (9) and verapamil (10) can also be used in conjunction with other therapy in some cases. In our case, blood glucose was controlled with diet, glucose infusion, steroids, and verapamil.

Finally, hypoglycemic patients are at a 25-times risk of developing severe pneumonia COVID-19 (11). Hypoglycemia depletes the energy needed to fight acute infection. Furthermore, glucose is needed to activate immune cells and maintain the antioxidant defense system through the maintenance of glutathione (GSH). As a result, low blood sugar leads to enhanced oxidative stress and impaired immune response (11). Hyperinflammation and hypercoagulable state develop as oxidative stress is enhanced and endothelial dysfunction takes place (12), which is detrimental to COVID-19 patients. This is true as in our patient, respiratory distress occurred because of pneumonia COVID-19.

CONCLUSION

Insulinoma in a hydrocephalus patient is rare, but it must be considered in a patient with documentation of recurrent hypoglycemia. Nonoperative management is paramount in a patient unable to undergo surgery, which is challenging to manage in the isolation room. Hypoglycemia must be prevented to avoid the poor prognosis of COVID-19 in insulinoma.

Declaration of interest

The authors have declared that no competing interests exist.

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Cardiac Tamponade: A Rare Manifestation of Lung Cancer. A Case Report

Taponamiento cardíaco: una rara manifestación de cáncer de pulmón. Reporte de un caso

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SUMMARY

Background: *Malignancy is the most common cause of non-inflammatory pericardial effusion that is usually neglected. Metastatic involvement of the pericardium is reflecting the advanced stage of the disease and generally associated with poor outcomes.*
Case presentation: *We report an unusual case of a malignancy patient with pericardial effusion complicated by cardiac tamponade. The patient was treated urgently with pericardiocentesis and cytology pericardial fluid aspirate showed malignant glandular cells. Computed tomography of the chest confirmed the presence of a malignant lung tumor.*
Conclusion: *Our case demonstrates the possibility of metastatic pericardial involvement in patient with malignancy that was successfully treated with pericardial drainage.*

Keywords: *Cardiac tamponade, neoplasms, pericardial effusion, pericardiocentesis.*

RESUMEN

Antecedentes: *La neoplasia maligna es la causa más frecuente de derrame pericárdico no inflamatorio que suele pasar desapercibido. La afectación metastásica del pericardio refleja la etapa avanzada de la enfermedad y generalmente asociada con malos resultados.*
Presentación del caso*: Presentamos un caso inusual de un paciente con derrame pericárdico complicado con taponamiento cardíaco. La paciente fue tratada de urgencia con pericardiocentesis y citología aspirada de líquido pericárdico que mostró células glandulares malignas. La tomografía computarizada de tórax confirmó la presencia de tumor pulmonar maligno.*
Conclusión: *Nuestro caso demuestra la posibilidad de afectación pericárdica metastásica en paciente con neoplasia maligna tratada con éxito con drenaje pericárdico.*

Palabras clave: *Taponamiento cardíaco, neoplasias, derrame pericárdico, pericardiocentesis.*

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INTRODUCTION

Metastatic pericardial effusion is common, but cardiac tamponade appears to be a rare manifestation which is an emergency case. Accumulation of fluid in the pericardial cavity in cardiac tamponade causes compression of the heart, decrease of cardiac output, and shock. Metastatic pericardial effusion is a sign of poor prognosis, with a mortality rate of more than 75 % within 12 months (1,2). Early detection and emergency measures such as percutaneous drainage or surgical management aim to reduce the symptoms.

Case Presentation

A 56-year-old female patient was admitted to the emergency unit because of continuous chest pain, on the left side, radiating to the back for 2 months. On the third day of admission, she complained of worsening shortness of breath, improving with a sitting position. She also complained of discomfort in the left side of the chest that feels like fullness, accompanied by penetrating pain that radiates to the back, with nausea-vomiting, and a decrease in appetite. She presented hypotension with BP 90/60 mmHg, tachycardia 125 bpm, tachypnoea with 28 breaths per minutes, and oxygen saturation was 96 % with a simple mask at 6 lpm. There was a distention of the jugular vein with muffled heart sounds from the cardiac examination. Her complete blood counts and electrolytes were normal. Electrocardiography showed sinus tachycardia 125 bpm with low voltage (Figure 1). Chest radiography showed an enlargement of the cardiac silhouette (Figure 2). Bedside echocardiography was done and showed a massive pericardial effusion with cardiac tamponade (Figure 3).

She underwent an emergent percutaneous pericardiocentesis and approximately 500 mL of bloody pericardial fluid was evacuated (Figure 4). A pericardial fluid sample was sent for cytology review and malignant glandular cells were found. The patient got better on the seventh day of treatment. There was no dyspnoea, nausea, or vomiting. On physical examination, the patient was awake and alert. The hemodynamic state was stable. The total pericardial fluid aspirated was about 1 241 mL. An echocardiogram was done for evaluation, and it showed moderate effusion without collapse of heart chambers, normokinetic left ventricle with an ejection fraction of 60 %, and normal diastolic function.

An evaluation chest computed tomography scan showed a malignant lung mass, with multiple nodules in both lungs and multiple lytic lesions at the sternum and corpus vertebrae (Figure 5). The lung mass encased the right pulmonary artery and adhered to the superior vena cava causing difficulty in tumor biopsy. The pericardial cell block was performed as an alternative and was sufficient for the EGFR mutation test, but no mutation was found. The patient was diagnosed with EGFR wild-type metastatic lung adenocarcinoma and was planning for getting chemotherapy.

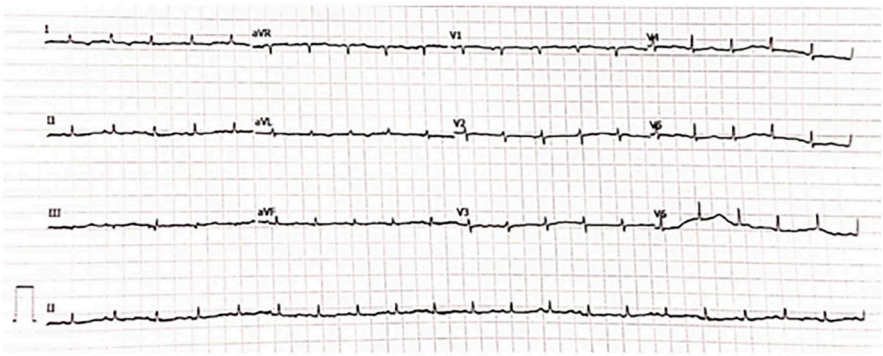

Figure 1. Electrocardiography examination showed sinus tachycardia with low voltage.

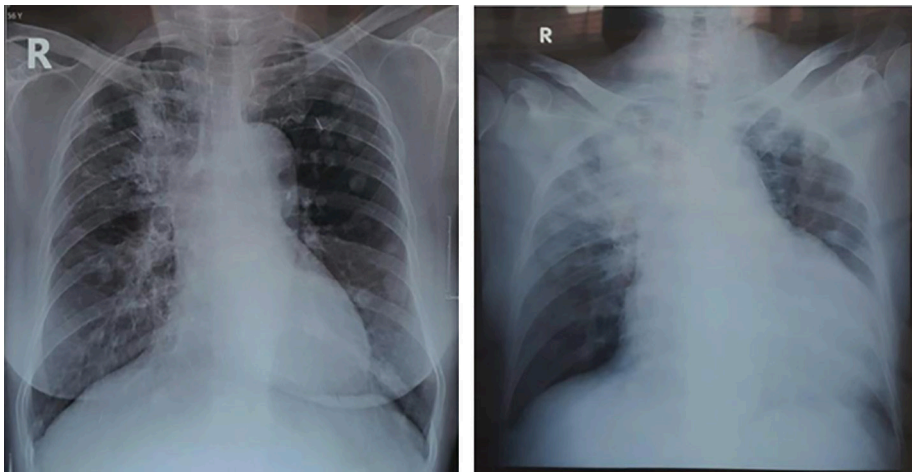

Figure 2. Comparison of the patient's first (October 2021) and second chest radiography (December 2021).

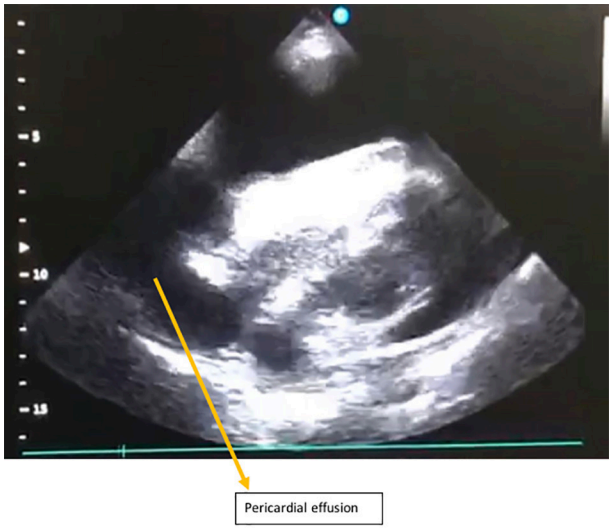

Figure 3. Echocardiography examination showed massive pericardial effusion.

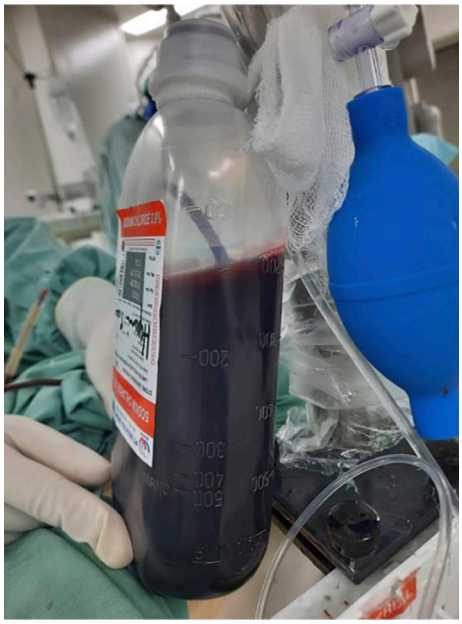

Figure 4. A volume of 500 mL bloody effusion was aspirated through pericardiocentesis.

DISCUSSION

Lung cancer is often asymptomatic in the early stages and causes a delay in diagnosis. The late diagnosis makes such a high mortality rate. Lung cancer metastases to distant organs and cause most deaths from lung cancer. Malignancy-associated pericardial effusion reflects an advanced stage of the disease and has poor outcomes with mortality of more than 75 % in 12 months (1-4).

Almost 95 % of malignant pericardial effusion (PE) was caused by a metastatic process, with lung and breast cancer as the most common cause.

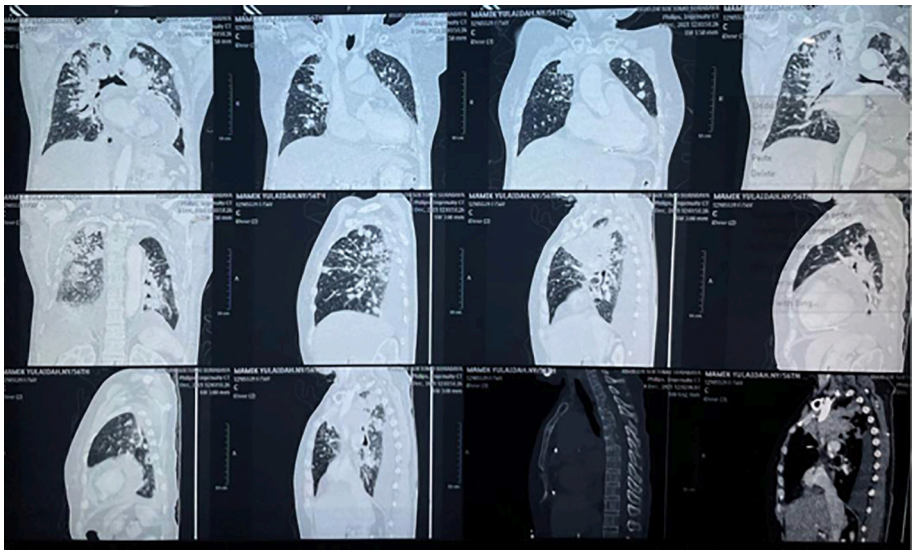

Figure 5. Thorax CT with contrast showed multiple nodules in both lungs, multiple lytic at sternum and vertebrae reflecting a metastatic process.

These two primaries along with hematologic malignancies such as leukemia and lymphoma are responsible for 75 % of malignant PE. Malignancy is the most common cause of non-inflammatory PE with a prevalence of 12 %-23 % One-third of PE cases were complicated by cardiac tamponade, in which the accumulation of pericardial fluid leads to impaired venous return, loss of left ventricular preload, and causes hemodynamic instability (5-8).

Cardiac metastases are usually asymptomatic in the early stages. The clinical signs of cardiac tamponade vary depending on the rate of fluid accumulation. In malignancy cases, pericardial fluid is built up at a chronic or subacute pace, with a volume that can be more than 1 000 mL without causing significant symptoms (1,2,9). As in this patient, a 1 241 mL volume of bloody pericardial effusion was collected after her symptoms emerged.

Classic symptoms of pericardial effusion are dyspnoea on exertion, which may progress to orthopnoea, chest pain, tachypnoea, and/or a feeling of fullness in the chest. Other symptoms can occur due to local compressions such as nausea-vomiting, dysphagia, hoarseness, and hiccups. Non-specific symptoms can be found such as cough, anorexia, palpitations, peripheral edema, and fatigue. Fever can be found in pericarditis cases (2,6,7,10,11). Classic signs of cardiac tamponade are Beck's triad of hypotension, distention of jugular veins, and muffle of heart sounds. Low voltage and electrical alternans can be seen on electrocardiography but are not sensitive nor specific. Mostly only seen as sinus tachycardia (1,2,6,10,11).

PE can be seen as an enlarged heart on chest radiography, but an enlarged cardiac silhouette only appears after the effusion reaches a moderate degree (~200 mL). Prior chest radiographs with normal cardiac silhouette can help to diagnose PE. This patient had prior chest radiography 2 months before admission and showed a normal size of the heart that supports the suspicion of new pericardial effusion (Figure 2). Transthoracic echocardiography is the first-line imaging in patients suspected of pericardial disease, which can detect pericardial effusion and its hemodynamic impact. Echocardiography not only can determine the right puncture point, but also the first choice for the evaluation of treatment (1,2,6).

Management of pericardial effusion depends on its etiology and its effect on hemodynamic.

Large volume effusion without any symptoms or causing unstable hemodynamic can be treated with conservative management, including periodic observation and treatment for underlying disease. PE with symptoms and collapse of the heart chamber are indications of drainage (2,6,10,12-14). The surgical approach is the definitive therapy of pericardial effusion, but because of its risks with variable recurrence, percutaneous intervention is recommended. Guided pericardiocentesis by echocardiography or by fluoroscopy is recommended to reduce the risk of injury to vital organs and determine the closest puncture point with the largest volume of effusions. CT-guided pericardiocentesis may be considered in cases of loculated effusions (10,14).

Isolated pericardiocentesis had a recurrence risk of up to 23 %. Pericardiocentesis with extended catheter drainage has lower recurrence rates of up to 10 %-14 %. Long-term use of a catheter can induce local inflammation, stimulate obliteration of the pericardial space, and significantly reduce the risk of fluid re-accumulation. However, the use of a drainage catheter for more than 7 days has a risk of infection. As in this patient, the drain catheter was removed after 6 days of insertion. An evaluation echocardiogram was done 1 month after that, and it showed minimal pericardial effusion at the base. She did another thorax CT 8 months later and it showed no recurrence of pericardial effusion (6,7,14).

Percutaneous pericardiocentesis with extended catheter drainage is the primary treatment for pericardial effusion in malignancy patients. Catheter revision or reimplantation can be done if there is a persistent or relapsing effusion. Several other procedures such as systemic antineoplastic, instillation of sclerotic or cytotoxic agents, percutaneous balloon pericardiotomy, pleuro-pericardiotomy, and radiation therapy, may be recommended if recurrence is found (10,13,14).

CONCLUSION

It has been reported a 56-years-old female with metastatic pericardial involvement that complicated by cardiac tamponade. The patient was successfully treated with pericardial drainage. Pericardiocentesis with extended catheter drainage showed lower recurrence than pericardiocentesis only. Early detection and proper management of cardiac tamponade determine the prognosis of the patient.

Author Contributions

All authors were involved in preparing this article regarding the conception, writing of the manuscript, and conducting a final proofreading.

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Conflict of Interest

There is no conflict of interest regarding the publication of this paper.

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Rare Manifestation of Acute Blindness in Ocular Toxoplasmosis: A Case Report

Manifestación raras de ceguera aguda en toxoplasmosis ocular: reporte de un caso

Dio Brimantyo[1], M. Vitanata Arfijanto[2]*

SUMMARY

Introduction: *Toxoplasmosis is one of the most common zoonoses worldwide. Clinical manifestations of ocular toxoplasmosis are highly specific. Atypical manifestations are not uncommon and are not always recognized as specific to ocular toxoplasmosis. Here, we present a rare manifestation of acute blindness in ocular toxoplasmosis in an immunocompetent patient.*
Case Illustration: *A 48-year-old female presented with a 1-week history of sudden blurry vision of the left eye. The patient denied any details about the redness or pain in the eye or the eye injury. Headache, fever, and abdominal pain were reported as the other symptoms. She has contact with the cat. The ophthalmological examination revealed abnormal visual acuity not improved by the pinhole and abnormal posterior segment. Anti-toxoplasma Immunoglobulin antibodies in serum were detected using a Chemiluminescence Microparticle Immunoassay (CMIA), which revealed positive. The diagnosis of neuro retinitis toxoplasmosis was established. The patient started treatment with clindamycin, pyrimethamine, and methylprednisolone. After 25 days of treatment, the patient had clinical improvement which is normal visual acuity, Ishihara color testing, and posterior segment.*
Conclusion: *Blurry vision can occur in ocular toxoplasmosis. Identification and adequate treatment can reduce the risk of permanent visual impairment, recurrence, severity, and duration of acute symptoms.*

Keywords: *Blindness, toxoplasmosis, ocular, immunocompetent.*

RESUMEN

Introducción: *La toxoplasmosis es una de las zoonosis más comunes a nivel mundial. Las manifestaciones clínicas de la toxoplasmosis ocular son muy específicas. Las manifestaciones atípicas no son infrecuentes y no siempre se reconocen como específicas de la toxoplasmosis ocular. Aquí presentamos una rara manifestación de ceguera aguda en la toxoplasmosis ocular en pacientes inmunocompetentes.*
Ejemplo de caso: *Una mujer de 48 años de edad se presentó con una historia de 1 semana de visión*

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borrosa repentina en el ojo izquierdo. La paciente negó cualquier detalle sobre el enrojecimiento o el dolor en el ojo o la lesión en el ojo. El dolor de cabeza, la fiebre y el dolor abdominal se informaron como los otros síntomas. Ella tiene contacto con un gato. El examen oftalmológico reveló agudeza visual anormal no mejorada por estenopeico y segmento posterior anormal. Se detectaron anticuerpos de inmunoglobulina anti-toxoplasma en suero mediante un inmunoensayo de micropartículas de quimioluminiscencia (CMIA), que resultó positivo. Se estableció el diagnóstico de neurorretinitis toxoplásmica. El paciente inició tratamiento con clindamicina, pirimetamina y metilprednisolona. Después de 25 días de tratamiento, el paciente tuvo una mejoría clínica como es agudeza visual, prueba de color de Ishihara y segmento posterior normales. **Conclusión***: La visión borrosa puede ocurrir en la toxoplasmosis ocular. La identificación y el tratamiento adecuado pueden reducir el riesgo de discapacidad visual permanente, recurrencia, gravedad y duración de los síntomas agudos.*

Palabras clave: *Ceguera, toxoplasmosis, ocular, inmunocompetente.*

INTRODUCTION

One of the most prevalent zoonoses in the world is toxoplasmosis. In adults, the seroprevalence of antibodies to *Toxoplasma gondii* ranges from 22.5 % to more than 80.0 % (1). Our poor understanding of the pathophysiology of ocular toxoplasmosis is reflected by our inability to unequivocally confirm a clinical diagnosis based on laboratory tests. Although the clinical manifestations of the disease are usually very specific, atypical manifestations are not uncommon, and these are not always recognized as specific for ocular toxoplasmosis even by experienced ophthalmologists. This situation raises questions about the sensitivity and specificity of clinical diagnosis, which, in the absence of sufficiently sensitive laboratory tests for this disease, are still considered the gold standard (2).

The diagnosis of ocular toxoplasmosis can be helped by the results of serological tests although this is not in itself conclusive. Patients with ocular toxoplasmosis are always positive for Toxoplasma-specific Immunoglobulin G (IgG), but also infected individuals who show no signs of ocular involvement. Therefore, the detection of Toxoplasma-specific IgG has a low diagnostic value (3). In some patients, Toxoplasma-specific IgM can be detected in the serum, which may indicate a recently acquired infection. However, in the case of acute infection, an equivocal or positive result has no diagnostic value. If serological data confirm the presence of a recently acquired infection, then the alternative of a reactivated latent state can be excluded. The absence of specific antibodies provides strong evidence for the origin of toxoplasmosis in ocular disease. The parasite itself has been detected in the peripheral blood of both patients with ocular toxoplasmosis and controls (4).

Ocular toxoplasmosis rarely results in blindness in immunocompetent patients and is usually asymptomatic. However, blindness can still occur. Appropriate identification and treatment can reduce morbidity in ocular toxoplasmosis patients. This case illustrates the rarity of the presentation of acute blindness in an ocular toxoplasmosis immunocompetent patient.

CASE ILLUSTRATION

A 48-year-old female came with a main complaint of a sudden blurred left eye in the middle pointing to the upper left like being covered by fog since 1 week ago. The patient reported only seeing the bottom of the eye with the left eye. Headache at the back of the head appeared intermittent since 1 week ago. Previously, the patient had a fever and abdominal pain 2 weeks ago for 3 days. The patient had no complaints of double vision, pain when glancing, fever, weakness, shortness of breath, joint pain, red face, nausea, vomiting, or diarrhea to exclude the presence of autoimmune disease. The patient has no history of trauma, diabetes mellitus, hypertension, stroke, autoimmune disease, cancer, and HIV. The patient frequently contacts her cat, which she pets at home.

Ophthalmological examination found visual acuity of 5/5 on the right eye and 5/20 but not improved by pinhole on the left eye, intraocular pressure of the right and the left eye were 19.3 and 19.5 mmHg, Ishihara color test of the right and the left eye were 14/14 and 1/14, the field of view (confrontation test) can count fingers

in all quadrants, ocular motility can be in any direction without pain, the tangent screen of the left eye found central scotoma, anterior segment examination was normal with a negative relative afferent pupillary defect on the right eye, posterior segment examination on the right eye was normal but the posterior segment on the left eye found superior and inferior nasal blurred optic nerve head margin, hyperemia, peripapillary hemorrhage, retina hemorrhage, peri-macular, and star-shaped exudate with negative macular reflects and still positive fundus reflects (Figure 1).

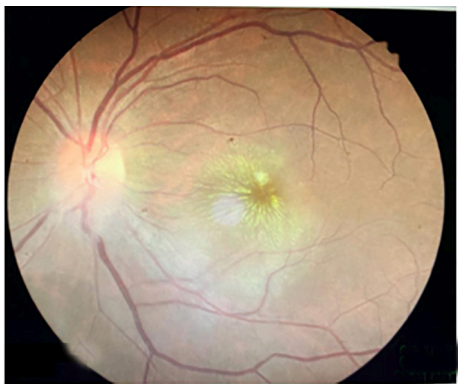

Figure 1. Posterior segment examination on the left eye before treatment. Fundoscopy showed a) hyperemic and blurred optic nerve head in the superior and inferior nasal border and b) star-shaped exudate with negative macular reflections.

Routinely laboratory examination was found. The patient was tested for antibodies with an Abbot Alinity tool® using a chemiluminescence microparticle immunoassay (CMIA) reagent. Toxoplasma and Cytomegalovirus (CMV) antibody was reactive (Table 1). Acquired immunosuppression was excluded. Serology for HIV was non-reactive. A head magnetic resonance imaging (MRI) was normal. The patient's assessment was neuro retinitis toxoplasmosis on the left eye with therapy initiated were clindamycin 300 mg orally every 8 hours, pyrimethamine 25 mg orally every 8 hours, methylprednisolone 62.5 mg IV bolus every 6 hours.

Table 1. Laboratory testing

Test	Result	Reference range
IgM-Toxoplasma	4.039	reactive >2.6
IgG-Toxoplasma	1.821	reactive >8
IgM-anti-CMV	2.73	reactive > 4.2
IgG-anti-CMV	3	reactive > 2

Outcome and follow-up

Four days later, the patient was re-evaluated and presented an improvement in her vision. The methylprednisolone dose was lowered to 62.5 mg intravenous bolus every 12 hours. On the seventh day of treatment, the patient's eyes have a significant improvement and the methylprednisolone dose was changed to 62.5 mg IV bolus every 24 hours. Patients were discharged on day 7 with the therapy of methylprednisolone 16 mg orally every 8 hours, clindamycin 300 mg orally every 8 hours, Pyrimethamine 25 mg orally every 8 hours, and maintained for 6 weeks. In outpatient follow-up, the patient's eyes have a significant improvement. Ophthalmology examination found improvement in visual acuity (10/20), and Ishihara color testing (5/14). However, posterior segment examination still found blurred superior and inferior nasal optic nerve head margin, hyperemic, and peripapillary hemorrhage in the left eye. On the twenty-fifth day of treatment, a significant improvement with normal visual acuity, Ishihara color testing, and posterior segment (Figure 2).

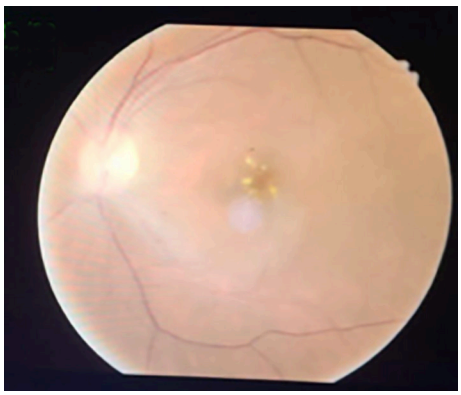

Figure 2. Follow-up of posterior segment examination on the left eye after treatment. Fundoscopy showed improvement, the exudate was decreased.

DISCUSSION

A common side effect of immunodeficiency conditions, such as those brought on by cancer, steroid and cytotoxic medication therapy, and AIDS, is disseminated toxoplasmosis. Ocular toxoplasmosis (OT) does not need immune suppression to occur. It is thought to represent either a reactivation of congenital infection or a postnatally acquired infection by a parasite (5). In immunocompetent patients, typical OT often presents with white focal retinitis and overlying vitreous inflammation (also known as the headlight in the fog sign) (6). Toxoplasma-associated chorioretinitis is usually a self-limiting infection and generally resolves spontaneously within 4-8 weeks (5). The most common cause of posterior uveitis is OT and is the result of acquired or congenital infection by the parasite *Toxoplasma gondii* with sources of infection are food and water contaminated with oocysts from cat feces or meat contaminated with tissue cysts. Congenitally acquired OT results from vertical transmission from mother to child, and may be evident at birth or later. Postnatally acquired OT becomes apparent when symptoms associated with active retinocortical lesions appear (7).

The prevalence of toxoplasma is estimated that 25 %-30 % of the world's population is infected (8). In immunocompetent patients in Brazil, the prevalence of OT ranges from 6 to 18 percent (9). In a prior study, 24 % of individuals with OT experienced legal blindness (10). More virulent *Toxoplasma* strains cause more frequent and more severe forms of OT in immunocompetent patients in tropical regions, especially in South America. Additionally, it has been demonstrated that IL17 inhibits parasite control while enhancing pathology in the eye (11). Most patients present with uveitis secondary to ocular toxoplasmosis in their second to fourth decades of life (12). The advanced age of the patient at the first manifestation has an impact on the risk of recurrence as well. The relative risk for individuals aged 40 years was significantly increased and may be related to reduced immune defenses in the aging host (13).

The most common manifestation of ocular toxoplasmosis is *Toxoplasma retinochoroiditis* (TR) which is usually a unilateral, unifocal retinocortical lesion associated with vitritis. Granulomatous anterior chamber inflammation is common, and retinal vasculitis (usually arteriolitis) occurs in about one-third of patients. Vision loss may be permanent due to macular scar formation or optic atrophy (14). Optic nerve involvement is less common but can cause severe visual field defects as well as loss of color vision. Scotoma is directly related to the size and location of the retinochoroidal scar during the inactive parasite stage. The classic ocular manifestations of toxoplasmosis are a fine white nidus, focal necrotizing retinitis, or contiguous retinochoroiditis with a variable pigmented chorioretinal scar. Often active lesions are obscured by severe vitritis resulting in the classic 'headlights in the fog' sign (15). In this case, it is in line with that we found visual acuity and the Ishihara color test is abnormal on the left eye, tangent screen found central scotoma and posterior segment examination on the left eye found superior and inferior nasal blurred optic nerve head margin, hyperemia, peripapillary hemorrhage, retina hemorrhage, peri-macular, and star-shaped exudate with negative macular reflects and still positive fundus reflects.

Serological testing is often the first step in diagnosis using IgG and IgM antibodies. IgM antibodies appear immediately after acute infection, increasing from 5 days to several weeks and reaching a maximum after 1 to 2 months, and decreasing more rapidly than IgG reaching a maximum in 1 month. If both IgG and IgM are negative, this indicates the absence of infection or a very recent acute infection. If the test shows positive IgG and negative IgM, this indicates a long-standing infection (infection more than 1 year ago). If both IgG and IgM are positive, this indicates a recent infection or a false positive test result. If an acute infection is suspected, retesting is recommended in 2 to 3 weeks. A 4-fold increase in IgG antibody titer between tests indicates recent infection (16). In this case, we found reactive IgM-Toxoplasma.

Even though the absence of IgG antibodies almost excludes the probability of ocular illness, false-negative results can occasionally be seen. In those with typical fundus characteristics but negative IgG test results, it is crucial to integrate several serological test systems. There may also be several unusual clinical signs and symptoms

of freshly acquired ocular toxoplasmosis (e.g., large active lesions without a scar). In many situations, determining the disease's cause requires laboratory validation. Setting a precise clinical diagnosis can be difficult because other conditions that can cause uveitis, including toxocariasis, multifocal choroiditis, punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, histoplasmosis, acute retinal necrosis syndrome (caused by the herpes simplex virus and varicella-zoster virus), tuberculosis, sarcoidosis, serpiginous choroiditis, syphilis, endophthalmitis, and ocular lymphoma may present with some clinical features of toxoplasma retinochoroiditis. In these circumstances, more laboratory testing is necessary to find additional potential infections (17).

Failure to respond to antiviral therapy leads clinicians to diagnose ocular toxoplasmosis (18,19). Treatment is recommended for lesions within the vascular arcade, adjacent to the optic disc, or larger than 2 optic disc diameters to reduce the possibility of visual loss (20). Antibiotics and corticosteroids have been the mainstay of pharmacologic therapy. Treatment is given to reduce the risk of permanent visual impairment (aiming to reduce the size of the retinochoroidal scar), the risk of recurrence, and the severity and duration of acute symptoms. Antibiotics are usually given for 6 to 8 weeks. Steroids are also sometimes used to decrease the severity of intraocular inflammation symptoms (21-23). Indications for corticosteroid use include severe vitreous inflammation, decreased vision, the proximity of the lesion to the fovea or optic disc, and large active lesion size. The preferred drug for oral corticosteroids is prednisone at a dose of 0.5-1.0 mg/kg/day (20,24). The combination of pyrimethamine and sulfadiazine has synergistic effects at different steps of nucleic acid synthesis in *T. gondii*, and corticosteroids have remained the classic 'triple drug therapy' (23). A study showed patients treated with triple-drug therapy showed a greater reduction in retinal lesion size compared with patients receiving other treatment regimens or no treatment (25). Clindamycin concentrates on the ocular tissue and penetrates the cyst wall of the tissue, often added to classic triple therapy as part of 'fourfold therapy' (20). Long-term intermittent treatment in immunocompetent patients decreased the recurrence of the disease from 24 to 7 % during a 20-month follow-up period (26). In this case, patients had resolution of active retinochoroiditis and improved vision with clindamycin, pyrimethamine, and methylprednisolone therapy.

Toxoplasmic chorioretinitis does not need immunocompromising to occur. Since ocular toxoplasmosis is a potentially blinding disease, preventive measures should be taken to avoid it. Proper washing of hands and strict food hygiene is important. In this case, a serological examination is performed to confirm the diagnosis so that the patient can be given the right therapy.

CONCLUSION

Ocular toxoplasmosis can cause blurry vision and potentially trigger permanent blindness. Recurrence, intensity, and duration of acute symptoms can all be decreased with early detection and appropriate treatment. Clindamycin, pyrimethamine, and methylprednisolone can be treatment options.

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Conflicts of interest

All of the authors declare no conflict of interest-

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CASO CLÍNICO

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Ovarian hyperstimulation syndrome with spontaneous bacterial peritonitis and thrombocytosis: A Case Report

Síndrome de hiperestimulación ovárica con peritonitis bacteriana espontánea y trombocitosis: reporte de un caso

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SUMMARY

Introduction: *To date, severe Ovarian Hyperstimulation Syndrome (OHSS) that can be associated with mortality only occurred in 0.1 % – 2 % of all OHSS cases. This paper reports one of those rare cases accompanied by spontaneous bacterial peritonitis and thrombocytosis.*
Case Presentation: *A 28-year-old female had OHSS as a complication of in-vitro fertilization. Clinical presentation fever, dyspnea, ascites, thrombocytosis, leukocytosis, and bilateral multiloculated cystic ovaries. Fluid analysis revealed polymorphonuclears 545 cells/mm³. Treatment includes antibiotics, human albumin serum, low molecular weight heparin, and abdominal paracentesis. The patient was discharged after one week of admission and there were no recurrent OHSS events thereafter.*
Conclusion: *In patients with severe OHSS, urgent treatment with multidisciplinary management is mandatorily needed. If left untreated, OHSS can result in serious complications and even death.*

Keywords: *Ovarian hyperstimulation syndrome, spontaneous bacterial peritonitis, thrombocytosis.*

RESUMEN

Introducción: *Hasta la fecha, el Síndrome de Hiperestimulación Ovárica (SHEO) severo que puede asociarse con mortalidad solo ocurrió en 0,1 % - 2 % de todos los casos de SHEO. Este artículo reporta uno de esos raros casos acompañados de peritonitis bacteriana espontánea y trombocitosis.*
Presentación del caso: *Una mujer de 28 años tuvo SHEO como complicación de la fertilización in vitro. Presentación clínica fiebre, disnea, ascitis, trombocitosis, leucocitosis y ovarios quísticos multiloculados bilaterales. El análisis de fluidos reveló polimorfonucleares 545 células/mm³. El tratamiento*

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incluye antibióticos, suero de albúmina humana, heparina de bajo peso molecular y paracentesis abdominal. El paciente fue dado de alta después de una semana de ingreso y no hubo eventos recurrentes de OHSS a partir de entonces.

Conclusión: *En pacientes con SHEO severo, es obligatorio el tratamiento urgente con manejo multidisciplinario. Si es tratada, el SHEO puede provocar complicaciones graves e incluso la muerte.*

Palabras clave: *Síndrome de hiperestimulación ovárica, peritonitis bacteriana espontánea, trombocitosis.*

INTRODUCTION

Ovarian hyperstimulated syndrome (OHSS) is an iatrogenic complication that, in some cases, can be a potentially fatal physiological complication caused by ovulation induction during *in vitro* fertilization (IVF) cycles. The hallmark of OHSS is characterized by a fluid shift from the intravascular to the third space due to increased capillary permeability, ovarian neoangiogenesis, and cystic enlargement of the ovaries (1,2). The syndrome appears several days after starting gonadotropin induction therapy. Capillary permeability to plasma proteins increases, resulting in a fluid shift from the intravascular to the extravascular compartment, which clinically manifests as ascites, pleural effusion, oliguria, hemoconcentration, and electrolyte imbalances. The prevalence of mild OHSS is 20 %-23 % of IVF cycles, medium OHSS prevalence is approximately 3 %-6 %, and rare cases of severe OHSS about 0.1 %-2 %, have been reported (3).

Serious infection can appear in patients with OHSS when predisposing factors such as plasma immunoglobulin are lower than the normal value (4). Increased capillary membrane permeability and acute third-space fluid loss derived from excessive production of ovarian hormones and vasoactive substances result in the consequence of decreased intravascular volume and hemoconcentration which can lead to thromboembolism and death (5). This paper describes a woman with OHSS who developed an unusual complication, a serious infection: spontaneous bacterial peritonitis (SBP) and thrombocytosis.

CASE PRESENTATION

A 28-year-old female was admitted to the hospital and complained of chest pain and palpitations. The patient was six weeks pregnant, nine weeks after IVF was performed at the secondary hospital in Surabaya, but ovarian stimulation and ovulation induction protocols from this hospital were unknown. One week before this admission, she was discharged from another hospital with the same symptoms, and had been diagnosed with moderate OHSS, suffered from ascites and pleural effusion, required hospitalization for abdominal and pleural paracentesis, and received human albumin serum two times. She had also noticed abdominal enlargement after four weeks of pregnancy.

She complained of stomach pain, fullness, nausea, vomiting, weakness, decreased urine output, fever, chills, and weight increase, 4 kg in the previous week. She also experienced diarrhea three times per day for five days, but two days before admission, it had completely stopped. She also noticed a marked reduction in urine production. She was awake and alert, with a blood pressure of 90/60 mmHg, palpitations, a heart rate of 110 beats per minute, a temperature of 38.8 °C, an increase in respiratory rate of 30 times per minute, and a decrease in oxygen saturation of 92 %. However, after receiving 3 L/min of nasal oxygen supplementation, her oxygen saturation increased. Physical examination revealed ascites and a swollen abdomen. Abdominal ultrasonographic examination at admission revealed bilateral multiloculated cystic ovaries with a diameter of the right ovary of 10.6 cm, an estimated volume of 82 cm^3 (Figure 1) and a diameter of the left ovary of 10 cm, an estimated volume of 78 cm^3 (Figure 2) and ascites as well. Right pleural effusions were observed on thoracic radiographs and ultrasound (Figures 3 and 4). There was hemoconcentration and a significant increase in leucocytes which is suspicion of infection. Thrombocytosis was present, and albumin serum was below the normal range. Alanine transaminase (ALT) levels were slightly increased but aspartate transaminase levels were normal. Procalcitonin (PCT) increased from the normal limit and the erythrocyte sedimentation rate increased. The results of the viral hepatitis serology were negative.

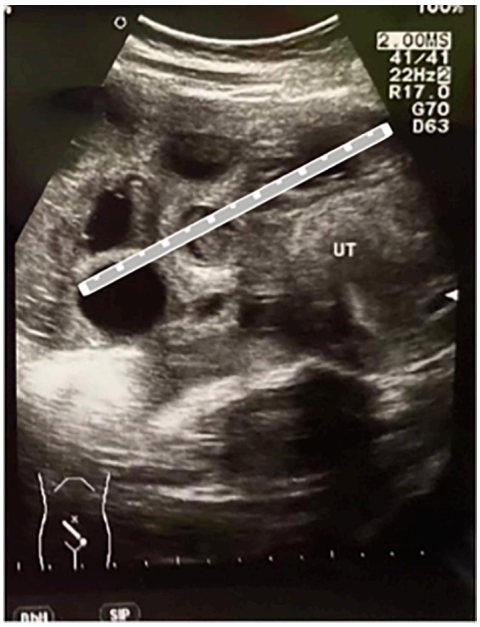

Figure 1. Right ovary diameter 10.6bcm, estimated volume 82 cm^3.

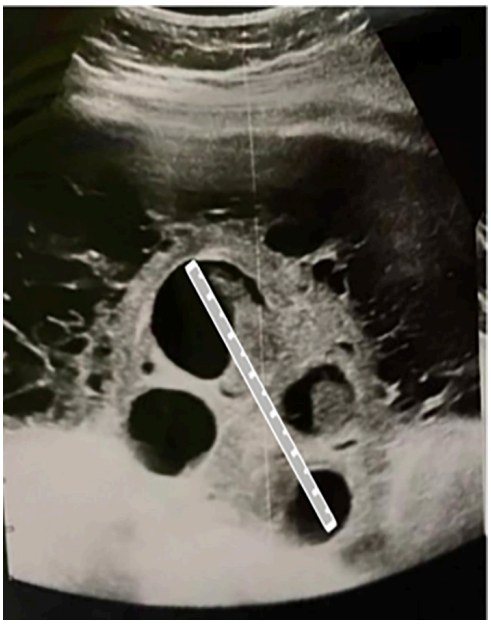

Figure 2. Left ovary 10 cm estimated volume 78 cm^3.

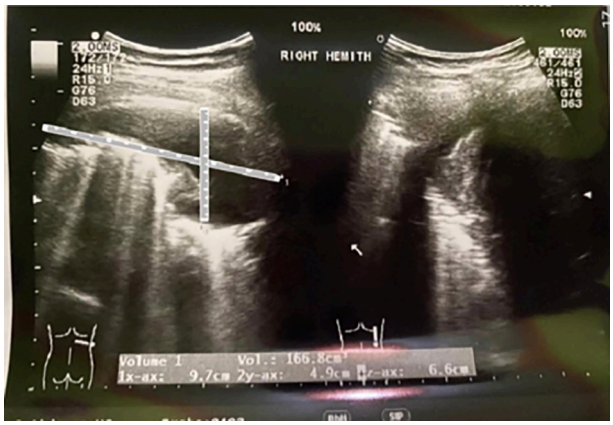

Figure 3. Right pleural effusion (9.7x6.6 cm), estimated volume 166.8 cm^3.

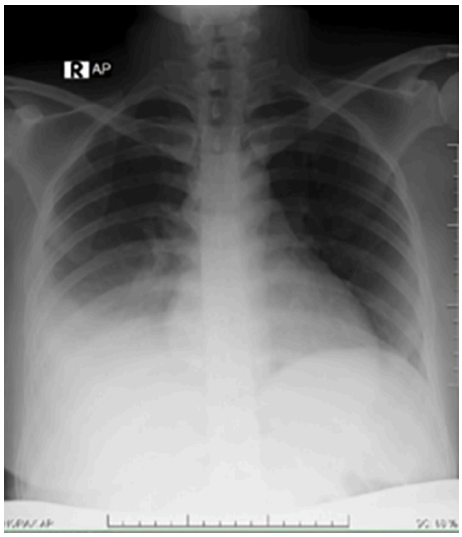

Figure 4. Right pleural effusion.

When OHSS was suspected, supportive care in the intensive care unit (ICU) was begun. At admission, 500 cm^3 of normal saline intravenous hydration and 25 % human albumin serum (100 mL/day) were started. The patient responded well, but his urine output was still insufficient. On the second day of admission, abdominal paracentesis with ultrasound guidance was performed, and 700 cm^3 of ascitic fluid were drained, followed by human albumin administration at a rate of 25 % 100 cm^3 per day. Ascites fluid analysis and culture were performed, as well as blood

culture. Cefotaxime was started at 2-g t.i.d. Fluid analysis revealed a significant increase in polymorphonuclears, indicating spontaneous bacterial peritonitis.

On the third day of admission, the patient was discharged to an internal ward after the hemoconcentration was resolved. For thromboembolic prophylaxis, low molecular weight heparin (fondaparinux sodium 2.5 mg once subcutaneously daily) was used. There were no thromboembolic events during treatment, oxygen saturation was normal after abdominal paracentesis, the patient no longer required oxygen supplementation, and the patient was able to perform her hospital activities independently. On the seven days of admission, blood culture and fluid ascites culture revealed no bacterial growth was found and platelets significantly decreased. Leucocytes also revealed normal, antibiotics were discontinued after seven days of treatment. The patient was discharged from the hospital after a total of seven days of hospitalization.

One week after being discharged from the hospital, the patient visited the outpatient department, in good condition, platelets decreased significantly, and the use of low molecular weight heparin was discontinued. On the second outpatient visit, she was in good health, her vital signs were normal, no ascites were found during the physical examination, and her platelets were normal (Summary laboratory tests performed upon admission were reported in Table S1 in the supplementary material).

DISCUSSION

The syndrome of ovarian hyperstimulation is an iatrogenic complication of supraphysiologic ovarian stimulation (6). The majority of OHSS is mild and causes little clinical concern in 20 % to 33 % of people. However, when OHSS is severe, it is occasionally associated with severe morbidity, and fatalities have been reported. Except in rare cases, OHSS occurs only after a luteinizing hormone surge or exposure to human chorionic gonadotropin (hCG). The reported incidence of moderate OHSS after gonadotropin superovulation for IVF is 3 % to 6 %, and for severe forms is 0.1 % to 2 %; the condition is potentially life-threaten. This case report defined SBP and thrombocytosis as complications of OHSS.

This case report presents a patient with a serious illness due to severe OHSS. OHSS was suspected when there was a recent history of ovarian stimulation followed by ovulation or hCG administration, according to The Society of Obstetricians and Gynecologists of Canada - Canadian Fertility and Andrology Society Clinical Practice Guidelines Committee. An ultrasound will reveal large ovaries with multiple luteal cysts. Classic symptoms of moderate to severe OHSS include bloating, abdominal pain, rapid weight gain, and decreased urine output. The phenomenon is caused by the movement of intravascular fluid into the extravascular compartment, resulting in intravascular volume depletion and hemoconcentration, and thus hypercoagulability. This patient fulfilled all these clinical diagnoses.

The disease has been classified into various stages based on the seriousness of the condition according to the Golan (7) criteria and modifications by Navot et al. (8) in Humaidan et al. (9).

"Mild OHSS: grade 1 (abdominal distention and discomfort), grade 2 (grade 1 disease plus nausea, vomiting, and/or diarrhea plus ovarian enlargement from 5 to 12 cm).

Moderate OHSS: grade 3 (features of mild OHSS plus ultrasonographic evidence of ascites).

Severe OHSS: grade 4 (features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax and breathing difficulties), grade 5 (all the above plus a change in the blood volume, increased blood viscosity due to hemoglobin concentration, coagulation abnormalities, and diminished renal perfusion and function).

Chronic OHSS: grade 6 (ascites ± hydrotonic, Hct >55 %, white blood cell counts 25 × 10/l, oliguria, creatinine =1.6, creatinine clearance <50 ml/min, renal failure, thromboembolism, ARDS)".

The severity, in this case, included ascites, breathing difficulties, change in blood volume, increase blood viscosity due to hemoglobin concentration, leucocytosis (white blood cell

Supplementary material
Table S1 Summary Laboratory Test Performed Upon Admission

Item	Values	Normal Values
At the emergency room (First-day admission)		
Hemoglobin	15.1 g/dL	12.0-16.0 g/dL
Hematocrit	45.3 %	37-47 %
Leucocyte	36.6 103 /μL	4.0-10.6 103 /μL
Neutrophil	91.8 %	50-70 %
Platelets	721 103 /μL	150-400 10^3 /μL
Sodium	130 mmol/L	135-145 mmol/L
Potassium	4.0 mmol/L	3.5-5 mmol/L
Creatinine	0.6 mg/dL	0.51-0.9 mg/dL
Albumin serum	3.4 g/dL	3.5-5.2 g/dL
SGOT (AST)	20 U/L	<=31 U/L
SGPT (ALT)	47 U/L	<=31 U/L
Procalcitonin (PCT)	0.69 ng/mL	<0.05 ng/mL
Second days admission		
Hemoglobin	10.7 g/dL	12.0-16.0 g/dL
Hematocrit	34.1 %	37-47 %
Leucocyte	29.22 103 /μL	4.0-10.6 10^3 /μL
Neutrophil	90.2 %	50-70 %
Platelets	863 103 /μL	150-400 10^3 /μL
Ascitic Fluid analysis		
• yellowish color		
• clear		
• polymorphonuclears (PMN)	545 cell/mm^3	
• protein	3.2 g/dL	
• glucose	98 mg/dlL	
Five days admission		
Hemoglobin	9.6 g/dL	12.0-16.0 g/dL
Hematocrit	30.5 %	37-47 %
Leucocyte	13.98 10^3 /μL	4.0-10.6 10^3 /μL
Neutrophil	89.7 %	50-70 %
Platelets	799 10^3 /μL	150-400 10^3 /μL
Seven days admission		
Hemoglobin	9.2 g/dL	12.0-16.0 g/dL
Hematocrit	29.0 %	37-47 %
Leucocyte	10.02 10^3 /μL	4.0-10.6 10^3 /μL
Neutrophil	70.3 %	50-70 %
Platelets	664 10^3 /μL	150-400 10^3 /μL
Blood culture	No bacterial growth was found	
Ascitic fluid culture	No bacterial growth was found.	
Seven days after discharge (On outpatient department)		
Hemoglobin	10.2 g/dL	12.0-16.0 g/dL
Hematocrit	30.6 %	37-47 %
Leucocyte	10.01 10^3 /μL	4.0-10.6 10^3 /μL
Neutrophil	70.2 %	50-70 %
Platelets	479 10^3 /μL	150-400 10^3 /μL
2 weeks after discharge (On outpatient department)		
Hemoglobin	11.2 g/dL	12.0-16.0 g/dL
Hematocrit	33.1 %	37-47 %
Leucocyte	9.8 10^3 /μL	4.0-10.6 10^3 /μL
Neutrophil	66 %	50-70 %
Platelets	357 10^3 /μL	150-400 10^3 /μL

count 36.600/μL), electrolyte imbalances (hyponatremia: sodium, 130 mmol/L), and elevated liver enzymes (10). OHSS is distinguished by increased capillary permeability, which results in ascites and effusion. Excess estrogens, progesterone, and cytokines are released because of hyperstimulation. This causes vascular endothelial growth factor secretion, which causes vascular hyperpermeability and a shift of fluids from the intravascular system to the abdominal and pleural cavities. As fluid accumulates in the third space, a patient may become hypovolemic and face circulatory problems (11). This is consistent with our patient's clinical presentation.

Fluid management is difficult in patients with severe OHSS due to the porous nature of the vascular bed. Women who can drink should, in general, be encouraged to drink to thirst rather than to excess. If the woman is unable to tolerate oral fluids, IV fluids such as normal saline should be started. Titrate the volume using the hematocrit as an indicator of hydration status. Excess intravenous fluids may aggravate the condition. The input/output balance must be constantly monitored (12). Diuretics should be avoided when there is hemoconcentration because they can cause critical OHSS. Diuretics should only be used when renal output is low despite normal hematocrit. Women with severe hemoconcentration (Hb >14 g/dL; Htc >45 %) need to be monitored (13).

In our case report, one of the complications of OHSS is evidence of SBP as a cause of sepsis, as determined by increased polymorphonuclears in fluid ascites analysis, which was successfully treated with antibiotics and intravenous human albumin administration. SBP is distinguished by the infection of ascitic fluid without an intraabdominal source of infection (11). The presence of more than 250 PMN cells/mm3 in the ascitic fluid indicates this condition and necessitates immediate treatment with antibiotics and human albumin serum. In 30 %-50 % of cases, ascitic fluid cultures are negative, and when positive, they typically grow gram-negative enteric bacteria (typically *Escherichia coli* and *Klebsiella pneumonia*). A lapse in antibiotic treatment could cause a significant and potentially fatal deterioration in clinical status. Infection can cause increased intestinal permeability, bacterial translocation into the bloodstream, changes in the systemic immune system, and impairment of ascitic fluid defense mechanisms. Patients with tense ascites that cause significant pain and/or respiratory compromise benefit from paracentesis. It can also improve oliguria caused by increasing intra-abdominal pressure and compromising blood flow to the kidney. The use of an indwelling pigtail catheter under ultrasound guidance eliminates the need for multiple drainage attempts and reduces the risk of infectious complications. The output of ascites should be recorded on daily basis. When paracentesis output begins to decrease as urine output increases, a clinical resolution occurs when the ascites output reaches 50 mL per day, the catheter can be removed. Ascites drainage will usually clear up a pleural effusion (13).

Thrombocytosis is an increase in platelets in the bloodstream. In severe cases, thrombocytosis can cause dangerous clots in blood vessels, thereby increasing the risk of a thromboembolic event. Secondary thrombocytosis is usually detected during routine laboratory testing, and most patients are asymptomatic. Patients may, however, experience symptoms related to the primary condition that causes thrombocytosis (14). Pregnancy is considered a hypercoagulable state due to the normal physiologic changes that affect coagulation. The pathophysiology of a thromboembolic event in OHSS is thought to be increased capillary permeability, resulting in hypovolemia and hemoconcentration, activation of the coagulation cascade, an increase in thrombin-antithrombin III, increased plasmin-antiplasmin complexes and increased platelets (12). Early detection and treatment are critical for both maternal and fetal health (15,16). The most serious life-threatening complication of OHSS is venous thrombosis. Preventive measures are recommended when there is a risk of thrombosis. Immobilization, pressure induced by large ovaries or ascites on pelvic vessels and hypercoagulable states due to pregnancy or high estrogen levels are all risk factors for thromboembolism in moderate-to-severe OHSS. Deep vein thrombosis is more common in patients who have a Leiden factor V mutation, antithrombin III deficiency, protein C

and S deficiency, and a personal or familial history of thrombosis (16,17). Using low-molecular-weight heparin improves the risk of thrombotic complications. Enoxaparin (40 mg/d) or dalteparin (5 000 IU/d) are recommended for thromboprophylaxis because they are easy to administer and do not require monitoring (17,18). Anticoagulation is advised for pregnant women and should be continued for at least the first trimester (19). There have been reports of late thrombosis up to 20 weeks after embryo transfer, and many researchers believe that heparin therapy should be continued for several weeks (20-22). Venous thromboembolism can occur even in mild OHSS, possibly due to the activation of the intrinsic coagulation cascade (23).

CONCLUSIONS

SBP, which results in sepsis, is a rare complication of OHSS. In OHSS, the combination of sepsis and capillary leakage causes hypovolemia and hemoconcentration, as well as activation of the coagulation cascade, which eventually leads to secondary thrombocytosis. To avoid further complications, such as thromboembolic events, immediate treatment with multidisciplinary management is required. When left untreated, OHSS can cause serious complications and even death.

Conflicting Interest(s)

The authors declare no conflict of interest.

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CASO CLÍNICO

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Arterioportal Fistula in Cirrhosis: A Case Report

Fístula arterioportal en cirrosis: reporte de un caso

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SUMMARY

Introduction: *Hepatic arterioportal fistula is a rare but treatable condition that may worsen pre-existing portal hypertension in cirrhosis patients. Embolization is the treatment of choice.*
Case Presentation: *A 60-year-old woman with a 6-year history of liver cirrhosis presented with upper gastrointestinal bleeding and an impaired level of consciousness. Endoscopic examination revealed large fundal varices. Computed tomography angiography of the abdomen revealed an incidental arterioportal fistula without prior history of abdominal trauma or liver procedure. Successful embolization was achieved.*
Conclusion: *This case highlighted the need to consider arterioportal fistula as an aggravating factor of existing portal hypertension through precise examination and treatment.*

Keywords*: Fistula, fibrosis, liver.*

RESUMEN

Introducción: *La fístula arterioportal hepática es una condición rara pero tratable que puede empeorar la hipertensión portal preexistente en pacientes con cirrosis. La embolización es el tratamiento de elección.*
Presentación del caso*: Una mujer de 60 años con antecedentes de cirrosis hepática durante 6 años se presentó con hemorragia digestiva alta y alteración del nivel de conciencia. El examen endoscópico reveló grandes venas varicosas en el fondo. La angiografía por tomografía computarizada del abdomen reveló una fístula arterioportal incidental sin antecedentes de trauma abdominal o procedimiento hepático. Se logró una embolización exitosa.*
Conclusión: *Este caso resaltó la necesidad de considerar la fístula arterioportal como un factor agravante de la hipertensión portal existente a través de un examen y tratamiento precisos.*

Palabras clave*: Fístula, fibrosis, hígado.*

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INTRODUCTION

Portal hypertension is a syndrome characterized by the formation of portosystemic collaterals due to cirrhosis or non-cirrhosis causes. The hallmark of portal hypertension is the formation of varices which are commonly found in the esophagus and gastric region, which are at risk of rupture and cause bleeding (1).

Gastric varices are less common (17 %-25 %) than esophageal varices in patients with liver cirrhosis, but bleeding from gastric varices tends to be more severe with an incidence of 16 %-45 % within 3 years and is associated with a high rate of rebleeding, high transfusion requirements, and high rates of higher mortality (1,2). According to Sarin's classification, GOV 2 and IGV 1 types are referred to as fundal varices because they are in the gastric fundus. Fundal varicose veins contribute to nearly 70 % of bleeding from gastric varices (1,3,4).

In cirrhosis patients, an abnormal connection between the hepatic artery and the portal vein termed arterioportal fistula (APF) may aggravate portal vein hypertension. APF can be a rare and reversible cause of pre-sinusoidal portal hypertension (5). The most common causes are abdominal trauma and iatrogenic cause due to interventional hepatic procedures (5). The diagnosis of APF in cirrhosis is often missed because portal hypertension is thought to be due to the natural course of cirrhosis itself (6). Identification of APF is important because it can contribute to lowering portal pressure in patients with cirrhosis if appropriate therapy is given (6-8). Embolization is the first-line therapy in APF. We presented a case of arterioportal fistula without prior trauma/invasive abdominal procedure that underwent embolization.

CASE PRESENTATION

A 60-year-old Javanese woman was admitted to the emergency department with an altered level of consciousness one day before admission. She appeared confused, disoriented and sometimes agitated. She vomited bright red blood and had an episode of black, tarry stool two days before admission. Her medical history included hepatitis B and liver cirrhosis diagnosed six years ago, routinely consuming Tenofovir 300 mg o.d. Patient denied any history of abdominal trauma or interventional hepatic procedure.

On physical examination, her Glasgow Coma Scale was 11 and her hemodynamic parameter was normal. She looked anemic but no blood flowed from the nasogastric tube. During the digital rectal examination, there was no blood on the gloves.

Her blood test revealed hemoglobin (Hb) concentration of 7.4 g/dL, platelets (Plt) 99 000/ μL, partial thromboplastin time (PPT) of 25.4 seconds (control 11.3 seconds), activated partial thromboplastin time (APTT) 36.8 seconds (control 25.3 seconds), and albumin 2.93 g/dL.

She was assessed initially with grade III hepatic encephalopathy, hematemesis melena due to variceal rupture, Child-Pugh B liver cirrhosis associated with Hepatitis B virus infection, and anemia. She was treated with oxygen, proton pump inhibitor injection, vitamin K injection, octreotide injection, L-ornithine-L-aspartate injection, and planned packed red cell transfusion.

On her 4th day of hospitalization, her consciousness had recovered and an esophago-gastroduodenal (EGD) examination was performed with the result of moderate portal hypertensive gastropathy with ulcers and fundal varices (Figure 1).

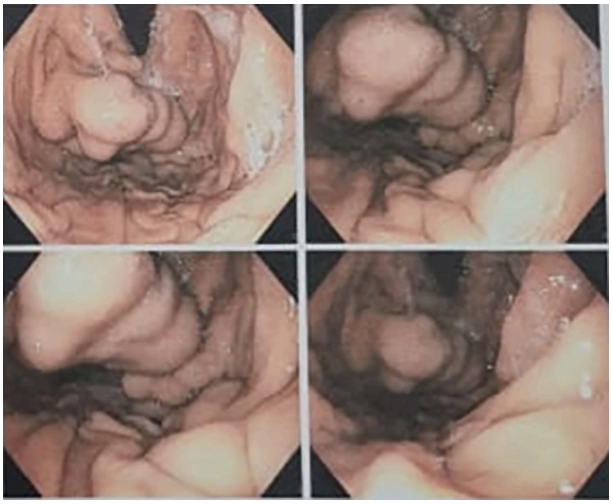

Figure 1. EGD revealed moderate portal hypertensive gastropathy with ulcers and fundal varices.

Abdominal Computed Tomography Angiography (CTA) examination was performed and revealed signs of portal hypertension (dilated portal vein diameter ± 17 mm, normal <13 mm) and an arterioportal fistula. Embolization of the right hepatic artery with polyvinyl alcohol (PVA) of 500-710 was performed by an interventional radiologist (Figure 2).

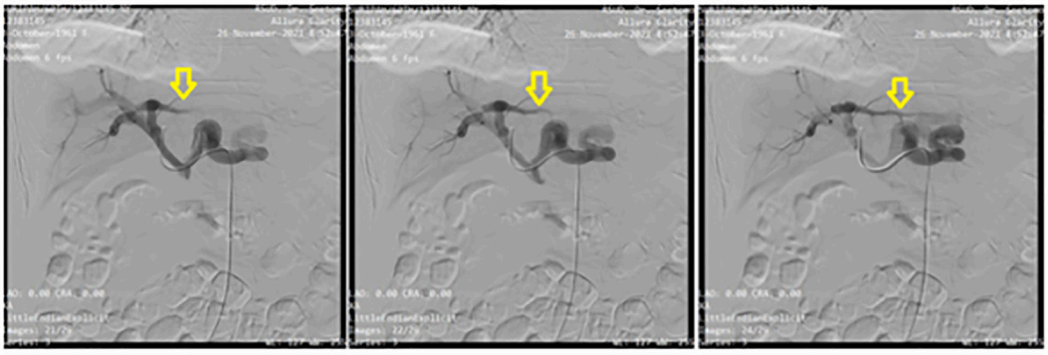

Figure 2. CTA revealed right hepatic artery fistulation to the portal vein.

After embolization, the right hepatic artery fistulation to the portal vein was no longer visible (Figure 3). Two days after embolization, she was discharged with Tenofovir 300 mg o.d. and propranolol 5 mg b.i.d. Despite the clinical improvement when discharged, the patient did not return to the outpatient clinic for further evaluation.

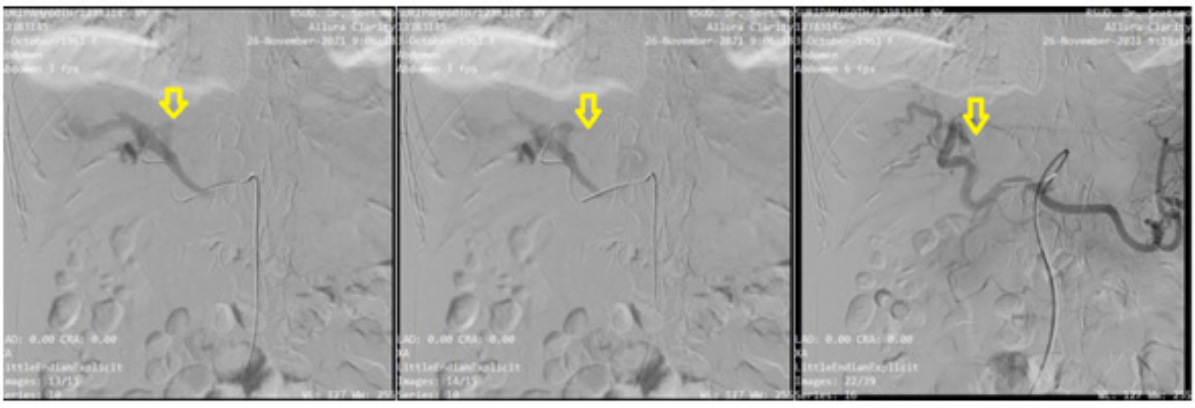

Figure 3. Angiography after embolization of the right hepatic artery with PVA 500-710, the fistula was no longer visible.

DISCUSSION

Portal hypertension can be defined as a portal pressure gradient (pressure difference between the portal vein and hepatic vein) of more than 5 mmHg. The pressure can be measured indirectly using the hepatic portal venous gradient (HVPG). HVPG is clinically significant if the value > 10 mmHg and may bleed when the pressure gradient is exceeding 12 mmHg (9).

In cirrhosis patients, increased liver resistance to portal blood flow due to structural and functional changes of the liver will culminate in increased portal vein pressure and cause typical portal hypertension clinical manifestations such as ascites (due to fluid escape into the peritoneal cavity) and development of collateral vessels (varices). Other factors that increased flow into the portal vein will further increase portal pressure and may worsen the degree of varices and subsequently gastrointestinal bleeding. To determine the cause of portal hypertension in symptomatic patients, risk factors for the underlying cause must be sought out (10).

The cause of portal hypertension is classified as prehepatic, hepatic, or post-hepatic depending on the location of the primary obstruction to portal blood flow. In hepatic (sinusoidal) causes such as cirrhosis, portal hypertension is caused by increased resistance to portal flow due to fibrosis and regenerative nodules and hyperdynamic flow of blood entering the portal vein. Pre-hepatic causes may include a portal or splenic vein thrombosis and arteriovenous fistula. Post-hepatic causes are Budd-Chiari syndrome or congestive heart failure. Non-cirrhosis causes of portal hypertension may include intra-hepatic or pre-hepatic lesions in the absence of liver cirrhosis, such as schistosomiasis, biliary cirrhosis, hepatoportal sclerosis, and congenital liver fibrosis (9,11,12).

One cause that may worsen portal hypertension that could go unnoticed in cirrhosis patients is APF because portal hypertension is already present in cirrhosis patients and clinical deterioration may be misinterpreted for the natural history of cirrhosis itself. An APF is an abnormal connection between the hepatic artery and the portal vein which can be a rare and reversible cause of pre-sinusoidal portal hypertension. APF can appear spontaneously in liver cirrhosis (5). In patients with liver cirrhosis, the diagnosis of APF is often underestimated because APF can be small and asymptomatic. APF is often caused by procedures that cause injury to the hepatic artery and portal vein such as percutaneous liver biopsy or penetrating liver trauma (6,7).

The majority of patients with APF are asymptomatic, however, when symptoms occur, it is usually due to the effects of increased portal pressure. The most common symptoms were gastrointestinal bleeding (33 %), ascites (26 %), congestive heart failure (4.5 %), and diarrhea (4.5 %). Bruits or thrills can also be detected in about 33 % of patients and are an early sign of APF. Thrill usually only appears when the diameter of the fistula is > 4 mm (5).

APF is classified based on its etiology, size, anatomy, and location. They can be classified as congenital or acquired, large or small, intra-hepatic or extra-hepatic, central or peripheral, and traumatic or spontaneous. Commonly, APF is classified into 3 types. Type 1 APF is usually small, peripheral, and intra-hepatic fistulas, usually asymptomatic, often occur after percutaneous liver biopsy, and may close spontaneously within 1 month. If the fistula remains open within 1 month and symptoms develop, then embolization therapy is needed. Type 2 APF is a larger, more central fistula, and occurs after penetrating abdominal trauma. Type 2 APF can cause portal hypertension and should be treated with embolization or surgery in cases where endovascular therapy fails or endovascular therapy is not available. Type 3 APF is a rare congenital fistula, usually intra-hepatic and diffuse, and can cause severe portal hypertension in childhood. Treatment options are hepatic artery ligation, embolization, hepatectomy, or liver transplantation (5).

Identification of APF is important because it may lower portal pressure in liver cirrhosis patients with appropriate therapy. The simplest screening is by color Doppler ultrasound examination. APF may be detected when there is a decrease in the resistive index and pulsatility index of at least 30 %-40 % in one lobe compared to the index in the other lobe and the blood flow in the intrahepatic branch of the portal vein of that lobe is opposite to the flow in the normal lobe (hepatopetal) (6,7).

Arteriography is the gold standard for diagnostics in APF. Pathognomonic signs include early visualization of the portal vein during aortic or celiac artery injection. Angiography often shows a single fistula with hepatopedal flow without evidence of portal hypertension, although cirrhosis may present with hepatofugal

flow. CTA shows premature filling of the veins during the arterial phase and a conspicuous focus on the hepatic arterial phase (5,8).

Our patient presented with a history of vomiting bright red blood and an episode of black, tarry stool caused by ruptured fundal varices. A possible cause of her gastrointestinal bleeding symptoms is increased portal hypertension due to liver cirrhosis (hepatic) and arterioportal fistula (prehepatic). Interestingly, CT angiography was initially performed to assess the afferent and efferent vessels of her fundal varices but instead found an arterioportal fistula. From the abdominal CT scan, we can also exclude additional prehepatic and post-hepatic causes of portal hypertension. The patient had no prior history of abdominal trauma or invasive abdominal procedure so APF in this patient may be occurred spontaneously related to her cirrhosis condition.

The initial management of acute bleeding from gastric varices is not different from that of esophageal varices, which includes fluid resuscitation, correction of coagulopathy, medical therapy with antibiotics and vasoactive drugs, and early intervention with endoscopy. Radiological management, balloon tamponade, and surgery are used in cases of hemostatic failure after endoscopic intervention and pharmacological therapy (4,13,14).

Endoscopic interventions include tissue adhesive with endoscopic cyanoacrylate glue injection (ECI), fibrin and thrombin therapy, endoscopic band ligation (EBL) and sclerosants including alcohol. ECI is the treatment of choice according to the Baveno VI consensus and is most often used in the management of gastric varices with a hemostatic rate of 91 %-100 % and a rebleeding rate of about 7 %-28 % (4). Although there are no strong recommendations and the risk of embolization, ECI can be used as primary and secondary prophylaxis of fundal variceal bleeding (13-15).

The choices of treatment for APF include surgery and minimally invasive interventions such as trans-catheter arterial embolization (TAE). TAE had lower morbidity and lower cost than surgery, therefore it became the first-line treatment for APF. Various embolic agents may be used with their advantages and disadvantages. Lipiodol agents may be useful in poor blood shunt but may easily occlude small blood vessels and induce liver ischemia. Polyvinyl alcohol (PVA) has to be combined with a contrast agent but is effective for long-term occlusion effects. Spring steel coils are typically used for long-term simple shunts because they may not reach the small distal vascular that are difficult to reach. Gelatin sponge particles are typically reabsorbed within 2-4 weeks, therefore had a high recanalization rate (16).

In a retrospective analysis of 97 cases of patients with hepatic arterioportal fistulas in China Hospital from January 2010 to January 2020, Cao et al. revealed that 64,9 % of APF patients treated with TACE showed comparable efficacy between the embolization agents such as polyvinyl alcohol, lipiodol combined with gelatin sponge, and spring steel ring (16). In our patient, we chose polyvinyl alcohol for embolization agents.

Complications that may occur with the embolization procedure are agent (coil) migration, vascular injury, liver failure, infection and subsequent abscess, portal thrombosis, and bile duct stricture (8,17). In cases where embolization fails, the choice is surgery with hepatic artery ligation or fistula ligation (8). In most patients with acquired APF, the prognosis is good due to the minimal physiologic changes associated with isolated APF and the currently effective treatments available (5,18). Our patient underwent embolization with no visible fistulation of the right hepatic artery to the portal vein.

CONCLUSION

APF is a rare condition that may cause increased portal pressure, mainly in a patient with underlying portal hypertension such as liver cirrhosis. Assessment of vascularity in gastric varices (including fundal varices) and identification of arterioportal fistulas are important to determine the appropriate management of the patient to stop active bleeding and prevent rebleeding. Embolization therapy is the treatment of choice for APF.

Academic Collaborations of the Authors

ZNH collected the data and wrote the manuscript, and BW conducted, supervised, and supported the project.

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Conflict of Interest

The author stated there is no conflict of interest.

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Severe Norwegian Scabies Infection in Psoriatic Arthritis Patient with Naïve Hepatitis B and Sepsis: A Case Report

Infección Severa de Sarna Noruega en Pacientes con Artritis Psoriásica con Hepatitis B sin Tratamiento Previo y Sepsis: Reporte de un caso

Dewinta Enggar Pramesthi[1*], Lita Diah Rahmawati[2]

SUMMARY

Introduction: *Norwegian scabies is an acute form of severe scabies infection seen in immunocompromised patients. Psoriasis arthritis (PsA) is a systemic autoimmune disease involving the synovial tissue and skin. Norwegian scabies with its complication that occurs in PsA patients can be difficult to diagnose and cause mortality if untreated.*

Case presentation: *A 39-year-old woman came to Dr. Soetomo's hospital with complaints of body aches, peeled white scales all over her body, and immobilization for months. Multiple macular erythemas that were covered by thick scales with indistinct borders and multiple ulcers with slough were found. The patient met CASPAR criteria for diagnosing PSA. Sarcoptes scabiei eggs were found on skin scraping. The patient also had naïve hepatitis B and severe sepsis. Low-dose methylprednisolone was given with ivermectin, antibiotic, tenofovir, and regular wound care. The patient responded satisfactorily to the treatment and clinical findings was getting better. The thick crust disappeared, and the patient was able to mobilize.*

Conclusion: *Diagnosing and treating Norwegian scabies in PsA remains challenging, and poor prognostic often follows. Proper and immediate treatment will give a good outcome.*

Keywords: *Norwegian scabies, psoriatic arthritis, sepsis, Naïve hepatitis B.*

RESUMEN

Introducción: *La Sarna Noruega es una forma aguda de sarna grave que se observa en pacientes inmunocomprometidos. La Artritis Psoriásica (PsA) es una enfermedad autoinmune sistémica que afecta el tejido sinovial y la piel. La Sarna Noruega con su complicación que ocurre en pacientes con PsA puede ser difícil de diagnosticar y causar mortalidad si no se trata.*

Presentación del caso: *Una mujer de 39 años acudió al hospital del Dr. Soetomo con quejas de dolores en el cuerpo, escamas blancas descamadas en todo el cuerpo e inmovilización durante meses. Se encontraron múltiples eritemas maculares que estaban cubiertos*

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por gruesas escamas de bordes indistintos y múltiples úlceras con esfacelos. El paciente cumplía criterios CASPAR para el diagnóstico de PSA. Se encontraron huevos de Sarcoptes scabiei al raspar la piel. El paciente también tenía Hepatitis B Naïve y sepsis grave. Se administró metilprednisolona en dosis bajas con ivermectina, antibiótico, tenofovir y cuidado regular de heridas. El paciente respondió satisfactoriamente al tratamiento y los hallazgos clínicos fueron mejorando. La costra gruesa desapareció y el paciente pudo movilizarse.

Conclusión: *El diagnóstico y el tratamiento de la Sarna Noruega en la APs sigue siendo un desafío y, a menudo, sigue un mal pronóstico. El tratamiento adecuado e inmediato dará un buen resultado.*

Palabras clave: *Sarna Noruega, artritis psoriásica, sepsis, hepatitis B Naïve.*

INTRODUCTION

Norwegian scabies, or hyperkeratotic scabies, is an acute form of severe scabies infection seen in immunocompromised patients. Psoriasis arthritis (PsA) is a systemic autoimmune disease involving the synovial tissue and skin. Patients with PsA tend to develop secondary infections more than healthy people. The immune system of patients with autoimmune diseases will attack the cells in their own bodies, and the immunosuppressant therapy given is a combination factor that makes patients with autoimmune diseases more susceptible to infection (1).

Human scabies is caused by an ectoparasite mite called *Sarcoptes scabiei var. hominis*, which belongs to the order Stigmata. Sarcoptes mites will enter the skin and lay several eggs in the canal and then a few days later nymphs will appear on the surface of the skin. This scabies infection can also be very easily transmitted to individuals around the patient. Scabies has been reported from various parts of the world, and the incidence is high, especially in developing countries. The main factors for the spread of this disease are overcrowding, poor personal hygiene, living in rural areas, and ignoring hygienic principles (2).

Norwegian scabies that occurs in PsA patients leads to sepsis due to secondary infection and death in untreated patients. Therefore, it is very important to carry out diagnostic and therapeutic management as early as possible, especially in patients with impaired immune systems, to avoid the severity of the disease and complications.

CASE PRESENTATION

A 39-year-old woman came to Dr. Soetomo hospital based on a referral from an internal medicine specialist with complaints of body aches and skin peeling all over her body. Initially, the patient complained of itchy legs accompanied by reddish patches, then spread throughout the body. After that, the skin is covered with white scales and peels off. Because the skin peels and the body aches, the patient was immobilized for the past 4 months. As a result, there was a wound on the right lower back. The patient also complains of joint pain in the right and left toes, especially in the morning after waking up. At the previous internal medicine specialist, the patient was previously treated with methylprednisolone tablets 16 mg/24 h for the last 2 weeks. From the social history, the patient lives with her husband at home and has 2 children. Her two children go to an Islamic boarding school and only come home when school is off.

On physical examination, the general condition was weak. Multiple ulcers were found in the sacrum region with a size of 7x5 cm, 3x2 cm, and 1x1 cm, with a dermis base and exudate. Ulcers were also found in the right trochanter region with a size of 10x6 cm, with a muscle base and slough. On the dermatological status of the whole body, there were multiple macular erythemas with indistinct borders and thick scales (Figure 1 a-d).

In laboratory examination, there were reactive HBsAg, leukocytes 32 780/cm^3, procalcitonin 6.39 ng/mL, CRP 27 mg/L, ESR 97 mm/h, ANA test 27.5 units (moderately positive), and negative rheumatoid factor. On x-ray examination, showed inflammatory joint disease in genu dextra. Due to the finding of multiple erythematous macules accompanied by thick scales, Dermatoveneorology colleagues performed a skin-scraping examination and found the formation of *Sarcoptes scabiei* eggs (Figure 2).

There were also found symptoms of infection, namely fever, accompanied by a focus of infection (purulent ulcer in the sacrum region) so the patient was examined for blood and pus

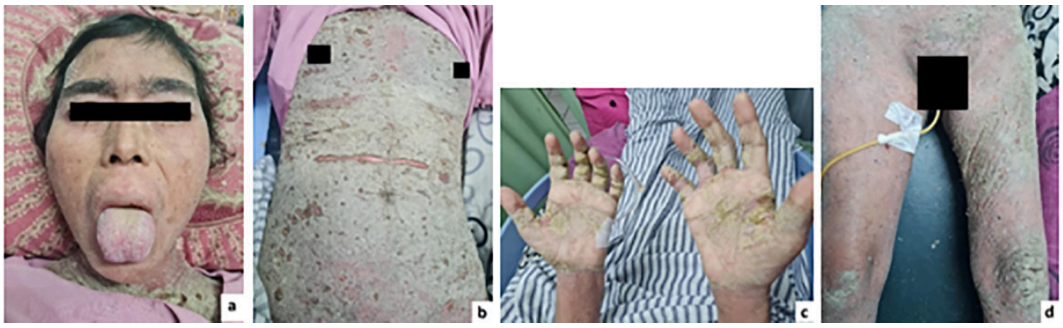

Figure 1 a-d. Clinical findings of multiple macular erythemas and thick scales all over the body, day 0 of treatment. (a: face, b: chest and abdomen, c: acral, d: lower limb).

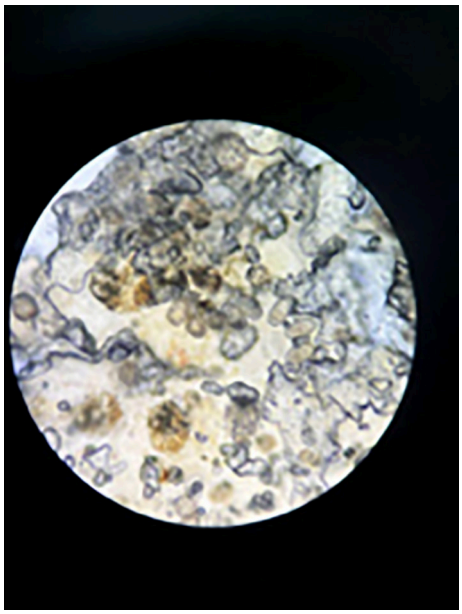

Figure 2. *Sarcoptes scabiei* eggs from skin scraping examination.

culture. Based on blood culture, MRSA was sensitive to linezolid and vancomycin and based on pus culture, ESBL was sensitive to amikacin, ampicillin-sulbactam, cefoperazone sulbactam, imipenem, tetracycline, amoxicillin, clavulanic acid, tigecycline, chloramphenicol, meropenem, and piperacillin. Through history taking, physical examination, and additional examination, the patient was diagnosed with PsA, Norwegian scabies, sepsis caused by infected decubitus ulcer of trochanter region dextra grade IV and sacrum region grade III, and naïve hepatitis B.

The patient was treated with methylprednisolone with an initial dose of 62.5 mg/24 h intravenous, then tapered down every 3 days to 8 mg/12 h orally, then 8 mg/24 h orally and paracetamol tablet 500 mg/8 h orally if in pain. For Norwegian scabies, the patient was initially given topical therapy with 5 % permethrin ointment which was applied to the entire lesion, but the patient complained that the skin was getting more painful and itchy, so finally the patient was given ivermectin tablet 12 mg/24 h given on day 1, 2, 8, 9 and 15 orally, accompanied by cetirizine tablets 10 mg/24 h every morning, CTM tablets 4 mg/24 h every night, sodium fusidate ointment 2 times a day, and wounds treatment regularly. The patient's family was also immediately directed to seek treatment from the community health center to prevent scabies from spreading. Previously the patient was given an empirical antibiotic which is ceftriaxone injection 1 g/12 h intravenously and due to the finding of MRSA in blood culture and ESBL in pus culture, the antibiotic was switched to vancomycin drip 1 g/12 h intravenously and cefoperazone sulbactam injection 2 g/12 h intravenously for 7 days. For treatment of naïve hepatitis B, tenofovir tablets were given 300 mg/24 h orally because the patient was receiving oral methylprednisolone therapy.

On the 7th day of treatment, the scales and peeling skin all over the body have reduced. Itchy and pain in the skin have also been reduced. Pus in the decubitus ulcer is still present but has decreased. Because there is still weakness

and pus in the decubitus ulcer, vancomycin drip of 1 g/12 h intravenously and cefoperazone sulbactam injection of 2 g/12 h intravenously were continued until day 10. After the 10th day of treatment, the clinical evaluation of the patient was found to be improving, so the patient was allowed to go home and undergo treatment in the outpatient clinic. When the patient came to the rheumatology outpatient polyclinic a week later, she found that complaints of pain were much reduced. The patient was able to do activities at home, the scales and erythema on the patient's skin were decreased, and the pus in the decubitus ulcer was also reduced. Patients received therapy with methylprednisolone 8 mg/24 h orally, cetirizine 10 mg/24 h orally, tenofovir tablets 300 mg/24 h orally, and wound treatment regularly for decubitus ulcers (Figure 3 a-d).

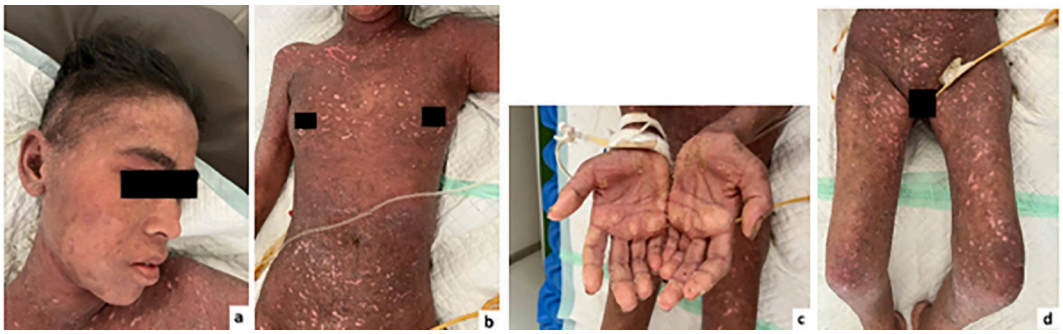

Figure 3 a-d. Clinical findings where erythema and thick scales have reduced, day 10 of treatment. (a: face, b: chest and abdomen, c: acral, d: lower limb).

DISCUSSION

PsA is a systemic autoimmune disease that can manifest in joints and skin (1). The diagnosis of PsA can be made using the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria, if there are 3 points out of the following criteria: present psoriasis (2 points; for all other criteria 1 point), history of psoriasis, family history of psoriasis, dactylitis, juxta-articular new bone formation as evidenced by radiological examination, negative rheumatoid factor, and nail dystrophy (3). Symptoms of PsA that are often found are pain, swelling, and stiffness in the joints. The severity of PsA symptoms varies from mild to severe irreversible inflammatory joint damage (4). On physical examination, inflammation of the joints can be found. The joints most commonly affected are the knees, ankles, and the joints of fingers, and toes. Diagnosis of psoriasis on the skin is more frequently found clinically because punch biopsy is rarely done. Clinical findings often found in psoriasis patients is the presence of well-defined, erythematous, thick scales with a diameter of > 0.5 cm, either as a single lesion or generalized throughout the body (5). The manifestations of psoriatic arthritis may precede the skin symptoms or occur together (6).

In this patient, the diagnosis of psoriatic arthritis can be made because it meets 3 points from the CASPAR criteria, namely the presence of current psoriasis and negative rheumatoid factor. Although a punch biopsy was not performed in this patient, the diagnosis of psoriasis can be made clinically, which is the presence of well-defined and thick scales that are generalized throughout the body, accompanied by erythematous skin underneath. Symptoms that are often found in PsA patients can also be found in this patient, namely pain in the toe joints.

Norwegian scabies is a rare form of massive manifestation caused by the infection of *Sarcoptes scabiei var hominis* due to inadequate host

response to mites. In common scabies, the number of parasites that attack the epidermis is relatively small. In Norwegian scabies, millions of parasites invade the epidermis and induce hyperplastic changes. Norwegian scabies is frequently found in immunocompromised patients, such as in patients with immunodeficiency syndromes or patients with transplants, patients with autoimmune, patients with infection (8), immobilized patients, and patients with paresis or severe arthropathy (7). With the increasing use of immunosuppressive therapy, the diagnosis of Norwegian scabies is more common (9). Cases have been reported on previous systemic corticosteroids (10) and tocilizumab therapy (11).

In this case, the patient has an autoimmune disease, which is PsA, where the patient's immune response is impaired. There was also a history of prolonged immobilization and previous therapy with oral corticosteroids which makes the patient susceptible to Norwegian scabies infection. Hepatitis B naïve in this patient also reduced immunity and make the patient susceptible to Norwegian scabies infection.

Clinically, Norwegian scabies is characterized by extensive hyperkeratosis and crustae, especially in the acral area. It can also cause severe itching and form a secondary infection that causes septicemia and mortality in untreated patients (12). Norwegian scabies can develop into erythroderma. Diagnosis can be complicated when this occurs in an autoimmune patient with the rash, thus skin scraping examination should be performed in autoimmune patients with hyperkeratosis and macular erythema, especially in patients with complaints of itching, to rule out the diagnosis of Norwegian scabies. When the diagnosis of Norwegian scabies is made, the patient must immediately undergo adequate therapy and isolation, because the disease is highly contagious (13).

This patient had macular erythema all over the body, accompanied by thick scales. This thick scale is formed from the process of hyperkeratosis. Skin scraping examination was performed on this patient and we found the formation of *Sarcoptes scabiei* eggs. When the diagnosis of Norwegian scabies was made, the patient was immediately treated in an isolation room. The patient's family at home was also immediately directed to check themselves at the community health center to break the chain of scabies infection transmission.

Therapy in PsA patients can be complicated in several circumstances, in this case with Norwegian scabies infection, sepsis, and comorbid hepatitis B infection. According to the American College of Rheumatology, non-pharmacological and pharmacological therapies can be given to PsA patients. Non-pharmacological therapies include physical therapy, occupational therapy, smoking cessation, weight loss, and exercise. Pharmacological therapies include oral small molecule, biologic tumor necrosis factor inhibitors (TNFi), biologic interleukin-17 inhibitors (IL-17i), biologic IL-12/23i, CTLA4-immunoglobulin, and JAK inhibitors. Symptomatic therapy includes Non-steroidal anti-inflammatory drugs (NSAID), systemic glucocorticoids, and glucocorticoid injections. Methotrexate (MTX) is recommended over NSAIDs in treatment-naive patients with active arthritis. NSAIDs can be used instead of MTX if there are contraindications in patients without severe psoriasis or severe PsA and in those at risk of liver toxicity (14) However, biological therapies such as TNFi, IL17i, and IL23i are contraindicated in patients with chronic infectious diseases, such as hepatitis B, HIV, and tuberculosis, because these patients are already immunocompromised. MTX therapy is also contraindicated in patients with chronic hepatitis B infection because it can cause further liver damage. In addition, cyclosporine therapy is also contraindicated in patients with immunocompromised states and active chronic infectious diseases, such as hepatitis B (14).

This patient was given therapy for PsA, but due to the presence of Norwegian scabies infection and naïve hepatitis B which indicates the patient is immunocompromised, the only therapy given was low-dose methylprednisolone. This is because the administration of cyclosporine, MTX, and biologic therapy is contraindicated in immunocompromised patients. Patients are also given paracetamol tablets 500 mg / 8 h when the patient feels pain and physical therapy with gradual mobilization exercises.

Treatment of Norwegian scabies was first carried out by administering a scabicidal agent, namely 5 % topical permethrin. It has been

previously reported in two cases of Norwegian scabies in similar autoimmune patients in Iran that topical use of 5 % permethrin for 2 weeks gave good results (12). If topical scabicide agents fail, oral ivermectin can be used for the treatment of Norwegian scabies (15). The use of ivermectin for Norwegian scabies has been shown to be safe and effective in a single oral dose (16). Ivermectin is used for the treatment of crusted scabies in doses ranging from 0.1 to 0.4 mg/kg. However, the general validated dose is 0.2 mg/kg (17). Ivermectin may be the drug of choice for scabies unresponsive to conventional topical therapy, which is common in patients with immunodeficiency syndromes or epidemic outbreaks.

Initially, this patient was treated with 5 % permethrin topically as a scabicidal agent, but the patient complained of worsening pain and itch. So we replaced it with oral ivermectin 12 mg / 24 h. After that, the thick scale began to disappear and the itch and pain felt by the patient began to decrease.

Generally, PsA is a disease with a mild condition. With proper management, joint stiffness, and pain can be resolved. However, in certain circumstances where PsA is accompanied by a secondary infection causing sepsis, it can be life-threatening. On the other hand, Norwegian scabies manifestations can occur in an atypical pattern, so it can cause delays in diagnosis and have a poor prognosis (18).

This patient had PsA manifestations accompanied by Norwegian scabies, naïve hepatitis B, decubitus ulcers, and sepsis. Due to the occurrence of PsA in this patient accompanied by other conditions that make the patient increasingly immunocompromised, this can lead to life-threatening for the patient and a poor prognosis. However, proper management and administration as early as possible prevent the patient from morbidity and mortality.

CONCLUSION

We reported a 39-year-old woman with complaints of body aches, peeled white scales all over her body, and immobilize for months. Multiple macular erythemas that were covered by thick scales with indistinct borders and multiple ulcers with slough were found. The patient met CASPAR criteria for diagnosing PsA. *Sarcoptes scabiei* eggs were found on skin scraping. The patient met CASPAR criteria for diagnosing PsA. The patient also had naïve hepatitis B and severe sepsis. Low-dose methylprednisolone was given with ivermectin, antibiotic, tenofovir, and regular wound care. The patient responded satisfactorily to the treatment and clinical findings were getting better. The thick crust disappeared, and the patient was able to mobilize. Diagnosis can be complicated when Norwegian scabies occurs in an autoimmune patient with the rash, thus skin scraping examination should be performed to rule out Norwegian scabies. Poor prognostic often follows Norwegian scabies in PsA, and treatment must be carried out with caution considering the many contraindications in autoimmune patients. Proper and immediate treatment will give a good outcome.

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Conflicts of Interest

The authors declare no conflict of interest.

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Liver Cirrhosis Patient with Complications of Hepatic Hydrothorax. Case Report

Paciente con cirrosis hepática con complicaciones de hidrotórax hepático. Reporte de caso

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SUMMARY

Introduction: *Hepatic hydrothorax is that occurs in individuals with decompensated cirrhosis of the liver. Approximately 5 % of cases of pleural effusion occur in patients with cirrhosis and ascites. Although quite rare, it is associated with higher morbidity and lower survival rates. The mechanism is not fully understood, but the most widely accepted pathogenesis involves the presence of portal hypertension, diaphragmatic defects, and negative intrathoracic pressure. In this case, the pleural effusion occurs because of the direct displacement of peritoneal fluid through the small openings in the diaphragm into the pleural space. We aimed to study its clinical features and natural history.*
Case Presentation: *We reported a 59-year-old woman with liver cirrhosis and hepatic hydrothorax complications. Patients experience shortness of breath and hematemesis. Examination of chest X-ray and chest CT scan found right pleural effusion. The patient was treated with repeated thoracocentesis, and a chest pigtail catheter was placed for pleural effusion, salt restriction, diuretics, and management of the underlying disease (liver cirrhosis). After the installation of the chest pigtail catheter, the fluid production reduced (less than 500 mL in a day). The results of the pleural fluid analysis showed an impression of the transudate.*
Conclusion: *This study reports the rare case of a patient with right pleural effusion due to hepatic hydrothorax in liver cirrhosis, who improved with comprehensive therapy (salt restriction, diuretics, repeated thoracocentesis, and then chest pigtail catheter application).*

Keywords: *Liver cirrhosis, hepatic hydrothorax, pleural effusion.*

RESUMEN

Introducción: *El hidrotórax hepático es el que se presenta en individuos con cirrosis hepática descompensada. Aproximadamente el 5 % de los*

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casos de derrame pleural ocurren en pacientes con cirrosis y ascitis. Aunque bastante raro, se asocia con una mayor morbilidad y menores tasas de supervivencia. El mecanismo no se comprende por completo, pero la patogenia más ampliamente aceptada involucra la presencia de hipertensión portal, defectos diafragmáticos y presión intratorácica negativa. En este caso, el derrame pleural se produce por el desplazamiento directo del líquido peritoneal a través de las pequeñas aberturas del diafragma hacia el espacio pleural. El objetivo fue estudiar sus características clínicas y su historia natural.

Descripción de caso: *Reportamos una mujer de 59 años con cirrosis hepática y complicaciones de hidrotórax hepático. Los pacientes experimentan dificultad para respirar y hematemesis. En el examen de radiografía de tórax y tomografía computarizada de tórax se encontró derrame pleural derecho. El paciente fue tratado con toracocentesis repetidas y se colocó un catéter pigtail (cola de cerdo) torácico por derrame pleural, restricción de sal, diuréticos y manejo de la enfermedad de base (cirrosis hepática). Después de la instalación del catéter de cola de cerdo torácico, la producción de fluidos se redujo (menos de 500 mL en un día). Los resultados del análisis del líquido pleural mostraron una impresión del trasudado.*

Conclusión: *Este estudio reporta el raro caso de un paciente con derrame pleural derecho por hidrotórax hepático en cirrosis hepática, que mejoró con terapia integral (restricción de sal, diuréticos, toracocentesis repetidas y luego aplicación de catéter de cola de cerdo torácico).*

Palabras clave: *Cirrosis hepática, hidrotórax hepático, derrame pleural*

INTRODUCTION

Hepatic hydrothorax is an excess accumulation of transudate fluid in the pleural cavity in patients with decompensated liver cirrhosis without pulmonary and pleural heart disease. The condition is localized to the right in approximately 85 % of cases and to the left alone in 13 % of cases, as only 2 % have effusions on both sides (1).

Hepatic hydrothorax is a rare complication of end-stage liver disease, accounting for 5 %-10 % of cirrhotic patients. There are already a few case reports describing the clinical features and treatment of hepatic hydrothorax, but current knowledge about this complication of cirrhosis is very limited. The pathogenesis and therapy of hepatic hydrothorax have not been well studied, and there are no randomized controlled trials that can provide the best treatment option, so evidence-based guidelines have not been published (2).

Patients with minimal pleural effusion may be asymptomatic or have pulmonary symptoms, such as shortness of breath, cough, chest discomfort, hypoxemia, or respiratory failure. Hepatic hydrothorax is prone to spontaneous bacterial pleurisy with or without spontaneous bacterial peritonitis. Hepatic hydrothorax indicates progression to decompensated cirrhosis and the need for liver transplantation consideration. The management of hepatic hydrothorax is still a problem because the condition of the liver tends to be poor (3). We present this case report to increase knowledge about liver cirrhosis complications, which are rare.

CASE PRESENTATION

A 59-year-old woman came from a hospital referral to the emergency room of Dr. Soetomo Hospital with complaints of vomiting blood one day before admission to the hospital. She vomited blood once in the form of fresh blood mixed with blood clots. The amount is approximately half a glass of mineral water (125 mL). The patient did not complain of abdominal pain, cough, or shortness of breath. There was no history of previous trauma or jaundice or urination like tea. The patient did not brush her teeth when she vomits.

The patient also complains of shortness of breath, but there was no cough or fever. The shortness of breath worsens when she sleeps, improving with a sitting position. The patient had had lung fluid removed while being treated in the internal medicine ward. The patient admitted that she had never looked yellow or had hepatitis before.

From the physical examination, the respiratory rate was 24x/minute. On examination of the head and neck, the conjunctiva was not anemic, not icteric. On chest examination, the development of the right chest wall lags behind the left. Auscultation of the thorax obtained decreased right vesicular breath sounds and no additional breath sounds. On abdominal examination,

there was no visible distention, *caput medusa*, or *collateral vein*. On auscultation, bowel sounds were normal. On percussion, neither *shifting dullness* nor undulation was found. Abdominal palpation revealed that the liver and spleen were not palpable.

From the results of laboratory tests, it was found that several tests were less or more than the reference values, which can be seen in Table 1.

Table 1. Laboratory result

Checking type	Parameters	Result
Hemoglobin	12.0-14.0 (F) 13.0-16.0 (M)	11.7 g/dL
Leukocytes	5 000-10 000	6360 u/mL
Neutrophils	39.8-70.5	76.30 %
Lymph	23.1-49.9	13.20 %
Platelets	150 000-450 000	83 000 u/mL
Blood Urea Nitrogen (BUN)	7-20	16 mg/dL
Serum creatinine	0.5-1.2	0.6 mg/dL
Sodium	136-146	140 mmol/L
Potassium	3.5-7.0	3.4 mmol/L
Chloride	94-111	102 mmol/L
AST <25 (M)	<21 (F) 149 units/L	
ALT <30 (M)	<23 (F) 70 units /L	
Albumin	3.4-5.0	2.98 g/dL
PPT	9-12	10.3 seconds
APTT	23-33	29.8 seconds
Random blood glucose	<200	117 mg/dL

From the investigation, HBsAg reactive, and COVID-19 PCR swab was not detected. The patient had undergone radiological investigations in the form of a chest X-ray with the results of pulmonary inflammation with right pleural effusion, and the heart did not show abnormalities (Figure 1). The ultrasound examination revealed normal liver size, heterogeneous increased echo-parenchymal intensity, irregular obtuse angles, no nodules, and an enlarged spleen that appeared ascites (Figure 2). There was an impression of hepatic cirrhosis with ascites. Transient elastography examination of the patient showed the results of 36.3 kPa, which is equivalent to the degree of fibrosis f4. The results of the initial ECG examination revealed rhythmic sinuses with a heart rate of 79 beats per minute, normoaxis.

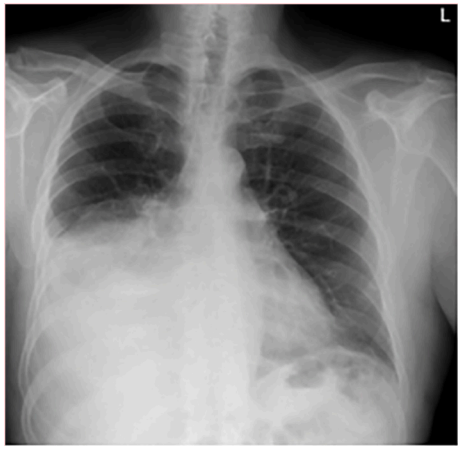

Figure 1. Chest X-ray (First admission).

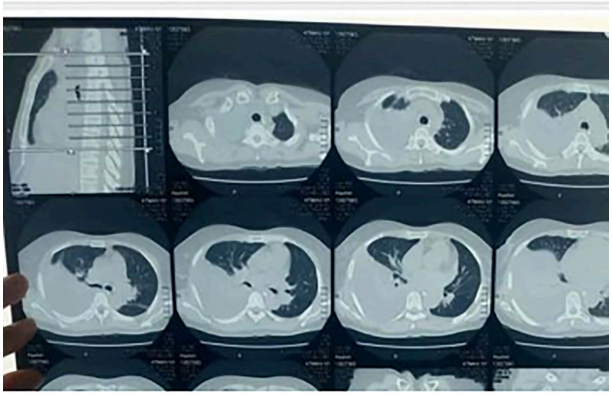

Figure 2. Thorax CT scan (First Admission).

From a chest X-ray examination and thorax CT scan, there is a right-sided pleural effusion, thickening of the left hilum, and ascites (Figures 1 and 2). On the fourth day of treatment, the patient complained of shortness of breath and black stool getting worst. The chest X-ray revealed the right pleural effusion, and the right lung was not visualized, suggesting a massive right pleural effusion. We gave additional therapy in the form of a somatostatin analog bolus of 50 mcg followed by a somatostatin analog drip of 25 mcg every hour and omeprazole in 40 mg every 6 hours and antibiotic (ceftriaxone injection of 2 g daily). On the tenth day of treatment, the

patient did not experience melena. Pleural fluid cytology results showed no malignancy, only powdered lymphocyte cells. The patient was then planned for endoscopy. The endoscopy showed esophageal and gastric varices (GOV-1) and gastropathy congestive. The patient was treated with an injection of histoacryl and lipiodol for gastric varices.

The patient was then planned for repeated fluid evacuation. On the fifth day of treatment, the patient underwent a second pleural fluid evacuation, 1 200 mL of lung fluid was obtained with a transparent color impression, and pleural fluid cytology was performed. The patient underwent a chest X-ray evaluation after the evacuation of pleural fluid. It was found on a chest X-ray of lung inflammation, right pleural effusion, and atherosclerosis. Because the estimated amount of lung fluid in the patient is still a lot, it is planned to install the right pigtail catheter in the patient. After the installation of the chest pigtail catheter, the fluid production reduced (less than 500 mL in a day). The results of the pleural fluid analysis showed an impression of the transudate.

DISCUSSION

Liver cirrhosis is a progressive, diffuse, fibrotic, and nodular condition that damages the entire liver structure (4). Cirrhosis is the final course of fibrogenesis in chronic liver disease. The liver changes from a normal state to a fibrotic condition, with cirrhosis being a complex process involving parenchymal and non-parenchymal components, the immune system, cytokines, proteinases, and their inhibitors (5).

Cirrhosis can be caused by various diseases, including alcohol, viral hepatitis infection (hepatitis B and C), and *Non-Alcoholic Fatty Liver disease* (NAFLD). Cryptogenic, metabolic (hemochromatosis or Wilson's disease), biliary disease, autoimmune, drug-induced hepatitis (e.g., methotrexate, amiodarone), and hepatic venous congestion (Budd Chiari syndrome, constrictive pericarditis) (6).

Cirrhosis and hepatocellular carcinoma (HCC) are two clinical outcomes of untreated chronic hepatitis B. This patient, although recently tested positive for hepatitis B, already has signs of chronic liver disease based on physical examination and investigations. This patient underwent a known HBsAg test in August 2020 and showed high ALT levels. The indications for treatment of hepatitis B infection were determined based on a combination of four criteria, including serum HBV DNA level, HBeAg status, ALT level, and liver histology. In patients with compensated cirrhosis, treatment was initiated in patients with HBV DNA >2 x 10^3 IU/mL. In contrast, decompensated cirrhosis should be treated promptly to prevent disease progression, regardless of HBV DNA or ALT (7). In this case, the patient is prescribed antiviral treatment in the form of tenofovir in a dose of 1 x 300 mg for life.

The natural course of cirrhosis is characterized by a phase of asymptomatic compensatory cirrhosis followed by a phase of decompensation, and this period of decompensation is characterized by the appearance of various symptoms, including ascites, bleeding, encephalopathy, and jaundice (8). The clinical picture of decompensated cirrhosis was assumed to result from a hemodynamically compromised overactive circulation syndrome caused by peripheral arterial vasodilation, particularly in the splanchnic circulation. Vasodilation impairs adequate blood volume and ultimately leads to hypoperfusion of peripheral organs, with the kidneys being the most affected (9).

One of the common complications of chronic decompensated liver disease is portal hypertension (10). Portal hypertension is defined as high pressure in the portal circulation characterized by an increased hepatic venous pressure gradient of >5 mmHg (9). Clinically, portal hypertension can be diagnosed in cirrhotic patients based on the presence of ascites, varicose veins, or both (11). In this case, the patient had minimal ascites detected by ultrasound. Endoscopic examination revealed varicose veins. The patient also experienced complications from esophageal and gastric varices. Effective volume reduction activates vasoconstrictors and water and sodium retention mechanisms such as the renin-angiotensin aldosterone system (RAAS), sympathetic system, and arginine-vasopressin secretion. This explains the main features of decompensated cirrhosis, such as sodium and

water retention, leading to ascites and Hepatorenal syndrome (HRS) (9).

Signs suggestive of portal hypertension include splenomegaly, portal vein dilatation, portal vein occlusion, decreased platelet count, and ascites with a serum albumin gradient more significant than 1.1 g/dL. The *Hepatic Venous Porto Gradient (HVPG) range* can provide useful clinical information for determining the prognosis of portal hypertension and its complications. Normal people have an HVPG range of 2-5 mmHg. Above 6 mmHg indicates portal hypertension, and an HVPG above 10 mmHg indicates significant portal hypertension (11).

Pleural effusion is a condition with excess fluid in the pleura. Fluid accumulates in the pleural space when the accumulation exceeds the absorption of the pleural fluid. Patients with suspected pleural effusion should undergo chest imaging studies to determine its severity. If a pleural effusion is found, efforts should be made to find the cause. The first step is to determine whether the fluid is transudative or exudative.

Pleural fluid was considered inflammatory fluid if it met at least one of the criteria for pleural protein level/serum protein level >0.5, pleural LDH/serum LDH >0.63, pleural LDH level more than 2-thirds of the upper limit of serum LDH (12). Based on the analysis results, the pleural fluid in the patient, in this case, did not meet the three criteria, so the patient's pleural fluid was transudate.

Hepatic hydrothorax is a complication of liver cirrhosis, which is very rare and usually has a relatively poor prognosis. Hepatic hydrothorax is a condition in which a large amount of fluid accumulates in the pleural cavity (generally more than 500 mL), which occurs in patients with cirrhosis and portal hypertension.

This patient had portal hypertension showing esophageal and gastric varices (GOV-1) and portal gastropathy on endoscopy. Physical examination showed no signs of liver chronicity, such as jaundice, redness of the palms, or the presence of collateral veins. Laboratory examination showed thrombocytopenia and hypoalbuminemia with positive hepatitis serology (HBsAg). Ultrasound revealed ascites.

The clinical examination may reveal pleural effusion in patients with ascites or without cirrhosis. We can diagnose hepatic hydrothorax early, mainly if the effusion is localized only to the right. Left-sided localization with fever and respiratory symptoms requires further investigation to rule out other diseases. Therefore, in cirrhotic patients with pleural effusion, a pleural puncture is necessary when symptoms occur to determine the type of pleural fluid transudate in the condition. The fluid in this state is similar to an ascitic fluid, but due to the difference in absorption speed, there is a slight difference in fluid analysis. Radioactive isotopes can be used to make decisions under suspicious circumstances (1).

The management principle of hepatic hydrothorax begins with salt reduction and diuretic therapy, similar to ascites, due to portal hypertension. This therapy principle is often inadequate because patients usually cannot tolerate the volume of pleural effusion. Symptomatic patients undergo thoracentesis to reduce dyspnea and/or hypoxia (13).

Diuretic therapy is usually initiated and gradually increased to furosemide 40 mg/day and spironolactone 100 mg/day, maintaining the ratio at 100 mg/day; 40 mg until the clinical response is adequate (14). In some cases, patients may be more comfortable with therapeutic thoracentesis if the pleural effusion is large enough (>1.5 L). This should be done with care to avoid drinking more than 2 liters of fluid with the risk of re-expansion, pulmonary edema, and hypotension. Diuretic therapy without repeated thoracentesis was sufficient for symptomatic relief in the natriuresis-matched group. However, in the group with significant sodium retention, thoracentesis may need to be repeated every 2-3 weeks to relieve symptoms (15).

Liver transplantation is the definitive treatment in severe cases when salt reduction and diuretic therapy have failed. Patients who are unable to undergo a liver transplant, or are waiting for an organ to become available, may experience a *transjugular intrahepatic portosystemic shunt* (TIPS) or *video-assisted thoracoscopy* (VATS) to correct a diaphragmatic defect (16). Selvan et al. (2021) reported indwelling pleural catheter-

based management for hepatic hydrothorax as a bridge to liver transplantation (17).

The patient, in this case, had been injected with Histoacryl-Lipiodol to prevent bleeding from esophageal and gastric varices (GOV-1). Salt restriction and diuretic therapy were also performed. This patient also received repeated thoracocentesis and the chest pigtail catheter for the pleural effusion. The evaluation was based on the amount of pleural fluid drained each day. The fluid production reduced (less than 500 mL) after chest pigtail catheter application and the patient got better. Diuretic therapy was gradually tapered off, and salt reduction was continued on discharge until the patient no longer produced a pleural effusion.

CONCLUSION

A 59-year-old female patient with liver cirrhosis and right pleural effusion due to hepatic hydrothorax has been reported. The patient did not find the cause of the heart and lung infection. The management of hepatic hydrothorax in this patient is comprehensive including treating the underlying disease (liver cirrhosis) and reducing the pleural effusion treated with salt reduction, diuretics, repeated thoracocentesis, and lastly chest pigtail catheter.

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Conflict of Interest

All the authors declare no conflict of interest.

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Small Vessel Vasculitis, an Uncommon Presentation of Systemic Lupus Erythematosus: A Case Report

Vasculitis de pequeño vaso, presentación infrecuente de lupus eritematoso sistémico: reporte de un caso

Chandra Adi Irawan Primasatya[1], Awalia Awalia[2,*]

SUMMARY

Introduction: *Systemic lupus erythematosus (SLE) has diverse clinical manifestations. Vasculitis is one of the clinical manifestations found in SLE. Vasculitis is present in different clinical forms, with purpura lesions seeming to be uncommon.*
Case Presentation: *We report a case of a 20-year-old male SLE patient who developed purpura on his extremities. Histologically, the lesions were suggestive of leukocytoclastic vasculitis.*
Conclusion: *Leukocytoclastic vasculitis is an uncommon manifestation of SLE. Physicians need to be aware that purpura can occur as a result of secondary vasculitis in SLE, even if the patient does not exhibit high disease activity.*

Keywords: *SLE, leukocytoclastic vasculitis, palpable purpura.*

RESUMEN

Introducción: *El lupus eritematoso sistémico (LES) tiene diversas manifestaciones clínicas. La vasculitis es una de las manifestaciones clínicas que se encuentran en el LES. La vasculitis se presenta en diferentes formas clínicas, pareciendo infrecuentes las lesiones de púrpura.*
Presentación del caso: *Presentamos el caso de un paciente masculino de 20 años con LES que desarrolló púrpura en las extremidades. Histológicamente, las lesiones eran sugestivas de vasculitis leucocitoclástica.*
Conclusión: *La vasculitis leucocitoclástica es una manifestación poco frecuente del LES. Los médicos deben ser conscientes de que la púrpura puede ocurrir como resultado de una vasculitis secundaria en el LES, incluso si el paciente no muestra una alta actividad de la enfermedad.*

Palabras clave: *LES, vasculitis leucocitoclástica, púrpura palpable.*

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INTRODUCTION

Systemic lupus erythematosus is a multisystem chronic autoimmune disease with an estimated 3.7 million cases globally. The incidence of

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SLE in the Asia-Pacific region is between 0.9 and 8.4 cases per 100 000 people per year, and the prevalence is between 3.7 and 127 cases per 100 000 people (1). SLE attacks women more than men (2). The annual incidence ratio of male and female SLE patients per 100 000 population is 0.7-1.5:7.9-9.3. Men with SLE often have aggressive clinical presentations, faster organ damage, and a worse prognosis than women with SLE (3).

SLE has diverse clinical manifestations, ranging from skin rashes to significant organ damage. Vasculitis is one of the clinical manifestations found in patients with SLE (4). Cutaneous vasculitis is not a rare manifestation of SLE, and SLE-related vasculitis can indicate a different clinical course. The spectrum of symptoms of vasculitis in SLE ranging from mild to severe is only limited to skin blood vessels, and the severe spectrum can attack other organs (5). A wide variety of antibodies are found in the serum of patients with SLE, and anti-nuclear antibodies (ANA) is one of the diagnostic characteristics in patients with SLE. Still, a positive ANA is not an absolute requirement for an SLE diagnosis (6).

This case showed that SLE can occur in men with manifestations of vasculitis and a negative ANA. Immediate therapy is paramount to reducing morbidity and mortality.

CASE PRESENTATION

The patient is a 20-year-old male, from Surabaya, unmarried, with a high school education, working as a self-employed employee, referred from Gotong Royong Hospital with a diagnosis of Henoch-Schönlein purpura and SLE. The patient complained of reddish patches on their hands and feet for two weeks (Figure 1), in addition to knee and ankle joint pain. The pain seemed to fade, improve with movement, and stiffen when at rest. For reddish patches and joint pain, the patient attended an internist and was prescribed ibuprofen 400 mg three times a day and methylprednisolone 8 mg three times daily. There was no improvement in the patient's complaints, therefore the dosages of ibuprofen and methylprednisolone were increased to 800 mg three times per day and 16 mg three times per day, respectively. Patients complained of nausea and vomiting for one day, and they threw up every food and liquid they consumed. No fever, cough, chest tightness, or throat pain was present.

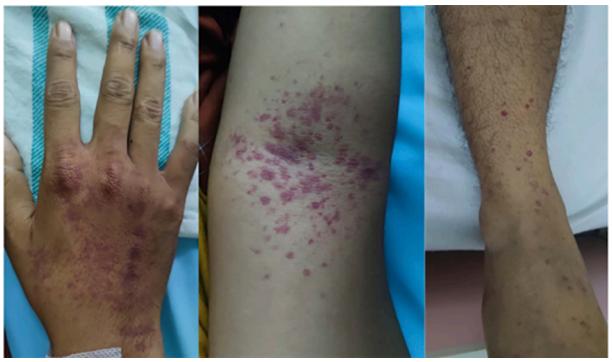

Figure 1. Reddish patches on the hands and feet.

The patient was then hospitalized at Gotong Royong Hospital and given intravenous fluids (NaCl 0.9 %), antibiotics (cefoperazone (1 gram twice daily intravenously), methylprednisolone (125 mg three times daily intravenously), pantoprazole (40 mg twice daily intravenously), ondansetron (4 mg three times daily intravenously), and paracetamol (500 mg three times daily) (1 gram three times a day). The patient experienced black feces up to one time after two days of treatment—a significant amount but not black vomit. Before 1.5 months ago, the patient had surgery to remove a cyst from behind the right ear. The patient presented with red eyes one month ago and was examined by an ophthalmologist, who diagnosed elevated eyeball pressure. The patient is receiving acetazolamide 500 mg twice a day, polyvinylpyrrolidone eye drops, and tobramycin 1 drop six times daily. At the 2-week follow-up, eyeball pressure was normal, and the dosage was reduced to acetazolamide 500 mg once per day, polyvinylpyrrolidone eye drops, and tobramycin 1 drop four times daily. The history of hair loss and facial flushing upon exposure to sunshine was denied. The patient's family history of diabetes, hypertension, cardiovascular disease, autoimmune disease, and cancer was denied. In the last five years, the patient has smoked one to

two cigarettes per day and used around one to two glasses of alcohol each week.

On examination, the patient's general condition was weak and moderately ill, with a GCS of 456, Body Mass Index (BMI) of 25.05, blood pressure of 130/70 mmHg, pulse rate of 100 beats per minute, respiratory rate of 24 beats per minute, an axillary temperature of 38 degrees Celsius, and a pain scale of 4. An examination of the head and neck revealed anemic conjunctiva without icteric sclera, cyanosis, and dyspnea. No retraction was observed throughout the thoracic examination, which was symmetrical. The cardiac examination revealed normal S1/S2 and no murmur or gallop. Both lungs were reported to have basic vesicular sounds and no wheezing, but rales. Examining the abdomen revealed normal bowel sounds, no pain, and no enlargement of the liver and spleen. Examining the patient's extremities revealed edema and purpura in both the superior and inferior extremities, which were warm with capillary refill time (CRT) less than 2 seconds.

The laboratory tests are listed in Table 1. On May 31, 2021, a chest x-ray (CXR) revealed a reticulogranular pattern in the right perihilar-paracardial and left paracardial regions, with interstitial lung edema and interstitial pneumonia serving as differential diagnoses.

The patient was diagnosed with Henoch-Schönlein Purpura (HSP), with vasculitis as a differential diagnosis, et causa systemic lupus erythematosus (SLE), post melena et causa suspect gastropathy and nonsteroidal anti-inflammatory drugs (NSAID), normochromic normocytic anemia, et causa gastrointestinal bleeding, and acute kidney injury (AKI). The patient has been administered a high-calorie, high-protein soft diet of 2 100 kcal with additional egg whites; an infusion of Ringer Dextrose 5 % (RD5) 1 000 mL every 24 h; ceftriaxone 1 g intravenously every 12 h; omeprazole 40 mg intravenously bolus every 6 h; tranexamic acid 500 mg.

On day two, the patient complained of coughing up mucus and continued skin redness. Normal vital signs were present. Still, a physical examination revealed purpura in both the upper and lower extremities. The laboratory tests are listed in Table 1. Examination of the urine reveals dysmorphic erythrocytes. Both hyperuricemia and hypocalcemia were added to the patient's evaluation. A pulse dose of methylprednisolone IV, 500 mg every 24 h; preemptive lamivudine, 100 mg orally once a day; allopurinol, 100 mg orally every 24 h; calcium carbonate ($CaCO_3$), 500 mg orally every 8 h, and packed red cell (PRC) transfusions, two bags per day, were added to the treatment until Hb was 10 mg/dL.

The redness of the skin diminished on day five (Figure 2). Laboratory analysis of procalcitonin at 0.52 ng/mL. The Chest X Ray (CXR) revealed pneumonia, a partially organized right pleural effusion, and pulmonary edema. Microbiological analysis of sputum revealed the presence of yeast. Fluconazole, 200 mg IV every 24 h, was added to the treatment regimen, and methylprednisolone was reduced to 62.5 mg IV every 24 h.

The redness of the skin diminished on the eighth day. Laboratory testing can be found in Table 1. CXR was unremarkable. The patient receives 16 mg orally every 8 h of methylprednisolone treatment.

The redness of the skin continued to improve on day 14. The sputum microbiology test revealed *Enterobacter cloacae* and *Klebsiella ozaena* (ESBL) which were sensitive to amikacin and meropenem, as well as *Candida tropicalis* was sensitive to fluconazole. Hospital-associated pneumonia (HAP) was added to the assessment, and amikacin was administered intravenously (IV) every 12 h.

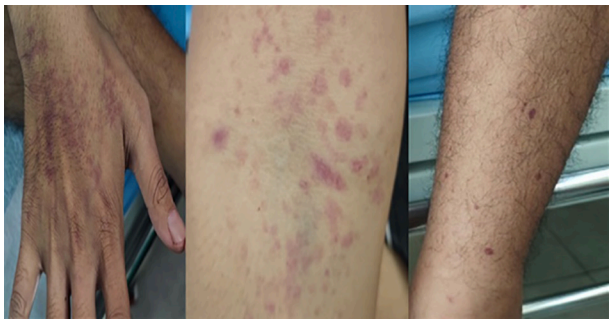

Figure 2. After a pulse dose of Methylprednisolone, the redness of the hands and feet improved.

On the sixteenth day, the patient had no symptoms and a normal physical exam. ANA profiles PM Scl100 (+) and Anti-neutrophil cytoplasmic antibody (ANCA) titers of 1:10 were detected in laboratory tests. Leukocytoclastic vasculitis was added to the patient's diagnosis after a skin biopsy revealed them. The patient was released on oral methylprednisolone 16 mg every 8 hours, oral allopurinol 100 mg every 24 h, oral $CaCO_3$ 500 mg every 8 h, and oral lamivudine 100 mg every 24 h.

Table 1. Laboratory test summary

Laboratory parameter	Day 1	Day 2	Day 5	Day 8
Hemoglobin (g/dL)	8.4	-	-	10.4
Leukocytes (/mm^3)	11 000	-	-	8 450
Neutrophils (/mm^3)	9, 55	-	-	6 125
Lymphocytes (/mm^3)	1 474	-	-	1 653
Platelets (/mm^3)	305 000	-	-	395 000
Sodium (mEq/L)	138	-	-	-
Potassium (mEq/L)	4.5	-	-	-
Chloride (mEq/L)	104	-	-	-
Blood sugar (mg/dL)	98	-	-	-
BUN (mg/dL)	86	-	-	31
Creatinine (mg/dL)	6	-	-	1.3
Total bilirubin (mg/dL)	0.87	-	-	-
Direct bilirubin (mg/dL)	0.3	-	-	-
AST (U/L)	20	-	-	-
ALT (U/L)	56	-	-	-
Albumin (g/dL)	2.86	-	-	-
Uric Acid (mg/dL)	-	12.3	-	-
Calcium (mg/dL)	-	7.5	-	-
Phosphate (mg/dL)	-	6.5	-	-
HBsAg	reactive	-	-	-
IgA (mg/dL)	184	-	-	-
ANA test (AU/mL)	-	12.7	-	-
C3 (mg/dL)	-	47	-	-
C4 (mg/dL)	-	4.7	-	-
Procalcitonin (ng/mL)	-	-	0.52	-
Urinalysis				
Color	Yellow with clear clarity			Yellow with clear clarity
pH	5.5			5.5
Specific gravity	1 006			1 006
Blood	+3			+2
Leukocytes	+2			Negative
Protein	+2			Negative
Bilirubin	Negative			Negative
Glucose	Negative			Negative
Ketone	Negative			Negative
Protein creatinine ratio (g/gCr)	≥ 0.5			<0.15
Albumin creatinine ratio (mg/gCr)	≥300			≥300

DISCUSSION

SLE is a chronic, systemic autoimmune disease with variable severity and the potential for flares. Damage to the kidneys, heart, blood vessels, central nervous system, skin, lungs, muscles, and joints can lead to morbidity and an increase in mortality. SLE has clinical symptoms, immunological and laboratory abnormalities,

disease progressions, and illness sequelae. The clinical symptoms of the skin, joints, kidneys, and other organ systems may not necessarily occur simultaneously. A T-cell imbalance is characteristic of SLE, an autoimmune disease. Disease activity is associated favorably with the Th17/Treg ratio. In the early phases of the disease, when clinical manifestations are minor, as in cases of ANA negativity or specific dominant organs, or in sporadic clinical presentations that can be lethal and necessitate prompt action, the diagnosis of SLE can be extremely difficult. A negative ANA test cannot eliminate the SLE diagnosis, as 20 % of patients have an ANA test (true or false negative) at different disease phases. However, lupus without ANA antibodies is less common. The diagnosis of SLE involves clinical symptoms backed by laboratory tests that reveal an immunological or inflammatory response in several organs (7,8).

The diagnosis of SLE is based on clinical symptoms and subsequently corroborated by laboratory tests that reveal immunological reactivation or inflammation in many organs. To guarantee that patient groups do not overlap, the most recent criterion categorization integrates the ACR-1997, SLICC-2012, and EULAR/ACR 2019 classifications. ANA or other positive immunological markers (autoantibodies or hypo-complements) are necessary to classify SLE according to SLICC-2012 and EULAR/ACR-2019, but not ACR-1997. SLE diagnosis does not require meeting categorization criteria. The SLICC-2012 and EULAR/ACR-2019 criteria are more sensitive than the ACR-1997 criteria in patients with early disease stages; however, some patients with potentially severe disease may still be missed (9). Modifying categorization criteria (Figure 4) can improve sensitivity, impose earlier diagnosis, and expedite treatment for patients with a high illness burden (7).

In this instance, the patient had an ANA-negative and hypo-complement test, along with arthritis as a clinical complaint. The 2019 EULAR/ACR criteria awarded this patient a total of 10 points (6 for arthritis and 4 for hypocomplementemia). This patient met the criteria for clinical SLE based on the diagnostic technique utilized for patients with SLE suspicion.

The incidence of vasculitis in SLE ranges between 11 and 36 percent. Vasculitis is characterized by inflammatory cell infiltration and necrosis of the blood vessel walls (Figure 3). Vasculitis can affect blood vessels of all sizes and organs, with prognoses ranging from mild to fatal. Lesions of the skin are more frequently associated with the involvement of tiny blood vessels (10). Purpura, urticaria, and lesions on the extremities might manifest as cutaneous vasculitis in SLE. The most prevalent kind of vasculitis is small-vessel vasculitis. Clinical symptoms of this leukocytoclastic vasculitis include hematuria and hemoptysis. The most prevalent lesions of cutaneous vasculitis are punctuated vasculitis lesions, which typically develop on the hands but can also manifest on the lower extremities. Purpura is the second most prevalent form of vasculitis of the skin. This purpura appears most frequently on the hands. HSP as cutaneous small vessel vasculitis with deposition of IgA and other immune components within the vessel walls is a possible differential diagnosis for skin vasculitis (10-12). SLE patients with renal vasculitis have glomerular lesions, hypertension, anemia, hematuria, and renal insufficiency, which progresses to kidney failure and high SLEDAI scores (13,14).

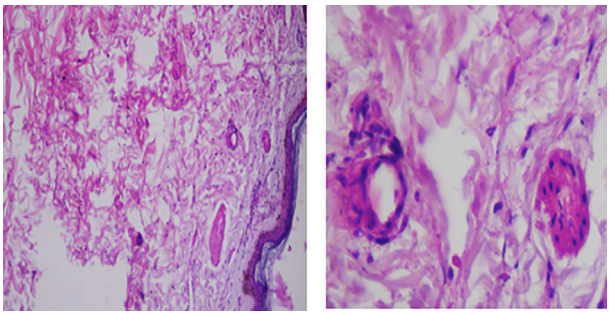

Figure 3. Leukocytoclastic vasculitis affecting superficial vessels from a skin biopsy patient.

Vasculitis treatment in lupus erythematosus is extremely restrictive, and time-consuming diagnostics restrict life-threatening clinical outcomes. Inflammation-related clinical indicators, such as the size of afflicted blood

vessels and organs, are associated with treatment. The treatment of cutaneous vasculitis with antimalarials is effective. The use of 200-400 mg of hydroxychloroquine per day is effective, particularly in patients with vasculitis, urticaria, and hypocomplementemia. Patients with minimal vasculitis of the skin react to the administration of colchicine (0.6 mg twice daily); however, relapses are possible following medication cessation. If there are contraindications to the use of earlier medications, then thalidomide and dapsone (50-200 mg per day) are effective alternatives (13). Long-term corticosteroids and immunosuppressants, such as cyclophosphamide, azathioprine, and mycophenolate mofetil, are used to treat visceral organ-afflicting vasculitis. Other effective treatments include intravenous immunoglobulins and biological medicines such as rituximab (10). Various types of vasculitis, including severe lupus cutaneous vasculitis that is resistant to conventional therapy, have been successfully treated with azathioprine (2 mg per kg body weight per day), despite its side effects, which include leukopenia, liver disorders, hypersensitivity reactions, and infections. In refractory, severe lupus vasculitis, immunoglobulin at a dose of 1 g per kg of body weight for 2 days followed by 400 mg per kg of body weight every month until the resolution of the disease — or pulse steroid therapy — is widely recognized. Methylprednisolone is administered intravenously at 10-30 mg per kg of body weight (maximum 1 g) once daily for three days, followed by an injection of 1 mg per kg of body weight per day for one week, and then tapered for one month until the least maintenance dose is reached. The gold standard of providing 1 mg of methylprednisolone per day for three days is associated with considerable infection-related consequences. 1.5 mg of methylprednisolone per day for three days is also useful for minimizing infection complications (11) for six months (13).

This patient had cutaneous purpura, kidney hematuria, and dysmorphic erythrocytes in urine sediments as signs of vasculitis. Patients with skin and visceral organs are administered a 500 mg methylprednisolone pulse daily. The patient's skin lesions improved after the use of steroids. The maintenance dosage of 62.5 mg of methylprednisolone per day was continued. The patient's skin biopsy revealed the presence of leukocytoclastic vasculitis, indicating that these patients have vasculitis due to SLE.

Reactivation of the hepatitis B virus is an immunosuppressive therapy adverse effect associated with higher mortality and morbidity in rheumatic disease patients. Reactivation of hepatitis B can be avoided through thorough screening and surveillance. Reactivation occurs in people with chronic hepatitis B infection (HBsAg-positive), but it can also occur in those who have recovered from hepatitis B infection (HBsAg-negative or anti-HBc-positive). The use of glucocorticoids is associated with an incidence of hepatitis B reactivation between 4 % and 50 % in patients with hepatitis B infection. Glucocorticoid administration with a dose of >20 mg of prednisolone and a period of >4 weeks poses a moderate risk of hepatitis B reactivation, and antiviral prophylaxis should be used. Prior to measuring immunosuppression, hepatitis B screening was required to prevent the reactivation of this disease. 1-2 weeks before beginning immunosuppressive medication is the optimal time to begin antiviral prophylaxis, particularly in individuals with a high viral load. Prophylactic therapy continues for up to 6 months following completion of antirheumatic therapy, or 12 months if rituximab is used (15,16). This patient's HBsAg was reactive. Before the pulse dose of Methylprednisolone (500 mg daily for three days), antiviral prophylaxis with Lamivudine, 100 mg once daily, was administered to the patient.

A male with SLE and vasculitis was discovered in this instance. 2019 ACR/EULAR criteria were used to identify patients with SLE (Figure 4). Men have a more aggressive clinical presentation and a poorer prognosis if diagnosed with SLE (3). Vasculitis occurs in just 11 %-36 % of SLE patients, and its symptoms range from moderate to life-threatening (10). Patient's urine was also found to have dysmorphic erythrocytes, indicating the presence of vasculitis that had progressed to the kidney and necessitated more intensive treatment.

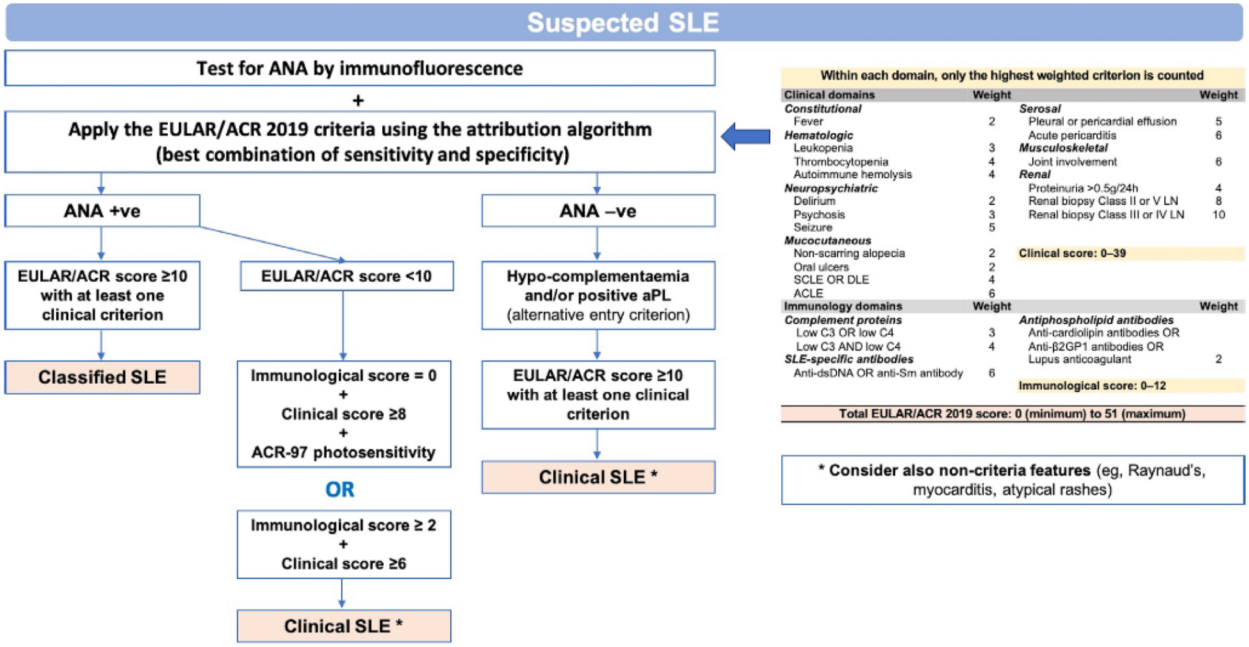

Figure 4. Approach to diagnosis in patients with suspected SLE (7).

CONCLUSION

The vasculitis of a 20-year-old male has been described as a symptom of SLE. Reddish patches on the patient's hands and feet led to a two-week hospitalization. A sample of the skin revealed leukocytoclastic vasculitis upon histopathological investigation. The patient's skin lesions improved following treatment with a pulse dose of methylprednisolone. This patient had chronic hepatitis B, and antiviral prophylaxis was used to avoid hepatitis B reactivation.

Conflicting Interest(s)

The authors declare no conflict of interest.

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Arthritis in Leprosy: A Case Report

Artritis en lepra: reporte de un caso

Aaron Tumewu[1], Awalia Awalia[2]

SUMMARY

Introduction: *Despite the third most common manifestations of leprosy, musculoskeletal manifestations are still underdiagnosed in leprosy patients, causing progressing and disfiguring disabilities.*
Case Presentation: *A 25-year-old woman presented with constant pain in both hands that had been worsening over the past month. She also reported progressive nodules over the face. Radiology revealed deformity of the second digit of her left hand and punch biopsy revealed a type II reaction of lepromatous leprosy. She later started treatment with oral steroids and a multibacillary leprosy regimen.*
Conclusion: *We presented a case of a painful swollen hand in a 25-year-old woman diagnosed with arthritis in leprosy.*

Keywords*: leprosy, arthritis, woman*

RESUMEN

Introducción*: A pesar de ocupar el tercer lugar entre las manifestaciones más frecuentes de la lepra, las manifestaciones musculoesqueléticas aún son infradiagnosticadas en los pacientes con lepra, provocando discapacidades progresivas y desfigurantes.*
Presentación del caso: *Una mujer de 25 años se presentó con dolor constante en ambas manos que había empeorado durante el último mes. También informó de nódulos progresivos en la cara. La radiología reveló una deformidad del segundo dedo de la mano izquierda y la biopsia con sacabocados reveló una reacción tipo II de lepra lepromatosa. Posteriormente inició tratamiento con esteroides orales y regimiento de lepra multibacilar.*
Conclusión*: Presentamos un caso de mano hinchada dolorosa en una mujer de 25 años diagnosticada de artritis en la lepra.*

Palabras clave: *Lepra, artritis, mujer.*

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INTRODUCTION

Leprosy is a chronic infectious disease known to attack the skin and peripheral nerves caused by *Mycobacterium leprae*. World Health Organization (WHO) reported the prevalence of leprosy cases undergoing therapy in 139 countries in the world 129 389 cases in 2020 (1).

Leprosy patients commonly present with typical cutaneous and neurological symptoms, although up to 75 % of leprosy patients may present with a musculoskeletal complaint with a number of atypical systemic symptoms such as fever, fatigue, or even paraesthesia's that may mimic symptoms of rheumatic disease. Laboratory examinations in leprosy patients also show positive autoantibody markers such as an antinuclear antibody (ANA), anticardiolipin (ACL), or rheumatoid factor (RF), making a definite diagnosis difficult at the onset of the disease. The wide manifestations of leprosy are caused by variations in the cellular immune response to Mycobacterium bacteria and are most often found in multibacillary (MB) patients (2,3).

A delay in diagnosis may lead to permanent nerve damage and irreversible deformity. Comprehensive clinical, laboratory and radiological examinations are needed for early diagnosis and appropriate therapy so that these events can be prevented (4).

We present a case of a 25-year-old leprosy woman with the main complaint of swollen and painful fingers in both hands.

CASE PRESENTATION

A 25-year-old woman Javanese female came to the rheumatology outpatient clinic with painful and swollen fingers in both hands since 2019 and worsening in the past 1 month. She also complained of finger stiffness and inability to clench her fists due to swelling. Finger stiffness is present mainly in the morning and improves after activities. She had a crack and yellow discoloration on the 4th fingernail digit of her left hand since 2020. One year ago, she felt her face become wider and small bumps appeared on the chin and cheeks. There were also complaints of fever and unintentional weight loss for 1 year. She took meloxicam 15 mg o.d. irregularly for her pain without any improvement. On physical examination, she was alert with a visual analogue scale (VAS) score of 6 and stable hemodynamic parameters. Facies leonina feature was observed on her face with non-tender small papules over her cheeks and chin. Her gait was normal. On hand examination, there was dactylitis on both hands with onycholysis on the 4th digit of her left hand (Figure 1). Her blood test revealed normochromic normocytic anaemia with haemoglobin of 9.9 g/dL and an elevated erythrocyte sedimentation rate (ESR) of 66 mm/h. The patient also underwent an anti-ds DNA and ANA test in 2020 with a negative result.

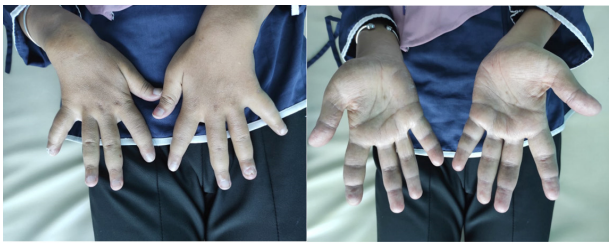

Figure 1. The patient presented with bilateral dactylitis and onycholysis on her 4th left digit.

Radiology examination showed deformity of the base of the 2nd right medial phalange and narrowing of the proximal interphalangeal joint of the 2nd right digit (Figure 2).

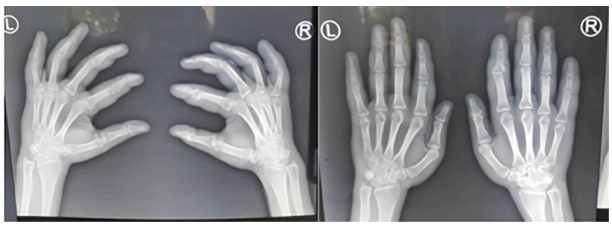

Figure 2. Radiology showed deformity of the base of the 2nd right medial phalange and narrowing of the proximal interphalangeal joint of the 2nd right digit.

A punch biopsy of the skin of her right manus showed a dermal layer full of foamy macrophages and lymphocytes in the dermo-epidermal junction to subcutaneous tissue, infiltration neutrophil cells in the capillary wall (vasculitis), Wade-Fite stain revealed an abundant amount of acid-fast bacilli. Conclusion: leprosy type Lepromatous Leprosy (LL) and leprosy reaction type II, or Erythema Nodosum Leprosum (ENL). A nail smear revealed infection of *Aspergillus flavus* and *Aspergillus niger*. She was assessed initially as LL-type leprosy and ENL with arthritis and tinea unguium. Multi-drug therapy (MDT) for leprosy and prednisone oral dose started from 1 mg/kg BW/day were initiated. After 4 months of MDT and prednisone therapy, the patient felt the symptoms were improving and the prednisone dose was lowered.

DISCUSSION

Leprosy generally causes skin symptoms such as macules, plaques, papules, or nodules that are usually hypopigmented and anesthetic in nature, and peripheral nervous system symptoms such as mononeuropathy, mononeuritis multiplex, or peripheral neuropathy. In LL, the lesions tend to be quite numerous (leproma) with symptoms of distal symmetrical hypoesthesia, resembling other diseases that can cause polyradiculoneuropathies, such as diabetes and hypothyroidism. At an advanced stage, the patient's face can also resemble a lion (facies leonina), and also finger deformities. Myositis and enthesitis of the intrinsic muscles of the hand due to intense inflammatory activity in LL. Musculoskeletal manifestations are the third most common clinical manifestation after dermatological and neurological manifestations in LL (5-7).

Manifestations of joint involvement in leprosy can be found in 75 % of cases and may be the initial symptom present. According to Chauhan et al., arthritis in leprosy may be classified into 5 types: acute polyarthritis due to leprosy reactions, syndrome of swollen feet and hands, chronic arthritis due to direct infiltration of *M. leprae*, Charcot arthropathy, and tenosynovitis (5).

The current hypothesis states that the reaction of type I and 2 leprosy and direct infiltration of *M. leprae* into the synovial joints are the basic mechanisms of joint damage. Two types of leprosy immunologic reactions can occur before, during, or after leprosy therapy. Type I leprosy reaction is a type 4 Gell-Coombs reaction (delayed hypersensitivity). This reaction is a cell-mediated immune response to the *M. leprae* antigen and is characterized by acute inflammation from pre-existing skin lesions or the appearance of new skin lesions and/or neuritis. In type I reactions, there is no systemic involvement (8).

Type I reactions can be found in one-third of leprosy patients and on histopathological examination can be found infiltration of CD4+ T cells that secrete IFN-γ and TNF-α in the skin, nerves, joints, and other tissues. This reaction can be a downgrading reaction (suppression of cell-mediated immunity) or a reversal reaction (increased cell-mediated immune activity). Reversal reactions usually appear in the first months to several years after initiation of therapy. Based on the existing cytokine profile, the type I reaction is mediated by Th1 cells (5).

Type II leprosy reaction, also known as ENL, is a type 3 (immune complex-mediated) hypersensitivity reaction in response to the *M. leprae* antigen. Clinical manifestations are painful skin lesions, joint damage, fever, and systemic manifestations. Systemic involvement can lead to arthritis, dactylitis, orchitis, uveitis, lymphadenitis, glomerulonephritis, proteinuria, and hepatitis (8).

Type II leprosy reactions lead to neutrophil infiltration and activation of the complement cascade, resulting in a severe inflammatory reaction. Although ENL can occur before a diagnosis of leprae is made or before therapy is given, up to 90 % of cases of ENL occur within 2 years of starting therapy. ENL papule biopsy shows vasculitis or panniculitis, and sometimes large numbers of lymphocytes are found. This type II reaction is mediated by Th2 cells (5).

A case-control study in Ethiopia published in 2017 revealed that the median percentage of activated CD3+, CD4+, and CD8+ T-cells were significantly higher in the peripheral blood mononuclear cells from ENL patients than from LL patient controls before treatment. The median percentage of central and activated memory T-cells was also increased significantly in patients

with ENL compared to LL patient controls before treatment. The percentage of naive T cells in patients with ENL was lower (27.7 %) than in the LL patient controls (59.5 %) ($P < 0.0001$) before treatment. However, after prednisolone treatment, naive T cells in patients with ENL had a higher median percentage (43.0 %) than LL controls (33.0 %) ($P < 0.001$). This study highlighted the role of T cells in the pathogenesis of ENL, which may explain why ENL may occur even before leprosy treatment (9).

Charcot arthropathy or neuropathic arthropathy is characterized by joint dislocation, pathological fracture, and severe deformity involving areas of weight-bearing joints such as the ankles and knees. It is estimated that about 10 % of leprosy patients have Charcot arthropathy due to untreated peripheral neuropathy (5,10).

The condition of acute polyarthritis due to leprosy reactions manifests as a symmetrical inflammation of the small joints of the hands and feet that resembles rheumatoid arthritis (RA). Knees, ankles, shoulders, and elbows may also be involved, although the prevalence is rare. Although the symptoms are similar to those of RA, there is usually no joint destruction. Type I leprosy reactions usually cause arthritis more often. Fever, exacerbation of skin lesions, and paresthesia predominate in the clinical presentation of type I and II reactions. In acute arthritis due to type I and II reactions, symptoms usually improve within 4 weeks (5,10,11). Painful swelling of the dorsal region of the hand with limited movement can be seen in leprosy patients. The mechanism of clinical symptoms is thought to be due to leprosy reactions and responds well to anti-leprosy drugs and glucocorticoid therapy (5,7).

Chronic polyarthritis due to basilar infiltration involves symmetrically small joints, mainly in the wrist, metacarpal, and proximal interphalangeal joints. As a result of this infiltration, irreversible joint damage can occur. The most common permanent damage is boutonniere deformity and swan neck deformity (5,10).

Tenosynovitis may also be seen in leprosy patients. The combination of arthritis, and tenosynovitis, with or without paresthesia or nerve thickening should be suspected as a clinical manifestation of leprae (5).

The immune response to *M. leprae* varies over time, in which the T cell response can increase or decrease, known as reactional states. This reaction can appear suddenly or be triggered by infection with other pathogens (viral, malaria, etc.), anemia, physical and mental stress, puberty, pregnancy, childbirth, or surgery (5,7).

The diagnosis of leprosy arthritis is a diagnosis of exclusion after successfully ruling out other possible causes. In patients living in endemic areas, it is necessary to take a detailed history regarding the existing skin lesions (hypo/anesthetic), a history of paresthesia's, thickening of the peripheral nerves, and symptoms of motor or sensory disturbances (5).

Due to prolonged fever accompanied by joint pain, our patient was diagnosed with an autoimmune disease and underwent anti-ds DNA and ANA tests in 2020 with a negative result. Despite no rheumatoid factor ever being obtained in this patient, the absence of extra-articular rheumatoid/psoriatic manifestations, response to anti-leprosy treatment, and punch biopsy results that were consistent with the ENL reaction of *M. leprae* infection were the clinical differentiator from RA and PsA in our patient.

Radiographic features that can be found in leprosy arthritis are destructive bone granuloma lesions, primary periostitis, honeycombing, subarticular erosions, concentric cortical erosions, and bone cysts. However, the radiological features of patients with leprosy arthritis may vary, ranging from normal joints to subluxation or destruction (10).

The gold standard of the diagnosis of leprosy arthritis is the finding of *M. leprae* in the joint fluid, although this is difficult to find. Arthrocentesis should be performed by a trained clinician under sterile conditions to minimize the risk of infection and contamination and ensure the accuracy of the joint fluid analysis. The results of joint fluid analysis of chronic leprosy arthritis may not show the presence of *M. leprae* bacilli (10).

Autoantibodies such as RF and ANA can be positive in leprosy patients. However, to differentiate from rheumatic diseases such as RA, the results of anti-CCP antibodies are negative in leprosy patients (5,7).

Our patient presented with joint pain combined with the appearance of facies leonina leading to a diagnosis of leprosy. Performed skin biopsy revealed LL type leprosy and type II reaction of leprosy. The joint pain was due to chronic leprosy.

In some study, arthritis in leprosy patients mainly mimics the manifestations of rheumatoid arthritis due to symmetrical polyarthritis presentations. The absence of nodules or extra-articular presentations, females being less commonly affected than males, and good response to anti-leprosy drugs are considered some of the distinguishing characteristics between them (12). The interesting part in our case was the presentation of dactylitis and onycholysis, which may be found in psoriatic arthritis. After a skin biopsy and nail smear, psoriatic arthritis was excluded.

The leprosy therapy recommended by WHO are MDT regimens, namely rifampin, clofazimine, and dapsone for MB-type leprosy. Leprosy and chronic arthritis must be diagnosed correctly because the treatment is different. In acute arthritis, in addition to MDT, glucocorticoids are also required, and clinical improvement should be noted within a few weeks of therapy. Chronic leprosy arthritis patients may not require steroids, but arthritis that occurs usually does not return to normal (10). Based on the 2018 WHO guidelines, therapy for multi-bacillary leprosy is with rifampin, clofazimine, and dapsone for 12 months, while for paucibacillary leprosy it is 6 months (13).

In leprosy arthritis, the main goals of treatment are to control the acute inflammation, relieve pain, and, if possible, restore nerve function. The recommended dose of prednisolone is 1 mg/kg body weight daily, then gradually reduced by 5 mg every 2-4 weeks. The duration of steroid administration depends on the clinical response and usually varies between 4-6 weeks. For type II leprosy reactions, MDT and prednisolone alone may not be sufficient, so clofazimine 300 mg/day or thalidomide 400 mg/day are needed (5,7).

In leprosy reactions, prednisolone treatment of ENL has been correlated with the downregulation of inflammatory cytokines, such as IL-1β, TNF, IFN-γ, and IL-17. Despite the widely used prednisolone treatment for ENL, clinical improvement varies. High recurrent and flare-up episodes are common in these patients. However, in a case-control study published in 2018, prednisolone significantly reduced TNF, IFN-γ, IL-1β, IL-6, and IL-17A expression in the blood and skin lesion of leprosy patients (14). Patients on prolonged steroid therapy may suffer some serious side effects. In a 2014 retrospective study In Ethiopia, patients taking steroid treatment for ENL has a 9 % mortality rate caused by steroid-related complications such as sepsis, and mostly happened in young people (15). Our patient was treated with an MDT regimen for multi-bacillary leprosy and prednisone for her type II leprosy reaction.

CONCLUSION

A leprosy patient with the main complaint of musculoskeletal symptoms may pose a challenge in diagnosis due to its atypical presentation. Arthritis in leprosy may mimic rheumatic diseases and need a proper examination to establish the diagnosis. MDT and steroids are the therapy of choice to manage arthritis in leprosy.

Academic Collaborations of the Authors

AT collected the data and wrote the manuscript, A conducted, supervised, and supported the project.

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Conflict of Interest

The author stated there is no conflict of interest.

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A Classic Dermatomyositis: A Case Report of Rare Idiopathic Inflammatory Myopathy

Una dermatomiositis clásica: reporte de un caso de miopatía inflamatoria idiopática rara

Satyawardhana[1], Awalia[2*]

SUMMARY

Background: *Dermatomyositis (DM) is a rare autoimmune disease and is one of the idiopathic inflammatory myopathies which predominately affects the skin and muscles. Its estimated incidence is less than 10 cases per million population with an overall female/male ratio is approximately 2:1. This case report presents a classic case of dermatomyositis in a male in Indonesia.*
Case Presentation: *A 38-year-old male was admitted to the Dr. Soetomo Hospital for weakness in all four extremities and dysphagia. Initial symptoms included a red-purplish rash around the eyes, further tests showed an elevation of a serum muscle enzyme and abnormal electromyography. The symptoms did not improve with a systemic corticosteroid but improved with an immunosuppressive agent. This patient had a typical clinical manifestation of classic DM.*
Conclusion: *Immunosuppressive agents including cyclophosphamide should be considered in refractory cases with corticosteroids.*

Keywords: *Myositis, dermatomyositis, cyclophosphamide.*

RESUMEN

Antecedentes*: La dermatomiositis (DM) es una enfermedad autoinmune rara y es una de las miopatías inflamatorias idiopáticas que afecta predominantemente la piel y los músculos. Su incidencia estimada es inferior a 10 casos por millón de habitantes con una relación global mujer/hombre de aproximadamente 2:1. Este reporte de caso presenta un caso clásico de dermatomiositis en un hombre en Indonesia.*
Presentación del caso*: Un hombre de 38 años ingresó en el Hospital Dr. Soetomo por debilidad en las cuatro extremidades y disfagia. Los síntomas iniciales incluyeron una erupción de color rojo púrpura alrededor de los ojos, las pruebas posteriores mostraron una elevación de una enzima muscular sérica y una electromiografía anormal. Los síntomas no mejoraron con un corticosteroide sistémico, pero*

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mejoraron con un agente inmunosupresor. Este paciente tenía una manifestación clínica típica de la DM clásica.

Conclusión*: Los agentes inmunosupresores, incluida la ciclofosfamida, deben considerarse en casos refractarios a los corticosteroides.*

Palabras clave: *Miositis, dermatomiositis, ciclofosfamida*

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INTRODUCTION

Dermatomyositis (DM), an idiopathic inflammatory myopathy, manifests as inflammation of the skin, muscles, and joints, and sometimes involves other organs such as the lungs, heart, joints, and gastrointestinal tract. Skin manifestation of DM occurs in patients with classic myositis or clinically amyopathic dermatomyositis (1). DM affects both children and adults with approximately a 2:1 ratio of female to male. In the last two decades, the number of DM has been reported more frequently compared to previously due to more precise diagnostic criteria and better health access and services. Although, the incidence of SM varies depending on study methodologies, female gender, and urban life are consistent risk factors (2). DM is a rare disease with an incidence of approximately 10 cases per million adults (3).

The pathophysiology of DM involves idiopathic inflammation mediated by muscle and/or connective tissue damage, along with the involvement of other organs. The causative factor is the idiopathic activation of the immune system, which causes immunological attacks on muscle fibers and endomysial capillaries (2). In this present case report, we report a male DM patient from Indonesia with classic presentations.

CASE PRESENTATION

A man, 38 years old, married, was referred to the Emergency Department of Dr. Soetomo, Surabaya, Indonesia with a chief complaint of weakness in all four extremities accompanied by swallowing difficulty. The patient's complaint began with weakness in both legs that started in the patient's thigh in the last two months and was getting weaker until he was unable to walk. Weakness in both arms was felt not long after and since the last month, the patient complained of difficulty swallowing and slurred speech in the past two weeks before hospital admission. At hospital admission, the patient was only able to drink fluid.

Five months before the muscle weakness, there were red-purple rashes around the eyes that were getting darker over time. The rashes were also found on the patient's chest and their appearance was not related to sun exposure. No complaint of numbness in the patient skin, hair loss, or pain in the joints previously. The patient admitted that within six months, he had intermittent fever. There were no complaints related to defecation or urination.

There was no history of hypertension or diabetes. The patient never had a history of stroke, history of trauma, or previous history of autoimmune disease. The patient worked as a driver for 18 years and is a heavy smoker (12 cigarettes per day) and currently lives at home with the patient's nephew. There was no history of similar illness or history of autoimmune disease in the patient's family.

On physical examination, the patient was weak, well aware of GCS E4V5M6, his body weight was 55 kg, height 165 cm with blood pressure 110/62 mmHg, pulse 82x/min, respiratory rate 22x/min, temperature 36.8 ºC, and oxygen saturation was 99 % with free air. Purplish red lesions were found around both eyes, pink papules over the metacarpal and interphalangeal joints, and erythematous patches were also seen in the upper chest and upper back (Figure 1). Examination of the thorax was found to be normal both in the lungs and heart. The abdomen was flat with normal bowel sounds, without tenderness. The extremities were warm, dry, and red with weakness in all four extremities with muscle strength in the upper extremities being 3/3 and the lower extremities being 2/2 without any sensory abnormalities.

Initial laboratory examinations revealed a level of hemoglobin 11.3 g/dL, leukocytes 11 450/mm^3 with 79 % neutrophils and 8 % lymphocytes, platelets 174 000/mm^3, sodium 13^9 mEq/L, potassium 4 mEq/L, chloride 10^3 mEq/L, blood glucose 10^9 mg/dL, creatinine 0.69 mg/dL, blood urea nitrogen (BUN) 25 mg/dL,

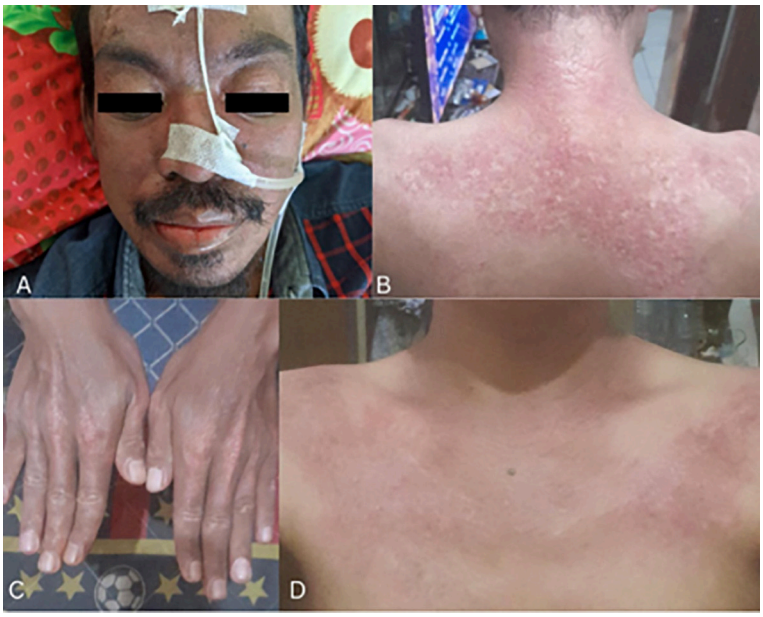

Figure 1. Pathognomonic skin manifestation of dermatomyositis. (A) Heliotrope rash, red-purplish erythema around both eyes involving upper eyelids, in the patient. (B) Shawl sign, erythematous macules, and patches over posterior shoulders, neck, and upper back. (C) Gottron's papules are pink papules over the dorsal side of the metacarpal or interphalangeal joints. (D) V-like sign, erythematous macules, and patches over the lower anterior neck and upper chest.

SGOT 121 U/L, SGPT 64 U/L, albumin 3.06 mg/dL, C-reactive protein (CRP) 0.2 mg/L, partial thromboplastin time (PPT) 27 sec, and activated partial thromboplastin time (aPTT) 14 sec. The chest X-ray showed no abnormalities in the lungs and heart.

Based on the above findings, the patient was diagnosed with susp dermatomyositis dd chronic inflammatory demyelinating polyradiculoneuropathy (CIPD) with elevated transaminase enzymes and hypoalbumin. The patient was planned to undergo further examinations including of anti-nuclear antibody (ANA) test, C3, C4, and creatine kinase. The patient was also planned to undergo skin biopsy, electromyography (EMG), and fiberoptic endoscopic evaluation of swallowing (FEES) examination.

The patient was given an infusion of NaCl 0.9 % 1 500 mL for 24 h, oral vipalbumin 500 mg every 8 h, and planned to receive an IV pulse dose of methylprednisolone 1 g every 24 h for 3 days. The high protein diet was given via nasogastric tube (NGT), Entrasol 100 mL each 2 h and increased gradually. In addition, the neurologist provided the IV mecobalamin 500 μg every 12 h and IV fursulthiamine 2.5 mg every 12 h.

The Antinuclear antibodies (ANA) test yielded negative results with an increased erythrocyte sedimentation rate (ESR) of 41 mm/h procalcitonin 0.32 ng/mL, slightly low C3 level (80 mg/dL), normal C4 (23 mg/dL), elevated creatinine kinase level (2,251 U/L) and negative for both HBsAg and anti-HIV screening test. The Electromyography (EMG) examination suggested demyelinating motor polyneuropathy with suspicion of muscle disease (Figure 2).

After receiving an IV pulse dose of 1 g methylprednisolone every 24 h for 3 days, no improvement was observed. The therapy continued with IV methylprednisolone 62.5 mg every 24 h, infusion of Asering: D5 %: Kalbamin 1: 1: 1 every 24 h, and B complex 1 tablet every 24 h.

Since no clinical improvement in the patient on the 6th day of admission (i.e., IV three days

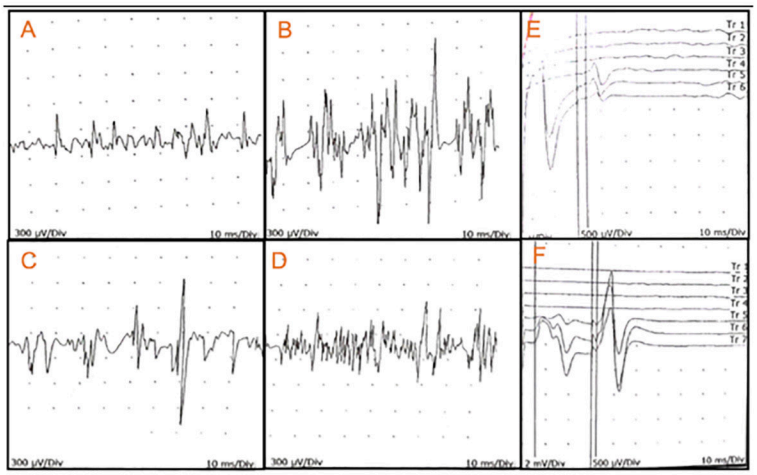

Figure 2. EMG showing polyphasic motor unit potential (A-D) and early recruitment (E, F). The EMG's impression was suspecting a muscle disease.

with pulse dose of 1 g methylprednisolone and three days of IV methylprednisolone 62.5 mg), the patient was treated with 1 g cyclophosphamide immunosuppressant. However, the patient refused to be treated and asked to be discharged. The patient was discharged with oral methylprednisolone 16-16-0 mg.

One day after the patient was discharged from the hospital, the patient came back to the Emergency Department of Dr. Soetomo Hospital with a chief complaint the body felt sore and could not eat because the a nasogastric tube (NGT) was detached. The patient was re-hospitalized with the plan of administering 1 g cyclophosphamide. The patient has been treated with the NGT diet with Entrasol 6x200 mL, infusion of Asering: D5 %: Kalbamin 1: 1: 1 every 24 h, IV cyclophosphamide 1 g within 4 h for 1 day, IV ceftriaxone 1 g every 12 h and vitamin B complex 1 tablet every 24 h.

At hospital admission, a skin biopsy was conducted on the skin lesion on the chest. The result showed a skin tissue lined with the atrophic epidermis, with flattened ridges, showing vacuolar degeneration in some of the basal cells. The dermis layer showed a mild infiltration of lymphocyte cells at the dermo-epidermal junction and was accompanied by the distribution of melanophages with a biopsy conclusion consistent with systemic lupus erythematosus. Initially, a muscle biopsy was planned, but the patient refused due to fear.

After being admitted for six days, the weakness was still present, the patient also complained that sometimes the body felt sore but improved. The patient was discharged with oral methylprednisolone 16-16-0 mg, oral hydroxychloroquine 200 mg every 8 h, and folic acid 1 mg every 24 h. The patient still had to use the NGT and was planned to be treated for six cycles of cyclophosphamide for six months and was scheduled for a cervical magnetic resonance imaging (MRI) examination and a fiberoptic endoscopic evaluation of swallowing (FEES).

The results of the cervical MRI of the patient revealed no lesion or mass in the nasopharynx, oropharynx, or hypopharynx. There was also no visualization of lesions or changes in the intensity of the neck muscles. The FEES examination concluded oropharyngeal dysphagia with severe penetration and aspiration. One month after the first cycle of cyclophosphamide, the weakness and swallowing difficulty remained unchanged. The patient returned to the hospital for the second cycle of cyclophosphamide, and the dose of methylprednisolone was tapered down to 8 mg every 24 h.

After the second cycle of cyclophosphamide, the patient was able to eat fine porridge, but the complaint of limb weakness still presented but improved slightly. The oral drugs included methylprednisolone 8 mg every 24 h, hydroxychloroquine was reduced to 200 mg every 24 h, folic acid 1 mg every 24 h, and $CaCO_3$ 500 mg every 24 h.

The patient was able to walk slowly with help after the administration of the third cycle of cyclophosphamide. The patient's condition continued to improve and after the fifth cycle of cyclophosphamide, the patient was able to walk without help and was able to eat soft rice. The muscle strength of the upper extremities was 4/4 and the lower extremities were 4/4. After the sixth cycle of cyclophosphamide, the patient was provided with oral azathioprine 50 mg every 12 h, methylprednisolone 8 mg every 24 h, folic acid 1 mg every 24 h, and $CaCO_3$ 500 mg every 24 h. During follow-up in the outpatient clinic, the patient said that the condition was not recovered as before, but gradually improved and was being still routinely monitored by the rheumatologist.

DISCUSSION

DM is one of the subgroups of idiopathic inflammatory myopathy (IIM) (5). Patients with DM are subclassified according to the disease subtype into classic dermatomyositis (CDM), amyopathic dermatomyositis (ADM), clinically amyopathic dermatomyositis (CADM), CADM that progressed to CDM, dermatomyositis hypomyositis (HDM), and juvenile dermatomyositis (JDM) (6,7). Our patient can be classified as a CDM of which five months before the muscle weakness onset, the patient had a red-purplish rash around the eyes and on the patient's chest (Figure 1). A CDM is characterized by skin manifestation with evidence of proximal muscle weakness occurring within six months of the onset of the skin (5). According to the patient history and clinical data, our patient can be classified into definite DM based on Bohan and Peter Diagnostic Criteria (6): 1) typical rash of DM; 2) symmetrical weakness of limb-girdle; 3) elevated CK enzyme; and 4) EMG pattern suspecting a muscle disease. The EMG of the patient had early recruitment and a polyphasic motor unit potential supporting the confirmation of the diagnosis. The patient also can be classified as a definite case of idiopathic inflammatory myositis (IIM) according to EULAR/ACR classification criteria for adult and juvenile IIM with a score of 8.1 without a muscle biopsy. Its classification can be further sub-grouped into DM based on EULAR/ACR classification. The patient presented pathognomonic DM clinical and laboratory symptoms, including symmetric proximal muscular weakness with pathognomonic cutaneous signs and a significant increase of muscle enzymes, which satisfied the needed criteria for DM diagnosis (8).

The exact pathomechanism of DM is remained unknown and traditionally has been viewed as a humoral-mediated vasculopathy disease. Similar to most other autoimmune disease, there is a combination of certain genetic predisposition and an exogenous factor (including infection) that trigger the disease. The strongest genetic risk for DM susceptibility is presumed to be the human leukocyte antigen (HLA), specifically HLA-D related (DR) antigen. Exogenous factors for DM include ultraviolet (UV) radiation, medication (NSAID), smoking, and viral infections (9).

The immune activation in DM is not completely understood, but it is likely to be the result of inappropriate complement activation resulting in capillary destruction in the endothelial cells near the endomysium, leading to muscle ischemia and damage (9). The initiating event is the activation of the completer-3 factor (C3), which forms C3b and C4b. This is followed by the formation of the C3bNEO neoantigen and the C5b-C9 membrane attack complex (MAC). This membrane attacks the complex deposits on the walls of blood vessels and causes inflammation. Hypoxic injury to muscle fibers leads to atrophy of muscle fibers, especially muscle fibers in the periphery that are distant from the vascular supply. Over time, the density or density of the capillaries decreases, and muscle fibers begin to undergo necrosis and degeneration (10).

The skin manifestations of DM include the pathognomonic finding of Gottron's papules and heliotropic rashes. Other skin manifestations are the "shawl sign" of the upper back and "V sign" of the anterior neck and upper chest and the "holster sign" of lateral thighs and psoriasiform erythema and scaling of the scalp (11). The

muscle weakness gradually worsens over weeks to months but is usually symmetrical and proximal, with distal muscle weakness occurring late in the course of the disease. A head drop occurred if the neck extensor muscles are affected and in more severe diseases, patients may experience dysphagia, dysphonia, and weakness of the respiratory muscles (12). Our patient had a presentation of heliotropic rash, which is a pathognomonic finding of DM. The muscle weakness started from both thighs, gradually worsening to both legs, which is consistent to DM characteristics which are symmetrical and proximal. Two weeks before admission, there was a complaint of dysphagia which indicated a progressing muscle weakness.

One of the most frequently performed laboratory tests in patients with suspected autoimmune disease is serum complement level. Serum complement exists in the circulation in an inactive state and can be activated when there is a formation of auto-antibodies and immune complexes, resulting in consumption and decreased levels of the complement system in the serum (13,14). ANA status is also tested in patients with suspected autoimmune diseases including DM, although the clinical significance of this status in DM is still unknown. More than 50 % of confirmed cases may have a positive ANA test. However, the serum of patients with an autoimmune disease may produce a negative result while having clear signs and symptoms of the disease. This can be due to current immunosuppressive treatment, the influence of antigenic deficiency in a testing substrate, or loss of IgG through the kidney (15,16). The more specific autoantibody for DM, called myositis-specific autoantibodies (MSA), is currently identifiable in 80 % of adult cases. The frequency of the MSA varies depending on the population studied (3). In our patient, the result of the ANA test was negative with a decreased serum complement level. The patient has not been tested for MSA due to limited funds. The symptoms of dysphagia and heliotrope rash can be observed clearly in this patient and are consistent with a previous cohort study which stated that its frequency is higher in ANA-negative patients (15,16).

Skin biopsy findings in dermatomyositis are similar to those found in systemic lupus erythematosus (10). The most consistent histologic findings of dermatomyositis include an increase in dermal mucin, vacuolar changes of the basal cell layer, and a mild to moderate inflammatory mononuclear cell infiltrate (17).

The goals of DM management are focused on treating muscle weakness, skin disease, and treating other underlying complications (10). There is still no treatment recommendation for DM based on randomized controlled trials (RCTs). The treatment of DM is mainly based on expert opinion or consensus. The current choice of first-line therapy is glucocorticoids (14,18). A high dose of prednisone (1-1.5 mg/kg/day), dexamethasone, or methylprednisolone can be used for autoimmune disease including all IIM subtypes. An intravenous pulse dose of methylprednisolone (500 – 1 000 mg IV daily for 2-4 consecutive days) may be necessary if the disease activity is severe, in the case of IIM is when muscle involvement is severe. A combination with steroid-sparing agents like methotrexate and azathioprine is often used for additional immunosuppressive action and to facilitate steroid tapering (11,19).

A similar case of classical DM in Nepal showed a good clinical response to steroids, the patient was given 50 mg of prednisolone and has shown muscular improvement and a decrease in muscle enzyme (20). Our patient failed to show adequate response to the steroid. Patients who do not respond satisfactorily to steroid therapy and azathioprine or methotrexate are considered refractory. Treatment options for resistant cases include rituximab, mycophenolate mofetil, calcineurin inhibitors, intravenous immunoglobulin, and cyclophosphamide (10). Cyclophosphamide has strong cytotoxic and immunosuppressive effects and has been reported to be useful in severe DM. A cohort study of 123 DM patients has shown a significant improvement in disease activity through the administration of cyclophosphamide (14).

Most patients with DM will require lifelong treatment. DM has a 63 % of 5-year survival rate and a 53 % of 10-year survival rate. Adult-onset DM is said to be associated with underlying malignancy (around 25 % of cases). With an increased risk for lung, breast, ovarian, nasopharyngeal, cervical, colorectal,

or esophageal malignancies reported among DM patients. The mortality of this disease will increase when there is a known malignancy. Our patient didn't have any signs or symptoms of an underlying malignancy. The chest x-ray showed no suspicious lesion and the FEES examination revealed no evidence supporting nasopharyngeal malignancy, which may indicate a better prognosis. However, a thorough scan for malignancy such as a PET scan should be performed to predict the prognosis better, but the test was not available in our hospital. In patients receiving immunosuppressant therapy, the risk of infection is increased. In a previous study, respiratory distress due to pneumonia infection contribute as the third most common cause of death in DM patients (21). This consequence is linked to an increased risk of infection or aspiration as a result of dysphagia, which can lead to pneumonia.

Unfortunately, we didn't evaluate the enzyme creatine kinase (CK) after the course of cyclophosphamide. However, our approach to this case has shown that in the case of DM with steroid resistance, a stronger immunosuppressant drug should be considered to achieve a better clinical response.

CONCLUSIONS

A 38 years-old male with a chief complaint of weakness on all four extremities and difficulties in swallowing was reported. Five months before those complaints, skin rashes appeared on my face and chest. The patient had a typical clinical manifestation of classic DM and was later supported by the laboratories, EMG, and skin biopsy findings. An immunosuppressive agent such as cyclophosphamide therapy could improve the clinical manifestations in the patient when there is steroid resistance. This case highlights the complexity of the diagnosis and management of the DM and early diagnosis of the cases could prevent the progression of the disease.

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Conflict of interest

The authors have no conflict of interest.

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Immune Thrombocytopenic Purpura Secondary to Peritoneal Tuberculosis Patient with Anti-Tuberculosis Drug-Induced Liver Injury. A Case Report

Púrpura trombocitopénica inmune secundaria a tuberculosis peritoneal en paciente con daño hepático inducido por drogas antituberculosas. Reporte de un caso

Fitria Yulistiawati[1], Muhammad Vitanata Arfijanto[2*]

SUMMARY

Introduction: *Various haematological abnormalities commonly occur in active tuberculosis (TB) but immune thrombocytopenic purpura (ITP) secondary to extrapulmonary TB is exceedingly rare.*
Case presentation: *We reported an 18-year-old male patient who presented with fever, abdominal pain, and thrombocytopenia. From the physical examination, there was found slight abdominal distention and diffuse tenderness. Peripheral blood smear and Immature Platelet Fraction (IPF) investigations were suggestive of ITP. His abdominal Ultrasound (US) and contrast computerized tomographic (CT) suggested peritoneal tuberculosis. He was treated with methylprednisolone orally for his ITP which showed a good response and was treated with isoniazid, pyrazinamide, and ethambutol for his peritoneal tuberculosis. He experienced Drug Induced Liver Injury (DILI) after Anti-Tuberculosis Therapy (ATT) was given. The initial ATT regimen was stopped and initiated again with a different ATT regimen (streptomycin, isoniazid, ethambutol) when there was a lowering of ALT and AST in 2 weeks. His steroid treatment was tapered off and his new regiment of ATT was continued for 10 months. In his follow-up visits, the patient reported improvement in abdominal symptoms and contrast abdominal CT evaluation.*
Conclusion: *ITP is a rare but potentially treatable presenting manifestation of extrapulmonary tuberculosis infection. A combination of ATT and steroids showed good results in this patient. The occurrence of DILI in this patient brought a new challenge in his peritoneal tuberculosis treatment but was resolved by switching initial ATT to a new ATT regimen.*

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RESUMEN

Introducción: *Varias anomalías hematológicas ocurren comúnmente en la tuberculosis (TB) activa,*

pero la púrpura trombocitopénica inmune (PTI) secundaria a la TB extrapulmonar es extremadamente rara.

Presentación del caso: *Reportamos un paciente masculino de 18 años que presentó fiebre, dolor abdominal y trombocitopenia. Al examen físico se encontró ligera distensión abdominal y dolor difuso a la palpación. Las investigaciones de frotis de sangre periférica y fracción de plaquetas inmaduras (IPF) sugirieron PTI. Su ultrasonido abdominal (US) y tomografía computarizada (TC) de contraste sugirieron tuberculosis peritoneal. Recibió tratamiento con metilprednisolona por vía oral para su PTI que mostró una buena respuesta y fue tratado con isoniazida, pirazinamida y etambutol para su tuberculosis peritoneal. Experimentó lesión hepática inducida por fármacos (DILI) después de que se le administró la terapia antituberculosa (ATT). El régimen inicial de ATT se suspendió y se inició de nuevo con un régimen de ATT diferente (estreptomicina, isoniazida, etambutol) cuando hubo una disminución de ALT y AST en 2 semanas). Su tratamiento con esteroides se redujo gradualmente y su nuevo régimen de ATT continuó durante 10 meses. En sus visitas de seguimiento, el paciente refirió mejoría de los síntomas abdominales y evaluación por TC abdominal con contraste.*

Conclusión: *La PTI es una manifestación de presentación rara pero potencialmente tratable de la infección tuberculosa extrapulmonar. Una combinación de ATT y esteroides mostró buenos resultados en este paciente. La aparición de DILI en este paciente supuso un nuevo reto en su tratamiento de la tuberculosis peritoneal, pero se resolvió cambiando el ATT inicial por un nuevo régimen de ATT.*

Palabras clave: *Púrpura trombocitopénica inmune secundaria, tuberculosis peritoneal, lesión hepática inducida por fármacos.*

INTRODUCTION

Tuberculosis is a multi-system disease, 90 % of which is located primarily in the lung. Extrapulmonary tuberculosis accounts for 5 of all cases of tuberculosis. The low incidence of extrapulmonary tuberculosis in national registers may be caused by poor identification and atypical symptoms. Abdominal tuberculosis is one of the common presentations of extrapulmonary tuberculosis and affects the gastrointestinal tract, peritoneum, mesentery, abdominal lymph nodes, liver, pancreas, and spleen (1).

Extrapulmonary tuberculosis can present with a wide variety of haematological manifestations such as anaemia, leukopenia, pancytopenia, thrombocytopenia, myelofibrosis, and hemophagocytic syndrome. Severe isolated thrombocytopenia in extrapulmonary tuberculosis is relatively uncommon (2). In one study, it was found around 1 % of TB patients had symptomatic ITP related to TB. And all those cases constituted around 7 % of all cases of ITP diagnosed over the same period. In endemic regions, TB should be considered an underlying cause of ITP (3).

Pulmonary TB represented the most common clinical presentation having occurred in 33 % of cases, followed equally at 19 % by disseminated TB and lymphadenitis. Tuberculosis-induced immune thrombocytopenic purpura (ITP) is rare, with few cases reported in the literature and only one case reported in the context of intestinal tuberculosis (4,5). Eighty-one and 35 % of patients presented with a platelet count under 20 × 109/L and 5 × 109/L, respectively. Lastly, one of the characteristics that are shared with most reports of TB-related ITP was an initial failure to identify TB as a putative cause of thrombocytopenia (4).

CASE PRESENTATION

An 18-year-old male was admitted with a high fever that was started 6 days prior he came to the hospital. The patient reported weight loss, loss of appetite, and night sweats for the last 6 months. He also presented with generalized abdominal pain, nausea, and vomiting. The abdominal pain was reported as non-localized and vague. Diarrhea and constipation were not reported. The patient did not report any respiratory symptoms or bleeding. There was no history of any haematological, hepatic, or other chronic illness. There was no history of contact with a known case of tuberculosis or any routine medication intake in the recent past.

The physical examination revealed a blood pressure of 103/73 mmHg, a pulse of 102/min and regular, a temperature of 37.6º Celsius, and his oxygen saturation was 98 % while the patient was breathing ambient air. The patient appeared undernourishment. His body mass index (BMI) was 15.6 kg/m^2 (underweight). On physical examination, the abdomen was slightly distended with diffuse tenderness. Bowel sound

was normal. There was no lymphadenopathy or hepatosplenomegaly. The remainder of the physical examination was unremarkable.

The initial complete blood count revealed a white blood cell count of 4 270/μL with 82.7 % granulocytes, 8.8 % lymphocytes, 8.3 % monocytes, 0.0 % eosinophils, and 0.2 % basophils, haemoglobin 10.9 g/L with an MCV of 75.0 and an MCH of 24.1, and platelet count 11 000/μL. A peripheral smear demonstrated microcytic normochromic red blood cells, markedly decreased platelets with giant platelets, and no atypical cells. Immature Platelet Fraction (IPF) was 13.8 % (normal 1-8.99 %). The erythrocyte sedimentation rate was 15 mm/h (normal: 0 -10 mm/h). Serum albumin was 2.7 g/dL (normal: 3.4 – 5.0 g/dL). The following laboratory studies were normal or negative: PT/PTT, ANA test, C3 and C4, anti-HIV, HbsAg, IgM, and IgG Dengue. Serum electrolytes and liver and kidney function tests were normal.

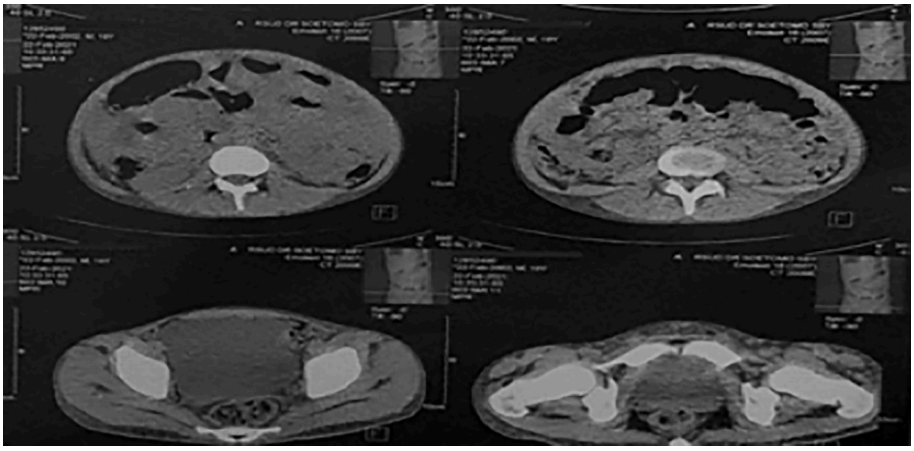

Figure 1. Axial contrast-enhanced CT: Mild ascites; thickening of the peritoneum, omentum, and small bowel's wall; adhesion of small bowel, mesenteric, and omentum.

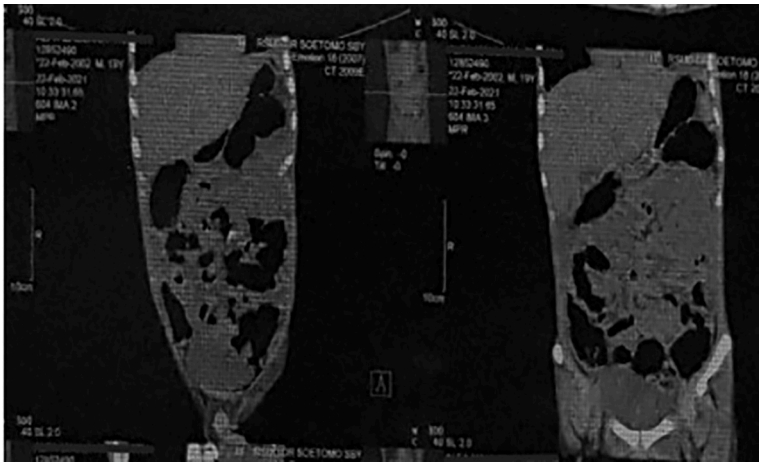

Figure 2. CT of the abdomen (coronal view) demonstrating densely-loculated ascites.

A chest X-ray demonstrated bilateral pleural effusions without fibro infiltrates (Fihure 1). A CT scan of the abdomen showed ascitic fluid has high attenuation values of 27 HU (normal: 20-45 HU) (Figure 2). The peritoneum was thickened. There was adhesion of the small

bowel, mesenteric, and omentum. The small bowel's wall was thickened, and the small bowel seemed dilated. There were proofs of mesenteric and omental involvement with characteristic multiple, fine, mobile septations. CT scan of the abdomen also demonstrated enlarged aortocaval lymph nodes. Abdomen ultrasound reveals free, loculated ascites, and thickening of the peritoneum and omentum. We diagnosed the patient with TB peritoneum.

Peritoneal biopsy and subsequent pathological or microbiologic confirmation were ideally performed to diagnose peritoneal tuberculosis as it is the gold standard for definitive peritoneal tuberculosis. We diagnosed the patient with peritoneal tuberculosis only based on imaging examinations. Colonoscopy was planned, but eventually, we did not perform a biopsy to obtain tissue for histological examination. The decision was made because the patient's condition greatly improved since we introduced steroids and ATT into the patient's treatment. This fact proved our diagnosis of peritoneal tuberculosis.

During hospitalization, thrombocytopenia worsened despite repeated platelet transfusions. There was no increase in platelets (8 000/μL) despite the transfusion of 10 units of platelets for two days. Administration of methylprednisolone 16 mg every 8 h orally was started. After the indication of tuberculosis infection, Anti-Tuberculosis Therapy (ATT) was started. He was given Isoniazid 300 mg once daily, Pyrazinamide 1 000 mg per 24 jam, and Ethambutol 500 mg once daily. Five days after methylprednisolone was given, the platelet count had increased to 33 000/μL. Methylprednisolone 16 mg every 8 h orally was continued.

The patient was diagnosed with ITP after the exclusion of other causes of thrombocytopenia. Abdomen ultrasound findings that indicated tuberculosis infection, thrombocytopenia worsening after platelet transfusion, and increase of platelet count (PC) after administration of steroids and ATT supported the diagnosis of ITP secondary to TB infection.

On 3rd day of anti-tuberculosis therapy, there was an increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 2.5 times the normal upper limit (ULN). ALT increased from 20 mg/dL to 283 mg/dL and AST increased from 48 mg/dL to 239 mg/dL. Anti-tuberculosis therapy was stopped. On the 8th day after the steroid was given, the platelet continues to increase to 52.000/μL He has discharged with methylprednisolone 16 mg every 8 hours orally. On 1st follow-up visit, the platelet count continued to increase to 106.000/μL. And on 2nd follow-up visit, ALT had decreased to 59 mg/dL and AST had decreased to 94 mg/dL. Because the ALT level had decreased to lower than 2 times the normal upper limit, ATT was started again with a new regimen that was less hepatotoxic. The new regimen consisted of Streptomycin 1 000 mg once a day was given intramuscularly, Isoniazid 300 mg once a day orally, and Ethambutol 750 mg once a day orally. He planned to take this ATT regiment for 2 months. Because the level of AST and ALT increases as he received ATT for 3 days and then decreased as ATT was stopped, we concluded that the patient had experienced ATT-induced liver injury. His steroid therapy started to taper off.

On a follow-up visit 3 months later, he went through an abdominal CT scan with contrast re-evaluation. It showed multiple mesenteric nodules and gave an impression of improvement in his TB peritoneum compared to the previous CT scan. His laboratory evaluation also showed platelet count within normal limit and liver function test that return to normal. He reported no gastrointestinal or systemic symptoms. He also reported gaining more weight in the last 3 months. He didn't consume any more steroids to maintain a normal platelet count. Because these facts and other causes of thrombocytopenia had been excluded, we diagnosed the patient with immune thrombocytopenic purpura secondary to tuberculosis. He continues to take ATT with a regiment of Isoniazid 300 mg once a day orally and Ethambutol 750 mg once a day orally for 10 months.

DISCUSSION

ITP can be defined as a platelet count less than 100.000/μL with other causes of thrombocytopenia excluded (5,6). ITP is an autoimmune disease characterized by thrombocytopenia as the only haematological manifestation. The two main diagnostic criteria for ITP are thrombocytopenia

in the context of a normal blood count, a normal smear, and the exclusion of primary conditions capable of causing thrombocytopenia (7). ITP is further differentiated into primary ITP or secondary ITP (6). Common secondary causes of ITP include autoimmune diseases like SLE, infections (HIV/hepatitis C), drugs (rifampicin), and lymphoproliferative disorders but tuberculosis per se is a very rare condition (8).

In the study conducted by Salib et al. (9), there was improved agreement about the diagnosis when 2 criteria were met: (1) the patient had a very low platelet nadir (<20 000/μL), and (2) the platelet count increased following treatment with intravenous immunoglobulin (IVIG), corticosteroids, or treatment of the underlying cause of secondary ITP. In our patient, the diagnosis of secondary ITP is based on very low platelet (11.000/μL) and also an increase in platelet counts following corticosteroid treatment. Besides those facts, history taking, physical examination, and laboratory investigation also supported the diagnosis of secondary ITP (2).

Reticulated platelets (RPs) and the immature platelet fraction (IPF) have been suggested as the platelet equivalent of red cell reticulocytes. In disorders in which thrombocytopenia is caused by platelet underproduction, the RP percentage and IPF are often low, whereas, in disorders of increased platelet turnover, the RP percentage and IPF are often elevated (6). In our patient, IPF was found to increase as a sign of platelet turnover.

The ITP in extrapulmonary tuberculosis can be either due to the production of platelet antigen-specific antibodies or platelet surface membrane immunoglobulin G, which is generated by proliferating lymphocytes as a part of the immune response to infection (2). Toxic thrombocytopenia might be related to the direct effect of the infecting organism, the acid-fast bacilli, or of immune complexes on the platelets during the most toxic period of infection (10). Previously suggested mechanisms included the production of antiplatelet antibodies and molecular mimicry during the regular immune response to TB (3).

Peritoneal TB can be a challenge to diagnose if it is not suspected. The clinical features include abdominal distension, abdominal pain, features of intestinal obstruction, and systemic symptoms like fever, weight loss, anorexia, and occasionally abdominal lump (11). Abdominal pain is a common presenting symptom and is frequently accompanied by abdominal distension. It is usually non-localized and vague (12). From the patient's physical examination, there were abdominal symptoms like abdominal pain and abdominal distention and systemic symptoms like fever and weight loss. Those supported peritoneal TB diagnosis.

Ascites is said to be the most common finding with 73 % of TB peritoneum patients having ascites. While ascites formation is a common phenomenon in patients with tubercular peritoneal involvement, the condition can also occur without ascites and may be characterized by thickening and nodularity of the omentum, mesentery, peritoneum, and clumping of bowel loops (11).

Ultrasonography (US) is a useful modality, and it can detect minimal ascites, collections, and thickening of the omentum and peritoneum (11). US is superior to CT in revealing the multiple, fine, mobile septations characteristically found in TBP (12). Computed tomography (CT) is often preferred for evaluation of the peritoneum and other intra-abdominal viscera including the gastrointestinal tract. The peritoneum is commonly thickened and nodular. Thickened mesentery with mesenteric lymph nodes is seen in most cases. Ha et al. reported 69 % sensitivity in the diagnosis of peritoneal TB by CT scan (11). CT scan highlights the peritoneal, mesenteric, or omental involvement. The ascitic fluid in peritoneal TB has high attenuation values on computerized tomographic (CT) imaging (20-45 HU) (12). High attenuation ascites were also found in our patient from ultrasonography and CT abdomen. The rest patient's abdominal ultrasonography and CT findings supported the diagnosis of peritoneal TB.

No established standard therapy for ITP due to tuberculosis has been recognized. Anti-tuberculosis treatment and corticosteroids are effective in many cases. The prognosis of ITP due to tuberculosis is generally good. Weber et al. concluded that early diagnosis and initiation of treatment for tuberculosis should be given the highest priority to reduce the use of immunosuppressants, transfusion,

and the risk of haemorrhage. In adults, the treatments of secondary ITP differ depending on the underlying disease (3). Secondary ITP with infectious diseases does not tend to remit spontaneously (13). The treatment in secondary ITP must be focused to obtain complete remission of the underlying cause and not treating the decreased platelet number (14).

The absence of recurrent thrombocytopenia after the withdrawal of corticosteroids in the patient strongly supports the etiologic role of TB in producing ITP and reinforces the need for anti-tuberculous therapy in all patients with TB-related ITP (4). The patient received metil prednisolone 16 mg every 8 hours orally after thrombocytopenia failed to remit spontaneously and had the tendency of worsening with platelet transfusion.

In cases of tuberculosis associated with ITP, the most important therapy is antituberculosis treatment. This treatment regimen can be combined with corticosteroids according to the degree of thrombocytopenia or the presence of bleeding (5). Adjunctive steroids may offer benefits by minimizing inflammation and preventing post-inflammatory fibrosis. Early trials showed that when corticosteroids were given in combination with antituberculosis medications there was no progression of TB (12,15). In patients, the combination of steroids and ATT did not worsen their peritoneal TB, instead, there was a reduction of abdominal symptoms and resolution of the disease.

The time from initiation of anti-tuberculosis treatment to PC recovery ranged from 2 days to 3 months (3). In cases that are responsive to treatment, there is usually an increase in the platelet count after one week of therapy, and a peak platelet count occurs in two to four weeks (5). An increase in platelet count was observed on 3rd day of steroid treatment in our patient. Steroids started to be tapered off when the patient's platelet count was above 100.000/ μL which was achieved in 3 weeks.

The available data strongly suggest that regimens, which are curative for pulmonary TB, are also sufficient for peritoneal TB. There are currently five drugs that are considered first-line medications: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), ethambutol (EMB) and streptomycin (SM). In most circumstances, the treatment regimen for adult patients with previously untreated TB should consist of a 2-month initial phase of INH, RIF, PZA, and EMB given daily. This is followed by a continuation phase where INH and RIF are again given daily for another 4 months (13). The patient was treated with isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB) as 1st ATT regimen for his peritoneal TB.

DILI may occur with all currently recommended regimens for the treatment of TB infection, including isoniazid and rifampin (16). The presence of hepatotoxicity is confirmed if the increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or bilirubin is more than 2.5 times the upper limit of normal (ULN) with or without symptoms of hepatitis (17,18). There was an increase of AST and ALT more than 2.5 times the upper limit of normal (ULN) after the patient received ATT in 3 days. ATT was stopped. The AST and ALT patient decreased after ATT was stopped which confirmed the diagnosis of ATT-induced liver injury. ATT with a new regimen which consisted of Streptomycin, Isoniazid, and Ethambutol, was given after AST and ALT levels decreased below 2 times of ULN.

Thrombocytopenia may arise during therapy as an adverse effect of antitubercular drugs, especially rifampicin, and, rarely, ethambutol and pyrazinamide (19,20). Considering the side effect of thrombocytopenia of rifampicin, our patient also did not receive rifampicin as his ATT regimen which prolong his ATT therapy from 6 months to 12 months.

Tuberculosis can be associated with severe immune-mediated thrombocytopenia. Besides primary ITP, tuberculosis needs to be included in the differential diagnosis of a patient presenting with severe thrombocytopenia, especially in Indonesia as it is a highly endemic country. Thrombocytopenia as one of the side effects of ATT must be considered when we treat a patient with tuberculosis infection with thrombocytopenia as one of its manifestations. Recommended ATT regiment may be needed to be adjusted. In our patient, DILI which happened during ATT administration brought more challenges in our patient's tuberculosis management.

Our case highlights the importance of suspicion of tuberculosis infection as one of the causes of thrombocytopenia. Active pulmonary tuberculosis is usually the cause of ITP secondary, but in our patient peritoneal tuberculosis is one that caused thrombocytopenia. The limitation in our case report is that we can only diagnose the patient with probable peritoneal tuberculosis because we failed to obtain evidence of *M. tuberculosis* bacilli via GeneXpert faces, or chronic inflammation with granulomas and acid-fast bacilli from the histopathological analysis. We could not perform the adenosine deaminase (ADA) test because of the difficulty of obtaining ascites fluid due to it being minimal and loculated. We also did not perform a bone marrow biopsy or aspiration to exclude primary ITP, but only did an immature platelet fraction (IPF) test to examine platelet production in the bone marrow. But in a country with limited resources like Indonesia, the lack of availability of examinations needed for exact diagnosis should not hinder the management of the disease which can be lifesaving.

CONCLUSION

Thrombocytopenia in our patient was caused by TB-associated secondary ITP. The platelet count improved a few days after starting anti-tuberculosis and steroids. The diagnosis of tuberculosis in our case was based on clinical symptoms and radiological evidence. Response to therapy in the form of increased platelet count with steroid use and resolution of abdominal symptoms and improvement in CT scan abdomen with contrast re-evaluation with anti-tuberculosis drugs confirmed the diagnosis of ITP and peritoneal tuberculosis. During the disease, the patient experienced side effects of DILI due to ATT which brought a new challenge in his ITP and peritoneal TB treatment. Adjustment ATT regimen was needed and resulted in the resolution of the patient's ATT-induced liver injury, recovery of platelet count, and improvement in peritoneal TB.

Informed consent statement

Informed written consent was obtained from the patient for the publication of this report and any accompanying images.

Conflicts of interest

The authors report no conflict of interest and no financial and non-financial interest in the subject matter or materials discussed in this manuscript. The authors alone are responsible for the content and writing of this article.

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Autoimmune Hemolytic Anemia, Amoebic Dysentery, And Intracranial Hemorrhage as Rare Manifestations of Smoldering Multiple Myeloma: A Case Report

Anemia hemolítica autoinmune, disentería amebiana y hemorragia intracraneal como manifestaciones raras de mieloma múltiple latente: Reporte de un caso

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SUMMARY

Background: *Smoldering multiple myeloma (SMM) is in asymptomatic stages before overt multiple myeloma (MM) but it also has an increased risk of thrombosis, infection, autoimmune, and hemorrhage. SMM is usually recognized coincidentally during the workup of a variety of symptoms.*
Case Presentation: *A 37-year-old male patient presented to the hospital with bloody diarrhea for two weeks. He was diagnosed with SMM with autoimmune hemolytic anemia (AIHA) and amoebic dysentery and treated for approximately 18 days then discharged to continue as an outpatient but he never attended. Seven months later he returned to the hospital with seizures. Computed tomography (CT-scan) was conducted, conforming had an intracranial hemorrhage and progressed to hydrocephalus.*
Conclusion: *This case report shows that nowadays SMM needs to be aware even in the absence of progression to overt MM. Exploring medical history, physical examination, laboratory, and imaging examination need to be paid attention to carefully to diagnose SMM considering that it is often found coincidentally among various manifestations.*

Keywords: *SMM, AIHA, amoebic dysentery, intracranial hemorrhage.*

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RESUMEN

Antecedentes: *El mieloma múltiple latente (SMM) es una etapa asintomática antes del mieloma múltiple (MM) manifiesto, pero también tiene un mayor riesgo de trombosis, infección, autoinmunidad y hemorragia. SMM generalmente se reconoce coincidentemente durante el estudio de varios síntomas.*

Presentación del caso*: un paciente masculino de 37 años se presentó en el hospital con diarrea sanguinolenta durante dos semanas. Fue diagnosticado con SMM con anemia hemolítica autoinmune (AIHA) y disentería amebiana y fue tratado durante aproximadamente 18 días, luego fue dado de alta para continuar como paciente externo, pero nunca asistió. Siete meses después volvió al hospital con convulsiones. Se realizó una tomografía computarizada (CT-scan), conforme tuvo hemorragia intracraneal y progresó a hidrocefalia.*

Conclusión: *Este caso muestra que hoy en día SMM debe ser consciente incluso en ausencia de progresión a MM manifiesto. Se debe prestar atención a la exploración de la historia clínica, el examen físico, el laboratorio y el examen de imágenes para diagnosticar la SMM, ya que a menudo se encuentra coincidentemente entre varias manifestaciones.*

Palabras clave: *SMM, AIHA, disentería amebiana, hemorragia intracraneal.*

INTRODUCTION

Smoldering Multiple Myeloma (SMM) is a precursor asymptomatic state of Multiple Myeloma (MM). There is no organ or tissue damage found in SMM, unlike MM who may develop signs and symptoms. Patients with SMM may experience a slow disease course (1). Because of incidence SMM data is unknown, The Iceland Screens, Treats or Prevents Multiple Myeloma (iStopMM) study screened a large (N>75 000) population-based, and it showed the prevalence of SMM is 0.5 % in persons 40 years or older (2). Smoldering multiple myeloma is an entity between monoclonal gammopathy of undetermined significance (MGUS) and MM. Unfortunately, there are no specific pathologies or molecular abnormalities that can be used to differentiate between SMMs who have a high risk of developing MM (3).

This case is unique because a young adult male suffered from SMM who initially came because of bloody diarrhea and autoimmune hemolytic anemia which later developed into intracranial hemorrhage and then progressed to hydrocephalus. Although SMM is a precursor to MM, it caused several risks including autoimmune, infection, and hemorrhage.

CASE PRESENTATION

A 37-year-old male patient came to the Emergency room at Dr. Seotomo Teaching Hospital. He was referred patient from a rural hospital presenting bloody diarrhea for two weeks. The frequency of diarrhea was more than 3 times per day to 10 times per day, with a great amount volume of liquid stool, and no mucus. He admitted that his appetite had decreased. He also had nausea and abdominal pain. He also lost weight, from 63 kg to 58 kg. He had a history of mild hemorrhoids which rarely bled. He had a history of difficulty finding a suitable blood donor from the previous hospital because he suffered from anemia. He denied any fever or family medical history of the same disease.

The patient had abnormal physical examination findings, such as tachycardia 115 x/min, anemic conjunctiva, and increased bowel sounds. The abnormal laboratory finding was hemoglobin (Hb) 8.1 g/dL, platelets 134.000/μL, leucocytes 40.860/μL with lymphocytes 16.7 %, monocytes 34.1 %, eosinophils 0.6 %, basophils 0.1 %, neutrophils 48.5 %. Albumin serum was decreased to 1.7 g/dL. The liver enzyme, urea, and creatinine serum were normal. Increased levels of C-reactive Protein (CRP) and LDH 12.4 ng/dL and 334 U/L, respectively, normal total bilirubin 0.18 and calcium 7.2 mg/dL were not increased. Stool examination showed macroscopically: blood (+), soft consistency, mucus (+), brown color; microscopically: amoeba (-), bacteria (3+), erythrocytes > 100, fungi (2+), cysts (-), leukocytes > 100, fat (2+), parasites (-), worm eggs (-), food waste (3+). He had positive direct and indirect Coomb tests. Peripheral blood smear: erythrocytes: normochromic anemia anisopoikilocytosis, leukocytosis with plasmablasts 9 % and plasma cells 27 %,

thrombocytopenia suggested suspicious of a plasma cell leukemia and normal Chest x-ray (CXR).

From the data above, at first, we diagnosed the patient with autoimmune hemolytic anemia (AIHA) caused by plasmacytoma colon with differential diagnoses of multiple myeloma, inflammatory bowel disease (IBD), and/or infectious diarrhea. We also planned additional tests such as protein electrophoresis, Beta 2 microglobulin, bone marrow aspiration, bone survey (Figure 1), fecal calprotectin, abdominal CT scan with contrast, and colonoscopy. He was treated with an intravenous (IV) drip of ceftriaxone 1 gram every 12 h, IV bolus of methylprednisolone 125 mg every 8 h, IV bolus of omeprazole 40 mg IV every 12 h, albumin transfusion, packed red cell (PRC) transfusion, and fentanyl patch for reducing pain.

On the second day of treatment, he still complained of bloody diarrhea, stomach cramps, and nausea. The results of the protein electrophoresis examination showed a decrease in albumin, alpha 2, and beta globulin fractions with an increase in alpha 1 and monoclonal gamma globulin (suspecting a monoclonal gammopathy) with the amount of M-protein 5 g/dL (Figure 1).

On the fifth day of treatment, He still complained same symptoms but less severe. His laboratory evaluation results showed improvement, Hb 10.7 g/dL, leukocytes 9430/µL, platelets 180 000/mm^3, albumin 2.6 g/dL. Fecal calprotectin and beta 2 -Microglobulin were performed, it reached >2000 (<50 μg/g) and 2.57 mg/L (0.81-2.19), respectively. Both tumor markers were normal, CEA < 0.5 mg/mL (<= 5) and Ca 19-9 4.8 U/mL (< 37). HIV infection is also excluded, confirmed by a negative HIV test. Bone marrow aspiration results reflected 8.28 % plasma cells. The results of the bone survey did not show any lytic lesions (Figure 2). CT scan of the abdomen with contrast: asymmetrical wall thickening with a maximum thickness of ± 1.5 cm in the rectosigmoid, ± 5.5 cm long with a distance of ± 5.2 cm from the anus, and spondylosis of lumbar. On colonoscopy examination, it was found that there was an edematous mucosa accompanied by whitish patches, the mucosa was fragile and bleeds easily, there was no intraluminal mass, no ulcer was seen, and suspicious pseudomembranous colitis. On the 8th day of treatment, an anatomical pathological examination of the rectosigmoid from colonoscopy found mucosal of the partially ulcerative colon, lamina propria with scattered inflammatory cells of lymphocytes, histiocytes, plasma cells, and neutrophil cells. Necrotic tissue was found on the mucosa and among them there was trophozoite entamoeba histolytica. There were no signs of malignancy. An IV bolus of Methylprednisolone was reduced to 62.5 mg per 8 h, IV antibiotic was replaced with an IV drip of ciprofloxacin 400 mg every 12 h and an IV drip of metronidazole 500 mg every 8 h.

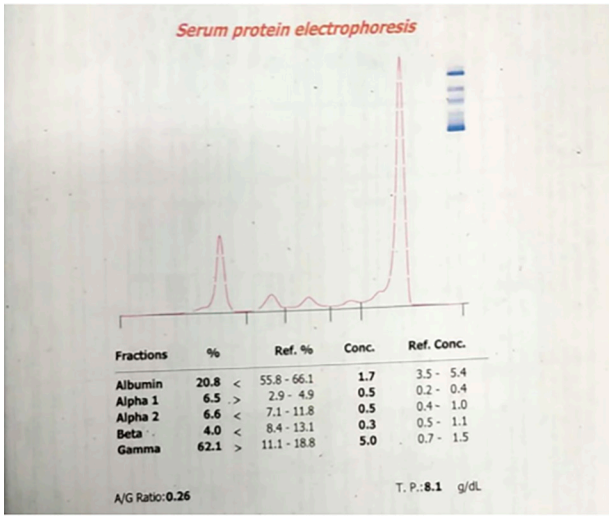

Figure 1. Serum Electrophoresis Protein.

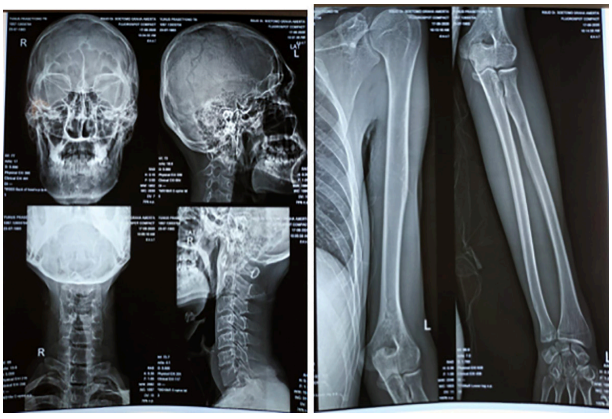

Figure 2. No evidence of bone lytic lesions on the bone survey.

He had unremarkable complaints on the 18th day of treatment then he was discharged from the hospital. Light chain examination was performed that showed kappa free light chain 9.96 (3.30-19.40 mg/L), lambda free light chain 57.99 (5.71-26.30 mg/L), kappa/lambda ratio 0.17 (0.26-1.65 mg/L), increased lambda light chain with decreased kappa/lambda ratio, suggested of monoclonal lambda gammopathy. Immunofixation test showed IgG Lambda monoclonal gammopathy (Figure 3).

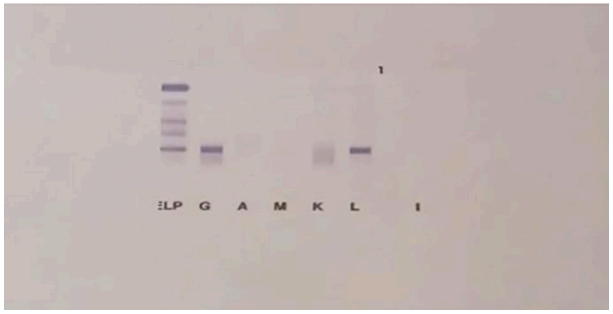

Figure 3. Serum Immunofixation.

In the end, he was diagnosed with smoldering multiple myeloma, AIHA, and amoebic dysentery. He was educated in routine control at the outpatient clinic, but he never attended. Then he came to the emergency room 7 months later with seizures. The general examination was decreased consciousness with GCS 346, blood pressure 100/60, pulse 105 x/min, temperature 37° C, respiratory rate 20 x/min. Complete blood count showed Hb 9.9 g/dL, leucocytes 13 380, and platelets 122 000. A CT scan of the head showed multiple lesions with perifocal edema accompanied by intra-tumoral and peritumoral hemorrhage in the subcortex of the left parietal lobe, left frontal lobe, right left temporal lobe, right cerebral tonsil, which could be multiple metastases with intra-tumoral hemorrhage and peritumoral hemorrhage with multiple simultaneous intracerebral hemorrhage (SIH) (Figure 4).

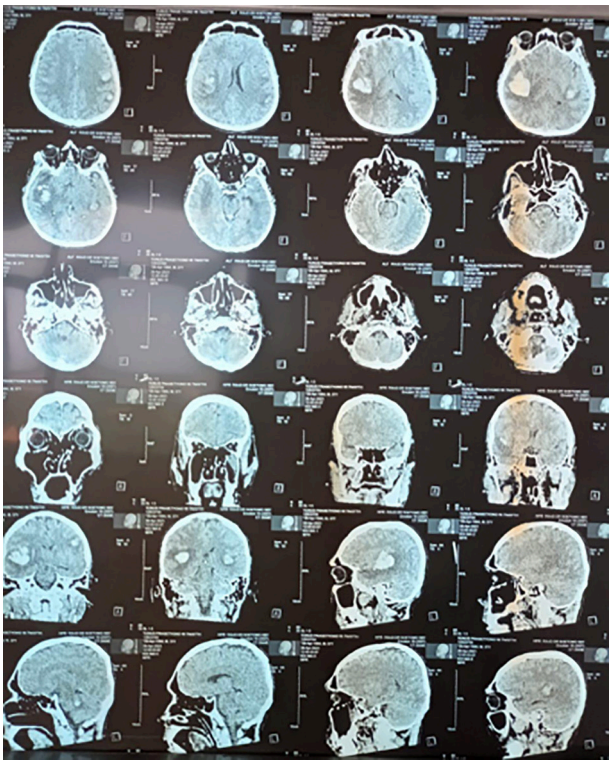

Figure 4. Head CT-scan.

Then after the general condition improved, the patient underwent bortezomib chemotherapy for 3 cycles. Six months later, he came to the ER again with complaints of profuse vomiting, headache, and decreased consciousness, CT scan of the head without contrast found active communicating hydrocephalus and brain edema. The patient's course of the disease was briefly explained in Figure 5.

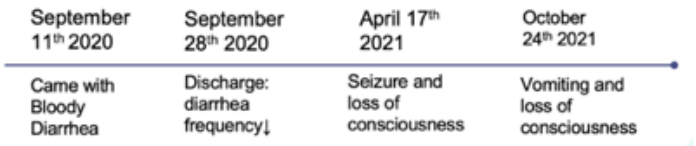

Figure 5. Patient's disease course.

DISCUSSION

The duration of diarrhea can provide information on the etiology of diarrhea. Based on the duration of diarrhea, is divided into three (1), acute diarrhea: 14 days, (2) persistent diarrhea > 14 days, and (3) chronic diarrhea > 30 days. Acute diarrhea is usually caused by viral and bacterial infections. If the duration of diarrhea is prolonged, you should start thinking about causes other than infection. A non-infectious etiology should be considered when no pathogen is found, and diarrhea becomes chronic. If there is profuse diarrhea that results in hypovolemia, diarrhea with blood, fever, > 6x/day, and severe abdominal pain, in the elderly > 70 years, in immunocompromised patients, an additional examination is necessary to find the etiology of diarrhea (4).

The role of endoscopic examination in acute diarrhea is to (1) differentiate inflammatory bowel disease (IBD) and infectious diarrhea because IBD can initially appear as acute diarrhea, (2) the presence of a pseudomembrane in toxic patients to diagnose *C. difficile* while waiting toxin stool test but it should be noted that colonoscopy can cause perforation in patients with impaired intestinal integrity, (3) immunocompromised patients are at risk for opportunistic infections such as cytomegalovirus (CMV) (4). We also had a running of Fecal Calprotectin which is a biomarker to assess intestinal inflammation (5). Direct Coomb's Test is used to detect autoantibodies on the surface of red blood cells characterized by the presence of C3 and/or IgG that bound to red blood cells while indirect Coomb's test can detect about 80 % of antibodies in serum. Transfusion is not an absolute contraindication in AIHA patients, but corticosteroids should be given before the transfusion (6).

A study conducted by Kristinsson et al. showed a new perspective that MGUS significantly increases the risk of infection. A high concentration of M protein at diagnosis shows an association with a high risk of infection (7). Some studies also show inflammatory/infectious states such as pneumonia, sepsis, meningitis, and osteoarthritis increase the development of MGUS and some cases progress to MM (8). This indicates that a severe inflammatory process can trigger the development of MGUS and myeloma. Infection is known to cause clonal proliferation by triggering certain genetic translocations (9).

Smoldering multiple myeloma criteria based on the International Myeloma Working Group (IMWG) must meet two of these criteria (1). Serum monoclonal protein 3 g/dL or urinary monoclonal protein ≥ 500 mg/24 h and or bone marrow plasma cells 10 %-60 % and (2) No incidence showing myeloma/amyloidosis (10).

MGUS is characterized by the presence of monoclonal gammopathy < 3 g/dL, bone marrow aspiration with plasma cells < 10 %, and the absence of CRAB criteria as in MM. According to IMWG, MGUS is subdivided into Non-IgM MGUS, IgM MGUS, and light chain MGUS. The diagnostic criteria for light chain MGUS were abnormal free light chain (FLC) ratio (<0.26 or >1.65), increased light chain (increased FLC in patients with FLC ratio > 1.65 and increased FLC in patients with FLC ratio < 0.26), no heavy chains were found on immunofixation examination, no organ damage, plasma cells on bone marrow aspiration < 10 %, and urine monoclonal protein < 500 mg/24 h based on the IMWG, the diagnostic criteria for MM are plasma cells in the bone marrow 10 % or proven by bone biopsy or extramedullary plasmacytoma and one or more of the following events: (1) Calcium > 0.25 mmol/L (1 mg/dL) higher than normal or > 2.75 mmol/L (> 11 mg/dL), (2) Renal insufficiency (creatinine > 2 mg/dL or 177 mmol/L) or creatinine clearance < 40 mg/dL, (3) Anemia (Hb < 10 g/dL or Hb>2g/dL below normal limits), (4) One or more osteolytic lesions on bone radiography, CT, or FDG PET/CT, (5) Bone marrow plasma cells 60 %, (6) FLC involved : uninvolved ratio > 100, (7) > 1 focal lesion on MRI 5 mm (10).

MM/MGUS is often accompanied by autoimmune diseases, including AIHA. Inflammation that occurs in autoimmune diseases can trigger the occurrence of MGUS and MM. In addition, genetic influences also influence the development of both autoimmune diseases and MM/MGUS (11). MGUS is known to initiate MM with an estimated 1 % risk that it will develop into MM (12). Although some MGUS did not develop into real MM. There is evidence that immune dysregulation or continued immune

stimulation may play a role in the development of MM/MGUS (13). A population-based study and a case series demonstrated that several immune-mediated conditions are associated with a risk of developing MGUS (14).

Several cases have been reported that AIHA and Evan syndrome was found in MM patients. The possible mechanism that can occur is M-protein type IgG that causes hemolysis, but this is not yet known for sure. It is not known whether the acquired autoimmune manifestations are events caused by MM or just coincidence. There was a study that showed that the M-Protein known at that time was a type of IgG kappa that attacks red blood cells. MM is known to be a B-cell malignancy accompanied by an immune disorder that causes clones to develop and produce antibodies against erythrocyte surface antigens (15).

Management of SMM can be treated earlier before MM occurs by doing risk stratification. There are 3 risk stratifications, low, medium, and high risk. Risk stratification aims to determine how often patients with SMM are monitored and when to start therapy, and earlier intervention to prevent progression to active MM and to achieve complete remission. High-risk SMM is an indication for therapy (1). High-risk criteria according to the Mayo clinic are 20/2/20, the percentage of plasma cells in the bone marrow > 20 %, M-protein > 2 g/dL, and FLC ratio > 20 (16).

There are no reports that discuss SMM patients in young patients, and how the prognosis and management are, but there is a study that discusses where patients diagnosed with MM at a young age are important for optimal treatment to improve good outcomes and minimize treatment-related toxicity (17).

No one has described a case of SMM with the central nervous system affected. However, there is a case report from Kumar et al., describing a 52-year-old woman presenting with headache and loss of consciousness. After further examination, a primary cerebral plasmacytoma with a bleeding tumor without progressing to MM was found because there were no lytic lesions in the bone and only 1 % plasma cells were found on bone marrow aspiration. However, in this case, an excision of the tumor was carried out, histopathological and immunohistochemical examinations were performed and it showed a plasmacytoma (18).

Another case reported by Onodera et al. was an intracranial plasmacytoma secondary to MM with cerebral hemorrhage without the involvement of bone lesions. In this case, coagulability disorders are caused by MM itself and the side effects of chemotherapy and radiotherapy that also cause massive hematomas (19). MGUS, SMM, and MM may have complications in the form of thrombosis or bleeding. The bleeding may be related to the presence of monoclonal protein immunoglobulins. Characteristics of specific paraprotein affinity with coagulation factors or platelet surfaces have been associated with bleeding in some cases of severe bleeding with monoclonal gammopathy (20).

ICH in this case can cause by platelet dysfunction or coagulation disorders, although the patient data cannot be proven due to the limitations of the examination in our hospital.

CONCLUSION

SMM needs to be aware even in the absence of progression to overt MM. Exploring medical history, physical examination, laboratory, and imaging examination need to be paid attention to carefully to diagnose SMM considering that it is often found coincidentally among various manifestations. Further research is required to study early treatment in high-risk SMM to prevent progression to active MM.

Conflicting interest

The authors declare that there are no conflicts of interest.

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Diagnostic Problem of Facial Malignancy in The Elderly: A rare case

Problema diagnóstico de malignidad facial en el anciano: Un caso raro

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SUMMARY

Introduction: *Lymphoma can occur in adults and the elderly, this will affect the condition of both diagnosis and therapy. Plasmablastic lymphoma (PBL) is a subtype of diffuse large B-cell lymphoma (DLBCL), the case is rarely found and often overlaps the anatomical pathology picture similar to plasmacytoma. It is aggressive and often relapses.*
Case Presentation: *A 50-year-old man, complained of a lump on the right cheek extending to the left cheek and left eye. Irregular shape, hard, painful, accompanied by lumps of the right and left submandibular glands, difficulty breathing and swallowing, so a tracheostomy and gastrostomy were performed. The first anatomical pathology results in extraosseous Plasmacytoma and the second Plasmablastic lymphoma with IHC CD138 (+) CHOP chemotherapy and radiation. After chemotherapy, the patient experienced improvement.*
Conclusion: *Plasmablastic lymphoma is difficult to diagnose because the anatomical pathology picture overlaps with plasmacytoma in the gold standard IHC CD138 (+), which is aggressive and relapses.*

Keywords: *Plasmablastic Lymphoma, plasmacytoma, CD 138.*

RESUMEN

Introducción: *El linfoma puede ocurrir en adultos y ancianos, esto afectará la condición tanto del diagnóstico como de la terapia. El linfoma plasmablástico (PBL) es un subtipo de linfoma difuso de células B grandes (DLBCL), el caso rara vez se encuentra y muchas veces se superpone al cuadro de la patología anatómica similar al plasmocitoma. Es agresivo y con frecuencia recae.*
Presentación del caso: *Un hombre de 50 años se quejó de un bulto en la mejilla derecha que se extendía a la mejilla izquierda y al ojo izquierdo. Forma irregular, dura, dolorosa, acompañada de nódulos en glándulas*

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submandibulares derecha e izquierda, dificultad para respirar y deglutir, por lo que se realizó traqueotomía y gastrostomía. La primera patología anatómica resulta en plasmacitoma extraóseo y el segundo linfoma plasmablástico con quimioterapia y radiación IHC CD138 (+) CHOP. Después de la quimioterapia, el paciente experimentó una mejoría.

Conclusión: *El linfoma plasmablástico es difícil de diagnosticar debido a que el cuadro anatomopatológico se superpone con el plasmacitoma en el patrón oro IHC CD138 (+), el cual es agresivo y recidivante.*

Palabras clave: *Linfoma plasmablástico, plasmacitoma, CD 138.*

INTRODUCTION

Lymphoma disease can occur in adults and the elderly, this will affect the condition of both diagnosis and therapy, because these cases are rare and there is often in the determination of diagnoses, the case is discussed. Plasmablastic lymphoma is a malignancy with the highest prediction in HIV-positive and immunocompetent patients such as transplantation. Several cases of Plasmablastic lymphoma are non-HIV (1). Plasmablastic lymphoma is a progressive disease, destructive and refractory of chemotherapy. This malignancy has a poor prognosis where the survival rate in HIV patients is not much different, which is about 8-15 months. The mean survival in HIV-positive patients was 10 months, 11 months in immunocompetent and HIV-negative patients, and 7 months in post-organ transplant patients (2).

CASE PRESENTATION

The patient named Mr. P is 60 years old. The patient's address is in a Nganjuk district and works as a carpenter. The chief complaint was a lump on the right cheek. For nine months after being admitted, the patient complained of a lump on the right cheek. Initially the size of chicken eggs with hard palpation. accompanied by pain in the upper right molars. The patient went to the dentist, and it was said that the swelling was due to a perforated molar tooth. However, it did not improve after almost three months of visiting the dentist until the patient was advised to see a surgeon.

One month later, the patient went to Rumah Sakit Islam Aisyiyah Nganjuk, RSI Nganjuk (Aisyiyah Islamic Hospital Nganjuk), the doctor's surgery did a biopsy, and the results of anatomic pathology were 1 month later. After a biopsy, the patient underwent a CT scan of the tumor area. Three weeks later after that, the patient came to the division of Oncology medicine with referral and examination results from RSI Nganjuk. At that time the patient's tumor had not covered the eyes and nostrils. A review of anatomic pathology at Dr. Soetomo's hospital was carried out from the result of an anatomical pathology biopsy at Nganjuk hospital. The results showed a primary extraosseous plasmacytoma, so the patient is planned for a Bone Marrow Aspiration examination. The patient complained that the tumor was getting bigger in the eyes, nose, and mouth area. The patient complained of difficulty breathing for 1 month. The patients could only drink and eat the milk with a straw. One month ago the patient complained of weakness and increasing difficulty breathing, the patient's family was taken to the Emergency Unit Dr. Soetomo Hospital. The patient was treated by digestive surgery and the head and neck underwent a tracheostomy and gastrostomy 6 days later. After that, the patient was transferred to the internal medicine board.

During treatment at Dr. Soetomo Hospital, a control patient in Medical Oncology Room. The patient never complained of a stuffy nose, bed smell, headache, or nose bleeds. The family history of the disease is the patient's sister suffering from uterine cancer. The patient's job is an owner of a home industry, namely wooden furniture.

The patient was admitted to the Internal medicine room. The patient's general condition when received was weak with Glasgow Coma Scale (GCS) 456; BP 100/60; pulse 84x/ min; RR 20x/ min; temperature: 37 ^{o}C. BW before the illness is 97 kg, BW now is 55 kg, height 160 cm.

On the head, there was a bumpy tumor on the right side of the face that extended to cover both eyes with an ulcer with a depth of 0.5 cm on the right cheek. There is an enlarged right submandibular lymph node measuring 6 x 6 cm, palpable hard, not mobile, and painless. There is an enlarged left submandibular lymph node

measuring 1 x 1 cm palpable hard, not mobile, and painless. A tracheostomy is attached (Figure 1). The thorax appears symmetrical and there is no retraction. Normal heart sounds, no murmurs, and gallops. Breath sounds vesicular, with no crackles and wheezing. Abdomen flat, flexible, normal bowel sounds. Attached gastrostomy, liver, and spleen were palpable. In the extremities, warm dry red acral was found.

Figure 1.

Head multi-slice CT (MDCT) result with contrast from RSI– Nganjuk (photo results not found, only photo readings are there) resulted in a solid mass of the right maxillary sinus that extends predominantly anteriorly, and destroys the right sphenoid bone. Right maxillary bone and the medial wall of the left maxillary sinus. Enlargement of the right jugular lymph node. An anatomical pathological examination was carried out from the biopsy results, it was concluded that it was a differential diagnosis of Rhabdomyosarcoma, Malignant Lymphoma, and Small Cell Carcinoma and was recommended for Immunohistochemical Examination.

Immunohistochemical was carried out at Dr. Soetomo with desmin results; negative tumor cells, and positive CD 138 on tumor cell membranes. Impression: morphologically and the location of the tumor favors a primary interosseous plasmacytoma. Fine-needle aspiration biopsy (FNAB) nodular submandibular region dextral. In Dr. Soetomo's hospital, with infiltration of plasmacytoid cells that morphologically resemble tumor cells in the cheek. Because the result of the immunohistochemistry (IHC) was Plasmacytoma (Figure 2), further investigations were carried out on the possibility of Multiple Myeloma, namely with a complete blood count, kidney function, protein electrophoresis, calcium, bone survey, and bone marrow aspiration.

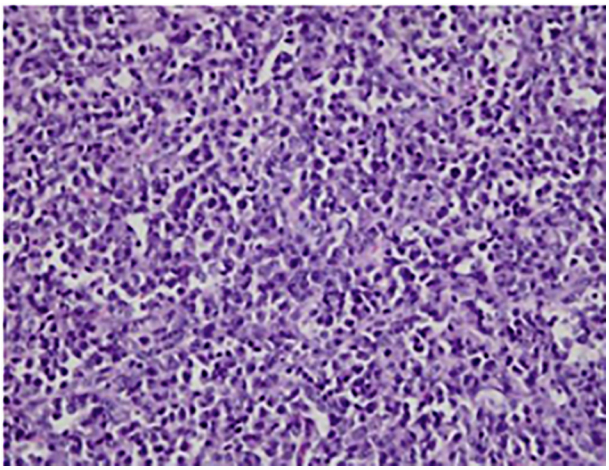

Figure 2. Fine-needle aspiration biopsy (FNAB) objective 40x.

Laboratory Examination Results showed Hb 10.8 g/dL; WBC 11.5; PLT 726 000; Albumin 3.4; BUN/creatinine serum 18/0.8; Calcium 8.2; Phosphate 3.0; Protein Bence Jones: negative; LED 71; LDH 219; HBsAg Non-Reactive; Anti HCV Non - Reactive; HIV rapid non-Reactive. Examination of serum protein electrophoresis revealed a decrease in the albumin fraction accompanied by a slight increase in the beta globulin fraction. On bone survey examination only found abnormalities in the ap/lat skull; complete fracture of the right superior mandibular ramus left mandibular body irregularity of the right mandibular bone, and multiple lytic lesions on the right and left mandibular bones. Soft tissue swelling of the right buccal region. As in other bones, there is no destruction, osteolytic or osteoblastic.

Bone Marrow Aspiration concluded a normocellular, M/E ratio of 5:1. Erythropoietic system normal impression, Myelopoiesis system normal impression with Myeloblast 4.5 %; Promyelocyte 4.3 %; Metamyelocyte 6 %; Rods 36 %; Segments 12 %; Plasma cells 1.3 %; Lymphocytes 17.8 %. Thrombopoietic system: normal impression. Bone Marrow Aspiration corresponds to the picture cells 1.3 %.

Two months after the installation of tracheostomy and gastrostomy a contrast-enhanced CT scan of the head was performed, the result showed an enhancing solid mass in the right maxillary sinus which extended medially, destroyed the medial wall of the maxillary sinus, filled the right nasal cavity. Destroyed the lamina papyracea. Filled the sinus ethmoid, destroys the lateral wall of the right maxillary sinus. Extends to the masticator space, infiltrates m. right temporal maxillaris, m. right buccinators and m. right masseter, infiltrating the right and left subcutaneous regions of the frontal region, right left maxillary and left naso-orbital right left maxillary, and left right mandibular, the mass destroys the superior wall of the right medullary sinus extending to the right maxillary sinus extending to the retro-orbital attached no m. right lateral rectus with firm boundaries pushed bulbus oculi as far as 1.5 cm, attached bulbus oculi and optic nerve with firm borders, mass destroying orbital roof extended to the right frontal sinus. Mass destroying right maxillary attached to soft palate to the right hard palate, nodules size was 0.5 cm in the left mandible, 6x6x6 cm in the right submandibular to the right and jugular, 0.7 cm in the left upper jugular, 0.7 cm in the left upper jugular 0.3 cm in the left upper jugular 0.5 cm in the left mind jugular, 0.9 cm in the right supraclavicular (AJCC staging 8th edition T4N3M0).

Thorax X-Ray: with the expression of an infiltrate in the right pericardial can be 2 differential diagnoses metastatic proses (pneumonic type), lung inflammation, no bone metastatic were seen, can't do not appear abnormal.

Follow up immunohistochemical examination was carried out on the results of the discussion of the Hematology Division with the anatomical pathology department because of the previous histopathology. The result did not support the patient's clinical manifestations. Further IHC examination showed CD 79A positive, CD 20 negative on tumor cell membranes, CD 45 positive on tumor cell membranes, and a Ki 67 proliferation index of 65 %. There was restriction for the kappa light chain, the conclusion supports a Plasmablastic Lymphoma.

The patient was diagnosed with plasmablastic lymphoma of the right maxillary region stage II BE. The patient was given the first CHOP (Cyclophosphamide, Epirubicin, Vincristine, Prednisone) chemotherapy with a dose of cyclophosphamide 1 000 mg, epirubicin 60 mg, vincristine 2 mg, and methylprednisolone 3x16 mg for 5 days. Before chemotherapy, the patient was in good general condition. During chemotherapy, the patient did not experience any side effects of chemotherapy drugs such as nausea, vomiting, urticaria, fever, and anaphylaxis. The chemotherapy went well for about 2 hours. The patient was then given an NS infusion of 1 500 mL. 24 hours, ranitidine injection 50 mg/12 h, and methylprednisolone tablet 3x16 mg. The patient's condition after chemotherapy was good.

On day 3rd after chemotherapy, the tumor on the patient's face seemed to have shrunk with the size of the tumor, at first was barely able to open the left eye, but now it can be opened. The patient did not complain of nausea and vomiting. The general condition of the patient is good with GCS 456; Blood pressure 120/70 mm/Hg; Pulse 80x/m; RR 20 x/m; Temperature 36.8 ºC. Laboratory results: Hb 11.2; WBC 6 400; Plt 209 000; SGOT 22; SGPT 22; BUN 15; SK 0.8; Uric acid 4.8; Sodium 138; Potassium 4.0; Chloride 100; Calcium 8.6.

On 5 the day after chemotherapy, the tumor on the patient's face seemed to be getting smaller with the remaining tumor size only on the forehead with a diameter of 5 cm and on the right cheek with a diameter of 10 cm. The patient a left eye can be opened and can see with vision OS 6/60. OD 2/6-. The patients did not complain of nausea and vomiting. the general condition of the patient is good with GCS 456, blood pressure 120/70, pulse 80x/m, RR20x/m, temperature 36.8 ºC. Laboratory results of the patient the days after chemotherapy with Hb 11, 0; WBC 6330; Plt 199 000; SGOT 24; SGPT 22; BUN

15; Creatinine serum 0.8; Uric acid 4.8; Sodium 138; Potassium 4.8; Chloride 100; Calcium 8.4.

On the 7th day after chemotherapy, the tumor on the patient's face got smaller with the remaining tumor on the right cheek with a diameter of 10 cm. The patients can see, eat through the mouth, and speak, and enlargement of the right submandibular lymph nodes began to shrink to a size of 3x3 cm. Enlargement of the left submandibular gland was not palpable. The patient didn't complain of nausea and vomiting. The general condition of the patient is good with GCS 456, blood pressure 120/70, pulse 80x/m, RR20x/m, temperature 36.8 ºC, Laboratory results of the patient the days after chemotherapy with blood Hb 11.8; WBC 6 700; Plt 214 000; SGOT 20; SGPT 19; BUN 15; Creatinine serum 0.8; Uric acid 4.3; Sodium 138; Potassium 4.0; Chloride 100; Calcium 8.5. The patient was planned outpatient with the second schedule of chemotherapy two weeks later.

After the second and third chemotherapy, the lump got smaller with a final diameter of 6 cm. The patients can see, speak, and eat smoothly. There were no side effects from chemotherapy drugs. However, after the fourth and fifth chemotherapy, new lumps began to appear at the side of the old tumor. The longer lump got bigger with a diameter of 4 cm and almost closed the patient's right eye. The patient was planned to receive adjuvant radiotherapy. After completing 8 cycles of chemotherapy plus adjuvant radiotherapy, the new tumor disappeared with the old tumor shrinking to 4 cm in size and there were no side effects from chemotherapy with radiotherapy. Namely dry mouth that the patient could tolerate (Figure 3).

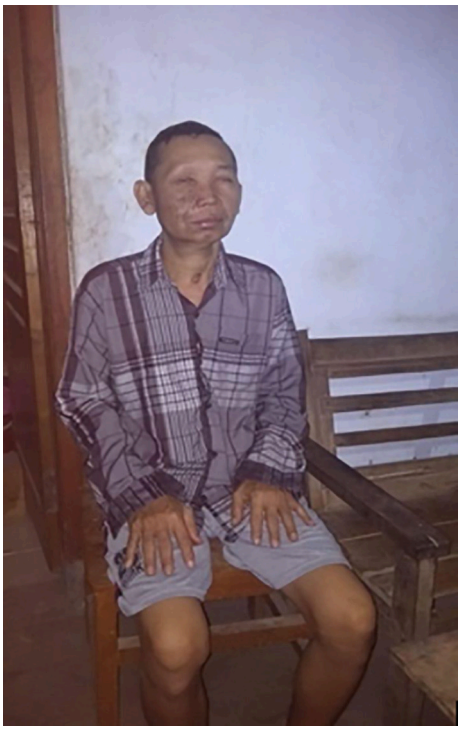

Figure 3. After 8 cycles of chemotherapy and adjuvant radiotherapy.

DISCUSSION

The diagnosis of the head and neck malignancy can be established through anamnesis, physical examination, and supporting examination, and supporting examination with the gold standard in the form of anatomical pathology biopsy results. The general history of patients with suspected malignancy is an appearance of a lump that is getting bigger and bigger, facial asymmetry, headache, oral manifestations, sometimes fever, and weight loss. Head and neck malignancies are more common in men than women 4:1 ratio, Risk factors for head and neck malignancies include smoking, alcohol consumption, exposure to industrial gases, wood dust, leather industry tanning fluids, and the Epstein Barr virus. Exposure to industrial gases and minerals as well as wood dust is a particular risk factor for the incidence of sinonasal malignancies (3). The commonly affected lymph nodes were cervical (78 %), Axillary (46.6 %), and mediastinal glands (21.8 %) (3).

Patients generally come with complaints of lymph in the oral cavity or sinonasal area then the patient comes to the dentist which does not improve with treatment. This tumor is clinically purplish in color with clear borders. Lymph node involvement is common with the most predilection being in the neck area. Investigations that can help are CT scans and often there is the destruction of the facial bones and the tumor extends to the ethmoid sinus, orbit, and masticator muscle (4).

From the patient's history, it was found that the lump was getting bigger and bigger for about 9 months before the was admitted to the hospital. The lump started from the right cheek the size of a chicken egg until when it came it experienced facial asymmetry and there were lumps on the oral cavity in the buccal and palate areas. The patient's work history as an owner of wooden furniture is often exposed to wood dust and wood tanning paint. There was a weight loss of 12 kg over 9 months. There were no complaints of fever, stuffy nose, frequent nosebleeds, and ringing in the ears before. Considering the results of the anamnesis, it can be assumed that the type of tumor is of sinonasal origin.

The patients found facial asymmetry. enlarged submandibular neck lymph nodes, airway obstruction due to shifting of the nasal bones, lumps in the palate and buccal area, and swallowing disorders. In the patient, rhinoscopy and indirect laryngoscopy were not possible because the tumor had invaded almost the entire face.

In the patient, the results of a CT scan from RSI Nganjuk were a solid mass of the right maxillary sinus that extended predominantly anteriorly, destroying the right sphenoid bone, the right maxillary bone, and the medial wall of the left maxillary sinus. Right jugular lymph node enlargement. The most common types of head and neck malignancies are squamous cell carcinoma, lymphoma, and adenocarcinoma, squamous cell carcinoma most often arises in the oral cavity and oropharynx, whereas lymphoma often arises from the sinonasal tract and tonsils. Neck lymph node involvement is common in lymphoma. Definitive diagnosis of the tumor type was carried out by anatomical pathology biopsy followed by immunohistochemistry (5).

Anatomical pathology examination was carried out from the biopsy results, it was concluded that it was a malignant round cell tumor with a differential diagnosis of Rhabdomyosarcoma, malignant lymphoma, and small cell carcinoma and it was recommended for immunohistochemistry examination from Nganjuk Hospital. The results of the immunohistochemical examination at the general hospital of Dr. Soetomo with desmin results negative on tumor cells, and positive CD 138 on tumor cell membranes (Figures 4 and 5).

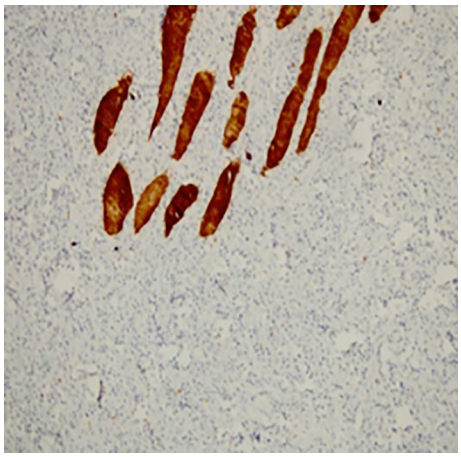

Figure 4. Desmin Staining Preparation.

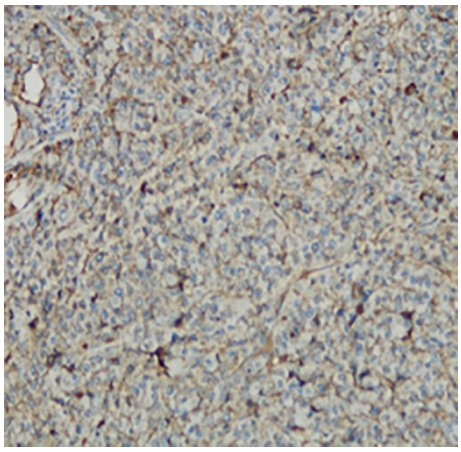

Figure 5. Preparation Antibody Desmin 138.

Impression morphologically and the location of the tumor favors a primary extraosseous plasmacytoma. One type of lymphoma that is difficult to diagnose is Plasmablastic lymphoma. The diagnosis of Plasmablastic lymphoma can overlap with that of Plasmacytoma both can occur in the upper respiratory tract and oral cavity. From protein electrophoresis, 14 %-25 % of cases of plasmacytoma found monoclonal components while the rest were normal. In Plasmablastic lymphoma, no abnormalities were found on protein electrophoresis. Kidney function, calcium, and blood laboratory result are within normal limits. Other important radiological

examinations included anatomical pathology, chest X-ray, and bone survey (6).

Both Plasmablastic lymphoma and Plasmacytoma show a strong positive CD138 on immunohistochemical examination with light chain restriction, which could be either Kappa or Lamda chains. In Plasmacytoma, if bone marrow aspiration is performed, the plasma cells are less than 5 % without forming a clone. There is almost no bone marrow involvement in Plasmablastic lymphoma. From the results of the biopsy, Plasmacytoma can be found in plasma cells that form a clone. Expression of B-cells was not found in Plasmablastic lymphoma or Plasmacytoma which was shown to be CD 20 negative. Expression of CD 79a can still be found in Plasmablastic lymphoma, while CD 45, a marker got that identification of hematopoietic or lymphoid neoplasm, can be underexpressed or weakly positive.

Almost all lymphoid cells are reactive to CD 45 The indicator of cell proliferation namely Ki 67 which increased by 75 %-905, indicated Plasmablastic lymphoma (7-9).

The results of the patient's bone marrow aspiration obtained cellularity with plasma cells at 1.3 %. Further immunohistochemistry results showed positive CD 79a(-), CD 20(-) on the tumor cell membrane, positive CD 45 on the tumor cell membrane, Ki 67 proliferation index 65 %, Kappa and Lamda had light chain restriction for Kappa. The conclusion supports a Plasmablastic lymphoma. The low Ki 67 results in these patients may be due to the immunocompetent status of the patients so that the proliferation of tumor cells is not specific staging for Plasmablastic lymphoma. Tumor staging was performed according to the ann arbor criteria for Lymphoma (3).

In this patient, the primary tumor was in the maxillary sinus with right and left submandibular lymph node involvement and systemic symptoms. Such as weight loss of 15 kg within 9 months so this patient was diagnosed with Plasmablastic lymphoma dextral maxillary region stage IIBE.

The presence of CD 45 expression is reported to provide a better prognosis but there is no standard therapy for Plasmablastic lymphoma it is a rare case. Several cases were reported using CHOP (cyclophosphamide, Vincristine, Doxorubicin, Prednisone). In which CHOP was considered suboptimal therapy.

The National Comprehensive Cancer Network® (NCCN) guideline recommends more aggressive therapy such as EPOCH (Etoposide, Vincristine, and doxorubicin, with bolus cyclophosphamide and prednisone). CODOX-MIVAC (Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, alternating with ifosfamide, etoposide (Cyclophosphamide, Vincristine, Doxorubicine, Ethrotexate) and cytarabine. However, some cases with EPOCH therapy did not provide a better benefit than CHOP (10).

The Response to chemotherapy in the patient is a partial response, where the tumor rapidly shrinks within 2-3 weeks after chemotherapy, The patient also received 35 cycles of adjuvant radiotherapy with good results (partial response).

CONCLUSION

We report a 50-year-old man with Plasmablastic lymphoma in the right maxillary region, Plasmablastic lymphoma is a malignancy that is difficult to diagnose because it overlaps with (plasmacytoma and lymphoma. This disease often attacks the oral cavity and upper respiratory tract, Plasmablastic lymphoma are common in HIV and non – immunocompromised patients, in this case, Plasmablastic lymphoma is destructive to bone and invasion of other tissue.

The gold standard was obtained from anatomic pathology and immunohistochemistry biopsy examinations. There is no standard therapy for Plasmablastic lymphoma, CHOP chemotherapy is still considered suboptimal but chemotherapy that is more aggressive than CHOP such as EPOCH has also been reported to have not increased median survival. Plasmablastic lymphoma has a poor prognosis where the median survival is between 8-15 months. Giving adjuvant radiotherapy can improve the response to therapy in the patient.

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Conflicts of Interest

The authors declare no conflict of interest.

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The first case reported in Southeast Asia of Huge Frantz's Tumor

El primer caso reportado en el Sudeste Asiático de tumor de Frantz enorme

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SUMMARY

Introduction: *Solid pseudopapillary pancreatic tumor (Frantz's Tumor) is a low-grade malignancy, that lacks clinical symptomatology. It was treatable with a favorable prognosis.*
Case presentation: *A young female patient presented with increasing abdominal pain three years ago. Abdominal examination revealed a lump palpable. Contrast-enhanced Computed Tomography abdomen reported a solid mass measuring 13.9 cm x 13.2 cm x 8.9 cm from the pancreas with an enhancing cystic component. Fine-needle aspiration biopsy yielded a cellular sample comprising pseudopapillary neoplasm of the pancreas. A distal pancreatectomy was performed; she was discharged in satisfactory condition.*
Conclusion: *A multidisciplinary team improves treatment accuracy and effective management. Prognosis over 95 % cure rate, so it is important to distinguish it from other pancreatic neoplasms.*

Keywords: *Solid pseudopapillary pancreatic tumor, Frantz's tumor, Diagnosis, Prognosis.*

RESUMEN

Introducción: *El tumor sólido pseudopapilar de páncreas (Tumor de Frantz) es una neoplasia maligna de bajo grado, sin sintomatología clínica. Era tratable con pronóstico favorable.*
Presentación del caso: *Una paciente joven se presentó con dolor abdominal cada vez mayor desde hace tres años. El examen abdominal reveló un bulto palpable. La tomografía computarizada de abdomen con contraste reportó una masa sólida de páncreas de 13,9 cm x 13,2 cm x 8,9 cm con un componente quístico realzado. La biopsia por aspiración con aguja fina arrojó una muestra celular que comprende una neoplasia pseudopapilar de páncreas. Se realizó una Pancreatectomía distal; la paciente se dio de alta con condiciones satisfactorias.*
Conclusión: *Un equipo multidisciplinario mejora la precisión del tratamiento y el manejo efectivo. Pronóstico superior al 95 % de tasa de curación, por lo que es importante distinguirlo de otras neoplasias pancreáticas.*

Palabras clave: *Tumor sólido pseudopapilar de páncreas, tumor de Frantz, Diagnóstico, Pronóstico.*

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INTRODUCTION

A solid pseudopapillary pancreatic tumor (SPPT) also known as 'Frantz tumor' is a very rare neoplasm of the pancreas. It was first described in 1959 by pathologist Virginia Kneeland Frantz (1). The term SPPT was introduced in 1996 by the World Health Organization (WHO) for the International classification of tumors of the exocrine pancreas (2). Although SPPT classification as an epithelial pancreatic tumor, in many cases.

Commonly misdiagnosed as a pancreatic pseudocyst and curative with total surgical resection. However, it was not recognized by the WHO as a low-grade epithelial malignant neoplasm until 2010 (2). Although the 5-year survival rate of more than 90 %, some cases may be locally aggressive; infiltrative with local recurrence, or distant metastases to the liver, lung, and skin (3).

Degenerative cystic changes and hemorrhagic areas are typical. On histological examination, the tumor is a solid mass with pseudopapillary and pseudocystic structures with rich microvascular in variant proportion (4). With the widespread availability of high-quality imaging systems and a better understanding of its pathology, the number of cases reported in the literature has been steadily increasing in recent years (5). Here, we reported the first case for Southeast Asia (Indonesia) of a Huge Frantz tumor in a young female patient who presented a rare indolent tumor.

CASE PRESENTATION

An 18 year old female patient presented with a dump upper abdominal mass in the outpatient clinic of our hospital, which was started 3 years ago. The patient noticed abdominal distension increasingly lasted one month before (along with weight loss of > 10 kg). At that moment, she denied any history of vomiting, change in bowel habits, weight loss, night sweats, scleral or urine discoloration, and menstrual irregularity. She was afebrile with a normal pulse and blood pressure. There was a palpable abdominal tenderness occupying most of her abdomen. No history of hepatic-biliary or pancreatic disease or other malignancy in her family was noted. Laboratory data were within normal limits. Due to prolong epigastric pain, an upper gastrointestinal study was performed in January 2022 with the conclusion of narrowing duodenal bulbus due to extralumen mass (Figure 1). Contrast-enhanced Computed Tomography (CT) abdomen (Figure 2) reported a large solid mass with enhancing cystic component and necrotic area, measuring 13,9 cm x 13,2 cm x 8,9 cm from corpus pancreas. A large mass was compressing the stomach superiorly, also compressing the portal vein, inferior cava vein, and abdominal aorta without any evidence of thrombosis. There was no evidence of distant metastases. Fine-needle aspiration biopsy yielded a cellular sample comprising pseudopapillary neoplasm of the pancreas. Intraoperatively was noted a rounded tumor, which revealed a huge mass occupying most of the abdominal cavity and displacing the stomach. A radical resection of the distal portion of the pancreas was performed. The patient was discharged in satisfactory condition. Post-1-year follow-up patient is doing well, with no signs of tumor recurrence locally and distance.

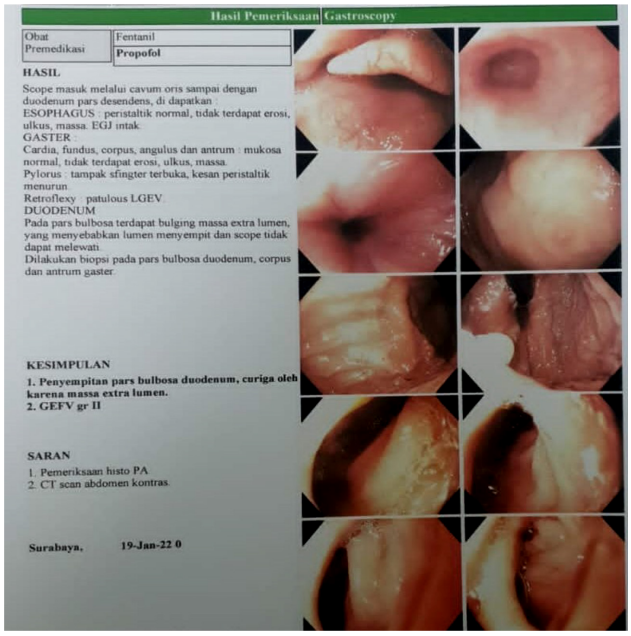

Figure 1. Upper gastrointestinal finding in endoscopy found narrowing duodenal bulbus due to extra luminal mass.

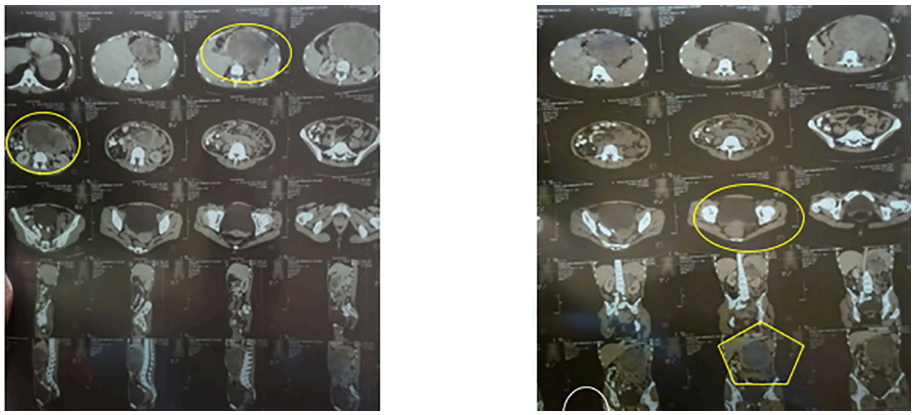

Figure 2. CT scan abdomen shows an enlargement mass from the pancreas compressed superiorly to gaster, well-marginated, encapsulated, solid and cystic mass.

DISCUSSION

SPPT can be found asymptomatic, and slow growing with an indolent course. Characterized by a long asymptomatic course and non-specific symptoms. The clinical presentation of the tumor is a palpable abdominal mass with uncharacteristic abdominal pain, and epigastric pain. Most commonly located in the body and tail (7). This case describes an indolent course from three years before admission because of non-specific symptoms and came to the hospital because palpable huge abdominal mass. SPPT is usually a well-demarcated tumor with a diameter ranging from 1,5 from 30 centimeters (cm) (average 10 cm). In our cases were 13.9 cm x 13.2 cm x 8.9 cm. Contrast Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) is superior in identifying capsule (8,9). SPPT is well-encapsulated from the pancreas, with large spongy areas of the hemorrhage on its cut surface alternating with both solid and cystic degeneration. The tumor contains a mixture of solid, cystic, and pseudopapillary patterns in various proportions. Both capsule and intratumoral hemorrhage are important clues to the diagnosis because these features are rarely found in another pancreatic tumor (10). Park et al. studied CT imaging features of SPPT in males and females which resulted in a lobulated shape that is more common among males and an oval shape in females (12,13)35.0 years.

Immunohistochemically, SPPT is typically positive for vimentin (Vim), a-1-antitrypsin (AAT), a-1-antichymotrypsin (AACT), and neuron-specific enolase (NSE) (14,15) which is consistent with the finding. However, the unique immunohistochemical features with an expression of CD56 and CD10 have not reached an agreement in a recent study (15). SPPT cells may also reveal focal immunoreactivity for cytokeratin (CK) and synaptophysin (Syn), abnormal nuclear location of β-catenin, and presence of progesterone receptors (PR), and may express galectin-3, all of which are useful in differentiating SPT from the endocrine pancreatic tumor (16,17).

The pathophysiology behind the development of SPN and its cellular origin is still a matter of debate with multiple purposed and hypotheses (7,18). One of the theories that have been suggested is the role of sex hormones in the pathogenesis of this tumor. It was proposed based on the higher female predominance rate that has been reported, particularly during the reproductive age, along with the fact that SPPT was usually positive for these receptors (19). During normal pancreas development, beta-catenin signaling within the beta-catenin/Wnt pathway is necessary and in the adult organ, this pathway is usually downregulated (20). The majority (85 %-90 %) of SPPT have exon-3 mutations and 10-15 % of mutations are present in other exons. The aberrant protein expression in SPPT is strongly

correlated with mutations in the beta-catenin gene (19,21). Mutations in beta-catenin gene exon-3 lead to Wnt signaling activation which plays an important role in the development of SPPT. Cell cycle-associated proteins like cyclin D1 and cyclin D3 are overexpressed in SPPT because of the deregulation of the cell cycle (22). The low tumor growth rate in SPPT is explained by the role of cyclin-dependent kinase inhibitors P^{21} and P^{27} in controlling the activated Wnt/beta-catenin signaling pathway (19,21,22). SPPTs are considered hormone sensitive because they express progesterone receptors (23). P^{21}, P^{27}, and cyclin D1 expression are influenced by estradiol and progesterone (24,25). At pathology, a solid pseudopapillary tumor is usually large and encapsulated and is composed of a mixture of cystic, solid, and hemorrhagic components. Both capsule and intratumoral hemorrhage are important clues to its diagnosis because they are rarely found in other pancreatic neoplasms.

Surgical management with free surgical resection margins is the mainstay of treatment even with metastasis and vascular invasion, surgical excision should be performed whenever feasible (26). In this case, attention to complications due to total resection probably wound infection; consider the patient at a young age. The recurrence rate after surgical resection has been reported to be 3 %-9 % (27). Regardless, the patient should be promptly followed up due to the risk of potential recurrence or emergence of metastatic lesions with serial imaging examination as the best recommendation. The prognosis of SPPT is generally excellent with a 95 % cure rate following complete surgical resection. In this case, abdominal discomfort with a palpable mass starts at an early puberty age (16 years old) when progesterone hormone is still low. From the literature 700 reported cases show a range of ages starting from 20 years old. All data show resection (even in the metastatic stage) preserves a good prognosis until 15 years old.

CONCLUSION

Solid pseudopapillary tumor of the pancreas is a rare primary neoplasm with unknown etiology, characterized by a paucity of clinical symptomatology, and can reach a large size. Radically curable with complete resection, distinguished from other tumors with a similar location because of its characteristic clinical and histopathologic features. The literature review supports the concept surgical resection offers an excellent prognosis.

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Conflict of Interest

The authors declare no conflict of interest.

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Patient Consent

Obtained.

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