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Arthritis in Leprosy: A Case Report

Artritis en lepra: reporte de un caso

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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.

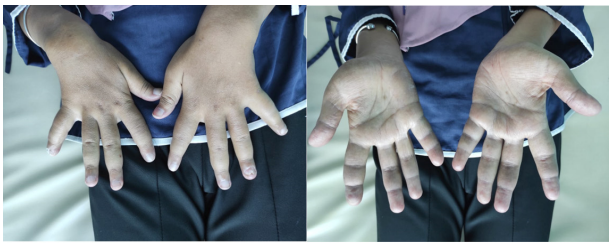

Figure 1. The patient presented with bilateral dactylitis and onycholysis on her 4th left digit.

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).

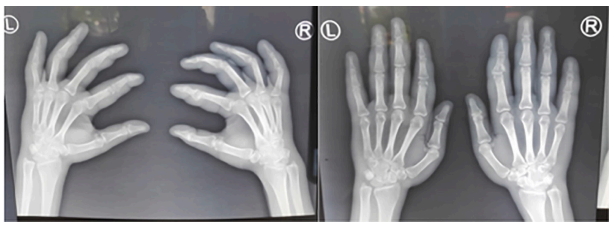

Figure 2. Radiology showed deformity of the base of the 2nd right medial phalange and narrowing of the proximal interphalangeal joint of the 2nd right digit.

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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