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Mucinous Adenocarcinoma (Signet Ring Cell Carcinoma) of the Urinary Bladder in Young Male: A Case Report

Adenocarcinoma mucinoso (carcinoma de células en anillo de sello) de vejiga urinaria en varón joven: reporte de un caso

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SUMMARY

Primary mucinous adenocarcinoma of the urinary bladder is a rare malignancy and accounts for less than 2 % of all malignant urinary bladder tumours. This malignancy occurs more commonly in males, with a peak incidence in the sixth decade of life. Herein, we report a case of a 29-year-old male presenting with pain in the symphysis pubis, urinary frequency, and haematuria. Clinical, laboratory, and radiology findings lead to suspicion of urinary bladder malignancy with bilateral hydronephrosis and chronic kidney disease. The histopathology examination revealed the tumor mass consisted of proliferative single and small groups of neoplastic epithelial cells in the pool of mucin. The cells are round to oval in shape, the cytoplasm contains mucin that pushes the nucleus to the edge, providing a signet ring cell morphology, and infiltrative to perivesical tissue. Immunohistochemical examination of CK7 stained weakly in the cytoplasm and β-catenin stained dominantly in cell membranes. Radical cystectomy has been performed and the patient is currently undergoing chemotherapy with the FOLFOX regimen. Based on clinical and pathological findings, the patient was diagnosed with primary mucinous adenocarcinoma (signet ring cell carcinoma) of the urinary bladder, pT3, stage III, with a poor prognosis.

Keywords: *Mucinous adenocarcinoma, signet ring cell carcinoma, urinary bladder.*

RESUMEN

El adenocarcinoma mucinoso primario de la vejiga urinaria es una neoplasia poco frecuente y representa menos del 2 % de todos los tumores malignos de la vejiga urinaria. Esta neoplasia maligna se presenta con mayor frecuencia en varones, con una incidencia máxima en la sexta década de la vida. Presentamos el caso de un varón de 29 años que consulta por dolor en la sínfisis del pubis, polaquiuria y hematuria. Los hallazgos clínicos, de laboratorio y radiológicos hacen sospechar una neoplasia maligna de vejiga urinaria con hidronefrosis bilateral y enfermedad renal crónica. El examen histopatológico reveló que la masa tumoral consistía en grupos pequeños y únicos proliferativos de células epiteliales neoplásicas en el conjunto de mucina. Las células son de forma redonda a ovalada, el citoplasma contiene mucina que empuja el núcleo hacia el borde, proporcionando una morfología de células en anillo de sello e infiltrante al tejido perivesical. El examen inmunohistoquímico de CK7 se tiñó débilmente en el citoplasma y la β-catenina se

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tiñó predominantemente en las membranas celulares. Se ha realizado cistectomía radical y actualmente el paciente se encuentra en tratamiento quimioterápico con la pauta FOLFOX. En base a los hallazgos clínicos y patológicos, el paciente fue diagnosticado de adenocarcinoma mucinoso primario (carcinoma de células en anillo de sello) de vejiga urinaria, pT3, estadio III, de mal pronóstico.

Palabras clave: *Adenocarcinoma mucinoso, carcinoma de células en anillo de sello, vejiga urinaria.*

INTRODUCTION

Primary adenocarcinoma of the urinary bladder is a malignancy derived from the urothelium with a histologically pure gland phenotype. This type of malignancy is rare and accounts for less than 2 % of all malignancies in the urinary bladder, is more common in males, and has a peak incidence in the 6th decade (1,2). Urinary bladder cancer is very rarely diagnosed in patients less than 40 years of age. The percentage of urinary bladder adenocarcinoma based on the histological subclassification where adenocarcinoma is not otherwise specified is 28 %, mucinous is 41 % (including signet ring cell 17 %), enteric is 19 %, and mixture is 13 % (3,4).

Primary adenocarcinoma of the urinary bladder has very aggressive behavior and less response to radiotherapy and chemotherapy. This tumor has overlapping histologic characteristics with adenocarcinoma derived from other primary sites such as colorectal, prostate, and gynecology. Diagnosis is often delayed because it is very difficult to determine its primary location, so palliative chemotherapy becomes a possible therapy in nearly 50% of patients (5-7). We will report a case of primary mucinous adenocarcinoma (signet ring cell carcinoma) of the urinary bladder that occurred in a 29-year-old male.

CASE DESCRIPTION

A 29-year-old man was referred to Sanglah Hospital with pain in the symphysis pubic area and hematuria. This patient had a history of recurrent urinary tract stones. Eleven years before admission for these complaints, the patient underwent surgery twice to remove stones from his bladder. In 2016, a doctor found stones in both patients' kidneys and performed an Extracorporeal Shock Wave Lithotripsy procedure. The patient did not have any congenital disorder or history of prior infection in the urinary tract.

Urological ultrasonography concluded the patient had bilateral hydropyonephrosis and clot retention with a differential diagnosis of a mass (Figure 1A). Abdominal CT scan without contrast showed lobulated thickness on the right, left, and posterior bladder wall causing obstruction in the right and left ureterovesical junction (UVJ) and bilateral hydronephrosis. There was no expansion of the lesions to the intestines, and surrounding organs (Figure 1B, 1C).

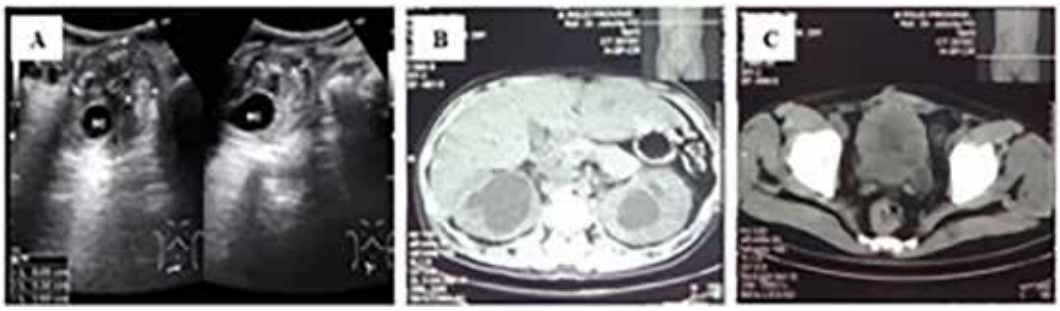

Figure 1. A. Urological ultrasonography concluded the patient had bilateral hydropyonephrosis, and clot retention with a differential diagnosis of a mass. B. Abdominal CT scan without contrast showed bilateral hydronephrosis. C. Lobulated thickness on the right, left and posterior bladder wall, expansion of the lesions to the intestines, and surrounding organs.

Clinical findings, radiological findings, and other examinations lead to suspicion of urinary bladder malignancy and chronic renal failure stage V. Hemodialysis, nephrostomy, and radical cystoprostatectomy were performed on this patient. After radical cystoprostatectomy, the urinary bladder was sent for a histopathology examination. The surgeon sent a urinary bladder, with both ureter and prostate (Figure 2) and the appendix for examination. The size of the urinary bladder was 8,5 x 7 x 6 cm, the diameter of each ureter was 0,8 cm, and the prostate's size was 2,5 x 2 x 2 cm. A gelatinous exophytic mass filled the whole of the urinary bladder. The length of the appendix was 6 cm and 0,8 cm in diameter. No mass was found in the appendix.

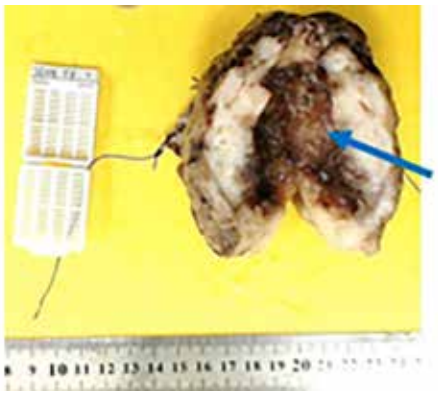

Figure 2. Urinary bladder, with both ureter and prostate. Gelatinous exophytic mass filled the whole urinary bladder (blue arrow).

Microscopic examination revealed the urinary bladder contained tumour mass consisting of proliferative single and small groups of neoplastic epithelial cells in the pool of mucin. The cells are round to oval, with cytoplasm containing mucin that pushes the nucleus to the edge, providing a signet ring cell morphology (Figure 3A), and infiltrative until the perivesical tissue (Figure 3B). There was no infiltration of these cells into the prostate and vesicula seminalis (Figure 3C), but the distance of malignant cells to the prostate edge was 1 mm (Figure 3D). An immunohistochemical examination of CK7 and β-catenin was performed. CK7 was stained weakly in the cytoplasm and β-catenin was stained dominant in the cell membranes (Figure 4) which supported the diagnosis that this malignancy was primarily from the urinary bladder. Based on clinical and pathological findings, the patient was diagnosed with primary mucinous adenocarcinoma (signet ring cell carcinoma) of the urinary bladder, pT3, stage III.

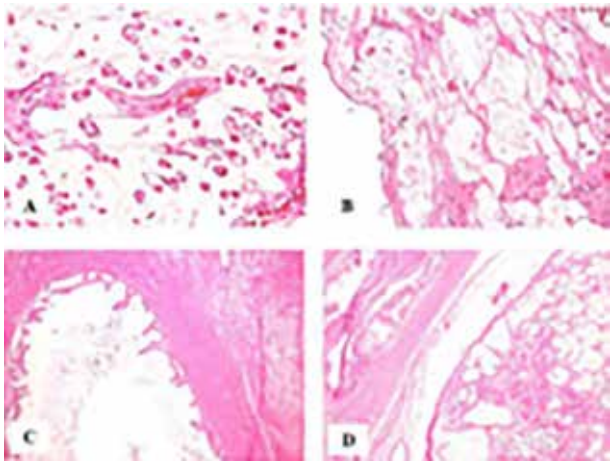

Figure 3. Microscopic examination with Haematoxylin and Eosin stain. A. Signet ring cell in the pool of mucin (x400). B. The neoplastic epithelial cells are infiltrative into perivesical tissue (x400). C. No infiltration of the malignant cells into vesicula seminalis (x40). D. No infiltration of the malignant cells into the prostate, but the distance of malignant cells to the prostate edge is 1 mm (x100).

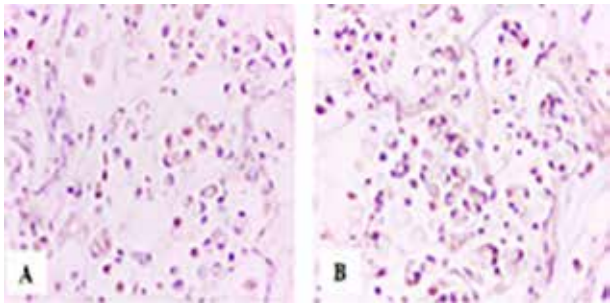

Figure 4. Immunohistochemical examination. A. CK7 was stained weakly in the cytoplasm. B. β-catenin was stained dominant in cell membranes.

DISCUSSION

Umbilical primary adenocarcinoma of the urinary bladder is very rare, accounting for only 0,5 %-2 % of all malignancies in the urinary bladder. This malignancy usually occurs in adults, with a peak incidence in the sixth decade, and the male: female ratio is 2,7:1 (8). Haematuria is the most common symptom, associated with symptoms of irritation when urinating. Mucusuria may also occur in some patients (1,8,9). In this case, a 29-year-old male came to the hospital with pain in the symphysis pubic area and hematuria.

Two hypotheses are accepted to explain the occurrence of this tumor. First, this tumor is progressing from mucinous metaplasia to mucinous adenoma and adenocarcinoma mucinous; however, no research confirms this hypothesis, and the second, persistent embryology of endodermal intestinal tissue (10). This lesion is associated with long-term intestinal metaplasia, chronic irritation, and obstruction such as schistosomiasis and non-functioning urinary vesicles. Pelvic lipomatosis is also mentioned as a risk factor (8,11). This patient did not have any congenital disorder but the patient had a history of recurrent urinary tract stones.

Rigorous clinical evaluation and other supporting examinations must be performed to establish the diagnosis and exclude other organs as the primary site (such as colorectal and prostate). Colonoscopy is the most specific examination to distinguish primary or secondary urinary bladder adenocarcinoma from colorectal adenocarcinoma (1,12). In this case, colonoscopy was not performed but urological ultrasonography concluded hydropyonephrosis, and clot retention with a differential diagnosis of a mass. An abdominal CT scan without contrast showed lobulated thickness on the right, left, and posterior bladder wall causing obstruction in the right and left ureterovesical junction (UVJ) and bilateral hydronephrosis. There was no expansion of the lesions to the intestines and surrounding organs.

Adenocarcinoma can occur anywhere in the urinary bladder, but in most cases is often involved in the posterior wall and trigonum (13). The macroscopic picture of this tumor may be exophytic, papillary, sessile, ulcerated, infiltrative, or gelatinous. Vesical extrophy and persistent uracal remnants can also be found as well as a risk factor associated with vesical adenocarcinoma (14). Macroscopic examination revealed a gelatinous exophytic mass filled the whole of the urinary bladder. We did not find a sign of vesical extrophy and persistent uracal remnants.

According to the WHO Classification 2016, these tumors are histopathologically classified into enteric adenocarcinoma, mucinous adenocarcinoma, and mixed adenocarcinoma. Enteric adenocarcinoma has an identical feature to gastrointestinal adenocarcinoma. The glands are lined by pseudostratified mucin-secreting epithelium with various degrees of pleomorphism and with central necrosis. In mucinous adenocarcinoma, the tumor cells form nests floating in abundant extravasated mucin. Sometimes single cells with signet ring cell morphology can be seen (8,15). The most common type is mixed adenocarcinoma which has a combination of enteric and mucinous patterns. If the gland has no specific type it can be classified as not otherwise specified (NOS) (8). Microscopic examination of this case revealed the urinary bladder contained tumor mass consisting of proliferation of dispersed single-epithelial neoplastic cells, some forming small groups in the pool of mucin. The morphology of the cells is round oval, the cytoplasm containing the mucin that pushes the nucleus to the edge, providing a signet ring cell morphology.

The differentiation of adenocarcinoma in the urinary bladder is determined based on the degree of gland differentiation and pleomorphia and is divided into well-, moderately- and poorly differentiated (13). We did not find any glandular differentiation in all preparat, we only found cells with signet ring cell morphology floating in abundant extravasated mucin which indicates poor differentiation (high grade). The TNM classification is used for tumor staging (Tables 1 and 2) (8). In this case, the neoplastic cells are infiltrative until perivesical tissue. There was no infiltration of these cells into the prostate tissue, vesicula seminalis, and appendix. There was no evidence of metastasis of this tumor to the lymph node and other organs. Therefore, this case is incorporated into pT3a and stage III.

The most important differential diagnosis is metastasis adenocarcinoma from other organs, for which the most common sites are colorectal and prostate for males and females and genital tract, breast, and colon for females (13). Expansion from the prostate can be ruled out in this case because microscopic examination did not find any malignant cells in the prostate tissue. Expansion from the colorectal also can be ruled out because exploration-based clinically and radiologically, did not find any mass. Besides clinical and other supporting examinations, immunohistochemical studies are important examinations for the exclusion of adenocarcinoma from elsewhere. Adenocarcinoma of the urinary bladder is usually positive for CEA, CDX-2, MUC-1, MUC-2, and MUC-3, as well as adenocarcinoma of the colon, and positive for CK7 and CK20. A typical colon adenocarcinoma is usually negative for CK7 and positive for CK20, but in 29 % of cases of primary adenocarcinoma in the urinary bladder, there are also similar expression patterns. Thrombomodulin (thrombin endothelial receptor) is a sensitive marker for the urothelial.

Wang et al. reported 90 % expression of thrombomodulin in urothelial carcinoma and expressed only in 59 % of cases of adenocarcinoma of the urinary bladder, and unexpressed in cases of colon adenocarcinoma (5,8,13). The staining of CK20, CK7, and CDX2 is not able to distinguish both of them. Nevertheless, β-catenin usually shows nuclear reactivity in colon cancer but membranous and cytoplasmic staining in primary bladder adenocarcinoma, thus becoming a very helpful tool in this respect (16). In this case, CK7 was stained weakly in the cytoplasm and β-catenin was stained dominantly in cell membranes, which supports the diagnosis of primary malignancy in the urinary bladder.

The treatment modalities for primary adenocarcinoma of the urinary bladder are surgery, radiotherapy, and chemotherapy. Types of surgery that can be performed include transurethral resection, partial cystectomy, and radical cystectomy (10). Adjuvant chemotherapy can improve long-term survival in patients who get early cystectomy. Until now there is no standard chemotherapy for primary adenocarcinoma of the urinary bladder due to their rarity (5,10). Cobo-Dols et al. reported a case of primary signet ring cell carcinoma treated successfully with total cystectomy followed by systemic chemotherapy with cisplatin and gemcitabine, a standard combination for transitional carcinoma of the urinary bladder (10). Recent evidence has shown that oxaliplatin plus fluoropyrimidine regimen (FOLFOX) should be considered in the case of failure of first-line chemotherapy treatment (5). A FOLFOX regimen is commonly used for metastatic colorectal cancer and appeared like a reasonable frontline choice after being supported by a sporadic successful therapy experience (16). In this case, radical cystectomy was performed and the patient is currently undergoing chemotherapy with the FOLFOX regimen.

Table 1

TNM classification of carcinomas of the urinary bladder (8)

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumour"
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis propria
T2a	Tumour invades superficial muscularis propria (Inner half)
T2b	Tumour invades deep muscularis propria (outer half)
T3	Tumour invades perivesical tissue:
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades the prostatic stroma, seminal
T4b	vesicles, uterus, or vagina
	A tumour invades the pelvic wall or abdominal Wall
	N- Regional lymph nodes
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to a single lymph node in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node)
N2	Metastasis to multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node)
N3	Metastasis to common iliac lymph node(s)
	M- Metastasis
M0	No distant metastasis
M1	Distant metastasis

Table 2

Stage grouping of carcinomas of the urinary bladder (8)

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a-b	N0	M0
Stage III	T3a-b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-3	M0
	Any T	Any N	M1

The prognosis of mucinous adenocarcinoma in the urinary bladder is generally poor and depends on the stage when the diagnosis is established, and therapy is given. In general, the 5-year survival rate is 40 %-50 %. Tumors composed of a signet ring cell without extracellular mucin have a worse prognosis than other histologic types (8,14). This patient was diagnosed with High-Grade Mucinous Adenocarcinoma (signet ring cell carcinoma) pT3a, stage III, which generally has a poor prognosis.

CONCLUSION

Primary mucinous adenocarcinoma (signet ring cell carcinoma) of the urinary bladder in a young male is a rare case. Comprehensive exploration from clinical and other supporting examinations is needed to exclude the primary possibility from other organs. In addition, immunohistochemical studies of CK7 and β-catenin may help exclude the primary possibilities from other organs. The main therapeutic modality for primary adenocarcinoma in the urinary bladder is surgery. Adjuvant chemotherapy can improve long-term survival in a patient who gets early cystectomy but until now there is no standard chemotherapy so further studies are really needed. The prognosis of mucinous adenocarcinoma in the urinary bladder is generally poor.

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