CASE REPORT

Synchronously detected secondary signet ring cell urinary bladder malignancy from the stomach masquerading as genitourinary tuberculosis

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SUMMARY

Secondary bladder neoplasms are very rare and represent 1% of all malignant bladder tumours. Among secondary bladder tumours, metastasis from the stomach accounts for about 4% of cases. These secondary tumours are generally detected during follow-up of patients already treated for gastric cancer. We report a case of metastatic adenocarcinoma of the urinary bladder from an occult primary poorly differentiated signet ring cell type gastric carcinoma masquerading clinically as genitourinary tuberculosis. Our case illustrates the importance of obtaining a bladder biopsy in suspected chronic inflammatory conditions such as urinary tract tuberculosis before starting medical management to avoid the serious consequences of missing a bladder malignancy.

BACKGROUND

The stomach is one of the rare sites of primary malignancy that can cause secondary bladder cancer with very few cases reported in the literature. In most of these reported cases, the metastases were a metachronous event in patients already

diagnosed with gastric cancer, unlike in the case of our patient.¹ When there is diffuse infiltration of bladder by the tumour, the metastases can present clinically as an inflammatory process and can lead to a diagnostic misinterpretation. Second, uncommon histology such as adenocarcinoma itself can cause a diagnostic dilemma as to whether the bladder malignancy is a primary or a secondary tumour. It is important to differentiate between the two, as an organ-confined primary bladder tumour is best treated surgically while secondary bladder cancer is ideally managed with palliative chemotherapy.^{1 2} This case also illustrates that in suspected chronic inflammatory conditions such as urinary tract tuberculosis, medical treatment should not be started on clinical grounds alone, even in endemic areas. A bladder biopsy must be obtained before starting medical management to avoid the serious consequences of missing a bladder cancer.

CASE PRESENTATION

A 60-year-old man who was being evaluated for lower urinary tract storage symptoms of 2 months'

Figure 1 CECT of the abdomen, axial section, showing diffuse thickening of stomach and urinary bladder wall with ascites.

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Figure 2 (A) Bladder biopsy showing poorly differentiated carcinoma (H&E×100). (B,C,D) Immunohistochemistry showing neoplastic cells strongly positivity for cytokeratin 7(B), CDX2(C) and negative for p63(D) (×100).

duration was detected to have a positive urinary PCR study for tubercular bacilli. He was subsequently referred to our clinic with a suspicion of genitourinary tuberculosis. His physical examination did not reveal anything significant.

INVESTIGATIONS

The patient's blood urea and serum creatinine levels were found to be elevated, and ultrasonography revealed bilateral asymmetrical hydronephrosis and a diffusely thickened small capacity bladder. Urine analysis revealed pyuria and microscopic haematuria but was negative for acid-fast bacilli. The patient subsequently underwent cystoscopy that showed a smooth wall, diffusely erythematous small capacity bladder. Bilateral ureteric orifices were not visualised. His renal parameters improved after urinary diversion. Contrast-enhanced CT (CECT) of abdomen and pelvis showed a diffusely thickened stomach, greater omentum and urinary bladder with ascites (figure 1). Urinary bladder biopsy showed a poorly differentiated malignancy that was positive on immunohistochemistry for panCK, CK7, CDX2, but negative for p63, suggesting a poorly differentiated adenocarcinoma likely from the upper gastrointestinal tract (figure 2). Considering the biopsy report and CECT findings, the patient was subjected to upper gastrointestinal endoscopy, which revealed an ulcerative lesion along the lesser curvature of the stomach (figure 3). A biopsy obtained from the ulcer was reported as primary poorly differentiated signet ring cell adenocarcinoma of the stomach (figure 4). Thus, a final diagnosis of primary gastric cancer with secondary gastric cancer in the bladder was made, and the patient was started on palliative chemotherapy.

DIFFERENTIAL DIAGNOSIS

- ▶ Genitourinary tuberculosis;
- ▶ Chronic cystitis;
- ▶ Primary bladder cancer.

TREATMENT

Combination chemotherapy with epirubicin, oxaliplatin and capecitabine.

OUTCOME AND FOLLOW-UP

The patient has responded well to chemotherapy but remains with bilateral nephrostomy tubes.

DISCUSSION

Primary adenocarcinoma of the bladder comprises only 0.5–2% of all epithelial tumours, and a primary SRC carcinoma has an estimated prevalence of 0.24% of all primary bladder cancers.³ Secondary urinary bladder malignancy accounts for 1% of all bladder neoplasms.¹ The stomach is one of the rare primary foci that produces metastases in the urinary bladder, with about nine cases of metastatic gastric signet ring cell carcinoma to the urinary bladder being reported in the literature (table 1).^{1 4–9} The most common mode of metastasis in a secondary bladder adenocarcinoma is by direct infiltration, peritoneal seeding or haematogenous spread. In our patient, haematogenous spread seems the most probable mechanism, as demonstrated by the diffuse bladder wall thickening. Secondary bladder cancers are

Figure 3 Upper gastrointestinal endoscopic image demonstrating an ulcerative lesion along the lesser curvature of the stomach.

Figure 4 Biopsy from the stomach showing a poorly differentiated signet ring cell gastric adenocarcinoma with overlying normal gastric glands. (A) (H&E×40). (B) (H&E×400).

classified as protuberant and diffuse type based on radiological findings and macroscopic appearance. The protuberant type commonly presents with gross haematuria facilitating its diagnosis, while the less common diffuse type is characterised by storage lower urinary tract symptoms without gross haematuria. The diffuse type can be confused with inflammatory conditions such as chronic cystitis and genitourinary tuberculosis.¹⁰ On cystoscopy, secondary tumours are mostly solitary (54%), located in the region of the bladder neck or trigone.

Primary and secondary SRC type carcinomas of the urinary bladder are difficult to distinguish on histopathology because they are fairly similar to their counterparts in other organs such as the stomach, colon and breast. The presence of urothelial carcinoma or squamous cell carcinoma in the adjacent mucosa goes in favour of primary bladder cancer whereas an overlying intact urothelium could suggest a secondary tumour.^{11–13} Primary bladder adenocarcinoma, to an extent, can be differentiated from secondary bladder adenocarcinoma on immunohistochemistry. Most gastrointestinal adenocarcinomas express CDX2 and villin, and stain positive for one or both of these markers in bladder biopsy could suggest a secondary bladder malignancy in appropriate clinical settings. Immunohistochemistry for CDX2 and villin are thus useful additions to the limited list of diagnostic markers (including CK7, CK20, thrombomodulin and β -catenin) for the distinction between primary and secondary adenocarcinomas of the bladder.^{14 15}

These secondary bladder malignancies of a diffuse type can often be confused with inflammatory diseases such as genitourinary tuberculosis, particularly in tropical countries. These inflammatory conditions are generally diagnosed on clinicoradiological grounds and laboratory investigations, however, neither of these methods is 100% accurate. Urinary PCR for *Mycobacterium tuberculosis* DNA has a sensitivity of 87–100% and a specificity of 92.2–98%. The most common cause of a false-positive PCR is carryover amplicon contamination.¹⁶ Thus, supportive evidence in the form of bladder biopsy should be aimed for in these clinical situations so as not to miss an underlying malignancy. Bladder biopsy by itself is diagnostic in only 18–45% of cases of genitourinary tuberculosis.¹⁷ Alternatively, coexistence of genitourinary tuberculosis with malignancy could have resulted in a positive urinary PCR. However, in this case we could not find any histopathological evidence of tuberculosis.

The treatment of organ-confined primary adenocarcinoma of the urinary bladder is primarily radical cystectomy while that of metastatic cancer in the urinary bladder is with palliative chemotherapy. Various trials have shown improved overall survival for an average of 6 months with combination chemotherapy over supportive care alone. Currently, combination chemotherapy regimens with epirubicin, cisplatin and capecitabine and epirubicin/and cisplatin, capecitabine and epirubicin or oxaliplatin and capecitabine, are preferred. These regimens have been found to be superior to the earlier gold standard of fluorouracil, doxorubicin and mitomycin.¹⁸

Table 1 Clinical profile of reported cases of metastatic signet ring cell gastric carcinoma in the urinary bladder

Reference	Clinical data	Macroscopic/radiological presentation	Interval between primary and metastatic tumour
Vigliar <i>et al</i> ¹	38/M on combination chemotherapy for poorly differentiated adenocarcinoma	Growth at trigone	7 months
Nakamura <i>et al</i> ⁴	55/M underwent gastrectomy for poorly differentiated adenocarcinoma, signet ring cell type	Diffuse type	9 Months
Saba <i>et al</i> ⁵	52/M underwent subtotal gastrectomy for poorly differentiated adenocarcinoma, signet ring cell type	Protuberant type	7 years
Uemura <i>et al</i> ⁶	59/M underwent gastrectomy for mucinous adenocarcinoma	Diffuse type	21 Months
Puerta <i>et al</i> ⁷	52/F underwent gastrectomy for poorly differentiated adenocarcinoma, signet ring cell type	Diffuse type	2 years
Antunes <i>et al</i> ⁸	63/F underwent partial gastrectomy for poorly differentiated adenocarcinoma, signet ring cell type	Diffuse type	21 months
Bates and Baithun ⁹	Two similar cases reported	Data not available	—
Sharma <i>et al</i> ¹⁰	30/M underwent D2 partial gastrectomy for signet ring cell variant of poorly differentiated mucoid adenocarcinoma	Protuberant type	2 years

F, Female; M, Male.

Learning points

- ▶ Patients of advanced age with clinical profiles suggesting inflammatory lower urinary tract/bladder pathology of recent onset should have a more detailed evaluation including bladder biopsy so as not to miss identifying malignancy.
- ▶ In patients with such an uncommon histology, evaluation of the clinical history, in depth radiological assessment and immunohistochemistry is critical so as to avoid diagnostic misinterpretation and unnecessary surgical treatment.
- ▶ Urinary PCR for acid-fast bacilli, though highly specific, can yet be falsely positive and in atypical presentations definitive evidence in the form of biopsy should be aimed for.

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Patient consent Obtained.

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