

# Negative pathology of ureteral carcinoma significantly delaying the diagnosis of the primary tumor of osteoblastic metastases: A case report and review of the literature

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**Abstract.** Ureteral urothelial carcinoma (UC) is a rare malignant tumor. The most common clinical manifestations of ureteral UC are hematuria, increased urinary frequency, dysuria and pain. The diagnosis of ureteral UC is made via radiography, endoscopy and pathology. Although osteoblastic destruction is usually observed in metastasis of prostate cancer, UC can also be a reason for osteoblastic metastasis. The present study reports the case of a 66-year-old man presenting with osteoblastic metastases, in which the primary tumor was finally diagnosed as a ureteral UC. However, the lack of pathological evidence significantly delayed the diagnosis of the primary tumor (>6 months), even though the results of radiographic examination, and the type and mode of bone metastases significantly suggested a ureteral UC. The case reveals that a suitable screening test should be recommended for patients at high risk due to the possibility of a negative pathology result for ureteral UC. Additionally, a more efficient diagnostic method is required. Moreover, the possibility of new diagnostic criterion that do not rely on the pathology of primary foci in ureteral UC should be considered in future.

## Introduction

Urothelial carcinoma (UC) is a common tumor that is identified most frequently in patients aged 50-80 years, and which

has a 2:1 male predominance (1). UC can be located in the bladder, renal pelvis or ureter with a relative frequency of 50:3:1 (2). The natural history of upper tract urothelial carcinoma (UTUC) differs from that of bladder cancer; 60% of UTUCs are invasive at diagnosis compared with only 15-25% of bladder tumors (3,4). The majority of UCs are detected in the early stage, such that the patients often show long-term survival (5). For metastatic UC, systemic chemotherapy is recommended (5).

Ureteral UC is a rare malignant tumor, which accounts for ~6% of all tumors of the upper urinary tract (1). The diagnosis of ureteral UC is made via radiography, endoscopy and pathology. Urinary obstruction is one of the typical imaging features (2). Although osteoblastic destruction is observed in the metastasis of prostate cancer, UC can also be the reason for osteoblastic metastasis. The treatment for metastatic ureteral UC is also systemic chemotherapy, and the same regimens used for bladder UC are recommended (5,6). The present study reports the case of a 66-year-old male presenting with osteoblastic metastases, in which the primary tumor was finally diagnosed as a ureteral UC. However, the lack of pathological evidence significantly delayed the diagnosis of the primary tumor. Written informed consent was obtained from the patient's family.

## Case report

A 66-year-old man presented to the Outpatient Department of the West China Hospital (Chengdu, Sichuan, China) on December 25, 2012 due to a 1-year history of thoracodorsal pain and a 2-week history of left-upper limb numbness. Positron emission tomography/computed tomography (CT) performed at another hospital on August 30, 2012 had revealed an increased bone density and fluorodeoxyglucose (FDG) metabolism of the pelvis and several vertebrae, increased FDG metabolism of enlarged lymph nodes inside the abdominopelvic cavity and a non-functioning right kidney (Fig. 1). Furthermore, enhanced magnetic resonance imaging of the abdominopelvic cavity had revealed several partly and unevenly enhanced nodules of the liver (the largest was 1.4 cm in diameter), and an unevenly enhanced stenotic right

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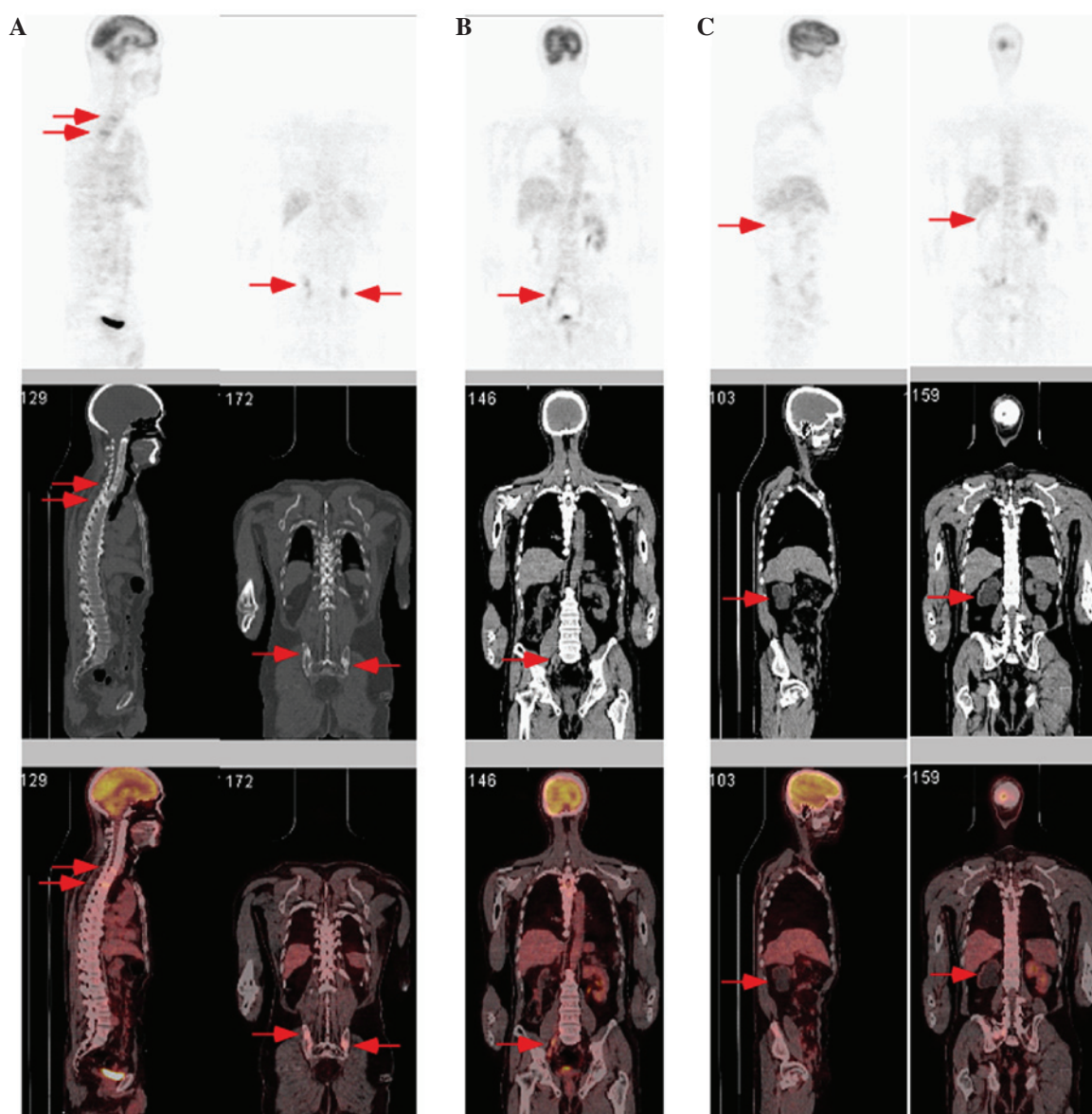


Figure 1. Results of positron emission tomography/computed tomography. (A) Increased bone density and fluorodeoxyglucose (FDG) metabolism of the pelvis and several vertebrae. (B) Increased FDG metabolism of several enlarged lymph nodes inside the abdominopelvic cavity. (C) The right kidney with dilated renal pelvis and atrophic renal parenchyma. Red arrows indicate the pathological foci.

ureter with a thickened wall. However, the ureteral endoscopy examination was negative, and pathological examinations of the prostate, bone marrow and voided urine had not detected any malignant cells.

In the Outpatient Operating Room of the West China Hospital, the patient received another multipoint biopsy of the prostate. However, a pathological examination of the prostatic biopsy, performed by the Department of Pathology at our hospital, found only low-grade prostatic intra-epithelial neoplasia and a few focal atypical glands. The patient then received another bone marrow biopsy (January 2, 2013), and smears revealed a large number of atypical cell clusters. A flow cytometric analysis of these particular cells, performed on January 3, 2013, showed negative results for cluster of differentiation (CD)45, CD2, CD5, CD7, CD16, CD56, CD10, CD19, CD20, CD38, light-chain immunoglobulin, CD34, human leukocyte antigen-antigen D related and CD117. However, immunohistochemical staining performed by the Department

of Pathology on January 14, 2013 showed positive results for pan cytokeratin (PCK), epithelial membrane antigen, CK7 and tumor protein 63 (p63), and negative results for CK5/6, CK20, thyroid transcription factor-1, prostate-specific antigen (PSA) and S-100 (Fig. 2A and B). Accordingly, the patient was diagnosed with malignant bone metastases, and the osteoblastic destruction was deemed not caused by prostate cancer.

The patient was hospitalized and administered drugs to control the pain (90 mg morphine hydrochloride sustained-release tablets every 12 h) and nerve symptoms (thrice daily 0.3 g oral gabapentin and once daily 10 mg intravenous dexamethasone for 4 days). The medical history revealed no family history of genetic diseases, but the patient was a retired employee of an oil company, therefore, contact was made with oil and various petroleum products during this time. To search for the primary tumor, the patient received thoracic and abdominal enhanced X-ray CT scans. The scans revealed liver metastases (3.9x3.0 cm), and suggested

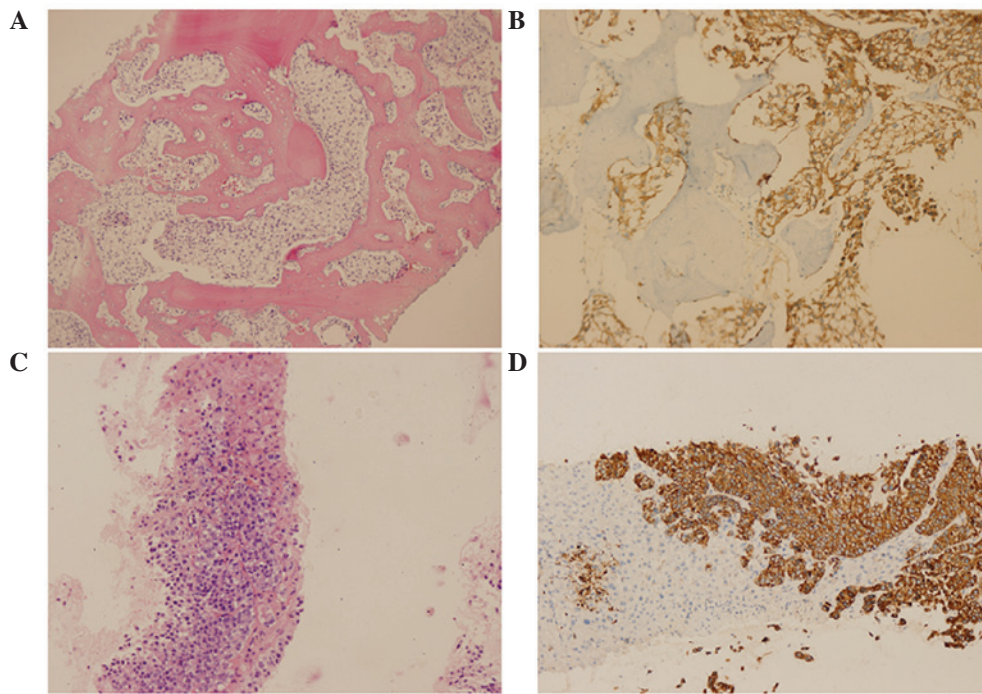


Figure 2. Pathological examinations of bone marrow and liver tissue. (A) Hematoxylin and eosin (HE) staining of bone marrow. (B) Immunohistochemistry staining of bone marrow for cytokeratin 7 (CK7). (C) HE staining of liver tissue. (D) Immunohistochemistry staining of liver tissue for CK7.

a right ureteral tumor. The patient subsequently underwent a percutaneous liver biopsy. Immunohistochemical staining of the liver tissue, performed on January 26, 2013, showed positive results for CK7 and p63, a punctuate positive result for CD10, a weakly positive result for homeobox protein CDX-2, a suspicious result for glypican-3, and negative results for hepatocyte, Cam5.2, and Arginase (Fig. 2C and D). Meanwhile, immunohistochemistry staining of the voided urine cytology (January 22, 2013) showed positive results for CK7 and CK20, and a negative result for PSA. On January 26, 2013, the patient was diagnosed with systemic multi-site metastases from ureteral UC.

Due to the patient's poor performance status, only two cycles of intravenous gemcitabine (1,800 mg, days 1 and 8, every 21 days plus cisplatin (500 mg, day 1 every 21 days) were administered. The patient succumbed to disease progression 4 months later (June 2013). From diagnosis to mortality, the patient survived for ~6 months.

## Discussion

The present study describes a delayed diagnosis of ureteral UC due to the lack of pathological evidence. As the patient refused to undergo endoscopic examinations again, it is unknown whether there were synchronous or metachronous ureteral tumors in other locations of the urinary system.

Ureteral UC is a rare malignant tumor. The most common clinical manifestations of ureteral UC are hematuria, increased urinary frequency, dysuria and pain. Pyuria and a palpable mass are much less frequently observed (1). Bone is one of the common metastatic sites of ureteral UC (7,8). Due to the drainage through the pelvic veins into the lumbar plexus, the bone metastases of ureteral UC most commonly affect the

spine (8). Although information on the type of bone destruction of ureteral UC is limited, an osteoblastic or a mixed osteolytic-osteoblastic pattern of bone destruction of transitional cell carcinoma from the bladder has been reported (9). UC should be therefore be preferentially considered as a primary tumor for osteoblastic metastasis of the spine besides prostate cancer.

However, all the typical clinical manifestations of ureteral UC were not observed in the present patient. The patient was not aware of the condition until thoracodorsal pain occurred when the disease progressed to bone metastases. The lack of pathological evidence significantly delayed the diagnosis of the primary tumor (the negative result of the first bone marrow biopsy may have been caused by an unsuitable puncture site), even though radiographic examination significantly suggested ureteral UC, and the bone metastases of the patient were osteoblastic and mainly involved the spine.

Currently, imaging and endoscopy, combined with pathological examination, are the main diagnostic approaches for UC (10-12). According to the present study, a more efficient diagnostic method is required. However, pathological evidence remains the current golden criterion for a ureteral UC diagnosis. Hence, the difficulty in achieving pathological evidence (as reported in the present study) will delay the diagnosis, no matter which diagnostic method the patient received or how efficient this was. Notably, in other tumors with the same situation (e.g., leptomeningeal metastasis), the National Comprehensive Cancer Network guidelines allow clinicians to make the diagnosis without pathological evidence (13). The guidelines offer multiple diagnostic criteria for such a unique situation. Accordingly, the possibility of new diagnostic criterion that do not rely on the pathology of primary foci should be considered in ureteral UC.



According to the medical history of the patient, the risk of UC was high in the present study. Although there is currently insufficient evidence to recommend a screening test for the whole UC population (14,15), a screening test should be recommended for the sub-population who are at high risk. Recently, UC of the bladder and the upper tract have been noted to represent two distinct diseases with practical, anatomical, biological and molecular differences (16). Hence, a screening test of UC should consider the differences between the two distinct diseases. From cytology to biomarkers, a number of novel approaches to screen UC in high-risk patients have been investigated (17,18). Compared with cytology, using cost-efficient high-performing urinary biomarkers may be more beneficial in these particular patients (14). Moreover, cytology may not be appropriate to be used as a single screening test on the basis of the current study results. Hence, more attention should be aimed at the investigation of using combination strategies for the screening test in the sub-population at high risk.

In conclusion, the present study reports the case of a patient with ureteral UC presenting with osteoblastic metastases, in which the diagnosis was delayed due to the lack of symptoms and pathological evidence. Considering the possibility of asymptomatic ureteral UC and negative pathology, a suitable screening test should be recommended for high-risk patients. Additionally, a more efficient diagnostic method is required. Moreover, the possibility of new diagnostic criteria that do not rely on the pathology of primary foci in ureteral UC should be considered due to the difficulty in achieving pathological evidence in certain patients.

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