Case Report

Diagnosis of Upper Urinary Tract Urothelial Cell Carcinoma by Urine Cytology in a Patient with Valvular Heart Disease: A Case Report

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A 58-year-old male was admitted to the hospital with severe gross hematuria and many comorbidities such as rheumatic heart disease and severe mitral valve stenosis. Because of atrial fibrillation, the patient took anticoagulant drug for stroke prevention. The patient was requested to stop anticoagulant agents and received blood replacement therapy for blood loss after hospitalization. Ureterorenoscopy was unable to visualize or biopsy the mass due to a massive blood clot. Urine cytology of left and right ureter showed high-grade urothelial carcinoma (HGUC) and few suspicious cells, respectively. Computed tomography angiography (CTA) of the whole abdomen revealed blood clot in the upper pole calyx and renal pelvis of the left kidney as well as the urinary bladder, but no abnormal enhancing lesion. The patient underwent the standard treatment for upper tract urothelial carcinoma (UTUC) with laparoscopic radical nephroureterectomy (RNU) with bladder cuff excision because the consulted cardiologist suggested to restart anticoagulant agents as soon as possible. Surgical pathology analysis revealed high-risk tumors with multiple low grade papillary urothelial carcinoma. The patient required long term follow-up. Here, the authors reported a case of UTUC with valvular heart disease, earlier diagnosed by using only positive urinary cytology, rather than by radiological examinations and/or related symptoms before definite treatment.

Keywords: Urine Cytology; Upper tract; Ureter; Ureteroscopy; Urothelial carcinoma; False positive; Nephroureterectomy

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Transitional cell carcinoma (TCC) of the upper urinary tract is less common and often presents a diagnostic challenge[1]. The gold standard diagnosis and treatment of upper tract urothelial carcinoma (UTUC) is surgical histopathological diagnosis and nephroureterectomy with excision of bladder cuff, respectively[2].

Imaging of the upper tract, urine cytology, and ureteroscopy may also play a key role in the diagnosis and initial workup of UTUC[3]. Computed tomography urography (CTU) of UTUC protocol is of critical importance in screening and staging of patients and has high sensitivity at 88% to 100% and specificity at 93% to 100%[4]. Actually, controversies exist for the proper management of patients with UTUC, including staging, surgical management, and prevention of bladder recurrence[5]. While urine cytology may give falsely positive results, urologists show reluctance to accept urinary cytology as a diagnostic procedure in urologic cancer[6]. Conversely, the authors highlight the present patient with rheumatic heart disease and severe mitral valve stenosis of UTUC diagnosed only with positive urine cytology before definite operation. The present study was approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (COA. MURA2022/407).

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Case Report

In 2022, a 58-year-old male patient presented with a background history of primary myelofibrosis,

thalassemia, G6PD deficiency, rheumatic heart disease, and severe mitral valve stenosis. The patient underwent mitral valve replacement in 2018 and paravalvular leaks (PVL) closure in 2020 due to severe prosthetic PVL. The patient suffered from atrial fibrillation and was on warfarin 35 mg/week for stroke prevention. The patient did not have a history of smoking.

On admission, the patient presented to the authors' hospital with severe painless gross hematuria for three days. Physical examination showed anemia and abdominal distention with marked splenomegaly, but no evidence suggesting malignancy was found. The patient was requested to stop anticoagulant agents after hospitalization and received blood replacement therapy for blood loss.

The patient underwent computed tomography angiography (CTA) of the whole abdomen, which showed no malignant lesion (Figure 1). Both kidneys were normal size and there was no change in a 1.5 cm right renal cyst at mid zone. Hyperdense contents were seen in the upper pole calyx and renal pelvis of the left kidney as well as at the dependent part of the urinary bladder lumen, considering hematomas or blood clots. No stone or enhancing mass was seen. In addition, the follow up computed tomography (CT) of the whole abdomen two weeks later revealed an irregularity of the upper pole calyx, where the blood clot was seen on the first CT scan (Figure 2).

Laboratory investigation indicated that urine voided cytology was negative for high-grade urothelial carcinoma (HGUC). Conversely, urine cytology of left and right ureter showed HGUC and few suspicious cells, respectively (Figure 3). Consequently, the patient underwent cystoscope and rigid ureteroscopic examination after stopping the anticoagulation more than a week, while the bleeding continued the second week. On cystourethroscopy, mild generalized cystitis with mild trabeculation and a 2.3 cm blood clot at the left ureteral orifice and no tumor or stone was found. These results indicated bleeding from the left upper urinary tract. However, ureteroscopic procedure was terminated explicitly due to bleeding with many clots and difficult visualization. Since the interruption of anticoagulation can increase the risk of thrombotic events during and after surgery, three week later the patient underwent left laparoscopic radical nephroureterectomy with bladder cuff excision. Unfortunately, the patient made an unplanned return to the operating room for evaluation of ongoing bleeding and a splenectomy was conducted due to a complication involving splenic injury. The

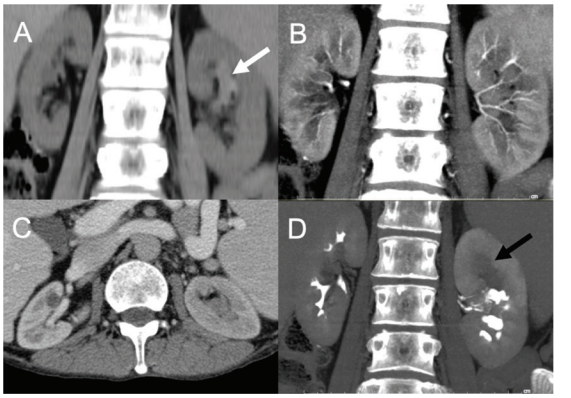

Figure 1. Computed tomography angiography (CTA) of the whole abdomen was performed on the admission date. Coronal view of non-enhanced image (A) revealed hyperdense contents (white arrow), 40 to 50 Hounsfield unit (HU) in the upper pole calyx and renal pelvis of the left kidney, representing blood clots. Coronal view of angiographic image (B) showed no active contrast extravasation. Axial view of venous image (C) showed no abnormal enhancing lesion of the left kidney. Coronal view of excretory phase image (D) revealed no or delayed contrast excretion into the upper pole calyx (black arrow). Multiple small contrast streaks in the left renal hilum represented pyelolymphatic backflow.

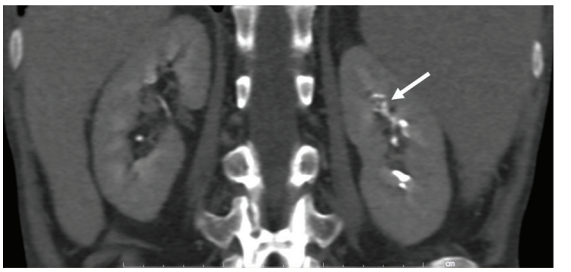

Figure 2. Computed tomography scan of the whole abdomen was performed two weeks later. On the excretory phase, the maximal intensity projection (MIP) image revealed an irregularity of the left upper pole calyx (arrow). Blood clots were resolved.

patient was safely discharged after 28 days from the hospital without recurrence of hematuria.

The authors could not find any macroscopic tumors in the gross features of the surgical specimen. However, microscopic pathologic analysis revealed non-invasive papillary urothelial carcinoma, which was interpreted as pathological stage pTa urothelial carcinoma (Figure 4). Tumor had three foci at 1) minor calyx, upper pole sized 0.3 cm in greatest dimension, 2) major calyx, middle pole sized 0.3 cm in greatest dimension, and 3) renal pelvis sized 0.45 cm in greatest dimension. Bladder cuff margin, vascular margin, and perinephric fat margin were uninvolved by carcinoma. The Hospital's Ethics Committee

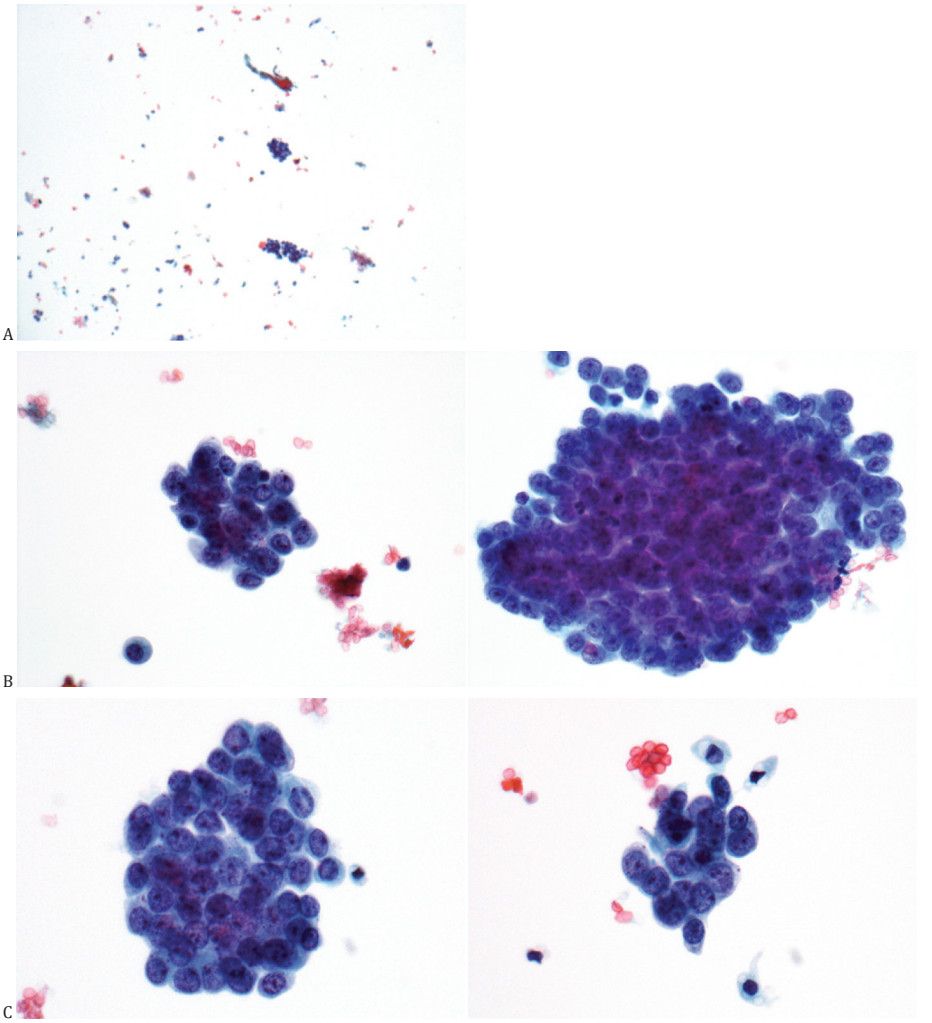

Figure 3. (A) The cytopathological examination showed occasional neoplastic cells in singles and loosely cohesive groups/background containing scattered red blood cells and minimal leukocytes: Low power 40x. (B) Neoplastic cells (arranging in loosely cohesive groups and single cells/showing medium to large oval to irregular hyperchromatic and pleomorphic nuclei, focal distinct nucleoli and scant cytoplasm; N/C ratio >0.7): High power 600x. (C) cytomorphologic details of neoplastic cells (medium to large oval to irregular hyperchromatic and pleomorphic nuclei, focal distinct nucleoli and scant cytoplasm; N/C ratio >0.7): Higher power 600x + close up.

Approved the present case study and informed consent was obtained from the patient.

Discussion

Primary UTUC is a malignant disease of the urothelial cell lining upper urinary tract from renal calyces, pelvises, and ureter down to the ureteral orifice. It commonly presents with hematuria[7]. UTUC is an uncommon cancer of the urinary tract and accounts for only 5% to 10% of UCs[8].

Urine cytology is an important investigation for the detection of urothelial neoplasia. There are two principal indications, as hematuria, and as a surveillance tool for patients with a history of TCC of genitourinary system[9]. For the Paris System (TPS) Working Group, the urine cytology was classified into six categories, negative for high-grade urothelial carcinoma (NHGUC), atypical urothelial cells (AUCs), suspicious for high-grade urothelial (SHGUC), HGUC, or low-grade urothelial neoplasm (LGUN), and other malignancies such as primary or metastatic and miscellaneous lesions[10].

The authors' institution reported a 95% accuracy rate for urine cytology for diagnosing invasive high-grade tumors and carcinoma in situ. Urine cytology has less sensitivity but high specificity to detect urothelial carcinoma[11]. However, false-positive results appear in patients with human polyomavirus

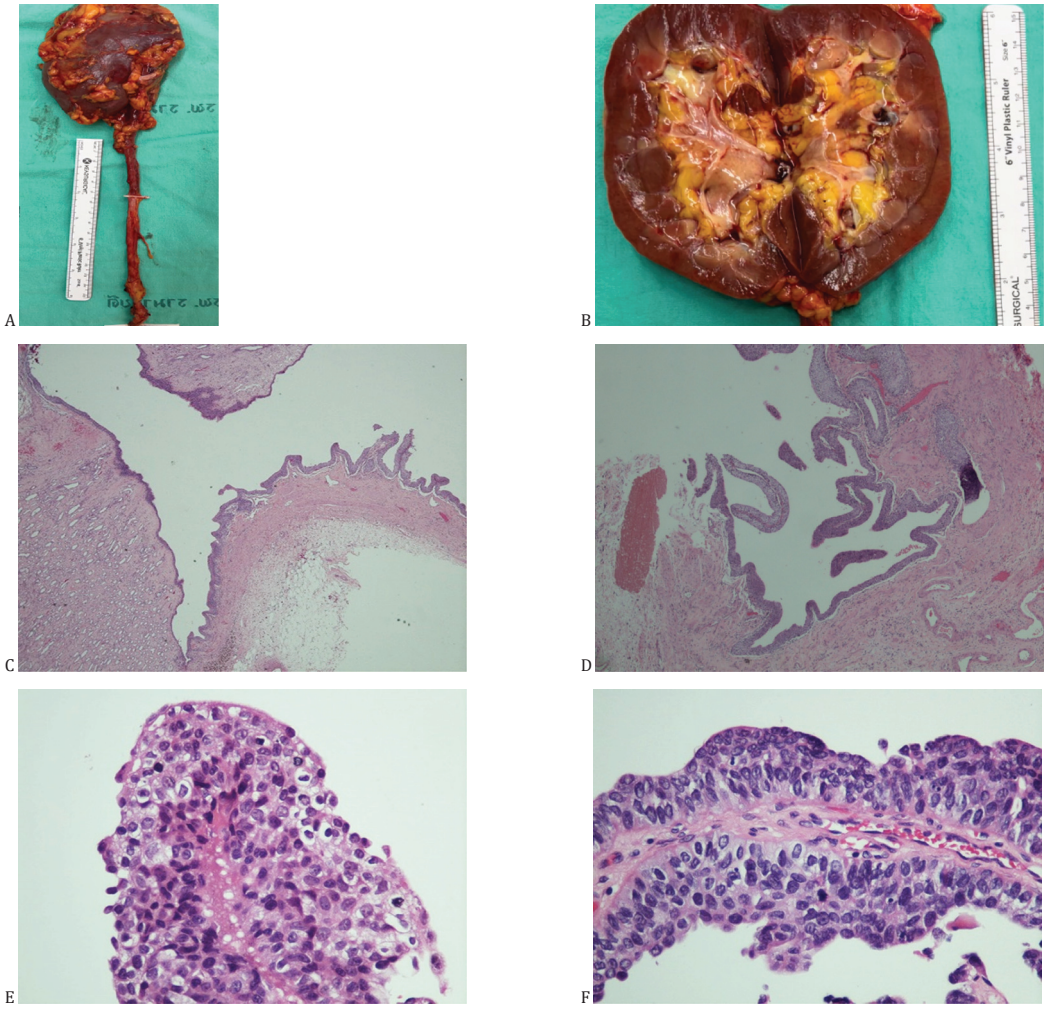

Figure 4. Postoperative view of specimen. (A) Gross specimen of left nephroureterectomy with bladder cuff excision. (B) Gross pathology of the resected kidney does not demonstrate any abnormality. (C, D) The histopathological examination of low power view showing small papillary excrescences of neoplastic urothelial cells project into the renal calyces. The base of lesions are smooth and show no evidence of subepithelial connective tissue invasion: H&E stain 20x, H&E stain 40x. (E, F) The histopathological examination of high-power view showing fibrovascular cores lined by stratified growth of neoplastic urothelial cells with nuclear size variation, moderate to marked nuclear pleomorphism, prominent nucleoli, and frequent mitotic activity: H&E stain 400x.

infection, bladder stones, and chemotherapy[12]. Therefore, a combination diagnosis of the patients' history, urine cytology, imaging of the upper tract, and histopathology are the appropriate practice for making a definite diagnosis, leading to proper management and follow-up of patients[11]. By contrast, ureteroscopic management (URS) has a clearly defined role in low-risk UTUC[13]. The present case demonstrated limited evidence for diagnosis with URS during acute and chronic bleeding form UTUC.

The purpose of the current study was to determine how to deal with patients suffering from rheumatic heart disease and severe mitral valve stenosis, on antithrombotic agents and that had only positive cytology for HGUC, but normal results of other examinations. The final clinical aims were to avoid over investigation and to prevent delayed diagnosis. Because of the most important ethical considerations in the present case before the definite operation, the authors discussed clearly with the patient and made decisions together. Incidentally, the surgeon pointed out that anticoagulation aggravated the tumor bleeding, not the underlying diseases. The patient and family agreed to undergo left laparoscopic radical nephroureterectomy with bladder cuff excision because the consulted cardiologist suggested to restart anticoagulant agents as soon as possible. The

patient accepted the possibility that urine cytology sometime produced false positive. However, the authors believed urinary cytology was a reliable procedure in the diagnosis of urologic malignancies as previously reported[14]. The patient was also informed that nephron-sparing treatments were not a valuable alternative or equivalent to the radical approach in the present case.

The present case needed a multidisciplinary approach including urology, anesthesiology, cardiology, and hematology[15,16]. The patient had comorbidities and was on warfarin 35 mg/week for stroke prevention. The urologist needed to understand the safe and effective use of oral anticoagulants (AC) and antiplatelets (AP) prophylaxis, and the risks associated with their withdrawal[17]. Douketis et al reported that most patients with atrial fibrillation on chronic anticoagulation, similar to the present case, did not require perioperative bridging in the absence of specific risk factors such as prior stroke[18]. Sfakianos et al reported that in patients undergoing nephrectomy on chronic anticoagulation who required bridging, there was a higher overall complication rate, transfusion rate, and length of stay than expected[19]. The present patient was requested to stop antithrombotic agents prior to the operative procedure and restart as soon as possible after surgery, which is usually done to prevent cardiovascular complication.

In addition, the follow up CT, which was two weeks later, revealed an irregularity of the upper pole calyx, where the blood clot was seen on the first CT scan. This abnormality could represent early urothelial neoplasm. Severe gross hematuria, unilateral/localized, in the present patient with early UTUC might be precipitated by anticoagulant therapy.

UTUC is a multifocal malignant tumor that tends to reoccur after treatment. In addition, the multicenter study demonstrated that preoperative positive urine cytology correlated with a significant 49% increased risk of intravesical recurrence[20]. Therefore, the patient was treated with Mitomycin C instilled into bladder after the operation to prevent recurrence of the cancer in the bladder.

Finally, a significant predictor of more advanced disease, non-organ confined disease, loco-regional, and distant recurrence is high-grade cytology as in the present case[21,22]. According to the EAU 2020 guidelines, the patient has high-risk if tumors included any high-grade status, thus, lesions larger than 2 cm, and presenting with multifocality[23]. The patient requires prolonged post-operative surveillance.

What is already known in this topic?

A 95% accuracy rate for urine cytology for diagnosing invasive high-grade tumors and carcinoma in situ. Urine cytology has less sensitivity but high specificity to detect urothelial carcinoma.

What this study adds?

The present case is the first to determine how to deal with patients who suffer from rheumatic heart disease, are on antithrombotic agents, and have only positive urine cytology. Since the interruption of anticoagulation can increase the risk of thrombotic events during and after surgery, the patient required definite treatment as soon as possible.

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Conflicts of interest

The authors declare no conflict of interest.

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