Case Report

The unusual nested carcinoma of the renal pelvis

Kiran Agarwal, Neha Kawatra Madan, Meenu Pujani, Meenakshi Rao

Department of Pathology, Lady Hardinge Medical College, New Delhi, India

Abstract Invasive urothelial carcinoma has a potential to show divergent differentiation. Several uncommon morphological variants have been described in the recent past. One such rare type is the nested variant of urothelial carcinoma. Most of the published reports depict occurrence of this variant in the urinary bladder. We report an unusual presentation of this uncommon entity in the renal pelvis of a 54-year-old lady who presented with widespread skeletal metastases without any urinary symptoms.

Key Words: Metastases, nested variant, renal pelvis

Address for correspondence:
Dr. Neha Kawatra Madan, Department of Pathology, Lady Hardinge Medical College and Associated Hospitals, New Delhi - 110 001, India.
E-mail: nehakawatramadan@gmail.com
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INTRODUCTION

Invasive urothelial carcinoma has a marked potential for divergent differentiation. In recent past, several uncommon morphological variants have been included in the recent WHO classification of urothelial tumors.[1,2] These include, the nested variant, micropapillary variant, plasmacytoid variant, lipoid cell variant, signet ring cell variant, urothelial carcinomawith rhabdoid features, with osteoclastic giant cells and with trophoblastic differentiation. Awareness of the morphological variants is essential in order to avoid misinterpretation in diagnosis, which may have a significant impact on patient risk stratification and management. The nested variant of urothelial carcinoma (NVUC) of the renal pelvis although extremely rare, is a special entity as this variant exhibits a bland morphology but carries a dismal prognosis. It constitutes 0.3% of all infiltrating urothelial tumors of the bladder.[3,4] However, its incidence in the renal pelvis is very rare, and to the best of our knowledge, only two cases have been reported in the literature.[5,6]

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The present report describes the clinical and pathological features of an unusual case of NVUC of the renal pelvis, with widespread bony metastases and no urinary complaints.

CASE REPORT

A 54-year-old postmenopausal lady presented with pain in the right arm and right upper thigh of three months duration. There was no history of trauma. General physical examination revealed bilateral axillary and inguinal lymphadenopathy. There was mild tenderness on palpation over the right arm and thigh; however, no definite swelling was noted. Rest of the systemic examination was normal. Complete hemogram, liver and renal function tests, and urinalysis were within normal limits.

The patient gave history of attending a primary health center where a provisional diagnosis of bone tuberculosis was made considering its high incidence in a developing country like india, and the patient was started on antitubercular therapy (ATT). The patient was referred to a higher center with no signs of improvement on ATT. Radiological investigations demonstrated a mass in the right radius and right iliac bone, and a fine needle aspiration cytology performed from these sites showed features of a metastatic carcinoma.

For further evaluation and investigation of the primary site, a whole body PET-CT and 99mTc-MDP bone scan were done. 99mTc-MDP bone scan exhibited abnormal increased tracer concentration in multiple hot spots in calvarium, ribs, right ilium, and right radius; suggestive of skeletal metastases. Whole body PET-CT scan showed metabolically active large lytic destructive lesions in multiple bones and a subtle enhancing soft tissue in midpolar region of left kidney. The patient was referred to our center for further management. Based on the above investigations, a clinical diagnosis of skeletal metastases with a possible primary in the kidney was considered. Three consecutive urine samples were sent for cytology, which was negative for malignant cells.

With the possibility of renal primary, the patient was taken up for laparotomy. Peroperatively, both kidneys appeared unremarkable, except that the left renal pelvis and upper one third of left ureter were indurated with adhesions present between them and the surrounding tissue. Rest of the visualized intra-abdominal structures were within normal limits. Hence, a left nephro-ureterectomy was performed.

Gross specimen consisted of left kidney with left adrenal gland and perinephric fat altogether measuring 9 × 6 × 5 cms, enclosed within the gerota's fascia with attached ureter of 11 cm length. On cutting open, a grey-white tumor was identified in the wall of the renal pelvis, which was extending into one of the calyceal walls and into the upper 7 cm of the ureter [Figure 1a]. No papillary growth was identified. Rest of the kidney and adjacent adrenal gland appeared uninvolved. Regional lymph nodes were not included in the specimen.

Microscopically, a tumor was seen arising from the urothelium with massive infiltration of the lamina propria [Figure 1b]. The tumor cells were arranged in the form of irregularly distributed variable-sized organized nests, few of which showed cribriform and microcystic pattern. The cells were medium-sized with mild to moderate anisocytosis, moderate amount of pale eosinophilic cytoplasm, rounded nuclei, granular chromatin with inconspicuous nucleoli in most of the cells. No significant nuclear polymorphism was noted in the majority of the tumor; however, few large tumor cells displaying some atypia were seen in the deeper areas. Mitoticfigure were rare with one mitoticfigure identified per 10 high power fields. Small irregular nests of tumor cells were seen invading in between the deep muscle bundles and also perineurally. Nests of tumor cells were seen invading into the pericalyceal areas of lower half of left kidney. Sections from pelvis and ureter showed tumor cells infiltrating through the wall of the pelvis and the ureter into the peripelvic fat. Renal vessels, resected margin of the ureter, and left adrenal gland were, however, free of tumor.

The differential diagnosis included the NVUC and neuroendocrine tumor, for which immunohistochemistry was performed. The tumor cells were diffusely immunoreactive for Pan CK, CK 7, CK 20 [Figure 2a] and were negative for neuroendocrine markers NSE and Chromogranin [Figure 2b]. Based on these findings, final diagnosis of nested variant of urothelial carcinoma was made.

In view of the widespread metastases, postoperatively, the patient was put on systemic chemotherapy including cisplatin and gemcitabine. Till date, she has received three cycles of chemotherapy, but her clinical condition has not improved in these three months.

DISCUSSION

Although majority of the urothelial carcinomas of the renal pelvis are of papillary nature, some rare histological variants have been identified, which are of clinical importance. One such rare variant as described in the index case is the nested variant. A number of cases of NVUC have been reported in the urinary bladder.[7-9] However, in a recent large scale study including 108 cases of high grade urothelial carcinoma of the renal pelvis, not even a single one turned out to be NVUC.[11]

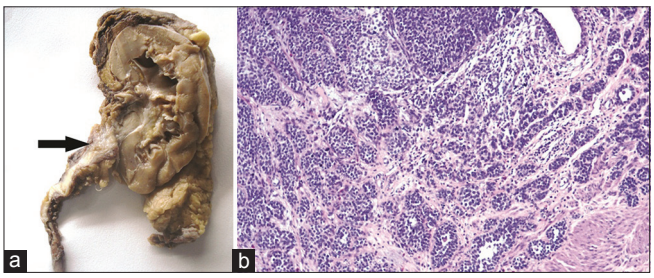

Figure 1: (a) Left panel – Gross specimen of left kidney showing a grey white tumor in the pelvis and ureter. (b) Right panel – tumor originating from the surface urothelium of renal pelvis with massive infiltration of lamina propria and muscle layer (H and E, ×40)

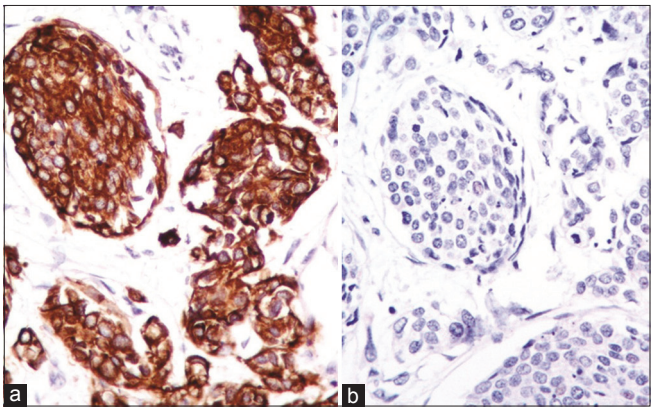

Figure 2: (a) Left panel – Tumor nests showing strong cytoplasmic positivity for CK 7 (IHC ×400). (b) Right panel – Tumor nests negative for Chromogranin (IHC ×400)

To the best of our knowledge, very few cases of NVUC have been reported in the renal pelvis so far.[5,6,12]

These few cases involved middle-aged males and females in whom the renal mass was incidentally discovered and was confined to the kidney. Most of the reported cases of NVUC show a male predominance with age range of 45-97 years, and gross hematuria is the most common sign. In the present case, a 54-year-old lady presented with widespread bony metastases before the lesion could be detected in the kidney. She did not have any urinary complaints, and repeated urine cytology was negative for malignant cells.

Microscopically, the nests of NVUC have a relatively bland appearance, which may occasionally show a microcystic or cribriform pattern and rarely small tubules.[13,14] The nuclei show mild anisonucleosis and relatively bland chromatin with a tendency for increasing atypia with increasing depth of invasion. The cytologic features of nested variant are subtle and can be confused with reactive changes, hence it can be missed on urine cytology.[10] Moreover, preference of this variant for a submucosal growth rather than an exophytic one can be a reason for the absence of urinary signs and symptoms leading to a possible delay in the diagnosis.

The differential diagnosis includes benign florid von Brunn's epithelial nests, cystitis glandularis, cystitis cystica on one hand and malignant tumors like carcinoid and paraganglioma on the other.[1,14]

The nests of NVUC are small, closely packed and irregularly distributed as opposed to florid Brunn's nests as described in NVUC of the urinary bladder.[8] But, in the renal pelvis, these two entities may show a strikingly similar morphology.[15] The distinguishing characteristics of NVUC are its infiltrative nature with deep muscle invasion, tendency for increasing cellular atypia in the deeper areas, and most importantly its high metastatic potential.[8,14,15] It has been suggested that these proliferating Brunn's nests could be the precursor of nested carcinoma. However, malignant transformation of these benign lesions has never been reported. Rather, a coexistent severe dysplasia of the urothelium has been observed in these patients as was seen in our case, but the exact urothelial origin is unclear.[14] For benign lesions, immunohistochemistry is not very helpful as they will stain positive for the cytokeratins and other epithelial markers, and no significant difference has been noted in their positivity for p53 and Ki67.[3] Thus, differentiation from benign Brunn's nests can be achieved on histomorphological features only.

Other differential diagnoses include neuroendocrine tumors like carcinoid and paraganglioma. Immunohistochemically, negativity for neuroendocrine markers: NSE and Chromogranin can differentiate these lesions from carcinoid and paraganglioma.

Wasco *et al*.[12] in their recent report on 30 cases of NVUC of the urinary tract concluded that, when compared with pure high-grade UC, NVUC was associated with high incidence of muscle invasion at transurethral resection, extravesical disease at cystectomy, and metastatic disease.

It is not certain whether the aggressive nature of the tumor cells, or the frequent delay in diagnosis is responsible for a more advanced stage of the disease at the time of presentation as compared to conventional urothelial carcinoma.[7,13]

Radical surgical resection followed by chemotherapy and radiotherapy is the treatment usually given, but the patients fare badly. Optimal management of this rare entity is yet to be determined.

Although NVUC of the renal pelvis is an extremely rare neoplasm, awareness of this unusual variant is important to distinguish it from classic urothelial carcinoma and other benign and low grade malignant lesions because of its deceptively bland appearance and worse prognosis.

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