Primary small cell carcinoma of the ureter

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Primary small cell carcinoma of the ureter is a rare clinico-pathological entity. We present a report of primary ureteric small cell carcinoma and pathological correlates.

Key Words: ureter, carcinoma, laparoscopy, chemotherapy

Background

Primary small cell neuroendocrine carcinoma (SCC) of the genitourinary system is rare. It has been reported to occur most commonly in the bladder, and very rarely in the prostate and kidney. Extrapulmonary SCC has been recognized as a clinico-pathological entity distinct from small-cell lung cancer (SCLC); however, they are both aggressive tumors with a high rate of metastasis. Several theories on the origin of extrapulmonary SCC have been postulated, but it remains unclear.[1] We report a case of primary SCC of the ureter, with the patient currently stable on adjuvant chemotherapy. Pathological correlates are reviewed.

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Case report

A 67-year-old Caucasian male was incidentally found to have left hydronephrosis while being worked up for loose bowel movements. His medical history includes hypertension, type II diabetes, smoking, and previous cholecystectomy. Intravenous pyelogram and retrograde pyelogram revealed hydronephrosis and filling defect of at the distal left ureter. The right kidney was normal. Cystoscopic examination showed an unremarkable bladder, except for evidence of a mass extruding from the left ureteric orifice. Urine cytology was inconclusive. A computerized tomography (CT) scan with contrast revealed moderate to severe left hydronephrosis, a large soft

tissue mass filling and obstructing the mid and proximal portion of the distal ureter measuring 3.5 cm x 2.8 cm x 6.0 cm Figure 1. There was also evidence of enlarged 2.7 cm mass in the retroperitoneum in a left periaortic location. Given his long-standing left hydronephrosis, a MAG3 nuclear renal scan was obtained to assess differential renal function prior to nephroureterectomy and his risk of post-operative dialysis. Function in the right kidney was 89% versus 11% in the left. Chest radiographs were negative for any evidence of metastatic disease.

We performed laparoscopic left radical nephrectomy and peri-aortic lymph node dissection, and open distal left ureterectomy and partial cystectomy. The laparoscopic portion of the operation was uncomplicated. At the time of the open procedure, we noted the tumor at the mid-ureter encasing and invading into the local mesentery of the

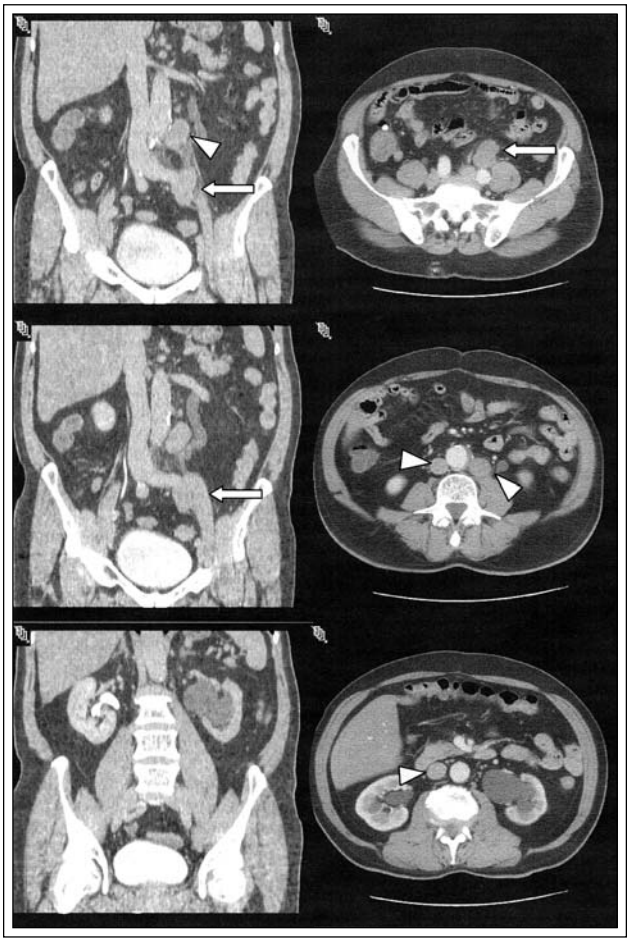

Figure 1. Preoperative computerized tomography scan revealed a mid-ureteral mass with adjacent extension (arrow) and enlarged peri-aortic lymph nodes (arrow head).

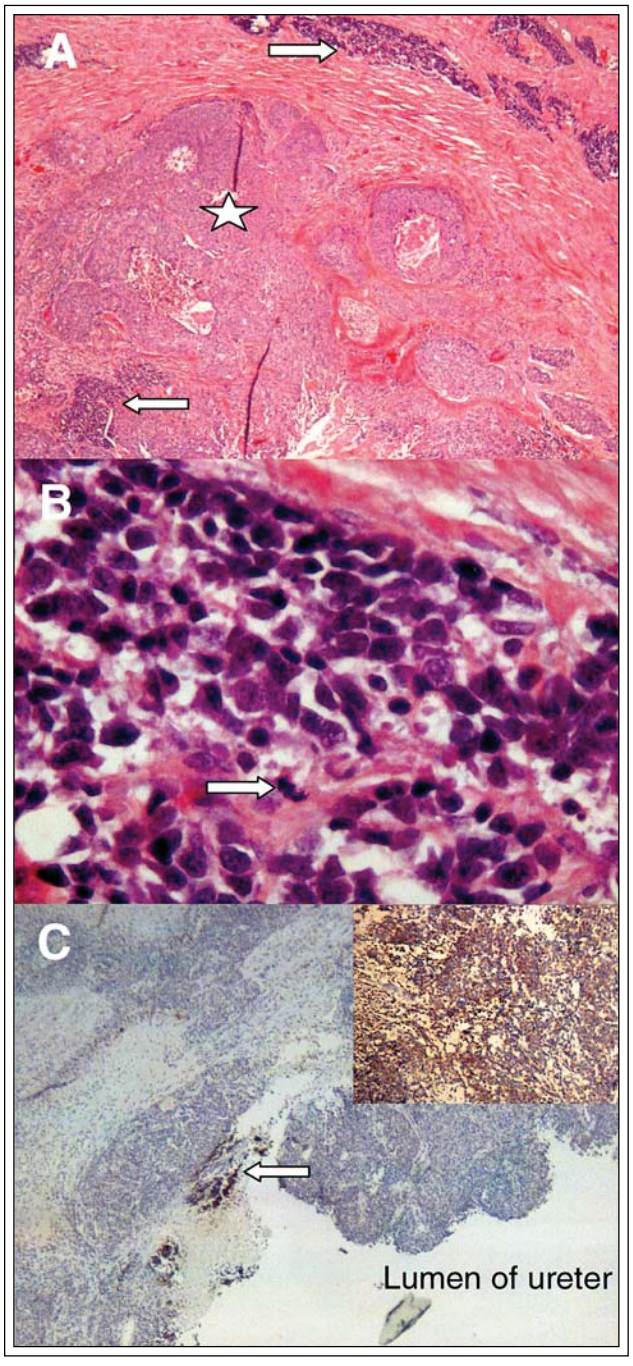

Figure 2. Histopathology. A. Low power image (25X) of ureter showing high grade transitional cell carcinoma (TCC) (star) with adjacent small cell carcinoma (arrows). B. High power image (400X) of SCC showing cells with high N/C ratio, nuclear molding, evenly dispersed chromatin, inconspicuous nucleoli and mitoses (arrow). C. Synaptophysin staining (25X). The high grade TCC is negative and the areas of SCC are positive (arrow). Inset (400X) shows another area of SCC strongly positive for synaptophysin.

bowel, and this was resected. The patient did well postoperatively and discharged home on post-operative day 4.

Microscopic examination of the mesentery, peri-aortic lymph nodes, and ureter showed extensive SCC. The cells had a high nuclear cytoplasmic ratio with nuclear molding and evenly dispersed chromatin. There was also high mitotic rate and abundant apoptosis. Immunohistochemistry showed staining for cytokeratin 7 and cytokeratin 20, as well as for the neuroendocrine markers synaptophysin, chromogranin, and equivocal staining for neuron specific enolase Figure 2. Thyroid transcription factor (TTF-1), a marker of lung and thyroid neoplasms, was negative. The cuff of bladder was negative for malignancy. The kidney had features of chronic pyelonephritis.

Referral was made to the Cancer Center, and adjuvant chemotherapy recommended. The patient has received monthly cycles of etoposide and platinum for 7 months with no evidence of recurrent disease (NED) on 6 month CT scan.

Discussion

Extrapulmonary small cell carcinoma has been reported in a variety of organ systems, including ovary, cervix, pancreas, colon, stomach, liver, larynx, breast, kidney, and prostate. The incidence of SCC of the bladder is estimated around 0.5% – 0.7% of primary bladder tumors (reviewed by Sved et al[1]). Although rare, these tumors behave as aggressively as SCC of the lung, and they both appear to be biologically related in that they may represent systemic disease processes and present with early metastasis. Interestingly, there are only few reports of SCC of the ureter in the world literature, namely in the Asian literature. SCC of the ureter was first reported in 1983 by Maeda et al,[2] and since then there have only been 16 cases reported in the literature. However, SCC of the ureter appears to share similar clinico-pathological features with SCC of the bladder.

The histological features of the case presented here fulfilled the criteria of SCC established by the World Health Organization.[3] The immunohistological features of SCC of ureter and bladder appear to be similar. Positivity for chromogranin has been shown to be the most specific marker of SCC.[4] Moreover, the pattern of cytokeratin staining has been used previously to characterize adenocarcinomas, particularly lung adenocarcinomas that display cytokeratin 7 positive/cytokeratin 20 negative staining pattern[5]. In addition to this cytokeratin phenotype, Chhieng et al suggested that a carcinoma is most likely of a primary lung tumor if it also demonstrates either positivity for TTF-1 or PE-10[6]. The pattern of cytokeratin 7 positive/cytokeratin 20 positive/TTF-1 negative seen in our case suggests that it was not of lung origin. The origin of SCC of the genitourinary system remains unclear, however, there have been speculations that it may arise from an urothelial stem cell rather than from a specific neuroendocrine precursor cell[7].

Prognosis of SCC of the bladder is poor and surgery is not curative. Cheng et al have reported the 1-year, 3-year, and 5-year specific survival rates to be 56%, 23%, and 16%, respectively.[7] There is, however, some evidence to suggest that preoperative chemotherapy with regimens containing etoposide (topoisomerase II inhibitor) and cisplatin (alkylating agent) may play a role in extending survival.[8] Our patient is currently being managed with monthly chemotherapy of etoposide and platinum and is doing very well 7 months after surgery with NED. Tsutsumi et al have employed similar approach with nephroureterectomy followed by etoposide and cisplatin with an 8-month recurrence free period.[9] However, Ishikawa et al attempted neoadjuvant methotrexate, epirubicin, and cisplatin followed by radical nephroureterectomy, but this patient died 5 months later.[10] Although there are limited clinical trials investigating the effectiveness of etoposide and cisplatin in the management of extrapulmonary SCC,[11] this regimen has become widely accepted for patients with small cell lung carcinoma. Recent results from a phase II trial have shown that this regimen achived up to 69% overall response rate and 39% 1-year survival rate in patients with SCLC.[12]

Thus, adjuvant etoposide and platinum-based chemotherapy following debulking surgery may extend survival of patients with SCC of the ureter. In summary, we present a case of primary SCC of the ureter with local mesenteric invasion, completely resected, and currently stable with NED on monthly maintenance chemotherapy. □

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