**CASE REPORT**

**CA125-producing Clear Cell Adenocarcinoma Arising From the Upper Ureter and Renal Pelvis**

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Clear cell adenocarcinomas similar to those found in the female genital organs can arise in the lower urinary tract of both women and men. Clear cell adenocarcinomas occurring in the upper urinary system are exceedingly rare. Here, we present a case of clear cell adenocarcinoma arising from the upper ureter and renal pelvis of a postmenopausal woman with a ureteral stone. The patient had elevated serum levels of cancer antigen (CA) 125 (103.80 U/mL) and CA19-9 (151.96 U/mL). The tumor showed typical features of tubulopapillary structures lined with clear-to-eosinophilic cytoplasm and frequent hobnail configuration. The tumor cells were immunoreactive for cytokeratin 7, cytokeratin 20, carcinoembryonic antigen and CA125, but negative for PAX-2 and α-methylacyl coenzyme A racemase. Given the presence of intestinal and squamous metaplasia of the adjacent urothelium, we propose that this clear cell adenocarcinoma developed through a metaplastic process. The tumor behaved so aggressively that the patient developed multiple metastases and died of the disease 5 months after radical nephroureterectomy. [J Chin Med Assoc 2010;73(1):40–43]

**Key Words:** CA125, CA19-9, clear cell adenocarcinoma, upper urinary tract

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**Introduction**

Clear cell adenocarcinoma of the female genital tract has been well known in association with prebirth exposure to diethylstilbestrol since 1971.¹ Clear cell adenocarcinoma is thought to originate from the Müllerian embryonal system.¹ Clear cell adenocarcinomas occur most often in the vagina, uterine cervix, endometrium and ovary. In the urinary system, similar tumors have been reported in the urethra, and urinary bladder with a female predominance.²⁻⁴ Clear cell adenocarcinomas arising in the upper urinary tract are extremely rare. We present an unusual case of cancer antigen (CA) 125-producing clear cell adenocarcinoma arising in the ureter and renal pelvis of a patient with a ureteral stone.

**Case Report**

A 73-year-old woman who had left flank pain for 3 months and a palpable mass over her left-side abdomen was admitted. Microhematuria and mild hypochromic anemia were noted. High serum levels of CA125 (103.80 U/mL; normal range, <35 U/mL) and CA19-9 (151.96 U/mL; normal range, <37 U/mL) were also noted, whereas the serum level of carcinoembryonic antigen (CEA) was within the normal range.

Intravenous pyelography, sonography and computed tomography demonstrated left renal and ureteral stones with severe hydronephrosis measuring up to 18 × 11 × 9 cm in renal size. No tumor mass could be detected anywhere including in the female genital tract using any of the imaging techniques above. The patient underwent nephrectomy and upper ureterectomy. Pathologic examination of the resected specimen revealed 2 stones, 1 measuring up to 2.0 × 1.5 × 0.7 cm in the renal pelvis and another spindle one measuring 1.5 × 0.7 × 0.6 cm impacted in the ureter just distal to the ureteropelvic junction. When the impacted ureteral stone was removed, an annular papillary tumor measuring 1.5 cm was found over the upper ureter, just distal to the stone (Figure 1). Microscopically, the superficial portion revealed papillary growth lined with a single layer...
Clear cell adenocarcinoma of the upper urinary tract of cuboidal cells, while the invasive portion consisted chiefly of tubulocystic structures (Figure 2A) with eosinophilic cytoplasm and frequent hobnail configuration (Figure 2B). A second component consisting of clear cells in a nesting pattern was present (Figure 2C). The tumor infiltrated the underlying smooth muscle wall of the ureter, nearby pelvic wall, and renal cortex (Figure 2D). Moderate nuclear atypia and occasional large nucleoli were observed. The stroma was desmoplastic and focally myxoid. The tumor cells were focally positive for periodic acid-Schiff and mucicarmine, and immunoreactive for cytokeratin 7 indicating a urothelial origin, cytokeratin 20 proving its enteric metaplasia, CEA proving its adenocarcinomatous nature, and CA125 indicating its relationship to high CA125 serum level and clear cell adenocarcinoma differentiation (Figure 3). The tumor was immunohistochemically nonreactive for vimentin which ruled out renal

Figure 1. An impacted ureteral stone just distal to the left ureteropelvic junction, and a 1.5-cm segment of annular villous tumor over the distal ureter contiguous to the ureteral stone.

Figure 2. (A) The superficial portion of the tumor revealed papillary growth lined with a single layer of cuboidal cells, while the invasive portion (arrowheads) consisted chiefly of tubulocystic structures (hematoxylin & eosin, 100×). (B) The tumor cells had eosinophilic cytoplasm with frequent hobnail configuration (arrows), and moderate nuclear atypia as well as occasional large nucleoli were observed (hematoxylin & eosin, 400×). (C) A second component consisting of clear cells in a nesting pattern was present (hematoxylin & eosin, 200×). (D) The tubulocystic tumor (arrows) diffusely infiltrated the hydronephrotic cortex (hematoxylin & eosin, 20×).
cell carcinoma, PAX-2 which excluded renal tubule derived tumor, and α-methylacyl coenzyme A racemase which excluded papillary renal cell carcinoma. The histomorphology and immunoprofile were typically consistent with those of clear cell adenocarcinoma. The adjacent urothelium exhibited squamous and intestinal metaplasia.

The patient did not receive adjuvant therapy because of her age and financial situation. Unfortunately, multiple pulmonary metastases were detected and she died of the disease 5 months later.

Discussion

Although clear cell adenocarcinomas resembling those in the female genital organs can occur in the lower urinary tract, such tumors are extremely rare in the upper urinary system. Reviewing the medical literature, only 2 cases have been reported in the renal pelvis and ureter under a diagnosis of “papillary adenocarcinoma” without specifying the histologic subtype. One of them was positive for CEA and CA19-9 and the other was also positive for CA125. Another ureteral tumor simply diagnosed as “adenocarcinoma” was reported to produce CA19-9. To our knowledge, there has not been a case specifically reported as clear cell adenocarcinoma in this anatomic location.

The tumor should be differentiated from other variants of glandular lesions of urothelial and renal cortical neoplasms. It is well known that urothelial carcinoma is capable of a wide range of divergent differentiation. Among the glandular types, the “not otherwise specified” and enteric types are the most common. Less frequent forms include mucinous, signet ring and villous tumors. These variants could be differentiated from ours by their distinctive histologic pattern. The tubulopapillary architecture and clear to granular cells with hobnail appearance are characteristic of clear cell adenocarcinoma. Our case lacked the conventional portion of urothelial carcinoma. The diagnosis is further supported by the high serum levels of CA125 and CA19-9, as well as the immunostaining of CA125 in the tumor cells except for the clear cell pattern. In addition, the tumor is unlikely to represent renal cell carcinoma. Clear cell renal cell carcinoma exhibits clear or granular cytoplasm, and both papillary renal cell carcinoma and collecting duct carcinoma may reveal tubulopapillary pattern. However, they have the immunoreactivity for α-methylacyl coenzyme A racemase, and never show hobnail configuration as clear cell adenocarcinoma does.

Another major differential consideration is nephrogenic adenoma. Clear cell adenocarcinoma, when well differentiated, may closely resemble nephrogenic adenoma. However, the presence of nuclear atypia, enlarged nucleoli, and invasive growth are incompatible with nephrogenic adenoma. Clinically, the tumor also behaved aggressively in contrast to the benign nature of nephrogenic adenoma. There has been 1 report providing molecular evidence suggesting the progression from nephrogenic adenoma to clear cell adenocarcinoma. Immunohistochemically, PAX-2 and α-methylacyl coenzyme A racemase, which are usually positive in nephrogenic adenoma, were negative in this case.

There have been several hypotheses regarding the histogenesis of clear cell adenocarcinoma in the urinary system. Recently, the tumor has either been considered to be malignant transformation of tissue originating from an aberrant Müllerian duct or to be of metaplastic origin from urothelium. Aberrant Müllerian tissue is unlikely to be found in the renal pelvis. On the other hand, since this clear cell adenocarcinoma was closely related to an impacted stone of the upper ureter and superficially contiguous with metaplastic squamous and intestinal type epithelium, the hypothesis of metaplasia is more plausible.

Finally, the possibility of clear cell adenocarcinoma from the female genital tract or reactive peritonitis inducing high CA125 serum level can be excluded by thorough clinical studies and immunostaining of CA125 in the tumor cells. The coexistence of superficial and contiguous deep parts, and the relationship of the superficial tumor with adjacent ureterorenal stones indicate a primary tumor rather than a metastatic tumor from
Clear cell adenocarcinoma of the upper urinary tract

other sites. Unfortunately, the postoperative reduction of the serum level of CA125 and CA19-9 was not checked to further confirm their relationship with this clear cell adenocarcinoma of the upper urinary tract.

In conclusion, we have demonstrated a primary clear cell adenocarcinoma occurring in the renal pelvis and upper ureter. Although it is rare, a tumor can develop in the upper urinary system, probably originating from a malignant transformation of metaplastic urothelium. High levels of CA125 and CA19-9 in serum might serve as markers of clear cell adenocarcinoma in organs other than the female genital organs, and as useful indicators during follow-up to determine whether the tumor has been eradicated or to look out for tumor recurrence.

Acknowledgments

We thank the staff at the Department of Pathology of National Taiwan University Hospital for their help in immunohistochemical staining of CA125.

References