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Case Report
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An Unexpected Case of Small Cell Neuroendocrine Carcinoma of the Ureter

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Abstract

With less than 30 cases reported in the literature, primary upper tract small cell neuroendocrine tumors are extremely rare. An 84-year-old woman with a history of ovarian carcinoma treated surgically and with adjuvant chemotherapy presents with right hydronephrosis discovered on surveillance imaging. Thought to be due to extrinsic compression, a ureteral stent was placed followed by routine exchanges until stent failure prompted ureteroscopy, which showed a mass in the mid ureter.

Keywords: Small cell neuroendocrine carcinoma; Upper tract

Introduction

Small cell neuroendocrine tumors are most commonly found in the lung, small intestine, adrenal gland and the thyroid. Primary small cell small cell neuroendocrine can also be found in the urinary tract, accounting for 0.7% of all bladder tumors [1] and less than 0.05% of all urinary tract malignancies [2]. Small cell neuroendocrine carcinoma of ureteral origin is extremely rare with fewer than 30 cases reported in the literature [3-6]. We report a case of primary small cell neuroendocrine carcinoma, initially presenting as ureteral obstruction of unknown etiology.

Case Presentation

We report a case of an 84-year-old woman with a history of Stage IIIC high grade serous ovarian carcinoma four years prior treated with total hysterectomy, pelvic lymphadenectomy, omentectomy and partial colon resection, as well as 6 cycles of carboplatin and paclitaxel chemotherapy. She was then randomized to the clinical trial AMG 386 for 18 months, which was completed in January 2015. In December of 2015, she underwent routine surveillance imaging, revealing new right-sided hydronephrosis (Figure 1). This was thought to be due to retroperitoneal fibrosis caused by her prior chemotherapy or due to ureteral stricture disease from her previous abdominal surgery.

A right retrograde pyelogram and right ureteral stent placement was performed in January 2016. Due to her spinal hardware, a clear location of her obstruction was not identified (Figure 2). She underwent a routine stent exchange 6 months later in July 2016.

In November 2016 at the routine follow-up with her gynecologist-oncologist, she was found to have increased right-sided hydronephrosis with deterioration in her renal function with a serum creatinine of 1.38 mg/dL from a baseline of 0.89 mg/dL. There was no evidence of recurrence of ovarian cancer on positron emission tomography scan and her cancer antigen-125 levels remained normal.

She then underwent a right retrograde pyelogram, ureteroscopy and stent exchange the following month. Retrograde pyelogram showed a massively dilated collecting system. Ureteroscopy revealed a fleshy mass within the mid right ureter. Cytology was collected and the mass was biopsied.

Hematoxylin and eosin stains showed small biopsy specimens containing crowded small to medium sized cells with indistinct cell borders and crush artifact in a background of scant stroma. Nuclei displayed hyper chromatic chromatin with indistinct nucleoli, nuclear molding and apoptotic debris. Due to the scant nature of the specimens limited immunohistochemical stains were performed but revealed positivity for synaptophysin. The case was reviewed at another major medical center, who also confirmed the diagnosis of small cell neuroendocrine tumor. (Figure 3-5).

After review of the small number of case reports, as well as extrapolating from the literature

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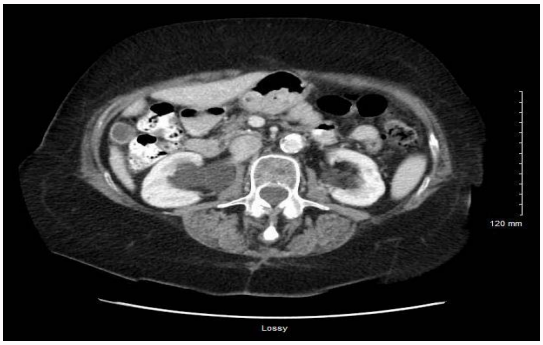

Figure 1: New right-sided hydronephrosis seen on routine CT scan performed for follow-up of ovarian carcinoma.

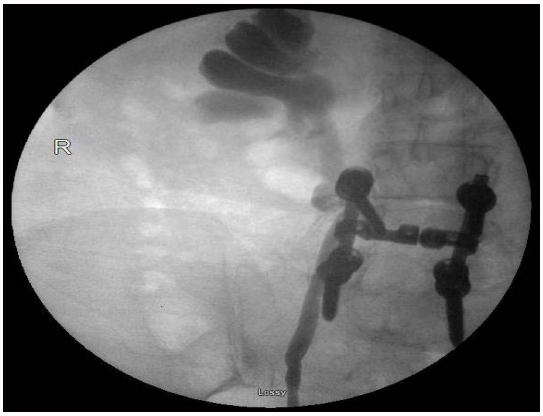

Figure 2: Right retrograde pyelogram. Clear source and location of obstruction not identified due to poor visualization secondary to spinal hardware.

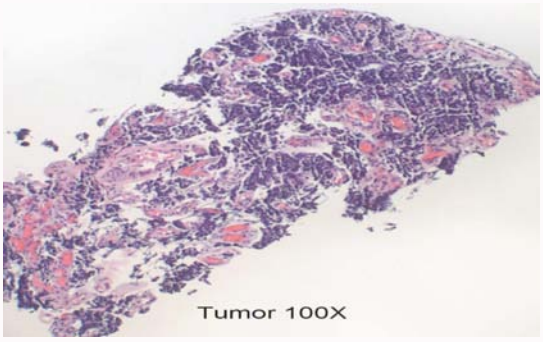

Figure 3: Diagnosis of small cell neuroendocrine tumor.

regarding small cell carcinoma of the bladder, conferring with our institution's multi-institutional tumor board, and counseling the patient, the treatment plan is for carboplatin chemotherapy with radiation. Follow-up imaging in May 2017 showed improved right-sided hydronephrosis and no evidence of metastatic disease.

Discussion

The exact etiology of neuroendocrine tumors is difficult to discern due to its rarity in the medical literature. However, it is hypothesized that urothelial cells may undergo a transformation to neuroendocrine cells or perhaps there is presence of trapped neural crest cells during embryological development [4].

The clinical presentation of primary small cell neuroendocrine

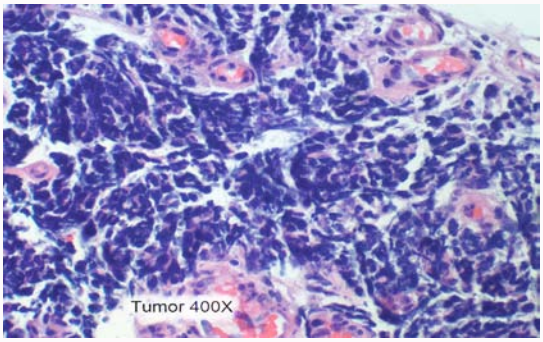

Figure 4: Diagnosis of small cell neuroendocrine tumor.

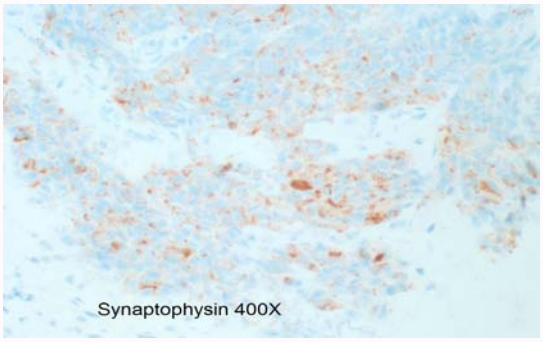

Figure 5: Diagnosis of small cell neuroendocrine tumor.

carcinoma of the upper tract is similar to that of other upper tract tumors: flank pain hematuria, weight loss, fatigue. Unlike other more common primary neuroendocrine tumors, primary small cell neuroendocrine carcinoma of the urinary tract is not associated with paraneoplastic syndromes [7].

Histologically, small cell neuroendocrine tumors are characterized by small to medium sized round/oval cells with minimal cytoplasm and indistinct cell borders. Nuclei displayed hyperchromatic chromatin with indistinct nucleoli, nuclear molding, mitotic figures and apoptotic debris. Crush artifact is common and characteristic of these delicate tumor cells. Immunohistochemical stains can also be helpful in the diagnosis. Classically, these tumors are positive for both chromogranin A and synaptophysin. In our case, the staining was negative for chromogranin; however, the positivity for synaptophysin in conjunction with the classic histomorphological features was enough to make the diagnosis of small cell neuroendocrine carcinoma. The largest meta-analysis of upper tract small cell neuroendocrine carcinoma reported a median age of presentation for upper tract small cell neuroendocrine carcinoma is 66.5 years with most patient presenting with either pT3 or pT4 disease. An aggressive disease, 54% of patients was reported to develop metastasis within 13 months of original diagnosis [4].

The treatment for small cell neuroendocrine carcinoma is extrapolated mostly from treatment of small cell carcinoma of the lung and is typically a multimodal approach, including surgery, radiation and adjuvant platinum-based chemotherapy. Median survival is reported to range from 8.2 to 23 months [1,3,4].

Interestingly, in our case, the patient's right-sided hydronephrosis was incidentally found, and then misdiagnosed initially as either extrinsic compression of the ureter due or ureteral stricture disease

from her previous extensive gynecological surgery. Sood et al. [5] also describe a similar situation of a woman diagnosed with primary ureteral small cell neuroendocrine carcinoma with a prior history of stage 1B mixed clear cell-endometroid cancer of uterus, treated with hysterectomy and adjuvant radiation. Both cases demonstrate the importance of having a high index of suspicion for less common reasons for radiographic hydronephrosis or clinical symptoms of obstruction.

Conclusion

Primary small cell neuroendocrine of the upper tract is a rare diagnosis. Diagnosis may be difficult initially, especially when other reasons for radiographic or clinical obstruction may be more likely. The paucity of literature makes for difficult treatment decision. More systematic study of treatments and outcomes for this rare condition would help guide management of future cases.

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