Primary Large Cell Neuroendocrine Carcinoma of the Urinary Bladder

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Reports of primary large cell neuroendocrine carcinomas of the urinary bladder are few; we identified only 2 cases in the literature. Both of these cases involved male patients with rapid progression of disease culminating in death with widespread metastases. We report a case of primary large cell neuroendocrine carcinoma of the bladder, with an admixed minor element of adenocarcinoma, in an 82-year-old man. This solitary lesion arose in a bladder diverticulum lateral to the left ureteric orifice. Two attempts at transurethral resection were unsuccessful at achieving local control. The patient underwent a partial cystectomy with left-sided pelvic lymphadenectomy following preoperative staging investigations that found no metastatic disease. Pathologically, the tumor invaded into the deep aspect of the muscularis propria, without extension into perivesical fat. The lateral resection margin was microscopically positive for tumor, but no malignancy was found in the pelvic lymph nodes. The adenocarcinoma comprised less than 5% of total tumor volume, and areas of transition between the neuroendocrine and adenocarcinoma components were apparent. The patient developed a local recurrence 8 months postoperatively, which was managed by a combination of transurethral resection and radiation therapy. Currently, the patient has no evidence of local or metastatic disease 2 years after initial diagnosis.

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Neuroendocrine tumors are most commonly encountered in the lungs and gastrointestinal tract. They belong to a spectrum that comprises carcinoid tumors, large cell neuroendocrine carcinomas (LCNECs), and small cell undifferentiated carcinomas (SCUCs). These tumors can arise in other anatomic locations, including the urinary bladder, a site in which they are rare relative to standard urothelial carcinomas. A not infrequent feature of neuroendocrine tumors in the urinary bladder is the coexistence of other forms of differentiation, such as urothelial carcinoma or adenocarcinoma. The most common neuroendocrine tumor of the urinary bladder is the SCUC; more than 100 cases have been described in the form of single case reports and small series. Although carcinoid tumors are much less common than SCUCs in the urinary bladder, several case reports exist. The least commonly described neuroendocrine tumor of the urinary bladder is the LCNEC; we found only 2 case reports in the English-language literature. The first report consists of a mixed adenocarcinoma-LCNEC, while the most recent description is that of a pure LCNEC. Both of these tumors were aggressive, culminating in death with widespread metastases.

In this article, we present a case of primary LCNEC of the bladder that contained an admixed minor component of moderately differentiated adenocarcinoma. In contrast to the previously published examples, this patient has had no evidence of metastasis during 2 years of follow-up.

REPORT OF A CASE

An 82-year-old white man presented with a 3-month history of gross hematuria. His medical history included type 2 diabetes mellitus and a remote history of cigarette smoking. Physical examination was unremarkable. Ultrasound studies revealed a 4.7 × 4.3-cm mass in the left lateral wall of the urinary bladder. Subsequent cystoscopy demonstrated a large polypoid tumor arising from a diverticulum immediately lateral to the left ureteric orifice. The tumor was partially resected transurethrally to the level of the mouth of the diverticulum. A second transurethral resection of bladder tumor (TURBT) procedure was carried out, removing more than 95% of the grossly visible tumor remaining in the diverticulum. Resection of more tumor was not possible due to the risk of perforating the diverticulum. Over a 2-month period, computed tomography demonstrated significant growth of tumor. Chest radiography, total body bone scan, and computed tomographic scan of the abdomen and pelvis showed no metastatic disease. The patient then underwent a diverticulectomy with left-sided pelvic lymphadenectomy in an attempt at more definitive local control. At operation, the bladder was opened in the midline, and tumor with abundant necrosis protruded from the diverticulum. The rest of the bladder mucosa was grossly normal. The friable exophytic component of the lesion was removed prior to excision of the diverticulum with a 1-cm margin of grossly uninvolved bladder mucosa that included the left ureteric orifice. The left ureter was reimplanted, and the patient experienced an uneventful immediate postoperative period. No adjuvant radiation or chemotherapy was given. He remained well with no evidence of local recurrence or metastasis through 3 months of follow-up. At 8 months of follow-up, he developed a 3-cm local recurrence in the left floor of the bladder, which was treated with TURBT. Complete restaging procedures showed no signs of metastatic tumor. The patient declined radical treatment.
A large cell neuroendocrine carcinomas of urinary bladder characterized by cells with large pleomorphic nuclei with coarse chromatin and prominent nucleoli, numerous mitotic figures, and abundant cytoplasm (hematoxylin-eosin, original magnification ×400). B, Area of glandular differentiation with focal papillary architecture (periodic acid–Schiff with diastase, original magnification ×100). C, Cytoplasmic and intraluminal mucin in the area with glandular architecture (periodic acid–Schiff with diastase, original magnification ×400). D, Immunohistochemical staining for synaptophysin (original magnification ×400).

MATERIALS AND METHODS

Formalin-fixed, paraffin-embedded tissue blocks were sectioned at 5 μm for histochemical and immunohistochemical analyses. Histochemical staining for hematoxylin-eosin, periodic acid–Schiff with diastase, and Mayer mucicarmine was performed. Immunohistochemical stains using primary antisera against cytokeratin AE1/AE3 (1:200, Dako Diagnostics, Carpenteria, Calif), vimentin (1:300, American Research Products, Belmont, Mass), leukocyte common antigen (1:80, Dako), prostatic acid phosphatase (1:3000, Dako), prostate-specific antigen (1:3000, Dako), neuron-specific enolase (1:1000, Dako), synaptophysin (1:100, Dako), and chromogranin A (1:400, ESBE Scientific [for Biomed Corporation], Toronto, Ontario) were carried out at the indicated dilutions using an automated staining method. Specific immunostaining was detected using the avidin-biotin peroxidase complex method. Fresh tissue samples were also fixed in glutaraldehyde, postfixed in osmium tetroxide, and embedded in epoxy resin for electron microscopy.

PATHOLOGIC FINDINGS

The 2 initial TURBT specimens consisted of multiple chips of pink-tan to hemorrhagic, soft, rubbery tissue with a combined aggregate weight of approximately 30 g. In both specimens, routine hematoxylin-eosin–stained sections showed a high-grade malignant epithelial neoplasm composed of large cells with abundant cytoplasm, large nuclei with coarse chromatin and variably prominent nucleoli, and a mitotic count greater than 50 mitotic figures per 10 high-power fields (Figure, A). Scattered bizarre gi-
ant cells were present, and many of the mitotic figures were abnormally formed. The tumor contained multiple foci of necrosis. There was extensive invasion of the lamina propria, but no invasion of the muscularis propria. Vascular space invasion was not present. The cells were arranged predominantly in diffuse sheets; however, foci showing vague glandular differentiation were present, in which the cells showed weak staining for intracytoplasmic mucin. The tumor cells showed positive immunoreactivity for cytokeratin (AE1/AE3) in both a diffuse cytoplasmic and a distinct dotlike perinuclear distribution (not shown). The cells were also positive for synaptophysin (Figure, D). Staining for chromogranin A, leukocyte common antigen, prostatic acid phosphatase, prostate-specific antigen, and vimentin was negative. Ultrastructurally, the tumor cells were tightly organized, but lacked cell junctions. Slender cytoplasmic processes were present between cells, some of which contained a few membrane-bound, dense-core granules with the surrounding halo characteristic of neurosecretory granules (not shown). Features of glandular differentiation were not identified.

The diverticulectomy specimen with residual tumor consisted of a cup-shaped portion of bladder wall measuring 6.5 × 5.0 cm with a thickness of 2.0 cm. The specimen also included separately received fragments of tumor, with an aggregate measurement of 5.5 × 4.0 × 1.5 cm, that were removed piecemeal prior to the actual diverticulectomy. The tumor had microscopic features similar to those of the TURBT specimens, but it also showed vascular space invasion that was not seen previously. In addition, there was a distinct focus of moderately differentiated adenocarcinoma characterized by irregularly shaped glandular structures with papillary projections and small glands with round lumina (Figure, B). Mayer mucicarmine and periodic acid–Schiff with diastase staining demonstrated the presence of intracytoplasmic and luminal mucin (Figure, C). The adenocarcinoma comprised less than 5% of total tumor volume. Only the adenocarcinoma component invaded the attenuated muscularis propria on the edge of the diverticulum. There was no extension of tumor into perivesical fat. Areas of transition between the LCNEC and adenocarcinoma, in which the cells shared features common to both elements, were identified. The lateral margin of resection of the diverticulum contained a microscopic focus of tumor; however, all other margins were free of tumor. The urothelium surrounding the mouth of the diverticulum was completely denuded, as were random biopsies of bladder mucosa remote from the tumor. As such, it was not possible to comment on the presence of associated intraurothelial neoplasia. No foci of cystitis cystica or glandularis were identified. The lymph nodes from the left-sided pelvic lymphadenectomy were negative for malignancy.

The TURBT specimen from the local recurrence at 8 months postdiverticulectomy showed only LCNEC with invasion of muscularis propria. A component with glandular differentiation was not present.

**COMMENT**

The light microscopic, immunohistochemical, and ultrastructural features in this case support a diagnosis of LCNEC with a focal element of adenocarcinoma. Neuroendocrine tumors of the urinary bladder are relatively rare and include carcinoids, LCNEC, and SCUC, the latter being by far the most common. The least commonly described entity is the LCNEC; we identified only 2 case reports in the literature. The diagnosis of LCNEC is based on criteria established for these tumors in the lung. The specific criteria include (a) cells of large size, polygonal shape, and low nuclear to cytoplasmic ratio; (b) coarse chromatin and frequent nucleoli; (c) mitotic activity in excess of 10 mitoses per 10 high-power fields with multiple areas of necrosis; and (d) immunohistochemical or ultrastructural evidence of neuroendocrine differentiation.8

The initial description of an LCNEC of the bladder by Abenoza et al2 was of a combined adenocarcinoma- LCNEC that arose in the dome of the bladder in a 55-year-old man. This patient underwent a radical cystectomy that showed transmural extension of tumor into perivesical fat and metastasis to a single iliac lymph node. Six months later, he developed a retroperitoneal recurrence that was treated surgically and with chemotherapy with partial response. Twenty-four months after initial diagnosis, he developed another local recurrence, which was treated with chemotherapy with poor response. Thirty months after initial diagnosis, the patient died with widely disseminated disease. Haillemariam et al8 described the second case in a 73-year-old man. This tumor was a pure LCNEC in a patient who had undergone a remote kidney transplant and radiation therapy for T2 N0 M0 prostatic carcinoma 3 years previously. The patient was treated by radical cystoprostatectomy, and there was transmural invasion of tumor with extension into perivesical fat. Adjuvant chemotherapy was not offered, and the patient died 2 months after surgery with widespread metastases.

As with the 2 previously reported cases, our patient was an adult male. Our case differs from the previous reports in that the lesion occurred in a diverticulum, it had a lower pathologic stage at surgery, and our patient has had no evidence of systemic disease during 2 years of follow-up. Local control appears to have been achieved with partial cystectomy, TURBT, and radiotherapy.

With only 2 reported cases, it is difficult to make statements regarding optimal treatment and prognosis for LCNEC of the urinary bladder, although both of the previously described patients had fatal outcomes. This behavior is thought to be similar to that observed for SCUC of the bladder, for which 2-year survival is reported to be in the range of 30% for advanced disease.4 The response of SCUC of the bladder to chemotherapy and/or radiation has been reported as variable at best.3,4 It is tempting to speculate that LCNEC of the bladder is merely an SCUC with larger cells. Data from a series of 40 patients with LCNEC of the lung suggest that this extrapolation may not be appropriate. In contrast to SCUC of the lung, LCNEC in this site tended to present at lower stage and have disease-free intervals and survival times after surgery that were not improved by adjuvant chemotherapy and/or radiation. Overall 5-year survival in this series was 13%.9 Clinical data from more cases of LCNEC in the bladder will determine if we can benefit from the experience in the lung.

The etiology of neuroendocrine tumors in the urinary bladder is unclear and has been widely discussed. The prevalent hypotheses include (1) an origin from a population of neuroendocrine cells normally present in urothelium, (2) an origin from multipotential undifferentiated stem cells within normal urothelium, and (3) an origin from metaplastic urothelium or high-grade urothelial carcinoma.2–4 The fact that upwards of 50% of SCUC of the...
bladder contain other forms of differentiation, including urothelial carcinoma and adenocarcinoma, would be consistent with either of the latter 2 theories. Additional support for this view is provided by case reports demonstrating coexistent adenocarcinoma across the complete spectrum of neuroendocrine tumors of the urinary bladder.

The differential diagnosis includes metastatic LCNEC from pulmonary or gastrointestinal primary sites, local invasion of the bladder by poorly differentiated prostatic carcinoma in male patients, and primary bladder lesions such as large cell lymphomas and high-grade, undifferentiated urothelial carcinomas. An immunohistochemical panel, supported by electron microscopy, allows one to distinguish these possibilities. As has been suggested for LCNEC of the lung, the true incidence of this entity in the urinary bladder may be underreported if the diagnosis is not considered and the appropriate diagnostic methods are not carried out. Prior to the advent of immunohistochemistry, these cases would most likely have been categorized as poorly differentiated, high-grade urothelial carcinomas. A retrospective review of archival poorly differentiated, high-grade urothelial carcinomas using neuroendocrine immunohistochemical markers might better define the true incidence, clinical behavior, and optimal management of this tumor.

References