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Case Report

Small-cell neuroendocrine carcinoma of the urinary bladder: A case report

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ABSTRACT

Primary neuroendocrine carcinomas of the urinary bladder are rare. A 60-year-old male presented with gross hematuria for the past 3 months. Diagnostic flexible cystoscopy revealed a papillary lesion above the right ureteric orifice. Transurethral resection of bladder tumor was performed and resected tissue was sent for histopathology that revealed high-grade urothelial carcinoma with small-cell neuroendocrine differentiation. Lamina propria, muscularis propria, and perineural invasion was seen which was later also confirmed by immunohistochemistry. The patient received neoadjuvant four cycles of chemotherapy and then underwent radical cystoprostatectomy with ileal conduit. The patient's recovery was uneventful and he is on regular follow-up from the past 12 months without any disease recurrence. Early detection and aggressive management can improve the survival and prognosis of these patients.

Keywords: Aggressive neoplasm, neuroendocrine carcinoma, radical cystoprostatectomy, urothelial carcinoma

Introduction

Bladder carcinoma is one of the most commonly diagnosed malignancies in men. In the past few decades, there has been rising in the incidence of bladder cancer cases globally. Small-cell carcinoma also known as oat cell carcinoma is an aggressive tumor with poor prognosis. Small-cell carcinoma mainly occurs in the lungs, but can also occur in other organs. Small-cell neuroendocrine carcinoma of the urinary bladder is extremely rare, accounting for just 0.5–1% of all primary bladder tumors.[1,2] Due to lacking typical clinical symptoms, early diagnosis is difficult to make. The patients often present with advanced metastasis at the time of diagnosis.[1,3,4]

In the previous reports regarding these rare cases, it has been found that this neoplasm has a strong male predilection and frequently arises between the fifth and ninth decades.[4-6] As far as, risk factors are concerned, mostly they are unknown, but these tumors are more evident in smokers; those suffering from long-standing cystitis and those harboring bladder stones. Due to its low incidence, it is difficult to establish a useful guideline for application in the clinic. It is common that it is misdiagnosed as another tumor type, and it is, therefore, necessary to accumulate more experience to determine the best treatment plan. The present study reports the case of a 60-year-old male patient with small-cell neuroendocrine carcinoma of the urinary bladder with coexisting high-grade urothelial carcinoma whose diagnosis was confirmed by histopathological examination. This patient report was important in a way to share our experience, treatment outcome, and follow-up regarding this rare entity.

Case Report

Our patient 60-year-old gentleman, a non-smoker without other significant comorbidities, presented with gross hematuria and dysuria. Furthermore, his serum electrolytes, renal function tests, and coagulation profile were normal. Apart from these, he had normal liver function tests. Urine culture was negative. Diagnostic flexible cystoscopy was done, which revealed small papillary lesion above the right ureteric orifice. It was unifocal, localized at the right lateral bladder wall, measuring 3 cm × 4 cm. Later on, transurethral resection was done and tissue sent for histopathology. It was mixed small-cell neuroendocrine carcinoma with high-grade transitional cell carcinoma, confirmed by immunohistochemistry with positive CD56, GATA3, Synaptophysin, and Ki-67 markers [Figures 1-3].

Radiological evaluation included a computed tomography (CT) chest abdomen and pelvis with and without contrast that showed a thickening of the right lateral bladder wall above the right ureteric orifice without any evidence of metastatic disease (no nodes in para-aortic areas seen and no other visceral metastasis seen on CT scan). A bone scintigraphy scan was also performed as a part of the initial staging and was found normal.

A mutidisciplinary meeting was conducted to discuss the case for future treatment plan. The patient was being informed

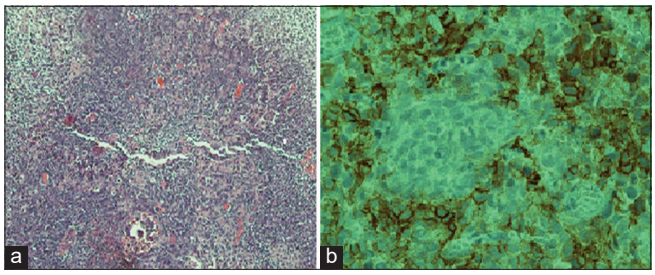

Figure 1: (a) Small-cell neuroendocrine bladder, (b) immunostain CD56 tumor mixed with high-grade urothelial Ca

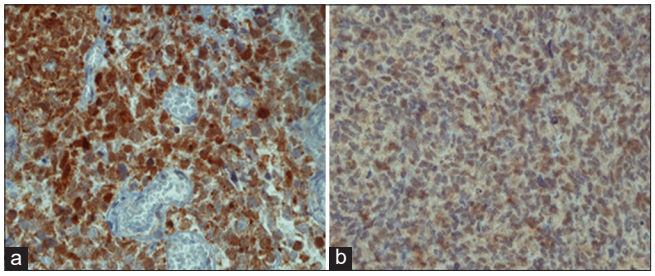

Figure 2: (a) Immunostain GATA3, (b) immunostain Synaptophysin

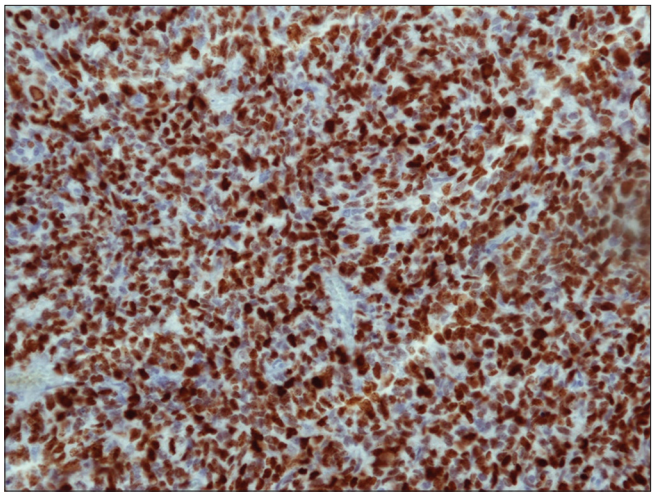

Figure 3: Immunostain Ki-67

regarding the associated morbidity and risks associated with treatment options. He decided to follow our treatment plan and he underwent four cycles of neoadjuvant chemotherapy with cisplatin/etoposide followed by cystoscopy and multiple biopsies from the previous resected area, random biopsies from the bladder walls, trigone, and prostatic fossa, but all were reported negative for malignancy. Later on, after taking the informed consent from the patient, radical cystoprostatectomy with ileal conduit was done after completion of the chemotherapy. The patient's post-operative recovery was uneventful, and currently, he is on regular follow-up for the past 13 months without any disease recurrence, progression, and metastasis.

Discussion

Urinary neuroendocrine localizations are rare and small-cell neuroendocrine tumors of the bladder represent only 0.5%– 1% of all bladder tumors.[1,2] This histological entity includes three subtypes, namely, neuroendocrine small-cell carcinomas, neuroendocrine large cell carcinomas, and differentiated neuroendocrine tumors such as carcinoid tumors.[5]

Clinical symptoms are non-specific, and most frequently found are gross hematuria, pelvic pain, and irritative voiding symptoms.[1,3,4] The diagnosis depends on histopathological recognition and reactivity for neuroendocrine markers such as Synaptophysin, chromogranin A, and neuron-specific enolase.[5] It has been reported that these tumors are diagnosed at a locally advanced stage in 70% of cases with lymph node involvement of 57% and with lung, bone, liver, or brain involvement in 28%–50% ofcases.[2,4] In our case, the radiological evaluation did not find evidence of metastatic disease at the time of diagnosis.

In the case of localized tumors, it has been seen that despite local treatment of a primary tumor, most patients develop metastasis. Sved *et al*. have reported disappointing results of patients treated only by radical cystoprostatectomy with 3 years overall survival rate of 16% and 5 years progression-free survival of 0%. However, a retrospective study from Mayo Clinic, in 2004, suggested that all patients with small-cell bladder carcinoma should undergo radical cystectomy except when metastatic disease is present with adjuvant chemotherapy based on cisplatin.[6]

Due to early metastatic potential, some authors have advocated the use of neoadjuvant chemotherapy. In a Phase II trial from M. D. Anderson Cancer Center in 2009, patients received four cycles of chemotherapy with ifosfamide, doxorubicin, etoposide, and cisplatin and noted a median survival of 58 months.[7] Similar results were found in another retrospective study that included 95 patients with cT4aN0M0 respectable neuroendocrine carcinoma of the bladder; the median overall survival was 159.5 months.[7,8]

The preferred local treatment for localized tumors is surgery. However, radiotherapy represents a good alternative in several centers. The largest retrospective study included 17 patients and complete response was observed in 15 patients (88%), with a median survival time of 32.5 months.[9] In the case of metastatic disease or relapse, chemotherapy with cisplatin-etoposide alone or in alternation with vincristine, doxorubicin, and cyclophosphamide remains the therapeutic standard.[10]

Thus, neuroendocrine small-cell carcinomas of the bladder are rare tumors with poor prognosis. Their management requires a multidisciplinary approach, in the absence of prospective trials; the best treatment cannot be established with certainty.

Conclusion

Small-cell neuroendocrine bladder tumor mixed with high-grade urothelial carcinoma is a rare malignant tumor with potential to metastasize early and has a poor prognosis.

Therefore, early diagnosis is imperative made by specialized histological examination. At present, multimodality therapy offers the best modality of treatment.

Conflicts of Interest

None.

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