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Large Cell Neuroendocrine Carcinoma of Urinary Bladder; Case Presentation

Mesanenin Büyük Hücreli Nöroendokrin Karsinomu; Olgu Sunumu

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ABSTRACT

Large cell neuroendocrine tumor of the urinary bladder is very rare. It is a type of neuroendocrine carcinoma that is morphologically different from small cell carcinoma.

This manuscript describes a 67-year-old man who presented with hematuria. Ultrasonographic and computer tomography revealed a 5 cm mass in right posterolateral wall of the bladder that invaded perivesical tissue and he subsequently underwent transurethral resection. Microscopic examination showed a tumor with a sheet-like and trabecular growth pattern comprising necrotic areas which infiltrated the muscularis propria. Tumoral cells had coarse chromatin, prominent nucleoli, moderate amount of cytoplasm and immunohistochemically stained strongly positive with synaptophysin, chromogranin and CD56.

There are only few case reports of large cell neuroendocrine tumor of the urinary bladder so the biological behavior and the treatment protocol of these tumors are still obscure. Appropriate management protocols and prognostic estimation could be achived by the increased number of cases being reported. Therefore in a case of a poorly differentiated tumor in bladder, although rare, it is important to consider large cell neuroendocrine carcinoma in differential diagnosis.

Key Words: Neuroendocrine, Carcinoma, Large cell, Small cell, Urinary bladder

ÖZ

Mesanenin büyük hücreli nöroendokrin tümörleri çok nadirdir. Bu tümörler küçük hücreli karsinomdan morfolojik olarak farklı olan ayrı bir nöroendokrin karsinom tipidir.

Bu makalede 67 yaşında hematüri nedeniyle başvuran erkek olgu sunuldu. Ultrason tetkiki ve bilgisayarlı tomografide mesane sağ posterior-lateral duvarda yaklaşık 5 cm çapında perivezikal alanı infiltre eden kitle izlendi ve hastaya transüretral rezeksiyon uygulandı. Mikroskobik olarak tabakalar ve trabeküler tarzda büyüme gösteren, muskularis propriayı yaygın olarak invaze etmiş arada nekroz odakları içeren tümör izlendi. Tümör hücreleri kaba kromatinli, belirgin nükleollu, kısmen bol sitoplazmalı olup immunohistokimyasal olarak sinaptofizin, kromogranin, ve CD56 ile kuvvetli pozitif idi.

Mesanenin Büyük Hücreli Nöroendokrin Karsinomu'na ait çok az sayıda olgu rapor edildiğinden, bu tümörlerin biyolojik davranışları ve tedavi protokolleri henüz belirsizdir. Rapor edilen olgu sayısının artması uygun tedavi protokollerinin geliştirilmesine ve prognozlarının tahmin edilmesine katkı sağlayacağından mesanede kötü diferansiye bir tümör varlığında, nadir olarak izlense de büyük hücreli nöroendokrin karsinomu akılda tutmak önem kazanmaktadır.

Anahtar Sözcükler: Nöroendokrin, Karsinom, Büyük hücreli, Küçük hücreli, Mesane

INTRODUCTION

Neuroendocrine (NE) tumors are a heterogenous group of tumors growing from NE cells. They are divided into sub-categories based on the organ they are derived from. NE tumors are observed basically as two types as carcinoid and small cell carcinoma in the urinary system (1) and make up less than 1% of bladder malignancies (2). In recent years, large cell neuroendocrine carcinoma (LCNEC) with different morphological characteristics than small cell carcinoma (SCC) as in the lung has been defined in the bladder (1). Our aim in this article was to present a 67-year-old male patient with a diagnosis of LCNEC in the bladder transurethral resection material together with the relevant literatures.

CASE REPORT

A 67-year-old male patient presented at the urology outpatients with hematuria and was admitted when a tumor was observed in the junction of the bladder side wall and dome of the bladder on abdominal ultrasonography. The patient's personal history included chronic obstructive lung disease and congestive heart failure for 15 years. The abdominal computed tomography (CT) revealed a

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mass of 5 cm in the largest dimension on the lateral wall of the bladder in the right posterior area infiltrating the perivesical region and a 3 cm lymphadenopathy in the right iliac region. Thorax CT findings were within normal limits. Positron Emission Tomography and Computed Tomography revealed a hypermetabolic mass 6x5 cm in size with irregular contours, filling the right half of the bladder and showing vegetative growth into the lumen. Cystoscopy and transurethral resection (TUR) was performed on the patient with these findings. All the TUR material 4 cc in volume was evaluated and microscobic examination revealed a sheet-like and trabecular growing tumor that had diffusely invaded the lamina propria and muscularis propria with occasional necrotic foci (Figure 1). Tumor cells showed coarse chromatin, prominent large nucleoli, quite large cytoplasm cytoplasm, and were polygonal shaped with high mitotic activity (Figure 2). Synaptophysin (1:100 dilution, Neomarkers, FremontCA), chromogranin (1:200 dilusyon, Neomarkers, Fremont, CA), CD 56 (1:50 dilution, Neomarkers, Fremont CA), Cytokeratin 7 (1:100, Neomarkers, Fremont, CA), Cytokeratin 20 (1:50, Novocastra, UK), p63 (1:100, Neomarkers, Fremont, CA), TTF-1 (1:100 dilution, Novocastra, UK), PSAP (Neomarkers, Fremont, CA, PASEI4l5) and PSA (Neomarkers, Fremont, CA, Ab-1(ER-PR8)) stains were applied by using the streptavidin-avidin-biotin histochemical method and the Leica-Bond Max automatic immunostaining device.

Tumor cells were widespread positive with synaptophysin (Figure 3A), chromogranin, CD56 (Figure 3B) and CK 7 (Figure 4A) and focal positive with CK 20 and p63 (Figure 4B). High molecular weight cytokeratin, TTF-1, PSA and

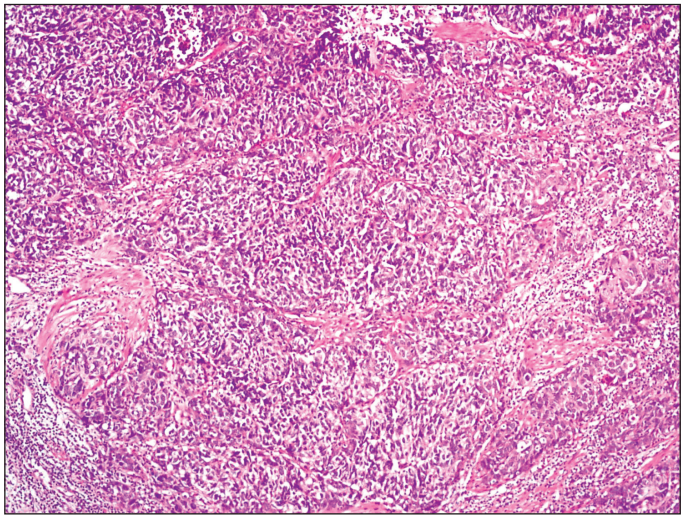

Figure 1: Tumor diffusely invaded the muscularis propria, showing sheet-like and trabecular growth (H&E x100).

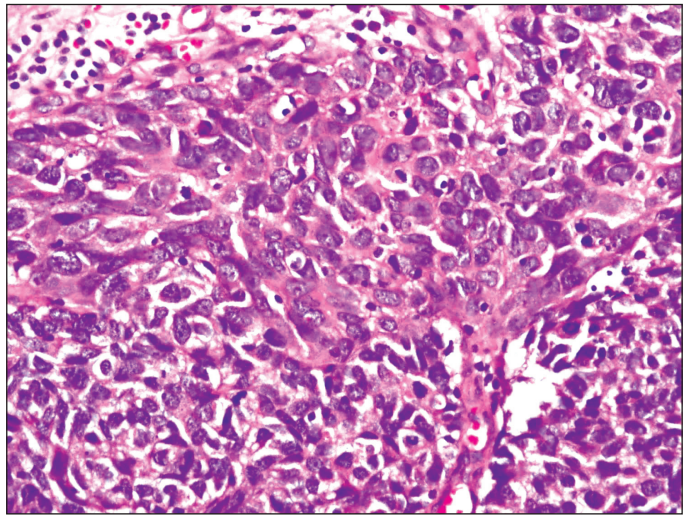

Figure 2: Large pleomorphic tumoral cells with active mitosis and pink or pale cytoplasm (H&E x400).

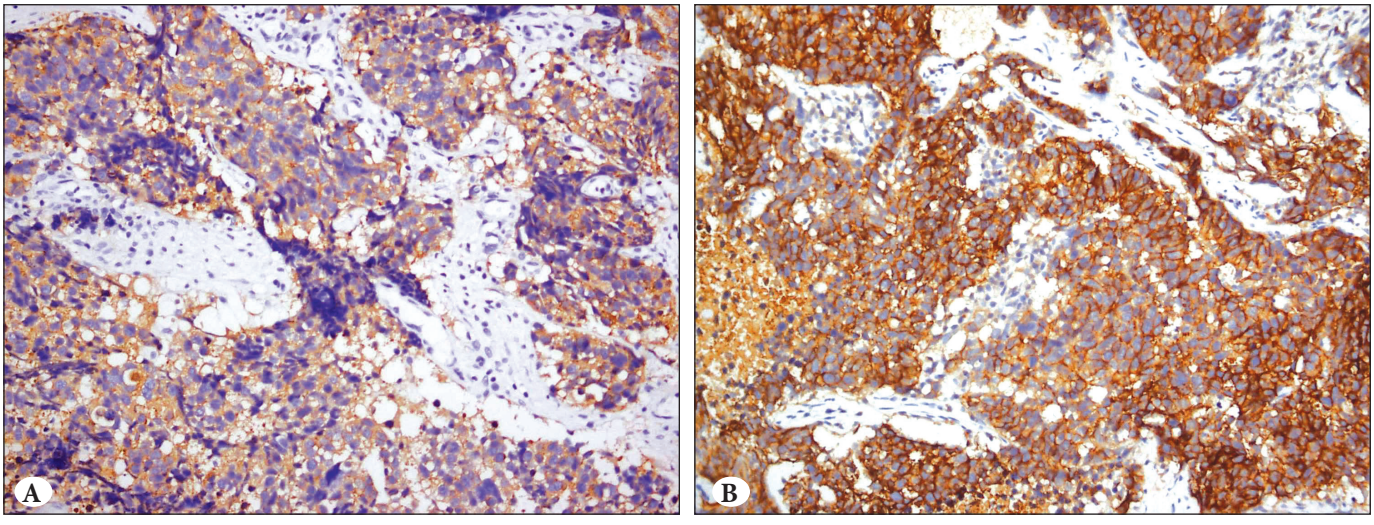

Figure 3: Tumor cells with **(A)** synaptophysin positivity (x200), **(B)** CD 56 positivity (x200).

PSAP were negative. An accompanying conventional urothelial carcinoma (UC) area was not observed. The patient was diagnosed with LCNEC, pT2 and died of heart faiure two weeks after the TUR surgery.

DISCUSSION

The most common type of bladder NE tumor is SCC and makes up 0.5-0.7% of primary bladder tumors (3-5). Bladder SCC shows microscopic and immunohistochemical features similar to pulmonary SCC. SCC may be accompanied by urothelial, squamous or glandular differentiation (4). Most patients are in the advanced phase at diagnosis, and metastases develop within a short time. The second most frequent NE tumor of the bladder is carcinoid, and about 20 cases have been reported so far (6-9).

LCNEC of the bladder was first described by Aboza et al. in 1986 in a 55-year-old patient and was reported to be associated with adenocarcinoma (10). Only four of the 14 LCNEC cases reported so far has been in the pure form (4, 5, 11) and other cases have been accompanied by adenocarcinoma, urothelial carcinoma, squamous cell carcinoma, carcinosarcoma, or lymphoepithelioma-like carcinoma (2, 3, 10, 12, 13). Clinicopathologic findings of the reported cases are summarized in Table I. LCNED was observed in a pure form in the TUR material in our case, but we could not rule out the presence of an accompanying carcinoma since there is a possibility of residue tumor in the bladder.

The basic features of LCNEC in organs other than the lung such as the bladder, uterus, thymus, stomach, larynx, parotid gland, prostate and kidneys, are histologically similar to their counterpart in the lung (2). The large size, polygonal shape, low nuclear/cytoplasmic ratio, coarse chromatin structure and frequent nucleoli are the most important features of the cells. More than 10 mitosis in 10 high power fields and necrosis are often present (2, 4). Synaptophysin, chromogranin and CD56 positivity are present immunohistochemically. LCNEC observed in the lung have been classified as large cell carcinoma variant by the WHO as they show morphological similarity with non-small cell lung tumors. However, they are clinically similar to SCC with a very poor prognosis, and similar response to cisplatin-based therapy (2). As in the lung, bladder SCCs have a poor prognosis and 5-year survival is approximately 8% (3). Bladder LCNECs also have a rapid course and poor prognosis like SCCs (3, 5). Bladder LCNECs are very rare tumors so there is no specific treatment protocol but studies with pulmonary LCNECs show they respond well to standard chemotherapy regimens administered to SCCs (14, 15).

The etiology of bladder NE carcinomas has not been elucidated as yet. The most widely accepted hypothesis is that neuroendocrine cells develop from stem cells or multipotent undifferentiated cells in the urothelium. Another theory is that they develop from metaplastic urothelium or high grade urothelial carcinoma (3). One of the finding which supports this theory is that besides bladder SCCs more than %50 of the bladder LCNECs are found to be associated with more differentiated cell forms such as urothelial carcinoma, and adenocarcinoma. The immunohistochemical heterogenity that both LCNEC and SCC show by staining with epithelial and neuroendocrine determinants to a certain degree also supports the multipotent stem cell theory (4). Although a conventional urothelial carcinoma area was not observed in our case, the positive staining of LCNEC areas with CK 7 and CK 20 (epithelial markers positive in urothelial carcinoma)

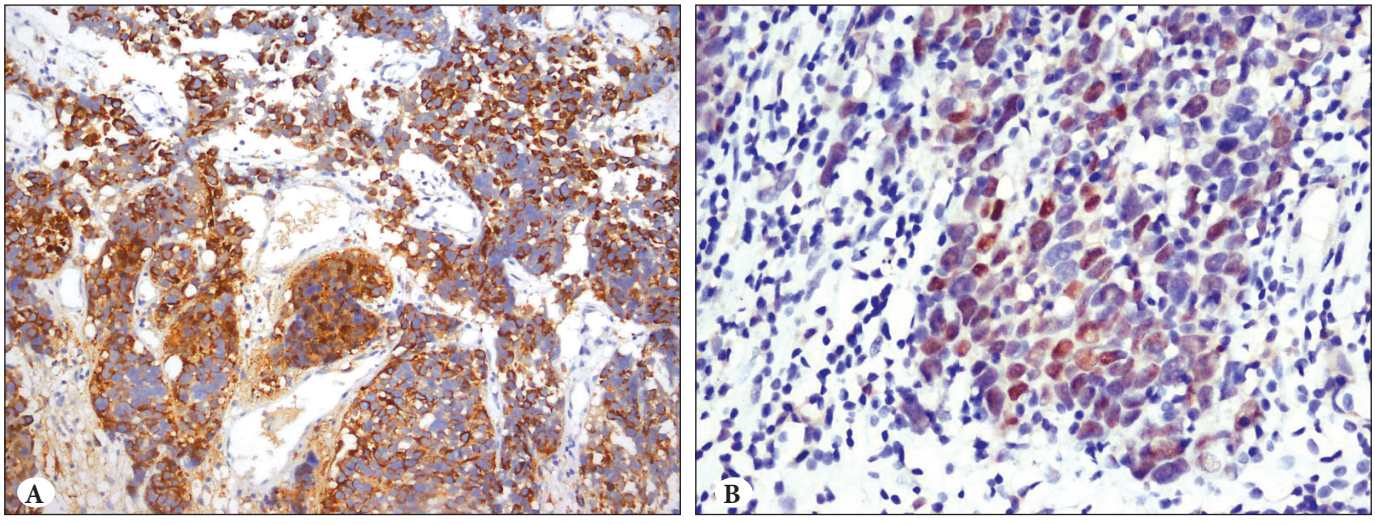

Figure 4: Tumor cells with **(A)** cytokeratin 7 positivity (x200), **(B)** P63 positivity (x400).

Table I: Published cases of bladder large cell neuroendocrine carcinoma

Reference	Age/ Gender	Symptom	Mix Histology	Surgery	Treatment	Follow-Up
(10)	55Y/M	Hematuria and Mucoid changes	Adenocarcinoma	RCx	CT	Died after 30 months of follow up
(11)	73Y/M	Hematuria	Pure	RCx	Could not be given as he was immunosuppressed for a renal transplant	Died 2 months after the surgery
(3)	82Y/M	Hematuria	Adenocarcinoma	PRx	CT RT	Alive without disease after 2 years of follow up
(12)	54Y/F	Hematuria and urethrargia	Lymphoepithelioma like carcinoma + UC	RCx	CT	Alive after 16 months of follow-up with lymph node metastasis,
(13)	61Y/E	Hematuria	Carcinosarcoma	RCx	No adjuvant treatment	Alive without disease after 8 months of follow-up
(16)	61-79Y 4M &1F	NI	2 cases PURE 3 cases UC	NI	NI	4 cases died due to the disease, 1 case alive after 24 months of follow-up
(4)	32Y/M	Hematuria	Pure	PCx	CT	Alive with lung and liver metastasis after 10 months of follow-up
(5)	40Y/M 28Y/F	NI	Pure Pure	RCx RCx	CT RT	Alive with the disease after 13 months of follow-up Died 12 months after the surgery
(2)	63M	Hematuria	Squamous cell carcinoma and UC	RCx	CT	Alive without disease after16 months of follow-up
Our case	67Y/M	Hematuria	Pure	TUR	RCx + CT were planned	Died 15 days later

M: Male, **F:** Female, **RCx:** Radical Cystectomy, **PRx:** Partial cystectomy, **CT:** Chemotherapy, **RT:** Radiotherapy, **TUR:** Transurethral resection, **NI:** No information, **UC:** Urothelial carcinoma.

in addition to neuroendocrine markers is consistent with the multipotent cell theory. P63 is an urothelial carcinoma determinant and was focal positive in our case. Although this seems to support the theory that LCNEC develops from high-grade urothelial carcinoma, there is no information available in the literature regarding p63 positivity in bladder LCNECs. Buza N. et al showed all 14 of their SCC cases except one to be negative for p63 in a study they conducted on bladder SCCs. However, that study defined p63 positivity as at least 10% of the tumor cells showing staining (17). More studies are needed to determine the meaning and role of p63 positivity in the differential diagnosis of bladder neuroendocrine carcinomas.

It is important to differentiate bladder LCNEC from metastatic LCNEC originating from other organs, poorly differentiated prostate adenocarcinoma or lymphoma showing local extension, and primary bladder tumors such as high grade UC and squamous cell carcinoma. In the presence of a tumor morphologically similar to LCNEC that needs to be differentiated from high-grade, poorly differentiated UC, the presence of immunohistochemical positivity for neuroendocrine determinants supports LCNEC. The most

significant histological features differentiating LCNEC from SCC with similar neuroendocrine characteristics are large cell size, prominent nucleoli, coarse chromatin, low nuclear/cytoplasmic ratio and trabecular organoid arrangement (2).

In conclusion, it is important to keep LCNEC in mind in the presence of a poorly differentiated tumor in the bladder as it has been reported that adjuvant chemotherapy, as well as surgical treatment can ensure long-term control in localized bladder LCNECs similar to pulmonary LCNECs (2). In addition, the increasing number of reported cases will contribute to the development of appropriate treatment protocols.

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