Neuroendocrine tumors of the urinary bladder

A case series and review of the literature

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Neuroendocrine tumors of the urinary bladder. A case series and review of the literature

Neuroendocrine carcinoma cases, more frequent in the GI tract, have rarely been reported *in extrapulmonary areas. Neuroendocrine carcinoma of the bladder is one of the malignancies with a poor prognosis, which is expected to cause rapid metastases. In addition, neuroendocrine carcinoma of the bladder constitutes < 1% of all bladder carcinomas.*
In this study, we present two rare cases, a combined small cell neuroendocrine carcinoma–high-grade urothelial carcinoma and a large cell neuroendocrine carcinoma, diagnosed at Çanakkale Onsekiz Mart University, Research and Practice Hospital Pathology Clinic, between November 2016 and January 2017.

KEYWORDS: Bladder, L cell neuroendocrine carcinoma, Pathological features, Small cell neuroendocrine carcinoma

Introduction

Neuroendocrine tumors are most commonly seen in the gastrointestinal tract, followed by the bronchopulmonary region [1]. Neuroendocrine carcinoma cases have rarely been reported in extrapulmonary areas. It is also rarely seen in areas such as the breast, bladder, and small intestine [2].
Neuroendocrine carcinoma of the bladder is one of the malignancies with a poor prognosis, which is expected to cause rapid metastases. In addition, neuroendocrine carcinoma of the bladder constitutes < 1% of all bladder carcinomas. Most of these are small cell neuroendocrine carcinomas, whereas large cell neuroendocrine carcinomas have also been reported recently [3].

In this study, we present two rare cases, a combined small cell neuroendocrine carcinoma–high-grade urothelial carcinoma and a large cell neuroendocrine carcinoma, diagnosed at Çanakkale Onsekiz Mart University, Research and Practice Hospital Pathology Clinic, between November 2016 and January 2017.

Case Reports

CASE 1

Polypoid lesions were seen in the bladder cystoscopy of a 67-year-old male patient, and TUR-M was performed. In the histopathological examination, two different tumor components were observed in the sections. The first component comprised a tumor with hyperchromatic and pleomorphic nuclei, comprising papillary structures with a fibrovascular core (Fig. 1), whereas the second component comprised highly mitotic, active, narrow cytoplasmic tumor cells with necrosis in the focal region, which were observed as solid islands (Figs. 2, 3). Immunohistochemical analysis revealed a widespread and strong positivity for synaptophysin and chromogranin in these solid areas (neuroendocrine areas) but no staining in the other tumor component (high-grade urothelial car-

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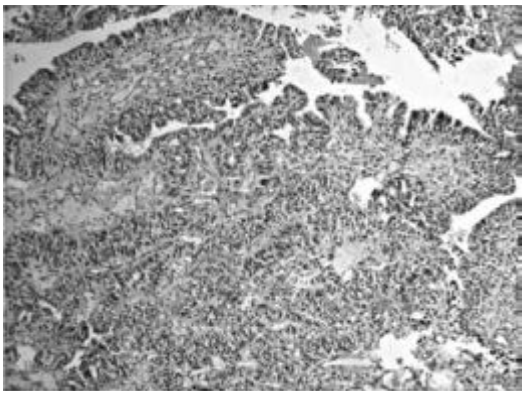

Fig. 1: Component comprising papillary structures in the high-grade papillary urothelial carcinoma areas (hematoxylin&eosin staining × 100).

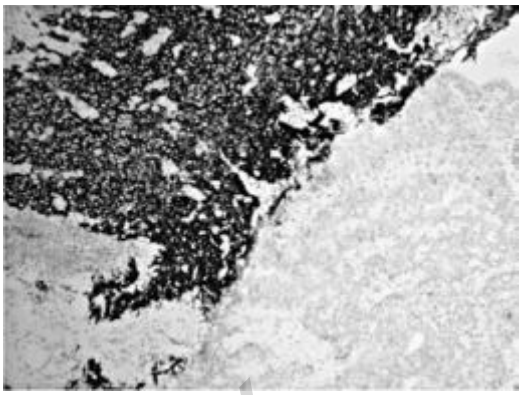

Fig. 4: Strong and widespread positivity in the small cell carcinoma component for synaptophysin, and negativity in papillary urothelial carcinoma areas (immunohistochemistry synaptophysin staining × 400).

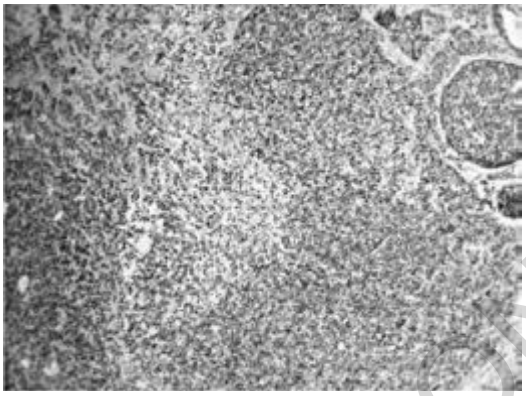

Fig. 2: Solid regions of the small cell carcinoma component (hematoxylin&eosin staining × 100).

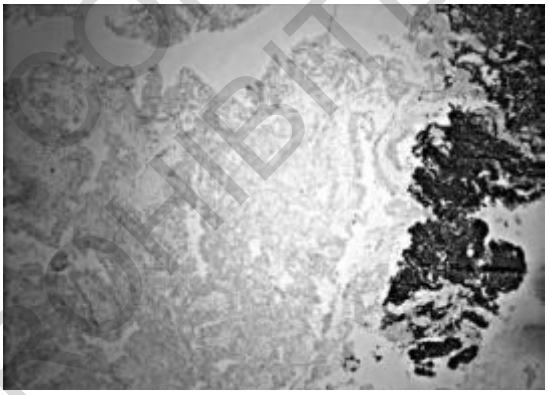

Fig. 5: Strong and widespread positivity in the small cell carcinoma component for synaptophysin, and negativity in papillary urothelial carcinoma areas (immunohistochemistry synaptophysin staining × 40).

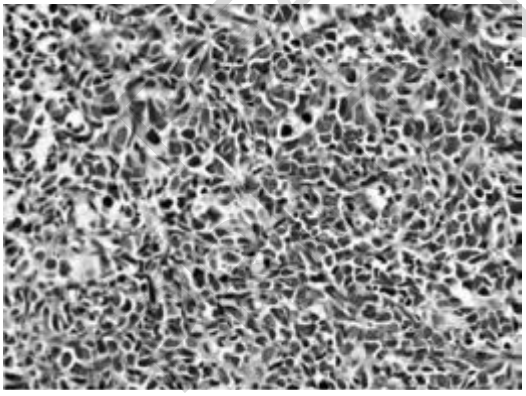

Fig. 3: Extensive mitoses in small cell carcinoma component regions (hematoxylin-eosin staining × 400).

cinoma areas) (Figs. 4, 5). In particular, the Ki 67 proliferation index was approximately 90%–100% in the neuroendocrine component. In addition, in situ carcinoma areas were noted in the peripheral bladder mucosa (Fig. 6). With these histopathological findings, the case was reported as "combined high-grade urothelial carcinoma/small cell neuroendocrine carcinoma." There was no invasion in the muscular layer in both components, and there was no lymphatic or vascular invasion. Cystoprostatectomy was not performed in the patient. The patient was referred to an oncology clinic where the treatment was continued.

Case 2

Suspicious masses were observed in the bladder cystoscopy of a 70-year-old male patient, and TUR-M was performed. TUR-M revealed carcinoma with muscle layer invasion, and cystoprostatectomy was performed in the patient. When sections of the cystoprostatectomy material were examined histopathologically, tumor nests with broad cytoplasm and salt-and-pepper chromatin, which were independent of the surface epithelium and showed infiltration as solid islands and small nests, were observed (Figs. 7, 8). Immunohistochemical analysis revealed a widespread and strong positivity for synaptophysin in these tumor cells (Fig. 9). With these

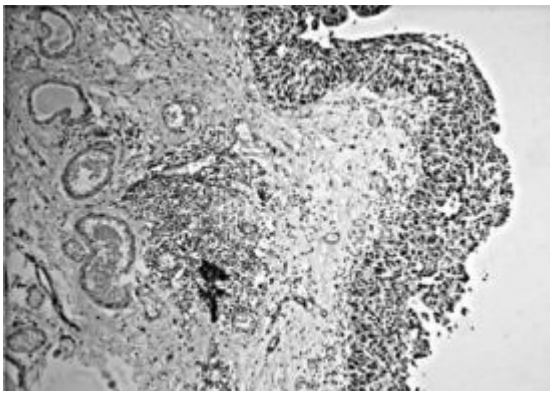

Fig. 6: In situ carcinoma areas of the epithelium in the non-tumor bladder mucosa (hematoxylin&eosin staining × 100).

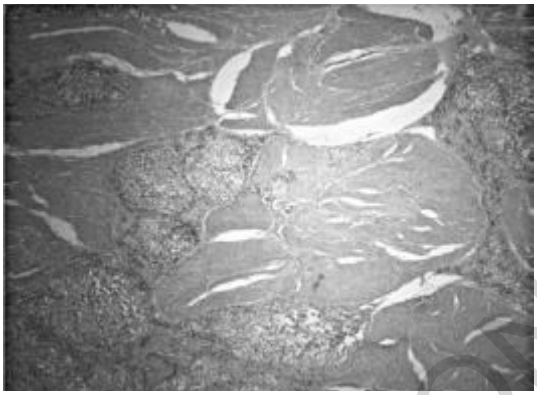

Fig. 7: Tumor islands showing infiltration in the deep muscle layer (hematoxylin&eosin staining × 40).

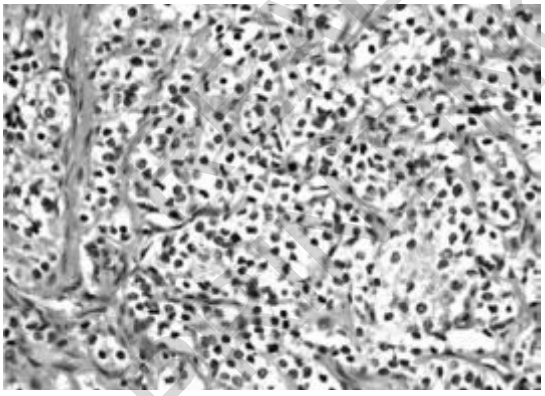

Fig. 8: Large cytoplasmic tumor cells showing infiltration in the form of nests in large cell neuroendocrine carcinoma sections (hematoxylin&eosin staining × 400).

histopathological and immunohistochemical findings, the case was reported as "large cell neuroendocrine carcinoma." In addition, extensive lymphatic/vascular invasion and prostate/vesicular seminalis carcinoma invasion were present in the patient. This patient was also referred to an oncology clinic for treatment.

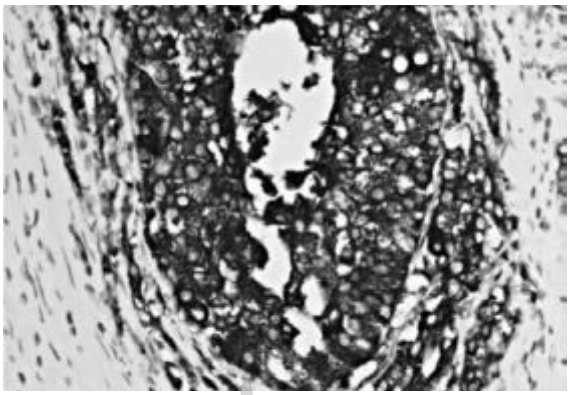

Fig. 9: Strong and widespread positivity for synaptophysin in tumor cells, as shown by immunohistochemical analysis (immunohistochemistry synaptophysin staining × 400).

Discussion

Neuroendocrine tumors are neoplasms that originate from neuroendocrine cells and are frequently seen in areas such as the gastrointestinal tract, lungs, larynx, salivary glands, breast, and kidney [3,5]. Although small cell neuroendocrine carcinomas of the lung are frequently seen, neuroendocrine carcinoma of the bladder is much rarer and is generally expected to be combined with adenocarcinoma, urothelial carcinoma, or sarcomatoid carcinoma [6]. In our case, small cell neuroendocrine carcinoma was combined with high-grade urothelial carcinoma. It is known that most neuroendocrine carcinomas are present in a mixed/combined form, and cases reported in the literature with pure neuroendocrine morphology are very rare [4]. The large cell neuroendocrine carcinoma case described in the present study had pure neuroendocrine morphology.

As in urothelial carcinomas of the bladder, male sex predominance has also been reported in neuroendocrine carcinomas, and it was generally seen in the sixth and seventh decade [6]. Both of our cases were male patients, and their ages were 67 and 70 years. It has been reported in the literature that most cases of neuroendocrine carcinoma of the bladder are expected to show invasion to the muscle layer during diagnosis [6,7]. In our cases, cystoprostatectomy-performed large cell neuroendocrine carcinoma showed invasion to the muscle layer, whereas the muscle layer was present in the biopsy material of the TUR-M-performed small cell neuroendocrine–high-grade urothelial carcinoma case, with no muscle invasion and no tumor presence in the biopsy taken separately from the tumor base.

When the pathogenesis of neuroendocrine carcinoma of the bladder is examined, molecular studies in the literature suggest that urothelial and neuroendocrine carcinomas originate from multipotent stem cells, and neuroendocrine carcinoma is also a variant of urothelial carcinoma [8]. According to other views, neuroendocrine car-

cinomas may be the result of malignant transformation of neuroendocrine stem cells in the bladder or neuroendocrine differentiation of urothelial carcinomas [9].
Although there is no standardized form of treatment for neuroendocrine carcinoma of the bladder, surgery, radiotherapy, or chemotherapy may be preferred. The cases should be investigated in detail with imaging methods and carefully examined to ensure that there is no other primary focus. If the cases are localized, performing cystectomy is debatable [10]. Cheng et al. reported that there is no significant difference in the survival of patients with and without cystectomy, whereas Sved et al. reported that the prognosis is poor only in cases with cystoprostatectomy [11,12]. Moreover, Siefker et al. reported that neoadjuvant therapy is beneficial in these cases [13]. Palliative chemotherapy is a preferred treatment option in patients with metastatic forms [14]. In our cases, while the patient with combined small cell neuroendocrine–high-grade urothelial carcinoma was referred to an oncology clinic without being operated, the patient with large cell neuroendocrine carcinoma was referred to an oncology clinic after cystoprostatectomy.
In conclusion, neuroendocrine carcinoma of the bladder is rare, and they are metastasis-prone tumors with a poor prognosis. Although there is no standardized treatment in these cases, an increase in the number of reported cases will be helpful in developing appropriate treatment protocols

Riassunto

Sono rare le segnalazioni di carcinomi neuroendocrini localizzati in aree extrapolmonari, e al di fuori del tratto gastroenterico. Quelli della vescica rappresentano una delle neoplasie maligne a prognosi cattiva, a causa della prevedibile rapida metastatizzazione. D'altra parte i tumori neuroendocrini della vescica rappresentano meno del 1% di tutti i carcinomi vescicale.
In questo studio presentiamo due casi rari, l'associazione di un tumore neuroendocrine a piccolo cellule con un carcinoma uroteliale di alto grado, ed un carcinoma neuroendocrine a grosse cellule, diagnosticati presso il Practice Hospital Pathology Clinic della Çanakkale Onsekiz Mart University tra novembre 2016 e gennaio 2017.

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