Case Report
Small cell carcinoma of the urinary bladder

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Abstract: Primary small cell carcinoma of the urinary bladder is very rare; only several studies have been reported in the English literature. A 62-year-old woman was admitted to our hospital because of hematuria and dysuria. Bladder endoscopy revealed a large polypoid tumor at the bladder base. Transurethral bladder tumorectomy (TUR-BT) was performed. Many TUR-BT specimens were obtained. Histologically, the bladder tumor was pure small cell carcinoma. Immunohistochemically, the tumor cells were positive for cytokeratin (CK) AE1/3, CK CAM5.2, CK8, CK18, neurone-specific enolase, chromogranin, NCAM (CD56), synaptophysin, Ki-67 (labeling=100%), p53, KIT (CD117), and platelet-derived growth factor receptor-α (PDGFRA). The tumor cells were negative for CK5/6, CK 34BE12, CK7, CK14, CK20, p63, CD45, and TTF-1. A molecular genetic analysis using PCR-direct sequencing showed no mutations of KIT (exons 9, 11, 13 and 17) and PDGFRA (exons 12 and 18) genes. No metastases were found by various imaging techniques. The patient is now treated by cisplatin-based chemotherapy.

Keywords: Small cell carcinoma, urinary bladder, immunohistochemistry, KIT, PDGFRA

Introduction

Primary small cell carcinoma of the urinary bladder is very rare; only a few studies have been reported in the English literature [1-5]. Like small cell lung carcinoma (SCLC), small cell carcinoma of the urinary bladder shows aggressive biological behavior and the prognosis is poor [1-5]. However, extensive immunohistochemical studies have not been performed in small cell carcinoma of the urinary bladder. KIT and platelet-derived growth factor receptor-α (PDGFRA) have been investigated only once [5] in small cell carcinoma of the urinary bladder.

Recent studies of SCLC showed that KIT protein is expressed in a significant percentage of SCLC [6-15]. In addition, one report showed that KIT gene mutations are present in SCLC [13], but others not [12, 14, 15]. PDGFRA protein in SCLC has not been reported. PDGFRA gene in SCLC has been investigated in one study [15], which showed no mutations.

KIT and PDGFRA, both mapped to 4q12, encode receptor tyrosine kinase oncoproteins called KIT (CD117) and PDGFRA, respectively [16-21]. Both molecules are transmembranous oncoproteins involved in tumorigenesis, in particular in gastrointestinal stromal tumor [16-21]. The author reports herein an autopsy case of small cell carcinoma of the urinary bladder with an emphasis on immunohistochemistry and on KIT and PDGFRA.

Case report

A 62-year-old woman was admitted to our hospital because of hematuria and dysuria. Bladder endoscopy revealed a large polypoid tumor at the bladder base. Transurethral bladder tumorectomy (TUR-BT) were performed. Many TUR-BT specimens were obtained. Histologically, the bladder tumor is pure small cell carcinoma consisting of small cells with hyperchromatic nuclei, inconspicuous nucleoli, molded nuclei, scant cytoplasm, and increased nucleo-cytoplasmic ratio (Figure 1A and 1B). An immunohistochemical study was performed with the used of Dako EnVision method as previously described [22-24]. Immunohistochemically, the tumor cells were positive for cytokeratin (CK) AE1/3 (Figure 2A), CK CAM5.2, CK8, CK18, neurone-specific eno-
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Table 1. Primer sequence

<table>
<thead>
<tr>
<th>Forward</th>
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<tr>
<td>KIT exon 9</td>
<td>5'-TCC TAG AGT AAG CCA GGG CTT-3'</td>
</tr>
<tr>
<td>5'-GAT CTA TTT TTC CCT TTC TC-3'</td>
<td>5'-AGC CCC TGT TTC ATA CTG AC-3'</td>
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<tr>
<td>5'-GCT TGA CAT CAG TTT GCC AG -3'</td>
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<td>5'-CTC CTC AAT CCT AAT GT-3'</td>
<td>5'-GTC AAG CAG AGA ATG GGT AC-3'</td>
</tr>
<tr>
<td>PDGFRA exon 12</td>
<td>5'-TTG GAT ATT CAC CAG TTA CCT GTC-3'</td>
</tr>
<tr>
<td>PDGFRA exon 18</td>
<td>5'-ACC ATG GAT CCA GTC TT-3'</td>
</tr>
<tr>
<td>5'-ACC ATG GAT CCA GTC TT-3'</td>
<td>5'-TGA AGG AGG ATG AGC CTG ACC-3'</td>
</tr>
</tbody>
</table>

A: Low power view of small cell carcinoma of the bladder. The tumor cells are medullary and consist of small cell with hyperchromatic nuclei. No differentiation is noted. Transurethral tumorectomy specimen, HE, x40. B: High power view of small cell carcinoma of the bladder. The tumor cells are small and show hyperchromatic nuclei, inconspicuous nucleoli, molded nuclei, scant cytoplasm and increased nucleo-cytoplasmic ratio. Transurethral tumorectomy specimen, HE, x200.

Discussion

The present urinary bladder tumor was apparent primary small cell carcinoma histologically. Immunohistochemical demonstration of neu-
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Ron-specific enolase, chromogranin, synaptophysin, NCAM (CD56) and KIT supports the diagnosis. Small cell carcinoma can occur in any organ, though the vast majority occurs in the lung. Small cell carcinoma of the urinary bladder is extremely rare. In general, small cell carcinoma is very aggressive tumor with poor prognosis.

There have been no comprehensive immunohistochemical studies in small cell carcinoma of the urinary bladder. The present case showed the immunoprofile. CK immunoprofile of bladder small cell carcinoma have not been reported. In the present case, the CK profile was CK AE1/3 +, CK CAM5.2 +, CK8 +, CK5/6 -, CK 34BE12 -, CK7 -, CK14 -, CK19 -, and CK20 -. The CK7-/CK20- pattern is compatible with primary bladder small cell carcinoma. Neuroendocrine antigens (chromogranin, synaptophysin, NCAM, neuron specific enolase) were all positive, indicating that the present tumor is small cell neuroendocrine carcinoma. p63 was negative, indicating that the present tumor is not urothelial carcinoma. Ki-67 labeling was 100%, indicating very high proliferative activity of this tumor. p53 was positive, suggesting p53 gene mutation. CD45 was negative, indicating that the tumor cells are not hematopoietic cells. TTF-1 was negative, suggesting that the present tumor is not metastasis from SCLC.

KIT and PDGFRα gene mutational status has been reported only once in small cell carcinoma of the urinary bladder [5]. The report showed no mutations of KIT and PDGFRα genes. KIT is expressed in various tumors including gastrointestinal stromal tumor (GIST), mast cell neoplasm, melanoma, germ cell tumor, hematopoietic malignancies and SCLC [16, 21]. The KIT protein expression in SCLC varies among researchers [6-15]; it is reported to be 100% [6], 73% [7], 37% [8], 60% [9], 78% [10], 53% [11], 40% [13], 64% [14], and 30% [14]. KIT expression without KIT gene mutations is thought to be due to KIT gene amplification [15]. The prognostic implications of positive KIT protein in SCLC is controversial and no definite conclusions were obtained [7-10, 13]. If activating KIT mutations are present, treatment of imatinib may be effective [15, 21]. KIT mutations are frequent in GIST, acute myeloid leukemia and mast cell neoplasms [21]. With regard to SCLC, one report showed KIT mutations [13], while others indicated no KIT mutations in SCLC [10, 12, 14]. Boldrini et al. [13] reported two mutations in exon 9 and three mutations of exon 11 in KIT gene were found in 60 SCLC. In contrast, Sihto et al. [15] showed no KIT mutations in 31 SCLC. More studies of KIT mutations remain to be performed in small cell carcinoma.

Figure 2. Immunohistochemistry. The tumor cells are positive for cytokeratin AE1/3 (A), NCAM (CD56) (B), synaptophysin (C), KIT (D), and PDGFRA (E). Immunostaining, x200.
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To the best of my knowledge, there is only one study of PDGFRA mutations in small cell carcinoma. Sihto et al. [15] found no PDGFRA mutations in 31 SCLC. The present case also showed no PDGFRA mutations. PDGFRA protein expression has not been reported in small cell carcinoma. The present case showed weak expression of PDGFRA, suggesting that a small amount of PDGFRA is present in small cell carcinoma. Much more studies remain to be done in PDGFRA expression and PDGFRA gene mutations in small cell carcinoma.

In conclusion, the author reported a case of primary small cell carcinoma of the urinary bladder with immunohistochemical studies and molecular genetic analysis of KIT and PDGFRA.

Conflict of interest statement

The author declares that he has no conflict of interest.

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References

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