Nested variant of urothelial carcinoma of urinary bladder strongly expressing NSE, KIT and PDGFRA

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Abstract The nested variant of urothelial carcinoma (NVUC) of urinary bladder (UB) is very rare and is characterized by the presence of benign-appearing urothelial carcinoma cells in lamina propria, sparing surface urothelial involvement. It shows aggressive clinical course despite the benign-looking histology. A 72-year-old woman presented with dysuria. Cystoscopy revealed papillary infiltrative tumor, and transurethral resection of UB tumor (TUR-BT) was performed. It was composed of small three fragments, two of which showed urothelial carcinoma (UC) of low grade (G1) atypia. In one section, NVUC was seen. The nested areas showed small clusters of UC of mild atypia. They were remote from surface urothelium. The tumor was mildly invasive, and the pathological stage was pT1. Immunohistochemically, tumor cells were positive for various types of cytokeratins, EMA, p63, p53, MUC1, NSE, KIT, PDGFRA, Ki-67 (43%), NCAM and synaptophysin. This is the first case of NVUC of UV with neuroendocrine features and expressions of KIT and PDGFRA.

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1. Introduction

Nested variant (NV) of urothelial carcinoma (UC) (NVUC) of urinary bladder (UB) is histologically characterized by bland, benign-looking UC in lamina propria with nested and tubular patterns and without overlying urothelial carcinoma of the surface urothelial layer [1,2]. Atypia of NVUC is relatively mild [1,2]. High grade neoplasms with focal nests and tumors with overlying carcinoma in situ should not be included in this variant [2]. NVUC should be differentiated from von-Brunn’s nest, nephrogenic metaplasia, prostatic carcinoma, and inverted papilloma [1,2]. Clinically, NVUC shows relatively aggressive course.

NVUC of UB (NVUC-UB) is very rare, and only less than 50 cases have been reported [1]. A PubMed search revealed only 8 reports [3–9]. There have no reports of NVUC-UB with neuroendocrine features and expression of KIT and PDGFRA. The author reports such a rare case of NVUC-UB.

2. Case report

A 72-year-old woman presented with dysuria. Urinary test revealed occult blood and glucose. UB cystectomy revealed a papillary infiltrative tumor and transurethral UB tumorectomy (TUR-BT) was performed.

The TUR-BT was composed of three fragments (Fig. 1A and B). The maximal length of the three fragment (Fig. 1A) was 12 mm, 6 mm, and 5 mm. Two of the free fragment showed ordinary urothelial carcinoma (UC) of low grade (G1) atypia. In one section, NVUC was seen. The nested areas showed small clusters of UC of mild atypia (Fig. 1B). They were discontinuous with the surface urothelium (Fig. 1A and B).

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The tumor was mildly invasive, and the pathological stage was pT1; no apparent muscular invasion was seen. An immunohistochemical study was performed[10]. Immunohistochemically, tumor cells were positive for CK AE1/3, CK CAM5.2, CK 34BE12, CK7, CK8 (Fig. 1C), CK 18, CK19, EMA, p63, MUC1, NSE, KIT (Fig. 1D), platelet-derived growth factor-alpha (PDGFRA) (Fig. 1E) and Ki-67 (labeling index = 43%), and moderately positive for NCAM and synaptophysin. The tumor cells were negative for CK5, CK6, CK14, CK20, CEA, CA19-9, MUC2, MUC5AC, MUC6, chromogranin, PSA, CD10, and CD45. The pathologic diagnosis was NVUC based on WHO classification [1].

A molecular genetic analysis of KIT and PDGFRA was performed by the PCR direct sequencing method, as previously reported. It revealed no mutations of genes of KIT (exons 9, 11, 13, and 17) and PDGFRA (exons 12 and 18) genes. The patient was considered to be cured and is now followed-up.

3. Discussion

The most important findings of the present NVUC are strongly positive expressions of NSE, KIT and PDGFRA. Because NCAM and synaptophysin were moderately expressed in the present tumor, the present NVUC has neuroendocrine features. This is the first report of NVUC of UB showing relatively extensive neuroendocrine differentiation. The significance of the neuroendocrine features of the present NVUC should be elucidated after accumulations of this rare variant of UC of UB.

The present case is the first case of NVUC of UB with strong expression of KIT and PDGFRA. Since recently KIT and PDGFRA are related to neuroendocrine and stem cell antigens, the expression may be related to the neuroendocrine differentiation in the present tumor. KIT and PDGFRA expression in UB is recognized in rare primary small cell carcinoma and sarcomatous carcinoma, which showed strong expression of KIT and PDGFRA. In these cases, KIT and PDGFRA genes were analyzed but no mutations of the KIT and PDGFRA were found. In the present study, no mutations of KIT and PDGFRA were seen in hot spots of exons of KIT and PDGFRA. However, broad studies including all exons and introns are necessary. If mutations would be found, it is possible that imatinib mesylate may be effective.

Usual urothelial carcinoma of the UB may show nested patterns of invasion. Such a tumor is not NVUC [1]. NVUC of UB should be free from surface epithelial involvement [1–10]. In the present cases, no surface involvements were seen. NVUC is characterized by the presence of tumor cells in lamina propria; tumor cells are bland and

Fig. 1 Histology of the urinary bladder tumor (A, B, arrows). A is low power and B is high power views. The vertical section shows nested variant of urothelial carcinoma. The surface epithelial cells show no apparent carcinoma in situ. The tumor cells are located in mucosa not attached the epithelial layer. The tumor cells characteristically show nested appearance. The atypia is mild. A: HE, × 20. B: HE, × 100. C, D, E: Immunohistochemical features of the tumor (C, D, E). Immunohistochemically, the tumor cells were positive for CK8 (C), KIT (D), and PDGFRA (E): ×200.
benign-looking [1–10]. The NVUC shows mild atypia in superficial part and relatively severe atypia in deep areas. However, anaplasia is seen in some areas in superficial parts. In the present case, atypia was mild. In the present tumor, p53 was positive and Ki67 labeling was high, suggesting malignant potentials of the present tumor.

NVUC must be differentiated from prominent von Brunn’s nest, cystitis glandularis and cystica, nephrogenic metaplasia, inverted papilloma, carcinoid, prostatic carcinoma, paraganglion and paraganglioma [1]. The present tumor is not proliferated von Brunn’s nests, because the tumor showed mild atypia and immunohistochemical findings of positive p53 and relatively high Ki67 labeling. The present tumor is different from cystitis glandularis and cystica morphologically and immunohistochemically. The present case is different from nephrogenic metaplasia because the tumor showed positive p53 and high Ki67 and negative CD10, a marker of nephrogenic metaplasia. The present tumor is different from inverted papilloma histologically and because the tumor is malignant. The present tumor is different from carcinoid tumor histologically. Although it showed neuroendocrine differentiation, the current tumor is not neuroendocrine tumor (NET) because of different histology. NET requires endocrine tumor cells >50% of all tumor cell population. The present case is not metastatic prostatic carcinoma because of negative PSA. The current tumor is different from paraganglion and paraganglioma because of positive cytokeratins.

Immunohistochemical study of NVUC was done in only one; Wasco et al. [3] demonstrated that NVUC was positive for CK7 in 93%, CK20 in 68%, and p63 in 92%. The present study is the first showing extensive immunohistochemical features of NVUC. In the present case, CK7 was positive, CK20 was negative and p63 was positive. The present study demonstrated the CK immunoprofile. Tp53 was positive in the present case and Ki67 labeling was relatively high in the present case, suggesting the p53 mutations and high cell proliferation. CD10 was negative, suggesting that the present tumor is not nephrogenic metaplasia. The negative reactions of CEA and CA19-9 suggest no glandular differentiation. The positive MUC1 apomucin does not imply glandular differentiation because MUC1 is transmembranous non-sec- retory mucins. The negative MUC2, MUC5AC and MUC6 suggest that MUC genes were not expressed in NVUC. CD45 negativity suggests that the tumor is not lymphoma.

Clinically, NVUC affects predominantly male [1–9]. Wasco et al. [3] showed that male to female ratio was 2.3:1. The present case was 72-year old female. NVUC showed aggressive clinical course in spite of deceptively benign-appearing histology [1–9]. The present case is now of free from tumor, although the follow-up is short (5 months). Strict follow-up is needed.

There are no previous studies of NVUC that attempted neuroendocrine features. Usually, diagnostic pathologists do not investigate the neuroendocrine (NE) antigens, but the author attempted NE antigen expressions in the present case because the author has studied NE features of various tumors of non-urogenital organs: the author always has performed NE expressions in relatively rare tumors. The tumor of the current case shows no features of NE tumor (carcinoid or NE carcinoma) on HE stains. The reason for this is unclear. However, it is well known that some carcinomas show immunohistochemical NE features (neuroendocrine differentiation) without no HE features of NE differentiation. Regrettfully, no electron-microscopic (EM) observations are done in the present tumor and other tumors. These issues are future problems. The NV-UC has been rarely been reported. The histological variability of bladder urothelial carcinoma is relatively wide. It is uncertain whether or not the clinicopathological entity of NV-UC is of value. One feature is the fact that NV-UC can resemble von-Brunn’s nest, cystitis glandularis and cystica, or non-invasive urothelial carcinoma invading into von Brunn’s nest. More accumulation of NV-UC cases is necessary to disclose histogenesis, diagnostic pathologic problems, and clinical course.

The author has no conflict of interest.

References