Case Report
Rhabdoid variant of urothelial carcinoma of the urinary bladder: a case report with emphasis on immunohistochemical analysis regarding the formation of rhabdoid morphology

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Received June 11, 2015; Accepted July 23, 2015; Epub August 1, 2015; Published August 15, 2015

Abstract: Various histological variants of urothelial carcinoma (UC) have been described. They are associated with different clinical outcomes and/or therapeutic approaches; in addition, recognition of these histological variants is also important in preventing diagnostic misinterpretations. Histological variants based on cytoplasmic features, such as plasmacytoid, rhabdoid, clear-cell, and lipoid-rich variants, have been described in invasive UC. Herein, we report an exceedingly rare case of a rhabdoid variant of UC arising in the urinary bladder of a 61-year-old man. Including UC, the presence of rhabdoid cells has been described in various types of malignant tumors. These tumors are regarded as more aggressive neoplasms than those without rhabdoid cells. It has been previously found that non-degraded aggregation of intermediate filaments and membrane proteins conjugated with ubiquitin and p62 is a noticeable finding in the formation of rhabdoid morphology. We have validated the existence of this mechanism in a rhabdoid variant of UC by extensive immunohistochemical analysis.

Keywords: Immunohistochemistry, p62, rhabdoid variant, ubiquitin, urinary bladder, urothelial carcinoma

Introduction

Urothelium can display a wide range of metaplastic changes and neoplasms arising from this epithelium show various morphologies, particularly in high-grade neoplasms [1]. The spectrum of morphology of urothelial carcinoma (UC) has been expanded to include several unusual histological variants. Recognizing histological variants in UC is important because some may be associated with different clinical outcomes and/or therapeutic approaches compared with conventional UC, and being aware of unusual histological variants may be crucial in preventing diagnostic misinterpretations [2]. Other than UC with squamous and/or glandular differentiation seen both in non-invasive and invasive components, histological variants are usually observed in invasive components, in which UC with unusual cytoplasmic features, such as plasmacytoid, rhabdoid, clear-cell (glycogen rich), and lipoid-rich features, are included [2].

The presence of rhabdoid cells has been documented in various types of malignant tumors of both mesenchymal and epithelial origins [3-7], in addition to extremely rarely encountered rhabdoid variant of UC [1, 2, 8, 9]; these tumors are regarded as more aggressive neoplasms than those without rhabdoid cells because rhabdoid cells probably reflect phenotypic deviation during tumor progression or dedifferentiation [10].

Herein, we report a case of a rhabdoid variant of UC arising in the urinary bladder, with an emphasis on the molecular mechanisms resulting in the formation of rhabdoid morphology. We applied various markers of immunohistochemistry (IHC) to reveal the mechanism, and present characteristics of rhabdoid tumor cells in UC.
Clinical summary

A 61-year-old man presented with hematuria persisting for 2 weeks. He had no other complaints. Urine cytology was performed, and it identified many atypical cells consistent with UC. On computed tomography, multiple protrusions suspicious of papillary UC were observed in the urinary bladder (Figure 1). Lymph node swelling and distant metastases were not found. Total cystectomy was performed with negative surgical margins. The pathological diagnosis was rhabdoid variant of UC, evaluated as pT2a. The patient’s postoperative course was uneventful, and he has been recurrence-free for 2 years.

Pathological findings

The surgically resected specimen revealed multiple elevated lesions extending nearly the entire length of the anterior and lateral wall (Figure 2A). The cut surface of it showed an apparently invasive lesion only at the anterior wall. The invasive lesion measured 12 × 10 × 8 mm (Figure 2B).

On histopathological analysis, approximately 90% of the tumor was composed of non-invasive UC in which an inverted growth pattern is prominent (Figure 2A). The tumor cells have a high nuclear to cytoplasmic ratio with intermediate grade nuclei (Figure 2A, inset). The invasive component accounted for approximately 10% with an abrupt transition between invasive and non-invasive components. The invasion reached the superficial layer of the muscularis propria. The tumor stroma was myxoid (Figure 2B). In the invasive area, tumor cells showed rhabdoid morphology, i.e., abundant eosinophilic cytoplasm with inclusion-like stained areas and eccentric nuclei containing distinct nucleoli (× 600).

Figure 1. Computed tomography findings. Multiple protrusions suspicious of papillary urothelial carcinoma are observed in the urinary bladder.

Figure 2. Histological findings. A. In the areas of non-invasive urothelial carcinoma, an inverted growth pattern is prominent (× 40). Inset: The tumor cells have a high nuclear to cytoplasmic ratio with intermediate grade nuclei (× 400). B. In the invasive area, the invasion reached the superficial layer of muscularis propria. The tumor stroma was myxoid (× 20). C. In the invasive area, tumor cells show rhabdoid morphology, i.e. abundant eosinophilic cytoplasm with inclusion-like stained areas and eccentric nuclei containing distinct nucleoli (× 600).
Upon IHC, the cytoplasm of the rhabdoid tumor cells showed inclusion-like immunoreactive patterns for CK7 (OV-TL 12/30, 1:100; Dako) (Figure 3A), CK20 (Ks20.8, 1:100; Dako) (Figure 3B), vimentin (V9, 1:100, Dako) (Figure 3C), E-cadherin (NCH-38, 1:100; Dako) (Figure 3D), β-catenin (β-catenin-1, 1:100; Dako) (Figure 3E), ubiquitin (polyclonal, 1:400; Dako) (Figure 3F), and p62 (ab-56416, 1:200; Epitomics) (Figure 3G). The rhabdoid tumor cells were negative for high molecular weight cytokeratin (34βE12, 1:100; Dako). Immunopositivity for p63 (4A4, 1:100; Dako) was observed in the nuclei of rhabdoid tumor cells. INI1 (BAF47, 1:100; BD Bioscience, Oxford, UK) (Figure 3H) expression was maintained in the nuclei of the rhabdoid tumor cells.

Although the tumor exhibited widespread extension in the urinary bladder with rather conventional cellular morphology, the diagnosis of rhabdoid variant of UC was made due to the results of the histological, immunohistochemical, and electron microscopy studies of the invasive area. Myxoid stroma of the tumor did not affect the diagnosis, since myxoid stroma was found to be associated with rhabdoid variant of UC in some cases [8].

Discussion

An abrupt transition was observed between the non-invasive component and the invasive component showing rhabdoid morphology in our case. In a previous study of renal pelvic UC with rhabdoid morphology by Fukumura et al., an abrupt transition was also described between non-invasive and invasive components [9]. They conducted loss of heterozygosity analysis and found that identical allelic losses/shifts were present in both components, suggesting a single clonal origin. It was also discovered that...
additional different allelic losses for each component were present, implying that tumor cells of each component gained different genetic alterations during progression after originating from the same clone [9]. In our case, a genetic analysis was not performed, but it was also supposed that the tumor cells with rhabdoid morphology developed from the same clone as that of the non-invasive tumor cells even though the transition between them was abrupt.

The prototype of a malignant tumor with rhabdoid morphology is malignant rhabdoid tumor of the kidney [11]. In addition to this tumor, atypical teratoid/rhabdoid tumors of the central nervous system are also a well-defined entity containing rhabdoid cells [12]. These tumors show lost expression of INI1, a member of the SWI/SNF complex, due to deletions and mutations involving the INI1/hSNF5 tumor suppressor gene on chromosome 22q11.2 [13]. Lost expression of INI1 has been documented in other tumors containing rhabdoid tumor cells [14-16]. In one study, lost expression of INI1 was suggested to occur as a result of additional genetic alteration of the SMARCB1/INI1 gene in rhabdoid tumor cells of renal cell carcinoma [15]. Another study reported some cases of clear cell renal cell carcinoma with rhabdoid tumor cells that had lost INI1 expression [16]. Therefore, genetic alteration of the SMARCB1/INI1 gene as evaluated by immunohistochemical INI1 expression may be involved in the formation of the rhabdoid morphology of tumor cells; however, it is not the only factor involved in the development of rhabdoid tumor cells. In fact, INI1 expression was maintained in our case. To the best of our knowledge, expression of INI1 in rhabdoid variant of UC has not been examined in other cases.

Another member of the SWI/SNF complex, BRG1, derived from the SMARCA4/BRG1 gene, may be involved in the development of rhabdoid tumor cells, as indicated by cases of renal cell carcinoma and endometrioid adenocarcinoma that have lost BRG1 expression in rhabdoid tumor cell components [15, 17]. In our case, although INI1 expression was not affected, other members of the SWI/SNF complex might be involved in the formation of rhabdoid cell components.

Membrane proteins, such as E-cadherin and β-catenin, might also be accumulating in cytoplasmic inclusions of rhabdoid tumor cells, in which aggregation of intermediate filaments is usually observed, based on a study of pancreatic anaplastic carcinoma with rhabdoid morphology by Sano et al. [18]. Resultant decreased expression of E-cadherin and β-catenin in the cellular membrane is reflected in the discontinuity of rhabdoid tumor cells [18]. In their study, intracytoplasmic aggregation of intermediate filaments, E-cadherin, and β-catenin were associated with ubiquitin and p62. p62 is associated with intracellular aggregation in a variety of diseases, such as Mallory bodies of alcoholic hepatitis and Lewy bodies of Parkinson’s disease [19], and aggregates containing both ubiquitin and p62 are degraded by the selective autophagy system [20]. It is thus postulated that intracellular aggregates containing ubiquitin and p62 reflect dysfunction of the autophagy system. In our case, aggregation of intermediate filaments, E-cadherin, and β-catenin in association with ubiquitin and p62 was also observed, the same pattern as that seen in the study by Sano et al. [18]. Thus, it is supposed that at least in certain cases of tumors with rhabdoid morphology, dysfunction of the autophagy system is contributing to the development of its morphology.

Prognosis of rhabdoid variant of UC is considered to be poor as is generally true of tumors with rhabdoid morphology, which was described in a study by Parwani et al. [8]. In our case, the patient has been recurrence-free for 2 years; it seems that the prognosis of the patient is not poor at present. This might be partly due to the fact that the size of the rhabdoid component is limited to 12 × 10 × 8 mm in our case and the size of it is much smaller than those described in the series of Parwani et al. [8]. In addition, the extension of the tumor in our case is restricted only to the superficial layer of the muscularis propria. However, very careful follow-up of our patient is required considering the generally accepted notion that tumors with rhabdoid morphology behave aggressively [10].

In conclusion, this is an exceedingly rare case of the rhabdoid variant of UC. Our report is the first case, other than some cases of pancreatic carcinoma, to describe aggregations of intermediate filaments and membrane proteins, such as E-cadherin and β-catenin, in the cytoplasm of carcinoma cells. The aggregations also contained ubiquitin and p62. This is thought to reflect dysfunction of the autophagy system and may be involved in the formation of rhabdoid morphology in some tumors. Although
expression of INI1 was maintained in our case, IHC of members of the SWI/SNF complex, including INI1, might provide important information when considering the genetic aspects of carcinoma cells with rhabdoid morphology as evidenced by cases of renal cell carcinoma.

Disclosure of conflict of interest

None.

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