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Case Report

Transition between urothelial carcinoma in situ and non-invasive micropapillary carcinoma as a pivot connection between diverse morphologies of bladder carcinoma: a case report of urothelial carcinoma with villoglandular differentiation

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Abstract: Urothelial carcinoma has numerous histological variants, and these variants may coexist in a single case. Here, we present a case of a 70-year-old man with urothelial carcinoma of the bladder with a maximal diameter of 5 mm that involved micropapillary and plasmacytoid variants, with villoglandular differentiation. The presence of these variants was confirmed by pathological examination of a transurethral resection specimen, and high-grade urothelial carcinoma was found as a minor component. Although this bladder carcinoma was classified as pT1, cystoprostatectomy, urethrectomy, and lymphadenectomy were performed due to the presence of the micropapillary and plasmacytoid variants, which are known to be aggressive. Examination of a surgically resected specimen revealed no carcinoma. A transition between urothelial carcinoma in situ and non-invasive micropapillary carcinoma was found to be a pivot point connecting the diverse morphologies of this bladder carcinoma, from which there existed two pathways. One pathway was from urothelial carcinoma in situ to the plasmacytoid variant through invasive high-grade urothelial carcinoma, and the other was from non-invasive micropapillary carcinoma to urothelial carcinoma with villoglandular differentiation or to the micropapillary variant. This is the 16th reported case of urothelial carcinoma with villoglandular differentiation in the literature. As urothelial carcinoma with villoglandular differentiation is often associated with aggressive variants, as shown in our case, it should be reported whenever encountered in routine pathological practice.

Keywords: Urinary bladder, urothelial carcinoma, non-invasive micropapillary carcinoma, urothelial carcinoma with villoglandular differentiation, micropapillary variant, plasmacytoid variant

Introduction

Urothelial carcinoma exhibits numerous histological variants such as the micropapillary, plasmacytoid, nested, microcystic, lymphoepithelioma-like, inverted papilloma-like, lipoid cell, clear cell, and sarcomatoid variants [1]. Among these, the micropapillary, plasmacytoid, nested, lipoid cell, and sarcomatoid variants are considered more aggressive [1]. The micropapillary variant was first described by Amin *et al.* in 1994 [2]. They also discussed non-invasive (surface) micropapillary carcinoma as a preinvasive state of the micropapillary variant. Since then, the aggressive nature of the micropapillary variant has been widely documented and has become well known [3]. The plasmacytoid variant was first noted by Zukerberg *et al.* in 1991 [4]. The aggressive nature of the plasmacytoid variant has been much more emphasized recently, and this variant might in fact be more aggressive than the micropapillary variant [3, 5].

Urothelial carcinoma with villoglandular differentiation was first documented by Lim *et al.* in 2009, and their report included 14 cases [6]. They pointed out the coexistence of urothelial carcinoma with aggressive variants, especially micropapillary and plasmacytoid. Since then,

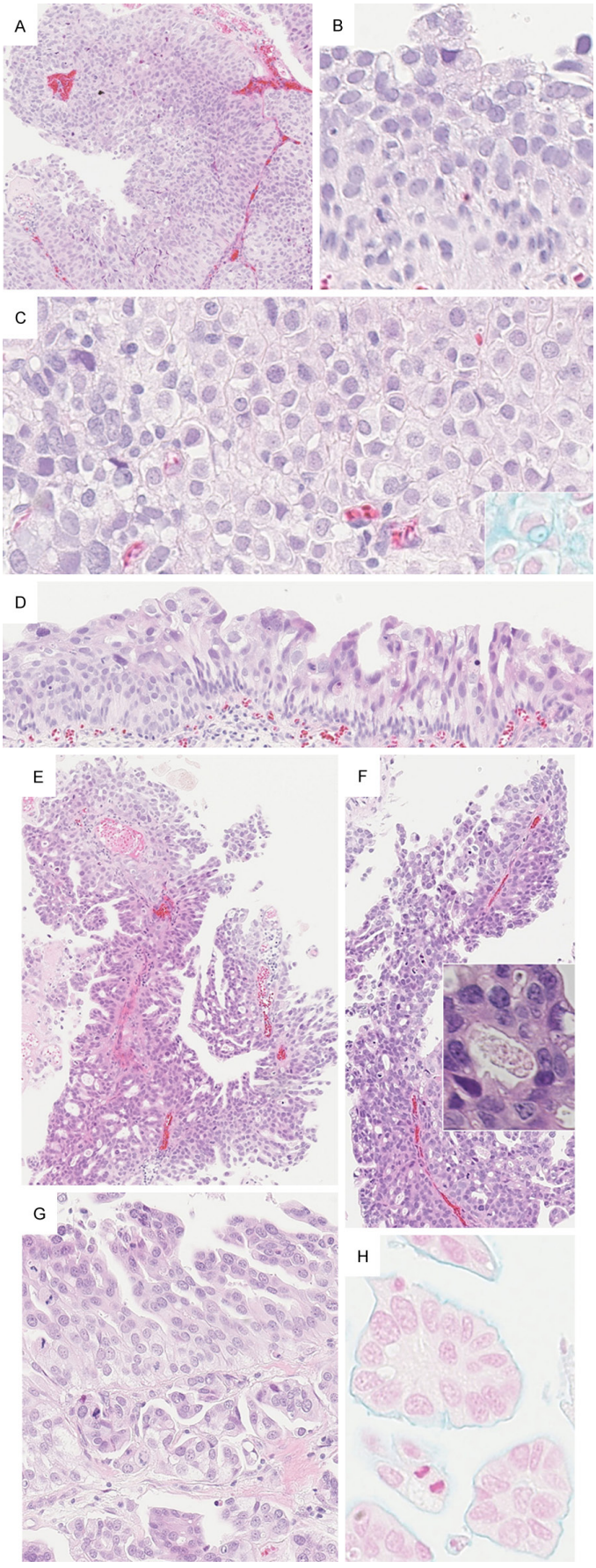

Figure 1. Microscopic findings. A. Non-invasive high-grade papillary urothelial carcinoma consisting of tumor cells with moderate-to-severe nuclear atypia, high nucleus-to-cytoplasm ratio, and distorted cellular polarity (× 40). B. Urothelial carcinoma in situ seen as a flattened lesion. It consists of tumor cells with moderate nuclear atypia and cellular dispolarity (× 400). C. A transition between invasive high-grade urothelial carcinoma with moderate-to-severe nuclear atypia (left) and the plasmacytoid variant (right) is observed. Nuclear atypia of the latter is mild-to-moderate and the nucleus-to-cytoplasm ratio is decreased due to the abundant, weakly eosinophilic cytoplasm. Inset: intracytoplasmic lumina stained blue with Alcian blue (× 400). D. Transition between urothelial carcinoma in situ (left) and non-invasive micropapillary carcinoma (right). The latter contains many small papillary clusters of tumor cells and cuboidal-to-columnar cells with moderate-to-severe nuclear atypia (× 200). E. Urothelial carcinoma with villoglandular differentiation composed of finger-like projections covered by tumor cells showing patchy cribriform gland formation (× 20). F. Another view of urothelial carcinoma with villoglandular differentiation (× 20). Inset: tumor cells form a lumen containing secretions and have moderate-to-severe nuclear atypia (× 400). G. Transition between non-invasive micropapillary carcinoma (upper) and the micropapillary variant (lower). The latter has seemingly floating tumor nests (× 200). H. Reversed apical membrane pattern of the micropapillary variant is observed on Alcian blue staining; the outer membranes of the tumor nests are stained blue (× 600).

only one case has been reported in the English literature, and this was in 2014 [7].

Here, we present a case of urothelial carcinoma showing diverse morphologies, one being an extremely rare urothelial carcinoma with villoglandular differentiation. The micropapillary and plasmacytoid variants were also present. We considered the transition between urothelial carcinoma in situ and non-invasive micropapillary carcinoma found in this case, which connected these different morphologies, to be very important. We also produced a schema illustrating the connections between components of this carcinoma.

Clinical summary

A 70-year-old man presented with dysuria. Ultrasonography was performed, and benign prostatic hyperplasia was suspected; a small mass was also detected in the bladder. Urine cytology revealed atypical cells. Subsequently, cystoscopy was performed, revealing a papillary tumor on the posterior wall of the bladder with a maximal diameter of 5 mm. Transurethral resection (TUR) was carried out at the same time. Although histopathological analysis of the TUR specimens showed high-grade urothelial carcinoma and its histological variants indicated aggressive behavior, invasion of the muscularis propria was not evident, and the tumor was thus classified as stage pT1. Because of concerns regarding potential recurrence, we performed cystoprostatectomy, urethrectomy, and lymphadenectomy, and carried out pathological examination, which demonstrated no residual tumor cells or lymph node metastasis. The postoperative course was uneventful and the patient now undergoes regular follow-up.

Pathological findings

Analysis of the TUR specimens revealed non-invasive high-grade papillary urothelial carcinoma (5%), urothelial carcinoma with villoglandular differentiation (15%), non-invasive micropapillary carcinoma (25%), urothelial carcinoma in situ (10%), the micropapillary variant (35%), invasive high-grade urothelial carcinoma (5%), and the plasmacytoid variant (5%). The non-invasive high-grade papillary urothelial carcinoma consisted of tumor cells with moderate-to-severe nuclear atypia and high nucleus-to-cytoplasm ratio; cellular polarity was distorted (**Figure 1A**). Urothelial carcinoma in situ, which was in the form of a flattened lesion consisting of tumor cells with moderate nuclear atypia and cellular dispolarity (**Figure 1B**), showed transition to invasive high-grade urothelial carcinoma with moderate-to-severe nuclear atypia; invasive high-grade urothelial carcinoma also showed transition to the plasmacytoid variant. The nuclear atypia of the plasmacytoid variant cells was mild to moderate and the nucleus-to-cytoplasm ratio was decreased due to abundant, weakly eosinophilic cytoplasm (**Figure 1C**). These cells had eccentric nuclei, and some contained intracytoplasmic lumina (ICL), which stained blue with Alcian blue (**Figure 1C**, inset). Urothelial carcinoma in situ also showed transition to non-invasive micropapillary carcinoma, which contained many small papillary clusters of tumor cells and comprised cuboidal-to-columnar cells with nuclei with moderate-to-severe atypia (**Figure 1D**). Non-invasive micropapillary carcinoma was focally continuous with the urothelial carcinoma with villoglandular differentiation. The latter was composed of finger-like projections covered by tumor cells showing patchy cribriform gland formation (**Figure 1E**, **1F**). Its tumor cells were cuboidal to columnar in shape with some glands containing secretions, and they had nuclei with moderate-to-severe atypia (**Figure 1F**, inset). Non-invasive micropapillary carcinoma also exhibited transition to the micropapillary variant. The former existed in the overlying mucosa and the latter was situated in the adjacent stroma as a form of invasion (**Figure 1G**). The micropapillary variant displayed seemingly floating tumor nests with a characteristic reversed apical membrane pattern and moderate-to-severe nuclear atypia in the constituent tumor cells. A reversed apical membrane pattern was observed with Alcian blue staining; the outer membranes of the tumor nests were stained blue (**Figure 1H**). The muscularis propria was present in the specimen, and showed no invasion. Therefore, the tumor was classified as stage pT1.

Immunohistochemical (IHC) analysis results indicated that the non-invasive high-grade papillary urothelial carcinoma, urothelial carcinoma in situ, and invasive high-grade urothelial carcinoma were positive for CK7 (OV-TL 12/30, 1:100; Dako, Glostrup, Denmark), CK20 (KS20.8, 1:100; Novocastra, Newcastle, UK), CD138 (5F7, 1:50, Novocastra), and p63 (4A4, 1:100; Dako). The plasmacytoid variant was positive for CK7 and CD138 (**Figure 2A**), and negative for CK20 and p63. E-cadherin (NCH-38, 1:100; Dako) was not expressed in the plasmacytoid variant (**Figure 2B**). Non-invasive micropapillary carcinoma, urothelial carcinoma with villoglandular differentiation, and the micropapillary variant were positive for CK7 and CD138, weakly positive for CK20, and negative for p63. EMA (E29, 1:100; Dako) and MUC1 (Ma695, 1:100; Novocastra) did not highlight the outer membrane of the tumor nests of the micropapillary variant because of its diffuse cytoplasmic staining.

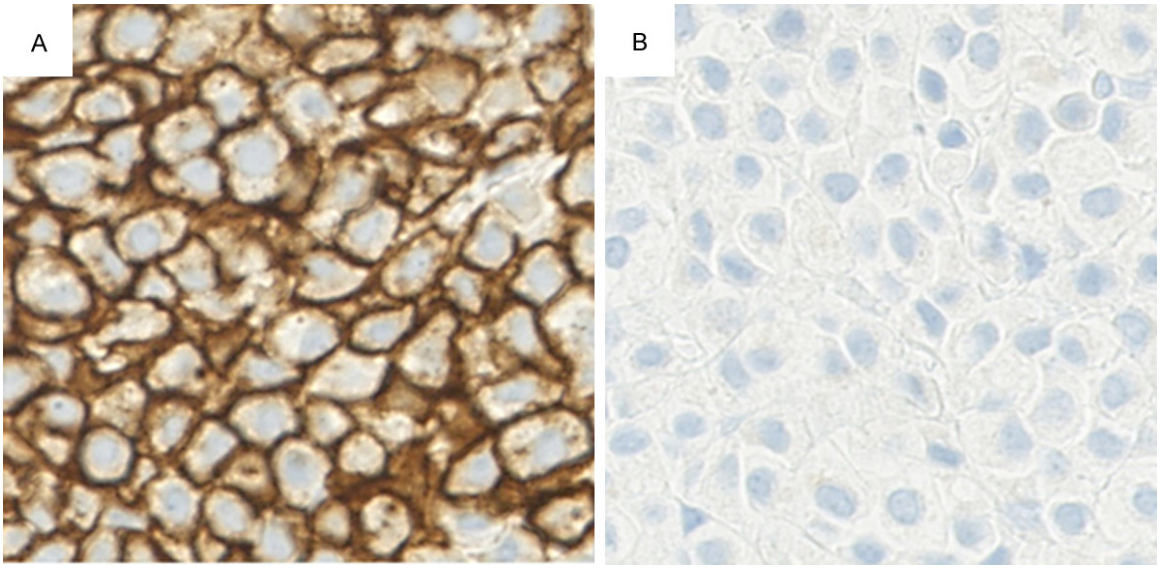

Figure 2. Immunohistochemical findings of the plasmacytoid variant. A. Positive for CD138 (× 400). B. Negative for E-cadherin (× 400).

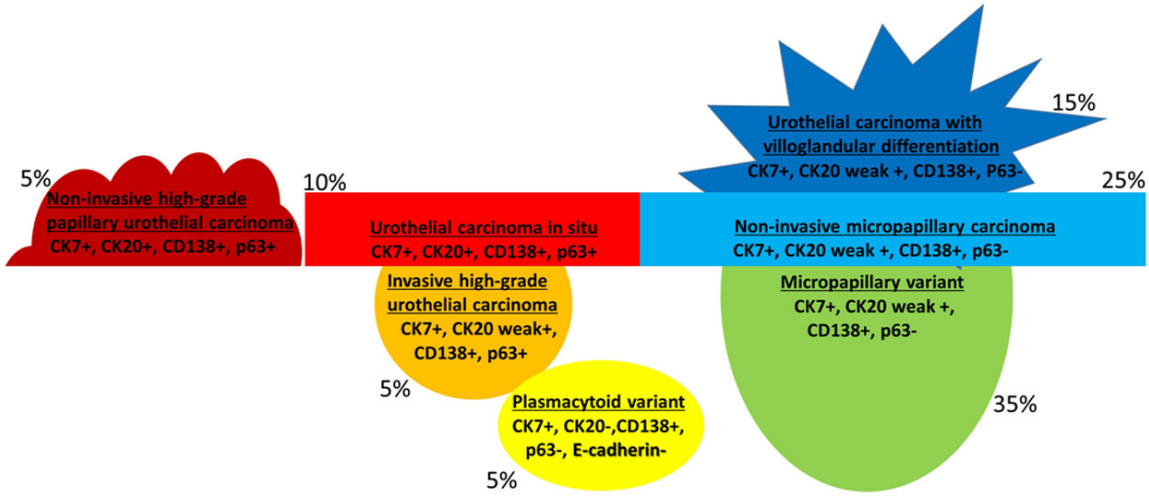

Figure 3. Schema of the bladder carcinoma in the present case. Careful microscopic inspection allowed us to speculate the tumor as a continuum, even from transurethral resection specimens. Transition between urothelial carcinoma in situ and non-invasive micropapillary carcinoma played a pivotal role, connecting all the components except non-invasive high-grade papillary urothelial carcinoma.

Cystoprostatectomy specimens revealed no carcinoma cells in the urinary bladder and prostate on macroscopic and microscopic examination. No lymph node metastasis was found.

Discussion

TUR specimens did not contain the entire tumor as a single mass, but careful microscopic inspection allowed us to speculate the original configuration of the tumor. The schema showing the speculated connections between the different tumor components is provided in **Figure 3**. In this schema, the transition between urothelial carcinoma in situ and non-invasive micropapillary carcinoma connects the diverse histological components observed in this case. Of note, non-invasive high-grade papillary urothelial carcinoma does not connect to other components. We considered the urothelial carcinoma with villoglandular differentiation and the micropapillary variant as showing a

type of glandular differentiation. The plasmacytoid variant, which is immunohistochemically characterized by CK7 and CD138 expression and decreased expression of CK20 [8] along with loss of E-cadherin [9], is also considered a tumor with a type of glandular differentiation [8, 9]. In fact, ICLs are often seen in the plasmacytoid variant, which can be easily observed using routine histochemical stains such as Alcian blue, PAS-D, and mucicarmine [8, 9]. The immunonegativity of p63 upon IHC analysis might be helpful when distinguishing these carcinomas with a type of glandular differentiation from conventional urothelial carcinomas [10]; this finding was observed in the present case. Therefore, except non-invasive high-grade papillary urothelial carcinoma, urothelial carcinoma in situ, and invasive high-grade urothelial carcinoma, which are frequently present as components of bladder carcinomas and occupied 20% of the mass in the present case, all the other components showed some degree of glandular differentiation. In this case, we suspect a field effect, which promotes a type of glandular differentiation of bladder carcinoma.

The urothelium can undergo phenotypic differentiation on the cellular and structural level through several pathways even in adults, which results from the embryonic origin of the bladder from the cloacal endoderm and the mesodermal Wolffian ducts, both of which are multipotent tissues [11]. A cell line study has also revealed that urothelial carcinoma is capable of undergoing glandular and squamous differentiation [12]. The potential for phenotypic differentiation on the cellular and structural level could be passed on to the carcinoma counterpart, which seems to be reflected in this case as a presentation with diverse morphologies.

Urothelial carcinoma with villoglandular differentiation tends to be associated with aggressive variants [6]. Including this case, the micropapillary variant was associated with it in 38% (6/16) of cases, while the plasmacytoid variant was present in 25% (4/16). The coexistence of the micropapillary and plasmacytoid variants was observed in 13% (2/16) of cases [6, 7]. Apart from the 2 cases containing urothelial carcinoma with villoglandular differentiation, only five cases harboring both micropapillary and plasmacytoid variants have been reported in the English literature [13-15]. Including our case, other aggressive variants and tumor subtypes, such as the sarcomatoid variant (6%; 1/16 cases), adenocarcinoma (25%; 4/16 cases), small cell carcinoma (6%; 1/16 cases) have been observed to be associated with urothelial carcinoma with villoglandular differentiation [6, 7]. Given its propensity for relationships with aggressive variants and tumor subtypes, the presence of urothelial carcinoma with villoglandular differentiation should be reported in the routine practice even when there is no invasive component; this situation is postulated when a tiny biopsy specimen derived from superficial tissue is submitted to pathological examination.

The differential diagnosis of urothelial carcinoma with villoglandular differentiation includes in situ adenocarcinoma and villous adenoma with coexisting adenocarcinoma [6]. In situ adenocarcinomas could display a papillary architecture, but do not have finger-like projections [16]. Villous adenoma has finger-like projections lined by pseudostratified columnar epithelium, which cannot be differentiated from villous and tubulovillous adenomas of the colon [17]. In villous adenoma, coexisting adenocarcinomas usually have an in situ component [18]; it is thus difficult to distinguish urothelial carcinoma with villoglandular differentiation from villous adenoma with an adenocarcinoma component. The lining epithelium is a distinguishable feature between these types. Urothelial carcinoma with villoglandular differentiation is not composed of columnar cells exhibiting nuclear pseudostratification, which is characteristic of villous adenoma [6].

In conclusion, in the present case there was a transition between urothelial carcinoma in situ and non-invasive micropapillary carcinoma. This finding connects a number of components showing a form of glandular differentiation, such as urothelial carcinoma with villoglandular differentiation, and the micropapillary and plasmacytoid variants. This is the 16th reported case of urothelial carcinoma with villoglandular differentiation. Because it tends to be associated with aggressive variants and tumor subtypes, urothelial carcinoma with villoglandular differentiation should be reported whenever encountered.

Disclosure of conflict of interest

None.

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