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= **Abstract** =

Cytologic Findings of a Plasmacytoid Variant of Urothelial Carcinoma of the Urinary Bladder in Voided Urine

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The plasmacytoid variant is an extremely rare form of urothelial carcinoma in which the malignant cells resemble those of plasmacytoma. We report the cytologic features of 3 cases of this disorder. All 3 patients were male and presented with painless macroscopic hematuria. The voided urine cytology revealed a few scattered clusters of tumor cells in a bloody background. Each tumor cell had an abundant amount of cytoplasm that was clear or densely stained and characterized by eccentrically located nuclei. A histological examination of tissue obtained from a radical cystectomy confirmed the cytologic diagnosis in each 3 case, revealing a diffusely infiltrating tumor composed of round, noncohesive tumor cells demonstrating a high nuclear grade. These cells had infiltrated the tunica propria in 2 cases, but were limited to the submucosa in 1 case. The tumor cells were plasmacytoid in appearance, each demonstrating an eccentric nucleus and dense cytoplasm, as seen in the cytologic findings. All of the tumors were immunoreactive for pancytokeratin, CK7, CK20; negative for epithelial membrane antigen (EMA), leukocyte common antigen (LCA), kappa, lambda, and CD79a. Thus, it is important to consider the plasmacytoid variant of urothelial carcinoma in addition to plasmacytoma or lymphoma as a diagnosis when encountering plasmacytoid tumor cells in a voided urine sample.

Key words: Plasmacytoid urothelial carcinoma, Urinary bladder, Urine, cytology

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INTRODUCTION

Urothelial carcinoma of the urinary bladder may differentiate into any of many histologic variants that have been described in recent years. The plasmacytoid variant of urothelial carcinoma was introduced by Sahin et al.[1] in 1991 and has rarely has been reported.1-6 In this article, we present 3 cases of this rare variant, which was diagnosed on the basis of cytologic findings in voided urine.

CASE

Clinical Findings

Case 1: A 47-year-old man presented with a history of painless macroscopic hematuria for 2 months. The additional medical history was nonspecific. A computed tomography (CT) scan of the abdomen showed a broad-based soft tissue density at the dome and along the both lateral walls of the urinary bladder and both hydronephroses. Cystoscopy and a retrograde pyelogram also revealed a diffusely infiltrating tumor involving the dome and both lateral walls of the urinary bladder. A cystoscopic biopsy was performed. The patient subsequently underwent a radical cystectomy, at which time of involvement multiple lymph nodes and metastasis to the liver were seen. He received 3 cycles of chemotherapy postoperatively. Three months after the operation, he died.

Case 2: A 70-year-old man with a history of macroscopic hematuria for 8 months was seen clinically with a luminal mass measuring 6 × 6 × 6 cm protruding from the dome of urinary bladder, as detected by CT scan. He underwent a cystoscopic biopsy and then a radical cystectomy, after which he received 3 cycles of chemotherapy. The postoperative follow-up at 3 years, including another CT scan, revealed no evidence of recurrent or metastatic disease.

Case 3: A 55-year-old man was admitted with a complaint of painless gross hematuria for 6 months. His past medical history was unremarkable. A cystoscopy revealed a sessile mass measuring 1.5×1.0×1.0 cm along the left posterolateral wall of the bladder. He underwent a transurethral resection and radical cystectomy 1 month later. The patient was well and without evidence of disease at a 2.5-year follow-up.

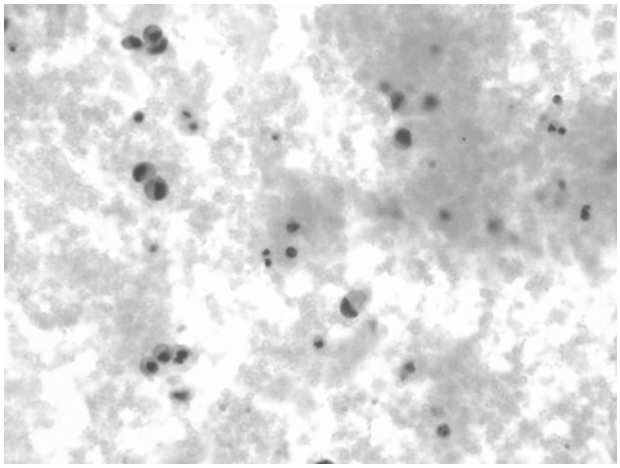

Fig. 1. Low-power cytologic finding in Case 1. The urinary sediment smear reveals large, individual, scattered tumor cells in a bloody background. (H-E)

Cytologic Findings

The voided urine samples in all 3 cases were submitted for screening before biopsy. Urinary sediment and cytospin smears were prepared with Papanicolaou and hematoxylin and eosin (H-E) stains. The slides revealed a few clusters or individually scattered monotonous large tumor cells on bloody background (Fig. 1). A few loosely cohesive clusters were also noted that demonstrated cordlike arrangements with nuclear moldings and overlaps. The scattered tumor cells had a high nuclear:cytoplasmic ratio with hyperchromatic, irregular, and eccentrically located nuclei (Figs. 2A and 2B). The cytoplasm of these tumor cells was abundant, clear, or condensed (Fig. 2C). The nuclear chromatin was coarse, and the nucleolus was inconspicuous.

Gross and Histologic Findings

In Case 1, the entire bladder mucosa showed a conglomerated nodular protruding mass with central

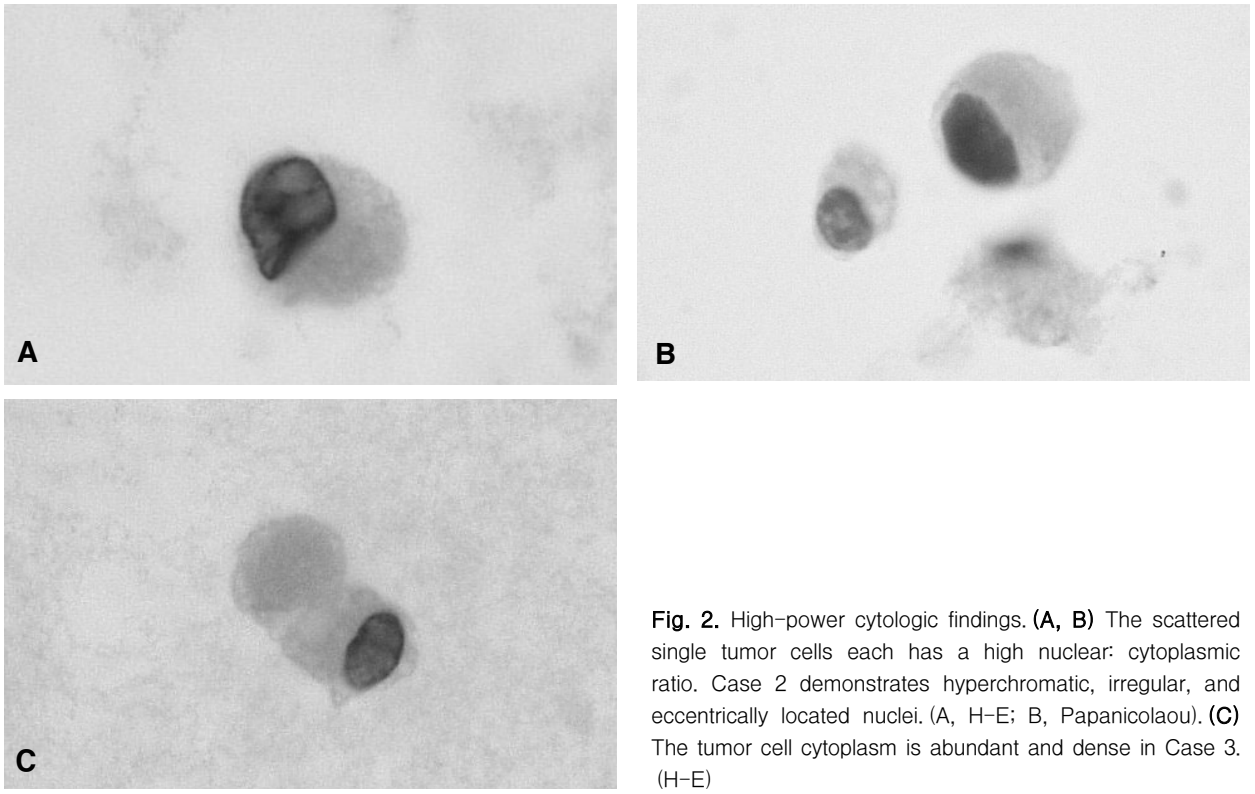

Fig. 2. High-power cytologic findings. (A, B) The scattered single tumor cells each has a high nuclear: cytoplasmic ratio. Case 2 demonstrates hyperchromatic, irregular, and eccentrically located nuclei. (A, H-E; B, Papanicolaou). (C) The tumor cell cytoplasm is abundant and dense in Case 3. (H-E)

ulceration. The tumor infiltrated one section of the bladder wall to reach the perivesicular adipose tissue (Fig. 3). A section of the tumor lesion demonstrated extensive necrosis. In Case 2, the luminal surface demonstrated a papillary mass growing at the dome that had infiltrated the deep muscle layer of bladder wall. In Case 3, the mass was located on the left lateral wall of bladder and had invaded the submucosal layer of connective tissue.

The histologic findings in all 3cases were similar. The tumor cells had diffusely permeated the bladder wall. They were monotonous and noncohesive in appearance, and contained eccentric nuclei with an abundant eosinophilic cytoplasm (Fig. 4). Most of the nuclei were round and enlarged with fine chromatin and distinct but not prominent nucleoli. Numerous mitoses were present. In Case 1, frequent lymphovascular tumor emboli were observed and metastasis was noted in 2 left iliac lymph nodes.

The immunohistochemical stains were performed on paraffin sections. Most of the tumor cells were positive for CK (AE1/AE3) (Fig. 5) focal reactive to CK7, CK20, and EMA antibodies and absolutely negative for kappa, lambda, LCA, HMB45, vimentin, and desmin antibodies in all 3 cases.

DISCUSSION

Urothelial carcinoma may take on any of a variety of histologic patterns and differentiations with a typical urothelial carcinoma component. The plasmacytoid variant of urothelial carcinoma is one in which the malignant cells resemble the cells of a plasmacytoma. This distinct morphologic appearance of plasma cells is the result of an accumulation of intracytoplasmic immunoglobulins in myeloma and an abundance of intermediate filaments that fill the cytoplasm and push the nucleus to one side, as seen in myoepithelial neoplasms,[7] or the result of the formation of signet-ring cell melanomas.[8] In a case presented by Sahin et al.,[1] electron microscopy revealed that the tumor contained a marked accumulation of amorphous intracytoplasmic material. However, Park et al.[6] reported that their case showed that

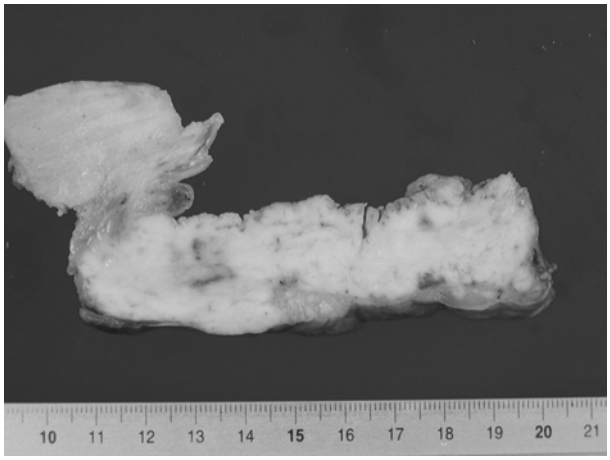

Fig. 3. Gross findings in Case 1. The cut surface shows a whitish infiltrating tumor invading perivesicular adipose tissue.

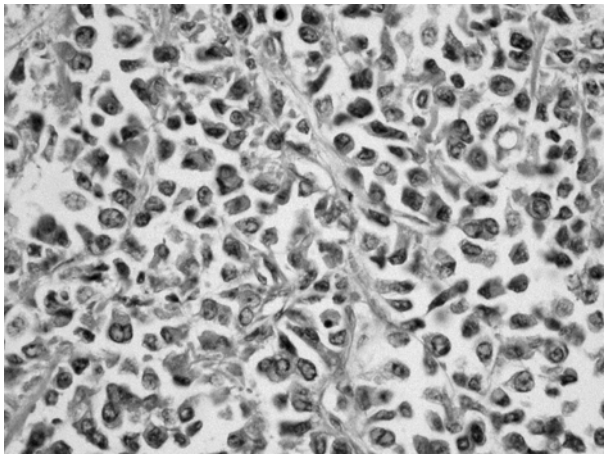

Fig. 4. Histologic findings in Case 1. The tumor is arranged in nests composed of noncohesive tumor cells containing eccentric nuclei and an abundant eosinophilic cytoplasm.

the tumor cell nuclei were displaced by an abundance of mitochondria.

This variant of urothelial carcinoma may cause a significant differential diagnostic dilemma. The importance of recognizing these variants lies not in mistaking them for plasmacytomas or lymphomas. Lymphomas and extramedullary plasmacytomas may rarely primarily involve the urinary bladder,[9,10] but more commonly will cause a secondary invasion of that organ. For this reason, a careful search for signs of urothelial carcinoma should be made. Sahin et al.[1] confirmed their diagnosis by observing urothelial carcinoma in situ in contiguous mucosa, immunohistochemical reaction for keratin, and electron microscopic confirmation of its epithelial origin.

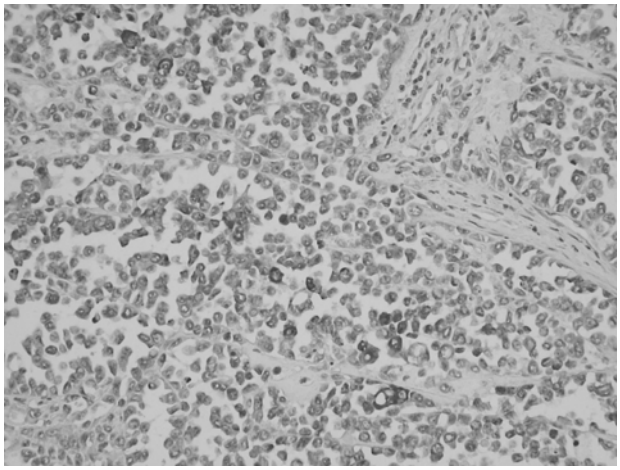

Fig. 5. Immunohistochemical stains for Case 1. Most of the tumor cells have a positive reaction for cytokeratin (AE1/AE3) in the cytoplasm.

Cytologic findings indicating plasmacytoid urothelial carcinoma were reported in 2 cases.[4,5] They were described as a few scattered, large, noncontiguous cells each with an abundance of cytoplasm and an eccentrically located hyperchromatic nucleus. Our patient also revealed a few clusters or isolated atypical cells, each of which contained a hyperchromatic nucleus with variable amounts of cytoplasm. Some of the tumor cells had eccentric nuclei with slightly abundant, dense cytoplasm. Immunohistochemical stains are helpful to identify nonepithelial malignancies. Mitsogiannis et al.[6] reported that an immunostain for CD138, which is considered a marker for tumors of plasma cell origin, was positive for aplasmacytoid urothelial carcinoma that might have been misdiagnosed.

When plasmacytoid tumor cells were found in voided urine specimens, they could not be diagnosed on the basis of a plasmacytoma or lymphoma morphology alone. However, several cytologic features favor a diagnosis of carcinoma.[2] First, the nuclear chromatin is finely dispersed, in contrast to the peripherally clumped chromatin commonly seen in lymphomas and plasmacytomas. Second, the nucleoli, although present, are not as prominent as they usually arein large-cell immunoblastic lymphomas. Finally, cohesive clusters that are typical of carcinoma could be identified by urine cytology.

Almost all reported cases have involved high-grade tumors and invasion of the musculature, except the case

reported by Zhang et al.,[4] in which the tumor invaded the lamina propria, and one of our cases, in which it invaded the submucosal layer. Although outcome information has been limited until now, this lesion may be associated with a worse prognosis than is usual for urothelial carcinoma.

Plasmacytoid neoplastic cells in voided urine specimens may be urothelial in origin, as in our cases. However, a nonepithelial neoplasm could not be excluded on the basis of cytologic features alone. Immuno-histochemical staining and other ancillary studies may be required to exclude other nonepithelial malignancies.

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