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A Case of Urinary Bladder Urothelial Carcinoma with Squamous, Glandular, and Plasmacytoid Differentiation

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Key Words
Bladder cancer · E-cadherin · Histological variant · Immunohistochemistry · p63 · Pathological diagnosis · Prognosis

Abstract
We report an extremely rare case of urothelial carcinoma (UC) of the urinary bladder with diverse histological differentiation into squamous, glandular, and plasmacytoid components. A 65-year-old man presented with gross hematuria. Cystoscopy showed a papillary-growing tumor with a wide-based stalk on the left wall of the urinary bladder. Based on the clinical diagnosis of locally invasive bladder cancer, the patient underwent radical cystectomy. Histological examination of the cystectomy specimen revealed UC with histological differentiation into multiple tumor subtypes. The tumor was composed of squamous cell carcinoma with marked keratinization, adenocarcinoma characterized by tall columnar cells with scattered goblet cells, conventional high-grade invasive UC and UC in situ, and plasmacytoid UC composed of discohesive cancer cells with eccentric nuclei and eosinophilic cytoplasm that diffusely infiltrated the bladder wall through the serosal surface. Immunohistochemically, the loss of membranous E-cadherin expression was noted only in the plasmacytoid UC component. The patient developed local recurrences 2 months postoperatively and died of the disease 6 months postoperatively. It is critical to correctly diagnose the histological variants of UC to predict a patient's prognosis and to determine the optimal treatment.
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Introduction

Urinary bladder urothelial carcinomas (UCs) may show diverse histological variation [1, 2]. Because the biological behavior of a bladder tumor with variant histology differs from that of conventional UC [3], an accurate histological diagnosis is important for an optimal patient management. We report a case of urinary bladder UC with diverse histological differentiation into squamous, glandular, and plasmacytoid components.

Case Presentation

A 65-year-old man presented with gross hematuria. Cystoscopy showed a papillary-growing tumor with a wide-based stalk on the left wall of the urinary bladder, and transurethral resection biopsy was performed. The pathological diagnosis was UC with muscularis propria invasion. Computed tomography and magnetic resonance imaging suggested the presence of extravesical invasion. Based on the clinical diagnosis of locally invasive bladder cancer, the patient underwent a radical cystectomy.

Gross examination of the cystectomy specimen revealed a protruding lesion measuring 4 × 4 cm on the left wall of the urinary bladder (fig. 1). Microscopically, the tumor was diagnosed as UC showing diverse histological differentiation into squamous, glandular, and plasmacytoid components (fig. 2). The protruding lesion was mainly composed of squamous cell carcinoma (SCC), which was characterized by atypical cells with marked keratinization (fig. 2b). Urothelial carcinoma in situ was observed in the flat mucosa around the protruding lesion. Well-differentiated adenocarcinoma composed of tall columnar cells with scattered goblet cells was found in the lamina propria (fig. 2c). A conventional high-grade UC component was also found in the bladder wall (fig. 2d). In addition, discohesive cancer cells with eccentric nuclei and eosinophilic cytoplasm reminiscent of plasma cells were observed to diffusely infiltrate the bladder wall through the serosal surface (fig. 2e). There were several foci of lymphovascular invasion. The prostate was not infiltrated by cancer cells, and no lymph node metastasis was found. The pathological stage was pT3b N0 [4]. The surgical margins were negative for cancer cells.

Immunohistochemistry for cytokeratin 7 (CK7; clone SP52; Ventana Medical Systems, Tucson, Ariz., USA; prediluted), cytokeratin 20 (CK20; clone SP33; Ventana Medical Systems; prediluted), CD138 (clone B-A38; Nichirei Biosciences, Tokyo, Japan; prediluted), p63 (clone 4A4; Nichirei Biosciences; prediluted), and E-cadherin (clone 36; Ventana Medical Systems; prediluted) was performed according to the standard techniques for a Ventana Benchmark® XT Autostainer (Ventana Medical Systems) [5]. The results of the immunohistochemical analysis are summarized in table 1, and representative photomicrographs are presented (fig. 3). CK7 and CD138 were positive in all components. CK20 was partially positive in the adenocarcinoma and plasmacytoid UC components but negative in the conventional UC and SCC components. p63 was positive in the conventional UC and SCC components but negative in the adenocarcinoma and plasmacytoid UC components. Membranous E-cadherin expression was completely lost in the plasmacytoid UC component but was retained in all other components.

The patient did not receive any adjuvant therapy. Two months after the surgery, computed tomography revealed two masses measuring up to 4 cm in the left pelvic cavity, suggesting local recurrence of the bladder cancer. The recurrent tumors grew rapidly, and the patient died 6 months postoperatively. An autopsy was not performed.

Discussion

It is well known that UCs may show diverse histological differentiation into a wide spectrum of components, including squamous, glandular, small cell, micropapillary, sarcomatoid, and plasmacytoid subtypes [1, 2]. In the present case, the urinary bladder UC showed histological differentiation into squamous, glandular, and plasmacytoid components. While plasmacytoid UC usually coexists with conventional high-grade UC [6, 7], this is the first report, to our knowledge, of a bladder tumor in which plasmacytoid UC has been found to coexist with SCC and adenocarcinoma.

Urothelial carcinomas with variant histological differentiation are more likely to present in an advanced stage and are associated with a worse prognosis [3, 8]. In particular, plasmacytoid UC, which has been included in the World Health Organization classification since 2004, represents one of the most aggressive variants of UC [1, 9]. Plasmacytoid UC is characterized by discohesive cells with a morphology closely resembling that of plasma cells [1]. A recent study by Shah et al. [2] suggested that plasmacytoid UC is one of the variants of UC that is underrecognized in community practice. Because plasmacytoid UC is a very aggressive variant with a dismal prognosis, as seen in the present case, a correct histological diagnosis is critical for an optimal patient management.

Several previous studies have examined the immunohistochemical features of plasmacytoid UC [6, 7, 9, 10]. CD138 is typically positive in plasmacytoid UC, as is the case in many other carcinomas as well as plasma cell neoplasia [7, 9]. Positivity for epithelial markers, including cytokeratins and epithelial membrane antigen, confirms the epithelial nature of plasmacytoid UC [6, 7, 9]. It has recently been reported that the majority of plasmacytoid UCs show negative or markedly reduced membranous staining for E-cadherin, which mediates cell-to-cell adhesion, suggesting that the loss of E-cadherin expression may be a prominent feature of plasmacytoid UC [9, 10]. In the present case, only the plasmacytoid UC component was negative for membranous E-cadherin, whereas the other histological components were positive for membranous E-cadherin, which is consistent with previous reports [9, 10]. In addition, we found that p63, a marker of the basal cell phenotype [11], was positive in the conventional UC and SCC components but negative in the adenocarcinoma and plasmacytoid UC components. In contrast, CK20 was partially positive in the adenocarcinoma and plasmacytoid UC components but negative in the conventional UC and SCC components. Immunohistochemical panels clearly confirmed diverse histological differentiation in the present case.

Because of its rarity, there is no established therapy for plasmacytoid UC. A few case reports have suggested that cisplatin-based chemotherapy is effective in the treatment of plasmacytoid UC [12]. However, a recent study by Keck et al. [13] showed that, in a prospective clinical trial cohort, the median overall survival of patients with plasmacytoid UC treated with cystectomy and adjuvant cisplatin-based chemotherapy was approximately half that observed in the patients with locally advanced conventional UC who received the same treatment. It has been suggested that the loss of E-cadherin as a sign of an epithelial-to-mesenchymal transition and the upregulation of transcriptional repressors of E-cadherin may contribute to a reduced sensitivity to chemotherapeutic agents [13–15]. The identification of the optimal therapy for plasmacytoid UC is still urgently needed.

In conclusion, we presented the previously unreported differentiation of urinary bladder UC into squamous, glandular, and plasmacytoid components. It is critical to correctly diagnose the histological variants of UC to predict a patient's prognosis and to determine the optimal treatment.

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Disclosure Statement

The authors declare no conflicts of interest associated with this paper.

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Table 1. Summary of the immunohistochemical analysis

	Conventional UC	SCC	Adeno-carcinoma	Plasmacytoid UC
CK7	+	+	+	+
CK20	–	–	+ (partial)	+ (partial)
CD138	+	+	+	+
p63	+	+	–	–
E-cadherin	+	+	+	–

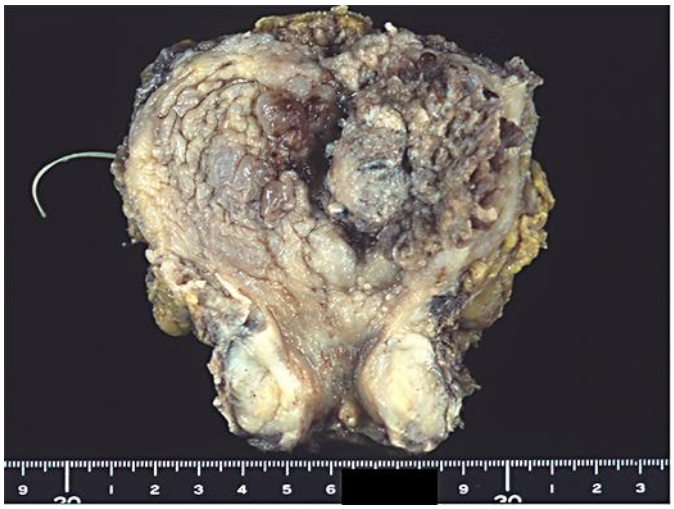

Fig. 1. Gross appearance of the urinary bladder tumor in the cystectomy specimen. A protruding lesion is observed on the left wall of the urinary bladder.

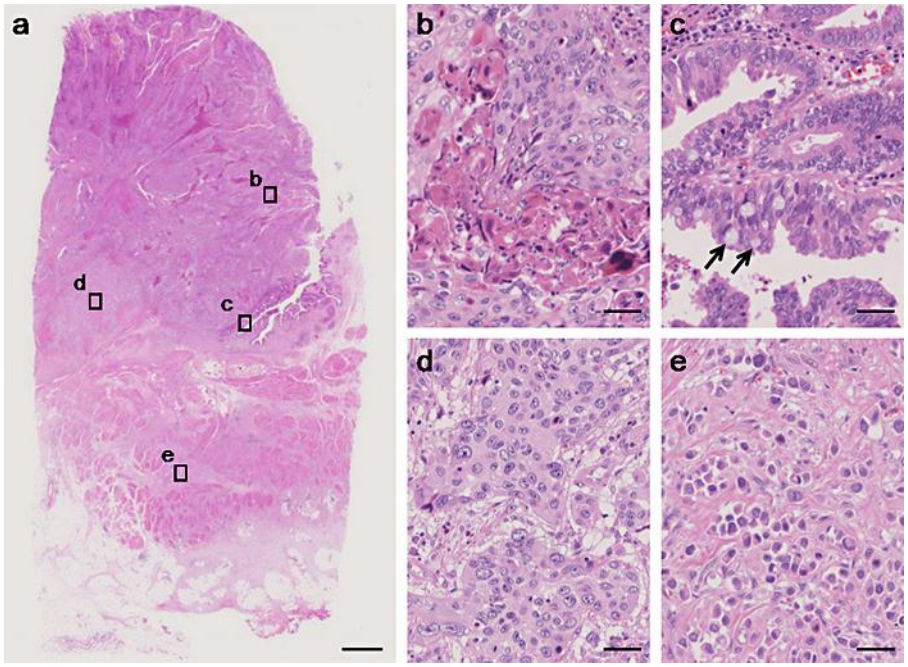

Fig. 2. Microscopic findings of the urinary bladder tumor (hematoxylin and eosin stain). **a** Low-power view of the lesion. High-power photomicrographs of the areas marked by squares are shown in **b–e**. Bar: 2 mm. **b** The protruding lesion is mainly composed of SCC showing marked keratinization. Bar: 50 μm. **c** Well-differentiated adenocarcinoma composed of tall columnar cells. Arrows indicate goblet cells. Bar: 50 μm. **d** Conventional high-grade UC component. Bar: 50 μm. **e** Plasmacytoid UC composed of discohesive cancer cells with eccentric nuclei and eosinophilic cytoplasm. Bar: 50 μm.

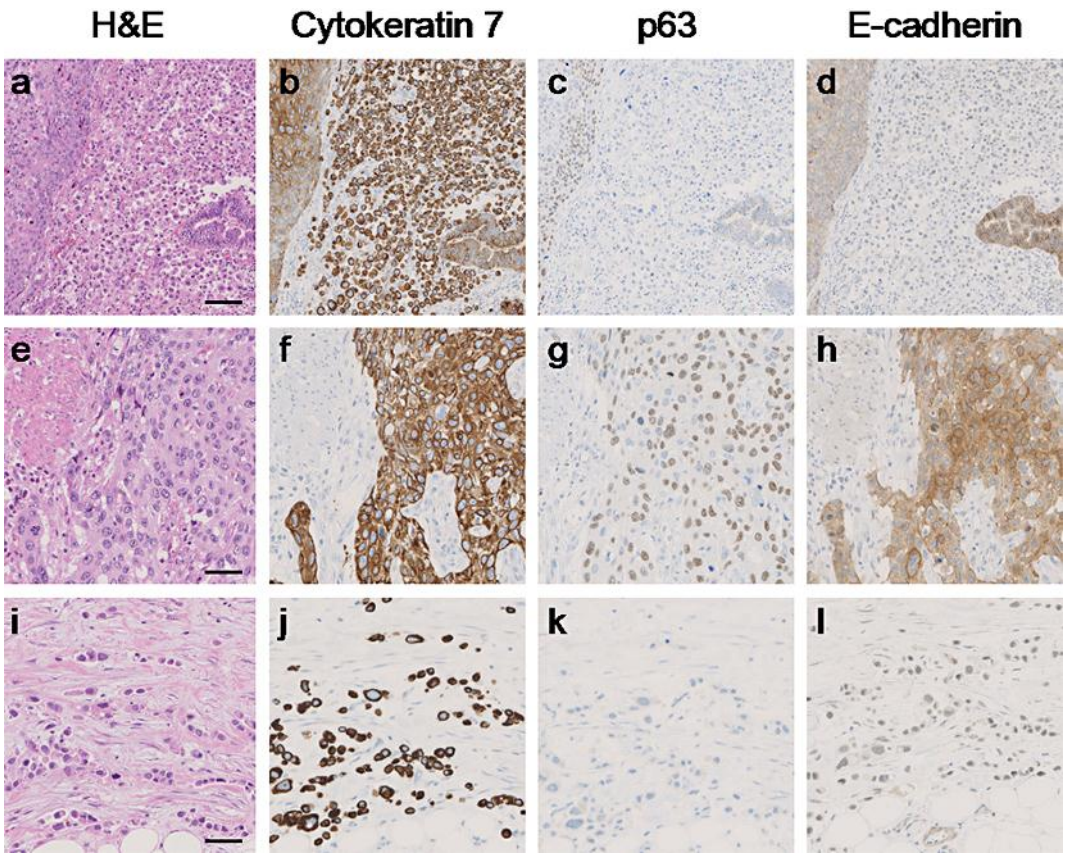

Fig. 3. Immunohistochemical findings (**a–d**). SCC (left), plasmacytoid UC (middle), and adenocarcinoma (right) components and the boundaries between them are shown. Bar: 100 μm. **e–h** Conventional UC. Bar: 50 μm. **i–l** Plasmacytoid UC. Bar: 50 μm.