

# Sarcomatoid variant of urothelial carcinoma: Cytological analysis of three cases

NAMIE ARITA\*, MITSUAKI ISHIDA\*, KEIKO YOSHIDA, AKIKO KAGOTANI,  
NOZOMI IWAMOTO, MUNEO IWAI and HIDETOSHI OKABE

Division of Diagnostic Pathology and Department of Clinical Laboratory Medicine,  
Shiga University of Medical Science, Shiga 520-2192, Japan

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**Abstract.** Sarcomatoid variant of urothelial carcinoma (SV-UC) is characterized by the presence of biphasic malignant neoplastic components exhibiting morphological and/or immunohistochemical evidence of epithelial and mesenchymal differentiation. SV-UC is a rare variant of UC and the cytological features of this tumor have not been well described. In the present study, we analyzed the cytological features of a series of SV-UC cases; 6 voided urine specimens from 3 patients with SV-UC were reviewed. Several characteristic cytological features were revealed: i) tumor cells were abundant in a necrotic background and while single tumor cells were predominant, small clusters of cells were occasionally present; ii) tumor cells were large-sized and round to polygonal in shape with ill-defined cell borders; iii) tumor cells had a high nuclear/cytoplasmic ratio and enlarged round to oval nuclei containing coarse chromatin and occasional nucleoli; and iv) spindle-shaped atypical cells were rarely identified (1/6 specimens). The cytological features of i), ii) and iii) are indistinguishable from those of conventional invasive high-grade UC. We hypothesize that these tumor cells originated from the conventional high-grade UC component of SV-UC as this component is usually present in this type of lesion, particularly on the surface of the tumor. Moreover, the sarcomatoid component of SV-UC is usually present in the deeper portion of the tumor and therefore detection of this component in the voided cytological specimen is low. Although cytodiagnosis of SV-UC is extremely difficult, cytodiagnosis of malignancy may prove possible due to the presence of a conventional UC component.

## Introduction

Sarcomatoid variant of urothelial carcinoma (SV-UC) is a rare variant of UC accounting for approximately 0.3% of all bladder malignancies (1). SV-UC is characterized by the presence of biphasic malignant neoplastic components exhibiting morphological and/or immunohistochemical evidence of epithelial and mesenchymal differentiation (2). The malignant mesenchymal component of SV-UC is usually composed of undifferentiated high-grade spindle cell neoplasm often resembling 'malignant fibrous histiocytoma', with the presence or absence of heterologous elements, including osteosarcoma, chondrosarcoma, rhabdomyosarcoma and liposarcoma (2). The sarcomatoid areas may merge with foci of overlying urothelial carcinoma *in situ* or conventional invasive UC.

The cytological features of SV-UC are not well known and only one cytological analysis of SV-UC has been previously reported (3). The present case study includes the first analysis of cytological features from a series of SV-UC cases and discusses possible differential diagnostic considerations. This study was approved by the Ethics Committee of Shiga University of Medical Science. Informed consent was obtained from the patients.

## Patients and methods

### Case reports

**Case 1.** A 64-year-old Japanese male presented with gross hematuria. Cystoscopy revealed multiple polypoid masses with ulceration in the bladder. Biopsies from these polypoid masses and subsequent total cystourethrectomy were performed. Following surgery, chemotherapy was administered. No recurrence or metastases were observed 6 months following surgery.

**Case 2.** An 80-year-old Japanese male presented with gross hematuria. Cystoscopy revealed a pedunculated papillary tumor in the bladder and tumor resection using a cystoscopy was performed. Two months following the initial procedure, second-look cystoscopy identified no residual tumor. No recurrence or metastases were observed 8 months following the initial cystoscopy.

**Case 3.** A 75-year-old Japanese male presented with persistent lower abdominal pain. Computed tomography

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*Correspondence to:* Dr Mitsuaki Ishida, Department of Clinical Laboratory Medicine and Division of Diagnostic Pathology, Shiga University of Medical Science, Tsukinowa-cho, Seta, Otsu, Shiga 520-2192, Japan  
E-mail: mitsuaki@belle.shiga-med.ac.jp

\*Contributed equally

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Table I. Cytological features of the sarcomatoid variant of urothelial carcinoma.

Case	Background	Number of neoplastic cells	Cellular arrangement	Cell size	Cell shape	Nuclear features	Spindle-shaped atypical cells
1	Necrotic	Abundant	Single >> small cluster	Large	Round to polygonal	Large round to oval with coarse chromatin and occasional prominent nucleoli.	Present
2	Necrotic	Few	Single	Large	Round to polygonal	Large round to oval with coarse chromatin and inconspicuous nucleoli	Absent
3	Necrotic	Abundant	Single > small cluster	Large	Round to polygonal	Large round to oval with coarse chromatin and occasional prominent nucleoli	Absent

demonstrated multiple tumorous lesions in the liver and hydronephrosis of the left kidney. Cystoscopy revealed an ulcerated polypoid tumor in the bladder and tumor resection using a cystoscopy was performed. A metastatic bladder tumor in the liver was clinically suspected and chemotherapy was administered.

*Cytological analysis.* Urine specimens from patients diagnosed histopathologically with SV-UC were retrieved. Six urine specimens from three patients were available in this study (two, one and three samples from case 1, 2 and 3, respectively). The specimens were voided urine samples obtained prior to surgical procedure or cystoscopy. Cytological specimens were Papanicolaou-stained and analyzed for cytological features, including background, number of neoplastic cells, cellular arrangement, cell size and shape, cellular border and nuclear features.

*Histological analysis.* Tissues from cystoscopic or surgical resections were fixed by formalin and embedded in paraffin. Tissue sections were stained with hematoxylin and eosin and subjected to immunohistochemistry using an autostainer (XT system Benchmark, Ventana Medical System, Tucson, AZ, USA) according to the manufacturer's instructions.

## Results

*Cytological findings.* Cytological features of the 3 cases are summarized in Table I.

*Case 1.* Two cytological specimens revealed abundant single tumor cells and a small number of tumor cell clusters in a necrotic background. Tumor cells were large-sized and round to polygonal in shape with ill-defined cell borders. The cells had a high nuclear/cytoplasmic (N/C) ratio and enlarged round to oval nuclei containing coarse chromatin and occasional prominent nucleoli (Fig. 1A). In addition, a few spindle-shaped atypical cells with enlarged oval nuclei containing coarse chromatin and dense cytoplasm were also observed in one specimen (Fig. 1B).

*Case 2.* One cytological specimen revealed a small number of single tumor cells, which were large-sized and round to polygonal in shape with ill-defined cell borders, in a necrotic background. The cells had a high N/C ratio and enlarged round to oval nuclei containing coarse chromatin and inconspicuous nucleoli. Tumor cell clusters and atypical spindle cells were not observed.

*Case 3.* Three cytological specimens revealed abundant single tumor cells and a limited number of small clusters of tumor cells in a necrotic background. Cells were large-sized and round to polygonal in shape with ill-defined cell borders. The cells had a high N/C ratio and enlarged round to oval nuclei containing coarse chromatin and occasional prominent nucleoli. No atypical spindle cells were observed.

*Histopathological findings.* Clinicopathological and immunohistochemical features of the 3 cases are summarized in Table II.

*Case 1.* Macroscopically, multiple polypoid lesions composed of proliferating atypical spindle-shaped tumor cells (Fig. 2A), with ulceration were present in the bladder. Tumor cells had hyperchromatic large nuclei with nucleoli and specific spindle-shaped tumor cells were observed to have rich eosinophilic cytoplasm and striation, which were immunohistochemically positive for desmin, indicative of presence of the rhabdomyosarcomatous component (Fig. 2B). The tumor was comprised of ~70% of the component and the residual area was conventional high-grade UC, which was largely present on the surface of the tumor (Fig. 2A). The tumor had invaded into the deeper portion of the muscular layer of the bladder (pT2b).

*Case 2.* The papillary tumor was largely composed of conventional invasive high-grade UC. In addition, proliferating spindle-shaped tumor cells with hyperchromatic large nuclei were observed (~20% of the tumor). No heterologous component was identified. The tumor had invaded into the muscular layer (>pT2).

*Case 3.* The polypoid tumor was composed of proliferating atypical spindle-shaped cells containing large nuclei with nucleoli (~80% of the tumor). The conventional invasive

Table II. Clinicopathological and immunohistochemical features of the sarcomatoid variant of urothelial carcinoma.

Case	Age/ Gender	Chief complaint	Histopathological features	Heterologous component	Depth	Immunohistochemical features	
						Sarcomatoid component	Conventional UC component
1	64/M	Gross hematuria	Sarcomatoid component >> conventional high-grade UC	Present (RD)	pT2b	CK (-), VM (+) desmin (+, RD)	CK(+), VM (-)
2	80/M	Gross hematuria	Conventional high-grade UC >> sarcomatoid component	Absent	≥pT2	CK (-), VM (+)	CK(+), VM (-)
3	75/M	Abdominal pain	Sarcomatoid component >> conventional high-grade UC	Absent	pT1	CK (-), VM (+)	CK(+), VM (-)

CK, cytokeratin; UC, urothelial carcinoma; RD, rhabdomyosarcoma; VM, vimentin.

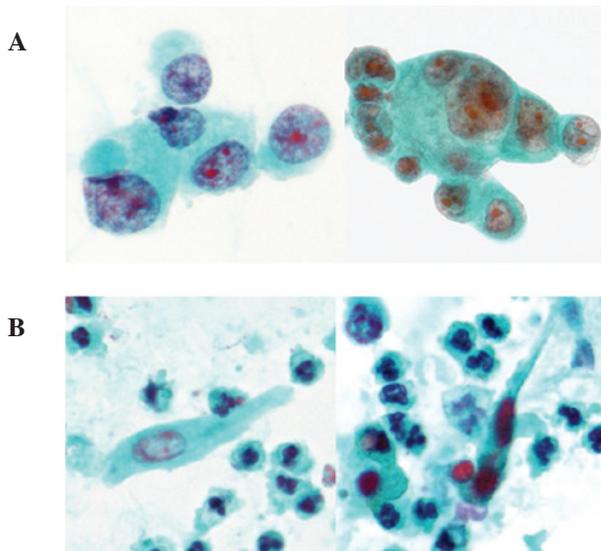


Figure 1. Cytological analysis of the sarcomatoid variant of urothelial carcinoma. (A) Single tumor cells (left) and small clusters of tumor cells (right) with a high nuclear/cytoplasmic ratio and large round to oval nuclei with coarse chromatin and occasional prominent nucleoli. (B) Spindle-shaped atypical cells are also present (Papanicolaou stain; magnification, x400).

high-grade UC component was also identified, largely on the tumor surface. No heterologous component was observed. The tumor had invaded into the subepithelial connective tissue, however, muscular invasion was not observed (pT1).

## Discussion

Cytological examination of urine specimens is important for the detection, diagnosis and follow-up of patients with UC. It is well recognized that cytological examination of urine specimens is highly sensitive for the detection of conventional high-grade UC (4). Moreover, the cytological features of rare histopathological variants of UC, including micropapillary and nested, were previously described (5-8). Although one cytological study of SV-UC has been previously reported (3),

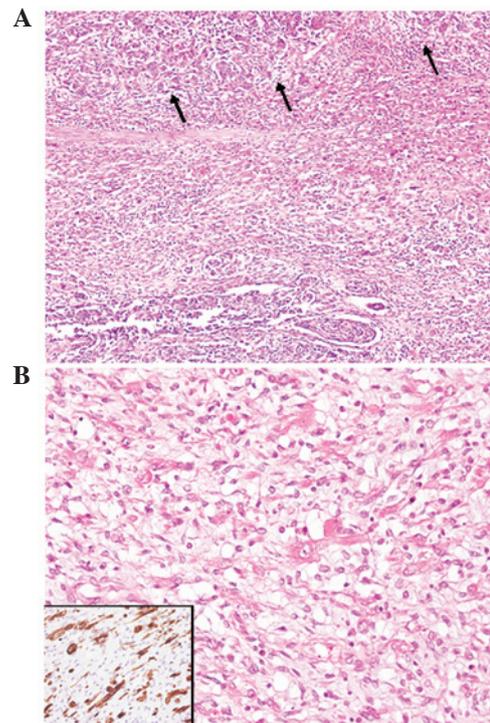


Figure 2. Histopathological and immunohistochemical analysis of the sarcomatoid variant of urothelial carcinoma. (A) Conventional invasive high-grade urothelial carcinoma components (arrows) and sarcomatoid component, which is composed of proliferating atypical spindle-shaped cells (hematoxylin and eosin; magnification, x100). (B) Rhabdomyosarcomatous component (hematoxylin and eosin; x200). Inset, desmin is positive (x200).

the cytological features of a series of SV-UC have yet to be described.

The present study revealed four cytological features of SV-UC: i) Tumor cells were abundant in a necrotic background and single tumor cells were predominant, although small clusters of tumor cells were occasionally present; ii) tumor cells were large-sized and round to polygonal in shape with ill-defined cell borders; iii) tumor cells had a high N/C ratio

and enlarged round to oval nuclei containing coarse chromatin and occasional nucleoli. iv) Spindle-shaped atypical cells were rarely identified.

Cytological observations in a previous report on SV-UC were consistent with features i), ii) and iii) from the present study (3). However, these cytological features are indistinguishable from those of conventional invasive high-grade UC. We hypothesize that tumor cells with features i), ii) and iii) may have originated from the conventional high-grade UC component of SV-UC, which usually contains conventional invasive UC and UC *in situ* components, particularly on the tumor surface. These components were present in all cases of this series, although it is unclear whether they were present in the previous report (3). The sarcomatoid component of SV-UC is generally present in the deeper portion of the tumor, therefore, the detection frequency of the sarcomatoid component in the voided cytological specimen may be low, as demonstrated in the present case study, in which spindle-shaped atypical cells representing the sarcomatoid component were observed in only one specimen.

In the present series, 5/6 specimens (cases 1 and 3) were initially diagnosed as malignant (UC) and the remaining specimen (case 2) was suspected to be malignant (suspicious for UC) due to a limited number of atypical cells. However, sarcomatoid component was not reported in any of the cases. The cytodiagnosis of SV-UC may be extremely difficult, however, cytodiagnosis of malignancy may prove possible due to the presence of a conventional UC component.

Cytological differential diagnosis of SV-UC includes UC accompanied by a squamous cell carcinoma (SCC) component and malignant mesenchymal tumors, including leiomyosarcoma and rhabdomyosarcoma. UC is occasionally identified to include a SCC component and pure SCC of the urinary bladder is rare. In voided urine specimens, atypical parakeratotic cells with high N/C ratio and enlarged hyperchromatic nuclei are observed in moderately to poorly differentiated SCC and in well differentiated cases, the presence of squamous cells demonstrating definite malignant features may be rare, although anucleated squamous and atypical parakeratotic cells have been previously observed (9). Spindle-shaped atypical cells are present in the urine specimen of UC with SCC and pure SCC cases, as well as SV-UC (9,10). However, parakeratotic atypical squamous cells are present in UC with SCC and pure SCC cases (10), but not SV-UC, although

SV-UC and UC with SCC contains a conventional high-grade UC component in urine specimens. These observations may facilitate clinical differentiation of SV-UC from UC with SCC. Leiomyosarcoma and rhabdomyosarcoma must also be included in differential diagnosis of SV-UC as these tumors reveal spindle-shaped tumor cells as well (11,12). However, due to the lack of a conventional high-grade UC component in leiomyosarcoma and rhabdomyosarcoma, differentiation from these tumors is simple and rapid.

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