Int J Clin Exp Pathol 2012;5(1):83-88
www.ijcep.com /ISSN: 1936-2625/IJCEP1108012

Case Report

Spindle cell carcinoma progressed from transitional cell carcinoma of the urinary bladder

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Received August 13, 2011; accepted November 25, 2011; Epub January 1, 2012; Published January 15, 2012

Abstract: The author reports a very rare case of spindle cell carcinoma (SpCC) of the urinary bladder progressed from ordinary papillary transitional cell carcinoma (TCC). A 63-year-old man complained of hematuria. A transurethral endoscopic examination revealed a papillary tumor, and transuthetral resection of bladder tumor (TUR-BT) was performed and was diagnosed as ordinary papillary urothelial TCC. Since then, he was treated with TUR-BT eight times. Chemotherapy, radiation, radical cystectomy and lymph nodes dissection were performed 16 years after the first TUR -BT. However, he developed rectal mucosal metastasis. He is now alive 17 years after the first presentation. All the TUR-BT specimens were ordinary papillary TCCs without invasion (pTa). Immunohistochemically, the TUR-BT specimens were positive for pancytokeratin, high molecular weight cytokeratin (CK), CK 5/6, CK 7, CK 18, CK 19, CK 20, p53, p63, Ki-67 (10%), and negative for other antigens examined including vimentin. The cystectomy bladder specimens show broad ulcers and polypoid lesions, and malignant spindle cells (SpCC) invading into muscular layer were present. No TCC elements were recognized. The tumor cells were positive strongly for vimentin, and less strongly for pancytokeratin, high molecular weight cytokeratin, CK 5/6, CK 14, CK 18, p53, p63 and Ki-67 (95%), and negative for other antigens examined. The rectal metastatic lesion showed SpCC without TCC elements, and were strongly positive for vimentin, and weakly positive for pancytokeratin, S100 protein, p53, p63, Ki-67 (90%), neuron-specific enolase, CD56, KIT and PDGFRA. It was negative for other antigen examined. It is strongly suggested that the present SpCC were progressed from ordinary TCC.

Keywords: Spindle cell carcinoma, urinary bladder, immunohistochemistry

Introduction

Sarcomatoid carcinoma of the urinary bladder is relatively rare. Of the sarcomatoid carcinoma, a subset of carcinoma composed largely of spindle cells are called spindle cell carcinoma (SpCC). Although SpCC can occur in any organ, SpCC of the urinary bladder is very rare; only eight cases have been reported in the literature [1-4]. Review of this literature has shown that SpCC cases have simultaneous areas of ordinary transitional cell urothelial carcinoma (TCC) or condyloma-like lesion in the urinary bladder [1-4]. Clinically, SpCC has been reported to be an aggressive tumor, and its survival is short compared with ordinary TCC [2]. The author herein reports a case of SpCC of the urinary bladder progressed from TCC.

Case report

A 63-year-old man complained of hematuria, and was admitted to our hospital for scrutiny. Transurethral endoscopic examination revealed a papillary tumor of the right lateral walls, and transuthetral resection of bladder tumor (TUR-BT) was performed. The pathological diagnosis was papillary urothelial TCC without invasion (pTa). Since then, he was treated with TUR-BT eight times for recurrent TCC of the right lateral walls, all of which were pTa TCCs. Chemotherapy, radiation, radical cystectomy, and lymph node dissection were performed 16 years after the first TUR-BT, and 3 years after the last TUR-BT. However, he developed rectal mucosal metastasis. He is now alive 17 years after the first presentation.

Materials and methods

The nine TUR-BT specimens, cystectomy bladder specimens, and metastatic rectal specimens were fixed in 10 % formalin and embedded in paraffin wax. Many 3-μm sections were

Table 1. Immunohistochemical reagents and results

Antigens	Antibodies (clone)	Sources	Bladder TCC	Bladder SpCC	Rectal metastatic SPCC
Pancytokeratin	AE1/3	Dako Corp, Carpinteria, CA, USA	+++	+	+
Pancytokeratin	Polyclonal wide	Dako	+++	+	+
Pancytokeratin	KL-1	Immunotech, Marseille, France	+++	-	-
HMWCK	34βE12	Dako	++	+	-
CK5/6	D5/16	Dako	+	+	-
CK7	N1626	Dako	+	-	-
CK14	LL002	Novocastra, New Castle upon Tyne, UK	-	+	-
CK18	DC10	Dako	++	+	-
CK19	RCK108	Progen, Heidelberg, Germany	++	-	-
CK20	K20.8	Dako	+	-	-
Melanosome	HMB45	Dako	-	-	-
EMA	E29	Dako	-	-	-
Vimentin	Vim 3B4	Dako	-	+++	+++
CEA	Polyclonal	Dako	-	-	-
Desmin	D33	Dako	-	-	-
S-100 protein	Polyclonal	Dako	-	-	+
ASMA	1A4	Dako	-	-	-
CD34	NU-4A1	Nichirei, Tokyo, Japan	-	-	-
P53 protein	DO-7	Dako	+	+	+
P63	4A4	Dako	+++	+	+
Ki-67	MIB-1	Dako	10%	95%	90%
Chromogranin	DAK-A3	Dako	-	-	-
Synaptophysin	Polyclonal	Dako	-	-	-
NSE	BBS/NC/VI-H14	Dako	-	-	+
CD56	UJ13A	Dako	-	-	+
CD68	KP-1	Dako	-	-	-
KIT	Polyclonal	Dako	-	-	+
PDGFRA	Polyclonal	Santa Cruz, CA, USA	-	-	+

+++、67-100% positive. ++、33-66%. +, 1-33% positive. -, negative.HMWCK, high molecular wight cytokerain. CK, cytokeratin, EMA, epithelial membrane antigen. CEA, carcinoembryonic antigen. ASMA, α-smooth muscle antigen. NSE, neuron-specific enolase. PDGFRA, platelet-derived growth factor receptot-α.

cut from each paraffin block, and one of them was stained with hematoxylin and eosin. The others were subjected to immunohistochimical staining, using Dako envision method (Dako Corp., Glostrup, Denmark) as previously described [5, 6]. The antigens examined are shown in **Table 1**.

Results

TUR-BT specimen

The nine TUR-BT specimens measured 0.5 cm to 3 cm in diameter and all showed ordinary papillary urothelial TCC without invasion (pTa) (**Figure 1**). The last bipopsy also showed papillary urothelial TCC (**Figure 1**). The nuclear grade was grade II. Immunohistochemically, tumor cells were positive for three pancytokeratins,

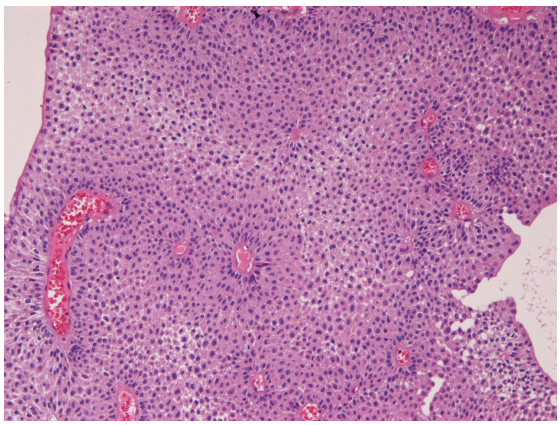

Figure 1. Histology of urothelial carcinoma obtained by transurethral resection of bladder tumor (TUR-BT). It is an ordinary papillary transitional cell carcinoma. HE, x200.

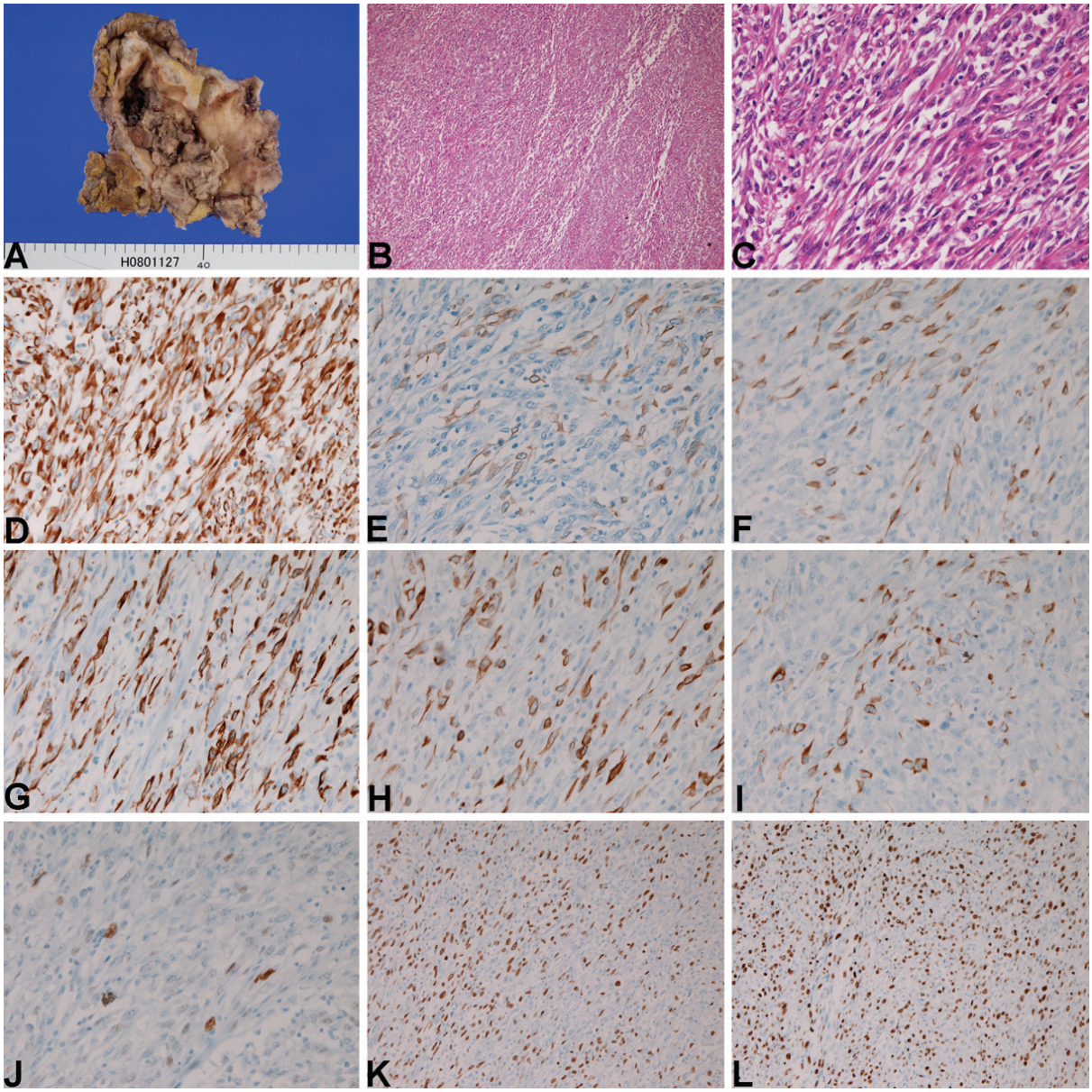

Figure 2. A. The gross features of resected bladder. It shows polypoid lesions and broad ulcer. B. Low power view of the bladder tumor. It is composed of malignant spindle cells. HE, x40. C. High power view of the bladder tumor. It is composed of malignant spindle cells with hyperchromatic nuclei and active mitotic figures. HE, x200. D. Vimentin is strongly expressed in the bladder tumor. Immunostaining, x200. E. Pancytokeratin is expressed in the bladder tumor. Immunostaining, x200. F. High molecular weight cytokeratin is expressed in the bladder tumor. Immunostaining, x200. G. Cytokeratin 5/6 is expressed in the bladder tumor. Immunostaining, x200. H. Cytokeratin 14 is expressed in the bladder tumor. Immunostaining, x200. I. Cytokeratin 18 is expressed in the bladder tumor. Immunostaining, x200. J. p53 protein expression in the bladder tumor. Immunostaining, x200. K. p63 is diffusely expressed in the bladder tumor. Immunostaining, x150. L. Ki-67 labeling is 95% in the bladder tumor. Immunostaining, x200.

high molecular weight cytokeratin (CK), CK 5/6, CK7, CK18, CK19, CK20, p53, p63, and Ki-67 (10%), and negative for other antigens examined including vimentin and mesenchymal markers (**Table 1**).

Cystectomy bladder specimen

Grossly, the resected urinary bladder showed extensive mucosal ulceration and polypoid lesions mainly in the right lateral walls (**Figure**

2A). The walls were thickened. Microscopically, the mucosa was entirely ulcerated, and malignant spindle cells were seen to proliferate and invade into the muscle layer (**Figures 2B** and **2C**). No residual TCC elements were recognized. SpCC of the urinary bladder was diagnosed. Immunohistochemically, tumor cells were positive strongly for vimentin (**Figure 2D**), and mildly for pancytokeratin (**Figure 2E**), high molecular weight cytokeratin (**Figure 2F**), CK5/6 (**Figure 2G**), CK14 (**Figure 2H**), CK18 (**Figure 2I**), p53 (**Figure 2J**), p63 (**Figure 2K**), and Ki-67 (95%) (**Figure 2L**). The tumor cells were negative for CK7, CK19, CK20, epithelial membrane antigen, melanosome, S-100 protein, CEA, desmin, CD34, α-smooth muscle antin, chromogranin, synaptophysin, neuron-specific enolase, CD56, CD68, KIT, and PDGFRA (**Table 1**).

Metastatic rectal lesion

The rectal lesion was an SpCC (**Figure 3**) similar to that of bladder tumor. No TCC elements were recognized. Immunohistochemically, tumor cells were strongly positive for vimentin, and weakly for pancytokeratin, S-100 protein, p53, p63, Ki-67 (90%), neuron-specific enolase, CD56, KIT, and PDGFRA. It was negative for other antigen examined (**Table 1**).

Discussion

The present tumors of the cystectomied bladder and rectal metastasis showed malignant spindle cells. Immunohistochemically, the tumor cells were positive for some fractions of CK and vimentin. They were also positive for p53 protein and Ki-67 antigen with very high labeling indices. In contrast, they were negative for other mesenchymal markers and neuroendocrine markers. Therefore, these tumors of the bladder and rectum were not sarcoma but a carcinoma. Thus, SpCC was a correct diagnosis.

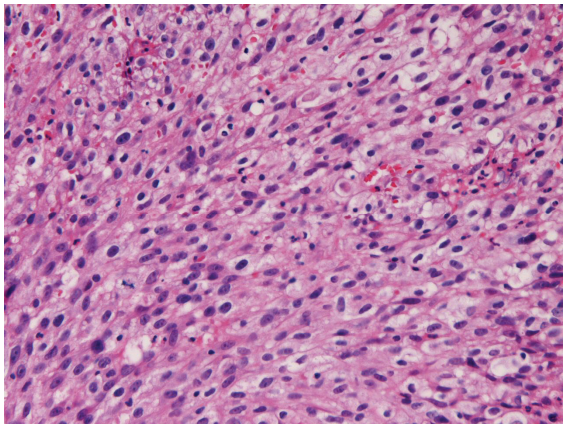

Figure 3. Histology of metastatic colon lesion. It is composed of malignant spindle cells, x200.

Sarcomatous progression of carcinoma can occur in any carcinoma, though the frequency is rare. In the urothelial carcinoma, Honda et al [1] found coexistence of TCC and SpCC in their case report. Barker et al [3] showed that condyloma accuminatum-like lesion of the urinary bladder progressed to invasive spindle cell carcinoma. Serino et al [2] found TCC or TCC in situ were present together with SpCC in the urinary bladder. In the present case, all nine TUR-BTs showed ordinary papillary TCCs, while cystectomied bladder consisted of only SpCC. In addition, the rectal metastasis was also composed of only SpCC. These finding strongly suggest that ordinary papillary TCC progressed to SpCC in the present case.

CK profiling has not been performed in bladder SpCC. The present report revealed that ordinary papillary TCC expressed a wide range of cytokeratin and its expression was strong. In contrast, SpCC of the bladder of the present case showed a relatively narrow expression of CK, and its expression was relatively weak. In addition, the metastatic colon SpCC revealed a very narrow range of CK expression. These observations indicated that the kinds and amounts of CK decrease along with the spindle cell progression of bladder carcinoma.

High molecular weight cytokeratin and CK 5/6 are relatively specifically expressed in TCC [7, 8]. In the present case, both CKs were expressed in the TUR-BT specimens and cystectomied bladder. This finding strongly suggests that the SpCC are progressed from TCC. In contrast to CK, vimentin expression was none in TCC, but it was strong in SpCC, indicating that vimentin emerge during the spindle cell progression of the bladder carcinoma.

Mesenchymal markers including melanosome, S-100 protein, α-smooth muscle actin, CD34 and desmin were not present in TCC and SpCC in the present case. This indicates that the bladder tumor is not melanoma or sarcoma but a carcinoma and that these antigens did not emerge in the spindle cell progression of the

bladder tumor. However, the rectal metastatic lesion in the present case mildly or minimally expressed S-100 protein, neuron-specific enolase, CD56, KIT and PDGFRA, suggesting that these antigens emerge in the progression and metastasis of SpCC of the bladder.

Present case was negative for epithelial membrane antigen and CEA, suggesting that these antigens were absent from bladder carcinoma. In the present case, TCC of the TUR-BT specimens SpCC of the bladder and metastatic colon lesion showed p63. p63 is a marker of basal cells, reserve cells, squamous cells, and TCC [8-12]. The finding strongly suggests that the SpCCs of the bladder and rectal metastatic lesion show features of urothelium and are progressed from TCC.

TCC expresses p53 protein and Ki-67 antigen [12-14]. The present study also showed p53 and Ki-67 antigen. High Ki-67 labeling predict poor prognosis [14]. In the present case, Ki-67 labeling of SpCC is 95%, suggesting a poor prognosis of the present case.

The present tumors were free of neuroendocrine markers (chromogranin, synaptophysin, neuron-specific enolase, and CD56) except for the metastatic colon lesion which showed neuron-specific enolase and CD56. Neuroendocrine carcinoma of the bladder has been reported [15-17]. The present findings indicate that the present tumors were not neuroendocrine tumors, but at least had acquired some neuroendocrine differentiation. The present case was negative for CD34, CD68, KIT and PDGFRA except metastatic rectal lesion, suggesting that the present tumor is not KIT-positive tumors such as gastrointestinal stromal tumor and other carcinomas and sarcomas. KIT expression is probably nonspecific.

Finally, recent researches have shown that sarcomatoid urothelial carcinoma shows monoclonal proliferation [18]. Sung et al [18] suggested that sarcomatoid urothelial carcinoma is monoclonal by X-chromosome inactivation and loss of heterozygosity (LOH) of various genes. In our case, it seems likely that the ordinary TCC and spindle cell carcinoma elements are monoclonal.

In summary, the author reported a very rare case of SpCC of the urinary bladder progressed from ordinary TCC.

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