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Micropapillary component of urothelial carcinoma detected in transurethral resection of bladder tumor (TUR-BT) tissues: a case report

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Abstract A case of urothelial carcinoma (UC) containing a micropapillary carcinoma (MPC) component in the urinary bladder of an 83-year-old man is reported. The MPC component of UC has been reported to be a variant featuring poor prognosis and rapid progression. In the present case, a characteristic MPC component with micropapillary growth, in association with a fine meshwork-like stroma, was observed in less than 10% of fragmented cancer tissues of UC, G3, obtained by transurethral resection of a bladder tumor (TUR-BT). Lymphatic invasion was also detected. UC cancer cells had invaded the prostatic glands and replaced the original epithelial cells. The unique "inside-out" feature of the MPC component was immunohistochemically obvious on staining with antibody to epithelial membrane antigen (EMA). On immunohistochemical study, cancer cells of both UC and MPC components were positive for pancytokeratin AE1/AE3 and cytokeratins 7 and 20. Carcinoembryonic antigen (CEA) and CAM5.2 were only focally positive in UC cells. MIB-1(Ki-67) labeling index was high, at 80%–90%, in cancer cells of UC. This was a case of UC, G3 with invasion to the muscularis propria layer of the urinary bladder and also to the prostate. MPC and MPC components in cancers should be recognized as a marker of poor prognosis, even when detected in less than 10% of UC within TUR-BT tissues, as in the present case.

Key words Urinary bladder · Micropapillary carcinoma · Urothelial carcinoma · Transurethral resection · Immunohistochemistry

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Introduction

Micropapillary carcinoma (MPC) was first reported as an entity associated with poor prognosis in cancers of the breast,[1] and then of the urinary bladder,[2] ovary,[3] lung,[4] colon,[5–7] ureter,[8] pelvis,[9] and other organs. This variant has also been found in urothelial carcinoma (UC), and to exhibit a poorer prognosis, more rapid progression, and higher frequency of metastasis than common UC.[10–13] These clinicopathological characteristics have also recently been demonstrated in colon cancer containing an MPC component.[6] The proportion of an MPC component in cancer tissues varies case by case, from less than 10% to almost 100%.[6,12] Among cases containing a focal MPC component, prognosis depends on the proportion of this component in cancer tissue.[12] It was demonstrated that a larger MPC component is associated with poorer prognosis, as was also shown in a comprehensive study of the urinary bladder.[12] In the colon, no relationship was found between prognosis and the proportion of MPC in cancer tissues.[6] Immunohistochemically, cancer cells in the MPC component were found to be similar to those of the original cancer cells. [6,12]

In the present study, we found an MPC component of UC in a tissue fragment obtained by transurethral resection of a bladder tumor (TUR-BT) from an 83-year-old male patient, and confirmed the unusual histopathological and immunohistochemical characteristics of the MPC component.

Materials and methods

An 83-year-old man was found to have hematuria, and papillary tumors were found in the urinary bladder on cystoscopy. TUR-BT was performed to resect as much of the tumor as possible.

The tissue fragments obtained by TUR-BT were fixed in 10% formalin solution, followed by dehydration in graded alcohols and embedding in paraffin; 4-μm dewaxed sections were then stained with hematoxylin and eosin (H&E).

Immunohistochemical staining was then performed, employing the labeled streptoavidin-biotin (LSAB) 2 kit/HRP (Dako, Kyoto, Japan) with diaminobenzidine as the substrate for horseradish peroxidase in accordance with the kit manual and as reported.[14,15] The antibodies used were to epithelial membrane antigen (EMA) (Dako; dilution 1:50, microwave-irradiated for 20 min at 95°C), carcinoembryonic antigen (CEA) (Dako; dilution 1:25, pretreated with pronase), AE1/AE3 (Boehringer-Mannheim Biochemical; dilution 1:400, pretreated by pronase), CAM5.2 (Becton-Dickinson; dilution 1:20, pretreated with pronase), CK7 (Dako; dilution 1:50, pretreated with pronase), CK20 (Dako; dilution 1:25, pretreated by autoclaving at 121°C for 15 min), CA125 (Dako; dilution 1:50, pretreated with pronase), and MIB-1 (Dako; dilution, 1:50, pretreated by autoclaving at 121°C for 15 min).

Results

Histopathological and immunohistochemical (Table 1) findings ars as follows.

Cancer cells had proliferated in large or small irregular solid nests (Fig. 1), with marked pleomorphism of cancer cells, which varied in size and shape (Fig. 1, inset), and many mitotic figures. Cancer cells were markedly invasive, as shown by anti-CK 7 immunostaining (Fig. 2), with invasion to the muscularis propria layer of the urinary bladder. Probable lymphatic invasion was found (Fig. 2, inset). In the region of the prostate, invading cancer cells proliferated in the prostatic glands, replacing the glandular cells (Fig. 3), and were positive on staining with antibodies to EMA, CK7, and CK20, to which glandular cells of the prostate were negative (Fig. 4). MIB-1 positivity of cancer cell nuclei was estimated to be approximately 80%–90% in total.

In the MPC component detected in one of the fragments of TUR-BT tissue, cancer cells had proliferated in small irregular nests associated with a fine stromal meshwork (Figs. 5, 6). The characteristic "inside-out" pattern of MPC was confirmed by staining with EMA antibody (Fig. 7). Peculiar linear positivity was detected on the outside of cell nests of the MPC pattern (Fig. 7), whereas no such findings were found on immunostaining for AE1/3, CK7, and CK20, although staining with these antibodies to cytokeratins was positive for all cancer cells, including those of the MPC component (Figs. 8, 9). Staining for antibody to CAM5.2 was positive only in a part of UC.

Staining for antibodies to CEA and CA125 was negative in all cancer cells, except small parts of UC in the case of anti-CEA antibody. Mitotic figures were often observed in cancer cells, even in the MPC component.

This case was diagnosed as UC, G3, with an MPC component in the urinary bladder, revealing immunohistochemical characteristics of an "inside-out" pattern on staining with anti-EMA antibody.

Table 1. Results of immunohistochemical staining

Antigens	UC	MPC	UB/Ep	Prostate/Ep
AE1/AE3	+	+	+	+
CAM5.2	(+)	–	– to (+)	+
EMA	+	+	– to (+)	– to (+)
CEA	– to (+)	–	–	–
CK7	+	+	+	+
CK20	+	+	+	–
CA125	–	–	–	–

UC, urothelial carcinoma; MPC, micropapillary carcinoma; UB/Ep, urinary bladder epithelium; Pr/Ep, prostate/epithelium; EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; CK7, cytokeratin7

Discussion

The MPC component was first reported in breast,[1] and then other organs including the urinary bladder.[2,10–13] Generally, this component appears to be a marker of poor prognosis. Indeed, the MPC component has been detected in TUR-BT tissues with invasion of the prostate, as in the present case.[12] This component metastasizes to lymph nodes and other organs at high frequency and is often found in metastatic foci.[4,6,12] Immunohistochemically, UC and MPC have displayed no marked differences on examination in various studies.[6,12] In the present study, no distinct difference was found between UC and MPC immunohistochemically. Only in the portion of tumor involved in invasion of the prostate was staining for anti-CK20 antibody positive in the part of invasive UC, with lack of staining in the prostatic epithelium. However, staining for anti-CK7 antibody was positive in both these tissues. Anti-CK20 antibody stain was thus very useful for examining invasion of the prostate. On staining with anti-CK20 antibody, MPC components in the urinary bladder were positive in the present case, as

Fig. 1. Cancer cells had proliferated in irregular nests, with marked invasion. *Inset:* Higher magnification of a part of a cancer cell nest, stained with anti-CK7 antibody. Hematoxylin and eosin (H&E) stain, ×200; *inset*, ×400

Fig. 2. Invasion to the muscularis propria layer of the urinary bladder, with probable lymphatic invasion, was seen (*arrows in inset*). *Inset:* Higher magnification of lymphatic invasion with staining for CK7. *Small arrow* more likely indicates the nuclei of endothelial cells. Anti-CK7 antibody stain with labeled streptoavidin–biotin complex (LSABC) method, ×200; *inset*, ×400

Fig. 3. In prostatic invasion, cancer cells were found with clear borders (*arrow*). H&E stain, ×200

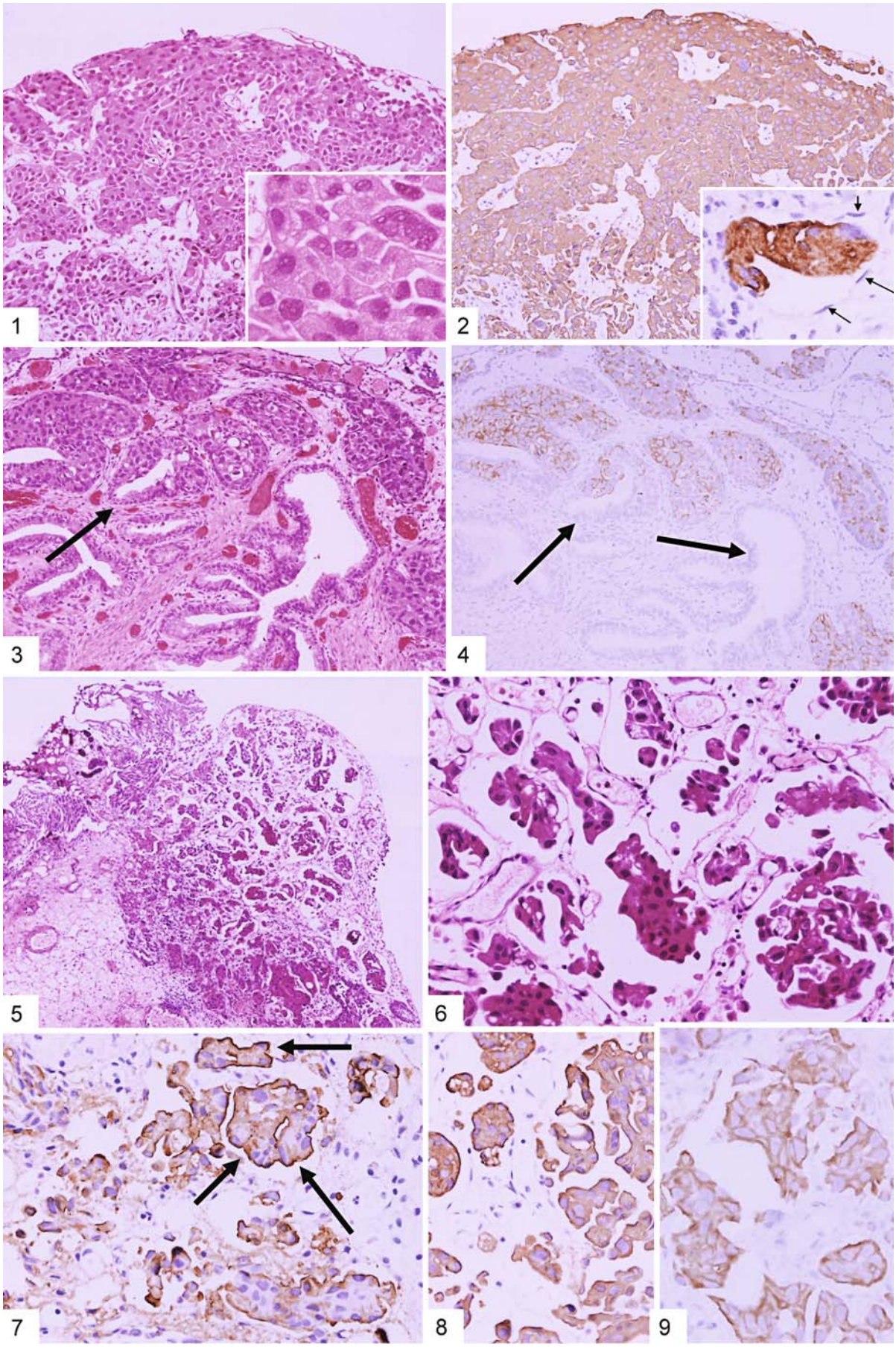
Fig. 4. Cancer cells were positive on anti-CK20 antibody staining (*upper half*), but not prostatic epithelial cells (*arrows*). Anti-CK20 antibody stain with LSABC method, ×200

Figs. 5, 6. In the micropapillary carcinoma (MPC) component (**5**), small irregular nests were embedded in a fine meshwork-like stroma with an invasive pattern. H&E, ×100. Higher magnification (**6**) demonstrates the MPC component clearly. H&E, ×400

Fig. 7. The characteristic "inside-out" pattern was apparent on anti-epithelial membrane antigen (EMA) antibody staining (*arrows*). Anti-EMA antibody stain with LSABC method, ×400

Fig. 8. Cancer cells were positive on anti-CK7 antibody staining. Anti-CK7 antibody stain with LSABC method, ×400

Fig. 9. Cancer cells were positive on anti-CK20 antibody staining. Anti-CK20 antibody stain with LSABC method, ×400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also reported,[12,16] although it has been reported that in the MPC component of lung cancer,[4] only 2 of 15 cases were positive, and that the MPC component was negative in breast cancer.[17]

A peculiar "inside-out" pattern was clearly found for MPC on staining with anti-EMA antibody, as shown in Fig. 7. This finding is of great importance in identifying the MPC component, as demonstrated previously.[12] In fact, lymphatic invasion and invasion of the muscularis propria layer of the urinary bladder were found in the present case, indicating a marked tendency toward deeper invasion, although the specimens examined included many fragments of TUR-BT tissues. The MPC component should be recognized as a marker of poor prognosis and aggressive proliferation, as suggested previously.[5,6,10–12] Pathologists should report the presence of the MPC component in cancers to clinicians to ensure careful and better care of patients.

This MPC pattern has been reported to be evidence of glandular differentiation in the urinary bladder.[12,17] However, cancer cells in the MPC component of the present case were negative on staining with cytokeratin CAM5.2 antibody, although only parts of UC were positive, as was the prostatic glandular epithelium. Staining for CEA and CA125 was negative in this case, but positive in other reported cases of urinary bladder.[12,17] To obtain clear evidence of glandular differentiation of the MPC component, further investigations are needed using MPC or cancers with MPC component in numerous tumors of various organs.

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References

1. Siliaunkgul S, Tavassoli FA (1993) Invasive micropapillary carcinoma of the breast. Mod Pathol 6:660–662
2. Amin MB, Ro JY, el-Sharkawy T, Lee KM, Troncoso P, Silva EG, Ordonez NG, Ayala AG (1994) Micropapillary variant of transitional cell carcinoma of the urinary bladder: histologic pattern resembling ovarian papillary serous carcinoma. Am J Surg Pathol 18:1224–1232
3. Burks RT, Sherman ME, Kurman RJ (1996) Micropapillary serous carcinoma of the ovary: a distinctive low-grade carcinoma-related serous borderline tumors. Am J Surg Pathol 20:1319–1330
4. Amin MB, Tamboli P, Merchant SH, Ordonez NG, Ro J, Ayala AG, Ro JY (2002) Micropapillary component in lung adenocarcinoma: a distinctive histologic feature with possible prognostic significance. Am J Surg Pathol 26:358–364
5. Sakamoto K, Watanabe M, De La Cruz C, Honda H, Ise H, Mitsui K, Namiki K, Mikami Y, Moriya T, Sasano H (2005) Primary invasive micropapillary carcinoma of the colon. Histopathology (Oxf) 47:479–484
6. Kim MJ, Hong SM, Jang SJ, Yu E, Kim JS, Kim KR, Gong G, Ro JY (2006) Invasive colorectal micropapillary carcinoma: an aggressive variant of adenocarcinoma. Hum Pathol 37:809–815
7. Kuroda N, Oonishi K, Ohara M, Hirouchi T, Mizuno K, Hayashi Y, Lee G-H (2007) Invasive micropapillary carcinoma of the colon: an immunohistochemical study. Med Mol Morphol 40:226–230
8. Oh YL, Kim KR (2000) Micropapillary variant of transitional cell carcinoma of the ureter. Pathol Int 50:52–56
9. Munakata S, Tahara H, Kojima K, Kishimoto T (2007) Micropapillary urothelial carcinoma of the renal pelvis: report of a case and review of the literature. Med Sci Monit 13:CS47–CS52
10. Johansson SL, Borghede G, Holmang S (1999) Micropapillary bladder carcinoma: a clinicopathological study of 20 cases. J Urol 161:1798–1802
11. Maranchie JK, Bouyounes BT, Zhang PL, O'Donnell MA, Summerhayes IC, DeWolf WC (2000) Clinical and pathological characteristics of micropapillary transitional cell carcinoma: a highly aggressive variant. J Urol 163:748–751
12. Samaratunga H, Khoo K (2004) Micropapillary variant of urothelial carcinoma of the urinary bladder; a clinicopathological and immunohistochemical study. Histopathology (Oxf) 45:55–64
13. Alvarado-Cabrero I, Sierra-Santiesteban FI, Mantilla-Morales A, Hernandez-Hernandez DM (2005) Micropapillary carcinoma of the urothelial tract. A clinicopathologic study of 38 cases. Ann Diagn Pathol 9:1–5
14. Ohtsuki Y, Terao N, Kuwahara M, Ochi K, Iguchi M, Kurabayashi A, Matsumoto M, Takeuchi T, Furihata M (2007) Eosinophil infiltration in posttransurethral resection prostatitis and cystitis with special reference to sequential changes of eosinophilia. Med Mol Morphol 40:29–33
15. Ohtsuki Y, Nakanishi N, Fujita J, Yoshinouchi T, Kobayashi M, Ueda N, Lee G-H, Furihata M (2007) Immunohistochemical distribution of SP-D, compared with those of SP-A and KL-6, in interstitial pneumonias. Med Mol Morphol 40:163–167
16. Kuroda N, Tamura M, Ohara M, Hirouchi T, Mizuno K, Miyazaki E (2006) Invasive micropapillary carcinoma of the urinary bladder: an immunohistochemical study of neoplastic and stromal cells. Int J Urol 13:1015–1018
17. Ramalingam P, Middleton LP, Tamboli P, Toroncoso P, Silva EG, Ayala AG (2003) Invasive micropapillary carcinoma of the breast metastatic to the urinary bladder and endometrium: diagnostic pitfalls and review of the literature of tumors with micropapillary features. Ann Diagn Pathol 7:112–119