Micropapillary Variant of Urothelial Carcinoma in the Upper Urinary Tract

A Clinicopathologic Study of 11 Cases

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Micropapillary urothelial carcinoma (MPUC) is a rare variant of urothelial carcinoma. Most studies of MPUC have focused on the urinary bladder, but MPUC of the upper urinary tract remains to be investigated.

Objective.—To investigate the pathologic features and clinical significance of MPUC in the upper urinary tract.

Design.—We searched the pathology files at our institution and identified 11 cases of MPUC of the upper urinary tract. The histology slides were reviewed, and the clinical information was obtained by review of medical charts.

Results.—The average age of the patients was 64.2 years (range, 22–76 years). The tumors were located in the renal pelvis (n = 5), ureter (n = 4), and ureteropelvic junction (n = 2). In all cases, MPUC accounted for an average of 45% (range, 10%–80%) of the tumor and was associated with conventional urothelial carcinoma. Lymphovascular invasion was present in all cases, and metastasis to lymph node was present in 4 of 5 patients whose lymph nodes were dissected. Two patients presented with pT2 disease, and both were alive without evidence of disease at 85 and 119 months after surgery. The other 9 patients presented with pT3 or pT4 disease: 4 of them died of disease at an average of 18 months; 4 surviving patients developed distant metastases; and 1 surviving patient with limited follow-up (6 months) showed no evidence of disease.

Conclusions.—Micropapillary urothelial carcinoma of the upper urinary tract often presents at an advanced stage with lymphovascular invasion and distant metastasis. The presence of MPUC, even focal, indicates a poor clinical course.

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U rothelial carcinoma is the most common tumor in the urinary tract. The majority of urothelial carcinomas arise from the urinary bladder, with 68,810 estimated new cases in the United States in 2008. In contrast, urothelial carcinomas of the upper urinary tract, which includes the renal pelvis and ureter, are relatively uncommon. It is estimated that urothelial carcinoma of the renal pelvis accounts for 10% of all renal tumors, with about 3000 new cases reported every year in the United States. In the ureter, urothelial carcinoma is even less common, with its incidence estimated to be only one third to a quarter of that in the renal pelvis. Because of their low incidences, most studies combine urothelial carcinoma of the renal pelvis and ureter into urothelial carcinoma of the upper urinary tract.

Micropapillary urothelial carcinoma (MPUC) is a rare variant of urothelial carcinoma. Amin et al first reported MPUC of the urinary bladder in 18 cases. They described 2 distinct histologic patterns of MPUC: (1) the noninvasive pattern characteristic of slender micropapillae on the surface of tumor and (2) the invasive pattern featured in small infiltrating clusters of micropapillary aggregates that were often present within lacunae or empty spaces. This variant demonstrated a high tendency to invade lymphovascular spaces and to metastasize to lymph nodes and other organs. They also found MPUC to be associated with advanced tumor stage and, therefore, a poor prognosis. Several other studies have confirmed these observations in MPUC of the urinary bladder.

Although MPUC has been well studied in the urinary bladder, there have been only a few studies of this tumor in the upper urinary tract, including the renal pelvis and ureter. To improve our understanding of this rare variant, we studied the pathologic and clinical features of 11 cases of MPUC in the upper urinary tract.

MATERIALS AND METHODS

After obtaining approval from the institutional review board, we retrospectively searched the pathology report database at our institution to identify patients treated between 1994 and 2006 for MPUC of the upper urinary tract, including the renal pelvis and ureter. We identified 11 patients who had undergone nephroureterectomy for this entity. These 11 patients accounted for approximately 2.3% of the 483 cases of nephroureterectomy performed during the period of this study.

In all cases, hematoxylin-eosin–stained histologic preparations were available for review. Parameters reviewed included tumor location, percentage of MPUC, tumor cell grade, depth of tumor invasion, lymphovascular invasion, presence of concurrent conventional papillary noninvasive or invasive urothelial carcinoma and urothelial carcinoma in situ, and presence of glandular, squamous, or another differentiation of urothelial carcinoma. Additionally, immunohistochemically stained sections of the MPUC were available in 3 cases. The immunohistochemical staining was performed using the avidin-biotin-peroxidase complex method in...
**Summary of Clinical and Histopathologic Characteristics of Micropapillary Variant of Urothelial Carcinoma (MPUC)**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y/Sex</th>
<th>Presenting Symptoms</th>
<th>Tumor Location</th>
<th>% of MPUC</th>
<th>Other Histologic Features</th>
<th>Depth of Invasion</th>
<th>Lymph Nodes</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76/M</td>
<td>Hematuria</td>
<td>Renal pelvis</td>
<td>80</td>
<td>Papillary UC</td>
<td>Peripelvic fat</td>
<td>3/5</td>
<td>25 mo; died of tumor</td>
</tr>
<tr>
<td>2</td>
<td>73/F</td>
<td>Hematuria, flank pain</td>
<td>Lower ureter</td>
<td>20</td>
<td>Papillary UC</td>
<td>Muscularis propria</td>
<td>0/3</td>
<td>119 mo; no evidence of disease</td>
</tr>
<tr>
<td>3</td>
<td>76/M</td>
<td>Flank pain</td>
<td>Lower ureter</td>
<td>70</td>
<td>Nonpapillary UC</td>
<td>Perireteral fat</td>
<td>NA</td>
<td>20 mo; died of tumor</td>
</tr>
<tr>
<td>4</td>
<td>73/F</td>
<td>Follow-up of bladder UC</td>
<td>Upper ureter, pelvis</td>
<td>60</td>
<td>Papillary UC</td>
<td>Renal parenchyma</td>
<td>NA</td>
<td>8 mo; metastasis to lung</td>
</tr>
<tr>
<td>5</td>
<td>58/M</td>
<td>Hematuria</td>
<td>Upper ureter, pelvis</td>
<td>70</td>
<td>Papillary UC</td>
<td>Muscularis propria</td>
<td>85 mo; no evidence of disease</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>74/M</td>
<td>Hematuria, flank pain</td>
<td>Renal pelvis</td>
<td>50</td>
<td>Papillary UC</td>
<td>Perinephric fat</td>
<td>NA</td>
<td>22 mo; died of tumor</td>
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<td>7</td>
<td>54/M</td>
<td>Flank pain</td>
<td>Renal pelvis</td>
<td>30</td>
<td>Papillary UC, adeno</td>
<td>Renal parenchyma</td>
<td>71 mo; local tumor recurrence in renal fossa</td>
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<tr>
<td>8</td>
<td>61/M</td>
<td>Flank pain</td>
<td>Mid ureter</td>
<td>10</td>
<td>Papillary UC</td>
<td>Periureteral fat</td>
<td>10/19</td>
<td>4 mo; died of tumor</td>
</tr>
<tr>
<td>9</td>
<td>69/M</td>
<td>Nephrosis</td>
<td>Upper ureter</td>
<td>30</td>
<td>Papillary UC</td>
<td>Periureteral fat</td>
<td>4/6</td>
<td>18 mo; metastasis to colon</td>
</tr>
<tr>
<td>10</td>
<td>22/M</td>
<td>Hematuria</td>
<td>Renal pelvis</td>
<td>10</td>
<td>Papillary UC, adeno, sq</td>
<td>Peripetal fat</td>
<td>NA</td>
<td>54 mo; metastasis to lung</td>
</tr>
<tr>
<td>11</td>
<td>70/M</td>
<td>Hematuria</td>
<td>Renal pelvis</td>
<td>30</td>
<td>Nonpapillary UC</td>
<td>Renal parenchyma</td>
<td>5/12</td>
<td>6 mo; no evidence of disease</td>
</tr>
</tbody>
</table>

* In cases 3 and 4, atypical cells were detected in urine cytology during follow-up of noninvasive papillary urothelial carcinoma of the bladder. UC indicates urothelial carcinoma; NA, nonapplicable; adeno, adenocarcinoma; and sq, squamous carcinoma.

A Dako AutoStainer (Dako, Carpinteria, Calif). The primary antibodies used were mouse monoclonal antibodies to podoplanin (D2-40; Signet Laboratories, Dedham, Mass), CD31 (1:20; Dako), and CD34 (1:100; Dako). The immunostaining was done using the LSAB2 peroxidase kit (Dako). To enhance the immunostaining, a heat epitope retrieval procedure was performed using a Black and Decker vegetable steamer (Towson, Md). The buffer solution used was Tris-EDTA buffer, pH 8.0. Enzymatic pretreatment with 0.2% protease, type XXIV (Sigma Chemical Co, St Louis, Mo) in Tris-buffered saline, pH 7.3, was performed. The antigen-antibody immunoreaction was visualized using 3-amino-9-ethylcarbazole as chromogen.

The following demographic and clinical information was obtained from patients’ charts or by communication with treating physicians: patient age and sex, presenting symptoms, type of therapy received, clinical course, and follow-up.

**RESULTS**

**Clinical Features**

Clinical information was available for all 11 patients in our study (Table). The average age was 64.2 years (range, 22–76 years), and there were 9 men and 2 women. Presenting symptoms included hematuria (n = 6), flank pain (n = 4), abnormal urine cytology (n = 3), and nephrotic syndrome (n = 1). The 3 patients who presented with abnormal urine cytology were identified during the follow-up study of previous noninvasive urothelial carcinomas of the urinary bladder, including urothelial carcinoma in situ (n = 2) and papillary urothelial carcinoma (n = 1). The tumors were located in the renal pelvis (n = 5), ureter (n = 4), and ureteropelvic junction (n = 2).

**Histologic Features**

When present on the urothelial surface, MPUC formed slender micropapillae, which usually lacked fibrovascular cores (Figure 1). Invasive MPUC was characteristic of small nests or clusters of tumor cells in lacunae (Figure 2, A). In these tumor nests or clusters, tumor cells had nuclei arranged at the periphery and cytoplasm at the center, creating a rosettelike pattern. Tumor cells were high grade, with marked nuclear atypia in all cases (Figure 2, B). Focal necrosis was present in 7 cases. In all cases, MPUCs were associated with conventional urothelial carcinoma, including papillary type (n = 9) and nonpapillary type (n = 2). Micropapillary variant urothelial carcinoma accounted for an average 45% of the tumor volume (range, 10%–80%). Other morphologic features included focal glandular differentiation (n = 2) and squamous differentiation (n = 1). Although they mimicked lymphovascular spaces, the lacunae actually resulted from retraction artifact. On routine hematoxylin-eosin stain, the lacunae lacked endothelial lining and blood cellular components (Figure 3, A). Immunostaining for endothelial markers, including CD31, CD34, and D2-40, also demonstrated that the lacunae lacked endothelial lining (Figure 3, B through D). However, true lymphovascular invasion was identified...
Figure 2. Micropapillary urothelial carcinoma of the ureter shows infiltrating tumor nests in lacunae (A) (hematoxylin-eosin, original magnification ×100) with marked nuclear atypia (B) (hematoxylin-eosin, original magnification ×200).

Figure 3. A, Lacunae lack endothelial lining and blood cellular components (hematoxylin-eosin, original magnification ×200). The lack of endothelial lining is highlighted on immunostaining for CD31 (B), CD34 (C), and D2-40 (D) (original magnifications ×200).

in all patients (Figure 4). Metastasis to lymph nodes was present in 4 of 5 patients whose lymph nodes were dissected (Figure 5). Tumors of the renal pelvis invaded into peripelvic adipose tissue or renal parenchyma in 4 cases and perinephric adipose tissue (pT4) in 1 case; tumors of the ureter invaded into muscularis propria (pT2) in 1 case and periureteral adipose tissue (pT3) in 3 cases; tumors of the ureteropelvic junction invaded into the muscularis propria (pT2) in 1 case and renal parenchyma (pT3) in the other case.
Patient Outcomes

Follow-up was available for all patients, with an average of 39 months (range, 4–119 months). All patients received chemotherapy after surgery. Both of the patients with pT2 tumors were alive without evidence of disease after 85 and 119 months of follow-up, respectively. Of the 8 patients with pT3 tumors, 3 died at an average of 16 months (range, 4–25 months) after surgery. Five patients were alive at an average follow-up period of 32 months (range, 6–54 months). Of these 5 patients, 4 developed distant metastases to lung, colon, or retroperitoneum; only 1 had no tumor recurrence at 6 months after surgery. The 1 patient with a pT4 tumor died of disease at 22 months after surgery.

COMMENT

Micropapillary variant urothelial carcinoma of the upper urinary tract exhibits histologic features identical to those observed in MPUC of the urinary bladder. The invasive pattern is characteristic of small infiltrating clusters of tumor cells within lacunae, whereas the noninvasive pattern features slender micropapillae on the surface of the tumor. In all of the cases we reviewed, tumor cells showed high nuclear grade, MPUCs were associated with conventional urothelial carcinoma, and true lymphovascular invasion was present. In addition, 4 of 5 patients who underwent lymph node dissection also had metastasis to lymph nodes.

One of the most prominent histologic features of MPUC is the presence of lacunae (small, round, empty spaces) surrounding infiltrating tumor nests. Although lacunae resemble vascular or lymphatic vessels, they are not true lymphovascular spaces. These empty spaces usually lack vascular features, such as an endothelial lining and cellular constituents of blood. Furthermore, immunohistochemical studies with factor VIII–related antigen and CD31 have generally failed to demonstrate endothelial cells.5,7,12 These retraction spaces are thought to be an artifact of fixation and are not seen on frozen sections.

Like MPUC of the urinary bladder, MPUC of the upper urinary tract is an aggressive variant of urothelial carcinoma, as evidenced by advanced tumor stage at diagnosis and high tendency to metastasize. In our study, 9 of 11 patients presented with pT3 or pT4 tumors, and 4 of these patients died of tumor within 2 years after surgery. For the 5 surviving patients, 4 developed metastases to the lung, colon, or retroperitoneum; only 1 showed no evidence of tumor, although that was within a short follow-up duration (6 months).

Interestingly, both patients with pT2 tumors were alive without evidence of disease after a long duration of follow-up (7 and 10 years, respectively). In fact, in a recent study of early-stage nonmuscle-invasive MPUC of the urinary bladder, Kamat et al13 reported that the 10-year survival rate reached 72% when patients received cystectomy as initial therapy. However, no patients survived 10 years when they received bacillus Calmette-Guérin as initial therapy followed by cystectomy. On the basis of this finding, the investigators recommended that patients with nonmuscle-invasive MPUC should be treated aggressively with radical cystectomy. Our study also suggests that nephroureterectomy may be curative in some patients in whom MPUC of the upper urinary tract is identified at an early stage.

Micropapillary variant urothelial carcinoma of the up-
per urinary tract is a rare variant, with fewer than 40 cases reported in the literature. In the 5 cases reported by Perez-Montiel et al., MPUC presented as an invasive pattern in 3 cases and as a noninvasive pattern in the other 2 cases. In the latter 2 cases, conventional urothelial carcinoma was also present and invaded into the renal parenchyma. All patients died of tumor from 3 to 24 months after initial diagnosis. Holmång et al. reported 26 cases of MPUC from 18 hospitals. All MUPCs presented as an invasive pattern. Twenty patients died of the disease; however, when compared stage by stage, the 5-year survival rate of patients with MUPC (23%) was not significantly worse than that of patients who had conventional urothelial carcinoma without MUPC (18%). Therefore, these investigators concluded that the poor prognosis of patients with MPUC might have been caused by the advanced stage of tumor. Their cases were collected from multiple hospitals, however, thus the treatment regimens might not have been uniform.

In addition to urothelial carcinoma, micropapillary pattern has been reported in carcinomas of the ovary, breast, lung, colon, and major salivary glands. In all of these organs, micropapillary pattern shares the distinct morphology that is characteristic of small infiltrating clusters or nests of tumor cells within lacunae. In these organs, micropapillary pattern is commonly mixed with conventional carcinoma or other variants. The aggressive nature of micropapillary pattern is evidenced by advanced tumor stage and high tendency to include lymphovascular invasion and metastasis, indicating a poor clinical outcome.

Because micropapillary carcinomas share identical morphologic features in most anatomic sites, it is important to exclude metastases with micropapillary features when making a definite diagnosis of primary tumor. Immunohistochemical stains are useful in identifying the primary tumor. Ramalingam et al. reported a case of a 59-year-old woman with a history of micropapillary variant of breast carcinoma following bilateral mastectomy. Two years after mastectomy, biopsies of this patient's urinary bladder and endometrium showed the presence of micropapillary carcinoma. The micropapillary components were morphologically identical in the breast, urinary bladder, and endometrium; however, the tumor cells from the breast, endometrium, and urinary bladder were positive for cytokeratin 7 and estrogen receptor and negative for cytokeratin 20. Therefore, the micropapillary tumors in the urinary bladder and endometrium were believed to be metastases from the breast primary.

It has been hypothesized that the highly aggressive behavior of micropapillary carcinoma may be attributed to a reverse in cell polarity in tumor nests where the stroma-facing (basal) surface of the cells acquires apical secretory properties. This reverse of cell polarization facilitates the direct release of molecules that are critical for tumor invasion into the stroma, leading to the dissemination of tumor cells. Luna-More et al. used electron microscopy to demonstrate the presence of a large number of microvilli at the surface of the cells facing the stroma. Furthermore, Nassar et al. used immunohistochemistry to demonstrate the presence of MUC1 on the basal surface of micropapillary carcinomas. As MUC1 is usually expressed at the apical surface of the cells in normal glandular epithelium, the presence of MUC1 on the basal surface supports the reverse in cell polarity in micropapillary carcinoma.

In summary, MPUC of the upper urinary tract is a high-aggressive variant of urothelial carcinoma. The histologic patterns of MPUC are characterized by slender micropapillae on the tumor surface and small infiltrating clusters of tumor cells surrounded by empty space in the deep tumor. MPUC frequently presents at an advanced stage with a high propensity for lymphovascular invasion and metastasis. It is uncertain whether MPUC is an independent prognostic factor for a patient's survival, due to the limited number of cases in our study. However, the presence of MPUC in the upper urinary tract, even focal, is associated with a poor outcome. When MPUC of the upper urinary tract is present at an early stage, aggressive therapy, such as nephroureterectomy, may be curative in some patients.

References


Micropapillary Urothelial Carcinoma—Guo et al