CASE REPORTS

Micropapillary urothelial carcinoma: an aggressive variant of urothelial carcinoma

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Abstract

Micropapillary urothelial carcinoma (MPC) is a rare variant of urothelial carcinoma (UC) with an aggressive clinical course, an advanced stage at first presentation and a high metastatic potential. The aim of our study is to present five illustrative cases of MPC, diagnosed among the 21 patients with UC treated by radical cystectomy in the Department of Urology, County Hospital of Tîrgu Mureş, Romania, between January 1, 2011 and December 31, 2013. The morphological and immunohistochemical features of this rare and aggressive variant of UC, as well as a brief review of the literature are all presented. All five cases were associated with lymph node metastases with micropapillary features, regardless of the microscopic aspect of the tumor on the surgical specimens [transurethral resection (TUR) or cystectomy]. Three of them had a micropapillary component in the TUR, on the cystectomy specimen, or in both, along with lymph nodes metastases. In two cases, the MPC features were present only in the lymph node metastasis, with a conventional UC on the TUR and on the cystectomy. Immunohistochemical staining demonstrated that both micropapillary and associated conventional UC were positive for CK7 and CK20. Ki67 was expressed in 40% of tumor cells and CD34 was positive in the endothelial cells and negative in the flattened spindled cells lining the retraction spaces around tumor cell nests. MPC is a highly aggressive variant of UC with specific morphological characteristics. Any amount of micropapillary component found in UC is significant, and should be reported because it encompasses an aggressive clinical behavior and a poor prognosis.

Keywords: urothelial carcinoma, micropapillary, prognosis.

Introduction

Urothelial carcinoma (UC) is the most common type of bladder cancer and it accounts for more than 90% of bladder tumors. UC has a propensity for divergent differentiation, so a whole spectrum of UC variants were described and recognized by the current 2004 WHO (World Health Organization) classification of urologic tumors [1].

The recognition of these variants is important because it can influence both prognosis and therapy.

Micropapillary urothelial carcinoma (MPC) is a distinct and rare variant of UC, accounting for 0.6–8.2% of all urothelial tumors [2, 3]. It has distinct morphologic features closely resembling to papillary serous carcinoma of the ovary [4], usually with an aggressive clinical course, an advanced stage at first presentation, a high metastatic potential and a poor outcome [5–7].

Because the clinical presentation is not different from conventional urothelial carcinoma, the pathological findings are crucial for a correct diagnosis and an appropriate therapeutic decision.

There are limited data available about the pathological characteristics and the clinical behavior of this variant with approximately 400 cases reported in the literature in few retrospective clinicopathological series and case reports [2, 4–11].

In this study, we analyze five consecutive cases of MPC in order to better define the morphological aspect and the behavior of this aggressive disease.

Patients and Methods

Twenty-one patients treated with radical cystectomy in the Department of Urology, County Hospital of Tîrgu Mureş, Romania, between January 1, 2011 and December 31, 2013 were evaluated. Of these, only five cases were included in the study, as they revealed micropapillary features, consistent with a diagnosis of MPC.

All cystectomy specimens were processed in the Department of Pathology, County Hospital of Tîrgu Mureş, according to the recommendations for handling and reporting bladder specimens [12]. For a better fixation and examination of the entire mucosa, the bladder was opened on the anterior face by performing a section from the urethra to the bladder dome. For all visible tumors, the size, location, macroscopic aspect (flat, papillary, ulcerated, or infiltrative), color and consistency were recorded. The tumor and the resection margins, including each ureter and the urethra, were sampled. In male patients, all the surgical specimens were cystoprostatectomies, in which the distal urethral margin is at the prostatic apex. The prostate was sampled and examined according to the protocol for pathological examination and reporting of radical prostatectomy specimens [13]. In one case of pelvic exenteration, besides the bladder, the uterus and the vagina were also evaluated, according to the standardized protocols for these organs [14].

In each case, the bladder tumor was entirely sampled in order to make an accurate histological typing, grading and staging. The histological type and the grade of the
exophytic component, if such a component was present, were established in line with the 2004 WHO (World Health Organization) classification [1]. The pathological stage (the depth of invasion) was established according to the 2009 TNM Staging System [15]. The presence of an associated carcinoma in situ (CIS) was also assessed in all patients. The attention was focused on the cases in which a micropapillary component was associated with conventional UC.

A diagnosis of micropapillary variant of UC was established if the following morphologic features were present: back-to-back lacunar spaces containing small nests of tumor cells, presence of multiple nests in a single lacunar space, small branching micropapillae and ring forms [16].

The percentage of the micropapillary component, representing the amount of this component out of the whole tumor (conventional UC), was evaluated.

According to the EAU (European Association of Urology) guidelines, radical cystectomy also includes the dissection of regional lymph nodes [17]. Therefore, all the lymph node specimens, sent in separate clearly labeled containers, and also the lymph nodes found in the perivesical fat were entirely included and evaluated.

Table 1 – Characteristics at initial presentation and tumor aspects on the radical cystectomy specimens for all five patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Transurethral resection</th>
<th>Radical cystectomy specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgical specimen</td>
<td>Lymph nodes</td>
</tr>
<tr>
<td>1.</td>
<td>Infiltrative UC with MPC (10%), stage pT1. Papillary and infiltrative (pushing margins infiltration type) UC with MPC (5%) in the bladder neck and in the lamina propria of the urethra. CIS in the prostatic urethra and prostatic glands.</td>
<td>1+ (UC and MPC) / 20</td>
</tr>
<tr>
<td>2.</td>
<td>Infiltrative UC with MPC (80%), stage pT1. CIS in the peritumoral mucosa. Infiltrative UC with MPC (10%) on the right lateral wall of the bladder. CIS extended in the prostatic urethra and prostatic glands.</td>
<td>6+ (only MPC) / 12</td>
</tr>
<tr>
<td>3.</td>
<td>Infiltrative UC, stage pT2. Infiltrative UC extended to the perivesical adipose tissue.</td>
<td>1+ (only MPC) / 9</td>
</tr>
<tr>
<td>4.</td>
<td>Infiltrative UC with glandular differentiation, stage pT2. Infiltrative UC extended to the perivesical adipose tissue with small foci of glandular differentiation.</td>
<td>18+ (only MPC) / 35</td>
</tr>
<tr>
<td>5.</td>
<td>Not available. Infiltrative UC with MPC (40%) extended to the uterus up to the myometrium. Ovarian metastasis. The extension and the metastasis had only micropapillary features.</td>
<td>4+ (only MPC) / 4</td>
</tr>
</tbody>
</table>

UC: Urothelial carcinoma, MPC: Micropapillary carcinoma, CIS: Carcinoma in situ.

When available, the transurethral resection (TUR) specimens were reviewed.

In some cases, immunohistochemistry (IHC) was necessary for differentiating MPC from other entities. Immunostaining with CD34, CK7, CK20, ER, WT-1 and TTF-1 antibodies was performed. The following staining patterns were considered positive: cytoplasmic for CK7 and CK20, nuclear localization for ER, WT-1, TTF1 and Ki67; cytoplasmic with membrane reinforcement for CD34.

Results

Five patients, four men and one woman, had a micropapillary component associated with the conventional UC, either on the cystectomy specimen or in the lymph nodes metastases. In three cases, the cystectomy was performed for a stage pT2 UC on TUR specimens. In two cases, although the tumor was infiltrating only the lamina propria (stage pT1), the cystectomy was recommended because a micropapillary component was identified. Table 1 summarizes the characteristics at initial presentation and tumor aspects on the radical cystectomy specimens for all five patients.

Discussion

Carcinomas with micropapillary features have been described in the uterus [18], breast [19] lung [20] and digestive tract [21, 22], the prototype pattern being the papillary serous carcinoma of the ovary.

In the bladder, micropapillary carcinoma is a variant described for the first time by Amin et al. in 1994 as a tumor closely resembling papillary serous carcinoma of the ovary [4].

Initial reports estimated that micropapillary variant of UC accounts for 0.6–2.2% of all urothelial tumors [2, 4]. The low incidence is probably because MPC was still little known and consequently underreported. Recently, the incidence has increased, more cases having been reported since 2000, when pathologists and oncologists became aware of its description and of its particular clinical behavior [3, 9]. The variable proportion reported by different authors is evidently due to a lack of established criteria for diagnosis, a low inter-observer reproducibility of this
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This histological variant of UC shows a male predominance (male to female ratio 5:1–10:1) which is higher than in conventional UC (3:1), with patient ages ranging from 50 to 90 and a mean age of 64.7 years [23]. Similarly, our series included four men and one woman, with ages ranging from 55 to 68 years and a mean age of 61.8 years.

By reviewing the literature on this subject, we did not find many studies on large numbers of patients with MPC. Approximately 400 cases reported in the literature are grouped in few retrospective clinicopathological series, summarized in Table 2, and in case reports.

Table 2 – Retrospective clinicopathological studies on micropapillary urothelial carcinoma

<table>
<thead>
<tr>
<th>Author, year [reference]</th>
<th>No. of patients</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amin et al., 1994 [4]</td>
<td>18</td>
<td>NA</td>
</tr>
<tr>
<td>Samarutunga et al., 2004 [8]</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Wang et al., 2012 [11]</td>
<td>73</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA: Not available.

It is natural to ask ourselves: Is this variant really so rare? Or is it still underreported? With the available data, we cannot answer this question, but in our small series of 21 patients who underwent a cystectomy over a period of two years, five (23%) patients had a micropapillary component, either in the bladder or in the lymph node metastases.

We have drawn attention to these cases because all the five cases had an aggressive behavior, all having lymph node metastases with micropapillary features, regardless of the appearance of tumor on surgical specimens (TUR or cystectomy), and regardless of the proportion of the micropapillary component in the bladder.

Gross features of MPC are highly variable and are not specific for this variant, ranging from papillary or polypoid tumor to an ulcerated or infiltrative mass [24, 25]. This heterogeneity was confirmed in our cases, with aspects varying from an extensive papillary tumor without evident muscle infiltration to an ulcerated mucosa with a visible infiltrative component.

At a microscopic level, two distinct morphological patterns of MPC can be encountered.

The most common is the invasive pattern consisting of small nests and papillae with atypical cells with high nuclear grade, surrounded by retraction spaces mimicking lymphatic vessels.

![Figure 1 – MPC associated with conventional UC. (A) Micropapillary component (back-to-back lacunar spaces with multiple small tumor cell nests in the same retraction space), HE staining, ×100; (B) Strong diffuse immunoreactivity of the micropapillary component for CK7, ×100; (C) Conventional UC revealing large nests of tumor cells with high pleomorphism, HE staining, ×100; (D) Strong diffuse immunoreactivity of the conventional component for CK7, ×100.](image-url)
The retraction spaces may be focally lined by flattened spindled cells or may be devoid of any lining. A small proportion of these spaces represents actual lympho-vascular invasion, which can be proven by IHC with endothelial markers such as CD31, CD34 and D2-40.

Although not present in all cases, reversed polarity of the nuclei to the external surface of tumor nests is another feature that may be seen in MPC.

The second morphological aspect is a non-invasive pattern composed of slender, filiform processes, usually devoid of fibrovascular core. When cut in cross-section, these pseudopapillae appear as glomeruloid bodies [24, 26].

All our patients presented an infiltrative pattern of MPC. Three of them had a micropapillary component either on the TUR or cystectomy specimen, or on both, along with lymph node metastases. In two cases, the MPC features were present only in the lymph node metastasis, with a conventional UC on the TUR and on the cystectomy.

Figure 2 – One patient with MPC infiltrative in the uterus, with lymph node and ovarian metastases. (A) MPC associated with conventional UC in the bladder, HE staining, ×40; (B) Infiltrative aspect of MPC in the bladder wall, HE staining, ×40; (C) Micropapillary component infiltrative in the uterus, HE staining, ×100; (D) Ovarian metastasis: multiple tumor cell nests in a retraction space, HE staining, ×100; (E) Micropapillary features in the ovary: ring forms, intracytoplasmatic vacuolization and peripheral orientation of the nuclei, HE staining, ×200; (F) The same micropapillary aspect in the lymph node metastasis, HE staining, ×100.
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Micropapillary urothelial carcinoma (MPC) is an aggressive variant of urothelial carcinoma (UC) characterized by a distinctive growth pattern with small nests or clusters of tumor cells, often associated with extracapsular extension and nuclear pleomorphism. The micropapillary pattern is described in literature as usually associated with UC, with varying proportions of MPC ranging from focal to almost exclusive. No established criteria for the cut-off proportion of micropapillary component to qualify a tumor as MPC have been set, with some authors suggesting 5% or 10% as the lower limit, while others concluded that the presence of any amount of MPC portends a poor outcome, and as a result it must be reported [10].

Associated CIS can be demonstrated in >50% cases according to literature [23], and must be reported as this also affects clinical outcome by predicting recurrence [10]. In our cases, CIS in the bladder was noticed in two cases, with extension in the prostatic urethra and prostatic glands.

Because MPC has a more aggressive clinical course, with high metastatic potential and a worse outcome than conventional UC, the most important differential diagnosis is its distinction from conventional UC with prominent retraction artifact. This was the case of two patients, both men, in our series. For the MPC diagnosis, the morphological features described by Sangoi et al., having the highest inter-observer reproducibility, were used: back-to-back lacunar spaces containing small tumor cell nests, multiple nests within a single stromal retraction space, epithelial ring forms, intracytoplasmic vacuolization and peripherally oriented nuclei. In contrast to these features, UC with extensive retraction characteristics are large nests and more confluent branching epithelium [16].

There are no immunohistochemical markers to differentiate MPC from conventional UC. Both express cytokeratins (CK7, CK20) epithelial membrane antigen, Leu-M1 and carcinoembryonic antigen [8, 24]. Some promising markers were described in the literature: MUC1, CA125 and Her2/neu [27, 28], but when comparing the expression of these three antibodies in MPC and UC with stromal retraction, Sangoi et al. concluded that they do not have great utility in the distinction between the two variants, and distinction should be based on morphology until more specific markers are identified [29].

The other critical differential diagnosis is a metastasis of micropapillary carcinoma from other organs in the bladder. In our study, two male patients presented a conventional UC in the bladder, with MPC features only in the lymph node metastasis. In this case, it was necessary to rule out a metastatic MPC from other organs such as the lung or digestive tract. As there was no clinical evidence for a lung or digestive tumor and because the tumor cells expressed CK7 and CK20 and were negative for TTF-1, a diagnosis of UC with MPC features in the lymph node metastasis was set in this case. Clinical data and immunohistochemistry were mandatory for a correct diagnosis.

Two series have addressed the issue of differential diagnosis of urothelial MPC from MPC primary originating in other organs [29, 30]. They found that in a metastatic setting, or when invasive MPC occurs in the bladder without an associated in situ or conventional UC components.
ponent, immunostaining for uroplakin, CK20 (bladder), TTF-1 (lung), ER, WT-1 and/or PAX8 (ovary) and mammaglobin (breast) is the best panel for determining the most likely primary site of MPC.

Johansson et al., Kamat et al., and Samaratunga and Kho reported on the clinical significance of micropapillary UC. These studies emphasized that patients have a variable course, with some patients dying rapidly and others experiencing prolonged survival, reflecting the fact that this entity is not fully well characterized or is not always correctly diagnosed [2, 5, 8].

The poor prognosis of these patients is evidenced by an overall 5-year survival rate of only 51% reported by Kamat et al. in the most representative study of MPC [5], and of 42.3% reported by Wang J and Wang FW in a recent population-based study on epidemiology, tumor characteristics and survival rates [31].

The propensity of for lymphovascular invasion and lymph node metastases is a characteristic feature of tumor aggressiveness in MPC. A complete and correct evaluation of all lymph nodes is decisive for a correct diagnosis and staging, considering the fact that the 2009 TNM Staging System defines nodal status based on the number and size of positive lymph nodes.

Our results are also supportive for an aggressive clinical outcome in patients with MPC. In our study, out of the 21 patients who underwent cystectomy, all five (100%) patients with MPC had an advanced disease at the time of diagnosis, with lymph node metastases, compared with 16 patients with conventional UC, of which only three (31%) presented lymph node metastases. Wang et al., in a recent study on 73 patients with MPC, had similar results with 50% patients with lymph node metastases in the MPC group vs. 10% in patients with conventional UC [11].

Given the fact that this variant of UC is almost invariably muscle invasive at the time of presentation, with frequent metastases to the lymph nodes, the treatment of choice for all patients with MPC is immediate radical cystectomy without adjuvant treatment [11].

Conclusions

Micropapillary urothelial carcinoma is very likely an underreported variant of UC, a highly aggressive one, with specific morphological characteristics. Any amount of micropapillary component found in UC is significant, and should be reported because it encompasses an aggressive behavior and poor prognosis. The presence of this component should alert urologists to apply an aggressive therapy, radical cystectomy being the only treatment that provides a chance of cure for these patients.

References


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