Micropapillary carcinoma of the urinary bladder

G. Glück¹, Monica Hortopan², R. Stoica¹, Manuela Chiriţă¹, I. Sinescu¹

¹ University of Medicine and Farmacy Carol Davila Bucharest
² Department of Pathology, Fundeni Clinical Institute, Bucharest, Romania

Abstract

Purpose: Micropapillary carcinoma of the urinary bladder is a rare and aggressive form of urothelial cancers that must be known by the urologist in order to adopt the most appropriate treatment pattern.

Materials and methods: A retrospective study had been undergone over a period of four years, between 2009-2012, including eight patients (one woman and seven men) diagnosed with invasive bladder cancer who benefited from radical cystectomy and in which cases the histopathological examination confirmed the presence of micropapillary carcinoma. The mean age reported was 60.2 years. Concerning the urinary diversion, there was a number of five cutaneous ureterostomies, two ileal conduits and one neobladder.

Results: The tumoral stage found was T2 for 3 patients, T3 for three patients and T4b for two patients. Pure micropapillary carcinoma was diagnosed in six cases, while the other two cases presented either squamous elements together with micropapillary carcinoma or squamous plus adenocarcinoma elements.

Negative lymph nodes were present in only two cases, the rest having positive lymph nodes as follows: two cases of N1, two cases of N2 and two cases of extra regional adenopathies.

Conclusions: Though micropapillary carcinoma is a rare form of urothelial cancer, it is very aggressive. Early diagnosis and radical surgical treatment can lead to acceptable results regarding survival.

Key words: bladder carcinoma, micropapillary, treatment

Correspondence: Glück Gabriel, M.D. PhD.
Center of Uronephrology and Renal Transplantation, Fundeni Clinical Institute,
258, Fundeni Street, Bucharest, Romania, 022328,
Email: gabrielgluck@yahoo.com, Tel: +40722973216.
**Introduction**

Micropapillary carcinoma is a rare subtype of urinary bladder cancer, being responsible for almost 0.6-12% of the urothelial cancers, with male preponderance (5-10:1). Therefore, in comparison with urothelial cancer where male to female sex ratio is 3:1, male preponderance is more frequent in micropapillary cases. [1, 6] Micropapillary carcinoma was first mentioned in literature in 1982 by Hendrickson, who described it as an aggressive form of endometrial adenocarcinoma.

The micropapillary architecture is a reminiscence of ovarian papillary tumours. Amin M.B. (from MD Anderson Cancer Center) was the first to report in 1994 a study consisting of 18 patients diagnosed with bladder cancer and histopathological examination positive for micropapillary carcinoma. [1]

**Materials and methods**

The study included eight patients (2%) – one woman and seven men - with anatomopathological diagnosis of micropapillary bladder carcinoma from a total of 389 patients with invasive bladder cancer, treated between 1990-2012. The mean age was 60.2 years. All patients underwent radical cystectomy. Concerning the urinary diversion, there was a number of five cutaneous ureterostomies, two ileal conduits and one neobladder.

**Results**

The tumor stage found was T2 for three patients, T3 for three patients and T4b for two patients. Table 1. Pure micropapillary carcinoma was diagnosed in six cases, while the other two cases presented either squamous elements together with micropapillary carcinoma or squamous plus adenocarcinoma elements. Negative lymph nodes were present in only two cases, the rest having positive lymph nodes as follows: two cases of N1, two cases of N2 and two cases of extraregional lymph nodes involvement.

**Table 1: Treatment, histopathological results and survival for patients included in the study**

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Surgical treatment</th>
<th>Date</th>
<th>Histopathological result</th>
<th>Survival</th>
<th>Adjuvant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>58</td>
<td>Radical cystectomy with cutaneous ureterostomy.</td>
<td>21-Dec-09</td>
<td>Micropapillary TCC + SCC pT2N1M0 - G3</td>
<td>Decease at 24 months. Extraregional adenopathy.</td>
<td>CG+R</td>
</tr>
<tr>
<td>M I</td>
<td>73</td>
<td>Radical cystectomy with cutaneous ureterostomy.</td>
<td>22-Dec-09</td>
<td>Micropapillary TCC pT2N1M0 - G2</td>
<td>23 months – alive</td>
<td></td>
</tr>
<tr>
<td>O I</td>
<td>56</td>
<td>Radical cystectomy with cutaneous ureterostomy.</td>
<td>02-Feb-10</td>
<td>Micropapillary TCC - pT4N2Mx - G3</td>
<td>Decease at 10 months.</td>
<td></td>
</tr>
<tr>
<td>M S</td>
<td>61</td>
<td>Radical cystectomy with cutaneous ureterostomy.</td>
<td>4-Apr-11</td>
<td>Micropapillary TCC + SCC + ADK - pT4bN2Mx - G3</td>
<td>Decease at 1 month.</td>
<td></td>
</tr>
<tr>
<td>Pr G</td>
<td>62</td>
<td>Radical cystectomy with cutaneous ureterostomy.</td>
<td>5-Apr-11</td>
<td>Micropapillary TCC - pT3N1Mx - G2</td>
<td>Decease at 7 months. Extraregional adenopathy.</td>
<td></td>
</tr>
<tr>
<td>D D</td>
<td>59</td>
<td>Radical cystectomy, ileal conduit, total penectomy and total ureterectomy.</td>
<td>07- Mai-12</td>
<td>Micropapillary TCC - pT3N0Mx G3</td>
<td>Corpora cavernosa metastasis at 6 months with local recurrence – alive.</td>
<td></td>
</tr>
<tr>
<td>G E</td>
<td>61</td>
<td>Radical cystectomy and ileal conduit.</td>
<td>12-Jun-12</td>
<td>Micropapillary TCC - pT3N2Mx G3</td>
<td>5 months - alive</td>
<td>GC 6 cycles.</td>
</tr>
<tr>
<td>PA</td>
<td>65</td>
<td>Radical cystectomy and neobladder.</td>
<td>August 2011</td>
<td>Micropapillary TCC T2N0G2</td>
<td>Bone metastasis at 4 months.</td>
<td></td>
</tr>
</tbody>
</table>

Survival: Two patients are still alive at 23, 6 and 5 months postoperatively, one patient developing local recurrence. There were five deaths recorded with a mean survival of 9.2 months. From this total, a number of four patients had G3 histological grading – in two cases there was macroscopic residual tumour and in other two cases the tumor staging was T4N2.
Discussions

Many patients with micropapillary bladder cancer present with locally advanced neoplasia. From the histological point of view, the micropapillary component can be found:

a) In noninvasive stage
b) Invasive stage
c) Metastatic stage

It can be described as focal, extensive (49%) or exclusive (over 50%). The extent of the micropapillary component can represent a negative prognostic factor. No criteria is mentioned in the literature concerning the pattern of micropapillary bladder carcinoma diagnosis and as a consequence, even histopathological specimens with 10% micropapillary component are considered to be micropapillary bladder cancer. It is a fact needed to be mentioned as it bears a great influence on prognosis and outcome.

Amin suggests that when making a diagnosis of micropapillary bladder cancer percentage, invasions, CIS component (present in more than 45% of cases) and glandular or trophoblastic differentiation must be mentioned [4].

The micropapillary aspect of urothelial cancers encompasses features such as:

1. Two different patterns: friable filiform processes with a fibrovascular base, at the surface and on section presenting as glomeruloid processes. In invasive or metastatic stages, the cells form small nests, narrow or spherical in shape.
2. Psammoma corpuscle (round shaped calcifications) – serous ovarian cancer characteristic, rarely present.
3. In invasive or metastatic forms the tumoural cells are assembled in gaps or stromal spaces, imitating vascular invasion. In the above mentioned stromal spaces can also be found flat cells or they can simply bare no insertion. This feature is specific for micropapillary invasion.
4. Micropapillary carcinoma constantly presents a high nuclear grade (according to WHO/ISUP classification), though the urothelial carcinoma component can display a low nuclear grade.
5. Lymph vascular invasion is detected in half of the muscle invasive micropapillary carcinoma.

Immunohistochemistry confirms the urothelial neoplasia subtype by using the CD 31 (endothelial marker) and D2-40 (lymphatic endothelial marker) markers. Because micropapillary gaps can imitate vascular invasion, it is important that such lesions must not be misinterpreted, as they associate worse outcomes. Moreover, it is of high importance that in women differential diagnosis includes serous cancer metastases from peritoneal tumors, abdominal lymph nodes or mesentery. An immunochemistry exam can be useful in making a diagnosis – CK 7, CK 20 and uroplakin III +. [3]

Micropapillary carcinoma diagnosis is essential because:

❖ This urothelial carcinoma subtype carries a much more aggressive clone.
❖ Such tumours present in an advanced tumoural stage, with vascular invasion and high nuclear grade.
❖ The micropapillary component has a greater DNA index compared with urothelial carcinoma and is expected to have worse outcomes.
❖ All metastases feature micropapillary areas.
If the histopathologist suspects that the tumour may be invasive and the biopsy specimen does not include muscle, re-TURBT is mandatory, with stage reevaluation. When taking into account the sensitivity of procedures, tumour biopsy seems to have an advantage in comparison with TURBT (54% vs. 48%). [5]

Data from literature suggests that non-muscle invasive tumours have a limited response to intravesical therapy, in which cases patients benefit from radical cystectomy. It appears that adjuvant therapy with BCG has no effect, disease progression being noted. The outcome is unfavorable, with 5 and 10 years survival of 51%, respectively 24%. [2]

Such premises are based on Kamat’s study, involving 100 patients with micropapillary bladder cancer, of whom 44 had non-muscle invasive tumours, 37 had muscle invasive tumours and 19 patients with unresectable tumours. In all 44 cases TURBT was performed. In this group, BCG therapy was administrated in 27 cases. During 8 months, 67% of patients with adjuvant BCG therapy progressed, necessitating radical cystectomy, with a 5 year survival of 60%. Only 5 patients with BGC intravesical treatment did not progressed over a period of 30 months (in all cases lymph vascular invasion was absent). A number of 12 patients from the total of 44 patients with TURBT underwent radical cystectomy with no adjuvant therapy, with a 5 year survival of 72%. The reported 5 year survival in the muscle invasive tumours and radical cystectomy group was 70% and 52% at 10 years. Neoadjuvant therapy did not influence the outcome.

Mayo Clinic study undergone by Wang J.K. (2012) [6] reported an incidence of micropapillary bladder cancer of almost 12%. His study included a number of 73 patients with this condition, of whom 66% presented with extravesical disease, 50% with adenopathies (vs. 10% in patients with common urothelial cancer) and 73% with lymphatic invasion (vs. 24% in patients with common urothelial cancer). When compared with common urothelial cancer the 10 years survival is 31% vs. 53%.

Lopez Beltran performed a study on 13 patients with micropapillary carcinoma. [7] Clinical manifestations consisted of dysuria (3 patients), hematuria and polyuria (4 patients). The ages varied between 61 and 83 years old (mean age – 68 years, median age – 63 years). The diagnosis was made on TURBT specimen in 3 cases and in 10 cases on TURBT and radical cystectomy specimen. No medical history of bladder cancer was recorded in any of the 13 cases. The surgical intervention was performed at 2-8 weeks after clinical manifestations began. Clinical tumoral stage was T2 in one patient, T3 in 7 patients and T4 in 5 patients. Positive lymph nodes were present in 8 cases (62%). Follow up was possible in all 13 cases, with a 2-21 month survival (mean survival – 10 months). Cancer related deaths were reported in 11 cases, survival varying between 2 and 14 months (mean survival – 6.2 months, median survival – 8 months). The patients still alive were diagnosed with metastases at 14 and 21 months. Moreover, 8 patients benefited from adjuvant chemotherapy, with no disease improvement.

Conclusions

It is fair to assume that micropapillary bladder cancer is often an underestimated form of urothelial cancer, though it associates a poor prognosis. TURBT histopathological specimen has an approximately 48% sensitivity, the lesion usually being mixed with high nuclear grade urothelial carcinoma and CIS. In rather many cases the tumoral stage is inappropriate and therefore the given treatment is inadequately – BCG therapy is inefficient. A high number of patients are diagnosed with extravesical tumoral extension, adenopathies and lymphvascular invasion. Some authors (A.Kamat) [2] advocate for radical cystectomy even in non-muscle invasive tumours. Neoadjuvant/adjuvant chemotherapy has proved to be inefficient. The low rate of such cases reflects in the lack of randomized studies covering this area and the establishment of precise treatment patterns.


References


