

## Micropapillary Variant of Urothelial Carcinoma of the Bladder: Four Case Reports and a Review of the Literature

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### ABSTRACT

Micropapillary carcinoma (MPC) of urinary tract is an uncommon histological variant of urothelial carcinoma. It is characterized by an aggressive clinical course, an advanced stage at first presentation and a high metastatic potential. Though MPC shows characteristic microscopic features, there exists interobserver variability and controversies concerning certain aspects of this rare tumor. The aim of our study is to present four cases of MPC treated by radical cystectomy in the Department of Urology, at the University Hospital Center of Rabat Morocco, during the period from January 2014 to December 2017. The clinical and morphological features of this rare and aggressive variant of urinary bladder carcinoma, as well as a brief review of the literature are all presented.

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### Introduction

Urothelial carcinoma (UC) is the most common type of bladder cancer who has a propensity for divergent differentiation, so a whole spectrum of UC variants were described and recognized by the WHO classification in 2004 [1]. Micropapillary urothelial carcinoma (MPC) is a distinct and rare variant of UC, accounting for 0.6–8.2% of all urothelial tumors [2]. It has distinct morphologic features, usually with an aggressive clinical course, an advanced stage at first presentation, a high metastatic potential and a poor outcome [3]. Herein reported are four cases of MPC with a brief review of the literature on this aggressive tumor.

### Methods

Four cases of micropapillary variant of urothelial carcinoma of the bladder were identified from the files of the department of Urology at the Ibn Sina University Hospital Center of Rabat from January 2014 to December 2017, and included in this study. All patients were treated and followed at the same institution. Age, gender, clinical presentation, pathological features, and follow-up were extracted from the medical charts.

### Results

Four patients were included in this study. They were all male and their median age was 62 years (ranging from 51 to 70 years). The initial presentation was the hematuria in all patients and two patients also complained of dysuria. Transurethral resection of bladder tumor (TURBT) was performed in all cases. Cystoscopy revealed papillary tumor in lateral walls in two patients and multifocal tumor in two cases. Histological examination showed micropapillary component associated with the conventional urothelial carcinoma (Figure 1) in three cases; and one case diagnosed on biopsy showed only conventional urothelial carcinoma. The proportion of micropapillary pattern was ranging from 10 to 50 %. In all cases the muscle was invaded pT2. CT scan was performed in all cases and did not show any distant suspected lesions except pelvic lymph node in two cases. No

patient underwent neoadjuvant chemotherapy. Radical cystectomy with pelvic lymphadenectomy was performed in all cases. There was no significant difference between initial resection and the radical surgery specimen except one case which showed pure urothelial carcinoma in the biopsy; however cystectomy showed 30% of micropapillary areas. Lymph nodes were invaded in all cases. Of these four cases, two patients were classified pT2N2 and two patients pT3aN2. Three patients received cisplatin based adjuvant chemotherapy; while one patient showed already metastases three months after cystectomy (lymph node and liver). Three patients progressed under treatment and died after 6, 10 and 12 months; and only one patient was alive without disease at 12 months of follow up.

### Discussion

Micropapillary carcinoma is a variant of urothelial carcinoma that was described for the first time by Amin et al. in 1994 as a tumor closely resembling papillary serous carcinoma of the ovary [4]. It is a rare entity but this low incidence is probably because it was still little known and consequently underreported. Recently, the incidence has increased, when pathologists and oncologists became aware of its description and of its particular clinical behavior [5]. This tumor predominantly affects male with male to female ratio of 5:1 to 10:1 which is higher than that for conventional UC which is 3:1, with patient ages ranging from 50 to 90 years and a mean age of 64.7 years [6].

Gross morphology of MPC is variable, and there are no unique features to distinguish it from conventional UC or other variants. MPC can present as papillary, sessile, polypoid, ulcerative, or infiltrative mass, and the size can also be variable from microscopic focus to over 10 cm [7].

The defining microscopic feature of MPC is micropapillary architecture reminiscent of the papillary configuration seen in ovarian papillary serous tumors [8]. The micropapillary pattern of MPC can present either on the mucosal surface as slender delicate processes which are

usually devoid of a fibrovascular core and appear as glomeruloid bodies on cross section or in the invasive component as small tight cell nests or balls contained in lacunae or stromal retraction spaces, mimicking lymphovascular invasion [8]. The nuclei of tumor cells are frequently of high grade, showing reversed polarity to the external surface of tumor nests [8]. Micropapillary pattern is described in literature usually associated with UC, the proportion of MPC ranging from focal to almost exclusive. There are no established criteria for the cut-off proportion of micropapillary component to qualify a tumor as MPC. Some authors suggest 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 [9]. Associated *carcinoma in situ* can be demonstrated in >50% cases according to literature, and must be reported as this also affects clinical outcome by predicting recurrence [9]. MPC may be admixed also with other variants of urothelial carcinoma [10].

There are no immunohistochemical markers to differentiate MPC from conventional UC. Both express cytokeratins (CK7, CK20) epithelial membrane antigen, Leu-M1 and carcinoembryonic antigen [11]. Some promising markers were described in the literature: MUC1, CA125 and Her2/neu, but when comparing the expression of these three antibodies in MPC and UC with stromal retraction, Sangoi et al. [12] 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.

The most important differential diagnosis for urinary tract MPC is its distinction from conventional UC with prominent retraction artifacts, which issue has been addressed in a consensus study by Sangoi et al. [13]. It is important to recognize the micropapillary pattern as it is regarded as a high-grade tumor with aggressive behavior. Metastasis of micropapillary carcinoma from other organs in the bladder is also a critical differential diagnosis. Clinical data and immunohistochemistry could be helpful for a correct diagnosis.

MPC is almost invariably muscle invasive at the time of presentation with frequent metastasis to lymph nodes and distant organs. Wang et al. [14] showed that lymph node invasion was more frequent in MPC with 50% patients with lymph node metastases in the MPC group vs. 10% in patients with conventional UC.

Conventional paradigm for treatment of UC is implementing radical surgery in the muscle invasive diseases and intravesical BCG administration after TURBT for the nonmuscle-invasive cases. While the conventional approach is applied in most institutions, early cystectomy for the nonmuscle-invasive MPC is advocated by one leading group on the ground that these tumors eventually develop muscle invasion and that the response to chemotherapy is limited when used as a secondary modality. Kamat et al. [15] reported a 10-year survival rate of 72% among patients who received early cystectomy for the nonmuscle-invasive disease, while none survived after the treatment according to the conventional paradigm. In a retrospective study, Masson-Lecomte et al. [16] reported that MPC was associated with higher recurrence rates after radical cystectomy and platinum-based adjuvant chemotherapy than that with pure UC.

When compared with UC, in a recent study Mitra et al. [17] showed that presence of MPC was associated with

higher pathologic stage and lymphovascular invasion at cystectomy. They showed also that MPC patients had poorer 5-year recurrence free survival (70% vs. 44%;  $P < 0.01$ ) and overall survivor (61% vs. 38%;  $P < 0.01$ ) [17]. However, on multivariable analysis, tumor histology was not independently associated with the risks of recurrence or mortality [17].

Micropapillary variant histology is known to have an aggressive clinical course, thus the treatment of choice for patients with MPC seems to be early radical cystectomy with lymph node dissection.

### Conclusion

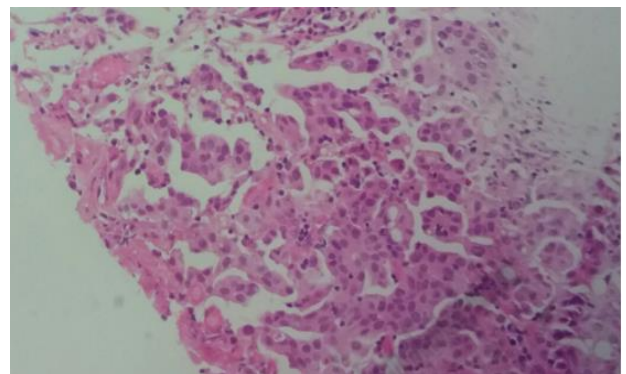
Micropapillary urothelial carcinoma is an aggressive variant of urothelial carcinoma, presenting frequently with deep muscle and lymphovascular invasion. The correct recognition of MPC and the differential diagnosis of MPC from UC are recommended in order to provide early radical therapy to this aggressive tumor.

### Competing Interests

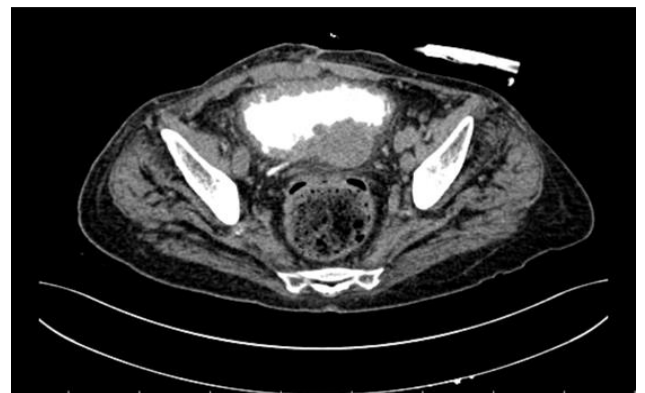
The authors declare that they have no competing interests.

### Author Contributions

All authors contributed in the development of this publication and approved the final manuscript.



**Figure 1.**High power view of micropapillary component of high grade urothelial carcinoma.



**Figure 2.**Computed tomography scan showing a tumor of the bladder in left posterolateral wall.

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