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Review

Micropapillary bladder cancer, a variant histology of the elderly

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Micropapillary bladder cancer is a rare variant of bladder cancer with dismal biological behavior. It most frequently affects the elderly and it is essential to define and report its morphological features at pathology since it demonstrates poor response to conventional treatments. This review aims to systematically explore and critically appraise the current state of the evidence regarding clinical features, pathology issues, prognostic factors and therapeutic perspectives in this difficult and peculiar variant of bladder cancer.

Key words: Bladder cancer, Micropapillary, Elderly

EPIDEMIOLOGY

Micropapillary bladder cancer (MPBC) was first reported in 1994 by Amin et al. [1] as a histological subtype of urothelial carcinoma (UC) which bears a strong resemblance to analogous neoplasms arising in the ovary and breast. As a rare variant of UC, its incidence has been estimated to represent 0.01-8.2% of all urothelial tumors [1-6].

MPBC is more frequent in old men, with a male-to-female ratio of 5-10:1 [1 4 5 7 8] and a mean age at first diagnosis of 67.6 years. According to a very large cohort of MPBC patients (baseline disease characteristics available for 869 patients, survival data available for 348 patients), median patients age was 69.9 years (58.9-80.9) [9]. Unfortunately, data on prevalence and mortality in patients > 65 years are not available.

There is no specific risk factor for MPBC, which shares the same risk factors of conventional of transitional cell carcinoma.

PATHOLOGY

Its gross appearance may vary, since it can occur as an exophytic (papillary, polypoid) mass or as a flat lesion (ulcerative or infiltrating), and its size may differ accordingly [4].

The diagnostic gold standard for MPBC is the detection of its peculiar morphological features at transurethral resection (TUR) biopsy, although the diagnosis is often challenging. Neoplastic cells usually appear as slender delicate papillary projections or small compact infiltrating nests from 4 to 5 cells lacking central vascular cores, floating within clear spaces similar to lymphatic channels due to the production of peritumoral stromal retraction artifacts, thus mimicking angiolymphatic invasion by neoplastic cells [5 7 15-17]. Such aggregates frequently show peripherally located high-grade nuclei and cytoplasmic vacuoles [8 18]; their inverted cellular polarity might result in apical secretory properties shifting

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to the basal surface of cells, ultimately leading to high tumor invasion [19,20]. Cold cup biopsy may miss a MPBC invading the muscle layer under the benign surface epithelium; thus deep biopsies are recommended [1,21,22]. Urine cytology smears are less informative though suggestive, showing papillary/spheroid aggregates of tumor cells with high nuclear grade along with rare single cells in a clear background [23]. Moreover, urine cytology is unable to detect neoplastic cells in cases of MPBC growing under normal mucosa [24].

Most MPBCs are found in association with conventional UC and carcinoma in situ (CIS) [24], as well as with other variants/histotypes of bladder cancer [3,12,14]. Like conventional UC, MPBC may be either non-muscle invasive or muscle invasive.

The immunophenotype of MPBC is similar to the one described in conventional UC; indeed, neoplastic cells usually express Cytokeratin 7 (CK7), uroplakin III, CK34βE12, CytoKeratin20 (CK20), Protein63 (P63), thrombomodulin, and Higth Molecular Weight Cytokeratin (HMWCK) [25,26]. Therefore conventional immunohistochemical markers have proven unsuccessful because of low specificity and sensitivity [24,27]. Useful markers in the differential diagnosis with other malignant neoplasms showing micropapillary morphology (such as lung, breast, ovary cancers) include Estrogen Receptor (ER), mammaglobin, Pired Box Gene 8 (PAX8), Thyroid transcription factor 1 (TTF1), Wilms Tumor protein1 (WT1) [1,26]. Finally, other prominent features of MPBC include activation of chromatin-remodeling complex RUVBL1 that may be related to the Epidermal Growth Factor receptor (EGFR), the luminal molecular sub-type profile, and downregulation of miR-296 [28], the latter suggesting that modulators of immune response may play a role in this disease like in other urological cancers [29,30].

According to Sangoi et al. [7], the interobserver agreement among uropathologists for the diagnosis of MPBC (especially "non-classic" forms) is only moderate even within a large academic center, with an overall concordance kappa score of 0.54. They pointed out It may be improved by taking into account the size and pattern of tumor cell aggregates (i.e. small multiple nests within the same lacunar space *vs* large branching). Limited interobserver agreement might also be partly due to a trend to under- or no- reporting variant histologies of UC, particularly outside of academic institutions [31], and partly to sampling error and tumor heterogeneity as TUR specimens have been reported to detect only 39% of variant histology [32,33].

CLINICAL FEATURES

Patients with MPBC usually present with hematuria, dysuria, urgency, frequency, urinary obstruction, urinary infection, weight loss and, as for upper tract tumors, flank pain [1,4,5,10-14]. Most MPBCs are diagnosed at an advanced stage with muscle-invasive or metastatic disease [1,3,5]. Even when they represent only a small fraction of the overall tumor volume [3,12,25,34] this feature confers a poor prognosis. Such aggressive behavior has been attributed to a high level of inherent chromosomal or genomic instability, with higher DNA contents than conventional UC [1,35]. Another putative explanation is the increased expression of molecular markers that are conventionally associated with poor prognosis, such as p53, MIB-1, Aurora-A, and surviving [36-40]. It would be interesting to test in this setting novel molecular markers currently under evaluation in the setting of prostate cancer [41-43].

The dismal prognosis of MPBC has been questioned by other studies comparing the clinical course of MPBC and conventional UC after cystectomy [44,45]. In a huge case series of more than 800 MPBCs, the median overall survival of these patients was nearly half that of conventional UC (44.7 *vs* 91.9 months; $p < 0.001$) 9. However, when stage matched the one of patients with pure UC, MPBC had similar rates of local/distant recurrence and cancer specific survival [46].

Vourganti et al. compared MPBC to conventional UC in a Surveillance, Epidemiology and End Results (SEER) based outcome study and found that stage for stage, MPBC had a similar survival profile to conventional UC except for non-muscle invasive disease which was associated with worse survival [47].

On the other hand, markers of an adverse clinical course such as occult nodal metastases and lymphovascular invasion are often reported in case series of MPBC, the latter typically found peripheral to the primary tumor mass 1 5. In such cases, 5- and 10-year survival rates may be as low as 25 and 24%, respectively [5,21,48].

The aggressive nature of this variant is supported by the occurrence of MP morphology in metastatic lesions and by the worse biological behavior of combined MPBC and conventional UC, supporting the aggressive nature of this variant [1,8,25,35]. In the latter case, mixed neoplasms with > 50% MPBC carry a relative mortality risk of 2.4 as compared with pure conventional UC or < 50% MPBC [12]. It is therefore recommended to report the presence and the proportion (in percentage) of MP component in the pathology report of a UC [35,49].

In a single study, a 10% cut-off of MPBC was reported to have a clinically significant effect on disease specific survival [25]; this has turned into reporting of even focal amounts of MPBC. However, many conflicting reports exist ranging from those stating that the mere presence of MPBC is clinically relevant [8] to others stating that focal MPBC portends better outcomes than extensive disease [10,50].

TREATMENT

The standard treatment for conventional urothelial MIBC is radical cystectomy (RC), possibly with neoadjuvant chemotherapy. Due to its poor prognosis, micropapillary MIBC is considered a strong indication to perform RC as a first-line therapy instead of neoadjuvant chemotherapy. The poor prognosis of MPBC and disparities in treatment response may be explained by underlying differences in tumor biology between UC and MPBC [28]. The available literature is limited to retrospective subgroup analyses of some randomized trials, thus leading to conflicting results [5 45]. Some studies, including a phase III trial [45 51] reported a better response to neoadjuvant chemotherapy in tumors with mixed histology and/or pure MPBCs than in pure UC (four cycles of gemcitabine and cisplatin in most cases), while other failed to demonstrate any significant difference in outcomes with the addition of neoadjuvant chemotherapy in patients with muscle-invasive MPBC undergoing RC [52 53]. On the other hand, a recent study of predictors of pT0 after neoadjuvant chemotherapy found that variant UC histology predicted against pT0 compared to pure UC (OR 0.09, 95% CI 0.021-0.380) [54]. A study of 82 patients treated at Memorial-Sloan Kettering found that neoadjuvant chemotherapy may be useful in muscle-invasive MPBC [45]. In their cohort, the 29 patients who received neoadjuvant chemotherapy (mostly gemcitabine-cisplatin) were more likely to have no evidence of residual disease at the time of RC when compared to immediate RC (pT0 rates of 45 *vs* 13%, respectively; p = 0.049), which is similar (38 and 15% respectively) to the pT0 rate seen in the neoadjuvant SWOG trial 8710 [55]. The study by Meeks et al. [45] failed to show any difference in survival between neoadjuvant chemotherapy and immediate RC but there was a significant improvement in overall survival for patients who achieved pT0 (2-yr CSS of 78 and 25% respectively, p = 0.05), though the follow-up was relatively short. Recently, Fernandez et al. [56] reported that neoadjuvant chemotherapy appears to confer benefit to patients with MPBC without tumor-associated hydronephrosis, while patients with cT1 disease may undergo standard surgical treatment.

The standard treatment for conventional urothelial NMIBC classified as high-risk is intravesical instillation of Bacillus Calmette-Guerin. The presence of micropapillary morphology seems in NMIBC has been reported to severely impair the efficacy of intravesical BCG treatment [3 5 24 48 57 58], although different studies yielded conflicting results. Kamat et al. [48] examined a series of 44 patients with non-muscle invasive MPBC, finding a non-significant trend towards improved survival in the immediate cystectomy group (5-yr CSS 60 *vs* 72%, p = 0.39). An update of the MD Anderson MPBC series in 2014 focused on 72 cases of cT1N0M0. Upfront RC was utilized in 36 (n = 26) while 55% (n = 40) received primary BCG [52]. In the primary BCG cohort, 45% progressed to muscle-invasive disease and 35% developed lymph node metastasis. At 5 years, disease specific survival was 62% for the delayed RC group compared with 100% for the upfront RC group (log rank p = 0.015). However, the Memorial Sloan Kettering Cancer Center reported on their experience with 36 patients with non-muscle invasive MPBC in 2014 [59]. Early RC was utilized in 15 and conservative therapy in 21. They found that five-year disease specific mortality (17% *vs* 25% respectively; p = 0.08) and the five-year incidence of metastasis (21 and 34% respectively; p = 0.09) were not significantly different between the groups. Other smaller retrospective series that contain patients with non-muscle invasive MPBC have been reported. Ghoneim et al. reported 10 patients diagnosed with cTis-cT1 disease, of whom 7 received intravesical BCG and 3 underwent upfront RC [60]. All 7 patients treated with BCG recurred (4 progressed) and underwent delayed RC with resultant pT3 disease. Furthermore, positive lymph nodes were detected in 6 patients. Comperat et al. reported on a 72 patients' cohort of MPBC including 12 cTa MPBC cases, of which 8 were treated with RC [8]. All 8 were found to have invasive carcinoma at the time of surgery including 5 (63%) with pT2-pT4 disease. A recent 120 patient SEER 17- based study also showed that non-muscle invasive MPBC was associated with worse overall and disease specific survival outcomes in a population based study when compared to conventional UC [47]. These studies all suggest that non-muscle invasive MPBC is associated with more aggressive disease and worse survival than would be expected for conventional NMIBC and may warrant more aggressive intervention.

Another study argues that non-muscle invasive MBPC may have a different histologic presentation than muscle-invasive MPBC as the authors suggest the former to be more "urothelial" in appearance than the often "glandular" muscle invasive MPBC [44]. Of the 18 patients in this report, treatment data was available on 13; 7 (54%) underwent primary intravesical therapy, 5 (38%) underwent initial surveillance only, and 1 (8%) underwent RC. Three patients progressed to muscle invasion (pT2, pT3, pT3N2). One patient died of bladder cancer, one died of other causes, and 64% are alive with an intact bladder after a median follow up of 14 months. In a report by Gaya et al. on 8 patients with non-muscle invasive MPBC, 6 (75%) patients (small proportion of MPBC relative to conventional UC) were reported to be disease free after BCG therapy with a 5-year DSS of 87.5% [50]. Despite the limited sample size, this report suggests that BCG may be appropriate for non-muscle invasive MPBC.

Overall, data suggest that the biology of non-muscle invasive MPBC is different from that of conventional UC and it's associated with an aggressive phenotype with high failure rates of intravesical therapy. This viewpoint is consistent with the opinion of the respondents to a survey developed in 2010 by the Translational Science Working Group of the Bladder Cancer Advocacy Network sponsored Think Tank meeting and distributed to members of the Society of Urological Oncology, with 80.5% advocating for early cystectomy (7.6% with neoadjuvant chemotherapy) for cT1 MPBC; this was one of the few therapeutic approaches with relative consensus [61].

Obviously, factors predicting disease outcome would be extremely welcome, ranging from simple clinical features, like smoking habits [62], to molecular markers representing different pathways potentially involved in tumor response to available treatments. Recent evidence suggests that such markers, apart from having predictive value, may represent novel potential therapeutic targets [63-68].

To conclude, MPBC is a rare variant of BC that usually affects the elderly. Correct pathology identification of this variant histology, including its stage and its percentage within the tumor, has prognostic value and therefore is essential to plan treatment. Non muscle invasive MPBC seems to have worse behavior than non muscle invasive conventional UC, thus requiring early aggressive treatment. In muscle invasive cases, the role of neoadjuvant chemotherapy before radical cystectomy is controversial. Like for other common urological conditions, case volume and treatment tailoring to patient and local clinical conditions remain a key issue [69-72].Insights into its peculiar behavior are crucial for a proper management.

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Conflict of interest

The authors declare no conflict of interest.

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