Perspective

Evolving concepts of micropapillary variant urothelial carcinoma

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Abstract: Micropapillary variant (MPV) urothelial carcinoma remains an uncommon, challenging to treat entity. Recent research has emerged that examines the genetic expression profile of MPV urothelial carcinoma and provides a new perspective on this challenging to treat form of bladder cancer. Ongoing research is necessary to determine the most appropriate treatment algorithms for managing patients with MPV urothelial carcinoma.

Keywords: Bladder; micropapillary variant (MPV); urothelial carcinoma; bladder cancer; variant histology; molecular genetics

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Introduction

Micropapillary variant (MPV) urothelial carcinoma has been reported as comprising up to eight percent of contemporary urothelial carcinoma cohorts (1-4). The majority of studies have reported that MPV urothelial carcinoma portends a worse oncologic prognosis and that the tumor demonstrates more aggressive histology (3,5-8). The optimal algorithm for patients diagnosed with MPV urothelial carcinoma remains poorly defined with many researchers arguing that even in the setting of non-muscle invasive disease, these patients should be taken for early extirpative management. As MPV urothelial carcinoma remains an uncommon entity, large and multi-institutional studies have not been conducted to evaluate the efficacy of neoadjuvant or adjuvant chemotherapy. However, retrospective institutional studies have suggested that MPV demonstrates a poorer response to standard neoadjuvant chemotherapy regimens when compared with pure urothelial carcinoma (9,10). The mechanism behind this has been poorly understood. The recent article by Guo *et al*. begins to explore the genetic differences in MPV compared with urothelial carcinoma (11).

Immunohistochemical evaluation

Previous immunohistochemical evaluations of MPV urothelial carcinoma have been performed to determine the best markers to identify MPV in bladder cancer specimens. *Figure 1* demonstrates an H & E stain of MPV urothelial carcinoma. GATA 3 (GATA binding protein 3) and uroplakin 3 have been reported as reliable markers for urothelial tumors although the sensitivity of uroplakin 3 is worse than for GATA 3. GATA 3 is a member of a family of transcription factors involved in embryogenesis and has been reported to be the most sensitive and specific for bladder cancer (12,13). Recent studies have reported that GATA 3 levels in MPV urothelial carcinoma are similar to levels in pure urothelial carcinoma (14). Interestingly, while GATA 3 levels are similar between MPV and pure urothelial carcinoma, GATA 3 levels have been reported to be significantly lower in other variants of urothelial carcinoma such as squamous differentiation variant and sarcomatoid variant (14,15). The reason for this difference is unclear but is likely more reflective of changes in the squamous differentiation variant.

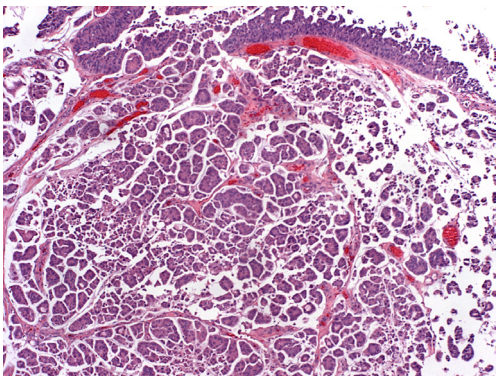

Figure 1 H & E stain of micropapillary variant (MPV) urothelial carcinoma. Original magnification ×100.

An additional marker of urothelial carcinoma is p63. Wang *et al.* recently reported that the presence of p63 was an independent predictor of worse survival in patients with urothelial carcinoma who underwent radical cystectomy with urinary diversion (16). Despite the majority of patients with pure urothelial carcinoma displaying expression of p63, recent studies have reported decreased p63 expression in patients with MPV, with between 27% and 54% of MPV tumors staining positive for p63 (15,17).

Choi *et al.* previously reported that muscle-invasive urothelial carcinoma can be divided into luminal, p53-like luminal, and basal subtypes which were predictive of response to chemotherapy and overall tumor behavior (18). The pure urothelial carcinoma cases with the basal subtype had overexpression of p63 and were more aggressive at presentation. These patients were additionally more sensitive to traditional neoadjuvant chemotherapy regimens (18,19). The luminal subtype demonstrated increased PPAR-γ expression and *FGFR* mutations. The p53-like luminal subtype tumors shared PPAR-γ expression and FGFR mutations but were notably chemo-resistant to current neoadjuvant chemotherapy regimens (18).

In the recent study by Guo *et al.*, it was reported that whereas in the pure urothelial carcinoma cohort 47.2% were basal subtype, 24.7% were luminal subtype, and 28.1% were p53-like luminal subtype, when examining the MPV urothelial carcinoma cohort, 2.3% were basal subtype (n=1), 51.2% were luminal subtype (n=22), and 46.5% were p53-like luminal subtype (n=20) (11). The MPV urothelial carcinoma tumors demonstrated, almost uniformly, GATA 3 and uroplakin 2. Furthermore, the tumors demonstrated increased PPAR-γ expression and downregulation of p63. When examining the response to chemotherapy among MPV tumors, 66% (n=4/6) of tumors in the luminal subtype and 45% (n=5/11) of tumors in the p53-like luminal subtype group demonstrated response to neoadjuvant chemotherapy, similar to prior studies suggesting that the p53-like luminal subtype was less likely to respond to chemotherapy.

Genetic alterations

Downregulation of miR-296, which is associated with upregulation of over 300 downstream genes, was found to be a driver in the expression of MPV in the recent study by Guo *et al.* (11). This may be a critical pathway that could be targeted to better identify patients with this uncommon variant of urothelial carcinoma. Downregulation of miR-296 has previously been reported to be associated with aggressive changes in other cancers including prostate cancer (20-23). As part of miR-296 downregulation, the RUVBL1 pathway is activated. This is known to be associated with genes that play critical roles in metastasis, cell growth, and DNA repair. Additionally, RUVBL1 acts via p53 to block p53 mediated cellular apoptosis (24). Furthermore, as the RUVBL1 pathway has been noted to be associated with poor response to traditional chemotherapy, it may serve as the mechanism of resistance to cisplatin based regimens. Both miR-296 and the RUVBL1 pathway could be intervened upon to prevent the aggressive changes seen with MPV urothelial carcinoma.

An additional potential intervenable pathway identified by the Guo *et al.* study is PPAR-γ (11). The study found that the majority of MPV urothelial carcinoma tumors, regardless of p53-like subset, demonstrate upstream PPAR-γ expression. PPAR-γ has been postulated as a target for muscle invasive bladder cancer and research is ongoing into its clinical relevance as a therapeutic target (25,26). Troglitazone, a PPAR-γ agonist, induces apoptosis and autophagy in bladder cancer cells (27); although more research is needed before these agents are used in clinical practice.

Clinical implications

A particularly interesting finding in the Guo *et al.* study is the fact that when examining tumors with MPV sections and pure urothelial carcinoma sections, the molecular signatures of the urothelial carcinoma sections were similar to the MPV sections (11). This finding would imply that regardless of the percentage of MPV in a tumor specimen, the patient will likely have a more aggressive clinical

progression of disease. Previously, authors have suggested that in the setting of only small volume variant histology (<5%), a patient could potentially be treated as if their tumor were pure urothelial carcinoma; however, the current study would suggest that these patients may be more similar to the higher volume MPV patients than previously understood and may benefit from early radical cystectomy with urinary diversion until new chemotherapeutic or immunomodulating agents are identified.

The lack of responsiveness to current chemotherapy regimens and molecular alterations indicative of an aggressive tumor suggest that patients with MPV urothelial carcinoma may benefit from early extirpative management. The approach to patients with MPV urothelial carcinoma will continue to evolve as new molecular targets are identified. As previously discussed, miR-296, RUVBL1, and PPAR-γ are potential targets that could revolutionize the way MPV urothelial carcinoma is approached.

Conclusions

MPV urothelial carcinoma remains an uncommon variant of bladder cancer that can be challenging to treat. Studies such as that by Guo *et al*. are landmark in building an understanding of the fundamental changes that occur in the development of MPV urothelial carcinoma. With subsequent studies of the molecular underpinnings and evaluation of therapeutic targets, management of patients with MPV will be revolutionized.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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