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Case Report

High-Grade Urothelial Carcinoma of Bladder Transforming to Micropapillary Variant on Follow-Up

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Abstract

Micropapillary variant of urothelial carcinoma (UC) of the bladder is an aggressive tumour, comprising 0.6-6% of all UC. It generally presents with high-grade and stage, and has been reported as having a worse prognosis when compared to traditional UC. We report the case of a 58-year-old man who presented with macroscopic haematuria. The patient was diagnosed with high-grade urothelial carcinoma and returned with recurrence after 16 months. Histopathology after transurethral biopsy revealed a non-muscle invasive high-grade bladder tumour at first presentation, whereas tumour recurrence was reported after 1.5years. The histopathology at recurrence revealed a high-grade, muscle invasive, micropapillary variant of urothelial carcinoma with focal adenomatous morphology. Immunohistochemical expression of $CK7^{+}$/$CK20^{+}$ in tumour cells and negativity for PSA, AMACR, and CDX2 in paraffin section helped in identifying the tumour as primary in the urinary bladder. Radical cystectomy was performed and the patient has no distant metastases on follow-up. The specific morphology even within the high-grade urothelial cancer cases is important to discern for proper treatment.

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Keywords ● Transitional cell carcinoma ● Micropapillary variant ● Bladder

What's Known

- Micropapillary variant is a less common presentation of urothelial cancer.

What's New

- Transformation of a known high-grade urothelial carcinoma case into micropapillary morphology.
- Multiple sections should be examined for any focus of transformation as the management changes with this morphology.

Introduction

Urothelial cancers (UC) are common and worldwide incidence is very high. Several histologic subtypes of bladder cancer such as microcystic, micropapillary, and nested variant are seen. Micropapillary urothelial carcinoma is a rare aggressive subtype of transitional cell carcinoma.[1] The presence of micropapillary component (MPC) in urothelial carcinoma was found to be associated with high-grade and advanced stage of tumour, though low-grade and non-invasive cases have been reported. Micropapillary variant was first described in 1994, though fewer than 300 cases have been reported. Micropapillary variant of bladder cancer (MPBC) occurs in only 0.6-6% of bladder cancer cases and shows a strong male predominance.[2,3] The histology of MPBC resembles that of micropapillary subtypes of breast, lung, stomach and colon, as well as serous ovarian carcinoma.[1] The micropapillary component of these tumours may be encountered on the surface of non-invasive component, the invasive

component of the tumour, or in metastatic sites. Immunohistochemical profile may help in the evaluation of final diagnosis in controversial cases. In primary tumour, the surface component often presents with delicate filiform projections with secondary or tertiary hierarchical branching. Standard recommendations for the treatment of locally advanced disease involve immediate cystectomy with or without perioperative chemotherapy.[4] However, the management of micropapillary variant of bladder cancer that is non-muscle invasive is more controversial. Here we report a case of micropapillary variant of urothelial carcinoma.

Case Presentation

A 58-year-old man presented with macroscopic haematuria, dysuria, and obstructive lower urinary tract symptoms in October 2013. Urine cytology showed the presence of epithelial cells 10-15/hpf, polymorphonuclear leucocytes more than 12/hpf, and a background of RBCs in the smear. Transurethral resection of bladder tumour (TURBT) was performed and the tissue was sent for histopathologic examination. Histopathologic examination revealed a high-grade urothelial carcinoma extending into the lamina propria, but not into the underlying detrusor muscle (figure 1A) and a diagnosis of pT1HGUC (high-grade urothelial carcinoma invading the lamina propria with no invasion into muscle) was rendered. The patient received intravesical BCG, completed the induction therapy of 6 weeks, and received 3 cycles of maintenance therapy at 3, 6, and 12 months of the initial dose. He missed the next dose and reported 6 months later with the complaint of haematuria in February 2015.

He underwent USG abdomen and was diagnosed with urothelial bladder mass (29×17mm) seen along the left lateral wall with mild adjacent perivesical fat stranding with small bilateral obturator nodes and prostomegaly. Preoperative CT-scan of the abdomen (liver, gall bladder, kidney, and prostate) was normal. The patient underwent TURBT again and the tumour tissue was sent for histopathologic examination.

Morphology showed glandular formations lined by a single layer of tumour cells along with micropapillary formations lined by 2-3 cell layer thick epithelium (figure 1B and C). Tumour cells had increased N: C ratio and mitosis was frequent. No mucin was present in the glands. However, occasional signet-ring cells were seen. The tumour cells were also seen in sheets invading into the detrusor muscle (figure 1D). Focal areas showed squamoid differentiation.

Immunohistochemistry was performed to rule out adenocarcinoma of secondary origin. The tumour cells were positive for CK7 and CK20 (figure 2A and B) and negative for CDX2, PSA and AMACR. Hence, a final diagnosis of urothelial carcinoma, micropapillary variant

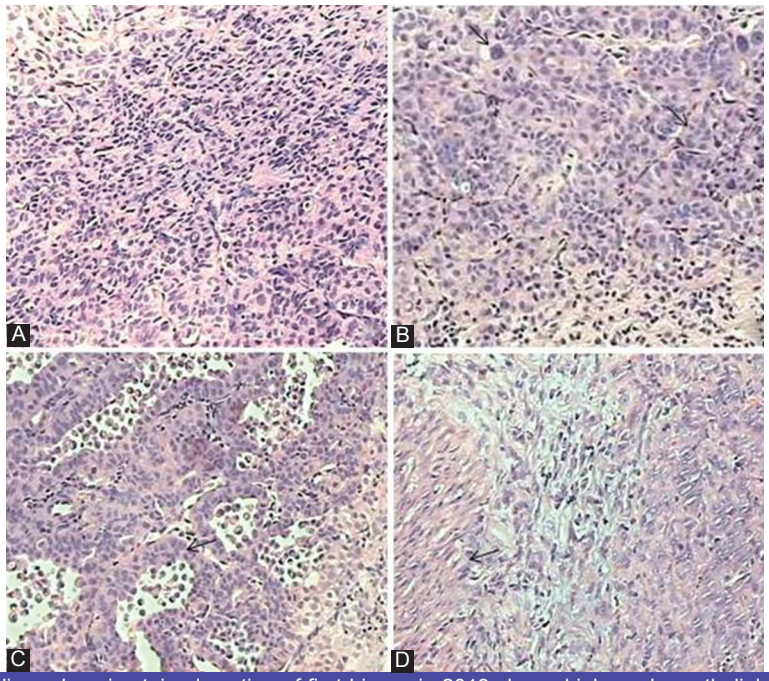

Figure 1: A) Hematoxylin and eosin stained section of first biopsy in 2013 shows high-grade urothelial carcinoma invading the lamina propria. B) Higher power (20×) view at this time shows nuclear pleomorphism (arrow). C) Biopsy at the time of recurrence in 2015 showed high-grade micropapillary carcinoma with arrow depicting the micropapillae. D) Tumour cells were seen invading the detrusor muscle (arrow).

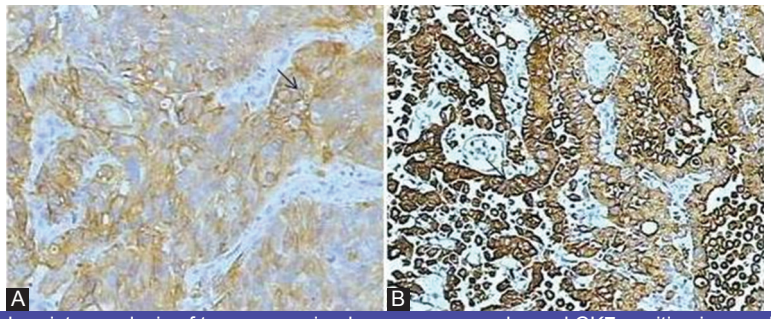

Figure 2: Immunohistochemistry analysis of tumour received on recurrence showed CK7 positive in membrane and cytoplasm of tumour cells (A), and CK20 positive in tumour cells of micropapillary variant of urothelium carcinoma (B).

with adeno and squamoid differentiation of high-grade, muscle-invasive stage (pT2HGUC) was given. The patient was treated with radical cystectomy and was found to have no nodal metastasis (N_0). Patient's consent has been obtained for reporting the case and all identifiers have been removed.

Discussion

Micropapillary urothelial carcinoma is recognized as a rare and aggressive variant of urothelial carcinoma, which often presents at a high-stage.[4] The poor prognosis in these cases was recognized to be due to the high incidence of lymphovascular invasion and the high clinical stage at presentation.[5] The morphology is reminiscent of micropapillary tumours primary at other sites. While usually invasive, non-invasive tumours have also been reported. WHO grade 1-2, non-invasive micropapillary urothelial carcinoma has also been reported in the ureter.[6] The presence of microcystic areas raised a few doubts about adenocarcinoma and the possible primary, hence immunohistochemical analysis was performed to confirm the origin. The most common adenocarcinomas metastatic to the bladder are from the prostate, therefore, markers PSA (prostate specific antigen) and AMACR (alpha-methylacyl-CoA racemase) which are positive for prostate origin, were performed. Micropapillary variant of colon carcinoma was considered and immunohistochemistry for CDX2 was performed. Analysis showed CK7 and CK20 expression in the tumour cells while PSA, AMACR, and CDX2 were negative.

The present case shows progression from a non-invasive lesion to a muscle-invasive lesion in 2 years of follow-up in spite of receiving intravesical therapy with BCG. While the pathogenesis of this tumour is unclear, some authors suggest that it could be a form of glandular differentiation of the tumour. This view is supported by reversed polarity seen in these cases where the tumour cells facing the stroma show secretory properties with the expression of MUC1. The 5-year and 10-year survival rates of 74% and 54%, respectively, with the conventional treatment show that the clinical course is poor. The patient was initially treated with intravesical BCG (induction and maintenance courses) after TURBT, as it was only diagnosed as high-grade carcinoma and the micropapillary areas were not discernible in the biopsy slide. The patient was non-responsive to BCG and progressed into muscle-invasive disease and the invasion was treated with radical cystectomy. The patient is well 3 months after surgery.

A poor prognosis has been reported for urothelial carcinoma with micropapillary and plasmacytoid morphology, but the case had extensive adhesions and peritoneal metastases at the time of surgery.[7]Extravesical extension has been reported in 60% of micropapillary UC cases.[8] However, our case presented only with frequent recurrences and muscle invasion, but no extravesical invasion, adhesions or distant metastases.

The loss of E-cadherin expression has been noted in high-grade lesions of other cancers. However, it is diffusely expressed in both micropapillary and high-grade urothelial carcinomas and does not contribute in differentiating the two entities.[8] Her2/neu gene amplification has, however, been found frequently in micropapillary carcinomas of urinary bladder suggesting that Her2 targeted therapy may be useful in suchpatients.[9,10]

Conclusion

The present case highlights the heterogeneous nature of the pT1HGUC cases as initially it was found to be the classical high-grade urothelial cancer. However, over time it developed into a more aggressive variant, which did not respond to immunotherapy. Initial treatment with radical cystectomy would have been the better option in this case even without the evidence of muscular invasion or perivesical stranding. The expression

of Her2/neu by both immunohistochemistry and FISH (fluorescence in situ hybridisation) in such cases may identify cases, which may benefit from Her2-targeted therapy.

Conflict of Interest: None declared.

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