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Case of the Month

Caveats in the diagnosis of suspected non-endemic verrucous carcinoma in the urinary bladder

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Case Conundrum

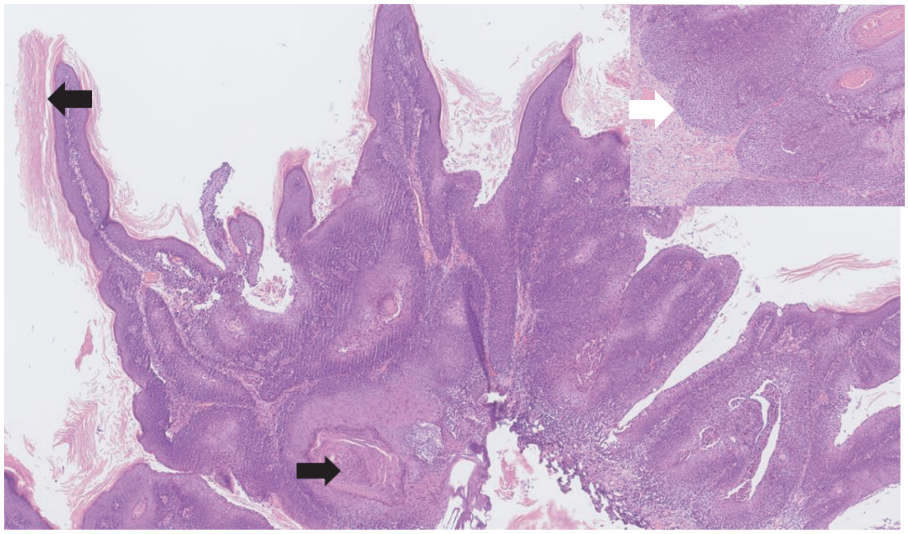
A 71-year-old male was diagnosed with high-grade, non-invasive, stage Ta urothelial carcinoma with squamous metaplasia. He was treated with transurethral resection of the bladder tumour (TURBT), followed by adjuvant BCG instillations. The inductive BCG instillations were administered at 6-week intervals and were uneventful.

Three months later, the man underwent follow-up flexible cystoscopy in the outpatient clinic. At this point, a voluminous necrotic excrescency was noted, growing from the right side of the bladder where the previous primary tumour had been resected. In addition to this finding, it was noted that a papillomatous protuberance was emerging under a layer of fibrin in the bladder dome as well as from the left side of the bladder wall around a diverticulum. Resection of the necrotic excrescency and biopsies were undertaken via TURBT 1 week later. Radical excision was not feasible and several small pathological areas remained after the TURBT.

Histopathological examination of the resected tissue from the right bladder wall showed papillomatosis and well-differentiated, acanthotic squamous epithelium with marked hyperkeratosis. No irregular invasive nests were found, but a 'pushing border' was observed in the specimens. The tumour was categorized as suspicious for verrucous carcinoma (VC; Fig. 1). The second biopsy sampled around the diverticulum showed papillary hyperplasia with keratinizing squamous metaplasia. Immunoreactivity for Ki67 indicated high proliferative activity in both specimens. The specimens were revised at a specialized tertiary university hospital because of the unusual findings. The suspicion of VC, however, remained. The patient had no history of travelling, and no *Schistosoma haematobium* eggs were identified in the specimens.

Transurethral resection of the bladder tumour was attempted again to re-resect the entire lesion and to obtain more specimens for histopathological assessment. A diagnosis of VC could still not be microscopically excluded as the tumour

Fig. 1 Material sampled by transurethral resection of bladder tumour shows an exophytic papillary process with well-differentiated squamous epithelium and marked hyperkeratosis (black arrow). Deep bulbous borders (white arrow) are present. The tumour was categorized as suspicious for verrucous carcinoma.



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tissue was resected only partially. Fluorodeoxyglucose (FDG)-positron emission tomography/CT was requested. It showed increased uptake of FDG in the bladder wall exclusively and thus excluded extravesical disease.

The patient had a long history of severe voiding symptoms, with invalidating urge and pollakiuria affecting his general well-being due to lack of sleep. The sleep deprivation further affected the symptoms he experienced due to orofacial dystonia (Meige syndrome), which was managed with botulinum toxin injections and a brain stimulator. The patient was a non-smoker and non-drinker, and had well-treated hypertension. As cystectomy could abate the causes of his daily discomfort and improve his general quality of life, this option was presented to and discussed with the patient. Given the diagnostic dilemma, the management strategy was further discussed during a multidisciplinary team meeting. In the interest of the patient and with his consent, it was finally agreed to proceed with an open cystectomy with an ileal conduit.

Histopathological examination of the cystectomy specimen showed small areas of non-invasive, papillary urothelial carcinoma, stage Ta and focal areas with keratinizing squamous metaplasia (Fig. 2). There were no findings of VC.

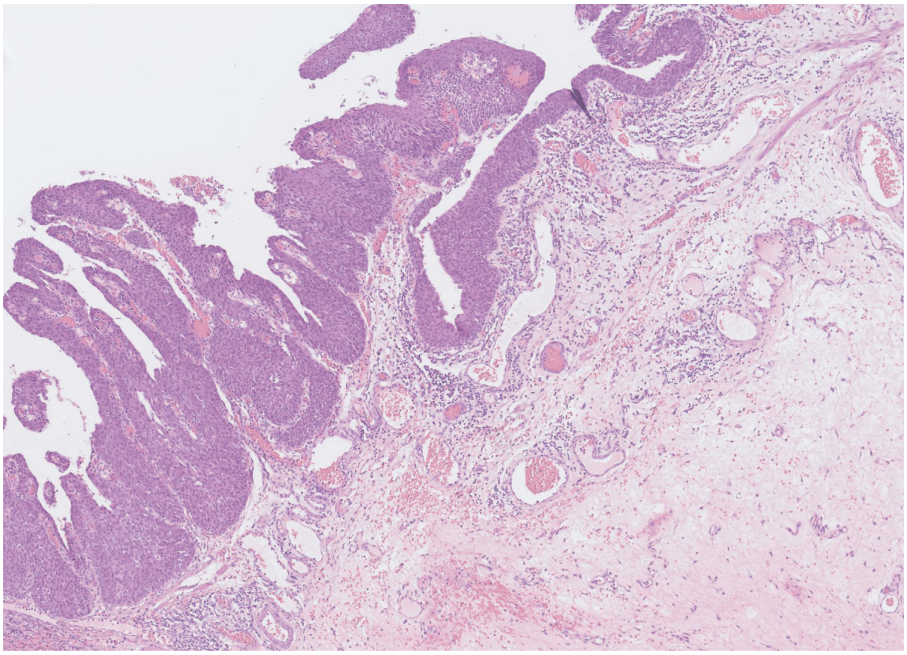
Discussion

Non-urothelial bladder carcinoma remains a diagnostic challenge, as illustrated by our case, where cystectomy was required to rule out the diagnosis of VC. This type of tumour is extremely rare in the bladder, and its sporadic occurrence does not ease the diagnostic challenges [1–3]. In areas without endemic schistosomiasis, only sporadic cases of VC in the bladder have been reported [2–4]. The aetiology of non-endemic VC remains unknown but it appears to be male predominated and age-dependent, typically presenting in the sixth decade in accordance with the case presented here [2–4].

Verrucous carcinoma is grossly characterized by an exophytic, fungating or filiform appearance, and is microscopically described by a hyperkeratotic well-differentiated squamous epithelium with an invasive front, reaching below the normal epithelium [1,2]. Predilection sites around diverticula and association with chronic bladder inflammation has been described [1,2]. All these features were noted in our case, but did not assist much in solving the diagnostic dilemma.

It should be acknowledged that these tumours may represent metastases from other sites, for which reason medical history should be thoroughly explored [1]. Secondly, differential diagnoses such as verrucous squamous hyperplasia or underlying squamous cell carcinoma (SCC) must be taken into account [1,5]. Metastases are not characteristic of VC, as opposed to SCC, where approximately 25% of patients have metastasis at the time of cystectomy [1]. Diagnostic precision often requires complete resection, however, this is a challenge in real life, where specimens are obtained by transurethral resection [1,5]. Biopsies or material sampled by TURBT are often inadequate, and caution should be taken when examining fragmentated specimens as the morphological

Fig. 2 Small areas of non-invasive, papillary urothelial carcinoma, stage Ta seen in the cystectomy specimen.



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picture may not reflect the findings in the surrounding tissue [5]. Obtaining sufficient diagnostic specimens turned out to be the core obstacle in our case, despite several attempts. Unfortunately, immunohistochemical markers are not helpful in assisting diagnostic accuracy [1].

As VC is characterized by the ability to invade nearby structures as reported by Flores et al. [4], and consequently may cause obstruction of the upper urinary tract, aggressive treatment is justified [5]. Thus, as in our case, when the histopathology remains ambiguous, partial or radical cystectomy may be warranted. In the case presented here, where lesions were found at multiple intravesical sites in a patient already treated for bladder cancer and with significant voiding symptoms, cystectomy rather than partial resection was agreed upon as the correct approach.

In conclusion, our case illustrates the difficulties in obtaining a conclusive morphological diagnosis in non-standard cases, and subsequently highlights the perplexity in management, resulting in an excessive management strategy when the histology remains equivocal. This caveat should be borne in mind whenever a rare bladder tumour is suspected.

Disclosure of Interests

The authors have no conflicting interests to declare.

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Abbreviations: FDG, fluorodeoxyglucose; SCC, squamous cell carcinoma; TURBT, transurethral resection of bladder tumour; VC, verrucous carcinoma.

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