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 excrescence 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 excrescence 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.
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 fragmented specimens as the morphological

![Fig. 2](image-url)
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.

Funding
The first author is funded by Aarhus University.

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