A spindle cell tumour in the bladder

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Abstract

Spindle cell lesions in the bladder can be challenging and present a wide differential diagnosis. We report a case of one of these diagnoses - sarcomatoid variant of urothelial carcinoma. We also describe how to differentiate between benign and malignant mimics and discuss the molecular features of sarcomatoid variant of urothelial carcinoma.

Keywords consensus classification of urothelial carcinoma; sarcomatoid variant of urothelial carcinoma; spindle cell lessions

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Case report

A 67-year-old woman underwent pelvic exenteration for a bladder tumour. Macroscopically there was a partly necrotic mass filling the bladder lumen and invading through the bladder wall. Microscopically, a malignant spindle cell tumour was seen. Focal urothelial carcinoma in-situ (CIS) was present and review of the initial trans-urethral resection of bladder tumour (TURBT) specimen showed a small focus of conventional high-grade papillary urothelial carcinoma (Figure 1). Immunohistochemistry showed patchy AE1/AE3 and p63 expression of variable intensity. Smooth muscle actin, desmin and S100 were not expressed. The final diagnosis was sarcomatoid variant of urothelial carcinoma.

Discussion

The sarcomatoid variant of urothelial carcinoma (SVUC) is rare, accounting for 0.1% of all bladder tumours. This variant is aggressive, often presents with pT3 or pT4 disease and has a five-year survival rate of 28.4%.[1] Microscopically conventional urothelial cell carcinoma (UCC) is often seen, and this may display divergent differentiation such as rhabdoid, squamous, chordoid or nested morphology. The mesenchymal element usually has a non-specific spindle cell pattern but myxoid or pseudoangiosarcomatous features can be seen. Rarely, osteoid is seen as a heterologous component. Chordoid epithelial differentiation and myxoid spindle cell morphology are each associated with a particularly poor prognosis.[2]

Spindle cell lesions in the bladder are a challenging diagnostic scenario encompassing benign and malignant processes (Table 1; reviewed comprehensively in references).[3,4] Inflammatory myofibroblastic tumour (IMT) and postoperative spindle cell nodule (PSCN) are two important benign entities that can mimic malignant processes in the bladder. Both can be differentiated from SVUC by the lack of a malignant urothelial component, minimal cytological atypia and the absence of necrosis in the deep component. IMT can display superficial ulceration and necrosis. Importantly, both IMT and PSCN can extend into the detrusor muscle; this feature does not indicate malignancy. Overall, the distinction between IMT and PSCN can be difficult in biopsy or TURBT specimens and there should be a low threshold for requesting levels or embedding remaining tissue.

Immunohistochemically, SVUC will typically show at least focal staining with broad spectrum cytokeratins. However, this has limited use in the differential diagnosis with PSCN and IMT as these entities can also express cytokeratins. Immunohistochemistry for anaplastic lymphoma kinase 1 (ALK1) may be useful. However, this marker is only expressed in 50% of IMT arising in the bladder, so a negative result does not rule out this diagnosis.[5] This is reflected at the genomic level as a similar proportion of cases have rearrangements at the ALK locus (2p23), as detected by fluorescence in-situ hybridisation. Malignant soft tissue tumours are also part of the differential diagnosis for a spindle cell neoplasm in the bladder. Leiomyosarcoma, rhabdomyosarcoma and angiosarcoma have all been reported at this site, and in the absence of a malignant urothelial component, immunohistochemistry is required to exclude these possibilities.

At a molecular level, SVUC is derived from the basal subtype of urothelial carcinoma and shows overexpression of basal markers including CD44 and cytokeratins 5, 6 and 14. Furthermore, SVUC has its own molecular subtypes and can be dichotomised into cases that retain basal markers and cases that lack expression of either

Practice points

- SVUC is recognised microscopically as a spindle cell neoplasm. This has a wide-ranging differential diagnosis comprising benign and malignant entities.
- SVUC belongs to the basal molecular subtype of UCC but a further subgroup of SVUC displays a 'double negative' phenotype and may have a worse prognosis.
- PARP inhibitors may be effective in cases of SVUC, in contrast to conventional UCC.

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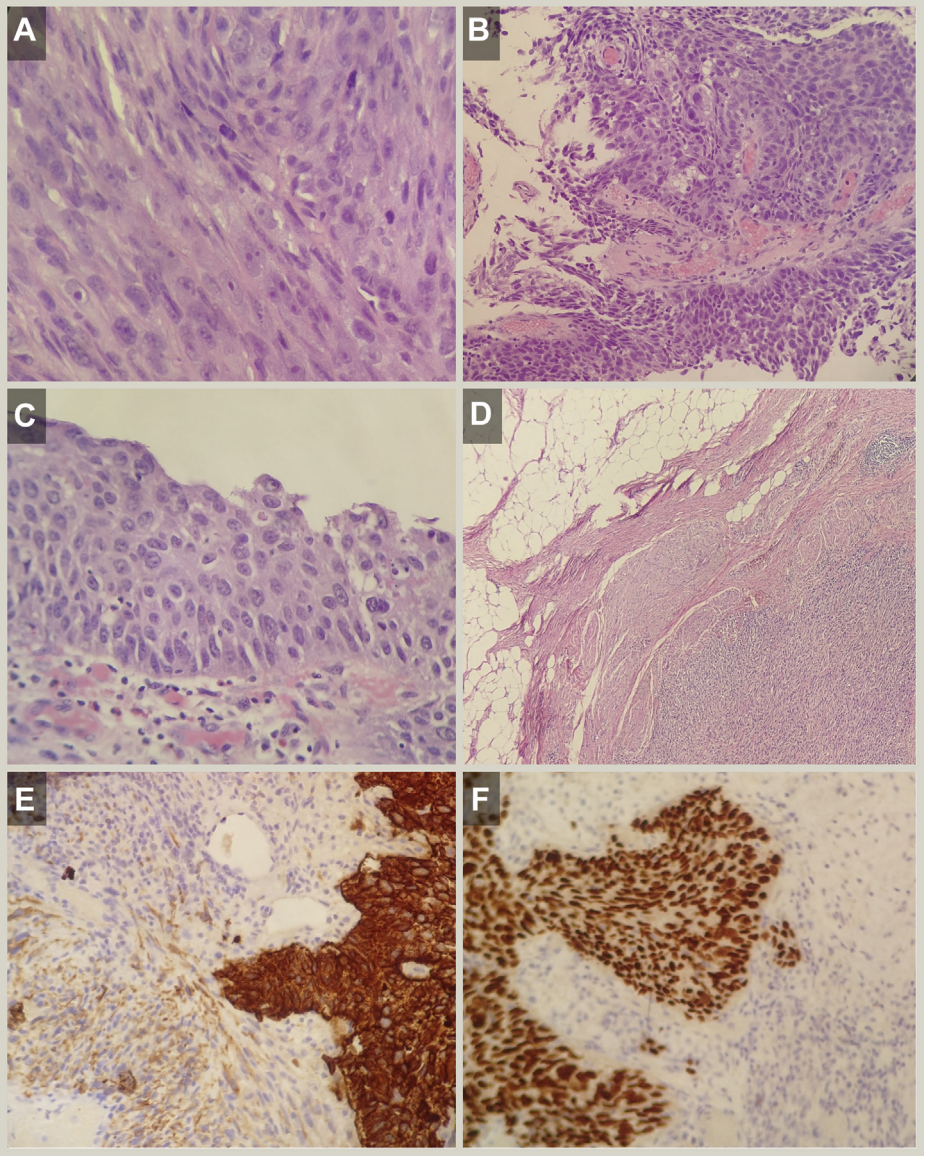

Figure 1 Morphological and immunohistochemical features of the sarcomatoid variant of urothelial carcinoma. A: Non-specific pleomorphic spindle cell pattern in the majority of the tumour, B: Focal high-grade papillary urothelial carcinoma in the TURBT specimen, C: Carcinoma-in situ in the cystectomy specimen, D: Invasion into perivesical adipose tissue, E and F: Immunohistochemistry for AE1/AE3 and p63 respectively, both showing patchy staining of variable intensity.

Differential diagnosis of spindle lesions in the bladder

Benign
Post-operative spindle cell nodule
Inflammatory myofibroblastic tumour
Leiomyoma
Solitary fibrous tumour
Neurofibroma
Malignant
Sarcomatoid urothelial carcinoma
Leiomyosarcoma
Rhabdomyosarcoma
Malignant peripheral nerve sheath tumour
Pleomorphic undifferentiated sarcoma

Table 1

luminal or basal markers.[6] This so-called 'double negative' group has a particularly poor prognosis with a mean survival of 10 months and is characterised by a gene expression profile of epithelial to mesenchymal transition (EMT). At a protein level, an immunohistochemical study of SVUC showed upregulation of the EMT markers SNAIL, vimentin and FoxC2.[2] This switch to an EMT phenotype may explain the widely invasive and aggressive nature of the sarcomatoid variant of urothelial carcinoma.

X chromosome inactivation studies have shown that SVUC arises from a urothelial carcinoma precursor rather than representing a collision between separate epithelial and mesenchymal tumours. Despite this, significant heterogeneity is seen between the epithelial and sarcomatoid elements. Divergent gene

expression patterns are seen, and this may translate to different responses to therapy for each component. In a recent study, sarcomatoid areas tended to have greater PD-L1 expression and had a drug response score in keeping with poly ADP ribose polymerase (PARP) inhibitor sensitivity when compared to adjacent conventional UCC.[7] This implies that multi-modal treatment including immunotherapy may be needed to treat both components. ◆

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Multiple choice questions

1 Which morphological pattern is associated with a particularly poor prognosis in sarcomatoid variant of urothelial carcinoma?

a) Osteoid as a heterologous mesenchymal component
b) Conventional urothelial carcinoma epithelial component
c) Rhabdoid morphology in the epithelial component
d) Non-specific spindle cell morphology in the mesenchymal component
e) Chordoid morphology in the epithelial component

Correct answer: e

2 What is the molecular subtype of sarcomatoid variant of urothelial carcinoma?

a) Luminal
b) Luminal papillary
c) Luminal infiltrated
d) Basal
e) Neuronal

Correct answer: d

3 Inflammatory myofibroblastic tumour can mimic sarcomatoid variant of urothelial carcinoma. Immunohistochemistry for ALK1 can be useful in differentiating between the two. This marker is positive in what proportion of inflammatory myofibroblastic tumours?

a) 1%
b) 25%
c) 50%
d) 75%
e) 99%

Correct answer: c

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