A snake in the grass
Rhiannon Trefor,1 Murali Varma2

CLINICAL QUESTION
A 77-year-old man presented with haematuria. Cystoscopy revealed a papillary tumour in the trigone region of the bladder. A TURBT was performed. Review the high-quality, interactive digital Aperio slide at http://virtualACP.com/JCPCases/jclinpath-2016-204015 and consider your diagnosis.

WHAT IS YOUR DIAGNOSIS?
A. Urothelial carcinoma pTa
B. Urothelial carcinoma pT1
C. Metastatic carcinoma
D. Prostatic adenocarcinoma
E. Prostatic polyp

ANSWER
B (plasmacytoid variant of urothelial carcinoma with lamina propria invasion)

DISCUSSION
The submitted section shows a non-invasive atypical glandular proliferation with features in keeping with high-grade non-invasive papillary urothelial carcinoma with glandular differentiation (pTa). There is prominent chronic inflammation in the lamina propria composed of lymphocytes and plasma cells. Within this inflammatory infiltrate are single cytologically atypical cells with eccentrically situated nuclei resulting in a plasmacytoid morphology. (figure 1A–E) These cells express cytokeratins confirming their epithelial nature (figure 1F). The final diagnosis is ‘non-invasive papillary urothelial carcinoma with glandular differentiation associated with plasmacytoid variant of urothelial carcinoma with lamina propria invasion (pT1)’. This small-cell aggressive malignancy tucked away within the lymphoid infiltrate is veritably a snake in the grass that poses a significant risk to the unwary pathologist.

Plasmacytoid urothelial carcinoma (pUC) is a rare histological variant of urothelial carcinoma characterised by an advanced stage at presentation and metastatic disease progression.1–3 The typical clinical presentation of pure pUC is an extensive linitis plastica-like involvement of the bladder such as AE1/AE3, EMA and CK7, GATA3, p53 and CD79, MUM-1 and light chains are negative in pUC recurrence is the peritoneum. Peritoneal recurrence is associated with raised serum CA-125 levels, which has been suggested as an aid to recognise early disease progression.1

The tumour cells of pUC are typically small to medium sized with abundant eosinophilic cytoplasm and eccentrically located often uniform nuclei resulting in a close resemblance to plasma cells.1,2 Some reports have described the presence of a paranuclear hof in pUC further mimicking plasma cells.1 Intracytoplasmic vacuolation is not uncommon and in some cases this mimics signet ring cells but extracellular mucin is not seen in pUC.1 Primary signet ring carcinoma of the bladder not associated with extracellular mucin is now included in the category of pUC as almost all cases are associated with a variable number of plasmacytoid cells.6

A variety of architectural patterns may be seen in pUC. These include small nests, larger sheets, cords, single files and diffuse discohesive growth patterns. Prominent retraction artefact around each tumour cell may be seen.1,2 Lymphoma-like and lobular carcinoma-like variants of urothelial carcinoma are now considered part of pUC category.

pUC with a diffusely discohesive growth pattern composed of isolated cells can be very difficult to identify at low power and in frozen sections, particularly when admixed with a chronic inflammatory infiltrate as in this case. Absence of a stromal reaction also renders low-power identification difficult. Metastatic pUC can pose a serious diagnostic challenge especially if the metastasis is in the bone where it can be readily misdiagnosed as plasmacytoma.

pUC often coexists with other subtypes of urothelial carcinoma such as conventional, micropapillary and nested with the extent of pUC component ranging from 15% to 100%;1,2 The associated component may be urothelial carcinoma in situ, non-invasive papillary urothelial carcinoma or invasive urothelial carcinoma.

The morphological differential diagnosis of pUC includes benign histiocytes or plasma cells, malignant lymphoma (including plasmacytoma) and signet-ring adenocarcinoma. Metastasis to the bladder of myeloma, multiple melanoma, lobular breast carcinoma and diffuse pattern of gastric carcinoma can also closely resemble pUC. Other neoplasms with a plasmacytoid morphology include medullary carcinoma, rhabdomyosarcoma, myoepithelial carcinoma and carcinoid tumours that are extremely rarely encountered in the bladder. The key to diagnosis is a limited immunohistochemical panel including cytokeratin antibodies and good clinical correlation.

pUC is immunoreactive for epithelial markers such as AE1/AE3, EMA and CK7, GATA3, p53 and p16.1,2 A well-recognised immunohistochemical pitfall is the expression of plasma cell marker CD138 in a significant proportion of pUC cases.6 Other markers of plasma cell differentiation such as CD79, MUM-1 and light chains are negative in pUC. The use of epithelial immunomarkers is recommended to distinguish cells of pUC from benign or malignant plasma cells. The proliferative index determined by Ki67 staining is usually high.

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Lim et al\textsuperscript{4} reported loss of E-cadherin expression in pUC. Al-Ahmadi et al\textsuperscript{5} confirmed loss of E-cadherin immunoreactivity in pUC and reported alterations of the \textit{CDH1} gene that encodes E-cadherin. \textit{CDH1} mutations are also frequently found in lobular breast carcinoma and diffuse gastric carcinoma, both of which morphologically resemble pUC. They concluded that the loss of E-cadherin expression, as a result of \textit{CDH1} somatic mutation or promoter hypermethylation, is associated with enhanced cellular migration, likely explaining the unique peritoneal pattern of disease dissemination and poor clinical outcome of patients with this variant of urothelial carcinoma.\textsuperscript{5}

Signet-ring cell carcinoma of the bladder without extracellular mucin, lobular carcinoma-like urothelial carcinoma and lymphoma-like urothelial carcinoma are now included within the category of pUC. These are all high-grade variants of urothelial carcinoma with similarities in their morphology, immunoprofile (most notably lack of E-cadherin expression) and prognosis.

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