Pink renal conundrum

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A 62-year-old man underwent a right radical nephrectomy for an incidentally discovered right renal tumour. Macroscopic examination of the specimen demonstrated an 11 cm diameter, well-circumscribed, tan-brown, solid tumour with focal haemorrhage. On immunostaining, the tumour cells were positive for AE1/AE3, Epithelial Membrane Antigen (patchy) and PAX8. No immunoreactivity was seen with CK7, CK20, CA9, CD10, CD117, AMACR, Melan A and HMB45. Review the high quality, interactive digital Aperio slide at http://virtualacp.com/JCPCases/jclinpath-2019-206260/ and consider your diagnosis.

WHAT IS YOUR DIAGNOSIS?

A. Eosinophilic solid and cystic renal cell carcinoma (RCC).
B. Eosinophilic variant of chromophobe carcinoma.
C. Eosinophilic variant of conventional (clear cell) RCC.
D. Oncocytoma.
E. Succinate dehydrogenase (SDH)-deficient RCC.

DISCUSSION

The submitted section shows a well-circumscribed unencapsulated tumour with a pushing border and peripheral entrapment of renal tubules (figure 1A,B). The tumour is composed of tightly packed cells with abundant, predominantly eosinophilic cytoplasm arranged in sheets and nests with cystic areas (figure 1C). No papillary architecture is seen. Many of the cells show a degree of cytoplasmic clearing, and cell boundaries are generally indistinct. The nuclei are generally uniform and round with occasional small nucleoli (figure 1D).

The differential diagnosis of a renal tumour with eosinophilic cytoplasm and solid pattern with low-grade cytology includes oncocytoma, chromophobe RCC, eosinophilic variant of conventional (clear

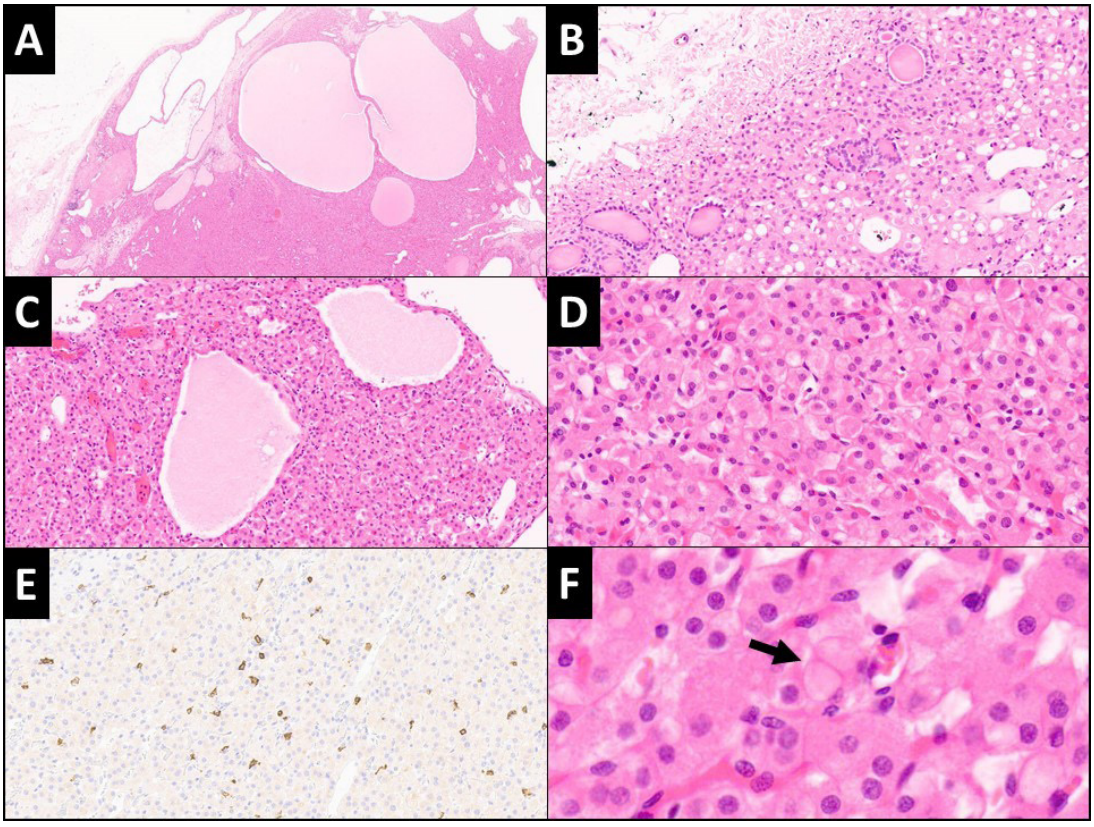

Figure 1 A well-circumscribed pseudoencapsulated lesion (A) with a pushing border and peripheral entrapment of renal tubules (B). The tumour shows a closely packed, solid-microcystic architecture (C) composed of oncocytic cuboidal cells with indistinct borders, and uniform nuclei showing dispersed chromatin and inconspicuous nucleoli (D). CD117 immunostain shows a prominent mast cell infiltrate; the tumour cells are immunonegative (E). High-power examination reveals distinctive flocculent cytoplasmic inclusions (arrow) characteristic of succinate dehydrogenase-deficient renal cell carcinoma (F).

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cell) RCC, epithelioid angiomyolipoma and eosinophilic solid and cystic RCC and SDH-deficient RCC.

We focus on the main differential diagnoses in the submitted case. More detailed discussion regarding the differential diagnosis of oncocytic renal tumours are available in recent reviews.[1 2]

The solid-nested architecture and uniform round nucleoli are suggestive of oncocytoma. However, the tumour cells show partly flocculent cytoplasm and lack the cytoplasmic granularity characteristic of oncocytoma (figure 1D). The submitted section also lacks the typical architecture of oncocytoma with small solid nests of cells within a myxoid or hyalinised stroma. Finally, in contrast to oncocytoma, this tumour was immunonegative for CD117 (figure 1E).

The solid growth pattern and degree of cytoplasmic clearing would raise the possibility of chromophobe RCC (eosinophilic variant). However, the tumour cells in the submitted case lack the distinctive prominent cell borders and irregular 'raisinoid' nuclei with binucleate forms typically seen in this entity. Moreover, unlike our case, chromophobe RCC typically shows diffuse CK7 immunoreactivity.

Conventional (clear cell) RCC is suggested by cytoplasmic clearing in some cells and the rich sinusoidal vasculature. However, the cytoplasm in the submitted tumour appears flocculent unlike the optically clear cytoplasm characteristic of clear cell RCC (figure 1D). In contrast to the submitted section, conventional RCC with eosinophilic cytoplasm is typically high grade with prominent nucleoli. Clear cell RCC is typically immunoreactive for CA9 and CD10.

Epithelioid angiomyolipoma (perivascular epithelioid cell neoplasm/PEComa) is another tumour that can manifest foci of cells with abundant eosinophilic cytoplasm arranged in solid sheets and nests. Smooth muscle bundles, thick walled blood vessels and fat, typical of classical angiomyolipoma may not be prominent in the epithelioid variant. However, epithelioid angiomyolipoma typically shows quite marked nuclear atypia, which is not seen in the submitted section. The rare oncocytoma-like angiomyolipoma generally has more prominent nucleoli.[3] PEComas are immunonegative for PAX8 unlike the submitted case.

Eosinophilic solid and cystic RCC is an emerging subtype of RCC that is composed of cells with abundant eosinophilic cytoplasm arranged in sheets and nests with a variable microcystic component. The nuclei are typically uniform round or oval with focally prominent nucleoli. This tumour type is commonly associated with small aggregates of histocytes and lymphocytes. On immunostaining, such tumours generally show CK20 immunoreactivity. In the submitted case, the tumour is not associated with an inflammatory infiltrate and is CK20 negative. Finally, unlike our case, this tumour type is commonly associated with macrocystic areas on gross examination.

Another eosinophilic renal tumour characterised by low grade cytology and solid-nested growth pattern is SDH-deficient RCC. Careful examination of the submitted section reveals flocculent cytoplasmic inclusions that impart a distinctive 'foamy' appearance to the cells (figure 1F). The 'neuroendocrine-like' nuclear features with dispersed chromatin pattern and inconspicuous nucleoli seen in this case are also characteristic of SDH-deficient RCC. CD117 immunohistochemistry also highlights the prominent mast cell component that is commonly associated with this tumour type (figure 1E). Genetic analysis of the tumour detected a heterogenous pathogenic variant, c.380T>G in the SDHB gene. Hence, the final diagnosis in the submitted case was SDH-deficient RCC.

The immunohistochemical hallmark of SDH-deficient RCC is loss of immunostaining for SDHB as mutation of any of the four subunits (A–D) of the SDH gene results in degradation of the SDHB subunit. These tumours are generally immunoreactive for PAX8 but negative for CD117, CK7, CK20, vimentin, CA9, RCC-Ma and neuroendocrine markers. Unlike most other RCCs (except MiT Family Translocation-Associated RCCs), the tumour cells are often either negative or only focally positive with epithelial markers (pancytokeratins and EMA).

The reader is referred to recent reviews for a more detailed discussion on this rare renal tumour that is part of a hereditary syndrome associated with pheochromocytomas/paraganglioma, gastrointestinal stromal tumour, RCC and pituitary adenoma.[4–7]

ANSWER

E. SDH-deficient RCC.

Take home messages

- Succinate dehydrogenase (SDH)-deficient renal cell carcinoma (RCC) is an oncocytic renal tumour that can closely mimic oncocytoma.
- The most characteristic morphological feature of SDH-deficient RCC is flocculent cytoplasmic inclusions or vacuoles.
- The immunohistochemical hallmark of SDH-deficient RCC is loss of SDHB expression.
- SDH-deficient RCCs are associated with a well-recognised clinical syndrome, with potential long-term implications for the patient and their wider family.

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