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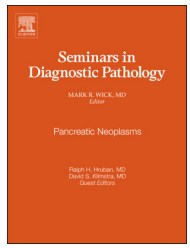

Distal nephron neoplasms

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ABSTRACT

Tumours of the distal nephron are uncommon but can create diagnostic difficulties. They may be divided into three groups—tumours of intercalated cell phenotype, those of principal cell phenotype and others with an unconfirmed distal nephron origin. Oncocytomas, chromophobe carcinoma and hybrid oncocytoma chromophobe carcinoma, all show features of intercalated cells and the distinction amongst these is one of the most common areas of diagnostic dilemma. Collecting duct carcinoma and renal medullary carcinoma are the most aggressive forms of renal cancer but recent evidence suggests they may respond to targeted therapy so their recognition becomes crucial to the management of these patients. There remains debate over the precise phenotype of both tubulocystic carcinoma and mucinous tubular and spindle cell carcinoma.

Introduction

It is generally accepted that the majority of renal epithelial tumours arise from the cells of the proximal tubule but there are some important, albeit uncommon, tumours which arise from the distal nephron.[1] Recognition of these unusual phenotypes is important because of their characteristic clinical behaviour and the potential for more specific therapy. Furthermore some pathological assessments need modification, grading criteria, in particular, are of limited value in assessing these neoplasms. The tumours fall into two main groups namely those arising from the intercalated cells (oncocytoma and chromophobe carcinoma) and those presumed to arise from the principal cells (collecting duct carcinoma and renal medullary carcinoma), and others for which the distal nephron origin is more debatable (tubulocystic carcinoma and mucinous tubular and spindle carcinoma).

Intercalated cell tumours

Their distal nephron origin is based on the close resemblance of the tumour phenotype to the intercalated cells of the collecting ducts. There are two main cell types in the collecting ducts—principal cells and intercalated cells. Intercalated cells constitute approximately a third of cortical collecting duct cells but that proportion falls along the length of the collecting ducts until their virtual absence in the deep medullary collecting ducts. They have a high density of mitochondria and are involved in the active secretion of H^+ into the urine to maintain internal pH balance. There are two main tumours in this group, oncocytoma and chromophobe carcinoma, and there is some merit in the argument that they represent the breadth of a spectrum from benign to malignant of tumours showing an intercalated cell phenotype.[2] Evidence supporting the intercalated cell origin of oncocytoma and chromophobe carcinoma includes the high density of mitochondria, the expression of the C isoform of carbonic anhydrase involved in acid secretion and of epithelial membrane antigen which is limited to the distal nephron and is consistently found in these tumours.[3,4]

Oncocytoma

The term oncocytoma has been applied to several organs to describe a neoplasm composed of oncocytes, cells with

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intensely eosinophilic granular cytoplasm. Renal oncocytoma was first proposed by Klein and Valensi[5] in 1976 and there ensued a debate concerning the diagnostic criteria and the behaviour of these tumours. Although the majority of renal oncocytomas appeared to behave in a benign manner, a few cases of metastasising oncocytoma were described.[6] The debate was largely resolved by the recognition of chromophobe carcinoma in 1985[7] and that most, if not all, the cases of "malignant" oncocytoma were chromophobe carcinomas. Renal oncocytoma diagnosed by accurate histological examination, supported when required by immunohistochemical and molecular methods is now considered to be a benign neoplasm with only two reports of possible metastases in the last 20 years.[8]

Oncocytomas account for slightly less than 5% of surgically excised renal tumours. They are more common over 50 years of age and are twice as common in men as women. Approximately 70% of oncocytomas are asymptomatic being detected by imaging during the investigation of other conditions. When symptomatic they may cause flank discomfort or pain and there may be a palpable renal mass. Haematuria is much less common than in renal carcinoma. Grossly, oncocytoma is well circumscribed and rounded, often with a central white scar contrasting with the tan-brown colour of the tumour. Haemorrhage may be seen but areas of necrosis should be viewed with caution. Multifocality and bilaterality are not uncommon and may raise the prospect of an inherited condition or of oncocytosis.

Oncocytoma has a characteristic morphology but presents two distinct diagnostic challenges namely the presence of "atypical" features and the distinction from the eosinophilic variant of chromophobe carcinoma. Oncocytoma typically has a solid or nested architecture (Fig. 1) with occasional tubular, cystic or trabecular areas.[9] In rare cases these minor architectural patterns may be the dominant morphology. In the typical oncocytoma the nested architecture predominates in the centre of the tumour while the periphery tends to be more solid. Between tumour nests and in the centre of the oncocytoma there is an oedematous loose stroma, in occasional cases this may occupy the bulk of the tumour. Coagulative necrosis is a rare feature although focal calcification may be seen in up to 10% of cases.[10]

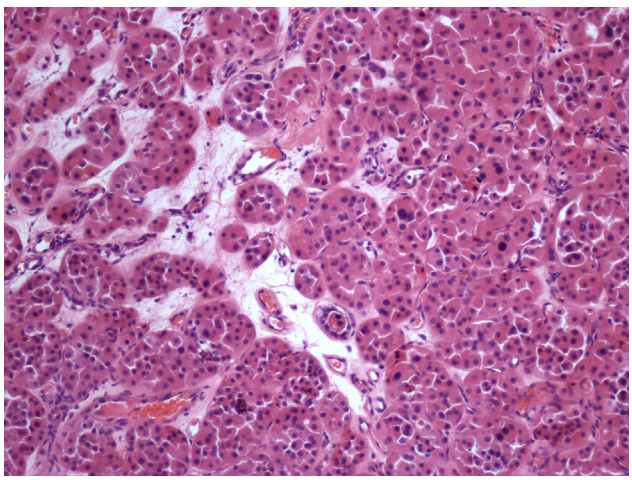

Fig. 1 – Oncocytoma consists of a nested arrangement of cuboidal cells with intensely eosinophilic granular cytoplasm with uniform round nuclei. Tubular areas are also seen (H&E, ×10 original magnification).

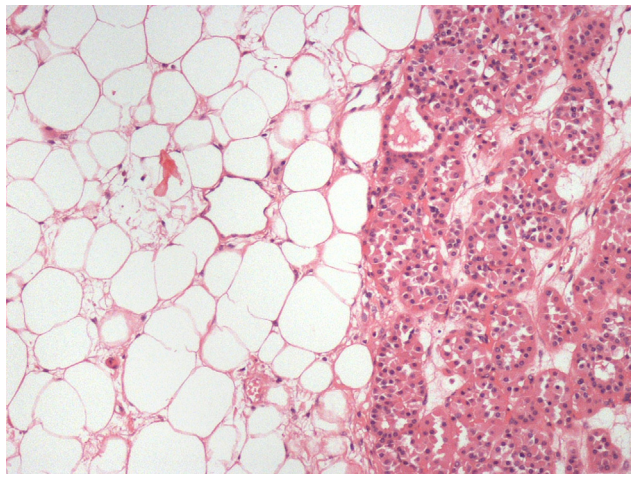

Fig. 2 – Oncocytoma will occasionally show invasion of perinephric fat with packeted oncocytes abutting the fat with no capsule and no inflammatory or desmoplastic reaction (H&E, ×20).

The cells are cuboidal with rather indistinct cell borders and oncocytic cytoplasm—intensely eosinophilic and granular. In poorly fixed specimens particularly in the centre of the tumour there may be marked discohesion but this is not seen in well-fixed tumours and around the tumour periphery. Nuclei are round with coarse clumping of chromatin often with small basophilic nucleoli. Focal nuclear atypia, with pleomorphism, hyperchromasia, intranuclear inclusions and multinucleation is seen is as many as 25% of cases but mitotic activity is absent.[9] These nuclei are often found in more degenerate areas of the tumour. Areas of the tumour containing smaller intensely staining cells have been described as oncoblasts[10] but this term carries no sinister connotation.

There are two features which may give rise to concern. Extension of oncocytoma into perinephric fat is common; Trpkov et al.[10] identified this feature in 15.6% of 109 cases of oncocytoma they reviewed. It typically consists of nests of oncocytes extending beyond the kidney infiltrating fat but without an inflammatory or desmoplasic reaction (Fig. 2). Less commonly vascular invasion (<5%) may be seen, this is usually microvascular invasion but can include invasion of muscle containing tributaries of the renal vein. Neither of these two apparently invasive features confers a malignant phenotype.

Chromophobe carcinoma

Chromophobe carcinoma was first identified in 1985[7] and it has been clear since then that there are two important issues with this tumour. These are the diagnostic confusion with oncocytoma and, although most cases of chromophobe carcinoma have a good outcome, the recognition of those likely cases to have a poor outcome.

They are well circumscribed tumours with a uniform brown or grey cut surface with areas of focal haemorrhage. They can