Part I: Primary malignant non-Wilms' renal tumours in children

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Part II: Management of primary malignant non-Wilms' renal tumours in children will be published in September 2007.

Non-Wilms' tumours form a small heterogeneous group of clinically significant renal malignancies in children, including renal-cell carcinoma, clear-cell sarcoma, (congenital) mesoblastic nephroma, rhabdoid tumour, and renal medullary carcinoma. Good progress has been made in the assessment of these tumours, which has led to a greater understanding of the molecular changes that occur in their development. This review is the first of two parts, and provides an updated review of the clinical presentation, imaging, and pathology of these tumours.

Introduction

Wilms' tumour represents about 6–7%[1] of all paediatric malignancies, and, for some time, this eponymously named renal tumour has dominated research efforts, with overall 3–5 year survival now approaching 90%. However, other primary renal malignancies, which represent a small proportion of all childhood cancer, also carry substantial mortality. This group is less well understood because its heterogeneity and rarity make formulating basic and clinical research difficult.[2,3] The advent of multicentre collaborations assessing Wilms' tumour—including the Children's Oncology Group (COG) in the USA (formerly National Wilms' Tumour Study Group [NWTSG]),[4] the Société Internationale d'Oncologie Pédiatrique (SIOP) in Europe, the UK Children's Cancer Study Group (UKCCSG), and many others—has produced substantial advances in the understanding and management of this tumour. Furthermore, such collaborations have also provided opportunities for learning more about non-Wilms' tumours.

This review is the first of two parts and provides a focused review of the clinical presentation (figure 1), imaging, and pathology of paediatric primary renal malignancies, including renal-cell carcinoma, clear-cell sarcoma, (congenital) mesoblastic nephroma, rhabdoid tumour of the kidney, and renal medullary carcinoma.

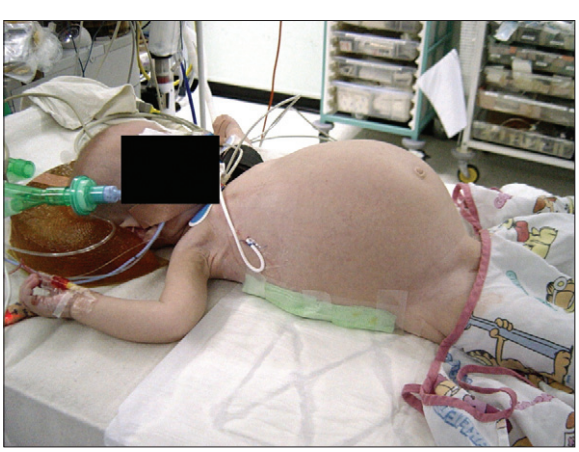

Figure 1: **Female child with large intra-abdominal mass shown to be a large, right, renal mass on CT**
Subsequent histology of nephrectomy sample showed clear-cell sarcoma of the kidney.

Part two will focus on the management of this group of tumours.

Renal-cell carcinoma

Clinical presentation

Renal-cell carcinoma (RCC) accounts for 2–5% of paediatric renal tumours, and 0·5–2% of all RCCs occur in those under 21 years of age.[5] The mean age of children with RCC varies from 9 to 15 years (this variation in age explains the differing age ranges used for inclusion in a particular series). Generally, there is no sex predominance, although one series has shown a female predominance of 2·7:1.[6] Patients present with frank haematuria, loin pain, and a palpable mass, although about a quarter are asymptomatic, with the tumour detected on imaging. This spectrum of presentation is similar to that of adult cases. Metastases in the lungs, bone, liver, or brain are identified in about 20% of patients at the time of diagnosis. Bilateral presentation can be associated with underlying conditions, such as von Hippel-Lindau disease, with which RCC is sometimes associated in younger patients.[7]

Imaging

Cross-sectional imaging shows a non-specific solid intrarenal lesion with little enhancement (figure 2A), although areas of haemorrhage and necrosis are sometimes seen (figure 2B). Calcification is more frequent in RCC than in Wilms' tumour (25% *vs* 9%, respectively).[3]

Pathology

RCC is generally smaller in size than Wilms' tumour, and, macroscopically, clear-cell RCC has a golden-yellow appearance compared with the fleshy appearance of Wilms' tumour. RCC has variable amounts of haemorrhage, necrosis, calcification, and cystic degeneration.

The WHO classification of renal tumours in adults was developed to take account of differing pathological and genetic abnormalities in distinct tumour entities.[8] Paediatric RCC can be classified according to this scheme, although, histologically, paediatric RCC is different from its adult counterpart (several series have identified a large frequency of paediatric tumours that do not have the usual histological features of adult RCC).[5,6,9,10,11] Therefore,

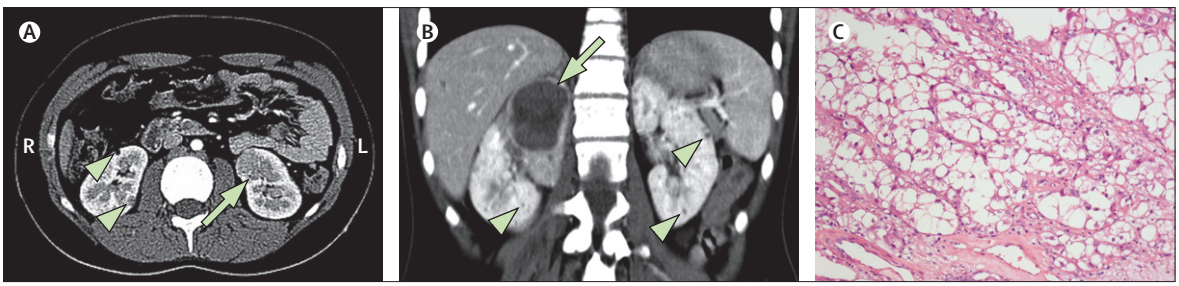

Figure 2: **Renal-cell carcinoma (RCC)**
(A) Cross-sectional CT scan showing typical features of RCC (left kidney mass [arrow] with little contrast uptake and absence of fat). (B) Coronal CT scan showing right RCC tumour (arrow) with large necrotic centre. These cases occurred in patients with associated angiomyolipomas (small peripheral fatty lesions visible in right kidney (arrowheads)). (C) Xp11.2-related RCC. Solid and papillary architecture is present with tumour cells showing voluminous clear cytoplasm (×40 magnification).

although two main morphological subgroups can be identified, namely papillary and clear-cell tumours, some RCCs (about 25%) show heterogeneous features that do not sit comfortably in either of these two WHO subcategories.[9,10]

Paediatric papillary RCC has the classic papillary architecture of its adult counterpart. This form is common, giving rise to between 20% and 50% of all paediatric RCCs, an incidence that is somewhat higher than that in the adult population.[11] Papillary RCC sometimes occurs in the setting of Wilms' tumour, metanephric adenoma, and metanephric adenofibroma. The other large group, clear-cell RCC, has classic clear-cell appearance.

However, this grouping into papillary and clear-cell subtypes predates molecular characterisation of RCC, and the two subgroups are less distinct if genetic translocation data is considered. Since the description of some paediatric RCCs with voluminous pale or clear cytoplasm as a specific entity (voluminous-cell variant),[9] many studies have shown that most RCCs can be subclassified according to specific genetic translocations. The RCC group is now accepted to include a subset of tumours with characteristic morphological features, which represent a group of genetic translocations.[12] However, a small number have conventional adult-type genetic mutations, with 3p25-26 (*VHL* locus) changes.

Xp11.2-related tumours and TFE3 fusions

Genetic translocations give rise to a third of paediatric RCCs, with many involving chromosome Xp11.2 and resulting in *TFE3* fusions.[13] The protein product of *TFE3* is a family member of the MITF-TFE family of basic helix-loop-helix leucine zipper transcription factors. The first reported translocation was t(X;1)(p11.2;q21), resulting in the fusion of *PRCC* and *TFE3*.[14] Other translocations have resulted in the fusion of *ASPSCR1* and *TFE3* (t[X;17][p11.2;q25]), *IGFBP7* and *TFE3* (t[X;1][p11.2;p34]), and *NONO* and *TFE3* (inv[X][p11;q12]).[15] *IGFBP7* and *NONO* are splicing-factor genes, but the function of *PRCC* and *ASPSCR1* have not yet been elucidated. Other translocations have also been reported.[13] A total of five gene fusions have so far been shown[13] and these Xp11.2-translocation carcinomas now form a distinct entity in the most recent WHO classification.[16] Morphologically, these carcinomas resemble conventional clear-cell renal carcinomas, but they also have areas of papillary architecture and granular eosinophilic cytoplasm, as well as small calcifications (figure 2C).

Translocation RCCs underexpress epithelial markers (cytokeratin and epithelial membrane antigen [EMA]) with only about half showing focal staining (a similar number show focal staining for vimentin).[17] The most consistent immunohistochemical feature is immuno-expression of the TFE3 protein.[18] Furthermore, the *ASPSCR1–TFE3*-fusion variant in t(X:17)(p11.2;q25) RCC is identical to the genetic change in alveolar soft-part sarcoma (ASPS). However, a study[19] has shown that the genetic pathways to pathogenesis are not necessarily identical in these two diseases. The investigators reported that immunohistochemical expression of the proteins human mutL homologue 1 (hMLH1) and human MutS homologue 2 (hMSH2), which are indicative of the activation status of the corresponding DNA mismatch repair genes *hMLH1* and *hMSH2,* was only patchy in RCC, suggesting that these factors do not have a role in the pathogenesis of translocation RCCs. By contrast, expression of these proteins was reported as positive in ASPS. These immuno-histochemical differences are not a consistent distinguishing feature between *ASPSCR1-TFE3* RCC and ASPS, but do point to a differing pathogenesis between the two diseases.[19]

t(6;11)(p21;q12) translocation tumours

The t(6;11)(p21;q12) translocation has not been fully characterised since its first description in 1996, and only a handful of cases have been reported, which show a less aggressive clinical course compared with Xp11.2-related tumours, many of which present at an advanced stage.[20]

Cells in t(6;11) tumours usually form nests and small acinar-like areas with clear, granular, eosinophilic cytoplasm and round nuclei. Other cells are also seen around hyaline nodules. However, despite this morphology,