

Rare non-Wilms' tumors in children

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Abstract

We report our institutional experience of the management of 2 cases of rare non-Wilms' tumors; a rhabdoid tumor in a 17-month old boy and a clear cell sarcoma in a 5-year old girl. The two patients were treated with ifosfamide/carboplatin/etoposide (ICE) alternating with vincristine/doxorubicin/cyclophosphamide (VDC) and cyclophosphamide/etoposide (CE) alternating with vincristine/doxorubicin/cyclophosphamide (VDC) and radiotherapy, respectively. Both patients showed full response with no significant adverse events. At 2-year follow up, they are disease and relapse free. Although contemporary treatment regimens are very promising, multicenter collaborative studies are needed in order to define a standard treatment for non-Wilms' tumors.

Introduction

Non-Wilms' tumors comprise a rare and heterogeneous group of renal malignancies in children, including renal-cell carcinoma, clear-cell sarcoma, (congenital) mesoblastic nephroma, rhabdoid tumor, and renal medullary carcinoma.¹ Malignant rhabdoid tumor of the kidney (MRTK) is a rare and aggressive pediatric malignancy. It was first identified in 1978 as an unfavorable histological subtype of Wilms' tumor and was eventually distinguished as a distinct pathological entity in 1981.² It accounts for 2% of childhood renal tumors mostly affecting children, predominantly males, under the age of two years.³

Clear cell sarcoma of the kidney (CCSK) is also considered a rare renal childhood malignancy, representing about 3% of pediatric renal tumors, and is associated with an unfavorable prognosis.⁴ It predominantly affects males and shows a tendency for distant metastasis, especially to bones.⁴ Treatment and prognosis of non-Wilms' tumors in infancy and

childhood are considered challenging compared to other pediatric malignancies. Between January 1995 and December 2009, a total of 14 renal tumors were managed in our department. Two of these were non-Wilms' tumors. We report our institutional experience on the management of these 2 cases, a rhabdoid tumor in a 17-month old boy and a clear cell sarcoma in a 5-year old girl, to provide further information about these rare tumors.

Case Report #1

A 17-month old male infant presented with vomiting and concurrent swollen scrotum. There was no significant past medical or family history and his growth and development had been normal. Abdominal ultrasonography demonstrated a huge left-sided intrinsic renal mass. A subsequent abdominal computed tomography (CT) scan confirmed the presence of a large mass arising from the left kidney. A left radical nephrectomy was performed revealing a tumor measuring a maximum 4.2 cm in diameter. Gross examination showed a tumor which was white in color with extensive necrosis, as well as subcapsular fluid collection together with intra-abdominal lymphadenopathy.

Histological examination demonstrated tumor cells with diffuse arrangement, containing eccentric nuclei with large *cherry-red* nucleoli and eosinophilic cytoplasm with paranuclear hyaline inclusions (Figure 1). Immunohistochemical stains showed dot-like cytoplasmic positivity for vimentin and epithelial membrane antigen. There was no positivity for desmin, myogenin, cytokeratins cam5.2 and AE1/AE3, synaptophysin, protein S-100 and antigen CD99. The findings were compatible with malignant renal rhabdoid tumor.

Intra-abdominal lymph nodes were tumor free. Metastatic dissemination was not found on subsequent imaging of the lungs and brain. Initial tumor staging was grade II, based on the NWT5-5 guidelines and the patient did not receive radiotherapy to the tumor bed. He did, however, receive chemotherapeutic treatment with ifosfamide/carboplatin/etoposide (ICE) alternating with vincristine/doxorubicin/cyclophosphamide (VDC). He showed full response with no significant adverse effects. At 2-year follow up, he remains disease and relapse free.

Case Report #2

A 5-year old girl presented with a 6-week history of microscopic hematuria that was initially attributed to urinary infection and received antibiotic treatment. There was no significant past medical or family history and

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her growth and development had been normal. Due to the persistence of hematuria, an abdominal ultrasonography was performed which revealed a large mass arising from the left kidney which was confirmed by abdominal CT. A left radical nephrectomy was performed revealing a tumor measuring 10.5 cm in diameter. The tumor mass was tan-grey in color, composed of small tumor cells with eosinophilic cytoplasm and a mixture of cord cells and septal cells with an extensive capillary network. There were areas with pattern of nests and cords, separated by spaced septa. Immunohistochemical staining was found positive to vimentin and BCL2 and negative to ceratins CAM5.2 and AE1/AE3, EMA, NSE, synaptophysin, CD34, CD117, which is compatible with the diagnosis of a clear cell sarcoma of the kidney (Figure 2). Bone scan was negative for bone metastases. The patient was treated with a regimen of cyclophosphamide/etoposide alternating with vincristine/ doxorubicin/ cyclophosphamide according to the ongoing COG AREN0321 with a minor modification, delivering vincristine and cyclophosphamide with doxorubicin at week 0, rather than administering doxorubicin alone and delaying effective therapy. Radiotherapy at a dose of 10.8Gy was administered at week 1. The patient completed treatment without any adverse events. During a 18-month follow-up period the patient remains relapse and metastases free.

Discussion

Non-Wilms' tumors represent a small proportion of all childhood malignancies and are associated with a poor prognosis. Rhabdoid tumors were initially described as atypical and aggressive variants of Wilms' tumors in early childhood. They are currently regarded as a distinct pathological entity that shares similar clinical and radiological findings with Wilms' tumors. Therefore, histological examination is considered mandatory for correct diagnosis.^{2,5} Moreover, mutation of the hSNF5/INI gene on chromosome 22, considered the hallmark of MRT tumors, and the lack of staining of the INI1 gene product, can help to confirm diagnosis with accuracy. In our cases, diagnosis of MRTK was based on clinical symptoms, radiographic findings and histopathology. Hematuria is a common presenting feature, but symptoms arising from metastases to distant organs are common initial findings as metastases occur in about 80% of patients, most frequently in lungs and brain.^{1,6} Hypercalcemia has also been reported in infants with MRTK.^{7,8} Computed tomography imaging of lungs and brain is recommended as part of the initial evaluation for all children with RTK. More recently, molecular genetics have revealed a mutation of the SMARCB1/hSNF5/INI1 gene which can help confirm diagnosis.⁸

Non-Wilms' tumors are associated with the

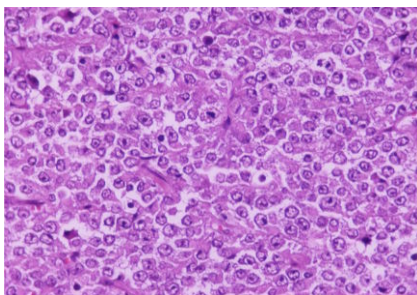


Figure 1. Typical histological features of malignant renal rhabdoid tumor (Haematoxylin & Eosin x400).

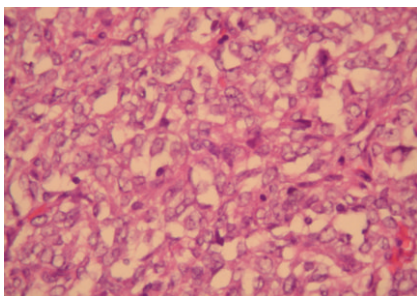


Figure 2. Clear spaces between tumor cells and empty nuclei (Haematoxylin & Eosin x400).

worst prognosis among all neoplasms involving the kidney in early life. Age is an important prognostic factor, and patients under the age of two years have the worst prognosis.⁹ Low stage and the extent of radical surgical excision are also important determinants for long-term survival. Historically, patients with MRTK were treated with National Wilms Tumour Study Group (NWTSG) protocols comprising vincristine, actinomycin and doxorubicin, with or without cyclophosphamide.^{4,10} Unfortunately, reported outcomes from both the NWTSG and SIOP (Society of Pediatric Oncology) protocols are poor. Recent reports have shown encouraging results with a combination of ifosfamide/carboplatin/etoposide (ICE) alternating with vincristine/doxorubicin/cyclophosphamide (VDCy).^{11,12} We followed this protocol and observed a full response and a 2-year period of disease free survival.

Clear Cell Sarcoma of the Kidney (CCSK) represents another rare renal childhood malignancy. It is a distinct clinico-pathological entity from Wilms' tumor. It is more commonly found in males with a peak incidence at 1-4 years of age, usually presenting as an abdominal mass. It shows a propensity to metastasize to the bones.⁴ Addition of doxorubicin to vincristine and actinomycin has shown a beneficial effect on survival according to NWTSG1,2,3,4. NWTSG-3 revealed no improvement in outcome when cyclophosphamide was added to a combination of vincristine, dactinomycin and doxorubicin but it is to be argued that cyclophosphamide was delivered at a relatively low dose and intensity. In NWTSG-5 (now the Children's Oncology Group, COG), patients with CCSK are treated with a protocol consisting of vincristine/doxorubicin/cyclophosphamide (VDC) alternating with cyclophosphamide/etoposide (CE).^{13,14} Our patient (Case Report 2) was treated according to that treatment regimen following nephrectomy combined with postoperative radiotherapy. Treatment outcome was excellent with the patient in remission at 18-month follow up. Nevertheless, metastatic progression or relapse remains a main concern in this patient.

Multicenter collaborative studies are required in order to create a standard for the management of non-Wilms' tumors, as well as to assess the safety and efficacy of new treatment regimens. In addition, long-term toxicity, together with the cost and psychological burden for the patients and their families need to be addressed in modern multimodal intensive therapies of patients with advanced stage disease.

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