UIJ UroToday International Journal®

Chromophobe Subtype Renal Cell Carcinoma in Childhood: A Case Report and Overview of the Literature

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Submitted November 23, 2012 - Accepted for Publication January 6, 2013

ABSTRACT

Introduction: Renal cell carcinoma (RCC) is the most frequent renal tumor in adults, and chromophobe represents the third most frequent subtype, following clear cell and papillary. However, they are extraordinarily rare in childhood, accounting for less than 2% of all renal tumors, and chromophobe subtype in particular is almost anecdotal.

Methods and results: We report the case of a 14-year-old child presenting with hematuria. Imaging tests revealed a large renal mass. After a percutaneous biopsy to exclude other entities, the patient underwent radical nephrectomy with lymphadenectomy and was diagnosed with an eosinophilic chromophobe RCC. At the 6-year follow-up, there was no evidence of recurrence.

Conclusions: RCC in childhood may represent a different entity from adult RCC, with distinct morphologic characteristics and unique genetic abnormalities. The role of the pathologist is crucial, as the diagnosis and classification of RCC in children is still a matter of discussion. New protocols are being tested that will provide more accurate knowledge and therefore may change the clinical management of pediatric RCC.

INTRODUCTION

Renal cell carcinomas (RCCs) are rare in children, accounting for approximately 2% of all new pediatric renal tumors with an annual incidence in children of approximately 4 per million. This is in contrast to the incidence rate in children of Wilms tumor, which is almost 30 times higher. Benign renal masses predominate in early infancy. Beyond the first year of life, Wilms tumor is the most common neoplasm. From adolescence, RCCs occur at a similar or higher frequency than Wilms tumor [1].

The most common subtype of RCC in children is the translocation RCC. A recent, up-to-date review suggests that conventional clear-cell RCCs are extraordinarily rare in childhood; many cases reported as clear RCC are in fact histologically atypical or have morphologic features of translocation RCC [2]. Chromophobe RCC is even less frequent than other RCC types in children, with less than 20 cases reported in the literature during the last 20 years [3-7].

METHODS AND RESULTS

We present the case of a 14-year-old male with no previous personal or familial medical history of interest. He was referred to our department because of a self-limiting episode of hematuria. The patient was feeling generally well, and no other urinary symptoms were reported. Physical examination did not reveal any significant findings. Blood tests were normal except for a lactate dehydrogenase (LDH) level of 1 540 U/L. Ultrasound imaging identified a solid, well-defined 15 cm x 14 cm x 12 cm mass in the upper pole of the left kidney with an area of calcification inside. A subsequent computed tomography (CT) scan revealed that the mass was enhanced with contrast dye and had a low-density central area that suggested necrosis (Figure 1). No evidence of lymphatic or vascular dissemination was

KEYWORDS: Renal cell carcinoma, chromophobe renal cell carcinoma, pediatric oncology

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CITATION: *UroToday Int J*. 2013 February;6(1):art 12. http://dx.doi.org/10.3834/uij.1944-5784.2013.02.12

Figure 1. The CT scan revealed a 15 cm x 14 cm x 12 cm mass in the upper pole of the left kidney that was enhanced with contrast dye and had a low-density central area that suggested necrosis

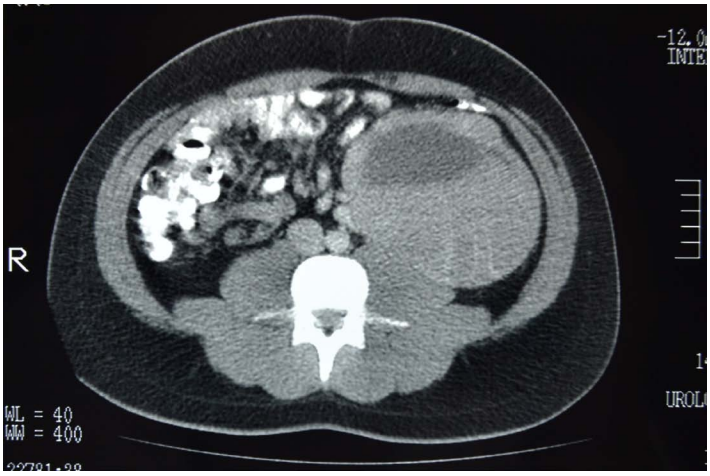
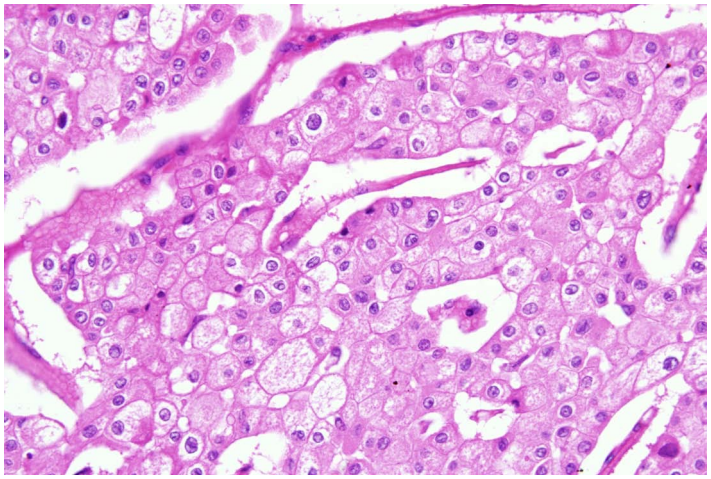
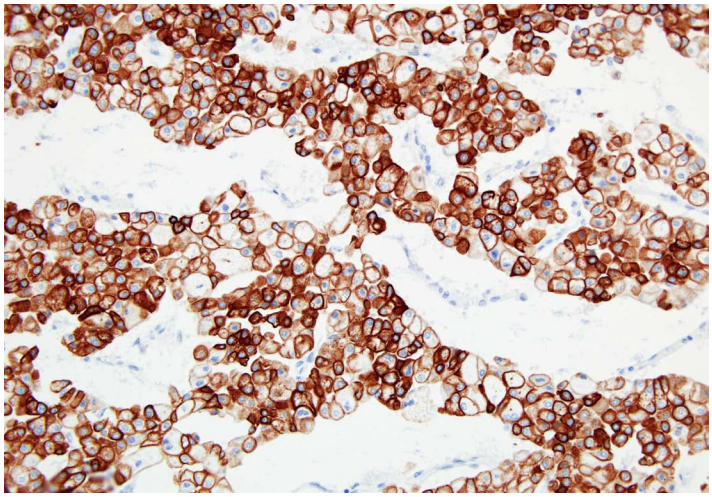


Figure 2. Classical chromophobe RCC findings were observed on hematoxylin-eosin staining: marked nuclear pleomorphism, a rasinoid nuclear membrane, a perinuclear halo, and a prominent cell border.



observed. We performed an ultrasound-guided percutaneous biopsy. Microscopic examination of the specimens excluded Wilms tumor and rhabdoid tumor, and led to a preliminary differential diagnosis between oncocytoma and an eosinophilic variant of renal cell carcinoma. The patient underwent an open left radical nephrectomy with lymphadenectomy (9 nodes). His postoperative course was unremarkable. The pathology examination revealed a chromophobe renal cell carcinoma, eosinophilic variant, Fuhrman grade II with disseminated calcification and necrotic areas (Figure 2 and Figure 3). The kidney-capsule limits were preserved and all regional and paraaortic nodes were free from neoplastic cells (pT2bN0M0). We followed the patient with periodic CT scans and ultrasound imaging. After a 6-year follow-up there was no evidence of local or distant recurrence.

Figure 3. Immunohistochemical staining for cytokeratin 7 is useful for the differential diagnosis with renal oncocytoma. Normally, whereas chromophobe RCCs exhibit strong cytoplasmic staining with peripheral cell accentuation, oncocytomas are entirely negative or show only weak and focal staining.



DISCUSSION

According to the data obtained so far, pediatric RCCs may be a different entity from adult RCCs, with distinct morphologic characteristics, unique genetic abnormalities, and, consequently, a different biology [3,4]. In accordance with this statement, up to 25% of pediatric RCCs cannot be categorized and elude precise classification. For this reason, classification and histologic diagnoses of RCC in children are difficult and remain a source of controversy.

Four subtypes of RCC are typically described in children. The most common subtype is the Xp11 (TFE3) translocation RCC (20 to 40%), followed closely by papillary RCC (30%), which includes types 1 and 2. Translocation RCC may occur following chemotherapy, and papillary RCC may appear in the setting of preexisting neoplasms, such as Wilms tumor, metanephric adenoma, or metanephric adenofibroma. The other two

subtypes are much less common: renal medullary carcinoma, which is a highly aggressive tumor arising in patients with the sickle cell gene; and oncocytic RCC, which has been identified in patients previously diagnosed with neuroblastoma [2]. Chromophobe RCC in children is extremely rare. It is thought to develop from the same type of cells as renal oncocytomas. There are also hybrid tumors with features common to both oncocytoma and chromophobe RCC [2].

Unlike adults, flank pain (55%), hematuria (30%), and abdominal masses (12.5%) are common presenting features of RCC in children. General symptoms such as fever (22%), weight loss (5%), vomiting/nausea (20%), anemia (10%), and malaise (10%) are also frequent. Only 15% of patients do not have specific symptoms at the time of diagnosis [6]. Normally, high levels of serum LDH are found only in cases with large tumors, as was observed in this case.

The mean age of presentation of RCC in children is 10 years. The typical solid intrarenal mass cannot be distinguished from a Wilms tumor in imaging tests. Ring-like calcifications within the mass are characteristic of RCC but are infrequent. A clinically relevant feature for distinguishing RCC from a possible Wilms tumor is the older age of the RCC patient [8]. The need of a percutaneous biopsy for the differential diagnosis is under discussion. It could be useful in the case of planning neoadjuvant chemotherapy for Wilms tumor [9].

RCCs in children normally present as a single lesion. Multifocality is unusual and suggests the presence of associated disorders. Up to one-third of the patients exhibit underlying syndromes such as Von Hippel-Lindau disease, tuberous sclerosis, hereditary leiomyomatosis, familial RCC, or RCC following other neoplasms (rhabdomyosarcoma, neuroblastoma, leiomyosarcoma). Chromophobe RCC may appear as part of 2 genetic syndromes: Birt-Hogg-Dubé syndrome (which can involve multifocal RCC, cutaneous fibrofolliculoma, lung cysts, and spontaneous pneumothorax), associated with the BHD gene; or hereditary pheochromocytoma or paraganglioma syndrome, associated with the SDH gene. It is important to note that RCCs associated with such syndromes are not frequently encountered in childhood but typically appear in adulthood. Some institutions encourage genetic screening when any of the above are suspected, but there is no agreed-upon recommendation about whether to perform a systematic genetic test or screen either the patient or their family members using ultrasound [1].

The higher incidence of regional lymph node involvement seen with pediatric RCC, reported to be between 25 to 33%, compared to 10 to 15% of adult RCC cases is an important distinguishing feature [10]. Thus, radical nephrectomy with lymphadenectomy and metastasectomy is the recommended treatment. In some small series, partial nephrectomy was chosen and exhibited similar results to radical nephrectomy. Nephrologically, this approach should ensure maximal preservation of renal function in patients with obviously extended life spans. Thus, partial nephrectomy could be an option in carefully selected patients with local, low-volume lesions [11]. However, there is not any long-term study in this regard that compares the experience of RCC in adults with children. Therefore, the risk-to-benefit ratio of potentially higher statistical chances of local recurrence will have to be compared to that of contralateral metachronous disease and renal insufficiency related to the functional residual mass after radical vs partial nephrectomy [11]. Additionally, although there are extremely limited reports of laparoscopic or robotic partial nephrectomy for oncologic surgery in children, another consideration should be if these goals could be accomplished with minimal invasiveness [10]. There is no evidence that adjuvant therapy is beneficial in children with positive nodes and no metastatic disease [12,13]. The treatment of non-surgical metastatic cases is as unsatisfactory as it is in adults. Radiotherapy is also not effective, and there are no targeted therapy protocols.

Another major difference between children and adults is the prognostic importance of local node involvement. Whereas adults exhibit a 5-year overall survival (OS) rate of 20%, children have up to a 75% 5-year OS rate when they have node involvement at the time of diagnosis [12]. The almost systematic lymph node dissection in children may in part facilitate such results, as current medical therapies are infrequently curative for unresected disease [10]. Nevertheless, other pathologic parameters typically associated with poor outcomes in adults, such as metastasis, high tumor stage, high Fuhrman nuclear grade, angiolymphatic invasion, and tumor necrosis do not seem to worsen the prognosis in children [14]. These data are in agreement with the hypothesis that pediatric RCCs have a different biology from adult RCCs.

CONCLUSIONS

Chromophobe RCC normally has an excellent prognosis after radical surgery, even when it is locally advanced. It is necessary to be aware of the possibility of underlying syndromes. Biopsy is useful to exclude other diagnoses, such as Wilms tumor, that could benefit from other management strategies. The role of the pathologist is crucial in the diagnosis of RCC in children. Although the limited number of cases and the discrepancy in diagnoses have thus far impeded the development of an adequate standard of care for these patients, new protocols from the Children´s Oncology Group are being tested that will provide more accurate knowledge and therefore may change the clinical management of RCC in childhood [2].

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