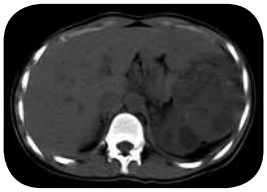

Renal Cell Carcinoma in Pediatric Age. Retrospective Evaluation of a Pediatric Hospital

Carcinoma de células renales en la edad pediátrica. Evaluación retrospectiva en un hospital pediátrico

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Summary

Renal cell carcinoma in childhood is a different disease from the adult›s form and represents around 2 % of all kidney tumors in children. The aim of the work is to show the cases assisted by this disease in our hospital. A retrospective review was performed of cases with renal cell carcinoma treated in our center between 1970 and 2013. 5 children were included (3 females) with an average age of 12.2 years (range 5-17). In 2 cases the affected kidney was the right. Stage: 1 case, stage I; 1 case, stage II; 2 cases, 2 stage III and 1 case stage IV. The first two cases were followed without evidence of disease for six and seven years, they did not go to more controls; the third, currently three years free of illness, the fourth died and the last, two years free of illness. Radical nefrectomy was carried out in the 5 patients. Clear cell was the histologic subtype in 4 cases and papillary in the last one. Many are diagnosed by ultrasound indicated by a different cause. Renal computed tomography is the preferred method of imaging. Nefrectomy continues being the main treatment.

Resumen

El carcinoma de células renales en la infancia es una entidad distinta a la del tipo adulto y representa solo alrededor del 2 % de los tumores renales en niños. Se muestran las características imaginológicas de los casos atendidos por esta entidad en un hospital pediátrico. A partir de una revisión de 43 años se incluyeron 5 niños (3 del sexo femenino) con una edad promedio de 12,2 años, rango de 5 a 17 años. Los hallazgos patológicos arrojaron 4 carcinomas de células claras y uno papilar. Estadio: 1 caso, estadio I; 1 caso, estadio II; 2 casos, estadio III y 1 caso estadio IV. Los 2 primeros casos se siguieron sin evidencias de enfermedad durante 6 y 7 años no acudiendo a más controles; el tercero actualmente 3 años libre de enfermedad, el cuarto falleció y el último, 2 años libre de enfermedad. Debe sospecharse en niños mayores de 5 años con masa renal. Muchos se diagnostican con un estudio ecográfico indicado por otra causa. El método radiológico preferible para su estudio es la tomografía computarizada. La extirpación quirúrgica continúa siendo el tratamiento principal.

Introduction

Renal cell carcinoma (RCC) occurs very rarely in children (1-5). It is recognized as an entity distinct from that manifested in adults, with different morphological characteristics, with genetic abnormalities and, consequently, with a biology and histopathology different from that of the adult (2,4-6). Efforts to clarify this issue are important, as therapeutic recommendations for RCC in children are often taken from experiences in adults. Age-dependent differences may mean different responses to therapy between the two age groups (1,6,7). Although any type of RCC can ap-

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pear at a pediatric age, translocation tumors are specific to it (8-10). In the pediatric age, the most common types are the papillary and the Xp11.2 translocation. The latter predominates in children and adolescents, and is rare in adults. In contrast, clear cells predominate in adults and are less frequent in children (4,7-9,11).

The experience of this disease in children is limited to case presentations or series of relatively few cases (12), hence the importance of being informed. Based on a review of the cases of RCC treated between 1970 and 2013 according to the registry of clinical documentation of the hospital. The characteristics found in five children are exposed.

Case 1. 5-year-old girl. Reason for consultation: fever of 38.5 °C one week evolution. Laboratory results: Hemoglobin (Hb) of 108 g / l; erythrocyte sedimentation rate (ESR) of 55 mm / h and leukocyturia. Urography: Left kidney silhouette enlarged; deformity of the excretory system with downward displacement by tumor of the upper pole of the left kidney (figure 1). Normal thorax Surgical treatment: total nephrectomy. Stage II: T2b N0 M0. Pathological anatomy: clear cell RCC. Non-specific chronic lymphadenitis. Evolution: Follow-up for 6 years free of disease, did not go to more controls.

Case 2. 7-year-old boy. Reason for consultation: Hematuria. Laboratory results: Hb of 105 g / l; VSG of 45 mm / hr. Macroscopic hematuria. Urography: increase in the silhouette of the right kidney; obliteration of the upper calyx of the kidney from its pelvic emergence (figure 2b). Angiography: the right renal artery with a superior concavity arch; its branches appear displaced downwards and limit a wide avascular zone in the upper half of the kidney (figure 2c). Surgical treatment: total nephrectomy. Stage I: T1a N0 M0. Pathological anatomy: clear cell RCC. Evolution: 7 years free of disease, did not go to more controls.

Case 3. Woman of 16 years of age. Reason for consultation: Right lumbar pain with urinary infection crisis. Laboratory results: Hb of 120 g / l; VSG of 60 mm / h. Lactic dehydrogenase (LDH) of 520 U / L. Leukocyturia, microscopic hematuria. Positive urine culture to Escherichia coli. Ultrasound: In the interpolar region of the right kidney a solid tumor of 3 × 3.5 cm with well-defined contours is observed, with calcifications in its interior (figure 3a) that compromises the anterior parenchyma and the sinus, and slightly dilates the calyceal group lower. Liver, pancreas, spleen, suprarenal glands and left kidney of normal structure. There is no regional adenomegaly. Normal inferior vena cava. Urography: Right kidney with moderate dilatation of the collecting system, subtle inferior displacement of the middle calyceal group (figure 3b). Computed tomography (CT): right kidney with mixed density image, maximum diameter 3.5 × 3.8 cm, with calcifications, which distends the capsule, compresses the excretory system and slightly dilates the lower calyceal group, compatible with renal tumor solid (figure 3c). Surgical treatment: total nephrectomy. Stage III: T1a N1 M0. Pathological anatomy: Clear cell renal carcinoma. Evolution: Currently 3 years free of disease.

Case 4. Man of 17 years of age. Reason for consultation: Increase in volume in the left clavicle. Laboratory results: Hb, 90 g/L; ESR, 120 mm/h; LDH, 1527 U/L. Microscopic hematuria Simple chest CT scan: bilateral supraclavicular adenopathies, metastatic infiltration of the medial end of the left clavicle (figure 4a), mediastinal lymph nodes, nodular images in both lungs. Abdominal CT: bulky mass (9 × 12 × 17 cm) that has almost completely replaced the left kidney; with soft tissue density, areas of necrosis or cystic and calcifications that have invaded the ipsilateral peri and pararenal spaces and some segments of the abdominal wall by their lateral and posterior sides (figures 4b and c). Surgical treatment: total nephrectomy. Stage IV: T4 N1 M1. Pathological anatomy: tumor metastasis (right and left supraclavicular) with appearance of renal cell carcinoma. Left kidney: renal cell carcinoma. Papillary variety. Infiltration of perirenal fat. Invasion of the renal vein. Tumoral infiltration of the para-aortic ganglion. Mesenteric ganglion: sinus adenitis, breast dilation. Ureter free of tumor. Evolution: The patient died.

Case 5. Woman of 16 years of age. Reason for consultation: menstrual disorders. Underwent gynecological sonography for dysmenorrhea, which revealed left renal mass, initially interpreted as

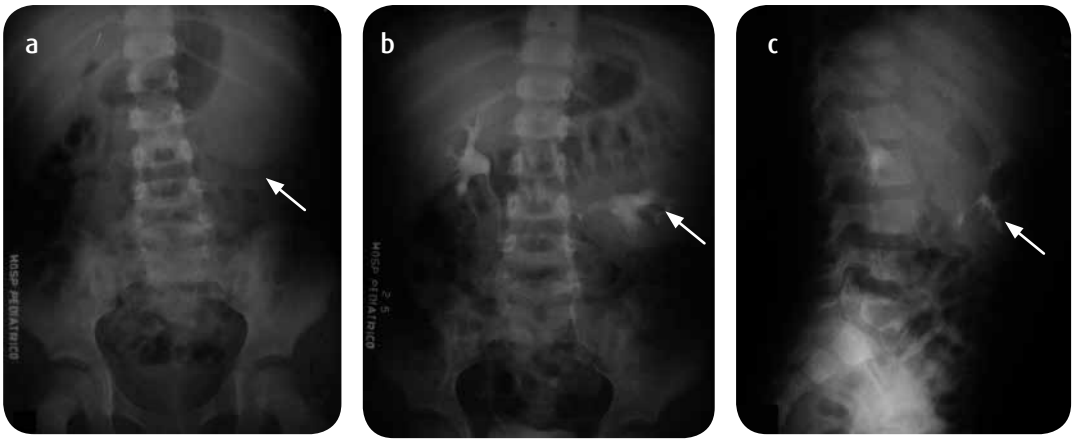

Figure 1. Left RCC in a 5-year-old girl. Stage II. Excretory urography. a) Simple study. Dense mass of soft tissues on the left flank due to nephromegaly. b) 25 minutes after the application of the contrast medium. Deformity and displacement of the excretory system and the left kidney down by tumor of the upper pole. Right kidney morphologically and functionally normal. c) Side view. Left kidney displaced downward and forward with distortion of the pellocalicial system.

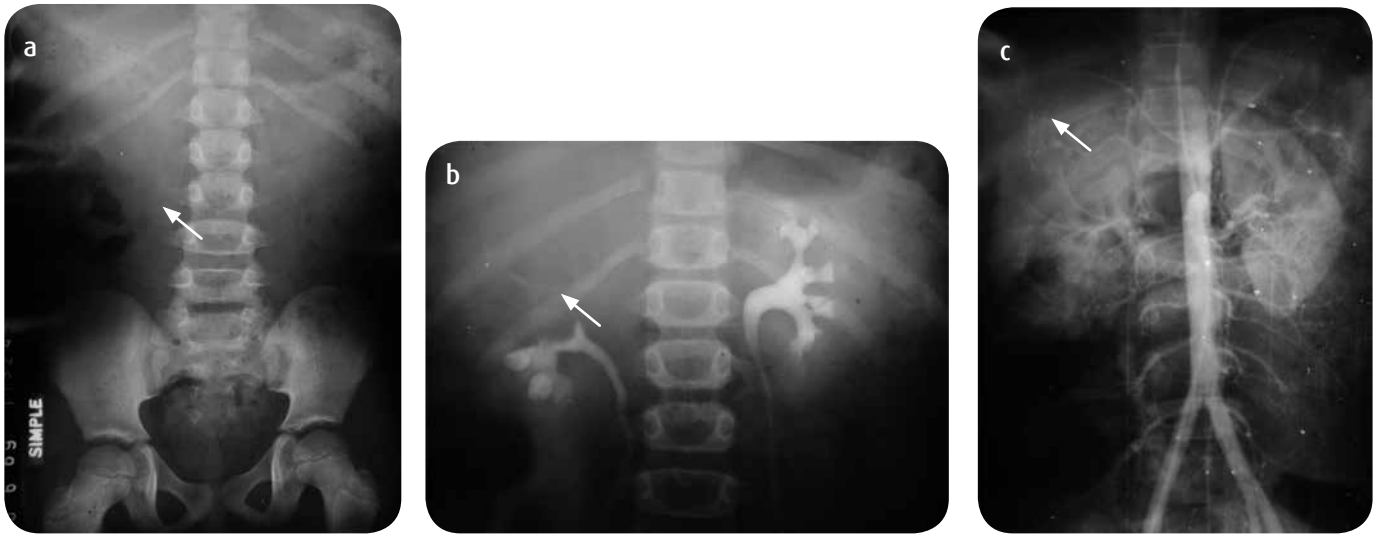

Figure 2. Right RCC in a 7-year-old boy. Stage I. Excretory urography: a) Simple view. Medial displacement of the right psoas by increasing the ipsilateral renal silhouette. b) 25 minutes after the application of the contrast medium. Amputation of the upper right calyceal group in its emergence from the pelvis. c) Angiography: Right renal mass, avascular with smooth surface and well-defined contours with arched displacement of vascular structures.

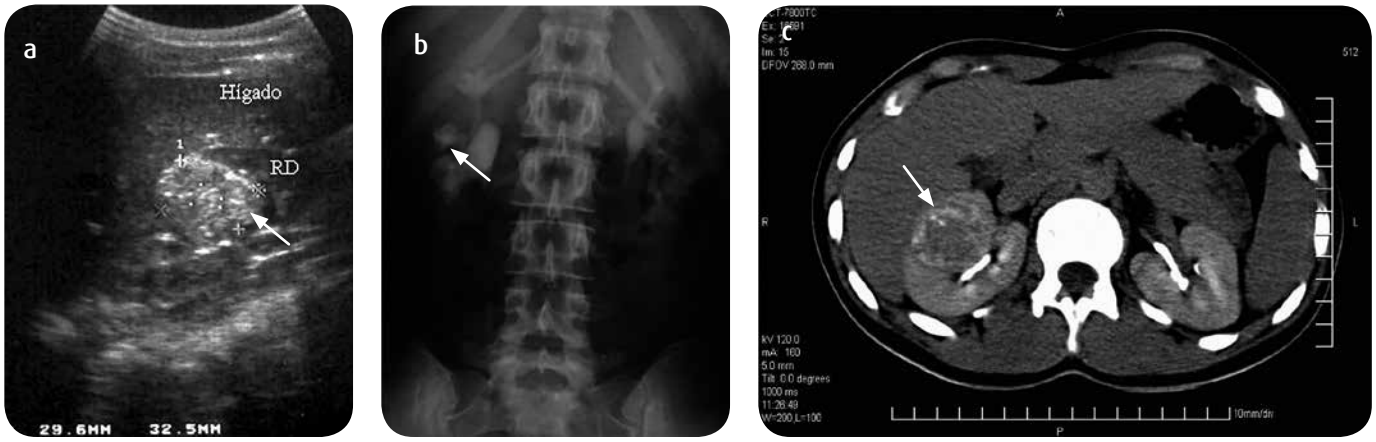

Figure 3. Right RCC in a 16-year-old patient. Stage III. a) Ultrasound: heterogeneous mass in the upper pole-interpolar region. b) Excretory urography: inferior displacement of the middle calyceal group and slight dilatation of the excretory system. c) Renal-CT: study after the application of the contrast medium: mass with heterogeneous enhancement towards the anterior aspect of the superior pole-interpolar region of the right kidney.

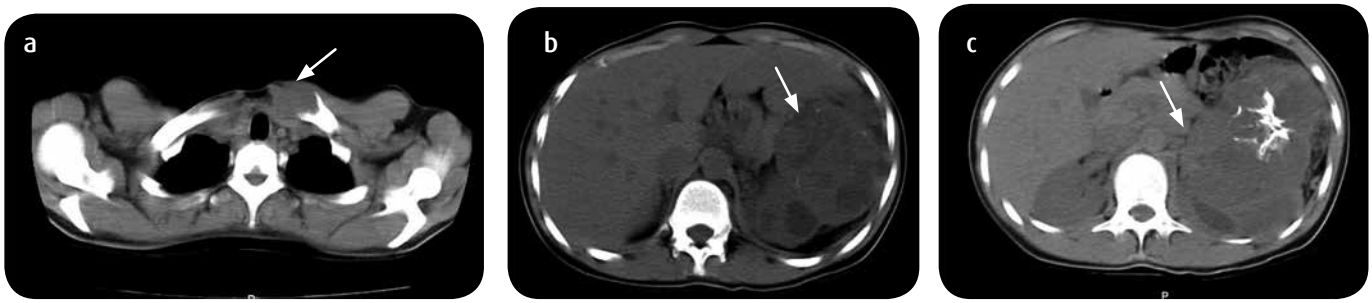

Figure 4. Left RCC in a 17-year-old adolescent. Stage IV. a) Single chest CT. Metastatic infiltration at the medial end of the left clavicle. b and c) Abdominal CT before application of contrast medium. Bulky mass in the left kidney with heterogeneous soft tissue density, with areas of necrosis or cystic and with calcifications.

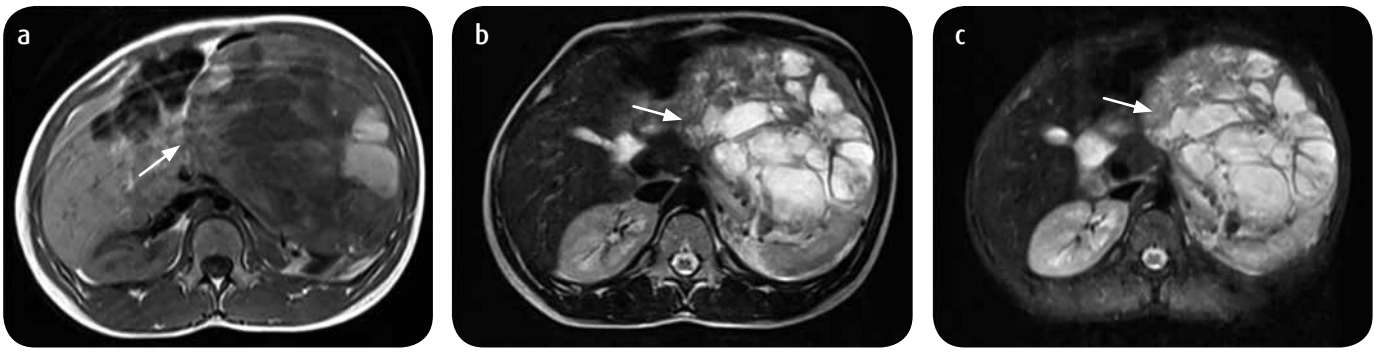

Figure 5. Left RCC in a 16-year-old patient. Stage III. MRI a) sequences with information T1 b) T2 and c) T2 with fat suppression. Large heterogeneous left renal tumor with areas of low signal with T1 information and high signal suggesting hemorrhages and intratumoral cystic lesions.

cystic dysplasia; it is sent for evaluation in our center, where the ultrasound suggests the tumor origin. Laboratory results: Hb, 102g/l; ESR, 73 mm/h; LDH, 780 U/L. Microscopic hematuria Magnetic resonance imaging (MRI): a large, well-encapsulated heterogeneous left renal mass that arises from the interpolar region and replaces a large part of the kidney with fundamentally anterior growth, exceeding the midline and compresses and displaces neighboring structures without infiltrating them, with areas of low signal and high signal in sequences with information in T1 suggestive of hemorrhages and intratumoral cystic lesions (figure 5). Surgical treatment: total nephrectomy. Stage III: T2b N1 M0. Pathological anatomy of the left kidney and left ureter: renal cell carcinoma. Tumor lesion composed of solid areas, multiple cystic cavities, papillae and abundant calcifications. Infiltration of a hilar ganglion. Tumor cells in the lumen of an artery of the renal hilum. No infiltration of perirenal fat is observed. Ureter without alterations. Evolution: 2 years free of disease.

Discussion

When the first two cases of this series were studied, ultrasound, MRI and CT techniques were not yet available. Between 1970 and 2011, only two cases had been seen in the hospital, the third was treated 41 years after the first, and the last three in a period of 2 years, between March 2011 and May 2013; the first two occurred during childhood and the last, in adolescence.

When evaluating children with renal masses, genetic predispositions and congenital syndromes with cancer risk or associated with it must be investigated (6). They constitute conditions associated with RCC: Von Hippel-Lindau disease, tuberous sclerosis, familial RCC, renal medullary carcinoma, rare subtype associated with sickle cell anemia; hereditary leiomyomatosis and a second neoplasm (1,4,13,14). Four of the ten pediatric RCC found by Downey et al. (1) and 16 of the 49 Selle et al. (15) —corresponding to the total registered in Germany in 25 years— had a recognized risk factor for the development of the RCC; in the cases of this series no hereditary background was found associated with the appearance of the tumor.

Among 46 RCC in children, Qiu and collaborators (5) found clear cells as the least frequent (nine cases). Selle (15), on the other hand, found only three of 49; while four of the cases found by the authors of this work corresponded to this histological stock. Due to the low incidence of these tumors, their differences with the adult type and the complexity and variability of their histological appearance, the work of children's pathologists must be assisted with immunohistochemical procedures for the study of antibody expressions and also with the study of genetic alterations (8).

The RCC can remain hidden for a good part of its course (6,16); in the cases of this series, similar behavior was observed. Three of them were diagnosed from nonspecific signs and symptoms, one in a metastatic stage with no clinical suggestive up to that point. Of the five cases, only one appeared at the early stage (4 cm cystic lesion with 1 cm nodule) with frank hematuria; the other case with small tumor (3 cm) was diagnosed by ultrasound during the study of a urinary tract infection and the remaining three reached the range of voluminous disease. The most common symptoms and signs in this entity are hematuria, fever, low back pain, weight loss and kidney tumor. The classic triad of flank pain, hematuria and palpable mass (16,17) was not found in the cases studied. Between 25 and 30% of patients are asymptomatic at the time of diagnosis and the carcinoma is incidentally in an imaging study, mainly by ultrasound (1), as in cases 3 and 5 of this series. Other signs and symptoms are: weight loss, fever, hypertension, night sweats, malaise and varicocele, usually left (16). The average age of the cases was 12 years, 2.5 months with a range of 5 to 17 years; VSG (ESR) did not rise significantly except in the case of bone metastasis; LDH was evaluated only in the last three cases and it was found to be elevated exclusively in the two tumors with the largest tumor size.

The information provided by the image is of paramount importance in the early diagnosis. The differentiation between benign or malignant lesion, the size and extension assessment, as well as for the decision making on the therapy, both localized and systemic disease; similarly, it is useful for assessing the degree of response to treatment.

Although a variety of examinations (ultrasound, excretory urography, MRI, angiography) can be used in the diagnosis, renal CT is the preferred method (1,16,17). In most cases, with only this test, the RCC stage can be diagnosed and determined and information for surgical planning can be provided without additional imaging studies, a concept in which the authors fully agree with Downey (1) and Purysko (17). Nuclear medicine techniques and CT in other parts of the body (for example, in thorax) are useful to establish the stage.

RCC has a very variable imaging appearance and there are very few published data on this aspect in children and adolescents; similarly, the diagnostic accuracy of imaging modalities in pre-treatment staging, which is of great importance in the establishment of the prognosis and in the decision of the appropriate treatment, is not well known in these ages (1). In ultrasound it can be iso-, hypo- or hyperechoic (1,17). Small lesions with less necrosis are more likely to appear with high echogenicity, as in the third of the cases studied (figure 3a). In the simple phase of CT, the tumor may appear low density, as in the fourth case of this series (figure 4b), also of low and high density; In addition, calcifications can be defined as in the fourth case studied (figure 4c). After administration of the contrast medium (figure 3c) they usually enhance between 10-20 Hounsfield units, (1,18,19). The volume of the tumor is an important criterion that influences any surgical decision; the definition of "small" in the adult refers to tumors smaller than 5 cm, while, it is difficult to define a diameter in children, given the considerable differences in the size of their kidneys (7); Downey and colleagues (1) found in their cases a maximum tumor diameter that ranged between 1.5 and 12.6 cm, while in this series that range was between 3.8 and 17 cm. In MRI (1,18,19) the RCC usually appears with medium or high signal in sequences with T1 information while in sequences with T2 information they are commonly high signal, often heterogeneous, as in the fifth case of this series (figures 5a and 5b). The necrosis or hemorrhage (figure 5) can modify the characteristic signal intensities.

Despite being usually smaller and calcified up to 25%, the imaging appearance of RCC can be indistinguishable from Wilms' tumor; Although the latter is the most common malignant renal malignancy in children, the differential diagnosis is extensive and includes benign and malignant lesions (1,3).

From the elements studied it is concluded that RCC is rare in pediatric age and should be suspected in children over 5 years of age with renal mass. The objective is to identify patients with resectable tumor. The information provided by the image is of cardinal importance. They can be diagnosed by an ultrasound study indicated by another cause. The preferred radiological method for evaluation is CT.

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