

Clear - cell renal carcinoma: review of literature in pediatric population

Carcinoma renal de células-claras: revisão bibliográfica na população pediátrica

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Abstract

Introduction: The first reports of renal tumors originated from the renal tubule epithelium date from 1855, Robin, and 1867, Waldeyer. However, at the same era, some pathologists wrong believed these tumors were originated from adrenal gland tissues due to the fat content of the tumor (hypernephroid tumor theory - origin above the kidney, 1894). The first diagnostic test for renal tumor was excretory urography. Over the years, with the emergence of ultrasonography (US), it has been replaced. Nowadays, after the US screening, all renal lesions should be evaluated, in a complementary way, with computed tomography (CT) - gold standard - in the pre-contrast, arterial, portal, nephrographic phases. This is necessary to characterize the presence of enhancement after contrast. A kidney injury that enhances more than 15 Housfield units (UH) is suspected of kidney cell cancer. There are different subtypes of renal tumors derived from various sites of the nephron. Clear cell Renal Cell Carcinoma (RCC) is one of the subtypes that originates from the renal cortex. It is a rare tumor in children. **Objective:** The aim of this chapter is to review de incidence, pathology, diagnosis and treatment in clear-cell renal carcinoma in pediatric population. **Methods:** The authors performed a literary review about clear-cell renal carcinoma in pediatric population using Pubmed Database and Campbell-Walsh Urology as source search.

Keywords: Renal cell carcinoma, Tumor, Pediatrics, Kidney, Nephrectomy

Resumo

Introdução: Os primeiros relatos de tumores renais originados do epitélio do túbulo renal datam de 1855, Robin, e 1867, Waldeyer. Contudo, na mesma época, alguns patologistas acreditavam erroneamente que esses tumores provinham dos tecidos das glândulas supra-renais, devido ao teor de gordura do tumor (hypernephroid tumor theory - origem acima do rim, 1894). O primeiro teste diagnóstico para tumor renal foi a urografia excretora. Ao longo dos anos, com o surgimento da ultrassonografia, esse teste foi substituído. Atualmente, após a leitura da ultrassonografia, todas as lesões renais devem ser avaliadas, de forma complementar, com tomografia computadorizada (TC) - padrão ouro - nas fases pré-contraste, arterial, porta e nefrográfica. Isso é necessário para caracterizar a presença de melhora após contraste. Uma lesão renal que aumenta mais de 15 unidades Housfield (UH) é suspeita de câncer de células renais. Existem diferentes subtipos de tumores derivados de vários locais do néfron. O carcinoma de células renais de células claras (CCR) é um dos subtipos originários do córtex renal. É um tumor raro em crianças. **Objetivo:** O objetivo deste capítulo é revisar a incidência, a patologia, o diagnóstico e o tratamento do CCR na população pediátrica. **Método:** Os autores realizaram uma revisão literária sobre carcinoma renal de células claras em população pediátrica usando a base de dados PubMed e o livro Campbell-Walsh de Urologia como fonte de pesquisa.

Palavras chave: Carcinoma de células renais, Tumor, Pediatria, Rim, Nephrectomia

Introduction

The first reports of renal tumors originated from the renal tubule epithelium date from 1855, Robin, and 1867, Waldeyer. However, at the same era, some pathologists wrong believed this tumors were originated from adrenal gland tissues due to the fat content

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of the tumor (hypernephroid tumor theory - origin above the kidney, 1894)⁽¹⁾.

Microscopically

From 1883 to 1928, several pathologists expanded the study of renal tumors to what is known today: there are different subtypes, derived from various sites of the nephron (clear cell and papillary variant are originated from proximal convoluted tubules; while chromophobe and collecting duct carcinoma are derived from the more distal components of the nephron). Each one has different biological and genetical bases⁽¹⁾.

Microscopically, it resembles renal tubules, and four major patterns of growth have been described: papillary, solid, cystic, and sarcomatoid. The papillary subtype predominates in children⁽¹⁾.

Clear cell Renal Cell Carcinoma (RCC) originates from the proximal convoluted tubules epithelium (renal cortex) and presents a predominantly expansile growth pattern.

Macroscopically

Macroscopically, it is a solid, yellowish lesion with variable degrees of internal necrosis, hemorrhage and cystic degeneration. Such findings are most frequently observed in large-volume, fast-growing tumors. Tumor calcifications may also be found (FIGURE 1).

Histologically, such lesions present clear cells because of their lipid- and glycogen-rich cytoplasmic content⁽²⁾. Frequently, such tumors also present eosinophil granular cytoplasm cell⁽²⁾.

Renal cell carcinoma is rare in pediatric population and the incidence is estimated in 0.1-0.3 % of all neoplasm and 1.8 - 6.3 % of malignant renal tumors⁽²⁾. It has the same incidence in male and female. Mean age presentation in children is 9-10 years. It corresponds to 1.4% of renal tumors in patients under 4 years old, between 5 and 9 years incidence is 15.2% and 52.6% between 10 and 15 years old⁽³⁾. In the second decade of life, it is as common as Wilms tumor. Since 1986, approximately 160 well-documented cases have been published in the literature⁽⁴⁾.

The more often seen subtype of RCC in children is renal medullary carcinoma; it occurs in patients with sickle cell disease and hemoglobinopathies. The mean age at presentation is 13 years or younger and its mortality is higher.

Despite the risk factors observed in adults (obesity, smoking, dialysis, hypertension, abuse of nonsteroidal anti-inflammatory drugs, syndromes such as tuberous sclerosis, radiotherapy for testicular tumors), there is no such correlation in children⁽³⁾.

Objective

The aim of this chapter is to review the incidence, pathology, diagnosis and treatment in clear-cell renal carcinoma in pediatric population.

Methods

The authors performed a literary review about clear-cell renal carcinoma in pediatric population using Pubmed Database and Campbell-Walsh Urology as source search.

Results

A) Genetic Association

Renal cell carcinoma in adults is often associated with tuberous sclerosis complex or the von Hippel-Lindau disease. RCC with nonpapillary histology is associated with translocations or terminal deletions of the short arm of chromosome 3 beginning at 3p13. This chromosomal 3p cytogenetic abnormality is uncommon in pediatric patients with RCC⁽⁴⁾. Several children with RCC associated with Von Hippel-Lindau syndrome or tuberous sclerosis have been reported⁽⁵⁾.

Using immunohistochemical staining, recent studies have reported Xp11.2 translocations in 20% to 70% of pediatric RCC⁽³⁾. There is also translocation related with PRCC-TFE3 gene and X chromosomes, which leads to overexpression of TFE3 protein in children and young adults. These findings can be related to different response to some chemotherapeutic agents (Table 1)^(1, 6-7).

B) Pathology

Renal cell carcinoma is circumscribed by a pseudo capsule of fibrous tissue. There is a classification of nuclear components which is based on nuclear size, shape and presence or absence of nucleoli. These features were gathered into a system graduation nominated Fuhrman's system, which is also an independent prognostic and predictor of outcome factor for clear cell renal carcinoma (Table 2)⁽⁸⁾.

C) Diagnosis

Renal cell carcinoma in children and young adults is more likely to be asymptomatic. About 50% to 68% of RCC patients are diagnosed incidentally. When the children is symptomatic, the tumor generally is advanced and has worst prognosis. The most common form of presentation of RCC in children is macroscopic hematuria and abdominal or flank pain. Other less

Table 1

Modified from 2004 World Health Organization histologic classification of RCC^(1,6-7).

Cytogenetic findings in Histologic Subtypes of RCC

Histologic subtype	Cytogenetic Findings
Clear cell RCC	3p deletions, von Hippel-Lindau gene mutations
Von Hippel - Lindau RCC	3p25-26
Papillary RCC	Trisomy of chromosomes 7 and 17, loss of Y chromosome
Hereditary papillary RCC syndrome	7q34 chromosome abnormality
Chromophobe RCC	Loss of multiple chromosomes: 1,2,6,10,13,17,21
Collecting duct carcinoma	Loss of multiple chromosomes: 1,6,14,15,22; gain of chromosome 3
Medullary carcinoma	Extracellular matrix gene loss
Mucinous tubular and spindle cell carcinoma	Loss of multiple chromosomes:1,4,6,8,13,14
Neuroblastoma-associated RCC	Multiple gene loss
Xp11,2 translocatio-TFE3 carcinoma	Translocations involving Xp 11,2

Table 2

Fuhrman's classification system in RCC⁽⁸⁾.

Grade	Nuclear Size	Nuclear Feature	Nucleoli
1	10 uM	Round and uniform	Absent
2	15 uM	Irregular	Small
3	20 uM	Irregular	Prominent
4	> 20 uM	Bizarre, mutilobed	Prominent with heavy chromatin clumps present

frequent symptoms are palpable abdominal mass, anemia, and fever⁽⁹⁻¹²⁾. Stachowicz-Stencel et al reported that 52.4% of pediatric RCC cases were asymptomatic and diagnosed during routine examination⁽¹⁰⁾. Paraneoplastic phenomena in adults are common and well reported but they are infrequently documented in children.

The complete clinical triad (gross hematuria, palpable mass, and flank pain) is seen in only 6% to 9% of affected children⁽⁵⁾.

Metastatic disease at presentation has the same incidence both children and adults. Lung and bone are the most common distant lesions and they are usually fatal⁽⁴⁾.

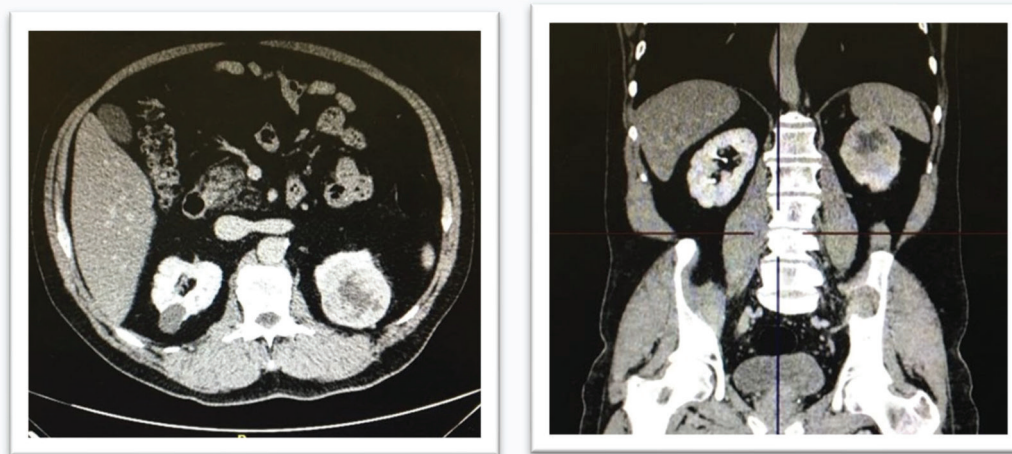


Figure 1. CT revealed a 7cm mass with high attenuation at the upper pole of left kidney. After contrast administration, the tumor was enhanced heterogenously (Fig. 1b)

D) Staging

Staging is based on Robson modified staging classification system. Stage I is disease confined by the renal capsule. Stage II disease invading renal capsule but confined by Gerota's fascia. Stage III is divided into A (involvement of renal vein or inferior vena cava) and B (regional lymph node involvement). Stage IV is metastatic disease (Tables 3 and 4)^(1,13).

Table 3

Renal carcinoma staging TNM (modified from Virchows Arch. 2018;472(4):519–31)⁽¹³⁾.

T: PRIMARY TUMOR

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1a	Tumor ≤4 cm and confined to the kidney
T1b	Tumor >4 but ≤ 7 cm and confined to the kidney
T2a	Tumor >7 but ≤ 10 cm and confined to the kidney
T2b	Tumor >10 cm and confined to the kidney
T3a	Tumor extends into the renal vein or its segmental branches, or tumor invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota fascia
T3b	Tumor extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota fascia I including contiguous extension into the ipsilateral adrenal gland)

N: REGIONAL LYMPH NODES

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

M: DISTANT METASTASIS

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

E) Radiological Exams

The first diagnostic test for renal tumor was excretory urography. Over the years, with the emergence of ultrasonography, it has been replaced. Ultrasound (USG) is a simple, low cost examination with good screening capability for potentially malignant lesions, in that it can differentiate solid lesions from cystic, characterize septa and calcifications, evaluate cystic

Table 4

Staging renal cell carcinoma. (modified from Campbell-Walsh 11 th edition, p. 1337)⁽¹⁾.

STAGE GROUPING

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	Any N	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

density and suggest greasy content. After the ultrasound, screening, renal lesions should be evaluated in a complementary way with computed tomography (CT) - gold standard - in the pre-contrast, arterial, portal, nephrographic phases (Figure 2). This is necessary to characterize the presence of enhancement after contrast. A kidney injury that enhances more than 15 Housfield units (UH) is suspected of kidney cell cancer.

However, up to 20% of the findings may be inconclusive, requiring other interventions. Magnetic resonance imaging is the alternative radiological modality, especially to those allergic to contrast. Evaluation of the enhancement is done by injection of gadolinium-labeled diethylenetriaminepentaacetic acid. Nephrogenic systemic fibrosis is a direct complication of contrast injection and occurs most commonly in patients with chronic kidney disease (Table 5).

Table 5

Possibilities of renal tumor presentation

Clear-cell renal carcinoma: image presentation
Complex cystic mass
Solid mass with intensive enhancement
Solid mass with moderate enhancement
Multifocal or bilateral mass
Calcified mass

F) Treatment

Treatment depends on tumor stage. In stage I, surgery can be curative. The completeness of the surgical resection with radical nephrectomy has been shown to be a significant prognostic factor, with survival rates as low as 10% after incomplete resection, given that current adjuvant medical therapies are not typically curative for unresected disease^(3, 12, 14).

If children present lymph node involvement, the resection may be useful to control tumor growth and staging. Depending on size and metastatic loca-

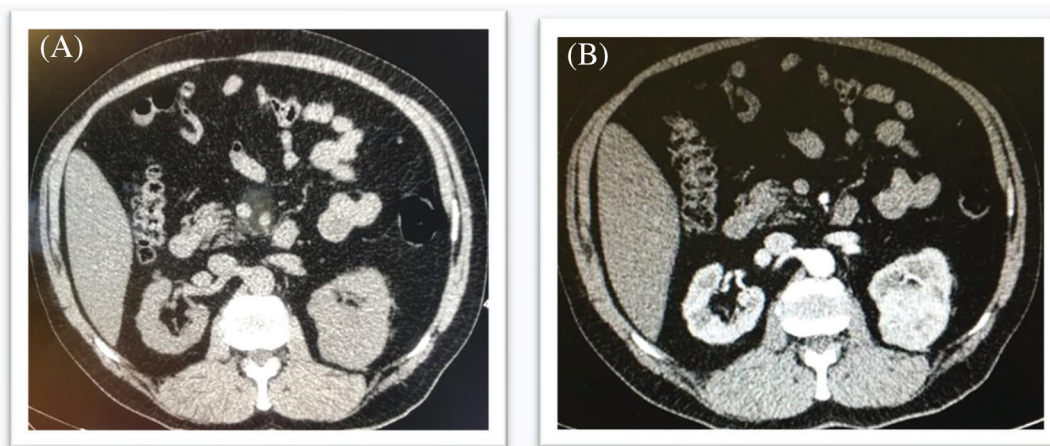


Figure 2. A - CT scan without contrast. B - Enhance of more than 15 HU is suggestive of clear cell carcinoma.

tion, it can be also useful to resect metastatic sites (metastectomy)⁽¹⁵⁾.

Immunotherapy based on interleukin-2 (IL-2) and interferon- alfa were used in the past to the treatment for advanced disease (stage III and IV), mostly used in combination. VEGF (vascular endothelial growth factor) inhibitors, mTOR inhibitors and monoclonal antibodies are currently gold standart in treatment of adult advanced tumors, with few literature based on evidence in its use for children. Table 6 represents combinations of targeted therapies in renal cell carcinoma⁽¹⁶⁻¹⁷⁾.

Chemotherapy with vincristine, vinblastine, actinomycin D, cisplatin, gemcitabine, and 5-FU are related with sucess in only a few cases, especially if related to renal medullary carcinoma^(2, 12). Cisplatin toxicity may lead to decreased creatinine clearance, hypomagnesemia, renal tubular acidosis.

Patients in stage II can be treated with radiotherapy of 2,000- 6,000 cGY to the renal bed and para-aortic region with and without chemotherapy.

Table 6

Ecog trial. Bevacizumab and other three drugs

Drug	Dose
Bevacizumab	10 mg/kg every 2 weeks
Temsirolimus + bevacizumab	25 mg/week + 10 mg/kg every 2 weeks
Bevacizumab + sorafenib	5 mg/kg every 2 weeks + 200 mg twice daily, 5 days weekly
Temsirolimus + sorafenib	25 mg weekly + 200 mg twice daily

G) Prognosis

The main prognosis factors are tumor stage and size, vascular invasion, age, location, celular sub-

type. However, tumor stage appears to be the most important factor for the survival⁽³⁾. Reports of RCC found overall survival rate of 56- 64% in pediatric population, which can be improved to 66.6% the use of adjuvant chemotherapy and radiotherapy. Regional lymph node involvement does not have the same poor prognosis as adult RCC.

Five years survival is more than 90% for patients with stage 1, 50-80% for patients with stages 2 (which is better than adult population) and 3 and less than 10% for stage 4⁽³⁾. Most recurrences occur in 2 years after diagnosis and the lung and liver are the sites that should receive careful monitoring⁽⁴⁾. There are recurrences described after 15 months from the time of diagnosis⁽⁴⁾.

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