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Renal clear cell sarcoma in the pediatric age: differential diagnosis and management.

ABSTRACT

Renal clear cell sarcoma is the second most frequent malignant renal tumor in pediatric age, after Wilms' tumor. It is a difficult to diagnose neoplasm, with nonspecific clinical presentation as palpable abdominal mass, abdominal pain and hypertension and hematuria. The imaging characteristics of this lesion are non-specific, so its diagnosis is made by anatomopathological study of the tumor. Its importance revolves around the diagnostic difficulty, since this tumor presents great histologic variability and few adequate immunohistochemical markers. Treatment includes neoadjuvant and post-surgical chemotherapy, with a prognosis that improves if the disease is diagnosed early.

Key words: sarcoma; renal neoplasms; pediatrics; adjuvant chemotherapy; surgery.

INTRODUCTION

Renal cancer accounts for 7% of renal neoplasms in children (1), a non-negligible percentage of solid tumors in this organ. Clear cell sarcoma (CCS) is the second most frequent renal cancer in this age group, preceded by nephroblastoma, also called Wilms' tumor (2), which accounts for 2-5% of renal neoplasms in this population. SCC predominates between 2 and 4 years of age, being infrequent before 6 months of age or in adulthood. It is characterized by being more frequent in males, in a 2:1 ratio (2).

Previously, it was thought to be a variant of nephroblastoma due to its nonspecific histology. It was not until 1970, when Kidd recognized it for the first time as a neoplasm distinct from nephroblastoma (3). This difference was recognized mainly because of its high incidence of bone metastasis (4). It was named SCC by Beckwith and Palmer, due to the presence of multiple intracytoplasmic vesicles (3).

The importance of this entity revolves around its difficult diagnosis, which often relegates it to the oblivion of the pathologist who manages pediatric tumors. This is dangerous because it is an aggressive tumor with a tendency to recur. In spite of being a generally symptomatic disease, characterized by abdominal pain, arterial hypertension and hematuria, these symptoms are non-specific and are shared with other renal tumors (2). At the anatomopathological level it has been a challenge, since it does not present a typical histological pattern; nor are there specific immunohistochemical markers for its diagnosis (5).

Differentiation from other renal neoplasms is essential for timely treatment; the difficulty in histologically distinguishing SCC from other

renal tumors such as nephroblastoma, mesoblastic nephroma, primitive neuroectodermal tumor or renal rhabdoid tumor, could result in inadequate or delayed treatment (5,6). The aim of this article is to carry out a bibliographic review of the most relevant findings in the diagnosis of SCC, as well as of the updates in its treatment, in order to clarify with the published evidence the difficulties in the timely diagnosis of this etiology.

METHOD

A systematic literature search was performed in Pubmed, Cochrane, Scielo and Google Scholar databases, using keywords such as "renal sarcoma" and "clear cell", combined with "clinical"，"diagnosis" and "treatment".

Articles published between 2014 and 2019 were selected. There was restriction on the language of the publications, only those written in Spanish, English and German that met the criteria described above were used.

Duplicates were eliminated. In addition, a manual search was made in the reference lists of the articles initially chosen to expand the available information. We reviewed the publications

selected through the analysis of the abstract and full text and the most relevant and outstanding ones were identified.

CLINIC

Clinically, CCS is usually symptomatic. Its main manifestation is usually palpation of an abdominal mass, usually associated with abdominal pain and hematuria (7). Other symptoms such as hypertension, vomiting, fever, constipation, anorexia or bone pain, due to metastases, are usually less frequent (8). It is characterized by presenting as a unilateral solid renal mass, with a cystic component. It frequently crosses the midline due to its size and it is unusual for it to present calcifications (7).

A considerable percentage of cases present metastasis at the time of diagnosis, the most common sites being lymph nodes (59%), bone (13%), lungs (10%) and liver (9%) (9). At the bone level, lytic lesions, sclerotic lesions or both are frequently observed (7).

DIAGNOSIS

No imaging method has been able to distinguish any distinctive or reliable feature to differentiate SCC from other pediatric renal tumors. Therefore, the diagnosis is made by anatomopathological and immunohistochemical study (4).

The International Society of Pediatric Oncology for Renal Tumors (SIOP- RTSG), developed in 2016 a protocol called UMBRELLA for the diagnosis, treatment and follow-up of childhood renal tumors. Recommendations for the diagnosis of SCC according to this protocol and the reviewed literature are summarized below (2,5,10).

ANATOMOPATHOLOGY

Macroscopically, it is observed as a soft, single,

large, pale gray mass that distorts the normal kidney, mainly located in the renal medulla and may contain cysts, hemorrhage and/or necrosis (2,4,8,11). SCC has highly variable histology and can mimic other pediatric renal tumors, so its histologic diagnosis can be very difficult.

This high morphological diversity, together with the scarcity of appropriate and specific tumor markers, is responsible for the diagnostic delay and for the fact that up to 22% of SCCs are initially diagnosed as other renal tumors (3-6,8,12).

The most frequent histological pattern, known as the classic variant, consists of ovoid cells with uniform chromatin and eccentric cytoplasm with multiple vesicles, arranged in trabeculae, separated by spaced and arborized fibrovascular septa with thin-walled capillaries within these septa, frequently described as a chicken wire pattern (4,7,8,11,13).

The other histologic patterns are: myxoid (50%), sclerosing (35%), cellular (26%), epithelioid (13%), spindle (7%), spindle cell (4%), and anaplastic (2.6%). The pattern variant does not identify prognostic correlation. The anaplastic pattern is defined as enlarged and hyperchromatic nuclei accompanied by abnormal mitosis, frequently found as a focal finding and presents immunoreactivity for the p53 protein (3,4).

Until very recently no immunohistochemical marker had proven to be useful in the diagnosis of SCC, presenting moderate immunoreactivity to vimentin and weak positive for actin, however, it has recently been found that the nerve growth factor receptor (NGFR) is a sensitive but non-specific marker for SCC (4,10,13).

Although the molecular pathology of SCC is still poorly understood, it is described that it has not been associated with syndromes or genetic predisposition, and currently no cases of familial SCC have been reported (1,6).

Gene expression analysis demonstrated the activation of genes involved in the Sonic Hedgehog (SHH) pathway, increased expression of nerve growth factor, as well as genes involved in neural development, SHH and nerve growth factor (NGF) have synergistic action and promote different events, including neural stem cell proliferation and tumor cell initiation and progression (6).

Currently, three categories are known according to the genetic alteration:

- The first: 85% have internal tandem duplications of the X-linked BCL-6 repressor gene (BCOR) that codes for the repressor complex that is mutated or translocated in human cancers, this finding has significant implications for future diagnostic and therapeutic approaches (5,11,14,15).
- The second category corresponds to 12% of SCC and is the t(10;17) (q22;p13) translocation involving the YHWAE and NUTM2B genes, however it has not been

possible to study the clinical phenotype of these cases (1,6,11,15).

- The third category corresponds to the minority of SCCs and are double negatives, which do not have any of the described mutations (15).

Table 1 International Society of Pediatric Oncology staging criteria for renal neoplasms**.**

Stadium	Criteria
1	l Tumor restricted to the kidney and completely resectable. l No evidence of renal vessel involvement.
	l Tumor extends beyond the kidney or its pseudocapsule, however, it is completely resectable. l Infiltration of renal sinus, blood vessels or renal lymphatics, but it is completely resectable. l Local extension into the vena cava. l No evidence of tumor tissue beyond the resection margins.
	At least one of the following: ¡ Evidence of tumor tissue beyond the margins of resection or macroscopically incomplete excision. ¡ Abdominal lymph node involvement. ¡ Tumor rupture prior to or during surgery. ¡ o Gradual elimination of intravascular tumor thrombus.
	l Hematogenous or distant lymphatic metastasis.
5	l Bilateral renal involvement at diagnosis.

Source: Chong WC, Cain JE. Lessons learned from the developmental origins of childhood renal cancer. Anat Rec. 2019;(March):1-17.

SCC can mimic the myxoid variant of synovial sarcoma, and with double positivity for CD99 and TLE1 was sufficient to rule out SCC, however, in 2018 a SCC presenting positivity for these markers was reported for the first time, so currently, when in doubt, histopathological assessment is necessary (15).

IMAGE STUDIES

Due to the low sensitivity and specificity of these studies for the diagnosis of SCC, their usefulness has been reserved for prognostic assessment and post-diagnostic follow-up.

A brain MRI is recommended due to the high risk of brain metastasis of this tumor, especially in relapses, where 40% of these are located at the cerebral level.

Whole-body positron emission tomography is recommended, as bone is one of the most common sites of metastasis (10,12).

GENETIC COUNSELING

It is not considered necessary to refer cases of SCC to a clinical geneticist because no syndromic association or familial cases have been reported (10).

However, recent molecular studies have characterized different mutations, including BCOR, TLE1, YWHAE-NUTM2B/E, TCF21, among others (5,6,14,15).

STAY

SCC, like other renal neoplasms, is classified into stages according to its presentation at the time of diagnosis, based on the criteria established by the International Society of Pediatric Oncology (**Table 1**).

Most cases are found in stages 1, 2 or 3; only 6 to 7% of children diagnosed with this neoplasm are found in stage 4 (4).

According to the Fifth National Wilms' Tumor Study (United States), at the time of diagnosis of SCC:

- 25% are in stage I
- 37% in stage II
- 34% in stage III
- 4% in stage IV

Only three cases of stage V (bilateral renal involvement) have been reported worldwide (9).

DIFFERENTIAL DIAGNOSIS

It is necessary to distinguish SCC from other typical primary renal tumors of childhood, for example: Wilms tumor (nephroblastoma), renal rhabdoid tumor and congenital mesoblastic nephroma, whose characteristics are described in **Table 2** (4).

Despite its low prevalence, CCS should be a differential diagnosis of any renal mass in the pediatric population, and it should not be forgotten that these patients may present with spontaneous bleeding (8).

TREATMENT

According to several studies and the UMBRELLA protocol, the mainstay of treatment is surgical resection of the tumor (1,4).

The UMBRELLA protocol includes chemotherapeutic regimens that have been shown to be useful in maintaining and improving survival in patients with localized SCC.

In addition, it aims to selectively decrease the intensity of standard therapy to minimize severe short- and long-term toxicity (4,10).

GENERAL RECOMMENDATIONS

According to the UMBRELLA protocol, it is ideal to continue treating patients between 6 months and 16 years of age with localized SCC with preoperative chemotherapy, actinomycin and vincristine, while patients with metastatic disease are recommended to be treated with actinomycin and doxorubicin.

Doxorubicin is also recommended as a postoperative regimen in all patients with SCC, as it has been shown to produce a significant improvement in outcome; however, with the aim of decreasing the cardiotoxicity of this drug, maximum cumulative total doses of 250mg / m2 in localized disease and 300mg/m2 for metastatic disease are recommended, as listed in **Table 3** (1,4,10).

Table 2 Differential diagnosis of clear cell sarcoma**.**

Tumor	Clinic	Macroscopic	Microscopic	Mutations
SCC	Severe abdominal pain, hypertension and hematuria.	Soft mass in renal medulla, which may be associated with hemorrhage or necrosis.	Ovoid cells, with clear cytoplasm and dispersed chromatin often arranged in cords, separated by a fibrovascular septum, positive for vimentin, cyclin D1, BCOR and NGFR, negative for epithelial membrane antigen.	YWHAE-NUTM2B BCOR

Nephroblastoma	Commonly asymptomatic.	Solitary lesion restricted to a single kidney, sometimes accompanied by necrosis, hemorrhage or cysts.	It presents monophasic, biphasic or triphasic morphology containing stromal, epithelial or blastemal elements, and may contain muscle, fat, bone or cartilage.	WT1, CTNNB1, WTX, DROSHA, DGCR8, SIX1, SIX2, MYCN, CREBBP, BRD7, HDAC4, TP53
Renal Rhabdoid Tumor	Asymmetric lower abdominal growth with hematuria	Multilobulated tumor mass with curvilinear calcifications. It may be associated with hemorrhage or necrosis.	Discohesive cells with prominent eosinophilic nuclei. Positive for CD99 and vimentin.	SMARCB1, SMARCA4
Congenital mesoblastic nephroma	Palpable abdominal mass, hematuria, hypertension, polyhydramnios	Non-encapsulated infiltrating tumor mass, with a spiral appearance.	Dense myofibroblastic cells, traversed by collagen fibers.	ETV6-NTRK3
Source: Chong WC, Cain JE. Lessons learned from the developmental origins of childhood renal cancer. Anat Rec. 2019;(March):1-17.				

Overview of the treatment of clear cell sarcoma according to stage.				
Stadium	Preoperative chemotherapy	Local resection surgery	Postoperative chemotherapy	Abdominal radiotherapy
I	AV	Yes	Isofosfamide alternating with cyclophosphamide, doxorubicin, etoposide and carboplatin.	No
II	AV	Yes	Isofosfamide alternating with cyclophosphamide, doxorubicin, etoposide and carboplatin.	Depending on the case
III	AV	Yes	Isofosfamide alternating with cyclophosphamide, doxorubicin, etoposide and carboplatin.	Depending on the case
IV	AVD	Yes	Isofosfamide alternating with cyclophosphamide, doxorubicin or vincristine, etoposide and carboplatin	Yes
Note: AV: Actinomycin + Vincristine, AVD: Actinomycin, vincristine and Doxorubicin. In the "Guideline for Radiotherapy" chapter of the UMBRELLA protocol, the cases in which radiotherapy is recommended for stage II and III patients are detailed.				
Source: Gooskens SL, Graf N, Furtwangler R, Spreafico F, Bergeron C, Ramirez-Villar GL, et al. Rationale for the treatment of children with CCSK in the UMBRELLA SIOP-RTSG 2016 protocol. Nat Rev Urol [Internet]. 2018;15(5):309-19				

Regardless of the stage of the disease, all patients should be treated postoperatively with alternating ifosfamide and cyclophosphamide in combination with etoposide, carboplatin and doxorubicin, to decrease nephrotoxicity

and to continue with treatments that penetrate the central nervous system, as the brain remains the primary site of metastasis.

(1,4,10) .

RECOMMENDATIONS FOR THE TREATMENT OF METASTATIC DISEASE

For patients with stage IV disease, hematogenous or lymphatic metastases outside the abdomino-pelvic region following preoperative chemotherapy, surgical resection of the metastases is recommended, regardless of the therapeutic response to preoperative chemotherapy or surgical treatment; radiotherapy is indicated in all cases with stage IV (1,10).

When the maximum cumulative dose of doxorubicin (300mg/m2) is exceeded, it will be replaced by vincristine to avoid cardiotoxicity (1,4,10).

RECOMMENDATIONS FOR THE TREATMENT OF RECURRENT DISEASE

Intensive treatment including chemotherapy, local control by surgery and radiotherapy appears to increase the survival of patients with recurrent SCC.

In addition, treatment with high-dose chemotherapy (melphalan at 200mg/m2 for one hour) followed by autologous stem cell transplantation appears to be valuable, although further studies are needed (10,13).

MONITORING AND FORECASTING

There is currently no record of any studies on surveillance in patients with SCC after completion of treatment, however, cohort studies support that relapses can occur up to 8 years after initial diagnosis, so surveillance even after 5 years from diagnosis is necessary.

Because the brain and bone are the most frequent sites of relapse, a complete neurological examination and MRI of the whole body is recommended during follow-up (9,10).

SCC has a markedly worse prognosis than Wilms tumor, particularly in patients younger than 1 year of age. Relapses occur in 20% to 40% of patients. Overall survival at 5 years is close to 90% and for stage I disease it is almost 100%, so early diagnosis and management are key points in this pathology (4,7,9,12,13).

CONCLUSIONS

In the literature review, it was observed that despite being a rare mesenchymal neoplasm in pediatric age, its aggressiveness and the possibility of recurrence and metastasis make the diagnosis of SCC a major problem.

Its clinical presentation is nonspecific, as are its imaging findings, so it must be ruled out in the histopathological examination of all renal masses in pediatrics.

This is at the same time a challenge for the pathologist, since it presents great histologic variability and few useful immunohistochemical markers.

Its diagnosis is difficult, since in many patients there are metastases in the initial evaluation, which worsens the prognosis for this group. Differential diagnosis with Wilms tumor is of utmost importance, since the treatments for both are very different. Due to advances in molecular pathology and the mutations detected, it is possible that immunotherapy treatments may be the best therapeutic option in the future. Currently, the UMBRELLA protocol is an international therapeutic proposal to improve toxicity and prognosis in patients with this diagnosis.

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