Cancer Association of South Africa (CANSA)

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Fact Sheet on Childhood Clear-Cell Sarcoma of the Kidney

Introduction

Sarcoma is a type of cancer that occurs in connective tissue (such as tendons), supportive tissue (such as bones), and soft tissue (such as muscle). Only about 1% of adults with cancer suffer from sarcoma, but 15% of children with cancer suffer from sarcoma. About one-quarter of children with sarcomas have a wide variety of soft tissue sarcomas, most of which are more commonly diagnosed in adults.

[Picture Credit: Sarcoma]

Due to the diversity of sarcoma types, they can be particularly challenging to diagnose accurately and thus treat appropriately.

Although they are often called *Paediatric Sarcomas* because of their prevalence in children, they can occur in adults as well. When children are diagnosed with cancer, they have special needs. This means that the entire family is affected in a way that is not altogether true for adults with cancer.

Childhood Clear-Cell Sarcoma of the Kidney (CCSK)

Clear cell sarcoma of the kidney (CCSK) is a rare type of kidney cancer comprising 3% of all paediatric renal tumours. Clear-cell sarcoma of the kidney can spread from the kidney to other organs, most commonly the bone, but also including the lungs, brain, and soft tissues of the body. Despite the similarities in names, *clear-cell sarcoma of the kidney* is unrelated to clear-cell sarcoma of soft tissue, also known as malignant melanoma of soft parts.

This tumour may recur many years after its initial diagnosis. The average age at diagnosis is 2 to 4 years. External tumours histologically identical to CCSK have been reported in rare instances. This tumour may be confused with other paediatric renal tumours including blastemal-predominant Wilms' tumour, malignant rhabdoid tumour, and cellular mesoblastic nephroma.

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Several histologic variants of CCSK are recognised. The most common variant is the Myxoid CCSK. The nuclear accumulation of p53 in anaplastic tumours is thought to represent evidence of p53 gene mutation, a finding that has been well-documented in anaplastic Wilms' tumours.

The frequency of different CCSK variants include:

- Myxoid pattern (50%)
- Sclerosing pattern (35%)
- Cellular pattern (26%)
- Epithelioid pattern (trabecular or acinar type) (13%)
- Palisading (verocay-body) pattern (11%)
- Spindle cell pattern (7%)
- Storiform pattern (4%)
- Anaplastic pattern (2.6%)

Aldera, A.P. & Pillay, K. 2020.
"Clear cell sarcoma of the kidney is an uncommon malignant pediatric renal neoplasm that typically presents in the 2- to 3-year age group and has a propensity for aggressive behavior and late relapses. Histologically, this tumor exhibits a great diversity of morphologic patterns that can mimic most other pediatric renal neoplasms, often leading to confusion and misdiagnosis. Until recently, adjunct immunohistochemical and molecular genetic tests to support the diagnosis were lacking. The presence of internal tandem duplications in BCL-6 coreceptor (*BCOR*) and a translocation t(10;17) creating the fusion gene *YWHAE-NUTM2B/E* have now been well accepted. Immunohistochemistry for BCOR has also been shown to be a sensitive and specific marker for clear cell sarcoma of the kidney in the context of pediatric renal tumors. Improved intensive chemotherapy regimens have influenced the clinical course of the disease, with late relapses now being less frequent and the brain having overtaken bone as the most common site of relapse."

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Aw, S.J. & chang, K.T.E. 2019.
"Clear cell sarcoma of the kidney is the second most common primary renal malignancy in childhood. It is histologically diverse, making accurate diagnosis challenging in some cases. Recent molecular studies have uncovered BCOR exon 15 internal tandem duplications in most cases, and YWHAE-NUTM2 fusion in a few cases, with the remaining cases having other genetic mutations, including BCOR-CCNB3 fusion and EGFR mutations. Although clear cell sarcoma of the kidney has no specific immunophenotype, several markers including cyclin D1, nerve growth factor receptor, and BCOR

(BCL6 corepressor) have emerged as potential diagnostic aides. This review provides a concise account of recent advances in our understanding of clear cell sarcoma of the kidney to serve as a practical update for the practicing pathologist."

Incidence of Childhood Clear-Cell Sarcoma of the Kidney
The South African National Cancer Registry (2017) does not provide any information regarding the incidence of childhood clear-cell sarcoma of the kidney.

Signs and Symptoms of Clear-Cell Sarcoma of the Kidney (CCSK)
The signs and symptoms of CCSK are very similar to that of Wilms' tumour and include:

A lump or mass in the abdomen of an otherwise well child.

- Abdominal pain
- Blood in the urine (haematuria)
- High blood pressure
- Fever
- Diarrhoea
- Weight loss
- Urogenital infections

Diagnosis of Clear-Cell Sarcoma of the Kidney
Manifestations in patients with clear cell sarcoma of the kidney (CCSK) are similar to those in patients with Wilms' tumour. Patients present with an abdominal mass, which is usually identified by a caregiver or family relative who has not seen the child in some time.

Often, abdominal swelling or the presence of an abdominal mass is noticed by a parent while bathing or dressing the child. Abdominal pain, gross haematuria, fever, and hypertension are other frequent findings.

Physical findings include a large palpable unilateral abdominal mass. Patients may have accompanying findings, such as hypertension and/or haematuria (gross or microscopic), depending on the size of the tumour. Extrarenal tumours with histologic features identical to those of clear-cell sarcoma of the kidney have been reported.

Khan, M.Z., Akhtar, N., Hassan, U. & Mushtaq, S. 2020.
Purpose. Clear cell sarcoma of the kidney (CCSK) is an uncommon malignant renal tumor. It is the second most common renal pediatric renal malignancy after Wilms tumor. It exhibits a heterogeneous morphology, with overlapping features with its close differentials, which results in diagnostic challenges. There was no specific immunohistochemical marker in the past, to help in this regard. BCOR antibody has recently been suggested to be helpful in the differential diagnosis. We aim to study the utility of the BCOR antibody in the diagnosis of CCSK.

Methods. We selected a total of 27 cases of CCSK (n = 12), Wilms tumor (n = 12), and congenital mesoblastic nephroma (n = 3). All cases were evaluated for the extent and intensity of nuclear labeling for BCOR antibody by immunohistochemistry (IHC).
Results. We found that BCOR IHC was positive in 11 out of 12 cases with diffuse and strong staining in 8 of the cases. None of the cases of Wilms tumor and congenital mesoblastic nephroma were positive. Only 2 cases of Wilms tumor showed minimal and weak staining in <5% of cells.
Conclusion. Diffuse and strong nuclear staining for the BCOR antibody is highly specific for CCSK among common pediatric renal malignancies. Our study confirms that BCOR IHC is a good IHC marker for the diagnosis of CCSK.

Chen, S., Li, M., Li, R., Cao, J., Wu, Q., Zhou, T., Cai, Z. & Li, N. 2020.
Background: Clear cell sarcoma of the kidney (CCSK) is a rare malignant tumor in children with uncertain histologic and immunohistologic traits. It mostly reveals atypical clinical symptoms similar to other familiar pediatric renal neoplasms, including abdominal mass, abdominal pain, hematuria, etc. Therefore, the lack of specificity in clinical symptoms may induce some challenging and controversial diagnoses.
Methods: Three cases of CCSK were acquired data from the First Affiliated Hospital of Bengbu Medical College (China) in recent years, accompanied by clinical symptoms and imaging manifestations without obvious specificity, while abdominal mass and abdominal pain were described as the main manifestations; even the initial clinical diagnosis of one case was Wilms Tumor (WT). Two of them underwent a radical nephrectomy. All 3 cases were detected by hematoxylin-eosin (H&E) staining and immunohistochemistry.
Results: Microscopic examination demonstrated the tumor component consisted of loose, locally dense tumor stroma and parenchyma composed of round or oval cells, which were separated by dendritic fibrosis. Afterwards, the unified immunophenotype were positive for Cyclin D1, Bcl-2, Vimentin, SATB-2, α-AACT, and Ki-67 (+, 30%, 40% and 80%, respectively).
Conclusion: Pathologic diagnosis of the disease should be comprehensively analyzed by multiple methods. More abundant morphologic, immunohistological, clinical and radiologic data can contribute to rigorous diagnosis and more accurate clinical treatment.

Treatment of Childhood Clear-Cell Sarcoma of the Kidney (CCSK)
The approach for treating clear-cell sarcoma of the kidney (CCSK) is different from the approach for Wilms' tumour because the overall survival of children with clear-cell sarcoma of the kidney remains considerably lower than that of patients with favourable-histology Wilms' tumour.

In the third National Wilms' Tumour Study (NWTS-3), the addition of doxorubicin to the combination of vincristine, dactinomycin, and radiation therapy resulted in an improvement in disease-free survival in patients with clear-cell sarcoma of the kidney.

NWTS-4 showed that patients treated with vincristine, doxorubicin, and dactinomycin for 15 months had an improved relapse-free survival rate compared with patients treated for 6 months (87.5% vs 60.6% at 8 y). The overall survival has improved for patients with clear- cell sarcoma of the kidney from NWTS-3 to NWTS-4 (83% vs 66.9% at 8 y). The 8-year relapse-free survival rate for localisd clear-cell sarcoma of the kidney stages I-III is 88%, but late relapses have been known to occur. In the NWTS-5 protocol, patients with all stages of CCSK are treated with the same regimen used in patients who have Wilms' tumour with diffuse anaplasia (excluding stage I);[1]this treatment consists of a radical

nephrectomy followed by radiotherapy and chemotherapy with cyclophosphamide, etoposide, vincristine, and doxorubicin for 24 weeks.

In the NWTSG series that was reviewed by Argani *et al*, a better prognosis was indicated in the subset of patients with clear-cell sarcoma of the kidney that was characterised by stage I tumours in patients aged 2-4 years in whom no tumour necrosis was identified.

In the current Children's Oncology Group protocol (AREN0321), all patients with clear-cell sarcoma of the kidney, except patients with stage IV, continue treatment as in NWTS-5. However, patients with stage I who undergo lymph node sampling do not undergo radiation therapy to the tumour bed. Any patient with stage I who has not undergone lymph node sampling is upstaged to stage II. Patients with stage IV undergo treatment with irinotecan and vincristine in an upfront window approach before treatment with cyclophosphamide, etoposide, vincristine, doxorubicin, and cyclophosphamide.

Surgical Care - at presentation, radical nephrectomy is the initial treatment of choice if the lesion is resectable. If the size or extension of the lesion is in question, a biopsy is performed, and chemotherapy is administered, followed by surgical resection after a response has been obtained

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Sources and References Consulted or Utilised

Aldera, A.P. & Pillay, K. 2020. Clear cell sarcoma of the kidney. *Arch Pathol Lab Med*. 2020 Jan;144(1):119-123.

Aldera, A.P. & Pillay, K. 2019. Clear cell sarcoma of the kidney. *Arch Pathol Lab Med*. 2019 Mar 27. doi: 10.5858/arpa.2018-0353-RS. [Epub ahead of print]

Atlas of Genetics and Cytogenetics in Oncology and Haematology
http://atlasgeneticsoncology.org/Tumors/t1017ClCellSarcID5412.html

Aw, S.J. & chang, K.T.E. 2019. Clear cell sarcoma of the kidney. Arch Pathol Lab Med. 2019 Jan 10. doi: 10.5858/arpa.2018-0045-RS. [Epub ahead of print]

Chen, S., Li, M., Li, R., Cao, J., Wu, Q., Zhou, T., Cai, Z. & Li, N. 2020. Clear cell sarcoma of the kidney in children: a clinopathologic analysis of three cases. *Int J Clin Exp Pathol*. 2020 Apr 1;13(4):771-777. eCollection 2020.

Children's Oncology Group
https://childrensoncologygroup.org/index.php/in-treatment-for-kidneywilms-tumor?id=192

Furtwängler, R., Gooskens, S.L., van Tinteren, H., de Kraker, J., Schleiermacher, G., Bergeron, C., de Camargo, B., Acha, T., Godzinski, J., Sandstedt, B., Leuschner, I., Vujanic, G.M., Pieters, R., Graf, N. & van den Heuvel-Eibrink, M.M. 2013. Clear cell sarcomas of the kidney registered on International Society of Pediatric Oncology (SIOP) 93-01 and SIOP 2001 protocols: a report of the SIOP Renal Tumour Study Group. *Eur J Cancer*. 2013 Nov;49(16):3497-506. doi: 10.1016/j.ejca.2013.06.036. Epub 2013 Jul 20.

Iver, V.K., Agwarwala, S. & Verma, K. 2005. Fine-needle aspiratioan cytology of clear-cell sarcoma of the kidney: study of eight cases. *Diagn Cytopathol*. 2005 Aug;33(2):83-9.

Khan, M.Z., Akhtar, N., Hassan, U. & Mushtaq, S. 2020. Diagnostic utility of BCOR antibody in clear cell sarcomas of kidney. Int J Surg Pathol. 2020 Aug;28(5):477-481.

Medscape
http://emedicine.medscape.com/article/993245-clinical
http://emedicine.medscape.com/article/993245-treatment

National Cancer Institute
http://www.cancer.gov/clinicaltrials/learningabout/what-are-clinical-trials

O'Meara, E., Stack, D., Lee, C.H., Garvin, A.J., Morris, T., Argani, P., Han, J.S., Karlsson, J., Gisselson, D., Leuschner, I., Gessler, M., Graf, N., Fletcher, J.A. & O'Sullivan, M.J. 2012. Characterization of the chromosomal translocation t(10;17)(q22;p13) in clear sarcoma of kidney. J Pathol. 2012 May;227(1):72-80. doi: 10.1002/path.3985. Epub 2012 Feb 17.

Sarcoma
https://littlefighterscancertrust.wordpress.com/2014/07/09/july-is-international-sarcoma-awareness-month/

Sarcoma Alliance
http://sarcomaalliance.org/what-you-need-to-know/children-with-sarcoma/

Sudour-Bonnange, H., Dijoud, F., Leclair, M.D., Rocourt, N. & Bergeron, C. 2016. Clear cell sarcoma of kidney in children. 2016. *Bull Cancer*. 2016 Apr;103(4):402-11. doi: 10.1016/j.bulcan.2016.01.017. Epub 2016 Feb 28.

The Liddy Shriver Sarcoma Initiative
http://sarcomahelp.org/clear-cell-sarcoma.html

Wikipedia
https://en.wikipedia.org/wiki/Clear-cell_sarcoma_of_the_kidney