

Solid Tumour Section

Review

Kidney: t(10;17) in clear cell sarcoma of the kidney

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Identity

Other names: bone metastasizing renal tumor of childhood

Clinics and pathology

Disease

Clear cell sarcoma of the kidney (CCSK) is a malignant renal tumor of childhood with a propensity to metastasize to bone and other organs. This tumor may also recur many years after its initial diagnosis. The average age at diagnosis is 2-4 years. CCSK is unrelated to the clear cell sarcoma of the soft tissue, also known as malignant melanoma of soft parts. Extrarenal tumors histologically identical to CCSK have been reported in rare instances. This tumor may be confused with other pediatric renal tumors including blastema-predominant Wilms' tumor, malignant rhabdoid tumor, and cellular mesoblastic nephroma.

Phenotype stem cell origin

Undifferentiated mesenchyme.

Embryonic origin

Mesoderm

Etiology

The tumor is composed of undifferentiated cells as illustrated by its relative lack of immunohistochemical reactivity. Its gene expression profile with a lack of WT-1 mRNA transcripts and elevated levels of IGF-2 mRNA further suggest that the tumor arises from an undifferentiated renal stem cell. Most studies fail to implicate the involvement of the p53 tumor suppressor gene.

Epidemiology

CCSK comprises 5 percent of primary pediatric renal tumors with the peak incidence in the second year of

life; however, patients' ages have ranged from 2 months to 54 years. Adult cases are extraordinarily rare. CCSK does not appear to be associated with genetic syndromes like Wilms' tumor (i.e. WAGR, Beckwith-Wiedemann, and Denys-Drash syndromes). Males appear to be more commonly affected than females. The National Wilms' Tumor Study (NWTS) has classified CCSK as one of the most common of the prognostically unfavorable histology tumors (others being anaplastic Wilms' tumor and malignant rhabdoid tumor of the kidney).

Clinics

The usual presentation of CCSK is a child with a flank mass with or without hematuria much like the typical signs and symptoms associated with Wilms' tumor. Abdominal pain and fever may also occur. In some instances, patients present with pathologic fractures due to metastatic tumor.

Pathology

Grossly, the tumor arises within the renal medulla has a mass of up to 3,000 grams. On cut section, the tumor is usually white-tan to gray and has a firm texture and is sharply defined from the surrounding renal parenchyma. Histologically, the classical CCSK (features present at least focally in over 90% of tumors) is composed of nests and cords of cells with scant cytoplasm and high nuclear-cytoplasmic ratios. The tumor has a prominent vascular network that may be highlighted with Ulex European I lectin or monoclonal antibodies specific for factor VIII or CD31. Adundant collagenous (sclerotic) extracellular matrix material is also a common finding in classical CCSK. The nuclei are characterized by a fine chromatin pattern and mitotic figures are generally rarely identified. Isolated nephrons are entrapped by the tumor. CCSK may be confused with Wilms' tumor, mesoblastic nephroma, and malignant rhabdoid tumor of the kidney.

Several histologic variants of CCSK are recognized. The most common variant is the myxoid CCSK. This histology features diffuse accumulation of mucopolysaccharide matrix material between tumor cells sometimes creating a cystic appearance. The sclerosing variant of CCSK is characterized by prominent collagen bundles that may isolate single or small groups of tumor cells in a dense matrix that may become hyalinized. The cellular pattern of CCSK is characterized by less extracellular matrix material between cells with overlapping of nuclei, a feature that may lead to confusion with a blastemal predominant Wilms' tumor or primitive neuroectodermal tumor. Mitotic activity is usually increased in this variant. The epithelioid CCSK variant may be confused with nephroblastoma due to condensation of tumor cell cords. The palisading pattern is described as having spindle cell nuclei in parallel linear arrays alternating with nuclear free zones, a feature that resembles Verocay bodies of schwannomas. The spindle cell and storiform patterns are relatively uncommon. Anaplasia is a rare finding in CCSK (3% of cases), and is characterized by the presence of enlarged, hyperchromatic polypoid nuclei with multipolar mitotic figures. The nuclear accumulation of p53 in anaplastic tumors is thought to represent evidence of p53 gene mutation, a finding that has been well-documented in anaplastic Wilms' tumors. The frequency of different CCSK variants is listed below:

- 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%).

Immunohistochemistry is rarely informative in CCSK. Immunoreactivity for the intermediate filament vimentin is usually present, however, reactivity with most other proteins including epithelial markers are negative.

Like other renal tumors of childhood, CCSK is staged by the National Wilms' Tumor Study staging scheme as follows:

Stage I (25% of CCSK): For stage I tumors, 1 or more of the following criteria must be met:

Tumor is limited to the kidney and is completely excised.

The surface of the renal capsule is intact.

The tumor is not ruptured or biopsied (open or needle) prior to removal.

No involvement of renal sinus vessels.

No residual tumor apparent beyond the margins of excision.

Stage II (37% of CCSK): For Stage II tumors, 1 or more of the following criteria must be met:

Tumor extends beyond the kidney but is completely excised.

No residual tumor apparent at or beyond the margins of excision.

Any of the following conditions may also exist:

Tumor involvement of the blood vessels of the renal sinus and/or outside the renal parenchyma.

The tumor has been biopsied prior to removal or there is local spillage of tumor during surgery, confined to the flank.

Stage III (34% of CCSK): For Stage III tumors, 1 or more of the following criteria must be met:

Unresectable primary tumor.

Lymph node metastasis.

Positive surgical margins.

Tumor spillage involving peritoneal surfaces either before or during surgery, or transected tumor thrombus.

Stage IV (4% of CCSK): defined as the presence of hematogenous metastases (lung, liver, bone, or brain), or lymph node metastases outside the abdomen/pelvic region.

Stage V (not yet reported for CCSK): defined as bilateral renal involvement at time of initial diagnosis.

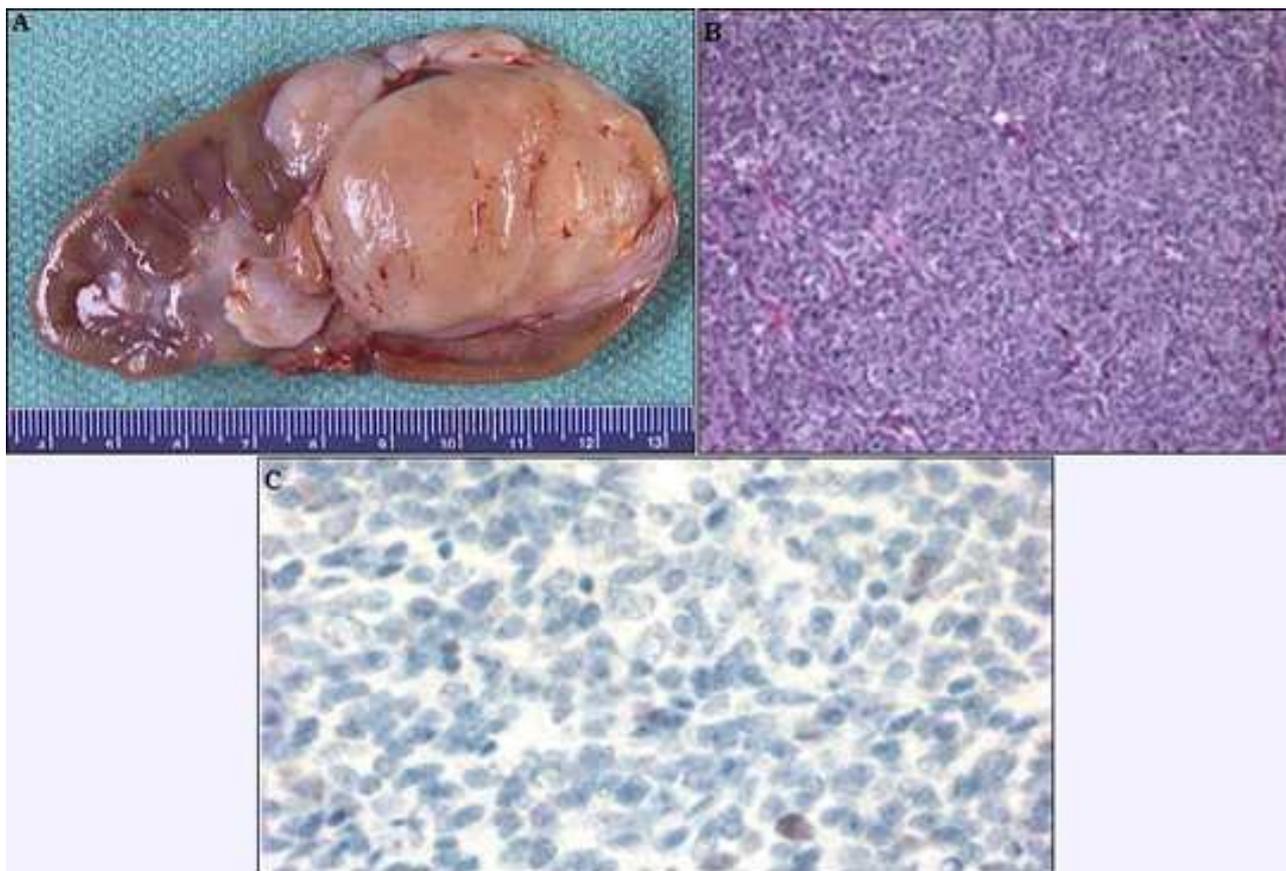
Treatment

Treatment of CCSK generally involves surgical intervention coupled with radiation and chemotherapy. CCSK commonly responds poorly to treatment with vincristine and actinomycin alone, but the addition of doxorubicin to chemotherapy regimens has improved survival rates. In the NWTS-5 protocol, patients with all stages of CCSK are treated with the same regimen used in patients who have Wilms tumor with diffuse anaplasia with the exception of stage I tumors. This treatment protocol is comprised of radical nephrectomy followed by radiotherapy and chemotherapy with cyclophosphamide, etoposide, vincristine, and doxorubicin for 24 weeks.

Prognosis

The prognosis for CCSK, particularly for low stage tumors, has improved with the addition of doxorubicin to chemotherapy regimens with a 66% reduction in overall mortality. Stage-dependent six-year survival is 97% for stage I tumors, 75% for stage II tumors, 77% for stage III tumors, and 50% for stage IV tumors.

Patients with tumors without areas of necrosis have a more favorable prognosis. Twenty-nine percent of patients with CCSK have lymph node metastases at the time of diagnosis, and bone metastasis is the most common form of relapse. Metastatic lesions have also been reported in the liver, brain, soft tissue sites, and lung with more unusual metastases to the skeletal muscle, testis, and salivary gland. Relapses of CCSK as many as 10 years after original diagnosis have been reported.

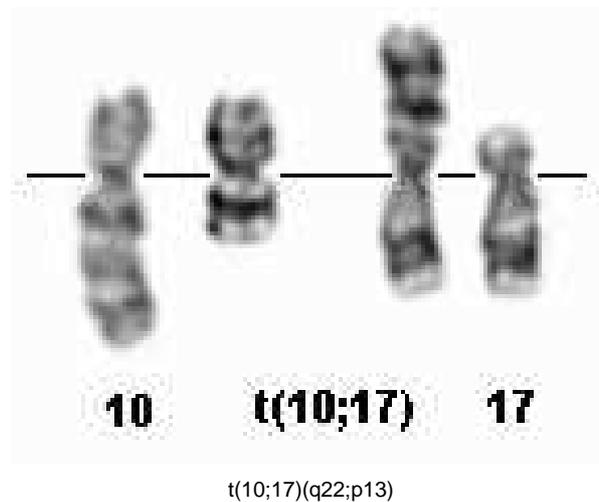


(A) Hemisection of kidney demonstrating large tan-yellow mass characteristic of CCSK. (B) Histologic section of CCSK characterized by hyperchromatic cells with high nuclear-cytoplasmic ratios and abundant extracellular matrix material. (C) p53 immunohistochemistry with only rare cells showing nuclear accumulation of protein.

Cytogenetics

Note: Only a small number of CCSK cases have been described cytogenetically. A clonal reciprocal 10;17 translocation t(10;17)(q22;p13) in CCSK was first reported in 1989. A CCSK with a complex karyotype including trisomy 9, deletions of chromosomes 16 and 22, and loss of chromosome 1p13 has been reported. In the same case, an interstitial deletion of chromosome 14 was reported: del(14)(q23). One of two 'sarcomatous Wilms' tumors' also contained a t(10;17)(q11;p12) as a part of an abnormal karyotype. Three of four other patients with CCSK were normal whereas one patient harbored a t(2;22)(q21;q11). Comparative genomic hybridization analysis of CCSK has documented quantitative chromosomal abnormalities in only 4 of 30 CCSK cases. These four cases included a gain of chromosome 1q and loss of 10q, gain of 1q and loss of terminal 4p, gain of 19p, and loss of chromosome 19. Later, another CCSK with a t(10;17)(q22;p13) was reported. Of five patients reviewed at this institution, karyotypes were available for four of these. One patient had a clonal balanced translocation 10;17 and an interstitial

deletion of the long arm of chromosome 14 as follows: 46, XY, t(10;17)(q22;p13)del(14)(q24.1q31.1). Three other patients had normal karyotypes. Fluorescent in-situ hybridization using a p53 probe was employed on the same cells harboring the clonal translocation above. This study documented the presence of two p53 signals on chromosome 17 indicating the absence of deletion or translocation of the TP53 tumor suppressor gene.



Genes involved and Proteins

Note: No gene has been implicated in the pathogenesis of CCSK. However, given the recurrent finding of clonal balanced translocations involving t(10;17)(q22;p13), gene(s) located within these regions may be related to CCSK pathogenesis. The chromosome 17p13 locus harbors the TP53 tumor suppressor gene, but several studies have failed to implicate mutations of p53 in CCSK. Tumor suppressor and oncogenes present on chromosome 10q22 include LCX and TET1. Both of these genes are involved in fusion gene products in acute myeloid leukemias. Tumor suppressor and/or oncogenes located in the deleted region of chromosome 14q24.1q31.1 include CHES1, a member of the forkhead family of transcription factors involved in cell cycle checkpoint control, hREC2, a gene encoding a protein with amino acid homology to a RAD51 involved in DNA double strand break repair, MAP3K9 or mitogen activated protein kinase, the MAX transcription factor, placental growth factor (VEGF-related protein), and transforming growth factor beta-3.

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