Clear Cell Sarcoma of the Kidney

Sze Jet Aw, MBBS; Kenneth Tou En Chang, MBChB, FRCPath

- 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 aids. 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. (Arch Pathol Lab Med. 2019;143:1022–1026; doi: 10.5858/arpa.2018-0045-RS)

In the late 1970s, a sarcomatous tumor of the kidney in childhood was recognized as distinct from the more common Wilms tumor because of its tendency to metastasize to bone.¹ This tumor was variously referred to as clear cell sarcoma, undifferentiated sarcoma of the kidney, and bone metastasizing renal tumor of childhood in separate publications from 1978, and the designation clear cell sarcoma of kidney (CCSK) was eventually adopted.² Accurate diagnosis of CCSK can be challenging because CCSK has diverse histologic features. An early study reported that up to about 50% of CCSK cases reviewed centrally were misdiagnosed by the original institutional pathologists.³ Accurate diagnosis is important because CCSK metastasizes to bone, brain, and other unusual sites and is associated with late recurrences.⁴ Additionally, CCSK chemotherapy regimens include doxorubicin with its associated cardiotoxic, nephrotoxic, and fertility risks.

CLINICAL FEATURES

Clear cell sarcoma of the kidney is the second most common pediatric renal malignancy, forming 3% to 5% of all primary tumors of the kidney in childhood.⁵ The age at presentation is similar to Wilms tumor, being most common in patients between 2 and 4 years old. The male to female ratio is 2:1.⁶ Only rare cases have been reported in adults.⁷ Some studies report that the right kidney is more commonly affected.⁸ The affected child often presents with abdominal distension, a palpable abdominal mass, abdominal pain, or gross hematuria.⁹ Most patients have stage 1, 2, or 3 disease at presentation, with only 6% to 7% presenting with stage 4 disease. Bilateral CCSK has not been reported. Metastasis, when seen at first presentation, affects mainly the ipsilateral renal hilar lymph nodes.

PATHOLOGY

Gross Pathology

Clear cell sarcoma of the kidney typically presents as a single, large renal mass with a white to pale tan-grey fleshy cut surface that distorts much of the adjacent healthy kidney (Figure 1). The mass may appear to have its epicenter at the renal medulla. Some tumors have soft, mucoid to cystic cut surfaces, with foci of hemorrhage or necrosis. The interface with adjacent healthy kidney tends to be well demarcated grossly, but histologic assessment may identify microscopic entrapment of native tubules and glomeruli at the tumor’s invasive edge. A few cases may feature gross evidence of renal vein invasion.

Cytologic Findings

Cytologic features of CCSK include ovoid tumor cells with evenly dispersed chromatin and eccentric cytoplasm with indistinct cytoplasmic boundaries (Figure 2). Fine nuclear grooves may be seen.⁹

Histologic Pathology

Clear cell sarcoma of the kidney has a highly variable histologic appearance and can mimic other pediatric renal tumors, making histologic diagnosis potentially challenging. Various histologic patterns have been described, but the classic pattern is most frequently identified and usually present, at least focally, in most cases of CCSK. The classic pattern consists of plump ovoid cells arranged in broad trabeculae or nests, separated by regularly spaced and arborizing fibrovascular septa. Those septa are often described as having a “chicken-wire” outline, featuring capillaries that are thin walled or encased within more amply thickened fibrocollagenous bands (Figure 3). The distinctive vasculature of CCSK is a helpful diagnostic feature because it is not prominent in the other pediatric renal tumors. The individual tumor cells have barely perceptible cytoplasm. Nuclei are fairly monomorphic and...
Figure 1. Nephrectomy specimen demonstrates a solitary well-circumscribed tumor with a fleshy pale-tan cut surface. Scale (bottom) in centimeters.

Figure 2. Cytologic smear of clear cell sarcoma of the kidney shows cells with wispy cytoplasm and ovoid nuclei with finely dispersed chromatin, occasional delicate nuclear grooves, and inconspicuous nucleoli (hematoxylin-eosin, original magnification ×400).

Figure 3. Clear cell sarcoma of the kidney, classic pattern (hematoxylin-eosin, original magnification ×300).

Figure 4. Clear cell sarcoma of the kidney, cellular pattern (hematoxylin-eosin, original magnification ×200).

Figure 5. Clear cell sarcoma of the kidney, myxoid pattern (hematoxylin-eosin, original magnification ×200).

Figure 6. Clear cell sarcoma of the kidney, sclerosing pattern (hematoxylin-eosin, original magnification ×200).
normochromic and contain finely dispersed chromatin without any conspicuous nucleoli. The nuclei, cytoplasm, or extracellular matrix may have a clear appearance from which the tumor derives its name. The variant histologic patterns include the cellular, myxoid, sclerosing, epithelioid, palisading, and spindle cell patterns.

The cellular pattern features closely packed tumor cells with overlapping nuclei and a decreased intercellular matrix (Figure 4). Mitotic activity tends to be high in this pattern, and confusion with other blastemal malignancies may occur. The myxoid pattern results from increased intercellular mucopolysaccharide matrix (Figure 5). This may coalesce to form cystic mucoid pools. The sclerosing pattern may be seen in up to one-third of cases and features deposition of acellular collagenous material that may be hyalinized and resemble osteoid (Figure 6), evoking the description of “osteosarcomatoid” in earlier publications. The epithelioid pattern features tumor cells aligned in tubules or elongated ribbonlike trabeculae, mimicking epithelial differentiation (Figure 7). However, these structures do not have an epithelial immunophenotype. The palisading pattern resembles Verocay bodies of schwannomas and is characterized by alignment of spindled nuclei forming parallel arrays, with adjacent nuclear-free zones (Figure 8). In the spindle cell pattern, the tumor cells lose their ovoid morphology and become more elongated and may resemble spindle cell sarcomas (Figure 9). These histologic patterns are not known to have significance in relation to disease course or survival.

Anaplasia may occur in CCSK and is defined by markedly enlarged and hyperchromatic tumor cell nuclei accompanied by abnormal multipolar mitoses. Anaplasia is typically a focal finding in a CCSK that is otherwise nonanaplastic. Immunoreactivity of anaplastic foci for p53 protein raises the possibility that such foci have an underlying TP53 mutation.

**Ultrastructural Features**

Ultrastructural analysis of CCSK is rarely undertaken nowadays. Electron microscopic findings of CCSK include a prominent extracellular matrix with variable amounts of collagenous fibers and ultrastructurally primitive ovoid tumor cells with small nucleoli, primitive cell junctions, and variable numbers of organelles that do not indicate any specific line of differentiation. The tumor cells tend to have extensions that surround pools of the matrix.

**ANCILLARY STUDIES**

**Immunohistochemistry**

Until recently, no particular immunohistochemical marker was known to be helpful in the diagnosis of CCSK, apart from stains serving to exclude differential diagnostic considerations. Clear cell sarcoma of the kidney has moderate to strong cytoplasmic immunoreactivity to the nonspecific marker vimentin and is weakly positive for actin. Moderate to strong cytoplasmic immunoreactivity to the nonspecific marker vimentin and is weakly positive for actin. Cyclin D1 typically stains the nuclei of CCSK tumor cells in an unequivocally strong and diffuse pattern (Figure 10).

Recent studies have explored the value of BCOR (BCL6 corepressor) immunohistochemistry in CCSK, but BCOR lacks complete sensitivity and staining is negative in a subset of genetically proven CCSK. BCOR immunoreactivity is also not specific for CCSK and can be seen in unrelated tumors, including CIC-DUX4 sarcoma, synovial sarcoma, and rhabdomyosarcoma.

Clear cell sarcoma of the kidney shows EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) messenger RNA overexpression and immunoreactivity. EZH2 is a catalytic component of PRC2 (polycomb repressive complex 2), and EZH2 overexpression may have both diagnostic and therapeutic applications.

**Molecular Pathology**

Early comparative genomic-hybridization studies showed a 1q gain in a few cases of CCSK, but no consistent recurrent copy-number alterations. Gene expression profiling studies showed upregulation of neural markers and activation of the Sonic hedgehog and phosphoinositide-3-kinase/Akt pathways, different from Wilms tumor, in which there is overexpression of genes primarily involved in metanephric development. A targeted study of imprinting showed loss of imprinting for the growth factor IGF2 in 43% of CCSK cases.

Sporadic reports of karyotyping findings of a recurrent balanced translocation t(10;17) emerged in 1989 and ensuing years. That translocation was eventually characterized as a translocation between the YWHAE (tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein e) gene on chromosome 17 and the NUTM2 (NUT family member 2A) gene on chromosome 10, resulting in an in-frame fusion transcript that incorporates exons 1 to 5 of YWHAE and exons 2 to 7 of NUTM2. The YWHAE-NUTM2 gene fusion is identified in only a few (approximately 12%) of CCSK cases, suggesting that still unknown genetic findings were lurking and awaiting discovery.

Although several genome-wide sequencing analyses were performed, those studies did not manage to identify the key mutation in CCSK. After an initial methylation profiling study of CCSK, the team of Ueno et al 24 (later Ueno-Yokohata et al 25) focused on BCOR, 1 of the 10 most hypomethylated genes they identified. Notably, an earlier study had already shown that BCOR was highly expressed in CCSK. Routine reverse transcriptase–polymerase chain reaction was performed to confirm the expression of BCOR in CCSK and, interestingly, yielded larger-than-expected polymerase chain reaction products. Sequencing the polymerase chain reaction products demonstrated an in-frame partial tandem duplication of the 3' end, and similar findings were identified in all 20 CCSK cases that they subsequently sequenced. This landmark mutational finding—an in-frame internal tandem duplication (ITD) of exon 15 of the BCOR gene—was rapidly confirmed by several other groups and was also found to be mutually exclusive with the YWHAE-NUTM2 fusion.

There is no explicit disease phenotype for CCSK with BCOR ITD versus those with the YWHAE-NUTM2 gene fusion.
Although most CCSK cases have BCOR ITD, and a few have the YWHAE-NUTM2 gene fusion, the remaining cases have diverse molecular findings. Recent reports describe CCSK with the BCOR-CCNB3 gene fusion. Recent reports describe CCSK with the BCOR-CCNB3 gene fusion. Those cases are histomorphologically, immunophenotypically, and transcriptomically indistinguishable from CCSK with BCOR ITD. Other reported genetic alterations in CCSK include IRX2-TERT gene fusion and EGFR gene amplification, point mutation (T790M), and internal tandem duplication, although it is not clear (apart from the single report of EGFR ITD) whether these alterations are mutually exclusive with the canonical BCOR and YWHAE-NUTM2 mutations.

In contrast to Wilms tumor, CCSK is not reported to be associated with any genetic predisposition syndrome, and no familial cases have been documented.

**DIFFERENTIAL DIAGNOSIS**

Clear cell sarcoma of the kidney needs to be distinguished from the other primary renal tumors of childhood, namely Wilms tumor, congenital mesoblastic nephroma, rhabdoid tumor, and primary renal Ewing sarcoma. Neuroblastomas may enter the differential diagnostic consideration because they affect patients in a similar age group, and larger locally invasive adrenal cases may appear to be centered in the subjacent kidney.

In pathology departments with a molecular pathology facility, identification of either the YWHAE-NUTM2 gene fusion or BCOR ITD would be definitive for a diagnosis of CCSK. Alternatively, a judicious panel of immunohistochemical stains comprising WT1, cyclin D1, INI1, and PHOX2B (pairedlike homeobox 2b) can provide the diagnosis in most situations.

Although triphasic Wilms tumor will not be confused with CCSK, blastemal Wilms tumor is the top differential diagnosis with CCSK. Cyclin D1 shows strong and diffuse nuclear immunoreactivity in CCSK (Figure 10) and is negative in the blastemal and stromal elements of Wilms tumor. Cyclin D1 is negative in rhabdoid tumor and Ewing
sarcoma and, coupled with their pathognomonic genetic changes of INI1 loss and EWSR1 (or FLIS) translocation respectively, leads to a clear diagnosis in both those tumors. Cyclin D1 is positive in neuroblastoma and congenital mesoblastic nephroma. Neuroblastoma can be distinguished based on clinical features and PHOX2B immunoreactivity. Classical mesoblastic nephroma is morphologically distinct with uniform fascicles of evenly spaced bland fibromatosis-like spindled cells, lacking the characteristic branching vasculature of CC SK. Cellular mesoblastic nephroma can have greater degrees of cellularity and cytologic atypia potentially resembling CC SK, and definitive diagnosis then rests on identification of the ETV6–NTRK3 or variant gene fusions. BCOR immunohistochemistry, if positive, can support a diagnosis of CC SK but, as discussed above, lacks sensitivity and specificity.

CURRENT TREATMENT

Treatment of CC SK, following Children's Oncology Group guidelines, consists of surgical resection of resectable tumors, and vincristine, cyclophosphamide, doxorubicin, and etoposide for disease that is in stages 1 to 3. Stage 4 disease receives intensified treatment with the addition of carboplatin. Local radiation therapy (10.8 Gy) is given for stage-2 and -3 disease. Follow-up care aims to identify disease relapse which can be late, and to identify treatment-related toxicity.

PROGNOSIS

With current, intensive treatment comprising multiagent chemotherapy and radiation therapy, outcome has improved with a 5-year event-free survival of 65% to 85% and a 5-year overall survival of 75% to 90%. Toxic effects of treatment include cardiotoxicity, infertility, obesity and metabolic dysfunction, and second malignancies; hence, there remains a need for continued research to identify molecular targets for more-targeted treatment strategies. Relapse occurs in about 16% of patients, and median time from diagnosis to relapse is about 17 months. With current treatment regimes, the most common sites of relapse are (in descending order) brain, lungs, and bone. Overall outcome after relapse remains poor.

References