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Original Article

Clear cell sarcoma of the kidney in children: a clinopathologic analysis of three cases

Shaohua Chen[1*], Ming Li[2*], Ran Li[1*], Jintao Cao[1*], Qiong Wu[1], Ting Zhou[1], Zhaogen Cai[1], Nan Li[1]

[1]Department of Pathology, The First Affiliated Hospital of Bengbu Medical College, Bengbu Medical College, Bengbu, Anhui, P. R. China; [2]Department of Endocrinology, Bengbu Second People's Hospital, Bengbu, Anhui, P. R. China. [*]Equal contributors.

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Abstract: 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.

Keywords: CCSK, histology, immunohistochemistry, diagnosis

Introduction

Renal clear cell sarcoma is the second most common kidney cancer in childhood, only after Wilms Tumor (WT), and typically presents mostly in children under 3 years old [1]. CCSK is an invasive tumor with a tendency to bone metastasis, brain metastasis, and can also spread to the lung and abdominal cavity, while the brain has replaced bone as the most common site of recurrence [2]. The propensity for aggressive behavior and late relapses gives a poor prognosis and high mortality [3]. Although some markers have emerged may act as potential diagnostic aides, the lack of accuracy and specificity constantly lead to inadequate situations. In consequence, an accurate diagnosis requires a high degree of suspicion and challenge before it can be distinguished from other pediatric renal tumors since accurate pathologic diagnosis dominates the treatment plan [2].

Materials and methods

We selected 3 cases of renal clear cell sarcoma from the First Affiliated Hospital of Bengbu Medical College from 2012 to 2017, aged 2, 4 and 12, including two boys and one girl. Clinical demographics were obtained from medical records and referral doctors, as well as the subsequent telephone follow-ups.

The selected specimens were fixed with neutral 10% formalin, paraffin embedded sections were stained with hematoxylin-eosin, and the paraffin sections of the samples were stained with Elivision method by immunohistochemistry. Antibodies and other supporting materials

Table 1. Sources of the antibodies involved in the immunohistochemistry analysis

Antibody	Clone[a]
CK	Monoclonal, clone AE1/AE3
EMA	Monoclonal, clone E29
Vimentin	Monoclonal, clone V9
NSE	Monoclonal, clone E27
Syn	Monoclonal, clone SP11
S-100	Monoclonal, clone 4C4.9
Ki-67	Monoclonal, clone MIB-1
CyclinD1	Monoclonal, clone SP4
CD34	Monoclonal, clone QBEnd/10
Bcl-2	Monoclonal, clone 8C8
Desmin	Monoclonal, clone D33
AACT	polyclone
SATB2	Monoclonal, clone EP281

[a]All antibodies were provided by Maixin Biotechnology Co., Ltd. (Fuzhou, China)

were purchased from Fuzhou Maixin Biotechnology Co., LTD (**Table 1**). Clinical records were obtained from medical records. The study was conducted by the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College.

Results

Clinical features

Three patients with CCSK were admitted to Department of Clinical Pathology of the First Affiliated Hospital of Bengbu Medical College from October 2012 to February 2017. All patients initially presented with complaints of unintentional detection of a mass in the left abdomen by the parents. One patient suffered marked abdominal distension. The duration was approximately 3 days, 2 weeks and 1 month, respectively.

Local computed tomography (CT) scan demonstrated the heterogeneous occupancy lesions of left kidney, which were considered as neoplastic lesions. The child was admitted to hospital with a preliminary diagnosis of WT. In another case, the contrast-enhanced CT illustrated a huge soft tissue mass measuring 10.8 cm × 7.6 cm × 8.4 cm occupying the location of the left renal parenchyma. Uneven enhancement could be observed after the enhanced scan, within small intracystic necrosis and low-density areas; mild uneven enhancement was observed during the arterial phase after the enhanced scan, while progressive enhancement was observed during the venous phase. The right renal cortex was significantly extruded and thinned (**Figure 1A**, **1B**). Intravenous urography: radiographic images were taken at different intervals after 76% Urografin was injected with 40 ml, representing the left pelvis and calyces that were displaced upward and compressed, and the deformation of the lumen. The size, shape, and position of the right pelvis and calyces were normal and no dilated hydrops was revealed. The bilateral ureters were unobstructed. The bladder was well-filled and the edges were smooth. Two patients underwent radical nephrectomy, one of whom died of bone metastasis after four cycles of COA chemotherapy (vinaxine cyclophosphamide epirubicin), the other died of multi-organ metastasis one year later without chemotherapy. One case lost contact after the pathologic diagnosis.

Gross and histologic features

Macroscopically, all abnormal renal volumes were significantly enlarged. The cortex and medulla of the smaller kidney was fairly clear. There were lumps of slightly soft texture in the section of the kidney, with long diameters of approximately 5 cm, 8 cm and 20 cm, respectively, located in the center of the kidney near the hilum. The kidney with the largest volume was almost completely occupied by the mass with a white to pale tan-grey fleshy cut surface and foci of hemorrhage or necrosis.

Microscopically, most of the tumor stroma was loose, filled with fibrous vessels, and some areas were slightly dense (**Figure 2A**). The neoplastic parenchyma was segmented into sheets or beams by fibrous vessels, abundant, dense, and epithelial. The parenchymal cells were mostly round or polygonal with lightly stained and transparent cytoplasm. The nucleus was round or oval while the chromatin was fine granular with vaguely visible nucleolus (**Figure 2B**).

In another case, the cells were spindle-shaped, arranged in a remarkably dense, mostly cord-like arrangement, with overlapping nuclei and unclear boundary. Cytoplasmic staining was light, almost without coloration, and the nucleus was rod-shaped, oval or slightly irregular,

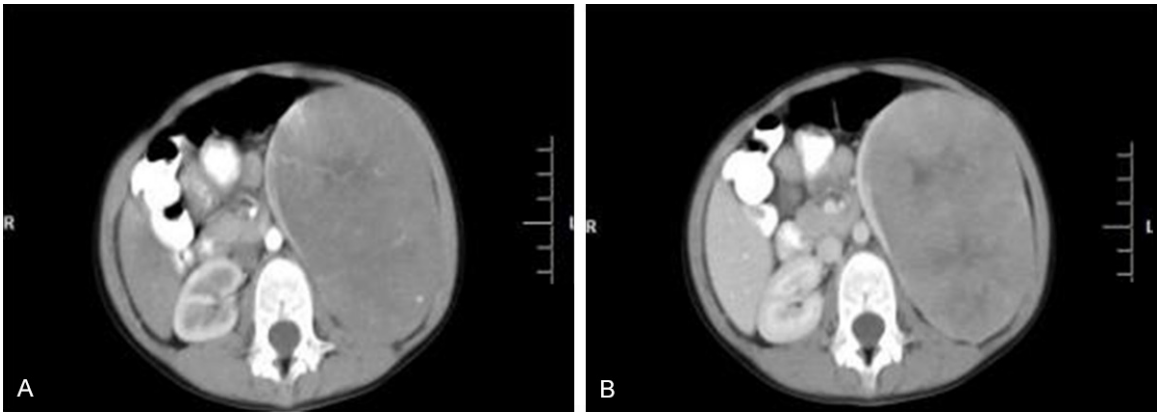

Figure 1. CT enhanced scan: A. Arterial phase CT scan. B. Venous phase CT scan. CT scan showed that there was a large soft tissue mass with uneven density in the parenchyma of the left kidney and small flaky low-density areas with necrotic cystic degeneration. After contrast-enhanced scan, there was slight uneven enhancement in the arterial phase, and continuous and progressive enhancement in the venous phase.

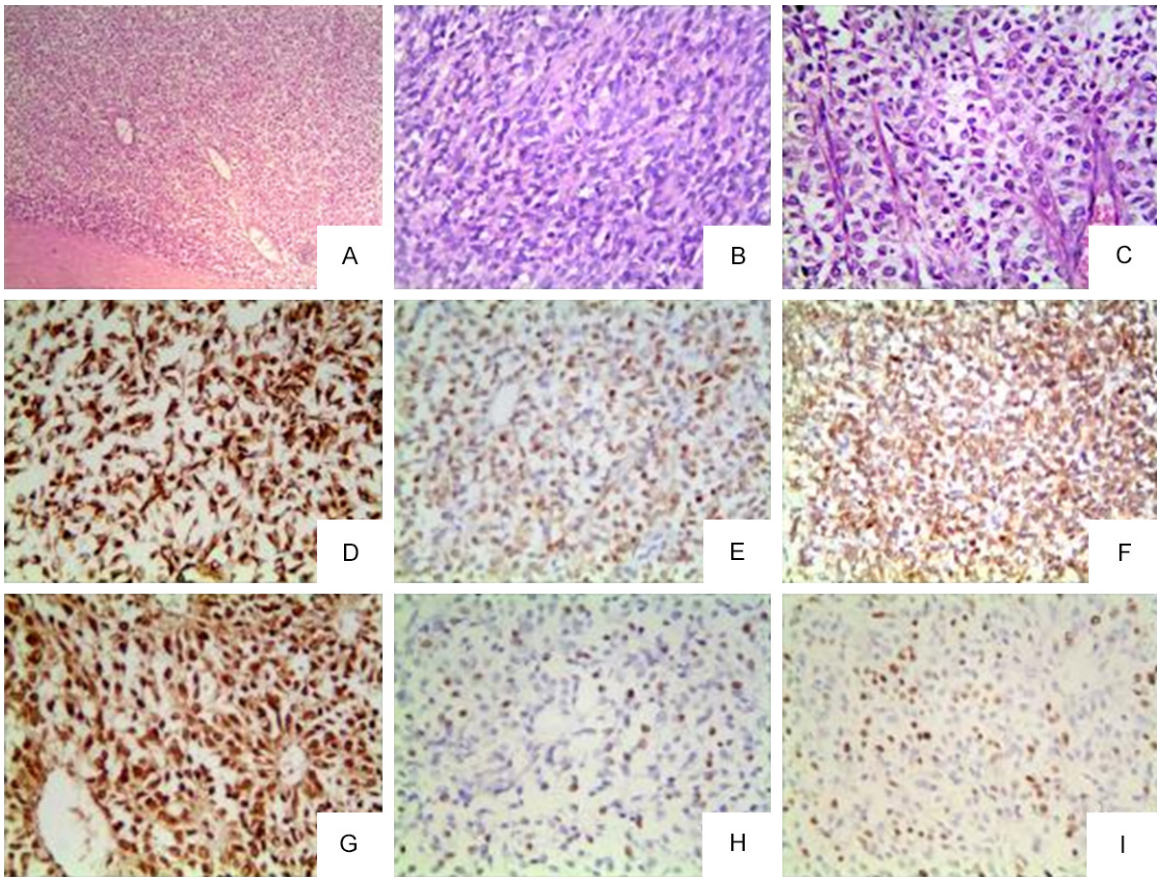

Figure 2. H&E stain and immunohistochemical photomicrographs. A. Loose tumor stroma filled with fibrous vessels, and some areas were slightly dense (hematoxylin-eosin ×100). B. Round or spindle cell bundles were visible, with oval to round vesicular nuclei and inconspicuous nucleoli (hematoxylin-eosin ×400). C. Tumor cells were separated by dendritic fibrosis, nested or strip-like (hematoxylin-eosin ×400). D. Vimentin co-receptor immunohistochemistry revealed diffuse nuclear staining (magnification, ×400). E. Moderately positive nuclear staining for Cyclin D1 in the tumor cells (magnification, ×400). F. Moderate cytoplasmic and membranous immunoreactivity for Bcl-2 (magnification, ×400). G. Alpha-aact was strongly staining the tumor cells in the cytoplasm (magnification, ×400). H. SATB-2 was highlighting focal areas in the nucleus (magnification, ×400). I. The proliferation index was about 30% in one case (magnification, ×400).

nuclear chromatin was fine. The nuclear membrane was thin and the nucleoli were not obvious. Nuclear division was indeterminate (**Figure 2C**).

Immunohistochemical features

Since there are no specific markers to diagnose CCSK to date, the majority of diagnoses were identified only after ruling out other potential diagnoses, that is, to distinguish them from other renal mesenchymal neoplasms. Thus vimentin took on an indispensable pathologic duty in renal clear cell sarcoma [4]. Immunohistochemistry in this study demonstrated that vimentin was moderately to strongly cytoplasmic positive, which was consistent with most of the literature reports (**Figure 2D**) [5]. Secondly, it has been reported that Cyclin D1 was a sensitive but not specific immunohistochemical marker, which had certain diagnostic value for CCSK and many other pediatric malignant carcinomas and neuroblastoma. Cyclin D1 is of great help in distinguishing between CCSK and embryo-rich WT [6, 7]. However, in this study, two cases were moderately positive for Cyclin D1 and one was weakly positive for immunohistochemistry (**Figure 2E**). In addition, two cases were positive for nuclear mechanism-related transcription factor SATB-2 and one was weakly positive for immunohistochemistry (**Figure 2H**). Alpha-aact was strongly positive in a cytoplasmic pattern (**Figure 2G**). All 3 cases depicted moderate cytoplasmic and membranous immunoreactivity for Inhibits apoptotic protein Bcl-2 (**Figure 2F**). Meanwhile epithelial markers CK, EMA, Neurogenic markers Syn, S-100, NSE, myogenic marker Desmin, vascular endothelial cell marker CD34, identification markers of nephroblastoma WT-1 were all negative. The proportion of proliferation index Ki-67 positive cells accounted for approximately 30%, 40% and 80% (**Figure 2I**), respectively.

Discussion

CCSK is a rare kidney malignancy in children and was first reported by Kidd in the 1970s, which comprises 3%-4% of pediatric kidney tumors, with an average age of approximately 36 months [1, 3]. Although genetically confirmed cases have occurred sporadically in adolescents, other hypothetical cases have been rarely reported in adults.

For the reason that CCSK lacks of specificity in the early clinical features and imaging manifestations, thus, it is easily misdiagnosed with other abdominal tumors. The common clinical manifestations of CCSK patients are similar to Wilms Tumor, including abdominal bulge or mass, abdominal pain and gross hematuria [8]. Other precise comorbid symptoms include fever, vomiting, constipation and hypertension. It was perceived in the investigation of clinical data of this study, among all the clinical symptoms, abdominal mass was the most prominent clinical symptom, which were mostly accidentally stumbled upon by parents while bathing and changing clothes for infants. Domestic reports describe the imaging manifestations of CCSK tend to be large, liquefied obviously, abundant blood supply, etc [9]. And yet since CCSK is relatively rare in clinic, consequently, before a definite pathological diagnosis, most children were misdiagnosed as other common renal occupied lesions, for instance the nephroblastoma or neuroblastoma. In this study, one case was misdiagnosed as WT before surgery and the postoperative pathological result was CCSK [10].

The prognosis of CCSK was naturally deemed to be unsatisfactory, mainly attributed to clinical features of aggressive, extensive metastasis, high rates of recurrence and mortality. CCSK has a predilection for osseous metastasis, also known as the bone metastasizing renal tumor of childhood, followed by the spine, pelvis, and rib cage, other parts such as the lung, liver, soft tissues and lymph nodes. Whereas, studies have also confirmed that the brain has surpassed bones as the most common site [11]. In addition to the common metastatic sites, it has been reported that bladder and other atypical sites may occurred as objects of metastases, likewise.

The diagnosis of CCSK still relies mainly on pathological histomorphometric analysis and immunophenotyping. In terms of the pathological features, the tumor is generally large, which could be lobulated, well-circumscribed, accompanied by an inconspicuous capsule. It often appears as tan-grey, or pale yellow-like fish-like on cut section.

Microscopic examination depicted an arrangement of tumor cells that is complex and varied, which may be divided into histologic patterns

according to the main cells. Generally, tumor is rich in smaller cellular components; while, the nucleus is mostly round to oval, with fine chromatin, inconspicuous nucleoli and imprecise capsule, and the cytoplasm is lightly stained or vacuolated. The tumor cells are nested, glandular, cord-like, beam-like or palisade-like, interspersed with branching fibrovascular interstitial, which could be mucoid degeneration, fibrosis, and hyaline degeneration. The tumor can be divided into epithelial-like, spindle-shaped, sclerotic, cystic, palisading, sinusoidal or pericytoma-like and polymorphic or anaplastic [5]. Among all these types, the prognosis will be worse with spindle cell type, polymorphism or variability.

Immunohistochemistry

Traditionally, immunohistochemistry naturally acts in the diagnosis of CCSK with a significant role to exclude other pediatric renal tumors. Immunohistochemical studies have interpreted that Vimentin positivity is a strong pathologic characteristic of CCSK [12]. Definite outcome suggests that moderate to strong cytoplasmic immunoreactivity, and nonspecific Vimentin positivity has been demonstrated. In this study, the results of tumor immunohistochemistry of all three cases demonstrated Vimentin positivity (**Table 1**), which was also consistent with most literature reports.

But this positivity is not specific. Similarly, cytokeratin, MIC-2, S-100, neural markers, desmin, and WT-1 are also negative [13, 14]. Cyclin D1, is recognized as a proto-oncogene and its overexpression can lead to uncontrolled and malignant cell proliferation. Cyclin D1 gene overexpression and amplification have been found in a variety of tumors, including mantle cell lymphoma, breast cancer, parathyroid tumor, lung cancer. Areva et al. [15] confirmed Cyclin D1, as well as nerve growth factor receptor (NGFR) immunohistological sensitivity to CCSK, but neither was a completely specific marker. Markers such as SATB2, Bcl-2, and CD10 also have a peculiarity of variable nonspecific positivity [7].

As yet, the pathogenesis of the disease has not been elucidated. Several studies suggested that ABCOR internal tandem duplication (ITD) has been identified as a factor associated with the progress of CCSK [16, 17]. Recent studies have explored the inextricable relationship between BCOR and CCSK, the corepressor of Bcl-6 [18]. The immunohistochemical diffuse strong positive marker of BCOR can more or less contribute to isolate CCSK from its main mimickers in pediatric renal mesenchymal tumors, including rhabdomyomas and posterior renal stromal tumors, also, covering epithelial-derived malignant tumors, such as renal clear cell carcinoma and WT [16]. However, there are also some scholars who raised objections; for instance the immunohistochemistry of BCOR lacks complete sensitivity and is even negative in some cases [19, 20]. Also, a part of adult renal sarcoma overexpressing BCOR is negative for BCOR gene changes which can be detected in other interstitial tumors conversely, including rhabdomyosarcoma, synovial sarcoma and undifferentiated sarcoma with small round cell phenotype with CIC gene rearrangement CIC-DUX4 sarcoma, etc. As well, the solitary fibrous tumor (SFT) has a significant overlap with CCSK in morphology and immunostains. The imprecise inclusion of malignant SFT in a list of tumors that are frequently presenting with BCOR overexpression indicates flaws in BCOR-based diagnosis [21].

The EZH2 gene (a member of Polycomb family) encodes a histone lysine-N-methyltransferase that is involved in DNA methylation to suppress transcription of other genes, which is often highly expressed in solid tumors and significantly associated with tumor malignancy and poor prognosis.

A related study has expounded the molecular mechanism of EZH2 inhibitors ineffective in the treatment of most solid tumors, and provided a possible synergistic inhibition of epigenetic interaction control solutions, as well as more specific and effective anti-cancer targeted therapies [22].

Similar studies on CCSK have noted overexpression of EZH2 messenger RNA and immunohistochemical positive expression, so it implies a diagnostic and therapeutic significance for EZH2. Further exploration is worthy of verification and expectation [23].

Hence, up to now, in addition to the staining used to rule out differential diagnostic considerations, no specific immunohistochemical

markers have been specific for the diagnosis of CCSK.

Genetic abnormalities have been illustrated, such as rearrangement of the YWHAE gene on chromosome 17 and dysregulation of the FAM22 gene on chromosome 10 [24], t (10; 17) (q22; p13/p12) 53 repeated translocation and 14q24q31 deletion [25], etc. Although a series of chromosomal translocations and genetic changes have been described in clear cell tumors, the identified molecular pathogenesis and cellular origin have not been elucidated.

CCSK is prone to metastasis and recurrence, while radical nephrectomy combined with enhanced chemotherapy is a very reliable treatment. In addition to the necessary surgical treatment, it is often inevitable to assist with postoperative radiotherapy and chemotherapy, either in combination or separately. At times, treatment decisions turn into a complicated situation by the fact that clear cell sarcomas are often confused with other renal interstitial neoplasms since there are no clinical or imaging techniques specific to clear cell sarcomas to date [26]. The survival rate is significantly improved with the application of adriamycin, cyclophosphamide, etoposide, and other chemotherapy drugs [1]. Younger and advanced stage of the disease increase the risk factors for palindromia. Recurrence basically predicts an unfavorable prognosis [27].

In summary, CCSK is notorious for its highly metastatic properties and poor prognosis. The vagueness and atypia of clinical symptoms, the diversity of histology, the lack of effective markers in immunohistology, and the impotence of molecular genetics have all brought about great obstacles to the diagnosis and treatment of the disease. In consideration of the rarity of the disease, the current diagnosis should be comprehensively analyzed by multiple disciplines, and clinical trials of metastasis, recurrence, and prognosis require international research and cooperation.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Nan Li, Department of Pathology, The First Affiliated Hospital of Bengbu Medical College, 287 Changhuai Road, Bengbu 233000, Anhui, P. R. China. Tel: +86-552-3070209; E-mail: linanangel100@sina.com

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