Case Report

Capicua transcriptional repressor (CIC)-rearranged sarcoma harboring *CIC-LEUTX* fusion with renal involvement: a rare case report

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Background: Capicua transcriptional repressor (CIC)-rearranged sarcoma (CRS) is a rare and highly aggressive undifferentiated small round cell sarcoma (USRCS), which genetically displays a characteristic gene fusion between *CIC* gene with other genes such as *DUX4*.

Case Description: We report a rare case with *CIC-LEUTX* fusion. The 45-year-old male patient presented to our department with frequent dry cough and lumbar pain. Computed tomography (CT) scan indicated multiple pulmonary nodules on both sides, hilar lymph node enlargement, left lower lobe infection and presence of pleural effusion in left quadrant. Enlargement and uneven density were seen in the left kidney, together with perinephric exudate, renal calculi, thickening and filling deficiency in renal veins, and small retroperitoneal lymph nodes. Immunohistochemistry (IHC) showed negativity in CK7, CK20, CD10, vimentin, PAX-8, P63, MelanA and synapatophysin, but GATA3 and CK were positive. RNA-based next generation sequencing (NGS) detection revealed CRS of gene fusion in *CIC* (exon 20) and *LEUTX* (exon 3). After treatment with a variety of targeted and chemotherapy drugs, the patient showed a poor response with a survival time of merely 7 months.

Conclusions: This case of USRCS harboring *CIC-LEUTX* fusion with renal involvement could help to expand our understanding on the diagnosis and treatment of CRS harboring *CIC-LEUTX* fusion.

Keywords: Capicua transcriptional repressor-rearranged sarcoma; gene fusion; *LEUTX* gene; case report

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Introduction

Capicua transcriptional repressor (CIC)-rearranged sarcoma (CRS), belonging to undifferentiated small round cell sarcoma (USRCS) in the 5th World Health Organization (WHO) Classification of Soft Tissue and Bone Tumors (1), represents a new entity harboring recurrent chromosomal translocation between *CIC* and double homeobox 4 gene (*DUX4*) in most of cases, such as t(4;19)(q35;q13) or t(10;19)(q26;q13) translocation (2-6). Except *DUX4*, the other CIC fusion partner genes include *FOXO4*, *NUTM1*, *NUTM2A* and *LEUTX* (7-9). To date, there are a few cases harboring *CIC-LEUTX* fusion (10,11), and the differential diagnosis of small round cell sarcoma (SRCS) can be challenging on account of overlapping cytological, immunohistochemistry (IHC), histological, and clinical features (12). Thus, we reported our experiences on the diagnosis of primary USRCS in left kidney harboring *CIC-LEUTX* fusion. Our study can provide helpful information for the subsequent diagnosis and treatment of this disease. We present this article in accordance with the CARE

reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-524/rc).

Case presentation

A 45-year-old male patient presented to our department with frequent dry cough and lumbar pain. Computed tomography (CT) scan indicated multiple pulmonary nodules, hilar lymph node enlargement on both sides, left lower lobe infection and presence of pleural effusion in left quadrant. In addition, enlargement and uneven density were seen in the left kidney, together with perinephric exudate, renal calculi, and thickening and filling deficiency in renal veins, as well as small retroperitoneal lymph nodes (*Figure 1*). Thus, renal cancer combined with tumor thrombosis in renal veins were considered. Multiple filling deficiency in both pulmonary arteries suggested a high probability of intra-pulmonary artery carcinoma thrombosis. Lung needle biopsy was performed and IHC showed negativity in CK7, CK20, CD10, Vimentin, PAX-8, P63, MelanA and synapatophysin, but GATA3 and CK were positive. The Ki-67 index was more than 80%. Thus, the patient was diagnosed with poorly differentiated carcinoma.

One month later, renal and pulmonary biopsy was performed, which showed irregular arrangement of tumor cells with various cell sizes in a large heterogeneity, presence of multinucleated and megakaryocytes, accompanied by hemorrhage and necrosis (*Figure 2*). IHC showed positivity of CD99, WT1, and Desmin, while SMA, S-100, CD31, CD34 and CK were negative (*Figure 3*). Then RNA-based next generation sequencing (NGS) procedures were performed including reverse transcription, end repair, dA-tailing, and adaptor ligation (NEB, Cat E7771 and E6111, Ipswich, MA, USA). Polymerase chain reaction (PCR) enrichment was performed using 269 specific primers targeting a panel of 60 genes frequently associated with solid tumors. The enriched PCR products were then sequenced on the NovaSeq 6000 platform (Illumina, USA). Sequencing reads were independently aligned to the human reference genome using STAR (version 2.7.10). Fusion gene prediction was conducted using StarFusion software (version 1.10.1). NGS assay showed *CIC-LEUTX* gene fusion between exon 20 of the *CIC* gene and exon 3 of the *LEUTX* gene. Finally, the patient was diagnosed with CRS with a *CIC-LEUTX* fusion. For the treatment, the patient received 1 cycle of chemotherapy using paclitaxel and carboplatin, 2 cycles using albumin paclitaxel, anlotinib and pabrolizumab, as well as 1 cycle with the combination of liposomal doxorubicin, vincristine, cyclophosphamide/etoposide and ifosfamide (VAC/IE). The patient showed a poor response to the regimen with a survival of 7 months. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Highlight box

Key findings

- We reported a case of undifferentiated small round cell sarcoma (USRCS) harboring capicua transcriptional repressor (CIC)-LEUTX fusion with renal involvement, which could help to expand our understanding on the diagnosis and treatment of capicua transcriptional repressor-rearranged sarcoma (CRS) harboring CIC-LEUTX fusion.

What is known and what is new?

- CIC-rearranged sarcoma is a rare and highly aggressive USRCS, which genetically displays a characteristic gene fusion between CIC gene with other genes such as *DUX4*. To date, there are a few cases harboring *CIC-LEUTX* fusion.
- We reported our experiences on the diagnosis of primary USRCS in left kidney harboring CIC-LEUTX fusion. Our study can provide helpful information for the subsequent diagnosis and treatment of this disease.

What is the implication, and what should change now?

- In the future, clinical trials with a large sample size are urgently required to establish appropriate treatment regimens for the CRS harboring various fusions.

Discussion

The 2 most common translocations among CRS patients are t(4;19) and t(10;19), resulting in *CIC* fusions with either *DUX4* and *DUX4L* paralog, respectively (13). Up to now, other rare variant fusion genes have also been reported, such as *FOXO4*, *NUTM1* and *LEUTX* (11). In this study, we reported a rare CRS case with renal involvement harboring *CIC-LEUTX* fusion, which could expand the spectrum of CIC-rearranged neoplasia.

CRS represents a rare disease that occurs mostly in children and young adults, especially males. Most CRS occurs in soft tissues, mainly in the trunk and extremities, followed by visceral sites, rarely in bone. It is highly

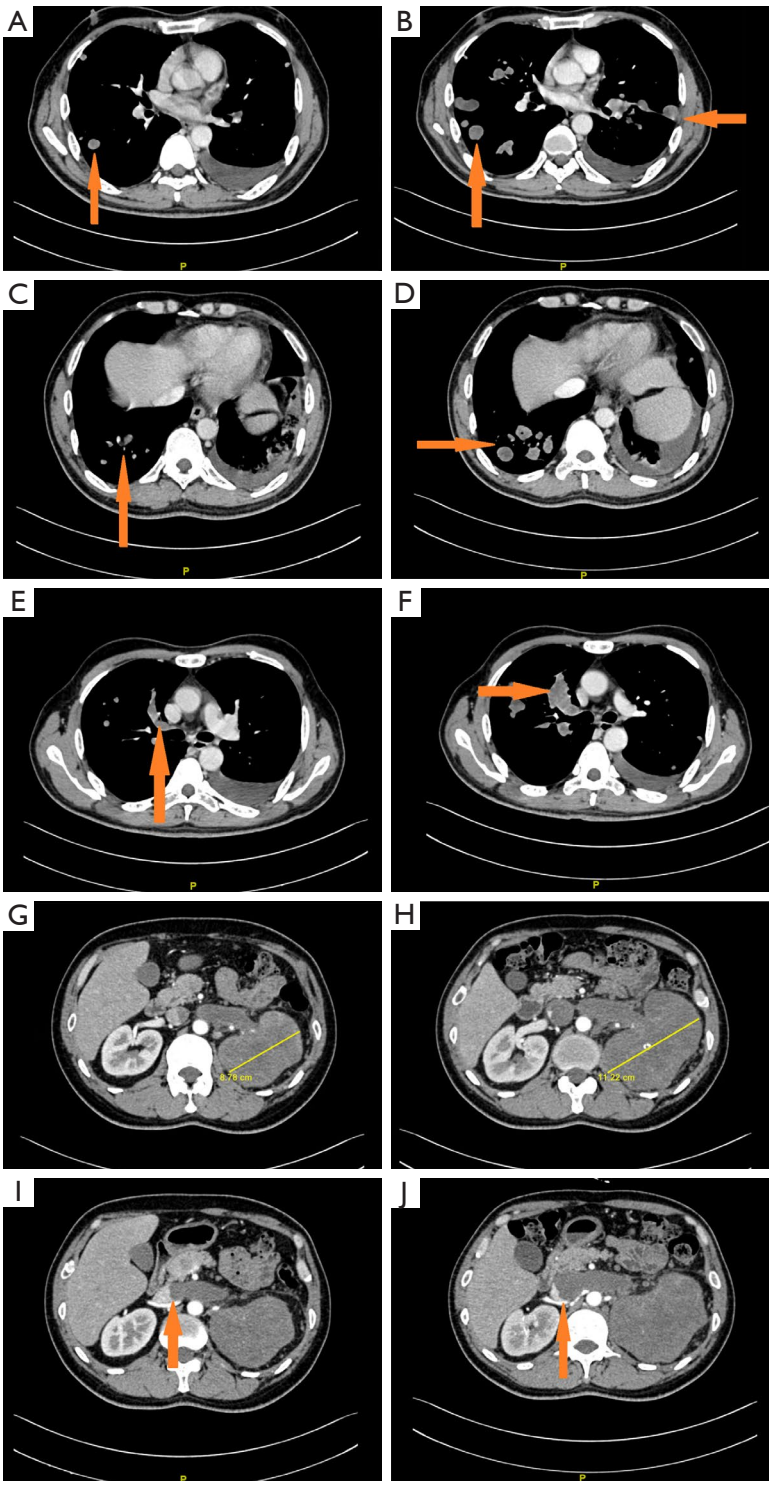

Figure 1 CT imagings of the patient's lungs and kidneys at the initial visit and a month later. Orange arrows indicate (A,C) lung metastases, (E) a pulmonary artery cancerous embolus, and (I) a renal vein cancerous embolus at the time of initial diagnosis. One month later, orange arrows indicate (B) new lung metastases on the left side, enlarged lung metastases on the right side, (D) enlarged lung metastases, the progression of the (F) pulmonary artery cancerous embolus and (J) renal vein cancerous embolus. The size of the patient's left renal lesion was (G) 8.78 cm at the initial diagnosis and (H) increased to 11.22 cm 1 month later. CT, computed tomography.

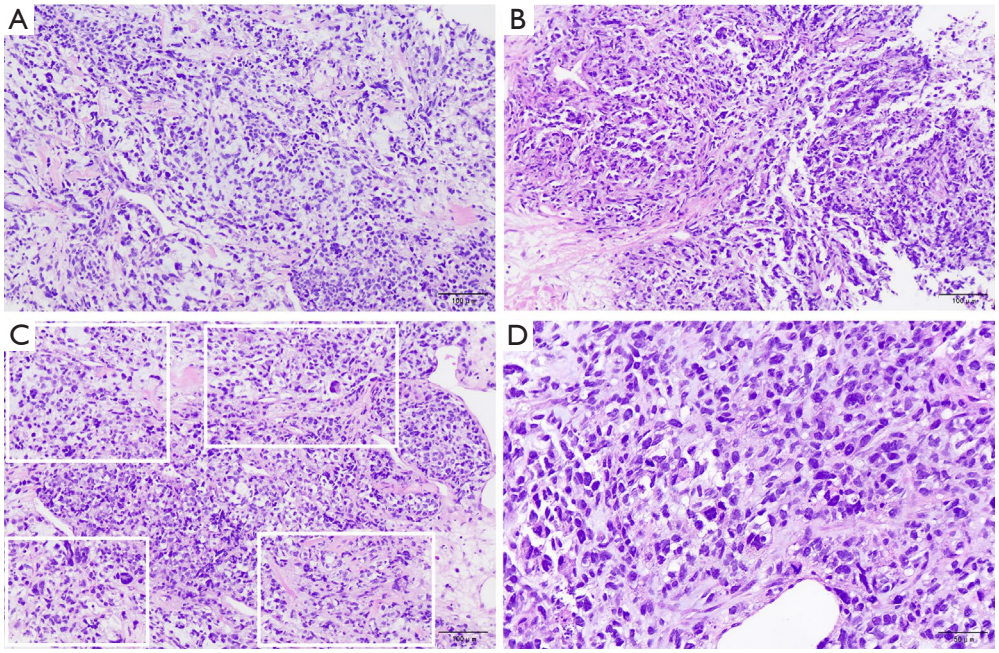

Figure 2 Histological images of lung biopsy with hematoxylin and eosin stain. (A) Focal myxoid stroma interstitium (20×), (B) focal cells are lobulated (20×), (C) focal cell pleomorphism (20×), (D) mitotic index 10–12/10 HPF (40×).

invasive, with about 40% of cases being diagnosed at an advanced stage, with distal metastasis in lung, bone, liver, brain, and lymph nodes (1,14). Most patients usually present to the hospitals due to unbearable pain, while on some occasions it may be ignored as a minor injury in sports or daily life. Some patients with soft tissue SRCS are usually painless but it grows rapidly, making them less noticeable (12). In this study, our case presented to our department due to frequent lumbar pain. A huge mass in the left kidney was found at the first diagnosis, multiple metastases in both lungs were found, combined with renal venous tumor thrombus and pulmonary embolism. CT performed one month later indicated disease progression.

The diagnosis of CRS is still a challenge due to disease rarity, intrinsic complexity, and harsh technical demanding. Besides, its diagnosis relies on multiple procedures involving morphological, IHC and diagnostic molecular pathological tests (15). CRS is similar to Ewing sarcoma (EWS) that shows the main morphologic features of uniformly monotonous round cells, round nuclei, fine chromatin, inconspicuous nucleolus, and opaque cytoplasm (16). CRS cells are distinctly pleomorphic, showing a round, epithelioid, and spindle morphology. Most tumor cells exhibit a round and ovoid cell morphology, and occasionally, they may present spindled and epithelioid/rhabdoid phenotype, combined with multiple myxoid stromal changes (1,17). CD99 could be used as a robust marker for EWS, which is positive in a strong and diffuse manner (18). Approximately 20% of CRS patients express CD99 in multifocal or local lesions or even in a diffused manner (1,17,19). Nuclear immunoreactivity for WT1 is presented in most CRS cases, and the expression of claretinin and NKX2.2 also contributes to the differential diagnosis between CRS and EWS (16,20). In this case, the tumor cells are morphologically atypical with low differentiation and lamellar arrangement of cells with positivity to CD99. The final diagnosis of CRS is clearly made by the molecular characteristic changes detected by the combination of NGS and IHC.

CIC-DUX4 fusion is the most common form in CRSs. The *CIC* (19q13) gene is highly conserved, which encodes a transcriptional suppressor. *DUX4* (either 4q35 or 10q26.1) encoded protein is reported to function as a transcriptional activator. The fusion of *DUX4* with *CIC* can upregulate several *PEA3* family genes, including *ETV1*, *ETV4* and *ETV5* genes, which may contribute to tumorigenesis (10). Besides *DUX4*, *CIC* fusion partner genes include *LEUTX*, *FOXO4*, *NUTM1*, and *NUTM2*. There are only a few cases of *CIC-LEUTX* gene fusion. For example, Huang *et al.* reported 1 case of CRS that was diagnosed by histomorphologic and

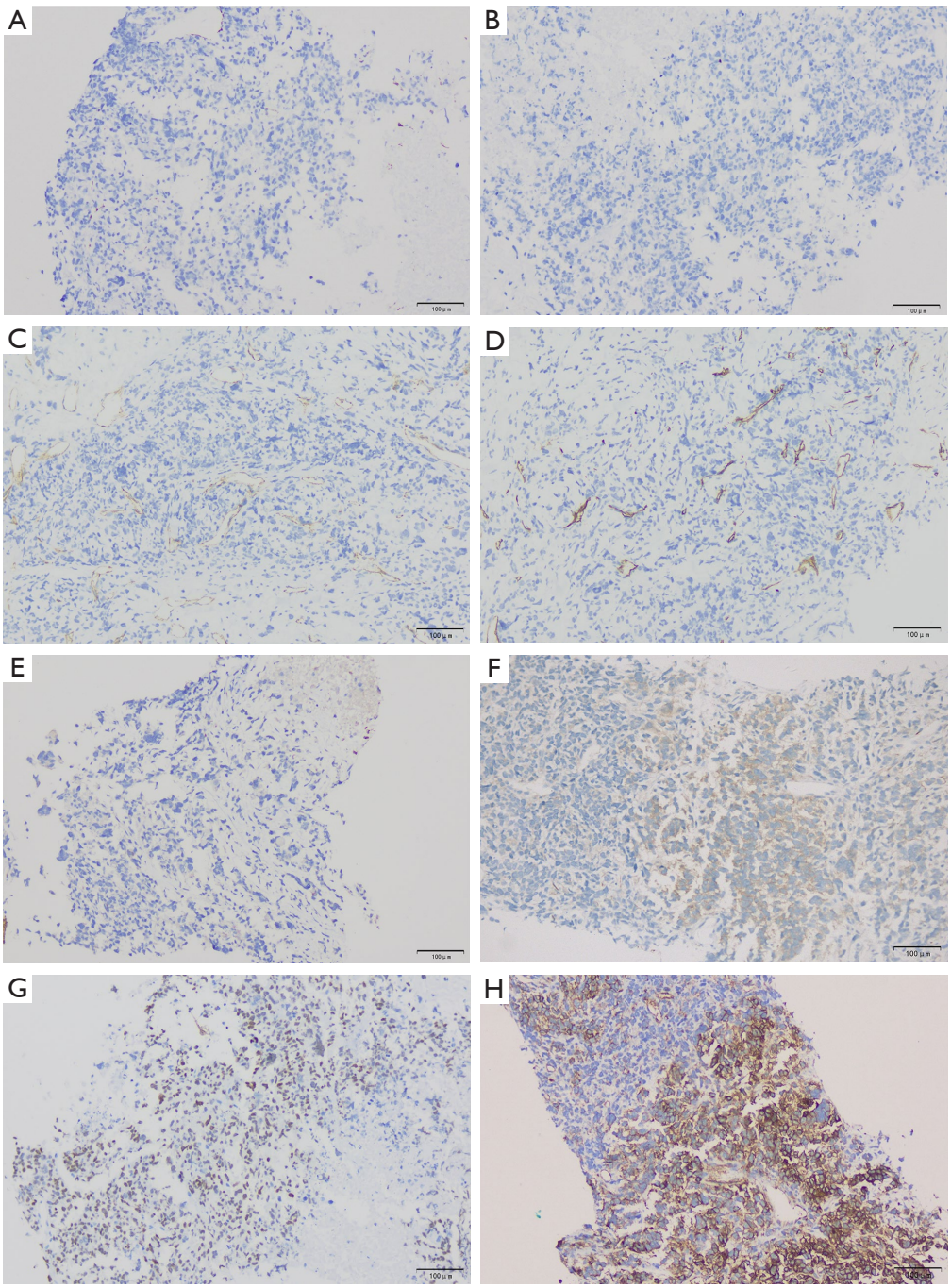

Figure 3 IHC results (20×). (A) SMA, (B) S-100, (C) CD31, (D) CD34 and (E) CK were negative, (F) Desmin were partly positive, (G) WT1 and (H) CD99 were positive. IHC, immunohistochemistry.

molecular detection harboring *CIC-LEUTX* fusion (21). Lake *et al.* reported two cases in childhood gliomas harboring *CIC-LEUTX* fusion, in which one was anaplastic ganglioglioma and the other was anaplastic astrocytoma with epithelioid GBM features (22). Moreover, Song *et al.* reported a 16-year-old man presented CRS with *CIC-LEUTX* gene fusion in intraspinal extramedullary subdural (10). Furthermore, Hu *et al.* reported a unique

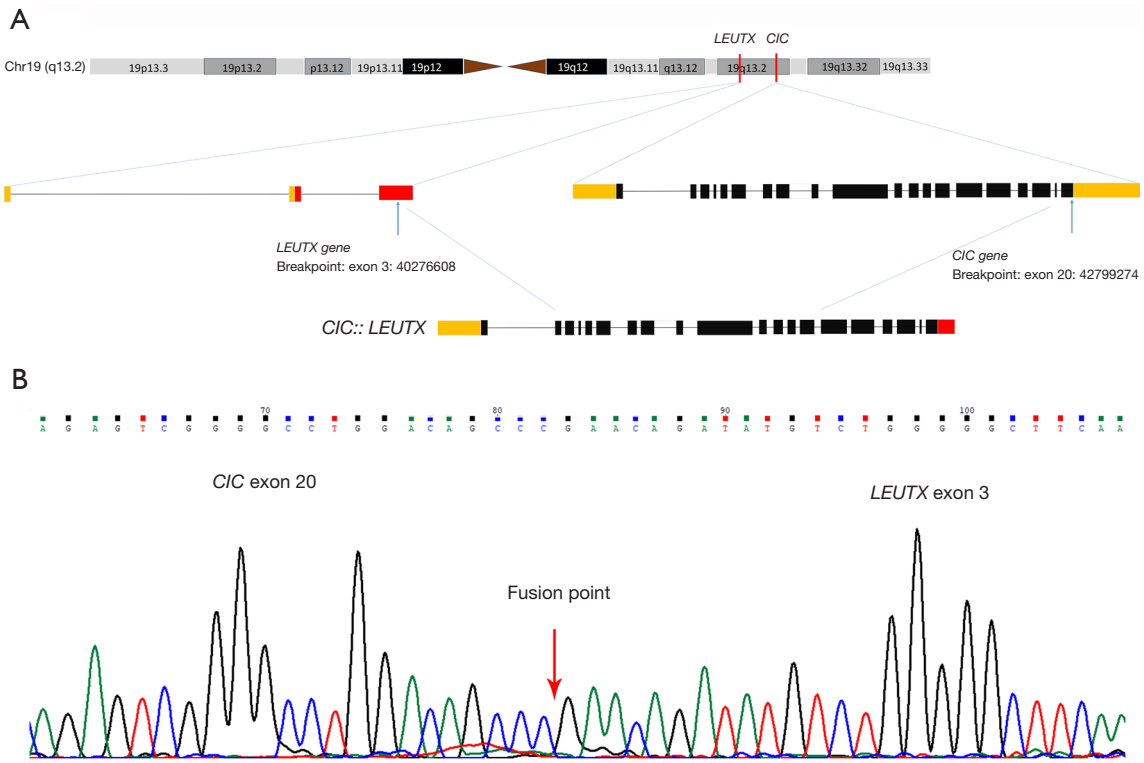

Figure 4 Gene fusion between *CIC* (exon 20) and *LEUTX* (exon 3). (A) Schematic diagram, (B) the result of sanger sequencing in order to validation fusion site. The breakpoints are at chr19: 42799274 and chr19: 40276608 for *CIC* and *LEUTX*, respectively.

pediatric case of central nervous system embryonal tumor harboring the *CIC-LEUTX* fusion (11). All these expanded our understanding on the *CIC-LEUTX* gene fusion in CRS.

The mechanism of *CIC-LEUTX* fusion may be similar with that of *CIC-DUX4* fusion, which is featured by fusion between exon 20 in *CIC* and exon 3 in *LEUTX* (*Figure 4*). The two genes are 2.5 Mb apart in distance at the 19q13.2 locus with similar transcriptional orientation (21). *LEUTX* plays an important role in embryonic genome activation and its expression is mostly repressed after birth. The fusion of the two genes thereby disrupting the C1 motif, of which its function is required for *CIC* to inhibit the DNA binding ability of target genes such as the transcription factor ETV family, affects the repressive activity of *CIC*. *CIC* protein is overexpressed and target genes such as *ETV1*, *ETV4*, *ETV4* are upregulated (21).

There is a lack of optimal chemotherapy regimens and prospective data for CRS patients, especially those with distal metastasis. CRS patients are routinely treated in the same way as EWS using neoadjuvant and adjuvant anthracycline-based multiple chemotherapy regimens, surgery and radiotherapy. Although some sporadic well-treated cases have been reported, patients with CRS still have a poor prognosis, showing a lower 5-year overall survival (OS) than that of the EWS (50% *vs.* 80%). In views of non-cytotoxic treatment, tyrosine kinase inhibitors could be given, but some patients show rapid progression with no response. Available data suggest that CRS is even less sensitive to chemotherapy (23). Our case showed a rapid progression, with an OS of merely 7 months after combined treatment with a variety of chemotherapeutic and targeted drugs. In the future, clinical trials with a large sample size are urgently required to establish appropriate treatment regimens for the CRS harboring various fusions.

Conclusions

In conclusion, we reported a rare case of USRCS harboring *CIC-LEUTX* fusion with renal involvement. RNA-based NGS indicated *CIC-LEUTX* gene fusion between exon 20 of the *CIC* gene and exon 3 of the *LEUTX* gene. The patient showed a poor response after treatment, with an

OS of merely 7 months. This case helps to expand our understanding on the diagnosis and treatment of CRS harboring *CIC-LEUTX* fusion.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-524/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-524/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-524/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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