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Case Report

A case of CIC-rearranged sarcoma with *CIC-LEUTX* gene fusion in spinal cord

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A 16-year-old male was admitted to the hospital for weakness of both lower extremities. Magnetic resonance imaging revealed an intraspinal extramedullary subdural mass at the thoracic 9 level. Microscopically, the tumor cells were small to medium sized and round to ovoid in shape. They were distributed in diffuse sheets or showed nodular appearance. The nucleus of the tumor had mild-to-moderate atypia, with vesicular chromatin and prominent nucleoli. A smaller proportion of tumor cells demonstrated rhabdoid morphology. Focal myxoid stromal change was present, in which tumor cells exhibited spindle shapes. Approximately two mitoses were counted per 10 high-power fields. No necrosis was observed. The tumor cells were focal positive for CD99; multifocal positive for WT1; diffuse positive for nestin, synaptophysin, and D2-40; partial positive for GFAP; focal positive for desmin and SSTR2; and scattered positive for S-100 protein. The Ki-67 labeling index was approximately 20%. Genetic testing revealed *CIC-LEUTX* gene fusion. Considering the patient's history, clinical data, pathological findings and genetic findings, we rendered a rare tumor named CIC-rearranged sarcoma with *CIC-LEUTX* gene fusion.

Key words: *CIC-LEUTX* fusion, immunohistochemistry, RNA-based next generation sequencing, sarcoma, spinal tumor.

INTRODUCTION

CIC-rearranged sarcomas are classified as undifferentiated small round cell sarcomas and uncertain differentiation tumors in mesenchymal tumors of non-meningeal epithelial origin in the 5th edition of the WHO Classification of Tumors of the Soft Tissue and Bone and Tumors of the Central Nervous System, respectively.[1,2] CIC-rearranged sarcomas are most common with *CIC-DUX4* fusions[3] and other rare partner genes, including FOXO4, LEUTX, NUTM1, and NUTM2A.[4–7] Most tumors arise in the deep soft tissue of the trunk and extremities, followed by visceral location. Only two cases of CIC-rearranged sarcoma located in the spinal cord have been reported so far, both of which were *CIC-DUX4* fusion.[8,9] However, the CIC-rearranged sarcomas with *CIC-LEUTX* fusion in the spinal cord have not been reported, and this is the first case.

CLINICAL SUMMARY

The patient, a 16-year-old male, was admitted to the hospital due to acute onset of weakness of both lower extremities for 20 days and aggravation for five days. The patient experienced bilateral lateral thigh soreness and discomfort without obvious predisposing factors 20 days previously, but it resolved spontaneously, followed by weakness of both lower extremities, which was not taken seriously. Then he gradually developed dragging while walking. Five days before presenting at the hospital, the patient was unable to walk or stand, which continued without relief. There was no obvious abnormality in cranial computed tomography (CT), cranial magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) and lumbar MRI, and no special treatment was given in other hospitals. For further diagnosis and treatment, the patient came to the outpatient department of the hospital and planned to be admitted to the neurology department with myelitis. On admission, MRI of the thoracic spine revealed mass isointensity on T1 and T2-weighted images at the level of thoracic 9. The spinal cord was compressed, and the subdural space above and below the lesion was widened (Fig. 1A,B). The mass displayed obvious enhancement onT1-weighted contrast-enhanced images and was approximately 1.2 cm in diameter (Fig. 1C). He was then transferred

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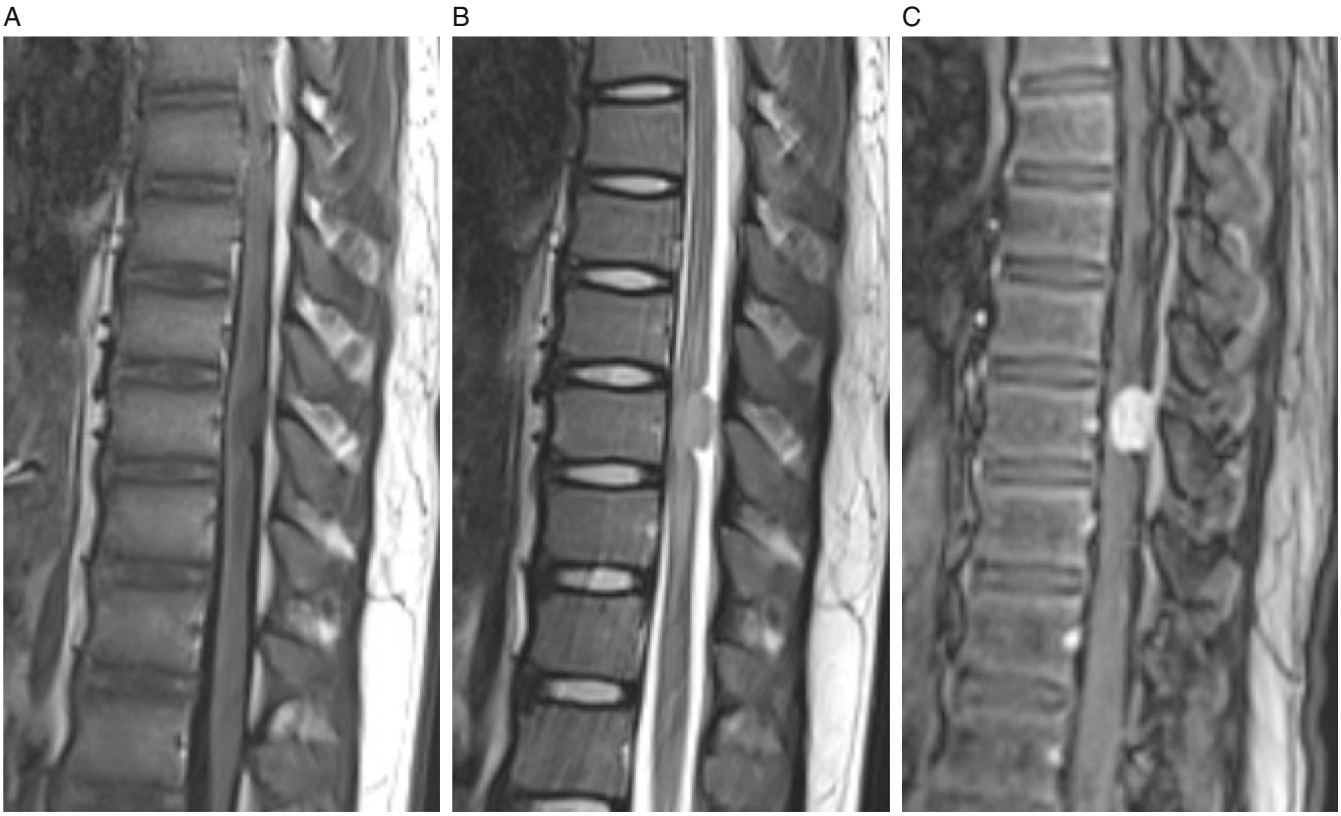

Fig 1 (A) T1-weighted sequences reveal an isointense mass. (B) T2-weighted sequences reveal an isointense mass. (C) The mass displays obvious enhancement in T1-weighted contrast-enhanced images.

to the department of neurosurgery for further surgical treatment. The thoracic 6–9 segments were opened by surgery, and the tumor tissue in the thoracic 9 thoracic canal was found. The tumor was located under the dura mater and related to dura mater closely. The tumor was rubbery and rich in blood supply. The tumor was closely adhered to the spinal cord on the left ventral side, and the boundary was unclear. The boundary was carefully separated to protect the spinal cord, and the tumor was then completely removed. The size of the tumor was approximately $1.2 \times 1.2 \times 1.5$ cm. After the operation, the limb weakness and sensory disturbance were significantly improved, and the patient could walk independently. Two months after the operation, spinal canal radiotherapy and ifosfamide and liposome doxorubicin chemotherapy were performed. Postoperative follow up was uneventful, and the thoracic spine MRI revealed no tumor recurrence at five months.

PATHOLOGIC FINDINGS

On macroscopic examination, the lesion showed a pile of gray-white tissue, measuring $1.5 \times 1 \times 0.4$ cm in size. On hematoxylin and eosin (HE) staining, the case comprised solid proliferation with sheets of tumor cells and exhibited a nodular appearance with thick collagenous septa separating the tumor into compartments locally (Fig. 2A). The tumor cells were small to medium sized and round to ovoid in shape with clear or mildly eosinophilic scant cytoplasm. They were relatively uniform in appearance, but the nuclei showed pleomorphism focally. The nuclei showed coarse chromatin and prominent nucleoli (Fig. 2B). A smaller proportion of tumor cells demonstrated rhabdoid cells with eccentrically located nuclei and extensive eosinophilic cytoplasm (Fig. 2c). The tumor showed focal prominent myxoid stromal change with spindle-shaped cells (Fig. 2D). The mitoses were approximately 2/10 high-power fields, and no hemorrhage or necrosis was observed. In the tumor tissue adjacent to the dura, pigment granules could be observed. Antibodies used for immunohistochemical staining are listed with their hosts, clones, dilutions, and sources in Table 1. The tumor cells were focal positive for CD99 (Fig. 3A); multifocal positive for WT1 with unequal strength (Fig. 3B); diffuse positive for nestin, synaptophysin (Fig. 3C); and D2-40 (Fig. 3D); partial positive for GFAP (Fig. 3E); focal positive for desmin and SSTR2; and scattered positive for S-100 protein. The Ki-67 labeling index was approximately 20% (Fig. 3F). Nuclear INI-1 staining was retained (Fig. 3G), whereas STAT6, PR, EMA, CK, Olig2, PLAP, CD45, HMB45, Melan-A, CD34, CD31, and ERG were negative.

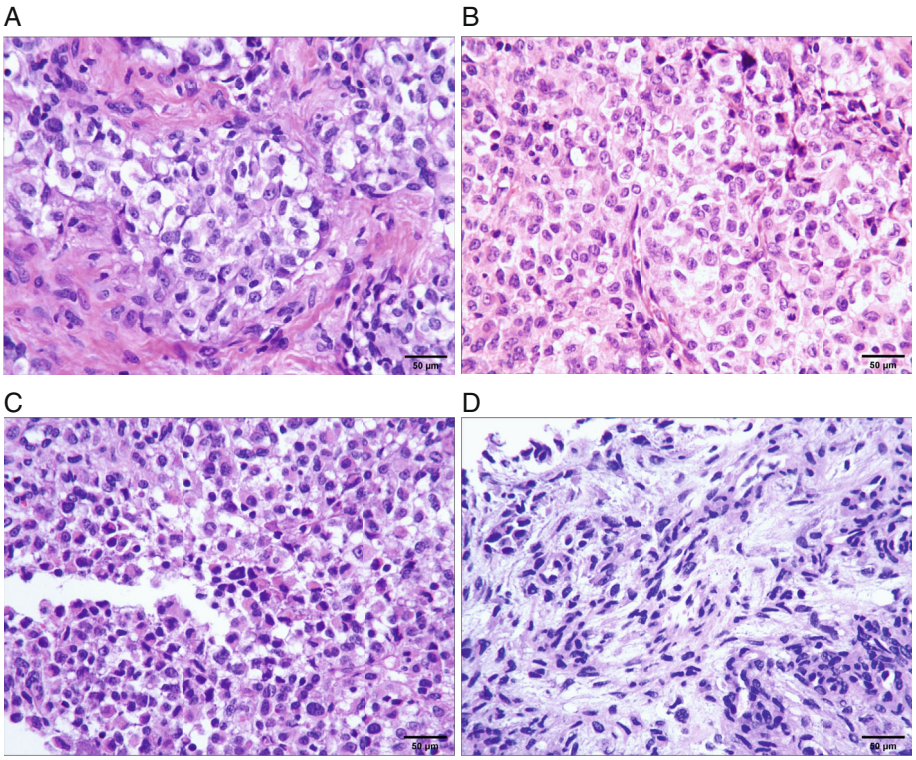

Fig 2 HE staining. (A, B) The tumor shows a nodular appearance or diffuse sheets. The tumor cells are relatively uniform in appearance, but the nuclei show pleomorphism focally. The nuclei shows coarse chromatin and prominent nucleoli. (C) A smaller proportion of tumor cells demonstrates rhabdoid cells with eccentrically located nuclei and extensive eosinophilic cytoplasm. (D) The tumor shows focal prominent myxoid stromal change with spindle-shaped cells.

GENETIC FINDINGS

Fusion testing was performed using an RNA-based next generation sequencing (NGS) assay at Genetron Health (Beijing). Gene test results showed that a fusion of *CIC-LEUTX* genes located in exon 20 of the CIC gene and exon 3 of the LEUTX gene. The breakpoints were at chr19: 42799216 and chr19: 40276580 for CIC and LEUTX, respectively (Fig. 4). Using the same detection method, no mutation was found in IDH1/2, BRAF, TERT, H3F3A, HIST1H3B, and HIST1H3C.

Table 1 List of antibodies used for immunohistochemical staining

Antibody	Host	Clone	Source	Dilution
CD99	Mouse monoclonal	O13	ZSGB, Beijing, China	Prediluted
WT1	Mouse monoclonal	MX012	Maxim, Fujian, Fuzhou, China	Prediluted
nestin	Rabbit monoclonal	EP287	ZSGB, Beijing, China	Prediluted
synaptophysin	Rabbit monoclonal	EP158	ZSGB, Beijing, China	1:300
D2-40	Mouse monoclonal	D2-40	ZSGB, Beijing, China	Prediluted
GFAP	Rabbit monoclonal	EP13	ZSGB, Beijing, China	Prediluted
SSTR2	Rabbit monoclonal	EP149	ZSGB, Beijing, China	Prediluted
S-100 protein	Mouse monoclonal	4C4.9	Celnovte, Henan, Zhengzhou, China	1:300
Ki-67	Mouse monoclonal	MIB-1	ZSGB, Beijing, China	1:300
INI-1	Mouse monoclonal	25	ZSGB, Beijing, China	Prediluted
STAT6	Rabbit monoclonal	EP325	ZSGB, Beijing, China	Prediluted
desmin	Rabbit monoclonal	EP15	ZSGB, Beijing, China	Prediluted
PR	Mouse monoclonal	C4D10	Celnovte, Henan, Zhengzhou, China	1:400
EMA	Mouse monoclonal	GP1.4	ZSGB, Beijing, China	1:100
CK	Mouse monoclonal	AE1/AE3	Celnovte, Henan, Zhengzhou, China	1:400
Olig2	Rabbit monoclonal	EP112	Celnovte, Henan, Zhengzhou, China	1:800
PLAP	Rabbit monoclonal	SP15	ZSGB, Beijing, China	Prediluted
CD45	Mouse monoclonal	2B11&PD7/26	Celnovte, Henan, Zhengzhou, China	1:400
HMB45	Mouse monoclonal	HMB45	Chang Dao, Shanghai, China	Prediluted
Melan-A	Mouse monoclonal	A103	Chang Dao, Shanghai, China	Prediluted
CD34	Mouse monoclonal	QBEnd/10	Celnovte, Henan, Zhengzhou, China	1:300
CD31	Mouse monoclonal	MX032	Maxim, Fujian, Fuzhou, China	Prediluted
ERG	Rabbit monoclonal	MXR004	Maxim, Fujian, Fuzhou, China	Prediluted

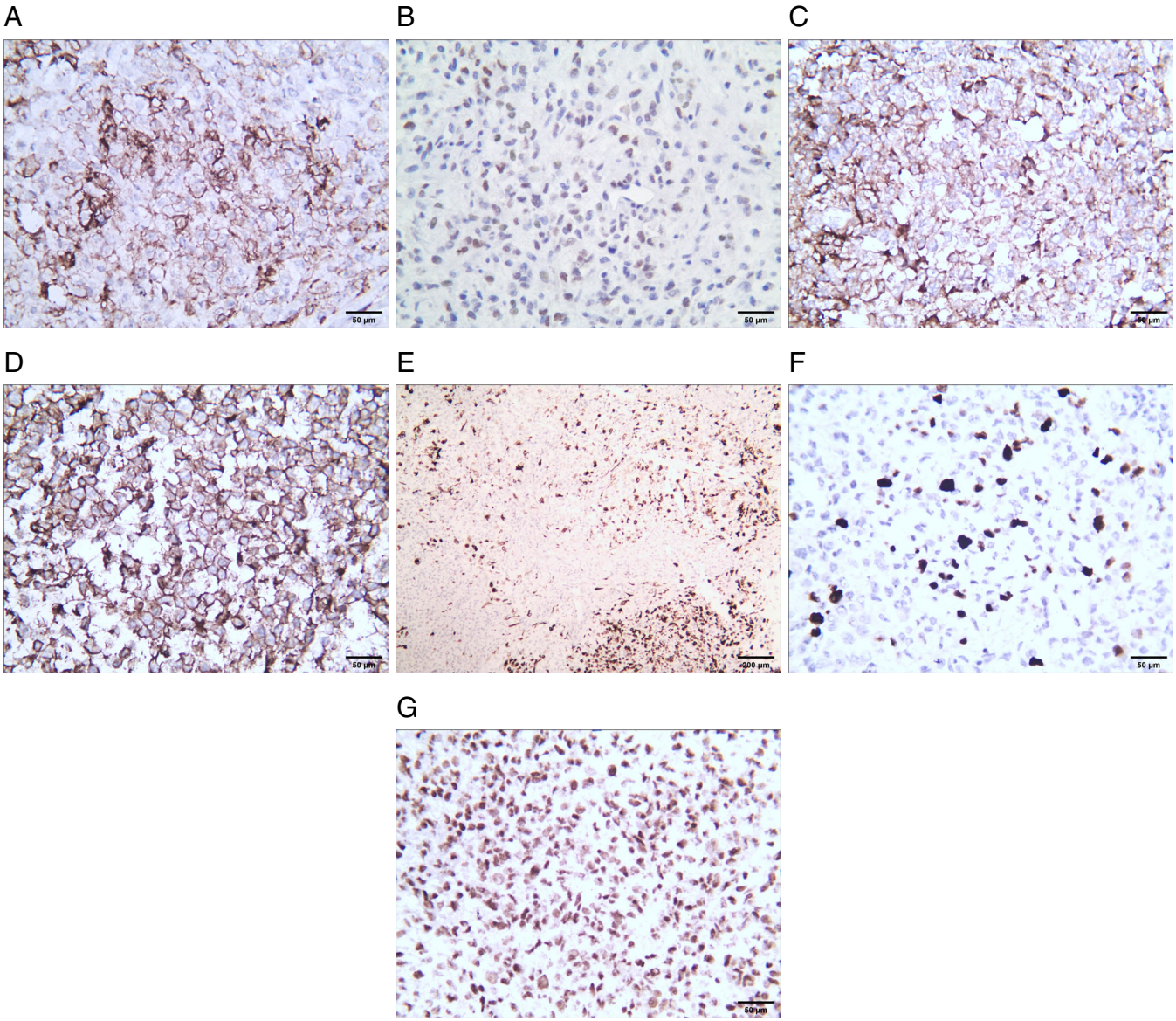

Fig 3 Immunohistochemical staining. (A) CD99 immunostaining is focal positive. (B) WT1 immunostaining is multifocal positive. (C) Synaptophysin immunostaining is diffuse positive. (D) D2-40 immunostaining is diffuse positive. (E) GFAP immunostaining is partial positive. (F) The Ki-67 labeling index is approximately 20%. (G) Nuclear INI-1 staining is retained.

Chromosome 7 was not amplified, and chromosome 10 was not deleted. Chromosome 1p/19q was intact.

DISCUSSION

The first case of t(4;19)(q35;q13.1)-associated sarcoma was reported by Richkind *et al.*[10] in 1996 in a 12-year-old boy who presented with an ankle soft tissue mass and synchronous lung metastases and died within 10 months. In 2006, Kawamura-Saito *et al.*[11] also discovered two cases of *CIC-DUX4* fusion round cell sarcoma diagnosed as Ewing-like sarcoma with chromosomal translocation t(4;19)(q35;q13). However, Choi *et al.*[12] did not recommend the appellation "Ewing-like sarcoma" for *CIC-DUX4* sarcoma despite its superficial resemblance. First, the location of the tumor is different. Ewing sarcoma (ES) most often presents as a primary bone tumor, whereas *CIC-DUX4* sarcoma is most frequently reported in soft tissue tumors. Second, in terms of treatment and prognosis, unlike ES, which is sensitive to chemotherapy, *CIC-DUX4* sarcoma usually appears to quickly develop chemoresistance and has a more aggressive clinical course. In addition, the two types of tumors differ in histology, immunohistochemistry, and molecular characteristics. Specht *et al.*[13] also believed that the distinct gene signature and immunoprofile of *CIC-DUX4* sarcoma suggested a distinct pathogenesis from ES.

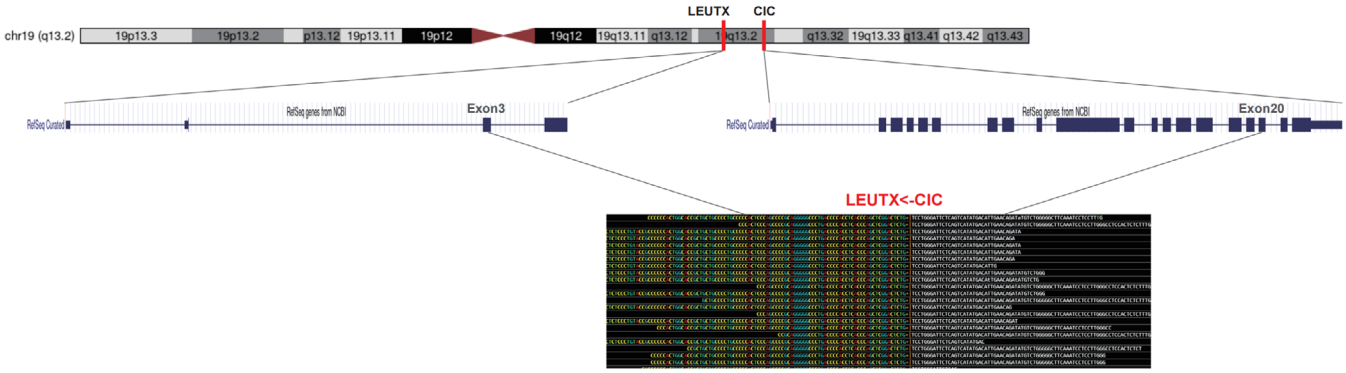

Fig 4 A fusion of CIC-LEUTX genes located in exon 20 of the CIC gene and exon 3 of the LEUTX gene. The breakpoints are at chr19: 42799216 and chr19: 40276580 for CIC and LEUTX, respectively.

Most CIC-rearranged sarcomas occur in the deep soft tissues of the limbs or trunk, followed by the head and neck, retroperitoneum, or pelvis; uncommonly in the viscera including kidney, gastrointestinal tract, or brain; and only rarely with primary osseous involvement. A case of primary cardiac CIC-rearranged undifferentiated sarcoma in an infant was reported recently.[14] There is a wide age range but a predilection for young adults, and there is a slight male predominance.[3] CIC-rearranged sarcomas are typically composed of diffuse sheets of undifferentiated round cells, displaying at least in part a lobulated growth pattern, divided by fibrous septa. A minor component of spindle or epithelioid/ rhabdoid cells may be seen. The tumor cells have relatively uniform cytomorphology but often reveal mild nuclear pleomorphism, with vesicular chromatin and prominent nucleoli. The cytoplasm is lightly eosinophilic or clear. Stromal myxoid change is a common finding, in which tumor cells exhibit reticular or pseudoacinar arrangements. Necrosis is common, and mitotic activity is brisk. Changes in histomorphology after therapy have been reported, included focal pleomorphism cells, eosinophilic cytoplasmic globules, nuclear pseudoinclusions and hyaline cartilage formations.[8,15] Immunohistochemically, these tumors usually show weak CD99 positivity and absent NKX2.2 expression. Hung *et al.*[16] evaluated the expression of ETV4 and WT1 in CIC-rearranged sarcomas and found that the sensitivity and specificity of ETV4 expression were 90% and 95%, respectively. While the sensitivity and specificity of WT1 were 95% and 81%, respectively. It is concluded that diffuse ETV4, along with at least focal WT1 expression, is helpful to distinguish CIC-rearranged sarcoma from ES and other histologic mimics. In addition, a small number of cases can express myogenic markers and cytokeratin, calretinin, neurofilament protein, S-100 protein, ERG, FLI1, MUC-4, and D2-40, but there is no specificity.[3,4,9,13,15] The histomorphological and immunohistochemical findings in this case were similar to those described in the literature. However, pigment granules can be seen in the tumor tissue adjacent to the meninges, which need to be differentiated from melanoma, and the relevant melanoma markers were all negative, which excluded this diagnosis. In this case, GFAP was partially expressed in tumor cells, and there is no report that CIC-rearranged sarcoma expresses GFAP. The tumor location was extramedullary, and glioma-related genes were all negative. Therefore, gliomas were excluded, and it may be caused by a heterogeneous expression of tumor cells.

The CIC gene on 19 q13 encodes a transcriptional repressor with a high-mobility group box. *CIC-DUX4* fusion is the most common form in 95% of CIC-rearranged sarcomas, with DUX4 either on 4q35 or 10q26.[1] The DUX4 fusion to CIC upregulates PEA3 family genes, such as ETV1, ETV4, and ETV5 genes, which might play an important role in tumorigenesis.[11] There are several other rare non-DUX4 partner genes, such as FOXO4, LEUTX, NUTM1, and NUTM2A. It is worth noting that in a report on angiosarcomas, three cases were found to have CIC rearrangement, and one of them had the *CIC-LEUTX* fusion gene.[5] Still, these three cases lacked angiogenesis, and their histology was similar to CIC-rearranged sarcoma. Only vascular-related immunohistochemical markers CD31 and ERG were positive, and these cases were thus classified as angiosarcoma. It is more appropriate to classify them as CIC-rearranged sarcomas based on histomorphological and molecular detection. Two other reports on *CIC-LEUTX* fusion gene occurred in the central nervous system, but neither was a CIC-rearranged sarcoma. One article included two cases of childhood gliomas: one case of anaplastic ganglioglioma and one case of anaplastic astrocytoma with epithelioid GBM features.[17] The other article was a case of an embryonal tumor of the central nervous system in a child. This case not only had the *CIC-LEUTX* fusion gene but also had NBN germline mutations and TSC2 lineage mutations.[18] So far, there are only three reports on

Table 2 Reported cases of tumors with CIC-LEUTX fusion

Reference	Age/sex	Location	Immunohistochemistry	Pathological diagnosis	Genetic alteration	Therapy	Follow up (Month)	Status
Huang *et al*., 2016	26/F	Thigh	Positive:CD31, ERG Negative:CD99,S100, desmin	Angiosarcomas	CIC-LEUTX	NA	10 33	Recured Died
Lake *et al*., 2020	19/F	Frontoparietal	Positive: synaptophysin, NSE	anaplastic ganglioglioma	CIC-LEUTX	GTR RT + TMZ → STR + RT (CSI) + Carboplatin→ cytoxan/doxo/ifos/ etoposide	10 56	Progression Alive, progressive disease
Lake *et al*., 2020	12/F	intraventricular	Positive: GFAP, synaptophysin, CD34	anaplastic astrocytoma with epithelioid GBM features	CIC-LEUTX	GTR + RT/TMZ	3	Alive, on therapy
Hu *et al*., 2020	2/M	left temporal lobe-basal ganglia and left parietal lobe	Positive: synaptophysin Negative: GFAP	CNS embryonal tumor	CIC-LEUTX, TCS2 and NBN	GR (CTX + CBP + VCR/DDP + VP-16), RT, and TSC2 targeted drug (everolimus)	1 11	Progression Alive
This case	16/M	Intraspinal extramedullary subdural	Positive:CD99, WT1, nestin, synaptophysin, D2-40	CIC-rearranged sarcoma	CIC-LEUTX	GRT + RT+ ifos/LD	5	Alive, on therapy

CBP, carboplatin; CSI, craniospinal irradiation; CNS, central nervous system; CTX, cyclophosphamide; DDP, cisplatin; doxo, doxorubicin; GBM, glioblastoma; GR, gross resection; GTR, gross total resection; ifos, ifosfamide; LD, liposome doxorubicin; NA, not applicable; NSE, neuron-specific enolase; RT, radiotherapy; STR, subtotal resection; TMZ, temozolomide; VP-16, etoposide; VCR, vincristine.

CIC-LEUTX fusion tumors, with a total of four cases, and this case is the fifth case (Table 2). The LEUTX gene is located on 19q13. LEUTX plays an important role in embryonal genome activation, and its expression is mostly suppressed postnatally. The fusion with KAT6A was discovered earlier, and it was reported in acute myeloid leukemia.[19] Recent studies suggested that *CIC-LEUTX* fusion mechanisms might be similar to those of *CIC-DUX4* fusion because both LEUTX and DUX4 belong to the same class of paired (PRD) homeobox genes.[5] Barresi *et al.*[20] recently reported a case of malignant epithelioid peripheral nerve sheath tumor in a child with *BRD4-LEUTX* fusion. Increased levels of LEUTX transcripts in the tumor could be detected in this case, suggesting that the *BRD4-LEUTX* fusion leads to LEUTX reactivation.

Only six original articles and a total of nine case reports can be found concerning the CIC-rearranged sarcoma located in the central nervous system.[6,8,9,14,21,22] As to the CIC-rearranged sarcoma located in the spinal cord, only two case reports can be found.[8,9] Genetic testing revealed that both cases were *CIC-DUX4* fusions. The first case was a 15-year-old female with a T5–T6 epidural tumor, and the second case was a 23-year-old male with a C3–C5 intramedullary tumor. Our case was a 16-year-old male, and the tumor was located in the extramedullary subdural space at the T9 level. Because of the location of the tumors, the clinical manifestations of patients were different. The clinical symptoms were back pain, weakness in the extremities, and weakness in both lower extremities separately. Radiological findings also varied in the three patients. MRI revealed hypointensity and isointensity on T1-weighted images in the second case and our case, respectively. After gadolinium administration, the tumors both displayed enhancement. On T2-weighted images, MRI revealed hyperintensity in the other two cases and isointensity in our case. Tumor resection and radiation therapy were performed in all three patients. The first patient and our patient were also treated with chemotherapy. The first patient died of disease after 22 months. The second patient and our patient have survived without tumor progression for 10 and five months, respectively. Maximal safe tumor resection and adjuvant radiation therapy might play an essential role in the management of this rare tumor.[9] The other seven cases were located in the brain, and five of them were detected in *CIC-NUTM1* gene fusion. *CIC-NUTM1* fusion seems to exhibit significant tropism for the central nervous system.

CIC-rearranged sarcomas should first be differentiated from ES. Although both are small round cell tumors and may have glycogen-rich cytoplasm. CIC-rearranged sarcomas showed significantly higher degrees of lobulation, nuclear pleomorphism, the prominence of the nucleoli, spindle cell elements, and myxoid changes. The CD99 expression was focal and heterogenous in the CIC-rearranged sarcomas, whereas in the ES, its expression was diffuse and strong.[14] Yoshimoto *et al.*[23] found that CCND2 and MUC5AC are reliable biomarkers to distinguish *CIC-DUX4* sarcoma from ES. In addition, it should be differentiated from other small round cell tumors and epithelioid cell tumors, such as atypical teratoid/rhabdoid tumors, sarcomas with BCL-6 interacting corepressor genetic alterations, alveolar rhabdomyosarcomas, poorly differentiated synovial sarcomas, lymphoma, desmoplastic small round cell tumors, carcinomas, and melanomas. There is clinicopathologic overlap between these tumors, and they can be initially identified by immunohistochemistry. The final diagnosis needs to rely on genetic testing. Fluorescence *in situ* hybridization analysis had a significant risk of false-negative results, while NGS-based diagnostic methods were more sensitive.[24] CIC-rearranged sarcoma can be accurately classified by DNA methylation array analysis.[25,26]

The prognosis of CIC-rearranged sarcoma is aggressive in clinical course and is prone to metastasis, most often to lung, liver, brain, lymph nodes and bone. CIC-rearranged sarcoma has a significantly worse prognosis than ES and has a poor response to chemotherapy for ES.[1,3,14] With the in-depth study on the molecular mechanism of CIC-rearranged sarcoma, targeted molecular therapy based on precision therapy has made progress. Oyama *et al.*[27] found that bortezomib and crizotinib can significantly suppress tumor cell growth in *CIC-DUX4* sarcoma *in vitro*. Yoshimoto *et al.*[23] found that palbociclib and trabectedin can block the growth of *CIC-DUX4* sarcoma in mice. The optimal treatment for patients with CIC-rearranged sarcoma remains to be further clarified, and a large number of clinical trials and comprehensive analysis of multi-institutional data is required.

DISCLOSURE

The authors declare no conflict of interest.

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