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Teaching case

Primary undifferentiated small round cell sarcoma of the deep abdominal wall with a novel variant of t(10;19) *CIC-DUX4* gene fusion

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ABSTRACT

We experienced a 38-year-old Japanese male with t(10;19) *CIC-DUX4* –positive undifferentiated small round cell sarcoma in the deep abdominal wall. Three months before his first visit to our hospital, he noticed a mass in his right abdominal wall. Computed tomography on admission revealed a solid abdominal tumor 70 × 53 mm in size and multiple small tumors in both lungs. The biopsy of the abdominal tumor revealed undifferentiated small round cell sarcoma, suggestive of Ewing sarcoma. Under the clinical diagnosis of Ewing-like sarcoma of the abdominal wall with multiple lung metastases, several cycles of ICE (ifosfamide, carboplatin and etoposide) therapy were performed. After the chemotherapy, the lung metastases disappeared, while the primary lesion rapidly grew. Additional VDC (vincristine, doxorubicin and cyclophosphamide) therapy was carried out without apparent effect. Although the surgical removal of the primary lesion was done, peritoneal dissemination and a huge metastatic liver tumor appeared thereafter. The patient died of disease progression two months after the surgery. The total clinical course was approximately one year, showing that the tumor was extremely aggressive. The tumor cells of the surgical specimen were positive for CD99, WT1, calretinin, INI1, ERG and Fli1 by immunohistochemistry. Fusion gene analyses using the frozen surgical material revealed negativity for *EWSR1-Fli1*, *EWSR1-ERG* and t(4;19) *CIC-DUX4* fusions, but positivity for t(10;19) *CIC-DUX4* fusion. Thus, we made a final pathological diagnosis of t(10;19) *CIC-DUX4* –positive undifferentiated small round cell sarcoma. To our knowledge, this is the 13th case of t(10;19) *CIC-DUX4* undifferentiated small round cell sarcoma with precise clinico-pathological information. Especially in our case, two types of t(10;19) *CIC-DUX4* fusion transcripts were observed, both of which are in-frame and novel.

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1. Introduction

CIC-DUX4 –positive undifferentiated sarcomas are a group of *EWSR1* –negative small round cell tumors or Ewing-like sarcomas. They have fusion of human homologue of the *Drosophila capicua* (*CIC*) gene on chromosome 19 and the double homeobox 4 (*DUX4*) retrogene on chromosome 4 or 10 [1–4]. As the result of duplication event during evolution, one *DUX4* gene is present at the end of chromosome 4 (*DUX4*) and the other at chromosome 10 (*DUX4L*) [2]. Among *CIC* –rearranged sarcomas, 2 *CIC-FOXO4* (forkhead box O4 gene on X chromosome) fusion-positive sarcomas were also

reported [5,6]. These *CIC* –rearranged sarcomas mainly arise from the soft tissue. On the other hand, *BCOR-CCNB3* –positive Ewing-like sarcomas preferentially occur in children and in the bone [7]. Recently, undifferentiated small round cell sarcomas with novel *BCOR-MAML3* and *ZC3H7B-BCOR* gene fusions were found further [8]. Thus, atypical Ewing sarcomas with *EWSR1* –rearrangement are reported [9,10], while *EWSR1* –negative Ewing-like sarcomas also exist. In that context, *CIC-DUX4* –positive primitive small round cell sarcoma was identified. This discovery of *CIC-DUX4* –positive sarcoma is of great importance in the understanding of Ewing sarcomas and Ewing-like sarcomas. Using *CIC* break-apart fluorescent in situ hybridization (FISH), Yoshida et al., identified 20 cases of *CIC* –rearranged sarcomas [11]. They showed that the overall survival of 20 cases of *CIC* –rearranged sarcomas is significantly worse than that of 53 cases of *EWSR1* –rearranged Ewing sarcomas. They concluded that *CIC* –rearranged sarcomas should be considered as

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a separate clinicopathological entity rather than the tumors of the same family. Sprecht et al., also proposed that it is reasonable to regard *CIC-DUX4*-positive sarcomas as a stand-alone category [3]. Recently, Antonescu et al., also reported the same conclusion that *CIC*-rearranged sarcomas are a distinct pathological and molecular entity from *EWSR1*-rearranged Ewing sarcomas [12].

Here, we report a highly aggressive primitive small round cell sarcoma with *t*(10;19) *CIC-DUX4* fusion. Reverse Transcription-Polymerase Chain Reaction (RT-PCR) analyses identified the two types of transcripts, both of which are in-frame with 27-base difference. The fusion pattern is novel and the existence of the multiple fusion transcripts has not been reported yet.

2. Clinical presentation

A 38-year-old Japanese male noticed an enlarging mass in the deep soft tissue of his right abdominal wall 3 months before his

first visit to the Department of Orthopaedic Surgery, Hyogo College of Medicine. On admission, a soft tissue mass (Fig. 1A), 70 × 53 mm in size, was observed by abdominal CT (Fig. 1B), and chest CT indicated multiple tumors in both lungs (data not shown). Although the biopsy specimen of the tumor revealed undifferentiated small cell sarcoma suggestive of Ewing sarcoma, the fusion-gene analyses by RT-PCR using formalin-fixed paraffin embedded biopsy material showed neither *EWSR1-Fli1* nor *EWSR1-ERG* fusion. Under the clinical diagnosis of Ewing-like sarcoma of the deep abdominal wall with lung metastases, several cycles of ICE (ifosfamide, carboplatin and etoposide) therapy were performed. After the chemotherapy, lung metastases disappeared, while the primary lesion rapidly grew (143 × 99 × 82 mm in size on abdominal CT, Fig. 1C). The primary lesion further enlarged even after the additional VDC (vincristine, doxorubicin and cyclophosphamide) chemotherapy. Surgical resection of primary lesion combined with small intestine and right-sided colon (Fig. 1D) was performed. After the surgery,

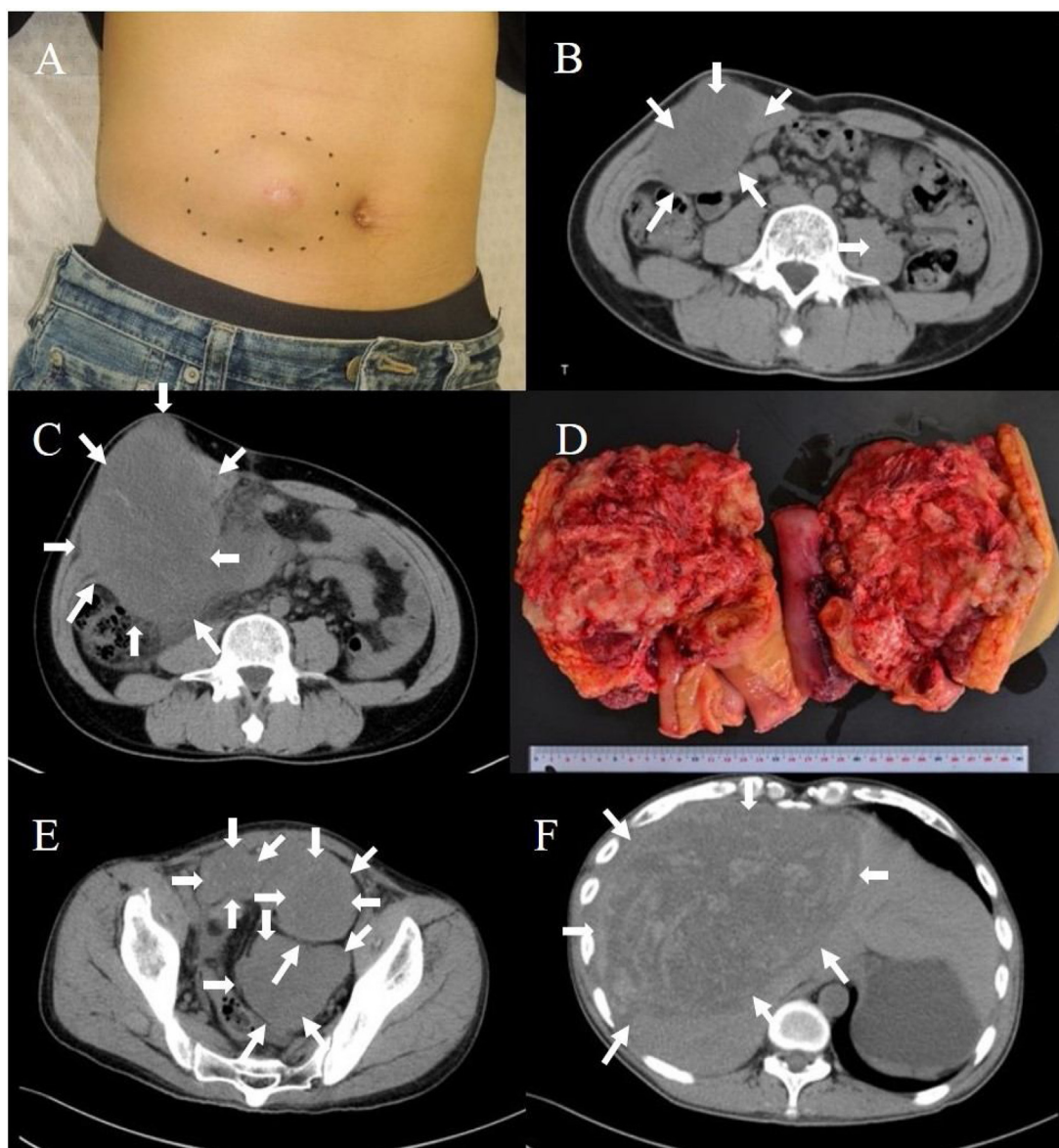


Fig. 1. Radiological and macroscopic findings.

Fig. 1A shows the photograph of the patient's abdomen at the first visit to our hospital. The tumor is pushing the skin upward. Radiographic findings on admission (Fig. 1B) and at 6 month later (Fig. 1C) show rapidly growing mass in the right deep abdominal wall. Surgically resected specimen shows the white tan cut surface of the tumor which invades the intestine (Fig. 1D). Two months after the surgical removal, multiple nodules in the pelvis and a huge hemorrhagic mass in the liver appeared (Fig. 1E & 1F).

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