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Secondary *CIC*-rearranged sarcoma responsive to chemotherapy regimens for Ewing sarcoma: A case report

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Abstract. Capicua transcriptional repressor *(CIC)*-rearranged sarcoma is an Ewing-like sarcoma with an aggressive clinical course and poor prognosis. No standard treatment has been established. The present study describes a case of *CIC*-rearranged sarcoma with lung metastases developing in a 24-year-old woman as a therapy-associated malignancy following chemotherapy for anaplastic large cell lymphoma at nine years old. This was treated with palliative regimens used for Ewing sarcoma. The patient achieved disease control for one year. Of note, ifosfamide and etoposide (IE), which were used as a second line treatment lead to a partial response. The case described in the present study indicated that treatment with Ewing regimens is a reasonable option for patients with metastatic *CIC*-rearranged sarcoma, including those with a second malignant case.

Introduction

Undifferentiated small-cell sarcomas are soft tissue malignancies which are characterized by small, round to ovoid cytomorphology with a high nuclear/cytoplasmic ratio. The most frequent one is Ewing sarcoma, which is characterized by EWS RNA binding protein 1 (*EWSR1*)-erythroblast transformation-specific (*ETS*) gene fusions, and others without theses fusions are called 'Ewing-like sarcomas'. Based on the discovery of novel molecular driving events, recent studies have enabled the identification of two distinct subgroups, these are, capicua transcriptional repressor (*CIC*)-rearranged sarcoma and BCL6 corepressor (*BCOR*)-rearranged sarcoma, within this previously uncharacterized group of Ewing-like sarcomas (1,2). In *CIC*-rearranged sarcoma, *CIC* is fused to double homeobox 4 (*DUX4*) with either t(4;19)(q35;q13.1) or t(10;19)(q26.3;q13) translocation, which are associated with oncogenesis, tumor development, and metastatic capability (1,3,4). On the other hand, *BCOR* is fused to mainly cyclin B3 (*CCNB3*) (5). These entities have different clinicopathological features. Of note, *CIC*-rearranged sarcomas are associated with an aggressive clinical course and poor prognosis compared to Ewing sarcoma (3). Median overall survival of patients with metastatic *CIC*-rearranged sarcoma is only 9-10 months (6,7). The efficacy of chemotherapy has not been prospectively evaluated, and no standard treatment has been established (7,8). Compared to *CIC*-rearranged sarcomas, *BCOR*-rearranged sarcomas have a much better prognosis (5,7), although no standard treatment for these tumors has been established either.

Here, we describe a case of metastatic *CIC*-rearranged sarcoma which developed years after chemotherapy for lymphoma that included alkylating agents and anthracycline, and was palliated with chemotherapy used for Ewing sarcoma.

Case report

The patient was a 24-year-old Japanese woman who had a past medical history of anaplastic large cell lymphoma at nine years old, treated with chemotherapy based on the ACLC99 protocol (9) and JACLS NHL-98 protocol (10), with subsequent autologous hematopoietic stem cell transplantation. These protocol regimens included cytotoxic drugs such as alkylating agents and anthracyclines. The cumulative dose of doxorubicin (DOX) was 150 mg/m^2. She had been in long-term complete remission.

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Abbreviations: Act-D, actinomycin-D; CPA, cyclophosphamide; DOX, doxorubicin; IE, ifosfamide and etoposide; TRB, trabectedin; VCR, vincristine

Key words: *CIC*-rearranged sarcoma, Ewing-like sarcoma, chemotherapy, ifosfamide, etoposide, secondary sarcoma

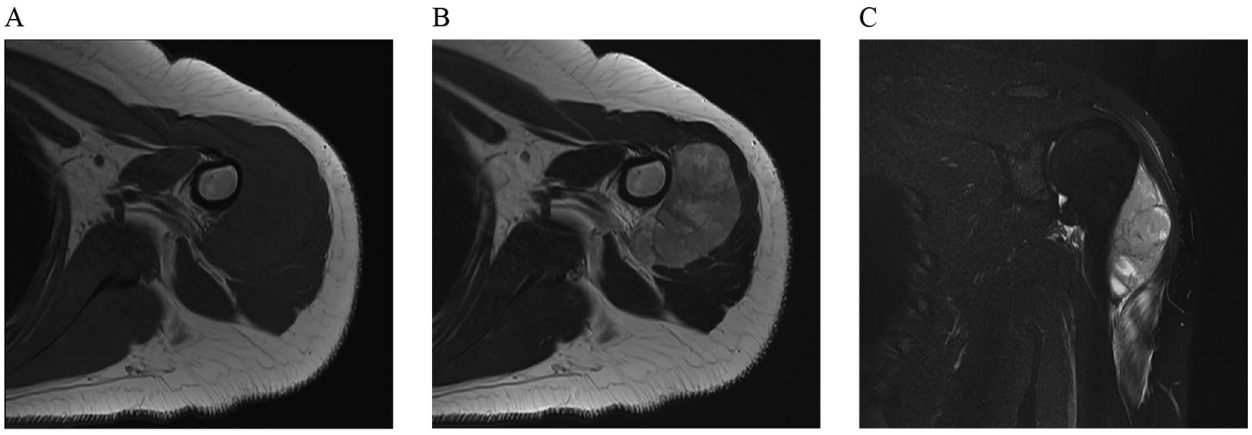

Figure 1. MRI of the tumor at presentation. A 5 cm long mass is isointense on (A) T1-weighted imaging, and (B) hyperintense on T2-weighted imaging and (C) short inversion time inversion recovery imaging.

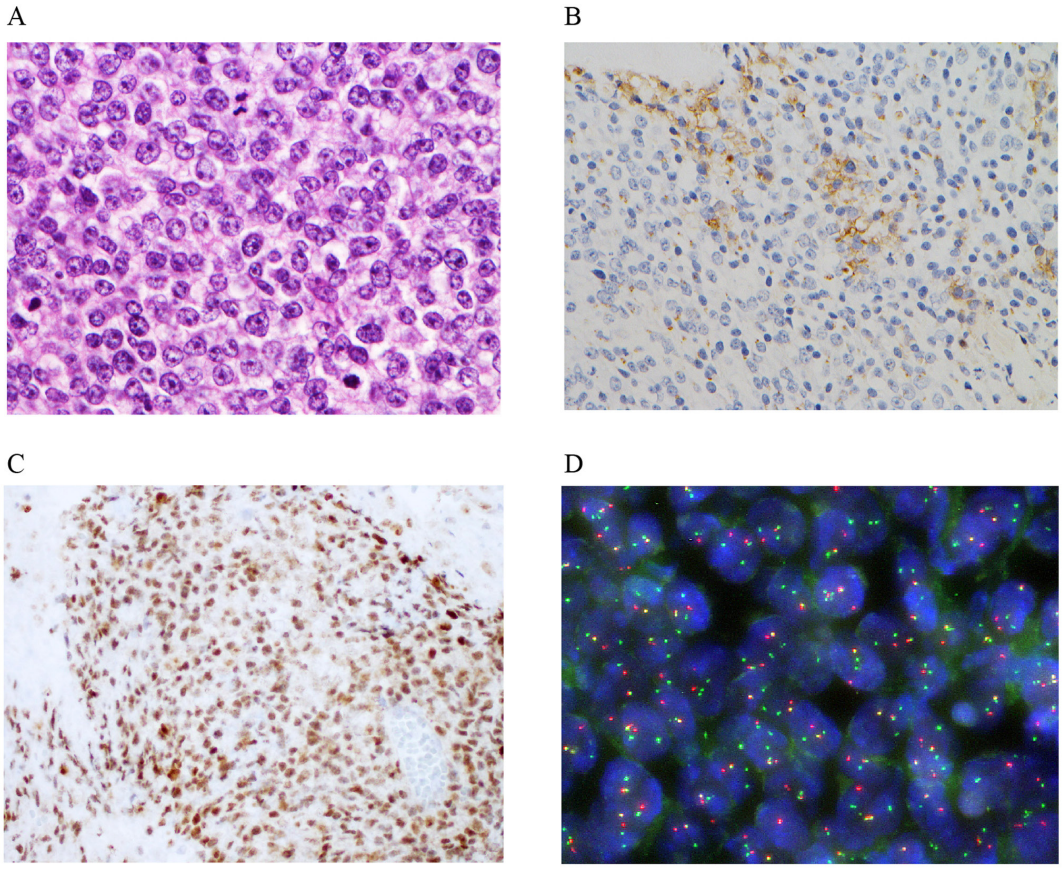

Figure 2. Small round atypical cells with a high nuclear/cytoplasmic ratio grow in sheets. (A) Hematoxylin and eosin stains. Magnification, x100. (B) Tumor cells are focally positive for CD99 and show strong and diffuse positive staining for (C) ETV4. Magnification, x40. (D) Fluorescence *in situ* hybridization shows the rearrangement of CIC gene. Split of green (5' part) and orange (3' part) signals. ETV4, ETS variant transcription factor 4.

She was referred to our hospital after presenting with pain and swelling of the left shoulder in May 2018. A magnetic resonance imaging (MRI) scan of the left shoulder revealed a 5 cm soft tissue mass located between the deltoid and humerus (Fig. 1A-C). Open biopsy was performed. Small round atypical cells with a high nuclear/cytoplasmic ratio grew in sheets (Fig. 2A) and formed alveolar structures with necrosis and fibrosis. Immunohistochemically, tumor cells were positive for WT-1, calretinin and ETS variant transcription factor 4 (ETV4), and focally positive for CD99 (Fig. 2B and C). Fluorescence *in situ* hybridization demonstrated *CIC* rearrangement (Fig. 2D). Based on these findings, the tumor was diagnosed as *CIC*-rearranged sarcoma. Detail of fusion partner did not be studied. CT scan revealed multiple nodules in the lungs, which were consistent with metastases.

The clinical course is summarized in Fig. 3A. First-line palliative chemotherapy with DOX, vincristine (VCR), and cyclophosphamide (CPA) was initiated in June 2018 (Fig. 3B).

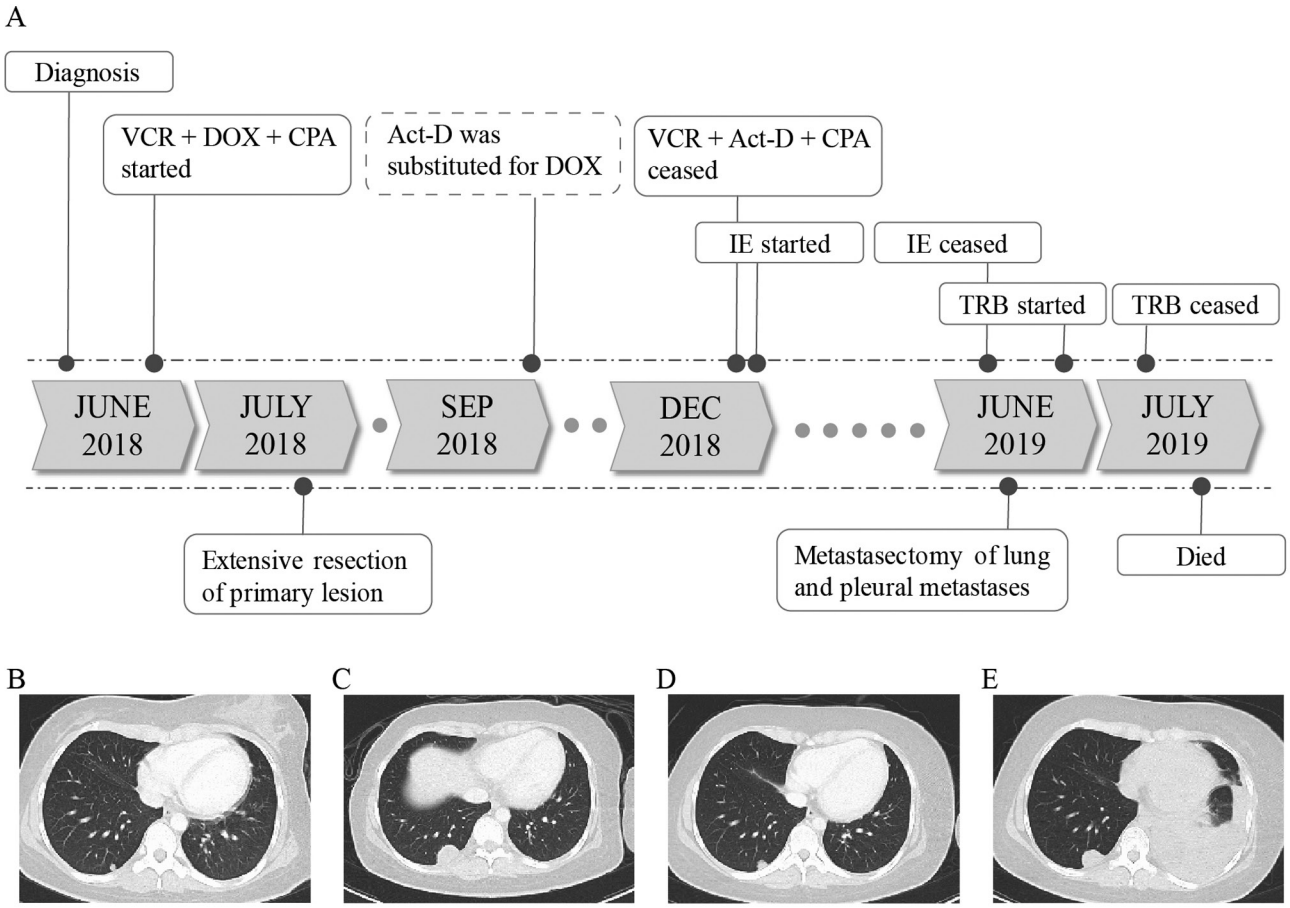

Figure 3. Summary of clinical course. (A) Course of treatment including chemotherapy and surgery. (B) Baseline CT scan in June 2018 shows small bilateral nodules. (C) A period of six months after the initiation of doxorubicin, vincristine and cyclophosphamide, progression of lung metastases is observed. (D) IE achieved a partial response confirmed in April 2019. (E) Disease progression was observed in June 2019. IE, ifosfamide and etoposide; VCR, vincristine; DOX, doxorubicin; CPA, cyclophosphamide; TRB, trabectedin.

After the first cycle, the lung metastases had shrunk, but the primary lesion had not changed. The patient underwent a wide resection of the primary lesion with replacement using artificial humeral head in July 2018 to improve her quality of life. Pathological response to initial chemotherapy was poor. DOX, VCR, and CPA were restarted. At the end of the third cycle, her cumulative lifetime exposure of DOX had reached 350 mg/m^2. We substituted actinomycin-D (Act-D) for DOX beginning with the fourth cycle to avoid cardiotoxicity (11). The *CIC*-rearranged sarcoma was well-controlled during six cycles, although adverse events occurred, including grade 3 febrile neutropenia and septic arthritis requiring debridement. Six months from the beginning of therapy, progression of the lung metastases developed (Fig. 3C).

We administered ifosfamide and etoposide as second-line treatment. We planned 1,800 mg/m^2 of ifosfamide per day for five days and 100 mg/m^2 of etoposide per day over the same five days every three weeks. Two cycles of IE achieved a good response in the lung metastases as seen on CT scan; this response lasted for 4 months (Fig. 3D). However, persistent grade 2 anorexia due to chemotherapy impaired her quality of life. In addition, some evidences have suggested that pulmonary metastasectomy may be associated with clinical benefit (12,13). As extrapulmonary metastases had not appeared, after careful discussion among the multidisciplinary team and the patient, we planned a pneumonectomy for pulmonary oligometastases for improvement of prognosis and quality of life with subsequent chemotherapy holiday after 5 cycles of IE. Despite rapid progression of the lung metastases, with a left pleural effusion appearing right before surgery (Fig. 3E), pneumonectomy and maximum debulking of the pleural metastases were performed. However, not all residual disease could be resected.

Following surgery, an aggressive clinical course was maintained. As rapidly progressive malignant pleural effusion developed, pleurodesis was performed. Although we started trabectedin (TRB) as third-line therapy, no clinical benefit was observed. She died one month later. Her overall survival from diagnosis was 13 months.

Discussion

No molecular-based targeted therapy or cancer immunotherapy for the treatment of *CIC*-rearranged sarcomas has been reported, and chemotherapy with cytotoxic agents is still generally used. The available data on treatment for metastatic *CIC*-rearranged sarcoma come from small retrospective studies. Because of the low incidence and variations in treatment, some cases were formerly diagnosed and treated as other sarcomas without pathognomonic molecular analysis (6,7,14). Palmerini *et al* reported that in first-line settings for metastatic *CIC*-rearranged

sarcoma, response rates to a Ewing regimen and another regimen (DOX and ifosfamide, unknown regimen) were 57% (n=8/14) and 0% (n=0/4), respectively (8). In addition, neoadjuvant chemotherapy with Ewing regimen achieved pathological response in 3 of 10 localized *CIC*-rearranged sarcoma (6). These findings suggest that chemotherapy with the Ewing regimens seems to be effective for patients newly diagnosed with metastatic *CIC*-rearranged sarcoma, albeit that further studies are warranted.

IE is an effective regimen for treatment of recurrent Ewing sarcoma (15). This regimen is not widely used in treatment for advanced soft tissue sarcoma (16,17), although minimum activity has been reported in small phase 2 trial (18). IE is commonly used with DOX, VCR, and CPA (VDC-IE) for treatment of localized Ewing sarcoma based on the results of a randomized phase 3 trial, but the same trial revealed that VDC-IE did not improve the outcome for patients with metastatic disease (19). Thus, we did not use VDC-IE in our first-line palliative treatment but did use it for second-line treatment. To our knowledge, this is the first case with a response to an IE regimen without DOX for refractory *CIC*-rearranged sarcoma. Unfortunately, the patients showed poor prognosis regardless palliative chemotherapy. However, Ewing regimens, especially IE regimen achieved clinically meaningful disease control in this case, considering to highly aggressive clinical course after IE regimen failure.

There is no established treatment for Ewing sarcoma refractory to both DOX, VCR, and CPA and to IE. TRB, a tetrahydroisoquinoline alkaloid, showed anti-tumor activity in *CIC*-rearranged sarcoma in a xenograft model (4). Preclinical and clinical studies have shown that TRB has an anti-tumor effect in several translocation-related sarcomas (20-22). Therefore, we used TRB as third-line palliative therapy based on these findings, but saw no clinical benefit. Interestingly, TRB did not demonstrate sufficient activity against relapsed Ewing sarcoma in a phase 2 trial (23). Of ten evaluable patients, there were no partial responses, one case of stable disease, and nine cases of progressive disease. Based on the above, the clinical response to chemotherapy in our case was concordant with the clinical chemosensitivity of Ewing sarcoma.

Our case is the first report of secondary *CIC*-rearranged sarcoma. Secondary sarcoma associated with prior chemotherapy is well known. Various treatment-related factors are associated with the development of secondary sarcoma, including exposure to alkylating agents and/or anthracyclines and a history of autologous hematopoietic stem cell transplantation (24,25). Most secondary sarcoma belong to the category with non-recurring genetic aberrations, including undifferentiated pleomorphic sarcoma, osteosarcoma, and malignant peripheral nerve sheath tumor (26). Ewing sarcoma accounts for only 5% of secondary sarcomas (24). However, *CIC*-rearranged sarcoma could have been overlooked in cases where pathognomonic molecular analysis was not performed. It is uncertain whether the clinical outcome differs between primary and secondary *CIC*-rearranged sarcoma. In our case, the previous treatment history restricted the use of DOX because of the patient's cumulative exposure.

In conclusion, we describe a case of metastatic *CIC*-rearranged sarcoma treated with palliative chemotherapy, beginning with an Ewing regimen, both VDC and IE. Our case and the best available clinical evidence suggest that treatment with Ewing regimens is a reasonable option for patients with metastatic *CIC*-rearranged sarcomas, including second malignant case.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

SK and YI made substantial contributions to the conception and design of the study. SK, YI, NK, HT, SM, TKo TH, MK, TKa, and HH substantial contributions to the acquisition of the data. SK and YI confirmed the authenticity of the raw data and drafted the manuscript. YFuj, YFun, MT and HM made substantial contributions to the analysis and interpretation of the data and were involved in revising the manuscript critically for important intellectual content. TH and MK contributed pathological diagnosis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of the clinical data and images.

Competing interests

The authors declare that they have no competing interests.

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