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Cardiac Tamponade as an Unusual Initial Clinical Manifestation of *CIC-DUX4* Sarcoma

Authors' Contribution:
 Study Design A
 Data Collection B
 Statistical Analysis C
 Data Interpretation D
 Manuscript Preparation E
 Literature Search F
 Funds Collection G

ABCDEF 1 **Akira Maekawa**
 ABDEF 1 **Tomoya Matsunobu**
 A 1 **Akira Nabeshima**
 B 2 **Suguru Fukushima**
 BC 3 **Kosuke Makihara**
 BC 4 **Masanori Hisaoka**
 AE 1 **Yukihide Iwamoto**

1 Department of Orthopedic Surgery, Kyushu Rosai Hospital, Kitakyushu, Fukuoka, Japan
 2 Department of Musculoskeletal Oncology, National Cancer Center Hospital, Tokyo, Japan
 3 Department of Pathology, Kyushu Rosai Hospital, Kitakyushu, Fukuoka, Japan
 4 Department of Pathology and Oncology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan

Corresponding Author: Tomoya Matsunobu, e-mail: matsunob@ortho.med.kyushu-u.ac.jp

Conflict of interest: None declared

Patient: **Male, 48-year-old**
Final Diagnosis: **Cardiac tamponade**
Symptoms: **Hypotension • tachycardia**
Medication: —
Clinical Procedure: —
Specialty: **Oncology**

Objective: **Unusual clinical course**

Background: *CIC*-rearranged sarcoma (CRS) is a recently described subset of undifferentiated small-round-cell sarcomas of bone and soft tissue. *DUX4* is the most common gene involved in CRS. CRS usually presents in the soft tissue of the trunk and extremities, and is recognized as being clinically aggressive, with poor prognosis. Our case highlights an unusual presentation of CRS with cardiac tamponade.

Case Report: A 48-year-old man presented with hypotension caused by hemorrhagic cardiac tamponade. ¹⁸F-fluorodeoxyglucose-positron emission tomography showed increased uptake in multiple lesions, including lesions in the left proximal humerus and several lymph nodes. Biopsy specimens of the humerus revealed proliferation of round-shaped cells. In addition, *CIC-DUX4* gene rearrangement was detected by polymerase chain reaction and direct sequencing, leading to a diagnosis of cardiac tamponade caused by CRS. Although the patient received systemic chemotherapy as well as radiotherapy to the mediastinal lesion and left humerus, he died of progressive disease 12 months after diagnosis.

Conclusions: Because CRS is a recently proposed entity that is distinct from Ewing sarcoma, the clinical presentation and outcome of CRS has not been well documented in the literature. This is the first case report of CRS presenting as cardiac tamponade. Although cardiac tamponade due to metastatic sarcoma is extremely rare, CRS can be included in the differential diagnosis.

Keywords: **Cardiac Tamponade • Sarcoma • Translocation, Genetic**

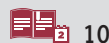
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Background

CIC-DUX4 sarcoma, the most common type of *CIC*-rearranged sarcoma (CRS), has been described as an aggressive soft-tissue tumor associated with *CIC-DUX4* fusion that results in either a t(4;19)(q35;q13) or t(10;19)(q26;q13) translocation [1]. Although CRS has a partial morphologic overlap with Ewing sarcoma, molecular data suggest that CRS has a distinct pathogenesis [2]. There is a wide age range at presentation (median age, 25-35 years) with a slight predominance in males, and CRS occurs in any site of deep soft tissue, including the limbs, trunk, and retroperitoneum, but primary osseous involvement is rare (<5%) [3]. CRS exhibits poor prognosis compared with other small-round-cell sarcomas, and its 5-year survival rate is less than 50%. However, the clinical presentation of CRS is still unclear [4].

Cardiac tamponade occurs when liquid that has accumulated in the pericardial sac restricts diastolic expansion and causes hemodynamic instability [5]. Malignant cardiac effusion with subsequent cardiac tamponade is an oncologic emergent condition. While cardiac tamponade is not infrequent in other advanced small-round-cell neoplasms such as lung cancer, malignant melanoma, and malignant lymphoma, it is quite rare in sarcoma [5,6]. Furthermore, there have been no reported cases in which CRS caused cardiac tamponade.

We herein report the case of a 48-year-old man who presented with cardiac tamponade caused by CRS.

Case Report

A previously healthy 48-year-old man presented to a nearby hospital with tachycardia and hypotension in July 2017. X-ray examination showed cardiomegaly. Massive pericardial effusion with a tumorous region in the pericardial space was detected by computed tomography (CT) (Figure 1). Routine serum chemistry testing at his first visit was almost within the normal range, and the complete blood cell count revealed pancytopenia (hemoglobin, 6.8 g/dL; total white blood cell count, $2.8 \times 10^9/L$; platelets, $13.6 \times 10^9/L$). Pericardiocentesis was performed, and 1900 mL of bloody fluid was aspirated. Atypical round-shaped cells were detected by cytological examination of the pericardial fluid. After pericardiocentesis, the patient's tachycardia and hypotension improved, but he began to complain of left shoulder pain. At that time, he was referred to our hospital for further evaluation and treatment. On admission, left shoulder pain was his only symptom. ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET) showed an increased uptake of FDG in multiple lesions, including those involving the left proximal humerus (the highest maximum standardized uptake value=20.9), left ilium, subcutis, and abdominal and mediastinal lymph nodes (Figure 2). X-ray examination showed an osteolytic lesion in the left proximal humerus (Figure 3). We performed a CT-guided needle biopsy of the left humerus. The biopsy specimen obtained from the humerus showed a diffuse, monotonous proliferation of atypical round cells with hyperchromatic nuclei (Figure 4). Immunohistochemically, the tumor cells were partially positive for *WT1* and *CD99*, and diffusely positive for *CIC* (Figure 5). Molecular analysis was conducted, and polymerase chain reaction showed no *EWSR1-FLI1*, *CIC-DUX4* gene rearrangement, which was further confirmed by direct sequencing (Figure 6). These results suggested CRS. The

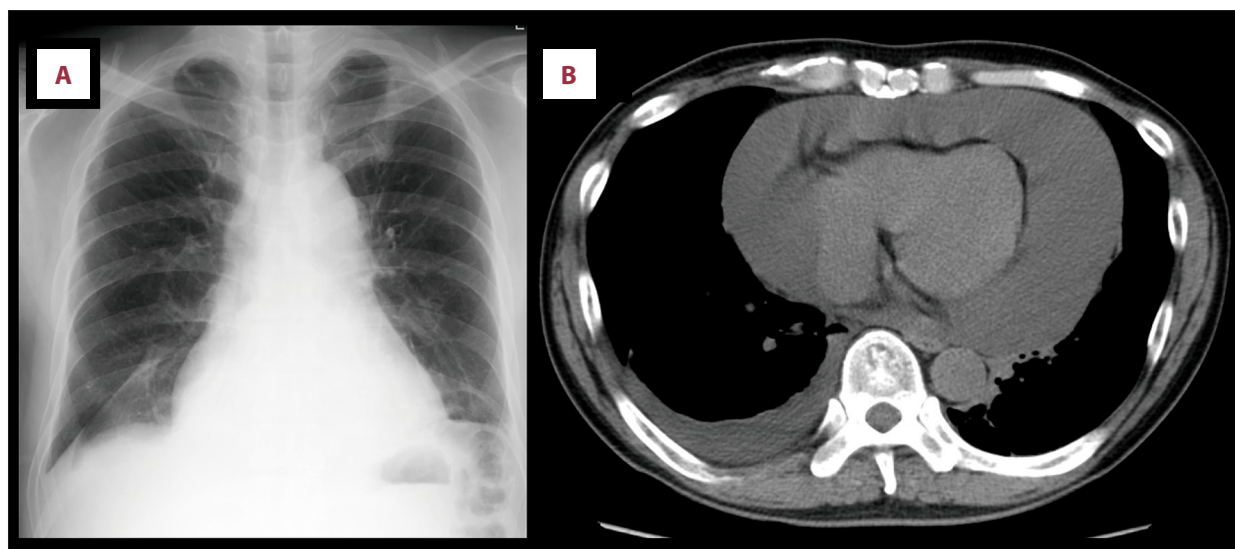


Figure 1. (A) Chest X-ray examination shows cardiomegaly. (B) Computed tomography examination shows massive pericardial effusion with a tumorous region in the pericardial space.

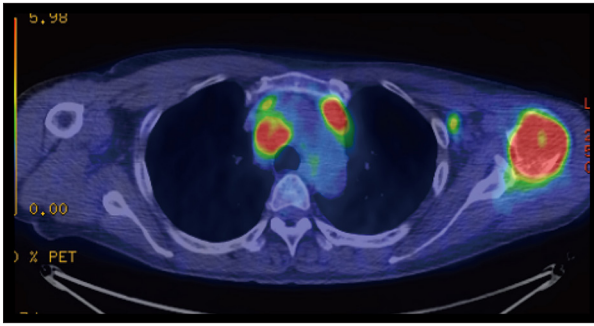


Figure 2. A representative axial image of ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET) shows increased uptake of FDG in multiple lesions, including those in the left proximal humerus and mediastinal lymph nodes.

patient received a course of palliative radiotherapy to the left humerus, and his pain was immediately relieved. X-ray examination showed bone formation after the irradiation. In addition to the radiotherapy, the patient was treated for advanced primary bone sarcoma with the same palliative chemotherapeutic regimen that would be used in Ewing sarcoma. His clinical

response was stable disease for 8 months, after which lymph node metastases progressed. To prevent the recurrence of lethal cardiac tamponade, the patient received radiation therapy for his mediastinal lesion. He died of progressive disease 12 months after diagnosis, although an autopsy did not detect the recurrence of cardiac tamponade.

Discussion

CRS is a recently recognized, genetically defined subtype of undifferentiated round-cell sarcoma that morphologically resembles the Ewing sarcoma family of tumors [1]. However, unlike Ewing sarcoma, CRS arises mostly in deep or superficial soft tissue and rarely in flat bone [4]. In our case, we were unable to determine whether the left humerus was the primary site of the tumor, even though the osteolytic lesion in the left humerus was the largest of the multiple lesions at the patient's first visit.

The patient in this case exhibited disease progression that was unlike that of more common sarcomas. In particular, cardiac

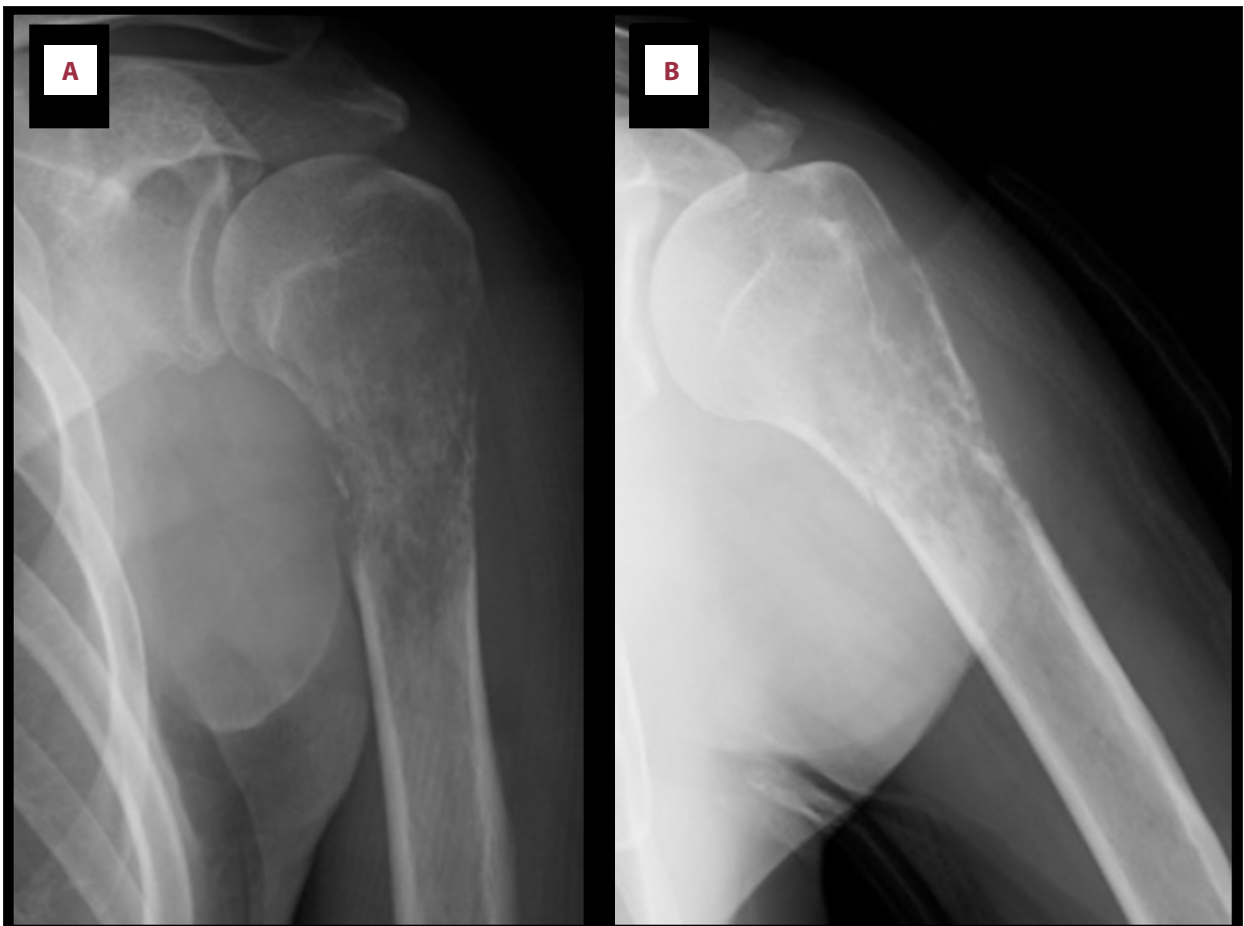


Figure 3. (A) Anteroposterior and (B) lateral views on plain X-ray show an osteolytic lesion in the left proximal humerus.

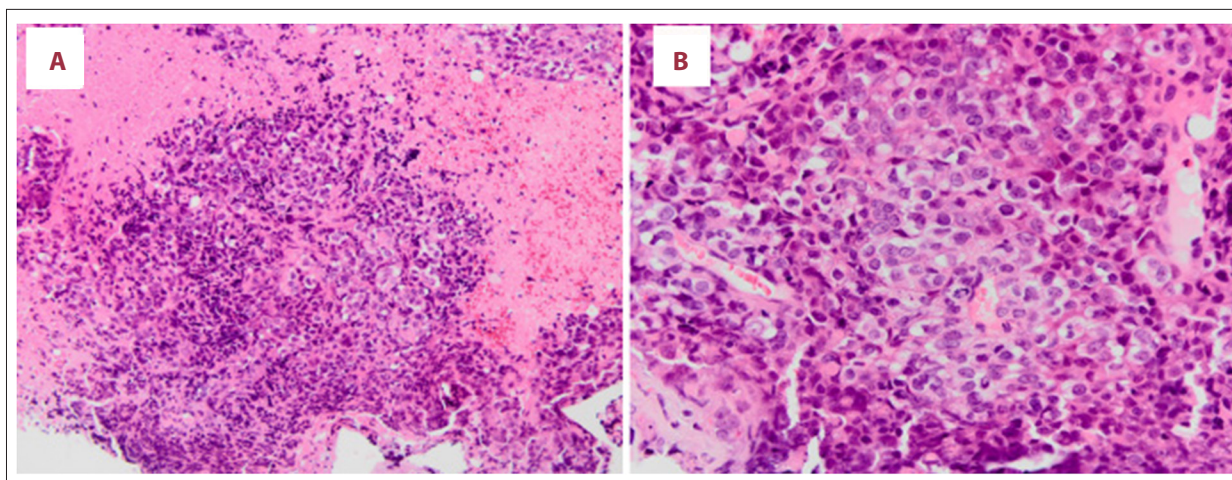


Figure 4. Microscopic images of the tumor specimen (hematoxylin and eosin staining). (A) Low-power magnification, showing sheets of a compact proliferation of tumor cells with necrotic areas. (B) A compact proliferation of atypical small-round cells in a high-power magnification.

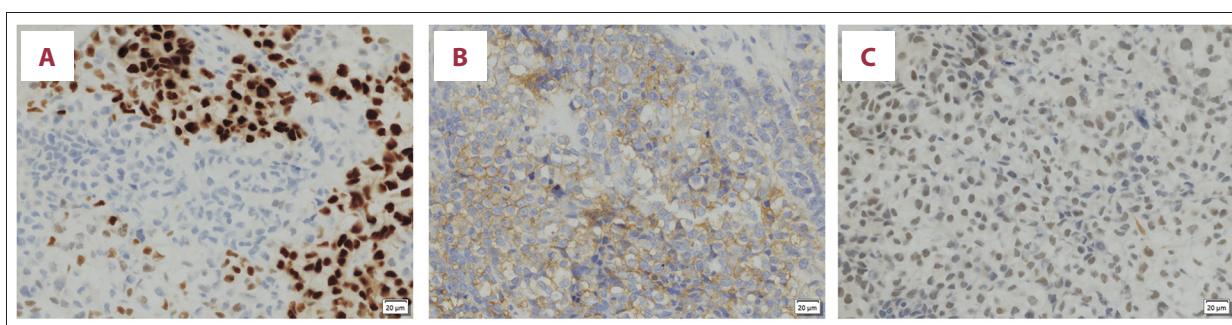


Figure 5. Immunohistochemical detection of (A) *WT1*, (B) *CD99*, and (C) *CIC*.

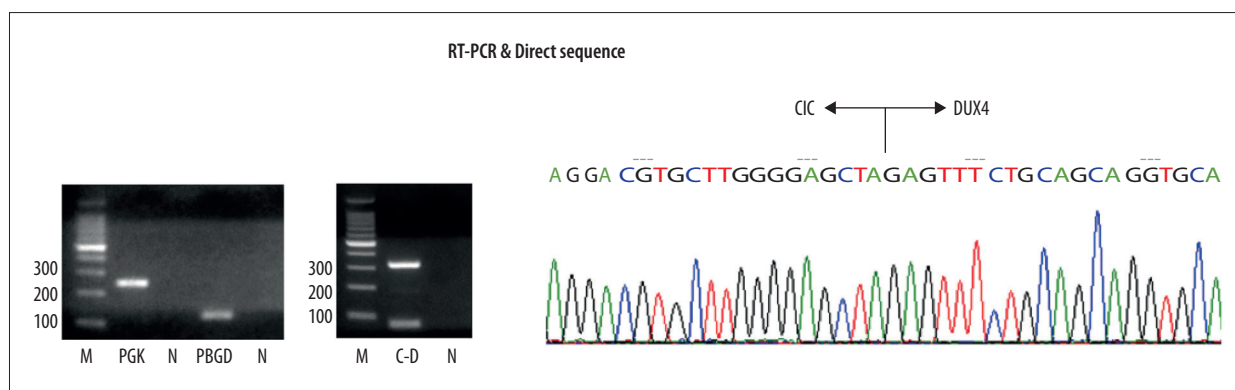


Figure 6. Reverse transcription-polymerase chain reaction (left and middle images) and subsequent direct sequence (right image), showing a transcript of the *CIC-DUX4* fusion identified. (M – size marker; PGK – phosphoglycerate kinase; PBGD – porphobilinogen deaminase; C-D – *CIC-DUX4*; N – negative control).

tamponade caused by sarcoma is extremely rare, and there are no reported cases of CRS causing pericardial effusion. In the few reported cases of cardiac tamponade in sarcoma patients, it was caused by pericardial extension [7] or direct cardiac wall invasion [8]. In the present case, we speculate that pericardial effusion may have arisen due to impaired lymphatic drainage

secondary to lymphomatous involvement of the mediastinal lymph nodes, as seen in other advanced small-round-cell neoplasms in which lymph node metastasis is common, such as lung cancer, malignant melanoma, and malignant lymphoma. Although previous reports showed that the frequency of lymph node metastasis in malignant soft tissue tumors was less

than 5% [9], a higher incidence was observed in some sarcoma subtypes [10], including the newly recognized CRS subtype.

CRS is considered to be a very aggressive tumor. In a review of 115 cases of CRS, Antonescu et al reported a 2-year overall survival (OS) rate of 53% and a 5-year OS rate of 43% [4]. These patients received multimodal treatment, including surgery, chemotherapy, and radiation, as is commonly applied in other small-round-cell sarcomas, such as Ewing sarcoma, but the response rates to these treatments were inferior compared with those of other round-cell sarcomas. In our case, irradiation effectively relieved pain caused by the humeral lesion. In addition, mediastinal irradiation successfully controlled the pericardial effusion until the end stage of the disease.

Because CRS is a recently recognized sarcoma, the optimal treatment strategy in advanced CRS is still unclear. Radiation therapy may be useful for disease control, a possibility that

warrants further investigation. Our case suggests that the progression pattern of CRS is very different from that of other conventional sarcomas, which should be taken into consideration when choosing treatments.

Conclusions

This is the first case report of CRS causing cardiac tamponade as the initial symptom. Cardiac tamponade is a rare presenting feature of sarcoma and may be misleading. Physicians and pathologists should include CRS in the differential diagnosis if the pericardial fluid in the context of cardiac tamponade contains atypical small-round cells.

Conflicts of Interest

None.

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