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Detection of Asymptomatic Cardiac Metastasis and Successful Salvage Chemotherapy Comprising a Prednisone, Etoposide, Procarbazine, and Cyclophosphamide Regimen in an Elderly Japanese Patient Suffering from a Delayed Recurrence of Diffuse Large B-Cell Lymphoma

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Key Words
Malignant lymphoma · Diffuse large B-cell lymphoma · Recurrence · Cardiac metastasis · Cardiac MRI · PET/CT · Salvage chemotherapy · Prednisone, etoposide, procarbazine, and cyclophosphamide regimen

Abstract
We report a case of facial diffuse large B-cell lymphoma (DLBCL) associated with recurrent metastasis in the heart and other sites in a 76-year-old Japanese woman. Initially, she developed DLBCL in her left upper eyelid that spread into the left orbit (Ann Arbor classification stage I). The lesion went into clinical regression after 4 cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy followed by radiotherapy. More than 3 years later, the lymphoma recurred in her facial skin, together with metastases in the mediastinal lymph nodes and the heart; the tumor in the heart was successfully detected by PET/CT and cardiac MRI. To treat the recurrent lesions, we performed a salvage chemotherapy regimen comprising prednisone, etoposide, procarbazine, and cyclophosphamide, which successfully induced tumor regression.

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Introduction

Detecting cardiac metastasis of malignant tumors is not easy, with most such cases diagnosed only at autopsy. Thus, it is rare that cardiac metastasis is correctly diagnosed after successful primary treatment with first-line chemotherapy. We recently encountered an elderly female patient suffering a recurrence of diffuse large B-cell lymphoma (DLBCL) involving the forehead, left eyelid, and orbit, and in whom heart metastasis was detected by PET/CT and cardiac MRI. She was successfully treated with the salvage oral combination chemotherapy regimen of prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C).

Case Report

A 76-year-old female patient presented at our hospital in July 2006 with swelling of the left upper eyelid, which was subsequently diagnosed histopathologically as DLBCL expressing CD20 antigen. MRI revealed extension of the tumor from the left upper eyelid into the orbital cavity, but CT imaging showed no other lesions. The tumor was graded as stage I according to the Ann Arbor classification [1], and the patient was treated accordingly with the standard chemotherapy regimen of 4 cycles of rituximab (Rit) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). She subsequently underwent radiotherapy to the left orbit (40 Gy/20 fractions). Following this initial treatment, no lesions were detected on imaging studies and the tumor was declared to be completely resolved.

There was no recurrence during the subsequent 3 years. However, in December 2010, our patient noted the development of red papules on her forehead, which spread to the left eyelid. Histopathologically, the lesions were again diagnosed as DLBCL, indicating a late recurrence. A PET/CT scan of fluorodeoxyglucose (FDG) uptake demonstrated additional tumors in the forehead and nasal cavity connected to the lesion on the left eyelid. Abnormal uptake was also found in the mediastinal lymph nodes and the heart (**fig. 1**); these findings were confirmed by CT (**fig. 2**). Cardiac MRI revealed the presence of abnormal masses in the right ventricular wall together with an infiltration of the right atrium, aortic root, and tricuspid valve (**fig. 3**). A recurrence of the facial DLBCL accompanied by metastasis to the heart and mediastinal lymph nodes was therefore diagnosed. Interestingly, the patient showed a good general state and no cardiac functional abnormalities by echocardiography or electrocardiogram.

Considering her age, the patient was started on PEP-C salvage chemotherapy according to Coleman et al.'s regimen [2]. This treatment consisted of daily oral administration of prednisone 20 mg after breakfast, cyclophosphamide 50 mg after lunch, etoposide 50 mg after dinner, and procarbazine 50 mg at bedtime, and it was continued until the white blood cell (WBC) count dropped below 3.0×10^9/l (**fig. 4**). Within one week, almost all of the forehead papules regressed, and on day 18 the metastatic cardiac tumor was also markedly reduced in size (fig. 3). At this stage, CD20 antigen expression remained and residual tumor was apparent, prompting the start of a new combined therapy of Rit plus the PEP-C regimen from day 22 (fig. 4). On day 37, PET/CT imaging showed partial remission of the residual tumor (fig. 1), although the patient's WBC count remained above 3.0×10^9/l. The daily oral medication was therefore continued until day 37. At this time, Japan was struck by the Great Eastern Earthquake, and all treatment was withheld until completion of the necessary infrastructure reconstruction. On day 56, the PEP-C regimen was reinstituted according to the maintenance phase of Coleman et al.'s regimen [2]. At the beginning of this maintenance phase, the dosing frequency was planned over 14 consecutive days with a one-week rest to constitute a Rit tri-weekly administration. On day 112, enhanced CT imaging showed a remarkable reduction in size of the numerous mediastinal lymph nodes together with near disappearance of the cardiac tumor (fig. 2). The patient finished the Rit therapy after 6 cycles of administration, and continued the PEP-C regimen as maintenance therapy.

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Discussion

In general, cardiovascular symptoms related to malignant lymphoma tend to appear only at the end stage of the disease [3, 4]. However, we report a unique case herein, whereby despite the presence of heart metastasis in the recurrent stage of DLBCL, the patient maintained a good general condition without noticeable cardiovascular symptoms. Moreover, we could only reach our final diagnosis thanks to the advanced nature of current diagnostic medical imaging technology such as echocardiography, PET/CT, CT, and cardiac MRI.

The incidence range of heart metastasis is 1.5–20.6% in patients with malignancies [5–8], although such metastatic tumors, and particularly those of malignant lymphoma, are mostly asymptomatic clinically and rarely diagnosed within the lifetime of the patient. Rosenberg et al. [9] reported that among 277 autopsy cases of cardiac malignant tumors, 63 had malignant lymphoma, indicating that its incidence is not rare, and none were diagnosed in a living patient. When Rafajlovski et al. [10] performed 11,403 autopsies from 1972 to 2004, malignant tumor was diagnosed in 2,928 of the autopsies and in 79 (2.7%) of these cases, heart metastasis was found. Even with this large number of patients, the diagnosis of heart metastasis was made only in 5 cases during the patients' lifetime. The highest frequency of heart metastasis was reported in cases of pulmonary carcinoma (18 cases), followed by leukemia, and then malignant lymphoma (8 cases each). According to Roberts et al. [3], only 5 of their 48 autopsied cases of malignant lymphoma had heart involvement that presented clinically with cardiovascular symptoms in their patients' lifetime. However, these symptoms were highly variable including pericarditis, pericardial effusion, angina, congestive heart failure, arrhythmia, and non-infectious endocarditis. Hanfling [11] indicated that even the cause of arrhythmia was dependent on the site influencing the conduction system of the heart rather than on tumor size. In addition, the manifestation of these cardiovascular symptoms tends to appear mostly at the end stage of the disease [3, 4].

The metastatic pathways of malignant lymphoma to the heart consist of hematogenous metastasis, direct invasion, and lymphatic metastasis [11], with the first mechanism being the most common. In the case of lymphatic metastasis, the tumor is thought to reach the heart by a retrograde flow through mediastinal and tracheobronchial lymphatic channels because the superficial lymph channels of the heart were filled with malignant cells in those reported cases of carcinomatous lymphangitis [3, 4]. In our present case, hematogenous metastasis is the most plausible causative mechanism because the primary lesion was found in the left eyelid. However, we cannot rule out the possibility of lymphatic metastasis from the mediastinal and tracheobronchial lymph nodes that showed swelling at the recurrence.

Finally, our literature search for cardiac metastasis of DLBCL that was detected during the patient's lifetime and treated with salvage chemotherapy revealed only a few reports. The most frequently reported cases involve the primary cardiac DLBCL or DLBCL with cardiac metastasis at the time of initial diagnosis. In these cases, CHOP or R-CHOP chemotherapy was employed. Coleman et al. [2] reported using PEP-C oral combination chemotherapy for 75 patients with DLBCL, 52 of whom showed complete or partial resolution despite one or more prior therapies. Our present case represents a successful response to PEP-C oral combination chemotherapy that was conducted as salvage chemotherapy for DLBCL in the elderly. The regimen proved to be effective and

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safe in the present elderly patient, and we therefore recommend this PEP-C regimen as salvage treatment for cardiac metastasis of DLBCL.

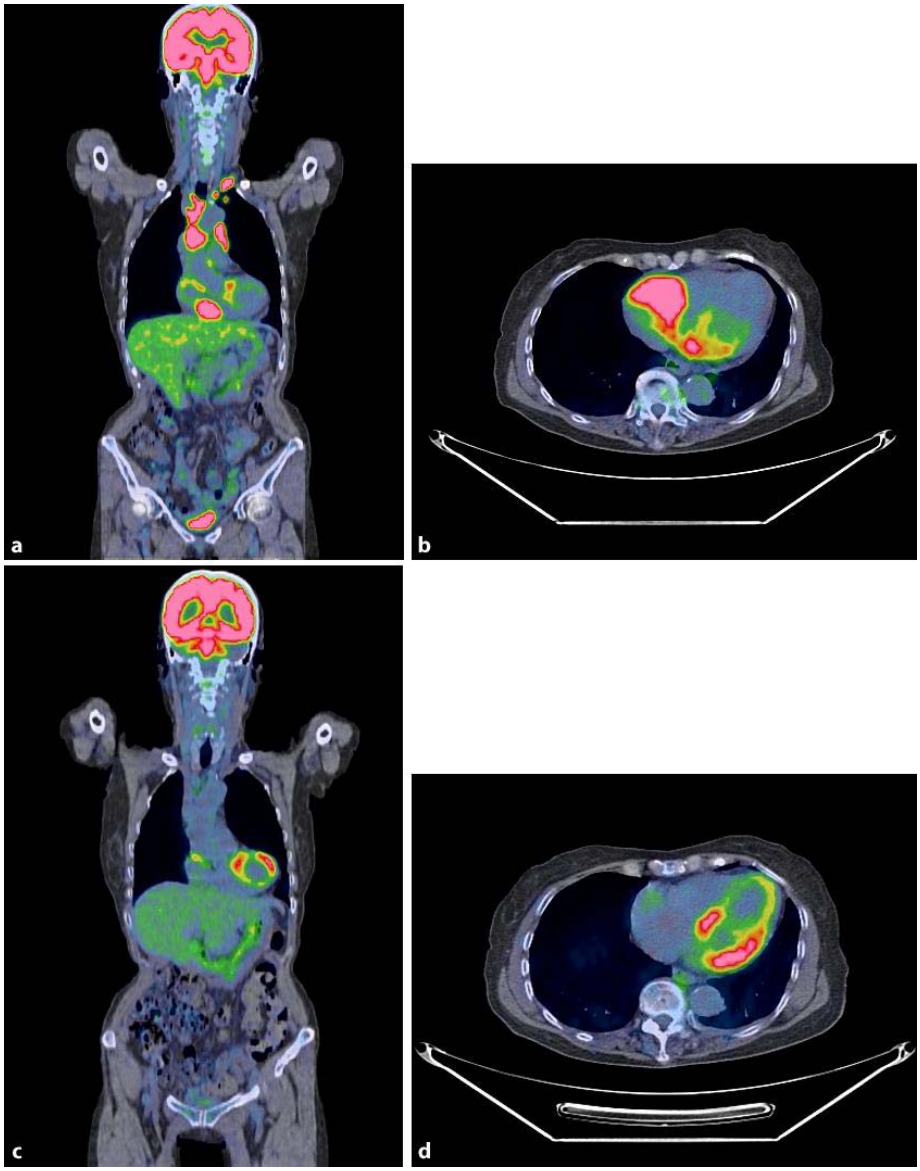

Fig. 1. Contrast PET/CT. **a**, **b** Abnormal uptake of FDG demonstrated the presence of tumor in the numerous mediastinal lymph nodes and in the heart. **c**, **d** On day 37 after the introduction of chemotherapy, FDG uptake had virtually disappeared.

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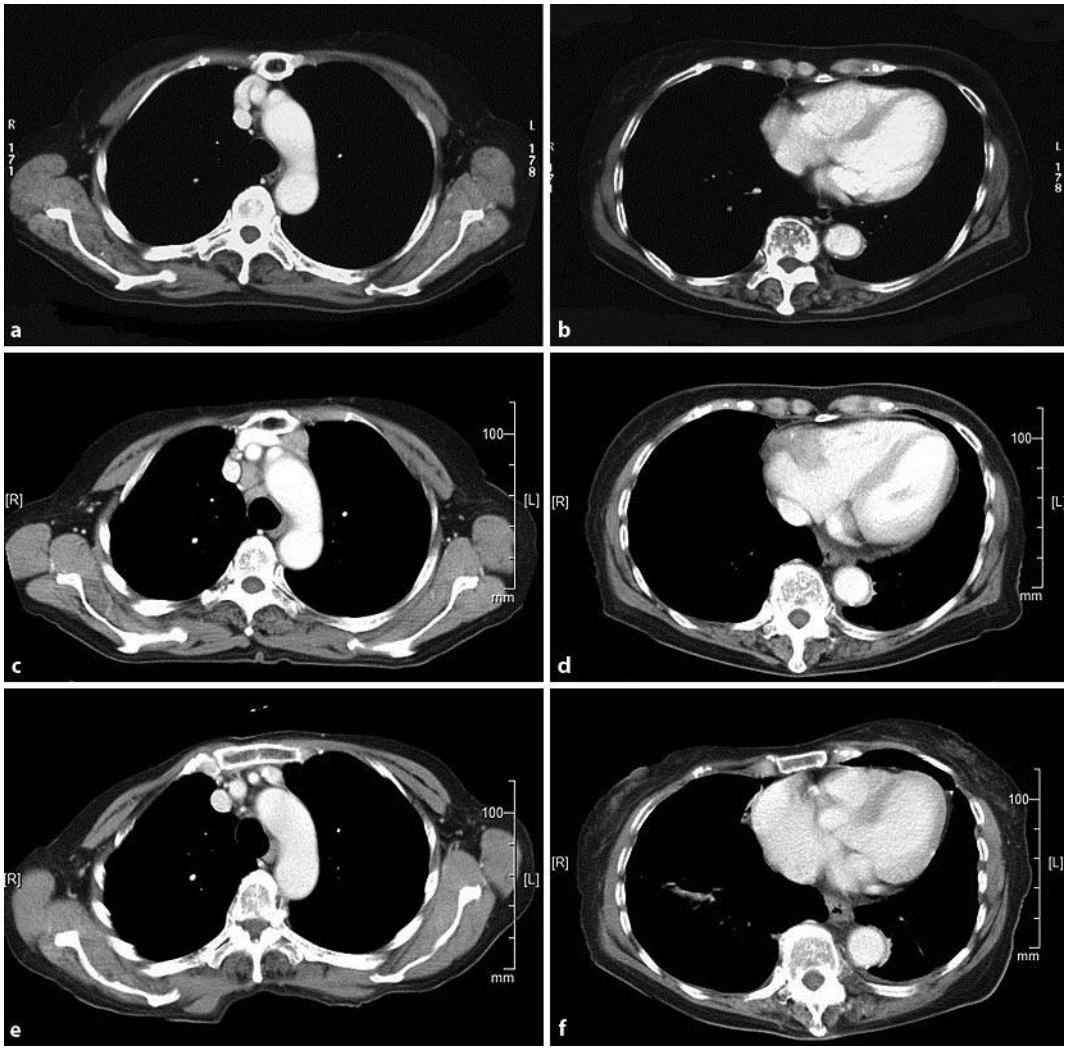

Fig. 2. Contrast-enhanced CT. **a**, **b** After the initial treatment, there were no abnormal findings. **c**, **d** In January 2011, there was a swelling of the mediastinal lymph nodes and an abnormal mass in the right ventricular wall. **e**, **f** On day 112 after the introduction of salvage chemotherapy, no swelling of the mediastinal lymph nodes was detected and the abnormal cardiac mass was diminished in size.

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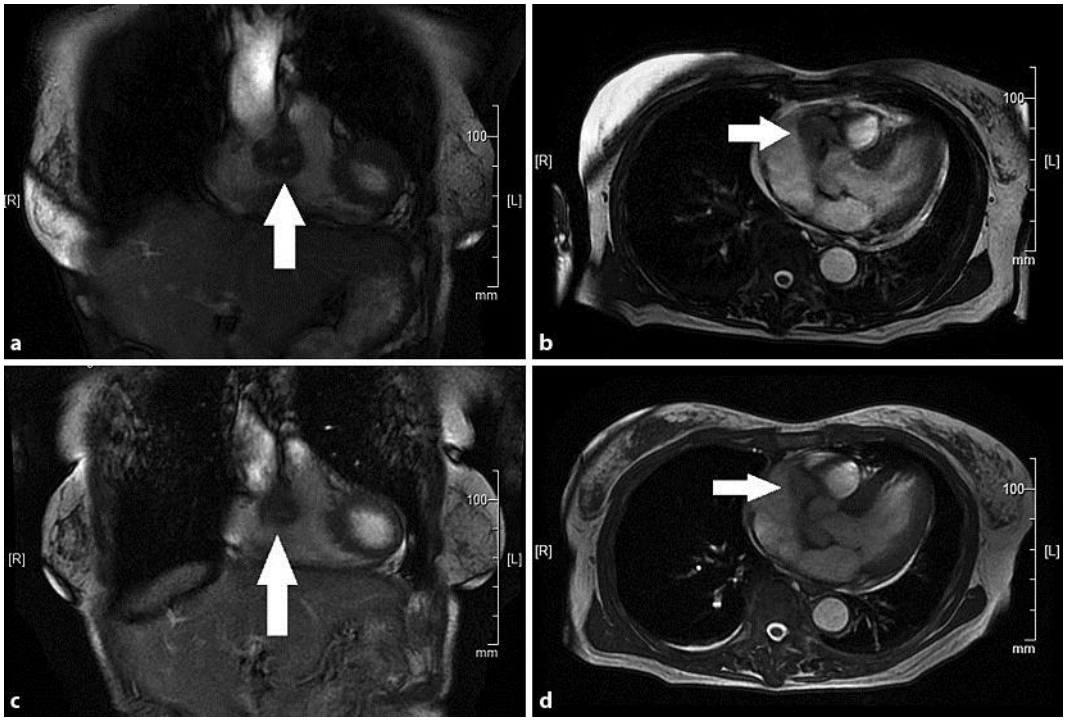

Fig. 3. Contrast cardiac MRI. **a**, **b** Abnormal mass in the right ventricular wall invading the right atrium, aortic root, and tricuspid valve. **c**, **d** On day 18 after the introduction of chemotherapy, the cardiac tumor remained, but had decreased in size.

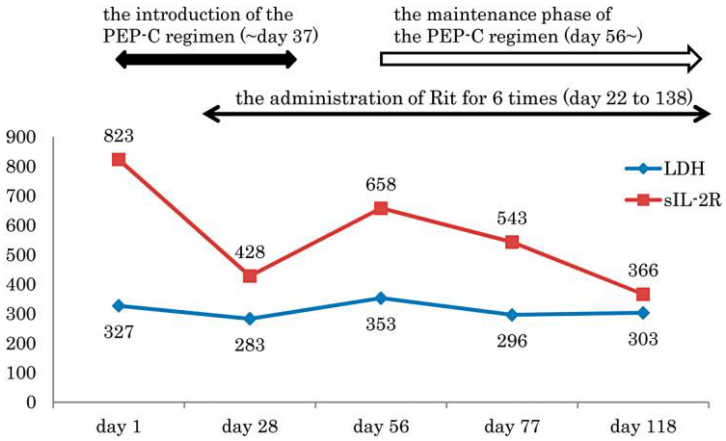

Fig. 4. Patient progress during treatment. The PEP-C regimen consisted of daily oral administration of prednisone 20 mg after breakfast, cyclophosphamide 50 mg after lunch, etoposide 50 mg after dinner, and procarbazine 50 mg at bedtime. The dosing frequency in the maintenance phase comprised administration for 14 consecutive days with a one-week rest, with the medications and doses given per day held constant according to the introduction of the PEP-C regimen. The frequency of Rit administration was tri-weekly from day 22. LDH = Lactic dehydrogenase (IU/l); sIL-2R = interleukin 2 receptor, soluble (U/ml).

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