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Case Study

High-dose chemotherapy with autologous stem cell transplantation following systemic chemotherapy, prophylactic intrathecal methotrexate, and radiotherapy prevents relapse and improves the outcome of advanced stage primary testicular lymphoma even with cardiac involvement

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Primary testicular lymphoma (PTL) is a rare but aggressive disease. Although most patients present in the early stage, their prognosis is poor. Similar with PTL, cardiac lymphoma is also an uncommon disease characterized by its aggressive clinical course and poor prognosis. We herein report an extremely rare case of advanced stage PTL with cardiac involvement, treated by high-dose chemotherapy with autologous stem cell transplantation (HDT-ASCT) followed by systemic chemotherapy, prophylactic intrathecal methotrexate (IT-MTX), and radiotherapy. A 48-year-old man presented with painless left scrotal swelling. He was diagnosed with PTL after orchiectomy, and the histological type was diffuse large B-cell lymphoma. For staging of lymphoma, positron emission tomography was performed, which revealed uptake in the right atrium and early cardiac metastasis within just 2 months after orchiectomy. He underwent 6 cycles of systemic chemotherapy that consisted of rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisolone (R-CHOP). He also received central nervous system prophylaxis 4 times with weekly IT-MTX during the first 2 cycles of R-CHOP. He achieved complete response after 6 cycles of R-CHOP, and underwent HDT-ASCT and radiotherapy as consolidation therapy without irreversible adverse effects. He is currently doing well, with a progression-free survival of 31 months. The above treatment strategy including HDT-ASCT may be one of the treatment options for advanced stage PTL with cardiac metastasis in patients younger than 65 years old.

Keywords: primary testicular lymphoma, cardiac involvment, high-dose chemotherapy, autologous stem cell transplantation

INTRODUCTION

Primary testicular lymphoma (PTL) is an uncommon malignant testicular tumor that accounts for less than 5% of testicular tumors and 1% of lymphomas overall.[1,2] Diffuse large B-cell lymphoma (DLBCL) is the most common subtype.[3] PTL has a high relapse rate even in the early stages.[2] A study reported that 41% of patients with PTL relapses had either central nervous system (CNS) or contralateral testicular involvement, even with systemic chemotherapy.[4] Although approximately 80% of PTL patients are diagnosed at an early stage, survival is poorer than predicted by the International Prognostic Index (IPI). Furthermore, the duration of survival after relapse is very poor (median, 4.5 months).[2] For these reasons, the prevention of relapse improves the outcome of PTL.

Primary cardiac tumors are very rare (0.02%, corresponding to 200 tumors in 1 million autopsies).[5] Most cardiac tumors are metastases from varying primary sites.[6] Approximately 8-15% of lymphoma patients have cardiac involvement.[6,7] As the rate of complete remission (CR) for primary cardiac lymphoma is only 37.5%, it has a poor prognosis.[8] Similarly, secondary cardiac lymphoma patients also have a very poor outcome due to the high risk of sudden death. Most patients die before the start of therapy.[9] For this reason, cardiac involvement should be diagnosed early. PTL with cardiac involvement is extremely rare. To the best of our knowledge, only one case has been reported to date.[10]

As patients with advanced PTL have an extremely poor prognosis, some authors have suggested that a more effective and intensive treatment strategy, such as high-dose therapy (HDT), should be tried, especially in younger patients.[4] The

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one and only prospective study reported the treatment strategy for early stage PTL.[11] In contrast, there is no reported consensus regarding the treatment strategy for advanced stage PTL.[4]

We present a rare case of advanced stage PTL with cardiac involvement that was successfully treated by an intensive strategy. To the best of our knowledge, this is the first case of advanced stage PTL in a patient under the age of 65 who was eligible for HDT followed by autologous stem cell transplantation (HDT-ASCT). Despite the interference caused by physiological accumulation of 18 fluoro-2-deoxyglucose (FDG) in the cardiac wall during the evaluation of cardiac lesions, positron emission tomography (PET) has been demonstrated as useful for the early detection of cardiac involvement, which enables the patient to receive chemotherapy before the development of cardiac dysfunction, as previously reported.[12,13] HDT-ASCT following the treatment for early stage PTL, including systemic chemotherapy, intrathecal methotrexate (IT-MTX), and radiotherapy (RT), contributed to improving the outcome of advanced stage PTL by preventing relapse.

CASE REPORT

A 48-year-old man with no notable medical history was referred to our institution with painless left scrotal swelling. There were no malignancies in his family history. His height was 171 cm, and his weight was 67 kg, with a body surface area of 1.74 m^2. His temperature was 35.7°C, heart rate was 95 beats per minute, blood pressure was 114/77 mmHg, and he had an oxygen saturation of 98% on room air. His Eastern Cooperative Oncology Group performance status was 0. Initial clinical laboratory data revealed a white blood cell count of 7,200/μL, hemoglobin of 15.8 g/dL, platelet count of 27.3 × 10^4/μL, and high serum lactate dehydrogenase (LDH) of 276 IU/L. However, there were no other abnormalities, including serum soluble interleukin 2 receptor, liver function, renal function, and disseminated intravascular coagulation markers. Serum antigens for human immunodeficiency virus (HIV) were negative. Serum antibodies to both HIV and human T cell leukemia virus-1 were also negative. Chest and abdominal contrast-enhanced computed tomography (CT) showed a well-defined solid mass in the left scrotum with diffuse uniform enhancement, which was considered a radiographic feature of malignancy. However, there was no evidence of cardiac metastasis in the right atrium (Fig. 1). For diagnosis, left orchiectomy was performed. The histological evaluation found infiltration of atypical large lymphoid cells that were positive for CD20, bcl-2, bcl-6, CD79a, and Mum-1, and negative for CD3, UCHL 1, CD10, CD30, CD5, c-kit, and EBER-ISH immunostaining, leading to the diagnosis of DLBCL (Fig. 2).

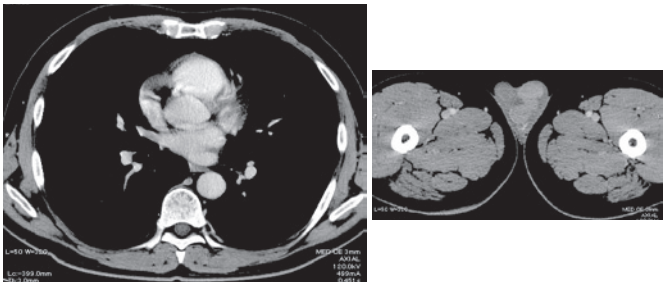

Fig. 1. Chest and abdominal computed tomography (CT) showed the left testicular tumor with the radiographic features of malignancy. There was no evidence of cardiac metastasis in the right atrium.

For DLBCL staging, FDG-PET was performed; hypermetabolic activity in the right atrium was observed (Fig. 3a). Tumor FDG uptake using the standardized uptake value was 10.9. Cardiac CT and magnetic resonance imaging (MRI) revealed that the tumor infiltrated the right atrium (Fig. 3b). The interval between the initial (Fig. 1) and repeat CT (Fig. 3b) scans was only 8 weeks. Transthoracic echocardiography also indicated that the tumor was situated on the free wall of the right atrium, but there was no evidence of abnormal left ventricular ejection fraction or tricuspid stenosis. There was no evidence of arrhythmia by tumor infiltration on the electrocardiogram. Bone marrow biopsy and lumbar puncture provided no evidence of lymphoma involvement. With these findings, a definite diagnosis of advanced stage PTL (Ann Arbor stage IV) was made. His age-adjusted IPI score was 3 (advanced stage, elevated LDH level), high-intermediate risk.

He was started on 6 cycles of R-CHOP-21 (375 mg/m^2 of rituximab, 50 mg/m^2 of doxorubicin, 750 mg/m^2 of cyclophosphamide, 1.4 mg/m^2 of vincristine on day 1, and 100 mg/body of prednisolone on days 1 to 5 of each cycle). He also received CNS prophylaxis with IT-MTX (12 mg), weekly for 4 times during the first 2 cycles of R-CHOP. PET-CT after chemotherapy indicated that he achieved CR. To prevent relapse, he underwent HDT-ASCT (375 mg/m^2 of rituximab, 300 mg/m^2 of ranimustine on day -8, 200 mg/m^2 of etoposide, 200 mg/m^2 of cytarabine on days -7 to 4, and 70 mg/m^2

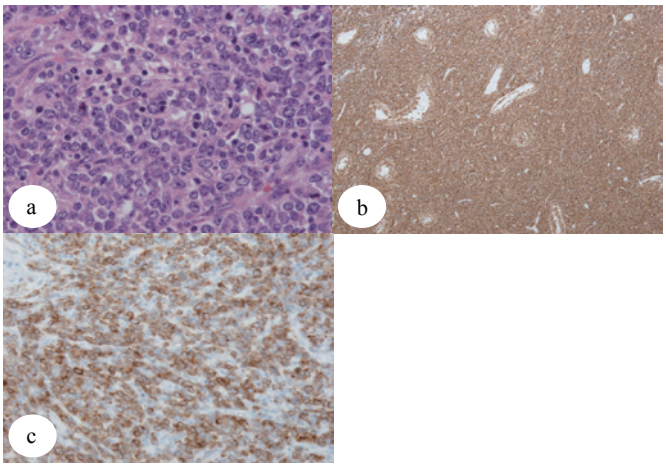

Fig. 2. Histological and immunohistochemical features of a biopsied sample of the left testis. Hematoxylin and eosin staining showed disruption of the lymph node architecture and diffuse proliferation of large-sized atypical cells. (***2a***) The large tumor cells were positive for CD20 and bcl-2, which indicated diffuse large B-cell lymphoma. (***2b & 2c***)

of melphalan on days -3 and -2, followed by peripheral blood stem cell transplantation on day 0). The patient developed hematological toxicity (grade 4 leukopenia, anemia, and thrombocytopenia) and grade 3 febrile neutropenia (FN) during HDT-ASCT, but these side effects were tolerable and reversible. Following HDT-ASCT, prophylactic RT of 30 Gy was delivered to the contralateral testis (Fig. 4). PET two months after RT indicated that CR was maintained. CT, MRI, and echocardiography findings were similar (Fig. 5). Currently, the patient visits the outpatient clinic regularly without definite evidence of relapse on follow-up imaging studies (CT, MRI, and echocardiography). At the time of writing (April 2017), he is doing well, with a progression-free survival of 31 months.

DISCUSSION

A case of advanced stage PTL with cardiac involvement in a patient who remains in CR following treatment including HDT-ASCT was presented. PTL with cardiac involvement is extremely rare. At present, the only case reported was in a 67-year-old man who achieved CR by 6 cycles of R-CHOP and 4 doses of IT-MTX.[10] The present report describes the first case of advanced stage PTL with cardiac involvement in a patient under the age of 65. The following important clinical suggestions come from the clinical course of this patient. HDT-ASCT following the treatment for early stage PTL contributed to improving the prognosis of advanced stage PTL by preventing relapse. As in previous reports, PET was useful for the early detection and diagnosis of cardiac involvement by lymphoma in the present case, which enabled this patient to avoid sudden death and receive the full dose of

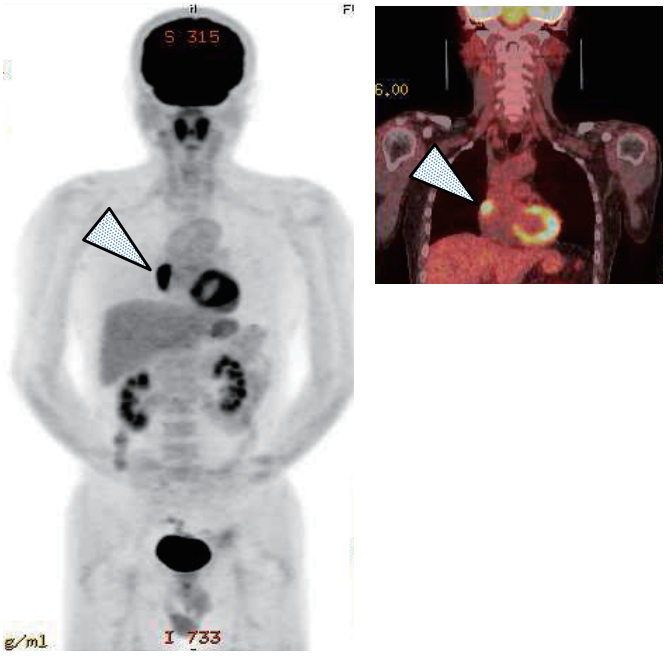

Fig. 3a. [18]Fluorine-labeled fluorodeoxyglucose positron emission tomography (FDG-PET)-CT showed hypermetabolic activity in the right atrium at presentation (*arrowheads*).

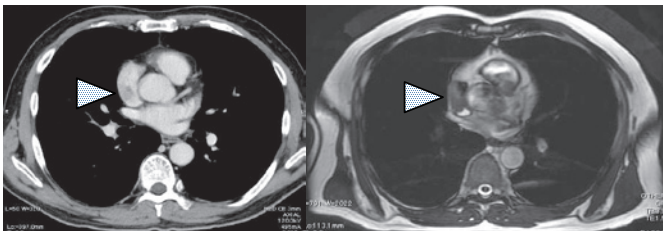

Fig. 3b. Left, Chest CT showed the tumor in the right atrium. Right (*arrowheads*), T1-weighted MRI of the chest also showed the tumor in the left atrium (*arrowheads*).

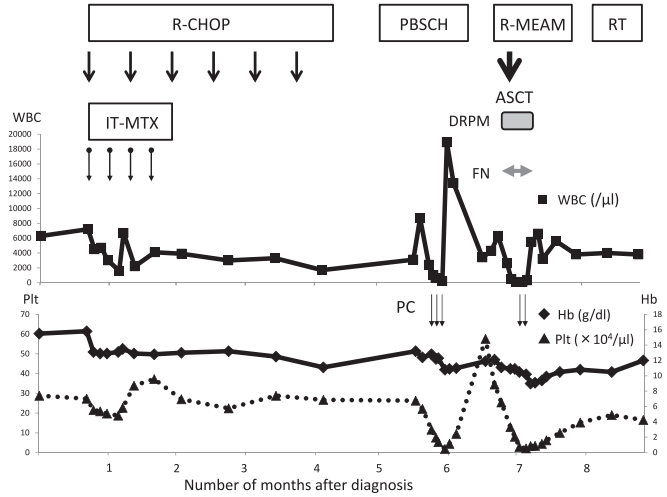

Fig. 4. Clinical course of the present patient
CT, MRI, and PET after 6 cycles of R-CHOP and 4 doses of IT-MTX demonstrated that the patient achieved CR. After systemic and CNS prophylaxis to prevent relapse, he underwent HDT-ASCT. Following HDT-ASCT, he received prophylactic RT of 30 Gy to the contralateral testis.
WBC, white blood cell; Hb, hemoglobin; Plt, platelets; R-CHOP, rituximab, doxorubicin, cyclophosphamide, vincristine, prednisolone; IT-MTX, intrathecal methotrexate; PBSCH, peripheral blood stem cell harvest; ASCT, autologous stem cell transplantation; R-MEAM, rituximab, ranimustine, etoposide, cytarabine, melphalan; RT, radiotherapy; DRPM, doripenem; FN, febrile neutropenia; PC, platelet transfusion.

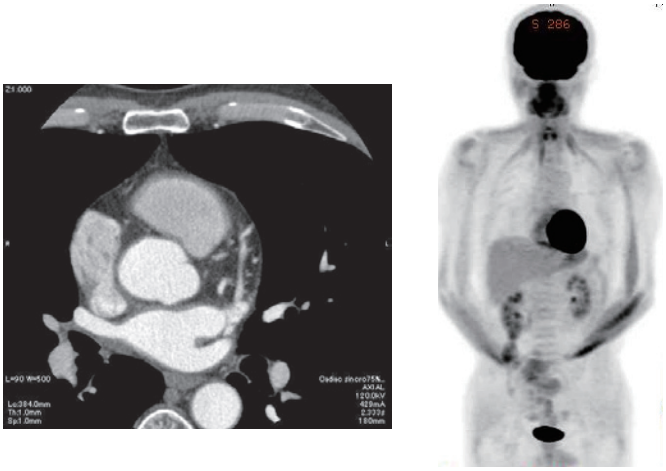

Fig. 5. Left, Chest CT showed disappearance of the right atrial tumor. Right, The complete disappearance of the right atrial tumor was also observed on FDG-PET.

chemotherapeutic drugs, such as doxorubicin, safely.

In the present case, HDT-ASCT following the treatment for early stage PTL improved the outcome of advanced stage PTL even with cardiac involvement by preventing early relapse. In 2009, Vitolo *et al.* first reported a prospective phase II trial of the treatment strategy for early stage PTL (Stage I, II).[11] In contrast with early stage, the treatment strategies for advanced stage PTL have not been established. Advanced stage PTL has a higher relapse rate and a very poor prognosis, with a median survival of 1.1 years.[2] A previous study demonstrated that HDT-ASCT as consolidation for aggressive NHL improved progression-free survival but not overall survival, probably because of the effectiveness of salvage ASCT.[14] Indeed, this study targeted aggressive NHL patients, but it did not refer to PTL patients. The clinical features of PTL, with its relapse and prognosis patterns, are very different from those of nodal DLBCL. Therefore, PTL should be considered biologically different from nodal DLBCL.[17,18] Furthermore, PTL had a high risk of CNS relapse.[4,15] Unfortunately, thiotepa, the active drug in regimens for HDT-ASCT for CNS relapse, cannot be used in Japan.[16] Thus, the effectiveness of salvage ASCT for CNS relapse was not expected in this patient. For these reasons, the prevention of relapse was markedly important for this patient to improve survival. In addition, a previous report found that HDT-ASCT prevented relapse and improved the prognosis of PTL that was predicted to have a poor outcome.[19] As the present patient was young and had good PS, he was eligible for HDT-ASCT.

The importance and usefulness of PET for lymphoma-involved sites have been widely reported.[12] Despite interference caused by physiological uptake of FDG in the cardiac wall during the evaluation of cardiac lesions,[13] PET was valuable in the early diagnosis of cardiac involvement in this patient. Lymphoma patients with cardiac involvement have a poor prognosis because of their high risk of sudden death, and the right side of the heart is a common site for lymphoma cardiac metastases.[9] In addition to obstructing circulation though the right side of the heart, right atrial tumors cause symptoms consistent with pulmonary emboli by releasing tumor fragments, which may be the cause of death before starting chemotherapy.[20,21] The early diagnosis of cardiac involvement enabled the patient to avoid death from several cardiac manifestations and to safely receive the full dose of chemotherapeutic drugs, such as doxorubicin, which may have improved his survival. Cardiac MRI is also useful in the diagnosis of cardiac tumors, but it should not be done without any cardiac symptoms.[22] In the present case, due to the early detection of cardiac metastasis, chemotherapy was started before the development of fatal cardiac events such as arrhythmia or pulmonary embolism. Due to its poor prognosis, some authors suggested that HDT-ASCT for cardiac lymphoma patients contributed to achieving CR and preventing relapse.[23]

The present patient exhibited an extremely rare case, the first case, of advanced stage PTL with cardiac involvement, and was successfully treated by HDT-ASCT following the treatment for early stage PTL. This treatment strategy including HDT-ASCT contributed to preventing early relapse and improved the prognosis of advanced stage PTL. In addition, the early detection of lymphoma cardiac metastasis contributed to improved survival by avoiding sudden death and allowing administration of the full dose of chemotherapy. At the time of writing (April 2017), this patient was still doing well, with a progression-free survival of 31 months. The clinical course of the present patient demonstrated the great efficacy and tolerability of the treatment strategy, including HDT-ASCT, for preventing relapse and prolonging progression-free survival of advanced stage PTL with rare but aggressive cardiac metastasis. Due to its rarity and aggressiveness, further investigation and more case reports are necessary to establish new treatment strategies for advanced stage PTL.

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CONFLICTS OF INTEREST

The authors have no potential conflicts of interest.

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