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Case Report

Cardiac tumor recurrence after orthotopic heart transplantation in primary cardiac lymphoma

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Abstract: Primary cardiac lymphoma is a rare malignancy. It is difficult to diagnose, and there is no standard mode of treatment, surgical resection is rarely performed. The prognosis is poor, because of the advanced stage of myocardial involvement at the time of presentation. We report a rare case of PCL diagnosed as DLBCL treated with orthotopic heart transplantation and 4 cycles of chemotherapy with R-COP. The patient achieved a complete response (CR), but suffered from a pulmonary fungal infection. A tumor occurrence was occurred in the mediastina and the transplanted heart, due to 2 months suspension of chemotherapy for the infection. Subsequently, the patient received a mediastinal intensity-modulated radiation therapy (IMRT) of 20 Gy in 11 fractions and a second-line chemotherapy with GEMOX with a partial response (PR). However, the patient finally died of tumor progression (in the mediastina, the neck, the thorax, and the abdomen) and serious fungal infection of lungs and survived for 11 months after diagnosis.

Keywords: Primary cardiac lymphoma, chemotherapy, radiotherapy, orthotopic heart transplantation

Introduction

Primary cardiac lymphoma (PCL) is an extremely rare malignancy, and more than 80% of PCLs are diagnosed as diffuse large B-cell lymphoma (DLBCL) [1]. While PCL can be detected by imaging, a biopsy is necessary to confirm the diagnosis. There is currently no established treatment paradigm for PCL. Chemotherapy is the most common treatment; surgical excision, heart transplantation, radiation therapy, and hematopoietic stem cell transplantation have also been reported. Nevertheless, the overall prognosis is poor and the median survival time after the initial treatment, regardless of treatment strategy, is approximately 7 months. Here, we report a case of PCL diagnosed as DLBCL treated with chemoradiotherapy after heart transplantation.

Case presentation

A 54-year-old male patient was initially admitted to a different hospital complaining of chest pain and dyspnea. An echocardiogram revealed a large tumor mass in the right atrium, encroaching on the right coronary artery. Pericardial effusion was also evident, and the ejection fraction was 71%. Computed tomography revealed the size of the lesion to be approximately 7.3 cm × 5.9 cm × 6.2 cm (**Figure 1A**, **1B**). With the exception of multiple lymph nodes on the neck, ultrasound examination showed no metastatic lesions or involvement in the other parts of the body.

Considering the high risk of cardiac rupture due to rapid tumor progression, and presenting a heart functional failure, orthotopic heart transplantation was performed for the patient. Intraoperatively it was observed that the tumor infiltrated the right atrium, the right ventricle, and the right coronary artery. The tumor size was approximately 8 cm × 7 cm. It encompassed the right atrioventricular cavity and had a "cauliflower-like" appearance. A biopsy of the cardiac tumor confirmed a diagnosis of DLBCL. The immunophenotype of the tumor was as follows: CD20+, PAX5+, MUMI+, CD3-, CD21-, CD10-, CD5-, BCL-, cyclin D1- and Ki67 (+80%).

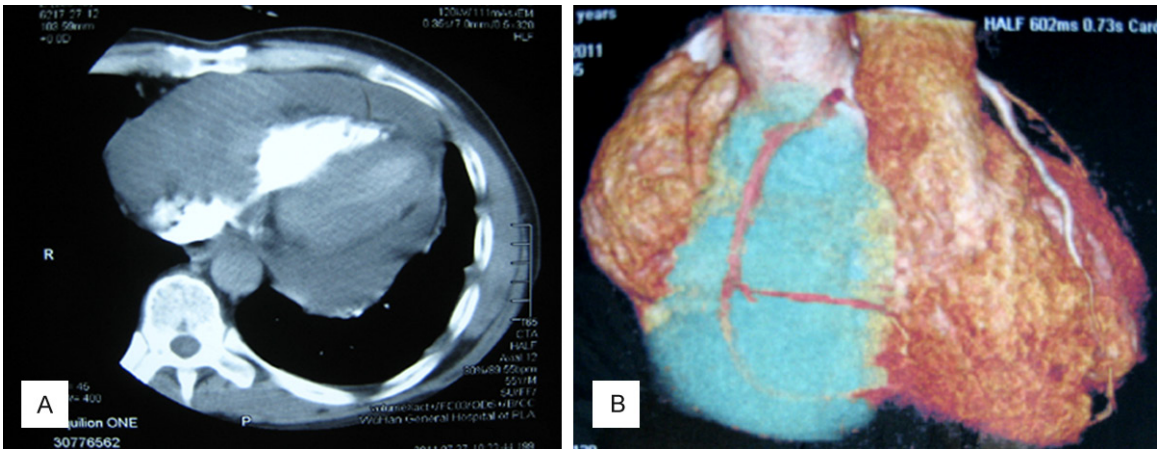

Figure 1. Computed tomography (CT) imaging of the heart before the surgery showing a mass in the cardiac space occupying approximately 7.3 cm × 5.9 cm × 6.2 cm. A: Tumor in the right atrium and hydropericardium (+), B: 3-D reconstruction for the CT images, the tumor is in blue.

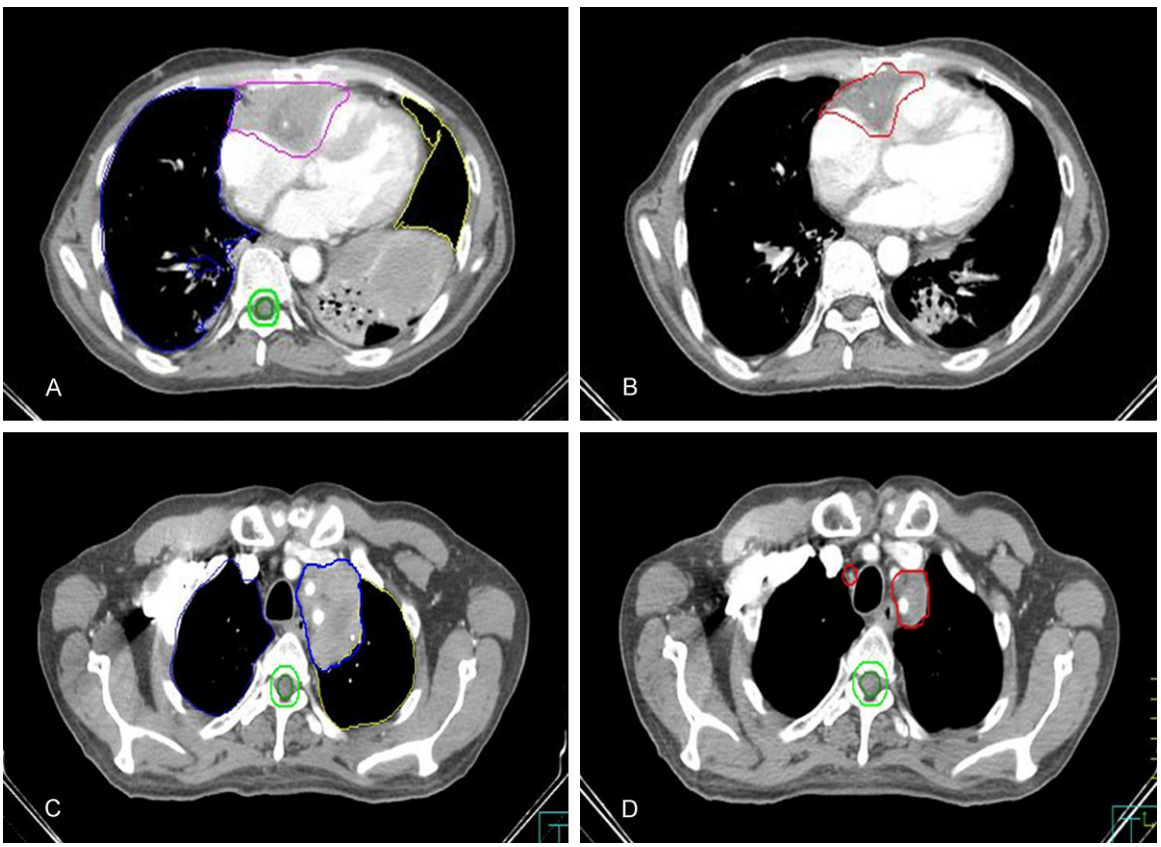

Figure 2. CT imaging. A: Anterior right ventricular tumor before radiotherapy, B: Reduction in the right ventricular tumor after radiotherapy, C: Upper left mediastinal trachea tumor before radiotherapy, D: Significant reduction in the upper left mediastinal trachea tumor after radiotherapy.

The patient received oral anti-rejection drugs and was re-examined by positron emission tomography (PET)-CT 1 month after the operation. PET-CT revealed abnormal increased metabolism in the right level I cervical lymph node. There was an abnormal rise in metabolism in the liver, inferior vena cava, left peritoneum and descending colon. The International

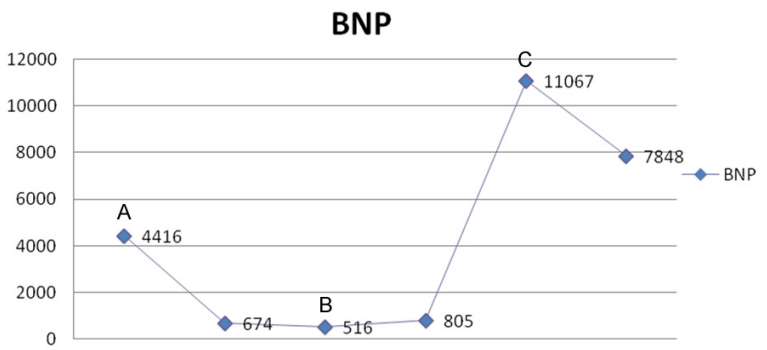

Figure 3. Changes in the levels of brain natriuretic peptide (BNP) in the patient after recurrence. A: Heart primary recurrence, B: Mediastinal radiotherapy, C: Pulmonary bacterial and fungal infection and tumor progression.

Prognostic Index score was 2. The patient subsequently received 4 cycles of chemotherapy with R-COP (rituximab 400 mg on day 1, cyclophosphamide 1000 mg on day 2, vincristine 2 mg on day 2, and prednisone 100 mg on days 2-6). Doxorubicin was omitted due to toxicity concerns given its immunosuppressive effects. Following completion of the chemotherapy regimen, the metabolic evaluation by PET/CT showed a complete response.

The patient responded well to chemotherapy, but he experienced degree III bone marrow suppression and had a pulmonary fungal infection after chemotherapy. An electrocardiogram (ECG) showed sinus tachycardia and a complete right bundle-branch atrioventricular block. Even though the patient's condition improved after anti-infection treatment, chemotherapy was suspended for 2 months. A CT scan of the thorax revealed multiple bilateral soft-tissue masses (**Figure 2A**, **2C**), while an ultrasonic cardiogram displayed multiple mediastinal masses. The dyspnea worsened, and he received R-COP chemotherapy for another 2 cycles. The patient's heart was weakening and his dyspnea was worsening. His chest and abdomen were re-examined by CT; this showed no change compared with his condition before chemotherapy.

The patient experienced progressive dyspnea and palpitations. Tumor recurrence in the transplanted heart and multiple metastases in the neck, thoracic, and abdominal regions were observed on CT images taken at the time of transfer to our hospital. The heart and mediastinal lesions were treated by regional radiation therapy to alleviate the heart compression symptoms. After the first round of intensity-modulated radiation therapy (20 Gy in 11 fractions), CT imaging showed that the heart and mediastinal masses were significantly reduced in size (**Figure 2B**, **2D**). The level of brain natriuretic peptide (BNP) was also significantly decreased (**Figure 3**). However, the abdominal mass continually progressed. The patient was then administered with the Gemox chemotherapy regimen (gemcitabine 1200 mg on day 1 and 8, oxaliplatin 150 mg on day 2). After this chemotherapy cycle, new mediastinal and abdominal lesions were seen on CT imaging. At that time, we proposed a second cycle of radiotherapy, but the patient had degree IV bone marrow suppression and pulmonary bacterial and fungal infections, and BNP and inosine levels were increased. An anti-infection treatment was administered, but the response was poor and his symptoms gradually worsened. The patient died within 11 months of the first PCL diagnosis.

Discussion

PCL is a rare malignancy and it accounts for less than 5% of non-Hodgkin's lymphoma (NHL), and 1-3% of all cardiac tumors [2]. PCL occurs more frequently in immunocompromised patients and those taking immunosuppressant drugs, cardiac transplant recipients, and male AIDS patients [3]. The most common site of origin is the right atrium of the heart, followed by the right and left ventricles and the left atrium [4]. The clinical presentation of PCL may vary according to the site of involvement, and symptoms include heart failure, arrhythmias, and pericardial tamponade [5]. Although it is difficult to diagnose, PCL can be detected by echocardiography, CT, magnetic resonance imaging, radioisotope scan and PET/CT. Nonetheless, the final diagnosis is made by pathological examination, this may include both cytologic examination of the effusive fluid and a tissue biopsy. DLBCL is expressed in a wide variety of B cell markers, such as CD19, CD20, CD22, CD79a, but may lose one or several of them. The expression of CD5 in 10% cases, CD10 in 25~50% cases, Bcl-2 protein in

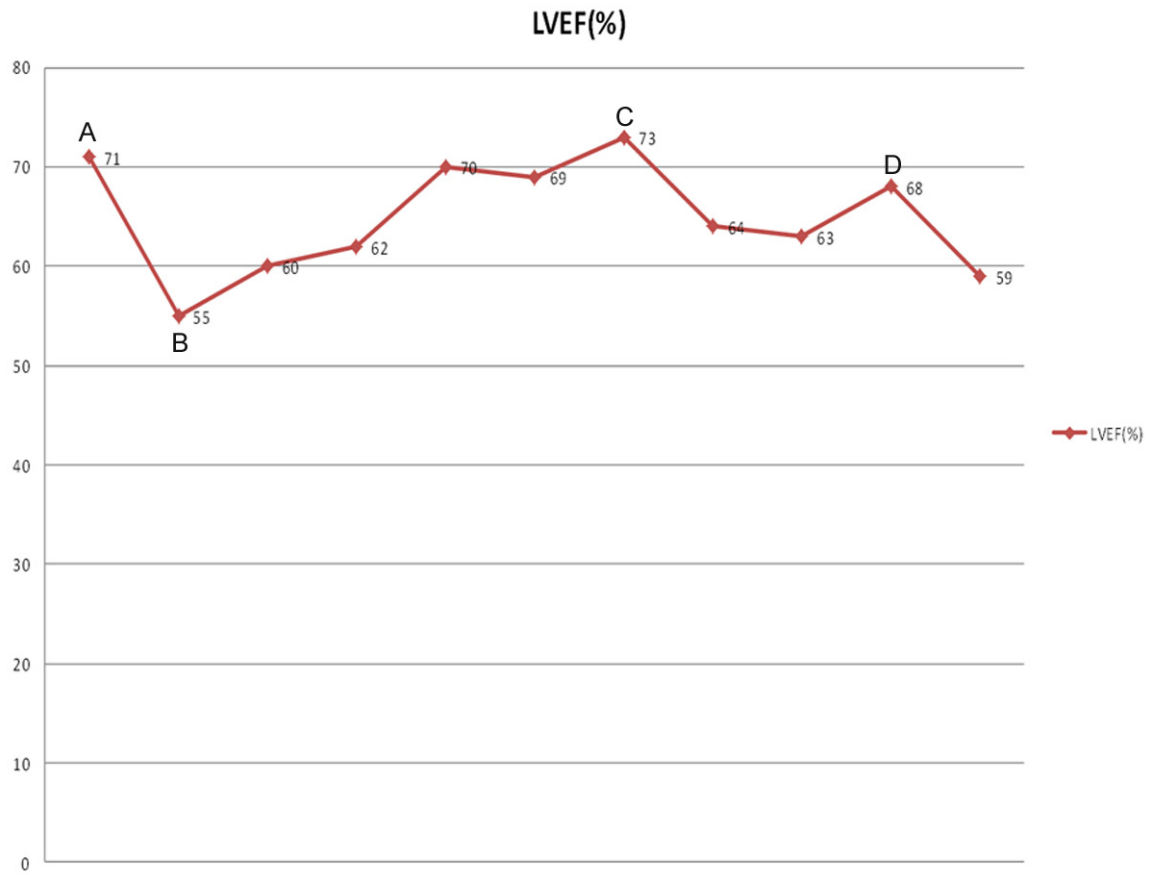

Figure 4. Left ventricular ejection fraction (LVEF) changes in the patient before and after surgery and chemotherapy; the change between approximately 50% and 70% is not obvious. A: Before the treatment, B: After the orthotopic heart transplantation, C: Cardiac recurrence, D: Mediastinal radiotherapy.

30~50% cases, the positive expression rate of Ki-67 was more than 40%, and a few more than 90%. Currently, there is no standard mode of treatment for PCL. Treatment strategies include chemotherapy, surgical excision, heart transplantation, radiation therapy, and hematopoietic stem cell transplantation, but the prognosis is poor for all of these treatment strategies. The median survival time from the initiation of treatment is approximately 7 months [6].

More than 80% of PCLs are diagnosed as DLBCL [1], which is usually sensitive to chemotherapy. Improved survival has been seen with the addition of rituximab to chemotherapy regimens for PCL [3]. A study by Seki et al. reported that rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) provided a greater survival benefit than CHOP alone [7].

However, chemotherapy can lead to adverse events in PCL patients. There have been many reports on gastrointestinal perforation occurring after treatment in patients with lymphoma involving the gastrointestinal tract [8]. Sudden death on the first day of chemotherapy has been described in patients with PCL [9], and tumor-associated cardiac wall rupture has also been reported in lymphomas treated with chemotherapy [10]. Considering the patient would have been at high risk for cardiac rupture following rapid tumor regression after chemotherapy, the doctor chose the orthotopic heart transplantation.

Moser et al. estimated that doxorubicin (total dose for most patients, <400 mg/m^2) increases the risk of chronic heart failure. In patients who received mediastinal radiotherapy (<40 Gy), there was no increased risk of chronic heart failure, myocardial infarction, or stroke [11]. Therefore, our case received chemotherapy with R-COP, and mediastinal radiotherapy after the cardiac recurrence.

After the orthotopic heart transplantation, the patient received oral anti-rejection drugs, chemotherapy, and suffered from bone marrow suppression and a pulmonary fungal infection; all of these contributed to decreased immune function that may have had an adverse effect on subsequent treatments.

In our case, the volatility of BNP (**Figure 3**) was more obvious than the left ventricular ejection fraction (LVEF, **Figure 4**). An analysis by Kuittinen et al. indicated that natriuretic peptides might be more sensitive than LVEF in reflecting acute, subclinical systolic dysfunction in NHL patients previously treated with chemotherapy [12]. Gimeno et al. reported that N-terminal-proBNP levels ≥ 900 pg/ml were significantly associated with a higher risk of death [13].

Conclusion

We propose local radiotherapy as an effective treatment option for the relief of heart failure symptoms in the PCL patient with cardiac recurrence who has undergone an orthotopic heart transplantation. However, patients who receive oral anti-rejection drugs after heart transplantation surgery have decreased immune function, which may have an adverse effect on subsequent treatments. These patients warrant additional vigilance during management.

Disclosure of conflict of interest

None.

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References

[1] Dawson MA, Mariani J, Taylor A, Koulouris G and Avery S. The successful treatment of primary cardiac lymphoma with a dose-dense schedule of rituximab plus CHOP. Ann Oncol 2006; 17: 176-177.

[2] Piccaluga PP, Vigna E, Placci A, Agostinelli C, Laterza C, Papayannidis C, Leone O, Martinelli G, Zinzani PL, Baccarani M and Pileri SA. Primary cardiac non-Hodgkin lymphoma presenting with atrial flutter and pericardial effusion. Br J Haematol 2006; 134: 356.

[3] Miguel C and Bestetti R. Primary cardiac lymphoma. Int J Cardiol 2011; 149: 358-363.

[4] Deepti A, Noone M, Mahadevan A, Naresh K, Yasha T, Satishchandra P, Muthane U and Shankar S. Primary cardiac cytotoxic T-cell lymphoma presenting with neurological deficits: a case report. Cardiovasc Pathol 2008; 17: 334-338.

[5] Gowda R and Khan I. Clinical perspectives of primary cardiac lymphoma. Angiology 2003; 54: 599-604.

[6] Mejhert M and Muller-Suur R. Primary lymphoma of the heart. Scand Cardiovasc J 2000; 34 606-608.

[7] Seki R, Ohshima K, Nagafuji K, Fujisaki T, Uike N, Kawano F, Gondo H, Makino S, Eto T, Moriuchi Y, Taguchi F, Kamimura T, Tsuda H, Ogawa R, Shimoda K, Yamashita K, Suzuki K, Suzushima H, Tsukazaki K, Higuchi M, Utsunomiya A, Iwahashi M, Imamura Y, Tamura K, Suzumiya J, Yoshida M, Abe Y, Matsumoto T and Okamura T. Rituximab in combination with CHOP chemotherapy for the treatment of diffuse large B cell lymphoma in Japan: a retrospective analysis of 1,057 cases from Kyushu Lymphoma Study Group. Int J Hematol 2010; 91: 258-266.

[8] Blackledge G, Bush H, Dodge O and Crowther D. A study of gastro-intestinal lymphoma. Clin Oncol 1979; 5: 209-219.

[9] Chim CS, Chan AC, Kwong YL, Liang R. Primary cardiac lymphoma. Am J Hematol 1979; 5: 209-219.

[10] Molajo A, McWilliam L, Ward C and Rahman A. Cardiac lymphoma: an unusual case of myocardial perforation--clinical, echocardiographic, haemodynamic and pathological features. Eur Heart J 1987; 8: 549-552.

[11] Moser EC, Noordijk EM, van Leeuwen FE, le Cessie S, Baars JW, Thomas J, Carde P, Meerwaldt JH, van Glabbeke M, Kluin-Nelemans HC. Long-term risk of cardiovascular disease after treatment for aggressive non-Hodgkin lymphoma. Blood 2006; 107: 2912-2919.

[12] Kuittinen T, Jantunen E, Vanninen E, Mussalo H, Vuolteenaho O, Ala-Kopsala M, Nousiainen T, Hartikainen J. Cardiac effects within 3 months of BEAC high-dose therapy in non-Hodgkin's lymphoma patients undergoing autologous stem cell transplantation. Eur J Haematol 2006; 77: 120-127.

[13] Gimeno E, Gómez M, González J, Comín J, Alvarez-Larrán A, Sánchez-González B, Molina L, Domingo-Domenech E, Garcia-Pallarols F, Pedro C, Abella E, Vilaplana C, de Sanjosé S, Besses C and Salar A. NT-proBNP: a cardiac biomarker to assess prognosis in non-Hodgkin lymphoma. Leuk Res 2011; 35: 715-720.