The usefulness of transesophageal echocardiographic observation during chemotherapy for cardiac metastasis of non-Hodgkin lymphoma complicated with left ventricular diastolic collapse

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Received 23 February 2008; received in revised form 14 August 2008; accepted 22 August 2008
Available online 14 October 2008

KEYWORDS
Non-Hodgkin lymphoma;
Cardiac metastasis;
Cardiac tamponade;
Left ventricular diastolic collapse;
Transesophageal echocardiography

Summary A 53-year-old man, who had been treated for penile origin diffuse large B cell type non-Hodgkin lymphoma (NHL), suffered from right femoral pain and dyspnea. Positron emission tomography (PET) revealed abnormal accumulation in his right femur and cardiac segments. Transthoracic echocardiography revealed massive localized pericardial effusion with the collapse of both ventricles and the mass-like echo in the left atrium. We performed emergent pericardiocentesis and diagnosed this case as a recurrence of NHL with cardiac metastasis. With the use of transesophageal echocardiography (TEE), we confirmed the mass-like echo around the inter-atrial septum, which directly invaded to the aortic ring and the right atrial wall. In order to evaluate the effect of chemotherapy, we performed TEE and observed the precise changes of intra-cardiac tumor size. With the use of TEE monitoring,
we could select the appropriate chemotherapeutic regimen, and the tumor became smaller and finally diminished. The femoral accumulation detected by PET also disappeared. We experienced a case of cardiac metastasis of NHL complicated with left ventricular diastolic collapse due to the massive localized pericardial effusion. TEE is a useful tool to evaluate precisely the efficacy of chemotherapy for intra-cardiac tumors.

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Case report

A 53-year-old man felt a tumor on his penis and visited our hospital in 2005. He was diagnosed as having diffuse large B cell type non-Hodgkin lymphoma (NHL) by the histological analysis of biopsy. He was treated with chemotherapy R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) for four cycles and radiation therapy, and achieved complete remission status. Nine months later, in mid-December 2006, he suffered from a painful right femoral tumor (10-cm diameter) and dyspnea on exertion. Positron emission tomography (PET; FDG 226.6 MBq) revealed abnormal accumulations in his right femur and cardiac segments. He gradually became dyneic at rest and was admitted to our hospital in late December.

At the time of admission, he was very obese (the height was 175 cm and weight 88 kg). The blood pressure was 124/78 mmHg, and the heart rate was 112 beats/min with pulsus paradoxus. The oxygen saturation showed 96% in the room air. Although he had no cardiac murmur, rales, leg edema, or lymph node swelling, he showed venous engorgement and the right femoral tumor. His extremities

Figure 1  Findings of pericardial effusion from each imaging modality in admission: (A) the chest roentgenogram showed marked cardiomegaly without lung congestion; (B) the chest computed tomography showed the massive localized pericardial effusion (arrows); (C) and (D) two-dimensional echocardiography showed the massive localized pericardial effusion at the posterior side of left ventricle (arrows), a little pericardial effusion at the anterior side of right ventricle, and the collapse of right ventricle (D: dotted arrows).
were clammy and cold indicating peripheral hypoperfusion.

Laboratory data indicated mild liver dysfunction due to congestion and low plasma brain natriuretic protein (BNP) level (51.7 pg/ml). The chest roentgenogram disclosed an enlarged cardiac silhouette and dull cardio-pleural angles (Fig. 1A). The electrocardiogram showed sinus tachycardia, low voltage in limb leads, incomplete right bundle branch block, and right axis deviation. The chest computed tomography (CT) demonstrated eccentric distribution of the pericardial effusion (PE), which localized to the anterior side of the right heart and the posterior side of the left ventricle (LV) (Fig. 1B). Transthoracic echocardiography (TTE) revealed the massive localized PE in the posterior side of LV and the mass-like echo (dotted arrow) in the septal side of left atrium (LA) (Fig. 2). In addition, diastolic compression of the right ventricle (RV) (Fig. 1C and 1D) and LV was observed. The frame analysis revealed that LV was collapsed in the early to mid-diastole as shown in Fig. 2. The LV diameter of end-diastole was slightly small (39 mm) and the size of the LA reached 51 mm. The percent respiratory change of trans-mitral peak early velocity was 38% and the diameter of the inferior vena cava was 28 mm with poor respiratory changes.

Judging from the clinical unstable status and TTE findings, we diagnosed that he was in clinical tamponade enough to need emergent pericardiocentesis. By substernal puncture, massive hemorrhagic fluid (1500 ml) was drained from the pericardial space and his symptoms dramatically improved. The fluid contained a lot of malignant lymphoma cells, which yielded the same histological findings as the primary penile lesion. Because the emergent TTE could not detect the invasion of the intra-cardiac tumor in detail, we performed transesophageal echocardiography (TEE) for the accurate diagnosis of the intra-cardiac tumor. We found that the tumor invaded into the inter-atrial septum, aortic rings, and right atrial wall and protruded to the atrial cavity (Fig. 3A).

According to these TEE findings, in order to prevent perforation of the inter-atrial septum and/or systemic embolization due to the rapid necrosis of the tumor, we initially treated him with R-COP regimen (rituximab, cyclophosphamide, vincristine, and prednisolone), and subsequently added methylprednisolone (mPSL) pulse therapy. Although the volume of fluid from pericardiocentesis gradually decreased, the size of intra-cardiac tumor did not change on TEE (Fig. 3B), and the femoral tumor became even larger. Therefore, we escalated the intensity of chemotherapy to R-CHOP regimen for one cycle. Since his cardiac tumor significantly reduced by this regimen without significant toxicity (Fig. 3C), we selected next R-EPOCH regimen (rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin) that included the similar drugs as R-CHOP regimen but

**Figure 2**  Serial echocardiographic images of left ventricular diastolic collapse. On the early to mid-diastole, the left ventricle was collapsed due to the massive posterior pericardial effusion from the apical long-axis view of transthoracic echocardiography. The feature of left ventricular free wall is normal at end-systole. During early to mid-diastole, however, the apical side of left ventricle started to dilate, but the posterior side of left ventricle was compressed inward by massive pericardial effusion (arrows). And on the end-diastole, the left ventricle enlarged normally. We could also detect the tumor in the left atrium (dotted arrows).
could reduce the cumulative toxicity of doxorubicin through continuous infusion of the drug [1]. Although two cycles of R-EPOCH reduced the size of cardiac tumor markedly, TEE revealed that there remained tumors in the inter-atrial septum and right atrium (RA) (Fig. 3D). Next we chose R-CHASE regimen (rituximab, cyclophosphamide, etoposide, cytarabine, and dexamethasone), which is the new salvage chemotherapy for patients with refractory or relapsed lymphoma. After four cycles of this regimen, we confirmed the disappearance of the cardiac tumor by TEE (Fig. 3E) as well as the lesions in the right femur and the heart by PET. Thus, a diagnosis of complete remission was made. Finally, we treated him with myeloablative high-dose chemotherapy by the use of the modified R-BEAM regimen (rituximab, ranimustine, etoposide, cytarabine, and melphalan), which was followed by autologous peripheral blood stem cell transplantation (PBSCT) rescue. He was discharged from our hospital in a stable condition in October 2007.

**Discussion**

It is reported that cardiac tamponade due to malignant disease is usually fatal [2]. A widely accepted echocardiographic sign of cardiac tamponade is the collapse of RA and RV associated with circumferential effusions [2], and the reports of left ventricular diastolic collapse (LVDC) are rare [3]. In this case, TTE showed the collapse of both ventricles. The mechanism of RV collapse is explained as that the early diastolic LV expansion compresses the fluid to right-side pericardial spaces, then increases RV pericardial pressure exceeds diastolic RV pressure and finally presses RV free wall [4]. Similar to RV diastolic collapse, LV diastolic collapse is caused by increased LV pericardial pressure via LV expansion in the limited space. It was reported that LVDC was sometimes observed in the case of the post-operation [5] or malignant tumors [6]. In such cases, it was reported that non-circumferential and localized PE was detected due to adhesion after operation or invasion of the tumor. This finding is
thought to be the difference of right- and left-side pericardial chamber compliance indicating partial adhesion of the heart and pericardium.

In our case, PE mainly located in the posterior side of LV as shown in Fig. 1B–D non-circumferentially. We thought that the tumor invaded and adhered to the cardiac wall and pericardial cavity, and then caused the localized PE. We, however, could not show the definite findings that indicate the adhesion or invasion on imaging modalities. After the pericardiocentesis, the patient’s symptoms were dramatically improved and LVDC was not detected. Therefore we thought that the localized PE due to adhesion and invasion of the tumor was mainly involved in the appearance of cardiac tamponade.

The diagnostic echocardiographic features of LVDC have been reported as follows. D’cruz et al. noted an abnormal diastolic contour of the left ventricular posterior wall such as paradoxical motion in M-mode echocardiography [7]. A similar finding was observed in M-mode echocardiography of an operative patient reported by Jones et al. on the late isolated left ventricular tamponade [8]. Hsu et al. reported that a case of LVDC caused by malignant PE showed the abnormal contour of the left ventricular posterior wall motion similar to our case by frame analysis of two-dimensional echocardiography [6]. These reports indicated that LVDC meant the existence of hemodynamically considerable cardiac tamponade.

Although we could not evaluate M-mode echocardiography because of the patient’s orthopnea on admission, we detected obvious LVDC of the posterior wall in the early to mid-diastole, by the use of two-dimensional echocardiography as shown in Fig. 2. Judging from LVDC and his severe symptoms, we diagnosed him in severe cardiac tamponade, and subsequently performed the emergent pericardiocentesis via the substernal approach. After the drainage from the anterior spaces of right heart, his symptoms were dramatically improved and both right- and left-side PE were decreased. It means that there were some communications between right- and left-side PE.

It has been reported that the frequency of primary cardiac tumor is only 20% of total cardiac tumors and the rest were metastatic cases [9]. Regarding the cases of malignant lymphoma, cardiac metastasis was reported to occur in 24% [10]. But the cardiac metastasis is often recognized for the first time in autopsy because of the difficulty to diagnose. Previous reports indicated that the recent advances in chemotherapy improved the prognosis of malignant lymphoma, when the appropriate therapeutic regimen was selected by the accurate evaluation of therapeutic effects. Regarding the chemotherapy, rituximab has been reported as an effective drug for cardiac lymphoma [11].

Our patient was followed up with PET after his first chemotherapy for the penile lesion of NHL, and we noticed the recurrence of NHL in the femur and the heart with PET. The finding with PET, however, only suggested the possibility of tumor existence in the cardiac segment. Regarding PET, we could judge the existence of cardiac tumor, but could not detect the extent of the size or the feature of tumor adequately. Furthermore, PET is too expensive for frequent monitoring of chemotherapeutic effects. As to CT, CT does not scan continuously and has a limitation in the slicing width. CT, therefore, could not have estimated the cardiac tumor in detail. If we had performed CT with a contrast medium, it might have caused renal failure in association with the side effects of chemotherapy. The most important problem in PET and CT scan is the exposition to radiation for the frequent repeat monitoring of the chemotherapeutic effect in a short period.

Thus, we selected echocardiography for monitoring the effect of chemotherapy. Because of marked obesity (BMI 28.7), although we could detect the existence of tumor in LA with TTE, we could not elucidate the feature, precise size, or infiltration of the intra-cardiac tumor. With TEE monitoring, on the other hand, we could find that the tumor invaded to the inter-atrial septum and the atrial cavity in detail, which was thought to be a risk factor for the perforation of the inter-atrial septum and systemic embolization. Although TEE might be a semi-invasive tool, we considered that the information of TEE performed by the well-trained operator exceeds the obscure images of TTE in this case. Therefore, we decided to use TEE for monitoring the cardiac tumor, and carefully changed the chemotherapy protocols according to TEE findings. As mentioned earlier, we could choose the appropriate five regimens, and the patient finally achieved complete remission of the disease.

In summary, this report highlights the usefulness of TEE for the evaluation of intra-cardiac tumor and the efficacy of chemotherapy. We also highlighted LVDC which was due to massive localized PE by cardiac metastasis of NHL.

References