

Case Report

Biatrial Double-Hit Lymphoma Presenting with Superior Vena Cava Syndrome

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Case Presentation

We report the case of a 67-year-old man affected by a double hit lymphoma presenting with a cardiac bi-atrial involvement at diagnosis.

Patient's medical history was positive for previous tobacco use and single-vessel coronaric heart disease.

In July 2014 he presented to his cardiologist with a three-month history of jugular compulsion. He performed an electrocardiography examination, an ergometric test and a coronarography without significant findings. In August 2014 he developed shortness of breath and face-neck oedema. Thus, the cardiologist ordered a chest Computed-Tomography (CT) scan that revealed a mediastinal mass in continuity with two hypodensities in the left and right cardiac atria.

The patient underwent a Positron Emission Tomography with

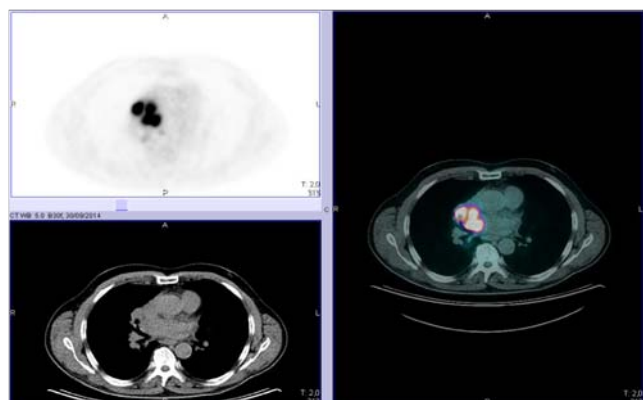


Figure 1: PET and PET/CT showing pathological increased uptake of the intra-atrial masses.

Abstract

Cardiac involvement is very rare in lymphomas and is typically characterized by a poor prognosis, largely due to delay in diagnosis and cardiac complications or venous/arterial thromboembolism.

This unusual presentation and other extranodal localizations are more likely to be found in aggressive lymphomas rather than indolent diseases. In this report we present the case of a patient with heart involvement by a biatrial double mass conditioning superior vena cava syndrome. Histological findings consistent with double hit lymphoma could explain the very aggressive behaviour and the extranodal tropism of this lymphoma. We are treating this patient with an intensified chemotherapy according to EPOCH regimen under carefully clinical and cardiological monitoring.

Keywords: Lymphoma; Double-Hit; C-Myc; Heart; Atrial Mass

Computed Tomography (PET/CT) which showed abnormally increased ¹⁸F-FDG uptake in the right hilar mass, involving the mediastinum and the atria (maximum standardized uptake value, SUV_{max}, 29) and pathological paratracheal and subcarinal lymphadenopathies (SUV_{max} 24) (Figure 1).

Eventually, A diagnostic Fine-Needle Aspiration Cytology (FNAC) of the hilar mass under endoscopic ultrasound guidance was performed. Histological findings were consistent with Diffuse Large B-Cell Lymphoma (DLBCL). On immunohistochemistry analysis, the large atypical lymphocytes were positive for CD20, BCL-2, BCL-6, CD10 stains and Ki-67 was higher than 90%. He subsequently started a steroid therapy. In October 2014 the patient was referred to our center in order to complete staging assessments and to start a cytoreductive treatment.

On admission to our hospital the patient presented with overt signs of superior vena cava syndrome: oedema of face and neck, bilateral jugular distention in standing position and changed voice tone due to vocal chords oedema. No venous collateral circulation was visible on the anterior chest wall.

Vital parameters were normal. Cardiac auscultation revealed no pathological sounds. Both blood counts and standard biochemical tests were normal. Of notice, Lactate Dehydrogenase (LDH) level was normal too (347 UI/L; normal value < 460 UI/L).

Contrast-enhanced total body CT scan confirmed the presence of a polycyclic expansion invading both left atrium (intra-atrial mass of 27 mm) and right atrium (42 mm) where it obstructed the superior cavoatrial junction. Azygos vein ectasia and paravertebral venous collaterals were present. There were no other radiological abnormalities in other anatomical districts (Figure 2).

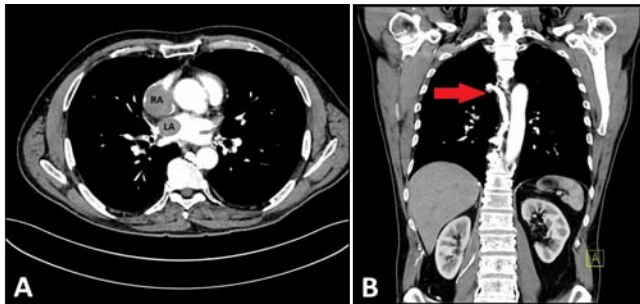


Figure 2: Contrast enhanced CT scan. Axial section (A): the lymphoma's mass in the Left Atrium (LA) and in the Right Atrium (RA). Coronal section (B): the dilated and tortuous azygos vein (red arrow) which drain superior vena cava blood flow into the paravertebral collaterals.

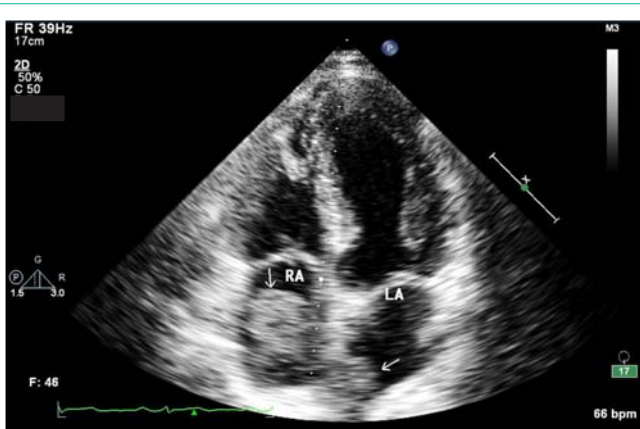


Figure 3: Two dimension (2D) echocardiography. It points out the Right and Left Atria (RA and LA), occupied by the neoplastic nodules (arrow).

Considering the extremely rare disease localization and in order to better assess cardiac involvement we also performed a transthoracic echocardiography (Figure 3). The examination properly visualized an echogenic solid mass in the left atrium (24 x 15 mm) between the top of the atrium and the interatrial septum, closed to the connection with the superior pulmonary vein. The right atrium was occupied by a polylobed mass (diameter 40 x 31 mm) which obstructed the venous return from superior *vena cava*. Ventricular ejection fraction, segmentary kinesis and global systolic function were normal

Bone marrow biopsy resulted negative for lymphoma infiltration.

The anatomopathological revision confirmed the diagnosis of DLBCL, germinal center like. Revised immunohistochemistry confirmed CD20, Bcl-2 and Bcl-6 positivity and showed over 70% *c-Myc* expression in the lymphoid cells. Fluorescent in Situ Hybridization (FISH) demonstrated the presence of *bcl2* and *bcl6* translocation whereas was negative for *c-Myc* rearrangements (Dual color break-apart probe for *c-myc*, *blc2*, *bcl6*) (Figure 4).

Thereby, a diagnosis of double hit DLBCL (by means of immunohistochemical analysis), Ann Arbor stage IVA, revised International Prognostic Index 2, because of age and stage, was performed.

In consideration of a very likely risk of cardiac perforation following chemotherapy, we decided to perform a mild debulking cytoreductive therapy with a single dose of doxorubicin 50 mg/sm

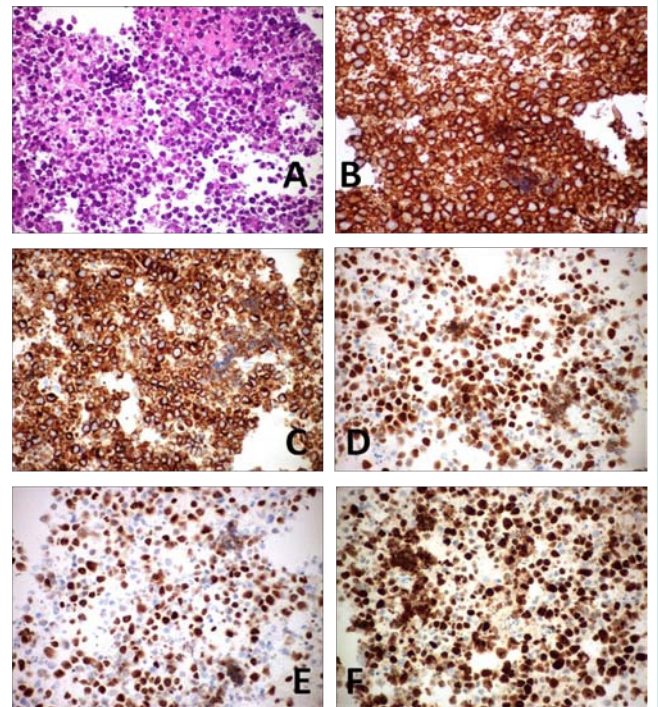


Figure 4: Hematoxylin and Eosin staining slide (A). Immunohistochemical staining demonstrating intense positivity of CD20 (B), BCL2 (C), BCL6 (D), C-MYC (E) and MIB-1 (F).

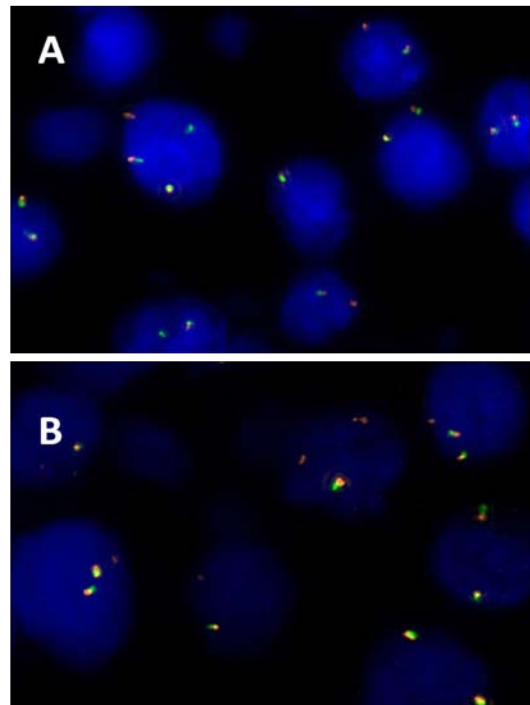


Figure 5: Fluorescent In Situ Hybridization (FISH) with dual color probe proves the presence of *bcl2* (A) and *bcl6* (B) translocations in lymphoma B cells.

before proceeding to immunochemotherapy. At starting therapy, we considered the risk of venous/arterial thromboembolism, of cardiac rhythm changes and tumor lysis syndrome and we started adequate

Table 1: Cardiac biatrial involvement in lymphoma: literature case reports.

| Reference | Year | Age (years) | Sex (M/F) | Clinical presentation | Histology | Treatment | Outcome, OS | Cause of death |
|-------------------|------|-------------|-----------|--------------------------------------|-----------------------|-------------------|-------------------|--|
| Somers [9] | 1960 | 66 | F | Dyspnea | NS | No treatment | Dead, 1 month | NS |
| Moore [10] | 1992 | 80 | M | Dyspnea, dysphagia | NS | No treatment | Dead, 1 month | NS |
| Chao [11] | 1995 | 57 | M | Dyspnea, atrial fibrillation | B cell lymphoma (NS) | Chemotherapy (NS) | Alive, NS | / |
| Jurkovich [12] | 2000 | 75 | M | Dyspnea, facial swelling, hemoptysis | DLBCL | Chemotherapy (NS) | Alive, NS | / |
| Mejhert [13] | 2000 | 59 | M | Dyspnea | NS | Chemotherapy | Dead, 10 months | NS |
| Saotome [14] | 2002 | 69 | M | Dyspnea | NS | Chemotherapy | Dead, 14 weeks | NS |
| Zakyntinos [15] | 2004 | 48 | M | Superior cavae vena syndrome | DLBCL (bcl2 + on IHC) | None | Dead, 8 days | Inferior vena cavae thrombosis, sepsis |
| Nascimento [16] | 2007 | 40 | F | Dyspnea, bradycardia | Follicular lymphoma | CHOP | Alive, 120 months | / |
| Lin [17] | 2010 | 42 | M | Syncopes | DLBCL | R-CHOP | Dead, 2 months | Sudden cardiac death |
| Cho [5] | 2012 | 63 | F | Dyspnea, facial swelling | DLBCL | R-CHOP | Alive, NED | / |
| Haji-Chahine [18] | 2014 | 70 | NS | NS | NS | NS | NS | NS |

therapy with aspirin plus low molecular weight heparin, allopurinol and hydration. The first chemo-treatment has been administered during continuous electrocardiographic monitoring. Chemotherapy was well tolerated without cardiac complications.

Two weeks later, the patient started immunochemotherapy with dose-adjusted EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin) plus Rituximab. He is currently on treatment with initial clinical evidence of response.

Discussion

Extranodal involvement in lymphomas has always been associated with a worse prognosis [1]. This feature could be present in almost every lymphoma subtype; however, aggressive diseases have a higher probability to present with such a rare phenotype. In particular, DLBCL, Mantle Cell Lymphoma (MCL) and Peripheral T Cell Lymphoma (PTCL) represent the subgroups with the highest rate of extranodal involvement [2]. The gastrointestinal tract, liver, bone, lungs and central nervous system represent the extra lymphatic regions/organs that are more likely to be sites of extranodal localization of disease [1].

Primary cardiac lymphoma represents only 1,5% of extranodal lymphomas while cardiac localization of systemic lymphoma could be present in up to 15% of patients as derived from post-mortem pathological studies [3]. In this very specific context, the most common cardiac involved sites are represented by right atrium followed by right ventricle, left ventricle, and atrial septum [4]. A biatrial involvement is almost unique and has been reported only by a few case reports in the whole medical literature (Table 1). Cardiac lymphoma localization has a poor prognosis essentially related to cardiovascular complications (pulmonary embolism, cerebrovascular ischemic disease, cardiac failure, cardiac perforation, myocardial infarction) [5].

Double-Hit Lymphomas (DHLs) are a subclass of lymphomas belonging to the heterogeneous DLBCL group. Morphologically they consist in large B cell lymphoid cells. Immunophenotypically they are similar to classic DLBCL (usually germinal center type). Clinically, DHLs present with signs of hyper proliferation (B symptoms, compression symptoms) or bulky disease. Moreover they

have a Ki-67 proliferation rate higher than 90%. These features make them similar to Burkitt Lymphoma (BL). The most distinguishing and diagnostic feature of DHLs is represented by positivity to *c-myc* (proliferative stimulus) plus *bcl2* rearrangements (antiapoptotic mechanism) by means of FISH. Recently, Green et al. have showed that also an Immunohistochemistry (IHC) positive for C-MYC or BCL2/BCL6 over expression, in the absence of a positive FISH, is a negative prognostic factor [6]. This is probably due to a more common presence of non-classic gene rearrangements that are not detected by standard FISH probes. Also epigenetic phenomena leading to gene over expression could play a role in this setting. Even if the prognosis of these double-hit “expression” lymphomas is not as worse as FISH-positive DHLs, many centers are treating both entities in the same way.

The more we learn to diagnose DHL, the more we find that they are not just in and between DLBCL and BL. They do have their own phenotypical features. In our clinical experience we noticed that DHLs have a more common extranodal presentation compared to DLBCL and BL. Our observation is confirmed by the few series reporting the incidence of extranodal disease in DHLs [7,8]. The incidence of extranodal involvement at diagnosis in this disease group ranges from 30% to 50% that is much higher compared to DLBCL (20%) (1) or BL (3-5%) [2]. This is of great interest when we consider that the presence of *c-myc* or *bcl2/bcl6* rearrangements alone are not sufficient to generate this phenotype. In fact, also follicular lymphoma, usually characterized by *bcl2* rearrangement, has a very low rate of soft tissue involvement (5-10%) [2]. Based on these observations, we could hypothesize that the sum of hyperproliferative and antiapoptotic signals conferred by altered C-MYC and BCL2/BCL6 expression are sinergic in making neoplastic cells independent by lymphoid (or bone marrow) microenvironment. This could eventually lead to a tropism to extranodal tissues and to soft tissue proliferation.

Conclusion

In conclusion, our report describes a rare case of biatrial lymphoma with a double mass conditioning superior vena cava syndrome. Besides their rare incidence, lymphoma with cardiac involvement represents a clinical challenge for the physician. In the presence of such a rare localization, an accurate pathological

assessment including search for *c-myc* and *bcl2/bcl6* rearrangements or over expression should be performed. Moreover, cardiologic and radiologic assessments represent helpful tools in order to better understand the bounds between the mass, the cardiac tissues and the vascular elements. Due to serious events correlated with the critical localization of the lymphoma mass, treatment of these patients requires carefully management. In this specific setting, a preferable chemotherapy does not exist but some reports describe a more favorable outcome with more aggressive therapies [8]. Even though the risk of cardiovascular complications is high, a DHL diagnosis could lead to an aggressive, and hopefully more effective therapeutic approach.

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