

Retraction Notice

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Expression of Concern:

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This paper is retracted by the editor handling error.

This article has been retracted to straighten the academic record. In making this decision the Editorial Board follows [COPE's Retraction Guidelines](#). Aim is to promote the circulation of scientific research by offering an ideal research publication platform with due consideration of internationally accepted standards on publication ethics. The Editorial Board would like to extend its sincere apologies for any inconvenience this retraction may have caused.

An Uncommon Case of Secondary Cardiac Lymphoma Manifested through Pre-Syncope, Syncope Episodes and Atrial Flutter

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Abstract

The most frequent metastatic malignancies to the heart are lung and breast carcinomas, followed by lymphomas. We herein report the case of a 62-year-old man with pre-syncope, syncope episodes and atrial flutter as the main symptoms of metastatic diffuse large B cell lymphoma, from the left kidney at the right atrium (RA). Laboratory data provided remarkable elevation of LDH, beta-2 microglobulin (B2M), cardiac enzymes and inflammatory biomarkers. The echocardiography revealed multilobulated mass extending from superior vena cava (SVC) to RA, while cardiac MRI showed invasion of RA and SVC from a tumor mass. Abdominal CT scan exhibited global enlargement, with total disorganization of renal architecture. The clinical presentation of cardiac lymphoma usually is nonspecific, going from the absence of symptoms, to heart failure, pericardial effusion or arrhythmias. Primary or secondary lymphoma should be kept in mind in patients presenting with symptomatic right-sided inflow lesions, pre-syncope, syncope episodes and arrhythmias. The elevated LDH and B2M levels, as well as high ratios of myocardial enzymes, would be considered alarming signs of cardiac involvement, as early diagnosis may be lifesaving and a chance for durable remissions or even cure.

Keywords

Atrial Flutter, Beta-2 Microglobulin, Heart, Kidney, LDH, Lymphoma, Syncope

1. Introduction

Cardiac involvement due to metastasis of malignant tumors is relatively uncommon and is associated with poor prognosis. Autopsy studies have shown up to 10% - 12% of cardiac involvement in all patients with malignancy [1]. The most frequent metastatic malignancies, in absolute terms, to the heart are lung and breast carcinomas, followed by lymphomas [2].

Primary cardiac lymphomas are rare and represent <1% of all lymphomas and up to 2% of all cardiac tumors [3]. Cardiac involvement has been reported in 8.7% to 28% of all patients with lymphoma [3]. Most secondary cardiac lymphomas are non-Hodgkin of T and B cell lineage.

The cardiac lymphoma usually presents as a mass in the right cardiac chambers and most frequently affects pericardium, myocardium and to a lesser degree endocardium. The clinical presentation usually is nonspecific, going from the absence of symptoms, to heart failure, pericardial effusion or arrhythmias. Ventricular arrhythmias are extremely uncommon and sparse cases have been reported so far. These arrhythmias usually are symptomatic and associated with significant hemodynamic instability [4].

The diagnosis of cardiac involvement can be difficult. Requiring high clinical awareness and antemortem diagnosis is challenging. MRI has become the gold standard imaging technique for all cardiac tumors with a sensitivity of 90%, permitting the differentiation between tumor and myocardium. Echocardiography and CT are also useful methods for cardiac masses identification. For the final diagnosis histological confirmation is required.

We herein report the case of a 62-year-old man with pre-syncope, syncope episodes and atrial flutter (AF) as the main symptoms of metastatic diffuse large B cell lymphoma (DLBCL), from the left kidney at right atrium (RA).

2. Case Presentation

A 62-year-old man with recent history of fatigue, progressive dyspnea, weakness, dysphagia and weight loss (20 kg in two months) was admitted to private medical centre. Chest radiography revealed mildly increased cardiothoracic ratio, whereas the pulmonary function tests were normal. The electrocardiogram (ECG) showed AF 2:1 at 150 bpm/min. The patient was admitted to General Hospital of Kavala for treatment of AF of unknown origin. Laboratory tests showed mild renal insufficiency (creatinine 1.8 mg/dL, range: 0.40 - 1.10 mg/dL, normal range: 0.6 - 1.2 mg/dL; urea 49 mg/dL, normal range: 0.8 - 2.0 mg/dL) and elevated CRP 2.20 mg/dL. The echocardiography examination was normal, probably due to technical reasons. He received b-blocker, digoxin and new oral anticoagulant, factor Xa inhibitor, [XARELTO® (rivaroxaban)] and was programmed for radiofrequency ablation and reevaluation in one month.

Few days after first discharge, the patient presented to the ER with syncope. The ECG showed sinus rhythm. After a brief hospitalization and stabilization, the patient had been discharged on b-blocker, digoxin and rivaroxaban with a recommendation for programmed reevaluation in 21 days. At the third admission to the ER, the patient was

presented with pre-syncope episode. ECG revealed idioventricular rhythm at 35 bpm/min. The administration of beta blocker and digoxin was discontinued and isoproterenol was administered. After the restoration of the rhythm to sinus, the combination of b-blocker and digoxin switched to sotalol (for rhythm maintenance).

He received isoprenaline hydrochloride (Isoproterenol) and underwent to normal sinus rhythm. The echocardiogram not revealed any pathological result, but “poor acoustic window” was noticed on the report. He was discharged on beta blocker, with the clinical diagnosis of tachycardia-bradycardia (“tachy-brady”) syndrome.

Sixteen days after last admission the patient was readmitted to the ER with syncope, hoarseness and dysphagia. The ECG at presentation showed atrial flutter with rapid ventricular response. The new echocardiogram revealed movable “cauliflower” like mass in the right atrium (RA) extending to the right ventricle, mild insufficiency of tricuspid valve (1+) and slight pericardial effusion. The thoracic CT scan showed lesion in the RA extending to right ventricle, mild pericardial effusion, mediastinal and paraesophageal lymphadenopathy. The abdominal ultrasound revealed enlargement of left kidney (17 cm) with heterogeneous enhancement.

The patient with the diagnosis of cardiac myxoma was admitted to the 1st Cardiology department of AHEPA University Hospital for further investigation and treatment. The patient was presented in the clinic with hoarseness, dyspnea, facial and hands edema, dysphagia and superior vena cava syndrome. The ECG showed sinus tachycardia with intermittent AF. A transthoracic echocardiography revealed multilobulated mass extending from superior vena cava to right atrium, interventricular septum and tricuspid valve. The tricuspid inflow was partially affected (1+: mild insufficiency). The left cardiac chambers and aorta was in normal range. The color Doppler examination revealed increased blood flow in the mass. Cardiac MRI showed invasion of RA and superior vena cava from a tumor mass, circular thickening of the wall of the RA and protruding polypoid masses in RA cavity (**Figure 1** and **Figure 2**). After intravenous contrast mild enhancement of lesion was detected. In the contrast-enhanced abdominal CT scan global enlargement, with total disorganization of renal architecture, was found. The lateral aortic lymph nodes around the origin of the left renal were also significantly enlarged. Laboratory tests showed elevated creatinine 1.7 mg/dL; urea 59 mg/dL; troponin T hs 169 ng/dL, normal range <14 ng/dL; CRP 19.100 mg/dL; LDH 1407 U/L, normal range: 135 - 214 U/L, erythrocyte sedimentation rate 41 mm/hr; normal range <20 mm/hr; ferritin 1709 ng/mL, normal range 13 - 150 ng/mL; serum beta-2 microglobulin 5.3 mg/L, normal range <3.5 mg/L and CPK 1407 U/L, normal range 0 - 167 U/L.

Since the differential diagnosis was kidney carcinoma with cardiac involvement, biopsy of the cardiac mass was performed via internal jugular vein, and the tissue fragments were sent for pathological examination. The biopsied material revealed a malignant tumor consisted of medium and large sized lymphoid cells with areas of necrosis and high number of mitotic figures. The neoplastic cells expressed, as revealed by immunohistochemistry the CD20, PAX5, CD45, Bcl2 and Bcl6 markers, whereas were negative for CD3, CD10, TdT, CD99 and Cyclin D1 markers. The Ki67 proliferation index was high (70%). Overall the diagnosis was consisted with non-Hodgkin diffuse

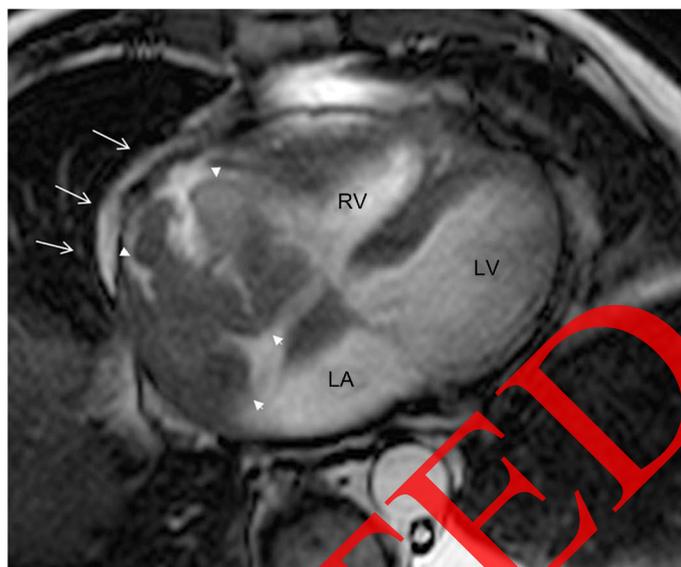


Figure 1. MRI of the heart in the four-chamber view, with the cine bright blood technique, demonstrates thickening of the right atrial wall (arrows) with a polypoid mass (arrowheads) occupying almost the whole cavity of the right atrium. LA (left atrium), LV (left ventricle), RV (right ventricle).

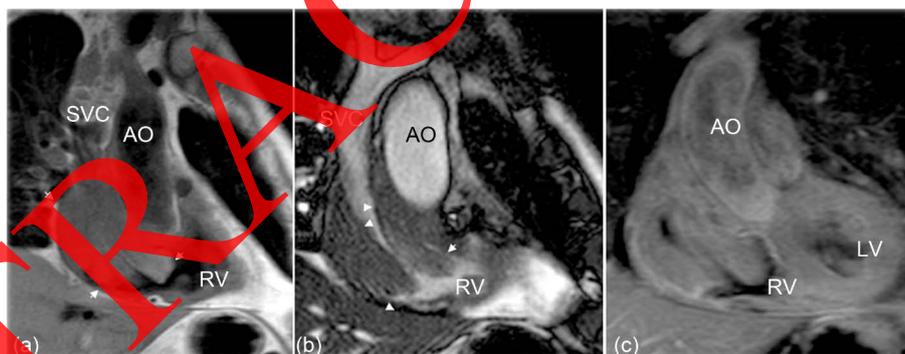


Figure 2. MRI of the heart in the long axis view with T1, cine bright blood and T1 with gadolinium injection with fat suppression techniques (from a to c), demonstrates the mass in the right atrium prolapsing in the right ventricle (RV) leaving a slit-like connection between the superior vena cava (SVC) and the RV. The mass demonstrates mild contrast enhancement. RV (right ventricle), SVC (superior vena cava), AO (aorta), LV (left ventricle).

large B-cell lymphoma (DLBCL). The followed biopsy of the left renal showed, as expected, massive infiltration from the DLBCL, whereas a bone marrow biopsy was negative for lymphomatous involvement (**Figure 3**).

The patient was treated with CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone) and died two days after the therapy admission.

3. Discussion

Primary cardiac tumors represent an extremely minority of human cancers, with an incidence of approximately of 0.001% to 0.3% in autopsy series [5]. The 2/3 of all primary

cardiac tumors are benign, with atrial myxomas to account for 75% of all primary cardiac tumors [5]. Secondary (metastatic) cardiac tumors are about twenty times more common than primary cardiac tumors [6] and are frequently diagnosed at later stages, since are manifested without pathognomonic symptoms or characteristic signs. The clinical presentation of the tumor is determined by several factors as anatomic location, size, growth rate, extent of invasiveness, and tumor friability [7].

Cardiac lymphoma, primary or secondary, is a rare disease, with the B cell non-Hodgkin lymphoma (NHL) to represent the vast majority of events. DLBCL followed by Burkitt lymphoma and CLL/SLL are the most commonly reported histologic types of cardiac NHL, both in primary and metastatic setting [8].

Primary renal lymphoma (PRL) accounts for 0.7% of all extranodal lymphomas, with less than 40 cases that fulfill the criteria of PRL, been reported in the literature. PRL represents less than 1% of all renal lesions and bilateral presentation is seen in 10% to 20% of the cases [9]. The most common PRL type is high grade B-cell NHL, particularly the large B-cell variant [9]. PRL spreads rapidly and up to 2/3 of the patients die within a year of diagnosis.

Cardiac involvement by lymphoma may occur in three pathways: a) direct extension

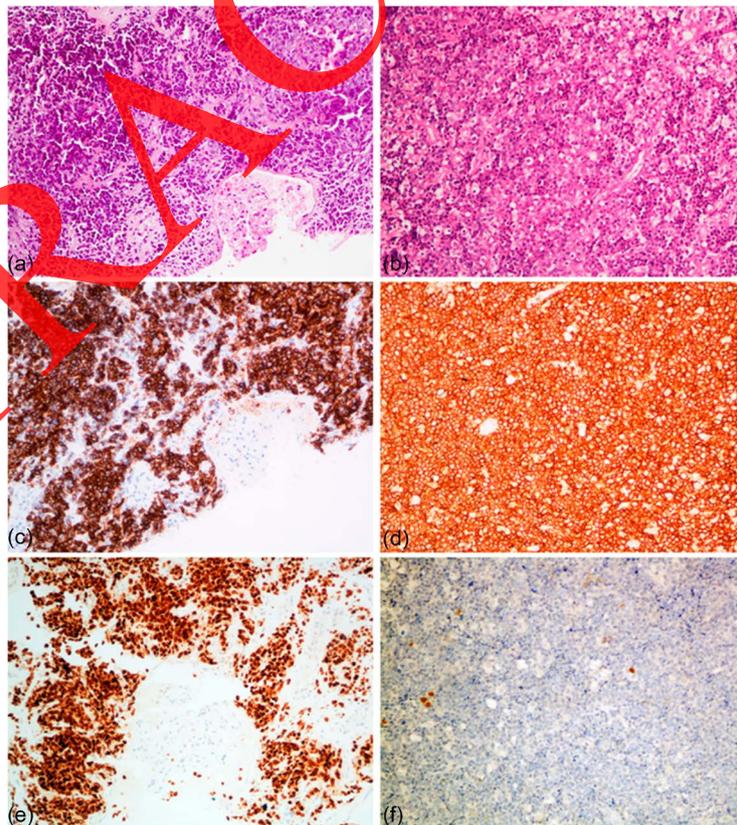


Figure 3. Representative illustrations from the renal lymphoma (a, c, e) and heart invasion (b, d, f). The neoplastic lymphoid cells were medium and large sized, mainly with centroblastic appearance (a, b), expressed CD20 (c, d) and PAX5 (e), whereas were negative for CD10 (f). a, b: H & E, magnification $\times 200$. (c)-(f): Immunohistochemistry, magnification $\times 200$.

from intrathoracic lesions through the parietal pericardium and then the heart; b) via lymphatic circulation along coronary arteries and epicardium; and c) by hematogenous-dissemination [2]. Lymphomatous infiltration can affect sinoatrial node and the atrio-ventricular system, and initiate conduction abnormalities which can drive to recurrent episodes of pre syncope and syncope, as presented in our patient. The syncope may also be due to SVC syndrome, cardiac involvement by the NHL and obstruction of the right atrium by the tumor mass.

Cardiac involvement by NHL is extremely uncommon, and symptoms are often sub-clinical or nonspecific [1]. As reported, in the largest case study of autopsy-proved cardiac lymphoma, only 32% of the cases involved a clinical cardiac manifestation [10]. The more common clinical symptoms of cardiac involvement include dyspnea, congestive heart failure, chest pain, pericardial effusion, Superior Vena Cava Syndrome, stroke, cardiac arrhythmias, nonspecific electrocardiographic abnormalities and sudden death [1] [8]. Other rare symptoms are abdominal pain, dizziness, sepsis, hemoptysis and pulmonary embolism [8].

Laboratory abnormalities such as elevated lactate dehydrogenase (LDH), erythrocyte sedimentation rate, and serum beta-2 microglobulin (B2M) are usually detected in NHLs, whereas raise in cardiac enzymes, as troponins and CPK are indicators of acute myocardial damage. In patients with aggressive NHL, the serum B2M level was reported to be increased in 40% - 55% of patients, whereas B2M level was elevated in 23% - 29% Hodgkin lymphoma [11].

Certain noninvasive examinations allow a quick assessment for cardiac disease. Three-dimensional echocardiography is a useful tool that may provide additional information or better visualization of intracardiac masses, whereas transthoracic echocardiogram is also a sensitive method for the identification of cardiac involvement by malignant tumors, which more commonly present as nodular or polypoid masses in right chambers, with variable myocardial infiltration, often with a pericardial effusion [2]. Cross-sectional imaging as computed tomography (CT) and magnetic resonance imaging (MRI), with the improved tissue and contrast resolution that offer, allow enhanced assessment of tissue on the basis of attenuation or signal intensity [1]. At CT, lymphoma commonly appear as an infiltrating epicardial or myocardial mass that is often isoattenuating to hypoattenuating relative to myocardium and commonly seen as a large, nodular mass that is isointense or hypointense relative to myocardium on both T1- and T2-weighted images which show heterogeneous enhancement after administration of gadolinium [1] [7]. The myocardial and pericardial infiltration is better depicted with MR imaging, however, it requires the patient's hemodynamic stability. Masses can be relatively hypointense on T1-weighted images and hyperintense on T2-weighted images however the appearance can be variable, and the presence of isointense signal relative to cardiac muscle is not uncommon [1].

For the final diagnosis of cardiac masses, and especially sarcomas and lymphomas, pathologic diagnosis is essential, since treatment varies for different tumor subtypes. Thoracotomy or less invasive procedures such as percutaneous endomyocardial biopsy

and fluoroscopy-guided endomyocardial biopsy can be used for obtaining tissue for pathological examination, whereas, in case of pericardial effusion, cytological examination is a useful tool for diagnosis.

The prognosis for patients with either primary or secondary cardiac lymphoma is usually poor, due to diagnostic delay and advanced stage of organ infiltration being major factors affecting the outcome. In the literature are included cases with treatment combinations including chemotherapy, chemotherapy plus radiation therapy, radiation therapy, surgery, surgery plus chemotherapy, and surgery plus chemotherapy plus radiation therapy [1]. Cases of complete remission after autologous stem cell transplantation were also reported [1]. The main chemotherapy regimen for cardiac lymphomas is CHOP, while the BACOP protocol (bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone) was also used [1]. The surgical resection and radiation therapy are less used as a primary choice of treatment in patients with cardiac lymphoma. Recently, the monoclonal CD20 antibody (rituximab) added with the standard CHOP protocol have provided higher survival rates in CD20-positive patients [1].

4. Conclusion

Though uncommon, the diagnosis of cardiac lymphoma, primary or secondary should be kept in mind in patients presenting with symptomatic right-sided inflow lesions, pre-syncope, syncope episodes and arrhythmias. The elevated LDH and serum beta-2 microglobulin levels, as well as high ratios of myocardial enzymes, would be considered alarming signs of cardiac involvement by lymphoma, as early diagnosis may be lifesaving and a chance for durable remissions or even cure.

Authors' Contributions

GK: Cooperated in the clinical case, collected the data and reviewed the manuscript. MB: Analyzed the data and drafted the manuscript. CS: Cooperated in the clinical case and reviewed the manuscript. TK: Cooperated in the clinical case. KK & AKF: Cooperated in the clinical case and interpreted the MRI and CT examinations. TZ & IK: Involved in histopathologic diagnosis of heart, renal and BM biopsies. VP: Cooperated in the clinical case and collected the laboratory data. SH: Cooperated in the clinical case and performed the endomyocardial biopsy. All authors read and approved the final manuscript.

Conflict of Interests

The authors declare that they have no conflict of interests.

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