Classical nodular sclerosis Hodgkin lymphoma presenting with atypical cardiac involvement

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Abstract

Primary and secondary cardiac involvements in lymphomas are extremely rare and sometimes ill-defined entities. Thorough clinical and imagistic investigation is crucial to evaluate disease extension and its impact on cardiac function. Chemotherapeutic agents with potential cardiovascular toxicity must be cautiously employed in high risk patients. We present the case of a young female patient with classical limited stage Hodgkin lymphoma and unfavorable prognostic factors, cardiac tumor mass with significant mediastinal extension, pleural effusion and subsequent cardiac dysfunction. Potentially cardiotoxic ABVD regimen yielded complete remission and progressive reversal of parameters of cardiac function.

Keywords: *Hodgkin lymphoma, cardiac tumor, Doxorubicin*

Introduction

Primary cardiac tumors represent rare entities with an estimated necroptic incidence of 0.05%-1%. Secondary cardiac involvement, regardless of the primary tumor histology, is more frequent (0.7-3.5% incidence) [1-4].

Little attention has been directed towards cardiac involvement in lymphoma patients [5]. Primary cardiac lymphoma represents roughly 1.8% of cardiac tumors; nevertheless, secondary cardiac determinations in patients with disseminated disease are more frequent [2]. The incidence of cardiac determinations in Hodgkin lymphoma (HL) remains unknown.

Clinical manifestations of cardiac tumors, irrespective of histological type, include palpitations, dyspnea, fatigue, chest pain and evidence of heart failure or pericardial effusion, reflecting the effect of the tumor mass on cardiac and pericardium anatomy and function. Common involved sites include the pericardium, atrial and ventricular walls, interventricular and interatrial septa. Tumor masses are usually polylobated and can present with either endocavitary expression and cardiac flow obstruction, or predominant pericardial involvement. Pericardial effusions are a common finding [6, 7].

Cardiac imaging techniques are of utmost importance in the diagnosis of cardiac tumors. Two-dimensional (2-D) transthoracic echocardiography (TTE) is commonly used due to its availability and general information provided concerning approximate tumor mass

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size, topography, overall impact on cardiac function and presence of pericardial effusion. Disadvantages of TTE include a potentially restricted field of view and underestimation of tumor extension. Cardiac computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) are further required to fully characterize tumor size and density, myocardial infiltration and metabolic activity [4, 8, 9].

Careful screening for myocardial dysfunction in patients with primary or secondary cardiac lymphomas is of utter importance, since it can limit the use of several therapeutic agents, including anthracyclins, commonly used in lymphoma therapy.

Case report

We present the case of a previously healthy 34 year-old female patient admitted in the cardiology department for fatigue, significant weight loss during the previous 8 months, sweating, rest dyspnea, productive cough and anterior thoracic pain. The onset of the disease was 3 months before admission and the symptoms gradually worsened.

Clinical examination revealed left supraclavicular 1.5 cm lymphadenopathy, 2 cm below the costal margin hepatomegaly, a grade 3 mitral systolic murmur and grade 2 turgid jugular veins.

Echocardiography showed a 70/28 mm tumor mass originating in the interatrial groove, with left ventricular wall extension, minimal mitral regurgitation and a left ventricular ejection fraction (LVEF) of 50%. No spontaneous contrast effect, indicative of possible thrombosis, was present. The patient presented also a circumferential pericardial effusion with 50 mm maximum posterior thickness.

A thoracic CT examination confirmed the presence of a 169/93/94 mm polylobated tumor mass originating in the visceral pericardium and infiltrating the subjacent myocardium. The tumor surrounded the emergence of the aorta, the aortic arch, left carotid and subclavian arteries and main pulmonary artery. A cranial expansion of the tumor engulfed the left carotid neurovascular bundle. Massive pericardial effusion, superficially situated from the tumor mass, was associated, as well as important inferior vena cava dilatation (30 mm) and mild hepatomegaly (Figure 1).

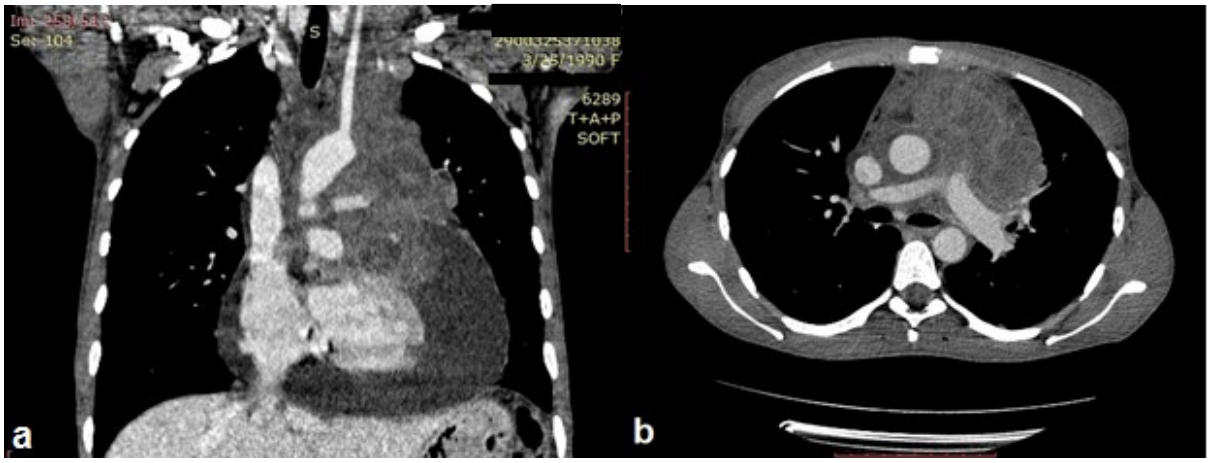

Fig. 1. Thoracic CT scan: **a)** coronal section and **b)** axial section in a patient with polylobated tumor mass originating in the visceral pericardium and infiltrating the subjacent myocardium with massive pericardial effusion. The tumor surrounded the emergence of the aorta, the aortic arch, left carotid and subclavian arteries and the pulmonary artery.

An emergency pericardiocentesis was performed and 2200 mL of pericardial fluid were evacuated during a 3 day period. Pleuro-pericardial window and pleural drainage were performed by video-assisted mini thoracotomy.

Pericardial biopsy revealed multiple nodules with interstitial hyalineosis containing a polymorphic infiltrate of small lymphocytes, rare eosinophils and Reed-Sternberg cells with CD30 and CD15 positivity (Figure 2).

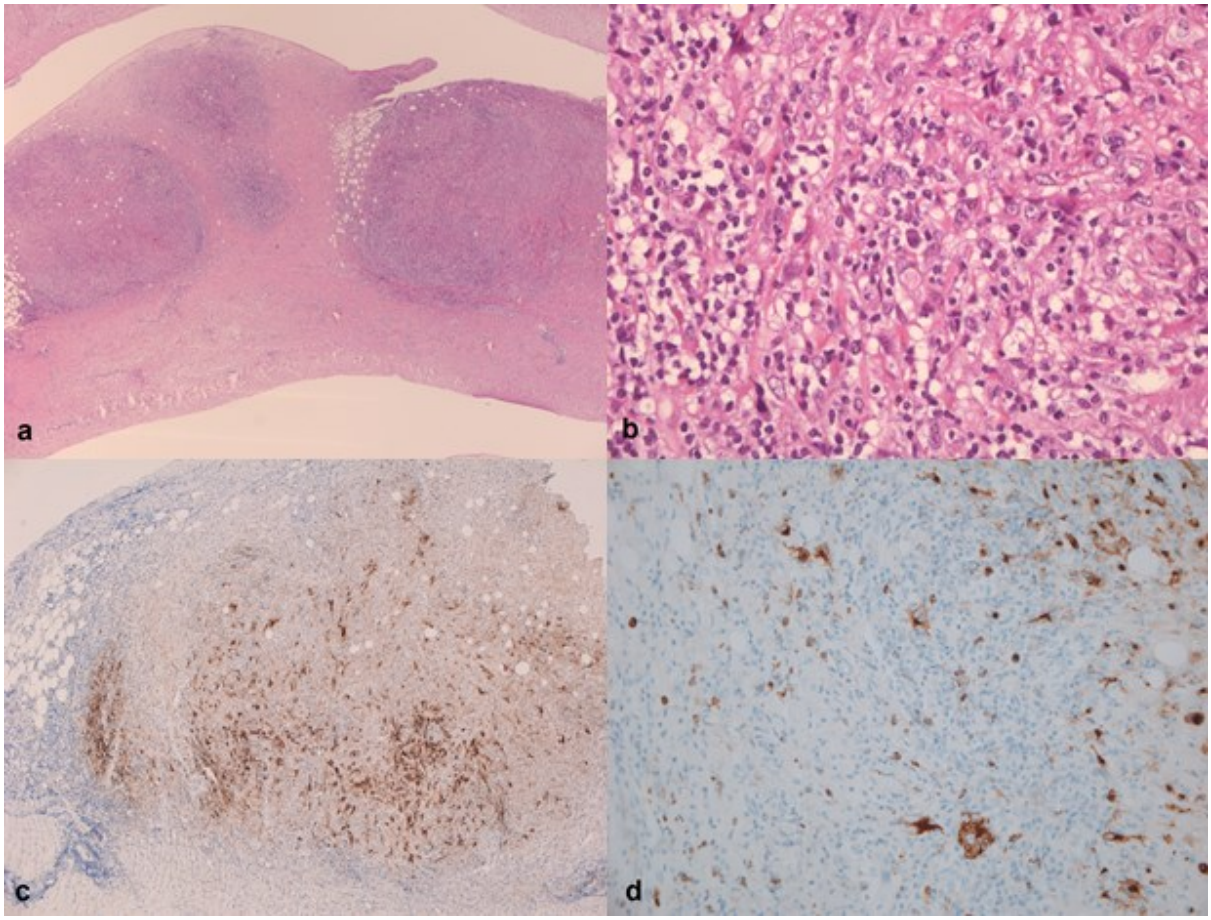

Fig. 2. Histopathological and immunohistochemical aspects: **a)** nodular pericardial infiltrates (HE, x25); **b)** Reed-Sternberg cells in a lymphocytic background (HE, x400); **c)** CD30 positive tumor cells (IHC, anti-CD30 Ab, x 50); **d)** CD15, Golgi staining of Reed-Sternberg cells (IHC, anti-CD15 Ab, x200).

Biologic evaluation revealed mild anemia (hemoglobin 11.6 g/dL) and inflammatory syndrome. Serum creatine kinase MB and MM isoforms were normal, as well as troponin T levels. High N-terminal prohormone of brain natriuretic peptide (NT Pro-BNP) serum levels of 2778 pg/mL suggested the severity of cardiac dysfunction [10]. A diagnosis of classical nodular sclerosis HL was thus established. No further tumor masses were discovered at abdominal and pelvic CT scan and bone marrow biopsy was normal, allowing us to define stage IIB_E at diagnosis [11]. Prognostic factors were evaluated according to the European Organization for the Research and Treatment of Cancer (EORTC) guidelines for early stage HL [12]. The patient presented 2 unfavorable features: 169/93/94 mm bulky tumor mass and elevated erythrocyte sedimentation rate (ESR > 50 mm/h).

Standard ABVD (Adriblastine 20 mg/m^2, Bleomycin 10 mg/m^2, Vinblastine 6 mg/m^2, Dacarbazine 375 mg/m^2) therapy was started and the patient received a total of 6 cycles, with no hematologic toxicity and immediate clinical improvement after first cycle.

Post therapeutic CT scan showed a restant mediastinal tumor mass (>50% reduction in size) and disappearance of cardiac involvement (Figure 3).

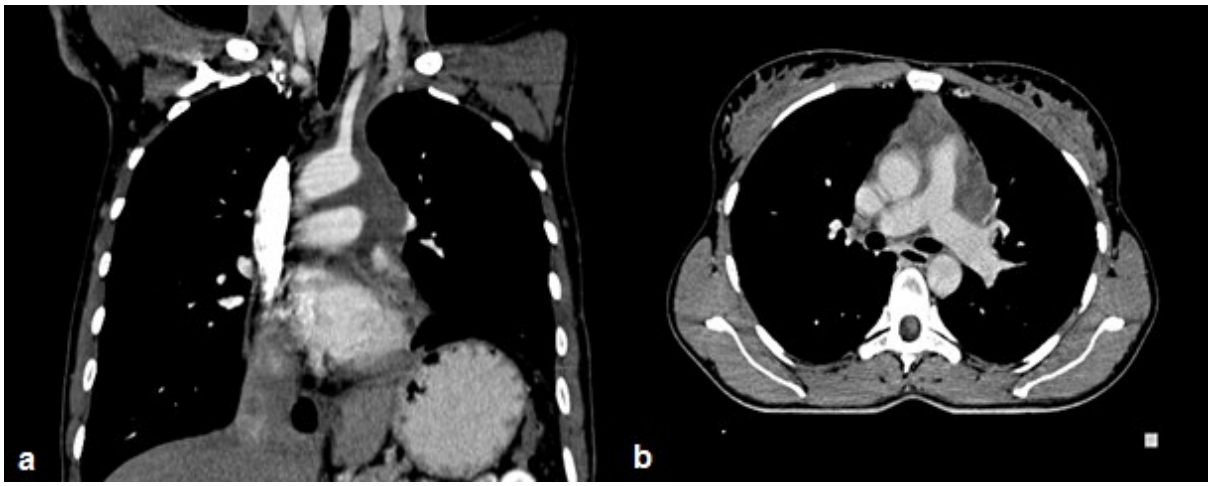

Fig. 3. Thoracic CT scan: **a)** coronal section and **b)** axial section in a patient with residual cervicomediastinal tumor mass. No pericardial effusion is seen. (Following chemotherapy completion).

PET scan revealed no metabolic activity of the residual tumor mass, confirming the complete therapeutic response (Figure 4).

TTE after chemotherapy completion revealed a normal LVEF of 70%, free cavities, intact septa and no pericardial effusion. Normal NT Pro BNP was noted at this moment.

The patient is currently in complete remission and is being reevaluated every 6 months according to our institutional protocol.

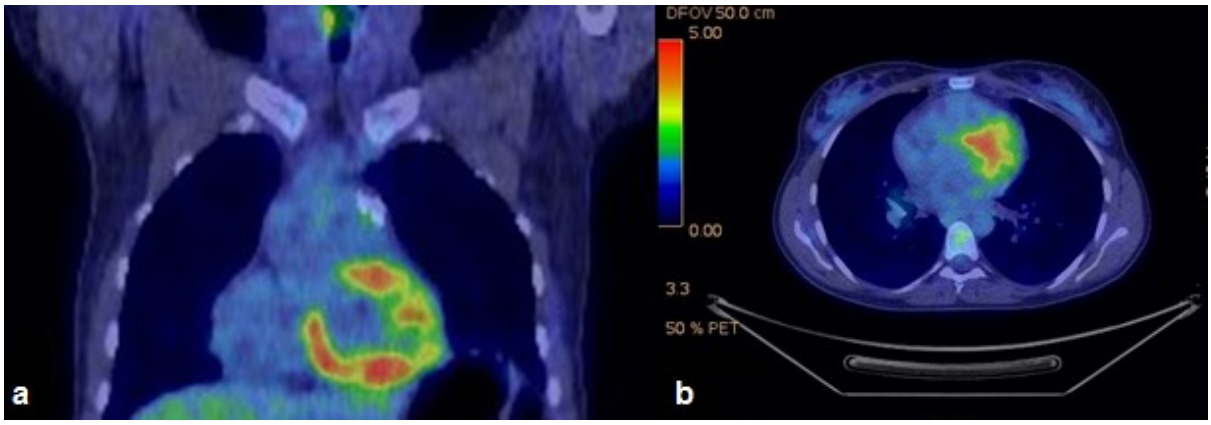

Fig. 4. Thoracic PET-CT scan: **a)** coronal section and **b)** axial section showing metabolic inactivity in residual mediastinal masses.

Discussion

Lymphomas account for 55.6% of hematological malignancies and HL represents 30% of total lymphoma cases [13]. Pulmonary, hepatic, cerebral and testicular tissues are among the most common extranodal determinations.

Cardiac involvement is rarely described in the literature. Amirimoghaddam et al. describes an isolated pediatric case of advanced stage HL with cardiac involvement in which tumour extension involved the entire heart tissue, liver, spleen and bone marrow [5]. The patient was treated with ABVD regimen and achieved complete remission. Lymphomas without extranodal determinations

are generally associated with chemosensitivity and better outcome. The presence of extraganglionar involvement has been linked to poorer prognosis, elevated serum lactate dehydrogenase (LDH) levels, advanced stage disease and central nervous system infiltration [12, 14].

Cardiac lymphomas have a greater incidence in Epstein Barr positive and immunocompromised individuals (acquired immunodeficiency syndrome patients, solid organ transplant recipients) [15]. Cardiac involvement can be either primary (tumor mass limited to myocardium and pericardium) or secondary [16]. Dissemination can occur by lymphatic, bloodstream or contiguous extension [2, 17]. Imagistic examination (ultrasonography, CT, PET/CT) has a significant role in establishing the degree of myocardial and pericardic infiltration, extracardiac dissemination and heart function [8].

HL staging is performed according to the Ann Arbor classification, allowing practitioners to distinguish between early stage (stages I and II) and advanced stage (stages III and IV) disease. The patient risk is further stratified by evaluating specific risk factors for limited and advanced disease [11]. Risk factors for early stage HL include bulky disease, involvement of more than 3 nodal sites, extranodal involvement and elevated ESR [12]. This classification has impact on treatment selection and must be thoroughly performed in HL patients [15].

Standard therapeutic guidelines in HL are promoting the anthracyclin - containing regimen ABVD as front line therapy in patients with stage II disease and unfavourable prognostic factors [18]. Doxorubicin is an anthracyclin antibiotic whose antineoplastic activity is based on its topoisomerase II inhibitory function. It is a highly cardiotoxic compound and may determine acute or chronic cardiac toxicity, should a total dose of 550 mg/m^2 be surpassed. Close patient monitoring is essential to decrease the incidence of anthracycline - induced cardiotoxicity, as is the early implementation of cardioprotective therapies in high risk individuals [19].

The most promising solution for preventing cardiotoxicity is the coadministration of dexrazoxane, an iron chelating agent that reduces the formation of anthracycline-iron complexes [20, 21]. It has been demonstrated that high dose doxorubicin in patients with preexistent cardiac dysfunction (evidenced by increased troponin I levels, a 10% LVEF decrease below the normal limit, 20% at any level or an absolute LVEF of 45%) is associated with further functional cardiac deterioration in the following 7 months [19, 22].

We presented the case of a young female patient with early stage classical HL and 2 unfavorable prognostic factors. Association of extranodal cardiac involvement with pericardial effusion and significant impairment of cardiac function, as indicated by LFEF and NT Pro BNP serum levels, is an aditional unfavourable feature, potentially limiting the use of cardiotoxic anthracyclines. Evaluation of patient eligibility for cardiotoxic therapy in cardiac lymphomas is not standardised and must be carefully weighed in each clinical setting. It should be noted that transthoracic ultrasonography can sometimes underestimate the actual quantity of pericardial fluid, underlining the utter importance of cardiac CT and IRM examination. Emergency pericardiocenthesis was indicated in this case, leading to immediate improvement of cardiac function.

The differentiation between a primary cardiac tumour with cervico mediastinal extension and a mediastinal tumour infiltrating the myocardium is difficult.

In this case, myocardial tumoral infiltration extending from visceral pericardium supports the first hypothesis. However, post therapy persistence of mediastinal tumor and disappearance of all heart masses could stand for mediastinal lymphoma with secondary cardiac infiltration. It should be noted that an actual unanimously accepted definition of primary cardiac lymphoma, allowing practitioners to separate this rare entitity from the more frequent mediastinal lymphomas with secondary cardiac involvement, does not exist.

In the absence of hepatic biopsy it is difficult to ascertain whether hepatomegaly represents the expression of secondary

lymphoma determination or the indirect result of retrograde vena cava pressure increase.

We opted for ABVD treatment after considering the bulky tumor mass, patient age and potentially favourable therapeutic following standard therapy. Doxorubicin was administred during intensive 24 hours surveillance in the intensive care unit.

Cardioprotective therapy in the form of dexrazoxane was not available. Nonetheless, no acute cardiac adverse events were noted and cardiac function was markedly improved after chemotherapy. Long term monitoring of cardiac function is required in such cases.

Conclusion

Cardiac involvement in lymphomas is a rare occurrence. We presented a case of classical HL in a young female patient with cardiac determination and bulky mediastinal tumor mass and unfavorable prognostic features. Despite the high risk of anthracyclin-related cardiac toxicity no cardiovascular adverse events were noted and post therapeutic imagistic evaluation revealed complete remission and reversal of cardiac dysfunction.

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