A CASE REPORT WITH FIBRIN-ASSOCIATED DIFFUSE LARGE B-CELL LYMPHOMA SECONDARY TO CARDIAC MYXOMA

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ABSTRACT

Aims: To raise awareness for differential diagnosis of fibrin-associated diffuse large B-cell lymphoma with patients that have sustained chronic inflammation or are immunocompetent with a previous Epstein-Barr virus infection. ***Case Report:*** A 58-year-old male patient was admitted to the Clinical Center of Sarajevo University, Cardiovascular Surgery Department with the symptoms of getting tired quickly accompanied by dyspnea. His echocardiography findings exhibited a large polymorphic clavicle type highly mobile formation in his left atrium with a size of 76x23mm, intermittently prolapsing the annulus of the mitral valve and reaching the middle of the extended left ventricle. After the detection of a cardiac mass, the patient underwent surgery and had a total excision of the mass. Histopathological analysis showed a tumor made of stellate cells that form complex structures resembling wires together with an islet of plasma cells embedded in a myxoid/fibrinoid background. Immunohistochemically, lymphoma cells were positively stained for CD20, CD30, MUM1, and EBER. After excluding all other systemic manifestations of any other diseases, the patient was diagnosed with fibrin-associated diffuse large B-cell lymphoma, as a primary cardiac lymphoma, and myxoma. ***Conclusion:*** In conclusion, we are reporting a very rare case seen approximately 3% of all lymphomas in the Western Population associated with Epstein-Barr virus B-cell Lymphoproliferative disorders, therefore making them harder to diagnose due to limited experience. Albeit being an infrequent disease fibrin-associated diffuse large B-cell lymphoma should be an entity included in the differential diagnosis of the patients that have sustained chronic inflammation or are immunocompetent with a previous Epstein-Barr virus infection. ***Keywords:*** Cardiac myxoma, diffuse large B-cell lymphoma, Epstein-Barr virus infection

INTRODUCTION

Primary cardiac lymphoma (PCL) is a rare entity comprising up to 0.5% of extranodal lymphomas and representing <2% of all primary cardiac tumors (1). Fibrin-associated diffuse large B-cell lymphoma (FA-DLBCL) is a PCL involving only the heart or pericardial sac which is listed in the 2016 World Health Organization (WHO) classification as a provisional entity associated with chronic inflammation and Epstein-Barr virus (EBV) type III latency (2, 3). Nevertheless, systemic manifestations of lymphomas involving the heart have been documented as well, often observed in terminally ill patients, and autopsies, existing in up to 10% of patients (3). It has been most commonly reported in men that are in their mid-sixties (2). Diffuse large B-cell lymphoma (DLBCL) has been demonstrated as the most common histological subtype (3).

On the contrary, primary cardiac neoplasms alone are very rare (1, 4). Unlike FA-DLBCL they predominantly occur in women between the fourth and sixth decade of life (4). They are 80%-90% benign and the most common type is cardiac myxoma (4). The classic triad of embolic events, intracardiac flow obstruction, and constitutional symptoms may be present in most patients, and around 10% are asymptomatic (1, 3, 4). Echocardiography is the first diagnostic modality of choice. The prognosis is excellent for patients that underwent surgical resection of the mass with a great reported postoperative recovery (4).

We report a 58-year-old patient exhibiting mild symptoms with two distinct tumors, one being a primary cardiac lymphoma developed through the base of a chronic inflammation induced by the second tumor, which is a myxoma located in his left atrium. We aim to increase the awareness of FA-DLBCL by Stellate-shape, to be an entity included in the differential diagnosis for the patients that have sustained chronic inflammation and/or are immunocompetent with a previous EBV infection.

CASE REPORT

A 58-year-old male patient was admitted to the Clinical Center of Sarajevo University, Cardiovascular Surgery Department with the symptoms of getting tired quickly accompanied by dyspnea. He suffered from this complaint for over 7 months. His past medical and family history was irrelevant. He was an ex-smoker (30 pack-a-year). On his performed echocardiography, there was a large polymorphic clavicle type highly mobile formation in his left atrium with a size of 76x23mm, intermittently prolapsing the annulus of the mitral valve and reaching the middle of the extended left ventricle (Figure 1). After the detection of a cardiac mass patient underwent surgery for total excision of the mass. His postoperative course was unproblematic, and he was followed in the cardiovascular surgery clinic.

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Histopathological analysis showed a tumor made out of stellate shaped cells which form complex structures resembling wires and nest fingers surrounding the varicose veins on a myxoid background. In addition to the myxoid cells, a portion of the tumor stranded with abundant plasma cells, and siderophores intertwined in the fibrin network were observed (Figure 2).

There can be seen an accumulation of large lymphocytes with prominent nucleolus of more abundant cytoplasm, large irregular nuclei, sporadic atypical mitoses, and also myxoma in a fibrinous background. Because of their centrally located nucleolus, lymphoma cells resemble immunoblasts (Figure 2).

Immunohistochemically, lymphoma cells were positively stained on CD20 (Figure 3), CD30 (Figure 3), MUM1, EBER (Figure 2), and had a high expression (80%) of ki-67. Cyclin-D1, CD10, BCL6, FOXp1, CD5, ALK, cMyc, and EMA were all negative. After excluding all other systemic manifestations, together with the morphological findings' patient was diagnosed with two distinct tumors: FA-DLBCL a primary cardiac lymphoma secondary to his initial diagnosis which was a cardiac myxoma.

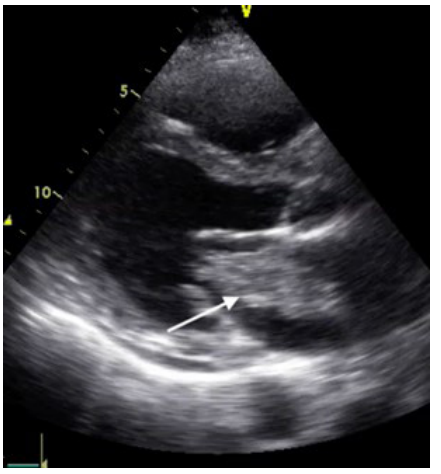

Figure 1: Large polymorphic clavicle type highly mobile formation in the left atrium with a size of 76x23mm (white arrow), prolapsing the annulus of the mitral valve and reaching the middle of the extended left ventricle.

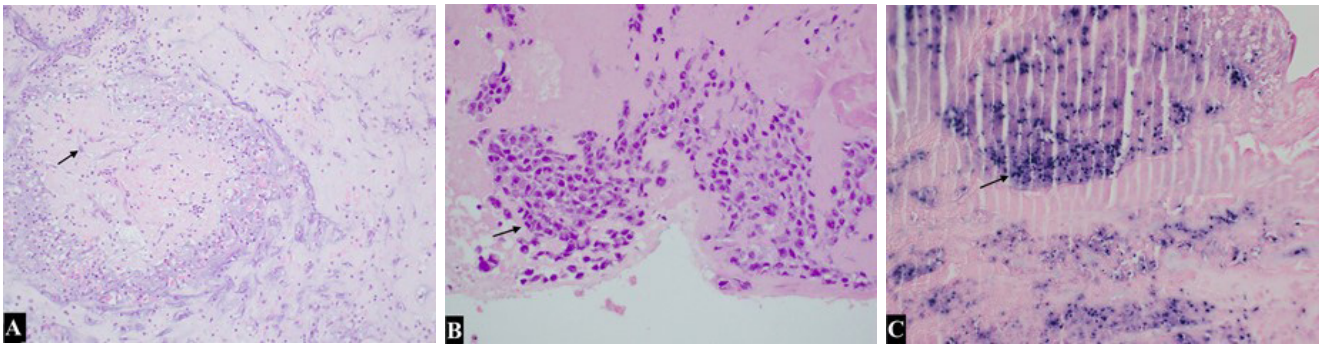

Figure 2: A: Stellate-shaped tumor cells (black arrow) of the myxoma surrounding varicose veins on a myxoid background with an infiltration of abundant plasma cells intertwined in a fibrinoid network (hematoxylin & eosin stain: x40 magnification). B: Plasmacytoid atypical lymphoid cell (black arrow) infiltration embedded in eosinophilic stained fibrinous material site (hematoxylin & eosin stain: x40 magnification). C: EBV-encoded RNA expression (EBER) in lymphoid cells (black arrow) (x40 magnification).

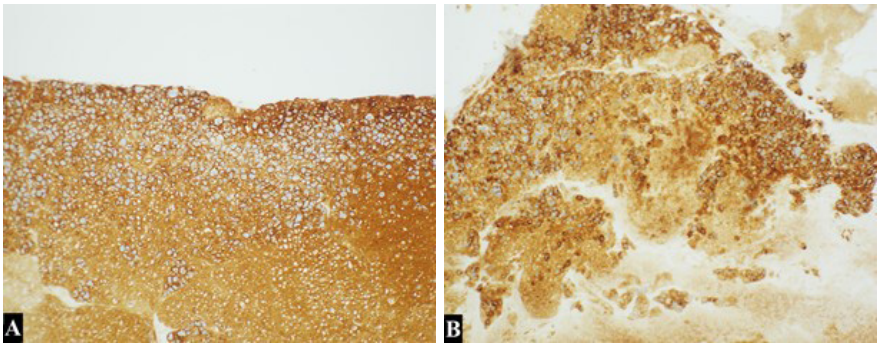

Figure 3: A: Diffuse positive staining for CD20 (x40 magnification). B: Diffuse positive staining for CD30 (x40 magnification).

DISCUSSION

Primary cardiac lymphomas' definition still differs among authors while some exclude extra-cardiac involvement, others permit a changeable amount of tumor outside the heart to be categorized as PCL either (2, 3). There has not been proposed a cutoff to quantify extra-cardiac disease, thus PCL's accepted definition is cardiac involvement of Hodgkin lymphoma (2, 5). Lymphoma involvement is usually in the right atrium and ventricle, found less on the left side. It may also extend to the inferior vena cava, superior vena cava, and jugular veins (6). Involvement can include all three layers of the heart. The most commonly reported age of the patients is the mid-sixties, most being men. Histologically most PCLs exhibit DLBCL being positive for CD20; although, few patients with T-cell and NK-cell origin have been reported as well (7, 8).

Diagnostic features for FA-DLBCL include a cluster of lymphoid cells with prominent apoptotic activity ingrained in a rich fibrinous background exhibiting non-germinal center B-cell phenotype, usually associated with EBV type III or a sustained chronic inflammation in a restricted anatomic space with an indolent clinical course (2, 7).

Pathogenesis is still a topic keeping its ambiguity on track with the need for further research. However, there have been several hypotheses presented. The most commonly accepted one has been the proliferation of EBV-positive B-cells in a localized immunosuppressed area (9). Boyer et al. (9) hypothesized a theory that EBV-positive B-cells are immortalized by the virus and lack the ability to grow autonomously in a restricted anatomic space. This was achieved through 7 of their patients showing type-III EBV latency with low or no expression of lytic protein BZLF-1, which is typically associated with immunodeficiency (10). It has been evident that telomerase-specific reverse transcriptase activity inhibits the EBV lytic cycle resulting in a maintenance of latency in infected cells (11, 12). Another important finding was how 6 (86%) patients out of 7 had positive PD-L1 stain in their immunohistochemical analysis (10). Therefore, by displaying a correlation between studies, we can elucidate how PD-L1 positivity plays a role in immune evasion in EBV-positive DLBCL and plasmablastic lymphoma cells (13). Hence, restricted anatomic space may further enhance the suppression of antitumor immunity in fibrin-associated EBV-positive large B-cell lymphoma. Protection from EBV-specific cytotoxic T cells in an immune-privileged environment could facilitate an unchecked proliferation of lymphoma cells.

Another key element in the development process of FA-DLBCL is chronic inflammation (14). There were cases reported with subdural hematoma, endovascular graft thrombi, adrenal gland pseudocyst and adjacent implanted prosthetic devices; the mutual finding of all cases is that they sustained chronic inflammation in an enclosed space (14). Furthermore, Hubackova et al. (15) has shown how interleukin 6 signaling, which plays a cardinal role in inflammatory processes, regulates the promyelocytic leukemia protein gene expression in both human and cancer cells. In this manner, inhibition of T-cell proliferation through cytokines like interleukin 10 could also provide an immunosuppressive effect resulting in a build-up of EBV-immortalized B-cells in restricted anatomic space (14). In our case, chronic inflammation induced by myxoma in the left atrium could have led to the advancement of tumor in an immune-privileged niche established by a previous EBV infection. Interestingly, there were cases reported with no immunosuppression nor EBV positivity and had no relation with a foreign body or chronic inflammation (9, 10).

The two most common clinical presentations are heart failure and pericardial effusion (1, 3). Due to tumors' location in the heart embolisms, thrombosis and stroke may develop as well. In advanced disease, there were cases reported with superior vena cava syndrome and myocardial infarction (16). Because the mass is not formed by lymphoid tissue, patients do not exhibit any signs of hematological malignancies like lymphadenopathy, organomegaly, or B-symptoms (9).

Diagnosis is difficult due to its unpredictable clinical manifestation; it is usually late or post-mortem (4). After a suspicious cardiac mass, detection of the tumor and pericardial effusion is best made by echocardiography (6). Other visualization techniques like electrocardiography-gated magnetic resonance or positron emission tomography may provide useful information for excluding the presence of other tumors that come in the differential diagnosis (6). Differential diagnosis may include neoplasm involving the heart such as malignant melanoma, angiosarcoma, metastatic carcinoma characterized by proliferation of large atypical cells that can be easily distinguished by immunophenotypic studies. In terms of malignant lymphomas, FA-DLBCL does not exhibit any systemic involvement, its characteristic features are that it originates from a base of chronic inflammation, usually associated with EBV, with lymphoma cells embedded in a fibrinous background. Nevertheless, a definitive diagnosis is made by a biopsy.

Due to its rarity, there has not been established a specific treatment protocol for FA-DLBCL. Different therapy methods such as are stem-cell transplantation, heart transplantation, and chemotherapy (R-CHOP) have been tried, with some of them resulting in complete remission (17). Nonetheless, with reported cases that had favorable outcomes with surgical excision (only according to WHO and other researchers), the question of whether patients must undergo high-dose chemotherapy arises because localized lesion does not have any clinical manifestation of secondary malignancy (1, 4). Thus, our patient underwent surgery where both tumors were resected, no further chemotherapy or radiation was administered.

In conclusion, we are reporting a very rare case seen in approximately 3% of all lymphomas associated with EBV B-cell lymphoproliferative disorders in the Western population, therefore, making them harder to diagnose due to their rarity (2, 7). As stated, pathogenesis is still a topic that requires further research. Albeit being an infrequent disease, FA-DLBCL should be an entity included in the differential diagnosis for patients that have sustained chronic inflammation or are immunocompetent with a previous EBV infection.

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