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Case Report

EBV+ diffuse large B-cell lymphoma arising within atrial myxoma in Chinese immunocompetent patient

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Abstract: The incidence rate of Primary cardiac lymphoma is very low. Primary cardiac lymphoma within myxoma is extremely rare disease. So far, these cases have been reported only eight in the world, which has not reported in Chinese so far. Hence, we reported the unique Chinese case of 52-year-old immunocompetent male with primary Epstein-Barr virus positive diffuse large B-cell lymphoma arising within atrial myxoma, and had no evidence of systemic lymphoma. The patient presented right sided body numbness, arm weakness no incentive and mouth twitch. A transthoracic echocardiogram revealed a large intraatrial mass, attached to the left atrial wall. The mass was removed by open thoracic surgery and subsequently diagnosed as malignant diffuse large B-cell lymphoma with myxoma by histopathology. This was the fourth case of discovered Epstein-Barr virus positive diffuse large B-cell lymphoma in a cardiac myxoma reported so far. The patient has been well by followed up for 5 months without chemotherapy. Now we discuss the importance of histodiagnosis and the proper treatment. Epstein-Barr virus positive diffuse large B-cell lymphoma arising within atrial myxoma is an extraordinary lymphoma for better prognosis, avoiding excessive treatment.

Keywords: Primary cardiac lymphoma, diffuse large B-cell lymphoma, atrial myxoma, Epstein-Barr virus, Chinese, histopathology

Introduction

Most heart tumors are benign. Myxomas are the predominant primary neoplasm of heart. It is derived from multipotential mesenchymal cells. In a retrospective report from 1995 to 2010, 170 cases cardiac tumors were benign in the 184 cases primary cardiac tumors, and myxomas were 168 cases among the benign tumors [1]. Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma among adults [2]. Primary cardiac lymphoma (PCL) is rare, only accounting for < 2% of all primary cardiac tumors [3-5]. PCL within myxoma is extremely rare, only 8 cases have been reported and it has not been reported in Chinese so far [3, 6-12]. The 8 cases included 5 cases of DLBCL, 1 case of plasmacytoid lymphoma, 1 case of chronic lymphocytic leukemia (CLL) and 1 case of atypical lymphoid proliferation. All the 5 cases of DLBCL included 2 cases of germinal center (GC) and 3 cases of non-germinal center (nGC). All non-germinal center diffuse large B-cell lymphomas (nGC-DLBCL) were infected with Epstein-Barr virus (EBV). In our research, we reported the fouth case of EBV positive nGC-DLBCL within myxoma, providing detailed immunohistochemical and clinical analyses in this immunocompetent patient.

Case report

A 52-year-old Chinese male presented with symptoms of right sided body numbness, arm weakness no incentive and mouth twitch, suggesting stroke cerebrovascular accident (CVA). Laboratory examination showed slight increased lactate dehydrogenase level (LDH 269U/l). Magnetic resonance imaging (MRI) of the brain revealed the left side of the thalamus infarction. A transthoracic echocardiogram (TTE) revealed a large intraatrial mass, attached to the left atrial wall, protruding through the left ventricle (**Figure 1**) suggestive of atrial myxoma. It was removed by open thoracic surgery. A 6.0 cm × 3.0 cm pedunculated mass and atrial septal defect (the diameter is about 1 cm) were discovered. The mass was excised en bloc with

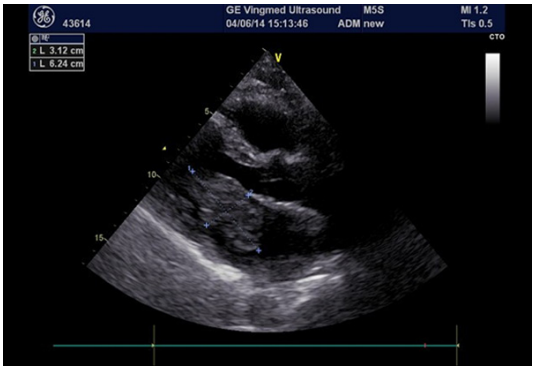

Figure 1. Transthoracic echocardiogram shows a 6.0 cm × 3.0 cm atrial myxoma.

part of the septum. The defect in the septum was repaired at the same time. TTE showed a mild mitral and tricuspid valve regurgitation after surgery. The patient was discharged a few days later without chemotherapy and was very well by followed up for 5 months after postoperation.

Macroscopically the tumor alternated with dull-red and pale yellow (**Figure 2A**). The section was gelatinous with focal areas of hemorrhage. Subsequent histopathology confirmed atrial myxoma showing a classic myxoid appearances (**Figure 2B**). Most of sparse cellular areas were composed of moderately and bland spindle or stellate cells with inflammatory cell infiltration. Partial spindle cells grew around thin-walled blood vessels in mucopolysaccharide-rich matrix. These spindle cells were overexpression of calretinin (**Figure 3A**) and CD34. A lot of peripheral hypercellular regions of mass harbored some high nucleoplasm ratio malignant cells (**Figure 2C**, **2D**). Malignant cells have a small amount of cytoplasm with round to oval nuclei and exhibit nuclear pleomorphism. These cells displayed prominent mitotic and apoptotic activity.

Immunohistochemical markers showed positive staining for CD20, CD79a, EBV, MUM1, Ki-67, PAX-5, BcL-2, CD30 in malignant cells, and negative staining for CK, CD3, Calretinin (CR), CD5, CD10, Bcl-6 and CyclinD1 (**Figure 3B-E**). In situ hybridization showed positive for EBER in large pleomorphism nuclei (**Figure 3F**). Overall immunohistochemical markers and morphological features confirmed the diagnosis of malignant nGC-DLBCL in the background of atrial myxoma. By careful staging, all physical examination showed no evidence of lymphoma at other positions and bone marrow indicating a true PCL.

Discussion

PCL is rare, about less than 2% of all primary cardiac tumors. Before diagnosis, it is necessary to exclude any metastasis from nodal or other extra-nodal site and primary malignant tumors in the heart such as angiosarcomas, undifferentiated sarcomas and metastatic tumors [1, 11]. The clinical feature is not unique, including symptoms of congestive heart failure, dyspnea on exertion, fever, embolisation, weight loss and fatigue. These clinical features together with the modern imaging technologies suggest the diagnosis of myxoma firstly. PCL can be easily overlooked on imaging and clinical feature even histopathology. Our case was first considered atria myxoma combining TTE with clinical feature, because only very little large cells and many inflammatory cells were found under microscope. We found nests and patches of large pleomorphism lymphoid cells in the mass peripheral zone after repeated pathology biopsy. And that PCL mainly occur in immunocompromised patients, such as HIV related or iatrogenic including solid organ or bone marrow transplantation. These patients were more fragile to get an acute clinical course and rapidly demise. And PCL, especially DLBCL are highly malignant, may lead to death through rapid growth and extensive infiltration of myocardium or obstruction heart blood flow. Therefore, early accurate diagnosis and proper treatment is crucial for medical prognosis. Preoperative biopsy or postoperative histopathology and immunohistochemistry are important to get the precise diagnosis.

The lymphoid malignancy within a myxoma has been reported on recent documents. All early cases and our presented case were summarized in **Table 1.** All the 9 PCLs were dated from B-cell derivation, 6 were typed as DLBCL, 4 of them were nGC cell phenotype and 2 of them were GC phenotype. One malignant lymphoma with negative CD20 and overexpression CD3 was diagnosed as lymphoplasmacytic lymphoma. One lymphoma overexpression CLA, CD20, LMP1 and occasionally CD79a and MUM1 was diagnosed Epstein-Barr virus (EBV) associated atypical lymphoid proliferation. Another lymphoma was atypical classified as CLL based on FISH analysis. All the masses in the 9 PCLs

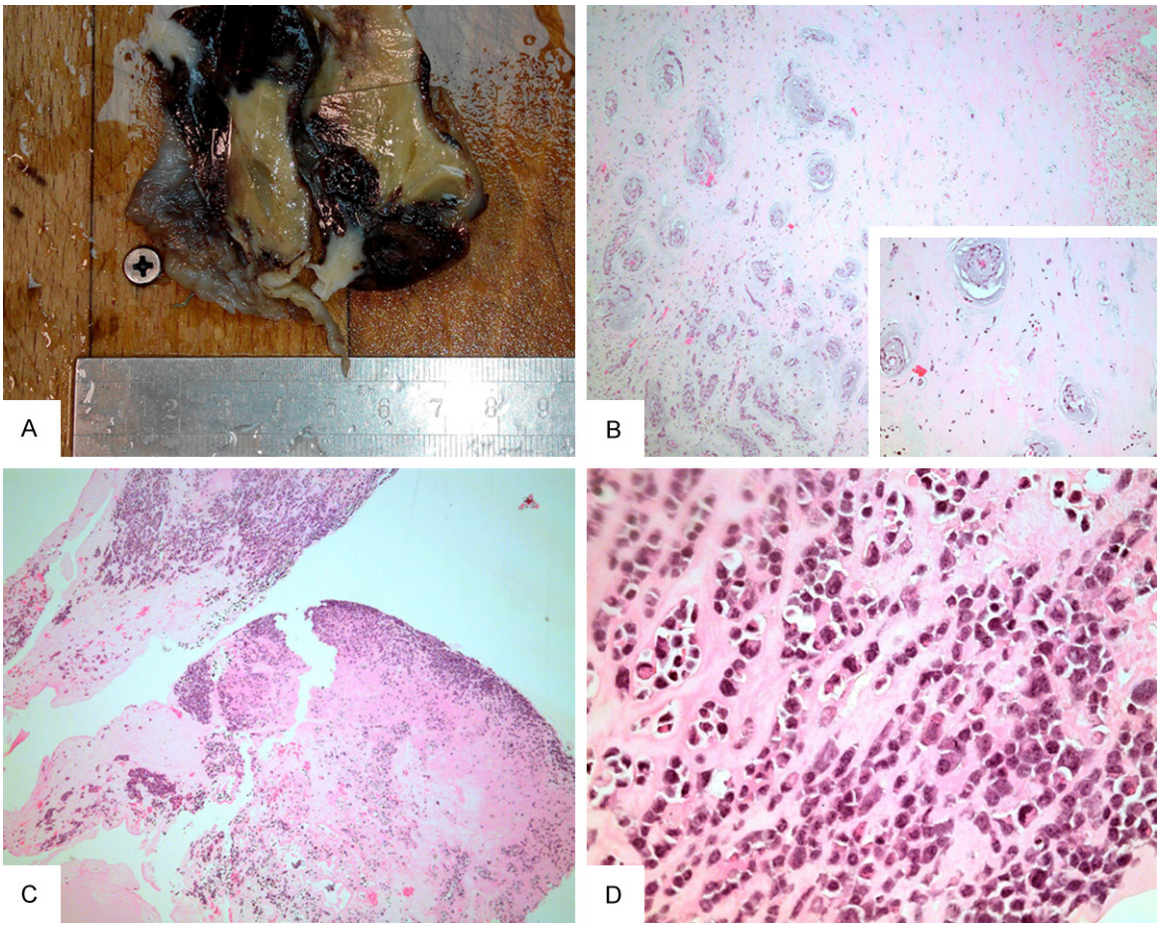

Figure 2. A. Excised surgical left atrial tumour macropathology. B. Hematoxylin and eosin stain shows a classic myxoid appearance (× 100) and a higher power magnification image on bottom right corner (× 200). C. Hematoxylin and eosin stain shows lymphoma arising into atrial myxoma (× 50). D. Higher power magnification of pleomorphic lymphoma cells (× 200).

located in left atrium. Preponderance of female gender with female: male ratio 6:3, age ranging from 49 to 81 years (mean 61, median 56). According to the 2008 WHO lymphoma Classification, the age cut-off was defined older than 50 in the EBV positive DLBCL of the elderly. 8 of 9 patients were older than 50 years old, 1 of 9 was 49 years old nearly 50 in line with this classification. 7 of 9 patients presented stroke or related symptoms, which maybe one of the most important clinical manifestations in lymphoma arising within atrial myxoma. All 4 non-germinal center DLBCLs and one atypical lymphoid proliferation were infected with EBV, 3 of them were Latency III, one of them was Latency II and one of them wasn't detected EBNA2 state. It is very interesting that EBV virus -associated lymphomas have previously been reported primarily in immunocompromised such as HIV-infected or post-transplant patients, while all the 9 PCLs within myxoma cases appeared uniformly to be immunocompetent. Recent reviews indicated that EBV virus infection is associated with lymphoproliferative disorders in immunocompromised and immunocompetent patients [9, 13]. Malignant lymphomas arising within myxoma possibility share pathogenic pathway driven by three sides. One is age-related senescence which is difficult to suppress the EBV infection or inflammation result in escaping immune surveillance. One is EBV presumably plays a crucial oncogenic role by alteration immunity, thereby creating a site-specific microenvironment conducive to lymphoma develop in the immunocompetent patients. Another is chronic inflammation, in which the transformation potential is unleashed in the cytokine-rich milieu of a myxoma [7-9]. Based on some cases reported observations, we proposed that chronic inflammation and

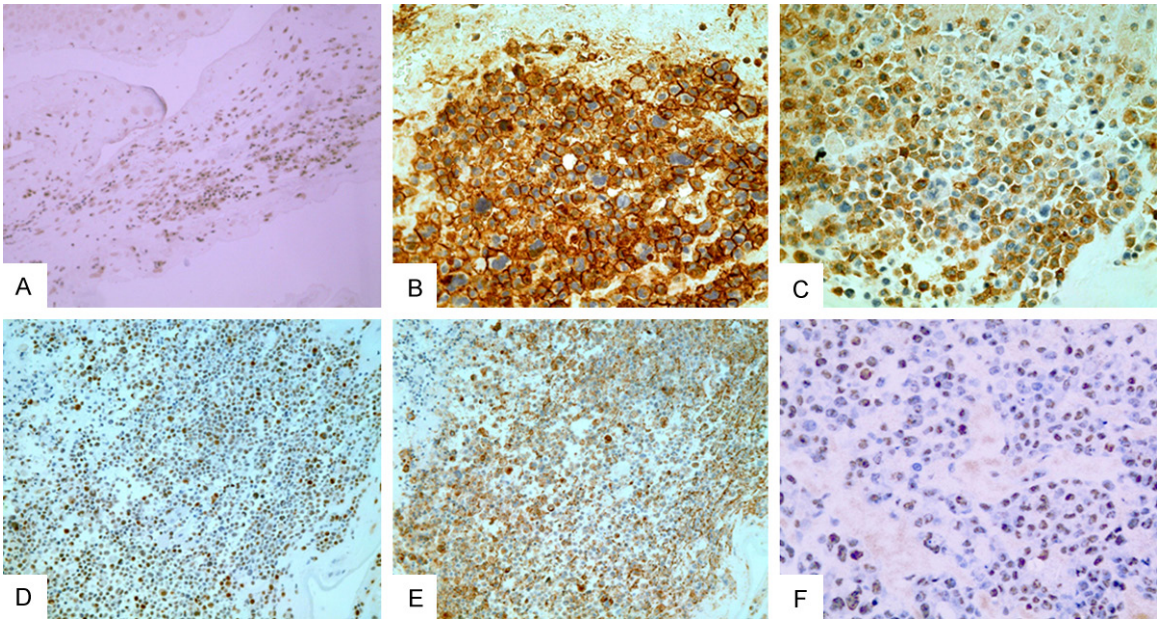

Figure 3. (A) The spindle cells of left atrial myxoma are positive for calretinin (× 100). (B-E) Immunohistochemical markers show positive staining for CD20 (B, × 400), CD30 (C, × 200), MUM1 (D, × 100) and EBV (E, × 200). (F) In situ hybridization shows lymphoma cells expression EBER (× 200).

EBV infection probably mutual promoted malignant transformation, through promoting interleukin-6 and interleukin-10 secretion to help EBV-transformed cells evading immune surveillance. It is maybe that chronic inflammation and aging forms immunodeficiency microenvironment, promoting EBV positive lymphoid proliferation [3, 6-10, 12, 14, 15].

It wasn't very clear that whether the patient of lymphomas within myxoma needed chemotherapy and what options suitable for them in immunocompetent patient due to the rarity of this compound disease and no long-term follow-up. 6 of 9 reported patients were treated with chemothearphy such as R-CHOP or CHOP. One patient died of illness associated with chemotherapy. The rest patients with or without chemothearphy was well in the subsequent partial follow-up. Moreover, one patient without any postsurgical chemothearphy was no recurrence at subsequent 6-year follow-up [14]. Our own patient was followed up for 5 months after surgery without adjuvant therapy, and no evidence of recurrence or metastases was found. Some reviews demonstrated the lymphoma has arisen within and remained localized at the previously formed atrial myxoma, which hampered invasion and generalization. Therefore, we proposed that these composite tumours may be indolent lymphoma and have good prognosis. It was possible appropriate to complete resect atrial myxoma with an EBV+ lymphoma in immunocompetent patients. The patient only needed initiation of combination chemotherapy when there had the evidence of recurrent disease [7-9, 14]. Treatment and prognosis of these composite tumors are possible different from common lymphoma. They needed frequent observation and follow-up.

In summary, we reported the unique case of DLBCL within an atrial myxoma in EBV+ of immunocompetent Chinese patients. The mass was resected completely without chemoradiotherapy. Stroke or related symptoms maybe one of the most important clinical manifestations. Our case further indicates that it is necessary to analysis histopathology and immunohistochemistry for all postoperative cardiac specimens to get the precise diagnosis. Based on above research, we propose that EBV positive DLBCL arising within atrial myxoma have good prognosis. It is sensible choice for postoperative observation and follow-up, avoiding excessive treatment. However, malignant lymphoma within an atrial myxoma is very rare event. The most appropriate treatment regimen needs further to research and follow-up.

Table 1. Review and updating characteristic of 9 PCLs within myxoma

Parameter	B-Lymphoma phenotype								
	GC-DLBCL		nGC-DLBCL				NON-DLBCL		
	1	2	1	2	3	4	ALBP	CLL	PL
Sex	F	M	F	F	M	M	F	F	F
Age	81	51	70	60	49	52	55	56	75
Major clinical feature	stroke	chest pain and acute breathe hard	Stroke cardiogenic shock and bradycardia	Weakness and stroke	Palpitations and stroke	stroke	fatigueand fever	Venous thrombus and stroke	Dyspnoea palpitations and stroke
Patient	IP	IP	IP	IP	IP	IP	IP	IP	IP
Position (atrium)	Left	Left	Left	Left	Left	Left	Left	Left	Left
Myxomas size (cm)	4 × 2	7.5 × 4.5	6.5 × 4	3.7 × 1.5	4.2 × 3.6	6 × 4	5.5 × 4.5	1.7 × 1	6 × 5
EBV/Type latency	NA	NA	EBER+LMP1+ EBNA2+III	EBER+LMP1+ EBNA2+III	EBER+LMP1+EBNA2+III	EBER+LMP1+ EBNA2cNA	EBER+LMP1+EBNA2-II	NA	NA
Treatment	R-CHOP × NA	CHOP × 6 cycles	CHOP × 4 cycles	CHOP × 6 cycles	CHOP × 6 cycles	None	None	FCR × NA	NA
Major IHC	CD20+CD79a+ CD10+BCL-2+ BCL-6+	CD20+CD10+	CD20+CD79a+ MUM1+BCL6+CD10-	CD20+CD79a+ MUM1+CD10-	CD20+CD79a+ MUM1+CD10-	CD20+CD79a+ MUM1+CD10- Bcl-6-	CD20+CD31+CD34+	CD20+CD5+CD-43+BCL-6-cyclinD-	CD31+CD3+ CD56-CD20-
Ki 67 (%)	80	100a	100	100	80	100	90	NA	NA many mitoses
Follow up (months)	None	None	5b	7	12	3	72	18d	None
Year [Ref]	2009 [5]	2010 [6]	2010 [11]	2012 [7]	2014 [8]	Our case	2013 [14]	2014 [9]	2010 [2]

nGC-DLBCL: non-germinal center diffuse large B-cell lymphoma; CLL: chronic lymphocytic leukemia; PL: plasmacytic lymphoma; ALBP: atypical lymphoid B-cell proliferation; IP: immunocompetent patient; NA: not available. a: Assessment by image; b: Died of illness associated with chemotherapy; c: Our case isn't detected EBNA2 state; d: local recurrence, she was undergochemotherapy with FCR, with clinical remission.

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Disclosure of conflict of interest

None.

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