CASE REPORT

A Malignant Lymphoma Growing Inside a Cardiac Mixoma: A Case Report

Sergio Pirola1*, MD; Stefano Fiori2, MD; Fausto Maffini3, MD; Giulia Mostardini1, RT; Giorgio Mastroiacovo1,4*, MD; Gianluca Polvani1,4, MD

Abstract

Introduction: Lymphomas arising from cardiac myxomas represent a particularly rare pathology, with only few cases reported in the literature.

Case presentation: We report a complete excision of a malignant lymphoma arising from a cardiac myxoma in a 44-year-old female patient. The myxoma presented like a floating mass within the left atrium with a maximum diameter of 3.5 cm. The clinical post-operative period was uneventful and the patient was dismissed on the 6th post-operative day.

Conclusion: This case reinforces the concept of radical excision of cardiac neoplasms.

Keywords: Myxoma. Lymphoma Heart Neoplasms. Epstein-Barr Virus. Postoperative Period.

INTRODUCTION

Cardiac myxomas account for the majority of cardiac tumours (50%) and mainly affect middle-aged women[1]. Primary cardiac lymphoma is a very rare neoplasm that accounts for 2% of all primary cardiac tumours[2]. Lymphomas growing in the context of cardiac myxomas are extremely rare mixed tumours, with just few cases reported in literature.

Case Presentation

A previously healthy 44-year-old female patient presented to our hospital from an outpatient cardiology clinic with an echocardiographic finding of a floating mass within the left atrium. She was symptomatic for a few months for asthenia, dyspnoea and dizziness. She denied lipotymia or syncope and any history of drug/alcohol abuse or recent travel. Her family history was negative for cardiovascular/neoplastic diseases.

The patient was in good clinical condition, NYHA class I and CCS 0. Cardiac auscultation revealed a classical diastolic ‘tumour plop’, not accompanied by another significant murmur.

An urgent transthoracic echocardiogram with 3D digital reconstruction of the images was performed and confirmed the primary diagnosis (Figure 1). The mass originated from the fossa ovalis on the left side of the interatrial septum.

The maximum diameter was 3.5 × 3 cm. The mass had a lobulated, polypoid architecture and a narrow implantation stalk, appearing to be unstable, and prolapsed across the mitral valve orifice during diastole.

To complete the diagnostic framework, cardiac, lung and brain computed tomography (CT) scans (Figure 2) were performed, without any pathological findings and recent cardio-embolic events were also excluded.

The patient was then scheduled for surgery. The operation was performed trough a left atriotomy. The tumour presented as a pale pink, grape-like, semi-transparent mass. It had a particularly gelatinous and friable consistency, with a high risk of fragmentation during surgical manipulation. Due to these atypical characteristics, we suspect the malignant nature of the neoplasm.

Abbreviations, acronyms & symbols

| Abbreviation | Full Form | Description |
|--------------|-----------|-------------|
| CCS          | Canadian Cardiovascular Society | |
| CT           | Computed tomography | |
| DLBCL-NOS    | Large B-cell lymphoma not otherwise specified | |
| EBV          | Epstein-Barr virus | |
| EBER         | Epstein–Barr virus-encoded small RNAs | |
| FA-DLBCL     | Fibrin-associated diffuse large B-cell lymphoma | |
| LMP1         | Latent membrane protein 1 | |
| NYHA         | New York Heart Association | |

This study was carried out at the Department of Cardiac Surgery, Centro Cardiologico Monzino, IRCCS, Milan, Italy.

Correspondence Address:

Sergio Pirola

E-mail: sergio.pirola@ccfm.it

Article received on February 7th, 2021.
Article accepted on February 22nd, 2021.
To perform a cautious removal of the mass, we started resecting it 2 mm from the implant base using a No. 11 scalpel blade to reduce the risk of tumour fragmentation.

The next step was to perform a radical full-thickness resection of the implant base, located in the atrial septum, leaving a safety margin of 5 millimetres. This was followed by repeated and extended washing of the left chambers of the heart to reduce the risk of embolization of the remaining tumour fragments. The redundant interatrial septum, though largely resected, was closed by a direct suture. No complications occurred in the postoperative period, and the patient was discharged on the 6th post-operative day to a rehabilitation facility.

At gross examination, surgical specimens included: a lesion with dimensions of 3.5 × 3 cm, pedunculated, translucent and with a villous surface, focally covered by fibrinous exudate; a 1.5 cm implantation stalk and a fragment of interatrial septum.

Histological analysis showed that the lesion consisted of myxoid matrix containing thin vessels and scattered stellate cells, without mitotic activity and cytologic atypia. Interestingly, the fibrinous layer focally covering the lesion contained few dense aggregates consisting of large, blastic lymphoid cells, with clear-cut atypical features (Figure 3).

On immunohistochemical staining, the stellate cells embedded in the myxoid matrix were positive for CD34 and negative for cytokeratins AE1/AE3, CD31 and CD45/LCA, and with a very low Ki67 proliferation rate (<2%). Such findings were consistent with cardiac myxoma.

Further immunohistochemical evaluation showed a B-cell phenotype (positive for CD20, PAX5, CD79A) of the atypical, blastic lymphoid cells, along with partial positivity for BCL6, IRF4, BCL2, CD30 and C-MYC (<40% of cells), negativity for CD10, CD5, ALKc and HHV8, and a very high Ki67 proliferation index (>80%). In situ hybridization for Epstein-Barr virus (EBV/EBER) was diffusely positive (Figure 3).

Histological features and incidental findings were all consistent with an EBV-positive fibrin-associated large B-cell lymphoma, arising within a cardiac myxoma.

The implantation stalk was focally involved by myxoma, but free of lymphoma, suggesting complete resection of the lesion.

Total body CT scan and 18-FDG positron emission tomography excluded distant metastases. Oncologic consultation did not indicate adjuvant chemotherapy or radiotherapy.

**DISCUSSION**

Myxoma is the most common type of tumour among all primary cardiac neoplasms. They usually...
Cardiac lymphomas are instead rare, amounting to only 0.6% of all cardiac tumours. Although several subtypes of lymphomas may arise in the heart, the most common is diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), usually associated with an aggressive biological behaviour. On the other hand, the most frequent lymphoproliferative disease associated with cardiac myxoma is fibrin-associated diffuse large B-cell lymphoma (FA-DLBCL), with 16 cases reported so far. FA-DLBCL is a recently recognized entity, included within the spectrum of diffuse large B-cell lymphomas associated with chronic inflammation and has highly distinctive features: it arises in fibrinous material covering or contained in sites of chronic inflammation (most commonly within the cardiovascular system), neither forming a mass nor producing specific symptoms. Typically, the diagnosis is incidental, during histologic examination. FA-DLBCL is invariably EBV-positive.

It is therefore likely that most of the previously reported cases of lymphomas arising in association with cardiac myxomas would be re-classified to FA-DLBCL according to the current classification of the World Health Organization, due to the concomitant positivity for EBV and for the typical location within the fibrinous material covering the myxoma. More importantly, despite aggressive histological features (large cell morphology, high proliferation rate), FA-DLBCL is a localized disease with an indolent behaviour and a favourable outcome even with surgical excision alone. The rare event of relapse and the associated risk of local invasion, however, reinforce the need for a complete surgical excision.

CONCLUSION

Our case report suggests that cardiac surgeons must be aware that even apparently benign cardiac masses can conceal malignant lesions, adopting a presumptive attitude of "malignancy until proven otherwise", which should prompt always an accurate and radical excision of the mass.

Recognition of a macroscopic unusual aspect of the lesion is of paramount importance, as all reported cases of lymphoid proliferation arising within a cardiac myxoma showed a partial or global gelatinous aspect of the neoplasm (especially in its peripheral areas) (Table 1).

The rarity of this disorder is an obstacle to prospective studies. Endocavitary masses with the peculiar macroscopic characteristics we have described could indicate a high probability of lymphocytic infiltration in the context of myxomatous masses. In this case, a specific, integrated diagnostic and therapeutic pathway should be followed, including: wide and radical resection and possibly a bone marrow specimen (easily collected during surgery from the sternal bone), to ensure a fast staging if the lesion would be proven malignant.
Table 1. Available literature data regarding cases of myxomas in which B-cell lymphomas were identified.

| First author | Location and size | Symptoms | Lymphoma | EBV type | Gross analysis | Follow-up |
|--------------|-------------------|----------|-----------|-----------|----------------|-----------|
| Bagwan[17]   | Left atrium (4 × 2 cm) | Multiple strokes | Diffuse large B-cell lymphoma | Not available | Gelatinous, grape-like, friable | Not available |
| Dimitrova[18] | Left atrium (7.5 × 4.5 cm) | Chest pain | Diffuse large B-cell lymphoma | Not available | Partially fimbriated surface, gelatinous and necrotic parts | Not available |
| Loong[11]    | Left atrium (6.5 × 4 cm) | Cardiogenic shock, ischemic stroke | Diffuse large B-cell lymphoma | Type III latency (EBER+, LMP1+) | Not described | Patient deceased for chemotherapy complications (neutropenia + pneumonia) at 5 months |
| Svec[12]     | Left atrium (3.7 × 1.5 cm) | Ischemic stroke | Diffuse large B-cell lymphoma | Type III latency (EBER+, LMP1+) | Not described | No evidence of disease at 7 months |
| Bartoloni[13] | Left atrium (5.5 × 4 cm) | Fever and progressive fatigue | Atypical lymphoid B-cell proliferation | Type II latency (EBER +, LMP1+) | Glistening, villous and gelatinous surface | No evidence of disease at 72 months |
| Tapan[14]    | Left atrium (4.2 × 3.6 cm) | Palpitations | Diffuse large B-cell lymphoma | Type III latency (EBER+, LMP1+) | Not described | No evidence of disease at 12 months |
| Aguilar[15]  | Left atrium (6.2 × 2.5 cm) | Transient ischemic attack | Diffuse large B-cell lymphoma | Type III latency (EBER+, LMP1+) | Not described | No evidence of disease at 42 months |
| Pineda[16]   | Left atrium (6.5 × 3 cm) | Coronary embolization | Diffuse large B-cell lymphoma | Not available | Reddish, gelatinous | Not available |
| Park[17]     | Left atrium (6.3 × 3.2 cm) | Peripheral arterial embolization | Diffuse large B-cell lymphoma | Type III latency, EBER + | Irregular surface, friable | Not available |
| Boyer[18]    | Left atrium (? cm) | Syncope | Diffuse large B-cell lymphoma | EBER+ | Not available | No evidence of disease at 130 months |
| Boyer[18]    | Left atrium (? cm) | Syncope, cough, dyspnoea | Diffuse large B-cell lymphoma | EBER+, LMP1+ | Reddish, gelatinous | Patient died at 2 months for cardiac cause |
| Boyer[18]    | Left atrium (? cm) | Dyspnoea, respiratory failure | Diffuse large B-cell lymphoma | EBER+, LMP1+ | Not available | Recurrent FA-DLBCL at mitral valve after 25 months. Patient died at 26 months (embolic stroke) |
| Yan[19]      | Left atrium (? cm) | Congestive heart failure | Diffuse large B-cell lymphoma | Type III latency, EBER+, LMP1+ | Myxoid appearance with an abundant fibrinous or mucinous background in the centre | No evidence of disease at 7 months |
| Yan[19]      | Left atrium (? cm) | Congestive heart failure | Diffuse large B-cell lymphoma | Type III latency, EBER+, LMP1+ | Myxoid appearance with an abundant fibrinous or mucinous background in the centre | No evidence of disease at 84 months |
| Yan[19]      | Left atrium (? cm) | Congestive heart failure | Diffuse large B-cell lymphoma | Type III latency, EBER+, LMP1+ | Myxoid appearance with an abundant fibrinous or mucinous background in the centre | No evidence of disease at 3 months |
| Yan[19]      | Left atrium (? cm) | Congestive heart failure | Diffuse large B-cell lymphoma | Type III latency, EBER+, LMP1+ | Myxoid appearance with an abundant fibrinous or mucinous background in the centre | No evidence of disease at 120 months |
| Present case | Left atrium (3.6 × 3 cm) | Asthenia, dyspnoea and dizziness | Diffuse large B-cell lymphoma | EBER+, LMP1+ | Gelatinous, grape-like, pale pink, semi-transparent, extremely friable | No evidence of disease at 4 months |

EBR=Epstein-Barr virus-encoded small RNAs; LMP1=latent membrane protein 1
No financial support.
No conflict of interest.

Authors' roles & responsibilities

SP  Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published

SF  Histological analysis of the surgical specimen, curation of the anatomopathological part of the paper

FM  Histological analysis of the surgical specimen, curation of the anatomopathological part of the paper.

GM  Radiological image processing and reconstruction with special editing software (MIMICS, Materialise)

GM  Collaboration in writing the paper and proofreading it, as well as editing the literature review

GP  Coordination and supervision of the entire work of the team of researchers and final endorsement to the publication of the paper

REFERENCES

1. Bogaert J, Dymarkowski S, Taylor A, Muthurangu V. Clinical Cardiac MRI. 2nd edn. Berlin: Springer;2012.
2. Miguel CE, Bestetti RB. Primary cardiac lymphoma. Int J Cardiol. 2011;149(3):358-63. doi:10.1016/j.ijcard.2010.02.016.
3. Pineda AM, Mihioc CG, Nascimento FO, Santana Q, Lamelas J, Bechar N. Coronary embolization from a left atrial myxoma containing malignant lymphoma cells. Tex Heart Inst J. 2015;42(6):565-8. doi:10.14503/THIJ-14-4619.
4. Patel J, Sheppard MN. Pathological study of primary cardiac and pericardial tumours in a specialist UK centre: surgical and autopsy series. Cardiovasc Pathol. 2010;19(6):343-52.
5. Lam KY, Dickens P, Chan AC. Tumors of the heart. A 20-year experience with a review of 12,485 consecutive autopsies. Arch Pathol Lab Med. 1993;117(10):1027-31.
6. Bruce CJ. Cardiac tumours: diagnosis and management. Heart. 2011;97(2):151-60. doi:10.1136/hrt.2009.186320.
7. Petrich A, Cho SI, Billett H. Primary cardiac lymphoma: an analysis of presentation, treatment, and outcome patterns. Cancer. 2011;117(3):581-9.
8. Zanelli M, Zizzo M, Montanaro M, Gomes V, Martino G, De Marco L, et al. Fibrin-associated large B-cell lymphoma: first case report within a cerebral artery aneurysm and literature review. BMC Cancer. 2019;19(1):916. doi:10.1186/s12885-019-6123-1.
9. Boyer DF, McKelvie PA, de Leval L, Edlefsen KL, Ko YH, Aberman ZA, et al. Fibrin-associated EBV-positive large B-cell lymphoma: an indolent neoplasm with features distinct from diffuse large B-cell lymphoma associated with chronic inflammation. Am J Surg Pathol. 2017;41(3):299-312. doi:10.1097/PAS.0000000000000775.
10. Yan J, Luo D, Zhang F, He J, Yao S, Luo X, et al. Diffuse large B-cell lymphoma associated with chronic inflammation arising within atrial myxoma: aggressive histological features but indolent clinical behaviour. Histopathology. 2017;71(6):951-9. doi:10.1111/his.13336.
11. Loong F, Chan AC, Ho BC, Chau YP, Lee HY, Cheuk W, et al. Diffuse large B-cell lymphoma associated with chronic inflammation as an incidental finding and new clinical scenarios. Mod Pathol. 2010;23(4):499-501. doi:10.1038/modpathol.2009.168.
12. Svec A, Rangaiah M, Giles M, Jakska R, McClay A. EBV+ diffuse large B-cell lymphoma arising within atrial myxoma. An example of a distinct primary cardiac EBV+ DLBCL of immunocompetent patients. Pathol Res Pract. 2012;208(3):172-6.
13. Bartolini G, Pucci A, Giorlandino A, Berretta M, Mignosa C, Italia F, et al. Incidental Epstein-Barr virus associated atypical lymphoid proliferation arising in a left atrial myxoma: a case of long survival without any postsurgical treatment and review of the literature. Cardiovasc Pathol. 2013;22(3):e5-10. doi:10.1016/j.carpath.2012.08.002.
14. Aguilar C, Beltran B, Quiñones P, Carbajal T, Wicapaza J, Yabar A, et al. Large B-cell lymphoma arising in cardiac myxoma or intracardiac fibrinous mass: a localized lymphoma usually associated with Epstein-Barr Virus? Cardiovasc Pathol. 2015;24(1):60-4. doi:10.1016/j.carpath.2014.08.007.
15. Tapan U, Pestana JB, Lee JC, Lerner A. Epstein-Barr virus-associated diffuse large B-cell lymphoma arising in atrial myxoma: a proposal for a modified therapeutic approach. Leuk Lymphoma. 2015;56(2):305-7. doi:10.3109/10428194.2014.919632.
16. Liu X, Liu P, Li J. EBV+ diffuse large B-cell lymphoma arising within atrial myxoma in Chinese immunocompetent patient. Int J Clin Exp Pathol. 2015;8(2):2159-64.
17. Bagvran IN, Desai S, Motherspoon A, Sheppard MN. Unusual presentation of primary cardiac lymphoma. Interact Cardiovasc Thorac Surg. 2009;9(1):127-9. doi:10.1510/icvts.2009.204628.
18. Dimitrova KR, Hoffman DM, Geller CM, Thiagarjah P, Master J, Berger M, et al. Malignant B-cell lymphoma arising in a large, left atrial myxoma. Ann Thorac Surg. 2010;89(2):626-9. doi:10.1016/j.athoracsur.2009.06.096.
19. Kameda K, Shono T, Takagishi S, Kono S, Aoki T, Ito Y, et al. Epstein-Barr virus-positive diffuse large B-cell primary central nervous system lymphoma associated with organized chronic subdural hematoma: a case report and review of the literature. Pathol Int. 2015;65(3):138-43. doi:10.1111/path.12194.
20. Park CK, Cho YA, Kim M, Shim HS. Malignant lymphoma arising in cardiac myxoma, presenting with peripheral arterial emboli. Cardiovasc Pathol. 2018;27:26-9. doi:10.1016/j.carpath.2017.10.001.