Fibrin-associated diffuse large B-cell lymphoma with plasmacytic differentiation: case report and literature review

Esther Moreno Moreno 1, Ana Ferrer-Gómez 1, Héctor Pian Arias 1, Irene García García 2 and Mónica García-Cosío 1*

Abstract
Background: Primary cardiac lymphomas are extremely rare entities (<2% of cardiac tumours) and the most frequent histologic type is diffuse large B-cell lymphoma (DLBCL). Fibrin-associated DLBCL (FA-DLBCL) is a very unusual form of DLBCL associated with chronic inflammation, and only case reports and small series have been described. In the heart, it usually occurs in the context of a cardiac myxoma or cardiac prostheses and it is not bulk forming. These lymphomas frequently present with non-germinal center phenotype and are associated with Epstein-Barr virus (EBV) type III latency.

Case presentation: We describe a case of FA-DLBCL arising in a cardiac myxoma, with plasmacytic differentiation and type I EBV latency.

Conclusions: Although they are very rare, FA-DLBCLs should be known for their diagnostic difficulty, due to its unspecified clinical manifestations, and for their more favourable prognosis, sometimes even without additional treatment after surgical resection.

Keywords: Myxoma, Primary cardiac lymphoma, Fibrin-associated diffuse large B-cell lymphoma, Epstein-Barr virus, Case report

Background
Primary cardiac lymphomas (PCLs) are extremely rare (<2% of cardiac tumours) [1, 2]. The most frequent histologic type is diffuse large B-cell lymphoma (DLBCL) [1]. Conventional PCLs, such as DLBCL, infiltrate myocardium or pericardium, with aggressive course and low median survival [2]. DLBCL associated with chronic inflammation (DLBCL-CI) occurs in the context of a localized and maintained situation of chronic inflammation and shows association with Epstein-Barr virus (EBV) [3]. The most representative example within this group is pyothorax-associated lymphoma [4]. Fibrin-associated DLBCL (FA-DLBCL) is a very unusual form of this entity, which is mediated by a local immunosuppression mechanism and can be found associated to cardiac myxoma or cardiac prostheses [1].

In FA-DLBCLs, tumour cells are arranged singly or in small clusters within fibrin material [2] or associated to chronic blood effusions [5], with a high proliferative index (Ki-67 > 90%), but without myocardial invasion [1].

The available literature about this entity is scarce and only case reports or small series have been published. These lymphomas usually present with non-germinal center phenotype and associated with EBV type III latency, having better prognosis than conventional DLBCL and DLBCL-CI [2].

We report a case of FA-DLBCL with plasmacytic differentiation and associated to EBV type I latency, arising in a cardiac myxoma and growing in small neoplastic nests. This entity should be know because of its favour
outcome, although the diagnosis can be very challenging
due to its paucicellular features and, in our case, also to
its plasmacytic phenotype with no expression of the
panB marker CD20.

**Case presentation**
We present a 57-year-old woman, with no significant
past medical history, who was hospitalized due to a sud-
den precordial pain and diagnosed with acute coronary
syndrome. Transthoracic echocardiogram revealed a 3
cm-polypoid lesion attached to left atrium. Angioplasty
and resection of the lesion were performed.

A 3.5 × 3 cm polypoid lesion with a 2.3 × 0.7 cm ped-
icle was resected. It showed a solid, yellowish, homoge-
neous cut surface, with a congestive area. Histological
study revealed a proliferation composed of a dense eo-
sinophilic substance with myxoid basophilic areas, in
which spindle and starry cells were observed. No atypia
or mitotic figures were identified. Once immunohisto-
chemical study was performed, these cells showed
positivity to Calretinin, CD31, CD34 and Vimentin, con-
firming the diagnosis of cardiac myxoma. Moreover,
within and in the periphery of the myxoma, small aggre-
gates of lymphoid cells were identified. These were large
sized cells, with vesicular nuclei and conspicuous nucle-
oli, showing several mitotic figures and nuclear debris
(Fig. 1 a-c). Given these findings, immunohistochemical
study was extended and in situ hybridization study for
EBV (EBERs) was performed. Such cellularity resulted
CD45+, OCT-2+, CD79a+, CD38+, CD20-, PAX5−,
MUM1+ and Kappa+, with a proliferation index (Ki67)
of 95% (Fig. 1 d-f). Other immunohistochemical
markers, such as CD30, CD3, CD138, CD19, Myeloper-
oxidase, HHV-8, TdT, CD14, CD68 and Lambda were
negative. In situ hybridization (HIS) stains for Kappa
and Lambda confirmed the kappa light chain restriction.
Immunoglobulin gene rearrangement analysis was per-
formed and it resulted clonal. EBERs study was positive
and immunohistochemistry for EBV Latent Membrane
Protein 1 (LMP1) was negative, with final diagnosis of

![Fig. 1](image)

**Fig. 1** a Macroscopic view of 3.5 × 3 cm solid, brownish polypoid specimen with a 2.3 × 0.7 cm pedicle. b HE (20x). Histological study revealed a proliferation composed of a dense eosinophilic substance with myxoid basophilic areas, in which spindle and starry cells were observed. No atypia or mitotic figures were identified. c HE (100x on oil). Within the myxoma, small aggregates of lymphoid-like cells were identified. High magnification showed vesicular nuclei and conspicuous nucleoli with several mitotic figures and nuclear debris. d CD79 (40x). Lymphoma cells were positive for CD79. e OCT2 (40x). Lymphoma cells were positive for OCT2. f MUM1 (40x). Lymphoma cells showed non-germinal centre phenotype, with MUM1 positivity.
fibrin-associated DLBCL within a cardiac myxoma, with EBV type I latency, plasmacytic immunophenotype and kappa light chain restriction (Fig. 2).

Programmed Death-Ligand 1 (PD-L1) study showed positivity in about 60% of the malignant cells.

Computed body tomography to staging was not performed, due to the patient was transferred to another hospital one month later.

Discussion and conclusions
We report an immunocompetent patient who presented with an EBV-DLBCL arising within a cardiac myxoma. She was treated with surgical excision with loss of follow-up 1 month later.

Primary cardiac solid tumours are very unusual entities, in which 77–90% of them are benign, being the most frequent cardiac myxoma [1, 6]. PCL represents 0.5% of extranodal lymphomas [2] and <2% of primary cardiac tumours. Lymphoproliferative disorders with secondary cardiac involvement are more frequently observed [1]. The most frequent PCL is DLBCL and it is presented as a bulk-forming neoplasm affecting myocardium or pericardium, most frequently in right cavities and clinically manifests as dyspnoea, chest pain due to pericardial effusion, among other symptoms [2]. Conventional PCL has been associated to immunodeficiency and it is diagnosed late in the course of the disease, with an overall survival of 12 months [2].

DLBCL-CI was defined as a new entity in the 2008 World Health Organization (WHO) Classification [3, 4]. These tumours are aggressive DLBCLs, EBV-associated and occur in an enclosed environment with a long-standing chronic inflammation [4], such a pyothorax-associated lymphoma. Few cases of FA-DLBCLs have been described such as case reports and small series (Table 1), usually within cardiac myxoma or associated to cardiac prostheses [7, 8]. Boyer et al. [4] and Svec et al. [9] reported an average age of 55 and 70 years, with a male: female ratio of 2:3 and 1:4, respectively. These tumours are considered a variant of chronic inflammation-associated lymphomas (2017 WHO Classification) [10, 11], with CD20 expression, non-germinal center phenotype, and associated with EBV type III latency, but with better outcomes than the former [2]. FA-DLBCLs occur in immunocompetent patients and appear to be produced by local immunosuppression mechanisms [1]. Characteristically these lymphomas are not bulk forming [2]. Although PCLs are very rare diseases, Gruver et al. [2] reported that fibrin-associated DLBCLs represent 50% of a series of 6 PCLs.

Boyer et al. [4] reported in a 12 cases series that FA-DLBCLs have several differences with DLBCL-CI. DLBCL-CI occurs in older patients, with longer latency and higher mortality. This series is one of the longest series published and this group supports the conclusion that FA-DLBCLs are different entities from DLBCL-CI. FA-DLBCLs arising in cardiac myxomas have lower genetic alterations than DLBCL-CI. Moreover, most FA-DLBCLs represent discrete foci of large B-cells without infiltration of normal tissue and with indolent clinical course [4].

Fibrin-associated DLBCLs are mostly non-germinal center B-cell lymphomas. There is only one case published in the literature diagnosed as lymphoplasmacytic

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**Fig. 2** a Kappa (HIS 40x) & b Lambda (HIS 40x). Malignant cells showed kappa light chain restriction. c EBV (40x). EBERs study was positive in malignant cells. d PDL1 (40x). Programmed Death-Ligand 1 (PD-L1) study showed positivity in about 60% of the malignant cells.
| Author                  | Cases | Age  | Sex | Location          | Diagnosis        | Phenotype | EBV latency | Stage     | Adjuvant treatment | Follow-up (months) |
|------------------------|-------|------|-----|-------------------|-------------------|-----------|-------------|-----------|-------------------|--------------------|
| Garces et al, 2019     | 1     | 50 M |     | Left atrial myxoma| FA-DLBCL          | Non-GC     | NA          | Localized | None              | 65-WER             |
| Zanelli et al, 2019    | 1     | 75 F |     | Adrenal pseudocyst| FA-DLBCL          | Non-GC     | NA          | Localized | None              | 130-WER            |
| Boyer et al, 2017      | 12    | 54 F |     | Left atrial myxoma| FA-DLBCL          | Non-GC     | Type III    | Localized | None              | Died 2 mo-WER      |
|                        |       | 55 F |     | Left atrial myxoma| FA-DLBCL          | Non-GC     | Type III    | Localized | None              | Died 26 mo-WER     |
|                        |       | 54 M |     | Left atrial myxoma| FA-DLBCL          | Non-GC     | Type III    | Localized | None              | Died 17 mo-WER     |
|                        | 56 M  |     |     | Aortic aneurysm   | FA-DLBCL          | Non-GC     | Type III    | Localized | R-CHOP × 6        | 24-persistent local disease |
|                        | 68 M  |     |     | Arterial thromboembolism | FA-DLBCL          | Non-GC     | Type III    | Localized | R-CHOP × 6        | Died 10 mo-WER     |
|                        | 71 M  |     |     | Aortobifemoral prosthesis | FA-DLBCL          | Non-GC     | Type II-III | Localized | None              | 10-WER             |
|                        | 79 M  |     |     | Testicular hematoma| FA-DLBCL          | Non-GC     | Type III    | Localized | None              | Died 17 mo-WER     |
|                        | 25 M  |     |     | Subdural hematoma  | FA-DLBCL          | Non-GC     | Type II-III | Localized | None              | 7-WER              |
|                        | 37 F  |     |     | Splenic pseudocyst | FA-DLBCL          | Non-GC     | Type II-III | Localized | R-CHOP × 6        | 32-WER             |
|                        | 73 M  |     |     | Retroperitoneal pseudocyst | FA-DLBCL          | Non-GC     | Type II-III | Localized | R-CHOP × 6        | 43-WER             |
|                        | 70 M  |     |     | Adrenal pseudocyst | FA-DLBCL          | Non-GC     | Type III    | Localized | None              | 14-WER             |
|                        | 44 M  |     |     | Retroperitoneal pseudocyst | FA-DLBCL          | Non-GC     | Type III    | Localized | CHOP × 5          | 84-WER             |
| Kirschenbaum et al, 2017| 1     | 81 M |     | Arachnoid cyst     | FA-DLBCL          | NA        | NA          | Localized | R-L x NA          | NA                 |
| Yan et al, 2017        | 4     | 46 F |     | Left atrial myxoma  | DLBCL-CI          | Non-GC     | Type III    | Localized | None              | 10-WER             |
|                        | 61 F  |     |     | Left atrial myxoma  | DLBCL-CI          | GC         | Type III    | Localized | None              | 7-WER              |
|                        | 54 M  |     |     | Left atrial myxoma  | DLBCL-CI          | Non-GC     | Type III    | Localized | None              | 7-WER              |
|                        | 46 F  |     |     | Left atrial myxoma  | DLBCL-CI          | Non-GC     | Type III    | Localized | None              | 3-WER              |
| Aguilar et al, 2015    | 1     | 52 M |     | Left atrial myxoma  | FA-DLBCL          | Non-GC     | Type III    | Localized | None              | 42-WER             |
| Tapan et al, 2015      | 1     | 49 M |     | Left atrial myxoma  | EBV-DLBCL         | Non-GC     | Type III    | Localized | R-CHOP × 6        | 12-WER             |
| Gruver et al., 2012    | 3     | 55 M |     | Aortic root graft  | FA-DLBCL          | Non-GC     | Type III    | Localized | R-CEOP × 8        | 16-WER             |
|                        | 56 M  |     |     | Left atrium        | FA-DLBCL          | Non-GC     | Type III    | Localized | R-CHOP × 6        | 8-WER              |
|                        | 75 M  |     |     | Mitral valve       | FA-DLBCL          | Non-GC     | EBV -       | Localized | R-CEP × 1 and R-CHOP × 6 | 39-WER             |
| Svec et al, 2012       | 1     | 60 F |     | Left atrial myxoma  | EBV-DLBCL         | Non-GC     | Type III    | Localized | R-CHOP × 6        | 7-WER              |
| Loong et al, 2010      | 4     | 29 M |     | Splenic cyst       | DLBCL-CI          | Non-GC     | Type III    | Localized | Rituximab × 6     | 6-WER              |
|                        | 88 M  |     |     | Right hydrocele    | DLBCL-CI          | Non-GC     | Type III    | Localized | NA                | Lost to follow-up  |
|                        | 70 F  |     |     | Left atrial myxoma  | DLBCL-CI          | Non-GC     | Type III    | Localized | R-CEP × 4        | Died 5 mo-WER      |
|                        | 78 M  |     |     | Knee prosthesis    | DLBCL-CI          | Non-GC     | Type III    | Localized | RT × 7            | 84 (7 y)-WER       |
| Present case           | 1     | 57 F |     | Left atrial myxoma  | Plasmacytic        | Non-GC     | Type I      | Localized | None              | 1-Loss of follow-up |

FA-DLBCL: fibrin-associated diffuse large B-cell lymphoma, DLBCL-CI: DLBCL associated with chronic inflammation, Non-GC: non-germinal center, GC: germinal center, NA: not available, WER: without evidence of recurrence, R-L: rituximab, lenalidomide, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone, R-CVP: rituximab, cyclophosphamide, vincristine and prednisone, R-CEP: rituximab, cyclophosphamide, etoposide, vincristine and prednisone, R-CEOP: rituximab, cyclophosphamide, etoposide, oncovin, and prednisone, RT: radiotherapy.
lymphoma, due to its B-cell derivation with loss of CD20 staining and aberrant expression of CD3 [9]. Our case was CD20 negative. Thus, it was diagnosed as fibrin-associated DLBCL, with plasmacytic differentiation.

The association with EBV infection suggests that fibrin-associated DLBCLs are predisposed by an underlying inflammatory background. Type III EBV pattern latency is typically observed in immunosuppressed patients. By contrast, these lymphomas occur in immunocompetent patients, so it is suggested a mechanism of local rather than systemic immunosuppression [1]. This mechanism is not well known, and it could be caused by local expression of proinflammatory cytokines, such as interleukin-6 (IL-6). IL-6 participates in B-cell maturation and several studies have reported that this cytokine is produced in cardiac myxomas. In an enclosed environment, chronic IL-6 exposure might favour the selection B-cells infected by EBV and the evasion of T-cell surveillance [1]. Other cytokines, such as interleukin-10, that inhibits T-cell proliferation, may contribute in local immunosuppression [3].

Despite the frequent association with EBV type III latency in the published cases (22/29 cases, see table), the negativity of LMP-1 in our case suggests a type I EBV latency. In the remaining published cases, EBV latency was not available and one case was EBV negative.

Moreover, it is thought that high levels of PD-L1 expression may contribute to the immune evasion of the EBV-positive B-cells. The study of PD-L1 expression in the reported FA-DLBCLs cases showed a 86% of positivity [4], similarly to our case, that displayed PD-L1 expression in 60% of the neoplastic cells. This may justify in part the type I EBV pattern latency, not associated to immunosuppression, observed in our case.

We present a case of FA-DLBCL with plasmacytic differentiation and type I EBV latency. Although they are very rare, FA-DLBCLs should be known for their diagnostic difficulty, due to its unspecified clinical manifestations and the not bulk forming features with paucity of neoplastic cells. Moreover, in our case the plasmacytic differentiation makes the diagnosis more challenging, because of the lack of expression of panB immunohistochemical markers.

More studies are needed to clarify the pathogenesis of FA-DLBCL, that is probably a different entity from DLBCL-CI in virtue of its excellent outcome, even without adjuvant therapy [1, 2, 4].

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s13000-020-01034-7.

Acknowledgments
We thank Dr. José Palacios Calvo for his critical review and Dr. Miguel Piris Villaespesa for his technical assistance.

Authors’ contributions
Esther Moreno and Ana Ferrer drafted the manuscript. Irene García-Cosío performed the interpretation of the histologic features and immunohistochemical results.

Competition of interest
The authors declare that they have no conflicts of interest.

Acknowledgments
The authors declare that they have no conflicts of interest.

Author details
1Department of Pathology, Hospital Universitario Ramón y Cajal, Ctra. de Colmenar Viejo km 9,100, Madrid 28034, Spain. 2Department of Haematology, Hospital Universitario Ramón y Cajal, Ctra. de Colmenar Viejo km. 9,100, 28034 Madrid, Spain.

Received: 24 July 2020 Accepted: 15 September 2020
Published online: 24 September 2020

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Funding
‘Not applicable’.

Availability of data and materials
‘Not applicable’.

Consent for publication
‘Not applicable’.

Additional file 1. CARE Checklist.
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