Case Report

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

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ABSTRACT

We report a case of left atrial cardiac myxoma harbouring an incidental atypical B-cell lymphoid proliferation. Histology disclosed classic myxoma cells embedded in a mucopolysaccharide-rich matrix and a micronodular lymphomatous proliferation under the surface of the mass. Myxoma cells were immunoreactive for calretinin, while lymphomatous cells expressed B lineage markers (CD 20+, CD79a), without evidence of clonality. Moreover, they were LMP1 positive; EBN2A negative; KSHV/HHV8 negative; and, by in situ hybridization, EBER/Epstein–Barr virus (EBV) positive and Kappa and Lambda negative. According to the 2008 WHO schemes, the present case shares close similarities either with diffuse large B-cell lymphomas growing in the context of long-standing chronic inflammation or with primary effusion lymphomas, solid variant, both associated with EBV infection. This is the sixth case of incidental atypical lymphoid proliferation discovered in a cardiac myxoma reported so far. The optimal treatment of such lesions remains undefined, but their clinical course is indolent. After an accurate staging workup, without any postsurgical treatment, the patient we observed has been well with no recurrence of the disease at 6 years of follow-up.

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1. Introduction

Primary cardiac tumors are rare, and cardiac myxomas are the most histotype among them [1]. Primary cardiac lymphomas are extremely rare [2,3], accounting for 2% of primary cardiac tumors and less than 5% of extranodal lymphomas [1]. Atypical lymphoid proliferations (ALPs), occurring within a cardiac myxoma, are an incidental finding in the surgical pathology practice and a very rare pathological condition. After a review of the pertinent scientific literature since 1980, we were able to find only five of such coincidental dual pathological lesion, in which the lymphoproliferative disorder, however, was diagnosed as primary lymphoma [4–8]. Based on these reported observations, lymphoproliferative lesions arising in a cardiac myxoma might represent a distinct unusual pathological entity characterized by indolent clinical course and good outcome or “early lesion” in the evolution of a lymphoid neoplasia [7]. Here we report a case of incidental ALP discovered in a cardiac myxoma. The patient is alive after a 6-year follow-up, by far the longest reported in the specific literature.

2. Case report

The patient, a 55-year-old Caucasian female, was admitted to the hospital because of a 3-month history of progressive fatigue and fever. After physical examination, an echocardiogram revealed a left atrial mass consistent with myxoma, typically attached to the oval fossa. Excision of the intraatrial tumor was carried out via median sternotomy, on cardiopulmonary bypass, with cardioplegic arrest. The tumor was removed with a full-thickness resection of the attached interatrial septum. The postoperative course was unremarkable, and the patient was discharged on postoperative day 6.

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Pathology confirmed the mass to be a cardiac myxoma, though having coincidental foci of atypical, pleomorphic lymphoid proliferation (see below). The patient proceeded to an accurate staging workup for lymphoma by physical examination, imaging studies, including computerized tomography, and bone marrow biopsy which showed no other sites of disease. There was no clinical history of recurrent infections or autoimmune disorders. Only a follow-up strategy was adopted without treatment. The patient is alive and well at 6-year follow-up.

3. Pathology

The 5.5×4.5×3.5-cm resected mass (Fig. 1A) showed glistening, villous surface with two whitish, nodular, firm areas (largest size 0.7 cm in diameter); the cut surface was gelatinous with focal areas of hemorrhage. Microscopic examination disclosed typical cardiac myxoma cells, embedded in a loose myxoid matrix, single scattered, or arranged in small nests, cord-like, or perivascular structures (Figs. 1B-D). The two grossly whitish nodules (Fig. 2A), which included multiple microscopic foci of tiny cellular aggregates close to the myxoma surface, were composed of large, pleomorphic lymphoid cells (Fig. 2C), with abundant atypical mitoses. The myxomatous and lymphoid proliferations were mainly arranged in a “collision” pattern (Fig. 2B) with abundant interposed inflammatory cells. Foci of haemorrhagic necrosis and hemosiderin-laden macrophages were mainly concentrated close to the lymphoid counterpart of the mass. The tumor attachment pedicle was composed only by myxomatous tissue, and no neoplastic cells infiltrated the resected...
interatrial myocardium. The immunohistochemical and in situ hybridization analyses performed to typify the lymphoid and myxomatous cells are summarised in Table 1. Myxoid “lepidic” cells were strongly positive for calretinin (Fig. 1E); intratumoral pseudo-vascular structures, typical of myxomatous architecture, were CD31 and CD34 positive (Fig. 1F). The large lymphoid cells were B-cells, without evidence of Kappa/Lambda clonality by in situ hybridization and immunohistochemistry, expressing CLA, CD20 (Fig. 2D), and, occasionally, CD79a and MUM1. They showed to be also LMP1 positive (Fig. 2E), but EBNA2 negative and HHV8 negative (data not shown). T-cell markers, including CD3 and CD5, were all negative. The cells were highly proliferative, with Ki67 being 90%. By in situ hybridization, lymphoid B-cells nuclei were positive for EBER (Fig. 2F). On the basis of the histological features and immunohistochemical profile, a final diagnosis of Epstein–Barr virus (EBV) associated atypical lymphoid proliferation was made, but the follow-up evaluation took into account the potential progression of the lesion in an overt diffuse large B-cell lymphoma (DLBCL).

4. Discussion

Though cardiac myxomas are the most frequent neoplasms encountered in the surgical pathology practice of cardiovascular surgery, the serendipitous discovery of a lymphoproliferative lesion in a left atrial myxoma: a case of long survival would be rare.
a cardiac myxoma is extremely rare. In the present case, it was possible to exclude, by careful staging, any lymphomatous involvement outside the heart and pericardium. Thus, such pathological entity “sensu strictiori” has to be considered primitive, with morphological and immunophenotypical features resembling a diffuse polymorphic lymphoproliferative B-cell lesion. Out of the five cases of coincidental dual pathological lesion that have been already reported, the diagnosis was plasmacytoid lymphoma in one [5]; in the remaining four cases, the diagnosis was DLBCL. In all cases, the lymphoid proliferations were, preferably, distributed close to the myxomas surface.

Regarding the coincidental myxoma, the immunophenotype disclosed the specific calretinin [9] and CD-34 positivities in “lepidic” myxomatous cells and pseudovascular structures, respectively [10]. The characteristic inflammatory features of myxoma were found only in the present case and in one other patient from the literature.

Lymphoproliferative lesions including ALPs, occurring in cardiac myxomas, were not considered in the 2008 WHO schemes [11], even though they share close similarities either with a special well defined category of DLBCL, growing in the context of long-standing chronic inflammation, or, alternatively, with primary effusion lymphoma, solid variant, both associated with EBV infection [12]. A proposed pathogenetic model suggests that chronic inflammation in the tumor microenvironment promotes malignant transformation, probably through autocrine/paracrine signaling by interleukin-6 and interleukin-10, allowing EBV-transformed cells to evade immune surveillance [7], in keeping with the key role of EBV infection in the disease progression. Intriguingly, the same pathogenetic mechanism underlies lymphoid malignancies associated with chronic inflammatory reaction after the implant of prostheses, another type of EBV-driven lymphoid proliferations [4,7,13]. In detail, intracardiac or endoarteric prostheses might be critically prone to EBV activity owing to the long-standing chronic inflammation of the prosthetic surface.

Table 1

<table>
<thead>
<tr>
<th>Antibody</th>
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<th>Results</th>
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<tr>
<td>CD3</td>
<td>Dako</td>
<td>Polyclonal</td>
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<tr>
<td>CD5</td>
<td>Novocastra</td>
<td>4C7</td>
<td>1:25</td>
<td>-</td>
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<tr>
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<td>Dako</td>
<td>CS1-4</td>
<td>1:200</td>
<td>+</td>
</tr>
<tr>
<td>CD34</td>
<td>Abcam</td>
<td>PE2</td>
<td>1:25</td>
<td>-</td>
</tr>
<tr>
<td>CD8</td>
<td>Ventana-Roche</td>
<td>13B10</td>
<td>1:25</td>
<td>-</td>
</tr>
<tr>
<td>CD77</td>
<td>Ventana-Roche</td>
<td>Inform EBER Probe</td>
<td>Ready to use</td>
<td>+</td>
</tr>
<tr>
<td>CD10</td>
<td>Dako</td>
<td>PD7/26+2B11</td>
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</table>

Table 2

Review and updating of lymphoid proliferations including primary lymphomas in cardiac myxomas

<table>
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<tr>
<th>Case</th>
<th>Age/gender</th>
<th>Ref.</th>
<th>Location</th>
<th>Pathological diagnosis</th>
<th>Inflammatory infiltrate/necrosis</th>
<th>Chemo/ radiotherapy</th>
<th>EBV</th>
<th>Follow-up</th>
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<td>1</td>
<td>81/F</td>
<td>[4]</td>
<td>Left atrial myxoma</td>
<td>DLBCL</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>Under surveillance</td>
</tr>
<tr>
<td>2</td>
<td>75/F</td>
<td>[5]</td>
<td>Plasmacytoid lymphoma</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>Under surveillance</td>
</tr>
<tr>
<td>3</td>
<td>51/M</td>
<td>[6]</td>
<td>Left atrial myxoma</td>
<td>DLBCL</td>
<td>Yes</td>
<td>Yes</td>
<td>+</td>
<td>Dead after 5 months (pneumonia)</td>
</tr>
<tr>
<td>4</td>
<td>70/F</td>
<td>[7]</td>
<td>Left atrial myxoma</td>
<td>DLBCL</td>
<td>Yes</td>
<td>Yes</td>
<td>+</td>
<td>Alive and well at 6 months</td>
</tr>
<tr>
<td>5</td>
<td>60/F</td>
<td>[8]</td>
<td>Plasmacytoid lymphoma</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>+</td>
<td>Alive and well at 6 years</td>
</tr>
<tr>
<td>6</td>
<td>55/F</td>
<td>Present case</td>
<td>Atypical lymphoid proliferation</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>+</td>
<td>Alive and well at 6 years</td>
</tr>
</tbody>
</table>

NA: not available.
to their specific intracirculatory exposure and chronic inflammatory reaction. Correspondingly intracavitary location of cardiac myxomas might represent the same predisposing condition. Moreover, inflammation in myxomas is only in part a reactive process being mainly induced by the intrinsic secretion of interleukin-6 and erythropoietin [14].

Tables 2 and 3 refer to a review of the literature concerning cases mostly diagnosed as DLBCL in cardiac myxoma (Table 2), DLBCL in aortic prosthetic valve and grafts, and other inflammatory processes (Table 3). A series of 13 patients (including the present one classified as ALP) share the common denominator of a morphologic DLBCL classification, limited disease, and the localization close to serous membranes or endothelial surface. In detail, among the proliferative lesions in cardiac myxoma, four cases were diagnosed as DLBCL and one as plasmacytoid lymphoma. The remaining seven (Table 3) were classified as DLBCL infiltrating several anatomical sites and associated with chronic inflammation (three of them occurring in cardiovascular prostheses).

The five previous reports of DLBCL in cardiac myxoma were published between 2009 and 2012 [4–8], and all patients, except one who died from pneumonia [7], were, to date, “under clinical surveillance,” thus preventing reliable prognostic conclusions for inadequate follow-up intervals. Concerning the remaining DLBCL cases and the present one, only the patient with tumor arising in a knee prosthesis warrants a 7-year follow-up (case 4 of Ref. [7]), comparable to that of the present study. In the same patient, Loong et al. [7] described ?PCR clonal immunoglobulin gene rearrangements, although notably the lymphoid proliferating cells did not show labeling for kappa or lambda mRNA, as in the present study. PCR clonality was not tested, in our case for suboptimal quality of extracted DNA. Out of the five DLBCL in cardiac myxoma patients and of the four DLBCL in cardiovascular prostheses patients, four died: one in the immediate postoperative course [14], and the remaining three, with a follow-up ranging from 5 to 18 months; died of fatal pneumonia related to chemotherapy (one patient) [7], long-distance rupture (6 months) of the prosthesis leaflets (one patient) [4], and a breast cancer (one patient) [13]. Chemotherapy was strictly related to the case of fatal pneumonia [7], and its potential role cannot be excluded in the case of leaflets rupture complicated by a prosthesis perivalvular fistula [4] as a consequence of postnecrotic changes. On the contrary, all untreated patients were alive. Concerning EBV markers detection in DLBCL in cardiac myxoma, infection was investigated only in two cases, both positive.

Although ordinary treatment for DLBCL (stage IE–II) and other similar subtypes like those associated with chronic inflammation and those referred as elderly types [11] is the rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone regimen, usually followed by radiotherapy [15], the lack of WHO classification criteria for lymphoproliferative lesions occurring in cardiac myxomas, their close similarities with self-limited EBV-related lymphoproliferative disorders, and the absence of malignancy-related complications strongly suggest a “wait and see” approach without chemotherapy or radiotherapeutic treatment.

Lymphoproliferative lesions in cardiac myxoma including ALP and the so-called DLBCLs occurring in cardiovascular prosthetic devices and membrane-associated miscellaneous inflammatory processes must be distinguished for their better prognosis, even though several authors [7,8,13] have suggested a similar statement, in the greater part of their cases, chemotherapy has been administered. The present study proposes that ALPs in cardiac myxoma may be managed with surgical treatment alone, lending support to the opinion that chemotherapeutic protocols in such cases with scanty tumor volume may be an overtreatment [16]. Hence, the “wait and see” strategy reserved for our patient might have allowed his excellent prognosis and follow-up.

In conclusion, ALPs in cardiac myxoma may effectively be treated with a complete surgical resection, and an accurate follow-up program could be more than adequate to assure a favorable prognosis. ALPs in cardiac myxomas and in cardiac prostheses, and lymphomatous and lymphomatous-like lesions in a background of inflammatory processes share an EBV-driven pathogenesis. Immunocompetence or immunocompromise plays a crucial role in the evolution and prognosis of these conditions, the former probably leading to self-limited reactive lymphoproliferative lesions and the latter to overt lymphomatous processes, mainly DLBCLs.

Although these conditions range from a reactive ALP to malignant, aggressive lymphomas, they might warrant a unifying pathogenetic concept of serous endothelial membrane-based extranodal lymphomas or reactive ALPs.

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References


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