Primary cardiac lymphoma: B- and T-cell cases at a specialist UK centre

J. Patel¹*, L. Melly² & M. N. Sheppard¹

¹Department of Histopathology, Royal Brompton Hospital and ²Department of Histopathology, Royal Free Hospital, London, UK

Received 25 July 2009; accepted 30 July 2009

Background: Primary cardiac lymphoma is a very rare malignancy, which is typically of a non-Hodgkin’s type, and involves only the heart and pericardium with no or minimal evidence of extracardiac involvement. In the past, they were frequently diagnosed at autopsy but modern imaging technology now permits early diagnosis and treatment which allows for improved prognosis.

Patients and methods: This report describes the wide spectrum of clinical presentation, difficulty with correct clinical diagnosis, complications of treatment and pathologic findings of one of the largest series of primary cardiac lymphomas at a specialist UK centre. Our series comprised five males and one female with an age range of 10–81 years.

Results: Most cases involved at least two chambers with the ventricles being the most common site. Clinical presentation included arrhythmias, valve incompetence, cardiac failure, pericardial effusion, embolic stroke and sudden death. Our study, in contrast to other series, included both B- and T-cell lymphomas.

Conclusions: All six cases illustrate the wide spectrum of clinical presentation of lymphomas presenting primarily in the heart and emphasise that histology of all mass lesions is essential. Other series are small like ours highlighting the rarity of these tumours in the heart with the emphasis on imaging, early diagnosis and treatment.

Key words: cardiac failure, cardiac lymphoma, heart, pericardium, pericardial effusion

Introduction

Primary cardiac lymphoma is a very rare malignancy, which is typically of a non-Hodgkin’s type, and involves only the heart and pericardium with no or minimal evidence of extracardiac involvement. It accounts for ~1% of the primary cardiac tumours and ~0.5% of extranodal lymphomas. Patients with primary cardiac lymphoma range in age from 18 to 77 years with equal sex distribution. Both B- and T-cell lymphomas have been reported. There has been an increase linked to acquired immunodeficiency syndrome (AIDS), immunosuppression and cardiac transplantation [1]. The right atrium and right ventricle are the two most frequently involved sites. Clinical presentation is heterogeneous and is generally related to the site of involvement in the heart.

Case reports are frequent, emphasising the rarity of these tumours as primaries. Few large series exist with the largest series to date being from the United States with five cases [2] and six cases from France [3].

In the past, they were frequently diagnosed at autopsy but modern imaging technology now permits early diagnosis and treatment which allows for improved prognosis [4]. Clinicians need to be aware of their variable presentation and the difficulty with diagnosis. This report describes the wide spectrum of clinical presentation, difficulty with correct clinical diagnosis, link to cardiac transplantation and valve replacement, complications of treatment and pathologic findings for one of the largest series of primary cardiac lymphomas at a specialist UK centre.

Patients and methods

Case 1

A 29-year-old man presented with arrhythmias. Magnetic resonance imaging (MRI) showed multiple lesions in his right and left ventricle with normal coronary arteries. Ventricular biopsy showed chronically inflamed granulation tissue with residual mesothelium, indicating destruction of the pericardium. A diagnosis of inflammatory ‘pseudotumour’ was made and the patient was treated with steroids and improved. Two months later, he re-presented with a skin lesion, which was diagnosed as an anaplastic large T-cell lymphoma. The myocardial biopsy was reviewed in view of this and it was found that the blood vessels on deeper sectioning contained lymphoid cells with convoluted nuclei, some of which had a cerebriform appearance with scattered cells in the granulation tissue. These cells showed strong cytoplastic positivity for CD30 and CD2 and strong nuclear and cytoplasmic positivity for activin receptor-like kinase-1. These cells were blocking the vessels resulting in widespread infarction with healing granulation in the walls of the left ventricle and interventricular septum, which obscured the diagnosis. The final diagnosis was vascular myocardial involvement by anaplastic large T-cell lymphoma (Figure 1A and B). The patient was treated but died 8 months later with widespread disease.
case 2

A 50-year-old man presented with aortic regurgitation (AR) and a history of aortic valve replacement (AVR) with a mechanical prosthesis and closure of a ventricular septal defect in 1989. He subsequently developed endocarditis on this mechanical valve and underwent a repeat procedure later in the same year. This was followed by redo-AVR first in 1993, then in 2004 and finally in 2005 with porcine stentless freestyle bioprosthesis for severe AR. Coronary arteriogram revealed normal coronary arteries. During the operation, ‘vegetations’ were seen to be completely covering the right and the left coronary leaflets of the aortic valve but sparing the noncoronary leaflet (Figure 2A). Histologically, the excised homograft revealed that instead of infection the vegetations were composed of large pleomorphic malignant cells with necrosis, apoptosis and abundant mitosis (Figure 2B). These cells invaded and destroyed two of the valve leaflets. They were positive for CD45, CD20 (Figure 2C), CD79a and CD10 with heterogeneous staining for BCL-2 and BCL-6. Approximately 80% of the tumour cells showed Ki67 expression. Immunostaining for Epstein–Barr virus (EBV)-latent membrane protein-1 was negative and there was no overexpression of p53. A diagnosis of diffuse large B-cell lymphoma was made. As staging revealed no evidence of disseminated disease or bone marrow involvement, this was considered to be primary cardiac diffuse large B-cell lymphoma. The patient received chemotherapy [rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)] but died 6 months later due to rupture of the bioprosthesis with dehiscence and fistula formation found at autopsy. There was extensive necrosis in the area of dehiscence, but no macroscopic or histological evidence of any residual lymphoma at autopsy.

case 3

A 53-year-old man had a cardiac transplant for dilated cardiomyopathy and died suddenly 5 years later. Macroscopic examination of the heart showed suture lines in aorta, pulmonary artery and atria with previous transplantation. Otherwise, the heart was structurally normal. Histology revealed nodular aggregates of lymphocytes throughout the myocardium as well as small lymphocytes with occasional large atypical cells with prominent nucleoli. The cells stained positively for leukocyte common antigen and CD20. A diagnosis of B-cell lymphoproliferative disease was made. No viral investigations could be done due to lack of tissue.

case 4

A 10-year-old boy presented with a 12-week history of progressive breathlessness. A chest X-ray showed marked cardiomegaly and an echocardiogram showed a large pericardial effusion, which was compromising the function of the heart. The patient became bradycardic shortly after the insertion of a pericardial drain, had a cardiac arrest and died. At post-mortem, there was a widespread malignant tumour involving the external surface of both ventricles (Figure 3A) with extension into the roof of the left atrium (Figure 3B) and adjacent visceral and parietal pericardium. He also had widespread involvement of all mediastinal lymph nodes. Histology showed infiltration of right and left ventricles by small malignant lymphoid cells (Figure 3C). The cells were small- to medium-sized lymphocytes with scant cytoplasm and condensed course chromatin. The cells stained positively for CD45, CD3, CD8, CD99 and terminal deoxynucleotidyl transferase with focal perinuclear epithelial membrane antigen positivity. A diagnosis of T-cell lymphoblastic lymphoma was made.

case 5

An 81-year-old female was referred with a history of multiple strokes associated with what looked like an atrial myxoma on echocardiography. A computed tomography (CT) scan of the brain revealed multiple bilateral middle cerebral artery infarctions. The left atrial myxoma looked exactly as expected at surgery, attached to the left atrial wall in the region of the fossa...
ovalis. This $40 \times 20 \times 8\, \text{mm}^3$ gelatinous, grape-like, friable tumour (Figure 4A) histologically showed a classic myxoid appearance in the centre and, but with more cellularity, at the periphery just underneath the surface. The myxoid areas showed the presence of calretinin-positive myxoma cells with no mitotic activity (Figure 4B). The appearances were typical of an atrial myxoma. Additionally, the cellular areas were composed of large pleomorphic lymphoid cells with high nucleus : cytoplasm ratio and abundant mitosis. These cells were admixed with the myxoma cells in place and were positive for CD20, CD79a, CD10, BCL-2 and BCL-6 but were negative for calretinin and CD3. Approximately 80% of the large cells showed Ki67 expression. The appearances were interpreted as being those of a coexistent diffuse large B-cell lymphoma within an atrial myxoma. Staging investigations revealed no evidence of lymphoma at other sites and there was no evidence of bone marrow involvement indicating this to be a true primary cardiac lymphoma. The patient has been commenced on R-CHOP chemotherapy for lymphoma.

case 6
A 54-year-old man was referred with a history of left shoulder pain and sweating. He had no other significant past medical or family history and he was an ex-smoker. An MRI showed multiple diffuse masses involving the left and right ventricles and atria encasing the aortic root, proximal ascending aorta and coronary arteries with inflammation and necrosis within the cardiac lesions. These findings indicated a diagnosis of cardiac lymphoma. Since his admission, the patient was treated for hospital-acquired pneumonia with a C-reactive protein $>300$ and worsening

Figure 3. (A) Widespread malignant tumour involving the external surface of both ventricles with (B) extension into the roof of the left atrium. (C) Histology showing infiltration of right and left ventricles by small malignant lymphoid cells (hematoxylin–eosin stain, magnification $\times 100$).

Figure 4. (A) The left atrial tumour shows a gelatinous, grape-like, friable appearance. (B) The myxoid areas showed the presence of small round cells arranged in cords and rings, representing an atrial myxoma (hematoxylin–eosin stain, magnification $\times 100$). Inset: the myxoma cells are positive for calretinin (arrows), whereas the large atypical cells in cellular areas are negative (magnification $\times 100$).
hypoxia. He also experienced three episodes of ventricular fibrillation, developed acute renal failure and had rising liver function tests. A biopsy was taken from the right ventricle and microscopic examination revealed fragments of myocardium infiltrated by atypical lymphocytes showing apoptosis and destruction in between myocytes, which appeared vacuolated and degenerate. Immunohistochemistry showed the cells to be positive to CD20 and CD45 with some reactive to CD3. Keratin and CD56 showed the cell to be negative, indicating it is not a small-cell carcinoma. These findings seemed consistent with a diffuse large B-cell lymphoma.

**discussion**

Cardiac involvement can occur in up to 20% of patients with diffuse nodal lymphoma [5, 6] but lymphomas first presenting in the heart are extremely rare and most are single-case reports emphasising the wide spectrum of presentation depending on the location and type and patient’s background history. With increasing use of imaging including transthoracic and transeosophageal echocardiography, CT and MRI, earlier diagnosis of these tumours now occurs with improvement in prognosis [1]. Lymphoma should always be among the differential diagnoses suspected when patients present with a cardiac mass or an unexplained refractory pericardial effusion. One should be suspicious of lymphoma when more than one chamber is involved as >75% of cases have involvement of more than one chamber [7], which was shown in our series also where five of the six cases involved at least two chambers. However, none of our patients had right atrium involvement, which was surprising considering the right atrium is the most commonly affected heart chamber [2].

The first case emphasised the difficulty of diagnosis when lymphomas are angiocentric. This case was originally reported as an inflammatory pseudotumour on imaging [8] with follow-up only revealing the true nature of the cardiac lesions. This is the first such case presenting in the heart. Other angiocentric T-cell lymphomas have presented in other sites as pseudotumour such as the orbit [9]. There is a case report showing widespread involvement in the brain, lungs and heart with initial presentation as seizures and myocardial infarction [10]. These are often aggressive tumours with a poor prognosis as our case illustrates.

In our second case where the lymphoma was involving the homograft, there was no indication of immunosuppression being involved in the process, and EBV was not present. It was presumed the leaking valve was due to endocarditis. Patients with homograft valves do not receive immunosuppressive therapy and no previous case of lymphoma involving a cardiac homograft has been reported. This case illustrates the importance of histology in all valve resections. It also illustrates complications of treatment in this case, which showed a complete tumour response (complete tumour disappearance on imaging analysis or by histological examination, lasting for at least 3 months) to chemotherapy but which led to necrosis with perforation.

Only case 3 had immunosuppression with B-cell lymphoproliferative disease, again as diffuse involvement of the myocardium. In immunosuppressed patients with AIDS and after transplant, there is a well-known increased incidence of lymphomas, both non-Hodgkin and Hodgkin types [11]. The tumours have a strong viral association, with viruses such as human immunodeficiency virus, EBV and human herpesvirus 8 [12], but we were not able to confirm this due to lack of tissue.

Case 4 illustrates presentation with pericardial effusion with widespread involvement of the heart, which is common with lymphomas [13], and also illustrates the risk of cardiac arrest with drainage [14]. This is also the first reported paediatric case of primary cardiac T-cell lymphoblastic lymphoma.

There have been case reports of primary cardiac lymphoma mimicking atrial myxoma and presenting as an atrial mass [15]. However, primary presentation of cardiac lymphoma occurring within an atrial myxoma (case 5) has not previously been described.

**conclusions**

All six cases illustrate the wide spectrum of clinical presentation of lymphomas presenting primarily in the heart and emphasise that histology of all mass lesions is essential. Other series are small like ours highlighting the rarity of these tumours in the heart [2, 3] with the emphasis on imaging, early diagnosis and treatment. All these tumours were B-cell lymphomas or anaplastic with no T-cell lymphomas reported. Histologically, nearly all cases of primary cardiac lymphomas reported thus far have been of B-cell origin. In contrast, our study included both B- and T-cell lymphomas. T-cell lymphomas have been reported as single-case reports in the heart but are extremely rare as a primary presentation [16–18]. Presentation with cardiac involvement is more frequent in lymphomas originating elsewhere [6] with T-cell lymphomas invading the heart more frequently and aggressively. Thus, our two cases are unusual in presenting first in the heart.

**funding**

Cardiac Risk in the Young.

**references**

9. Kato K, Matsuuchi T, Ishimaru T et al. [Rapidly progressive T-cell angiocentric lymphoma with CD56+ phenotype involving bilateral orbits and


