Virchows Archiv (2020) 477:603–607
https://doi.org/10.1007/s00428-020-02819-3

BRIEF REPORT

Occult primary cardiac lymphomas causing unexpected/sudden death or acute heart failure

Andrea De Martino[1] · Federico Del Re[1] · Carlo Barzaghi[1] · Uberto Bortolotti[1] · Luigi Papi[2] · Angela Pucci[3]

Received: 8 December 2019 / Revised: 4 April 2020 / Accepted: 16 April 2020 / Published online: 5 May 2020

Abstract

Three cases of unexpected/sudden death ($N = 2$) or acute heart failure ($N = 1$) were investigated in our centre. The first patient died unexpectedly after surgery for cardiac tamponade and constrictive pericarditis; at autopsy, gross features mimicked a pericardial mesothelioma. The second patient died suddenly after recovering from a respiratory insufficiency episode; autopsy revealed an epicardial mass encircling the right coronary artery. The third patient presenting symptoms mimicked a fulminant myocarditis and she underwent endomyocardial biopsy. In all cases, histology disclosed a diffuse large B cell non-Hodgkin lymphoma, localized to the pericardium together with the right ventricle and the conduction system, to the epicardium and the right coronary artery or to the myocardium, respectively. Histology was crucial for the diagnosis, the atypical presentation favouring other diagnostic hypotheses. Although primary cardiac lymphoma is uncommon and usually shows a sub-acute onset, it may also cause unexpected/sudden death or acute heart failure.

Keywords Cardiac lymphoma · Sudden death · Endomyocardial biopsy · Histology

Introduction

Primary cardiac lymphomas (PCL) are rare, accounting for 1–2% of the surgically resected heart tumors, their incidence ranging between 0.15 and 1% at post-mortem examination [1, 2]. The clinical symptoms are nonspecific and mainly related to the tumor location whereas the prognosis largely depends upon early diagnosis and treatment [2, 3]. Although the modern imaging techniques together with the endomyocardial biopsy and the cardiac surgery evolution have dramatically increased in vivo diagnosis of cardiac masses, cardiac tumors may still cause acute heart failure or even sudden death [2–6]. We herein describe three cases of PCL in immunocompetent patients, presenting with unexpected/sudden death or acute heart failure, the signs and symptoms mimicking other disorders. Histology was crucial for the diagnosis, the clinical presentation favouring other diagnostic hypotheses.

Case report

Case # 1 A 71-year-old man was referred to our Cardiac Surgery Department because of cardiac tamponade with atrial fibrillation. A pericardiocentesis, yielding 1200 cc of hematic fluid, resulted only in a temporary improvement and the patient underwent partial pericardiectomy that showed a severely and diffusely thickened pericardium (Fig. 1a). The hemodynamic conditions initially improved, but few hours later, the patient clinical conditions suddenly worsened; he developed irreversible heart failure, unresponsive to massive inotropic support and died shortly after. At a complete autopsy (including central nervous system examination), the pericardium showed a diffuse plaque-like thickening, highly suggestive of a pericardial mesothelioma and apparently infiltrating the right ventricle free wall (Fig. 1j). The heart (weight 380 g) was extensively sampled after gross examination of the cardiac chambers, valves and coronary arteries, by short axis cuts. Coronary arteries were transversely cut a 3–4 mm intervals and paraffin embedded in several blocks. The conduction

This article is part of the Topical Collection on Quality in Pathology

✉ Angela Pucci
angelapucci@libero.it

[1] Department of Cardiac Surgery, Pisa University Hospital, Pisa, Italy

[2] Department of Forensic Science, University of Pisa, Pisa, Italy

[3] Department of Histopathology, Pisa University Hospital, Pisa, Italy

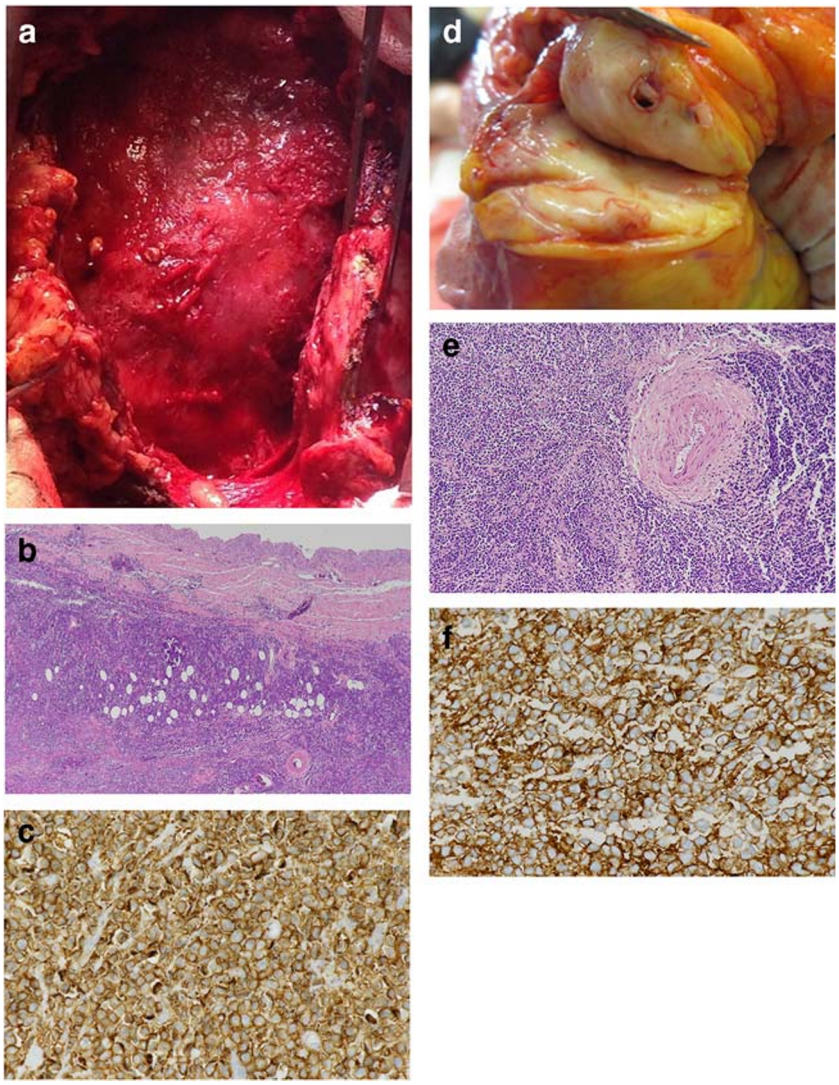

Fig. 1 First case: **a** gross features at surgery showing the diffuse thickening of the pericardium, mimicking mesothelioma; **b** histology shows a diffuse proliferation of large B cell lymphocytes that are (C) CD20 positive. Second case: **d** Gross appearance of the mass encircling the right coronary artery; **e** histology shows a diffuse infiltration by large B cell lymphocytes, encircling the right coronary artery and f CD20 positive. Third case: **g** four endomyocardial biopsy fragments at low magnification, two of them (at the right end side) with an infiltrate that at higher magnification, **h** shows a lymphoid morphology and is **i** CD20 immunoreactive. *Additional features from the 1st case*: **j** gross features after formalin fixation showing right ventricle infiltration by the mass, low (**k**; arrow, the atrio-ventricular node; ★, the right bundle branch) and higher (**l**) magnification pictures showing infiltration of the conduction system by the lymphoma (**b** hematoxylin and eosin, original magnification 4×; **c**, **f**, **i** immunoperoxidase technique with hematoxylin counterstaining, **c**, **f** original magnification 40×, **i** original magnification 20×; **e**, **l** hematoxylin and eosin, original magnification 20×; **g**, **k** hematoxylin and eosin, original magnification 2×; **h** hematoxylin and eosin, original magnification: 10×)

system, including the sinus atrial node region and the atrioventricular system, was investigated according to a standardized protocol; serial sections were stained by hematoxylin-eosin and examined [7]. On the myocardial specimens, Masson's trichrome, elastic van Gieson, Perls' and Congo Red histochemical stainings were also performed to assess fibrosis and to exclude infiltrative diseases such as hemochromatosis or amyloidosis. Histology of the mass showed a large and diffuse cell lymphoid proliferation infiltrating the pericardium, the adjacent right ventricle myocardium, the atrioventricular node region and the right bundle branch of the conduction system, (Fig. 1b, k, l). Immunophenotyping of the infiltrates showed a B cell proliferation with features (CD20+, CD79a+, Bcl2+, Bcl6+, CD3−, CD5−, CD10−; c-Myc positivity in 10% neoplastic cells; an MIB1 labeling index value of 90%) consistent with a diffuse large B cell non-Hodgkin lymphoma (Fig. 1c). Additional cardiac findings consisted of few mild to moderate atherosclerotic (class II–III) lesions in the right and left coronary arteries with no critical stenosis or ulceration, focal interstitial fibrosis in the

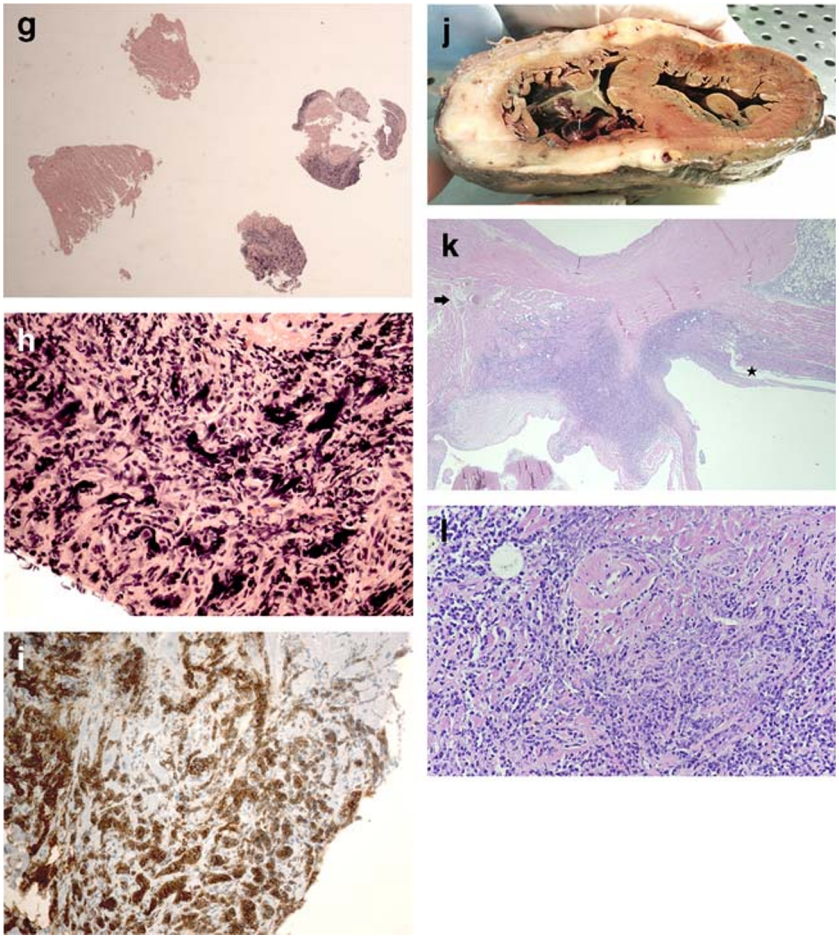

Fig. 1 continued.

free left ventricle myocardium [8]. No lymphadenopathy and no other significant lesion were shown in any other organ or tissue.

Case # 2 A 77-year-old woman with a history of severe chronic obstructive pulmonary disease (COPD) and systemic arterial hypertension died suddenly during transfer on ambulance from a general hospital to a rehabilitation centre. She had been previously hospitalized and successfully treated for a respiratory failure episode with stabilization of the respiratory function. The cardiac arrest was unresponsive to prompt resuscitation maneuvers and immediately preceded by ventricular tachycardia with oxygen desaturation. During the hospital stay, ECG did not show any significant alteration and a thoracic CT scan did not reveal any pericardial or pleural effusion, nor mediastinal lymphadenopathy. A complete autopsy (including central nervous system examination) showed an epicardial mass measuring 8 × 3 cm, encircling and compressing the proximal third of the right coronary artery from its origin (Fig. 1d). The heart (weight 290 g) was grossly examined and then sampled, together with the epicardial mass, the coronary arteries and the conduction system, as described in case #1. Histology and immunohistochemistry of the mass disclosed a diffuse large B cell lymphoma (immunophenotype: CD20+, CD79a+, Bcl2+, Bcl6−, CD3−, CD5−, CD10−; MIB1 labeling index value of 90%) (Fig. 1e, f). The lymphoma did not involve the conduction tissue or any other cardiac structure, organ, or tissue. Additional cardiac findings consisted of mild dilatation of the right cardiac chambers, focal interstitial fibrosis with mild compensatory myocyte hypertrophy in both ventricles; the epicardial coronary arteries showed mild fibrous intimal thickening or thin fibroatheromas (class I–III atherosclerotic lesions) with no critical stenosis [8]. In the lungs, features consisting with COPD were found, i.e., areas of emphysema, alveolar wall thickening and bronchiectasis. No lymphadenopathy and no other significant lesion were shown in any other organ or tissue.

Case #3 A previously healthy 55-year-old woman was admitted to our Emergency Department with recent and rapidly worsening tachycardia and dyspnea, unresponsive to medical treatment. ECG showed sinus rhythm and minor ST-T nonspecific alterations. Laboratory tests revealed a slight increase

of HS troponin (194 ng/L) and CRP (5.2 mg/dL) whereas an angio-CT excluded pulmonary embolism. A 2D echocardiography evidenced normal sized ventricles with diffuse kinetic alterations. A fulminant myocarditis was suspected, and the patient underwent a right endomyocardial biopsy. Four endomyocardial biopsy samples were obtained by the percutaneous procedure, formalin-fixed and paraffin-embedded. Serial sections were obtained and stained with hematoxylin-eosin, Masson's trichrome, Elastic van Gieson, Congo Red and Perls' stainings, together with immunoperoxidase stainings for lymphocytic (CD3 and CD20) and monocytic antigens (KP1 clone) according to a previously established protocol [4]. But histology showed a diffuse large cell lymphoid infiltrate in two out of four biopsy samples, in the endocardium and the adjacent myocardium. No other significant finding was detected by histology. Based on histology and immunohistochemistry (immunophenotype: CD20+, CD79+, Bcl2+, Bcl6+, CD3−, CD5−, CD10−; c-Myc positivity in 12% neoplastic cells; MIB1 labeling index value of 90%) results, a diffuse large B cell non-Hodgkin lymphoma was diagnosed (Fig. 1g–i). No lymphadenopathy or other organ involvement was evidenced by further investigations. The patient was then addressed to standard chemotherapy (R-CHOP regimen, i.e. cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab) and she is recovering well at 12 months, without evidence of residual or recurrent disease.

Discussion

PCLs are uncommon and usually show a sub-acute onset [1–3, 9]. So far, sudden/unexpected death or acute heart failure presentation are quite rare and very few cases have been recently reported [5, 10, 11]. In case #1, unexpected death occurred after pericardiectomy that was initially followed by a temporary recovery; the diffuse infiltration of either the pericardium and the ventricular wall (causing diastolic dysfunction) together with the involvement of the conduction constituted the anatomical substrate of the rapid worsening after surgery leading to the unexpected death. As to case #2, it could be hypothesized that the right coronary artery involvement played a major role in causing the fatal arrhythmia and the sudden death of the patient, in absence of conduction system involvement.

In the immunocompetent patients with PCL, the most common symptoms are represented by chest pain, dyspnea, pericardial effusion and arrhythmias [2, 12–14]. In these three immunocompetent patients, PCL, causing sudden/unexpected death or acute heart failure, showed an atypical presentation mimicking other disorders. Histology was then crucial for the definite diagnosis and allowed a prompt treatment in the patient undergoing endomyocardial biopsy.

Histology is considered the gold standard for the differential diagnosis of cardiac masses; apart from rhabdomyoma of the infants and foetuses, it is required for either adequate treatment or prognosis of cardiac tumours [1, 4–6]. Diffuse large B cell lymphoma represents the most frequent PCL and often involves the right heart as it was in all three cases of the present report [1–3, 12]. The pericardial infiltration has been previously reported in PCL whereas the involvement of the proximal right coronary artery that we observed in the case #2 is uncommon [2, 9]. In the case #1 showing a diffuse pericardial infiltration that grossly mimicked a pericardial mesothelioma, the pericardial involvement was very likely preceding the ventricle invasion.

The mean reported survival of PCLs is 23 months, but prognosis has been improving in the last decade because of earlier diagnoses, prompt and appropriate treatments as it was in our third case [12–14]. Late diagnosis that negatively influences the prognosis was obviously the circumstance of our first two cases with *post-mortem* diagnosis, whereas the patient with in vivo diagnosis by endomyocardial biopsy showed a PCL limited to the heart (stage I) that could benefit the treatment.

In conclusion, an atypical presentation favouring other diagnostic hypotheses characterized these three cases, PCL causing unexpected/sudden death or acute heart failure in three immunocompetent patients; histology was crucial for the diagnosis on endomyocardial biopsy or at *post-mortem* investigations. The early and prompt diagnosis of lymphoma by endomyocardial biopsy influenced positively the outcome of the PCL mimicking fulminant myocarditis.

Authors' contributions Andrea De Martino: collection of data, preparation of the manuscript, surgical procedures. Federico Del Re: collection of data, surgical procedures. Carlo Barzaghi: surgical procedures, data collection. Uberto Bortolotti: revision and analysis of data. Luigi Papi: autopsy procedure analyses. Angela Pucci: histology and immunohistochemistry analyses on endomyocardial biopsy, surgical and autopsy samples, writing and revision of the manuscript

Compliance with ethical standards

Informed consent The study was conducted according to our Institutional Review Board and in adherence to the Declaration of Helsinki. A written informed consent was obtained from all patients or their closest relatives.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Burke AP, Veinot JP, Loire R, Virmani R, Tazelaar H, Kamiya H, Araoz PA, Watanabe G (2015) Tumours of the heart. In: Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG (eds) WHO classification of tumours of the lung, pleura, thymus and heart, 4th

edn. Lyon, France, International Agency for Research on Cancer, pp 249–288
2. Carras S, Berger F, Chalabreysse L, Callet-Bauchut E, Cordier JF, Salles G, Girard N (2017) Primary cardiac lymphoma: diagnosis, treatment and outcome in a modern series. Hematol Oncol 35:510–519
3. Bruce CJ (2011) Cardiac tumours: diagnosis and management. Heart 97:151–160
4. Leone O, Veinot JP, Angelini A, Baandrup UT, Basso C, Berry G, Bruneval P, Burke M, Butany J, Calabrese F, d'Amati G, Edwards WD, Fallon JT, Fishbein MC, Gallagher PJ, Halushka MK, McManus B, Pucci A, Rodriguez ER, Saffitz JE, Sheppard MN, Steenbergen C, Stone JR, Tan C, Thiene G, van der Wal AC, Winters GL (2012) 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. Cardiovasc Pathol 21:245–274
5. Olds K, Heath K, Miliauskas J, Byard RW (2018) Occult cardiac lymphoma and sudden death. Forensic Sci Med Pathol 14:551–554
6. Pucci A, Botta G, Sina N, Tibaldi M, Valori A, Grosso E, Zonta A, Giudici M, Agnoletti G, Bergamasco L, Abbruzzese PA, Bartoloni G (2013) Life-threatening tumors of the heart in fetal and postnatal age. J Pediatr 162:964–969
7. Yanagawa N, Nakajima Y (2009) A simple dissection method for the conduction system of the human heart. Anat Sci Ed 2:78–80
8. Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W Jr, Rosenfeld ME, Schaffer A, Schwartz CJ, Wagner WD, Wissler RW (1994) A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. Arterioscler Thromb 14:840–856
9. Miguel CE, Bestetti RB (2011) Primary cardiac lymphoma. Int J Cardiol 149:358–363
10. Tikka J, Vaittinen S, Pakanen L, Lunetta P (2018) Sudden unexpected death from unusually large primary cardiac B-cell lymphoma. Am J Forensic Med Pathol 39:161–163
11. Cheng JF, Lee SH, Hsu RB, Yu SC, Shun CT, Huang PS, Chen YH, Lee CM (2018) Fulminant primary cardiac lymphoma with sudden death: a case report and brief review. J Formos Med Assoc 117:939–943
12. Pérez Baztarrica G, Nieva N, Gariglio L, Salvaggio F, Porcile R (2010) Primary cardiac lymphoma: a rare case of pulmonary tumor embolism. Circulation 121:2249–2250
13. Lee GY, Kim WS, Ko YH, Choi JO, Jeon ES (2013) Primary cardiac lymphoma mimicking infiltrative cardiomyopathy. Eur J Heart Fail 15:589–591
14. Oliveira GH, Al-Kindi SG, Hoimes C, Park SJ (2015) Characteristics and survival of malignant cardiac tumors: a 40-year analysis of >500 patients. Circulation 132:2395–2402