Review

Primary cardiac sarcoma

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Summary

Primary malignant lesions of the heart are rare. Although myxomas have been extensively described, there is a paucity of large studies on non-myxomatous cardiac tumours. On the other hand, there are several case reports on specific histopathological variants, in small numbers. Consequently there exists no consensus on therapeutic modalities for cardiac sarcomas. The prognosis for these lesions remains dismal, despite the enhanced diagnostic ability of newer technology. The reasons for the dismal prognosis are (1) the advanced tumour stage at presentation, (2) non-specific symptomatology, (3) insufficient awareness of these lesions, due to their rarity, (4) delayed diagnosis and/or misdiagnosis, which leads to (5) advanced tumour stage at presentation. Thus a vicious cycle is created. This article addresses these issues, deals with the surgically relevant modes of presentation, rather than the histopathology, and reviews the diagnosis and management options for the various sarcomas, categorized by the site and extent of cardiac involvement. Clinicians should be familiar with the presentation of these tumours and have a high index of suspicion, since the potential for long-term survival following resection does exist. Wide surgical resection remains the cornerstone of sarcoma therapy. Complete characterization of tumour extent using echocardiography and CT/MRI is mandatory to achieve this goal. Radical resections such as ‘bench surgery’ and transplantation may reduce local recurrence, but the risk of metastatic disease remains. The clinical experience with such approaches is limited. The role of adjuvant therapy is not yet established. In no other field of cardiac surgery would a multidisciplinary approach be more useful, in achieving cure or long-term palliation.

Keywords: Cardiac sarcomas; Lymphoma; Autotransplantation; Transplantation

1. Introduction

Primary cardiac tumours are rare with an incidence between 0.0017% and 0.019% [1,2]. Twenty-five percent of cardiac tumours are malignant [3]. Surgeons rarely encounter cardiac sarcomas. This is a review on cardiac malignancy and excludes myxomas which are extensively described. Most studies on cardiac sarcomas have limited numbers, deal with specific histopathological variants and provide little information on clinical outcomes [4—10]. This disease oriented approach bears little relation to a surgically relevant clinical presentation, and is akin to approaching the problem in reverse.

Cardiac sarcomas are often asymptomatic until advanced, and even then produce non-specific symptoms and mimic other pathology. The dismal prognosis results from extensive local invasion and/or distant metastases at presentation. Early recognition and characterization of their pathoanatomy is crucial. This article co-relates the modes of presentation with the site and extent of cardiac involvement and the subsequent management.

2. Manifestations

Cardiac sarcomas manifest by one of four mechanisms [11]:

(1) Obstruction to blood flow and interference with valve function.

(2) Local invasion causing arrhythmias [12,13] or pericardial effusion with tamponade. Twenty-nine percent of patients have pericardial effusions at presentation.

(3) Embolic phenomena—cerebral, coronary, and retinal emboli from tumour fragments or peri-tumoral thrombus.

(4) Symptoms like dyspnoea [14], syncope, chest pain, fever, malaise, and weight loss.

Right-sided tumours may be the source of pulmonary emboli. The absence of risk factors or evidence for thrombosis arouses suspicion of non-thrombotic pulmonary embolism [15].

Pulmonary hypertension can result from extensive tumour embolism, or pulmonary venous obstruction. Pulmonary artery (PA) or right ventricular outflow tract (RVOT) lesions cause right heart enlargement and failure. Complete valve obstruction can cause cardiac arrest.
3. Types of sarcoma

The characteristic features of the common tumours are listed in Tables 1 and 2. Other histopathological variants include malignant fibrous histiocyta, malignant mesenchymoma [16], myxosarcoma, chondrosarcoma and carcinosarcoma.

3.1. Lymphoma

Primary cardiac lymphoma (PCL) is defined as a non-Hodgkin's lymphoma (NHL) involving only the heart/pericardium or as a NHL with the bulk of the tumour located in the heart [17]. PCL is rare in immunocompetent patients [18].
The commonest presentation is refractory cardiac failure. Manifestations include dyspnoea [19,20], arrhythmias [21], superior vena cava (SVC) obstruction, pericardial effusions [19], tamponade [20], and chest pain.

Lymphomas commonly arise in the right atrium [19], and ventricle [19]. CT reveals pericardial effusion [19] and thickening, polyloid masses or ill-defined infiltrative lesions [22]. On MRI, lymphomas have a similar or lower intensity than that of cardiac muscle. Contrast MRI reveals heterogenous enhancement due to central necrosis.

Cytology of pericardial effusion is diagnostic in 67% of the cases. While thoracotomy is diagnostic in all cases, less invasive procedures have high false-negative rates.

The pathology can be established by transvenous [23—25] or transthoracic biopsy with ultrasound guidance [26], especially with right heart tumours. Echo guided transvenous tumour biopsy can be complicated by tumour embolism. With US-guided transthoracic needle biopsy, the rate of misdiagnosis is lower, but this technique is restricted to right ventricular free wall lesions. Complications described are cardiac perforation, tamponade, and coronary artery injury [26].

SVC syndrome due to PCL is caused by SVC obstruction [23]. SVC obstruction has been treated with expandable metallic stents [23], and surgery. The involved venous structures are resected, followed by reconstruction with expanded polytetrafluoroethylene grafts [23]. This is perhaps the only cardiac malignancy where gross resection has no role. Early anthracycline-containing chemotherapy and radiotherapy appears to improve survival [19].

Most PCL’s are aggressive B-cell lymphomas [19,20]. Immunohistochemistry is positive for common leukocyte and L26 antigens which are specific for B cell lymphoma.

4. Differentiation from benign tumours

Imaging features suggestive of malignancy include a broad base of attachment, absence of a pedicle, combined intramural and intracavity location, an aggressive growth pattern such as extension into the pulmonary veins or the atrial septum, or epicardial infiltration. In contrast to benign tumours, sarcomas tend to involve multiple chambers and destroy valves by direct extension.

4.1. Myxoma imitators

Literature analysis reveals several instances where cardiac sarcomas were diagnosed as myxoma [27,28], mitral stenosis [29,30], or endocarditis.

4.2. Echo

Transthoracic echocardiography is the screening modality of choice. Transesophageal echocardiography shows tumour size, location, mobility, and attachment, and better depicts the posterior left atrium, atrial septum, the right heart and the descending aorta. The diagnostic sensitivities of transthoracic and transesophageal echocardiography are 93.3% and 96%, respectively [31]. However, cases have been described where cardiac sarcomas have eluded diagnosis by echocardiography and were eventually demonstrated by CT or by open tumour biopsy [32,33] TOE guides transvenous tumour biopsies especially with right atrial masses [34], thereby avoiding invasive diagnostic procedures [35].

4.3. 3D echo

3D echo is useful in planning surgical access, provides simulation of various intra-operative views, and provides exact spatial information about the shape and surface of intracardiac masses [36].

4.4. Angiography

Selective coronary arteriography demonstrates tumour blood supply and distortion of coronary anatomy [37]. However, CT and echocardiography in combination make angiography unnecessary. Cardiac catheterization is associated with the risk tumour embolism [38].

4.5. CT and MRI

Magnetic resonance imaging (MRI) and computerized tomography (CT) are complementary to TOE in aiding the diagnosis of cardiac malignancy. They reveal infiltrative growth and extracardiac extent of sarcomas, criteria that help distinguish benign from malignant lesions and assess resectability [39].

CT shows myocardial infiltration, compression of cardiac chambers [40], pericardial [41], and great vessel involvement [42,43], and depicts calcification and fat [44]. MRI allows better soft-tissue characterization than CT, is the modality of choice for evaluating myocardial and pericardial involvement [45], and provides functional information such as flow direction and velocity in large vessels [46]. MRI has diverse capabilities including multiplanar imaging, and can also assess tumour volume [47], tumour burden and response to surgery, radiation, and chemotherapy [48]. The differences in signal intensity between the heart and the adjacent structures permit MRI to define mediastinal invasion [49]. Central necrosis in sarcomas is demonstrated on contrast MRI’s with gadopentetate dimeglumine [49]. Tissue perfusion imaging with MRI or ultrafast CT can distinguish neoplasm from thrombus and evaluate tumour extent [50].

4.6. Surgical approach

Median sternotomy and cardiopulmonary bypass (CPB) using bicaval cannulation, moderate hypothermia, and cardiopulmonary arrest are routinely used. Standard approaches to the cardiac chambers involved are employed. Surgical resection ranges from open biopsy, to palliative debulking to complete gross resection. The ideal resection encompasses the tumour and a portion of the normal cardiac tissue.

4.7. Pathology

The precise classification of sarcomas may be difficult. Immunohistochemical staining is useful in distinguishing malignant from benign lesions and detailed characterization of sarcomas.
5. Great vessel sarcomas

5.1. Caval sarcomas

Vascular leiymosarcomas arise as proliferations of smooth muscle cells within the media [51]. The commonest site is the inferior vena cava (IVC). They also occur in the SVC andazygous veins. IVC sarcomas occur in women (mean age, 49 years), with symptoms of pain, venous thrombosis, and IVC syndrome. Metastatic sites include the lungs, kidneys,pleura, chest wall, liver, and bones [52].

Radiographic findings range from an intraluminal lesion with IVC obstruction to an extraluminal mass extending from the media into the surrounding tissue. Extraluminal growths appear as lobulated, encapsulated heterogeneous tumours on contrast CT. They show intermediate to high signal intensity on T1 and T2-weighted MRI. With intraluminal growths, both CT and MRI demonstrate IVC dilatation, and can differentiate tumour extent from thrombus. Surgical resection with wide margins offers the only chance of cure. Most IVC sarcomas react with antibodies to actin, desmin, and vimentin [52].

In a small series of 14 patients, age, gender, tumour size, grade, and lymph node status did not impact survival [53]. The 5-year cumulative survival was 53% [53]. Survival was worse in those with positive surgical margins. Radiation diminished local recurrence, while chemoradiation improved survival in this series, although they have been variably effective in other series [54].

5.2. PA sarcoma (PAS)

Primary malignancy of the pulmonary arteries (PA) is rare. In several instances, the diagnosis has been made by default, following exclusion of other diagnoses and treatment for other conditions. PAS arises from the multipotential mesenchymal cells of the intima [55]. They are either undifferentiated (34%) or leiomyosarcomas (20%) [56]. PAS can be intimal, intraluminal, or adventitial. Positive staining for factor V11-related antigen suggests primary endothelial origin.

The mean age at presentation is 52 years. PAS occur in the pulmonary trunk, the branch pulmonary arteries (PA), the pulmonary valve or the RVOT [57]. They spread intraluminally along the direction of blood flow [58]. Transmural extension into the adjacent lung, bronchi or lymph nodes occurs in 50% of cases [48]. Systemic metastases occur in 20% of cases and include the kidneys, brain, and lymph nodes. Sixty percent have lung metastases. Most patients die of right heart failure secondary to outflow obstruction, or distal thromboembolism.

Due to their tendency to mimic common conditions and the relative non-specific symptoms (dyspnea, chest pain, cough, syncope, hemoptysis, right ventricular failure), PAS are frequently misdiagnosed, particularly as pulmonary thromboembolism. Hemoptysis and pleuritic pain are due to pulmonary infarction. Sudden death due to obstructing PAS has been reported [59]. Other differential diagnoses include pulmonary stenosis, Takayasu and giant cell arteritis, fibrosing mediastinitis, and lung cancer, but these invade the pulmonary vessels from outside. The definite diagnosis is often delayed by 12–17 months, leading to a high proportion of advanced lesions.

Echocardiograms reveal pulmonary hypertension and right ventricular overload [60]. Chest X-rays may be normal, or may reveal a pulmonary nodule, hilar mass, PA enlargement, decreased vascularity, or parenchymal infiltrates. A hilar mass causing unilateral PA enlargement should suggest a PAS.

Angiography shows PA occlusion and suggests pulmonary embolism [60,61]. A pedunculated mobile lesion suggests PAS rather than thromboembolism, although distinction is difficult with sessile tumours, covered with thrombus. Increased tumour uptake on FDG-PET (fluorine-18-2-fluoro-2-deoxy-D-glucose) is consistent with neoplasm.

Contrast CT outlines a filling defect in the PA, which may be indistinguishable from pulmonary thrombus. Thromboembolism appears as an abrupt vascular cut-off instead of the continuous soft tissue filling of the PA with sarcomas. PAS have heterogenous contrast enhancement due to necrosis and haemorrhage. A unilateral mass continuously filling the PA, vascular distension, and extravascular invasion suggest PAS, especially in the absence of coagulation disorders.

Normal coagulation tests, venograms or Doppler ultrasound investigations can exclude venous thrombosis. Lung scans show multiple perfusion defects indistinguishable from thromboembolism. Unlike thromboembolism, nuclear scan abnormalities of PAS tend to remain unchanged on serial examinations. On T1 and T2-weighted MRI, PAS appear as intraluminal masses of intermediate to high signal intensity. Contrast MRI helps differentiate tumour from thrombus [62]. Diagnosis can be made by aspiration biopsies during pulmonary angiography.

There are several reports of PAS that were initially diagnosed as thromboembolism and treated with anticoagulants [63] or IVC filters [65]. Such patients have subsequently developed respiratory failure and been referred for emergency ‘pulmonary embolectomy’.

The management is primarily surgical. Historically, the surgical approach was pneumonectomy through a thoracotomy or sternotomy. Redmond et al. [65] described pneumonectomy with suction extraction of the tumour fragments from the proximal PA. Although combined pneumonectomy for tumour propagation beyond the first hilar branch or for recognized distal tumour emboli has been described, the higher operative risk should mandate careful consideration in such cases. Pneumonectomy may be followed by recurrence in the other lung due to the proximal tumour location.

As these tumours are predominantly intimal, resection via sternotomy and CBP is being used increasingly. For early intimal lesions endarterectomy may result in complete tumour removal, and is perhaps a simpler approach, because microscopic distal embolisation is common. The obstructive tumour plus associated thrombus is stripped from the luminal wall through a vertical arteriotomy. However, these resections have been incomplete, can be complicated by post-perfusion endobronchial haemorrhage, and recurrence has been uniform. Frozen section analysis to determine vessel wall involvement is useful.

The principles of surgery for PAS include minimal tumour manipulation, PA dissection on CPB, and early transection of the distal PA to minimize distal embolization [66]. For advanced lesions, total excision of the pulmonary trunk and
reconstruction is recommended. RVOT reconstruction with homografts has been described [67,68]. In the absence of distal disease, resection of isolated pulmonary metastases after obtaining local control may provide a survival benefit.

Heart–lung transplantation is potentially curative in patients with disease confined to the PA, but the numbers have been small. RVOT tumours can recur even after palliative debulking, and chemo-radiotherapy [69]. Balkin and Imoto [69] reported treatment of recurrent RVOT obstruction by stents, which however provide temporary palliation, due to tumour ingrowth, compression, or over-growth beyond the stent.

Incomplete resection, or advanced tumour stage are associated with poor prognosis.

Mean survival without therapy is about 1.5 months, but can be extended by as much as 3–5 years following complete resection [70,71]. As distal microembolisation is common adjuvant chemotherapy would seem appropriate. However, there is no good evidence that chemotherapy or radiotherapy have benefits [72], although improved survival has been reported with adjuvant therapy [73,74].

5.3. Aortic sarcoma

Aortic sarcomas present in the seventh decade (mean age, 62 years) and show no gender predilection. They exhibit extensive surface growth but tend to localize to the intima [75]. These lesions are categorized as intimal and mural. They present as embolic phenomena, including limb and mesenteric vessel occlusion. The diagnosis is sometimes established after embolectomy. The lungs are not affected as the metastases are arterial [76]. There are reports of tumour arising in association with Dacron grafts [77,78]. Nanjo et al. [79] reported a patient with aortic sarcoma who died of acute myocardial infarction caused by left main coronary obstruction.

MRI can distinguish tumour from thrombus. The sarcoma may extend through the aortic wall and metastases occur in the adrenal, kidney, liver, spleen, pancreas, pelvis and mesentery [76], and bone [80]. Histological subtypes include myofibroblastic, histiocytic, leiomyogenic and endothelial forms. Immunohistochemistry is positive for actin and vimentin, and sometimes FVIIIIRag. The mean survival rate for the 87 reported cases of aortic sarcomas was 14 months.

5.4. Left atrial (LA) and pulmonary vein (PV) sarcomas

Pulmonary vein sarcomas occur mostly in women (mean age, 56 years). They are attached to the pulmonary veins, where they may be intraluminal and/or intramural, with variable extension into the posterior LA, the mitral valve, the lung hilum and parenchyma. Pulmonary sarcomas can extend into the LA [81], complicating attempts at resection due to tumour embolism and incomplete resection [82]. Clinical manifestations include chest pain, dyspnoea, pulmonary hypertension, congestive failure and stroke. Most PV sarcomas are leiomyosarcomas, which react immunohistochemically to vimentin, desmin, and actin.

Large tumours make assessment of the precise site of origin difficult. Echocardiograms and CT/MRI are useful to delineate the sites and extent of involvement, which determine the surgical approach. With predominant pulmonary parenchymal, minimal pulmonary venous and no left atrial involvement, an appropriate lung resection through a thoracotomy is appropriate.

Pulmonary venous and LA involvement warrant a more radical resection, through a sternotomy, using CPB. Surgery involves en bloc resection of the tumour, the PV, LA free wall, and the septum (if involved) followed by LA reconstruction, usually with a pericardial patch [83]. No consensus exists regarding the best operative strategy [81].

Local recurrence and metastases have appeared despite the use of adjuvant therapy and radical resection. Marvasti et al. [84] reported a LA resection in a patient with osteogenic sarcoma, who subsequently required a pneumonectomy as a separate procedure.

5.5. Valve sarcomas

Atrioventricular valve involvement by primary or recurrent tumour, warrants valve replacement with resection of the subvalvular apparatus. The pathology of primary valve tumours is difficult to determine pre-operatively. Huang et al. [85] reported two malignant mitral tumours, which were misdiagnosed as benign lesions, and treated by a mitral valvuloplasty, instead of mitral replacement. Both patients died a year later—one of local recurrence and the other of cerebral metastasis. Frozen sections are useful in such situations.

6. Surgery for local recurrence

Multiple resections have been described for local recurrence, but the outlook is poor. Okita et al. [86] reported six resections for an LA sarcoma, following which the patient died. Putnam et al. [87] reported seven cases of repeat resection, but none survived beyond 30 months.

6.1. Autotransplantation

The overriding problem with resection for malignancy is extensive involvement precluding resection or anatomic location hindering access for complete resection and reconstruction, particularly in LA tumours. Incomplete resection results in recurrence. To achieve complete resection, Reardon et al. [88] used a technique of cardiac explantation, extracorporeal tumour resection with cardiac reconstruction, and autotransplantation. This approach permits an aggressive and complete resection. Although their patient died of metastatic disease, there was no evidence of local recurrence at autopsy. Others have reported this technique [89,90].

6.2. Transplantation

Cardiac transplantation is an option for inoperable sarcomas, but is not routinely considered due to concern about recurrence and the possibility that immunosuppression may stimulate further tumour growth or new neoplasia. The incidence of lymphoma ranges from 2.3% to 13% in cardiac allograft recipients, and 3.8% to 33% following combined
heart and lung transplants [91]. Patients should undergo a pre-operative metastatic evaluation, to rule out extracardiac disease.

Despite the absence of extracardiac disease at transplantation, many patients die of metastases. Gowdamarajan and Michler [91] in a review reported 21 patients who underwent transplantation for inoperable cardiac malignancy. Although overall mean survival was 12 months, there were 7 patients who survived a mean of 27 months without recurrence. Thirteen patients died of recurrent disease or metastases.

Survival up to 3 years has been reported using adjunctive chemotherapy and radiotherapy [91]. Uberfuhr et al. [92] in their experience with four patients indicated that transplantation followed by post-operative chemotherapy did not affect the long-term outcome. However, they indicated that pre-operative chemotherapy induces regression in chemosensitive lesions, facilitates curative resection and potentially eradicates early micrometastases. Transplantation in responders offers a chance of long-term survival.

Experience with transplantation for cardiac sarcomas is limited. In view of the difficulty in determining resectability pre-operatively, attempts at resection should be coordinated with donor availability. Should resection prove feasible, a second recipient should be available to avoid wasting a donor heart.

6.3. Heart and lung transplantation

Talbot et al. [93] investigated the role of combined heart and lung resection followed by en bloc heart and bilateral lung transplant, in four patients where the sarcoma extended beyond the cardiac borders of cardiectomy. All patients had neoadjuvant chemotherapy. All patients developed local recurrence (n = 1) or metastases (n = 3). Median survival after transplant was 31 months. Although heart lung transplant for sarcoma was technically feasible, the limited experience with this aggressive approach was disappointing.

6.4. Management of bleeding

Radical surgical resection for cardiac sarcomas can be complicated by severe bleeding. Conventional techniques of blood conservation include return of all residual CPB circuit blood, intra-operative salvage using cell savers and reinfusion of shed mediastinal blood. The use of these techniques is, however, controversial in patients with cardiac malignancy. The possibility of tumour dissemination would be a cause for concern. Drugs commonly used to decrease blood loss are aprotinin, epsilon-aminocaproic acid, and tranexamic acid. Nielson et al. [94] described an innovative technique to control haemorrhage after right atrial reconstruction with a pericardial patch in a patient with primary angiosarcoma. A Dacron patch was initially placed around the right atrium and ventricle to tamponade the bleeding. When this failed, a type of Cabrol fistula was formed with a tube graft from the Dacron patch to the left innominate vein. This acted as a conduit back into the venous system. Construction of funnel grafts to deliver shed blood into the venous system has been described in relation to other cardiac surgical procedures [95,96].

6.5. Adjuvant therapy

Given the likely inadequacy of surgical margins and the risk of metastases, adjuvant chemotherapy and radiotherapy have been recommended. Systemic therapy is indicated for those with advanced, recurrent or persistent tumours, or for resections with positive tumour margins. Several chemotherapeutic regimens like CYVADIC (cyclofosfomide, vincristine, Adriamycin, imidazole carboxamide) [97] have been used with variable results. In the absence of randomised clinical trials, the benefits of adjuvant therapy following ‘curative’ surgery are unknown. Complete surgical resection was the only factor that influenced survival [80,87]. In the French experience [98], postoperative doxorubicin based chemotherapy failed to modify prognosis.

The role of radiation in malignant cardiac tumours is less well defined. Radiation with chemotherapy is appropriate for PCL. In less sensitive lesions, the potential gain of radiotherapy must be weighed against the risk of myocardial damage. Most studies show a decrease in local recurrence rates, with minimal or no influence on survival.

7. Prognosis and results

Mean survival for most sarcomas is about 9–11 months [80,99]. Bakaee et al. [99] reported actuarial survivals at 1 and 3 years of 47% and 24%. Median survival ranges from 24 months after complete resection versus 10 months after incomplete or no resection. Putnam et al. [87] reported that survival doubled in patients after complete resection with adjuvant therapy. In hospital mortality ranges from 5% to 22% [99].

Predictors of long-term mortality include NYHA class III and IV. Factors determining survival, in the Armed Forces Institute of Pathology series [80], were left sided lesions, absence of necroses or metastases, and low mitotic count. In Burke’s series [80], age, sex, differentiation and histology had no effect on prognosis.

8. Conclusion

The prognosis with cardiac sarcomas is perceived to be dismal due to the advanced tumour stage at presentation. Non-specific symptoms and misdiagnosis partly contribute to the delayed presentation and diagnosis. Approaching these lesions with the probable diagnosis of a myxoma or thromboembolism is not ideal, and could compromise the extent and type of resection, which influence outcome. In this era, delayed diagnosis is unacceptable, given the current status and availability of imaging technology.

Clinicians should be familiar with the presentation of these tumours and have a high index of suspicion, since the potential for long-term survival following resection does exist. Wide surgical resection remains the cornerstone of sarcoma therapy. Complete characterization of tumour extent using echocardiography and CT/MRI is mandatory to achieve this goal. Radical resections such as ‘bench surgery’ and transplantation may reduce local recurrence, but the risk of metastatic disease remains. The clinical experience with
such approaches is limited. Counselling patients on the benefits of adjuvant therapy is complicated by the paucity of hard data. In no other field of cardiac surgery would a multidisciplinary approach be more useful, in achieving cure or long-term palliation.

References


