CHAPTER 4

Tumours of the Heart

Although tumours of the heart do not contribute significantly to the overall tumour burden, they may cause a variety of cardiac and systemic symptoms. Clinical features depend not only on the size, but, to a significant extent, on the anatomic location. Small, benign neoplasms may have devastating clinical consequences if in a critical location.

Progress in imaging and cardiac surgery have considerably improved the prognosis. However, cardiac sarcomas are still life-threatening diseases.

Due to the low frequency, there is no specific grading scheme for malignant heart tumours. This volume largely follows the principles of classification and grading detailed in the WHO Classification of Tumours of Soft Tissue and Bone.
WHO histological classification of tumours of the heart

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1 Morphology code of the International Classification of Diseases for Oncology (ICD-O) (6) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
Epidemiology
The estimated frequency of cardiac tumours ranges from 0.0017–0.33% (2165). In a review of 22 autopsy-based series of primary cardiac tumours a frequency of 0.021% was identified among 731,309 patients (1656). In one 20-year (1972-1991) review of 12,485 autopsy cases, there was a 0.056% incidence of primary tumours and a 1.23% incidence of secondary tumours (1116). However, these data may have a high referral bias and may not reflect population-based incidence rates (2079). At the Mayo Clinic, the autopsy incidence of primary cardiac tumours from 1915 to 1931 was 0.05%, but more than tripled to 0.17% between 1954 and 1970 (2165); again, referral bias may have played a role in this change.

When most cardiac tumours were diagnosed at autopsy, myxomas and sarcomas were reported at a similar frequency. With the utilization of cardiopulmonary bypass and surgical excision, the reported frequency of myxomas as opposed to cardiac sarcomas has increased substantially (249,1568). In a review of surgical series, cardiac myxomas constitute 77% of surgically excised tumours, and cardiac sarcomas, 10% (249).

In children, cardiac tumours are not common and most are benign (249). The most common pediatric tumours include rhabdomyomas, fibromas, myxomas, and teratomas (249,356). Secondary cardiac tumours, either metastatic or by direct invasion, outnumber primary cardiac neoplasms (1116). A review of 3,314 autopsies found a 2.9% frequency of metastatic tumours involving the heart (12). The most common primary sites are lung, breast, and cutaneous melanoma.

Clinical features
Cardiac neoplasms may cause a variety of signs and symptoms (1225,1791,2079). The clinical presentation depends on the size of the tumour and its anatomic location. Growth rate, friability, and invasiveness are also important factors that determine clinical features (737). Large tumours may be relatively silent, whereas small tumours in a critical location may give rise to devastating clinical consequences. Left atrial tumours, especially those that are mobile or pedunculated, may lead to systemic embolism involving the coronary, cerebral and peripheral circulations (737,1568,2077), resulting in myocardial infarction, stroke or ischemic viscera or limbs. Left atrial tumours may also interfere with mitral valve function resulting in mitral stenosis or regurgitation. Cardiac murmurs and a characteristic tumour “plop” may be auscultated. Valve dysfunction manifests as left-sided heart failure with shortness of breath, orthopnea, paroxysmal nocturnal dyspnoea, pulmonary edema, fatigue, cough, and chest pain (356).

Intramural left ventricular tumours may be asymptomatic or present with a mass effect. With protrusion into the cavity, hemodynamic compromise may result (1225). Local extension of the tumour may cause conduction or coronary artery compromise with chest pain, myocardial infarction, arrhythmia, heart block or sudden death (356,737,1225,1791). Right atrial or right ventricular tumours may result in right heart failure from atrioventricular or pulmonary outflow obstruction, resulting in peripheral edema, hepatomegaly, ascites, shortness of breath, syncope and sometimes, sudden death (737). If the tumours interfere with valve function they may result in regurgitation or stenosis (1791).

Right-sided cardiac tumours may emboize to the lungs and present as pulmonary emboli with chest pain, pulmonary infarction and haemoptysis (1634,1791). Chronic embolization may also mimic chronic thromboembolic disease with signs and symptoms of pulmonary hypertension.

Pericardial tumours may cause chest pain typical of pericarditis (1225,1568). The tumours may be haemorrhagic and cause pericardial effusion and tamponade (1634). However, constrictive pericarditis may also result from tumour infiltration.

Rarely, tumours such as myxoma, cause systemic symptoms, including anorexia, weight loss, fatigue and malaise which may mimic a variety of systemic disorders (356,737,1774,2077). Interestingly, they may also cause haematologic abnormalities, including anemia, polycythemia, leukocytosis, thrombocytosis and elevated sedimentation rate (1225). Tumour production of mediators, including interleukins, has been reported (1774).

Imaging
Primary tumours of the heart and pericardium may be detected as an abnormal finding on a chest radiogram or another imaging test obtained for an unrelated reason. Once detected cardiac imaging is needed to define (1) tumour location, extent and boundaries; (2) relationships with adjacent key cardiac structures such as valves and coronary arteries; (3) tumour type; and (4) presence and degree of functional impairment. The main non-invasive imaging modalities for evaluating primary cardiac tumours each have advantages and disadvantages. They are often used together in a complementary manner for diagnosis and surgical planning.

Echocardiography
The primary advantage of echocardiography is that it has the best spatial and temporal resolution and provides excellent anatomic and functional information (492,705,1070,1162,2104,2215). It is the optimal imaging modality for small masses (<1 cm) or masses arising from valves. A second major advantage of echocardiography is the ability to image velocities with Doppler, which allows for assessment of presence, degree, and location of obstructions to blood flow or valve regurgitation. Echocardiography is typically the modality used for the initial evaluation of cardiac tumours and may be the only diagnostic test required in some patients. Disadvantages include
suboptimal image quality in patients with poor acoustic windows, inability to image extent of disease outside of the mediastinum, and relatively low soft tissue contrast, which limits detection of tumour infiltration and characterization of tumour tissue. Also, intravenous contrast agents are not routinely used with echocardiography, which limits the ability to characterize tumour vascularity.

Magnetic Resonance Imaging (MRI)
The primary advantage of MRI is its excellent soft tissue contrast which makes it the most sensitive modality for detection of tumour infiltration. MRI has more manipulable imaging parameters than other imaging modalities. Because of this, MRI is the best modality for characterizing tumour tissue [1003,1768,1831,2156]. For example, a T2-weighted standard or fast spin echo sequence distinguishes tumours with high water content, such as haemangioma, from tumours with low water content, such as fibroma. A third advantage of MRI is the ability to characterize tumour vascularity with intravenous contrast. Though not as flexible as echocardiography, MRI does allow assessment of wall motion and assessment of velocities through large vessels. This allows for characterization of ventricular function, inflow or outflow obstruction and valve regurgitation. The primary disadvantage of MRI is long examination times, which translates into the need for sedation in children, and the need for reliable ECG gating. MRI should be considered when the tissue type, exact location, or the relationships of the tumour with neighbouring structures are not completely defined by echocardiography or when surgical resection of the tumour is considered.

Computed Tomography (CT)
ECG gated CT scans with the latest generation of multidetector scanners or with electron beam scanners are also very useful for cardiac imaging [65,275]. In many ways, the advantages and disadvantages of CT are intermediate between those of echocardiography and MRI. Modern CT scanners have excellent spatial resolution, which is better than that of MRI, but not as high echocardiography. CT has better soft tissue contrast than echocardiography, and can be used to definitively characterize fatty content and calcifications; however, the overall soft tissue contrast and ability to characterize tumour infiltration and tumour type is less than that of MRI. Intravenous contrast can provide information about tumour vascularity, an advantage CT shares with MRI. CT may be used as an adjunct to both echocardiography and MRI.

Cardiac Catheterization
This is seldom required for diagnosis of cardiac tumours, but may be performed in adults to exclude coronary artery disease. Angiography provides indirect and nonspecific imaging based on filling defects within the cardiac chambers and displacement of the coronary arteries [347,1840]. Two exceptions are worth noting. First, endomyocardial biopsy for tissue typing may be considered in selected patients. Second, selective coronary angiography is helpful when planning surgical resection of an intramycocardial tumour.

Tumour grading and staging
Given the low frequency of malignant cardiac tumours, there is no grading scheme specifically referring to malignant heart tumours. This volume uses the criteria published in the recent WHO Classification of Tumours of Soft Tissue and Bone [590]. The concept of grading sarcomas was first introduced in 1977 (1712). Several grading systems have since been proposed which have shown to correlate with prognosis [412,1247,1418,2031,2070]. The two most important parameters in non-cardiac soft tissue seem to be the mitotic index and extent of tumour necrosis [1793,2031,2070]. Most pathologists recognize three grades of malignancy: G1, low grade; G2, intermediate grade; and G3, high grade. Some use a 4-tiered system. The two most widely used systems are those of the NCI (U.S. National Cancer Institute) [412,413] and the FNCLCC (Fédération Nationale des Centres de Lutte contre le Cancer) [387-389,748,2031].

According to the methodology defined in 1984 [412] and refined in 1999 [413], the NCI system uses a combination of histologic type, cellularity, pleomorphism and mitotic rate for attributing grade 1 or 3. All the other types of sarcomas are classified as either grade 2 or grade 3 depending on the amount of tumour necrosis, with 15% necrosis as the threshold for separation of grade 2 and grade 3 lesions. The FNCLCC system is based on a score obtained by evaluating three features: tumour differentiation, mitotic rate and amount of tumour necrosis [2031]. A score is attributed independently to each parameter and the grade is obtained by adding the three attributed scores. Tumour differentiation is highly dependent on histologic type and subtype. The reproducibility of this system has been tested by 15 pathologists: the crude proportion of agreement was 75% for tumour grade, but only 61% for histologic type [748]. Because of the limitations and pitfalls of grading, the following guidelines have been suggested to improve reliability:

> Grading should be used only for untreated primary soft tissue sarcomas.
> Grading should be performed on representative and well-processed material.
> Grading is not a substitute for a histologic diagnosis and does not differentiate benign and malignant lesions. Before grading a soft tissue lesion, one must be sure that one is dealing with a true sarcoma and not a pseudosarcoma.

Parameters of the grading system for sarcomas of the Fédération Nationale des Centres de Lutte contre le Cancer (FNCLCC).

<table>
<thead>
<tr>
<th>Tumour differentiation</th>
<th>Score 0: No necrosis</th>
<th>Score 1: &lt;50% tumour necrosis</th>
<th>Score 2: ≥50% tumour necrosis</th>
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<tr>
<td>Score 0: Total score 2.3</td>
<td>Grade 2: Total score 4.5</td>
<td>Grade 3: Total score 6, 7, 8</td>
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Modified from Trojani et al [2031].

*A high-power field (hpf) measures 0.1734mm²

Fig. 4.01 Parameters of the grading system for sarcomas of the Fédération Nationale des Centres de Lutte contre le Cancer (FNCLCC).
The WHO Classification of Tumors of Soft Tissue and Bone [590] offers additional information on the grading of soft tissue sarcomas. There is no TNM classification for cardiac malignancies.

**Treatment and prognosis**

In general, surgical resection, when possible, is the treatment of choice for primary cardiac tumours in symptomatic patients. It is also highly desirable for patients whose tumours are identified incidentally because of the ever-present risk of sudden death, embolism, obstruction, or arrhythmia [307,952]. In patients with rhabdomyomas and so called histiocytoid cardiomyopathy, predominantly children, there are some who suggest that surgical intervention is only necessary in the face of life-threatening symptoms, as these tumours are benign and known to regress with age [1880].

Surgical strategy varies by tumour type. Cardiac myxomas arise mainly from the left atrial septum, and the surgical strategy usually includes complete tumour resection with underlying stalk. Sometimes reconstruction using a prosthetic patch is necessary [952]. The prognosis of patients with cardiac myxomas is excellent. They may occasionally recur, especially in patients with Carney complex, an autosomal dominant syndrome characterized by associated skin lesions, endocrine abnormalities and other unusual tumours [1018]. It is difficult to suggest a regular surgical strategy for other cardiac tumours as they arise in various locations. The prognosis for other benign tumours is generally favourable with low recurrence, and it is quite good even if incompletely excised [307,952,1880]. Orthotopic heart transplantation is an option if tumour resection and reconstruction would be expected to cause irreparable damage to essential cardiac structures [731]. For malignant cardiac tumours, complete resection is often impossible because of local spread [2071]. The prognosis of patients with primary malignant cardiac tumours is very poor even if complete resection is attempted [952,2071]. Adjuvant chemotherapy and irradiation are usually also given, but these are not effective in most cases [2071]. Favourable results of heart transplantation for primary malignant cardiac tumours have been reported despite immunosuppression [731,733,1962,2071].
Benign tumours with myocyte differentiation

**Rhabdomyoma**

**Definition**
A benign tumour of the cardiac myocyte, which can be solitary or multiple. The cells typically contain large glycogen filled vacuoles.

**ICD-O code**
8900/0

**Epidemiology**
Cardiac rhabdomyoma is commonly associated with tuberous sclerosis, an autosomal dominant disorder with a high mutation rate. It involves multiple organs including brain, kidney, pancreas, retina and skin. In autopsy series, patients with tuberous sclerosis have a 30% incidence of cardiac rhabdomyoma [571]. However, the actual incidence is likely higher since series that have evaluated patients with echocardiography have found an incidence between 40% and 86% [119,492,777]. The presence of multiple cardiac rhabdomyomas prenatally may be the earliest manifestation of tuberous sclerosis.

**Localization**
Rhabdomyomas are firm, white, well-circumscribed lobulated nodules that occur in any location in the heart, but are more common in the ventricles. In patients with tuberous sclerosis, tumours are usually multiple (> 90%) and can consist of numerous miliary nodules measuring less than 1 mm; in this instance, the term “rhabdomyomatosis” has been used. The most common locations are the left ventricle and ventricular septum, although 30% will have atrial wall or right ventricular involvement [1602]. In contrast to patients with tuberous sclerosis, approximately 50% of sporadic rhabdomyomas occur singly.

**Clinical features**

**Signs and symptoms**
Rhabdomyomas are the most common tumours in the pediatric age group. They are also the tumours most commonly diagnosed during the prenatal period by foetal echocardiography. Intrauterine as well as sudden death after birth has been attributed to these tumours. Clinical and hemodynamic findings are related to the number, position, and size of the tumours. For instance large intramural or intracavitary tumours may obstruct valvular orifices, or occlude intracavitary spaces [1254]. Foetal dysrhythmias or non-immune hydrops may be identified as early as 21 weeks by ultrasound [863]. The tumours may cause infant respiratory distress, congestive heart failure, or low cardiac output. Right-sided tumours that cause obstruction may cause cyanosis, or features suggestive of tetralogy of Fallot or pulmonary stenosis [41,583]. Left-sided tumours may present as subaortic obstruction, or hypoplastic left heart syndrome [2068]. Rarely they can be associated with structural cardiac defects [2113]. Patients with “rhabdomyomatosis” or diffuse microscopic involvement of the myocardium may present as though they have a cardiomyopathy. Spontaneous regression is a common feature [1254,1840].

**Electrocardiographic abnormalities** will vary depending on location, but evidence of ventricular hypertrophy and ST-T wave abnormalities consistent with ischemia and/or strain are common. The conduction abnormalities consist of bundle branch block, preexcitation, and first to third degree atrioventricular block.

**Imaging**
At echocardiography rhabdomyomas appear as homogeneous, well-circumscribed echogenic masses in the ventricular myocardium, possibly protruding into the ventricular cavity. Although uncommon, extensive rhabdomyomas can be associated with ventricular dysfunction. Given that the finding of multiple cardiac masses is diagnostic of rhabdomyoma, especially in patients with tuberous sclerosis, and that the tumours are not infiltrative, echocardiography usually provides adequate information for diagnosis and clinical management. If there is question of tumour type or of tumour invasion, MRI or CT may be used to further define the tumours. At MRI, rhabdomyomas appear as well-circumscribed masses with signal characteristics similar to that of normal myocardium [155,737,1003]. Compared with the signal from uninvolved myocardium, the masses are hypointense on post-gadolinium imaging. At CT, rhabdomy-
omas also appear as multiple nodules, which may be hyper or hypotenuating compared to normal myocardium. With MRI or CT, the rest of the body can be imaged for signs of tuberous sclerosis. However, because rhabdomyoma has many imaging features similar to normal myocardium, echocardiography, MRI, and CT may be complementary as rhabdomyomas that are not visible by one modality may be visible on another [737].

Macroscopy
Single or multiple, they are well-circumscribed, non-capsulated white or grey white nodules which may vary in size from millimeters to several centimeters. Tumours can become quite large, especially in sporadic cases. In one series of 14 cases, the range was 0.3-9.0 cm, with a mean of 3.4 cm [248]. They most often occur in the ventricle, but can be found in the atria, at the cavoatrial junction and on the epicardial surface. Large tumours may obliterate and distort a ventricular cavity.

Histopathology
Cardiac rhabdomyomas are well-demarcated nodules of enlarged cardiac myocytes with cleared cytoplasm. In some cells, strands of eosinophilic cytoplasm stretch from a central nucleus to the cell membrane giving rise to cells that resemble a spider (“spider cells”). The majority of cells show vacuolization with sparse myofilaments. There is a strong reaction with periodic acid-Schiff reagent, reflecting the presence of abundant intracellular glycogen.

Immunoprofile
Immunohistochemical studies document the striated muscle characteristics of rhabdomyoma cells, which express myoglobin, desmin, actin, and vimentin. Tumour cells do not express cell proliferation markers such as Ki-67 and PCNA, indicating that the lesions are more likely hamartomas as opposed to neoplasms [248].

Electron microscopy
By electron microscopy, the cells resemble altered myocytes. They possess abundant glycogen, small and sparse mitochondria, and cellular junctions resembling intercalated disks surround the cell periphery. In contrast, the intercalated disks of differentiated myocytes are located exclusively at the poles of the cell. Intercalated discs and myofibrils or collections of Z band material are present. Rarely one may observe there primitive T-tubules. Leptomeric fibers close to the sarcolemma may also be identified.

Differential diagnosis
The diagnosis of cardiac rhabdomyoma in infants and young children is straightforward. In patients with multiple non-calciﬁng masses, especially with other manifestations of tuberous sclerosis complex, a tissue diagnosis is unnecessary. However, because the tumours have been shown to regress with age and multiple biopsies do not allow for evaluation of the morphologic changes that characterize this process, the relationship between persistent rhabdomyomas and so-called adult rhabdomyoma...
omas and hamartomas is not clear. In the rare examples of rhabdomyomas in older children, there is often a paucity of spider cells, resulting in a tumour with some characteristics of adult rhabdomyomas, but without the proliferative activity. Hamartoma of mature cardiac myocytes, which, like rhabdomyoma, is a non-proliferative hamartomatous lesion, occurs in adults. These tumours lack circumscription and spider cells.

**Genetic alterations**
The familial form of tuberous sclerosis, which is present in up to 50% of patients with cardiac rhabdomyoma, exhibits autosomal dominant inheritance. Two disease genes have been identified: TSC-1 at chromosome 9q34, and TSC-2 at chromosome 16p13 [1613]. The TSC-1 gene encodes hamartin, and TSC-2 tuberin, proteins involved in tumour suppression. Loss of heterozygosity is often found at these loci in tumours from patients with tuberous sclerosis. The precise roles of TSC-1 and TSC-2 in the development of cardiac tumours and regulation of embryonic and neonatal cardiomyocyte growth remain to be elucidated.

**Treatment and Prognosis**
Rhabdomyomas have a natural history of spontaneous regression [204,556,1840]. However, serious symptoms may precipitate the need for surgical resection. When arrhythmias are the presenting symptom, treatment with anti-arrhythmic drugs is commenced. If control is achieved by that means, then drugs can be continued until the arrhythmias or tumours regress. If drugs fail to control arrhythmias, surgical resection is indicated. When a tumour is causing intracardiac obstruction, surgery is necessary [180,525,538,1289].

**Histiocytoid cardiomyopathy**

**Definition**
Histiocytoid cardiomyopathy is a rare, but distinctive arrhythmogenic disorder caused by a neoplastic or hamartomatous proliferation of cardiac cells with some Purkinje cell characteristics.

**Synonyms**
Purkinje cell hamartoma, arachnocytosis of the myocardium, infantile cardiomyopathy, infantile xanthomatous cardiomyopathy, oncocytic cardiomyopathy, focal lipid cardiomyopathy, isolated cardiac lipidosis, infantile cardiomyopathy with histiocytoid changes, myocardial or conduction system hamartoma, foamy myocardial transformation, and congenital cardiomyopathy.

**Epidemiology**
Histiocytoid cardiomyopathy occurs predominantly in the first two years of life; 20% of cases are diagnosed in the first month, 60% in the first year, and less than 3% after two years of life. The prevalence of this disease may be higher than the reported cases would suggest, since some cases are undoubtedly diagnosed as Sudden Infant Death Syndrome (SIDS).

The female preponderance is 3:1. In approximately 5% of cases there seems to be a familial tendency.

**Clinical features**
Histiocytoid cardiomyopathy is an arrhythmogenic disorder; 70% of published cases the patients present with a spectrum of arrhythmias and electrical disturbances including: paroxysmal atrial tachycardia, atrial fibrillation, ventricular fibrillation, ventricular tachycardia, premature atrial contractions, premature ventricular contractions, Wolff-Parkinson-White syndrome, and right or left bundle branch block.

Approximately 20% of patients present as sudden death and often such cases have been misclassified as Sudden Infant Death Syndrome (SIDS). Other infants experience flu-like symptoms preceding or accompanying the cardiac manifestations. The majority of patients (95%) display cardiomegaly, but may also have a number of associated anomalies, including cardiac malformation (16%): ventricular and atrial septal defects, hypoplastic left heart syndrome; and endocardial fibroelastosis. Extracardiac anomalies occur in 17% of patients including corneal opacities, microcephaly, cataract, aphakia, hydrocephalus, agenesis of the corpus callosum, cleft palate, laryngeal web, and linear skin defect. Combined cardiac and extracardiac anomalies occur in 4%, and 7% show extracardiac histiocytoid cells in exocrine and endocrine glands [1794].

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**Fig. 4.05** Histiocytoid cardiomyopathy. **A** Gross picture of the heart, showing multiple histiocytoid nodules in the aortic valve leaflets, endocardium, and papillary muscles (arrows). **B** Macroscopic photograph of a heart demonstrating the left ventricle and portion of the mitral valve. Note pale tan endocardial nodules at the level of the annulus.
Etiology
Many theories of the etiopathogenesis have been proposed, including viral infection, myocardial ischemia, toxic exposure, and metabolic disorders such as glycogen storage disease, cardiac lipidosis, and various mitochondrial myopathies. However, the clinical, gross, microscopic, and ultrastructural findings show clear differences between the above-mentioned disorders and histiocytoid cardiomyopathy. The clinical presentation (arrhythmia), the distribution of histiocytoid cells, and their ultrastructural and immunohistochemical characteristics, all point to the cardiac conduction system as playing a key role. The primitive Purkinje cells of the developing heart show a striking resemblance to histiocytoid cells. Both types of cells show strong positivity for cholinesterase by frozen section histochemistry and for neutral lipids with the Sudan Black stain. Cholinesterase is present only in the conduction tissue of the heart; it is not present in contractile myocytes (1794).

Macroscopy
Single or multiple subendocardial yellow-tan nodules or plaques ranging from 1-15 mm may be seen in both ventricles, the septum, and on all four cardiac valves. Although these nodules are mainly seen beneath the endocardium following the distribution of the bundle branches of the conduction system, they can also be seen in the inner myocardium and subepicardial areas. Lesions may be grossly inapparent as nodules, but multiple cross sections of the myocardium may show a mottled appearance with irregular ill-defined yellowish-tan areas.

Histopathology
Histiocytoid cardiomyopathy lesions appear as multifocal, ill-defined islands of large polygonal cells with granular eosinophilic cytoplasm, small round to oval shaped nuclei containing occasional nucleoli. The cytoplasmic appearance is due to extensive accumulation of mitochondria. The cells are distributed along the bundle branches of the conduction system. The sinoatrial and atrioventricular nodes are involved in 28% of cases; however, these areas are not sampled routinely (1794).

Immunoprofile
Histiocytoid cardiomyopathy cells react with antibodies to desmin, myoglobin, myosin, and muscle specific actin. There is no expression of macrophage or histiocytic antigens (CD68, CD69, MAC 387, LN3, HAM-56). The cells also fail to react with antibodies to vimentin and cytokeratin (CAM-5.2), whereas S-100 protein reactivity is variable. Cell proliferation markers (Ki-67 and MIB-1) are usually negative (682,1713).

Electron microscopy
Ultrastructurally, the cells of histiocytoid cardiomyopathy show poorly developed intercellular junctions. Their cytoplasm contains a superabundance of swollen mitochondria with disorganized cristae and dense membrane bounded granules, which push the diminished myofibrils to the periphery of the cell. The cytoplasm also contains lipid droplets of variable size, scattered desmosomes, intercalated discs, and leptometric fibers.

Differential diagnosis
The disease has been confused with mitochondrial cardiomyopathy. However, there are major gross, light microscopic, and ultrastructural differences between the two diseases. Mitochondrial cardiomyopathy shows no discrete nodules as present in histiocytoid cardiomyopathy. Additionally, in mitochondrial cardiomyopathy, all myocytes are affected, but to a variable degree, whereas in histiocytoid cardiomyopathy, only focal areas of the heart are involved, but the affected cells are affected totally. The ultrastructural changes in histiocytoid cardiomyopathy cells consist of increased numbers of mitochondria with and without structural changes and reduced myofibrils. In mitochondrial cardiomyopathy, the mitochondria are consistently abnormal in a variety of ways. They are enlarged, show variation in size and shape, contain occasional glycogen particles, and have cristae which are increased in number and on cross section, are arranged in a concentric circular fashion (like growth rings of a tree) surrounding occasional dense bodies.

Genetic susceptibility
Familial recurrence of histiocytoid cardiomyopathy in 5% of cases has led to several proposals of a genetic mechanism. The female preponderance of cases suggests an X-linked mutation causing prenatal lethality in the homozygous male (168,234,1898). A female infant with “oncocytic cardiomyopathy” and microphthalmia with linear skin...
defects showed monosomy for Xp22 (1543). Biochemical (1543) and molecular (mitochondrial DNA) (57) evidence suggest a defect of complex III (reduced coenzyme Q-cytochrome c reductase) of the respiratory chain in cardiac mitochondria. Such a mechanism could be responsible for the mitochondrial changes observed by light and electron microscopy, and the systemic involvement in some patients. It has been suggested that the disease is due to a mutation in Sox6 gene (p100H), which is associated with widespread myopathies (385). From reported cases with known ethnic background, histiocytoid cardiomyopathy appears to be more common in Caucasian (80%) followed by African-American (15%), and Latin-American infants (3%); it is rare in Asian infants (1794).

Prognosis and predictive factors
Histiocytoid cardiomyopathy causes incessant ventricular tachycardia in small children and can result in sudden death. Surgical excision or direct-vision cryoablation of the multiple small nodular tumours is required for long-term cure (665). Surgical intervention, electrophysiologic mapping, and ablation of the arrhythmogenic foci result in a survival rate of approximately 80%. Some authors have found that aggressive anti-arrhythmomic treatment may allow the tumours to regress without subjecting patients to surgery. A few patients with extensive disease have undergone cardiac transplant (664,678,984,1286).

Hamartoma of mature cardiac myocytes

Definition
The term “hamartoma” has been loosely applied to several cardiac tumours, most commonly histiocytoid cardiomyopathy (“Purkinje cell hamartoma”). The term has also been applied to lesions or malformations composed of a variety of cardiac elements, and other tumours composed primarily of a single cell type (e.g., rhabdomyoma). The term hamartoma of mature cardiac myocytes is used for a distinct tumour in adults, composed of cardiac myocytes. This lesion may be single or multiple.

Etiology
The etiology of cardiac hamartoma is unknown. Some have suggested that these tumours may represent maturing congenital rhabdomyomas. However, there has been no association of hamartoma of mature cardiac myocytes with other syndromes including the tuberous sclerosis complex, making this unlikely.

Localization
Hamartomas of mature cardiac myocytes may occur in the ventricles or atria, and may be single or multiple (243). Unusual examples of diffuse multiple tumourlets similar to so-called rhabdomyomatosis, have also been described.

Clinical features
As is the case with most cardiac tumours, the clinical features depend on the location. Tumours in the atria may result in supraventricular arrhythmias and Wolf Parkinson White syndrome, and those in the ventricles sudden death, or no symptoms at all.

Macroscopy
They are usually poorly demarcated firm white masses and range in size from 2 mm to 5 cm in greatest dimension. They resemble normal myocardium, but the bundles of muscle may appear disorganized and associated with bands of connective tissue.

Histopathology
They are composed of enlarged myocytes with obvious cross striations, and contain enlarged, irregular nuclei. They are poorly demarcated and may interdigitate with normal myocytes at the edges of the tumour. The interstitium demonstrates increased collagen. Interspersed fat cells may be present in small numbers.

Immunoprofile
The tumours are similar to normal cardiac myocytes, and express actin and myosin. Abnormal accumulations of these intermediate filaments may be appreciated, particularly of actin. There is no evidence of proliferation by immunohistochemical stains for Ki-67 or PCNA.

Electron microscopy
The cells show features of myocytes, but abnormal accumulations of actin and myosin may be identified.

Differential diagnosis
The disorganized hypertrophied muscle fibers of a hamartoma are also reminiscent of the disarray characteristic of hypertrophic cardiomyopathy, but with rare exception (apical variant), hypertrophic cardiomyopathy is not associated with a focal mass lesion.

Prognosis and predictive factors
These tumours are benign neoplasms and can be excised, resulting in cure. However, arrhythmias and sudden death may be the initial presentation.

Fig. 4.07 Histiocytoid cardiomyopathy. A Electron microscopic illustration showing histiocytoid cells packed with mitochondria. The diminished myofibrils are displaced to the periphery of the cell (arrows). B Higher magnification showing abundant swollen mitochondria with disorganized cristae and dense membrane bounded granules.
**Adult cellular rhabdomyoma**

**Definition**
Adult cellular rhabdomyoma is a benign neoplasm of striated myocytes. A similar tumour frequently occurs in the head and neck region (extracardiac rhabdomyoma).

**ICD-O code**
8904/0

**Epidemiology**
The adult form of extracardiac rhabdomyoma occurs primarily in the head and neck region of men and women over 40 years. Four cases of “extracardiac” rhabdomyomas have been described in the heart [241,2226].

**Clinical features and localization**
Three of the four reported cases of adult cellular rhabdomyoma have occurred in the atria, and all have occurred in adults from 35-55 years of age. Common to any heart tumour, the mode of presentation is often electrical disturbance such as supraventricular tachycardia or nonsustained ventricular tachycardia. The masses may be identified incidentally.

**Macroscopy**
They range in size from 2–5 cm. The tumours are soft, bulging, tan to brown and have a pseudocapsule. These features distinguish these tumours from other cardiac tumours with muscle differentiation.

**Histopathology**
These tumours are histologically distinct from cardiac rhabdomyomas, and are composed of tightly packed, round to polygonal cells with eosinophilic, finely granular cytoplasm, occasional vacuoles and occasional spider cells. Conversely, cardiac rhabdomyomas are composed of large cells with clear cytoplasm containing abundant glycogen and many spider cells.

**Differential diagnosis**
In contrast to congenital rhabdomyomas, adult cellular rhabdomyomas occur in adults, demonstrate evidence of cellular proliferation e.g. by expression of Ki-67 antigen, and contain relatively few vacuolated or spider cells. Unlike hamartoma of mature cardiac myocytes, the tumours are well circumscribed, and although not as frequent as in congenital rhabdomyoma, some vacuolated cells are usually present. Furthermore, the disorganized masses of myofilaments characteristic of hamartoma of mature cardiac myocytes are not seen. Rhabdomyosarcoma shares some features with adult cellular rhabdomyoma. Despite the evidence of cell proliferation in the latter tumours, the absence of tumour necrosis, mitotic figures, myogenin expression, and the presence of a well-defined pseudocapsule help to distinguish it from rhabdomyosarcoma.

**Histogenesis**
The lesion is believed to be a true neoplasm of striated muscle origin.

**Somatic genetics**
Due to the rarity of these lesions, molecular and genetic characterization has not been undertaken. In extracardiac rhabdomyoma, a reciprocal translocation between chromosomes 15 and 17 and abnormalities of the long arm of chromosome 10 have been described [680].

**Prognosis and predictive factors**
The prognosis of adult cellular rhabdomyoma is unknown, but presumed to be benign, based on the biologic behaviour of extracardiac rhabdomyomas in adults. Late recurrences have been described in extracardiac rhabdomyoma [680].
Benign tumours of pluripotent mesenchyme

**Cardiac myxoma**

**Definition**
Myxoma is a neoplasm composed of stellate to plump cytologically bland mesenchymal cells set in a myxoid stroma.

**ICD-O code**
8840/0

**Epidemiology**
Cardiac myxoma represents one of the most common benign cardiac tumours [2013,2165]. In most surgical series, they account for almost 80% of cases [249,1986]. In large registries and repositories with significant referral bias myxomas represent between 20 and 40% of primary cardiac tumours [249,1338]. Patient age ranges from 2-97 years. Mean age at presentation is 50 years [1133]. About 90% of individuals are between the ages of 30 and 60 years [2165]. A recent analysis of 1,195 individuals with myxomas revealed that 67% were female and 33% were male [2212].

**Clinical features**
Clinical presentation is diverse and dependent upon tumour location and to a lesser extent morphology [175,643, 1598,1616]. About 20% of cardiac myxomas are asymptomatic; they are usually smaller than 40 mm [722,736].

*Cardiac symptoms*
In over 50% of patients left atrial myxomas cause symptoms of mitral valve stenosis or obstruction (dyspnoea and orthopnoea from pulmonary oedema or heart failure). Right atrial myxomas may obstruct the tricuspid valve and cause symptoms of right-sided heart failure. The majority of patients have an abnormal physical examination, most characteristically a diastolic or systolic murmur. A “tumour plop” may be occasionally heard in early diastole [722,1598,1616]. Abnormal, but nonspecific electrocardiographic changes may be identified in 20-40% of patients and include atrial fibrillation or flutter and left and right bundle branch block [643,1616]. Chest roentgenograms also show only nonspecific findings, including cardiomegaly, chamber enlargement, and pulmonary oedema [1616].

*Embolism*
Embolic phenomena are the second most common manifestation (30-40% of patients). Frequent sites of embolization include the central nervous system, kidney, spleen and extremities. Coronary embolism may result in myocardial infarction [524,1542]. There is some evidence that fibrous lesions are more likely to produce valvular obstruction while polypoid and myxoid ones are more likely to embolize [722,736].

*Systemic symptoms*
These are possibly related to IL-6 production by tumour cells. They are seen in approximately 20% of patients and include myalgia, muscle weakness, arthralgia, fever, fatigue and weight loss. Although infection of a myxoma is rare, when present the initial manifestations mimic those of infective endocarditis, and can include fever, chills, petechiae, subconjunctival haemorrhages, Osler nodes and positive blood culture. Anaemia, leukocytosis and elevated erythrocyte sedimentation rate are the most common laboratory findings [175,1616]. Most myxomas are sporadic, although syndromic and familial cases (Carney or myxoma complex) are well recognised. In familial cases, the patients present at a younger age, they occur in unusual locations and have a higher recurrence rate than in non-familial cases [296,2114].

**Imaging**
At echocardiography cardiac myxomas typically appear as a mobile mass attached to the endocardial surface by a stalk, usually arising from the fossa ovalis. Myxomas with this appearance can be confidently diagnosed by echocardiography and further imaging is not necessary [1298]. In fact, because the tumours are usually small and mobile, myxomas are typically better defined by echocardiography than by either MRI or CT, because echocardiog-
Cardiac myxoma has the best spatial and temporal resolution. If the narrow stalk is not visible, the diagnosis cannot be made by echocardiography and further imaging, usually MRI, is necessary to show the tumour’s margins and to exclude tumour infiltration. At MRI and CT myxoma appears as an intracavitary heterogeneous, lobular mass. As with echocardiography, if the narrow stalk is visible, myxoma can be diagnosed by MRI or CT.

Macroscopy
Cardiac myxomas are intracavitary masses that occur most often in the left atrium. They arise from the endocardium of the atrial septum near the fossa ovalis in 85-90% of cases. Most of the remainder are located in the right atrium. Rarely, they arise in the ventricles.

Multiple tumours occurring at sites other than fossa ovalis and ventricles are generally found in the inherited form of cardiac myxoma. Very rarely, cardiac myxomas have also been documented to occur on valves and chordae tendineae.

The external appearance, consistency, size and weight are extremely variable. They may be as small as a few millimeters and as large as 14 cm in diameter. The weight ranges from 2-250 gm. Tiny cardiac myxomas may be totally asymptomatic and discovered incidentally at surgery for another purpose or autopsy. Extravasated red cells, foci of recent and organizing haemorrhage and hemosiderin deposition are frequent. Hemosiderin is seen free within the stroma, within histiocytes and myxoma cells. Variable numbers of lymphocytes, plasma cells, macrophages, dendritic cells, and mast cells may be present. Gamma-Gandy bodies as seen in chronic venous congestion of the spleen may be encountered infrequently. Calcification and metaplastic bone formation may also occur. The latter are more frequent in right atrial myxomas. The surface is usually composed of a single layer of flattened cells, but multilayering and tufting may occur.

Myxomas are ovoid, globular, lobulated or polypoid. They may be smooth and glistening or have multiple papillary, villous, finger-like projections. They may be grey white and fibrous, gelatinous and myxoid, or a combination of both. The papillary structures may be quite friable increasing the risk of embolisation. Superficial thrombi also embolize. Marked variation in colour is characteristic. Pale grey, pearly white or yellow brown areas are frequently admixed with haemorrhagic dark brown or red areas. Tumour consistency depends on the quantity and distribution of fibrous tissue, and calcification. Rarely, the bulk of the tumour becomes calcified.

Histopathology
The myxoma cells may be arranged singly, in cords, or in vasoformative ring structures. The cells can be elongated, fusiform or stellate. They contain modest amounts of eosinophilic cytoplasm. Nuclei are oval, round, or elongated and mitoses are very rare. Myxoma cells have a tendency to form primitive or differentiated vessels, reflected in expression of endothelial markers. Less myxoid stroma often forms a halo around the vascular formations. The stroma contains variable amounts of proteoglycans, collagen and elastin. It shows strong reactivity with alcian blue, resistant to predigestion by hyaluronidase. The vessels within the tumour are thin-walled and lack pericytes. Occasionally, cavernous vascular spaces containing blood or proteinaceous material are encountered. Thick walled blood vessels with prominent muscular walls are present predominantly at the base of tumour and in the stalk. Extravasated red cells, foci of recent and organizing haemorrhage and hemosiderin deposition are frequent. Hemosiderin is seen free within the stroma, within histiocytes and myxoma cells. Variable numbers of lymphocytes, plasma cells, macrophages, dendritic cells, and mast cells may be present. Gamma-Gandy bodies as seen in chronic venous congestion of the spleen may be encountered infrequently. Calcification and metaplastic bone formation may also occur. The latter are more frequent in right atrial myxomas. The surface is usually composed of a single layer of flattened cells, but multilayering and tufting may occur.
Heterologous components
Well-defined columnar epithelium, occasionally forming glands occurs in about 2% of myxomas. The epithelium may show moderate cytologic atypia, mitotic activity and express cytokeratin. Age and sex distribution of patients, signs and symptoms, frequency of syndromic association and sites of occurrence are similar for cardiac myxoma with or without glands. Recognition of the glands as a component of a myxoma is important since these structures may be confused with metastatic adenocarcinoma. The glandular cells are positive for PAS-diastase, alcian blue and mucicarmine; they stain for cytokeratin (diffuse cytoplasmic staining with antibodies to cytokeratin 7, AE1/AE3, 4betaE12 and Cam 5.2; and focal staining for cytokeratin 20), EMA (diffuse cytoplasmic), and CEA (apical cell border). Reactivity for CA19.9 has also been observed on the apical epithelial membrane of the glandular component of a myxoma from a patient with elevated serum CA19{1190}. Foci of extramedullary haematopoiesis may be seen in 7% of myxomas{245}. Thymic rests have also been observed{245}.

Immunoprofile
The cells are cytokeratin negative, variably S-100 positive, and variably positive for smooth muscle and endothelial markers e.g. CD 34 and CD31{362,1269,1625,2013}. Calretinin is expressed in about 75% of cardiac myxomas{16}.

Histogenesis
Some years ago myxomas were considered nothing more than organised thrombi. Their neoplastic nature is supported by the presence of chromosomal abnormalities{489}, abnormal DNA content{1226} and the presence of microsatellite instability{1853}. The presence of heterologous elements, however, still suggest to some that they may be reactive or hamartomatous{1925}. The origin of myxoma cells is unclear. They are thought to arise from subendothelial vasosoformative reserve cells or primitive cells which reside in the fossa ovalis and surrounding endocardium. The minute endocardial structures described by Frichard{1618} do not seem to correspond to the hypothetical subendothelial pluripotent vasosoformative reserve cells from which the myxomas would arise, because they do not share the immuno-histochemical properties of myxoma cells{15,16}. On the other hand, cardiomyocyte-specific transcription factor mRNAs have been recently found in RNA extracted from myxoma lysates, suggesting cardiomyogenic differentiation in myxoma cells and a possible origin in cardiomyocyte progenitor cells{1037}.

Genetic susceptibility
Although most myxomas are sporadic, some have been associated with the myxoma complex{295,483}. This autosomal dominant syndrome has been reported under the acronyms NAME (nevus, atrial myxoma, myxoid neurofibroma, ephelides), LAMB (lentigines, atrial myxoma, mucocutaneous myxomas, blue nevi), and more recently as Carney syndrome{295,299,530}. This syndrome includes cardiac myxomas and extracardiac manifestations: abnormal skin pigmentation (lentigines and blue nevi), calcifying Sertoli-Leydig testicular tumours, cutaneous myxomas, myxoid breast fibroadenomas, pigmented adrenal cortical hyperplasia, pituitary hyperactivity, psammomatous melanotic schwannoma and thyroid tumours{295}. Familial myxomas are estimated to account for 7% of atrial myxomas{299}, are more often multiple, recurrent and right sided, as compared to sporadic myxomas. The affected patients are also younger, most presenting at 20-30 years of age{530,1133,1544}.

Somatic genetics
The chromosomal patterns of sporadic cardiac myxoma are characterised by extensive intratumour heterogeneity. In the seventeen cases published to date,
multiple unspecific chromosome aberrations have been reported, including dicentric chromosomes and, in particular, telomeric associations [489,497,498, 502]. Intratumour heterogeneity, as found in a variety of tumour types and grades [688], is considered a sign of genetic instability presumably resulting from disruption of genes that control genomic integrity. Studies of cardiac myxomas suggest that the chromosomal regions 12p1 and 17p1 may play a specific role in the development of these neoplasms since they are frequently rearranged [497].

Cytogenetic analyses of three cases of cardiac myxoma derived from patients with the myxoma syndrome reveal chromosome patterns similar to those observed in sporadic cases [489,1658, 1882]. Whether there is a common genetic mechanism underlying sporadic and familial cardiac myxomas is unclear. Based on linkage analysis, 2 loci have been proposed for genes causally related to the myxoma syndrome: 2p16 [1882] and 17q2 [299]. Recently, a gene located at 17q24 was cloned that showed mutations in myxoma patients [122,598,1018]. This gene, PRKAR1A, represents a putative tumour suppressor gene, coding for the type 1 alpha regulatory subunit of protein kinase A (CNC1, OMIM #160980). No causal gene has been identified at the 2p16 locus, and some families that were initially thought to have disease related to this locus actually have chromosome 17q24 PRKAR1A mutations [122]. At least one further locus remains to be identified. As yet, neither mutations of PRKAR1A nor loss of heterozygosity of markers at 17q2 and 2p16 have been found in sporadic cardiac myxomas [598].

Flow cytometry shows abnormally high tetraploid DNA patterns in all cases of syndromic myxomas, whereas in sporadic myxomas it is present only in about 20%.

**Prognosis and predictive factors**

There is a remarkably different prognosis between patients with sporadic and familial myxomas. Patients with sporadic tumours have a good prognosis, with 1-3% recurrence rate [1275,296,2227]. However, about 10% of patients with familial myxomas either have recurrent tumours or develop another tumour in a different location [1276,1598]. The recurrence interval in one series was 47.8 months [296]. The probability of recurrence has been related to DNA chromosomal pattern [296,1276]. Patients with a familial tumour need to followed long term.

Emboli are the major complication of myxoma and may result in ischemic symptoms in a variety of arterial beds. Intracranial aneurysm due to embolization is also a rare, but potentially morbid, complication. The etiology of these aneurysms is unclear but histologic verification of myxoma cells in arterial walls has been reported [1758].

**Treatment**

Immediate surgical resection is advised when the diagnosis of cardiac myxoma is suspected [1454], because of the risk of embolism [2001]. The tumour is removed under cardiac arrest with cardiopulmonary bypass. Minimal manipulation and gentle management of the heart is recommended so as not to precipitate embolism. After the tumour is resected, the cardiac chamber should be irrigated with saline solution to wash out residual tumour fragments.

The approach to a left atrial myxoma is usually through a vertical incision. When the tumour is not large, a transseptal approach useful, whereas a transseptal biatriotomy [516] is recommended for a large tumour. As the majority of left atrial myxomas arise from the interatrial septum, the tumours can be removed en bloc with a 5 mm margin of normal tissue. The fossa ovalis, where the pre-tumour cells of myxomas are thought likely to exist [2102], should also be excised if possible. For a right atrial myxoma, direct caval cannulation avoids tumour fragmentation. When direct cannulation to the inferior vena cava is impractical, a cannula should be inserted from the femoral vein for the inferior vena cava. Tumour resection with the full thickness of the septum and patch repair is required for tumours with a broad based attachment. However, when the tumour originates from the atrial wall, resection of the attachment, and 5 mm of normal tissue including endocardium and underlying myocardium are recommended.

**Papillary fibroelastoma**

**Definition**

An endocardial based papilloma lined by endothelial cells with proteoglycan rich avascular stroma, usually rich in elastin.

**Synonyms**

Giant Lambl excrescence, fibroelastic papilloma

**Epidemiology**

Papillary fibroelastoma is a rare and benign tumour representing less than 10% of primary cardiac tumours [121,247]. The true incidence is difficult to determine, as the tumour may be overlooked and there is morphologic overlap with Lambl excrescences, a reactive age-related valvular lesion [249,2080]. In recent series of surgically excised cardiac tumours papillary fibroelastoma represents the second most frequent benign lesion. Papillary fibroelastoma is the most common primary tumour of cardiac valves. In two recent series of primary valve tumours, papillary fibroelastoma constituted 73% and 89% of cases [531,1714]. Mean age of patients is 60 years (range, newborn to 83 years) and there is an equal gender predilection [1714, 1903].
Etiology
The histogenesis continues to be a source of controversy. Various gross, microscopic, and molecular characteristics of papillary fibroelastoma have led to the lesions’ being described as neoplasms, hamartomas, organized thrombi, and unusual endocardial responses to trauma. The histochemical presence of fibrin, hyaluronic acid, and laminated elastic fibers within the fronds supports the hypothesis that papillary fibroelastomas may be related to organizing thrombi. Evidence favouring the hamartoma hypothesis includes a histologic appearance that suggests the proliferation of miniature tendinous cords and apparent congenital papillary fibroelastomas associated with other congenital cardiac anomalies. Due to the presence of dendritic cells and cytomegalovirus in the intermediate layers of some papillary fibroelastomas, a recent study proposed that papillary fibroelastomas may be related to a chronic form of viral endocarditis [734].

Repetitive hemodynamic trauma may contribute to their development as they have been reported in association with diseases resulting in abnormal flow of blood in the heart including rheumatic heart disease, hypertrophic cardiomyopathy, mitral valve prolapse and atrial septal defect, among other diseases. However, the mechanisms by which such hemodynamic abnormalities contribute to papillary fibroelastoma growth are unclear. There is increasing evidence that at least a subset (18%) of these tumours develop as a result of iatrogenic factors, including thoracic irradiation and open-heart surgery (subaortic septal myectomy, valve repair, valve replacement and repair of congenital defects [1105]. In contrast to sporadic cases, which are most common on cardiac valves, iatrogenic papillary fibroelastomas tend to occur in a variety of non-valvular endocardial surfaces, usually in close proximity to the predisposing iatrogenic factor, e.g. in the chamber most closely associated with the site of surgery.

Localization
Ninety percent of papillary fibroelastomas occur on heart valves, including aortic, posterior and anterior mitral leaflets [531,597,842,1397,1819,2015], mitral chordae and papillary muscles [313,659]. Unusual locations include the tricuspid and pulmonary valves, right and left atrial and ventricular endocardial walls, Chiari’s network, and coronary ostia {43,202,254,913,977,1179,1770,2249}. Autopsy series show an equal right and left heart distribution [205,531,1274]. However, surgical series have a high prevalence (81%) of left sided papillary fibroelastomas because left-sided lesions are much more frequently symptomatic.

Tumours are found most commonly (69.5%) on diseased valves - 37.8% post-rheumatic valves and 62.2% valves with fibrosis and calcification [1903]. Papillary fibroelastomas have been likened to Lambl excrescence, but unlike Lambl excrescences, which occur at the line of closure of semilunar valves, papillary fibroelastomas occur anywhere on the valve surface.

Clinical features
The clinical diagnosis of papillary fibroelastoma can be difficult because embolic complications can mimic a variety of underlying diseases [1714]. Integrity of the superficial endothelial layer of the fronds has been demonstrated to be the main element leading to occurrence of embolic events [734]. Embolism is related to the aggregation of platelets and fibrin [567,734,742]. Lesions adjacent to coronary ostia may prolapse resulting in angina, syncope or sudden death [205,262]. The majority of surgically excised cases occur in patients with symptoms related to cerebrovascular ischemia. The diagnosis is made by multiplanar transthoracic and transesophageal echocardiography [713,1151,1770,2015]. High-resolution echocardiography shows an echolucent centre.

Table 4.02
Immunohistochemical profile of cardiac papillary fibroelastomas.
From D. Grandmougin et al. [734]

<table>
<thead>
<tr>
<th>Marker</th>
<th>Central fibrous core</th>
<th>Intermediate layer</th>
<th>Endothelial border</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vimentin</td>
<td>(+)</td>
<td>(+)</td>
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<tr>
<td>S 100 Protein</td>
<td>(-)</td>
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<tr>
<td>CD 31</td>
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<tr>
<td>CD 34</td>
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<tr>
<td>Factor VIII</td>
<td>(-)</td>
<td>(-)</td>
<td>(+)*</td>
</tr>
<tr>
<td>CMV-LMP-1</td>
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<tr>
<td>EBV-LMP-1</td>
<td>(-)</td>
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*Staining intensity decreased in comparison to the adjacent normal endocardial endothelium with an immunoreactivity ratio of 0.4

Macroscopy
Papillary fibroelastomas range in size from 2-50 mm in greatest dimension, although the majority are less than 10 mm. They are generally opalescent white, but this colour may be obscured by thrombus. They are usually attached to the endocardial surface by a short single stalk, but those with more than one attachment to the endocardium have been observed. Papillary fibroelastomas have multiple papillary fronds and, particularly when immersed in water, they resemble a pom-pom or sea anemone. Papillary fibroelastomas most often occur singly (80-90%), but among patients with iatrogenic tumours, multiple tumours (2 to greater than 40) occur with great frequency (67%). Such tumours are less likely to occur on the valves and have been reported in a wide variety of locations (on papillary muscles, tendinous cords, and atrial and ventricular septal and free walls).

Histopathology
Papillary fibroelastomas have a superficial endothelial layer, an intermediate...
layer rich in proteoglycans and a central avascular core. The inner layers contain fibroblasts and occasional inflammatory cells including macrophages and dendritic cells (742,1703). Elastic fibres are most prominent in the core but may be sparse or absent in the distal parts of the papillae. Acute and organizing thrombi may be seen on the surface and obscure the papillary surfaces.

**Immunohistochemistry**

Immunohistologic studies demonstrate a disparity between surface and deeper layers. Surface endothelial cells express vimentin and CD34 with some loss of intensity for CD31 and factor VIII related antigen in comparison to normal endocardial endothelium. It has been proposed that the decreased expression of endothelial markers indicates endothelial trauma or dysfunction (734,1200,1703). Spindle cells in deeper layers may focally express S100 protein. The S100 cells likely represent competent antigen presenting dendritic cells. The presence of T cells has not been investigated in these regions.

Fig. 4.14 Papillary fibroelastoma. A Location at the aortic valve. B Movat pentachrome stain demonstrating an incidental papillary fibroelastoma on the surface of the valve. In this example, there is little elastic tissue within the papillae. C Papillary fibroelastoma showing multiple fronds with prominent elastic tissue cores (elastic van Gieson). D Fibroelastic papilloma with young vegetations.
Haemangioma

**Definition**
Haemangiomas (angiomas) are benign tumours composed predominantly of blood vessels. The histologic classification includes those composed of multiple dilated thin-walled vessels (cavernous type), smaller vessels resembling capillaries (capillary type), and dysplastic malformed arteries and veins (arterio-venous haemangioma, cirrroid aneurysm). Cardiac haemangiomas often have combined features of cavernous, capillary and arteriovenous haemangiomas, and many contain fibrous tissue and fat. These features are reminiscent of intramuscular haemangiomas of skeletal muscle.

**ICD-O code** 9120/0

**Clinical features**
Most cardiac haemangiomas are discovered incidentally but patients may present with dyspnoea on exertion, arrhythmias, right-sided heart failure, pericarditis, pericardial effusion, and failure to thrive. Patients may have associated vascular syndromes e.g. Kasabach-Merritt [675].

**Imaging**
At echocardiography, haemangiomas are usually hyperechoic, circumscribed, and intracavitary solitary masses. At MRI, hemangiomas may be intermediate to high on T1 weighted images, often are very intense on T2 weighted images, and also enhance brightly with contrast administration [1003]. At CT the tumors are usually circumscribed, low attenuation, heterogeneous and also enhance brightly with contrast administration [737]. The circumscribed, non-infiltrative appearance of haemangioma, particularly on MRI which is most sensitive to tissue infiltration, can be used to suggest that the neoplasm is benign, but a specific diagnosis cannot be made with imaging.

**Localization**
The most frequent locations are the lateral wall of the left ventricle (21%), the anterior wall of the right ventricle (21%), the interventricular septum (17%) and occasionally, the right ventricular outflow tract [226].

**Macroscopy**
The tumours are often large and gross appearance depends on the size of the vascular spaces in the tumour. The capillary type is frequently slightly raised from the endocardial surface and appears red to purple. Intramuscular types will appear infiltrative. Cavernous haemangiomas are usually large and are also poorly circumscribed.

**Histopathology**
Capillary haemangiomas are composed of nodules of small capillary-size vessels, each of which is subserved by a “feeder” vessel. This lobular or grouped arrangement of vessels is helpful for distinguishing these benign from malignant vascular proliferations. Mast cells and factor XIII-positive interstitial cells are a consistent feature. Intramuscular cardiac haemangioma has superficial resemblance to arteriovenous malformation, with the presence of heterogeneous vessel types, including muscularized arteries, veins, and capillaries. In contrast to capillary haemangioma, they are infiltrative lesions and occur within the myocardium. They are histologically identical to intramuscular haemangiomas within skeletal muscle, and may possess, in addition to the vessels, fat and fibrous tissue. Because of the latter features, some intramuscular cardiac haemangiomas are misclassified as lipomas or fibrolipomas.

Cavernous haemangiomas are composed of large dilated vascular spaces. They tend to infiltrate the myocardium. The lining cells are bland and flattened and mitotically inactive.

**Genetic susceptibility**
Genetic susceptibility to cardiac haemangiomas has not been identified. Extracardiac haemangiomas occur in a variety of contexts. They may be single sporadic lesions or multiple lesions that are components of complex genetic syndromes. Capillary haemangiomas occur in up to 10% of live births and are the most frequent tumour in newborns [1409]. When these tumours occur in the absence of associated syndromes, they may represent manifestations of an autosomal dominant mendelian trait (OMIM #602089) [7]. Linkage analyses [224, 2101] of multiplex kindreds affected by hereditary capillary haemangiomas have identified loci on chromosome 5 (q31-q33 and q13-q22) that appear to contain as yet unidentified causal disease genes.

A wide array of complex syndromes, such as von Hippel Lindau syndrome (OMIM #193300) and SC phacomelia/Roberts syndrome (OMIM #269000), that
can be transmitted in a mendelian fashion include haemangiomas as components of their clinical presentations. The Klippel-Trenaunay-Weber syndrome, in which cutaneous haemangiomas occur in the setting of osseous hypertrophy, shows familial clustering, but a clear mode of inheritance has not been established. Autosomal paradominant and dominant modes of inheritance have been proposed (306,775). Translocations (2105-2130) have been identified in 2 Klippel-Trenaunay-Weber patients, t(5;11) (q13.3;p15.1) and t(8;14)(q22.3; q13), but specific gene defects remain to be identified.

**Somatic genetics**
Specific genes have been associated with two disorders involving arteriovenous malformations. Mutations in the gene on chromosome 9p21 encoding the endothelial cell-specific receptor tyrosine kinase TIE2 cause the autosomal dominant Bean or “Blue rubber-bleb nevus” syndrome (OMIM #112200) and familial multiple cutaneous and mucosal venous malformations (OMIM#600195) (2084). At least some cases of hereditary cerebral cavernous malformations (OMIM #116860) are caused by mutations in the chromosome 7q21-q22 Krev interaction trapped-1, KREVIT-1, gene (1110). KRIT1 normal binds to RAP1A, a Ras GTPase, and the disease causing mutations appear to disrupt these interactions. Other genetic loci for this disorder have been identified at chromosomes 17p15-p13 and 3q25.2-q27 and remain to be studied. The genetic and clinical relationship of this disorder to hereditary neurocutaneous angioma (OMIM #106070) is unclear.

**Syndromic associations**
The majority of cardiac haemangiomas are sporadic, without evidence of extracardiac vascular lesions. Rarely, there may be extracardiac haemangiomas of the gastrointestinal tract and port-wine stain of the face. Giant cardiac haemangiomas can result in thrombosis and coagulopathies (Kasabach-Merritt syndrome) (239,675).
Benign tumours with myofibroblastic differentiation

Cardiac fibroma

Definition
Fibroma is a rare primary heart tumour composed of fibroblasts or myofibroblasts with a matrix containing collagen. It almost exclusively occurs within the myocardium of the ventricles or ventricular septum. It is not clear whether it is a hamartoma or a true neoplasm. Because most cases occur in infants and children it is likely congenital.

ICD-O code 8810/0

Synonyms
Fibroelastic hamartoma, fibrous hamartoma.

Epidemiology
Most cardiac fibromas are discovered in children and often before one year of age (737,1944). Prenatal diagnosis with sonography is possible (121,134,538). However, cases are also reported in adults (307) and even as an incidental finding in the elderly (2093). There is no sex predominance. The incidence is very low with only about 200 cases reported to date.

Localization
The most common site of cardiac fibroma is the ventricular septum, but the free walls of the left and right ventricle are other common locations. Atrial fibromas are quite rare.

Clinical features
One-third of cardiac fibromas cause symptoms because of their mass effect, either through obstruction of blood flow or interference with valvular function and patients present with cardiac failure or cyanosis. In another third of the cases, cardiac fibromas, whatever their location, cause significant arrhythmias, syncope or sudden death. The remaining patients are asymptomatic and tumours are discovered because of heart murmur or a radiographic abnormality. Embolic phenomena are not a feature of cardiac fibromas (121,134,538,737,1944).

Imaging
At echocardiography fibromas typically appear as a large, well-circumscribed, solitary mass in the septum or ventricular free wall (1010,1242) and in some cases may be confused with hypertrophic cardiomyopathy (66). The tumors are frequently very large and may cause obstruction, which can be assessed by colour Doppler. MRI likewise shows a large, solitary, homogeneous myocardial mass centered in the ventricles (1003, 1215,1660). Because of the fibrous nature of the tumour, the signal intensity is often less than that of adjacent uninvolved myocardium, and contrast-enhanced imaging usually demonstrates a hypoperfused tumour core. CT also shows a large, solitary, ventricular mass, which is usually low attenuation on CT. Unlike other imaging modalities CT may detect calcification which is a helpful feature in making a confident diagnosis (66). Overall, the imaging finding of a

Fig. 4.19 Cardiac fibroma. A The tumour fills the left ventricular cavity, which is obliterated. The right ventricle and tricuspid valve are on the left. B Cardiac fibroma with prominent whorled surface.

Fig. 4.18 Cardiac fibroma. A Left ventricular fibroma in a 6-month-old infant. A. ECG-triggered breath-hold proton-density fast spin echo MRI with double inversion recovery sequence in the axial plane showing a large inhomogeneous mass involving the left ventricular free wall. B MRI of left ventricular fibroma in a 6-months-old infant. Post-gadolinium imaging shows enhancement of the uninvolved myocardium and the tumour’s periphery. Note the hypoperfused tumor core. C Echocardiogram of an infant with a large right ventricular fibroma causing right ventricular outflow tract obstruction.
A solitary, very large, hypovascular mass in a child is suggestive of a cardiac fibroma.

**Macroscopy**

They are typically rounded masses that are fibrous, white and whorled, reminiscent of uterine leiomyomas. The margin may be either circumscribed or infiltrative. In some cases, fibromas are massive and can obliterate ventricular cavities. They are nearly always mural, although polypoid endocardial based lesions have been reported. Most occur singly. The mean diameter is 5 cm.

**Histopathology**

Fibromas are composed of bland-looking spindle cells forming loose intersecting bundles. They are not encapsulated and extend into the surrounding myocardium. Even in grossly circumscribed cases, entrapped myocytes can often be seen deep within the tumours, far from the gross margins (244,451). The fibroma cells have oval or tapered nuclei without nucleoli. Their cytoplasm is pale. These cells are associated with abundant collagenous stroma, which increases with the age of the patient. Cellular lesions are observed in infants during their first months of life, while fibromas in older patients contain large amounts of collagen. Mitoses and foci of extramedullary haematopoiesis may be present in cellular tumours (451). Calcification is observed in lesions from patients of all ages, but is somewhat more common in older individuals. Wavy elastic fibers are frequent and may be prominent. Focal myxoid change in the stroma and chronic inflammation may also be present (244).

**Immunoprofile**

Tumour cells express vimentin and smooth muscle actin, both in cellular and fibrous lesions. They do not express desmin, CD34 or S-100 protein. Reactivity for markers of proliferation, are much more frequent in cellular tumours than in the fibrous ones (451).

**Somatic genetics**

A clonal translocation has been described in cell cultures of a subepicardial fibroma resected from an infant. Cytogenetic analysis in this tumor showed a clonal reciprocal translocation, 46,XY,t(1;9)(q32;q22),inv(9)(p11q12)c (572).

**Genetic susceptibility**

Approximately 3% of patients with Gorlin syndrome have cardiac fibromas (418, 547,716). Gorlin syndrome (or nevoid basal cell carcinoma syndrome) is an autosomal dominant disorder characterized by generalized body overgrowth, jaw keratocysts, developmental abnormalities of the skeleton, and a predisposition to neoplasms, specifically cardiac fibroma. Gorlin syndrome results from germline mutations in the PTC gene, which maps to chromosome 9q22.3 and is homologous to the Drosophila patched (ptc) gene (756). The ptc gene encodes a transmembrane protein in Drosophila that represses the Hedgehog signaling pathway to control cell fate, growth, and development (756,893). These data suggest that the PTC gene not only functions as a tumour suppressor gene, but also plays a critical role in development. However, the precise role of the PTC gene in myocardial cell growth and differentiation and its role in the development of cardiac fibroma remains to be defined (2077).

Associated hydrocephalus, cleft lip and palate, and Sotos syndrome (megalencephaly with gigantism) have been reported (446,1242).

**Prognosis and predictive factors**

The cardiac fibroma is benign, but its nature of slow but continuous growth...
may cause conduction defects and arrhythmias. Extension into the ventricular free walls may result in atrioventricular valve inflow or arterial outflow obstruction. Spontaneous regression as can occur with congenital rhabdomyoma has not been observed.

**Treatment**
Operative intervention is usually required \{451,615,2071\}. When the tumour proves unresectable, heart transplantation is an option \{731,2071\}. However, favourable late results even after incomplete excision have been reported \{132,307,1880\}.

**Inflammatory myofibroblastic tumour**

**Definition**
Inflammatory myofibroblastic tumour is composed of myofibroblasts accompanied by a variable number of inflammatory cells including lymphocytes, macrophages, plasma cells and eosinophils.

**ICD-O code** 8825/1

**Synonyms**
Plasma cell granuloma, inflammatory pseudotumour and possibly inflammatory fibrosarcoma

**Epidemiology**
These tumours are very rare in the heart, and only small series and case reports appear in the literature.

**Localization**
Although there is a predilection for the ventricles, especially the right ventricular outflow tract, any site in the heart may be involved \{1177\}.

**Clinical features**

**Signs and symptoms**
There are no specific signs or symptoms related to cardiac inflammatory myofibroblastic tumour, as these are related to location within the heart. One cardiac inflammatory myofibroblastic tumour has been reported in a patient with systemic vasculitis and another tumour regressed spontaneously.

**Macroscopy**
Inflammatory myofibroblastic tumours of the heart are large lesions, measuring up to 8 cm \{451\}. Grossly, they tend to have relatively narrow attachments to the endocardium and project into the ventricular lumen.

**Histopathology**
Inflammatory myofibroblastic tumour is composed of spindled myofibroblasts, fibroblasts, chronic inflammatory cells and sometimes eosinophils. Various combinations of these cell types make these tumours quite variable from one case to another. Occasional mitoses and foci of necrosis may be present.

**Immunoprofile**
The tumour cells strongly express actin and vimentin, but not desmin, CD34, S-100 protein and p53. It is unknown if ALK-1 expression is diagnostically useful in cardiac inflammatory myofibroblastic tumours as is the case with extracardiac tumours.

**Differential diagnosis**
In contrast to fibromas, inflammatory myofibroblastic tumours are endocardial lesions, and there is often organizing fibrin thrombus on the surface. In addition the tumours are more histologically variable, the spindle cells are larger than in fibromas and the cells often have nucleoli.

**Prognosis and predictive factors**
The biologic behavior of inflammatory myofibroblastic tumour is that of a low-grade lesion with the propensity for recurrence, but overt malignancy is rare. No case of metastases arising from cardiac inflammatory myofibroblastic tumour has been reported.
Cardiac lipoma

**Definition**
Benign tumour composed of mature, white adipocytes.

**ICD-O code** 8850/0

**Epidemiology**
Cardiac lipoma is rare and found in fewer than 1 in 10,000 autopsies [1116]. Lipomas generally account for only 0.5-3% of excised heart tumours [121,573, 952,1257,1672]. Higher estimates of up to 10% of heart tumours are likely because lipomatous hypertrophy, a separate entity, has been included [1257,1628]. Lipomas occur in children, but account for less than 2% of heart tumours similar to the relative incidence in adults [134].

**Localization**
Cardiac lipomas may occur anywhere in the heart. There is a predilection for the pericardium and epicardial surfaces [540,1125,1628,2060], where they may attain enormous sizes. Other sites include the ventricular septum [1869], and cardiac valves. When they involve the latter site, the designation “fibrolipoma” has been used [149,280,1562].

**Clinical features**
As is the case with other heart tumours, the presentation is varied, and depends on location. Many cardiac lipomas are incidental findings, or cause a variety of arrhythmias, syncope and electrocardiographic abnormalities [342,638,1383, 1562,1735]. Rarely, outflow tract obstruction may occur [1869]. Computed tomography and magnetic resonance imaging may establish the fatty nature of the tumour [1383]. Recurrences are rare [2146].

**Imaging**
The echocardiographic appearance of cardiac lipomas varies with their location. Lipomas in the pericardial space have variable echogenicity but are often hypoechogenic, while intracavitary lipomas are typically echogenic [66]. The reason for this difference is unknown. At echocardiography, intracavitary lipomas are usually circumscribed but cannot be differentiated from other circumscribed cardiac masses. However, MRI and CT both allow for very specific identification of fat and therefore can be used to definitively diagnose lipomas [66].

**Histopathology**
Similar to extracardiac lipomas, cardiac lipomas are circumscribed masses of mature adipocytes. Unusual histologic variants of lipoma have not been described in the heart, with the exception of pediatric cardiac lipoblastoma in a child, which possessed immature and mature adipocytes, with focal vascular myxoid areas containing lipoblasts [500].

**Differential diagnosis**
The main differential is lipomatous hypertrophy, a non-encapsulated lesion composed of mature fat and adipocytes resembling brown fat cells intermixed with enlarged cardiac myocytes occurring solely in the interatrial septum. Lipomatous hypertrophy is most often an incidental finding at autopsy, but may uncommonly be the cause of unexplained atrial arrhythmias, congestive heart failure, or superior vena cava obstruction [242,365]. The differential diagnosis also includes the intramuscular variant of haemangioma, which may contain variable numbers of adipocytes.
Cystic tumour of atrioventricular node

Definition
Congenital multicystic tumour or rest located at the base of the atrial septum in the region of the atrioventricular node. Lining cells may be derived from primitive endoderm.

ICD-O code 8454/0

Synonyms
Mesothelioma of atrioventricular node, lymphangioma, endothelioma, inclusion cyst, Tawarian node, benign mesothelioma of Mahaim, endodermal rest, congenital polycystic tumour of atrioventricular node, intracardiac endodermal heterotopia.

Epidemiology
The mean age at presentation is 38 years (range birth–78 years) and women are more frequently affected than men (approximately 3:1). One patient with long standing heart block survived to age 95, at which time the diagnosis was made at autopsy [64].

Etiology
Because most patients have a history of congenital heart block, they likely are congenital rests. In 10% of patients the tumours occur in association with other midline defects [240,1189,1617,1719,2021]. The precise intrauterine migration defect is unknown. The cell of origin is foregut endoderm, not mesothelium as previously believed. Because diagnosis in advanced years occurs, the congenital nature is not proved in all. Evidence that limited cell proliferation occurs in some cases may explain presentation later in life, and patients may live for decades with complete heart block [64].

Localization
By definition they occur adjacent to the atrioventricular node. Similar lesions have not been described elsewhere in the body.

Clinical features
Two-thirds of patients present with complete heart block, 15% with lesser degrees of atrioventricular block, and 10% with sudden death without documented history of heart block [240]. The remainder are incidental findings in newborns and infants with structural heart defects. Only rarely are atrioventricular nodal tumours detected in patients with normal sinus rhythm. Most tumours have first been diagnosed at autopsy but in vivo diagnosis has been reported [102].

Macroscopy
They range in size from 2-20 mm and are multicystic, the cysts often barely perceptible.

Histopathology
They arise in the inferior interatrial septum and generally respect the boundaries of the central fibrous body, and do not involve ventricular myocardium or the valves. Tumour cells occur in nests or line the variably sized cystic spaces. Cells can interdigitate with myocytes within the inferior septum, resulting in degenerative changes within the myocytes. Cells may be cuboidal, transitional, squamoid or show sebaceous differentiation. Multilayering may occur along the cyst walls [240,1157,1189].

Immunohistochemistry
The cells strongly express cytokeratin, epithelial membrane antigen, carcinoembryonic antigen and B72.3. Cells may also express calcitonin and serotonin [465,523,1173,1345].

Electron microscopy
Two cells types are characteristic. Within the solid nests, cells have well formed basement membrane, cytoplasmic tonofilaments and desmosomes. Cells lining the spaces are also connected by desmosomes, have short microvilli and may contain electron dense material [240].

Prognosis
The tumours are benign neoplasms but may result in significant arrhythmias or sudden death. Surgical excision has been reported in a few patients [951,1541].
Cardiac sarcomas

Angiosarcoma

Definition
Angiosarcoma is a malignant tumour whose cells display endothelial differentiation.

ICD-O code
9120/3

Synonyms
Haemangioendothelioma, malignant haemangioendothelioma, haemangiosarcoma, haemangioendothelial sarcoma, malignant haemangioma and malignant angioendothelioma [1179].

Epidemiology
Angiosarcomas are the most common malignant differentiated cardiac neoplasms [259,691]. They occur over a wide age range (36 months to 80 years) [259,1693] with a peak incidence in the fourth decade. It occurs with equal frequency in men and women.

Localization
It most often arises in the right atrium near the atrioventricular groove (80%), but has been reported in the other three chambers as well as in the pericardium [921,1654]. Left atrial involvement is unusual though it has been reported [203,478,799]. In one series the right atrium was involved in 55.6% and showed co-involvement of the right ventricle (6.5%), pericardium (6.5%), and the left atrium (0.9%) [1653].

Clinical features

Signs and symptoms
Clinical features reflect location, size and the extent of regional involvement, and the presence or absence of metastases [259]. Most are initially silent. Because of frequent pericardial involvement [1653], dyspnoea is not an early symptom as is the case with other cardiac sarcomas. The most common presenting symptom is chest pain (46%) [259]. Right-sided heart failure, often associated with hemopericardium and supraventricular arrhythmias are also frequent [1128A, 1398A]. A significant number of patients present with or have co-existent haemorrhagic episodes, coagulopathy, anaemia, persistent haematomas or easy bruising [25]. Sometimes, early pericardial involvement may lead to pericardial biopsy during emergency surgical cardiac decompression for tamponade. Cardiac rupture may occur, but is rare. Presentation with lung metastases is not uncommon [23,186,2216]. In 10% of cases, fever, weight loss, and fatigue remain unexplained for several months, resulting in delayed diagnosis, large tumour size, and advanced stage when surgery is performed.

Imaging
At echocardiography angiosarcomas typically appear as an echogenic, nodular or lobulated mass in the right atrium. Pericardial effusion or direct pericardial extension/invasion are frequently seen [66]. At MRI angiosarcoma also usually appears as a heterogeneous, nodular mass in the right atrium. MRI imaging sequences sensitive for hemorrhage (T1 weighted images) may show areas of hemorrhage which may be diffuse or nodular [65]. After administration of intravenous contrast (gadolinium-DTPA) enhancement along vascular lakes may be seen which has been described as a “sunray” appearance [527]. Like echocardiography, MRI may also show pericardial effusion or direct pericardial invasion, though MRI is more sensitive than echocardiography for distinguishing between pericardial fluid and pericardial tumour. CT findings are similar to the MRI findings. CT usually shows a heterogeneous, nodular mass in the right atrium.

Fig. 4.24 Cardiac angiosarcoma. A. CT section at the level of the aortic valve demonstrates a soft tissue mass completely filling the right atrium. B. Cardiac angiosarcoma arising in right atrioventricular groove, forming a papillary right atrial mass. Note the extensive pericardial involvement. C. Metastatic angiosarcoma to the lung, forming multiple haemorrhagic subpleural nodules (courtesy of Dr. William D. Edwards).
Tumours of the heart - Sarcomas

with possible pericardial effusion or invasion. At CT angiosarcomas are usually low attenuation due to necrosis but may have focal high areas of attenuation due to hemorrhage. CT may show a similar pattern of contrast enhancement as MRI. With MRI or CT, the presence of a hemorrhagic, irregular right atrial mass is very suggestive of angiosarcoma, especially if accompanied by a pericardial effusion [66].

Macroscopy

Angiosarcomas usually form lobulated variegated masses in the right atrial wall, protruding into the chamber. They range from 2.0 cm to several centimeters. The masses are classically dark, grey-brown to black in colour and may resemble a melanoma [249], but tumours with less well-developed vascular spaces may appear firm, yellow-white in colour, lacking the classic hemorrhagic appearance. The pericardium is frequently involved and hence a hemorrhagic pericardial effusion is a frequent accompaniment. While involvement of the tricuspid valve and extension or invasion of the vena cavae is reported, involvement of the pulmonary artery and interatrial septum are unusual. In rare instances, the pericardium is the sole site of involvement.

Histopathology

Over two-thirds of cardiac angiosarcomas are well to moderately differentiated showing well-formed vascular channels and papillary structures. The vascular channels are irregular, anastomosing, and sinusoidal. The lining cells are usually pleomorphic and atypical. They may form cord-like structures in which lumina are difficult to demonstrate. Mitoses are usually present [249,259,590]. The remaining third are poorly differentiated and composed predominantly of anaplastic spindle cells. In angiosarcoma with a focal or dominant spindle cell pattern, poorly formed vascular channels and extravascular red blood cells can usually be identified focally. Generous sampling may be necessary in order to identify diagnostic areas in such cases [249]. Often, metastatic as opposed to primary lesions, show areas of better differentiation. Angiosarcoma with a solid pattern of growth and individual cells having epithelioid features have been reported [2059]. In these cases the neoplastic cells have eosinophilic cytoplasm with occasional cytoplasmic vacuoles. The nuclei in this variety are usually large, hyperchromatic and have prominent eosinophilic nucleoli. The stroma can be abundant and hyalinized.

Immunoprofile

Immunohistochemical staining is important for the definitive diagnosis of vascular lesions, especially those with poorly differentiated patterns in which vascular channels are difficult to identify. Most angiosarcomas express, to variable degrees, usual endothelial cell antigens including factor VIII (von Willebrand factor), CD31 and CD34. Of these, CD31 gives the most consistent results, has good specificity and excellent sensitivity (approximately 90%) [462,2119]. Vascular channels may be highlighted by the use of laminin and type IV collagen. Cytokeratin and epithelial membrane antigen may be focally positive in conventional angiosarcoma and may be diffusely positive in epithelioid angiosarcomas [2247].

Electron microscopy

With the wide availability of immunohistochemistry, ultrastructural study is less critical for diagnosis. The classic ultrastructural feature of endothelial cells, the Weibel-Palade body, is not demonstrable.

Fig. 4.25 Cardiac angiosarcoma. A Cardiac angiosarcoma with papillary features. Serpiginous and gaping vascular spaces lined by plump hyperchromatic endothelial cells. B Cardiac angiosarcoma with irregular vascular spaces lined by atypical hyperchromatic, somewhat epithelioid endothelial cells.

Fig. 4.26 Epithelioid angiosarcoma. Note the prominent eosinophilic cytoplasm (arrows).
in most neoplastic cells. However, pinocytotic vesicles, abundant intermediate filaments, and a moderate amount of rough endoplasmic reticulum and Golgi apparatus may be identified. Pericytes may be demonstrated adjacent to tumour cells [1291].

**Differential diagnosis**
In cases with a dominant spindle cell pattern distinction from an unclassified spindle cell sarcoma, fibrosarcoma or malignant fibrous histiocytoma may be difficult. The detection of endothelial vacuoles or papillary structures are helpful. Immunohistochemical stains for laminin, type IV collagen and even reticulin stains may help highlight the vascular lumina [545]. The increasing incidence of Kaposi sarcoma makes differentiation from the spindle cell areas of angiosarcoma essential, though cardiac Kaposi sarcoma is usually metastatic. Pericardial angiosarcomas can be mistaken for mesotheliomas [1277] and clumps of reactive mesothelial cells may be trapped in areas of an angiosarcoma. Stains for cytokeratin, calretinin, cytokeratin 5/6 and CD31 can help to differentiate the two populations of cells.

**Genetics**
Genetics studies involving cardiac angiosarcomas are rare and they only analyze isolated patients with heart primary tumours. Cytogenetic analyses of cardiac angiosarcoma show no consistent chromosomal abnormality [590]. A case of right atrial angiosarcoma demonstrated hyperdiploid clonal populations with changes in chromosome number, as follows: 55, XY, +der (1;17) (q10;q10), +2,+7, +8, +19, +20, +21, +22, as well as polysomy of chromosome 8 [2247]. Other chromosomal changes reported are gains of 5pter-p11, 8p12-qter, 20pter-q12 and losses of 4p, 7p15-pter-y and abnormalities involving 22q (310,590). Molecular analyses on tumour tissues have focused on genetic alterations of TP53 and K-ras. The few reports available show that TP53 is more frequently altered than K-ras. Mutations of the TP53 tumour suppressor gene have been revealed by PCR-SSCP and sequencing studies and by immunohistochemical staining in up to 50% of tumours studied [662,1428,2247]. A K-ras mutation has also been documented in heart angiosarcoma [662]: a G-to-A transition at the first base of codon 13, which resulted in one amino acid substitution (Gly-13-Ser), in 2 relatively young patients (31 and 36 years old).

**Prognosis and predictive factors**
Cardiac angiosarcomas have an especially poor prognosis because they typically present in the face of advanced disease [249]. In one study, 80% of patients had metastatic disease at the time of diagnosis and 90% survived less than nine months [921]. A mean survival of ten months after surgical excision, with or without adjuvant therapy, has been reported in another study [823]. In soft tissue angiosarcomas, morphologic features that have statistically correlated with poor outcome include age, large size and high proliferative (Ki-67) index [478,590]. Metastases occur most frequently to the lung (70%), then liver. No significant correlation has been reported between DNA ploidy patterns and clinical outcome [590].

**Treatment**
There are no randomized treatment trials, but patients are generally treated by a combination of surgery and radiation with or without sarcoma-type chemotherapy. Surgical resection is necessary, but complete excision cannot be achieved in most cases, because lack of a dissection plane and myocardial encroachment of tumoural tissue. However, even partial resection (with possible valve repair) may provide some months of symptom-free survival. However, local recurrence is the rule, even when resection was thought to be complete. Heart transplantation has been used to treat cardiac angiosarcoma, but without long-term survival [1654, 2043].
Pleomorphic malignant fibrous histiocytoma (MFH) / Undifferentiated pleomorphic sarcoma

Definition
Malignant fibrous histiocytoma or undifferentiated pleomorphic sarcoma is high-grade malignancy showing fibroblastic or myoblastic differentiation and areas of marked cellular pleomorphism. Malignant fibrous histiocytomas and fibrosarcomas represent a broad spectrum of mesenchymal tumours and the degree of cellular pleomorphism is the major distinguishing feature.

ICD-O code
Malignant fibrous histiocytoma 8830/3

Synonym
Malignant fibrous histiocytoma is now regarded as synonymous with undifferentiated pleomorphic sarcoma, as many tumours formerly classified as MFH have been found to have evidence of myogenic or other more specific differentiation.

Epidemiology
Malignant fibrous histiocytoma, as historically defined, is the second most common malignant cardiac sarcoma in adults and, if considered with all undifferentiated sarcomas represents the most common sarcoma. There is no gender predilection and the mean age is around 45 years (range, 20-80 years). Rare cases have been reported in infants.

Localization
Malignant fibrous histiocytoma tends to be located in the left atrium of the heart, most commonly the posterior wall and / or interatrial septum {1056,1142,1526}.

In a recent review, 81% of 47 cases were left atrial {1508}. The other reported locations included the pericardial space (3 cases), right ventricle/ pulmonary valve (3 cases), right atrium (1 case), and left ventricle (1 case) {1508}. Although the majority occur in the left atrium, where they most often present like cardiac myxomas, they more commonly arise along the posterior wall in comparison to the septum {1056,1142,1526}.

Fig. 4.28 Malignant fibrous histiocytoma. A Primary malignant fibrous histiocytoma with osseous differentiation (osteosarcoma). B Malignant fibrous histiocytoma with osseous differentiation (osteosarcoma). C Large nodules in the right atrium.

Fig. 4.29 Malignant fibrous histiocytoma (pleomorphic undifferentiated sarcoma). A In this example, there is a myxoid background and a prominent vascular pattern reminiscent of myxoid malignant fibrous histiocytoma found in soft tissue. B Malignant fibrous histiocytoma arising in left atrium where it initially mimicked a cardiac myxoma. Note mitotic activity. C Note pleomorphic growth pattern. D Malignant fibrous histiocytoma with osseous differentiation (osteosarcoma). Note formation of the mature bone trabeculae. E Osteoid formation. F Cartilagenous differentiation.
Clinical features
Most occur on the left side of the heart and cause signs and symptoms related to pulmonary congestion, mitral stenosis and pulmonary vein obstruction. Tumours may also present with metastases and the lungs, lymph nodes, kidney and skin are common sites. Constitutional signs and symptoms may precede symptoms referable to the heart. Diagnosis of cardiac sarcoma rests on echocardiography; MRI is helpful preoperatively to determine precise tumour size, location, and adjacent tissues invasion, and post-operatively for assessment of excision and recurrence.

Macroscopy
Malignant fibrous histiocytoma typically presents as a soft or firm polyloid endocardial based tumour. It may be sessile or pedunculated, simulating myxoma, but unlike myxoma, may form multiple masses not obviously part of the same tumour (1142). The mass may distend the atrium and impinge upon the mitral valve. Extension into the pulmonary veins and lung parenchyma may be present (1056) They may be uniform tan-white or variegated due to haemorrhage and necrosis. Calcification is uncommon.

Histopathology
Malignant fibrous histiocytoma or undifferentiated pleomorphic sarcoma is a diagnosis of exclusion, and immunohistochemical studies are important in ruling out metastatic myogenic, melanocytic and neurogenic tumours as well as sarcomatoid carcinomas. Of the subtypes of malignant fibrous histiocytoma described in the soft tissue, the pleomorphic (greater than 90%) and giant cell subtypes have been recognized in the heart. The tumours are heterogeneous in appearance and are variably cellular. The constituent cells may be spindle or epithelioid and sometimes have abundant eosinophilic cytoplasm. Intermixed giant cells are common. A storiform arrangement of tumour cells is common and they usually have marked pleomorphism. Mitotic activity is easy to find.

Osteosarcoma
Undifferentiated pleomorphic sarcomas demonstrate areas of osseous differentiation in 15% of cases. There is debate as to whether these tumours should be classified as extra skeletal osteosarcomas or undifferentiated pleomorphic sarcomas with osteosarcomatous differentiation. Virtually all osteosarcomas of the heart reported thus far have occurred in the left atrium. Like skeletal osteosarcoma, areas of malignant giant cell tumour (giant cell malignant fibrous histiocytoma), chondroid differentiation, and osseous differentiation have been found to coexist in variable amounts in a single lesion.

Genetics
Genetic studies of cardiac sarcomas are limited. In studies of extra cardiac malignant fibrous histiocytoma, the common signature of genetic alterations includes recurring low-level copy number increases at new sites on chromosome 7, and losses of chromosome 2 sequences (1546). Genomic imbalance at chromosome 13 has also been observed, with high gains for Xp and bands 1q21-22, 1p31, 3q27 and 9q3. The losses at chromosome 13 were observed in a large proportion at regions 13q12-14 and 13q21-22 (1131,1224). Specific losses in regions that harbour tumour suppressor genes like INK4a (9p21) and RB1 (13q14) have been revealed by Southern blot and comparative genomic hybridization (1828). RB1 gene is probably implicated in tumourigenesis of malignant fibrous histiocytoma due to the high correlation between absence of RB1 protein expression and chromosome 13 losses and mutations found in this gene (353). Mutations localized to the core domain of TP53 have been found by immunohistochemical and sequencing procedures (1982), as have other abnormalities like protein accumulation (1647). TP53 mutations and accumulation of p53 protein have been detected in tumours with MDM2 gene amplification (1647).

Prognosis and predictive factors
For malignant fibrous histiocytoma and fibrosarcoma there is some evidence that grading is useful in predicting survival, but the majority of patients with these tumours die of either local or metastatic disease (731,952,1508). The mean post-operative survival is 5-18 months. The cause of death may be related to metastatic disease, bulky intracardiac recurrences, or general debilitation.

Fibrosarcoma and myxosarcoma

Definition
Fibrosarcoma is a malignant tumour composed of fibroblasts with variable amounts of intercellular collagen and a classic herringbone architecture. Some fibrosarcomas with abundant myxoid stroma have been called myxosarcomas but are not considered malignant variants of cardiac myxoma. Tumours with marked pleomorphism, or a prominent vascular or storiform pattern are better classified as malignant fibrous histiocytoma.

ICD-O code
Fibrosarcoma 8810/3

Fig. 4.30 A Myxosarcoma from the left atrium. Cut surface showing variable solid, soft and haemorrhagic regions. B Fibromyxosarcoma. A portion of the tumor near the endocardial surface shows an undifferentiated spindle cell sarcoma without prominent vascularity or pleomorphism and an abundant proteoglycan matrix.
Epidemiology
Fibrosarcoma represents 5-10% of all cardiac sarcomas depending on the criteria used for diagnosis. Fibrosarcomas are less frequent, and occur over a broader age range than malignant fibrous histiocytoma, some having been reported in children.

Localization
Fibrosarcomas are most common in the left atrium, but have been reported to arise in all chambers. Fibrosarcomas may also infiltrate the pericardial space, thus mimicking mesothelioma (1034).

Clinical features
The clinical features of fibrosarcomas have not been well-delineated from related cardiac sarcomas such as malignant fibrous histiocytoma (undifferentiated pleomorphic sarcoma) as the classification of these lesions has not been standardized in large series. As with other sarcomas, signs and symptoms vary depending on the location of the tumour. Because most occur on the left side of the heart, signs and symptoms related to pulmonary congestion, mitral stenosis and pulmonary vein obstruction are most frequent. Rarely, cardiac fibrosarcoma may present with metastases in the lungs, lymph nodes, skin, and kidney.

Macroscopy
Fibrosarcoma typically presents as a soft polyoid tumour projecting into the chamber from whose walls they arise. They have a gross appearance similar to MFH (329), but haemorrhage, necrosis, and variegation are less common.

Histopathology
Fibrosarcoma of adult type is composed of spindle shaped cells arranged in sweeping fascicles that are often arranged at angles to one another resulting in a “herringbone” pattern. The nuclei are usually elongate with tapered ends and darkly staining. Mitotic activity is variable. In the myxoid variant tumour cells spindling is less pronounced and cells may take on a stellate or ovoid configuration. However in all types pleomorphism is minimal and prominent vascularity is absent.

Differential diagnosis
The differential diagnosis for the typical variant of fibrosarcoma includes monophasic synovial sarcoma, inflammatory myofibroblastic tumours and localized fibrous tumours, and for the myxoid variant, other myxoid sarcomas (MFH, leiomyosarcoma, etc.) and cardiac myxoma. The latter is generally distinguished by the presence of myxoma cells, abundant organizing hemorrhage, and absence of mitotic figures and high cellularity. Fibromas are easily distinguished from typical fibrosarcoma by lack of cellularity and abundant collagen.

Rhabdomyosarcoma
Definition
Rhabdomyosarcoma is a malignant tumour with striated muscle differentiation.

ICD-O code
8900/3

Epidemiology
Rhabdomyosarcoma is a very rare subtype of cardiac sarcoma. In the past, before immunohistochemical documentation of tumour histogenesis was routine, it was stated that a large proportion of cardiac sarcomas were rhabdomyosarcomas. However, in more recent series, the proportion is less than 5% (250), and in one recent series of cardiac sarcomas with rigorous immunohistochemical documentation, none of 24 was classified as rhabdomyosarcoma (509).

Localization
Rhabdomyosarcomas occur anywhere in the heart. Approximately 50% occur in the atria, and 50% in the ventricles. The frequency of ventricular involvement is greater than other cardiac sarcomas. Contrary to sarcomas with fibro- or myofibroblastic differentiation, they are not usually intracavitary tumours, but are more often mural.

Clinical features
Cardiac rhabdomyosarcomas are usually of the embryonal variant and, there-
fore, occur most frequently in children and young adults; it is the most common primary cardiac malignancy in children. The mean age at presentation is approximately 20 years, compared to 40-50 years of age for other subtypes of cardiac sarcoma. Rhabdomyosarcoma is more likely than other primary cardiac sarcomas to involve the valves. The clinical presentation, as with other cardiac tumours, depends on the cardiac location.

Macroscopy
Cardiac rhabdomyosarcomas are bulky, invasive tumours that may be grossly mucoid or gelatinous, similar to cardiac myxoma, or soft and necrotic, with variation and heterogeneity. They usually arise within the myocardium and are less likely than sarcomas with myofibroblastic or fibroblastic differentiation to be endocardial based, luminal tumours.

Tumour spread and staging
Sites of metastatic spread are, in order of descending frequency: lungs, regional lymph nodes, central nervous system, gastrointestinal tract, kidney, adrenals, thyroid, ovary, bone and pancreas.

Histopathology
Cardiac rhabdomyosarcomas are almost exclusively embryonal. Embryonal rhabdomyosarcoma is small cell neoplasm with variable numbers of PAS-positive rhabdomyoblasts (tadpole or strap cells). Well-differentiated embryonal rhabdomyosarcoma has numerous tadpole-shaped rhabdomyoblasts. Nuclear staining with antibodies against myogenin greatly facilitates the diagnosis (1630). Desmin is also useful in documenting muscular differentiation. Alveolar rhabdomyosarcoma, characterized by a collagenous stroma and a paucity of rhabdomyoblasts, has been described in the heart generally as a metastatic lesion. Sarcoma botryoides, with characteristic grape-like structures and a so-called cambium layer, a form of embryonal rhabdomyosarcoma, has also been described in the heart (760).

Differential diagnosis
The differential diagnosis includes other cardiac sarcomas, especially undifferentiated lesions and metastatic small round cell tumours in children and young adults. Immunohistochemical stains are vital in identifying rhabdomyoblasts. Adult cellular rhabdomyomas, in contrast to rhabdomyosarcoma, lack significant mitotic activity, necrosis, and do not express myogenin.

Electron microscopy
The diagnostic features are thick and thin filaments reminiscent of normal striated muscle. Internal A and I banding may or may not be present, but Z-bands are frequently well formed. Plentiful glycogen granules and abundant mitochondria are also present. Tumour nuclei are lobulated, containing variable amounts of condensed chromatin. Occasionally, several grids must be examined before rhabdomyoblasts are identified.

Somatic genetics
At exon 1 of K-ras, a mutation at the first base of codon 13 (G to A transition) has been detected in cardiac rhabdomyosarcoma (662).

Treatment
Surgery
Surgical resection of the tumour is usually indicated even if it is considered as palliative to relieve obstruction to cardiac blood flow and to clarify the diagnosis (301,470,952). Total orthotopic heart transplantation may offer relatively long-term survival (67,701,733) if there are no distant metastases.

Chemotherapy
Although the outcome of chemotherapy on cardiac rhabdomyosarcoma has not been fully studied, due to the rarity of the tumour, there have been advances in the treatment of soft tissue rhabdomyosarcoma (423,529, 1194,1749) with a three-year progression-free survival of approximately 65%. Neoadjuvant chemotherapy may optimize a surgical approach (1749).

Radiotherapy
Adjuvant radiotherapy is commonly mandatory to preclude local relapse or to optimise the results of a surgical approach. However radiotherapy may be used preoperatively to decrease tumor size and allow surgical resection.

Prognosis and predictive factors
Specific prognostic microscopic features have not been devised for cardiac rhabdomyosarcomas. However, grading is similar for other subtypes of cardiac sarcomas, and includes an assessment of mitotic activity and necrosis (509). The
prognosis is poor, with recurrence and eventual metastasis with death of the patient within months the rule [1944]. The mean survival rarely exceeds 12 months.

**Leiomyosarcoma**

**Definition**
A malignant tumour composed of cells with distinct smooth muscle features.

**ICD-O code**
8890/3

**Epidemiology**
Cardiac leiomyosarcoma is uncommon, representing less 10% of cardiac sarcomas. There is no sex predilection, and most occur in patients between 40 and 50 years of age.

**Clinical features**
Dyspnoea is the main clinical feature. Sometimes patients present with chest pain, cough, atrial arrhythmias, or haemoptysis.

**Macroscopy**
Most of them are located in the left atrium (posterior wall) and invade pulmonary veins or mitral valve. But, tumours can arise elsewhere, including the right atrium and ventricle, or pulmonary valve or trunk. The tumours tend to be firm, fleshy, grey and sessile. They may present as multiple intra-cavitary nodules.

**Histopathology**
Leiomyosarcoma is composed of compact bundles of spindle cells that possess blunt-ended nuclei and are often oriented at sharp angle or 90° to one another. Inconstant characteristic features include the presence of cytoplasmic glycogen and perinuclear vacuoles. Pleomorphic and giant cells may be present. Zones of necrosis and mitotic figures are generally plentiful. Usual immunohistochemical markers of neoplastic cells are smooth muscle alpha actin and desmin. Alpha actin also shows numerous normal little vessels in the tumour tissue. There may occasionally be aberrant expression of cytokeratin and epithelial membrane antigen. Demonstration of smooth muscle cell derivation virtually confirms malignancy, as leiomyomas remain undescribed in this location.

**Treatment and prognosis**
Treatment consists of surgical excision, almost always incomplete. This may allow some patients several months of symptom free survival, typically less than one year. Chemotherapy and radiation therapy may provide palliation.

**Synovial sarcoma**

**Definition**
Synovial sarcoma is a biphasic tumour composed of spindled and epithelioid areas, characterized by X;18 chromosomal translocations.

**ICD-O code**
9040/3

**Epidemiology**
Synovial sarcomas account for approximately 5% of cardiac sarcomas [173, 300,400,1466]. The true incidence has probably been underestimated, as molecular studies can now confirm the diagnosis in the monophasic variant, which is the most common form in the heart. An association between cardiac synovial sarcoma and asbestos exposure has been reported [1144].

**Localization**
There is a predilection for the atria and pericardial surfaces.

**Clinical features**
Clinical symptoms may arise from obstruction, embolism, and tamponade.

**Macroscopy**
Synovial sarcomas are bulky, infiltrative tumours that are typically firm and white. Necrosis or hemorrhage may be present.

**Histopathology**
The classic lesion is biphasic, but the monomorphic variant is especially common in the heart. The spindle component resembles a fibrosarcoma, but alternating cellular and oedematous areas are typical. The spindle cells are small, compact, and often infiltrated by sparse mononuclear lymphoid cells. The epithelioid cells form clusters and nests, and occasionally larger gland-like spaces which may show branching. Immunohistochemically, cytokeratin and epithelial membrane antigen are strongly expressed in the epithelioid cells. Staining for these markers in the spindle cells may be very focal. Spindle cells express vimentin and occasionally smooth muscle actin. The cells do not express CD34.
Differential diagnosis

Distinction of synovial sarcoma from mesothelioma, another biphasic tumour, can usually be made on the basis of tumour location (mesotheliomas do not occur within the atria) and growth pattern (synovial sarcoma is usually a circumscribed solitary lesion while mesothelioma tends to grow diffusely over the pericardium. Additionally, the spindle cell areas of synovial sarcoma tend to be relatively monomorphous. The X;18 translocation may be confirmed on formalin fixed, paraffin embedded tissues and has a high degree of sensitivity and specificity (1506). Reactivity for calretinin has been described in both mesothelioma and synovial sarcoma, and is not helpful in the differential diagnosis. Unlike mesothelioma, solitary fibrous tumour is generally lower-grade, usually expresses CD34 antigen, is less cellular and tends to have alternating hyper- and hypocellular areas.

Somatic genetics

Cytogenetically the reciprocal translocation t(X;18)(p11.2;q11.2) is seen in more than 90% of soft tissue synovial sarcomas (1330). This is considered to be the primary cytogenetic abnormality and specific for synovial sarcomas. The breakpoints of the t(X;18) have been cloned, and it has been shown that this translocation results in fusion of SS18 gene (previously described as SYT or SSXT) at the chromosome 18q11.2 to either of two genes, SSX1 or SSX2, at Xp11.2. This rearrangement of genes produces a chimeric SS18/SSX transcript, which could be implicated in tumorigenesis (375). The SS18/SSX transcripts can be specific markers of synovial sarcoma that can be detected by the reverse transcriptase-polymerase chain reaction (RT-PCR). The transcripts can be identified in almost all synovial sarcomas when there is adequate tumour RNA (837). This molecular diagnostic method also can be applied to paraffin-embedded tissue (747).
Cardiac lymphomas

Definition
Primary cardiac lymphoma (PCL) is an extra-nodal lymphoma involving only the heart and/or the pericardium. A less restrictive definition includes small secondary lesions elsewhere, with the vast bulk of the tumour arising in the heart. It is clinically defined as a lymphoma presenting as cardiac disease with the bulk of the tumour being intra-pericardial. Cardiac involvement by disseminated non-Hodgkin lymphoma should be excluded.

Epidemiology
PCL is an uncommon malignancy, accounting for 1.3% of primary cardiac tumours and 0.5% of extranodal lymphomas [249,273,1679]. The published series account for about 80 cases, while cardiac involvement in disseminated lymphoma has been documented in nearly 20% of autopsy cases [1280]. The appearance of PCL in patients with AIDS [1736] and in a kidney recipient [1667] suggests that immunodeficiency may be a predisposing factor. However, the heart is an uncommon site for immunodeficiency-related lymphoma. Most PCL arise in immunocompetent patients. The median age of the reported cases is 62 years (range, 5-90 years) with a male-to-female ratio of 3:1. The clinical course is generally short, with a mean survival of 7 months (range, 0-48 months).

Clinical features
Signs and symptoms
The clinical course is generally acute in onset. There is no pathognomonic clinical presentation and patients are generally investigated because of chest pain, pericardial effusion, refractory heart failure, arrhythmia, or lightheadedness and syncope due to a myxoma-like intracavitary mass [308]. Superior vena cava obstruction [363], multiple pulmonary emboli and infarction [1832] and hypertrophic cardiomyopathy [266] have also been reported as initial diagnosis in patients with PCL. Complete atrio-ventricular block may be the major clinical presentation [1416].

Imaging
Because the gross pathologic features of primary cardiac lymphoma are variable, the imaging findings are variable. Cardiac lymphomas most commonly manifest as circumscribed, nodular masses in the myocardium, often with an associated pericardial effusion. These findings are usually well seen at echocardiography, MRI, and CT. Lymphoma may also manifest as an ill-defined, infiltrative mass, in which case, they are typically best depicted with MRI because of its superior soft tissue contrast [66]. Internal imaging features and contrast enhancement patterns are very variable with cardiac lymphomas. Lymphomas may have high or low signal on MRI, may have similar attenuation as muscle or lower attenuation than muscle on CT, and may show increased, or decreased contrast enhancement. In some cases, pericardial effusion or pericardial thickening may be the only findings. In addition to echocardiography, MRI, and CT, nuclear medicine techniques may be useful procedures for the non-invasive assessment of cardiac lymphomas. Gallium-67 uptake is non-specific, though a marked accumulation in the heart without extracardiac uptake can suggest the diagnosis of PCL [1680].

Diagnostic approach
When pericardial effusion is present its drainage may have both palliative and diagnostic purposes. Lymphoma cells may be detected in serous fluid in up to 88% of cases [308]. When cytology is not available, the diagnosis of PCL is usually assessed by explorative thoracotomy with cardiac mass biopsy. Recently, less invasive procedures have been performed, such as transoesophageal echocardiography (TEE) guided percutaneous intracardiac biopsy [46,947].

Macroscopy
PCL may arise in either atrium or ventricle. Usually the tumour is large, infiltrating myocardium and extending into the right atrium and ventricle in the form of multiple intracavitary polypoid nodules, which may eventually obliterate the cavi- ties. The right atrium is involved in more than 2/3 of patients. The pericardium is usually thickened by white-greyish tumour infiltration. Pericardial effusion, which is generally massive, may be isolated (12.5% of cases) or associated with a heart mass (near half of cases) [737].

Cytology
A diagnostic cytologic sample is obtained in less than 20% of primary cardiac lymphomas (PCL) [1680]. It may be difficult to differentiate PCL from benign reactive lymphocytosis by cytology alone. Immunocytochemical staining [1724], cytogenetic studies [1] and polymerase chain reaction [964] have been performed successfully to confirm the lymphoid lineage and detect the presence of a monoclonal population.
Histopathology
Diffuse large B-cell lymphoma is the subtype most frequently observed (80% of published cases). Non-cleaved small cell lymphoma has been reported in a few cases; the histopathology was unspecified in the other cases. Recently two cases of diffuse large B-cell lymphoma with CD5 expression have been reported [317]. This is a recently identified subgroup of diffuse large B-cell lymphomas, which differs for clinical characteristics (elderly, female and extranodal involvement) and aggressive clinical course [2181]. One case of Burkitt lymphoma in an immunocompetent patient has been described [317].

Somatic genetics
A complex abnormal karyotype containing t(8;14) (q24;q32) has been reported in a case of diffuse large B-cell lymphoma mainly involving the heart with cells which were CD5+ and CD20+ with a c-myc rearrangement [1948]. In situ hybridization for EBER-1 was negative.

Prognosis and predictive factors
Late diagnosis appears to be a major factor in the poor outcome in PCL patients. Irrespective of the treatment applied, 60% of the patients died of their tumour 1.8 months after diagnosis [317]. Prompt anthracycline-based chemotherapy results in near 60% of complete response (mean follow-up 17 months; range 3-40 months). PCL should be treated like other aggressive lymphomas arising in other primary sites.
Metastatic tumours to the heart

G. Rolla
F. Calligaris-Cappio

Definition
Malignant cardiac neoplasm with a non-pericardial or myocardial primary site. Metastatic tumors that infiltrate myocardium are frequently accompanied by pericardial metastases, especially in the cases of carcinomas, which additionally involve mediastinal lymph nodes.

Epidemiology
In a series of 133 surgically resected cardiac tumors, 14% were metastatic (1411). In a recent review, cardiac metastases were present in 12% of autopsies performed for widespread malignancy (12). Primary tumors in decreasing order of frequency include carcinomas of the lung, lymphomas, carcinomas of the breast, leukemia, carcinomas of the stomach, malignant melanoma, hepatocellular carcinoma and carcinomas of the colon. The following tumors have an especially high rate of cardiac metastasis if the incidence of the primary tumor is considered: leukemia, melanoma, thyroid carcinoma, extracardiac sarcomas, lymphomas, renal cell carcinomas, carcinomas of the lung and carcinomas of the breast. These tumors all had a greater than 15% rate of cardiac metastasis in a large autopsy study (1398). The rate of cardiac involvement by metastatic disease has not appeared to change over a 14-year period, indicating that current treatment modalities may not have a significant effect on the rate of metastatic malignancy to the heart.

Clinical features
The cardiac location of the tumor greatly affects the signs and symptoms. These can include symptoms related pericardial effusions, arrhythmias, or congestive heart failure. Obstruction of the mitral or aortic valve may cause syncope. Involvement of the right heart and tricuspid valves may give rise to right-sided failure.

Localization
Malignancies spread to the heart by direct extension, usually from mediastinal tumor; haematogenously; via lymphatics; and rarely by intracavitary extension from the inferior vena cava or pulmonary veins. Lymphatic spread is generally accompanied by involvement and enlargement of pulmonary hilar or mediastinal lymph nodes. Haematogenous spread is characterized by myocardial involvement.

Epithelial malignancies typically spread to the heart by lymphatics. Melanoma, sarcomas, leukemia and renal cell carcinoma metastasize to the heart by a haematogenous route. Melanomas, renal tumours, including Wilms’ tumour and renal cell carcinoma, adrenal tumours, liver tumours, and uterine tumours are the most frequent intracavitary tumours. Metastatic cardiac tumours affect the right side of the heart in 20-30% of cases, the left side in 10-33% of cases, and show bilateral or diffuse involvement in approximately 30-35% of cases. The endocardium or chamber cavities are involved in 5% of cases (1398). The most common epithelial malignancies to metastasize to the heart are carcinomas of the breast and lung. In most cases there is pericardial involvement with superficial myocardial infiltration. The valves and endocardium are usually spared. Generally, the heart is not the only organ involved, and metastatic deposits are usually present in extracardiac sites.

The myocardium is involved in virtually 100% of cases of metastatic melanoma, and there is less frequent infiltration of epicardium. Leukemic and lymphomatous infiltrates are typically widespread, involving the epicardium (61%), and myocardium diffusely. The left ventricle is involved in 55%, and right atrium in 54% of cases. Sarcomatous deposits are found within the myocardium (50%), pericardium (33%), or both myocardium and pericardium (17% of cases). Valvular metastases are uncommon (764). Osteosarcoma, liposarcoma, leiomyosarcoma, unclassifiable sarcomas, rhabdomyosarcoma, neurofibrosarcoma, synovial sarcoma, and malignant fibrous histiocytoma have been reported to involve the heart secondarily.

Pathologic findings
Metastatic deposits may be diffuse, multinodular, or consist of a single dominant mass. Especially with carcinomas, there may be diffuse studding and thickening of the pericardial surfaces. This pattern can grossly be confused with mesothelioma, or benign fibrosing pericarditis. The tumour burden in the heart is the highest with melanoma, as compared to any other malignancy. Carcinomatous spread in the myocardium is frequently most prominent in subepicardial lymphatics, whereas melanomas, sarcomas, renal cell carcinomas and lymphoid neoplasms form intramyocardial interstitial tumours. The histopathologic distinction between primary and metastatic sarcoma may be impossible upon surgical resection of a cardiac tumour. Most sarcomas metastatic to the heart cause symptoms at their primary site before cardiac symptoms are evident, however (764). Although primary sarcomas of the heart are uncommon, extracardiac sarcomas presenting as cardiac metastases are even rarer.

Fig. 4.38 Metastases of a large cell carcinoma of the lung in the heart.
**Pericardial tumours**

**Solitary fibrous tumour**

**Definition**
An uncommon, spindle-cell, fibroblastic tumour which often shows a prominent haemangiopericytoma-like vascular pattern.

**ICD-O code**
Solitary fibrous tumour 8815/1

**Synonyms**
Benign mesothelioma, fibrous mesothelioma, submesothelial fibroma

**Localization**
The most common locations, outside the pleura, include the head and neck, especially orbit, soft tissue, especially abdomen, extremities, and meninges {233,1384,1473}. As with any lesion common to the pleura, there have been examples of solitary fibrous tumour reported in the pericardium and rarely within the heart.

**Clinical features**
Clinical features are related to pericardial mass effect.

**Macroscopy**
Solitary fibrous tumours tend to be well-circumscribed, firm, fleshy or white although diffuse mesothelial surface involvement has been described.

**Histopathology**
Histologic variability is the rule and multiple growth patterns have been described. Most tumours will have a predominant monomorphic spindle cell pattern resembling low-grade fibrosarcoma although broad tumour cell fascicles are rare. Areas of hypercellularity typically alternate with those that are less cellular. The less cellular areas can by myxoid or contain abundant collagen {459}. Typically the nuclei of tumour cells are closely apposed to collagen bundles. A haemangiopericytoma-like vascular pattern may be conspicuous, present in a small portion of the lesion, or absent. The differential diagnosis includes other monomorphic spindle cell tumours, including neurogenic tumours, spindle cell mesotheliomas, monophasic synovial sarcoma, and fibrosarcoma {1311}. Recently, desmoid tumour of the pleura has been added in the list of differential diagnostic considerations {2151}. See pleural section for additional information.

**Immunoprofile**
Solitary fibrous tumours are CD34 and bcl-2 positive. They are consistently negative for epithelial markers, muscle specific actin, desmin, CD31, CD117 (c-kit), S-100 protein calretinin, and inhibin {596,772,1473,2127}.

**Differential diagnosis**
Sarcomatous mesotheliomas of the pericardium are distinguished from solitary fibrous tumours by their diffuse growth pattern, and keratin and calretinin reactivity. On the other hand, solitary fibrous tumour may closely mimic monophasic synovial sarcoma and low-grade fibrosarcoma. Fibrosarcoma tends to be more architecturally monomorphic and negative for CD34. Monophasic synovial sarcoma has higher grade cytology, plumper nuclei and shows focal keratin reactivity. Endometrial stromal sarcoma, and metastatic granulosa cell tumour may be excluded by negative reactivity for cytokeratin, estrogen and progesterone receptors, and inhibin.

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Fig. 4.39 Mesothelioma of pericardium. A Note the extensive tumour encasing the pericardium. B In many cases, the pericardial mass is in continuity with pleural mesothelioma.

Fig. 4.40 Localized fibrous tumor of the mesothelium is identical in appearance to those of the pleura. Note the spindle cell growth with prominent vascularity and variable cellularity.
Prognosis and predictive factors
The prognosis is generally good, although recurrences and local spread have been reported. Criteria for malignancy of pleural tumours include necrosis and a mitotic count of greater than 4 per 10 high powered fields, but the applicability of these criteria to tumours in the heart and pericardium is unknown.

Malignant mesothelioma

Definition
Malignant mesothelioma arises from mesothelial cells or demonstrates mesothelial differentiation. The definition of primary pericardial mesothelioma stipulates that there is no tumour present outside the pericardium, with the exception of lymph node metastases.

ICD-O code 9050/3

Epidemiology
Mesothelioma of the pericardium represents approximately 0.7% of malignant mesotheliomas [831]. As with mesotheliomas in other sites, the incidence may be increasing, due to the latency between asbestos exposure and tumour development [1074].

Etiology
Like pleural mesotheliomas, a large proportion of mesotheliomas of the pericardium are induced by asbestos [1074]. Iatrogenically induced pericardial mesotheliomas have been reported decades after exposure to pericardial dusting with asbestos and fibreglass as a treatment for angina pectoris. Therapeutic radiation for breast cancer and mediastinal lymphoma has also been implicated in rare patients. However, there remains a subset of patients with mesothelioma who have no known exposure history.

Clinical features

Signs and symptoms
The mean age of patients with pericardial mesothelioma is about 45 years, with a wide age range, including elderly, older children and young adults. The initial course is usually related to pericardial effusions. Tamponade may eventually occur [1202].

Imaging
Echocardiography usually shows pericardial effusions and may show pericardial thickening. However, because pericardium is at the periphery of the field of view obtainable with echocardiography, MRI or CT are usually necessary. MRI and CT usually demonstrate pericardial fluid as well as pericardial thickening and/or pericardial masses [737].

Macroscopy
Malignant mesotheliomas of the pericardium can form bulky nodules that fill the pericardial cavity. The tumour can also spread diffusely over the pericardial surface and completely encase the heart. They can further encircle the great vessels and may obstruct the venae cavae.

Histopathology
Malignant mesotheliomas of the pericardium resemble pleural mesotheliomas. Although the majority are of the epithelioid type, forming tubules, papillary structures, and cords of infiltrating cells that can incite a desmoplastic response, the sarcomatous variant is also common. Variants similar to those described in the pleura may also be seen in the pericardium e.g. microcystic, adenomatoid, deciduoid [1649,1802].

Immunoprofile
The immunohistochemical profile of pericardial mesothelioma is similar to that of pleural mesothelioma. Expression of mesothelial antigens, such as calretinin, and cytokeratins 5/6 are helpful in the diagnosis, as are negative reactions for adenocarcinoma markers, such as carcinoembryonic antigen.

Electron microscopy
Ultrastructurally, mesothelioma cells from epithelioid areas contain branched, bushy microvilli. Cytoplasmic tonofibrils are present in approximately 50% of tumours. Asbestos bodies may be identified within pericardial mesothelioma, but are of no diagnostic utility.

Differential diagnosis
The distinction between mesothelioma and pleural-based lung adenocarcinoma can be quite difficult, and is generally based on immunohistochemical findings. Distinction from reactive mesothelial cell proliferations may also be difficult; in comparison to reactive pleural mesothelial proliferations, reactive pericardial mesothelial cells may be more deeply “invasive”. Reactive stromal cells may also often attain bizarre and pleomorphic shapes, confusing the histopathologic picture. Other malignancies that may be confused with mesothelioma include pericardial-based angiosarcoma, which may elicit a prominent mesothelial response, malignant solitary fibrous tumour and synovial sarcoma. Immunohistochemistry is invaluable in such circumstances. Mesothelioma lacks the X;18 translocation of synovial sarcoma.

Prognosis and predictive factors
The prognosis of pericardial mesothelioma is poor. Fifty per cent of patients
survive 6 months, and an exceptional patient may live as long as 48 months (248).

**Germ cell tumours**

**Definition**
A neoplasm of germ cell origin classified by histologic type into seminoma (dysgerminoma), embryonal carcinoma, yolk sac tumour (endodermal sinus tumour), choriocarcinoma, and teratoma.

**Epidemiology**
Approximately 100 cases of intrapericardial germ cell tumours have been reported, over 90% within the pericardium, and the remainder in the myocardium. The majority are pericardial teratomas (248), and the remainder are yolk sac tumours (411,1178). Reports of intrapericardial teratoma describing the presence of only one or two germ cell layers may represent misclassified bronchogenic cysts.

**Clinical features**
Patient age ranges from intrauterine life to 66 years (411). Teratomas generally occur in infants while adults tend to have malignant germ cell tumours. Over 75% of cardiac teratomas occur in children under age 15. There is a slight female predominance. Symptoms include respiratory distress, pericardial tamponade, and cyanosis. Occasionally mediastinal teratomas in adults may secondarily involve the pericardium. Due to the routine use of fetal echocardiography, an increasing number of pericardial teratomas are being diagnosed in second and third trimester fetuses (1615, 1786,2005). Neonates may die at birth from cardiac tamponade and cardiac compression. Prenatal resection and intruterine pericardiocentesis have been successfully accomplished (1615, 1935). Intramyocardial teratomas have occurred in the newborn period or in the first 6 years of life (1615). Most patients are symptomatic and present with congestive heart failure; rarely, a patient may be asymptomatic, or sudden death may be the first symptom, due to acute arrhythmia caused from the tumour’s interventricular location.

**Macroscopy**
Cardiac teratomas may be massive, measuring up to 15 cm. They have a smooth surface and are lobulated. The tumours are multicystic with intervening solid areas. The tumours usually displace the heart and rotate it along its longitudinal axis. Intrapericardial teratomas are usually located on the right side of the heart, displacing the organs to the left and posteriorly; those located on the left side will produce the opposite effect. Teratomas are usually attached by a pedicle to one of the great vessels with arterial supply directly from the aorta.

**Histopathology**
Teratomas of the heart are similar to extracardiac teratomas. A minority of germ cell tumours of the pericardium are yolk sac tumours (248,411,1792).

**Histogenesis**
The cell of origin of extragonadal teratoma, including pericardial teratoma, is the primordial germ cell. Although normal germ cells migrate from the yolk sac to the gonad, they may lodge early in embryogenesis in midline structures such as the mediastinum.

**Treatment**
Surgical excision is the only effective treatment for cardiac teratoma. Since the blood supply is usually from the root of the ascending aorta, the surgeon must perform a careful dissection and ligation of these vessels to prevent massive hemorrhage. Intracardiac teratomas, because of their location in the interventricular septum, are more difficult to remove than pericardial teratomas. Malignant germ cell tumours require standard chemotherapy.

**Metastatic pericardial tumours**
A high percentage of pericardial biopsies occur in patients in whom the diagnosis of malignancy has not yet been made, either for life-threatening tamponade or to establish the cause of pericarditis (1201,1499). In about two-thirds of patients with positive pericardial biopsy, the clinical diagnosis is pericarditis,
and in the remainder, tamponade. False negative biopsies may occur due to sampling, and it is not uncommon to have a positive cytology and a negative biopsy. Most adenocarcinomas presenting as pericardial metastases originate either in the lung or an undetermined primary site. Breast carcinoma, unlike lung carcinoma, usually manifests as pericardial disease only after the primary site is known. Other tumours found in pericardial biopsies include lymphoma, melanoma, multiple myeloma, thymoma, metastatic seminoma (121,249,1398). The sites of origin of tumours discovered initially at pericardial biopsy are shown in Table 4.03.

The distinction between reactive mesothelial hyperplasia and metastatic carcinoma can be difficult, and is assisted by immunohistochemistry. The presence of carcinoembryonic antigen, berEP4, B72.3 antigen, and Leu M1 favour carcinoma over mesothelial hyperplasia. Calretinin and cytokeratin 5/6 reactivity favour the diagnosis of a mesothelial process.

The treatment of malignant pericardial disease includes establishing a pericardial window, sclerosis with tetracycline or other agents, and radiation therapy (1069). Malignant pericardial effusions are generally a sign of rapidly progressive disease, necessitating emergency treatment. Patients with metastatic pericardial disease have a mean survival of 4.3 months (1201). In contrast, patients with pericardial malignant lymphoma or with involvement by thymoma often fare significantly better.

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Number</th>
<th>Fraction</th>
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<td>68%</td>
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<tr>
<td>Adenocarcinoma</td>
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</tr>
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<td>Sarcoma</td>
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<td>9%</td>
</tr>
<tr>
<td>MFH</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Angiosarcoma</td>
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</tr>
<tr>
<td>Leiomyosarcoma</td>
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<tr>
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</tr>
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<tr>
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<td><strong>Total</strong></td>
<td><strong>80</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
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Table 4.03
Malignant tumours diagnosed at pericardial biopsy (1201).

Fig. 4.44 Metastatic pericardial tumors. Gross large metastatic nodules in cardiac chambers and myocardium (renal cell carcinoma).