Prevalence and pathology of primary cardiac tumours

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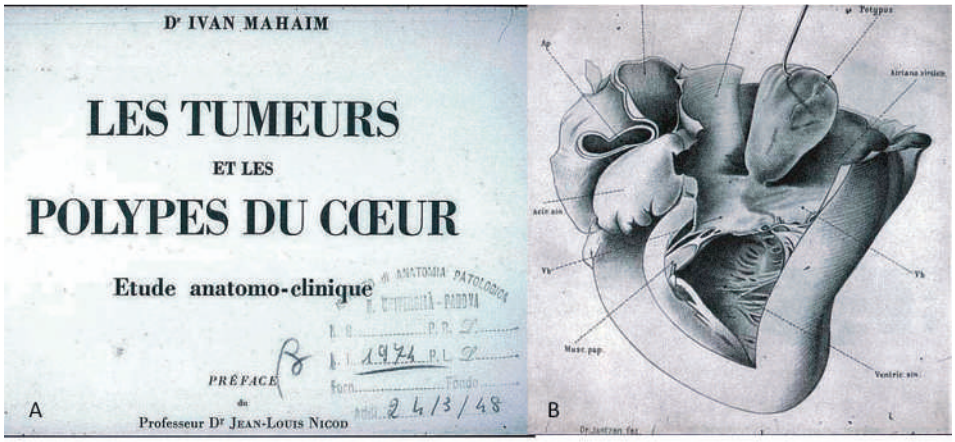
Summary

Primary cardiac tumours are rare clinical observations, different from secondary neoplasms (ten times more frequent), and 90% of all primary cardiac tumours are benign. Myxoma is by far the most frequent benign tumour (75%), typically located in the left atrium, and manifests with intra-cavitary obstruction, embolism and constitutional symptoms, but it may also be silent and discovered incidentally by echo. Papillary fibroelastoma is a tumour usually arising on the valvular or mural endocardium, which, although quite small, may become symptomatic through embolic events. Typical tumours of the paediatric age group are fibroma, rhabdomyoma and teratoma.

Primary malignant neoplasms account for 10% of all primary cardiac tumours and are represented by sarcomas (angiosarcoma, leiomyosarcoma, fibrosarcoma, liposarcoma, rhabdomyosarcoma undifferentiated pleomorphic sarcomas) and primary lymphomas. They usually infiltrate the cardiac walls, but may be also solely intra-cavitary, mimicking myxoma. Non neoplastic masses may consist of thrombi and infections, which again can be identified by a thorough surgical pathology examination. Cardiac non invasive imaging through transthoracic and transesophageal echocardiography easily detects heart masses. Cardiac magnetic resonance imaging and computed tomography are helpful complementary investigations, for refining diagnosis and in the post-surgery follow-up. Histology with immuno-histochemistry of any cardiac mass is mandatory for diagnosis, therapy and prognosis. Endomyocardial biopsy may be of help for histological investigation without thoracotomy particularly in right sided masses.

Key words: cardiac tumours; pathology; biopsy

Figure 1
The front page of the first book on cardiac tumours by Ivan Mahaim, published in 1945 [2] (A) with the original drawing of the left atrial myxoma ("le polype du coeur") (B).



Introduction

Although the term tumour generally recalls the idea of "cancer", at a cardiac level most primary tumours are biologically benign and malignancy is mostly haemodynamic, due to obstruction of the blood flow because of intra-cavitary growth and embolism following neo-

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plastic fragmentation with ischemic damage of several organs [1, 2]. The first book on cardiac tumours was published in 1945 by Ivan Mahaim, Professor at the University of Lausanne [2]. It was a collection of post-mortem observations and a thorough review of the literature (fig. 1). While treating atrial myxoma ("Le polype du cœur"), the most frequent cardiac tumour (nearly two-thirds of primary heart neoplasms), he said "…surgical resection of atrial polyp encounters apparently insurmountable difficulties. However, we should not give up because of this feeling. In any field of science, with technological progress, the impossible is just a moment during the evolution of our powers. As Mummery said about alpinism, the inaccessible peak becomes an easy route for ladies…". In fact, some years later the era of "surgical pathology" started with the advent of cardiac imaging and open heart surgery in the '60s, when cardiac neoplasms were diagnosed during life and not only in the autopsy room and became surgically resectable with excellent long-term survival [3, 4]. Nowadays, the pathologist is on call to achieve the *in vivo* diagnosis on endomyocardial or surgical biopsies, by establishing the nature (benign, malignant, or non-neoplastic, usually thrombi or vegetations) and the histotype, and to make the differential diagnosis with secondary tumours. The purpose of this review is to discuss the actual prevalence and pathology of primary cardiac tumours.

Epidemiology

Epidemiological data of primary cardiac tumours are still based on post-mortem studies. The incidence and prevalence of cardiac neoplasms, in general, have shown little change over time. Since the early report in 1934 [5], the reported prevalence is very low, ranging from 0.0017 to 0.28% in autopsy series, with the variability being strongly influenced by when and where the data have been collected and according to diagnostic methods [6–8].

Cardiac and pericardiac masses include benign and malignant tumours, both primary and secondary, and non-tumoural lesions [9, 10].

The prevalence of cardiac tumours differs among age groups: myxoma is the most common cardiac neoplasm in adults, whereas in childhood fibromas and rhabdomyomas are the most frequent [11].

Metastatic involvement is much more common than primary cardiac tumours with a reported prevalence of 2.3–18.3% [12–16]. At the Institute of Pathology of the University of Padua in the time interval of 1967–1976, on 7,460 autopsies the prevalence of primary cardiac tumour was 1 out of 2,000 and that of secondary tumours was 1 out of 100 autopsies, with a secondary/primary ratio of 20:1 [1]. Bussani et al. [14] reported 662 cases among 7,289 with malignancies (9.1%), with a decreasing occurrence with age (16.8% in people <64 vs 8.5% in people >85), probably due to less biological aggressiveness in the elderly. Any extracardiac malignant tumour may metastatise to the heart, however, melanoma, lung and breast carcinoma show the highest cardio-tropism, reflecting also the most common incidence of these cancers. Metastatic involvement of the heart can occur due to direct infiltration by mediastinal and lung malignancies; haematic pathway, in the case of distant primary neoplasm; lymphatic pathway due to a spread through the tracheamediastinal lymphatic network, especially in case of lung carcinoma (pericardial "carcinosis"); and endocavitary diffusion through the inferior vena cava (renal carcinoma and hepatocarcinoma) and pulmonary veins.

Concerning the epidemiology and prevalence of various histotypes of primary cardiac tumours, in a consecutive series of 210 primary cardiac neoplasms studied at the University of Padua, 89% were benign and 11% malignant [17].

According to the histological classification by the World Health Organisation (WHO) in 2004 [7] (table 1), among the benign cardiac tumours, the majority (63%) were myxomas, followed by papillary fibroelastomas (8%). Primary neoplasms, all benign, were also observed in the paediatric age group (<18 years) in 13%

Table 1

WHO Classification of primary tumours of the heart.

Benign tumours and tumour-like lesions	
Rhabdomyoma	8900/0
Histiocytoid cardiomyopathy	
Hamartoma of mature cardiac myocytes	
Adult cellular rhabdomyoma	8904/0
Cardiac myxoma	8840/0
Papillary fibroelastoma	
Haemangioma	9120/0
Cardiac fibroma	8810/0
Inflammatory myofibroblastic tumour	8821/1
Lipoma	8850/0
Cystic tumour of the atrioventricular node	
Malignant tumours	
Angiosarcoma	9120/3
Epithelioid haemangio-endothelioma	9133/3
Malignant pleomorphic fibrous histiocytoma MFH / Undifferentiated pleomorphic sarcoma	8830/3
Fibrosarcoma and myxoid fibrosarcoma	8840/3
Rhabdomyosarcoma	8900/3
Leiomyosarcoma	8890/3
Synovial sarcoma	9040/3
Liposarcoma	
Cardiac lymphoma	
Pericardial tumours	
Solitary fibrous tumour	8815/1
Malignant mesothelioma	9050/3
Germ cell tumours	

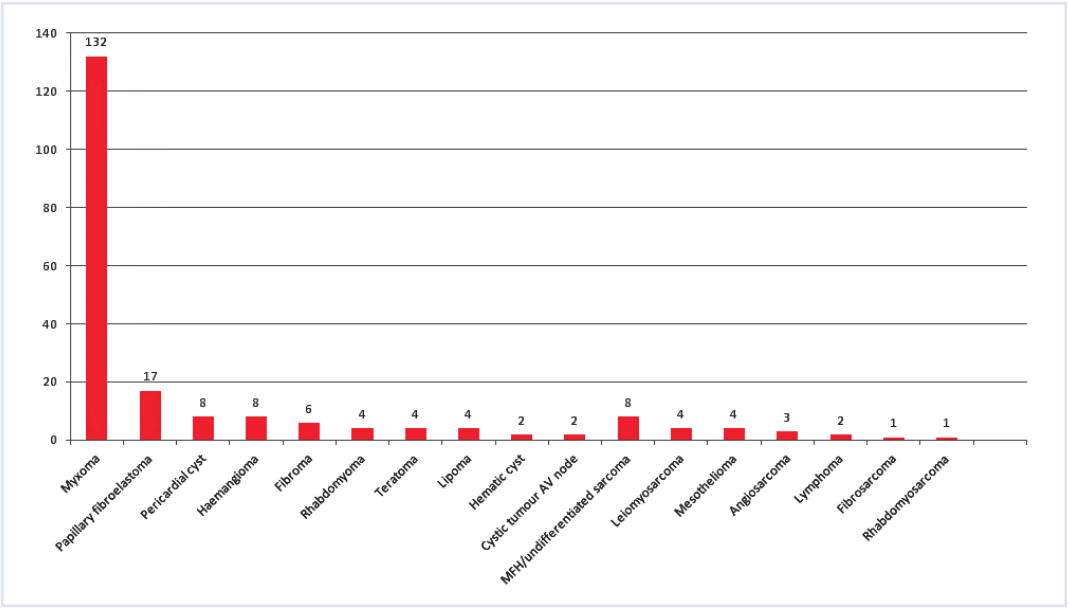


Figure 2
Primary cardiac and pericardial tumours at the Cardiovascular Pathology Unit, University of Padua (1970–2004): total n = 210 cases.

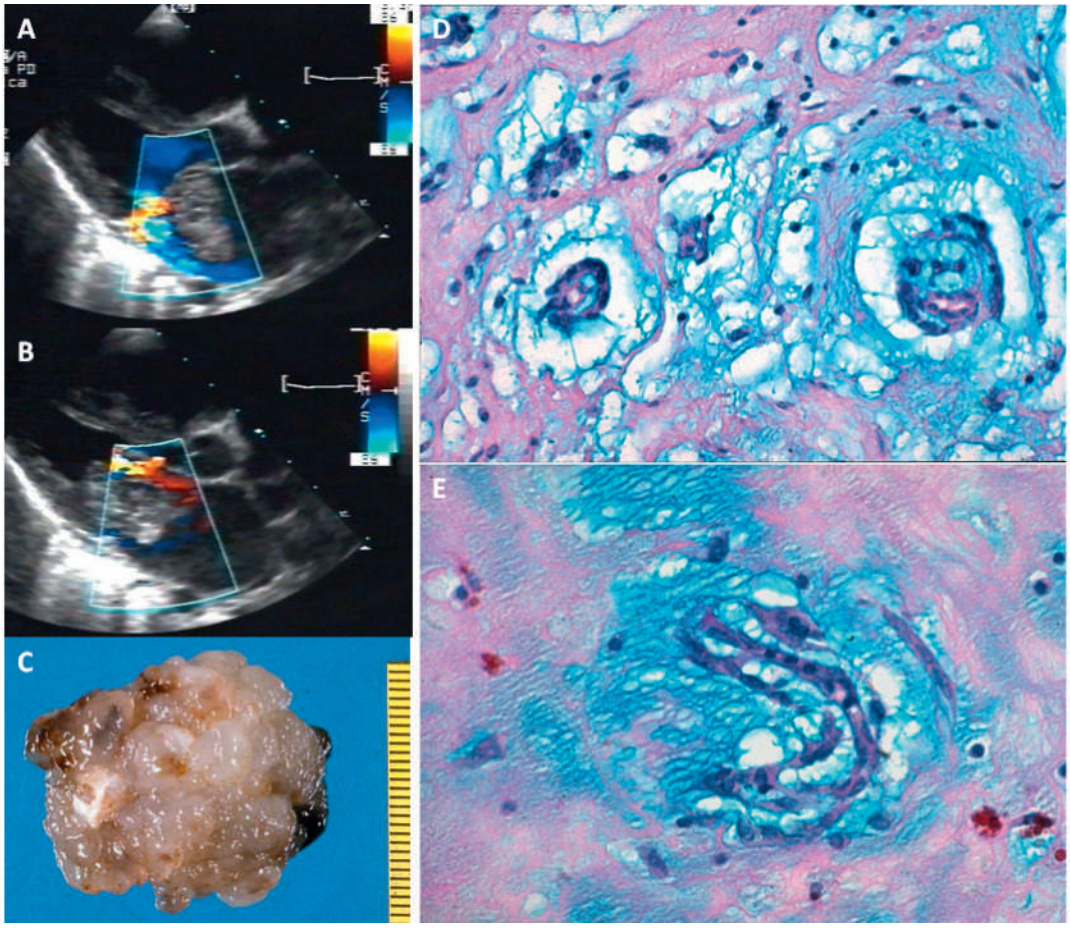


Figure 3
Surgically resected left atrial myxoma in a 6-year-old child. (Modified from: Padalino MA, Basso C, Moreolo GS, Thiene G, Stellin G. Left atrial myxoma in a child: case report and review of the literature. Cardiovasc Pathol. 2003;12:233–6.©2003, Reprinted with permission from Elsevier.)

A 2D echocardiography, long axis parasternal view, in systole.

B 2D echocardiography, long axis parasternal view, in diastole: note the prolapsing mass.

C Smooth, gelatinous mass resected at surgery.

D Histology of the myxoma shows abundant mucoid extracellular matrix with angioblastic-like structures (Alcian Pas stain).

of cases and atrial myxoma was still the most frequent one. Leiomyosarcoma, malignant fibrohistiocytoma, angiosarcoma and mesothelioma represented the main malignant primary cardiac tumours (fig. 2).

Although cardiac tumours are considered "rare" diseases, they are increasingly detected *in vivo* thanks to the widespread use and increased sensitivity of non-invasive cardiac imaging techniques. Differentiation between mass histotypes is primarily suggested by the clinical and imaging features, which include the appearance, the location (intracavitary or intramural), the number of detectable masses and the tissue char-

acteristics. None of these features are sensitive and specific for a diagnosis of malignancy; benign and malignant tumours can have overlapping features. Excision of the lesion and pathologic examination, including cytology of pericardial fluid or transvenous biopsy of the mass, remains the gold standard to achieve a definitive diagnosis of a cardiac mass.

Primary benign cardiac tumours

Myxoma

Myxoma is the paradigm of a benign intra-cavitary cardiac tumour, probably originating from residual embryonic cardiac jelly [18]. Myxomas are in fact mostly found in the left atrium followed by the right atrium, and occasionally in the ventricles. In our experience, myxoma was located in the left atrium in 80% of cases and in the right atrium in 18%; "biatrial" myxoma was observed only twice [17]. Although myxomas have been reported in both genders and in all ages, they are more common in women and in the sixth decade of life [17, 18]. According to our experience, 60% presented with obstructive symptoms, 30% with constitutional symptoms, and 16% with embolism, whereas 25% of cases were asymptomatic and discovered incidentally at echo. In the elderly, the "silent myxoma" may undergo calcification ("lithomyxoma"), like a sort of a self-healing [19, 20].

The majority of cardiac myxomas are sporadic. A familial incidence has been described, accounting for up to 7% of all cardiac myxomas, associated with Carney complex, an autosomal dominant hereditary disease, due to mutation in the gene PRKAR1A, located at 17q24 [21, 22]. The subjects are younger than those with sporadic myxoma, have no female prevalence, present multiple chamber involvement and have a tendency of recurrence after surgery.

On a large scale, cardiac myxomas are widely vari-

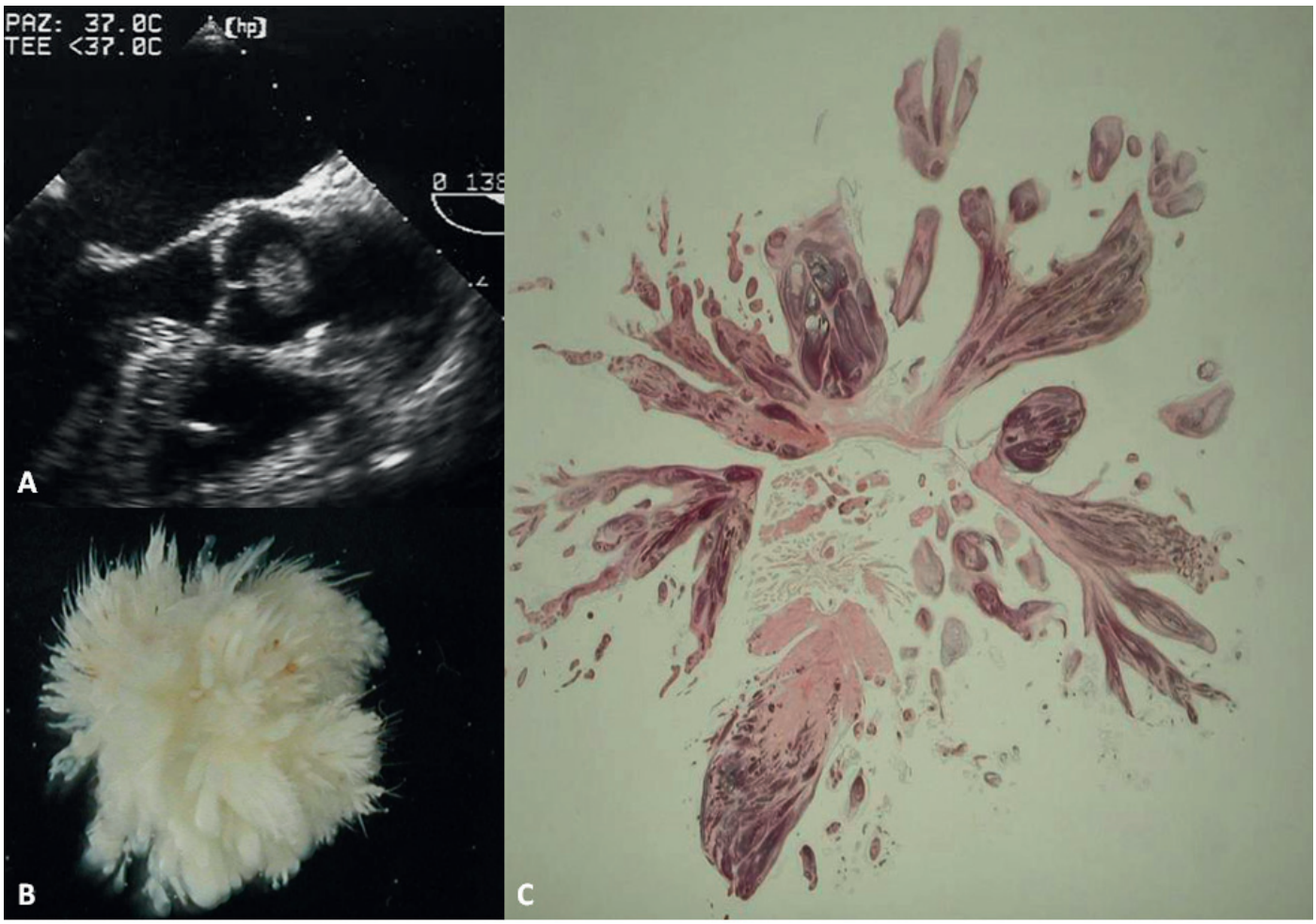
Figure 4

Papillary fibroelastoma of the aortic valve in an asymptomatic 77-year-old woman (incidental finding). Modified from: Bottio T, Pittarello D, Bonato R; Thiene G, Gerosa G, Casarotto D, Basso C. Echocardiographic diagnosis of aortic valve papillary fibroelastoma. Tex Heart Inst J 2004;322–23.© 2004 by the Texas Heart Institute, Houston.)

A Trans-oesophageal echocardiography showing a small mass attached to the non-coronary aortic cusp

B The resected mass, viewed under water, resembles a sea-anemone.

C Histology shows multiple fronds with a fibroelastic axis (elastic van Gieson stain).



able in size, both sessile or peduncolated [23, 24], with a smooth or villous surface (respectively 65% and 35% in our experience) [17] (fig. 3). These tumours are grey or yellow-brown, often with areas of haemorrhage on cut sections.

Microscopically, the cells (so called "lepidic cells") are polygonal with scant eosinophilic cytoplasm occurring in clusters in a vascular myxoid stroma rich in Alcian-PAS positive acid mucopolysaccharides [25–27] (fig. 3). Lacking a fibrous axis, the risk of systemic emboli is high in patients with myxomas, due to detachment of tumour fragments or thrombus layered on the surface. Due to the embolic potential, surgical removal is indicated. Recurrence of a myxoma can be prevented with an adequate resection encompassing a button of normal endocardium around the tumour stalk, sometimes necessitating patch reconstruction of the atrial septum.

Papillary fibroelastoma

Papillary fibroelastoma, known also with the name of endocardial papilloma, is the second primary cardiac tumour following myxoma in our series (8%) [17] and it is the most common primary heart valve tumour [28–30] (fig. 4). Gowda et al. reviewed 725 cases of cardiac papillary fibroelastoma reported in the literature, and found that the valvular endocardium was its predominant location [31]. More than 95% arise in the left heart. The aortic valve (29%), mitral valve (25%), tricuspid valve (17%) and pulmonary valves (13%) are involved [31, 32], but also the mural non-valvular endocardium may be the site of growth, in the latter case being difficult to differentiate from thrombus and myxoma. It is predominant in the 4th and 5th decades of life and in males [31]. On gross examination, it is a small intra-cavitary neoplasm usually single, firm, with a short pedicle and multiple papillary fronds similar to a sea anemone when under water [33]. At histopathology, it is a papillary lesion with a thin layer of mucopolysaccharide matrix and avascular stroma composed predominantly of elastic fibres and a small amount of collagen, covered with a single layer of endothelial cells (fig. 4) [34]. Recent or organised thrombi may be observed, entrapped within the fronds, having the potential to lead to thrombo-embolic events.

Once an incidental finding at autopsy, nowadays papillary fibroelastoma is becoming a frequent observation at echo, either following an unexplained murmur or embolism, or during an ultrasound procedure for other reasons. Differential diagnosis is with Lambl's excrescences, which typically are located on the line of closure of the valve leaflets, while papillary fibroelastoma can occur anywhere on the valve surface. The differential diagnosis with valvular endocarditis is based on the absence of signs of infection, valvular destruction or abnormal valvular function.

Due to the small size, papillary fibroelastoma rarely presents clinically with signs of obstruction. A very rare complication, even at risk of sudden death, is represented by the wedging of the aortic valve papilloma into a coronary ostium, when located at the free edge of a coronary cusp. The potential embolic risk is such that the neoplasm should not be considered "innocent" and indication for surgery is mandatory, at least for left-sided lesions.

Lipoma

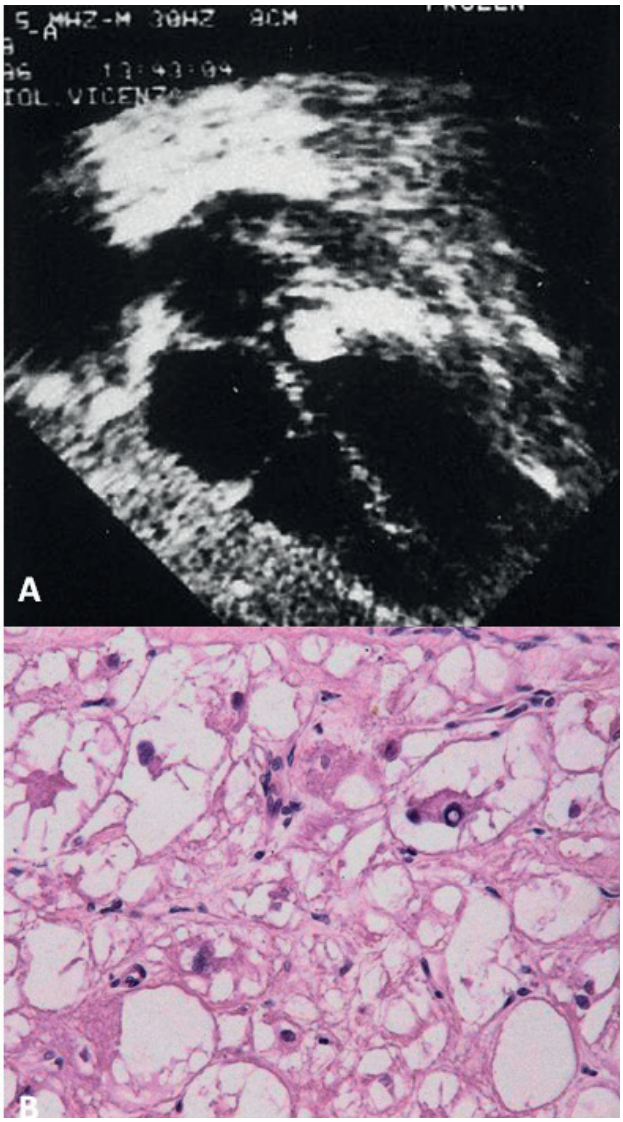
Lipoma was first described by Orth in 1886. It is a benign tumour made up of mature fat cells, reported at

Figure 5

Rhabdomyoma in a 7-month-old male infant with systolic murmur. (Modified from: De Dominicis E, Frigiola A, Thiene G, Menicanti L, Bozzola L, Finocchi G. Subaortic stenosis by solitary rhabdomyoma. Successful excision in an infant following 2D echocardiogram and doppler diagnosis. Chest. 1989;95:470–2. © 1989 American College of Chest Physicians.)

A 2D echocardiography reveals a sub-aortic endocavitary round mass.

B The resected mass resulted to be a rhabdomyoma: note the typical "spider" cells (haematoxylin-eosin stain).



any age with an equal frequency in both genders, with an incidence of 8% [9, 35]. Cardiac lipoma can occur in any location, on which depend the clinical manifestations, including compression, obstruction and arrhythmias. The true lipoma, which are single or multiple capsulated fatty masses, yellow, soft, and originating from the endocardium, epicardium or myocardium, should be kept distinct from so-called lipomatous hypertrophy of the interatrial septum. The latter, which should not be considered a proper tumour, is a non encapsulated adipose tissue thickening, probably an intracardiac extension of the sub-epicardial fat of the right atrioventricular sulcus, usually observed in obese, old people [36]. Histologically, lipoma consists of mature adipocytes enmeshed in a fine fibrovascular network, rather than lipomatous hypertrophy which shows myocardial tissue with wide-spread infiltration of fat-cells [36, 37]. Magnetic resonance imaging (MRI) is quite helpful in the diagnostic workup due to its properties of tissue characterisation with clear demonstration of fatty tissue.

Haemangioma

Haemangioma accounts for approximately 1 to 5% of all benign cardiac tumours in different series [9, 38]. It occurs mostly in adults, and the clinical presentation varies depending on the location and size of the tumour [38, 39]. A total of 75% present with an intramural growth and 25% are sessile or polypoid, projecting into the atrial or ventricular cavities, sometimes mimicking myxoma. Epicardial location is also reported. Coronary angiography may be useful in detecting the distribution of the afferent vessels to the tumour. The histologic appearance is that of a proliferation of blood vessels lined by endothelial cells, which may be small capillaries (capillary haemangioma), large thin walled vessels (cavernous haemangioma, the most common type) or dysplastic malformation of arteries and veins (arteriovenous haemangioma or cirsoid aneurysm). Mixed forms are frequent [40]. The prognosis of these tumours is unpredictable; they may even resolve [41, 42], stop growing, or proliferate indefinitely. There is always the risk of recurrence, especially if there has been incomplete resection at initial surgery.

Rhabdomyoma

Rhabdomyoma is considered the most common paediatric cardiac neoplasm, accounting for 90% of primary benign tumours in this age group [43–46]. Nevertheless, in our experience [1, 17, 47], only 15% of paediatric cardiac tumours were rhabdomyoma, since usually there is no indication for surgery because of spontaneous regression of the neoplasm along the natural history. Cardiac rhabdomyoma are found in up to 80% of cases affected by tuberous sclerosis [48], consisting of a classical clinical triad, i.e. neurofibromatous lesions, mental slowing and cutaneous lesions and due to mutation of genes coding for two tumour suppressors, amartin (9q34) and tuberin (16p 13.3) [1].

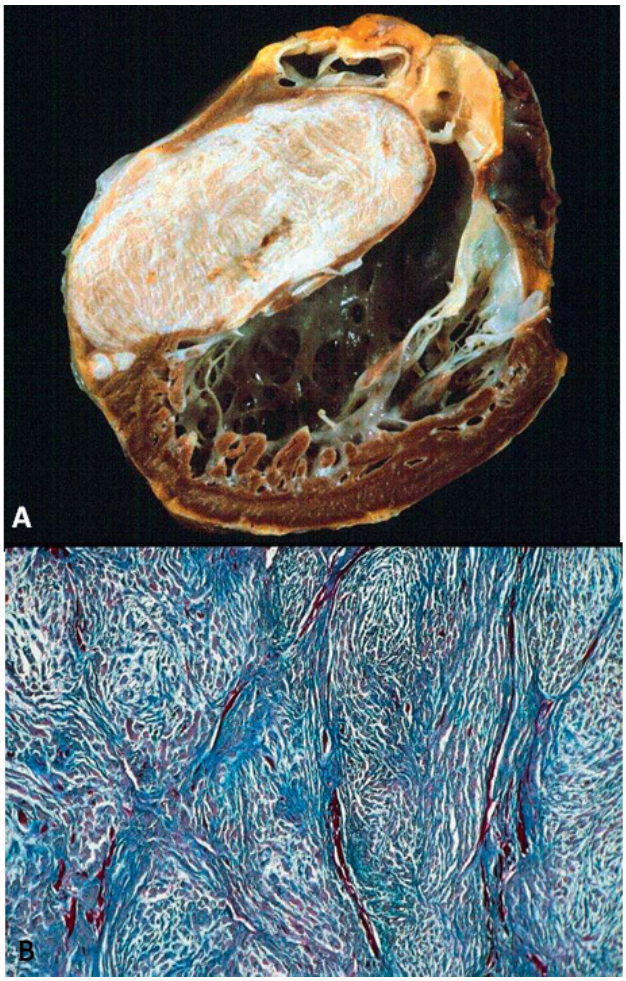
The diagnosis is frequently prenatal by foetal echocardiography, in case of arrhythmias, hydrope, retarded intrauterine growth and familiarity of tuberous sclerosis. Rhabdomyomas are single or, more frequently, multiple non-capsulated nodules, white or grey, up to 1–2 cm in diameter, usually intramural within the ventricular myocardium, but also intra-cavitary because of growth from the sub-endocardium (fig. 5). The latter are often symptomatic due to intracardiac obstruction as to require surgical resection. Histologically, they consist of large, vacuolated, clear myocytes full of glycogen, with residual cytoplasm stretching from the central nucleus to the membrane,

Figure 6

Cardiac fibroma in a 40-year-old woman who underwent to cardiac transplantation due to congestive heart failure with a misdiagnosis of hypertrophic cardiomyopathy with sub-aortic obstruction. (Modified from: Valente M, Cocco P, Thiene G, et al. Cardiac fibroma and heart transplantation. J Thorac Cardiovasc Surg. 1993;106:1208–12. © 1993 reprinted with permission from Elsevier.)

A Long axis section of the native heart reveals an intramural huge, firm, white, oval mass and two satellite small nodules within the interventricular septum.

B The mass at histology consists mostly of collagen bundles (Heidenhain trichrome stain).



giving rise to a spider appearance ("spider cells"). More than a proliferation of cardiomyocytes, the rhabdomyoma is a localised storage disease of glycogen, which may account for severe contractile ventricular dysfunction.

Fibroma

Fibroma is the second most common tumour in the paediatric population after rhabdomyoma [43–46, 50]. In a study of 27,640 children evaluated by echocardiography an incidence of less than 0.02% was reported [45]. It represents nearly 20% of paediatric cardiac tumours in our experience [1, 17, 47]. Most fibromas are solitary, well circumscribed, firm, located within the left ventricular free wall or interventricular septum, thus producing compression of the conduction system, reentry ventricular arrhythmias or obstruction of the ventricular lumen [45, 46, 50–53] (fig. 6). Sudden death has been reported as the first manifestation of the disease.

Histopathologically, cardiac fibromas are composed of spindled cells with variable amounts of fibrous stroma, entrapping cardiomyocytes at the periphery; calcific deposits are frequent [49, 52]. When feasible, complete resection is usually recommended. Debulking (partial resection) and heart transplant in non-resectable forms have also been advocated [47, 52, 53].

Cystic tumour of the atrioventricular (AV) node

The cystic tumour of the atrioventricular (AV) node, first described in 1911 [54], involves the atrioventricular node selectively. It is also known as tawarioma (from Tawara, who discovered the AV node) or celothelioma (mesothelioma of the AV node) reflecting its controversial histogenesis [55–58]. The mean age of clinical presentation is nearly 40 years. A total of 75% of patients present with complete and 15% with incomplete AV block, whereas in 10% sudden death is the first clinical manifestation [59]. On a large scale, the tumour appears multicystic, with size varying from 2 to 20 mm. Histologically, the tumour is located on the right side of the central fibrous body, infiltrating and compressing the AV node. The cysts are filled by a mucoid substance and are lined by epithelium, cytokeratin and epithelial membrane antigen positive [60]. Diagnosis is usually achieved at post-mortem or after cardiac transplantation [61] through histological examination of the conduction system, but occasionally *in vivo* or during surgical resections [62].

Intracardiac blood cyst

Intracardiac blood cysts are rare, usually small and asymptomatic lesions, located in the endocardium most frequently along the closure rim of the atrio-ventricular valves in newborns and infants, particularly under 2 months of age, due to blood entrapped in the leaflet. The cysts are single blood-filled spaces lined by a layer of endothelial cells. They may regress spontaneously, thus are rare in adults. Occasionally, the blood sequestration may increase and the cyst assumes a huge endocavitary dimension, creates obstructive symptoms and requires surgery [63, 64].

Figure 7

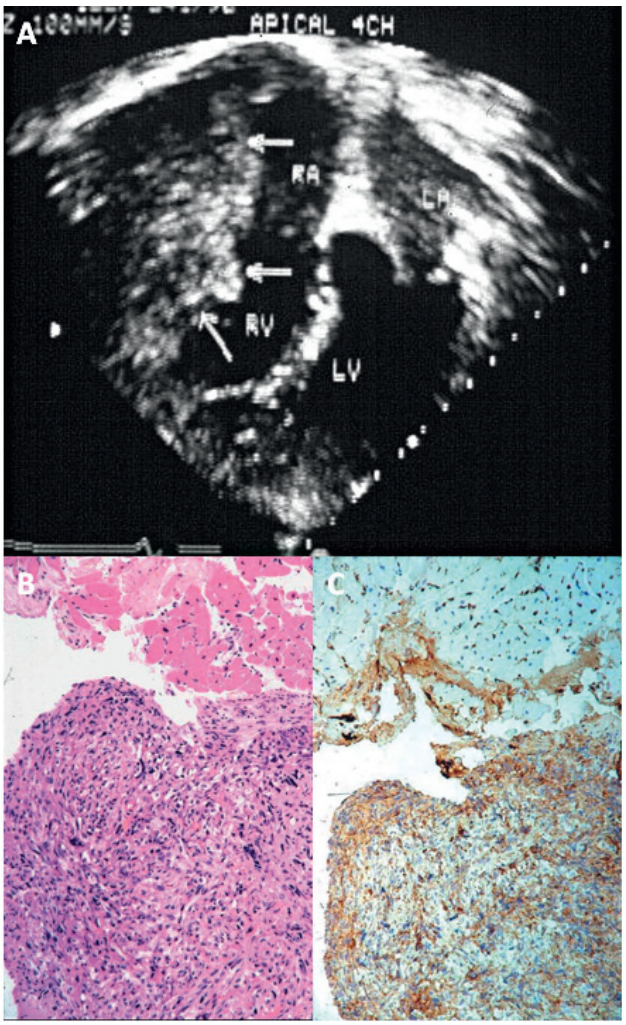
Right atrial angiosarcoma diagnosed at endomyocardial biopsy in a 36-year-old woman with dyspnoea. (Modified from: Poletti A, Cocco P, Valente M, Fasoli G, Chioin R, Thiene G. In vivo diagnosis of cardiac angiosarcoma by endomyocardial biopsy. Cardiovasc Pathol. 1993;2:85–91. © 1993, reprinted with permission from Elsevier.)

A 2D echocardiography, four chamber view, showing an intramural, irregular mass protruding into the right atrial and ventricular cavities.

B Transvenous endomyocardial biopsy sample showing the myocardium (on the left) infiltrated by a neoplastic proliferation of pleomorphic, spindle cells with frequent mitoses, forming vascular-like structures (haematoxylin-eosin stain).

C Immuno-histochemistry with diffuse positivity for endothelial cell markers (factor VIII).

RA = right atrium; RV = right ventricle; LV = left ventricle.



Primary malignant cardiac tumours

Primary malignant cardiac tumours are very rare, representing nearly 10% of all primary cardiac neoplasms

[8]. Sarcomas represent 95% of these tumours (20% of all primary cardiac tumours), angiosarcomas and unclassified sarcomas being the most common accounting for 76%, and primary lymphomas and mesotheliomas make up the remaining 5% [1, 9, 17, 65–70] (table 1). All varieties of soft tissue sarcomas have been reported to arise in the heart.

Primary cardiac sarcomas can occur at any age, but are more frequently diagnosed between the third and fifth decades, and equally in men and women [66], whereas they are extremely rare in the paediatric age group. Surgical excision is the most effective treatment for primary cardiac malignancies. However, prognosis is very poor in spite of additional treatments, such as radiotherapy and chemotherapy, with a median survival of less than one year and 80% of patients already present diffuse infiltration of the heart and metastases at the time of diagnosis [67–70]. A less-aggressive course seems related to the left atrium location, a low histologic grading with scarce cellular pleomorphism and low-mitotic activity, absence of necrosis, and absence of metastasis at diagnosis [7].

Angiosarcoma

Angiosarcoma is the most common primary malignant cardiac tumour, with a peak in the 4th decade and no sex predilection [71]. The most frequent location is the right atrial chamber. The presenting signs and symptoms are non-specific and may include right sided heart failure, symptoms of pericardial involvement or vena cava obstruction. Echocardiography usually demonstrates a broad based right atrial mass near the inferior vena cava. On computed tomography (CT) and MRI they show arterial phase enhancement permitting a definitive diagnosis. Pulmonary metastases are frequent, and survival after diagnosis rarely exceeds 6 months. On a large scale, it is an intramural neoplasm, brownish and lobulated, infiltrating the wall and the

Figure 8

Left atrial malignant pleomorphic fibrous histiocytoma in a 68-year-old man with fever and fatigue. (From: Thiene G, Valente M, Lombardi M, Basso C. Tumours of the Heart. In: Camm JA, Luscher TF, Serruys PV, eds. ESC Textbook of cardiovascular Medicine. Oxford: University Press, 2009. © Oxford University Press.)

A 2D trans-oesophageal echocardiography shows a round, non infiltrating, intra-cavitary mass in the left atrium.

B Gross view of the resected mass: note the rough surface and non-gelatinous appearance.

C At histology, bizarre, pleomorphic cells, frequently giant multinuclear, with high mitotic activity are visible.

D Immuno-histochemistry points to an undifferentiated mesenchymal cell (vimentin positivity).

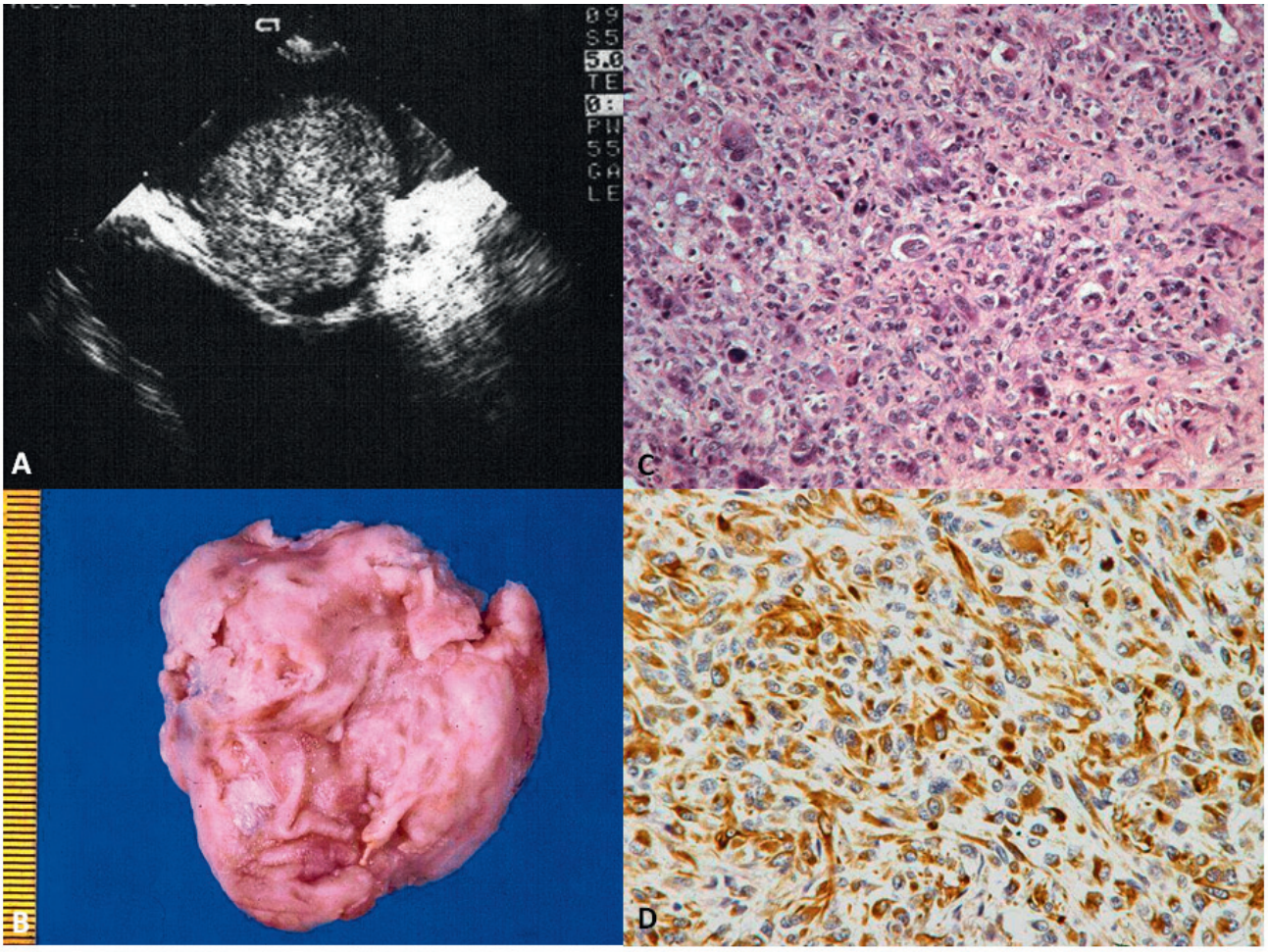


Figure 9

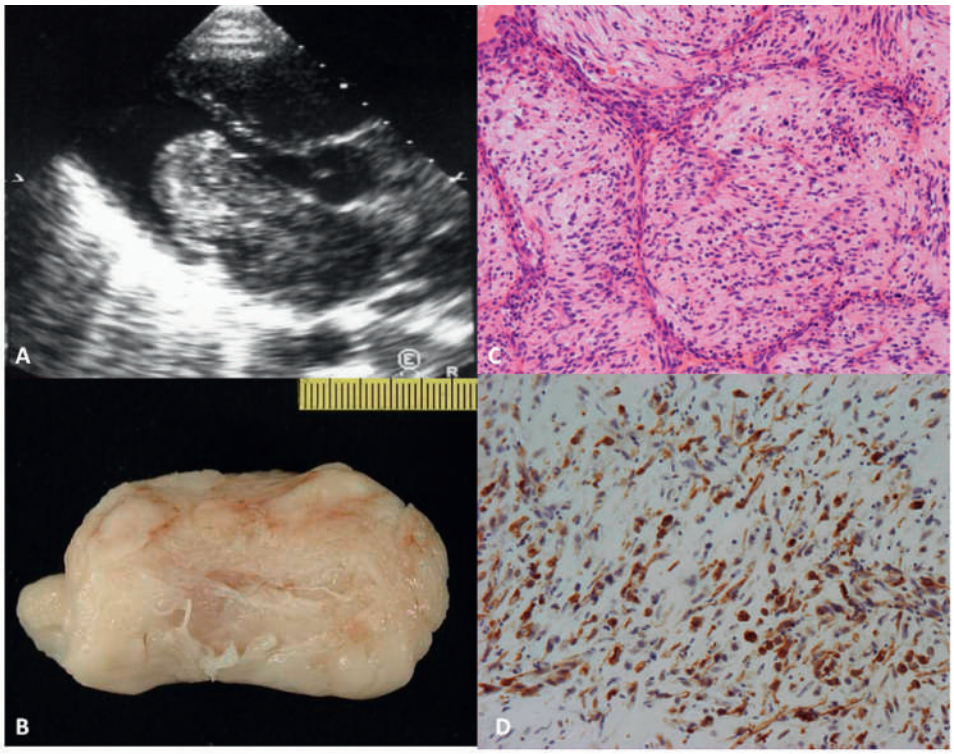
Leiomyosarcoma of the left atrium in a 21-year-old woman with acute pulmonary oedema and preoperative diagnosis of left atrial myxoma. (Modified from: Mazzola A, Spano JP, Valente M, Gregorini R, Villani C, Di Eusanio M, et al. Leiomyosarcoma of the left atrium mimicking a left atrial myxoma. J Thorac Cardiovasc Surg. 2006;131:224–6. © 2006, reprinted with permission from Elsevier.)

A 2D echocardiography long axis parasternal view: note the tumour prolapse during diastole into the left ventricular cavity.

B Cut surface of the mass with whitish appearance and irregular surface.

C Pleomorphic cells arranged in a storiform pattern within a myxoid background.

D Immunohistochemical staining showing tumour cells positivity for desmin.



pericardium, and protruding into right cardiac cavities, with invasion of the inferior vena cava and the tricuspid orifice. The site is ideal for *in vivo* diagnosis through endomyocardial biopsy [72] (fig. 7). At histology, two thirds of angiosarcoma are well to moderately differentiated and show an irregular, anastomosing, vascular network, lined by pleomorphic, atypical cells with frequent mitoses. In one third of cases, the tumour is poorly differentiated, consisting of anaplastic spindle cells within a hyaline stroma, containing focally extravascular red cells. In this case, immunohistochemistry plays a crucial role in diagnosis, confirming the endothelial nature of malignant cells, strongly positive with factor VIII, CD31 and CD34.

Malignant pleomorphic fibrous histiocytoma (MFH) / undifferentiated pleomorphic sarcoma

Malignant pleomorphic fibrous histiocytoma (MFH) / undifferentiated pleomorphic sarcoma accounts for one-third of all cardiac sarcomas and have been incorporated in the malignant fibrous histiocytoma/pleomorphic sarcoma subgroup [6, 7]. This is an exclusion diagnosis, when all the immunohistochemical stains fail to give evidence of specific differentiation. Once, when immunohistochemistry was not available, undifferentiated sarcoma represented 50% of all cardiac malignancies, but in more recently published series it has almost disappeared. Most frequently it arises in the left atrium, with an endocavitary growth, mimicking left atrial myxoma at echocardiographic examination (fig. 8). Differential diagnosis should also consider intracavitary thrombi. Macroscopically, the mass is clearly distinguishable from myxoma because it may be multiple, whitish with a rough surface and hard consistency, in the absence of gelatinous appearance. Microscopically, it consists of pleomorphic cells, frequently giant multi-nuclear, with high mitotic activity and positivity only for vimentin at immunostaining.

Leiomyosarcoma

Leiomyosarcoma is a primary sarcoma of smooth muscle cells and accounts for nearly 10% of all cardiac malignancies, with a peak in the 5th decade and no sex prevalence [1, 7].

There are two usual sites of origin. One is the left atrium, where it may present as a single or multiple endocavitary mass, mimicking the left atrial myxoma although usually attached to the atrial roof rather than the atrial septum [73] (fig. 9); the second, is the pulmonary infundibulum and artery, mimicking pulmonary embolism [74]. On a large scale, the mass is irregular, solid, and whitish or grey. Histologically, fascicles of spindle cells, smooth muscle actin and desmin positive, with blunt-ended nuclei, oriented at right angle with mitoses are visible. Pleomorphism, giant cells and necrosis are focally present.

Fibrosarcoma

Fibrosarcoma consists of a malignant proliferation of mesenchymal cells with fibroblastic features and a storiform, herring-bone pattern with a collagen stroma [1, 7, 75, 76]. They represent nearly 5% of all primary cardiac malignancies. The most frequent location is in the atria (particularly the left), with both intracavitary and mural location. A pericardial form does exist (solitary malignant fibrous tumour of the pericardium), which may mimic a mesothelioma. As with other sarcomas, clinical presentation depends on the site and size of the tumour. Being mostly left sided, signs and symp-

toms of pulmonary congestion, mitral stenosis and pulmonary vein obstruction are the most frequent [76].

Microscopically, the fibrosarcoma consists of a collagen stroma and monomorphic spindle cells, with variable mitotic index. Pleomorphism, giant cells and vascularisation are absent.

Immuno-histochemistry is positive for vimentin and frequently also for actin, in keeping with a myofibroblastic differentiation.

The prognosis is poor (mean survival 5 months), even in intracavitary cases in which surgical resection is apparently radical.

In the AFIP Atlas, the term myxosarcoma has been applied to undifferentiated cardiac malignant sarcomas with myxoid stroma. Myxoid fibrosarcoma is nowadays equivalent to the extra-cardiac soft tissue myxofibrosarcoma and fibromyxoid sarcoma at a low grade of malignancy, which are grouped among fibroblastic/myofibroblastic neoplasms.

Rhabdomyosarcoma

Rhabdomyosarcoma is a rare malignant tumour of striated muscle, most frequently encountered in children with male prevalence [1, 7, 9]. Rhabdomyosarcomas arise de novo, not from malignant degeneration of a rhabdomyoma. It often diffusely infiltrates the myocardium at any location, presenting with cardiac obstructive phenomenon, arrhythmias or pericardial effusion.

Embryonal rhabdomyosarcoma is the most frequent at cardiac level thus explaining the younger age at presentation. Within a rich proliferation of round cells with frequent mitoses, PAS positive rhabdomyoblasts are visible with the typical feature of "tadpole" and positive at immunohistochemistry for vimentin, muscle-specific actin, desmin and myogenin. Electron microscopy reveals cells containing contractile filaments with a "Z-band-like" appearance.

Liposarcoma

Liposarcoma is a rare entity (1% of primary malignant tumours of the heart) [1, 7, 9] that predominantly appears as a bulky endocavitary left atrial mass, mimicking myxoma, with early signs of local invasion and haemodynamic disturbance.

On a large scale, it looks like an intramural, sessile or pedunculated mass, gelatinous and un-encapsulated. Microscopically, it consists of lipoblasts, irregular cells, with large pleomorphic nuclei and cytoplasmatic fat vacuoles, S100 positive at immunohistochemistry.

Cardiac lymphoma

It represents 5% of primary cardiac malignant neoplasms, which means 1% of all cardiac primary tumours. It occurs in ages from 5 to 90 years (median 60), the male/female ratio is approximately 3:1, and it does not necessarily occur in immune-deficient people. It may arise in any cardiac chamber, but in 2/3 of cases the right atrium is the site of involvement with an intramural, whitish infiltrating mass extended to pericardium with massive effusion.

Primary cardiac lymphoma is an extranodal non-Hodgkin's lymphoma. The subtype most frequently observed (80% of cases) is B-cell lymphoma with huge, CD20 positive cells, whereas the remaining 20% are CD3 positive T-cell lymphomas. Cytology of pericardial effusion may be of help for diagnosis, by using molecular techniques to differentiate B and T-cell lymphomas from reactive lymphocyte hyperplasia. Primary cardiac lymphomas should be promptly treated like aggressive lymphomas in other sites, since a late diagnosis is the major determinant of a poor prognosis. It is worthwhile to note that primary cardiac lymphomas, with chemotherapy, are the only malignant cardiac neoplasms to present a fairly good prognosis [77].

Tumours of the pericardium

Primary pericardial tumours are rare, and include benign (cyst, teratoma, fibroma, angioma and lipoma) and malignant (mesothelioma and sarcoma) forms. More frequently, the pericardium is secondarily involved by direct extension, retrograde lymphangitic spread or hematogenous dissemination. The patients present with pericardial effusion and occasionally pericardial tamponade [78].

Pericardial cyst

A pericardial cyst is a relatively frequent mass, uni- or multi-loculated, full of serous liquid, probably disontogenetic in origin, but symptomatic in adult age because of increasing storage of fluid within the cystic cavity. Histologically, the thin wall consists of highly vascularised connective tissue covered by mesothelium on both sides [79].

Teratoma

Teratoma is a tumour of germinal cells, which represents nearly 10% of all paediatric cardiac tumours. In 90% of cases it is located within the pericardial cavity, usually at the base of the heart. Diagnosis is usually achieved within one month of age because of severe obstructive symptoms by compression of the arterial pole and lungs. Pericardial effusion may occur and lead to cardiac tamponade. On a large scale, they appear as cystic lesions, clearly visible with clinical imaging. Histologically, proliferation of various tissues from two or three embryonic leaflets is visible (gastrointestinal, cartilagineous, bony, bronchial, nervous), easily identified by immunohistochemistry [43, 79].

Malignant mesothelioma

Malignant mesothelioma is the most common primary malignancy of the pericardium. It accounts for only

about 1% of all mesotheliomas. It affects individuals of any age (mean 45 years), with a male predominance. The role of asbestos in pericardial mesothelioma is unclear. A role for radiotherapy for mediastinal neoplasms and breast cancer has also been advocated [80]. Mesothelioma arises from the serous epithelial cells of the mesothelium. It occurs most frequently as diffuse pericardial thickening, encasing the heart. The cells are large pleomorphic cells with abundant pale cytoplasm and well demarcated cell borders, positive for cytokeratin, vimentin, epithelial membrane antigen and calretinin and negative to carcinoembryonic antigen, the latter being instead positive in pericardial metastasis of adenocarcinoma. It is in fact imperative to rule out any neoplasm with secondary pericardial involvement [78].

Conclusions

Primary cardiac tumours are very rare compared to metastatic tumours; most primary neoplasms are benign and the majority are myxomas. The clinician should be aware that cardiac masses should not be considered as benign myxomas or thrombi just because they are intra-cavitary. All cardiac tumours should be subjected to histological examination in order to confirm the diagnosis and rule out malignancy, thus planning the best treatment. None of current cardiac imaging techniques are able to provide a definitive diagnosis. 50 years ago the role of pathologists in the oncological field at a cardiac level was confined to the autopsy room, whereas today they have an important and expanding role in the diagnosis and treatment of surgically resected cardiac tumours. Ongoing research on molecular genetics and the mechanism of cardiac tumourigenesis could be of help not only to revise the classification of cardiac neoplasms but also to achieve successful, new, molecular-targeted therapies associated with specific tumour histotypes.

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