# Primary Cardiac Malignancies: Epidemiology and Pathology

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## 20.1 Epidemiology

Primary tumors are uncommon in the heart and malignancies are even more uncommon and mostly metastatic. Therefore, before making a diagnosis of primary cardiac malignancies, the metastasis from extracardiac origin must be excluded through extensive clinical and imaging investigations.

One must remember, however, that at the level of the heart, even benign cardiac tumors may lead to significant morbidity and mortality by affecting blood flow and causing arrhythmias and embolism (hemodynamic malignancy).

If in the past virtually all cardiac tumors were diagnosed after death, nowadays these tumors are detected frequently in vivo and have become often surgically curable thanks to recent advances in diagnostic imaging modalities and cardiac surgical techniques.

The exact incidence and prevalence of cardiac tumors are unknown. Knowledge of the prevalence of cardiac tumors is still based on postmortem studies. The prevalence of primary cardiac tumors is estimated on 0.001–0.3 % in autopsy reports [1–7]. In a 20-year study (1972–1991) of 12,485 autopsy cases, there was a 0.056 % incidence of primary tumors and a 1.23 % incidence of secondary tumors [8]. Based upon the data of 22 large autopsy series reported by McAllister et al., the frequency of primary cardiac tumors is approximately 0.02 % [9]. In a study carried out in the Institute of Pathology of the University of Padua in time year interval 1967–1976, among 7460 autopsies the cause of death was due to malignancies in 1181, in 74 of which cardiac metastases occurred (1 % of all the autopsies and 6 % of those with any malignancy). Thus, we can approximately say that autopsy prevalence of primary cardiac tumor is 1 out of 2000 and that of secondary cardiac tumors is 1 out of 100 autopsies, with a secondary/primary ratio of 20:1 [10]. A review of 3314 autopsies found a 2.9 % frequency of metastatic tumors involving the heart, arising by direct extension of adjacent organs or spreading via hematogenous, lymphatic, or intracavitary routes [11]. The most common primary sites are the lung, breast, and cutaneous melanoma [12, 13]. Available data from single-center studies vary with a reported prevalence between 3 and 28.7 % [14–16]. However these data may have a high referral bias and may not reflect population-based incidence rates. The rate of malignant cardiac tumors is frequently erroneously reported up to 30 % among all primary cardiac tumors, when based upon data derived from pathology tertiary centers, where the most difficult cases are sent for consultancy [17]. Surgical pathology data certainly underestimate tumors that do not require surgery (e.g., rhabdomyomas and metastases), as well as tumors possibly revealed by sudden death.

In 2015, the World Health Organization (WHO) updated the classification of cardiac tumors as reported in Table 20.1 [1]. The WHO classifies tumors of the heart into three types: benign tumors and tumorlike lesions, malignant tumors, and pericardial tumors. The major changes in malignant tumors of the heart have been: the removal of the term "malignant fibrous histiocytoma" as synonymous with undifferentiated pleomorphic sarcoma, incorporation of epithelioid hemangioendothelioma as an angiosarcoma with low-grade malignance, remarkable expansion of the cytogenetic and molecular genetic characterization of many cardiac tumors, and reintroduction of the primary cardiac osteosarcoma and myxofibrosarcoma subtypes. Intimal sarcoma has been recently reported in the heart as the most frequent sarcoma histotype and, as in large vessels, is characterized by overexpression of MDM2 as well as alterations in genes like PDGFRA and EGFR that could be targets for novel therapeutic approaches [18]. However this

**Table 20.1** WHO classification 2015 of cardiac tumors [1]

| | |
|---|---|
| *Benign tumors and tumorlike lesions* | |
| Histiocytoid cardiomyopathy | |
| Hamartoma of mature cardiac myocytes | |
| Rhabdomyoma | 8900/0 |
| Adult cellular rhabdomyoma | 8904/0 |
| Cardiac myxoma | 8840/0 |
| Papillary fibroelastoma | |
| Hemangioma, NOS | 9120/0 |
| Capillary hemangioma | 9131/0 |
| Cavernous hemangioma | 9121/0 |
| Cardiac fibroma | 8810/0 |
| Lipoma | 8850/0 |
| Cystic tumor of the atrioventricular node | 8454/0 |
| Inflammatory myofibroblastic tumor | 8825/1 |
| Granular cell tumor | 9580/0 |
| Schwannoma | 9560/0 |
| *Germ cell tumors* | |
| Mature teratoma | 9080/0 |
| Immature teratoma | 9080/3 |
| Yolk sac tumor | 9071/3 |
| Paraganglioma | 8680/1 |
| *Malignant tumors* | |
| Angiosarcoma | 9120/3 |
| Undifferentiated pleomorphic sarcoma | 8830/3 |
| Osteosarcoma | 9180/3 |
| Myxofibrosarcoma | 8811/3 |
| Leiomyosarcoma | 8890/3 |
| Rhabdomyosarcoma | 8900/3 |
| Synovial sarcoma | 9040/3 |
| Miscellaneous sarcomas | |
| Cardiac lymphomas | |
| Metastatic tumors | |

**Table 20.1** (continued)

| | |
|---|---|
| *Tumors of the pericardium* | |
| Solitary fibrous tumor | 8815/1 |
| Malignant | 8815/3 |
| Angiosarcoma | 9120/3 |
| Synovial sarcoma | 9040/3 |
| Malignant mesothelioma | 9050/3 |
| Germ cell tumors | |
| Teratoma mature | 9080/0 |
| Teratoma immature | 9080/3 |
| Mixed germ cell tumor | 9085/3 |

clinical–pathological entity has been not included in the new WHO classification since it requires further investigation.

Up to 90 % of primary tumors are benign and 10 % malignant, with the majority of these being sarcomas (90 %) arising from the parenchymal or mesenchymal cells of the structural elements of the heart such as the blood vessels, muscle, connective tissue, fat, and even bone. Lymphoma and primary pericardial mesothelioma represent most of the remaining cases.

Concerning the epidemiology and prevalence of various histotypes, we refer to the experience of the University of Padua [6, 10]. In the time interval 1970–2010, 267 consecutive primary cardiac neoplasms were studied, 213 (89.5 %) of which were benign and 26 (10.5 %) malignant. This is mostly a biopsy-based experience (89.5 % of cases), just to emphasize that nowadays cardiac tumors are rarely fatal, with exception of primary malignancies. Among the benign cardiac tumors, the majority (66 %) were myxomas, followed by papillary fibroelastomas (9.5 %). There was a female predominance (88, 62.5 %), mean age 54 years. As far as malignant primary cardiac tumors, leiomyosarcoma and angiosarcoma ranked first (19 % each). There was a male predominance, mean age 50 years. As far as metastatic cardiac tumors, lung carcinoma was by far the leading one in our experience (32.5 %), especially as pericardial carcinosis with effusion, followed by lymphoma and leukemia (16 %), breast carcinoma (5 %), hepatic carcinoma (5 %), and kidney carcinoma (4 %).

More important than the cell type is the proximity of the tumor to vital intracardiac structures. Two different types of growth are found:

- Intramural, producing conduction abnormalities and arrhythmias as well as heart failure due to systolic and diastolic dysfunction
- Intracavitary, with obstruction to blood flow or embolization of thrombi or tumor cells

## 20.2 Clinical Features

Patients with cardiac tumors may present with cardiovascular-related or constitutional symptoms, through any of the four mechanisms:

- Mass effect: they can obstruct intracardiac blood flow or interfere with valve function.
- Local invasion: leading to arrhythmias or pericardial effusions with tamponade.
- Embolization: parts of tumor or thrombi can embolize, causing systemic or pulmonary infarctions (if on the left or right side of the heart respectively).
- The tumors may cause constitutional symptoms or hematologic abnormalities.

Moreover, cardiac malignant tumors may also present with problems related to metastatic disease. In rare cases, the first manifestation of a cardiac tumor is sudden cardiac death. Some tumors produce no symptoms and are incidental findings during an imaging investigation performed for an unrelated indication.

## 20.3 Surgical Pathology

Histopathology is mandatory in any resected cardiac mass, to establish the benign or malignant nature and the precise histotype. This information may be crucial in the case of malignancy for the choice of therapy and prognosis. Masses may be neoplastic, but even thrombotic, calcific, septic, and infective. The employment of traditional histological and histochemical stainings should be accompanied by immunohistochemistry with a large panel of antibodies, for establishing the histotype of tumor cell proliferations, particularly in the setting of malignant unresectable masses that require histological characterization before starting chemotherapy [1]. In rare cases of cardiac sarcoma, electron microscopy may also be of help. Consultancy in tertiary referral centers of cardiovascular or soft tissue tumor pathology is advisable. Before surgery, tissue diagnosis can be achieved through percutaneous endomyocardial biopsy, particularly in the setting of right-sided cardiac masses. Moreover, endomyocardial biopsy can be useful for unresectable tumors requiring histological characterisation before chemotherapy.

## 20.4 Tumor Grading and Staging

Due to the low frequency of malignant cardiac tumors, as far as histologic grading of malignancy, there are no specific parameters, and we have to refer to soft tissue neoplasms [19]. A histologic grading system has been put forward by the French Federation Nationale des Centre de Lutte Contre le Cancer (FFNCLCC) [20], which is based upon a cumulative score deriving from three parameters, i.e., (a) tumor differentiation (score 1, sarcomas closely resembling normal adult mesenchymal tissue; score 2, sarcomas for which histological typing is certain; score 3, undifferentiated sarcoma, angiosarcoma), (b) mitotic count (score 1, 0–9 mitoses per 10 high-power field, HPF, measuring 0.1734 mm2; score 2, 10–19 mitoses per 10 HPF; > or =20 mitoses per 10 HPF), and (c) tumor necrosis (score 0, no necrosis; score 1, <50% tumor necrosis; score 2, > or = 50% tumor necrosis). Three grades of malignancy are thus recognize: G1, low grade (total score 2, 3); G2, intermediate grade (total score 4, 5); G3, high grade (total score 6, 7, 8),

## 20.5 Treatment and Prognosis

The prognosis of patients with primary malignant cardiac tumors is very poor even if complete resection is attempted. Adjuvant chemotherapy and irradiation are usually also given, but these are not effective in most cases, with the exception of primary cardiac lymphoma which shows a better survival compared with sarcomas. Favorable results of heart transplantation for primary malignant cardiac tumors have been reported. Cardiac autotransplantation (cardiac explantation, ex vivo tumor resection, reconstruction, and reimplantation) may represent an option in many primary malignant cardiac tumors [21].

## 20.6 Key Points

- Cardiac tumors are rare with a frequency that varies in postmortem studies between 0.0017 % and 0.33 %.
- Consist of both primary and secondary tumors.
- Secondary cardiac tumors (metastases) are 20 times more common than primary cardiac tumors.
- The majority of primary cardiac tumors are benign, most being myxomas, accounting for up to 90 % of all cardiac tumors.
- The most common malignant primary cardiac tumor is sarcoma.
- Primary lymphoma of the heart is exceedingly rare, but with a better survival.
- Symptoms are nonspecific and can mimic many other heart diseases.
- The clinical presentation depends on the size, location of the cardiac tumor, and type of growth (intramural or intracavitary).
- "Histological examination of any resected cardiac mass is mandatory to achieve a certain diagnosis and to plan the proper treatment".

## 20.7 Cardiac Sarcomas

Sarcomas are mesenchymal tumors of various histologic morphologies and constitute most of primary malignant cardiac tumors [1, 6, 7, 10, 17, 22, 23]. By definition, they are confined to the heart or pericardium at the time of diagnosis without any evidence of extracardiac primary neoplasm. They occur in adults and have no predilection for either sex.

Primary cardiac sarcomas may occur in any chamber of the heart, although the right heart is the most frequent site of origin. Histologic type shows no consistent relation to the location within the heart, except for angiosarcoma, which has a predilection for the right atrium. Although arising from the endocardium or pericardium more often than from the myocardium, malignant tumors rapidly infiltrate all layers of the heart, invade adjacent mediastinal structures, and metastasize. Systemic metastases, particularly to the lungs and mediastinal lymph nodes, are present in 80 % of cases when first diagnosed. This growth pattern makes cardiac sarcomas often unresectable and thus the prognosis is poor. Survival is measured in weeks or months.

## 20.7.1 Angiosarcoma

### Definition

20.7.1.1 Angiosarcoma is a malignant tumor with endothelial differentiation. According to the new WHO classification [1], there are two types, with distinctive histological and genetic features: angiosarcoma (high-grade sarcomas) and epithelioid hemangioendothelioma (low-grade sarcomas).

### Epidemiology

20.7.1.2 Angiosarcomas are the most common primary malignant cardiac neoplasms, accounting for 40 % of primary cardiac malignancies. The peak incidence is in the fourth decade with slight male predilection.

### Localization

It most often arises in the right atrium, close to the atrioventricular groove (80 %) [4, 24, 25], but has been reported in the other heart three chambers as well as in the pericardium. Cardiac epithelioid hemangioendothelioma typically occurs in the atria and may present as an incidental mass or embolism.

### Clinical Features

Symptoms tend to develop late in the course of the disease and are often nonspecific. Clinical symptoms usually relate to cardiac tamponade or right heart failure secondary to intracavitary obstruction. Affecting the right heart, angiosarcoma often produces right-sided heart failure, superior vena cava obstruction, and pericardial effusion. Presentation with lung metastases is not uncommon. The predominant right-sided location allows for diagnosis by endomyocardial biopsy [26] (◘ Fig. 20.1).

### Pathology

Macroscopically, it is a large mural, lobulated, and brown-reddish mass with a necrotic or hemorrhagic appearance, that widely infiltrates the wall and the pericardium and protrudes in right cardiac cavities, with invasion of the inferior vena cava and the tricuspid orifice. Histologically, two thirds of angiosarcoma are moderately to well differentiated and are composed of irregular vascular spaces with papillary intraluminal tufting lined by pleomorphic and atypical cells. Mitoses are frequent. In one third of cases, the tumor is poorly differentiated, without discrete vascular structures, and consists of anaplastic spindle cells within a hyaline stroma, containing focally extravascular red cells. No definite Weibel-Palade bodies are identified with electron microscopy. However, pynocytotic vesicles, abundant intermediate filaments, and a moderate amount of rough endoplasmic reticulum and Golgi apparatus may be found.

Epithelioid hemangioendothelioma is composed of epithelioid cells arranged in short strands or solid nests. The constituent endothelial cells are round or oval, contain small intracellular lumina, and frequently infiltrate the vessels.

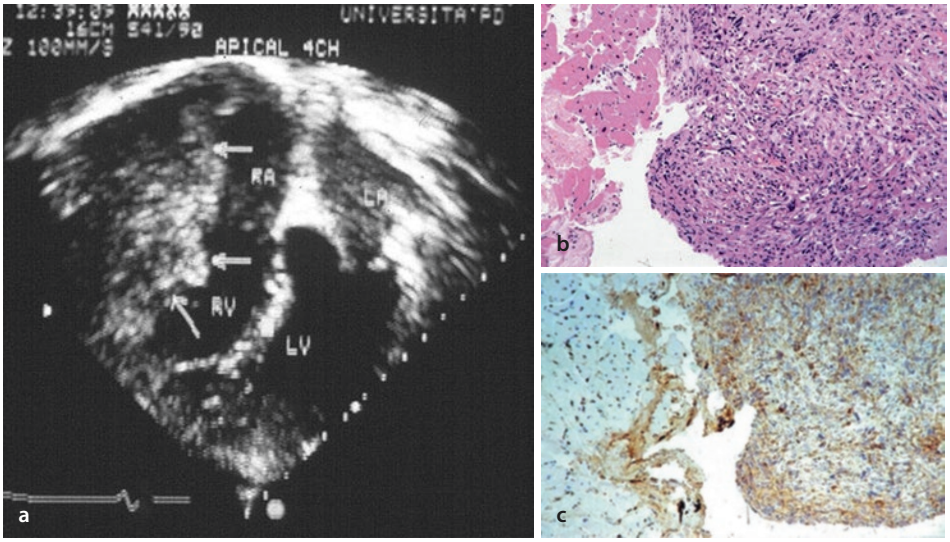



**Fig. 20.1** Angiosarcoma in a 36-year-old woman, suffering from dyspnea and fever (Modified from Poletti et al. [26]). **a** Two-dimensional echocardiogram, four-chamber view, showing an endocavitary and intramural large mass in the right atrium extending into the right ventricle, measuring 6 × 8 cm. **b** Photomicrograph of transvenous biopsied tumor: the myocardium was infiltrated by pleomorphic spindle cells with hyperchromatic nuclei forming vascular spaces. **c** Tumor cells arranged in vascular channels were positive for factor VIII

## Immunohistochemistry

Angiosarcomas typically express endothelial markers, including von Willebrand factor, CD34, CD31, and VEGF.

## Differential Diagnosis

Differential diagnosis includes fibrosarcoma, undifferentiated pleomorphic sarcomas, and Kaposi sarcoma. The detection of endothelial vacuoles or papillary structures is helpful. Immunohistochemistry plays a crucial role in diagnosis, especially in undifferentiated forms. Kaposi sarcoma generally forms small nodules involving the pericardium with minimal invasion of the myocardium. Pericardial angiosarcomas can be mistaken for mesotheliomas. Stains for cytokeratin, calretinin, cytokeratin 5/6, and CD31 can help to differentiate the two populations of cells. The intracellular lumina of epithelioid hemangioendothelioma may mimic the vacuoles of adenocarcinoma, which should be initially considered in the microscopic differential diagnosis.

## Genetics

Molecular analyses on tumor tissues have focused on genetic alterations of TP53 and K-ras [27].

## Prognosis

Prognosis is poor, usually because of delayed diagnosis and metastases, with a median survival of less than 1 year, even after surgical exeresis and adjuvant therapy.

**Key Points: Angiosarcoma**

- Angiosarcoma (high-grade sarcoma) is the most common primary cardiac malignant tumor.
- Epithelioid hemangioendothelioma is a subtype with low-grade malignancy.
- Male predominance and a peak incidence in the fourth decade.
- Right atrial free wall and atrioventrentricular groove are involved in 80 % of cases, allowing diagnosis by endomyocardial biopsy.
- Hemorrhagic mass composed by multiple, irregular vascular channels lined by pleomorphic and atypical cells, CD31, von Willebrand factor, and CD34 positive.

## 20.7.2 Undifferentiated Pleomorphic Sarcomas

### Definition

High-grade malignant cardiac sarcomas showing fibroblastic or myofibroblastic differentiation and areas of marked cellular pleomorphism, with no specific histologic and immunohistochemical markers [1]. Malignant fibrous histiocytoma is a synonym.

### Epidemiology

Undifferentiated pleomorphic sarcoma is the second most common malignant cardiac sarcoma in adults with a reported prevalence of 24–37.5 %. There is no gender predilection and the mean age is around 45 years (range, 20–80 years).

### Localization

Undifferentiated pleomorphic sarcomas tend to be intracavitary, located in the left atrium of the heart, where they most often present like cardiac myxomas, but most commonly arise along the posterior wall in comparison to the septum.

### 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. Constitutional signs and symptoms may precede symptoms referable to the heart. They may also present with metastases and the lungs, lymph nodes, kidney, and skin are common sites.

### Pathology

Undifferentiated pleomorphic sarcoma typically presents as a soft or firm polypoid endocardial-based tumor. It may be sessile or pedunculated, simulating myxoma, but unlike myxoma, may form multiple masses. The mass may distend the atrium and impinge upon the mitral valve. Extension into the pulmonary veins and lung parenchyma may be

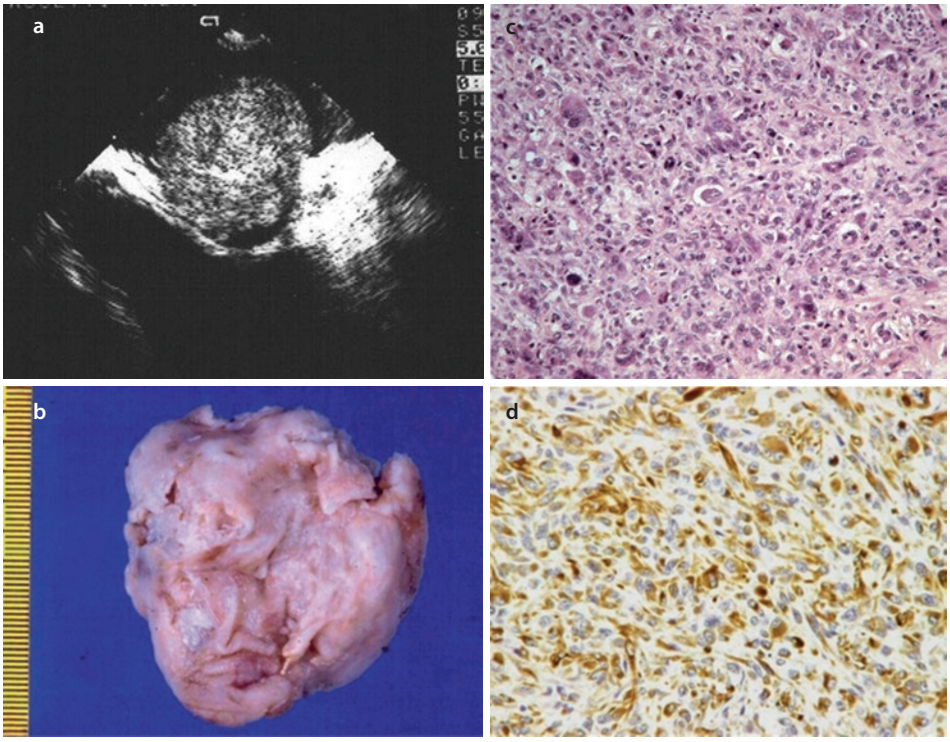



**Fig. 20.2** Left atrial undifferentiated pleomorphic sarcoma in a 68-year-old man, presenting with fever and increased serum level of flogistic markers. **a** Echocardiogram: endoluminal round mass in the left atrium, simulating a myxoma. **b** Grossly, the surgical resected mass showed a rough and irregular surface. **c** At histology, bizarre cells with pleomorphic nuclei admixed to giant cells and spindle-shaped cells, with high mitotic rate, are seen. **d** At immunohistochemistry, tumor cells are positive for vimentin

present. They may be uniform whitish or variegated due to hemorrhage and necrosis, with hard consistency. Calcification is uncommon. The diagnosis of Undifferentiated pleomorphic sarcoma is achieved by exclusion, when the use of a large panel of immunohistochemical stains fails to give evidence of myogenic or other specific differentiations (endothelial, cardiomyocyte, smooth muscle cells, fibroblast, adipose, nerves, epithelial). Microscopically, the proliferation consists of bizarre, pleomorphic cells, frequently giant multinuclear, with high mitotic activity (Fig. 20.2).

## Prognosis

The prognosis of undifferentiated pleomorphic sarcoma is very poor, because surgical resection is often incomplete. Chemiotherapy and radiotherapy give only temporary improvement. Survival patients ranges from 5 to 18 months. Most patients die of metastasis or local recurrence.

**Key Points: Undifferentiated Pleomorphic Sarcomas**

- Undifferentiated pleomorphic sarcomas are malignant neoplasms with fibroblastic or myofibroblastic differentiation and areas of marked cellular pleomorphism, with no specific histologic and immunohistochemical markers.
- The second most common primary malignant cardiac sarcoma in adults with a prevalence of 24–37.5 %.
- No gender predilection, mean age 45 years.
- The left atrium is frequently involved with an intracavitary growth.
- Proliferation of bizarre, pleomorphic cells, frequently giant multinuclear, with high mitotic activity.
- Diagnosis is achieved by exclusion, when immunohistochemical stains fail to give evidence of specific differentiation.

### 20.7.3 Osteosarcoma

#### Definition

Primary cardiac osteosarcoma originates in the heart and produces the osteoid or bone, occasionally with chondroblastic differentiation. These have been grouped in the past WHO classification within malignant pleomorphic fibrous histiocytomas/undifferentiated pleomorphic sarcomas with osteosarcomatous differentiation, but nowadays they represent a distinct subtype [1]. Osteogenic sarcoma, osteoblastic osteosarcoma and extraskeletal osteosarcoma are synonyms.

#### Epidemiology

Osteosarcomas are quite rare, making up approximately 10 % of primary cardiac sarcomas. Cardiac osteosarcomas occur most commonly between the second and fifth decades of life, with a mean patient age of 40 years, and do not show any gender predominance.

#### Localization

Primary osteosarcomas are more frequently left sided and may be mistaken for atrial myxomas. The second most common location is the right atrium, with extension into the vena cava.

#### Clinical Features

Due to the left atrial location, initial symptoms are most frequently related to mitral valve obstruction. Dyspnea, chest pain, palpitations, dizziness, murmurs, and congestive heart failure have been reported.

## Pathology

Cardiac osteosarcomas usually present as nodular masses with infiltrative margins. The cut surface is heterogeneous, firm, and white, with areas of hemorrhage and necrosis. They may have osteo-, chondro-, or fibroblastic differentiation. The bone-forming areas range from well-differentiated trabeculated osteosarcoma to poorly differentiated sarcomas with stromal osteoid. Chondrosarcomatous areas are also present in about half of all cases.

## Immunohistochemistry

Most tumors express smooth muscle actin; S100 protein is expressed in chondroid areas. Epithelial membrane antigen can be focally positive in epithelioid areas.

## Differential Diagnosis

Atrial myxomas, given the left-sided location and presence of calcification.

## Prognosis

Prognosis of cardiac osteosarcoma is poor, with survival rarely beyond 1 year due to early metastases to lungs, skin, and skeleton.

**Key Points: Osteosarcoma**

- Malignant tumor that produces the osteoid or bone, occasionally with chondroblastic differentiation
- 10 % of primary cardiac sarcomas
- No gender predominance, mean age 40 years
- Left-sided tumor with intracavitary growth
- Osteo-, chondro-, or fibroblastic differentiation

### 20.7.4 Myxofibrosarcoma

## Definition

Myxofibrosarcoma is a low-grade cardiac sarcoma composed of spindle cells in a myxoid matrix [1, 28] Myxoid malignant fibrous histiocytoma, fibromyxosarcoma and myxoid fibrosarcoma are synonyms. It should be not considered a malignant variant of myxoma, the latter basically being a benign tumor.

## Epidemiology

Because of the various terms that have been used for this tumor, the precise incidence rate is uncertain, but myxofibrosarcoma probably accounts for about 10 % of cardiac sarcomas, making it the fourth most common cardiac sarcoma (after angiosarcoma, undifferentiated pleomorphic sarcoma, and osteosarcoma).

## Localization

The most common location for cardiac myxofibrosarcoma is in the atria (particularly the left), followed by the right ventricle, and the ventricular septum.

## Clinical Features

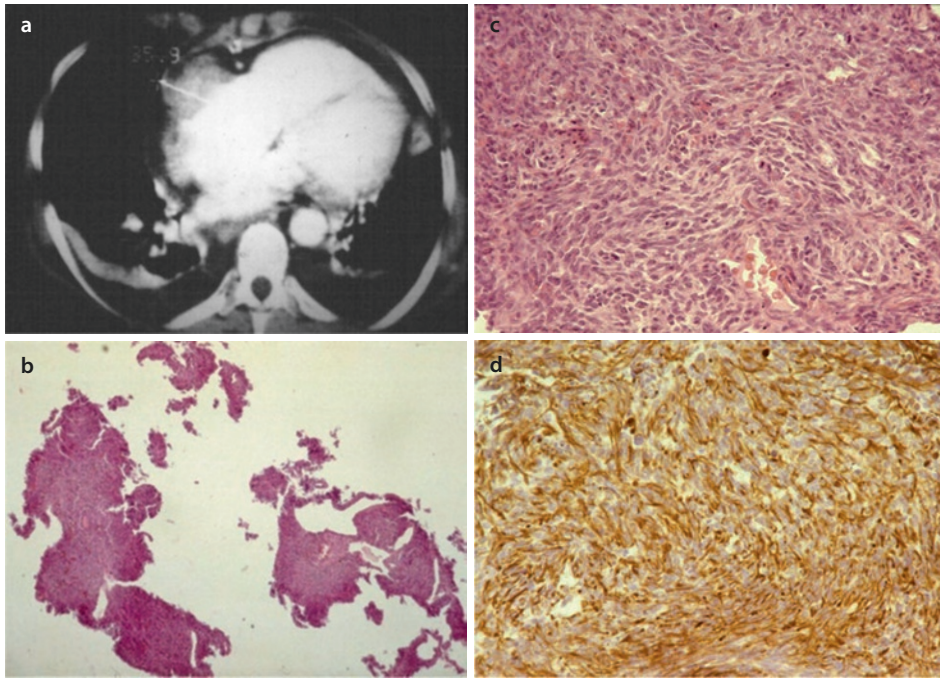
Cardiac myxofibrosarcomas have been described most frequently in the left atrium with both intracavitary and mural growth, typically causing obstruction and symptoms of mitral stenosis.

## Pathology

Myxofibrosarcoma is typically an endocardial-based tumor with little necrosis or hemorrhage, with intracavitary growth. Histologically, myxofibrosarcomas show spindle or rounded cells often within a myxoid matrix, without significant pleomorphism (◘ Fig. 20.3).

## Immunohistochemistry

Immunohistochemical staining is not helpful in the diagnosis, except to exclude other tumors, being positive only vimentin.




◘ **Fig. 20.3** Fibrosarcoma of the right atrium in a 62-year-old woman, suffering from weakness and effort dyspnea. **a** CT showing a mass infiltrating right atrial free wall. **b** Transvenous endomyocardial biopsy: note the elevated number of bioptic specimens. **c** At higher magnification, note atypical spindle cells within fibrous stroma. **d** Tumor cells are immunoreactive to vimentin

## Differential Diagnosis

Myxoma may be confused with myxofibrosarcoma because of the proteoglycan-rich matrix. Because myxofibrosarcoma may be histologically bland, the absence of pleomorphism is not a distinguishing feature between myxoma and myxofibrosarcoma.

## Prognosis

In spite of surgery is often possible, survival is poor, but slightly better than angiosarcoma of the heart.

**Key Points: Myxofibrosarcoma**

- Low-grade cardiac sarcoma composed of spindle cells in a myxoid matrix.
- About 10 % of cardiac sarcomas.
- The left and right atrium are the main location with intracavitary and mural growth.

### 20.7.5 Leiomyosarcoma

## Definition

Leiomyosarcoma is a malignant tumor with smooth muscle cell differentiation [1, 29, 30].

## Epidemiology

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

## Localization

It has a predilection for the left atrium and pulmonary infundibulum.

## Clinical Features

The commonest manifestation is dyspnea and cardiac failure from mitral obstructive symptoms. Pulmonary embolism may occur in case of right-sided tumors.

## Pathology

The tumors appear firm, fleshy, gray, and sessile. They may present as multiple intracavitary nodules. Leiomyosarcoma consists of compact bundles of spindle cells with blunt-ended nuclei, glycogen, and perinuclear vacuoles, often oriented at sharp angle or 90° to one another. Zones of necrosis and mitotic figures are frequent.

## Immunohistochemistry

The spindle cells show reactivity for alpha smooth muscle actin and desmin (Fig. 20.4).

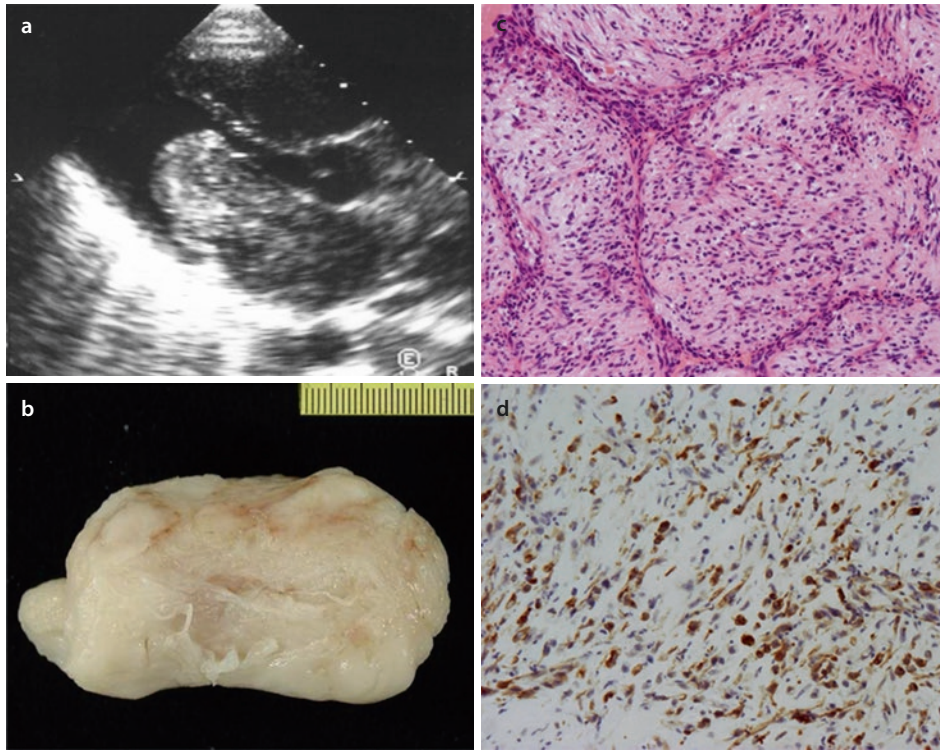



**Fig. 20.4** Leiomyosarcoma of the left atrium in a 21-year-old woman with acute pulmonary edema and preoperative diagnosis of left atrial myxoma. **a** Echocardiogram: endoluminal mass in the left atrium prolapsing in the left ventricular cavity during diastole, simulating a myxoma. **b** Gross features of the cardiac mass resected at the surgery, showing rough and irregular surface. **c** Pleomorphic cells arranged in a storiform pattern within a myxoid background. **d** Immunohistochemical staining showing tumor cell positivity for desmin

## Prognosis

Surgical resection is usually palliative in association with adjuvant chemotherapy and radiotherapy. The reported mean survival time is about 1 year.

### Key Points: Leiomyosarcoma

- Malignant tumor with smooth muscle cell differentiation
- No sex predilection, 40 and 50 years of age
- Predilection for the left atrium and pulmonary infundibulum
- Bundles of spindle cells with blunt-ended nuclei, often oriented at sharp angle or 90° to one another, and alpha smooth muscle actin and desmin positive

### 20.7.6 Rhabdomyosarcoma

#### Definition

Rhabdomyosarcoma is a malignant tumor with striated muscle differentiation [1]. Rhabdomyosarcomas arise de novo, not from malignant degeneration of a rhabdomyoma.

#### Epidemiology

Rhabdomyosarcoma is a rare subtype of cardiac sarcoma (less than 5 %) [31], but remains the most common pediatric cardiac malignancy. In the past, before immunohistochemical analysis, a large proportion of cardiac sarcomas were wrongly considered rhabdomyosarcomas.

#### Localization

Rhabdomyosarcomas may arise from any location in the heart, but ventricular involvement is greater than other cardiac sarcomas. They are usually mural tumors.

#### Clinical Features

The clinical presentation, as with other cardiac tumors, depends on the cardiac location. Pericardial effusion, dyspnea, conduction disturbances and extracardiac metastases are the usual presentation.

#### Pathology

Cardiac rhabdomyosarcomas are large, bulky, infiltrative tumors that may be grossly mucoid or gelatinous, similar to cardiac myxoma, or soft and necrotic, highly heterogeneous. In the heart there are two distinct histologic types: embryonal, which occur mainly in children and adults, and a pleomorphic, which are much less frequent and occur in adults. Embryonal rhabdomyosarcoma is a small-cell neoplasm with variable numbers of PAS-positive rhabdomyoblasts (tadpole or strap cells). Alveolar rhabdomyosarcoma has been described in the heart as a metastatic lesion. Sarcoma botryoides, with characteristic grape-like structures, has also been described in the heart [32] At electron microscopy, the diagnostic features are thick and thin filaments and Z-bands.

#### Immunohistochemistry

Immunohistochemical staining shows positivity for desmin and myogenin.

#### Differential Diagnosis

The differential diagnosis includes other cardiac sarcomas, especially undifferentiated lesions and metastatic small round cell tumors in children and young adults. Immunohistochemical stains are vital in identifying rhabdomyoblasts.

## Somatic Genetics

Cytogenetic analysis shows mutation at exon 1 of K-ras.

## Prognosis

Surgical rection is palliative due to local and distant metastases. Response to adjuvant chemotherapy and radiation is poor. In selected cases, cardiac transplantation is considered.

**Key Points: Rhabdomyosarcoma**

- Malignant tumor with striated muscle differentiation that involves the myocardium.
- The most common cardiac malignancy in pediatric population.
- Embryonal rhabdomyosarcoma is the most frequent variant in the heart, characterized by small cells and variable numbers of PAS-positive rhabdomyoblasts (tadpole or strap cells), with positivity for desmin and myogenin.

### 20.7.7 Synovial Sarcoma

## Definition

Synovial sarcoma is a biphasic tumor composed of spindle and epithelioid cells, characterized by X;18 chromosomal translocations.

## Epidemiology

Synovial sarcomas account for approximately 5% of all primary cardiac sarcomas. The male-to-female ratio is 3:1. The mean patient age at diagnosis is 37 years, ranging from 13 to 70 years.

## Localization

Most common site for synovial sarcoma is the lower limb. Synovial sarcoma of the heart is extremely rare. There is a predilection for the atria and pericardial surfaces. Right side synovial sarcoma is twice more common than the left side [33, 34].

## Clinical Features

The clinical presentation is nonspecific, so the diagnosis is almost always at advanced stage in most of the cases. Left-sided tumor manifests earlier than right-sided tumor due to their mass effect and obstruction to pulmonary veins.

## Pathology

On macroscopic examination synovial sarcomas are firm, whitish, infiltrative tumors with areas of necrosis and hemorrhage. The size of tumor varies from 2.9 to 15 cm. Left-sided tumors are comparatively small. Cardiac synovial sarcoma may be biphasic or monophasic.

The latter is the most common form in the heart. The classical biphasic synovial sarcoma has epithelial and spindle cell components in varying proportion. The classical monophasic variant contains only spindle cell component.

## Immunohistochemistry

Immunohistochemically, cytokeratin and epithelial membrane antigen are strongly expressed in the epithelioid cells. Spindle cells express vimentin and focally smooth muscle actin. The cells do not express CD34.

## Differential Diagnosis

Differential diagnosis includes sarcomatoid mesothelioma, solitary fibrous tumor, and fibrosarcoma. Distinction of synovial sarcoma from mesothelioma, another biphasic tumor, can usually be made on the basis of tumor location (mesotheliomas do not occur within the atria) and growth pattern (synovial sarcoma is usually a solitary mass, while mesothelioma tends to grow diffusely over the pericardium). Additionally, the spindle cell component of synovial sarcoma tends to be relatively uniform. The SS18/SSX transcripts are specific markers of synovial sarcoma and can be detected by the reverse transcriptase–polymerase chain reaction (RT-PCR) [35].

## Genetics

Cytogenetically the reciprocal translocation *t*(X;18) (p11.2;q11.2) between SYT gene on chromosome 18 and SSX1 or SSX2 gene on chromosome X is seen in more than 90 % of soft tissue synovial sarcomas.

## Prognosis

Primary cardiac synovial sarcoma is an extremely rare malignancy, with a very poor prognosis due to high local recurrence and metastasis rate. Chemotherapy with or without radiotherapy seems to improve survival.

### Key Points: Synovial Sarcoma

- Synovial sarcoma is an extremely rare and highly aggressive tumor composed of epithelial and spindle cells.
- Male-to-female ratio is 3:1, mean age 37 years.
- Right side synovial sarcoma is twice more common than the left side.
- Cardiac synovial sarcoma may be biphasic (epithelial and spindle cell components) or monophasic (only spindle cell component), the latter being the most common form in the heart. The epithelioid cells express cytokeratin and epithelial membrane antigen, while spindle cells vimentin and smooth muscle actin.
- X;18 chromosomal translocations is seen in more than 90 % of soft tissue synovial sarcomas.

### 20.7.8 Miscellaneous Sarcomas

#### Definition

Miscellaneous sarcomas include rare primary cardiac sarcomas: malignant peripheral nerve sheath tumor (MPNST), liposarcoma, extraskeletal Ewing sarcoma/primitive neuroectodermal tumor/the Ewing family of tumors (EFTs), carcinosarcoma, desmoplastic small round cell tumor (DSRCT), extrarenal rhabdoid tumor/malignant extrarenal rhabdoid tumor (MERT), and chondrosarcoma [1].

## 20.8 Primary Cardiac Lymphoma

### 20.8.1 Definition

Primary cardiac lymphoma is defined as an extranodal non-Hodgkin lymphoma that involves only the heart and/or the pericardium.

### 20.8.2 Epidemiology

Primary cardiac lymphomas represent about 1 % of all primary cardiac tumors. The median age is 60 years, with male/female ratio approximately 3:1, and it occurs not necessarily in immune-deficient people [36].

### 20.8.3 Location

Primary cardiac lymphomas may arise in any cardiac chamber, but in two thirds of cases, the right atrium is the site of involvement with an intramural, whitish infiltrating mass extended to the pericardium with massive effusion.

### 20.8.4 Clinical Features

The clinical presentation has usually an acute onset, with chest pain, pericardial effusion, congestive heart failure, arrhythmias, syncope, and even complete AV block.

### 20.8.5 Pathology

Usually the tumor is large, infiltrating myocardium and forming multiple intracavitary polypoid nodules, which may eventually obliterate the cavities. The pericardium is usually thickened by white–grayish tumor infiltration with massive pericardial effusion.

### 20.8.6 Immunohistochemistry

Histopathologically, the subtype most frequently observed (80 % of cases) is diffuse large B-cell lymphoma with CD20-positive cells, whereas the remaining 20 % are CD3-positive T-cell lymphomas. Immunocytochemical staining, cytogenetic studies, and polymerase chain reaction are necessary to differentiate B- and T-cell lymphomas from reactive lymphocyte hyperplasia, detecting the presence of a monoclonal population.

### 20.8.7 Differential Diagnoses

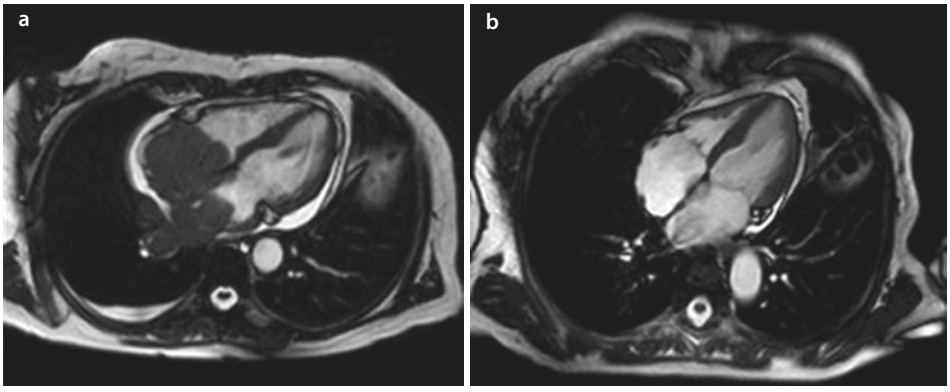
The differential diagnoses include secondary cardiac involvement by a primary mediastinal large B-cell lymphoma and primary cardiac sarcomas.

### 20.8.8 Prognosis

The prognosis is poor, with a mean survival of 7 months. Chemotherapy can often improve the patient's survival (◘ Fig. 20.5).

### 20.8.9 Key Points: Primary Cardiac Lymphoma

- Defined as an extranodal non-Hodgkin lymphoma involving primarily and only the heart and pericardium.
- Secondary cardiac involvement by lymphoma is more common than primary cardiac lymphoma.
- Primary cardiac lymphoma typically involves the right heart and more than one cardiac chamber.
- Diffuse large B-cell lymphoma with CD20-positive cells is the most frequent subtype.
- Chemotherapy is the main treatment.




◘ **Fig. 20.5** Magnetic resonance imaging in a case of primary cardiac non-Hodgkin lymphoma. **a** At diagnosis the mass occupied both atria, extending to pulmonary veins. **b** After R-CHOP chemotherapy there was complete remission

## 20.9 Tumors of the Pericardium

Pericardial tumors in WHO classification [1] include solitary fibrous tumor, malignant mesotheliomas, germ cell tumors, sarcomas (angiosarcomas and synovial sarcoma), and metastatic pericardial tumors.

Pericardial tumors are most likely to be metastatic in nature or an extension of primary tumors from the surrounding structures, in most cases from lung and breast tumors, melanoma, or hematologic malignancies.

Pericardial teratomas and malignant mesotheliomas are the most common primary pericardial tumors.

Pericardial tumors often cause symptoms related to pericardial effusion.

The combination of cytologic fluid analysis and histologic pericardial biopsy is necessary to making the final diagnosis.

### 20.9.1 Solitary Fibrous Tumor

#### Definition

A spindle cell tumor with a hemangiopericytoma-like vascular pattern. Localized fibrous tumor and haemangiopericytoma are synonyms.

#### Localization

Solitary fibrous tumors usually arise from the pleura, but also in various sites. Rare examples have been reported in the pericardium and within the heart [37].

#### Clinical Features

Clinical features are related to pericardial mass effect, including pericarditis and pericardial effusion.

#### Pathology

Macroscopically, solitary fibrous tumor is firm and well circumscribed. Histopathologic examination shows spindle cell proliferation with often a hemangiopericytoma-like vascular pattern. Areas of hypercellularity typically alternate with myxoid or fibrous areas.

#### Immunohistochemistry

Solitary fibrous tumors are CD34 positive. STAT6 nuclear expression is a specific and sensitive marker for solitary fibrous tumor.

#### Differential Diagnosis

Malignant mesotheliomas of the pericardium show diffuse growth pattern and keratin and calretinin reactivity. Fibrosarcoma tends to be more monomorphic and negative for CD34. Monophasic synovial sarcoma has higher-grade cytology and focal keratin reactivity.

## Prognosis

The prognosis is good, although recurrences after surgical resection and local spread have been reported.

**Key Points: Solitary Fibrous Tumor**

- Spindle cell tumor showing alternating hypercellular and hypocellular areas, with hemangiopericytoma-like patterns.
- Diffuse positivity for CD34 and STAT6.
- Prognosis is good.

### 20.9.2 Malignant Mesothelioma

## Definition

A malignant tumor derived from mesenchymal tissue showing a mesothelial differentiation. The definition of primary pericardial mesothelioma requires that there is no tumor present outside the pericardium, with the exception of lymph node metastases.

## Epidemiology

Pericardial mesotheliomas represent less than 1 % of all malignant mesotheliomas, but they are the most common primary pericardial tumor, with a higher incidence among men than women and a mean age of 45 years. Risk factors for malignant mesothelioma include asbestos exposure, therapeutic radiation, and pericardial dusting as a treatment for angina pectoris.

## Clinical Features

Symptoms usually result from constriction of the heart and diastolic impairment or compression of surrounding structures either from hemorrhagic pericardial effusion or direct infiltration. Cytological examination is a poor method for detection of mesothelioma. Although clinical data and imaging are very helpful for the diagnosis of pericardial mesothelioma, a definite diagnosis still relies on pericardial biopsy or postmortem examination [38].

## Pathology

Macroscopically, malignant mesotheliomas of the pericardium may present as localized nodules that fill the pericardial cavity or may spread diffusely over the pericardial surface encasing the heart and the great vessels. At histology, the majority are of the epithelioid type, forming tubules and papillary structures. The sarcomatous variant is also common. Ultrastructurally, mesothelioma cells contain microvilli.

## Immunohistochemistry

Expressions of mesothelial antigens, such as calretinin and cytokeratins 5/6, are helpful in the diagnosis. Negative are the reactions for adenocarcinoma markers, such as carcinoembryonic antigen.

## Differential Diagnosis

The distinction between mesothelioma and metastatic adenocarcinoma can be difficult and is generally based on immunohistochemical findings. Distinction from reactive mesothelial cell proliferations may also be difficult. Malignancies that may be confused with mesothelioma include pericardial angiosarcoma, which may elicit a prominent mesothelial response, malignant solitary fibrous tumor, and synovial sarcoma. Mesothelioma lacks the X;18 translocation of synovial sarcoma.

## Prognosis

The median survival of patients with pericardial mesothelioma is approximately 6 months [39].

**Key Points: Malignant Mesothelioma**

- Primary malignant pericardial mesothelioma is extremely rare; however, it is the most common primary malignancy of the pericardium.
- No constant relationship between the asbestos exposure and the development of pericardial mesothelioma.
- Male-to-female ratio of 3:1, mean age 45 years.
- Progressive encasement of the heart causing breathlessness and chest pain, often with clinical signs of pericardial constriction and/or tamponade.
- Prognosis is poor.

### 20.9.3 Germ Cell Tumors

## Definition

Tumors of germ cell origin arising within the myocardium or pericardial cavity.

## Epidemiology

The great majority of germ cell tumors are benign teratomas and the remainders are yolk sac tumors. Teratomas typically affect infants and children. Its occurrence in adults is very rare, <1 % [40, 41], with a peak incidence in the second and third decades of life and a male predominance.

## Localization

Approximately 90 % of the cardiac teratomas involve the pericardium [1].

## Clinical Features

The main clinical findings relate to pericardial effusion. Intramyocardial teratoma often manifests with congestive heart failure or arrhythmias.

## Pathology

Macroscopically they have a multicystic and lobulated appearance, with intervening solid areas. The size goes from a few millimeters up to 15 cm.

Histologically, teratomas contain elements derived from the three embryonic layers (endodermal, ectodermal, and mesodermal) in varying degrees. If more than 50 % of the tumor is comprised of well-differentiated elements, then the tumor is referred to as a mature teratoma. The immature teratoma is less well differentiated, with components resembling fetal-type tissues. Malignant areas may be observed within a benign teratoma, with features of yolk sac tumor.

## Immunohistochemistry

Immunohistochemical staining positive for alpha-fetoprotein suggests the diagnosis of a germ cell tumor.

## Differential Diagnosis

The differential diagnosis of intra cardiac teratomas is cystic tumor of the atrioventricular node; however, the latter does not contain mesodermal or ectodermal structures.

## Prognosis

Recurrence or malignant degeneration is rare. The prognosis depends upon the extension of malignant areas. Yolk sac tumors metastasize at an early stage and invade the surrounding structures and organs.

**Key Points: Germ Cell Tumors**

- Tumors of germ cell origin that contain endodermal, mesodermal, and ectodermal elements.
- Strong predilection toward pediatric population.
- Most of them are intrapericardial benign teratomas.
- Areas of malignant degeneration ("yolk sac tumor") secreting alpha-fetoprotein may be present.
- Prognosis depends on these malignant areas.

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