The 2021 WHO Classification of Tumors of the Heart

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Introduction

The fifth edition of the WHO Classification of Thoracic Tumours presents an updated classification of cardiac tumors, detailed in Table 1. As in previous iterations, the tumors are stratified into benign and malignant varieties, with a separate section to address hematolymphoid neoplasms of the heart.

New to the fifth edition is an extensive collection of online whole slide images that exhibit examples of each of the cardiac entities classified in this volume. In addition, a new online format makes the content even more accessible to clinicians and scientists globally, in the hopes of facilitating adoption. It is only through these common definitions and language that we can hope to better understand these rather uncommon lesions.

Advances in our understanding of cardiac tumors were the guiding principle in determining the optimum classification. To reduce redundancy, some mesenchymal entities of the thorax were removed from the site-specific subsections of the book and placed within a general section on the topic. Similarly, syndromic tumors are now discussed separately in a section on genetic tumor syndromes involving the thorax.

Here, the changes made in the fifth edition will be summarized. Essential and desirable diagnostic criteria are provided for each entity in Supplementary Table 1. Brief commentaries on the clinical relevance of these changes are provided, with final comments on potential directions for further study in this area.

Changes in the Fifth Edition

Updates to each of the main categories of cardiac tumors were made in the fifth edition, resulting in some entities being combined with others and some being newly established. Malignant primary cardiac neoplasms have been an area of growing controversy in the past decade. As detailed subsequently, the entities of intimal sarcoma and undifferentiated pleomorphic sarcoma (UPS) have been formally separated, reflecting a better understanding of their biology and a better reflection of their anatomical sites of occurrence. Intimal sarcoma has been relocated to the Lung Section of the Thoracic Volume and the Intimal Sarcoma chapter of the WHO Classification of Soft Tissue and Bone Tumours.

Although many sarcomas have been described in the heart, only a few are encountered with regularity. Most of the other rare types have been relocated to a specific section on Mesenchymal Tumors of the Thorax or can be found in the Soft Tissue volume. These include rhabdomyosarcoma (embryonal and pleomorphic subtypes), osteosarcoma, dedifferentiated liposarcoma, malignant peripheral nerve sheath tumor, and Ewing sarcoma.

There has also been increasing debate on the neoplastic nature of papillary fibroelastomas (PFEs). It is currently the most often excised heart tumor, nearly twice as frequently encountered as cardiac myxoma.
Updates on the biology of these lesions have allowed for their reclassification and an altered bioepidemiologic landscape of cardiac neoplasms.

Another reclassification occurred with the lesion formerly referenced as histiocytoid cardiomyopathy, which is now recognized as a primarily tumoral condition, the conduction system hamartoma. Several other hamartomatous lesions (mesenchymal cardiac hamartoma and lipomatous hamartoma of the atrioventricular valves) were also added to the classification because of their distinctive clinical and pathologic presentations.

As mentioned previously, a detailed section on thoracic tumor syndromes, including their clinical presentation and molecular genetics, is now present within the text. Specifically, apropos to cardiac neoplasms, is the subsection on Carney complex (CNC), which provides the reader with more detail on the genetic implications of this diagnosis and the contemporary testing or screening strategy.

Summary of Cardiac Metastases

Defined as a malignant neoplasm arising outside of the heart and pericardium, cardiac metastases occur in up to 10% of patients with cancer. Metastases are far more common than primary cardiac tumors and generally portend a poor prognosis. Most encountered are malignant melanoma and supradiaphragmatic epithelial neoplasms, most notably lung and breast carcinomas. Other reported primary malignancies metastatic to the heart include but are not limited to thyroid, thymic, gastrointestinal, renal, endometrial, ovarian, and urinary bladder. Metastases of nonepithelial tumors may include sarcomas (including angiosarcoma [AS]), mesothelioma, and lymphoma.

Radiologic-pathologic correlation studies confirm that metastatic tumors to the heart and pericardium may occur by means of several different mechanisms, including direct extension, hematogenous or lymphatic spread, or transvenous extension. The most common mechanism is metastasis through mediastinal lymphatic channels to the heart, resulting in epicardial deposition of the tumor.

The visceral pericardium contains a high density of lymphatic channels draining the pericardial space, which merge at the root of the aorta. A pericardial effusion results when metastatic tumor deposits obstruct the lymphatic system. Acute and chronic pericarditis can be found owing to this impaired lymphatic drainage or direct irritation. Prominent thickening of the pericardium is more often observed in the context of mesothelioma (either metastatic or primary) (Fig. 1) or chronic fibrosing pericarditis.

The clinical presentation of cardiac involvement in metastatic disease includes shortness of breath and hypotension which may be out of proportion to radiographic findings in patients with pericardial effusion. Patients may also present with cough, chest pain, or peripheral edema. Metastatic involvement of the heart and pericardium may go unrecognized until autopsy. Impairment of cardiac function occurs in approximately 30% of patients and is usually attributable to pericardial effusion.

Cytologic evaluation of pericardial effusion specimens after pericardiocentesis is frequently the initial procedure of choice to diagnose a metastatic malignancy involving the heart, although it has a rather low sensitivity with a false-negative rate approaching 15%. Nevertheless, when tumor cells are detected, it provides an excellent way of differentiating metastatic

Table 1. ICD-9-O Topographic Coding of Heart Tumors

<table>
<thead>
<tr>
<th>Benign Tumors</th>
<th>Malignant Tumors</th>
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<tbody>
<tr>
<td>8820/0 Papillary fibroelastoma</td>
<td>9120/3 Angiosarcoma</td>
</tr>
<tr>
<td>8840/0 Myxoma, NOS</td>
<td>8890/3 Leiomyosarcoma, NOS</td>
</tr>
<tr>
<td>8810/0 Fibroma, NOS</td>
<td>8802/3 Pleomorphic sarcoma</td>
</tr>
<tr>
<td>8900/0 Rhabdomyoma, NOS</td>
<td>8000/6 Neoplasm, metastatic</td>
</tr>
<tr>
<td>8904/0 Adult cellular rhabdomyoma</td>
<td>Hematolymphoid tumors</td>
</tr>
<tr>
<td>8850/0 Lipoma, NOS</td>
<td>9680/3 Diffuse large B-cell lymphoma, NOS</td>
</tr>
<tr>
<td>Lipomatous hypertrophy of the atrial septum</td>
<td>9680/3 Fibrin-associated diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Lipomatous hamartoma of atrioventricular valve</td>
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<tr>
<td>Hamartoma of mature cardiac myocytes</td>
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<tr>
<td>Mesenchymal cardiac hamartoma</td>
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<tr>
<td>9120/0 Hemangioma, NOS</td>
<td></td>
</tr>
<tr>
<td>9122/0 Venous hemangioma</td>
<td></td>
</tr>
<tr>
<td>9131/0 Capillary hemangioma</td>
<td></td>
</tr>
<tr>
<td>9123/0 Arteriovenous hemangioma</td>
<td></td>
</tr>
<tr>
<td>9121/0 Cavernous hemangioma</td>
<td></td>
</tr>
<tr>
<td>Conduction system hamartoma</td>
<td></td>
</tr>
<tr>
<td>8454/0 Cystic tumor of atrioventricular node</td>
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carcinoma, melanoma, sarcoma, mesothelioma, and reactive processes such as mesothelial hyperplasia, especially with use of adjunct immunohistochemistry and molecular studies. New ancillary studies such as BAP1 and MTAP immunohistochemistry and p16/CDKN2A fluorescence in situ hybridization are excellent for distinguishing malignant mesothelial proliferations from their benign counterparts (Fig. 2 A and B).9

**Figure 1.** Primary pericardial mesothelioma. The neoplasm diffusely involves the visceral pericardium and focally infiltrates the superficial myocardium.

Summary of Benign Cardiac Neoplasms

Most primary cardiac tumors are benign. These benign tumors reflect a broad array of neoplasms and hamartomas that are diagnosed throughout life, ranging from in utero diagnosis to centenarians.

The most common among these is the PFE. The classification of this lesion was changed from “growth” to “neoplasm” in the fifth edition, reflecting contemporary understanding that a significant proportion of these tumors harbor canonical oncogenic driver mutations in KRAS.10,11 High-resolution imaging has also led to increased detection of these tumors, causing them to usurp the cardiac myxoma as the most common cardiac neoplasm.9 PFEs may arise on any endocardial-lined surface, with the aortic valve being most often affected. Damaged endocardial surfaces are also particularly susceptible to PFE development.12 These papillary tumors look like sea anemones on both imaging and gross examination (Fig. 3 A and B), owing to their avascular, endocardium-lined fronds. Most patients with PFE are asymptomatic, and the PFE is found incidentally during a routine echocardiogram or cardiac computed tomography done for other indications. When symptomatic, the classic presentation is neurologic event (20%–30%), such as stroke or transient ischemic attack, followed by angina and myocardial infarction, sudden death, and rarely pulmonary embolism, retinal embolism, and even more rarely mesenteric ischemia, peripheral emboli, and renal infarction.3

Cardiac myxomas are benign neoplasms that most often arise on the septum of the left atrium. They can be lobulated or villiform (Fig. 4 A and B) and variable in size and shape. The lesional cell is the myxoma cell, occurring singly or in clusters, embedded in a myxoid matrix typically rich in proteoglycan, collagen, and elastin (Fig. 5). Immunoreactivity with calretinin is found in nearly all cases. Myxomas arising in a non-left atrial site or that are multicentric should always raise the suspicion for CNC, a syndrome resulting from underlying germline mutations in PRKAR1A. PRKAR1A immunostaining provides a useful surrogate to screen for CNC and can help direct future screening of patients with...
myxoma and their families (Fig. 6). Although incidental discovery on imaging is possible, nearly 70% of patients with myxoma will present with significant symptoms, such as stroke, peripheral embolization, or myocardial infarction. Obstructive symptoms, leading to heart failure, chest pain unrelated to exercise, palpitations, syncope, and sudden death may occur. Constitutional symptoms are also not infrequent, found in up to a third of patients, and may include fever, weight loss, fatigue, myalgias, arthralgias, and even Raynaud’s phenomena.

Cardiac rhabdomyoma is the most common pediatric cardiac neoplasm, up to 70% to 90% of which are associated with tuberous sclerosis. It is a benign hamartomatous lesion of striated cardiac myocytes without proliferative activity. They typically arise in multiples and frequently are associated with obstructive symptoms or arrhythmias. Histologically, they consist of enlarged, vacuolated “spider cells” that form circumscribed nodules. Spontaneous regression is common, thus a conservative approach to management is often taken; however, mTOR pathway inhibitors have been found to hasten tumor regression. Cardiac fibroma is the second most common pediatric cardiac tumor. Its diagnostic characteristics did not undergo significant revision from the previous classification. These tumors usually arise in the ventricular septum, where they have a large, grossly circumscribed, tan-white, and whorled appearance. Most often, they arise as a single mass with characteristic calcification that can sometimes be found on imaging. Histologically, cardiac fibromas consist of benign fibroblasts admixed with collagen fibers that increase as the lesion ages. The tumor is frequently associated with an arrhythmic presentation, but it responds

Figure 3. Papillary fibroelastoma. (A) Echocardiogram revealing the left atrial tumor (white arrow) with its numerous fronds. (B) The resected tumor exhibits a classic “sea anemone” appearance of the papillary fibroelastoma.

Figure 4. Cardiac myxoma. (A) These tumors can have a lobulated, smooth surface or (B) a villiform architecture. The latter is far more likely be associated with thromboembolic phenomena.
favorably to resection with a low rate of tumor recurrence. Cardiac fibromas are associated with germline or somatic PTCH1 mutations, the former of which occur in the setting of Gorlin (nevoid basal cell carcinoma) syndrome.

Adult cellular rhabdomyoma is a rare neoplasm that occurs in adults more than 20 years old. In contrast to the more common cardiac rhabdomyoma, adult cellular rhabdomyoma has no known syndromic association and lacks the pathognomonic vacuolated “spider cells” of its pediatric counterpart (though sarcoplasmic vacuolization may be encountered). Instead, it consists of striated muscle cells with histologic resemblance to extracardiac rhabdomyomas. Grossly, the tumors are circumscribed, tan, homogenous masses that may protrude into adjacent cardiac chambers. Histologically, they seem more cellular than the cardiac rhabdomyoma, with sheet-like growth of ovoid-to-spindled striated myocytes and a prominent vascular background. Immunoreactivity with desmin and myogenin is the rule. Ki-67 staining usually reveals a low proliferation index, generally between 1% and 20%.

The two primary cardiac adipocytic tumors, cardiac lipoma and lipomatous hypertrophy of the atrial septum (LHAS), are now discussed in the same section in recognition of the fact that some cases of LHAS have been found to harbor molecular genetic alterations similar to those found in lipomas. Lipomas tend to be epicardial, but they can occur in any layer of the heart. Histologically, a lipoma is an encapsulated mass composed of mature adipocytes; LHAS is instead an unencapsulated collection of fat (including brown fat) and atrial myocytes expanding the atrial septum that is rarely itself symptomatic.

Lipomatous hamartoma of the atrioventricular valve is a new entity in the fifth edition. These lesions are uncommon, presumably congenital hamartomatous expansions of the mitral and tricuspid valves. Grossly, atrioventricular leaflets seem thickened and billowing, with nodular protuberances. Histologically, they consist of disorganized mature adipose tissue and fibroconnective tissue with thin-walled vasculature. This entity contrasts from cardiac lipoma by its lack of a capsule, causing it to have an infiltrative or expansive appearance on light microscopy.

Hamartoma of mature cardiac myocytes is a benign disorganized growth of cardiac myocytes characterized by a poorly defined, pale-gray myocardial mass, usually arising in the ventricular myocardium.

Mesenchymal cardiac hamartoma is a newly recognized entity in the fifth edition. In contrast to the aforementioned hamartoma of mature cardiac myocytes, mesenchymal cardiac hamartoma consists of cardiomyocytes and disorganized mature elements native to the myocardium, including the fat, nerve, vasculature, smooth muscle, and collagen. Grossly, the lesion forms a discrete tan-pink mass, most often occurring in the ventricular myocardium. Ventricular arrhythmias and sudden death have been documented with these lesions.

Cardiac hemangiomas are benign vascular tumors (or vascular malformations) with capillary, cavernous, and arteriovenous types. Their location is variable, but they arise most frequently in the ventricular free walls. Histologically, they are composed of thin-walled vascular spaces, without atypia. Expression of vascular markers (CD31, CD34, and ERG) is found in all cases. Clinically, patients present in the fifth decade and may be asymptomatic or symptomatic with dyspnea, syncope, or angina.
Conduction system hamartoma was renamed from its previous designation as "histiocytoid cardiomyopathy," in recognition of the fact that it is primarily tumoral in presentation rather than cardiomyopathic. Grossly, yellow-tan subendocardial nodules follow the distribution of the conduction system. Histologically, the lesions are composed of large, pale polygonal cells with granular sarcoplasm, ovoid nuclei, and variably prominent nucleoli, which have patchy reactivity with S100 immunohistochemistry. Underlying mutations in the NDUF gene family, encoding components of the oxidative phosphorylation pathway, have been described.20 Cardiomegaly is almost always present, including a high rate of arrhythmogenic disorders and sudden death in the young.21

Cystic tumor of the atrioventricular node is a benign, congenital, endodermal developmental rest forming a cystic in the region of the atrioventricular node which (although often <3 mm in size) can result in sudden death. It consists of multiple, variable cysts lined by columnar, transitional, or squamous cells, without cellular atypia.

Summary of Cardiac Malignancies

Malignant neoplasms represent the minority (≤10%) of primary cardiac neoplasms, and, excluding tumors of the pericardium (now covered in the section entitled Tumors of the Pleura and Pericardium), fall essentially into two histologic groups—sarcomas and lymphomas.

Although a wide variety of sarcomas have been reported to occur primary to the heart, cardiac AS, cardiac UPS, and cardiac leiomyosarcoma (LMS) are the most common, representing approximately three quarters of all cardiac sarcomas. Cardiac AS and UPS each account for approximately a third of cases, with LMS accounting for approximately 10%.22–24 As a group, these sarcomas generally present between the fourth and sixth decades of life; however there is a wide age range, including pediatric patients. UPS and LMS occur most often in the left atrium with no sex predilection, whereas AS occurs in the right atrium disproportionately in men.25–27 Patients will often present with chest pain, dyspnea, weight loss, and malaise, which are nonspecific and will delay the diagnosis. These blood vessel-rich tumors may also cause catastrophic hemorrhage with cardiac tamponade (Fig. 9), which is notably devoid of characteristic cytology. Of all the cardiac sarcomas, AS portends the worse prognosis, with a 5-year overall survival of approximately 10%.27 The remaining cardiac sarcomas include various differentiated sarcomas which occur rarely in a primary cardiac location and have been condensed into a summative entry entitled Other Sarcomas That May Involve the Heart.
Immunohistochemistry remains the mainstay for the classification of differentiated cardiac sarcomas along with hematoxylin and eosin morphology. Cardiac AS typically has immunoreactivity for the endothelial markers (ERG and CD31) and LMS exhibits reactivity with smooth muscle markers (desmin and smooth muscle actin).28,29 As the name implies, cardiac UPS has no areas of specific tissue differentiation by light microscopic appearance or immunohistochemistry. Epithelioid hemangioendothelioma, which occasionally enters the differential diagnosis, can be distinguished from epithelioid AS by the presence of the CAMTA1-WWTR1 fusion.30

As of yet, there are no diagnostic or prognostic molecular aberrations in the three most common cardiac sarcomas. Cardiac AS typically has complex karyotypes, and point mutations in a variety of genes have been identified, including the well-known tumor suppressor TP53 and oncogene KRAS and less well-known PLCG1 and the MLL/KMT2 family of genes.30,31,32 Recently, recurrent POT1 mutations have been found in cardiac AS in the setting of Li-Fraumeni–like syndrome.33

Although involvement of the heart can occur in up to 25% of disseminated lymphomas, primary cardiac lymphoma is rare. As a group, it is defined by its primary involvement of the heart and encompasses a variety of T-cell and non–Hodgkin B-cell lymphomas.36,37 In contrast to the previous WHO classification that addressed cardiac lymphomas summatively, the new edition focuses on diffuse large B-cell lymphoma (DLBCL), representing greater than or equal to 80% of cardiac lymphomas, along with a specific entry of a rare and recently described subtype, fibrin-associated DLBCL (FA-DLBCL).

Cardiac DLBCL occurs most often in men in the sixth and seventh decades of life.36,38 FA-DLBCL is strongly associated with infection of lesional B cells by Epstein-Barr virus and is distinguished from other DLBCL subtypes by its lack of mass formation and tissue infiltration, being almost always restricted to the fibrin within an anatomical space (including around prosthetic devices and tumors such as myxomas). It is usually diagnosed incidentally on histologic examination.39 Other DLBCL subtypes which seem overrepresented in the heart are those associated with Epstein-Barr virus and chronic inflammation.40,41 As a group, the prognosis of cardiac DLBCL is generally poor. FA-DLBCL represents a notable exception and is considered an indolent neoplasm with no directly related deaths reported to date.

Areas of Needed Further Study

Although many advances have been made in our understanding of cardiac tumors since the publication of the fourth edition of The WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, much remains to be understood. As has always been the case, the rarity of these tumors has limited their wholesale study. Nevertheless, advances in molecular technology, which allow interrogation of increasingly smaller samples, including those that have been formalin fixed and paraffin embedded, will undoubtedly facilitate further advances in this field.

Specifically, a better understanding of the molecular genetic drivers that underpin the most lethal of these lesions, the cardiac sarcomas, is paramount given the fact that they affect such devastating outcomes on an otherwise relatively young and healthy population.

Figure 9. Cardiac angiosarcoma. The infiltrating mass within the right atrioventricular groove (white arrow) may rupture and bleed into the pericardial space leading to hemopericardium (white asterisk) and tamponade.
Furthermore, molecular insights into the pathogenesis also afford the opportunity for refinement of classification and nomenclature in these rare neoplasms. In addition to malignancies, better understanding of benign lesions such as PFEs is also critically important given their incidence and the potential they have for causing devastating sequelae (e.g., strokes, myocardial infarctions). Fortunately, the need for fresh tissues for such investigative work is being reduced as our technologies are increasingly allowing for interrogation of formalin-fixed, paraffin-embedded specimens.

The classification outlined in this fifth edition of the WHO Classification of Thoracic Tumors serves as a common language to level-set investigators around the world. Continued study of these entities will preemptively guide the sixth edition of the classification of these lesions, thus allowing for better care of the patients they afflict.

CRediT Authorship Contribution

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**Cristina Basso, Melanie C. Bois, Carolyn Glass, Kyle W. Klarich, Charles Leduc, Fabio Tavora**: Writing—original draft, Writing—review and editing.

**Robert F. Padera**: Writing—review and editing, Visualization.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at [www.jto.org](http://www.jto.org) and at [https://doi.org/10.1016/j.jtho.2021.10.021](https://doi.org/10.1016/j.jtho.2021.10.021).

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