

# Primary Malignant Cardiac Tumors: A Rare Disease With an Adventurous Journey

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*It is very rare or almost impossible that an event can be negative from all points of view —Dalai Lama XIV*

Cardiac masses and tumors have always fascinated pathologists and cardiovascular physicians/surgeons alike. Before the mid-1950s, primary cardiac tumors were usually reported at autopsies. With the development of echocardiography, the imaging and diagnosis of tumors like myxoma became a possibility. With advancements in cardiopulmonary bypass, their resection and thus a cure became an exciting reality. Further developments in imaging, particularly echocardiography, 3-dimensional echocardiography, multidetector cardiac computed tomography (MDCT), and cardiac magnetic resonance imaging (CMR), have facilitated antemortem diagnosis of cardiac tumors.

## The Magnitude

Primary cardiac tumors are rare; the reported prevalence is between 0.0017% and 0.028%.<sup>1</sup> Approximately one quarter of all primary heart and pericardial tumors are malignant.<sup>2,3</sup> Except mesothelioma or primary malignancy of the pericardium, the primary malignancy of the heart consists of various sarcomas and lymphomas.<sup>2,3</sup>

Metastatic involvement of the heart is not uncommonly encountered in a hospital-based cardiology practice. Overall, 10% of noncardiac malignancies metastasize the heart, and of these only, 10% develop signs/symptoms of cardiac

dysfunction (noniatrogenic). Thus, only 1% of total malignancies have clinically symptomatic cardiac involvement.<sup>4</sup> This is mostly encountered in the patients with cancers of lung, breast, lymphoma, and leukemia. Malignant melanoma and malignant germ cell tumors more often spread to the heart.<sup>4</sup> Usually, the spread results from hematogenous routes, direct tumor invasion, or tumor growth through the vena cava into the right atrium. The patients are largely symptomatic because of their primary tumors, although rarely cardiac metastasis could be the earliest symptom. A high index of suspicion is warranted when dealing with a patient with such malignancies. Cardiac or pericardial metastases should always be thought of whenever such patients rapidly develop any new cardiovascular symptoms or signs. The new signs and symptoms may point to the site of cardiac involvement as well. The manifestation is predominantly pericardial effusion (90% of cases) with/without cardiac tamponade.<sup>4</sup> The prognosis is poor once cardiac symptoms develop.

## Clinical Signs and Symptoms of Primary Cardiac Tumors

Most primary benign cardiac tumors produce symptoms in one of the following ways: via obstruction; when located near or affecting the conduction system, producing conduction disturbances or arrhythmia; embolization (usually systemic); myocardial or pericardial infiltration; invasion of adjacent structures, like lung/mediastinum; or symptoms may be constitutional or systemic. Patients with benign cardiac tumors may present with cardiac symptoms either in isolation or as a constellation of symptoms, like shortness of breath, atypical chest pains, sometimes with syncope, and embolization or constitutional symptoms. Thus, no specific signs or symptoms exist for such tumors. The symptoms depend on the tumor location, size, and potential for embolization, and not by their histopathological characteristics. Myxomas usually present with obstructive features, with/without constitutional symptoms, whereas papillary fibroelastomas often present with systemic embolization.

In patients with primary malignant cardiac tumors, clinical features depend on tumor location, size, invasiveness, friability, and rate of growth. Most tumors are sarcomas.

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Primary sarcomas arising in the heart generally are rapidly progressive and produce early death through infiltration of the myocardium, obstruction of circulation, or distant metastases to lungs, lymph nodes, and liver. When feasible, treatment is surgical, although most of these tumors recur rather rapidly, limiting survival to a year.<sup>5</sup> However, long-term survival is reported for complete resection, particularly with low-grade sarcomas.<sup>5,6</sup> Primary cardiac lymphomas present with cardiac tamponade, atrial fibrillation, features of right heart failure, and superior vena cava syndrome. The prognosis is better than sarcomas, as 40% of patients are reported to have a complete response to systemic therapy.<sup>7</sup> Therefore, when a cardiac tumor is identified (benign or malignant), a complete differential diagnosis must be entertained.

Although overall prognosis is poor, early diagnosis, particularly of low-grade removable sarcoma and cardiac lymphomas, may improve prognosis. A high index of suspicion coupled with a detailed and careful echocardiographic study, followed by MDCT and/or CMR, are the main pillars of a diagnostic workup. Occasionally, incidental findings at chest roentgenogram or echocardiography, or MDCT or CMR, may raise alarm. In medical school, we are taught: when one hears hoofbeats, one must think of horses, not zebras. It is important to bear in mind zebras do exist, and must be considered, after excluding commonly encountered horses.

Many conditions may appear to be cardiac tumors, but are not, such as vegetations, pericardial cysts, thrombi, sarcoid deposits, myocardial abscesses, and at times lipomatous hypertrophy of interatrial septum. Other rare conditions, so-called pseudoneoplasms, must also be borne in the mind.<sup>8</sup> These include inflammatory myofibroblastic tumor, hamartoma of mature cardiac myocytes, calcified amorphous tumor, and mesothelial/monocytic incidental cardiac excrescences. Alarmingly unlike lipomatous hypertrophy, these tumors require resection to distinguish them from neoplasms or to prevent embolization or obstruction to flow of blood. Although a rare intracardiac blood cyst also presents this way.

## The Journey

The detection of cardiac masses at echocardiographic examination is not infrequent. Once a cardiac tumor is identified, echocardiography remains the initial tool of investigation, although MDCT and/or CMR are commonly necessary to confirm or to rule out the diagnosis. Notably, at CMR, the T1- and T2-weighted sequences indicate the chemical microenvironment within a tumor, thereby helping to identify the nature of the tumor.<sup>9</sup> In studies involving  $\approx 2000$  patients with cardiac tumors, characteristic radiographic appearances and tissue densities accurately facilitated the diagnosis of myxomas, other benign tumors, and sarcomas.<sup>10–13</sup> Coronary

artery angiography may be necessary to assess the blood supply and vascularity of a tumor arising from epicardium or invading it. This is an essential step in planning for the excision of the tumor. Furthermore, significant involvement of coronary arteries may need resection and grafting of such arteries.<sup>14</sup> Positron emission tomography is also useful to detect cardiac involvement with metastatic tumors,<sup>15</sup> atrial myxomas, and lipomatous septal hypertrophy. Usually, a preoperative cardiac biopsy is not considered appropriate, although occasionally it could be considered if the potential benefits clearly outweigh its risks. Despite increased awareness of cardiac tumors and improved diagnostic techniques, clinical manifestations could be so protean that discovery of the cardiac tumor may be incidental during surgery/autopsy.

The literature is replete with autopsy studies, case reports, and observational studies involving a series of cases with cardiac tumors (either single center or multicenter).<sup>1–6,10–14,16</sup> The diagnosis, surgical removal, and outcomes (short- and long-term) for benign tumors, like myxomas or papillary fibroelastomas, and for cardiac metastasis are well documented in the literature.<sup>2</sup> However, there is a conspicuous absence of data on primary malignant cardiac tumors. Sufficient data to inform guidelines do not exist; thus, there is no guideline-directed management of primary malignant cardiac tumors.

In this issue of the *Journal of the American Heart Association (JAHA)*, the original article by Antwi-Amoabeng and coworkers<sup>17</sup> is a timely addition to the limited existing literature. As the disease is rare, authors collected the data (from 1973 to 2015, over 41 years) from the largest cancer registry in the United States (ie, SEER [Surveillance, Epidemiology, and End Results] 18). This registry captures cancer data from 18 cancer registries in the United States. This is the largest registry-based data set, with 694 patients with primary malignant cardiac tumors of a total of 7 384 580 cases of cancer included in the registry (prevalence, 0.0094%). The study concludes: primary malignant cardiac tumors are rare in both men and women, with no difference in survival between men and women over past 4 decades. Sarcomas are the most common primary cardiac malignancy; however, those with primary cardiac lymphomas have better outcomes.<sup>17</sup> It would have been interesting to note response to therapy among those with sarcomas (how many could be excised and cured or recurred?) and lymphomas (how many responded to the treatment?). However, despite the limitations (the details of the treatment and follow-up) of this registry-based data, the study provides important data on primary malignant cardiac tumors. This report confirms the findings of one earlier registry-based (the same registry from 1973 to 2011) study in 2015, with 551 patients described by Oliveira and coworkers,<sup>18</sup> that this is a rare disease (incidence, 34 cases per 100 million people) and has a poor prognosis. This prior study also points out that with extracardiac cancers of similar histopathological

characteristics, the patients with primary malignant cardiac tumors are relatively younger and have worse survival.

No age is immune to cardiac tumors. Interestingly, they are reported in all age groups, including among fetuses. Although it is rare that they are incidentally discovered at prenatal echocardiography, they are generally benign. Unlike adults, tumors identified in utero are usually nonmyxomatous growths, like teratoma, rhabdomyoma, fibroma, and hemangioma, and are removed with good results.<sup>19</sup> Malignant tumors (sarcomas, rhabdomyosarcoma, and fibrosarcoma) are also reported and often have poor outcomes despite surgical resection.<sup>20</sup>

## The Technology Imperatives: A Promising Future

The eyes see what the mind knows. Undoubtedly, primary malignant cardiac tumors are rare. However, their existence reminds us to be aware and to explore/investigate a cardiac mass/growth or rapidly developing pericardial effusion with/without cardiac tamponade or treatment-resistant rapidly progressing heart failure. This exploration is interesting, at times challenging, and can be a highly rewarding experience. A remote possibility of subtle mass/growth while investigating a patient with unexplained arrhythmia or conduction disturbances should also be kept in mind at the time of echocardiographic study/CMR/MDCT study. The upcoming technologies hold a great promise: development of artificial intelligence to facilitate an early and precise diagnosis and 3-dimensional printing to precisely identify the extent of the growth may be invaluable in preoperative planning. Excellent outcomes with benign tumors and fair outcomes with certain primary malignant cardiac tumors, like low-grade sarcomas (removable ones) and systemic therapy-responsive lymphoma, raise the hope in the hearts of the patients and treating cardiologists/surgeons alike.

## Disclosures

None.

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