JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 2, 2018

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Neoplasia and the Heart

Pathological Review of Effects With Clinical and Radiological Correlation

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ABSTRACT

The intersection of oncological and cardiovascular diseases is an increasingly recognized phenomenon. This recognition has led to the emergence of cardio-oncology as a true subspecialty. This field is not simply limited to primary cardiac tumors or complications of chemotherapeutic medications. Rather, it also encompasses metastatic cardiovascular complications and secondary cardiovascular effects of the underlying neoplasia. This review will broadly cover primary and metastatic cardiac neoplasms, as well as secondary cardiovascular effects of extracardiac neoplasia (e.g., amyloidosis, carcinoid valvulopathy, and chemotherapeutic cardiotoxicities). (J Am Coll Cardiol 2018;72:202–27)

The emerging discipline of cardio-oncology covers the intersection of neoplasia and heart disease. This includes neoplasms directly involving the heart as well as indirect effects neoplasms may exert on cardiac structure and/or function (**Central Illustration**, Panel A). Indirect effects encompass both substances elaborated by neoplasms that can affect the heart, as well as therapeutic complications that arise in the treatment of cancer, such as those seen with chemotherapy or radiation (**Central Illustration**, Panel B).

Cardiac neoplasms can be categorized according to their histological characteristics (benign or malignant) and their site of origin (metastatic or primary). Metastatic lesions are exponentially (20- to 30-fold) more common than primary lesions and uniformly malignant. In contrast, primary lesions can be either benign or malignant, with the former about 10× more common than the latter.

In 2015, the World Health Organization revised the classification of cardiac neoplasms (1) to incorporate contemporary data regarding their morphology and prognosis. Additionally, it brought the nomenclature into accord with similar neoplasms that arise in extracardiac sites. Since publication of this revised classification, our understanding of the incidence and pathobiology of many of these lesions has further advanced. This review will focus on the new classification scheme and also provide some insight into some of the emerging data on these tumors. Although a detailed discussion of every primary cardiac neoplasm is not possible, a listing of such is included in **Table 1**.

With respect to indirect effects of neoplasms, the increased recognition of cardiac amyloidosis, a diagnosis that should prompt evaluation for an underlying neoplastic etiology, as well as the development of newer-generation chemotherapeutic agents (immune checkpoint inhibitors) have spurred the growth of cardio-oncology. Consequently, this review will also discuss, at a high level, the presentation, evaluation, and pathology of these entities, in addition to carcinoid valvulopathy.

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Manuscript received March 2, 2018; revised manuscript received May 1, 2018, accepted May 3, 2018.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.05.026

METASTATIC NEOPLASMS

The reported incidence of metastatic disease to the heart is between 0.7% and 3.5% in the general population, 9.1% in patients with metastatic cancer, and as high as 14.2% in those who have high-stage disease (2-6). Advances in diagnostic imaging and therapeutic interventions in oncology patients are at least partially responsible for increasing recognition of cardiac metastasis (3,4). Due to their relatively high prevalence and aggressiveness, lung, breast, and hematological tumors and melanoma are among the malignancies that most frequently metastasize to the heart (4,6-8). In contrast, indolent malignancies, such as prostate cancer, rarely metastasize to the heart. Mechanistically, malignancies can move to involve the heart in a number of ways, including direct extension (e.g., lung carcinoma), hematogenous seeding (e.g., melanoma, lymphoma), retrograde lymphatic seeding (e.g., breast carcinoma), and venous extension (e.g., renal carcinoma) (6,9,10).

CLINICAL PRESENTATION. Clinical presentation of cardiac metastasis is often nonspecific and depends largely on tumor location and the extent of involvement (4,5,9). The majority of cases remain clinically silent and are only discovered at autopsy (4-6,8). When present, symptoms are generally related to tumor location.

Pericardial metastases, responsible for >60% of cases of cardiac metastasis, may cause pericarditis or effusion, resulting in clinician signs and symptoms of such (6,7). Myocardial metastases account for about one-third of cases and can cause arrhythmia, chest pain, or other symptoms mimicking acute coronary syndrome (5,6,11). Moreover, extensive myocardial invasion can inhibit myocardial contractility and result in heart failure or, rarely, cause myocardial rupture with catastrophic results (5). Endocardial involvement is rare, seen in 3% to 5% of cases, but may still have significant consequences, including obstruction and/or embolization (6,7).

Paraneoplastic phenomenon, such as hypercoagulability (particularly in the setting of mucinous neoplasms of the ovary or gastrointestinal tract), can also occur. This may manifest as nonbacterial thrombotic endocarditis and present as recurrent thromboembolism or even as a sudden death. Select other phenomena will be discussed later in the section "Secondary Neoplastic Effects on the Heart."

IMAGING CHARACTERISTICS. Metastatic lesions vary substantially in imaging appearance based on tumor type and location. Often, the patient has a known primary tumor and additional metastases at presentation, facilitating a correct diagnosis. Imaging is often useful to confirm the presence of metastatic lesions incompletely imaged with other modalities (such as whole-body positron emission tomography or chest computed tomography [CT]); distinguish malignant from benign lesions; evaluate complications, such as ventricular or valvular dysfunction, inflow or outflow obstruction, or pleural or pericardial involvement; or evaluate response to therapy.

Echocardiography is usually the first-line cardiac imaging for evaluation of potential masses because of its widespread availability (12). Both transthoracic echocardiography (TTE) and transesophageal echocardiography have the advantages of assessing hemodynamics as well as the anatomic location of a mass. The modality is relatively limited, however, in tissue characterization and in the ability to evaluate extracardiac structures.

Cardiac magnetic resonance (CMR) is usually considered the most sophisticated modality to evaluate masses because of its tissue characterization potential and multiplanar capability. The imaging features of primary and metastatic lesions overlap substantially, although a few features may help narrow the differential diagnosis. Metastatic melanoma frequently demonstrates intrinsic T_1-hyperintensity on CMR, which can be considered a defining feature. Highly cellular tumors, such as many carcinomas, will usually demonstrate restricted diffusion. Blood vessel-rich metastases (e.g., renal cell carcinoma) tend to demonstrate avid contrast enhancement. Assessing change in enhancement patterns after an intervention may be useful as a marker of response to therapy (**Figure 1**).

CT scans are also increasingly used to evaluate metastatic lesions. The diagnosis is often known or suspected, and the tissue characterization potential of CMR may not be as critical for metastases as for primary tumors. Rather, careful anatomic delineation of the mass may be sufficient. Advantages of CT include substantially higher spatial resolution, 3-dimensional volumetric coverage, and better ability to visualize epicardial coronary arteries and mediastinal structures, which may help in planning surgery. Additionally, cardiac CT may be combined with standard chest CT, which many oncology patients routinely undergo during the course of their care.

PATHOLOGY. The histopathology of cardiac metastases largely recapitulates that seen at the primary site. Traditional light microscopy is the gold standard for diagnosing the type of neoplasm involving the heart. This often includes using ancillary studies,

ABBREVIATIONS AND ACRONYMS

AL = amyloid light chain

ATTR = transthyretin amyloidosis

CMR = cardiac magnetic resonance

CNC = Carney complex

CT = computed tomography

LHAS = lipomatous hypertrophy of the atrial septum

LVEF = left ventricular ejection fraction

PCL = primary cardiac lymphoma

PFE = papillary fibroelastoma

TSC = tuberous sclerosis

TTE = transthoracic echocardiography