Review

Metastases to the heart

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Primary tumors of the heart are rare, occurring at a frequency of ∼0.02% in pooled autopsy series [1]. Histologically, three-quarters of primary heart tumors turn out to be benign, almost half of them being myxomas [2]. Whether benign or malignant, the majority of primary cardiac tumors are intracavitary and preferentially develop in the left atrium, thereby leading to left ventricular inflow obstruction. Embolism is also common. Secondary or metastatic heart tumors occur comparatively more frequently, with an at least 100 times higher incidence than primary tumors of the heart [3]. Intracavitary growth of secondary heart tumors, however, is unusual. Therefore, despite their frequency, metastatic heart tumors only rarely gain clinical attention. However, signs of cardiac involvement are often overlooked, since the symptoms of disseminated tumor disease prevail. Thus, like primary tumors of the heart, metastases may imitate valvular heart disease or cause cardiac failure, ventricular or supraventricular heart rhythm disturbances, conduction defects, syncope, embolism, or, quite often, pericardial effusion. Not infrequently, cardiac tumor invasion contributes to the mechanism of death in affected patients [4]. Today, two-dimensional echocardiography makes the detection of cardiac involvement in neoplastic diseases much easier.

Definition

Neoplasms of the heart may be primary or secondary. Secondary or metastatic tumors are per se malignant. Carcinomas of the heart are, by definition, metastatic. Sarcomas or mesotheliomas have to be considered metastatic if an extracardiac tumor site has already been or will be revealed by clinical examination, by diagnostic procedures, or post-mortem.

Incidence

Reflecting the age distribution of malignant diseases, cardiac metastases predominantly occur in patients in the sixth and seventh decade of life. There is no sex preference. Cardiac metastases mostly appear in patients with disseminated tumor disease; solitary metastases to the heart are very rare. The frequency of cardiac metastases is generally underestimated: varying from series to series, cardiac metastases were found in up to 25% of post-mortem patients who had died of malignancies [3–19]. Better diagnostic tools and aggressive treatment of localized malignant tumors by surgery and/or radiotherapy has led to longer survival of tumor patients; in tumors with a high propensity to spread metastases, however, this is with the downside of a higher probability that the patient finally goes through diffuse tumor disease. Therefore, the incidence of cardiac metastases has increased during recent decades [3–19]. Furthermore, metastases to the heart, whether microscopic or macroscopic, are increasingly taken into account nowadays, and are looked for thoroughly during post-mortem examinations [11, 15, 20].

Tumors of origin

In principle, every malignant tumor can metastasize to the heart. To date, only tumors of the central nervous system have not been proven to develop cardiac metastases. The most common tumors with cardiac metastatic potential are carcinomas of the lung, the breast and the esophagus, malignant lymphoma, leukemia, and malignant melanoma [3–8, 13–17, 19, 21, 22]. Owing to their high propensity to generalized hematogenous spread, malignant melanomas frequently metastasize to the heart, and represent the tumor with the highest rate of cardiac metastases (in more than half the cases) [20]. This rate is increasingly lower in carcinomas of the lung, breast, thyroid gland, kidney and esophagus, and malignant lymphomas. Cardiac infiltrates are also identified in about one-third of patients that die of leukemia. Figure 1 shows the relative incidence of cardiac metastases in four large post-mortem series classified by the tumor of origin.

Morphology and topography

Cardiac metastases are usually small and multiple; however, single large tumor lesions are also observed. In carcinomas, metastatic deposits may lead to diffuse thickening of the pericardium. Focal as well as diffuse tumor infiltration of the pericardium and/or myocardium and/or endocardium have been observed in hematological malignancies: in contrast to leukemic infiltration, lymphomatous deposits are usually grossly discernible. Although it is assumed that the right side of the heart is more frequently involved than the left [6, 20, 23], there are numerous cases where left-sided involvement is found [4, 5, 7, 9, 24]. In most cases, diffuse bilateral spread is found. In descending order of frequency, pericardium, myocardium and endocardium are involved [4, 5, 8–10, 17–19]. Whether pericardial or myocardial metastases develop depends on the preferential metastatic pathway of the tumor of origin.

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Metastatic pathways

Metastases may reach the heart via the lymphatic or hematogenous route, or by direct or transvenous extension. Lymphatic spread tends to give rise to pericardial metastases, hematogenous spread preferentially gives rise to myocardial metastases. Only rarely are endocardial tumor deposits found. Tumors such as the bronchial or esophageal carcinoma, which develop near the heart, may expand by direct extension into the heart, but these tumors predominantly attain to the heart by the lymphatics. Similar observations were made for carcinomas of the breast. Via mediastinal lymph nodes, tumor cells invade at first the epicardial, and then the myocardial lymphatic system [12]. Owing to their topography and prevalence, carcinomas of lung and breast are the most common tumors originating cardiac metastases. Owing to their preferred metastatic pathway, both preferentially affect the pericardium. Cardiac metastases of infradiaphragmatic tumors are markedly less frequent. Malignant melanoma, lymphoma, leukemia, soft tissue and bone sarcoma usually spread hematogenously. Secondary heart tumors that have partial or total intracavitary growth are very rare; when they do occur, they are often covered by thrombotic material [25–40]. Even more rare are clusters of tumor cells on heart valves. This type of tumor infiltration has led to heart valve stenosis or regurgitation only in isolated cases [20, 41–43].

Extracardiac tumors may also reach the atria and even the chambers of the heart by transvenous extension. Intraluminal growth of renal cell carcinoma (hypernephroma) through the vena renalis and vena cava inferior into the right atrium (in 1% of these tumors) has been reported [29, 44–47]. Furthermore, hepatocellular carcinoma [48], leiomyoma of the uterus [49, 50], nephroblastoma (Wilm’s tumor) [51, 52], pheochromocytoma [53] and carcinoma of the adrenal cortex [54–56] have been observed to extend through the inferior, and carcinoma of the lung and thyroid gland [57, 58] through the superior vena cava into the right atrium. Rarely, bronchial carcinoma spreads through the pulmonary veins into the left-side heart cavities [59, 60].

Symptomatology

Since the clinical picture is chiefly dominated by generalized tumor spread, cardiac metastases usually remain clinically silent, particularly as the vast majority of cardiac metastases are small. Frequently, cardiac involvement is not noticed until after death. In retrospective studies, only about one-tenth of patients who died of tumor disease and showed cardiac spread as identified at post-mortem examination presented with symptoms or findings indicative of cardiac involvement [7, 11]. Obviously, there is no strong correlation between the extent of cardiac involvement and clinical manifestations. Not infrequently, post-mortem findings reveal cardiac involvement to be more extensive than clinical findings have suggested.

At the time when malignant disease is diagnosed, cardiac metastases are the clinically prevailing finding in a few single cases only [13, 26, 29, 61, 62]. Occasionally, however, metastases to the heart are detected during initial tumor staging. On the other hand, they may not become apparent clinically until many years after cancer diagnosis, if at all. For example, heart metastases of sarcomas have caused clinical symptoms not before 11 and 25 years after resection of the original tumor, respectively, just as metastases of malignant melanomas not before 14 and 22 years, respectively [63–67]. Heralds of metastases to the heart are a rapid increase in heart size by pericardial effusion, new signs of heart failure or valve disease, conduction defects, and atrial or ventricular heart rhythm disturbances [3, 5, 10, 11, 13, 20, 21, 28]. Symptoms such as dyspnea or tachypnea, and clinical findings such as systolic heart murmur, peripheral edema, pleural or peri-
cardial effusion, or ascites, however, may also be the result of tumor-associated anemia and hypoproteinemia, or of lung metastases.

It is less the histological type than the localization of metastases that determines the symptomatology. Pericardial involvement can lead to pericarditis with pericardial effusion, which can be serosanguineous or hemorrhagic and may lack hemodynamic compromise. However, in cases of rapid increase in pericardial fluid and low compliance of the pericardium, cardiac tamponade can result and necessitate immediate pericardiocentesis [5, 9, 18, 20, 29, 62, 68–71]. Cardiac output can only be maintained as long as the reduction in stroke volume due to increasing pericardial pressure can be compensated for by tachycardia and peripheral vasoconstriction. Hypotension, dyspnea and peripheral cyanosis, pulsus paradoxus (systolic blood pressure decreases by more than 10 mmHg during inspiration), and venous congestion are also hallmarks of clinical diagnosis. Venous congestion is manifested by distended neck veins and paradoxical increase in venous pressure during inspiration (Kussmaul’s sign), as well as epigastric pain caused by hepatic congestion. In cases of a slow increase in pericardial fluid, the pericardium may stretch and the pericardial sac may take in more than 3 l. In these cases, pericardial effusion can remain asymptomatic for a long time. Pericardial tumor growth itself can cause constriction of the heart in the same way [10, 22, 25, 68, 70, 71]. Other causes of heart failure in patients with cardiac metastases may be replacement of myocardium and, in cases of intracavitary growth, the obliteration of heart chambers or the obstruction of the ventricular inflow or outflow tract suggestive of valvular heart disease [5, 10, 20, 25–28, 35–37]. An association between tumor infiltration and myocardial rupture has been reported only in isolated cases [72, 73].

Cardiac metastases can provoke atrial and ventricular heart rhythm disturbances, as well as conduction defects. These include complete atioventricular block by invasion of the cardiac conduction system or of the providing coronary artery [5, 7–11, 20, 25, 28, 41, 68, 69, 74, 75]. Syncope and sudden death have been reported [9, 10, 20, 25, 28, 36, 68, 75]. Angina pectoris and myocardial infarction can be the result of coronary embolism, but also of invasion or compression of a coronary artery [3, 10–12, 20, 22, 41, 63, 65]. Alternatively, retrosternal pain may be due to pericarditis. Furthermore, intracavitary right-sided heart metastases can lead to pulmonary, and left-sided heart metastases to systemic embolism [26, 27, 29, 30, 47, 63]. However, this occurs less frequently than in cases of the benign myxoma.

The most common tumors of origin, carcinoma of the lung and breast, metastasize preferentially to the pericardium, thereby leading to pericardial effusion. Therefore, when signs and or symptoms of cardiac dysfunction are present, the vast majority results from pericardial, and only rarely from myocardial or intracavitary, metastases.

Diagnosis

There are no physical or laboratory examinations that specifically detect cardiac metastases in diffuse tumor disease. In cases of intracavitary metastases, systolic and or diastolic murmurs can occur in relation to their location, size and mobility [10, 33]. The nature of the murmur in mobile tumors may change with body position. Diastolic murmurs reflect tumor-related obstruction of the left or right ventricular filling, and systolic murmurs the interference with the closure of atioventricular valves or the narrowing of the ventricular outflow tract. In cases of heart failure, gallop rhythm can develop; in cases of pericarditis, pericardial friction; and in cases of larger pericardial effusion, heart sounds often diminish [7, 8, 11].

Electrocardiographic recordings are usually unspecific but may document possible ventricular or supraventricular arrhythmias, or conduction defects. Pericarditis is rarely accompanied by the typical ST-segment elevations. Not infrequently, only non-specific ST-segment changes are found. Pericardial effusion can cause low voltage and electrical alternans [5, 7–11, 20, 68, 69, 71, 74, 75]. Q-waves can occur as residues of tumor-related myocardial infarction; an electrocardiographic picture of infarction can also result from infiltration or displacement of myocardium by the tumor [7, 11, 65, 71].

Chest radiography may reveal an increase in cardiac silhouette through pericardial effusion or peri- and/or paracardial tumor growth, as well as a pleural effusion resulting from heart failure or a lung tumor [7–9, 76]. Because they contain bone, cardiac metastases of the rare osteogenic sarcomas can be visualized by radiography [28].

In cases of larger size only, intracavitary tumors may appear as filling defects under radionuclide or contrast medium angiography [25, 39, 77]. Probing of the tumor-bearing heart chamber, however, should be avoided, since tumor fragments or tumor-adherent thrombotic material may be embolized. Nevertheless, in individual cases, diagnosis of intracardiac metastasis has been established by catheter biopsy, usually under fluoroscopic guidance [61, 65, 78]. Biopsy of intracardiac lesions has also been performed with the help of transthoracic or transesophageal echocardiography [79, 80]. Tumor vessels can be dyed in cases in which coronary arteriography is included in the diagnostic procedure.

The method of choice to detect cardiac metastases and their complications, however, is two-dimensional echocardiography [27, 29, 31, 37, 81, 82]. Echocardiography can show dense pericardial bands reflecting the pericardium being thickened by inflammation or tumor infiltration. Pericardial effusion can be proven quickly, with high sensitivity. Pericardial metastases may project in a cauliflower-like pattern into the fluid-filled pericardial space [83]. Pericardiocentesis can be performed under ultrasound guidance, and thereby more safely and accurately. Tumor cells within the pericardial fluid may verify diagnosis of metastatic pericardial involvement [10, 29, 68–71]. Negative cytologic findings, however, do not exclude a malignant origin of the effusion, and pericardial biopsy might then be necessary. Because sonographic examination is comfortable for the patient and inexpensive, it is appropriate for the follow-up of pericardial effusions. In cases of larger myocardial metastases, regional wall motion abnormalities can be revealed by ultrasound. Intracavitary lesions can also be detected with high sensitivity. In cases of peri- or paracardial lesions, the transesophageal approach is superior to the transthoracic approach [81, 84].
Supplemental diagnostic imaging methods are computer tomography and magnetic resonance imaging. These two methods provide sections of cardiac, mediastinal, pulmonic and thoracic structures in any desired plane, without overlapping. Thus, size and extension of paracardial or transpericardial tumor growth can be determined more precisely than by sonography. In addition, and in contrast to ultrasound, tissue differentiation is partly possible between solid, liquid, hemorrhagic or fatty lesions [64, 81, 82, 85, 86], and myocardial metastases can be better demarcated.

In cases in which a malignant tumor was resected many years before detection of a cardiac tumor mass, exploratory thoracotomy and open biopsy might be necessary to confirm the diagnosis of metastasis [76].

**Differential diagnosis**

The differential diagnosis of intracavitary mass lesions includes benign and malignant primary cardiac tumors. Since an intracardiac lesion is detected by ultrasound, the differential diagnosis must include thrombus, vegetation and a foreign body. However, intracardiac metastases, even though rare, should also be included in the differential diagnosis, as well as infectious and non-bacterial thrombotic or marantic endocarditis. Intramural metastases should be considered in the differential diagnosis of myocardial infarction and pericardial metastases in the differential diagnosis of pericardial effusion. However, myocardial or pericardial damage can also be caused by radio- or chemotherapy. Thus, pericarditis with effusion, pericarditis constrictiva, myocardial or valvular fibrosis may be attributable to radiotherapy, and cardiomyopathy to anthracyclines such as doxorubicin and daunorubicin.

**Treatment**

In the vast majority of cases, cardiac metastases manifest in patients with advanced tumor disease, with the heart being involved in the generalized tumor spread. At this stage of the disease, many patients will already have undergone surgical treatment for the tumor of origin, or radio- or chemotherapy. Cardiac treatment is mostly confined to palliative measures. Surgical resection is only indicated in exceptional cases of solitary intracavitary heart metastases, leading to obliteration of cardiac chambers or valve obstruction if the tumor of origin was surgically resected in toto and the patient appears to have a good prognosis [32, 63, 64, 66, 77, 87, 88]. Frequently, however, complete resection fails, and postoperative mortality is high [89, 90]. Coil embolization of the supplying coronary branch may be an alternative option in circumscribed intracardiac masses [91]. Tumors invading the right atrium by the transvenous route, however, have been successfully removed surgically in a large number of cases [44–47, 49, 52, 53, 55, 56, 89]. Mitral valve replacement because of high-grade mitral insufficiency due to tumor infiltration has been reported casuistically [42]. Furthermore, tumor-related complete AV-block has been managed by pacemaker implantation [75]. Tumor-related AV-block, however, may occasionally be rescinded by radiotherapy [10]. Usually, cardiac infiltrates in leukemia and lymphoma respond well to radio- or chemotherapy [10, 69].

Not infrequently, pericardial involvement requires specific efforts. Malignant pericardial effusion may be diminished by local radiotherapy or systemic chemotherapy [10, 69, 71]. Cardiac tamponade, however, makes percutaneous pericardiocentesis necessary as soon as possible [68–71]. The immediate success rate is high (>95%) and complications are rare, and include puncture of a coronary artery or the myocardium, rhythm disturbances or pneumothorax [92]. Nearly half of effusions can be definitely controlled by this approach [92]. If not, chemotherapeutics or radioisotopes may be instilled through the catheter to prevent recurrence of the effusion (by direct cytostatic and/or by sclerosing activity with adhesion of the visceral and the parietal pericardium as a result of inflammatory reactions) [70, 71, 92–95]. For this purpose in particular, bleomycin sulfate [96–98], cisplatin [99–102], mitoxantrone [103], thiotepa [104, 105], mitomycin C [106], 5-fluorouracil [100, 107] and tetracycline derivatives [94, 96, 98, 100] (see also Table 1), as well as chromic phosphate 32P for a dose of 185 to 370 MBq [108, 109], were evaluated. Among the chemotherapeutics, cisplatin seems to be the most efficacious, especially in lung cancer patients [100, 102]. However, instillation of antitumor agents or tetracyline derivatives can result in severe pain, arrhythmias and bone marrow toxicity, and in unpredictable sclerotic processes. Radioisotopes have been shown to be safe, without noteworthy side effects and of high efficacy, but the technical expenditure is high [92, 108, 109]. In cases of failure to control pericardial effusion by pericardiocentesis, alternatively, percutaneous balloon pericardiostomy can be considered [110, 111]. Today, more invasive procedures, such as open surgical drainage through a subxiphoid pericardial window or anterolateral thoracotomy with pericardiotomy, in these terminally ill patients are only rarely performed.

Symptomatic improvement, however, is not infrequently lessened by cardiopulmonary side effects: radiotherapy may lead to fibrosis of the lung or myocardium, and the latter may be associated with disturbance of the conduction system. Frequently, radiotherapy is accompanied by pericarditis. Cardiotoxic side effects well known for the chemotherapeutic agents doxorubicin, daunorubicin and cyclophosphamide (in high doses) may induce recalcitrant myocardial failure.

**Summary**

Secondary heart tumors are common in patients with metastatic tumor disease, afflicting up to one-quarter of them. Clinically, secondary heart tumors usually remain silent. However, ultrasound examination of the heart should be performed as soon as symptoms of heart failure, angina pectoris, embolism or rhythm disturbances develop, or a new heart murmur becomes audible, or as soon as heart size increases radiologically. Additional information may be obtained by computer tomography or nuclear magnetic resonance imaging. To note cardiac involvement does not only have prognostic implications: even if only exceptionally curative
therapy may be available, palliative measures may improve the quality of life of affected patients.

Acknowledgements

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References


Table 1. Substances used for pericardial sclerosis treatment, and their doses and side effects

<table>
<thead>
<tr>
<th>Substance</th>
<th>Single dose</th>
<th>Frequency of application</th>
<th>Side effects</th>
</tr>
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<tbody>
<tr>
<td>Tetracycline derivates</td>
<td>15 mg/kg body weight (500–1000 mg)* in 20–50 ml normal saline solution</td>
<td>1–5×</td>
<td>Fever &gt;38.5°C, thoracic pain, atrial arrhythmia</td>
</tr>
<tr>
<td>Bleomycin sulfate</td>
<td>5–60 mg in 10–20 ml normal saline solution</td>
<td>1–2×</td>
<td>Fever</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>10 mg in 20 ml normal saline solution; or 30 mg/m² in 100 ml normal saline solution</td>
<td>1–5×</td>
<td>Pain, nausea, myocardial ischemia, atrial arrhythmia</td>
</tr>
<tr>
<td>Thiopeta</td>
<td>15 mg in 20 ml sterile water; or 30 mg in 20 ml sterile water</td>
<td>1×</td>
<td>Leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>8 mg in 10 ml normal saline</td>
<td>1–3×</td>
<td>Pericardial constriction</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>10–20 mg</td>
<td>1–3×</td>
<td>None</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>250 mg in 20 ml normal saline</td>
<td>1×</td>
<td>Neutropenia</td>
</tr>
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*Previous instillation of 100 mg lidocaine intrapericardially advisable.


