Unusual aspects of cardiac myxoma

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Abstract

A cardiac myxoma may manifest as miscellaneous and uncharacteristic presentations. These unusual aspects of cardiac myxomas can be rare clinical presentations, special patient populations, unusual locations, and special pathology, which may lead to a delayed diagnosis, improper checkups, and subsequent untimely treatment, eventually resulting in unexpected poor prognosis. Therefore, the diagnosis of cardiac myxomas can be challenging because of these unusual aspects. In order to get a better understanding of a cardiac myxoma and to facilitate an early diagnosis and proper treatment, the unusual aspects of cardiac myxomas are described here. *(Anatol J Cardiol 2017; 17: 241-7)*

Keywords: cardiovascular diagnostic techniques; heart neoplasms; myxoma; pathology

Introduction

Cardiac myxomas are the most common primary cardiac tumors, accounting for 50% of cases. The classic triad of symptoms, including obstructive, embolic, and constitutional symptoms, is the common manifestation of a cardiac myxoma (1). The differential manifestations of left and right atrial myxomas in terms of systemic and pulmonary embolic predilections have drawn attention (2). A cerebrovascular complication such as a neurological deficit or sensory impairment as an onset symptom may prompt a suspicion of a cardiac myxoma much earlier (3). Nevertheless, the high false-negative rate of cranial computed tomography during the early onset of stroke may adversely influence the early diagnosis of its cardiac myxoma origin (4). In addition, the miscellaneous and uncharacteristic clinical manifestations of a cardiac myxoma vary considerably on a case-to-case basis. This peculiarity of the presenting symptoms often leads to delayed presentation and a delayed diagnosis, eventually resulting in unexpected poor prognosis (5). Therefore, a comprehensive understanding of the usual aspects of cardiac myxomas is extremely important for an early diagnosis and prompt treatment.

Rare clinical presentations

Fever of unknown origin

A cardiac myxoma is a rare causative disease of fever of unknown origin. A comprehensive collection of the pertinent literature on cases of a cardiac myxoma presenting with fever of unknown origin until October 2016 resulted in 58 articles including 62 patients. The patients' temperature during hospitalization was 38.8±0.7°C (range, 37.4°C–40°C; median, 38.9°C) (Fig. 1). The temperatures of the patients were in a normal distribution (Fig. 2). The duration of fever (time interval from the onset of fever to presentation) was 6.4±14.6 months (range, 5 days–8 years; median, 2 months) (Fig. 3). Laboratory findings may reveal leukocytosis, thrombocytosis or thrombocytopenia, anemia, and elevated erythrocyte sedimentation rate and C-reactive protein levels. In this patient setting, the time of diagnosis (time from the onset of fever to diagnosis) of a cardiac myxoma was 6.0±6.1 months (range, 0.5–24 months; median, 3.2 months) and that from presentation to diagnosis was 1.4±2.6 months (range, 0.07–10 months; median, 0.33 months). It is reasonable that the time from the onset of fever to diagnosis is equal to the time from onset to presentation plus the time from presentation to diagnosis. However, because of the lack of necessary data from the literature, the final statistics showed a smaller time interval from the onset of fever to diagnosis than that from the onset of fever to presentation.

This resulted in a misdiagnosis, missed diagnosis, and delayed diagnosis in 19.4% (12/62), 6.5% (4/62), and 1.6% (1/62) patients, respectively. Of them, 14.5% were cases of infected cardiac myxomas. A poor response to antibiotic treatments was seen in nearly one-third of the patients, and unnecessary extensive laboratory investigations were performed in the context of a delayed diagnosis or misdiagnosis in more than one-fourth of the

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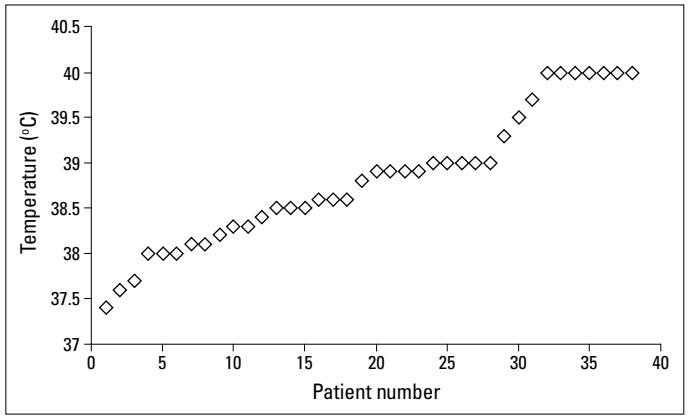

Figure 1. Body temperatures of cardiac myxoma patients presenting with fever of unknown origin

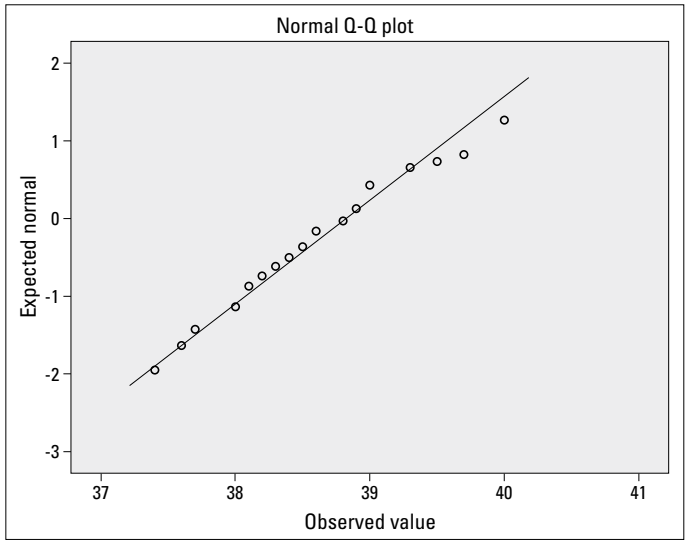

Figure 2. Normal distribution of body temperatures of cardiac myxoma patients presenting with fever of unknown origin (Only 38 out of 62 patients had their temperatures reported digitally, while for other patients, the temperatures were verbally recorded as "low-grade fever," which could not be included in statistical analysis)

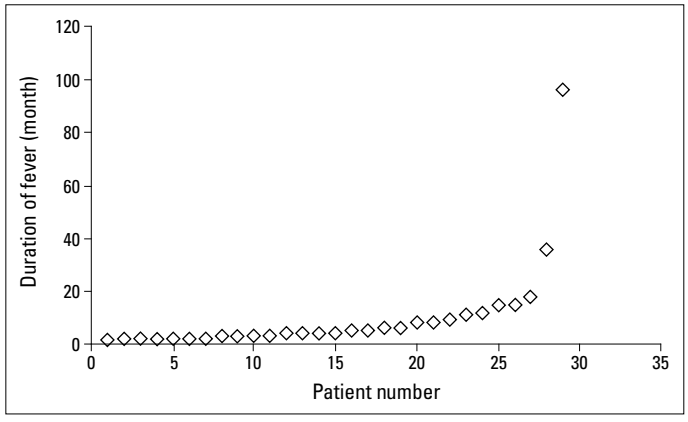

Figure 3. Duration of fever of cardiac myxoma patients presenting with fever of unknown origin before presentation to a physician

patients. Repeated missed diagnoses of fever of unknown origin in patients with a cardiac myxoma resulted in complications

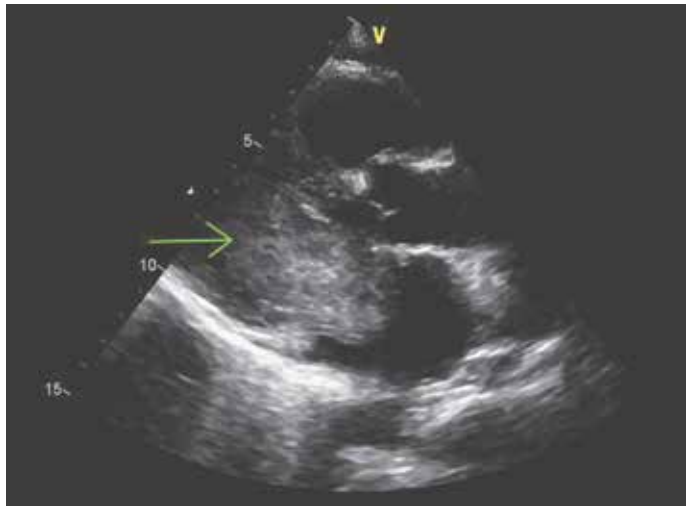

Figure 4. Transthoracic echocardiography (a long-axis view) showed a huge left atrial myxoma (arrow) prolapsing into the left ventricle in a 56-year-old female patient presenting with fever of unknown origin

such as mycotic aneurysm of the middle cerebral artery requiring craniotomy, peripheral embolic events, and eventual death. Although the diagnosis was prompt in some patients, peripheral embolic events occurred 48 h after admission because of the lack of a timely surgical resection. Moreover, during the process of delayed diagnosis, unnecessary extensive laboratory investigations were performed with workups for infectious, oncological, or collagen tissue disorders. The fever subsided 2–7 days after cardiac myxoma resection. As a result, 88.9% of the patients underwent cardiac myxoma resection, and all of them survived. A recent report of a case of a huge left atrial myxoma presenting with fever of unknown origin demonstrated that the diagnosis was not made until transthoracic echocardiography was performed (Fig. 4). In this report, it was emphasized that there was a relationship between fever and the elevations of inflammatory biomarker levels, particularly C-reaction protein and interleukin-6 levels (6). A re-review of the histological sections of the resected tumor revealed patchy coagulation necrosis and hemorrhages (Fig. 5). This pathological phenomenon has not been described previously.

Infected cardiac myxoma

In 1998, Revankar et al. (7) classified infected cardiac myxomas into 3 levels based on the clinical and pathological findings of myxomas (Table 1). The 3 levels accounted for 85%, 12.5%, and 2.5% cases of infected cardiac myxomas, respectively, as reported by Revankar et al. (7) and 87.2%, 10.3%, and 2.6% cases of infected cardiac myxomas, respectively, as reported in a recent review (8). Fever was the most common symptom, accounting for 97.3% of all cases, and constitutional symptoms were more frequent than obstructive or neurological symptoms. The duration of fever before admission was 1.6±1.7 months (range, 0.1–6 months; median, 1 month) (8), which was much shorter than the duration of fever (6.0±6.1 months) in patients with cardiac myxoma presenting with fever of unknown origin. Fever of unknown origin

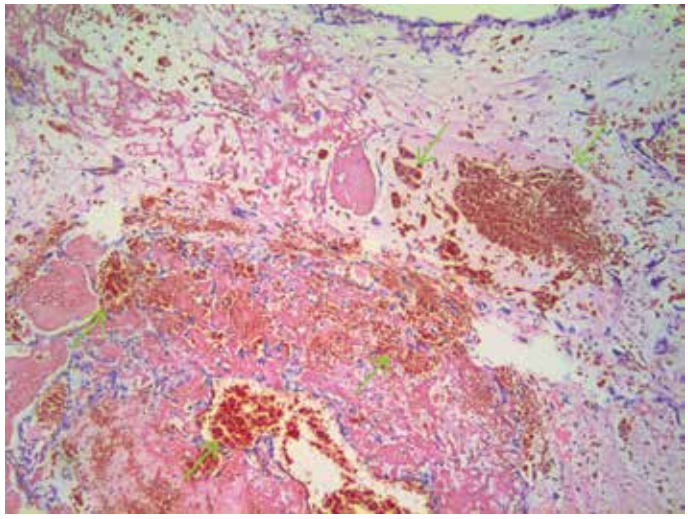

Figure 5. Histological examination of the large left atrial myxoma in the patient with fever of unknown origin showed patches of alternating coagulation necrosis and hemorrhages (arrows). HE ×200

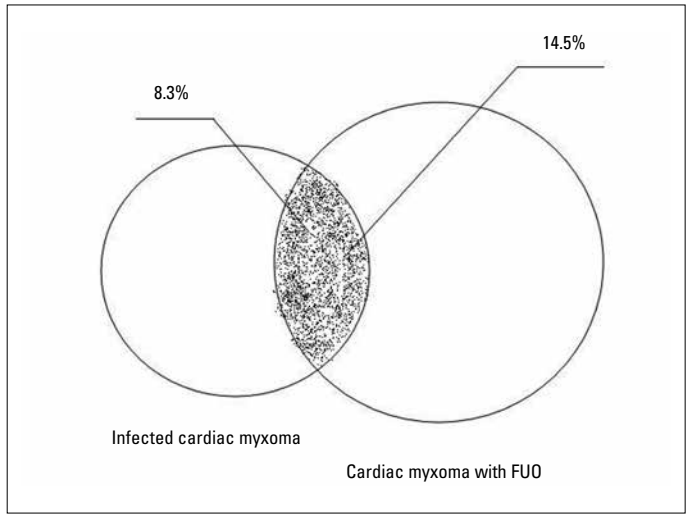

Figure 6. Overlapping of cardiac myxoma with fever of unknown origin with infected cardiac myxoma. FUO - fever of unknown origin

Table 1. Levels of infected cardiac myxoma

Levels of infected cardiac myxoma
Definite infected cardiac myxoma
1. Documented myxoma by pathology and
2a. Microorganisms seen on pathology or
2b. Positive blood cultures and inflammation on pathology
Probable infected cardiac myxoma
1. Documented myxoma by pathology and
2. Positive blood cultures or inflammation on pathology
Possible infected cardiac myxoma
1.Characteristic appearance by transthoracic or transesophageal echocardiography and
2. Positive blood cultures

was observed in 8.3% (3/37) of patients with infected cardiac myxomas (8) in comparison with 14.5% (9/62) of infected cardiac myxomas in the cardiac myxoma patients presenting with fever of unknown origin (Fig. 6). The causative pathogens could be investigated by culture of blood or resected tumor tissues, by pathological examinations of the resected tumor, or by polymerase chain reaction. All patients with infected cardiac myxomas underwent surgical resection of the myxomas with pre- and postoperative antimicrobial therapies including vancomycin, penicillin, and ampicillin. The updated series showed few incidences of moderate-grade fever and abnormal heart sound but more incidences of uncommon microorganisms and more embolic events as well as significantly decreased overall mortality.

Acute myocardial infarction

A cardiac myxoma rarely causes acute myocardial infarction. A comprehensive review comprising 48 patients with cardiac myxoma-related acute myocardial infarction revealed that most patients had an acute onset of symptoms, with chest pain being the prevailing onset symptom in 75.6% of the cases. Cardiac myxoma-related myocardial infarction differed from atherosclerotic myocardial infarction in 3 ways: 1) a normal coronary artery was evidenced by a coronary angiogram in nearly half of the patients; 2) the culprit coronary arteries were mostly the circumflex artery (38.1%) and right coronary artery (28.6%) other than the left anterior descending coronary artery itself; therefore, the hypokinetic/akinetic ventricular wall was mostly the inferior wall; and 3) the patients were much younger. Neovascularization of cardiac myxomas could be noted in two-thirds of the patients who underwent a coronary angiogram. Sudden death occurred in 4.2% of the patients who therefore could not undergo surgical treatment. Surgical resection of the myxoma was performed in 95.7% of the patients, 35.4% of which were also managed with conservative (thrombolytic and/or coagulant) therapy for myxoma-related coronary lesions (9). Treatment with thrombolytic agents was recommended for acute-onset patients because of the risks of peripheral embolism. There may be failure with regard to recanulation (10), but no complications were noted in relation to thrombolytic agents (11). The timing of surgical resection of the cardiac myxoma in patients with dual antiplatelet therapy may be in accordance with the recommended guidelines for patients for coronary artery bypass grafting: aspirin was continued through surgery and clopidogrel was ceased 5 days before surgery and was recommenced as early as possible after surgery (12). Prognostic analysis showed that the event-free survival rate was 88.4%, the survival rate with disabilities was 7.0%, and the mortality rate was 4.2% (9).

Stroke of a cardiac myxoma origin

It was reported that embolic stroke was observed in 9%–22% of atrial myxoma cases (13). A female predominance was demonstrated in this patient setting according to a recent review (4), which revealed that 56.7% of the patients presented

within 24 h, while the remaining patients had a delayed presentation at 3 days to 2 years after the onset. The false-negative rate of computed tomography was significantly higher than that of magnetic resonance imaging for illustrating stroke of a myxoma origin. Logistic regression analysis showed that peripheral embolic events and nonsurgical resection of the cardiac myxoma had a significant correlation with mortality (accounting for 15.3% of the whole group) (4). There are a few reports on intravenous thrombolytic therapy with a recombinant tissue plasminogen activator for cerebral embolism caused by a left atrial myxoma. Although the radical therapy is open heart tumor resection, there is no clear guideline for patient management during the period from cerebral infarction to surgery (14). However, the mortality of patients would be considerably reduced if the cardiac operation could be postponed to more than 4 weeks after an embolic stroke (13). Rao et al. (15) planned cardiac myxoma resection 3 weeks after cerebral infarction to prevent from the risks of secondary hemorrhage in the cerebral-infracted region following thrombolytic and anticoagulant therapies. However, re-infarction occurred during the waiting period. The operation was performed in advance, and the patient was uneventful postoperatively. A cardiac myxoma could be the underlying cause of rostral brainstem infarction or "top of the basilar" syndrome characterized by visual, oculomotor, and behavioral abnormalities, often with insignificant motor dysfunction (1). The top of the basilar artery consists of 2 posterior cerebral arteries, 2 superior cerebellar arteries, and the top of basilar artery at the top of the basilar artery (16). The top of basilar territory is usually within a 2-cm-diameter circle surrounding the 5-forked junction, which is the predisposing invading location of cardiac myxoma debris as a result of the special anatomical features (Fig. 7) (17).

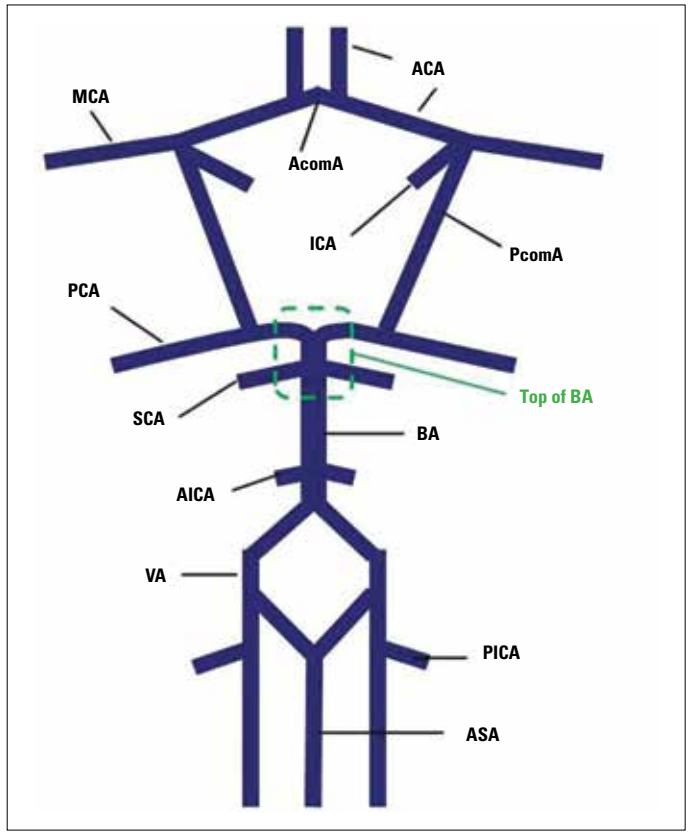

Figure 7. Schematic drawing of "top of basilar artery" (17).
ACA - anterior cerebral artery; AcomA - anterior communicating artery; AICA - anterior inferior cerebral artery; ASA - anterior spinal artery; BA - basilar artery; ICA - internal carotid artery; MCA - middle cerebral artery; PcomA - posterior communicating artery, PCA - posterior cerebral artery; PICA - posterior inferior cerebral artery; SCA - superior cerebral artery; VA - vertebral artery

Dysphagia

A large left atrial myxoma is a very rare cause of repetitive dysphagia (18). Mishima et al. (19) reported a patient in whom dysphagia was caused by the compression of a large left atrial myxoma and resolved after myxoma resection.

Special patient populations

Familial cardiac myxoma

A familial cardiac myxoma is a rare syndrome, which accounts for approximately <10% of all cardiac myxomas. Syndrome myxoma or Carney's syndrome also consists of extracardiac myxomas in the breast or skin, spotty pigmentation, and endocrine overactivity. Patients with Carney's syndrome are often younger (20 years old) and the cardiac myxomas are usually multiple and recurrent, involving more than 1 cardiac chamber and unusual locations (20, 21). Familial cardiac myxomas appear to have an autosomal dominant transmission. Recurrent cardiac myxomas are highly intrinsically aggressive with greater interleukin-6 production despite their smaller size (22).

Cardiac myxoma in pregnancy

A cardiac myxoma in pregnancy was rare. One-fifth of the pregnant patients were asymptomatic, while four-fifths were symptomatic, presenting with 1 or 2 of Goodwin's triad symptoms (23). Bryukhina et al. (24) described that embolic events developed in 29.0% of pregnant patients with a cardiac myxoma, which was likely to be associated with a delayed cardiac myxoma resection. Debates regarding the timing of cardiac myxoma resection continue with regard to the fates of both the mother and baby. Primary studies of surgical resection of the myxoma did not reveal any difference before or after delivery or simultaneous in 1-stage with cardiac operation performed. All pregnant patients with a cardiac myxoma were alive. No significant differences were noted in the prognosis in the pregnancy termination and delivery groups (23).

Fetal cardiac myxoma

Fetal cardiac myxomas are extremely rare lesions, and their prevalence is difficult to be determined. To date, only 31 cases of fetal cardiac myxomas have been reported from 26 articles worldwide. Fetal cardiac myxomas could be diagnosed by fetal echocardiography at an early stage (18-week gestational age)

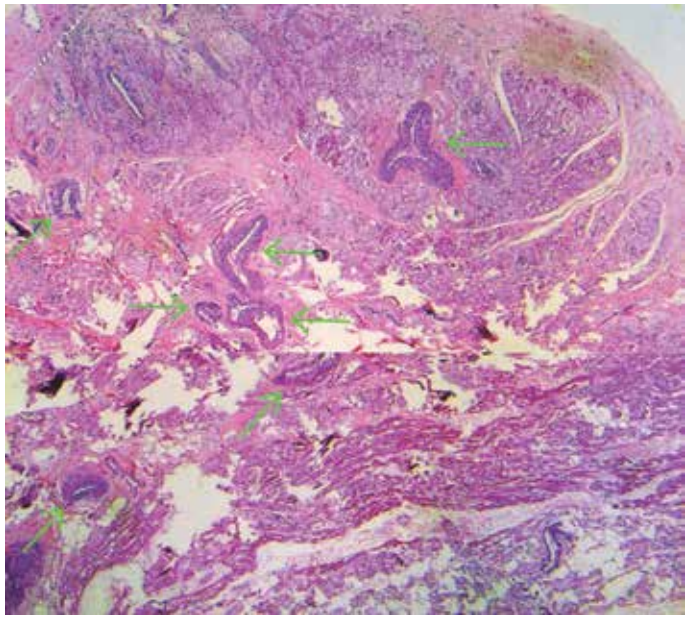

Figure 8. Histological examination of the resected glandular cardiac myxoma from a 51-year-old female patient demonstrated well-formed glandular structures (arrows) and typical myxoma tissues. HE ×40

(25). Most of the cases were noted by prenatal screening echocardiographic examinations. Only a few of the cases presented with pericardial effusions, ventricular inflow obstruction, or arrthymias, while most remained asymptomatic. Unfortunately, most pregnant women chose to terminate pregnancy as long as they noted a fetal cardiac myxoma. In 2 cases, the presence of a fetal cardiac myxoma caused intrauterine death because of deteriorated fetal conditions (26, 27). Only 3 cases underwent postnatal cardiac myxoma resection; 2 of them survived (25, 28) and 1 died during the operation (29). Management strategies should be individualized based on the patient's conditions. The asymptomatic cases with a small and immobile cardiac myxoma may warrant a close follow-up, and the symptomatic cases with large tumors, flow obstruction signs and embolic potentials should be surgically treated during pregnancy (28).

Unusual locations

A cardiac myxoma may arise from any of the 4 cardiac chambers. Most tumors are solitary, and a few involve more than 1 cardiac chamber. Most cardiac myxomas arise within the left atrium, accounting for 75% of cases. The right atrium is the second most common location of a cardiac myxoma among the 4 cardiac chambers from which a cardiac myxoma arises. About 15%–20% of cardiac myxomas are located in the right atrium. Only 3%–4% of cardiac myxomas are found in the left ventricle and 3%–4% in the right ventricle (30). Moreover, valvular myxomas are even rarer. Mitral myxomas are the most common valvular myxomas (31). Two-thirds of the mitral myxomas are solitary and one-third is multiple (32). Tricuspid valve myxomas have a lower incidence, and even sporadic cases have been instantly reported (33). Aortic valve myxomas are even rarer (34). Pulmonary valve myxomas and pulmonary artery myxomas have been occasionally reported (35).

Special pathology

Glandular cardiac myxoma

Glandular cardiac myxomas are rare, representing only 5% of cardiac myxomas. The morphological studies on glandular cardiac myxomas are helpful for understanding the pathogenesis of the cardiac myxomas as a possible morphologic diversity arising from intracardiac endodermal heterotopia or representing entrapped foregut rests (36). A glandular cardiac myxoma is composed of well-formed glandular structures and typical myxoma tissues (Fig. 8). Unlike the areas of glands in carcinoma cells, nuclear atypia and mitosis are rarely observed in glandular myxoma cells (37). Cytoplasms of the glandular cells are immunoreactive for epithelial and soft tissue tumor antigens (38). Immunohistochemical studies of our patient with glandular cardiac myxoma revealed the following: vimentin: strongly positive; epithelial membrane antigen (EMA), CD34, and carcinoembryonic antigen (CEA): moderately positive; cytokeratin 7: mildly positive (Fig. 9); and desmin, cytokeratin, and smooth muscle actin (SMA): negative.

Discussion

The diagnosis of a cardiac myxoma poses challenges on many occasions. The clinical manifestations actually depend on the natures of the maxoma (size, location, shape, growth speed, length of the pedicle, mobility, falling debris, pathological and secondary degenerative changes inside the tumors (such as hemorrhage or necrosis), and patients' response) (39). Muthiah (40) described that the secondary degenerative changes included tumor necrosis and calcification, which accounted for 8% and 10–20% of cases, respectively, and complete calcification of cardiac myxoma rarely occurred. The progression of tumor necrosis and calcification is mutually promoted, especially during the interruption of blood supply to the cardiac myxoma.

Smith et al. (41) comprehensively considered the concept of the paraneoplastic effects of cardiac myxoma, including vasculitis, hematological changes, constitutional symptoms, and some system disorders. According to them, fever of unknown origin is a paraneoplastic effect of cardiac myxoma. They also proposed that these paraneoplastic effects of cardiac myxoma may be related to tumor-secreted cytokines, including interleukins, vascular endothelial growth factor, basic fibroblast growth factor, and monocyte chemotactic protein-1, implicating in tumor growth, recurrence, and distant metastasis. Distant metastases of cardiac myxomas have been found in the brain, lungs, bones, and soft tissues either prior to the diagnosis or several years after the surgical resection of the primary cardiac myxoma.

In particular, the relationships between the tumor and constitutional symptoms are probably determined by the interleukins

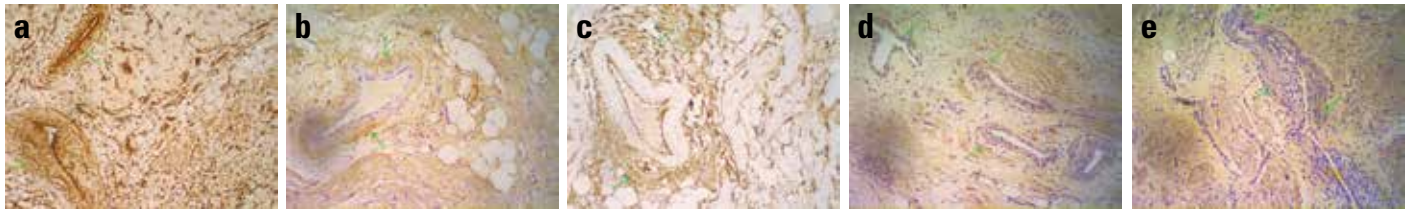

Figure 9. Immunohistochemistry of glandular cardiac myxoma: (a) The entire glandular structures as well as the mucous substances inside the glandular lumen showed an extremely strongly positive reaction to vimentin (arrows). (b) The connective tissues of the glandular structures showed a moderately positive reaction to epithelial membrane antigen (EMA) (arrows). (c) The glandular structures (the transitional epithelium and connective tissues) showed a strongly positive reaction to CD34 (arrows). (d) The glandular structures showed a strongly positive reaction to carcinoembryonic antigen (CEA) (arrows). and (e) The glandular structures showed a mildly positive reaction to cytokeratin 7 (arrows). EnVision ×200

(interleukin-4, -6, and -12p70) synthesized and secreted by the tumor itself. Interleukin-6 acts as a pro-inflammatory cytokine and an anti-inflammatory myokine, being a main substance in the acute phase response, interfering in the pathophysiological processes of fever, leukocytosis, complement activation, and coagulation reaction. Moreover, immunohistochemically, 74% of cardiac myxomas expressed interleukin-6, while 17% showed an abnormal deoxyribonucleic acid content (42). The difference in the diagnostic time between cardiac myxoma patients with fever of unknown origin and those with infected cardiac myxoma implied the diagnostic puzzles of the former.

Preoperative differential diagnoses of cardiac myxoma pose important clinical implications for appropriate treatment for the underlying diseases. Imaging features could reliably predict primary versus secondary and benign versus malignant cardiac tumors (43). The diagnosis of cardiac tumors relies on transthoracic and transesophageal echocardiography, radiographic examinations, surgery, and pathological findings, with echocardiography being the most commonly used method of preoperation (44). Echocardiography should be performed to confirm the diagnosis of a cardiac myxoma when (i) there is a diastolic murmur in the apex changing with time and posture in the absence of a rheumatic disease history; (ii) there are repeated arterial embolic events; (iii) there is syncope in relation to a change of posture; (iv) there is prolonged low-grade fever, accelerated erythrocyte sedimentation rate, anemia in the absence of rheumatic fever, or infective endocarditis; and (v) there is refractory heart failure with poor response to medical treatment.

Cardiac myxomas differ from other benign or malignant cardiac tumors in several ways, e.g., prevalence, locations, and clinical, histological, and immonohistochemical characteristics. Cardiac myxomas most commonly arise from the left atrium on the rim of the fossa ovalis, usually with a regular appearance, with very few chances of pleomorphic nuclei or atypical mitose, even in glandular cardiac myxomas. Immunohistochemical studies may show positive reactions to intermediate filament proteins and epithelium-related markers. Some reports have described tumor recurrence, local invasion, peripheral tumor mass, or distant metastasis of cardiac myxomas (45). Cardiac papillary fibroelastomas and intracardiac thrombus are often valvular (43, 46, 47). The cavernous hemangiomas are isointense masses on magnetic resonance imaging (43, 48). However, malignant cardiac tumors, most commonly cardiac rhabdomyosarcomas, angiosarcomas, myxosarcomas, and malignant fibrous histiocytomas, resemble a myxoma on echocardiography; therefore, differential diagnoses is likely to be difficult (43). Malignant tumors show rapid tumor growth, predilections of distant metastasis, and recurrence as well as poor survival (49). Cell differentiation, atypical mitoses, and pleomorphic nuclei are often observed (49). The prevalence of tumor necrosis is very high. Most often, tumors are positively reactive to the intermediate filament proteins and myogenic and endothelial markers, which constitute the major distinguishing criteria from benign cardiac tumors (49). Surgical tumor resection with chemotherapy is a preferred treatment strategy of choice for malignant tumors. Prompt therapeutic measures for cardiac myxomas are essential to prevent potential embolic events (42). It is believed that refinement of prompt diagnosis and timely management may result in better patient outcomes.

Conclusions

Unusual presentations of cardiac myxomas pose challenges for the physicians in terms of diagnosis and differential diagnosis and often lead to a delayed or missed diagnosis, improper checkup, untimely treatment and even poor prognosis. A better understanding of the uncharacteristic nature of cardiac myxomas would definitely facilitate the proper management and improve prognosis. Because of the malignant potentials, timely surgical resection is warranted in all patients without contraindications upon making a diagnosis. The port-access approach is an alternative to the conventional open heart surgical technique in terms of its minimally invasive purpose for myxoma resection.

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