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Review article

Cardiac myxoma induced paraneoplastic syndromes: A review of the literature

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ABSTRACT

Background: Atrial myxomas are the most common benign tumors of the heart and may present with a wide variety of symptoms. Although 45% of patients present with neurological symptoms, a diverse range of systemic symptoms also occur.
Methods: A systemic review of the literature related to the diagnosis, treatment, pathogenesis, and symptoms associated with atrial myxomas was performed.
Results: Here we summarize the current state of understanding about myxoma pathogenesis and treatments are described. We review the common and rare local and systemic effects of myxomas. Additionally, we review the paraneoplastic and metastatic potential of myxomas.
Conclusions: A better understanding of the diverse disease presentations, paraneoplastic syndromes, and side effects of cytokine abnormalities stemming from myxomas will aid the physician in earlier detection and monitoring of disease recurrence.
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1. Introduction

Primary cardiac tumors are very rare with an incidence ranging from 0.0017% to 0.19% in one autopsy series [1]. Atrial myxomas are the most common cardiac tumors and comprise 50% of all benign cardiac tumors [2,3]. In this review, we will review all aspects of myxomas including location and nature of myxomas, pathogenesis, diagnosis, and treatment. Further discussion will include the metastatic potential and paraneoplastic manifestations that complicate myxomas.

The name myxoma is derived from its appearance as a cell-poor, myxoid neoplasm with a mucopolysaccharide-rich extracellular matrix. Myxomas range in size from 1 to 15 cm and are typically round, oval, or lobulated with a smooth surface and a narrow pedicle attaching to the cardiac tissue [4]. Broad-based features and a frond-like appearance have also been reported [4].

The most common locations for myxomas are the left atrium (60–75%), the right atrium (20–28%) and, rarely in both atria and ventricles. Typically, myxomas arise close to the fossa ovalis of the interatrial septum, although a few arise from free walls of the atria or from atrioventricular valve leaflets [5]. There is a 2:1 female predominance and diagnosis is typically between 50 and 70 years of age [6].

Although atrial myxomas occur sporadically, at least 10% of the cases are familial, the most common of which is the Carney syndrome [7]. This autosomal dominant syndrome consists of multiple cardiac myxomas, a variety of pigmented skin lesions, extra-cardiac tumors and melanotic schwannomas. Patients with Carney's triad are usually younger and more likely to have myxomas outside the left atrium. Carney syndrome is also associated with increased risk of myxoma recurrence, approaching 25%, after tumor resection [8]. Mutations in the tumor suppressor gene, protein kinase A (PKA) type-1 regulatory subunit (R1A) PRKAR1A, occur in >50% of cases while linkage to chromosome 2p16 occurs in other families [9–12].

The mechanisms by which atrial myxomas produce symptoms include constitutional symptoms, systemic embolization, and mitral valve obstruction. Although 10% of patients may be asymptomatic, most patients present with constitutional symptoms such as fever, weight loss, weakness or myalgias [6]. Cardiac symptoms usually manifest as dyspnea, palpitations or syncope. These symptoms are related to obstruction to left ventricular inflow or elevated left atrial pressures. Neurological manifestations are frequent and have been reported in 25–45% of cases [13]. The neurological signs and symptoms are usually a result of embolization. Tumor mobility, not size, appears to be related to embolic potential. Rarely, neurological complications may be due to embolized tumor fragments instead of surface thrombi [14,15].

2. Pathogenesis

There are two main gross anatomical types of atrial myxomas, a solid type that is firm and smooth and a gelatinous type that is soft and friable [16]. Shimono et al. found that clinical presentation correlated with the gross tumor appearance [17]. Patients with solid

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tumors were more likely to present with congestive heart failure symptoms while patients with gelatinous tumors were more likely to present with cerebral and peripheral embolization [17]. Solid myxomas are highly vascular tumors with a tendency to undergo internal hemorrhage secondary to repetitive contact with the mitral valve annulus. In a histopathology review of 19 atrial myxoma cases, organizing blood clots were noted on the surfaces of 8 solid tumors, hemosiderin-laden macrophages were identified in 16 tumors (3 papillary, 13 solid) and hemorrhage was found in 17 tumors [18]. Internal hemorrhage may lead to a very rapid increase in myxoma size that can further compromise cardiac output. Other studies have reported surface thrombi in up to 40% of all myxomas [15]. The presence of surface thrombi further contributes to neurological and systemic embolization (Fig. 1).

Several cytokine abnormalities have been documented to be elevated in cardiac myxomas and are thought to be causative in recurrence, local and systemic invasion, and paraneoplastic manifestations (Table 1). Interleukin 6 (IL-6), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and monocyte chemotactic protein-1 (MCP-1) have all been implicated in the pathogenesis of myxomas [19]. Excessive production of IL-6 is associated with local myxoma growth, frequent recurrence, and occurrence of distant myxoma metastases [20–24]. Mendoza et al. performed a prospective study to evaluate the correlation of interleukin-6 serum levels with preoperative constitutional symptoms and the possible role played by this cytokine in tumor recurrence. The results of the study showed a strong correlation between IL-6 and the constitutional symptoms associated with atrial myxomas. Furthermore, IL-6 levels may be used as a marker for recurrence [20,23,24]. IL-6 acts as an autocrine growth factor for myxoma cells and may also contribute to the pathogenesis of ventricular hypertrophy [24].

VEGF has also been implicated in the pathogenesis of myxomas. Kono et al. analyzed 15 myxomas for VEGF expression by immunohistochemistry and found high expression in all of the tumors [25]. Furthermore, VEGF expression was inversely proportional to tumor size and correlated to microvessel density of the tumor [26]. Additionally, neutralizing anti-VEGF antibodies inhibit cardiac myxoma growth in vitro [26]. These studies substantiated the close link between VEGF stimulation and myxoma cells.

bFGF and its receptor, FGFR-1, have also been shown to have increased expression in the majority of myxomas, 73.3% and 67.7% respectively [27]. Similar to VEGF, increased microvessel density occurred in myxomas with high bFGF or FGFR-1 expression [27]. As with VEGF, it appears as though bFGF and the FGFR receptor play an important role for tumor angiogenesis and proliferative activity.

Myxoma angiogenesis also correlates with the expression of MCP-1 and thymidine phosphorylase (TP). Evaluation of 17 resected cardiac myxomas revealed increased microvessel density in myxomas with a high proportion of cells expressing MCP-1 and TP [28]. These results indicate that MCP-1 and TP may be regarded as important angiogenic signals accompanying tumor growth. Thus, IL-6, VEGF, bFGF, MCP-1, and TP may all contribute to the pathogenesis or recurrence of myxomas. Despite these advances, there are no published studies on anti-cytokine therapies directed at the humoral factors produced by myxomas.

Table 1
Proposed humoral mediators.

Cytokine	Association
Interleukin-12p70 (IL-12p70)	Constitutional symptoms [22]
Interleukin-8 (IL-8)	Myxoma associated stroke or myocardial infarction [70]
Interleukin-6 (IL-6)	Contributes to myxoma growth [20] Satellites distant from primary tumor [71] Increased recurrent disease [6] Constitutional symptoms [72] Ventricular hypertrophy [22]
Interleukin-4 (IL-4)	Constitutional symptoms [22]
Basic fibroblast growth factor (FGF) and its receptor (FGFR-1)	Increased microvessel density and tumor size [27]
Monocyte chemotactic protein −1 (MCP-1)	Increased microvessel density and tumor size [28]
Thymidine phosphorylase (TP-2) and chemokine receptor-2 (CCR-2)	Increased microvessel density and tumor size [28]
Vascular endothelial growth factor (VEGF)	Inversely associated with tumor size [26] Increased microvessel density [26]
Interferon gamma	Constitutional symptoms [22]
Tumor necrosis factor (TNF)	Constitutional symptoms [22]

3. Diagnosis and treatment

Until 1977 when echocardiography became readily available, a means of noninvasive diagnosis was unavailable. Previously atrial myxomas had been described postmortem, as was the case with the first atrial myxoma described in the literature by Goldberg et al. in 1952 [29]. Even today, the diagnosis of atrial myxoma can be challenging given the variety of nonspecific symptoms patients may have. Echocardiography remains the most frequently used imaging modality to detect atrial myxomas. Trans-esophageal echocardiography (TEE) is preferred over trans-thoracic echocardiography (TTE) due to increased sensitivity. One multicenter study reported TEE to be 100% sensitive for detecting atrial myxomas [30]. Cardiac MRI and gated ultrafast cardiac CT scan have also been used to image atrial myxomas [31,32].

Once a myxoma has been diagnosed, urgent surgical removal should be considered due to the risk of embolization. Long term survival after wide resection of myxomas is excellent with survival rates between 80% and 98% at 10 years [33–35]. For sporadic myxomas, annual echocardiography is suggested for a period of 3–4 years, at which time recurrence is the greatest [36]. Atrial myxomas recur in only 1% to 3% of sporadic cases often due to inadequate resection [6]. The recurrence rate is much higher in the familial cases such as Carney complex which has a recurrence rate of 25% [37].

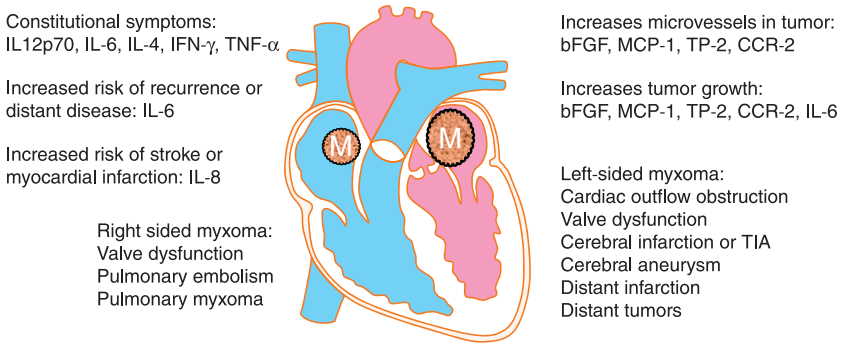

Fig. 1. Associated symptoms and humoral mediators of atrial myxoma. Several cytokines are associated with particular pathogenic tumor features or pathological symptoms. Right and left atrial myxoma have distinct disease manifestations.