RESEARCH ARTICLE

Clinical and Histopathological Analysis of 66 Cases with Cardiac Myxoma

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Abstract

Background and Purpose: Cardiac myxoma is a major primary heart tumor which often causes unexpected symptoms or sudden death. This present study was designed to investigate its clinical pathological features and biological behavior. Methods: A retrospective analysis of the clinical pathologic and immunohistochemical features of 66 cases with cardiac myxoma was conducted. Results: In 66 patients with cardiac myxoma, 61 cases had involvement of the left atrium, one case in both the right ventricular and left atria. The female: male ratio was 2.7:1. Patients had symptoms of blood flow obstruction and systemic alterations with performance of arterial embolization. Tumors were spherical, lobulated or irregular in shape, and soft and brittle. Immunohistochemical markers of vimentin and CD34 in tumor cells were positive. Conclusion: Cardiac myxoma always exists in the left atrium and is more common in women, with diverse clinical manifestations and pathomorphism. Although proliferative activity and the recurrence rate are low, in addition to thorough surgical resection, strengthened review is important for young patients.

Keywords: Cardiac myxoma - clinical features - histopathology

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Introduction

Primary cardiac tumors are rare. Its incidence accounts for about 0.3% of patients with cardiac surgery. In cardiac tumors, the cardiac myxomas (CMs) are most common accounting for about 50% (Molina et al., 1990; Elbardissi et al., 2008; Tasoglu et al., 2009). The annual incidence rate is 0.5/per million, always in adults aged 30 to 60. Women have a higher incidence, of which 4.5% to 10% are due to familial nature (Salcedo et al., 1992; Lamba et al., 2012). CMs always occur in the left atrium, about 75% to 83%, mostly in a single place, 1.3% of which have bi-atrial myxomas (Pinede et al., 2001; Lamba et al., 2012). Due to the tumor size and location in the different chambers of heart, the clinical sign of cardiac myxoma is the obstruction of blood flow resulted in cardiac soufflé, left ventricular or right ventricular dysfunction, orthostatic syncope or sudden death, and embolism performance due to drop of tumor debris and embolus of tumor thrombus (Kuroczyński et al., 2009; Tasoglu et al., 2009). From histomorphology, the tumor cells were stellate, fusiform, or polygonal in shape; had small clusters, strips cords, and mesh-like arrangement in which filled with pink or light blue staining myxoid material, while some concomitant morphological changes such as calcification, ossification, adenoid metaplasia are very rare (Singh et al., 2012). Although the overall incidence is low and mostly benign, it brought popular attentions that the CMs often cause sudden symptoms or sudden death. Its biological behavior and tissue origin has not been elucidated. In recent years, the detection rate of this disease significantly increased with a wide application of echocardiography. This study was designed to collect 66 cases with surgical resection of cardiac myxoma and observe these samples from clinical features, pathological and immunohistochemical staining to investigate the features of clinical pathology, tissue and biological behavior.

Materials and Methods

General Information

This study was designed to conduct a retrospective analysis to 66 cases with surgical resection of cardiac myxoma in First Affiliated Hospital of Xi'an Jiaotong University between May in 1985 to October in 2011. The subjects were 48 females and 18 males, aged 3 to 74 years (median age was 45.5 years). The course was 5 days to 17 years.

Clinical manifestations

There were three categories of lesion found: (1) symptoms of flow obstruction: palpitation after exercises, shortness of breath, chest tightness, syncope, leg edema; (2) systemic symptoms: fever, fatigue, anemia, fast ESR; (3) symptoms of arterial embolism: performance of cerebral embolism.

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Diagnosis and surgical treatment

All 66 cases were diagnosed with echocardiography showing quasi-circular ground shape echo with varying sizes in atrial and ventricular cavity which had clear boundary and the reciprocating movement in the heart cavity with the heart beat. 2 patients with symptoms of cerebral embolism diagnosed with cerebral MRI had left atrial myxoma as embolic etiology with heart ultrasound. All patients accepted the heart surgery underwent the resection of both tumor and basement tissue of tumor, and had no family history.

Pathology and immunohistochemical staining

Collected surgical specimens were fixed in 10% neutral formalin, embedded in paraffin to slice and observed after HE staining. 35 samples had 8 kinds of immunohistochemical staining: AE1/AE3 (1:50); Vimentin (1:80); EMA (1:150); Calretinin (1:30); CD34 (1:30); F8 (1:50); SMA (1:70); Ki67 (1:50). The first antibody and SP kits were purchased from Fuzhou Mai xing Biotechnology development Co., Ltd, which all have a positive and negative control.

Results

Clinical features

The occurrence sites: 61 cases had the myxoma in the left atrium; 3 cases had it in the right atrium; 1 patient had it in the nearly apical part of left ventricular; 1 case had it in the both right ventricular and left atrial. Clinical manifestations: (1) All patients had blood flow obstruction symptoms including palpitation after exercises, shortness of breath, chest tightness history (100%) with nine cases of lower extremity edema, seven cases of syncope history, four cases of hemoptysis history; (2) 15 cases of fatigue, anemia, rapid ESR and systemic symptoms (22.72%); (3) 2 cases associated with cerebral embolism and the hemisensory obstacles (0.03%). There were 0 case of cardiac function grade I, 21 cases of grade II, 38 cases of grade III and 7 cases of grade IV. 51 cases had diastolic rumbling murmur in apex area of heart with physical examination, the first heart sound hyperthyroidism and similar signs of mitral stenosis, 10 cases had 3/6 systolic in the heart area and diastolic mid-murmur. 57 cases in 66 patients with cardiac myxoma had tumor basement whose length was 0.3 to 1.2cm, width was 0.8~2.5 cm. 9 cases had no tumor basement and were broad-based. The tumors of 54 cases attached to the fossa ovalis or the upper edge of them. The tumors of 7 cases attached to the lower portion of the atrial septum. 3 cases' attached to the atrial side of the mitral annulus. 1 case's attached to the interventricular septum of near apex of heart. 1 case's attached to the vicinity of the tricuspid annulus.

Pathological features

Gross examination: tumors were spherical, lobulated or irregular-shaped; surface of seven cases had pseudocapsule with smooth surface; two cases had blood clots adhered to the surface. Appearance of these tumors was yellowish translucent jelly and shiny, parts between which had dark red hemorrhagic foci scattered with different sizes, soft and brittle. The volume atrial tumors in 64 cases were 1.5cm x 1.5cm x 0.5cm ~ 12cm × 7cm × 5cm, of which 57 cases had the basements; one case had the smallest tumor (0.7cm x 0.7cm x 0.4cm) without a basement. Cut surface is light yellow and dark red jelly. The different sized cysts whose diameters were 0.2cm~1.0cm appeared in some tumors. The contents were dark red blood clot-like materials. Some tumors had gray fibrosis area and sallow calcification stoves. The tumor pedicle was tough, some with little myocardial tissue.

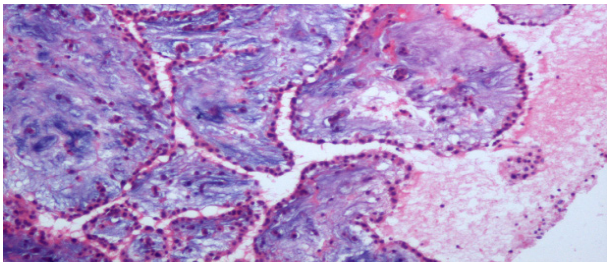

Figure 1. Papillary Structure on the Surface (HE×100)

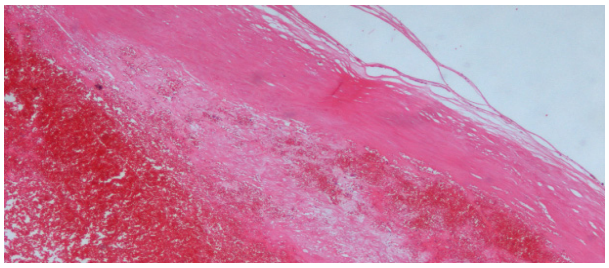

Figure 2. Fibrous Pseudocapsule on the Surface (HE×40)

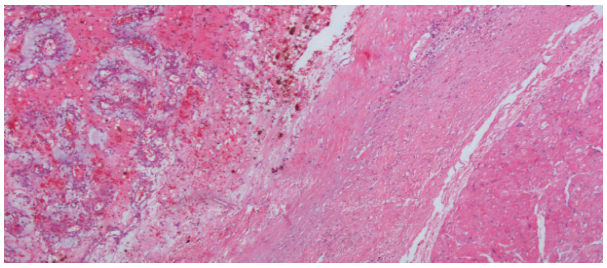

Figure 3. Tumor Pedicle and Myocardium Separated by Fiber Layer (HE×40)

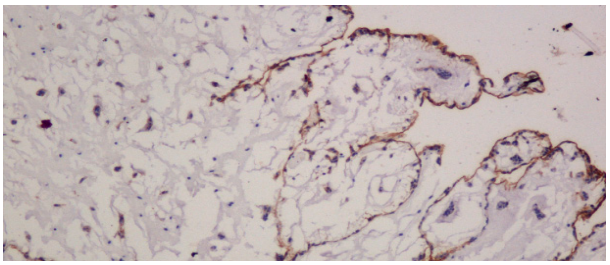

Figure 4. Cells and Parenchyma Cells were Coated on the Surface of Tumor CD34(+) (SP×100)

Histologic morphological observations

The tumor surfaces of 57 cases were coated with single- or multi-layer cuboidal or flat epithelial cells, which grew towards with crypt-like shape. Some associated with interstitial growth and formed the papillary structures (Figure 1) on the surface. 2 cases' surfaces had visible bleeding and were coated with fiber. 7 cases' surfaces had pseudocapsule layer of hyperplasia formation of fibrous

tissue (Figure 2). Tumor cells were stellate, spindle-shaped, round or polygonal. The nuclear was cylindrical, oval with clear nuclear membrane and no mitotic stage. The cytoplasm was stained pink. Single tumor cell was scattered, or in the form of small clusters and cords, mesh arrangement. The pink or light blue staining myxoid material filled with the tumor cells. The central tumor tissue in one case had tubular glands and cysts lined with mucous columnar epithelial cells and low cuboidal epithelial cells. Most interstitial in oncology centers had different amount of lymphocytes, plasma cells and tissues cells. 10 cases had chronic hemorrhage, deposition of hemosiderin and iron salt and fibrosis in the center of tumors, of which 6 cases were accompanied with necrosis in the tumor tissue; 3 cases had spotty calcification; 1 case had ossification and fat metaplasia. There was fiber layer separation between tumor pedicle and myocardial fiber layer, obvious proliferation of collagen fibers in pedicle and more thick-walled small arteries (Figure 3).

Results of immunohistochemical staining

This study was designed to make immunohistochemical staining to specimen of 35 cases. Vimentin and CD34 of coated cells on the surface of the tumor cells and myxoma cytoplasm had positive expression (35/35) (Figure 4). CK in the adenoid structure and EMA in cytoplasm and membrane were stained positive. The rest of the tumor cells were negative. F8 in tumor vascular endothelial was positive while tumor cells were negative (0/35). The SMA and Calretinin of coated cells on tumor surface and mucus tumor cells were negative. The SMA in the vascular smooth muscle was positive (0/12). Ki67 were all negative.

Follow-up

42 cases received postoperative follow-up. The period of follow-up was between 1 to 24 years. The patients were all alive. 5 cases recurred during two years after surgery, of which one case recurred three times.

Discussion

Cardiac myxoma is the most important cardiac tumor. The annual incidence was 0.5 per million. This tumor can occur at any age, but more common in adults aged 30 to 60, and women have a higher incidence. The ratio of female to male is 2:1 to 3:1. 4.5% to 10% of patients are the familial. The youngest patient in this group was 3 years old which is rarely reported in literature. Most of the 66 cases were women. The ratio of female to male was 48:18, also 2.7:1. The median age was 45.53 years old. Those were consistent with reports in the literature (Elbardissi et al., 2008). The tumor always occurs in the left atrium, multi originates in the fossa ovalis of atrial septal which were connected to basement accounting for about 75% to 83%. 12.7% of tumors occurred in the right atrium, mostly in a single side. 1.3% of tumors occurred in the both atrium. There is also report that tumors occur more common in the right atrium than in the left ventricular (Tasoglu et al., 2009). It is rare that the tumors appear in multiple chambers of the heart (Leonhardt et al., 1977). In this group of 66 cases, 61 tumors occurred in the left atrium accounting for 92.42%, of which 54 tumors adhered to the fossa ovalis, while 2 tumors existed in mitral annular atrial side, 1 located in the apex of left ventricle and 1 in the right ventricle which were rare. One case occurred in the left and right ventricles accounting for 0.015%. 3 cases occurred in right atrial accounting for 0.045%. One case of 21-year-old patient occurred in multiple cavities. The tumors located in the left atrium and right ventricle. 57 patients had varying length of the basement membrane. The visible hyperplasia fiber and thick-walled small blood vessels existed under the basement of sessile tumor.

Signs of cardiac myxoma were different with the tumor size and located heart chamber, and tumor can have a heart murmur of the blood flow obstruction within the heart and clinical manifestations. Due to blocked atrioventricular canal, left ventricular or right ventricular may have dysfunction, and the patients may have orthostatic syncope or sudden death. Pathology observed cardiac myxoma specimens were soft, crunchy, and had the jelly-like appearance with the uneven surface. Thus tumor debris and tumor thrombus emboli can easily fall off to cause embolism, about 50% of patients with embolic performance. Due to hemodynamic factors, the right atrial myxoma mainly caused pulmonary embolism, while the left atrial myxoma can cause systemic embolism, of which the most common is cerebral embolism (Salcedo et al., 1992). 100% patients in this group had the symptoms of flow obstruction including syncope, lower extremity edema, hemoptysis, and etc. 2 cases were accompanied with cerebral embolism and symptoms of hemisensory disorder accounting for 0.03%. Those results prompted that people who suffered unexplained syncope, embolism, heart murmur, and etc. should go to receive examination with B-ultrasound. Echocardiography is the most valuable means to diagnose this disease with the sensitivity up to 98%.

66 cases of myxoma had the following features in addition to a general morphological appearance: 7 cases had a layer of fibrous tissue hyperplasia formed pseudocapsule on the tumor surface, which was consistent with the smooth surface in larger tumors described by Lamba et al (Lamba et al., 2012); 10 tumors had the central fibrosis and hemosiderin deposition; 3 cases had spotty calcification; one patient had ossification and fat metaplasia. These performance and analysis was related with tumor growth for a long time, which was also rare. 6 cases were accompanied with necrosis in the tumor tissue, which may be associated with rapid tumor growth and lack of blood supply. Most tumors stromal had different amount of lymphocytes, plasma cells and tissue cells, which may be related to the body's reaction. Author (Pucci et al., 2000) had summarized that in the 53 cases with cardiac myxoma, two cases had the spotty adenoid differentiation parts in the tumor basement. In this group, adenoid structure was identified in a 3-year-old child, which is rare in the cardiac myxoma and due to metaplasia from tumor cell, or differentiation from pluripotent stem cells.

The stained Vimentin and CD34 of the monolayer of flat or cuboidal cells on the tumor surface and tumor cells in vivo were positive. F8 in the tumor vascular

endothelial was positive while tumor cells were negative. The results showed that the coated cells on the tumor surface were same class with the tumor cells in the body. Vimentin and CD34 expression suggested these cells were mesenchymal-derived. In 35 cases, F8 was only positive in vascular endothelium but negative in tumor cells, which indicated that the tumor did not origin from vascular endothelium. There are fewer reports about CD34 detection in the literature. The results in this group showed that the tumor cells were CD34-positive, supporting the idea of origin from primitive mesenchymal cells of Berrutti etc. (Berrutti et al., 1996). Calretinin of tumor cells was negative, which was different from the results of Val-Bernal et al. (2003), and thus whether the Calretinin can be an indicator of the diagnosis of cardiac myxoma needed further study. CK, EMA in adenoid structure area was positive, which confirmed that the differential ability of tumors to epithelium.

It has been controversial about the tissue origin of cardiac myxoma. There are mainly two views: (1) derived from pluripotent primitive mesenchymal cells (Pucci et al., 2000; Amano et al., 2003); (2) from the endocardial nerve tissue (Sakamoto et al., 2004). Some study put forward the idea that simplex virus type I (HSV-1) infection may be related with sporadic atrial myxoma In this study, tumor cells were CD34 positive, which support the idea of origin from the primitive mesenchymal cells with the ability to differentiate endothelium in the first view.

It is still a problem about whether cardiac myxoma is benign or malignant. There had been a study to analyze the DNA in 35 of the 37 cases with cardiac myxoma with flow cytometry to find that 17% of them had abnormal DNA components (Acebo et al., 2003), as well as another study reported that the tumor cells had aneuploidy DNA with high proliferative activity and malignant possibility (Kotyloet al., 1991). Ki-67 immunohistochemistry tests of 35 patients in our group were all negative, indicating the tumor had not a high proliferative activity. The recurrence rate of this tumor is low, only 2-5% (Pinede et al., 2001; D'Alfonso et al., 2008). Therefore chemotherapy is not recommended because that the embolism is not a true transfer. Study found that detection of MUC5AC in cardiac myxoma with immunohistochemical method can mean the low incidence of embolism (Chu et al., 2005). We followed up 42 cases. 5 cases had recurrence in local, of whom 4 cases aged less than 43 years old, consistent with Lamba et al. (2012) who mentioned that young people are easy to relapse. However, the cases in our study were all single lesion without family history. Vaideeswa et al. (2012) analyzed 20 patients of non-typical myxoma with multifocal lesions and characteristics, of whom four cases had recurrence, suggesting that young people with multiple lesions or family history are more likely to relapse. Such patients should always receive routine echocardiography examination throughout their life. Because that the patients with the cardiac myxoma are prone to blood flow obstruction and arterial embolization there is the risk of relapse and recurrence, these patients should therefore receive clinical treatment to malignant state (Amano et al., 2003) with thorough resection of pedicle. In addition to the surgical removal, the newly proposed molecular targeted therapy is expected to become a treatment (Barh et al., 2009), especially for those patients who already have distant embolization and recurrence, and are hard to receive surgery.

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