Trends in the Clinical and Morphological Characteristics of Cardiac Myxoma
— 20-Year Experience of a Single Large Tertiary Referral Center in Japan —

Satoshi Yuda, MD†; Satoshi Nakatani, MD; Chikao Yutani, MD*; Masakazu Yamagishi, MD; Soichiro Kitamura, MD**; Kunio Miyatake, MD

The purpose of this study was to clarify whether or not a change in the clinical characteristics of cardiac myxoma has occurred during the past 2 decades. The clinical records of 57 patients (22 men, 35 women; age, 52±14 years) with myxoma that had been surgically treated between May 1978 and July 1997 at the National Cardiovascular Center in Japan were reviewed. All myxomas were discovered by transthoracic echocardiography. They were divided into an early group (n=30) treated in the first decade (1978–1987) and a late group (n=27) treated in the second decade (1988–1997). The incidence of myxoma, patient characteristics, preoperative symptoms and echocardiographic features did not differ between the 2 groups. In contrast, the maximal dimensions of myxoma in the early group were significantly larger than those in the late group (6.3±2.7 cm vs 4.3±1.3 cm, p=0.012). The weight of myxoma in the early group tended to be heavier than that in the late group (76±80 g vs 25±18 g, p=0.054). The incidence of patients with asymptomatic myxoma also tended to increase in the late group (7% vs 26%, p=0.07). Although there was no difference in the incidence of myxoma, smaller and asymptomatic myxomas were more frequent during the last decade, probably as a result of the development of cardiac imaging, particularly echocardiography. (Circ J 2002; 66: 1008–1013)

Key Words: Cardiac myxoma; Cardiac surgery; Clinical characteristics; Two-dimensional echocardiography

Myxoma is the most common cardiac tumor, comprising approximately half of all primary benign cardiac tumors.1,2 Despite its benign pathologic nature, however, catastrophic results can occur because of systemic embolism (eg, cerebral and myocardial infarction) and intracardiac obstruction (eg, syncope and sudden death).3–4 Recently, the close relationship between the morphological characteristics of myxoma and systemic embolism has been shown,3 and therefore, the significance of assessment of myxoma has increased.

Although the clinical characteristics of myxoma have been reported in many studies,2,5–11 most have been only comprehensive reviews5–7 and there are limited studies that have focused on the temporal trends in the clinical characteristics of myxoma.8–11 Further, previous studies of the trends of myxoma have shown mainly an increased incidence of detectable myxoma after the introduction of echocardiography8–10 and few have mentioned changes, if any, in the clinical characteristics of myxoma after the widespread introduction of echocardiography.11

Ultrasound technology has been constantly progressing and the quality of echocardiographic images has improved almost year by year, which has lead to the early detection of myxomas and asymptomatic patients. The purpose of this study was to clarify whether changes in the clinical and morphological characteristics of myxoma have occurred during the past 2 decades in which echocardiography became a standard imaging technique. The National Cardiovascular Center is one of the best places to approach this subject because it is a large tertiary referral center with the most recent models of echocardiography equipment.

Methods

Patient Group
During the decades from May 1978 to July 1997, 68

Fig1. Number of patients with and without symptoms associated with myxoma diagnosed at the National Cardiovascular Center between 1978 and 1997.
patients underwent surgical excision of primary cardiac tumors at the National Cardiovascular Center and all tumors were diagnosed histologically. Of those, 8 patients with malignant tumors (5 angiosarcomas, 1 malignant fibrous histiocytoma, 1 malignant lymphoma and 1 hemangiopericytoma) and 3 with benign non-myxoma tumors (1 fibroma, 1 neurofibroma and 1 rhabdomyoma) were excluded, leaving 57 patients with cardiac myxoma (22 men, 35 women; mean age 52±14 years, range: 2 months to 74 years) to be enrolled (Fig 1). The clinical characteristics, such as patient characteristics, preoperative symptoms, laboratory findings, echocardiographic findings and outcome, were reviewed retrospectively. Elevated erythrocyte sedimentation rate (ESR >20 mm per time period) and C-reactive protein level (>0.3 mg/dl or >0.5+), and leukocytosis (white blood cell count >10,000/mm^3) were identified on admission. The follow-up data were obtained from the patient’s medical charts and/or by questionnaire. The patients were divided into an early group (n=30) treated in the period 1978–1987 and a late group (n=27) treated in the period 1988–1997.

**Ultrasound and Computed Tomography Examination**

All patients underwent transthoracic echocardiography examination with a commercially available ultrasound system before surgery. The left atrial and left ventricular (LV) end-diastolic and end-systolic diameters were determined from M-mode or B-mode echocardiograms, and the LV fractional shortening was measured. Dilatation of the left atrium, LV and the right ventricle were defined according to previous reports. Further, we examined the morphological characteristics of myxoma including mobility and shape. Here, we defined the prolapsing type as a myxoma prolapsing through the mitral or tricuspid valve during diastole, and the polypoid type as a myxoma characterized by a soft and irregular shape with a mobile surface, according to the previous study. Enhanced computed tomography (CT) was performed on 10 patients (18%) before surgery. The myxoma surface assessed with enhanced CT was compared with the pathological findings.

**Pathology**

Morphological (surface, dimension and weight of the excised tumor) and histological features (hemorrhage, necrosis and calcification) of the myxoma were also studied. The surface types were defined as villous or smooth, according to the previous study. The villous type had an irregular surface that consisted of multiple fine villous, gelatinous and fragile extensions. The smooth type had a regular and round surface.

**Statistical Analysis**

All data are expressed as mean±SD. Continuous variables were compared by the Student’s unpaired t test, and the size of myxoma was compared by the Mann-Whitney U-test. Categorical variables were analyzed with the chi-square test or Fisher’s exact test when the number of patients was small. All results were considered significant when the p value was less than 0.05.

**Results**

**Clinical Characteristics of Myxoma (Table 1)**

Of the 57 myxomas, 52 were located in the left atrium, 4 were in the right atrium, and 1 was in the right ventricle. Of the 52 left atrial myxomas, 48 (92%) arose from the fossa ovalis of the atrial septum, 3 (6%) from the posterior wall and 1 (2%) from the left atrial appendage. Three of the right atrial myxomas arose from the fossa ovalis of the atrial
The prolapsing type myxoma was found in 13 and the polypoid type in 5 patients. We found 24 patients with a murmur in 2, acute myocardial infarction in 1, arrhythmia in 4, heart murmur in 3 and hypertension in 2. Of these, 20 (35%) were discovered by routine echocardiography, 4 by transthoracic echocardiography, and 10 by enhanced CT followed by transthoracic echocardiography. Right bundle branch block was noted in 2 patients (4%) and atrial premature contraction was noted in 1 (2%).

Ultrasound and CT Findings
All myxomas, except one that was discovered by enhanced CT followed by transthoracic echocardiography, were first discovered by transthoracic echocardiography. Of these, 20 (35%) were discovered by routine echocardiographic examination after admission to hospital for other purposes (cerebral infarction in 8, heart failure in 7, heart murmur in 2, acute myocardial infarction in 1, arrhythmia in 1 and infective endocarditis in 1). We found 24 patients (53%) had dilatation of the left atrium, 5 (11%) had dilatation of the LV and 12 had dilatation of the right ventricle. (53%) had dilatation of the left atrium, 5 (11%) had dilatation of the right ventricle, and 5 (11%) had dilatation of the right ventricle.

Before the surgical procedure, sinus rhythm was noted in 45 (79%) of the 57 patients and 12 had atrial fibrillation. Right bundle branch block was noted in 2 patients (4%) and ventricular premature contraction was noted in 1 (2%).

Histologically, hemorrhage and/or necrosis and calcification were observed in 17 (30%) and 5 (9%) patients, respectively. Echocardiography identified hemorrhage and/or necrosis in 5 patients (30%) of the 17 as a heterogeneous mass and calcification in 2 (40%) of the 5 as a high echo region.

Trends in the Clinical Characteristics
The incidence of myxoma in the early and late years appeared comparable (3.0 patients per year in the early group and 2.7 patients per year in the late group) (Fig 1). Table 1 shows there was no significant difference between the 2 groups in age, gender, preoperative symptoms, laboratory findings or echocardiographic features. However, the maximal dimensions of the myxomas in the early group were significantly larger than in the late group (6.3±2.7 vs 4.3±1.3 cm, p=0.012) (Fig 2), and the weight of myxoma tended to be heavier than in the late group (76±80 vs 25±18 g, p=0.054) (Fig 2). The incidence of asymptomatic myxoma (7% vs 26%, p=0.07) and that of the patients with a normal C-reactive protein concentration (23% vs 52%, p=0.07) also tended to increase in the late group (Table 1).

Relationship of Symptoms to the Size of Myxoma
The size of an asymptomatic myxoma was not significantly different from that of a symptomatic tumor (5.3±2.7 vs 4.1±2.1 cm, p=0.15 for the maximal dimension, 58±85 vs 34±34 g, p=0.55 for the weight). The maximal dimension in myxoma accompanied by dyspnea (6.0±2.6 cm) tended to be larger than that for myxoma without dyspnea (4.4±2.9 cm, p=0.051). The incidence of the polypoid type was significantly higher in patients with systemic embolization than in those without embolization (20% vs 3%, p=0.047), as was the incidence of the villous type (57% vs 10%, p=0.001). However, no relationship was found between the surface type or size of myxoma (the maximal dimension and weight) and other symptoms. The ESR and C-reactive protein concentration did not correlate with the maximal dimension and weight of myxoma, and the incidence of patients with elevated ESR, C-reactive protein concentration or leukocytosis was not significantly different between patients with and without embolism and/or dyspnea.

Follow-up and Survival
There were no hospital deaths. Follow-up was available in 56 of the 57 patients (98%) and the mean follow-up period was 6.0±4.8 years (range, 3 months to 17.3 years). Six patients (11%) died during follow-up: one developed systemic metastasis of the myxoma at 5.3 years after surgery; one patient who had brain and skin metastases died from respiratory failure at 6 years; the other patient died because of a traffic accident at 3.5 years. Three other patients died at 5.5, 6.6 and 15.1 years after surgery, respectively, but the cause of death was unknown. Metastasis of myxoma was found in 2 patients (4%) both of whom had no malignant characteristics histologically: brain and skin metastases occurred in one patient at 3 and 10 months, respectively, and an esophageal metastasis occurred in the other patient at 2.8 years after the operation. Of the 56 patients who underwent postoperative transthoracic echocardiography (mean, 3.4±3.0 years; range, 1 month to 13.9 years), 1 patient (2%) whose 7.5×3.5 cm myxoma with a stalk was resected had a recurrence in the left atrium at 2.1 years after the operation.

Fig 2. Comparison of the maximal dimension (Left) and weight (Right) of myxoma between the early (1978–87, open column) and late (1988–97, solid column) groups.
Discussion

We compared the clinical and morphological characteristics of cardiac myxomas treated in the early (1978–1987) and late (1988–1997) periods of echocardiography use. Although no difference in the incidence of myxoma was found, smaller myxomas were more frequently found in the late period, and the incidence of myxoma without any symptoms tended to also increase in the late period.

Incidence of Myxoma

Before 1970, the preoperative diagnosis of myxoma was difficult and 2-thirds of myxomas were first discovered at surgical operation or autopsy. In contrast, the recent progress in cardiac imaging has led to a dramatic improvement in diagnostic capability and a preoperative diagnosis can be established in almost all cases of myxoma, which is consistent with our results.

It has been the introduction of echocardiography that has led to the increase in the incidence of myxoma diagnosed preoperatively. Fyke et al reported that the mean rate of preoperative diagnosis of myxoma increased from 1.6 (1968–1976) to 3.5 myxomas per year (1977–1983) after the introduction of 2-dimensional echocardiography, and Pinede et al also found an increase in the incidence of myxoma diagnosed preoperatively from 0.7 (1959–1977) to 4.7 myxomas per year (1978–1998). However, the temporal trend in the incidence of myxoma after the introduction of intensive use of echocardiography has been unclear and we found that the incidence had not changed significantly between the early and late periods, chosen for investigation. Thus, despite the development of ultrasound imaging technologies, it has not been sufficient to significantly enhance the detection rate.
Size and Weight of Myxoma

Previous studies\(^1,6-11,14-27\) of the size and weight of myxoma are reviewed in Table 2. The averaged maximal dimension and weight of myxoma ranged from 3.7 to 5.6 cm (maximal dimension) and from 34.8 to 71.6 g (weight), which is comparable with our present results. Most of those data have been accumulated during the past 3 decades and the temporal trend in the size of identified myxomas has not been fully elucidated. There are few studies on the trends in the clinical characteristics of myxoma. Endo et al investigated 161 primary cardiac tumors (including 91 myxomas) diagnosed between 1993 and 1994 in Japan\(^1\) but they only compared the size of myxoma to that of previous studies and suggested that there had been a decrease in the size of myxoma after the widespread introduction of echocardiography. We obtained similar results at a single center and we also found a decrease in the weight of myxoma detected during the past decade, which suggests that qualitative changes in the identified myxomas have occurred during that decade.

One of the major factors is the shortening of the time interval from the onset of symptoms to diagnosis, which was not assessed in this study. Before the introduction of echocardiography, the time interval between the onset of symptoms and diagnosis was 5.5–12 months\(^1,10,14\) and there has been a trend toward shortening of that interval (ranging from 3.0 to 3.5 months) after the use of echocardiography became widespread.\(^1,10\) Because the growth rate of myxoma ranges from 0.02 to 0.53 cm per month or from 0.79 to 1.6 g per month,\(^1,26\) early diagnosis by echocardiography will contribute to the reduced size of myxoma resected at operation.

Asymptomatic Myxoma

We reviewed the previous studies on asymptomatic myxoma (Table 3).\(^1,3,5,7-10,14,17-20,25,29-31\) The incidence of asymptomatic myxoma was from 0 to 20% (mean 5%), which is consistent with our present results. As well as the trends in the size and weight of myxoma, the trend in the incidence of asymptomatic myxoma has not been well known and to the best of our knowledge, this is the first report to examine it and clarify the increase tendency of asymptomatic myxoma. Surprisingly, approximately 25% of myxomas in the late group did not have symptoms and it is the extensive use of echocardiography for medical check-ups or as preoperative screening for non-cardiovascular disease that has contributed to this.

Clinical Implications

The size of the myxoma is a significant determinant of dyspnea, but not of embolism, whereas the polypoid type is a risk factor for embolism.\(^9,10,22,24,29,31\) When the morphologic characteristics of myxoma are assessed, these findings must be taken into consideration for risk stratification (eg, systemic embolism and heart failure).

We found the size of myxoma in the last decade was smaller than that in the earlier decade, suggesting that it is being detected earlier than before. Nakano et al found a positive correlation between the weight of myxoma and both preoperative mean pulmonary artery pressure and New York Heart Association functional class.\(^24\) Thus, although no difference in the incidence of dyspnea was observed between the early and late groups in the present study, the reduction in the size of the myxoma at diagnosis may have contributed to the decrease in patients with severe heart failure associated with myxoma in the late group. The morphology (eg, polypoid type) of myxoma, not its size, is a significant risk factor for embolism;\(^10,22\) and therefore, the size of the tumor will have little influence on the incidence of embolism.

Constitutional symptoms occurred in only 10% in the late group, which corresponded to the low incidence in previous reports that has varied from 5% to 47%.\(^5,7-10,18-21,25-27,29-31\) The reason for that low incidence can be explained by the fact that we could identify myxomas when they were small enough not to produce constitutional symptoms. Although the number of myxoma with constitutional symptoms (n=5) was too small for statistical analysis, a previous study\(^9\) has shown that large myxomas are associated with constitutional symptoms and abnormal laboratory findings (eg, elevated ESR and increased gamma globulin concentration). Further, a recent study\(^32\) has demonstrated that the plasma interleukin-6 concentration correlated positively with both the myxoma size and constitutional symptoms.

Study Limitations

This is the experience of a single center, although it is a large tertiary referral center and many cardiac patients are referred from all over Japan. Further, because it is a National center, we have the latest ultrasound machines and so we believe our experience well reflects the temporal trend in clinical and morphological characteristics of myxoma in Japan. We have not determined the clinical significance of small and asymptomatic myxoma in relation to surgical outcome, because of the relatively small sample size, and excellent short-term and long-term prognosis.\(^7,10,18,26\) Although the echocardiographic measurements are useful for the risk stratification of systemic embolism, we assessed the incidence of myxoma from the pathologic features. The good correlation between the echocardiographic and pathologic measurements of myxoma has been reported.\(^31\)

Conclusions

We retrospectively reviewed 57 cases with surgically removed myxomas during a 20-year period during which the use of diagnostic echocardiography became widespread. Although the incidence of myxoma did not change between the early decade and the later 10 years, small-sized and asymptomatic myxomas were more frequently found during the later decade, which can be explained by the development of cardiac imaging, particularly echocardiography.

Acknowledgments

This work was supported by a Research Grant from the Japan Cardiovascular Research Foundation.

We thank Nobuo Shirahashi, MS, for assistance in the statistical analysis.

References

5. Blondeau P. Primary cardiac tumors: French studies of 533 cases.