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Characteristics of Cardiac Myxoma with Constitutional Signs: A Multicenter Study in Japan

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Summary

Background: A relationship between constitutional signs in patients with cardiac myxoma and interleukin-6 has been noted. However, there is little information about characteristics of cardiac myxomas associated with constitutional signs.

Hypothesis: The objective of this study was to clarify the characteristics of myxoma patients who had constitutional signs.

Methods: Questionnaires were sent to cardiology or cardiovascular surgery divisions at university hospitals throughout Japan. Constitutional signs were considered present when a patient had fever, weight loss, or elevations of C-reactive protein or gammaglobulin. In addition, interleukin-6 concentrations were evaluated in some patients.

Results: Data were obtained in 249 patients with primary cardiac tumors (204 myxomas, 15 other primary benign tumors, and 30 primary malignant tumors), confirmed histologically between 1993 and 1996. Fever and weight loss were observed in 15 and 6% of patients with myxoma, respectively, while C-reactive protein and gammaglobulin were increased in 39 and 21%, respectively. This amounted to a prevalence of constitutional signs in 49%. All constitutional signs disappeared after tumor resection. Age, gender, tumor site, and frequency of thrombosis did not differ between patients with and without constitutional signs. Tumors associated with constitutional signs were significantly more likely to be large, multiple, or recurrent than those unassociated with constitutional signs.

Conclusions: Constitutional signs are present in about half of patients with myxoma. Large or multicentric tumors are likely to induce constitutional signs, which are reversible upon resection. These might suggest that constitutional signs result when interleukin-6 concentrations exceed a certain threshold.

Key words: cardiac myxoma, constitutional signs, autoimmune disease

Introduction

Remarkable progress of cardiovascular imaging, especially echocardiography, has increased the frequency of identification of cardiac tumors.[1–3] Cardiac myxoma is the most common histologic type, accounting for 75 to 90% of primary cardiac tumors.[1, 4, 5] Clinical features of myxomas reflect a triad of systemic arterial embolism, obstruction of intracardiac blood flow, and constitutional signs. Constitutional signs characteristic of myxoma include fatigue, fever, weight loss, and laboratory abnormalities such as elevated serum C-reactive protein (CRP) and globulin concentrations and the presence of autoantibodies.

Recent studies demonstrated that the myxoma itself can produce interleukin (IL)-6, which may be associated with autoimmune abnormalities.[6–8] Parissis *et al.* reported that patients whose myxomas showed increased IL-6 mRNA expression had immunologic abnormalities, while those with tumors low in IL-6 mRNA expression were free of autoimmune disorders.[6] The resulting elevation of IL-6 is thought to be the cause of constitutional signs, since overproduction of IL-6 is known to increase serum concentrations of acute-phase proteins and gammaglobulin, favor occurrence of autoantibodies, and cause fever.[9, 10] While previous studies investigated the relationship between cardiac myxoma and constitutional signs,[3, 11, 12] the relatively small patient numbers interfered with identifying the characteristics of patients with myxoma with constitutional signs. The purposes of our large population study were to determine the frequency of constitutional signs in patients with myxoma, to verify whether these constitutional signs disappear after tumor resection,

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and to determine characteristic differences between patients with myxoma with and without constitutional signs.

Materials and Methods

Questionnaires were sent to divisions of cardiology or cardiovascular surgery at 238 university hospitals throughout Japan. Patients included were selected on the basis of criteria requiring primary cardiac tumors confirmed by histology that were diagnosed during life. Data were obtained for 249 such patients with primary cardiac tumors (90 men and 159 women; mean age ± standard deviation [SD], 56.5 ± 16.8 years) diagnosed and histologically confirmed between the years 1993 and 1996. In these patients, we evaluated fever (temperature exceeding 37˚C at least once a day), weight loss of more than 2 kg, and elevations of CRP or gammaglobulin as constitutional signs. The normal range for laboratory data was determined by each institution. When at least one abnormal finding was present, the patient was classified as having constitutional signs. Other patients with none of the three abnormalities were defined as not having constitutional signs; any remaining patients with incomplete information were classified as undetermined. In addition, data concerning IL-6 elevation were available for some of the patients diagnosed during 1995 and 1996. Finally, we examined changes in constitutional signs noted during follow-up after tumor resection.

Statistical Analysis

Continuous variables were expressed as mean values ± SD, and categorical variables were expressed as percentages. Categorical differences between groups were assessed by chi-square analysis or Fisher's exact test. Student's *t*-test was used for comparing continuous variables. All analyses were performed with a commercially available statistical program (StatView Version 5.0; SAS Institute, Cary, N.C., USA). Differences were considered significant when p values were < 0.05.

Results

Histologic diagnoses of the cardiac tumors are shown in Table I. Of the 249 patients, 219 (88%) had primary benign tumors, while 30 (12%) had primary malignant tumors. Myxoma (n = 204) was the most common histologic type, accounting for 82% of all primary cardiac tumors and 93% of primary benign tumors.

Frequency of Constitutional Signs

Frequency of constitutional signs is summarized in Table II. In patients with myxoma, fever and weight loss were observed, respectively, in 29 of the 195 patients (15%; 9 cases were unconfirmed) and 7 of the 115 patients (6%) with available data. The serum CRP concentration was increased in 72 of 187 patients (39%). However, these abnormal findings were observed more frequently in patients with primary malignant cardiac tumors (Table II). Hypergammaglobulinemia and increased IL-6 were observed in 21 and 46% of patients with myxoma, respectively. In contrast, among patients with benign cardiac tumors except for myxoma, only one exhibited elevation of CRP (7%); other constitutional signs were not observed.

In all cases of myxoma for which follow-up data were available (74 of 90 patients with constitutional signs), all constitutional signs disappeared after tumor resection. On the other hand, in patients with primary malignant cardiac tumors, only

TABLE I Histology of primary cardiac tumors in 249 patients

Histological type	Numbers
A. Benign	(219)
Myxoma	204
Hemangioma	4
Rhabdomyoma	3
Lipoma	3
Fibroma	1
Pericardial cyst	3
Dermoid cyst	1
B. Malignant	(30)
Angiosarcoma	9
Malignant lymphoma	5
Rhabdomyosarcoma	4
Malignant fibrous histiocytoma	3
Malignant mesothelioma	3
Papillary fibroelastoma	2
Leiomyosarcoma	1
Synovial sarcoma	1
Chondrosarcoma	1
Paraganglioma	1

TABLE II Frequency of fever, weight loss, and elevations of C-reactive protein, gamma-globulin, and IL-6

	Benign tumors		Malignant tumors
	Myxoma	Others	
	No.	No.	No.
Fever (%)	29/195 (15)	0/15 (0)	15/26 (58) [b]
Weight loss (%)	7/115 (6)	0/11 (0)	7/16 (44) [b]
Elevated CRP (%)	72/187 (39)	1/15 (7) [a]	21/28 (75) [b]
Elevated gamma globulin (%)	26/125 (21)	0/10 (0)	6/21 (29)
Elevated IL-6 (%)	12/26 (46)	0/0 (0)	0/2 (0)

[a] $p < 0.05$ vs. myxoma.
[b] $p < 0.01$ vs. myxoma.
Abbreviations: CRP = C-reactive protein, IL-6 = interleukin-6, Myxoma = patients with myxoma, Others = patients with primary benign cardiac tumors except for myxoma, Malignant tumors = patients with primary malignant cardiac tumors.

3 of 11 patients (27%) showed diminution of their abnormal signs after the tumor was removed (7 cases had no such signs initially, and 12 cases had insufficient information).

Comparison between Patients with Myxoma with and without Constitutional Signs

Among patients with myxoma, at least one constitutional sign was observed in 90 patients (49%). Ninety-two patients (51%) had no constitutional signs, and 22 cases were classified as undetermined. Comparisons between patients with and without constitutional signs are shown in Table III. No significant differences in age, gender, site of tumor, or frequency of thrombosis were seen between the two groups. However, tumor size (evaluated as the mean of long and short dimensions) was significantly larger in patients with than in those without constitutional signs ($p < 0.001$). Among patients with constitutional signs, multicentric tumors (three cases with multiple tumors, two recurrences, and two cases with both multiple tumors and recurrence) were more frequent than among patients without constitutional signs (only one case with multiple tumors). Of the patients with myxoma with IL-6 measurements, all but one patient with constitutional signs had an increased serum IL-6 concentration. In contrast, serum IL-6 was not elevated in patients without constitutional signs.

Discussion

The main findings in this study were that about half of patients with myxoma exhibited constitutional signs, and that all of these manifestations disappeared after tumor resection. Further, in patients with myxoma with constitutional signs, tumors were larger and more likely to be multiple or recurrent than in patients without constitutional signs.

Cardiac myxoma has been known to show constitutional signs that can mimic autoimmune diseases;[13, 14] such signs were observed in 20 to 55% of patients with myxoma in relatively small studies.[3, 11, 12] In our large survey, elevation of CRP was the most commonly observed manifestation (39% of cases), followed in descending order by elevation of gammaglobulin, fever, and weight loss. Several previous studies found that constitutional signs in patients with cardiac myxoma disappeared after the tumor was removed.[7, 8, 11] Increases in serum IL-6, IL-6 antigen, and IL-6 mRNA expression in myxoma tissue were also reported in association with immunologic abnormalities.[6–8, 11, 15] These abnormalities underwent remission with return of circulating serum IL-6 to undetectable amounts after tumor resection.[7, 8, 11] Our multicenter investigation of a large population verified the disappearance of constitutional signs in patients with myxoma after tumor resection. Furthermore, when serum IL-6 was not elevated, constitutional signs were uncommon (one case). Soeparwata *et al.* reported a significant correlation between plasma IL-6 and tumor size in patients with myxoma.[16] In our study, patients with myxoma with constitutional signs had significantly larger tumors than patients without constitutional signs. These results might suggest that production of IL-6 increases in proportion to tumor size, and that constitutional signs result when IL-6 concentrations exceed a certain threshold. If elevation of IL-6 is not seen in patients with large tumor, the tumor may not be myxoma. Thus, we speculate that the measurements of IL-6 are helpful in selected cases of cardiac tumors with large size to distinguish between myxoma and other cardiac tumors.

Cardiac myxoma is histologically benign, but sometimes this tumor has multicentric origin as documented by both multiple and recurrent myxoma. Tumors with these features sometimes are referred to "complex" myxomas.[17] Such complex myxomas have been reported to show more constitutional signs than the simple type.[18] In our study, we confirmed that patients with myxoma with multicentric tumor origin frequently showed constitutional signs, and that serum IL-6 elevations were common in patients with such signs. If patients with "complex" myxoma have high circulating concentrations of IL-6, constitutional signs or measurement of serum IL-6 could be used to monitor patients for recurrences.

TABLE III Clinical characteristics of patients with myxoma with and without constitutional signs

	Constitutional positive (n = 90)	Constitutional negative (n = 92)	p Value
Age (years)	57 ± 15	59 ± 14	NS
Gender (M/F)	28 / 62	30 / 62	NS
Tumor size (mm)	40 ± 17	32 ± 13	< 0.001
Single LA site (%)	74 (82)	84 (91)	NS
Single except LA site (%)	11 (12)	7 (8)	NS
Multicentric origin (%)	7 (8)	1 (1)	< 0.05
Thrombosis (%)	14 (16)	15 (16)	NS
Elevated IL-6 (%)	12 / 13 (92)	0 / 13 (0)	< 0.0001

Data are expressed as mean value ± standard deviation or number (%) of patients.

Abbreviations: Constitutional positive = the group of myxoma patients with constitutional signs, Constitutional negative = the group of myxoma patients without constitutional signs, M = male, F = female, LA = left atrium, Single LA site = single tumor existed only in LA site, Single except LA site = single tumor existed except for LA site, Multicentric origin = multiple or recurrent myxomas, IL-6 = interleukin-6, NS = not significant.

Limitations

Several limitations are present in this study. First, since this is a retrospective multicenter survey, some cases had incomplete data. Therefore, we could not classify all patients with myxoma into groups with or without constitutional signs, leaving some patients in an undetermined category. Second, serum IL-6 was measured only in a small number of patients; therefore, we could not determine direct relationships between constitutional signs and IL-6. To verify our results, a prospective multicenter study is necessary.

Conclusions

We investigated 249 patients with primary cardiac tumors that were diagnosed histologically between 1993 and 1996. About half of patients with myxoma exhibited constitutional signs. All of these features disappeared after tumor removal. Patients with myxoma with constitutional signs had larger tumor size and more frequent multicentric origin than those without constitutional signs.

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