

## Cardiac Myxoma: Its Origin and Tumor Characteristics

Jun Amano, MD, PhD, Tetsuya Kono, MD, PhD, Yuko Wada, MD,  
Tianshu Zhang, MD, PhD, Naohiko Koide, MD, PhD, Minoru Fujimori, MD, PhD,  
and Ken-ichi Ito, MD, PhD

Cardiac myxoma is most common among primary cardiac tumors, and its origin and tumor characteristics have been gradually elucidated by recent advances in molecular biology. Prichard's structure in the interatrial septum which was reported to be a candidate for the origin of cardiac myxoma, was revealed to be age-related changes. In hereditary cardiac myxoma "Carney complex", chromosomal abnormalities involving chromosomes 2p, 12 and 17q have been reported, however, no genetic abnormalities of these locus were found in the development of sporadic cases. Cardiac myxoma has multiple differentiating potentials, and recently various amounts of cardiomyocyte-specific transcription factor genes were identified. This indicates that cardiac myxoma might arise from mesenchymal cardiomyocyte progenitor cells. Various cytokines and growth factors such as vascular endothelial growth factor, basic fibroblast growth factor, monocyte chemoattractant protein-1 and interleukin-6 were involved in tumor growth and angiogenesis. Although cardiac myxoma usually presents as a benign neoplasm, reports suggesting its malignancy, including recurrence of the tumor, locally invasive myxoma, extension from the heart, and distant metastasis are increasing.

These genetic and molecular approaches to cardiac myxoma may prompt the development of therapeutic modalities for treatment of malignancies and cardiac cell regeneration. (*Ann Thorac Cardiovasc Surg* 2003; 9: 215–21)

**Key words:** cardiac myxoma, Carney complex, angiogenesis, cytokine

### Introduction

Primary tumors of the heart are rare, however, among them cardiac myxoma is the most common tumor accounting for half of the primary cardiac neoplasms.<sup>1,2</sup> About 75% of cardiac myxomas are located in the left atrium, and 25% are located in the right atrium. These are thought to be arising from remnants of subendocardial vasoformative reserve cells or multipotential primitive mesenchymal cells in the fossa ovalis and surrounding endocar-

dium, which can differentiate along a variety of cell lineages including epithelial, hematopoietic, and muscle cells.<sup>1,2</sup> Although some cases are discovered incidentally by echocardiographic examination, it was recognized in most of the patients by various symptoms caused by the release of inflammatory cytokines such as interleukin-6 (IL-6), obstruction of intracardiac blood flow, or embolization.<sup>3,4</sup> Cardiac myxoma has many undetermined interesting issues about its origin, nature as a tumor, varying clinical manifestations, and the presence of both sporadic and familial types. Recent evidence revealed that cardiac myxomas are benign neoplasms and slowly proliferating lesions. The existence of its malignant counterpart is controversial, however, recurrence after surgical excision or metastasis is reported. This review provides current knowledge of the origin of cardiac myxoma and its tumor characteristics.

*From Department of Surgery, Shinshu University School of Medicine, Nagano, Japan*

Received June 9, 2003; accepted for publication June 20, 2003.  
Address reprint requests to Jun Amano, MD, PhD: Division of Cardiovascular Surgery, Department of Surgery, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan.

## Origin of Cardiac Myxoma

In search for candidate cells or tissues as precursor cells of cardiac myxoma, in 1951 Prichard described a kind of microscopic endocardial structure of the atrial septum, which was suggested to be related to cardiac myxomas.<sup>5</sup> To confirm the existence of Prichard's structures and to clarify their role in the genesis of cardiac myxomas, Acebo et al. examined histologically the fossa ovalis and performed an immunohistochemical study of the endocardial abnormalities.<sup>6</sup> Histological study of 100 atrial septa and an immunohistochemical study of three out of the 12 endocardial abnormalities that were detected, as well as of four conventional cardiac myxomas were accomplished. Antibodies were used to detect vimentin, CD31, CD34, alpha-smooth muscle actin, S100 protein, thrombomodulin, calretinin and c-kit (CD117), and a tyrosine kinase growth factor receptor for stem cell factor usually expressed by embryonic/fetal endothelium. They found structures similar to the ones described by Prichard in 12% of septa, most of them in the left side of the fossa ovalis. The hearts with these structures were from patients 10 years older than the ones without them ( $72 \pm 10$  versus  $62 \pm 16$  years,  $P=0.006$ ). Immunohistochemically the cells comprising Prichard's structures were positive for vimentin, CD31, CD34 and thrombomodulin, and negative for alpha-smooth muscle actin, S100 protein, calretinin and c-kit. Therefore, these cells seem to be mature endothelial cells, but not primitive multipotential mesenchymal cells. Furthermore, these cells were not found in the atrial tissue from the bases of any of cardiac myxomas. From these results, they concluded that there is no apparent relation between Prichard's structures and cardiac myxomas, and that Prichard's minute endocardial deformities are age-related phenomena. Even from this meticulous study, the presence of nests of pluripotent primitive mesenchymal cells in the interatrial septum are still mysterious, and a search for primitive cells differentiating myxoma cells should be continued.

## Genetic Abnormalities in Cardiac Myxoma

Most sporadic cardiac myxomas arise as an isolated left atrial mass from the fossa ovalis in middle-aged women.<sup>7</sup> However, approximately 7% of cardiac myxomas arise as components of a heritable disorder with spotty pigmentation of the skin and endocrinopathy, which is recently referred as Carney complex.<sup>8,9</sup> Carney complex is an autosomal dominant disorder and is previously de-

scribed cardiac myxoma syndromes such as LAMB (lentiginos, atrial myxoma, mucocutaneous myxomas and blue nevi)<sup>10</sup> and NAME (nevi, atrial myxoma, mucinosis of the skin and endocrine overactivity).<sup>11</sup> Carney complex myxomas may be single or multiple and frequently recur in the initial resection site and also distant to the initial operative site.<sup>12,13</sup> In Japan, several cases of Carney complex have been reported.<sup>14,15</sup> Carney complex myxomas have been shown to have heterogenous clonal telomeric rearrangements and other chromosomal abnormalities primarily involving chromosomes 2p16, 12 and 17q22-24.<sup>16</sup> Using linkage analysis, Stratakis et al. identified several families affected by the disorder and proposed that an unidentified gene defect resided within a 6.4-cM interval on chromosome 2p.<sup>16</sup> Basson et al. subsequently demonstrated that the syndrome is genetically heterogeneous, that a chromosome 2p locus cannot account for all Carney complex families,<sup>17</sup> and that a major genetic locus for Carney complex maps to chromosome 17q2.<sup>18</sup> Most recently, Casey et al. have demonstrated that mutations in the *PRKAR1 $\alpha$*  gene encoding the R1 $\alpha$  regulatory subunit of cAMP-dependent protein kinase A cause autosomal dominant Carney complex.<sup>19</sup> All mutations identified to date produce *PRKAR1 $\alpha$*  haploinsufficiency, and therefore diminished *PRKAR1 $\alpha$*  gene dose, and the consequent reduction in protein results in a predisposition to cardiac tumorigenesis. Although *PRKAR1 $\alpha$*  is thought to function in this disorder as a tumor suppressor gene, other interacting gene products are candidates to be studied for somatic mutation in Carney complex tumors.

In contrast to the study for searching for genetic abnormalities in Carney complex, Dijkhuizen et al. performed cytogenetic analysis on 2p16 and 17q2 in 15 sporadic cardiac myxomas.<sup>20</sup> Ten of these cases revealed abnormal karyotypes with clonal and nonclonal rearrangements including dicentric chromosomes and telomeric associations. However, no cytogenetic evidence was found for a role of 2p16 in the development of sporadic cases. Region 17q2 was involved in structural rearrangements, but to a lesser extent than other regions. They concluded that structural rearrangements involving regions 12p1 and 17p1 are more frequently present, and might therefore harbor important genes for the development of sporadic cardiac myxomas. Fogt et al. also analyzed sporadic cardiac myxomas to evaluate whether the genetic alterations seen in Carney complex are present in non-Carney complex cardiac myxoma.<sup>21</sup> They studied microdissected material from 13 patients with cardiac myxomas for the mark-

ers PRKAR1 9CA, D2S2153, D2S2251 and D2S123. None of the cases demonstrated loss of heterozygosity or definite band changes suggestive of microsatellite instability for any of the markers used. They conclude that sporadic cardiac myxomas are genetically not related to Carney complex, and genetic alterations of Carney complex are not present in sporadic cardiac myxomas. However, identification of PRKAR1 $\alpha$  mutations that cause cardiac myxomas provides insight into basic intracellular signaling pathways that regulate cardiac growth and differentiation. Manipulation of such protein kinase-dependent pathways suggests therapeutic options to target cardiomyocyte regeneration in the myopathic heart, or therapeutic modalities for malignancies.

### Multiple Potential Differentiations in Cardiac Myxoma

In the course of tumor generation and its growth, multiple potentials of differentiation toward a variety of cells such as endothelial, fibroblastic, hematopoietic, glandular, neurogenic and smooth muscle cells have been reported.<sup>22)</sup> Recently, Kodama et al. investigated five cases of cardiac myxoma and one case of cardiac undifferentiated sarcoma by light and electron microscopy, in situ hybridization, immunohistochemical staining, and reverse transcriptase-polymerase chain reaction for cardiomyocyte-specific transcription factors, Nkx2.5/Csx, GATA-4, MEF2, and eHAND.<sup>23)</sup> Immunohistochemistry for Nkx2.5/Csx, GATA-4, and eHAND was slightly to intensely positive in all myxoma cases. MEF2 immunoreactivity was observed in all cases including the case of sarcoma, thus suggesting myogenic differentiation of myxoma or sarcoma cells. In situ hybridization for Nkx2.5/Csx also revealed that all myxoma cells, but not sarcoma cells, expressed mRNA of Nkx2.5/Csx. Furthermore, nested reverse transcriptase-polymerase chain reaction demonstrated that the Nkx2.5/Csx and eHAND gene product were detected in all cases, and in three of six cases, respectively. They concluded that cardiac myxoma cells were found to express various amounts of cardiomyocyte-specific transcription factor gene products at the mRNA and protein levels, thus suggesting the concept that cardiac myxoma might arise from mesenchymal cardiomyocyte progenitor cells. All these reports studying tumor origin by specific antigen expression may reflect one facet of the tumor, and in a neoplasm originating from multipotential primitive mesenchymal cells, phenotypic expression may be variable and does not nec-

essarily reflect the tumor origin.

### Angiogenesis and Proliferation of Cardiac Myxoma

Angiogenesis is a complex biological process regulated by a number of cytokines or growth factors secreted by tumor and/or stromal cells, and is indispensable to tumor development and proliferation. We evaluated the association between angiogenesis and the clinicopathologic features in cardiac myxoma, vascular endothelial growth factor (VEGF) expression by using reverse transcriptase polymerase chain reaction and immunohistochemistry, and the microvessel density.<sup>24)</sup> All of the seven analyzed myxomas were positive for VEGF mRNA, whereas atrial septum and atrium tissues were negative. Positive immunohistochemical reaction for VEGF was also observed in the cells of all 15 myxomas. The size of myxomas with high VEGF expression was smaller than that of myxomas with low VEGF expression. The microvessel density in myxomas with high VEGF expression was greater than that in myxomas with low VEGF expression. There was an inverse correlation between the tumor size and the ratio of the microvessel density in the central part to the microvessel density in the peripheral part of myxomas. Furthermore, there was an inverse correlation between PCNA (proliferating cell nuclear antigen)-labeling index and the tumor size, and the PCNA-labeling index in myxomas with high VEGF expression was higher than that in myxomas with low VEGF expression. These data suggested that cardiac myxomas produce VEGF, which probably induces angiogenesis for tumor growth.

We also studied expression of basic fibroblast growth factor (bFGF) and its receptor-1 (FGFR-1) in cardiac myxoma to evaluate the significance of bFGF in angiogenesis and proliferative activity, the expression of bFGF and FGFR-1 were immunohistochemically examined.<sup>25)</sup> Basic FGF and FGFR-1 were observed in 73.3% and 67.7% of the myxomas, respectively. There was a close correlation between the expression of bFGF and FGFR-1. This co-expression was frequently observed in the myxoma cells around the microvessels appearing as a ring structure. The microvessel density in the myxomas with bFGF or FGFR-1 expression was higher than that in myxomas without it. The PCNA-labeling index in myxomas with bFGF expression was higher than that in myxomas without it, and the PCNA labeling index tended to be higher in myxomas with FGFR-1 expression than that in myxomas without it. From these data, bFGF and/or

FGFR-1 was expressed in some cardiac myxomas, and may be an important role for tumor angiogenesis and proliferative activity.

Another of our studies was to examine whether the expression of monocyte chemotactic protein-1 (MCP-1) and of thymidine phosphorylase (TP) correlates with the angiogenesis and clinicopathologic features in cardiac myxoma.<sup>26)</sup> Paraffin-embedded specimens of 17 resected cardiac myxomas were immunohistochemically stained for MCP-1, CC chemokine receptor-2 (CCR-2), TP, CD31, and CD68. Immunohistochemical analysis revealed that MCP-1 and TP were expressed in myxoma cells, as well as in stromal cells such as infiltrating cells, fibroblast-like cells and endothelial cells. CCR-2 was abundantly expressed in stromal infiltrating cells in all myxomas and occasionally in the endothelial cells. In the tumor stroma, the major sources of MCP-1, TP and CCR-2 were macrophages, and the sites of positive staining for MCP-1, TP and CCR-2 matched in most of the myxomas. The proportions of MCP-1-positive myxoma and stromal cells, and TP-positive myxoma and stromal cells significantly correlated with an increased microvessel count. And also the proportions of MCP-1-positive myxoma and stromal cells significantly correlated with the proportion of TP-positive stromal cells. Small tumors ( $\leq 55$  mm in diameter) exhibited high MCP-1 or TP expression, and the microvessel count in small tumors was significantly higher than in large myxomas. These results indicate that in cardiac myxoma, MCP-1 and TP may be regarded as important angiogenic signals.

Since the initial report of Hirano et al., many other studies have confirmed that cardiac myxomas produce IL-6 constitutively, which is a possible explanation for the inflammatory and immune features observed in patients with this tumor.<sup>27)</sup> Interleukin-6 is a multifactorial cytokine that produces differentiation and proliferation of normal and malignant cells, induction of the acute-phase response and fever. Mendoza et al. studied the correlation of IL-6 serum levels with preoperative constitutional symptoms and immunologic abnormalities, and the possible role played by this cytokine in tumor recurrence.<sup>28)</sup> They measured IL-6 serum levels by enzyme-linked immunosorbent assay method preoperatively, and one and six months after surgery in eight consecutive patients with nonfamilial myxoma. Two of the cases involved recurrent tumor; one patient had undergone his first surgery at a different institution and died during the second procedure, so his data were incomplete. Although patients with a first occurrence of tumor demonstrated a

positive correlation between IL-6 serum level and tumor size, the two patients with recurrent tumors appeared to have higher IL-6 levels regardless of tumor size. Once the tumor was surgically removed, IL-6 levels returned to normal values, and this was associated with regression of clinical manifestations and immunologic features. According to this study, the overproduction of IL-6 by cardiac myxomas is responsible for the constitutional symptoms and immunologic abnormalities observed in patients with such tumors, and might also play a role as a marker of recurrence. This study also suggests that recurrent cardiac myxomas form a subgroup of cardiac myxomas with a highly intrinsic aggressiveness, as implied by their greater IL-6 production despite their smaller size.

There are vascular myosin heavy chain isoforms; SM2 expression is specific to mature smooth muscle cells, while SMemb is a nonmuscle-type isoform which is expressed in immature mesenchyme cells.<sup>29)</sup> We studied in situ IL-6 transcription in embryonic nonmuscle myosin heavy chain expressing immature mesenchyme cells of cardiac myxoma.<sup>30)</sup> Expression of SMemb in cardiac myxoma was increased but SM2 expression was not in the vascular-like channels of myxoma. Increased IL-6 transcription was observed in the SMemb expressing cells in the channel. Therefore, mesenchymal cells with immature phenotype in the vascular-channels may play a pivotal role in the inflammatory responses and vasculogenesis of cardiac myxoma.

### **Malignant Character in Cardiac Myxoma**

Although cardiac myxomas usually present as a benign neoplasm, there are many reports suggesting its malignancy, including recurrence of the tumor, locally invasive myxoma, extension from the heart, and distant metastasis or peripheral tumor mass.<sup>31-36)</sup> Cardiac myxomas are generally thought curable by surgical resection of the primary tumor, but recurrence can occur at the site of the original tumor, at multiple intracardiac lesions, and at sites outside the heart. Recurrence of cardiac myxoma has been observed in about 3% of patients in sporadic cases, and 20% in Carney complex. Cardiac recurrence may be secondary to incomplete resection of the tumor, implantation from the original tumor, unrecognized multicentric origin, or the new growth of pretumor or reserve cells.<sup>31)</sup> These recurrences may grow faster and be more infiltrative than the original tumor. Gerbode et al. first reported recurrence of left atrial myxoma four years after initial

excision.<sup>32)</sup> They postulated incomplete removal at the first operation and recommended wide resection of the interatrial septum around the base or stalk of the tumor. In English literature, Shinfeld et al. collected 584 patients with cardiac myxomas and found 42 patients with first recurrence, and they found very few cases (1.3%) of repeated recurrence.<sup>33)</sup> They reported the age range at the time of first surgical resection was 7 to 62 years (mean, 32.7 years), and reoperation was performed at between 3 months and 14 years afterwards (average, 3.9 years). Of the 42 cases of recurrence after left atrial myxoma, the second tumor appeared in the left atrium in 83%, in the right atrium in 14%, and at other sites in the heart in 7%. The tumor recurred at, or close to, the original site of the left atrium in 85% of cases.

Tumor emboli may go to any vascular bed and tumor cells may remain viable at the site of embolization, thus forming distant metastasis or peripheral tumor mass. As a benign tumor character of cardiac myxoma and tumor location of it in the cardiac chamber, its metastasis is usually intravascular and present delayed occurrence after resection of the cardiac lesion. Dang and Hurley pointed out that malignancy of atrial myxomas is predicated on biologic behavior rather than on histologic appearance.<sup>37)</sup> Read et al. described a case of metastatic myxoma to soft tissue and bone.<sup>38)</sup> Cerebral metastasis from myxoma has also been reported.<sup>38)</sup> Wada et al. reported a case of a 70-year-old man who had an atrial myxoma and two metastatic myxomas in the brain.<sup>39)</sup> The intracranial lesions were in fact diagnosed before the cardiac myxoma, since the patient developed hemiparesis before his cardiac symptoms occurred. Histopathological examination showed all lesions to be benign myxomas. Interestingly, high concentrations of IL-6 were present in the patient's serum and cardiac myxoma. Thus, they suggested that IL-6 may possibly potentiate metastasis of cardiac myxoma. Failure of constitutional symptoms to resolve and of elevated gamma globulins and sedimentation rates to return to normal after technically successful resection of a primary cardiac tumor may suggest residual extracardiac tumor and may serve as a means of identifying the malignant cardiac myxoma.

The potential for malignant change in cardiac myxoma is controversial. Shinfeld et al. reported same-site recurrence with more aggressive histology, then second recurrence with multiple smaller myxomas elsewhere in the left atrium.<sup>33)</sup> Although the first lesion was typically benign, the second recurrence was clearly malignant, and the patient died with extensive left atrial sarcoma. Se-

quential malignant transformation of cardiac myxoma is very rare. Kasugai et al. reported a 44-year-old Japanese man, who died after developing metastases in the skin, brain and muscle.<sup>40)</sup> Although the primary heart tumor showed typical benign cardiac myxoma, the recurrent cardiac tumor, which was partly resected three months before the patient's death, showed apparently malignant characteristics resembling malignant fibrous histiocytoma (MFH). A gradual but significant increase in the cellularity was observed over the course of five years. Immunohistochemically, tumor cells in the muscle metastasis contained vimentin and factor VIII-related antigen, and multinucleated giant cells in the recurrent heart tumor contained desmin, which is rarely detectable in MFH. Therefore, they speculated that the present case represented malignant transformation of benign cardiac myxoma. Kaynak et al. also reported a 22-year-old woman who had a history of three cardiac operations for resection myxoma and a bilateral femoral embolectomy for recurrent cardiac myxoma and myxoma embolism, who was admitted to the hospital with multiple immobile peripheral masses.<sup>41)</sup> The mass in the left inguinal region was extirpated and chemotherapy was effective to the inoperable other masses. Pathological examination of the inguinal mass revealed myxoma showing malignant features such as pleomorphism, prominent mitotic activation and perineural invasion. Some authors feel that although emboli from myxomas do occur, vascular invasion by myxomatous emboli is highly unlikely in view of a benign histology. There is controversy as to whether invasive cases of myxoma have been a misdiagnosed case of myxosarcoma, chondrosarcoma, fibromyxosarcoma, or MFH. Microscopic features which should suggest that a malignant tumor is mimicking a myxoma include direct cardiac muscle invasion by tumor, increased cellular pleomorphism in the area of muscle invasion, and abnormal mitoses.

In addition to these clinical and biological behaviors of a cardiac myxoma mimicking a malignant tumor, molecular approaches to evaluate the oncogenes or tumor suppressor genes have been reported. Suvarna and Royds evaluated 10 archive cases of cardiac myxoma for proliferative activity, metastatic potential and expression of oncogene/tumor suppressor gene products by means of PCNA, MIB1, nm23, p53, Bcl-2 and Rb-1 immunohistochemistry.<sup>42)</sup> The myxomas showed variable proliferative activity (PCNA 0-41%, average 12.6%; MIB1 0-13%, average 3.2%) contrasting with the absence of mitotic activity histologically. All the myxomas showed nm23

staining. None showed p53 reactivity. Eight cases were negative for Bcl-2 expression, with two cases giving weak cytoplasmic staining. Rb-1 reactivity showed a variable pattern (staining indices 0-86%) paralleling the cases with proliferative activity. The cardiac myxoma is interpreted as a weakly proliferative lesion with little metastatic potential and no modulation of oncogene/oncogene suppressor products. They concluded that whilst not excluding a neoplastic aetiology, cardiac myxomas are considered more in keeping with a reactive/hamartomatous process. Karga et al. also evaluated ras oncogenes and p53 tumor suppressor gene mutations in cardiac myxoma.<sup>43</sup> Paraffin-embedded tissues from 19 cardiac myxomas were investigated for the presence of ras oncogenes and p53 tumor suppressor gene abnormalities. Immunohistochemical analysis was used to identify the accumulation of p21-ras and p53 proteins. A polymerase chain reaction was used to amplify exons 1 and 2 of the ras genes and exons 5 to 8 of the p53 gene. The PCR products were analyzed by single strand conformation polymorphism analysis and by direct DNA sequencing. Three of 19 myxomas showed strong positive staining for the ras p21 protein. In contrast, nuclear p53 was not detectable in any of the myxomas. Among the ras p21 immunopositive myxomas, 2 were heterozygous for a missense point mutation of the K-ras, Gly 12 Asp. Further screening of the remaining myxomas showed no mutation or even silent polymorphism in any exon of the ras and p53. They concluded that although genetic alterations of ras oncogenes and p53 are uncommon events in cardiac myxomas, ras mutations may be involved in the pathogenesis of a subgroup of this type of tumor.

### Future Aspects in Cardiac Myxoma

The origin of cardiac myxomas is still unknown. To search for a possible candidate for a mesenchymal progenitor cell in the interatrial septum, further histological and molecular approaches are necessary. In Carney complex, genetic abnormalities are gradually elucidated, however, it should be addressed whether genetic instability is present in sporadic myxoma. Such studies searching for new oncogenes or tumor suppressor genes in cardiac myxoma may contribute to develop therapeutic modalities for malignancy. Malignant transformation or presence of malignant myxoma are still controversial. Although such malignant type of cardiac myxomas are reported, histological diagnosis of the primary tumor is very important to differentiate from other malignant cardiac

tumors or metastatic cardiac tumors. Cardiac myxoma cells have multiple potentials of differentiation and produce growth factors and cytokines. From the studies of these tumor characteristics, cardiac myxoma cells can be used for cardiac cell regeneration.

Most of the studies on cardiac myxoma were targeted at myxoma cells themselves, and the quantitative and qualitative analyses of gelatinous matrix occupying most of the tumor tissue were rare. The study on the composition of extracellular matrix may contribute to evaluate the mechanisms of tumor growth, recurrence of cardiac myxoma or malignant potential of histologically benign cardiac myxoma.

### References

1. Reynen K. Cardiac myxomas. *N Engl J Med* 1995; **333**: 1610–17.
2. Blondeau P. Primary cardiac tumors: French studies of 533 cases. *Thorac Cardiovasc Surg* 1990; **38** (Suppl 2): 192–5.
3. Molina JE, Edwards JE, Ward HB. Primary cardiac tumors: experience at the University of Minnesota. *Thorac Cardiovasc Surg* 1990; **38** (Suppl 2): 183–91.
4. Centofanti P, Rosa ED, Deorsola L, et al. Primary cardiac tumors: early and late results of surgical treatment in 91 patients. *Ann Thorac Surg* 1999; **68**: 1236–41.
5. Prichard RW. Tumors of the heart: review of the subject and report of one hundred and fifty cases. *Arch Pathol* 1951; **51**: 98–128.
6. Acebo E, Val-Benal JF, J J Gómez-Román. Prichard's structures of the fossa ovalis are not histogenetically related to cardiac myxoma. *Histopathology* 2001; **39**: 529–35.
7. Yoon DHA, Roberts WC. Sex distribution in cardiac myxomas. *Am J Cardiol* 2002; **90**: 563–5.
8. Carney JA, Hruska L, Beauchamp GD. Dominant inheritance of the complex of myxomas, spotty pigmentation and endocrine overactivity. *Mayo Clin Proc* 1986; **61**: 165–72.
9. Carney JA, Ferreiro JA. The epitheloid blue nevus. A multicentric familial tumor with important associations, including cardiac myxoma and psammomatous melanotic schwannoma. *Am J Surg Pathol* 1996; **20**: 259–72.
10. Rhodes AR, Silverman RA, Harrant TJ, et al. Mucocutaneous lentiginosities, cardiocutaneous myxomas, and multiple blue nevi: the "LAMB" syndrome. *J Am Acad Dermatol* 1984; **10**: 72–82.
11. Koopman RJ, Happle R. Autosomal dominant transmission of the NAME syndrome (nevi, atrial myxoma, mucinosis of the skin, and endocrine overactivity). *Hum Genet* 1991; **86**: 300–4.
12. McCarthy PM, Piehler JM, Schaff HV, et al. The significance of multiple, recurrent, and "complex" car-

- diac myxomas. *J Thorac Cardiovasc Surg* 1986; **91**: 389–96.
13. Carney JA. Differences between nonfamilial and familial cardiac myxoma. *Am J Surg Pathol* 1985; **9**: 53–5.
  14. Yokomuro H, Takanashi Y, Suzuki N, Yoshihara K, Koyama N, Komatsu H. A case of “familial” type cardiac myxoma. *Nippon Kyobu Geka Gakkai Zasshi* 1994; **42**: 427–32. (in Japanese)
  15. Ohshima N, Yamada T, Nakahara H, et al. Familial cardiac myxoma with multiple and contralateral recurrence. *Kyobu Geka* 1990; **43**: 1060–6.
  16. Stratakis CA, Carney JA, Lin JP, et al. Carney complex, a familial multiple neoplasia and lentiginosis syndrome: analysis of 11 kindreds and linkage to the short arm of chromosome 2. *J Clin Invest* 1996; **97**: 699–705.
  17. Basson CT, MacRae CA, Korf B, et al. Genetic heterogeneity of familial atrial myxoma syndromes (Carney complex). *Am J Cardiol* 1997; **79**: 994–5.
  18. Casey M, Mah C, Merliss AD, et al. Identification of a novel genetic locus for familial cardiac myxomas and Carney complex. *Circulation* 1998; **98**: 2560–6.
  19. Casey M, Vaughan CJ, He J, et al. Mutations in the protein kinase A R1 alpha regulatory subunit cause familial cardiac myxomas and Carney complex. *J Clin Invest* 2000; **106**: R31–8.
  20. Dijkhuizen T, de Jong B, Meuzelaar JJ, Molenaar WM, van den Berg E. No cytogenetic evidence for involvement of gene(s) at 2p16 in sporadic cardiac myxomas: cytogenetic changes in ten sporadic cardiac myxomas. *Cancer Genet Cytogenet* 2001; **126**: 162–5.
  21. Fogt F, Zimmerman RL, Hartmann CJ, Brown CA, Narula N. Genetic alterations of Carney complex are not present in sporadic cardiac myxomas. *Int J Mol Med* 2002; **9**: 59–60.
  22. Lindner V, Edah-Tally S, Chakfe N, Onody T, Eisenmann B, Walter P. Cardiac myxoma with glandular component: case report and review of the literature. *Pathol Res Pract* 1999; **195**: 267–72.
  23. Kodama H, Hirotsu T, Suzuki Y, Ogawa S, Yamazaki K. Cardiomyogenic differentiation in cardiac myxoma expressing lineage-specific transcription factors. *Am J Pathol* 2002; **161**: 381–9.
  24. Kono T, Koide N, Hama Y, et al. Expression of vascular endothelial growth factor and angiogenesis in cardiac myxoma: a study of fifteen patients. *J Thorac Cardiovasc Surg* 2000; **119**: 101–7.
  25. Fujisawa H, Koide N, Kono T, et al. Expression of basic fibroblast growth factor and its receptor-1 in cardiac myxoma. *J Cardiovasc Surg (Torino)* 2002; **43**: 589–94.
  26. Zhang T, Koide N, Wada Y, et al. Significance of monocyte chemoattractant protein-1 and thymidine phosphorylase in angiogenesis of human cardiac myxoma. *Circ J* 2003; **67**: 54–60.
  27. Hirano T, Taga T, Yasukawa K, et al. Human B-cell differentiation factor defined by an anti-peptide antibody and its possible role in autoantibody production. *Proc Natl Acad Sci U S A* 1987; **84**: 228–31.
  28. Mendoza CE, Rosado MF, Bernal L. The role of interleukin-6 in cases of cardiac myxoma. Clinical features, immunologic abnormalities, and a possible role in recurrence. *Tex Heart Inst J* 2001; **28**: 3–7.
  29. Nagai R, Kuro-o M, Babij P, Periasamy M. Identification of two types of smooth muscle myosin heavy chain isoforms by cDNA cloning and immunoblot analysis. *J Biol Chem* 1989; **264**: 9734–7.
  30. Suzuki J, Takayama K, Mitsui F, et al. In situ interleukin-6 transcription in embryonic nonmuscle myosin heavy chain expressing immature mesenchyme cells of cardiac myxoma. *Cardiovasc Pathol* 2000; **9**: 33–7.
  31. Gray IR, Williams WG. Recurring cardiac myxoma. *Br Med J* 1985; **53**: 645–9.
  32. Gerbode F, Kerth WJ, Hill JD. Surgical management of tumors of the heart. *Surgery* 1967; **61**: 94–101.
  33. Shinfeld A, Katsumata T, Westaby S. Recurrent cardiac myxoma: seeding or multifocal disease? *Ann Thorac Surg* 1998; **66**: 285–8.
  34. Hannah H, Eisemann G, Hyszczynskij R, Winsky M, Cohen L. Invasive atrial myxoma: documentation of malignant potential of cardiac myxomas. *Am Heart J* 1982; **104**: 881–3.
  35. Markel ML, Armstrong WF, Waller BF, Mahomed Y. Left atrial myxoma with multicentric recurrence and evidence of metastases. *Am Heart J* 1986; **111**: 409–13.
  36. Hou YC, Chang S, Lo HM, Hsiao CH, Lin FY. Recurrent cardiac myxoma with multiple distant metastasis and malignant change. *J Formos Med Assoc* 2001; **100**: 63–5.
  37. Dang CR, Hurley EJ. Contralateral recurrent myxoma of the heart. *Ann Thorac Surg* 1976; **21**: 59–62.
  38. Read RC, White HJ, Murphy ML, Williams D, Sun CN, Flanagan WH. The malignant potentiality of left atrial myxoma. *J Thorac Cardiovasc Surg* 1974; **68**: 857–68.
  39. Wada A, Kanda T, Hayashi R, Imai S, Suzuki T, Murata K. Cardiac myxoma metastasized to the brain: potential role of endogenous interleukin-6. *Cardiology* 1993; **83**: 208–11.
  40. Kasugai T, Sakurai M, Yutani C, et al. Sequential malignant transformation of cardiac myxoma. *Acta Pathol Jpn* 1990; **40**: 687–92.
  41. Kaynak K, Besirli K, Arslan C, Ozguroglu M, Oz B. Metastatic cardiac myxoma. *Ann Thorac Surg* 2001; **72**: 623–5.
  42. Suvarna SK, Royds JA. The nature of the cardiac myxoma. *Int J Cardiol* 1996; **57**: 211–6.
  43. Karga H, Papaioannou P, Karayianni M, et al. Ras oncogenes and p53 tumor suppressor gene analysis in cardiac myxomas. *Pathol Res Pract* 2000; **196**: 601–5.