A Case of Interleukin-6-producing Malignant Fibrous Histiocytoma Originating in the Heart

Hitoshi Deguchi¹, Bunzo Sato¹, Masato Ohshima², Asao Seki², Masahiro Yamamoto¹, Hiroshi Naito³, Naoki Nishida⁴, Chikao Yutani⁴ and Soichiro Kitamura⁵

¹Third Department of Internal Medicine and ²Department of Pathology, Nissay Hospital, Nippon Life Saiseikai Foundation, Osaka, ³Third Department of Surgery, Nara Medical University, Kashihara, Nara and Departments of ⁴Pathology and ⁵Surgery, National Cardiovascular Center, Suita, Osaka, Japan

Primary cardiac malignant fibrous histiocytoma is extremely rare and its pathophysiological characteristics remain largely unknown. We treated a female patient with persistent fever and disseminated intravascular coagulation. Since ultrasonic echocardiography revealed the presence of a cardiac tumor and her serum interleukin-6 level was elevated, we speculated she had a cardiac myxoma. Histological examination of the surgically resected specimen, however, revealed that the tumor was malignant fibrous histiocytoma. Although her disseminated intravascular coagulation and heart failure were transiently improved after operation, local recurrence and systemic metastasis occurred and she died 7 weeks after operation. Using the autopsied specimen, we examined whether the malignant fibrous histiocytoma constitutively synthesized interleukin-6. The interleukin-6 content in the tumor was high, consistent with interleukin-6 production by the tumor. This was confirmed by immunohistochemical analysis. To our knowledge, this is the first report demonstrating interleukin-6 production by a cardiac malignant fibrous histiocytoma.

Key words: malignant fibrous histiocytoma – primary cardiac tumor – disseminated intravascular coagulation – interleukin-6

INTRODUCTION

In this paper, we present the first evidence that a primary cardiac malignant fibrous histiocytoma (MFH) can constitutively produce IL-6. This production of IL-6 may have been related to the systemic symptoms of the affected patient. Primary cardiac tumors are less frequent than those metastatic to the heart. It is estimated that the ratio of primary to metastatic tumors in the heart falls somewhere between 1:20 and 1:40. Some estimate that the ratio could be as low as 1:500. One-third of primary cardiac tumors are malignant (35%, 137/386) and most malignant tumors are sarcomas (95%, 137/144). The frequency of MFH among primary cardiac sarcomas is 11.7% (16/137), making MFH the second most common primary cardiac sarcoma (1).

Pathologically, the concept and definition of MFH have changed. The prevailing understanding is that MFH does not necessarily express a histiocytic phenotype. Rather, it is now established to be an undifferentiated fibrous tumor composed mainly of bizarre cells with a closer phenotypic link with fibroblasts (2). MFH is a malignant tumor of fibroblasts and pleomorphic histiocytoid cells that assume a characteristic storiform growth pattern in some areas of the tumor (1).

Although infrequently, earlier studies have demonstrated that any region can be the primary site of MFH (3,4). To date, only 38 cases of primary cardiac MFH have been reported (5–9). It is known that primary cardiac MFH most frequently originates in the left atrium (5–7), although a few cases occurring in the right or left ventricle have been reported (8,9). Over 90% arise in the left atrium, most commonly on the posterior wall. Because of this location, the symptoms of cardiac MFH are related to pulmonary congestion due to pulmonary vein obstruction, mitral stenosis, mitral regurgitation and right ventricular failure (1). In addition, patients with cardiac MFH reportedly exhibit systemic symptoms such as fever (6), the pathological mechanism of which remains unclear. Since cardiac myxoma has been demonstrated to elicit such systemic symptoms through interleukin-6 (IL-6) production (10,11), it would be useful to examine whether cardiac MFH can synthesize IL-6.
CASE REPORT

CLINICAL HISTORY

A 77-year-old Japanese female (135 cm, 35 kg) was admitted to our hospital because of chest discomfort and low-grade fever. Chest radiographs taken upon admission revealed right lower bronchogenic pneumonia and bilateral small pleural effusions with a cardiothoracic ratio (CTR) of 0.58. The patient's body temperature was 37.2°C and her blood pressure was 150/70 mmHg. The cardiac rhythm was atrial fibrillation with a ventricular rate of about 90 beats/min. A series of hematological and serum tests revealed that she also had slight anemia, thrombocytopenia (5.6 × 10^4/μl) and increased LDH (750 IU/l) and CRP (0.87 ng/ml). No other abnormalities in blood chemistry, including immunoglobulin level, were detected. While antibiotic therapy in conjunction with diuretics improved the pneumonia and heart failure, the platelet count continuously declined and low-grade fever persisted. Moreover, findings of decreased fibrinogen (143 mg/dl), increased fibrin degenerative products (FDP) (120 μg/ml) and D-dimer (9.8 mg/ml) as well as thrombocytopenia were suggestive of disseminated intravascular coagulation (DIC), the condition of which was improved by cardiac surgery.

Thrombocytopenia, which was apparent at the time of admission, progressed for 6 weeks and reached 2.4 × 10^4/μl. Ultrasonic echocardiography (UCG) and magnetic resonance imaging (MRI) revealed multiple cardiac tumors in the patient: a large tumor in the left atrium and a smaller one in the left ventricle (Fig. 1). Hexakis(2-methoxyisobutyl isonitrile)technetium cardiac scintigraphy revealed multiple myocardial hypoperfusion and cardiac failure [left ventricular ejection fraction (LVEF) of 59%].

A series of preoperative examinations (chest radiography, CT, MRI, abdominal ultrasonography, MRI and pelvic CT) detected no tumors in other sites including the ribs, liver and soft tissue, indicating that the patient's tumors originated in the heart. Her serum IL-6 level was 12 pg/ml (normal level <4.0 pg/ml). In view of the cardiac failure and the presence of therapy-resistant DIC, surgical resection was performed under the preoperative diagnosis of cardiac myxoma. The cardiac tumors were resected through atrioseptal and right-sided left atrial approaches (Fig. 2). The extirpation of cardiac tumors resulted in a remarkable improvement in her DIC: the platelet level gradually increased to 2.5 × 10^5/μl and FDP decreased to 10 μg/ml on the 14th postoperative day. However, local recurrence and multiple metastases to the liver, ribs and tonsils occurred with simultaneous reappearance of DIC 3 weeks after surgery. Adjuvant chemotherapy with cisplatin and etoposide was not effective. She died of cardiac failure due to tumor recurrence and systemic metastasis 7 weeks after surgery.

METHOD

IL-6 levels in the serum and the tumors were measured by a highly sensitive chemiluminescent enzyme immunoassay (CL-EIA) using mouse monoclonal antibodies against recombinant IL-6 (Fujirebio, Tokyo, Japan). The assay format was based on the two-step sandwich CL-EIA method, as follows: 50 μl of sample were added to 250 μl of a suspension of ferrite microparticles coated with a monoclonal antibody against IL-6 as
a solid phase and incubated for 10 min at 37°C. The particles were separated magnetically and washed, then 250 µl of another monoclonal antibody against IL-6 conjugated with alkaline phosphatase were added to the particles. After 10 min of incubation at 37°C, the particles were washed in the same manner. Subsequently, the substrate solution [3-(2-spiroadamantane)-4-methoxy-4-(3-phosphoryloxy)phenyl-1,2-dioxetane disodium (AMPDD)] was added at 37°C. After 5 min of incubation, the chemiluminescent signal was photon counted. The assay was performed with a Lumipulse 1200 or Lumipulse f system (Fujirebio), a fully automated CL-EIA analyzer. The assay exhibited a linear response for up to 1000 pg/ml of IL-6. The detection limit of IL-6 in the present assay was 0.2 pg/ml (12). A tumor extract was prepared according to the conventional method. Briefly, about 0.4 g of tumor tissue was homogenized four times with 3.0 ml of phosphate-buffered saline (PBS) and then centrifuged for 30 min at 4°C at 105 000 g. The supernatant was subjected to IL-6 measurement. Immunohistochemical studies were performed with mouse anti-human CD68 monoclonal antibody, monoclonal mouse anti-human IL-6 antibody (IgG1 class) (Genzyme Diagnostics, Cambridge, MA, USA) and the Universal Streptavidin/Biotin Immunoperoxidase System with DAB Chromogen (MaxiTags kit, Lipshaw, Pittsburgh, PA, USA) according to the manufacturers’ instructions for use.

**PATHOLOGICAL FINDINGS**

The surgically removed cardiac tumors in the left atrium and the left ventricle weighed 85 and 5 g, respectively. The tumors were elastic and soft and the cut surfaces were yellow–white and partially necrotic (Fig. 2). Unresected tumors were still present on the left atrium and in the left ventricle.

The tumors were composed of large polygonal and spindle-shaped cells with dense nuclear chromatin and irregular marginal nuclei. These tumor cells proliferated with fibrous stroma and exhibited a storiform pattern, frequent mitosis, nuclear atypia and marked pleomorphism. Cells with bizarre nuclei were intermingled. Multinucleated osteoclast-like giant cells and mitoses were also observed (Fig. 3). Histiocytoid cells and giant cells with ground-glass nuclei and relatively broad cytoplasm were also included. An apparent focus of venous involvement was detected in the area of invasion of the myocardium. Minimal necrosis and hemorrhage were observed. On reticulin staining, these tumor cells demonstrated a non-epithelial pattern. These findings were consistent with MFH of storiform–pleomorphic type (Fig. 4). The hemangiopericytomatous pattern sometimes observed in MFH was not detected.

No typical myxoma cells or deposition of hemosiderin was found, although myxoid stroma was observed focally. No adipose tissue, atypical lipoblasts or differentiation into smooth muscle cells were detected. Since the tumor cells were negative for markers indicating specific differentiation, such as α-smooth muscle actin, muscle actin (stained by HHF-35 monoclonal antibody) and desmin and no malignant endothelial cells forming papillary structures or abnormal vascular channels were identified, smooth muscle tumor and angiosarcoma could be ruled out.

PAS and immunohistochemical staining revealed diastase-resistant PAS-positive hyaline droplets. Histiocytoid atypical cells were positive for α1-antichymotrypsin and lysozyme. Staining for CD68, a panhistiocytic marker detected by monoclonal antibody KP-1, was markedly positive (Fig. 5), although staining for keratin was negative. Results of staining also supported the diagnosis and are summarized in Table 1.

Autopsy revealed recurrent cardiac tumors with the same microscopic findings: larger tumor in the left atrium (4.5 × 2.5 × 1.5 cm) had invaded into septum and aorta and another tumor (4 × 2 × 2 cm) in the left ventricle had invaded to the myocardium. The cut surface of the tumor was solid, elastic hard and white–gray. Hemorrhage and necrosis were not conspicuous. The right and left pulmonary veins (PV) were involved and at least two branches of the PV were completely obstructed. Huge hepatic metastases were found in both the left and right lobes. They were yellow–white and large (5 cm in diameter in the left and 7 cm in the right lobe). The other sites of metastasis were the small intestine, left tonsil and right seventh rib.
Figure 5. Immunohistochemical staining. Anti-CD68 antibody reacted positively with histiocytoid atypical cells.

Figure 6. Immunohistochemical detection of IL-6 production in MFH cells. The specimen was stained with anti-IL-6 monoclonal antibody. Mouse preimmune serum (IgG fraction) used as a control yielded no staining (data not shown).

Table 1. Results of PAS and immunohistochemical staining

<table>
<thead>
<tr>
<th>Staining/antigen</th>
<th>Dilution</th>
<th>Antibody source</th>
<th>Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS</td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>α-1-Antichymotrypsin</td>
<td>1:100</td>
<td>DK</td>
<td>+</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>1:100</td>
<td>DK</td>
<td>++</td>
</tr>
<tr>
<td>CD68</td>
<td>1:50</td>
<td>DK</td>
<td>+++</td>
</tr>
<tr>
<td>Keratin</td>
<td>1:50</td>
<td>DK</td>
<td>–</td>
</tr>
<tr>
<td>α-Smooth muscle actin</td>
<td>1:50</td>
<td>DK</td>
<td>–</td>
</tr>
<tr>
<td>Desmin</td>
<td>1:50</td>
<td>DK</td>
<td>–</td>
</tr>
<tr>
<td>S-100 protein</td>
<td>1:200</td>
<td>DK</td>
<td>–</td>
</tr>
<tr>
<td>EMA</td>
<td>1:50</td>
<td>DK</td>
<td>–</td>
</tr>
</tbody>
</table>

PAS, periodic acid–Schiff; EMA, epithelial membrane antigen; DK, DAKO Japan.

IL-6 PRODUCTION IN MFH

In view of the elevated serum level of IL-6, the possibility that this MFH constitutively synthesized IL-6 was examined. The tumor extract contained a high level of IL-6 (170 pg/g tissue), suggesting IL-6 production in MFH. To confirm this, an immunohistochemical analysis was carried out. Most of the MFH cells were stained with monoclonal anti IL-6 antibody (Fig. 6). These findings demonstrated that this MFH could synthesize IL-6.

DISCUSSION

Primary cardiac MFH is a very rare disease (1,13). This, in turn, makes preoperative diagnosis of primary cardiac tumors difficult. Given the well-known clinical observation that approximately 50% of primary cardiac tumors are cardiac myxomas (14), we initially speculated preoperatively that this patient had a cardiac myxoma. The elevated serum level of IL-6 supported our preoperative diagnosis, since cardiac myxoma cells have been found to synthesize IL-6 (10). However, histological analysis clearly demonstrated the presence of cardiac MFH in this patient. Our case therefore suggests that MFH should be considered in addition to cardiac myxoma when diagnosing primary cardiac tumor with an elevated serum IL-6 level.

The highly malignant clinical character of MFH has been reported, along with the difficulty of its preoperative diagnosis. In our case, the primary tumor in the left atrium appeared to have metastasized to the left ventricle with resultant mitral valvular regurgitation. Although pulmonary dissemination was not detected, we believe that the tumor in the left ventricle, in turn, metastasized to the thoracic aorta, followed by dissemination to the small intestine, left tonsil, costal bone and liver. Considering these findings together, the multiple metastatic lesions revealed by autopsy strongly suggest the postoperative hematogenous metastatic and highly malignant clinical character of MFH.

In order to distinguish MFH from cardiac myxoma, the serum IL-6 levels in the two diseases can perhaps be compared. Allegedly, serum IL-6 levels in patients with cardiac myxomas are two to six times the reference value on bioassay (14,15) and 3–81 pg/ml on ELISA (10,16). The serum IL-6 level in our patient, however, suggests a problem with the use of serum IL-6 level as an indicator of cardiac myxoma in the diagnosis of cardiac tumors. Patients with cardiac myxoma have been reported to present with weight loss, fever, anemia, collagen disease-like symptoms and elevated serum globulin levels (17) and the severity of these signs and symptoms is positively correlated with serum IL-6 level. This suggests that the malignant counterpart of myxoma exhibits MFH-like morphology, as reported in a case of malignant transformation of cardiac myxoma (18), since MFH is now regarded as a form of poorly differentiated sarcoma. It may also be possible that once malignant transformation occurs, the tumor can become highly aggressive, as in the case of neurogenic sarcoma derived from neurofibroma. However, the frequent
mitosis, nuclear atypia, necrosis and hypercellularity with pleomorphism detected in the present case were suggestive of MFH. Negative staining for desmin and S-100 also supported the diagnosis of MFH. It must be noted that DIC has not been reported to be a common sign of cardiac myxoma. Although the precise incidence of DIC in cardiac MFH cannot at present be determined owing to its rarity, we believe that DIC is a systemic sign of MFH in patients with primary cardiac tumor.

The results of our immunohistochemical analysis and the intra-tumor content of IL-6 led us to conclude that cardiac MFH is capable of constitutively synthesizing IL-6. To our knowledge, this is the first report demonstrating that cardiac MFH cells are able to synthesize IL-6. We believe that this IL-6 production may partly explain the patient's systemic symptoms including DIC, since extirpation of her cardiac tumor resulted in transient improvement of her DIC. As discussed above, however, IL-6 production alone seems insufficient to explain her DIC. Some biologically active molecules such as proteolytic enzymes other than IL-6 could have been secreted from this MFH.

The presence of multinucleated cells in this MFH may be explained by IL-6 production in the tumor, since IL-6 has been reported to play an important role in the generation of multinucleated osteoclast-like cells: IL-6 is an osteotropic factor that can preferentially stimulate the formation of multinucleated cells expressing the osteoclast phenotype by inducing IL-1 release (Fig. 3) (19).

Since constitutive production of IL-6 in cardiac MFH was found in this study, the next important question is whether MFHs originating at other sites generally synthesize IL-6. Notably, there is a case report of an IL-6-producing mediastinal MFH (20). Future studies of IL-6 production by MFH at other sites should be encouraged, particularly in bone, since bone MFH frequently causes pathological fracture. Considering the well-characterized effects of IL-6 on bone (21), the possibility that MFH-induced bone fracture is mediated through the production of IL-6 in MFH cells should be thoroughly examined in future studies.

Acknowledgments

We thank Tomoko Senjyu for secretarial help and Ayako Goto for expert care as a social worker.

References