Abstract. The patient is a 62-year-old man who was diagnosed with myasthenia gravis and invasive thymoma at the age of 45 years, and had received treatment by extended thymectomy and radiotherapy. At the age of 61, he had suffered from a myasthenic crisis, and been administered immunoadsorption therapy under managed ventilatory care. Treatment had then been continued with steroids; however, due to subsequent deterioration of his diabetic state, treatment was switched to the immunosuppressant drug tacrolimus. Three months after the commencement of tacrolimus administration, the patient developed generalized malaise and dyspnea. The serum creatine phosphokinase (CPK) level was abnormally elevated, and abnormal electrocardiographic findings were noted, including atrioventricular dissociation and ventricular escape contraction. Steroid pulse therapy was therefore initiated, however, 4 days later, the patient suddenly died. Autopsy examination revealed inflammatory cell infiltration with giant cells in the myocardium, diffuse myocardial degeneration, and polymyositis. The case was therefore considered as one with the syndrome of myasthenia gravis, polymyositis, giant cell myocarditis, and thymoma. (Keio J Med 53 (1): 30–42, March 2004)

Key words: myasthenia gravis, thymoma, polymyositis, giant cell myocarditis
patient while receiving treatment with a steroid. In January 2002, he again developed exacerbation of his myasthenic condition along with increase in the serum level of the antiacetylcholine receptor (AChR) antibody. His diabetic state was found at this time to have worsened markedly, therefore, tacrolimus administration was started at the daily dose of 3 mg, in order to avoid increasing in the steroid dose. An electrocardiograph (ECG) obtained at this time revealed nonspecific ST-T changes, but no abnormal echocardiographic findings were observed, and monitoring of the clinical course was continued on an outpatient basis.

On April 9, 2002, a routine blood examination revealed elevation of the serum CPK level to 563 mg/dl, even though there was no change in his symptom status. On April 13, he developed generalized malaise and dyspnea. On April 15, he presented to our outpatient clinic with epigastralgia, generalized malaise and exacerbation of dyspnea. He was suspected to have a myasthenic crisis, and was admitted immediately, on an emergent basis, to our department.

As for past history of medical illness, the patient had steroid-induced diabetes. At the age of 61 years, he had also been diagnosed to have tongue cancer and had undergone resective surgery. In the same year, he had also undergone polyectomy for colonic polyps.

The family history was unremarkable. As for the personal history, he was not habituated to either smoking or drinking.

Dr. Tanahashi: Any questions at this point?

Mr. Niihara (3rd-grade student): Was any test conducted for infectious diseases at the last admission?

Dr. Sato (H): We did not determine the antibody titers of any viruses that could potentially cause myocarditis.

Dr. Tanahashi: This patient was diagnosed as having MG in 1985. Do you have any comments about this diagnosis? The patient had shown double vision, ptosis, muscle weakness, and easy fatigability. When MG is suspected, what kind of tests should be conducted?

Mr. Nishi (3rd-grade student): It is important to detect waning phenomenon of the electrical muscle activity on an evoked electromyogram (EMG).

Dr. Tanahashi: How about the result of this examination early in the course of this patient’s disease, Dr. Sato?

Dr. Sato (H): According to his medical record from 1985, decrementing response during repetitive nerve stimulation was observed, and the patient was also positive for the Tensilon* test and his serum anti-AChR antibodies level was elevated.

Dr. Tanahashi: The diagnosis of MG was thus made in 1985 in the early stage of the clinical course of this patient. At this time, thymoma was also present, and extended thymectomy and radiotherapy were carried out. Is there any description regarding the thymoma in the early stage of the clinical course?

Dr. Kawamura (Surgery): Chest CT revealed pleural dissemination on the left side. Extended thymectomy was performed, as standard surgical fashion for thymoma with extensive dissection of the adipose tissue in the following regions: around the ligament extending from the upper pole of the thymic gland (thymus) to the lower pole of the thyroid gland (thyro-thymic ligament) on the cephalic side, at the level of the right and left phrenic nerves on the lateral side, and in the mediastinum, at the level of the diaphragmatic on the caudal side. Since the thymus gland is also converted into adipose tissue in association with thymic regression in adults, it is impossible to precisely differentiate the adipose tissue surrounding the thymus from the residual thymus gland. This is the reason why extensive adipose tissue dissection, as described above, was conducted. With regard to the pleural dissemination, although they could also be treated by total pleuropneumonectomy if radical surgical treatment is desired, usually, however, such an extensive procedure is not employed; in this patient, the disseminated thymus were resected and radiotherapy was administered postoperatively.

Dr. Satoh (T) (Internal Medicine): Dr. Kawamura, please tell us whether or not the heart was also irradiated, and if it was, what was the radiation dose employed?

Dr. Kawamura: Keio University Hospital follows its own radiotherapeutic protocol for thymoma associated with pleural dissemination. The pleural dissemination in these cases usually occurs unilaterally. Therefore, hemithorax irradiation is applied on the side of dissemination; the entire thorax on the affected side, extending from the apex of the lung to the lowest portion of the diaphragm (up to the posterior aspect of the liver on the right side and the level of the spleen on the left side) is widely irradiated at a daily dose of 1 Gy, over 10 sessions. This procedure is considered to allow reasonably satisfactory regression of the pleural metastases.

Irradiation at a higher daily dose of 2 or 3 Gy is often associated with serious radiation pneumonitis, because the irradiation field is very wide. Slow irradiation, i.e., irradiation at a daily dose of 1 Gy over 10 sessions, is considered to allow adequate irradiation with a relatively lower risk of pneumonitis. I repeat that the irradiation field in these cases is much wider as compared with that which is usually the case. The wide-ranging irradiation field includes the mediastinum as well. Subsequently, however, the irradiation field is narrowed to cover the mediastinum alone, which is irradiated with approximately another 20 Gy. Finally, the irradiation field is narrowed down even further to only the site of the primary lesion, which is then irradiated at a total dose of approximately 40–45 Gy. Accordingly, the
heart may receive a total radiation dose of approximately 30 Gy during the course of such radiotherapy.

**Dr. Tanahashi:** Although the patient showed remission initially, he developed a myasthenic crisis in May 2001, and was treated with a mechanical ventilator and immunoadsorption and steroid pulse therapy. Do you have comments on that?

**Ms. Nishiyama (3rd-grade student):** Myasthenic crisis may be induced by various factors, including infection and stress under the condition that physical state is deteriorated. Since the physical condition is associated with respiratory muscle failure in myasthenic crisis, artificial ventilatory support is essential.

**Dr. Tanahashi:** During a crisis, in particular, artificial ventilatory support is very essential. This patient was also administered immunoadsorption therapy and steroid pulse therapy for the myasthenic crisis. Dr. Sato, could you please explain to us why the immunoadsorption therapy and steroid pulse therapy was done for the myasthenic crisis in this case?

**Dr. Sato (H):** MG is generally treated with immunosuppressant drugs, because the condition is believed to be an autoimmune disease. During a crisis, when the patient develops respiratory failure due to respiratory muscle failure and/or bulbar palsy, mechanical ventilatory support and suppression of the associated immunological abnormalities are essential. As a rule, both must be continued until recovery from the crisis.

**Dr. Tanahashi:** The patient survived the crisis, and follow-up was continued on an outpatient basis while he was under treatment with a steroid. In January 2002, the patient’s condition deteriorated again, but this time, it was not a myasthenic crisis, was it? The serum level of anti-AChR antibody was found to be elevated. What was the level?

**Dr. Sato (H):** It was increased to 200 nmol/ml.

**Dr. Tanahashi:** What are the normal levels of this parameter?

**Dr. Sato (H):** 0.2 nmol/ml or less.

**Dr. Tanahashi:** So, the anti-AChR antibody level was markedly elevated to 200 or so nmol/ml; however, since the patient, already known to be a diabetic, showed marked deterioration of his diabetic state, the steroid dose was not increased; instead, administration of tacrolimus, an immunosuppressant drug, was started.

**Mr. Harasawa (3rd-grade student):** Some MG patients do not respond to steroid therapy following thymectomy, and such patients, as well as those with severe adverse reactions to steroids would be candidates for receiving immunosuppressant drugs.

**Dr. Tanahashi:** Thereafter, the patient’s condition was monitored by serial echocardiography, and no distinct electrocardiographic abnormalities, including ST-T changes were noted. However, elevated CPK levels were detected during a routine blood examination conducted on an outpatient basis on April 9 last year.

The serum CPK level was 563 mg/dl. What can we make out from this level?

**Mr. Harada (3rd-grade student):** The normal range for serum CPK is 67–210 mg/dl. Thus, the level in this patient was markedly elevated; when the MB fraction is elevated, skeletal myopathy and endocrine-disease-induced myopathy are considered. When the MB fraction is elevated, cardiac muscle disease is considered.

**Dr. Tanahashi:** On April 13, the patient developed generalized malaise and dyspnea, and on April 15, he visited our outpatient clinic with the complaints of epigastralgia, malaise, and dyspnea. Based on the clinical findings, he was suspected to have a myasthenic crisis, and was admitted to our department.

On admission, he was found to have dyspnea, and the serum CPK level was markedly elevated, and a myasthenic crisis was suspected. Please explain the clinical course of the patient from the time of admission until observation of the abnormal echocardiographic findings.

**Dr. Sato (H):** Physical examination at the time of admission revealed a pulse of 88 per minute, blood pressure of 146/90 mmHg, and a respiratory rate of 30 per minute; thus, the patient had tachypnea. Alopecia involving the entire body, including the scalp, (alopecia totalis) was observed, and the patient had very severe generalized muscle tenderness. He could scarcely move his body.

On neurological examination, because of severe muscle tenderness, it was difficult to definitively evaluate his muscle strength, but no definite phenomenon of fatigue was noted on test of repetitive grasping.

Laboratory examination revealed elevation of the red blood cell count, hematocrit and serum hemoglobin. These findings associated with elevation of the serum creatinine and blood urea nitrogen levels suggested hemoconcentration, i.e., the patient was in a dehydrated condition. The white blood cell count was also markedly increased to 18,200 per c.mm, and the serum CRP was 7.42 mg/dl. From these findings, some inflammatory reaction was assumed. The serum CPK was markedly elevated to 9835 IU/l, and the serum myoglobin and troponin T derived from myocardium levels were also elevated to 16,400 ng/ml and 3.24 ng/ml, respectively. These findings suggested skeletal myopathy and/or cardiomyopathy.

The serum anti-AChR antibody level was 56.0 nmol/ml, which was less than the level noted at the previous examination. The blood level of tacrolimus was 6.2 ng/ml, which was within the reference range.

Arterial blood gas parameters were within normal range even when the patient was breathing room air:
pH, 7.406; pCO₂, 40.2 Torr; pO₂, 86.8 Torr; HCO₃, 24.7 mEq/l; BE, 0.6 mEq/l.

**Dr. Tanahashi:** So, myasthenic crisis was not considered as the diagnosis at this time point, was it?

**Dr. Sato (H):** Because the patient didn’t present typical features of myasthenic crisis such as bulbar palsy. When we started to treat him, we could not rule out myasthenic crisis.

**Dr. Tanahashi:** Laboratory examination revealed marked elevation of some myogenic enzymes; CPK, 9,800 IU/l, MM fraction, 96%, myoglobin, 16,400 ng/ml, and troponin T, 3.24 ng/ml. What disease conditions would be considered from these values?

**Mr. Niihara:** The serum CPK level was high, in particular, the MM fraction, in the present examination. In this situation, skeletal myopathy and endocrine-disease-induced myopathy should be considered. In cardiac diseases including acute myocardial infarction, elevation in the MM fraction is rare. Therefore, muscular disorders should be suspected.

**Dr. Tanahashi:** Do you mean that disorders of the skeletal muscle should be considered? How about serum troponin T? What are the conditions in which the serum level of troponin T is elevated?

**Mr. Niihara:** Serum troponin T is elevated in cases of myocardial disease or myocardial infarction.

**Dr. Tanahashi:** So, the laboratory test data are suggestive of skeletal myopathy or cardiomyopathy. Will you please present the roentgenographic, ECG, and echocardiographic findings now, Dr. Sato?

**Dr. Sato (H):** ECGs taken in February 1997 (Fig. 1A), November 2000 (Fig. 1B) and January 2001 (Fig. 1C) showed slight ST-T change, left axis deviation and left atrial overload. The ECG taken in January 2002 (Fig. 1D) showed ST segment depression in precordial leads V3, V4, V5 and V6. The ECG recorded at the present admission (Fig. 1E) revealed atrioventricular dissociation (P/QRS dissociation). There is widening of the QRS complexes. The contour of the QRS complexes is suggestive of left bundle branch block. Subsequently, QRS complexes had become wider (Fig. 1F).

**Dr. Tanahashi:** The ECG findings seem to show considerable variability, don’t they? ST-T changes associated with conduction disturbances and various other changes. Can the ECG findings be considered to be specific for any morbid condition, Dr. Sato?

**Dr. Satoh (T):** No, the changes are nonspecific, and various causes must be considered.

**Dr. Tanahashi:** Now then, will you please explain the chest x-ray findings and echocardiographic findings?

**Dr. Sato (H):** These are the chest X-rays. This one was taken in January 2002 (Fig. 2). A nodular shadow in the lung and a shadow along the chest wall are observed. There is evidence of repeated relapses and remissions of the malignant thymoma. The size of the cardiac shadow has remained unchanged, and there is no evidence of pulmonary congestion.

An echocardiogram taken on April 16, 2002 showed the disturbance of left ventricular wall motion. The left ventricular ejection fraction was 57.5%. The inferior vena cava (IVC) diameter was 1.3 cm, suggestive of slight venous stasis. The respiratory fluctuations in the vein diameter are attenuated.

**Dr. Tanahashi:** Please explain the course after admission and the course before the death, Dr. Sato.

**Dr. Sato (H):** Blood gas analysis was conducted on several occasions within the first 24 hours after admission on April 15, 2002. A progressive increase in the arterial CO₂ tension and severity of acidosis was noted.
Since consciousness disturbance also worsened, tracheal intubation was performed, and the patient was connected to a ventilator. Based on all the information and data available, it was considered highly probable that the patient had myocarditis and myositis associated with MG. Under this assumption, steroid pulse therapy was initiated. However, since the blood sugar shot up to over 700 mg/dl the steroid pulse therapy was discontinued, and instead the patient was initiated on high-dose immunoglobulin therapy, which was then continued.

As for the heart, treatment with catecholamines was initiated, but signs of cardiac decompensation, including low blood pressure, persisted. Echocardiographic monitoring at the bedside also revealed daily worsening of the left ventricular wall motion. On the dawn of April 19, 2002, the patient complained of an oppressive sensation on the chest, and soon thereafter, died of cardiac arrest.

**Dr. Tanahashi:** The patient died relatively suddenly, about 4 days after admission. Serial echocardiograms revealed gradual worsening of the left ventricular wall motion. The patient was treated under a presumptive diagnosis of generalized myositis and myocarditis. Steroid pulse therapy was also employed for suspected myasthenic crisis, while the patient was under artificial ventilation. Cardiac conduction disturbances began to be observed, and the patient eventually developed ventricular tachycardia and died.

Then, what do you think about the course of the patient from the cardiological standpoint, Dr. Sato?

**Dr. Sato:** Several diseases should be ruled out; one is the ischemic heart disease, which is responsible for the rapidly progressive ventricular dysfunction. He is old enough to have ischemic heart disease. However, he had few risk factors and no past history of chest pain, nor left ventricular wall motion abnormality was not consistent with the area perfused by any particular coronary artery. These evidence are against the ischemic heart disease. Under these circumstances, the probability of ischemic heart disease seemed to be low.

On admission, the patient had mild hypertension. There was no distinct past history of the condition, but hypertensive heart disease must be enumerated in the differential diagnosis. However, the eventual course of the patient did not conform to this diagnosis. Then, the possibility of myocarditis must also be considered. Troponin T, one of the myocardial enzymes, is highly specific for myocardial damage. The serum troponin T level may also be elevated in the presence of heart failure alone. The level of 3.24 ng/ml was high for heart failure, and the serum CPK-MB level was approximately 4%, which is borderline, but this value should still be considered as high. Therefore a morbid condition causing rapidly progressive damage of myocardium should be considered. If ischemic heart disease is not probable, myocarditis should be considered.

The diagnosis of myocarditis is often made from the characteristic ST segment elevation on ECG. Because this patient had persistent VT, the ST segment could not be assessed properly. Definitive diagnosis could have been made by cardiac catheterization and myocardial biopsy, but this was impossible because of the patient’s serious condition. Gallium scintigraphy might also have been specific if the patient had been positive, but this was also difficult to perform. Therefore, a myocarditis was most strongly suspected, but it could not be confirmed. The progression was rapid. Because the patient was on immunosuppressant drugs, he may have been predisposed to viral myocarditis, the commonest cause of myocarditis.

Myocardial dysfunction due to irradiation may also be considered. Radiation cardiomyopathy is frequently associated with pericarditis and pericardial thickening; however, in this case, no pericardial thickening was observed on CT. Therefore, the possibility of this condition would also be low. As another possibility that must be ruled out, tacrolimus-induced cardiomyopathy can be enumerated, because the frequency of tacrolimus use has recently increased. This possibility may not be completely ruled out, but because of the rapid progression of the disease, this drug can hardly be considered to be the cause of the myocardial dysfunction. Under these circumstances, the diagnosis of myocarditis was considered to be most probable.

**Dr. Tanahashi:** So, Dr. Sato has indicated that myo-

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**Fig. 2** The chest X-ray film taken in January, 2002. A nodular shadow in the lung and pleural thickening were observed.

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carditis was suspected to be the cause of the rapidly progressive cardiomyopathy in this case. As to the etiology of the myocarditis, in turn, he suggests the possibility of viral infection. He has also taken into consideration various other causes, including immunosuppressant drug administration, radiation, etc. . . . In any event, whatever the cause, the suspected diagnosis was myocarditis.

The patient’s course towards death was very rapid; progression of the cardiac condition rather than MG were considered to be responsible for the rapidly fatal course.

**Dr. Sato (H):** Circulatory-respiratory failure may be caused by heart failure due to myocarditis. It is difficult to determine whether or not myasthenic crisis was also present, because the Tensilon test could not be conducted after the patient was connected to a ventilator. The question therefore remained unresolved until the end.

**Dr. Tanahashi:** The present patient who had MG associated with invasive thymoma developed symptoms of acute heart failure during the course of observation. The heart failure was suspected to be caused by myocarditis. Dr. Kawamura, do you have any remarks to make?

**Dr. Kawamura:** After extended thymectomy for MG, we have often encountered patients who develop either myasthenic crises or cholinergic crises postoperatively, regardless of the presence or absence of a thymoma. On the other hand, we have never encountered myocarditis or acute heart failure in these cases.

**Dr. Tanahashi:** Dr. Shimoda from the Department of Pathology, will you please explain the pathological findings?

**Dr. Shimoda (Pathology):** The present patient was followed up for more than ten years after being diagnosed to have MG associated with invasive thymoma. At autopsy, recurrent invasive thymoma, giant cell myocarditis, polymyositis and alopecia totalis were observed in addition to MG. The autopsy findings are summarized in Table 1.

The invasive thymoma had invaded the pericardium and the left pleura in the surgically resected tissue in 1985. Histologically, the tumor consisted of lymphocytes and epithelial cells, arranged in compartments formed by fibrous septa (Fig. 3A, B). Some areas of this tumor showed medullary differentiation. The tumor was diagnosed as invasive thymoma. At autopsy, the invasive thymoma recurred in the anterior septum, invaded to the epicardium and metastasized to the bilateral lungs and the left pleura (Fig. 3E). The recurrent tumor was composed of lymphocytes and epithelial cells in compartments formed by fibrous septa (Fig. 3C, D). As compared to the findings in the specimens resected during the operation, there is very marked proliferation of the epithelial cells, and on the other hand, the lymphocytes were decreased. The epithelial cells showed significant nuclear atypia, compared to that observed in the specimens resected at surgery. In terms of these histological features, we have to distinguish invasive thymoma from thymic carcinoma. It is said that thymoma retains the function of the thymus to attract immature T cells from bone marrow to make them mature whereas thymic carcinoma has lost this function. In the present tumor, numerous CD1a-positive immature lymphocytes and CD99-positive immature lymphocytes were observed by immunohistochemistry. Therefore, we could rule out the possibility of thymic carcinoma, and diagnosed the tumor as recurrent invasive thymoma. As for the atypia of the lymphocytes in the recurrent tumor, the possibility of the influence of chemotherapy that the patient received during the clinical course must be considered.

### Table 1  Summary of Anatomical and Histopathological Findings

<table>
<thead>
<tr>
<th>Major findings</th>
<th>[Major findings]</th>
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<tbody>
<tr>
<td>1. Myasthenia gravis</td>
<td></td>
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<tr>
<td>2. Invasive thymoma</td>
<td></td>
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<tr>
<td>a) primary site: Anterior mediastinum, 5.5 × 5.3 × 2.8 cm</td>
<td></td>
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<tr>
<td>b) Recurrence at autopsy: Anterior mediastinum, 3.0 × 3.1 × 1.0 cm</td>
<td></td>
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<tr>
<td>c) Invasion &amp; metastasis: Epicardium, lungs (660 g, 650 g), left pleura</td>
<td></td>
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<tr>
<td>d) Therapies: Surgical resection, radiation therapy and chemotherapy</td>
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<tr>
<td>3. Giant cell myocarditis</td>
<td></td>
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<tr>
<td>a) Inflammatory cell infiltration, severe</td>
<td></td>
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<tr>
<td>b) Electron microscope: No particle of virus was seen at autopsy.</td>
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<tr>
<td>c) Related lesions: Congestion: Liver (1140 g), kidneys (150 g, 145 g) and lungs</td>
<td></td>
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<td>4. Polymyositis</td>
<td></td>
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<tr>
<td>a) Inflammatory cell infiltration: Iliopsoas muscle, diaphragm (severe) pectoralis major muscle, intercostal muscle, muscles of neck (moderate)</td>
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<tr>
<td>b) Related lesions: Myoglobinuria</td>
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<tr>
<td>5. Alopecia totalis</td>
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<tr>
<td>6. Tongue carcinoma</td>
<td></td>
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<tr>
<td>a) Primary site: Margin of the tongue, right side, 1.5 × 1.0 cm</td>
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<tr>
<td>Modately differentiated squamous cell carcinoma with ulcer formation, stromal invasion (+)</td>
<td></td>
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<tr>
<td>b) Recurrence: No recurrence was seen at autopsy</td>
<td></td>
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<tr>
<td>c) Therapy: Surgical resection</td>
<td></td>
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<tr>
<td>7. Hemorrhagic infarction, inferior lobe of right lung, 3.0 × 3.0 × 3.0 cm</td>
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[Minor findings]

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<td>7. Hemorrhagic infarction, inferior lobe of right lung, 3.0 × 3.0 × 3.0 cm</td>
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At the time of autopsy, giant cell myocarditis and polymyositis were observed. The heart showed a widespread mononuclear inflammatory infiltrate containing multinucleated giant cells with massive myocardium degeneration (Fig. 4A–C). Although electron microscopy was carried out, viral particles were not detected.

All the muscle tissue specimens collected from the diaphragm, iliopsoas muscle, pectoralis major muscle, intercostal muscle and muscles of neck at autopsy showed mononuclear inflammatory cellular infiltrate containing giant cells with degeneration and necrosis of the muscle (Fig. 4D, E). Immunohistochemical studies showed that
The giant cells were positive for myoglobin, suggesting that these cells are derived from muscle.

The alopecia totalis had been present for one year and ten months before death. At autopsy, lymphocyte infiltration around the hair follicles and the skin appendages was observed (Fig. 5). Hair follicles were observed, but no hair tissue was observed within the hair follicles. Immunohistochemical studies revealed that these lymphocytes were mostly T cell lymphocytes, and CD8-positive cells predominated over all others.

In summary, we have presented a case of giant cell myocarditis and polymyositis associated with invasive
thymoma and MG. In previous literatures, some cases of the syndrome of giant cell myocarditis and polymyositis associated with invasive thymoma and MG have been reported. The present case is also thought to belong to this syndrome.

Dr. Nogawa (Internal Medicine): As for the origin of the giant cells in the myocardium and skeletal muscle, some literature has demonstrated that they are derived from macrophages, is that right?

Dr. Shimoda: Yes, that is right.

Dr. Nogawa: The cells were myoglobin-positive giant cells. How was the origin of the cells determined, i.e., whether they were derived from macrophages or myocytes?

Dr. Shimoda: Both origins can be considered; i.e., macrophages and myocytes, but we did not screen the giant cells of the myocardium. In the skeletal muscle, there were relatively more numerous giant cells that were positive for myoglobin and negative for CD68, a surface marker of macrophages. Therefore, the giant cells in the present case were considered to have fundamentally been derived from myocytes.

Dr. Nogawa: Sarcoïdosis should also be excluded as a differential diagnosis, judging from the overall picture. The presence or absence of epithelioid cells should be considered. In the present patient, can we exclude sarcoïdosis of the myocardium?

Dr. Shimoda: With regard to the histological findings in the myocardium, no typical granulomas. Characteristic asteroid bodies were not observed either. Clinically as well, there is no description of elevation of the serum level of angiotensin-converting enzyme, or other characteristic clinical features. Therefore, sarcoïdosis may be excluded based on the clinical and pathological findings.

Dr. Satoh (T): I have two questions; first, I reviewed the cardiac lesions complicated with MG. There have been many cases of chronic myocarditis reported. In this patient, the ECG findings suggested rapid deterioration of the myocardial lesion over the last 2–3 years. Did you find any evidence of chronic myocarditis in this case?

Dr. Shimoda: Since some parts of the apex of the heart show marked fibrosis, there is the possibility that the patient had chronic myocarditis. But we also have to take into consideration the possibility of myocardial infarction.

Dr. Satoh (T): Are there any abnormalities of the coronary arteries?

Dr. Shimoda: No, there is no thickening or other abnormalities of the coronary arteries.

Dr. Satoh (T): The second question. In spite of very severe heart failure, the patient showed no evidence of pulmonary congestion. Right-heart catheterization also showed normal pulmonary arterial pressure and normal left atrial pressure. From these findings, it was clinically estimated that the right ventricle was more severely damaged. How about the pathological findings?

Dr. Shimoda: Both the left and right ventricles showed very severe inflammatory cellular infiltration. No marked differences were noted between the two ventricles.

Dr. Tanahashi: So, in this case, the features are consistent with the syndrome of invasive thymoma, MG, myocarditis, and giant cell myocarditis or myositis. Could you please give some comments, including on the clinical findings, Dr. Nogawa, from the standpoint of the physician-in-charge.

Dr. Nogawa: MG is an autoimmune disease. Approximately 75% of MG patients are positive for AChR antibody (like this patient). The remaining 25% who are negative for the antibody are referred to as having “sero-negative” MG. It has recently been reported that an antibody to muscle-specific kinase (MuSK) is present in some cases of sero-negative MG. The characteristic clinical symptom in MG is diurnal fluctuation of the muscle strength, and in the Edrophonium (Tensilon®) test, recovery of muscle strength is noted following administration of this drug. On EMG, a waning response is observed to repetitive 3-Hz stimulation. Particularly noteworthy is the fact that 80% of the patients have abnormalities of the thymus gland, and 10% of the patients have a thymoma. As for other complications, various autoimmune diseases have been reported to be associated with MG. That is, abnormal thyroid function is associated with MG in 15–25% of the patients, and rheumatoid arthritis (RA) and idiopathic systemic lupus erythematosus (SLE), which are collagen diseases, are associated with MG in some cases. As for hematological diseases, pernicious
anemia, hemolytic anemia, pure red cell aplasia and idiopathic thrombocytopenic purpura have been reported to be associated with MG. In addition, insulin-dependent diabetes mellitus, nephritis, nephrotic syndrome and alopecia totalis (as observed in the present patient) or alopecia areata have also been reported in these cases. Vitiligo, ulcerative colitis, multiple sclerosis, and Lambert-Eaton myasthenic syndrome (LEMS) may occasionally be associated with MG.

The most common classification to describe the clinical severity of MG is Osserman’s classification. Types I, II, III, IV, and V refer to ocular, generalized, acute fulminant, late grave, and the atrophic type of MG, respectively. However, in actuality, classification according to this system may be rather difficult. The clinical classification of the MG Foundation of America has recently been published in Neurology; class I corresponds to the ocular type, and classes II, III and IV correspond to mild, moderate and severe MG, respectively, affecting other than ocular muscles. Subclass A in each class indicates the involvement of muscles of all the four extremities, and subclass B indicates the involvement of the pharyngeal and respiratory muscles. Myasthenic crisis, i.e., the morbid condition requiring intubation, is categorized as class V. Therefore, the present patient may be included in class V, based on the clinical presentation.

The important clinical observations in this patient before his death: Firstly, rapid progression of cardiorespiratory failure was observed. It became important to determine whether or not the patient was in myasthenic crisis. The patient had little or no exacerbation of ptosis, eye movement disorder, or swallowing difficulty, which are all typical of MG. Elevation in the serum level of the AChR antibody, which was observed earlier, was not marked during this admission. Therefore, myasthenic crisis was not considered to be the cause of the rapidly progressive respiratory failure. Secondly, the patient had acute heart failure, and on ECG, various abnormalities, including AV conduction block, were observed. Various causes for these abnormalities were considered: (1) Viral infection, (2) idiopathic cardiomyopathy, (3) myocardial ischemia, (4) infiltration of thymoma into the pericardium – this was revealed on pathological examination, but the extent of the infiltration was not sufficient to explain the condition, (5) cardiomyopathy due to tacrolimus [the present patient was the first case in which we used tacrolimus (FK-506) for MG], (6) autoimmune involvement, and (7) other-drug-induced, such as adriamycin, which exerts cardiotoxicity. Thirdly, marked hyper-CPKemia and myositis were present, but the muscle pain was not so severe. Therefore, the patient’s condition appeared to be slightly different from that typical of polymyositis (PM), which is a commonly encountered condition.

Fourthly, this patient has had alopecia totalis, and the symptom became manifest long after the commencement of administration of the anticancerous drugs. Therefore, the baldness could not have been caused by the anticancerous drugs. However, the patient did not have alopecia areata, which has been described in the literature, but alopecia totalis. This became an issue.

As described earlier by Dr. Shimoda, macroscopically, the myocardium showed fibrosis to a certain degree and the presence of chronic lesions, and microscopically, giant cells were observed. Based on these findings, patients with thymoma, which has been reported to be associated with (giant cell) myocarditis in the literature, were reviewed (Table 2). Nearly 20 cases have been reported worldwide to date, and the present patient was the 8th case of MG associated with myositis, myocarditis, and thymoma. The present patient was the 3rd case in Japan, suggesting that the patient is a very rare case.

The cases that have been reported as “giant cell cardiomyositis” were reviewed. Pathologically, lesions resembling granulomas, with giant cells but no epithelioid cells, are described. Myocardial necrosis and fibrosis are also observed. With regard to the origin of the giant cells, some reports have suggested that they are derived from macrophages, while others have suggested that they are derived from myocytes. The disease has been believed to be associated with autoimmune diseases, including thymoma, MG, SLE, abnormal thyroid function and RA. It must be differentiated from sarcoidosis, toxoplasmosis, myocytic infection, tuberculosis, syphilis, and Chagas’ disease. They show a common clinical course; some reports have indicated that many cases with this disease show rapidly progressive congestive heart failure or conduction disturbances, ST-T changes, and a fatal course. Although the mechanisms still remain unknown, it has been speculated in past reports that antimyocardial antibodies or antiskeletal muscle antibodies may be responsible for the abnormalities, because many patients of MG associated with thymoma are positive for these antibodies. About half of the cases with myositis are positive for antibodies to the ryanodine receptor (RyR) present in abundance in the myocardium. These reports suggest the involvement of autoimmune mechanisms, although the underlying mechanisms have yet to be clearly elucidated.

Regarding the recently established concept of the syndrome of MG, giant cell polymyositis and myocarditis associated with thymoma, please allow me to review this a little. In 1944, Giordano & Haymond reported the first autopsied case with the four diseases, MG, thymoma, giant cell polymyositis, and cardiomyositis. In 1969, Burke et al., who observed ST segment depression and T wave inversion on the ECG
in one case, reported that the patient suddenly died due to rapid progression of heart failure. Namba et al.\(^6\) summarized 13 cases of giant cell polymyositis, cardiomyositis and thymoma in an article entitled “Idiopathic giant cell myositis”. In this article, the presence of MG was not considered. In 1976, Dr. Hiromichi Suzuki\(^7\) of our University reported a patient with all of these diseases. In actuality, the present patient is considered to be the first case reported in Japan. In 1985, a neurologist, Dr. Tomimoto\(^8\) of (Faculty of Medicine) Kyoto University reported a similar case. Thereafter, a review of 11 patients was reported,\(^9\) and another report has called attention to the possibility of ventricular tachycardia occurring in these cases,\(^10\) and one report has referred to elevation of the ST segment.\(^11\) Recently, 14 cases have been reviewed in a report entitled “Giant cell myocarditis and malignant thymoma”,\(^12\) and another report has indicated the occurrence of cardiac block in a case of malignant thymoma.\(^13\) In a recent issue of Rincho Shinkeigaku, a case of MG associated with Hashimoto’s disease associated with the development of giant cell myocarditis was reported.\(^14\)

In this case, thymoma was absent.

Another noteworthy feature in the present patient was alopecia totalis. Figure 6 shows the present patient’s photograph taken when he was well. The head is completely bald (A). He was also found to have atrichia involving the hair of the axilla (B), the nostrils (C), and pubes. Figure 7 shows the mechanisms underlying the immunological abnormalities that may occur in cases of thymoma, \(i.e.,\) thymoma-associated syndrome. The following have become increasingly clear: The presence of thymoma induces abnormalities in the humoral immunity. When anti-AChR antibody or anti-MuSK antibody is produced, MG results; LEMS results when the anti-voltage-gated calcium channel (VGCC) antibody is produced. In the presence of anti-voltage-gated potassium channel (VGKC) antibody, neuromyotonia, \(i.e.,\) Isaacs syndrome occurs. As in the present patient, presence of antibodies to the skeletal muscle or myocardium may be associated with giant cell myositis or giant cell myocarditis. In particular, the anti-RyR antibody is drawing much attention.\(^3\) Furthermore, the present patient had alopecia totalis. Although this has not been reported yet, the condition (alopecia totalis) may occur if the anti-follicle antibody is produced. Pathological examination of tissue specimens revealed intrafollicular infiltration by CD8-positive cells, suggesting that abnormal cellular immunity occurring after thymectomy may be involved in such infiltration. Thus, as described above, while many issues still need to be resolved, very interesting conditions were observed in the present patient.

Ultimately, the present patient was the first case in which we used tacrolimus for treatment. The patient died only several months after the commencement of its administration. The blood concentration was within the normal range, but let me touch on the possibility of this drug having adversely influenced the patient’s condition. As described even earlier by Dr. Toru Sato,
Atkins et al.\textsuperscript{15} reported in 1995 that cardiomyopathy may occur with the use of tacrolimus. The underlying mechanism may be as follows: Calcium is stored in the sarcoplasmic reticulum (SR) in the myocytes and skeletal muscle cells. Intracellular recruitment of calcium induces further intracellular release of calcium via RyR type 2 on the SR surface [calcium-induced calcium release (CICR)]. Usually, FKBP12, a FK-506-binding protein, is bound to the RyR. It was reported in an issue of the journal Cell in 1994, that the bond of RyR to FKBP12 regulates CICR.\textsuperscript{16} However, when the level of intracellular cyclic AMP increases following catecholamine stimulation to activate PKA, the RyR becomes phosphorylated and FKBP12 is separated from the RyR, facilitating the release of calcium. Therefore, it has been speculated that the intracellular calcium concentration may be elevated by dissociation of FKBP which may result in cardiomyopathy, when tacrolimus is used. Another report has shown the induction of rhabdomyolysis in not only the myocardium, but also in the skeletal muscle.\textsuperscript{17} Recently, however, a report has suggested that tacrolimus does not induce cardiomyopathy.\textsuperscript{18} No definitive consensus has been arrived yet regarding the possibility of existence of tacrolimus-induced cardiomyopathy. In the present patient, the blood tacrolimus concentration was approximately one-third of that observed following administration of the drug at doses actually used for transplantations, and it remained consistently within the normal range. Changes in the ECG and echocardiogram were present even before tacrolimus administration was started. Light-microscopic observation suggested chronic fibrosis of the myocardium. Such a syndrome has been actually reported, and the present patient was the first case in which tacrolimus was used. Based on these circumstances, we believe that the possibility of tacrolimus

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure6.png}
\caption{The present patient’s photographs taken in January 2002. Alopecia of the scalp (A), the axilla (B), and the nostrils (C) was noted (alopecia totalis).}
\end{figure}
having been involved in the development of the cardiomyopathy is low. Furthermore, we also considered that it was possible that the drug predisposed the patient to viral infections because of its immunosuppressive actions. However, electron-microscopic examination showed the absence of viral particles. Therefore, this possibility was probably ruled out. Under these circumstances, along with the aforementioned pathological findings, the present patient is clinically considered to be a case with the syndrome of MG, giant cell myocarditis, myositis and thymoma.

Dr. Tanahashi: The present case was indeed a very interesting one. I now declare the CPC closed. Thank you very much for your participation.

References