Allergic Granulomatosis and Angiitis with Severe Cardiac Disease: A Case in Which Cardiac Function was Extremely Improved by Long-Term Steroid Therapy

Naohiko Takahashi, Masakazu Horita, Mari Tatsukawa, Toshihiro Maeda, Masataka Seike, Tetsunori Saikawa, Ryosaburo Takaki, Toshio Mori* and Shigeo Yokoyama**

A 38-year-old man with a history of bronchial asthma developed marked eosinophilia, mononeuritis multiplex and transient pulmonary infiltration. Pathological findings from the lung and nerve biopsy were helpful in determining the diagnosis as allergic granulomatosis and angiitis (AGA). Echocardiogram indicated dilation of the left ventricle with impaired systolic contraction. Coronary arteriography demonstrated significant stenosis only in the peripheral segment of the circumflex artery. After 1 year of corticosteroid therapy, echocardiogram revealed improvement of left ventricular contractility evaluated by ejection fraction (from 28% to 67%). To our knowledge, no previous reports have described amelioration of severe cardiac lesions during long-term steroid treatment in patients with AGA.

Key words: eosinophil, necrotizing angiitis, ejection fraction

Introduction

Allergic granulomatosis and angiitis (AGA) was first described by Churg and Strauss in 1951 as an independent disease that could be differentiated from classical polyarteritis nodosa (PN) (1). This disorder is characterized by eosinophilia and systemic vasculitis occurring in individuals with asthma. It has been infrequently described in the literature. Nagasawa and Yoshida reported 74 Japanese cases in a 1986 nationwide survey (2).

Although cardiac involvement is the major cause of mortality in patients with AGA (3), reports on this aspect of the disease are limited and therapeutic standards have not yet been established. Here, we report a patient with AGA who demonstrated improvement in severe cardiac lesions after protracted steroid therapy.

Case Report

A 38-year-old man was admitted to our hospital on October 6, 1989, because of fever, loss of body weight and numbness in the extremities. The patient had been well until 16 months before presentation, when he developed cough and dyspnea. He was diagnosed at a local hospital as having bronchial asthma with extreme leukocytosis and eosinophilia. Prednisolone (PSL) (20 mg/day) improved his symptoms. However, he experienced similar episodes on 5 subsequent occasions. The patient began to experience loss of appetite, loss of body weight (10 kg) and numbness in the extremities one month before entry. Two weeks later he was admitted to another hospital, where he was found to have fever and hepatosplenomegaly. Laboratory studies revealed that his white cell count was 31,000/mm³ with 58% eosinophils. Since resolution of his symptoms was not seen after 1 week of treatment with PSL (30 mg/day), he was referred to our hospital. He had no particular medical history. There was a family history of rheumatoid arthritis in his uncle. At admission, his body weight was 41 kg, his temperature was 36.6°C, and his pulse was 110/min. Blood pressure was 124/94 mmHg.

On examination, the patient appeared frail and ill. No lymphadenopathy was found. There were no abnormal findings in the heart and lungs. The abdomen was soft;
the edge of the liver descended 3 cm below the right costal margin. The spleen could not be felt. Neurologic examination revealed muscle weakness and atrophy in the extremities. Grasping power was 14 kg. The patient displayed severe gait disturbance. There was a prominent decrease in sensation below both ankle joints with respect to touch, pain and temperature. Deep tendon reflexes were absent in the extremities.

Laboratory data on admission are shown in Table 1. Blood cell counts showed leucocytosis (11,400/mm$^3$) with 26% eosinophils. The platelet count was 410,000/mm$^3$. Blood chemistry data included a total protein level of 6.2 g/dl with decreased A/G (0.95); increased levels of total bilirubin (1.2 mg/dl), glutamate pyruvate transaminase (GPT; 60 IU/l), γ-glutamyl transpeptidase (γ-GTP; 40 IU/l), lactic dehydrogenase (LDH; 505 IU/l) and decreased levels of sodium (135 meq/l).

<table>
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<tr>
<th>Table 1. Laboratory Data on Admission</th>
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<td>14.3 g/dl</td>
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Fig. 1. Electrocardiograms at the first (Oct. 7, 1989) and second (Nov. 7, 1990) admission.

Fig. 2. Clinical course.
Takahashi et al

and chloride (89 meq/l). Serological tests revealed the following: C-reactive protein 0.4 mg/dl, RA positive, RAHA × 320, anti-nuclear antibody negative and IgE 559 U/ml.

Poor R wave progression, ST segment depression and negative T wave in leads V4 to V6 were recorded on an electrocardiogram (Fig. 1) without any evidence of abnormalities on chest X-ray. Echocardiogram revealed slight hypertrophy and markedly decreased contraction of the left ventricle with an ejection fraction (EF) of 28%. Gastroscopic examination showed multiple ulcers in the antrum of the stomach. In addition, edema was noted in the gastrointestinal tract by upper abdominal CT. The patient continued to have loss of appetite with progressive hyponatremia after hospitalization. He displayed a low serum Na level of 123 mEq/l on November 6. The patient continued to lose body weight, weighing only 32.5 kg on November 19 (Fig. 2).

Bronchoscopic examination on November 1 indicated that the T lymphocyte subset ratio (OKT4/OKT8) in bronchoalveolar lavage fluid decreased to 0.42. Furthermore, the pathological findings of transbronchial lung biopsy manifested angitis (Fig. 3) and septal hypertrophy accompanied by lymphocyte and eosinophil infiltration. Marked decreases in myelinated fibers with axonal degeneration were observed on sural nerve biopsy (Fig. 4).

Based on a diagnosis of AGA, the administration of PSL (40 mg/day) was initiated on November 2, followed by the administration of a diuretic (furosemide) and digitalis. Infiltration shadows on X-rays of the chest, which appeared on the right lower lobe on November 2 and the left upper lobe on November 11 (Fig. 5), disappeared spontaneously. Since frequent ventricular premature contractions (VPCs) of Lown grade V were recorded in December, antiarrhythmic agents were administered. Although the frequency of arrhythmia was subsequently reduced, it remained at Lown grade III.

Coronary arteriography (CAG), which was performed on January 17, 1990, indicated slight irregularity of the artery wall in the main trunk of the coronary artery and significant stenosis in segment 15 of the circumflex artery (Fig. 6). Left ventriculography revealed severe hypokinesia (Fig. 6). The results of cardiac catheterization are shown in Table 2. Myocardial biopsy of the left ventricle showed focal myocardial fibrosis (Fig. 7). At discharge, the patient was receiving PSL (15 mg/day). His appetite was restored and body weight was increased to 45 kg. Symptoms of mononeuritis multiplex (gait disturbance and numbness of extremities) were improved. However, left ventricular contractility showed minimal

Fig. 3. Lung biopsy specimen showing angitis in the pulmonary arteriole (outlined by small arrows). The inner lumen is almost completely obstructed by thickening of the intima with eosinophil infiltration (large arrows) (hematoxylin and eosin stain, ×200).

Fig. 4. Cross-section of the sural nerve (toluidine blue stain, ×100). There is marked loss of myelinated fibers with axonal degeneration.

Fig. 5. Chest roentgenogram conducted on Nov. 11, 1989, demonstrated an infiltration shadow in the left upper lobe.
AGA and Cardiac Disease

Fig. 6. Coronary arteriograms (CAG, top) and left ventriculograms (LVG, bottom). Top left: right CAG, Top right: left CAG revealing stenosis in segment 15 of the circumflex artery (arrow). Bottom left: LVG end-diastole, Bottom right: LVG end-systole. Note markedly impaired systolic contraction of the left ventricle.

Table 2. Changes in Clinical Characteristics and Results of Cardiac Catheterization

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<tr>
<td>LVEDP (mmHg)</td>
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<tr>
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<td>SV (ml/beat)</td>
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<td>81</td>
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<td>EF (%)</td>
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NYHA: New York Heart Association classification, CTR: cardiothoracic ratio, HR: heart rate, mPCWP: mean pulmonary capillary wedge pressure, LVEDP: left ventricular end-diastolic pressure, C.I.: cardiac index, SV: stroke volume, EF: ejection fraction

The patient was readmitted 1 year after the first hospitalization to re-evaluate cardiac function. His PSL dosage at this time was 10 mg/day. Electrocardiogram demonstrated resolution of ST segment depression and negative T wave in leads V4 to V6 (Fig. 1). EF improved to 67% (Fig. 8). Left ventriculography indicated decreased wall movement, although there was distinct improvement compared with the results of the previous examination. CAG revealed lesions similar to the previous study. The results of cardiac catheterization are shown in Table 2.

Fig. 7. Myocardial biopsy revealing focal myocardial fibrosis (hematoxylin and eosin stain, ×100).
**Discussion**

Congestive heart failure, cerebral hemorrhage, gastrointestinal tract perforation or hemorrhage, and respiratory and renal failure have been reported as causes of death in patients with AGA (2, 3). Of the above-mentioned disorders, cardiac involvement is the major cause of mortality, especially in patients who have acute progression of AGA. Lanham et al investigated 164 cases of AGA and attributed 48% of the observed mortality to cardiac diseases (3). The studied patients presented acute pericarditis, constrictive pericarditis, cardiac failure and myocardial infarction as cardiac manifestations. According to the Third National Survey conducted by the Japanese Ministry of Health and Welfare in 1986, 31 (42%) of 74 Japanese patients with AGA suffered from cardiac manifestations such as cardiac failure, infarction and pericarditis (2). Of the 14 deaths (19%), 3 were due to cardiac failure. More than half of the patients with AGA had ECG abnormalities (3).

Although cardiac lesions are an important factor in AGA, investigations have not yet been fully focused on them. Only a few previous patients were subjected to cardiovascular angiography before death (5–7). CAG findings indicated pooling in the peripheral vessels of the coronary artery in one patient, whereas no abnormalities were noted in the other patients. Left ventriculography in both cases revealed decreases in left ventricular contractility. Cardiac catheterization has also been performed in other patients with pericardial diseases (7, 8). In the present case, the patient did not have any subjective symptoms, although cardiac function manifested a marked decrease in cardiac output with an EF of 28%. In CAG, part of the circumflex branch was stenosed and left ventriculography showed diffuse hypokinesis. The observed decrease in left ventricular contractility coincides well with previous reports and seems to be a characteristic cardiac finding in AGA. Furthermore, myocardial biopsy revealed focal myocardial fibrosis similar to that described in other cases (6, 8).

The mechanism of AGA-induced cardiac injury involves 1) myocardial necrosis caused by angiitis, and 2) direct damage inflicted on the endocardium and myocardium by eosinophils. These findings were also observed in a patient with isolated eosinophilic coronary arteritis and eosinophilic myocarditis (9). The role of these etiological factors has been advocated by pathological findings at autopsy. That is, necrotizing angiitis accompanied by marked infiltration of eosinophils in the vascular walls, granuloma formation in the myocardium, and myocardial necrosis with interstitial eosinophilic infiltration and diffuse fibrosis were the main cardiac findings in patients who died of AGA (4, 10, 11). Necrotizing vasculitis can be divided into 2 types, granulomatous and fibrinoid vasculitis. In AGA, the former is more characteristic and has a higher incidence, especially in the heart (12). Tissue damage by eosinophils is attributed to the cellular toxicity of major basic protein (MBP) and eosinophil cationic protein (ECP) contained within the granules (13). Previous studies in rats showed that such eosinophil granular proteins directly damage isolated myocardial cells. Moreover, it has been demonstrated that these granular proteins are present in myocardial lesions associated with eosinophilic myocardial disease.
Effective therapy for cardiac diseases in patients with AGA has not yet been established. Several reports followed the progress of cardiac lesions treated with long-term corticosteroids (5–8, 14). No improvement in cardiac function was seen during follow-up periods ranging from 6 months to 1 year in patients with myocardial lesions alone, while acute improvement has been reported in the cases with pericardial and myocardial disease. Although corticosteroid treatment was initiated at a comparatively low dosage in the present patient, amelioration of cardiac function (increase in EF from 28% to 67%) was achieved with long-term steroid administration. The mechanism by which cardiac function was gradually restored is not clear. It may have been brought about by the healing of cardiac and systemic angiitis, which resulted in 1) the recovery of cardiac contractility itself and 2) the reduction of cardiac pre- and after-load. The latter change was suggested by the decrease in high plasma renin-angiotensin levels (renin 17.6ng/ml/h, angiotensin I 2,500pg/ml < and angiotensin II 330pg/ml on admission versus renin 13.2ng/ml/h, angiotensin I 850pg/ml and angiotensin II 22pg/ml after 5 months and renin 8.0ng/ml/h after 1 year) (15, 16). The present case provides an important reference for future therapy in patients with AGA.

References