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| 著者                           | Araki Tsutomu, Konno Tetsuo, Soma Ryuichiro, Nakashima Akikatsu, Takimoto Hiroaki, Tofuku Yohei, Shimizu Masami |
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## Crow-Fukase Syndrome Associated with High-Output Heart Failure

Tsutomu ARAKI, Tetsuo KONNO, Ryuichiro SOMA, Akikatsu NAKASHIMA, Hiroaki TAKIMOTO, Yohei TOFUKU and Masami SHIMIZU\*

### Abstract

A 64-year-old woman was admitted with systemic edema and exertional dyspnea. High-output heart failure was diagnosed by right heart catheterization and she was treated with diuretics. After 3 weeks, her symptoms disappeared but a high cardiac output state persisted. A diagnosis of Crow-Fukase syndrome was made based on the presence of polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes. Her serum vascular endothelial growth factor (VEGF) level was markedly elevated after recovery from heart failure. We suspect that an elevated VEGF level and a high cardiac output state may play a role in the pathogenesis of heart failure in Crow-Fukase syndrome.

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**Key words:** POEMS syndrome, vascular endothelial growth factor (VEGF), systemic vascular resistance

### Introduction

Crow-Fukase (POEMS) syndrome is a plasma cell dyscrasia associated with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (1). Although about one-third of patients with this syndrome die as a result of heart failure (2), the etiology of their heart failure remains unclear. We herein report a case of Crow-Fukase syndrome associated with high-output heart failure, as determined by repeated right heart catheterization.

### Case Report

A 64-year-old woman was admitted to our hospital in June 2001, because of systemic edema and exertional dyspnea. She had been diagnosed as having hypertension at the age of 60 for

which she was treated elsewhere with a calcium antagonist. She had experienced progressive edema for the previous six months and a month before admission had developed exertional dyspnea. She had no personal or family history of any heart diseases.

The following were recorded at the time of admission: height, 153 cm; body weight, 63 kg; body temperature, 37.5°C; blood pressure, 160/80 mmHg; and a pulse rate of 80 beats/min and regular. Physical examination revealed severe pitting edema in the distal extremities and diffuse hyperpigmentation of the skin. The jugular veins were distended. A systolic murmur was audible at the fourth intercostal space near the left sternal border, and moist rales were audible in the bilateral lung fields. The abdomen was distended. Neurological examination revealed muscle weakness and glove and stocking type dysesthesia in the distal extremities. Patellar and achilles tendon reflexes were absent. Laboratory data were unremarkable, except for the presence of thrombocytosis ( $56.0 \times 10^4/\mu\text{l}$ ). The erythrocyte count was  $441 \times 10^4/\mu\text{l}$ , the hemoglobin values and hematocrit were 12.8 g/dl and 38.5%, respectively, and the leukocyte count was  $7,400/\mu\text{l}$  (neutrophils 74%; lymphocytes 20%; monocytes 5%). The serum C-reactive protein level was 0.1 mg/dl. Blood chemistry was as follows: total protein, 6.4 g/dl (albumin 55.4%;  $\gamma$ -globulin 18.4%); blood urea nitrogen, 12 mg/dl; creatinine, 0.6 mg/dl; aspartate aminotransferase, 8 IU/l; alanine aminotransferase, 5 IU/l; lactic dehydrogenase, 259 IU/l; alkaline phosphatase, 216 IU/l; creatine phosphokinase, 25 IU/l; total cholesterol, 112 mg/dl; and triglyceride, 100 mg/dl. The serum electrolytes and urine were normal. The fasting blood sugar was 104 mg/dl and HbA<sub>1c</sub> was 4.9%. Arterial blood gas analysis revealed mild hypoxemia (pH 7.409; PO<sub>2</sub> 61.9 mmHg; PCO<sub>2</sub> 40.3 mmHg), and a chest X-ray revealed cardiomegaly (cardiothoracic ratio=56%), mild pulmonary congestion, and pleural effusion (Fig. 1). Abdominal CT showed splenomegaly and mild ascites. An electrocardiogram was normal, except for flat T waves, and an echocardiogram showed left ventricular hypertrophy and dilatation with normal contractility (ejection fraction=76%), left atrial dilatation, and mild pericardial effu-

From the Department of Internal Medicine, Saiseikai Kanazawa Hospital, Kanazawa and \*Molecular Genetics of Cardiovascular Disorders, Division of Cardiovascular Medicine, Graduate School of Medical Science, Kanazawa University, Kanazawa

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Reprint requests should be addressed to Dr. Tsutomu Araki, the Department of Cardiology, Kanazawa Cardiovascular Hospital, 16 Ha, Tanaka-machi, Kanazawa 920-0007



Figure 1. Chest X-ray on admission revealed cardiomegaly, mild pulmonary congestion, and pleural effusion.

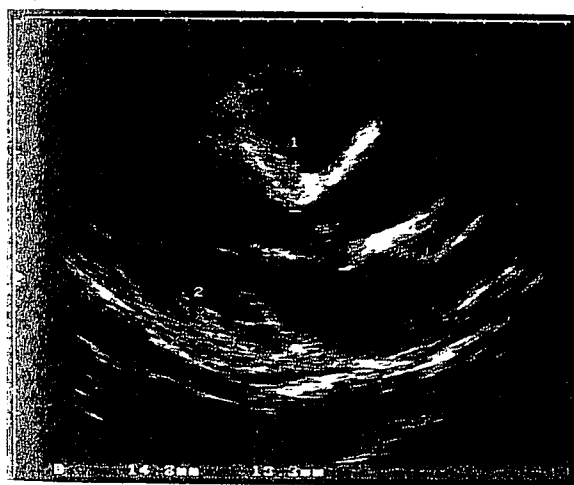


Figure 2. Echocardiogram on admission showed left ventricular hypertrophy and dilatation with normal contractility, left atrial dilatation, and mild pericardial effusion. Interventricular septal thickness: 14 mm, left ventricular posterior wall thickness: 13 mm, left ventricular end-diastolic diameter: 53 mm, left ventricular end-systolic diameter: 29 mm, left atrial diameter: 53 mm.

sion (Fig. 2). Moderate tricuspid regurgitation was detected by color Doppler echocardiography, and the maximal velocity of the regurgitant jet was 3.5 m/sec as determined by continuous wave Doppler echocardiography. Right heart catheterization was performed on the 2nd day, and the results are shown in

Table 1. Hemodynamic Findings

|         |   | Day 2     | Day 26   |
|---------|---|-----------|----------|
| PCW     | (mmHg)  | 14        | 6        |
| PA      | (mmHg)  | 42/18     | 30/10    |
| RV(EDP) | (mmHg)  | 43/7 (14) | 33/1 (5) |
| RA      | (mmHg)  | 10        | 5        |
| CO      | (l/min)                                       | 8.58      | 8.49     |
| CI      | (l/min/m <sup>2</sup> )                       | 5.23      | 5.34     |
| SV      | (ml/beat)                                     | 134       | 120      |
| SI      | (ml/beat/m <sup>2</sup> )                     | 82        | 75       |
| SVR     | (dynes-sec-cm <sup>-5</sup> )                 | 876       | 848      |
| SVRI    | (dynes-sec-cm <sup>-5</sup> /m <sup>2</sup> ) | 534       | 533      |
| BP      | (mmHg)  | 156/78    | 138/72   |
| HR      | (beats/min)                                   | 64        | 71       |
| BSA     | (m <sup>2</sup> )                             | 1.64      | 1.59     |

PCW: pulmonary capillary wedge pressure, PA: pulmonary artery pressure, RV: right ventricular pressure, EDP: end-diastolic pressure, RA: right atrial pressure, CO: cardiac output, CI: cardiac index, SV: stroke volume, SI: stroke index, SVR: systemic vascular resistance, SVRI: systemic vascular resistance index, BP: blood pressure, HR: heart rate, BSA: body surface area.

Table 1. Pulmonary hypertension, a high cardiac output and a decreased systemic vascular resistance were observed. The patient was diagnosed as having high-output heart failure and was treated with diuretics (Torsemide 8 mg/day). Her hypertension with left ventricular hypertrophy was treated with an angiotensin II receptor antagonist (Losartan 50 mg/day). The etiology of her high-output heart failure was not immediately clear, since her thyroid function was near normal (TSH 3.29  $\mu$ U/ml; free T<sub>3</sub> 2.4 pg/ml; free T<sub>4</sub> 1.16 ng/dl), and her serum thiamine level was 40 ng/ml (normal range: 20–50 ng/ml).

Three weeks after admission, the patient's heart failure symptoms disappeared and her body weight and blood pressure decreased to 58 kg and 140/70 mmHg, respectively. Her pulmonary congestion and pleural effusion also disappeared, but her cardiomegaly (cardiothoracic ratio=54%) persisted as revealed by chest X-ray. While her ascites disappeared, her splenomegaly persisted as determined by abdominal CT. Her pericardial effusion and tricuspid regurgitation disappeared, but left ventricular and atrial dilatation persisted on echocardiogram. Right heart catheterization was performed again on the 26th day, and the results are shown in Table 1. Pulmonary artery pressure was found to have decreased, but a high cardiac output and a decreased systemic vascular resistance persisted. Coronary angiography was normal, and a left ventriculogram showed left ventricular dilatation with normal contractility (ejection fraction=67%).

After improvement of her heart failure, the patient's muscle weakness and dysesthesia in the distal extremities worsened. Her nerve conduction velocities were severely delayed. She was referred to a neurologist with suspected Crow-Fukase syndrome because of her peripheral neuropathy, papilledema, splenomegaly, skin hyperpigmentation, and systemic edema. En-

**Table 2. Endocrinological Findings**

|                                    |            |             |               |             |            |      |
|------------------------------------|------------|-------------|---------------|-------------|------------|------|
| ACTH                               | 120 pg/ml  | (9–52)      | PRA           | 0.8 ng/ml/h | (0.3–2.9)  |      |
| Cortisol                           | 11.4 µg/dl | (4.0–18.3)  | PAC           | 40 pg/ml    | (29.9–159) |      |
| TSH                                | 8.53 µU/ml | (0.34–3.50) | Adrenaline    | 9 pg/ml     | (<100)     |      |
| Free T <sub>3</sub>                | 2.3 pg/ml  | (2.47–4.34) | Noradrenaline | 354 pg/ml   | (100–450)  |      |
| Free T <sub>4</sub>                | 0.86 ng/dl | (0.97–1.79) | Dopamine      | 13 pg/ml    | (<20)      |      |
| <75 g oral glucose tolerance test> |            |             |               |             |            |      |
|                                    |            | 0'          | 30'           | 60'         | 90'        | 120' |
| Blood sugar (mg/dl)                |            | 94          | 151           | 180         | 201        | 161  |
| IRI (µU/ml)                        |            | 4.6         | 9.4           | 14.4        | 20.4       | 17.4 |

ACTH: adrenocorticotropic hormone, TSH: thyroid stimulating hormone, T<sub>3</sub>: triiodothyronine, T<sub>4</sub>: thyroxine, PRA: plasma renin activity, PAC: plasma aldosterone concentration, IRI: immunoreactive insulin.

Endocrinological examinations revealed some disturbances including subclinical adrenal insufficiency, mild hypothyroidism, and glucose intolerance, as shown in Table 2. Serum immunoelectrophoresis revealed an M-protein component of the IgA-λ type. Based on these findings, she was diagnosed with Crow-Fukase syndrome. Bone X-rays and scintigraphy did not uncover bone lesions. Neither bone marrow nor lumbar punctures were performed. With regard to cytokines, the serum vascular endothelial growth factor (VEGF) level was markedly elevated (5,020 pg/ml; normal range: <280 pg/ml), and the serum levels of interleukin-1β, interleukin-6 and tumor necrosis factor-α were normal. In August 2001, she was referred to Kanazawa University Hospital for further examination and treatment of her Crow-Fukase syndrome.

### Discussion

Although heart failure is the main cause of death in patients with Crow-Fukase syndrome (2), its etiology remains unclear. Iwasaki et al (3) reported a case of Crow-Fukase syndrome that was associated with pulmonary hypertension and a normal cardiac index (3.5 l/min/m<sup>2</sup>) as determined by right heart catheterization, and suspected that pulmonary hypertension might have caused some of the cardiovascular symptoms in their patient. Okura et al (4) reported a case of Crow-Fukase syndrome that was associated with thiamine deficiency, pulmonary hypertension, and a high cardiac output (7.7 l/min), determined by radionuclide angiocardiology, and speculated that these factors play a role in the pathogenesis of heart failure in this syndrome. High-output heart failure is primarily caused by anemia, systemic arteriovenous fistulas, hyperthyroidism, and beriberi heart disease (5). In the present case, these conditions were not evident, and though this patient had hypertension, that condition is not known to cause high-output heart failure.

Niimi et al (6) reported a case of Crow-Fukase syndrome that was associated with pulmonary hypertension and a high

concentration of serum VEGF, and suggested that there was a close correlation between serum VEGF levels and pulmonary artery pressures. In the present case, the serum VEGF level was markedly elevated after recovery from heart failure. Since VEGF is a multifunctional cytokine that stimulates vasodilation, vascular hyperpermeability, and angiogenesis, and was reported to stimulate endothelial nitric oxide production (7), we suspect that VEGF may have decreased systemic vascular resistance in our patient resulting in the development of a high cardiac output state, which was followed by high-output heart failure. On the other hand, multiple myeloma was also reported to cause a high cardiac output state (8, 9). Since both multiple myeloma and Crow-Fukase syndrome exhibit plasma cell dyscrasia, and since cytokines are suspected in the pathogenesis of both of these diseases (10, 11), we suspect that there may be a common mechanism for the high cardiac output state in both multiple myeloma and Crow-Fukase syndrome, which might be mediated by VEGF. Further studies are necessary to clarify these points.

To our knowledge, this is the first reported case of Crow-Fukase syndrome that was associated with high-output heart failure, as determined by repeated right heart catheterization. Although exactly how serum VEGF levels relate to cardiac output is unclear, we suspect that an elevated VEGF level and a high cardiac output state may play a role in the pathogenesis of heart failure in Crow-Fukase syndrome.

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