CASE REPORT

Crow-Fukase Syndrome Associated with Pulmonary Hypertension

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Keishi Shimizu, Jone-Dae Lee, Takanori Ueda and Toru Nakamura

A 60-year-old woman suffering from heart failure was found to have Crow-Fukase syndrome. A precise cardiovascular study revealed the existence of pulmonary hypertension (PH), cardiomegaly and myocardial hypertrophy in addition to manifestations of this syndrome such as hyperpigmentation, hypertrichosis, finger clubbing, polyneuropathy, organomegaly and plasma cell dyscrasia. These findings suggest the possibility that patients with Crow-Fukase syndrome have cardiopulmonary disorders including PH and cardiomegaly which might cause some cardiovascular symptoms such as peripheral edema and finger clubbing.

(Key words: myocardial hypertrophy, organomegaly, plasma cell dyscrasia, mitochondriosis)

Introduction

Crow-Fukase syndrome, from the names of those who first reported it, has also been called PEP syndrome (a peculiar progressive polyneuritis associated with pigmentation and edema and plasma cell dyscrasia) (1), POEMS (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome (2), and Takatsuki syndrome (3). The symptoms are: 1) chronic progressive peripheral sensorimotor polyneuropathy; 2) skin changes such as diffuse hyperpigmentation, hypertrichosis and thickening; 3) anasarca such as pitting edema on the lower extremities, ascites and pleural effusion; 4) gynecostasia and impotence in men and amenorrhea in women; 5) hepatosplenomegaly and generalized lymphadenopathy; 6) papilledema with increased CSF protein; 7) slight fever, hyperhydrosis and finger clubbing (4). Though the syndrome includes some cardiovascular-like manifestations such as hyperhydrosis and finger clubbing, no accurate studies have been performed with respect to the cardiovascular dynamics. Here, we report the first case of Crow-Fukase syndrome with chronic cardiac failure and pulmonary hypertension (PH).

Case Report

A 60-year-old woman consulted our clinic because of severe dyspnea and anasarca. The patient had felt general malaise, appetite loss, leg edema and hypertrichosis from 2 years before consultation. After visiting several hospitals and clinics without an appropriate diagnosis, she was admitted to our hospital due to progressive dyspnea and systemic edema. A physical examination on admission revealed hyperpigmentation, finger clubbing, Guillain-Barré-type polyneuropathy and hypertrichosis. The heart rate was 80/min (regular) and blood pressure was 200/130 mmHg although the patient did not have a history of hypertension. Decreased oxygen and increased carbon dioxide partial pressures in the arterial blood were found by blood gas analysis (pH 7.44, PaO2 58.5 mmHg, PaCO2 50.2 mmHg). An echocardiogram showed moderate concentric left ventricular hypertrophy and the thickness of the left ventricular posterior wall (LVPW) and the interventricular septum (IVS) were both 15 mm (Fig. 1). Chest X-ray, posteroanterior view shows moderate cardiomegaly (cardio-thoracic ratio were 0.68) and mildly cephalad pulmonary blood flow pattern, and no interstitial pulmonary lesions were recognized. Physical examination and echocardiography showed no evidence of valvular disease or congenital heart disease. Emergency right cardiac catheterization revealed a markedly elevated pulmonary artery pressure and right ventricular pressure (main pulmonary artery (PA): 62/22 (35) mmHg (systolic/diastolic (mean)), pulmonary capillary wedge: (17) mmHg, right ventricle: 62/16 mmHg, right atrium: (10) mmHg, cardiac index 3.51 L/min/m²).

As we suspected the patient had Crow-Fukase syndrome, bone marrow aspiration was performed. The bone marrow aspirate revealed a normocellular marrow (NCC: 16.5×10⁹/mm³) containing 4.6% plasma cells. Some plasma cells were myeloma like, i.e. extraordinary large and contained two to four nuclei (Fig. 2), and showed gathering (Fig. 3). Abdominal

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Crow-Fukase Syndrome and PH

Fig. 1. Two-dimensional and M-mode echocardiogram showing left ventricular hypertrophy. ES: endystolic, ED: enddiastolic, IVS: interventricular septum, PW: posterior wall (LVDD 42mm, LVDS 29mm, EF 67%, LVPW 15mm, IVS 15mm, DDR 40mm/sec, Eamp 8mm, LAD 40mm, AOD 20mm).

computerized tomography (Fig. 4) and echography revealed bilateral pleural effusion, ascites, hepatosplenomegaly, pancreas swelling and adrenal gland swelling. Increased protein level (107 mg/dl) in the cerebrospinal fluid (CSF) and papilledema were also found. The serum protein level was normal and M-protein could not be detected in serum, urine or CSF by immunoelectrophoresis. Other hematological and biochemical data are shown in Table 1.

Fig. 2. Bone marrow aspirate obtained from sternal bone. Abnormal plasma cell with four nuclei (MG staining, x1,000).

Fig. 3. Bone marrow aspirate obtained from sternal bone. Gathering plasma cells are seen. Seven plasma cells are shown in this microscopic field (MG staining, x200).
Fig. 4. Computed tomography (CT) films at the level of the liver and spleen (left side) and the level of the pancreas (right side). These pictures show hepatosplenomegaly and pancreas swelling. Upper: plain CT; Lower: contrast enhancement CT.

Table 1. Hematological and Biochemical Data

<table>
<thead>
<tr>
<th>Peripheral blood</th>
<th>Bone marrow</th>
<th>Biochemistry</th>
<th>Serum</th>
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<tbody>
<tr>
<td>WBC 6,200/mm³</td>
<td>NCC 16.5×10⁹/mm³</td>
<td>Na 139 mEq/l</td>
<td>CRP (±)</td>
</tr>
<tr>
<td>band 11%</td>
<td>myel 1.4%</td>
<td>K 4.7 mEq/l</td>
<td>RA (-)</td>
</tr>
<tr>
<td>seg 60%</td>
<td>promy 2.6%</td>
<td>Cl 101 mEq/l</td>
<td>ASLO (-)</td>
</tr>
<tr>
<td>eos 0%</td>
<td>myel 14.8%</td>
<td>BUN 27 mg/dl</td>
<td></td>
</tr>
<tr>
<td>bas 0%</td>
<td>met 9.0%</td>
<td>UA 5.9 mg/dl</td>
<td></td>
</tr>
<tr>
<td>lym 19%</td>
<td>band 24.6%</td>
<td>Cr 1.7 mg/dl</td>
<td></td>
</tr>
<tr>
<td>mon 10%</td>
<td>seg 4.6%</td>
<td>T-bil 0.3 mg/dl</td>
<td></td>
</tr>
<tr>
<td>RBC 407×10⁶/mm³</td>
<td>eos 3.4%</td>
<td>GOT 9 IU/l</td>
<td></td>
</tr>
<tr>
<td>Hb 12.4 g/dl</td>
<td>bas 1.0%</td>
<td>GPT 9 IU/l</td>
<td></td>
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<tr>
<td>Ht 38.0%</td>
<td>mon 0.8%</td>
<td>LDH 316 IU/l</td>
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<tr>
<td>PLT 16×10⁹/mm³</td>
<td>lym 13.8%</td>
<td>ALP 206 IU/l</td>
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<tr>
<td>plas 4.6%</td>
<td>erybl 19.4%</td>
<td>γ-GTP 34 IU/l</td>
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<tr>
<td>erybl 19.4%</td>
<td>mgk 25/mm³</td>
<td>ChE 1.97 IU/l</td>
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<tr>
<td>M/E 3.16</td>
<td></td>
<td>TP 5.6 g/dl</td>
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<tr>
<td>pls 4.6%</td>
<td></td>
<td>Alb 59.7%</td>
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</tr>
<tr>
<td>α₁ 4.3%</td>
<td></td>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>α₂ 9.1%</td>
<td></td>
<td>ESR 22 mm/hr</td>
<td></td>
</tr>
<tr>
<td>β 9.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ 17.2%</td>
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<td></td>
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</tbody>
</table>

Pressure 130 mmH₂O
Cell count 0/mm³
Cl 129 mg/dl
TP 102 mg/dl
Glu 67 mg/dl
Others
ESR 22 mm/hr
The administration of diuretics, a vasodilator and digitalis or oxygen inhalation lowered the pulmonary capillary wedge pressure (PCWP) and improved her symptoms including hypoxia. However, the mean pulmonary artery pressure was still higher than the normal value [main pulmonary artery pressure: 48/16 (26) mmHg, PCWP: (5) mmHg]. Prednisolone administration dramatically improved her edema as well as neurological symptoms as shown in Fig. 5. The dose of prednisolone was decreased gradually from 40 to 10 mg/day. Right cardiac catheterization after administration of prednisolone revealed normalized PA pressure. Furthermore, hyperpigmentation, hypertrichosis, finger clubbing, papilledema, pleural effusion, ascites and organomegaly also improved following prednisolone treatment. However, the faint sensory disturbance in the bilateral feet still remained at a dose of 10 mg/day for one month. Because it has been reported that interferon-α was found to be effective for multiple myeloma (5), we administered interferon-α-2a and her sensory disturbance gradually improved. However, due to a side effect of gastric disturbance we could not continue this treatment. No remarkable changes in plasma cells were observed by bone marrow aspiration after prednisolone administration. Both postmedication thicknesses of LVPW and IVS were 14 mm. This figure was not improved compared with the premedication value, in other words, myocardial hypertrophy remained.

Endomyocardial biopsy was performed (6) after prednisolone administration to examine myocardial morphology using both light and electron microscopy. In the light microscopic section, the biopsied myocardium from the left posterior wall was composed of slightly hypertrophic myofibrils. Intermyocardial fibrosis was mild to moderate. Neither amyloid deposits nor disarray of myofibrils were seen. In transmission electron microscopic sections, lipofuscin granules found in the myocardium were adjacent to the poles of the elongated nuclei of myocardial cells. The number of lipofuscin granules were within normal limits and the size was also normal. However, severe sarcoplasmic reticulum hyperplasia and mitochondriosis were observed (Fig. 6) although these changes were nonspecific.

Thereafter, we observed that this patient had empty sella diagnosed by magnetic resonance imaging. Empty sella might have been the cause of various neurological disturbances and this is described in a previous report (7).

**Discussion**

Crow-Fukase syndrome, a unique, multisystem disorder, is reported to be associated with plasma cell dyscrasia which is generally used as an inclusive designation for monoclonal or unbalanced proliferation of immunoglobulin-secreting cells (8–10). Takatsuki and Sanada reported that “plasma cell
“organomegaly” is present even in patients without M-protein observed in routine electrophoresis and suggested that many symptoms in this syndrome are “remote” effects caused by plasma cell dyscrasia (8).

In the present case neither hypergammaglobulinemia nor M-protein were detected even by immunoelectrophoresis but a slight increase in atypical plasma cells in bone marrow was found suggesting the existence of plasma cell dyscrasia. A high frequency of complications of peripheral edema in the lower extremities (91%), ascites (62%), pleural effusion (40%) and finger clubbing (56%) has been reported by several investigators (4, 8, 11). These manifestations were similar to the cardiopulmonary symptoms and some patients with Crow-Fukase syndrome were reported to have died due to anasarca (8). These manifestations were thought to be due to the increased capillary leak (12), and it was reported that “systemic capillary leak syndrome” is a form of plasma cell dyscrasia by Atkinson et al (13). This syndrome may have the same status as Crow-Fukase syndrome. In the present case, as the major symptoms were those of heart failure, a precise cardiovascular study was performed showing PH with high PCWP and suggesting that such PH was associated with left heart failure. PH has not yet been reported in this syndrome. We tried to treat this heart failure patient with diuretics, vasodilator and digitalis. One month after treatment, PCWP improved (10 mmHg) but the mean PA pressure still remained higher (26 mmHg) than the normal value. The administration of prednisolone was effective for this patient’s abnormal status, i.e. not only hyperpigmentation, hypertrichosis and polyneuropathy but also for PH. These findings suggest that PH might also be related to the pathogenesis of Crow-Fukase syndrome. For example, finger clubbing, a major complication of Crow-Fukase syndrome, might be due to chronic hypoxia which is caused by PH.

Organomegaly is also a major complication in Crow-Fukase syndrome (4). Previous investigators have described hepatomegaly, splenomegaly and lymphadenopathy but cardiomegaly due to myocardial hypertrophy has not been reported yet. Ventricular hypertrophy as well as hepatosplenomegaly in this patient did not improve following prednisolone administration. Hepatosplenomegaly and myocardial hypertrophy have been thought to be caused by increased capillary leak. Because it is suspected that lung congestion is secondary to leakage of fluid into and the subsequent swelling of the lung, and then myocardial hypertrophy also causes secondarily PH; myocardial hypertrophy might also be a general complication in this syndrome. However, the phenomena in this syndrome has not been discussed from the cardiovascular point of view, and it was not possible to determine whether the myocardial hypertrophy was due to this syndrome or was secondary to hypertension. An electron microscopic study of the myocardium in Crow-Fukase syndrome has not been reported to data.

Endomyocardial degradation of myofibrils and Z-band abnormalities suggesting a hypertrophic cardiomyopathy were not detected but some abnormalities of the organelles which are qualitatively similar to changes in the hypoxic myocardium were found. It might be important to use morphometric techniques in such a case (14). In the present case, sarcoplasmic reticulum hyperplasia and mitochondrialosis were also detected. However, most of the changes in the myocardium detected by light and electron microscopy were nonspecific findings (15).

Thus, this case suggests that some of the manifestations of Crow-Fukase syndrome may be due to cardiovascular abnormalities. Further studies should be done to clarify this point.

References