Crow-Fukase Syndrome with Ischemic Cardiomyopathy

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Abstract

A 31-year-old man was admitted to our hospital for further evaluation of heart failure symptoms. Crow-Fukase syndrome was diagnosed on the basis of findings of polyneuropathy, hepatomegaly, monoclonal hypergamma-globulinemia, and hypertrichosis. Dipyridamole-stress thallium-201 perfusion imaging, contrast left ventriculography, and coronary angiography revealed a markedly dilated and dysfunctioning left ventricle, extensive reversible ischemia with fixed defect, and multiple coronary lesions. Histopathology of myocardial biopsy specimens demonstrated ischemia-induced myocardial necrosis. These findings suggested that ischemic cardiomyopathy, probably due to inflammatory reactions of coronary arteries in Crow-Fukase syndrome, was responsible for the heart failure symptoms and left ventricular dysfunction in this patient. (Internal Medicine 40: 726-730, 2001)

Key words: POEMS syndrome, congestive heart failure, myocardial ischemia, coronary artery disease

Introduction

Crow-Fukase syndrome is a plasma cell dyscrasia with polyneuropathy and organomegaly, endocrinological disturbances, M-proteinemia, and skin lesions (POEMS syndrome) (1-6). Although heart failure is a major cause of death in patients with this syndrome and several cases with cardiomyopathy have been reported (7-9), the pathogenesis of this disorder and mechanisms underlying the cardiac involvement have not been determined. We encountered a case of Crow-Fukase syndrome with congestive heart failure that was found to be due to ischemic cardiomyopathy. The findings in the present case suggested one of the possible mechanisms underlying cardiac involvement that leads to heart failure and poor clinical outcome in patients with Crow-Fukase syndrome.

Case Report

A 31-year-old man was admitted to the Neurology Department in our hospital for evaluation of progressive lower extremity paresthesias, low-grade fever, edema of lower limbs, and impotence that had persisted for two years. He had no major coronary risk factors other than cigarette smoking. The diagnosis of Crow-Fukase syndrome was made on the basis of findings of polyneuropathy, hepatomegaly, M-proteinemia, and hypertrichosis. He underwent an operation to remove a solitary plasma cytoma at the right femoral bone, which was possibly related to this syndrome. Despite the improvement in paresthesias and low-grade fever, dyspnea and tachycardia subsequently developed. He was transferred to our department for evaluation and treatment of the heart failure symptoms. His blood pressure was 94/68 mmHg and heart rate was 120 beats per minute. In addition to hepatosplenomegaly, pretibial edema, gynecomastia and diffuse skin hyperpigmentation, jugular vein distension, S3 gallop rhythm, and moist lung crackle were detected. Chest X-ray revealed cardiomegaly and pulmonary congestion (Fig. 1A) and an electrocardiogram showed a sinus tachycardia with a ST-segment depression and T-wave inversion in leads V4 through V6 (Fig. 1B). Results of laboratory examinations revealed a normochromic normocytic anemia with a hemoglobin level of 11.2 g/dl, increased white cell counts (16,100/mm³), and hypoproteinemia (5.0 g/dl). There were increases in the serum vascular endothelial growth factor (VEGF) level (1,410 pg/ml) and tumor necrosis factor-alpha (TNF-α) level (15.0 pg/ml) (10, 11), but after resection of solitary plasma cytoma, they decreased to 38 pg/ml and to less than 4.0 pg/ml, respectively. The results of immunoelectrophoresis showed a monoclonal protein of the IgA λ type and elevated cerebrospinal fluid protein level (130 mg/dl).

Dipyridamole-stress thallium-201 perfusion imaging demonstrated a markedly dilated left ventricle and extensive perfusion defects at anterior, septal, lateral, inferior, and apical walls with redistribution at the anterioapical and lateral walls (Fig. 2), indicating reversible ischemia with irreversible myocardial damage. Selective coronary arteriography showed diffuse and multiple coronary narrowings and thrombus with a luminal

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Internal Medicine Vol. 40, No. 8 (August 2001)
Ischemic Heart Failure in POEMS Syndrome

Figure 1. Chest radiograph shows cardiomegaly and bilateral pulmonary congestion (A), and an electrocardiogram (B) demonstrates sinus tachycardia at a rate of 109 beats per minute and ST-segment depression with T-wave inversion in leads V4 through V6.

Figure 2. In addition to a markedly dilated left ventricle, dipyridamole-stress thallium-201 perfusion tomograms show both fixed perfusion defects at apical and inferior walls and reversible perfusion abnormality at the lateral wall. The anteroapical region also has a partial reversible perfusion abnormality with a persistent perfusion defect.

narrowing of 75% or more at the relatively distal portions of the left anterior descending, left circumflex, and right coronary arteries (Fig. 3A). A contrast left ventriculogram also revealed a considerably enlarged left ventricular cavity and generally reduced wall motion with left ventricular ejection fraction of 32% (Fig. 3B). Histopathology of a right ventricular endomyocardial biopsy showed localized myocardial damage with fibrosis, coagulation necrosis, and contraction band ne-
Figure 3. (A) Selective coronary arteriography clearly demonstrates diffuse and multiple areas of coronary narrowing (small arrows) and thrombus formation (large arrows) with a luminal narrowing of 75% or more at the distal portions of left and right coronary arteries. LAD: left anterior descending artery, Lx: left circumflex artery, RCA: right coronary artery. (B) Contrast left ventriculogram indicates markedly enlarged left ventricle, generally reduced wall motion, and left ventricular ejection fraction of 32%.

crosis (Fig. 4) but no disarray nor deposition of abnormal protein suggestive of non-ischemic or idiopathic cardiomyopathy was found, indicating irreversible injury due to myocardial ischemia. These findings suggested that ischemic cardiomyopathy due to coronary lesions leading to microvascular dysfunction had resulted in ischemia-related left ventricular dysfunction and heart failure symptoms in this patient. Following the plasma cytoma resection, treatment with an anticoagulant (warfarin), nitrate, diuretic, angiotensin-converting enzyme inhibitor, and β-blocker for heart failure and myocardial ischemia was started. His heart failure and neurological symptoms gradually disappeared, and serum levels of VEGF, TNF-α and γ-globulin decreased. Eight months later, cardiac enlargement and dysfunction had improved; cardiothoracic ratio had de-
lesions, however, are unlikely to be associated with age-related coronary myocardial infarction were responsible for the myocardial in-
creased from 50% to 43%, left ventricular end-diastolic dimension had decreased from 61 mm to 58 mm, and left ventricular ejection fraction had increased from 32% to 41%. Repeated stress perfusion scintigraphy and coronary angiography, however, showed residual reversible ischemia and coronary narrowing, respectively.

Discussion

Crow-Fukase syndrome causes systemic disturbances due to plasma cell dyscrasia, including various kinds of cardiac involvement, such as coronary artery disease and "idiopathic" cardiomyopathy, leading to poor clinical outcomes (6–9). Nakanishi et al (6) reported that approximately one-third of the causes of death in 102 patients with this syndrome was heart failure and that the mean survival interval was 33 months. However, mechanisms underlying the cardiac involvement that lead to lethal outcomes in this disorder and the etiological implications of Crow-Fukase syndrome in coronary artery disease remain to be established (1–9). It is evident that our patient had heart failure attributed to ischemic cardiomyopathy because of diffuse and multiple coronary lesions with coronary thrombus and because of inducible myocardial ischemia with extensive irreversible damage, as clearly demonstrated by stress perfusion imaging. The fixed perfusion abnormality is likely related to a severe wall motion abnormality and to be consistent with the massive coagulation necrosis with contraction band formation histopathologically identified. These findings strongly suggest that severe and reversible ischemia and myocardial infarction were responsible for the myocardial injury and depressed cardiac function in this case. The coronary lesions, however, are unlikely to be associated with age-related arteriosclerosis, Kawasaki disease, idiopathic cardiomyopathy, or other types of non-ischemic cardiac diseases in this patient without major coronary risk factors.

Manning et al (12) suggested that abnormal immunoreactions are responsible for coronary lesions and myocardial infarction in this syndrome. Abnormal immunoglobulin bound to the endothelium or basement membrane of the coronary artery possibly leads to direct endothelial dysfunction, and coronary artery injury could be indirectly caused by subsequent inflammatory response (12). According to the result of recent studies, it is likely that this syndrome can be explained by abnormal immunoreactions mediated by cytokines, such as interleukin 6, VEGF, TNF-α, and immunoglobulins, that are produced by plasma cells (13–15). Notably, VEGF has been shown to have multiple biological effects on the endothelium, such as 1) a high affinity to endothelial cells, 2) potent and rapid induction of microvascular hyperpermeability and extravasation of plasma proteins, including fibrinogen and coagulation factors, 3) an increase in endothelial production of plasminogen activators, plasminogen activator inhibitor-1 (PAI-1) and so forth, and 4) increased production under a hypoxic condition (16, 17). Thus, it is possible that VEGF is responsible for impairment of endothelial function of the coronary artery and microcirculation in this disorder. The present patient actually had pathologic immunoreactions. Decreases in serum levels of VEGF, TNF-α, and monoclonal γ-globulin after surgical resection of solitary plasma cytoma appear to be related to improvement of neurological and cardiac symptoms and clinical signs, including cardiac function. In addition, despite the lack of major coronary risk factors and the relatively young age of the patient, his coronary arteries had complicated multiple lesions. These findings strongly suggest that abnormal immunoreactions via plasma cell dyscrasia caused coronary vasculitis and endothelial injury leading to ischemic cardiomyopathy in this patient with Crow-Fukase syndrome. These considerations also suggest that modification of immune reactions using immunosuppressants or other methods is a promising treatment for this disease. Coronary revascularization is an effective treatment for ischemic cardiomyopathy if angiographically indicated. In the present case, however, coronary intervention was not performed for several reasons. The coronary lesions had multiple distal areas of narrowing as well as proximal stenoses, multiple thrombus formation, and poor run-off; hypercoagulability and vascular inflammatory reactions are possibly involved in the coronary disease in this syndrome; and it was speculated that anticoagulant treatment would be effective and that vasculitis and immunoreactions could be normalized since the plasma cytoma had been removed. Further clinical and immunological investigation is, however, required to determine the immunological mechanisms underlying myocardial injury and coronary lesions in order to develop therapeutic and prophylactic strategies, including immunosuppression, against cardiac involvement responsible for lethal clinical outcomes in Crow-Fukase syndrome.

In conclusion, the clinical findings in this case of Crow-Fukase syndrome with congestive heart failure suggested that ischemic cardiomyopathy, probably due to immunological reactions of coronary arteries, was responsible for heart failure.
symptoms, cardiac enlargement, and left ventricular dysfunction.

References