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Case Report

Reversible Cardiomyopathy Associated with Multicentric Castleman Disease: Successful Treatment with Tocilizumab, an Anti–Interleukin 6 Receptor Antibody

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Abstract

Multicentric Castleman disease (MCD) is a rare lymphoproliferative disorder characterized by systemic lymphadenopathy and inflammatory symptoms that are associated with the overproduction of interleukin 6 (IL-6). Although several nonlymphoid organs can also be damaged in MCD, only a few cases with cardiac complications have been reported to date. We report a case of congestive heart failure in a female patient with MCD. On admission, her echocardiogram revealed a dilated and diffusely hypokinetic left ventricle. No stenosis was evident in the coronary angiogram. A histopathologic examination of a myocardial biopsy specimen showed mildly hypertrophic myocytes without infiltration of plasma cells or amyloid deposits. Repeated administration of an anti–IL-6 receptor antibody, tocilizumab (formerly known as MRA), gradually improved the ventricular wall motion over 6 months without any additional treatment for heart failure, suggesting the involvement of IL-6 in the pathogenesis of her cardiomyopathy. This report is the first of MCD complicated by heart failure treated successfully with tocilizumab. Administering tocilizumab in cases of MCD with unexplained cardiac dysfunction is worthwhile, because such a complication could be reversible.
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Key words: Multicentric Castleman disease; Anti–interleukin 6 receptor antibody; Heart failure

1. Introduction

Castleman disease (CD) was originally described by Castleman in 1956 as a solitary mediastinal tumor resembling thymoma and characterized by lymph node hyperplasia with germinal center formation and marked capillary proliferation [1]. Histopathologically, CD is classified into 2 groups, a hyalinized vascular type and a plasma cell type; the latter with systemic lymphadenopathy is called multicentric CD (MCD) [2]. MCD is usually accompanied by inflammatory symptoms such as fever, general fatigue, and appetite loss, as well as by abnormal laboratory findings, including an elevated serum C-reactive protein (CRP) level, hypoalbuminemia, and hypergammaglobulinemia. Dysregulated overproduction of interleukin 6 (IL-6) by B-cells in germinal centers has been speculated to play a pivotal role in the pathogenesis of MCD [3]. Although steroids and other immunosuppressants, such as cyclophosphamide, have been used to treat patients with MCD with limited efficacy, an anti–IL-6 receptor (IL-6R) antagonist, tocilizumab (MRA), has been shown to have a dramatic effect on alleviating symptoms of this disease [4].

Various vital organs, such as the lung and kidney, can be damaged in MCD. Only a few cases of MCD with cardiac complications have been reported to date, and the mechanism of these complications remains to be elucidated [5-9]. We report a case of MCD with chronic heart failure with features of dilated cardiomyopathy that was treated successfully with tocilizumab.

2. Case Report

A 21-year-old woman visited Kyoto University Hospital for general fatigue and low-grade fever. A physical examination showed systemic lymphadenopathy, and her laboratory

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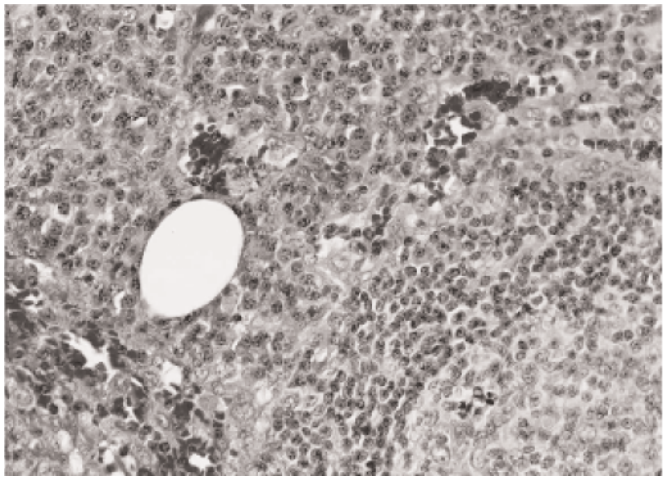

Figure 1. Hematoxylin and eosin staining of an axillary lymph node at diagnosis. A reactive germinal center and marked proliferation of plasma cells in interfollicular areas are observed (original magnification ×400).

data revealed elevated levels of serum CRP and IL-6 (39.0 pg/mL; normal range, <4 pg/mL). MCD of the plasma cell type was diagnosed on the basis of a histopathologic examination of an axillary lymph node (Figure 1). The results of a test for antibody to human immunodeficiency virus in the serum were negative. Results of polymerase chain reaction analyses for human herpesvirus 8 DNA in the lymph node and the peripheral blood were also negative. A bone marrow aspirate revealed a slight increase in plasma cells, accounting for 8% of all nucleated cells. An echocardiographic evaluation performed at diagnosis for tachycardia was normal (Table 1). Since then, the patient was treated with prednisolone, methotrexate, and cyclophosphamide without any remarkable improvement of her symptoms.

Three years after the initial diagnosis, the patient was admitted to Kyoto University Hospital because of exacerbation of fever, general fatigue, and dyspnea on effort. On admission, she was taking 15 mg of prednisolone per day. Her pulse rate was 152 beats/min, and her body temperature was 37.7°C. The S3 and S4 heart sounds were clearly audible as a gallop rhythm. Multiple lymph nodes (0.5 cm to 1.5 cm in size) were palpable bilaterally in the cervical, axillary, and inguinal areas. The patient's abdomen was soft and distended, and the liver was palpable 3 cm below the right costal margin. The results of a neurologic examination were negative. Laboratory examinations showed leukocytosis (white blood cell count, 13,700/μL) with 2% plasma cells in the peripheral blood and severe microcytic anemia (hemoglobin, 4.5 g/dL; mean corpuscular volume, 69.0 fL). A serum protein analysis revealed hypoalbuminemia (albumin, 1.6 g/dL) with polyclonal hypergammaglobulinemia (immunoglobulin G, 6646 mg/dL). No M protein was detected by immunoelectrophoresis. The levels of CRP, IL-6, and vascular endothelial growth factor (VEGF) were extremely high (28.9 mg/dL, 215 pg/mL, and 1121 pg/mL, respectively). Computed tomography scanning revealed multiple swollen lymph nodes in supraclavicular, axillary, mediastinal, and para-aortic regions, as well as hepatosplenomegaly and a small amount of ascites. The patient's electrocardiogram showed sinus tachycardia, and a chest radiograph revealed mild cardiomegaly (cardiothoracic ratio, 56%). Her echocardiogram revealed the left ventricle (LV) to be severely hypocontractile and mildly dilated (estimated LV ejection fraction, 32%; LV diastolic diameter, 53 mm), findings that were consistent with dilated cardiomyopathy (Table 1 and Figure 2). The serum levels of atrial natriuretic peptide and brain natriuretic peptide were elevated (60.6 pg/mL and 180.5 pg/mL, respectively). To elucidate the etiology of her heart failure, we performed a cardiac catheterization. No significant stenosis was evident in the coronary angiogram. Swan-Ganz catheterization revealed the pulmonary artery and pulmonary capillary wedge pressures to be normal (mean pulmonary artery pressure, 15 mm Hg; pulmonary capillary wedge pressure, 13 mm Hg), and the cardiac output and the cardiac index were 4.96 L/min and 3.75 L/min per m^2, respectively. A histopathologic examination of the endomyocardial biopsy specimen from the right ventricle showed focal fibrosis and mildly hypertrophic myocytes, without any deposits of amyloid or infiltration of plasma cells.

After patient admission, 4 units of red blood cells were transfused without any improvement of the general fatigue or tachycardia. We then administered 8 mg/kg of tocilizumab intravenously, which dramatically alleviated her symptoms, including the high-grade fever and general fatigue, without any complications. The CRP level decreased from 28.9 mg/dL to 2.6 mg/dL in 10 days (Figure 3).

After the first tocilizumab dose, the serum IL-6 level increased from 215 pg/mL to 1390 pg/mL, and the VEGF level

Table 1.
Changes in Echocardiogram Findings*

			Time After Admission		
	At Diagnosis	On Admission	1 mo	6 mo	9 mo
LVDd, mm	45	53	57	46	44
LVDs, mm	32	45	43	34	36
EF (Teichholz)	56%	32%	48%	51%	50%
IVSTd, mm	7	7	7	7	5
PWTd, mm	7	7	8	9	9

*LVDd indicates left ventricular internal dimension in diastole; LVDs, left ventricular internal dimension in systole; EF, ejection fraction; IVSTd, interventricular septum thickness in diastole; PWTd, posterior left ventricular wall thickness in diastole.

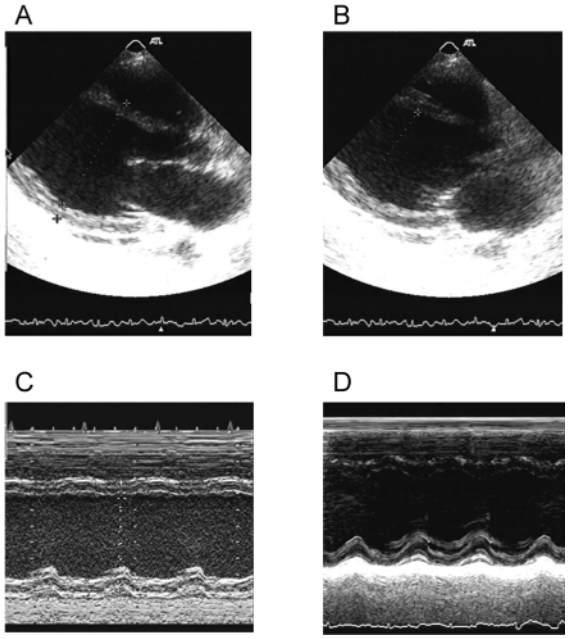

Figure 2. A and B, Parasternal long-axis B-mode view of the echocardiogram in end diastole (A) and end systole (B) on patient admission. The left ventricle was markedly dilated and severely hypokinetic. C and D, M-mode view of the left ventricle at the level of the tendinous cords on admission (C) and 9 months after the administration of tocilizumab (D).

decreased from 1121 pg/mL to 594 pg/mL. Tocilizumab began to be administrated in 2-week intervals. After the fourth dose of tocilizumab, we changed the interval to 1 week because its administration in 2-week intervals could not achieve a serum concentration sufficient to completely suppress the inflammatory reactions. The sizes of the lymph nodes and spleen gradually decreased, and her cardiac function improved steadily. The estimated ejection fraction increased from 32% to 51% in 6 months (Table 1, Figures 2 and 3). The serum levels of atrial natriuretic peptide and brain natriuretic peptide decreased in 1 year to 13.8 pg/mL and 4.9 pg/mL, respectively.

3. Discussion

Although multiorgan involvement, such as respiratory and renal damage, is frequently observed in MCD, cardiac complications are rare, with only 5 cases having been reported to date (Table 2) [5-9]. Diffuse hypokinesis of LV wall motion was evident on echocardiograms in all cases. Cardiac amyloidosis was diagnosed in 1 case by Congo red staining of the myocardium biopsy specimen, but the etiology of the cardiac dysfunction was not determined in the other 4 cases. In 2 of these cases, cardiac function and systemic symptoms were restored with the administration of corticosteroids.

In the current case, cardiac function was severely deteriorated at the time of patient admission, compared with the function at initial diagnosis. Angiographic and echocardiographic studies showed findings, including LV dilatation and diffusely hypokinetic LV wall motion, that were indistinguishable from those of dilated cardiomyopathy, and we observed neither amyloid deposits nor plasmacytic infiltration in the myocardial biopsy specimen. Repeated administrations of tocilizumab gradually improved the cardiac function without any specific treatment for heart failure. Simultaneously, the systemic inflammatory symptoms were resolved, and the abnormal laboratory findings were normalized. The increase in the serum IL-6 level and the decrease in the serum VEGF level after the first tocilizumab dose are consistent with the results of a previous report [10].

IL-6 is a pleiotropic cytokine with various biological activities, including immunoregulation, support of hematopoiesis, and induction of acute-phase inflammatory reactions. The binding of IL-6 to IL-6R induces the disulfide-linked homodimerization of gp130, leading to the activation of Janus kinase (JAK) and tyrosine phosphorylation of gp130. These events lead to the activation of multiple signal-transducing pathways, such as the signal transducer and activator of transcription 3 (STAT3), Ras and mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase pathways [11,12]. An association between IL-6 and cardiovascular diseases has been implicated in both clinical and experimental settings [13-15]. Cardiac myxoma is known to produce IL-6, which has been postulated to be involved in ventricular hypertrophy [13,16]. Hirota et al reported that the circulating level of IL-6 was elevated in patients with congestive heart failure, implying the association of IL-6 in the pathogenesis of cardiac dysfunction [17].

Ancey et al showed that human cardiomyocyte hypertrophy could be induced by gp130 stimulation in vitro, and this action was associated with IL-6 and STAT3 pathway activation [18]. Double-transgenic mice overexpressing both IL-6 and IL-6R showed constitutive tyrosine phosphorylation of gp130 and STAT3 in the heart, and concentric hypertrophy and a decreased LV volume were observed in these mice [19]. In addition to myocardial hypertrophy, acute and chronic

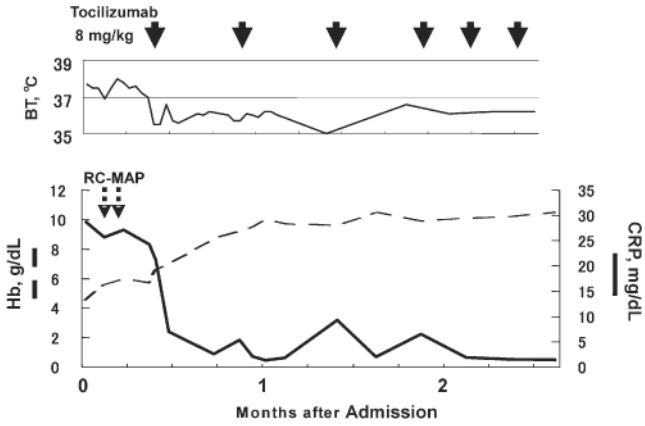

Figure 3. Clinical course after tocilizumab administration. Solid arrows indicate tocilizumab doses; dashed arrows indicate doses of red cell concentrate in mannitol-adenine-phosphate solution (RC-MAP). Solid and dashed lines indicate serum C-reactive protein (CRP) and hemoglobin (Hb) levels, respectively. BT indicates body temperature.

Table 2.
Cases of Castleman Disease Associated with Heart Failure*

Case No.	Reference	Age, y/Sex	Chest Radiograph	Echocardiography	CAG	Myocardium Biopsy	Clinical Course
1	[6]	70/F	Marked cardiomegaly, pulmonary congestion	EF, 30%; diffuse LV hypokinesis; increased echo-reflectivity of the endocardium	No stenosis	Mild hypertrophic myocytes with various sizes of nuclei	NS
2	[7]	50/M	CTR, 73%; bilateral pleural effusions	EF, 33%; dilatation of LV; diffuse LV hypokinesis; increased echo-reflectivity of the LV wall	NS	No abnormality	Steroid administration normalized cardiac function within 2 wk
3	[8]	72/F	CTR, 82.2%; mediastinal enlargement	EF, 41.8%; diffuse LV hypokinesis	No stenosis	Fibrosis and mildly atrophic and hypertrophic myocardium with fatty changes	NS
4	[9]	34/F	Bilateral pleural effusions, mediastinal enlargement	EF, 20%; diffuse LV hypokinesis; small pericardial effusion; increased echo-reflectivity of the endocardium	NS	Increased perivascular connective tissue and T-lymphocyte infiltration; Congo red staining indicated amyloid deposits	Administration of steroid relieved symptoms; EF was 51% at 1 y after steroid administration
5	[10]	65/NS	CTR, 66%; left pleural effusion	EF, 72%; mild diastolic dysfunction; pericardial effusion of LV wall	Not done	Not done	NS
6	Current case	24/F	CTR, 56%	EF, 32%; diffuse LV hypokinesis	No stenosis	Mild to moderate hypertrophied myocytes with various sizes of nuclei	EF and LV wall motion were improved within 6 mo after tocilizumab administration

*CAG indicates coronary angiogram; F, female; EF, ejection fraction; LV, left ventricle; NS, not stated; M, male; CTR, cardiothoracic ratio.

exposure to IL-6 has been shown to exert a reversible, negative inotropic effect on myocardiocytes through a nitric oxide–dependent pathway mediated by STAT3. Finkel et al showed that brief exposure to IL-6 inhibited the contractility of isolated hamster papillary muscles in a concentration-dependent and reversible manner. A nitric oxide synthase inhibitor, N^G-monomethyl-L-arginine, blocked this negative inotropic effect, indicating that this inotropic effect of IL-6 is mediated by nitric oxide synthase [20]. Yu et al showed that long-term exposure to IL-6 decreases contractile and sarcoplasmic reticular function through a nitric oxide–dependent mechanism in adult rat ventricular myocytes [21]. In our case, the severe hypokinesis of the LV observed on admission was mostly reversed by treatment with an IL-6R antibody, tocilizumab. These observations suggested that the main mechanism of hypocontractility of the LV wall in the current case was the negative inotropic effect of IL-6 on cardiomyocytes rather than irreversible myocardial changes.

Along with the IL-6–associated mechanisms, severe anemia might have promoted cardiac dysfunction in our case. The possibility of myocarditis following viral infection cannot be entirely excluded because the patient had been treated with prednisolone for a long period, which might have increased the incidence of viral infection. Another possible cause of heart failure in this case is the high serum level of VEGF. POEMS syndrome, which is characterized by polyneuropathy, organomegaly, endocrinopathy, M protein, skin lesions, and an elevated level of VEGF, has features that overlap with those of CD in terms of cytokine parameters and plasma cell dyscrasia [22]. Etiologies of heart failure associated with POEMS syndrome include cardiac amyloidosis, ischemic cardiomyopathy, and elevated serum VEGF levels, which can cause high-output failure or pulmonary hypertension [23,24]. Cardiac myxoma is another disease that produces VEGF [25]. In the current case, no characteristics of POEMS syndrome other than plasma cell dyscrasia were observed, nor were cardiac tumors detected with echocardiography, although VEGF involvement could not be ruled out in the etiology of heart failure.

Thus, various factors can cause heart failure in MCD. In the current case, we postulate that IL-6 might have been crucially involved in the pathogenesis of the patient's cardiomyopathy because treatment with tocilizumab clearly improved her cardiac function. Heart failure has been previously reported as one of the serious adverse events of tocilizumab therapy [26]; however, our current case suggests that administering tocilizumab with careful monitoring of cardiac function may be worthwhile, even in cases of MCD complicated with severe cardiac failure. Further studies are necessary to clarify the pathogenesis of cardiac complications in CD.

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