

A Case of Multicentric Castleman's Disease Having Lung Lesion Successfully Treated with Humanized Anti-interleukin-6 Receptor Antibody, Tocilizumab

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This report presents the case of a patient demonstrating multicentric Castleman's disease (MCD) with a lung lesion that was successfully treated with an anti-interleukin-6 receptor antibody, tocilizumab in combination with corticosteroid and tacrolimus. A 43-yr-old female with abnormal shadows on a chest X-ray was referred to the hospital for further examination. She was diagnosed as having MCD based on the characteristic pathology of inguinal lymph node, lung lesions, laboratory data, and undifferentiated arthritis. Corticosteroid and rituximab therapy did not fully ameliorate the symptoms; thus, the therapeutic regimen was changed to include tocilizumab, oral corticosteroid and tacrolimus. This regimen resulted in clinical remission and the dose of tocilizumab and corticosteroid could be tapered. Tocilizumab in combination with corticosteroid and tacrolimus may therefore be a beneficial treatment regimen for lung lesions associated with MCD.

Key Words: Giant Lymph Node Hyperplasia; Biological Products; Immunosuppressive Agents

INTRODUCTION

Castleman's disease is a lymphoproliferative disorder with benign hyperplastic lymph nodes characterized histologically by (A) follicular hyperplasia, and (B) capillary proliferation with endothelial hyperplasia (1). This disease has been classified histopathologically as hyalinevascular, plasma cell, or a mixed type variant of the two (2, 3). The plasma cell and mixed types are often associated with 'multicentric Castleman's disease' (MCD), which shows various systemic manifestations, such as fever, anemia, hypergammaglobulinemia, hypoalbuminemia, and an increase in acute phase proteins (2). MCD is often refractory to conventional therapeutic strategies, such as corticosteroid, cytotoxic agents, and/or radiation (4, 5). The frequency of MCD associated with a lung lesion among the Japanese population is high (~70%) (6) and such progressive lung lesions often lead to death (2, 7).

Interleukin-6 (IL-6) is a pleiotropic cytokine with a wide range of biologic activities, such as hematopoiesis, regulation of immune responses, and inflammatory responses (4). Patients with the plasma cell type Castleman's disease often generate large quantities of IL-6 in the germinal centers of hyperplastic lymph nodes (8).

'Tocilizumab' is a humanized anti-interleukin-6 receptor an-

tibody that neutralizes the pleiotropic actions of IL-6. It was approved for use in Japan for the treatment of Castleman's disease in 2005.

This report describes a case of MCD with an associated lung lesion, which responded dramatically to tocilizumab in combination with corticosteroid and tacrolimus.

CASE REPORT

A 43-yr-old female visited a nearby hospital because of abnormal shadows including multiple nodules and reticular shadows on chest radiography found at an annual medical checkup in 2005. A bronchoscopic examination was performed. They were unable to obtain a biopsy specimen from one of the nodules in S10 of the left lung because the patient had a strong bleeding tendency. She was referred to this hospital for further examination on June 30, 2005.

On admission, her height was 157.5 cm and weight, 50.3 kg. Her consciousness was clear. The conjunctivas were anemic and not jaundiced. Her heart sounds were normal. Fine crackles were audible in the right lower lung field. The abdomen was not distended. Her inguinal lymph nodes were palpable and no other superficial lymph nodes were palpable. She was experiencing slight polyarthralgia, however, radiography films showed no joint

anomalies.

The laboratory data were: erythrocyte sedimentation rate, 119 mm/1 hr; white cell count, 8,900/ μ L; hemoglobin, 8.4 g/dL; platelet count, 39.4×10^4 / μ L; serum aspartate aminotransferase, 22 IU/L; alanine aminotransferase, 22; total protein, 9.7 g/dL; albumin 2.6; creatinine, 0.48; PT, 13.1 sec (INR 1.45); aPTT, 39.6 (control, 10.4); fibrinogen, 750 mg/dL; KL-6, 277 U/mL (reference range <500); C-reactive protein, 11.7 mg/dL (<0.3); serum immunoglobulin (Ig)G, 4,570 (870-1740); IgA, 491 (110-400), IgM, 706 (35-220), CH50, 52.3 U/mL (30-50), soluble IL-2 receptor, 1,400; serum IL-6, 6.8 pg/mL (<4); rheumatoid factor (RF), 1,330 IU/mL (<20). Autoantibodies, including antinuclear antibody, anti-dsDNA, anti-Sm, anti-RNP, cytoplasmic antineutrophil cytoplasmic antibody (ANCA), and myeloperoxidase-ANCA were all negative. M-protein was not noted in serum immunoelectrophoresis. Bone marrow aspiration showed hyperplasia with no abnormal morphology on smear specimens.

Chest radiographs showed multiple nodules and reticular shadows mainly in the lower lung field. Chest CT scan disclosed a slight enlargement of the mediastinal lymph nodes, centrilobular nodules, thin-walled cysts, the thickening of the bronchovascular bundles, and ground-grass opacities, all of these find-

ings were compatible with those of lymphocytic interstitial pneumonia (LIP; Fig. 1A) (5, 9). ⁶⁷Gallium citrate scintigraphy did not reveal any evident accumulation.

A lung surgeon and a thoracic physician declined to perform a lung biopsy because of her bleeding tendency (bleeding time: 6 min 30 sec) and poor general condition. A biopsy of an inguinal lymph node was obtained for making a definite diagnosis (Fig. 2). She was diagnosed with MCD and undifferentiated arthritis based on the characteristic pathology of the specimen of the inguinal lymph node, CT findings of the bilateral lung lesions and laboratory data.

She was initially administered intravenous corticosteroid (methylprednisolone, 500 mg/day, 3 consecutive days) followed by oral corticosteroid (methylprednisolone, 16 mg/day), and, 375 mg/m² rituximab every week for 4 weeks. The polyarthralgia instantly disappeared; however, none of the other clinical and laboratory parameters were fully resolved. Therefore the therapeutic regimen was changed to tocilizumab (8 mg/kg, every 2 weeks), oral corticosteroid (methylprednisolone, 16 mg/day) on October 25, 2005. The patient requested that the interval between tocilizumab to be increased to more than every two weeks. The dose of corticosteroid in combination with tocilizumab should



Fig. 1. Chest CT findings (A) just before the second regimen, of tocilizumab in combination with corticosteroid and tacrolimus: centrilobular nodules, thin walled cysts, the thickening of the bronchovascular bundles and ground-grass opacities were noted; (B) Thirteen months after the continuation of the second regimen; (C) after twenty three months: most of the lesions had alleviated.

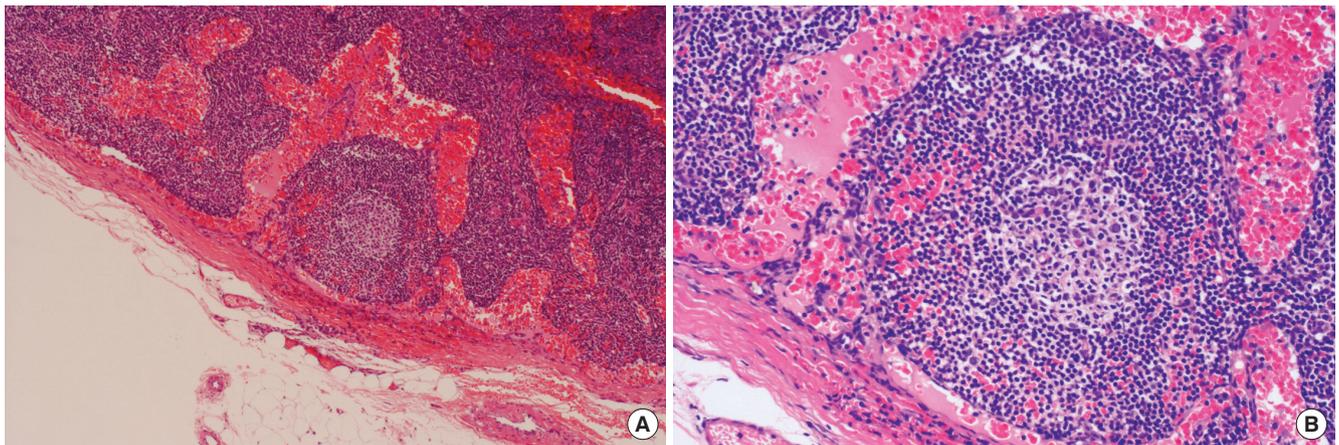


Fig. 2. The specimen obtained from the inguinal lymph node. Microscopic examination of the lymph node showed typical features of plasma cell type Castleman's disease (A, H&E stain, $\times 40$; B, H&E stain, $\times 200$).

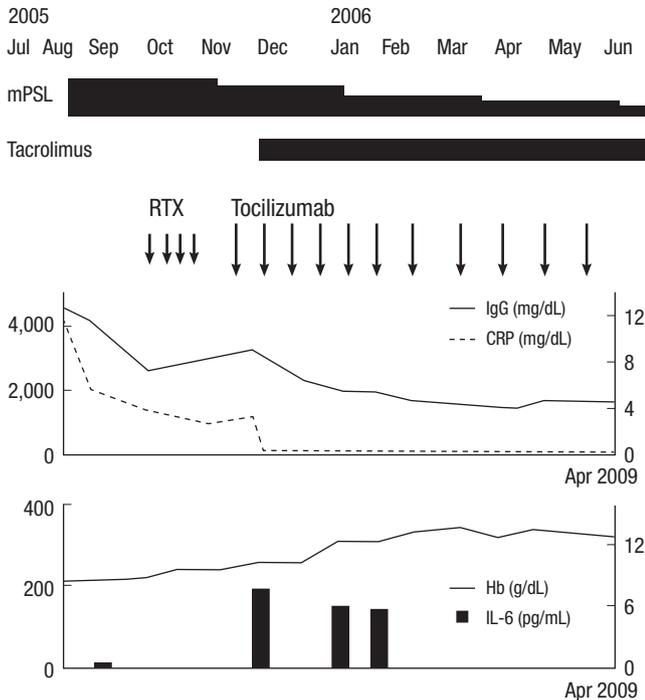


Fig. 3. Clinical course of the patient. mPSL, methylprednisolone; RTX, rituximab 375 mg/m²; tocilizumab, tocilizumab 6 mg/kg. The dose of mPSL could be gradually tapered from 16 mg/day to 4 mg/day.

be kept as low as possible to avoid various side effects, such as osteoporosis, hyperglycemia, and hypertension. It is indicated for the treatment of rheumatoid arthritis in Japan. The addition of tacrolimus to the regimen was considered to fulfill such requirements. Both the possible merits and demerits of the drug were explained to the patient and her oral consent was obtained. Tacrolimus (3 mg/day) was introduced on November 10, 2005. Laboratory findings, including anemia, hypergammaglobulinemia, and an increase in acute phase proteins responded to this regimen (Fig. 3). The enlargement of mediastinal lymph nodes and abnormal shadows were also partially alleviated (Fig. 1B, C). The intervals of the tocilizumab-administration sessions were extended from every 2 weeks to every 3 weeks from January 2006. Oral corticosteroid was gradually tapered from 16 mg/day finally to 4 mg/day. The dose of tacrolimus has been unchanged. The disease activity has been totally suppressed for 36 months by this maintenance regimen.

DISCUSSION

The treatment of MCD includes various therapeutic strategies such as corticosteroid, chemotherapy, rituximab, or tocilizumab. Rituximab, an immunoglobulin G1 (IgG1) κ monoclonal antibody to CD20, has the potential for B-lymphocyte depletion via antibody-dependent cell mediated-cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), and apoptosis. Kaposi's sarcoma-associated herpes virus (KSHV/HHV8) was thought

to be associated with the development of Castleman's disease, especially in patients infected with human immunodeficiency virus (HIV) and rituximab was reported to be effective in HIV-related Castleman's disease (11). The effectiveness of rituximab was limited in the present case because the patient was not infected with HIV. A humanized anti-interleukin-6 receptor antibody, tocilizumab, was shown to be effective for the treatment of MCD in an open label trial, and has been widely used in Japan (5).

The frequency of MCD associated with a lung lesion is relatively low (10-20%) in the United States. In contrast, Nishimoto et al. reported that 18 of 28 Japanese cases (=64.3%) had a lung lesion (6). The CT findings of intrathoracic involvement in MCD include bilateral hilar and mediastinal lymphadenopathy, centrilobular nodular opacities, thin-walled cysts, interlobular septal thickening, and ground-glass attenuation (9). Some reports have noted that the lung lesion in MCD is compatible with lymphocytic interstitial pneumonia (LIP) (5, 9).

Ohno et al. (12) reported a case of MCD with a lung lesion that responded to tocilizumab. In contrast, Akahane et al. (7) described that the administration of tocilizumab for 2 yr had no effect on the lung lesion in an MCD patient. The main target of calcineurin inhibitors is generally thought to be T cells. IL-6 production by the germinal center B cells in the swollen lymph nodes of patients with MCD is remarkable (8), but the roles of T cells are unknown. If T cells do participate in the pathogenesis, immunosuppressive drugs for T cells should be useful. In fact, MCD, which is classified as a lymphoproliferative disorder, has characteristics of an autoimmune disease, demonstrated by the production of autoantibodies. Several studies have shown that these drugs are active not only against T cells but also against other cells. For example, they are used for the treatment of RA. They suppress the promotion of IL-6 in the rheumatoid synovium where T cells are relatively scarce (13). They also suppress IL-6 production in monocytes, and TNF- α production in B cells (14, 15). Pham et al. (16) reported that inhibition of NF- κ B and NFAT activation in aggressive B-cell lymphomas by calcineurin inhibitors suppressed the CD40 ligand expression in B cells and lymphoma cell survival in an in vitro experiment. Some of these actions of tacrolimus, if not all, may be associated with the efficacy of the drug for the treatment of MCD. In fact, Miltenyi et al. (17) reported that non-cytostatic immunomodulatory therapy including corticosteroid, cyclosporine A and thalidomide treatment was effective for Castleman's disease.

The long-time use of tocilizumab and corticosteroid is necessary for the treatment of MCD. Corticosteroid has various dose-related side effects, and acquisition of drug resistance possible. P-glycoprotein (P-gp) plays a pivotal role in the latter. Peripheral lymphocytes in patients with autoimmune diseases could express P-gp on their cell surface. Calcineurin inhibitors have an antagonistic activity to P-gp: they may inhibit corticosteroid-

resistance in peripheral lymphocytes in vivo (18, 19). The dose of corticosteroid could be tapered in the current case, at least in part, due to the antagonistic activity to P-gp of tacrolimus.

In conclusion, this is the first report to describe that tocilizumab, in combination with corticosteroid and tacrolimus, shows a dramatic effectiveness in the treatment of a lung lesion in an MCD patient.

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