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Multicentric IL-5-positive Castleman Disease With Nephrotic Syndrome Relapsed After Rituximab Treatment

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Abstract. *Background/Aim: To date, no reports of interleukin (IL)-5-producing Castleman disease with nephrotic syndrome and moreover no reports of relapse after remission with rituximab treatment, have been published. Case Report: A 67-year-old male presented to the Osaka Medical and Pharmaceutical University Hospital with a history of low-grade fever, papules, and nephrotic syndrome. Lymph nodes were palpated in the inguinal region. The patient showed anemia, eosinophilia, polyclonal hypergammaglobulinemia, and elevated interleukin (IL)-6 levels. Patient's serum IL-5 and IL-6 levels were measured using ELISA and immunohistochemical staining of lymph nodes was performed with antibodies specific to CD134. Histological examination confirmed diagnosis of a plasma cell variant of Castleman disease. After a total of four weekly doses of rituximab, urinary protein disappeared, and skin symptoms improved. However, one month after rituximab treatment, the skin rash worsened again, and eosinophils and IL-5 were elevated significantly. Conclusion: This is the first report of recurrent Castleman disease with direct evidence of increased serum IL-5. It may be reasonable to use rituximab, an anti-CD20 antibody for treating the disease, however, for IL-5-producing cases the effect of rituximab may be partial.*

Castleman disease is a neoplastic and lymphoproliferative disease characterized by unregulated cytokine production. Fever, anemia, and multifocal lymphadenopathy are usually present. The disease presents in three subtypes based on the histopathology; the plasma cell dominant, the hyaline vascular, and the mixed type. It is reported that an inflammatory cytokine, interleukin (IL)-6 is over-produced by enlarged lymph nodes in the plasma cell dominant type of Castleman disease, increasing systemic inflammatory response (1-3). Castleman disease is also classified as localized type or multicentric type based on the distribution of swollen lymph nodes. The former pattern presents with localized lymphadenopathy with solitary masses and is often curable by surgical resection or radiation therapy. On the other hand, the latter pattern shows generalized lymphadenopathy and resistance to treatment (1-3). IL-5 along with IL-6 has been reported to play a role in the pathophysiology of the Castleman disease (2, 3).

There have been no reports of IL-5-producing Castleman disease with nephrotic syndrome and furthermore, no reports of relapse after remission with rituximab treatment. Hence, we discuss a case of plasma cell type, multicentric Castleman disease with eosinophilia and elevated immunoglobulin (Ig)E and IL-5.

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Key Words: Castleman disease, nephrotic syndrome, IL-5, eosinophilia, rituximab.

Case Report

A 68-year-old Japanese man was referred to the Osaka Medical and Pharmaceutical University Hospital with low-grade fever, leg edema, and papules. He had no history of asthma, parasite infections, or other allergic diseases which might have caused eosinophilia. Physical examination showed leg edema, palpable lymph nodes in the right inguinal region, and papules on the trunk and extremities. The abdomen was soft and non-tender. The spleen, liver, and kidneys were not palpable.

Upon admission, his body temperature was 37.7˚C and blood pressure was 139/81 mmHg. Table I shows the clinical data on admission. On admission, urinalysis showed mild proteinuria of 3.79 g/g creatinine (urine protein-to-creatinine ratio). Anemia (hemoglobin; 7.6g/dl) and severe eosinophilia (4,260/ml were observed. The inflammatory marker, C-reactive protein was found increased (CRP; 6.26 mg/dl). Increases in IgG were also observed (IgG; 1,957 mg/dl). Autoantibodies, such as rheumatoid factor, anti-cyclic

Table I. *Clinical data of patient on admission.*

Laboratory data	
White blood cells (10^3/μl)	6.10
Eosinophils (/μl)	4,260
Hemoglobin (g/dl)	7.6
Platelet (10^3/μl)	211
CRP (mg/dl)	11.77
Total bilirubin (mg/dl)	0.2
AST (IU/l)	18
ALT (IU/l)	30
LDH (U/l)	250
Albumin (g/dl)	1.5
BUN (mg/dl)	26
Creatinine (mg/dl)	1.4
Na (mEq/l)	131
K (mEq/l)	5.1
IgG (mg/dl)	1,957
IgA (mg/dl)	280
IgM (mg/dl)	122
C3 (mg/dl)	163
C4 (mg/dl)	34.8
RF (IU/ml)	<3
MPO-ANCA (EU)	<0.5
PR3-ANCA (EU)	<0.5
Anti-ds-DNA Ab (IU/ml)	1.9
Anti-Sm Ab (IU/ml)	<10.0
IL-6 (pg/ml)	26.7
Urinalysis	
pH	8.0
Blood	–
Protein	+
Urinary protein (g/g creatinine)	3.79

CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; Na: serum sodium; K: potassium; IgG: immunoglobulin G; IgA: immunoglobulin A; IgM: immunoglobulin M; C3: complement C3; C4: complement C4; RF: rheumatoid factor; MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibodies; PR3-ANCA: proteinase-3--anti-neutrophil cytoplasmic antibodies; Anti-ds-DNA Ab: anti-double stranded DNA antibody; Anti-Sm Ab: anti-Smith antibody; IL-6: interleukin-6.

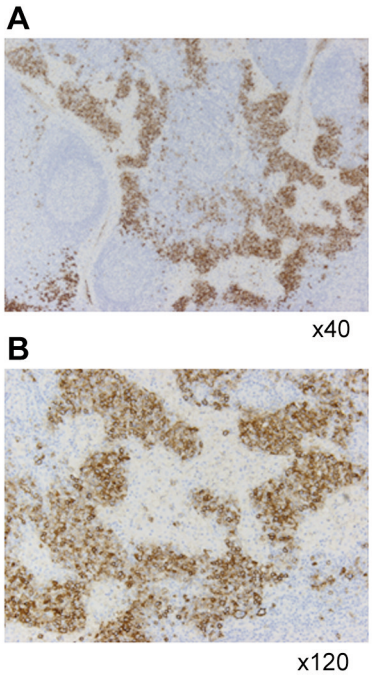

Figure 1. *Immunohistochemical staining of CD134 in lymph nodes. CD134, belongs to the tumor necrosis factor (TNF) receptor superfamily and positive cells were detected in the interfollicular area of the excised lymph node. (A) Magnification ×40. (B) Magnification ×120.*

citrullinated peptide antibody, anti-double stranded DNA antibody, anti-Sm antibody, and anti-cardiolipin antibody. Viral serological tests for hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV)-1 were negative.

A computed tomography (CT) scan revealed the presence of multiple swollen lymph nodes in the mediastinum and pelvis, ranging in size from 1 to 2 cm. Surgical biopsy of the swollen lymph nodes in the inguinal region was performed. Histopathological examination of the excised lymph nodes revealed follicular hyperplasia with thickening of mantle cells and expansion of plasma cells in the interfollicular area. CD134-positive cells, which belong to the tumor necrosis factor (TNF) receptor superfamily, function as a specific entry receptor for human herpes virus (HHV)-6B were detected by immunohistochemical staining. It is reported that HHV-8 or Kaposi's sarcoma-associated herpes virus infection is one possible cause of multicentric Castleman disease, especially in HIV-positive patients (4, 5). However, the HHV-8 antibody in this patient was a false-positive finding. Based on clinical symptoms and pathological analysis of lymph node tissue, a diagnosis of Castleman disease was made.

Treatment with rituximab, an anti-CD20 monoclonal antibody, for HHV-8 positive multicentric Castleman disease has been reported. Although HHV-8 antibody was false-positive, rituximab was administrated at weekly doses of 500 mg for 4 doses. After rituximab treatment, proteinuria was significantly decreased, and the nephrotic syndrome was in complete remission. Fever, papules, anemia, and lymphadenopathy dramatically improved. However, one month after the end of rituximab treatment, skin rash and fever flared up. Eosinophilia was prominent again (5,494/μl) and IgE was significantly increased (9,880 IU/ml). Based on these findings, we considered the possibility of IL-5-producing Castleman disease and measured levels of IL-5, which were elevated at 11.3 pg/ml, leading to a definite diagnosis of IL-5-producing Castleman disease. There have been few reports of IL-5-producing Castleman disease, but induction of prednisolone (40 mg/day) significantly reduced fever and improved skin rash. Furthermore, decreases in the

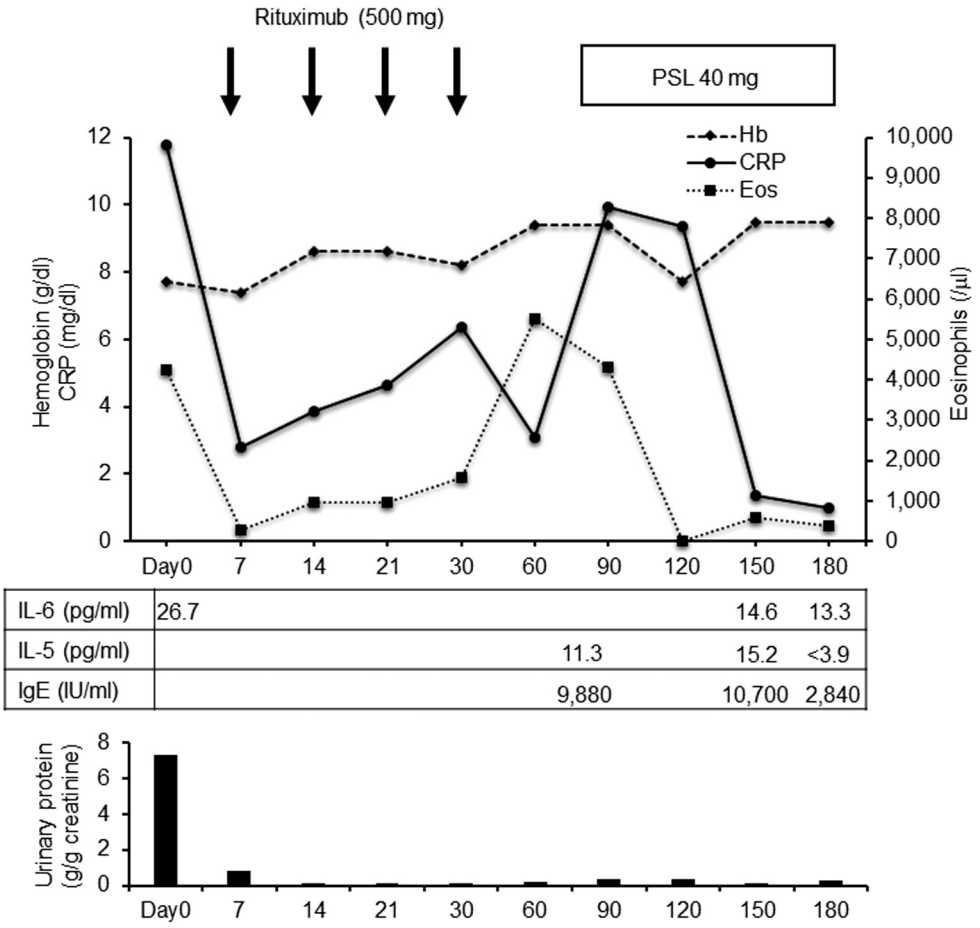

Figure 2. *Clinical course of the present case. Hb: Hemoglobin; CRP: C-reactive protein; Eos: eosinophils; IL-6: interleukin-6; IL-5: interleukin-5; IgE: immunoglobulin E; PSL: prednisolone.*

levels of laboratory markers, including CRP (0.98 mg/dl), eosinophil (398/μl), IgE (2,840 IU/ml), IL-6 (13.3 pg/ml) were recognized, and levels of IL-5 fell below the detection limit (Figure 1). Clinical course of the presented case is shown in Figure 2.

ELISA assay. Serum levels of IL-5 and IL-6 were measured using an ELISA kit by enzyme-linked immunosorbent assay (R&D systems, Minneapolis, MN, USA) and absorbance was read using ELISA reader at 450nm (TECAN, Zürich, Switzerland).

Biochemical examination. Blood biochemical analyses were performed on a Hitachi labospect 008 (Hitachi, Tokyo, Japan) autoanalyzer.

Calculation of eGFR. Levels of serum creatinine were measured using an enzymatic laboratory method, and the values are represented using two decimal places. The eGFR of each patient was calculated using the following formula: 194 × serum creatinine−1.094 × age−0.287 × [0.739 (if female)].

Lymph node biopsy. Lymph node specimens were fixed in 10% formalin, and immunohistochemical staining was performed with antibodies specific to CD134 using an established avidin-biotin detection method.

Discussion

Castleman disease is a hyperplastic lymphoproliferative disorder characterized by multicentric follicular hyperplasia and abundant plasma cell proliferation (6). Castleman disease is known for abnormal IL-6 secretion in lymph nodes, and increased expression of IL-6 can be recognized in germinal center cells as well as in the mantle zone and interfollicular region (7). The etiology of the disease remains unclear; however, a viral etiology is postulated that results in immune dysregulation and atypical lymphoproliferative processes.

Castleman disease's symptoms are thought to be due to release of various cytokines, including ILs and vascular endothelial growth factor (VEGF). Furthermore, IL-6 is believed to be of pivotal role in developing Castleman disease. The pathogenic feature of Kaposi's sarcoma-associated HHV-8 in association with cytokines; HHV-8 could produce an IL-6 homolog (8, 9). A previous report showed that mice receiving transplants of IL-6 retrovirus-infected bone marrow cells could increase plasma cell proliferation (10). IL-6 can increase VEGF secretion which plays a pivotal role in angiogenesis and vascular permeability (6, 11, 12). It is also involved in B cell proliferation and differentiation into antibody-producing cells, causing follicular hyperplasia and lymph node enlargement (13, 14). We reported that levels of IL-6 were increased in chronic kidney disease (CKD) model rodents (15, 16). Furthermore, VEGF expression has been reported to be increased in the glomeruli of CKD (17, 18). The precise mechanism of nephrotic syndrome development due to Castleman disease remains unclear, but one possibility is an increase in these cytokines, which have vascular and membrane permeability.

The role of IL-5 in the pathophysiology of Castleman disease has not been extensively studied. A role of IL-5 along with IL-6 in has been proposed in the pathophysiology of the disease; eosinophilia and remarkably elevated serum levels of IL-5 and IL-6 were observed in multicentric plasma cell-dominant Castleman disease. As in our case, induction of glucocorticoids normalized the levels of IL-5 and eosinophilia (2). Thus, IL-5 is considered to be related to Castleman disease and responsible for eosinophilia. IL-5 also stimulates B-cell growth and immunoglobulin secretion (19). At this point, it may be reasonable to use rituximab, an anti-CD20 antibody for the treatment of Castleman disease. However, the effect may be partial, since it may not directly suppress IL-5 production. Indeed, our case showed relapse of the disease after rituximab treatment.

In summary, we report a case of unicentric plasma cell variant of the IL-5-producing Castleman disease with eosinophilia and nephrotic syndrome. Furthermore, treatment with rituximab was partially effective and complete remission was achieved with glucocorticoids.

Conflicts of Interest

A. Mima received a speaker's honorarium from Novartis, Kyowa Kirin, Mitsubishi Tanabe, Torii, Kowa, Bayer, Eli Lilly, Mochida, Astellas, and Boehringer Ingelheim. A. Mima received research grants from Kyowa Kirin, Sumitomo Pharma, Otsuka, Torii, Daiichi-Sankyo, Kowa, Mitsubishi Tanabe, and Boehringer Ingelheim.

Authors' Contributions

A. Mima and R. Lee contributed to the conception and design of the study. Material preparation, data collection, and analyses were performed by A. Mima, A. Murakami, H. Gotoda, R. Akai, and S. Lee. The first draft of the manuscript was written by A. Mima.

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