We herein report the long-term outcome (30 years) of a human immunodeficiency virus- and human herpesvirus 8-negative Japanese man who was diagnosed to have multicentric Castleman disease (MCD) of the plasmacytic type after investigation of generalized lymphadenopathy at 34 of age in 1983. He received chemotherapy based on lymphoma regimens (combinations of prednisolone, vincristine, vindesine, cyclophosphamide, etoposide, melphalan, and ranimustine, etc.) for over 20 years. Although the systemic lymphadenopathy resolved, AA amyloidosis-related nephropathy occurred, with a serum creatinine (Cre) level of 0.9 mg/dL and urinary protein excretion (UP) of 7.5 g daily. Rituximab was started, but Cre increased to 2.6 mg/dL in 2010 and UP was unchanged. Therefore, treatment with tocilizumab was started. As a result, his hypergammaglobulinemia was well controlled, C-reactive protein became normal, UP decreased to 3.5 g daily, and Cre remained at 2.5 mg/dL in 2013. When AA amyloid nephropathy occurred after long-term chemotherapy, rituximab could not control it, but tocilizumab stopped the progression of nephropathy. This case suggests that MCD and AA amyloidosis may both have a close relationship to the overproduction of interleukin-6.

Key words: multicentric Castleman disease, humanized anti-IL-6 receptor antibody, tocilizumab, IL-6, rituximab

Table. Laboratory Tests.

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<tr>
<td></td>
<td>(34 years)</td>
<td>(54 years)</td>
<td>(60 years)</td>
<td>(64 years)</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>12.5</td>
<td>9.8</td>
<td>7</td>
<td>11.2</td>
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<tr>
<td>TP (g/dL)</td>
<td>10.2</td>
<td>9.2</td>
<td>8.4</td>
<td>6.9</td>
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<tr>
<td>Alb (g/dL)</td>
<td>1.7</td>
<td>1.9</td>
<td>1.8</td>
<td>3.2</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>5+</td>
<td>4.9</td>
<td>4.7</td>
<td>0</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>0.9</td>
<td>0.9</td>
<td>2.6</td>
<td>2.6</td>
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<tr>
<td>IgG (mg/dL)</td>
<td>8,422</td>
<td>4,388</td>
<td>3,734</td>
<td>1,523</td>
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<tr>
<td>IL-6 (pg/mL)</td>
<td>14.2</td>
<td>10.7</td>
<td>778</td>
<td>7</td>
</tr>
<tr>
<td>Urinary protein (g/day)</td>
<td>0.21</td>
<td>7.46</td>
<td>6.98</td>
<td>3.56</td>
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Figure 1. Cervical lymph node biopsy revealed hyperplasia of the lymphoid follicles with prominent infiltration of plasma cells between the follicles (original magnification x40).

Figure 2. Clinical course. PSL: prednisolone, VCR: vincristine, CY: cyclophosphamide, VP16: etoposide, VDS: vindesine, Mel: melphalan

rected against CD20 (rituximab) became available in the 2000s (5-11). In 2005, Nishimoto et al. demonstrated that a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody (tocilizumab) was another therapeutic option for MCD (12). They also reported that IL-6 overproduction plays a role in the etiology of this disease, since patients with MCD showed marked improvement on tocilizumab therapy (12, 13). However, there is still no gold standard treatment for MCD and no randomized trials have been conducted.

We herein report on an HIV- and HHV-8-negative Japanese man who was diagnosed with MCD of the plasmacytic type at 34 years of age. The long-term outcome of this patient over 30 years is discussed along with the various treatments (steroids, chemotherapy, rituximab, and tocilizumab) that he has received over time.

Case Report

In 1983, a 34-year-old Japanese man was admitted to our hospital for the evaluation of generalized lymphadenopathy and weight loss. Elevation of the zinc sulfate turbidity test (ZTT) and thymol turbidity test (TTT) had been detected by annual screening one year earlier.

On admission, his cervical, supraclavicular, axillary, and inguinal lymph nodes were palpable bilaterally. Laboratory tests showed a total protein (TP) of 10.2 g/dL, ZTT of 19.5 KU (normal: 2.3 to 12), TTT of 13.3 (normal: 0 to 5), qualitative C-reactive protein (CRP) of 5+ and hemoglobin of 12.5 g/dL. Urinary protein excretion was 0.21 g daily (Table). Cervical lymph node biopsy revealed hyperplasia of the lymphoid follicles with prominent infiltration of plasma cells between follicles (Fig. 1). Plasmacytic MCD was diagnosed based on the patient’s symptoms, laboratory findings, lymph node histology and exclusion of other conditions such as infection, autoimmune diseases and malignant tumors. Treatment was initiated with prednisolone (PSL) at a dose of 20 mg daily, but his anemia failed to improve and CRP remained high (Fig. 2). In 1985, his hemoglobin (Hb) declined to 9.5 g/dL. Microcytic hypochromic anemia without iron deficiency was diagnosed, with a mean corpuscular volume of 76.1 fl. Intravenous vincristine (1.5 g) and cyclophosphamide (500 mg) were added on a monthly basis. Vincristine was discontinued after two months because of fever after infusion, but cyclophosphamide was continued until 1990. In 1987, his TP remained around 10-12 g/dL and anemia also persisted. Etoposide (VP-16) (50 mg) was administered three times weekly for two months. In 1990, his Hb dropped to 5.9 g/dL and TP increased to 12.9 g/dL. Cyclophosphamide was discontinued. Intravenous vindesine (3 mg) and carboquone (3 mg) were started monthly, while PSL was increased to 40 mg daily. Carboquone was stopped in 1992, but vindesine and PSL were continued until 2005. In 1991, melphalan (6 mg per three weeks) was added, and was administered until 1998. In 1993, monthly intravenous ranimustine (50 mg) was started, and was continued until 1994. Also in 1994, plasma exchange with fresh frozen plasma was performed to treat hyperglobulinemia, but the effect was transient. Vindesine and PSL were continued because lymphadenopathy resolved, although total protein remained at 10 to 11 g/dL. In 2005, his proteinuria progressed. Laboratory tests revealed the following (Table): TP of 9.2 g/dL, albumin of 1.9 g/dL, urea nitrogen (UN) of 16 mg/dL, creatinine (Cre) of 0.9 mg/dL, CRP of 4.9 mg/dL,
IgG of 4,388 mg/dL, IgA of 648 g/dL, IgM of 266 mg/dL and IL-6 of 14.2 pg/mL. HIV and HHV-8 were negative. Urinary protein excretion (UP) was 7.5 g daily, and the urinary sediment contained one to five erythrocytes per high power field (HPF). Renal biopsy was performed.

**Renal biopsy findings**

A light microscopic examination revealed 19 glomeruli, among which four glomeruli showed global sclerosis. Deposits of amorphous material were seen in the glomeruli, small arteries and tubules (Fig. 3a). These deposits were positive by Congo red staining (Fig. 3b) and showed apple green birefringence under polarizing light. Immunohistochemical staining was positive for AA (Fig. 3c), but was negative for the kappa and lambda chains, beta-2 microglobulin and prealbumin. Electron microscopy showed randomly arranged fibrils measuring 8-12 nm in diameter in the deposits (Fig. 3d). Accordingly, AA amyloidosis was diagnosed.

**Clinical course**

Treatment with rituximab (600 mg) was initiated four times, but it was not effective (Fig. 2). In 2010, his renal function deteriorated with a UN of 35 mg/dL and Cre of 2.6 mg/dL. TP was 8.4 g/dL, albumin was 1.8 g/dL, IgG was 3,734 mg/dL, CRP was 4.7 mg/dL, Hb was 7.0 g/dL and UP was 6.98 g daily (Table). HIV and HHV-8 were negative. In June 2010, tocilizumab was initiated at a dose of 520 mg (8 mg/kg) every two weeks. This agent was effective and CRP became negative. In November 2014, his UN was 35 mg/dL and Cre was 2.6 mg/dL. In addition, TP was 6.9 g/dL, albumin was 3.2 g/dL, IgG was 1,523 mg/dL, CRP was 0.0, Hb was 11.2 g/dL and UP was 3.56 g daily (Table). Therefore, both anemia and hypergammaglobulinemia showed improvement while his renal function remained stable.

**Discussion**

The treatment outcomes in MCD are generally considered to be unfavorable. The change in the treatment regimens for patients with MCD will now be summarized. Chemotherapy based on non-Hodgkin’s lymphoma regimens, such as CHOP, has been performed for MCD and controls some systemic symptoms, but has not been shown to improve survival. Patients with MCD often die of multiple organ failure,
progressive KS, bacterial infection and non-Hodgkin’s lymphoma (1). Oksenhendler et al. evaluated 20 patients with HIV-positive MCD, and reported that single-agent chemotherapy with vinblastine was effective and may prolong survival. However, death occurred in 14 patients and the median survival time was only 14 months. Non-Hodgkin’s lymphoma developed in two patients and Kaposi’s sarcoma occurred in three patients (2). Scott et al. reported two patients with the HIV-positive plasma cell type of MCD. In case 1, treatment with paclitaxel and doxorubicin was ineffective. Etoposide (VP-16) (50 mg) was administered every other day and led to marked improvement of systemic symptoms, including weight loss, anorexia and relapsing fever and regression of lymphadenopathy after one year. In case 2, etoposide was administered as a first-line therapy, and the patient’s fever, lymphadenopathy and systemic symptoms subsided after three months. The long-term outcome of these patients remains uncertain (3). Simko et al. reported treatment using interferon-alpha for an 11-year-old boy with the plasma cell type of MCD. The patient was treated with 2 million units/m² of interferon-alpha every day and clinical improvement was dramatic. This patient has remained alive for eight years so far (4). Rituximab specifically binds to CD20 antigen, a 35-kDa transmembrane protein, which is involved in cell cycle progression and differentiation, and causes rapid depletion of CD20-positive B cells from the peripheral blood (5). Corbellino et al. reported a case of HIV-1-positive and KSHV-positive MCD (6). Treatment with an anti-herpesvirus agent, antituberculous chemotherapy and combination therapy with antiretroviral agents did not achieve durable clinical or virologic remission. In contrast, the administration of rituximab was well-tolerated and led to remission of clinical symptoms and KSHV viremia for 14 months (6). Marcelin et al. reported five patients with HIV-positive MCD who were treated by rituximab. Two of the patients died rapidly. The other three patients were considered to be in complete remission with no symptoms of MCD after follow-up for 4 to 14 months, but an aggravation of Kaposi’s sarcoma was observed in two patients (7). Gholam et al. reported the first case of HIV-negative and HHV-8-negative MCD that showed shrinkage of the involved lymph nodes after two cycles of combination chemotherapy (cyclophosphamide, vincristine and corticosteroids) and rituximab. However, there was no effect on cardiac and gastrointestinal amyloidosis, and this patient died (8). Ide et al. reported a 61-year-old man with HIV-negative MCD and bilateral orbital tumors, who showed a marked improvement after treatment with rituximab and PSL (9). Ocio et al. reported an HIV-negative and HHV-8-negative patient MCD with immune hemolytic anemia and Raynaud’s phenomenon who was successfully treated with rituximab alone (10). Robinson et al. obtained clinical data on 59 MCD patients who attended two MCD referral centers in the United States (US) between 2000 and 2009. There were 35 HIV-negative patients and six HIV-positive patients, while the HIV status of the others was unknown. During the first year of follow-up, the chief two systemic therapies were PSL and rituximab monotherapy, while steroids, rituximab and immunomodulatory agents (lenalidomide or thalidomide) were also given either alone or in combination with other agents. Both CVP (cyclophosphamide, vincristine and PSL) and CHOP were used. After a follow-up of two years, 92% of the patients were still alive. Rituximab is considered to be one of the best therapeutic options in the US, but the long-term outcome achieved with rituximab remains unknown. In addition, the effect of rituximab on MCD with AA amyloid remains unknown (11). Tocilizumab, a humanized anti-IL-6R antibody, is expected to normalize the levels of acute-phase proteins, including CRP, by inhibiting the IL-6R and thus ameliorate the symptoms of IL-6-related diseases such as rheumatoid arthritis and MCD. Nishimoto et al. reported on the effect of tocilizumab in 28 patients with plasmacytic MCD and systemic manifestations (12, 13). Two patients were seropositive for HIV-8, but none of them were seropositive for HIV. Fifteen patients had received prior treatment with PSL and four patients had received chemotherapy with agents such as cyclophosphamide, melphalan and PSL. The authors reported that MCD markedly improved by tocilizumab therapy. Of the 28 patients enrolled in the study, 27 patients (96.4%) have continued to receive tocilizumab for more than three years and have shown long-term improvement of lymphadenopathy and all inflammatory parameters. One patient withdrew from the study at 40 weeks because of aggravation of a concurrent disease (chronic myelomonocytic leukemia), and died at 57 weeks.

The relationship between MCD and AA-amyloidosis was reported by Ikeda et al. (14). They encountered a 21-year-old woman with MCD who was diagnosed with AA-amyloidosis by biopsies of liver tissues and gastric mucosa. Since both serum SAA and IL-6 decreased to within normal levels and all clinical abnormalities greatly improved, after surgical excision of a large retroperitoneal lymph node showing pathology of MCD, they hypothesized that abnormal production of IL-6 may stimulate the synthesis of an amyloid precursor (SAA), causing systemic reactive (AA) amyloidosis (14). This theory was also supported by Lachmann (15).

In conclusion, we herein described the long-term outcome (30 years) of an HIV and HHV-8 negative Japanese man who was diagnosed with MCD after an investigation of systemic disease at 34 years of age. Chemotherapy based on lymphoma regimens was performed for over 20 years, but AA amyloidosis-related nephropathy occurred. Rituximab could not control this patient’s nephropathy, but tocilizumab suppressed its progression. This case suggests that MCD and AA amyloidosis are both related to the overproduction of IL-6.

The authors state that they have no Conflict of Interest (COI).
Financial Support
This study was funded by the Okinaka Memorial Institute for Medical Research.

References

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