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CASE REPORT

Successful rituximab treatment of an elderly Japanese patient with HHV8-positive, HIV-negative multicentric Castleman disease

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Abstract

Human herpesvirus-8 (HHV8)-positive, human immunodeficiency virus (HIV)-negative multicentric Castleman disease (MCD) is a rare and age-related lymphoproliferative disorder caused by cytokine storm. Rituximab treatment is currently recommended because B-cell depletion eliminates the primary reservoir for HHV8. We report the first case of effective rituximab treatment of a Japanese patient (an 87-year-old woman) with this disorder. Her inflammatory symptoms and lymphadenopathy improved after medium-dose steroid therapy, but these symptoms recurred during steroid tapering. After one course of rituximab therapy, she achieved sustained remission. HHV8-associated MCD should be considered as a possible diagnosis in HIV-negative patients with inflammatory symptoms and lymphadenopathy.

Keywords Human herpesvirus-8 · Human immunodeficiency virus · Multicentric Castleman disease · Rituximab

Introduction

Multicentric Castleman disease (MCD), a rare lymphoproliferative disease, is a heterogeneous group of systemic hematological disorders that share characteristic lymph node histopathology [1, 2]. The annual incidence rates of MCD in the United States and Japan are 5.1–5.7 and 2.4–5.8 per million individuals, respectively [3, 4]. Although MCD has a long history, it is difficult to diagnose due to the lack of well-established diagnostic criteria, resulting in underestimation of its incidence [2, 4, 5].

According to the recent classification, MCD is divided into idiopathic MCD (iMCD), human herpesvirus-8 (HHV8)-associated MCD, and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes)-associated MCD. HHV8-associated MCD is further subclassified into HHV8-positive, human immunodeficiency virus (HIV)-positive MCD and HHV8-positive, HIV-negative MCD [1]. The peak of disease onset in the former is the fifth decade, whereas that in the latter is the seventh decade [1].

HHV8-associated MCD mainly develops in HIV-positive patients [6]. Therefore, there are limited reports on HHV8-associated MCD in HIV-negative patients [7]. The proportion of HHV8-positive, HIV-negative MCD cases may vary with the prevalence of HHV8 in the population. In the cohort of Dossier et al. [7], most patients (15/18) originated from a country with a high prevalence of HHV8. In Japan, the seroprevalence of HHV8 in the HIV-negative population is low (0.2%) [8]. This suggests that HHV8-positive, HIV-negative MCD is rare in Japan. Indeed, in the Japanese cohort of Suda et al. [9], there were no patients with HHV8-positive, HIV-negative MCD among 75 with MCD.

Uncontrolled HHV8 infection is an etiological driver of cytokine storm in HHV8-associated MCD [1, 2, 10]. Rituximab is currently recommended for the treatment of HHV8-associated MCD because B-cell depletion removes the primary reservoir for HHV8 [1, 2, 10]. Dossier et al. [7] reported the clinicopathological features and treatment results in 18 patients with HHV8-positive, HIV-negative

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MCD. In their cohort, most patients treated using rituximab had a favorable outcome. To the best of our knowledge, there is no other published series of patients with HHV8-positive, HIV-negative MCD and only 11 other patients treated using rituximab [11–20].

We report the first case of effective rituximab treatment of a Japanese patient with HHV8-positive, HIV-negative MCD. We also review the clinical features of the previously reported HHV8-positive, HIV-negative MCD patients who were treated using rituximab [7, 11–20].

Case report

An 87-year-old Japanese woman was admitted because of high fever and general fatigue. Her medical history was unremarkable. On examination, her body temperature was 38.4 °C. Physical examination revealed systemic lymphadenopathy and hepatosplenomegaly. There were no cutaneous manifestations. The results of laboratory tests are shown in Table 1. Anemia with an increased serum level of ferritin, thrombocytopenia, and highly increased serum levels of C-reactive protein and soluble interleukin-2 receptor were noted. Contrast-enhanced computed tomography (CT) demonstrated multiple enlarged lymph nodes and hepatosplenomegaly (Fig. 1). Based on these findings, we suspected malignant lymphoma and performed cervical lymph node biopsy. We also started oral prednisolone (PSL) therapy (20 mg/day) before making the definitive pathological diagnosis because of high fever.

After PSL treatment, her inflammatory symptoms and lymph node swelling improved. Lymph node biopsy revealed HHV8-positive MCD, the mixed cell type [1, 2, 7] (Fig. 2A, B). Immunohistochemistry for immunoglobulin light chains demonstrated a λ light-chain restriction pattern in the mantle zone (Fig. 2C, D). No evidence of Kaposi's sarcoma was noted. Polymerase chain reaction test for HHV8 in peripheral blood was positive (50,000 copies/mL). On further testing, the serum level of interleukin 6 (IL-6) was < 8 pg/mL (normal range: < 8 pg/mL), and both HIV antigen and antibody were negative. She was therefore diagnosed with HHV8-positive, HIV-negative MCD.

As she initially responded well to PSL monotherapy, the dose of PSL was reduced to 15 mg/day. She was discharged 28 days after the 1st admission. However, 13 days after discharge, she was readmitted because of the recurrence of fever, lymphadenopathy, and bicytopenia (hemoglobin: 9.1 g/dL; platelet count: 61,000/μL). We started rituximab therapy (375 mg/m^2 once a week for 4 weeks). No adverse effects of rituximab were observed. After this therapy, her symptoms improved completely. She was discharged 32 days after the 2nd readmission. Four months after discharge, PSL was discontinued at the outpatient clinic. She remains in complete remission 2.5 years after rituximab therapy.

Discussion

HHV8 is a human oncovirus classified as a gamma-herpesvirus that establishes lifelong latency in B cells, and is associated with Kaposi's sarcoma and some cases of MCD [1,

Table 1 Laboratory data on admission

Urinalysis		Blood chemistry	
Protein	−	Aspartate aminotransferase	36 IU/L
Occult blood	1 +	Alanine aminotransferase	19 IU/L
Red blood cells	5/HPF	Lactate dehydrogenase	348 IU/L
White blood cells	0/HPF	γ-glutamyltransferase	24 IU/L
Peripheral blood		Total protein	6.0 g/dL
White blood cells	8500/μL	Albumin	2.4 g/dL
Neutrophils (stab)	13%	Total cholesterol	73 mg/dL
Neutrophils (segmented)	57%	Blood urea nitrogen	19.5 mg/dL
Monocytes	13%	Creatinine	0.58 mg/dL
Lymphocytes	17%	Serology	
Red blood cells	396×10^4/μL	C-reactive protein	17.45 mg/dL
Hemoglobin	8.2 g/dL	Antinuclear antibody	−
Hematocrit	25.1%	IgG	1918 mg/dL
Platelets	43,000/μL	IgA	286 mg/dL
		IgM	115 mg/dL
		Ferritin	464.0 ng/mL
		Soluble interleukin-2 receptor	7572 U/mL (normal: 122–496)

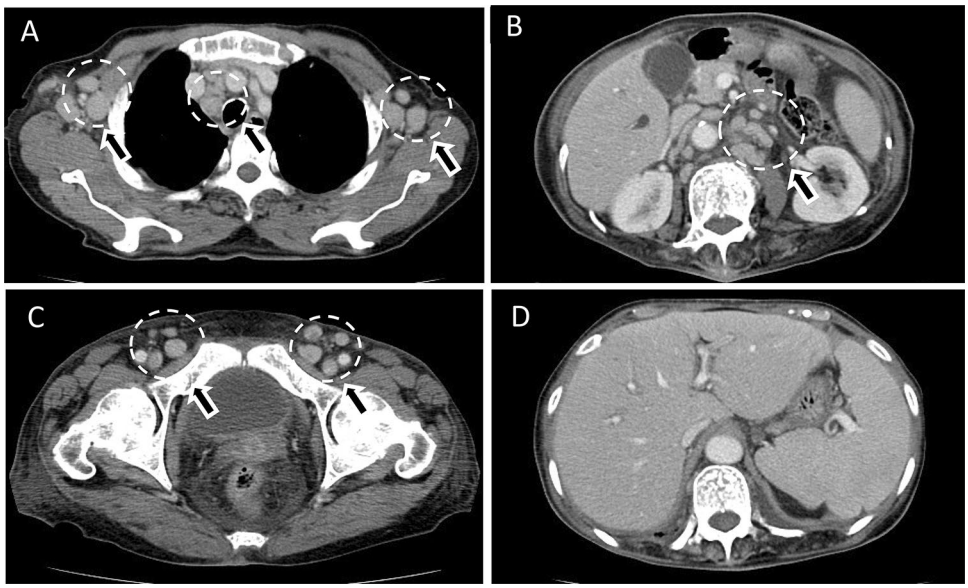

Fig. 1 CT findings on the first admission. **A**–**D** Enlarged lymph nodes in the axillary, mediastinal, para-aortic, and inguinal regions (arrows), and hepatosplenomegaly

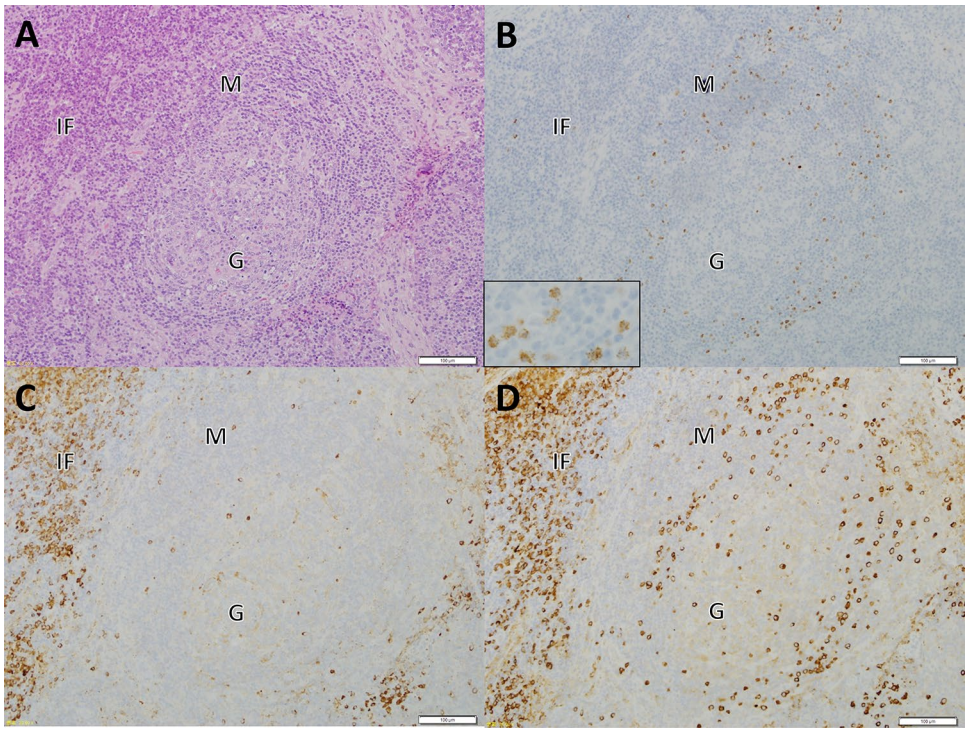

Fig. 2 Cervical lymph node biopsy findings. **A** A partially hyalinized germinal center with an expanded mantle zone (onionskin-like appearance) and abundant interfollicular plasma cells (Hematoxylin–eosin staining, original magnification × 200). **B** HHV8-infected large lymphocytes exhibiting nuclear anti-HHV8 positivity in the mantle zone (HHV8 latency-associated nuclear antigen 1 staining, original magnification × 200). High-magnification insert: stippled nuclear staining (original magnification × 600). **C** κ-positive cells in the interfollicular area (κ light-chain staining, original magnification × 200). **D** λ-positive cells in the mantle zone and interfollicular area (λ light-chain staining, original magnification × 200). *G* germinal center; *M* mantle zone; *IF* interfollicular area. The scale bars represent 100 μm

2, 6]. Unlike other viruses, HHV8 encodes several human homologues, including cytokines. Among the viral cytokines encoded by HHV8, the viral homolog of IL-6 (vIL-6) is one of the most important proteins in the pathogenesis of HHV8-associated diseases. In uncontrolled HHV8 infection, HHV8 can replicate in lymph node plasmablasts and transcribe vIL-6, which drives inflammatory symptoms and lymph node pathology along with a cascade of other cytokines, including human IL-6 [1, 2, 6, 10]. In our patient, vIL-6 may have played a major role in the development of acute inflammatory symptoms, although the serum level of human IL-6 was not examined before steroid therapy.

Infection with HHV8 alone may not be sufficient for the onset HHV8-associated diseases. Several factors, such as simultaneous infection with other viruses and an immunosuppressive state, may lead to the reactivation of HHV8 and promote the pathogenesis of MCD [2]. Dossier et al. [7] analyzed the clinicopathological features of 18 patients with HHV8-positive, HIV-negative MCD and suggested an age-related-specific immune deficiency leading to HHV8

Table 2 HHV8-positive, HIV-negative MCD patients treated with rituximab

Ref. (year) Country	Age/Gender Race	Complications associated with MCD	Previous therapies	Rituximab initial therapy	Rituximab maintenance therapy	Outcome
11 (2003) Italy	71/F	Acquired hemophilia	Steroid Cyclophosphamide Cidofovir	375 mg/m^2/week × 4 (2 courses)		Dead Cardiologic/neurologic complications
12 (2006) Spain	68/M	Kaposi's sarcoma		Rituximab dose: ND + CHOP × 8		CR (10 months) No worsening of Kaposi's sarcoma
13 (2006) Spain	75/F		CHOP	375 mg/m^2/week × 4		CR (9 months)
14 (2008) Italy	78/M			375 mg/m^2 + CVP × 6	375 mg/m^2/2 months × 4	CR (17 months)
15 (2009) Italy	78/M			375 mg/m^2/week × 4	375 mg/m^2/week × 4 every 6 months (2 years)	CR (30 months)
15 (2009) Italy	79/M	AIHA	Steroid	375 mg/m^2/week × 4		CR (9 months)
16 (2010) Australia	81/M Greek			375 mg/m^2 + CP × 6		Development of Kaposi's sarcoma after CR of MCD
17 (2012) Hungary	40/F Caucasian			Rituximab dose: ND + CVP × 4		No response TOC was effective
7 (2013) France	12 patients 42–78 (mean: 62) M/F: 8/4	RHS: 3 Kaposi's sarcoma: 2 AIHA: 2		375 mg/m^2/week × 4 + chemotherapies		Alive: 9 (2–151 months) Lost to follow-up: 3
18 (2016) Turkey	59/M			Rituximab dose: ND + CHOP × 6 + valganciclovir		CR
19 (2017) Australia	62/M Mediterranean descent	Kaposi's sarcoma	Steroid Lipo-DOX × 6 CEOP × 2	375 mg/m^2/week × 4 + CVP + valganciclovir		CR (> 5 years)
20 (2020) Greece	66/F			Rituximab (dose: ND)/week × 4 (3 courses)		CR (1 year)
Present case Japan	87/F Japanese		Steroid	375 mg/m^2/week × 4		CR (2.5 years)

AIHA autoimmune hemolytic anemia, *CEOP/CHOP* cyclophosphamide + etoposide (or doxorubicin hydrochloride) + vincristine + prednisolone, *CVP* cyclophosphamide + vincristine + prednisolone (or methylprednisolone), *F* female, *Lipo-DOX* liposomal doxorubicin, *M* male, *ND* not described, *RHS* reactive hemophagocytic syndrome, *TOC* tocilizumab

control loss. Their 18 patients exhibited histological features of MCD of the mixed cell type or of the plasma cell type, including depleted germinal centers, expanded mantle zones, and prominent infiltration of plasma cells in the interfollicular region. In the plasma cell type of HHV8-associated MCD, Dupin et al. [21] reported a λ light-chain restriction pattern in the mantle zone of B-cell follicles. Our case of the mixed cell type also had a similar pattern in the mantle zone.

Dossier et al. [7] further compared clinical features between HHV8-positive MCD and HHV8-negative MCD in their cohort. In HHV8-positive MCD, a relapsing and remitting course, splenomegaly, Kaposi's sarcoma lesions, severe anemia (related to autoimmune hemolytic anemia or reactive hemophagocytic syndrome), thrombocytopenia (associated with autoimmune thrombocytopenic purpura, thrombotic microangiopathy, or anti-phospholipid antibodies), and lymphoma were more frequently observed. Severe anemia and thrombocytopenia were also observed in our patient. As bone marrow examination and specific tests for autoimmunity were not performed, the exact underlying causes of anemia and thrombocytopenia were uncertain.

The clinical features of the previously reported 23 patients and our patient with HHV8-positive, HIV-negative MCD who were treated using rituximab are summarized in Table 2. Most reports were from Mediterranean countries [7, 11–15, 18, 20], and two patients reported from Australia originated from Mediterranean countries [16, 19]. This feature may be associated with an age-related high prevalence of HHV8 (34% in > 59 individuals) in Mediterranean regions [22]. The mean age of the patients was 66 years (range 40–87 years) and our patient is the oldest. Fifteen patients were male and nine were female. Regarding complications associated with HHV8-associated MCD, four patients had Kaposi's sarcoma, three had reactive hemophagocytic syndrome, three had autoimmune hemolytic anemia, and one had acquired hemophilia. Before rituximab therapy, some patients received combined chemotherapy including cyclophosphamide, antiviral drugs, or steroids. Most patients received rituximab according to the standard administration protocol (one course: 375 mg/m^2/week × 4 cycles) with or without chemotherapy, and achieved complete remission. Some of these patients were further treated using rituximab maintenance therapy. There were no adverse effects of rituximab, except in one patient who developed Kaposi's sarcoma after remission of MCD by rituximab therapy [16]. The patient reported by Kounatidis et al. [20] and ours suggest that HHV8-positive, HIV-negative MCD patients without serious complications can be treated using rituximab without combined chemotherapy or antiviral drugs. Our patient remains in remission without rituximab maintenance therapy 2.5 years after rituximab therapy. In a recent overview article of MCD [1], rituximab therapy was recommended as the first-line therapy for HHV8-associated MCD, whereas anti-IL-6-directed therapies were recommended for iMCD.

In summary, HHV8-associated MCD should be considered in the management of HIV-negative patients with inflammatory symptoms and lymphadenopathy, even in regions with a low prevalence of HHV8. HHV8-positive, HIV-negative MCD patients without serious complications may respond well to rituximab alone.

Declarations

Conflict of interest Dr. Naoto Takahashi reports that he received grants and personal fees from Novartis Pharmaceuticals, personal fees from Bristol Myers Squibb, grants and personal fees from Pfizer, grants and personal fees from Otsuka Pharmaceutical, and grants from Kyowa Kirin, Astellas Pharma, Chugai Pharmaceutical, Asahi Kasei Pharma, Ono Pharmaceutical, and Eisai Pharmaceuticals outside of the submitted work. The remaining authors state that they have no COI.

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