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Idiopathic multicentric Castleman disease treated with siltuximab for 15 years: a case report

Evan Lang, Brenda Sande, Samantha Brodkin and Frits van Rhee

Abstract

Human herpes virus-8 (HHV8)-negative, idiopathic multicentric Castleman disease (iMCD) is a rare lymphoproliferative disorder sustained by pro-inflammatory cytokines, including interleukin-6 (IL-6). According to the international evidence-based criteria developed by the Castleman Disease Collaborative Network (CDCN), siltuximab, which works by inhibiting IL-6, is the recommended choice for iMCD treatment. We report a case of a 63-year-old white male with iMCD who has been on maintenance therapy with siltuximab for 15 years – representing one of the longest treatment periods of any patient with iMCD treated with siltuximab. The patient initially presented with fatigue and night sweats, with progressive worsening of the symptoms. Whole-body positron emission tomography/computed tomography revealed hypermetabolic lymphadenopathy. The patient had histopathologically confirmed Castleman disease, plasma cell type, and was negative for HHV8 and human immunodeficiency virus. The patient had abnormally high C-reactive protein (CRP) levels, a surrogate measure for IL-6. The patient was treated with high-dose steroids but had recurring lymphadenopathy early on. He was enrolled in the phase I dose-finding clinical trial of siltuximab, during which he achieved marked clinical improvement and sustained inhibition of CRP. The patient was enrolled in the long-term safety study and continues to receive siltuximab at 11 mg/kg every 3 weeks. He is presently receiving commercial siltuximab and has remained asymptomatic, with no evidence of lymphadenopathy. The case study presented is consistent with the evidence that siltuximab is a safe and effective therapy for the long-term management of iMCD. In addition, this case highlights the importance of prompt diagnosis for patients with iMCD, as effective therapy is available for patients as described in the CDCN and National Comprehensive Cancer Network iMCD treatment guidelines.

Plain Language Summary

The case of a 63-year-old white male with idiopathic multicentric Castleman disease who was successfully treated with siltuximab for 15 years

Idiopathic multicentric Castleman disease (iMCD) is a group of rare lymphoproliferative disorders with shared histopathological features that affect lymph nodes in multiple regions of the body. The signs and symptoms of iMCD can be varied, with the disease being mild in some patients while life-threatening in others. A timely diagnosis of iMCD can be challenging but is required for effective management. We report a case of a patient who was diagnosed with iMCD. The patient was given high-dose steroids but continued to show progressive disease. He was then started on siltuximab, a targeted antibody therapy against a specific cytokine (interleukin-6) involved in inflammation. The patient

Correspondence to:
Evan Lang
Oncology Hematology Care, Inc., 5053 Wooster Road, Cincinnati, OH 45226, USA.
evan.lang@usoncology.com

Brenda Sande
Samantha Brodkin
Medical Affairs, EUSA Pharma, Burlington, MA, USA

Frits van Rhee
Myeloma Center, University of Arkansas for Medical Sciences, Little Rock, AR, USA

responded well to the treatment, has shown evidence of long-term disease control, and has not reported any serious adverse events related to long-term siltuximab use. He has received 11 mg/kg of siltuximab every 3 weeks for the past 15 years. This case emphasizes the value of using siltuximab therapy for long-term management of this rare disorder. In addition, it highlights the importance of prompt diagnosis for patients with iMCD, as effective therapy is available, as described in iMCD treatment guidelines.

Keywords: angiofollicular hyperplasia, case report, Castleman disease, IL-6 therapy, siltuximab

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Introduction

Multicentric Castleman disease is an uncommon disease.[1] Diagnosis can be challenging and treatment options are limited.[2,3] Combined with prompt and accurate diagnosis, siltuximab has offered hope for disease control and improvement of quality of life.[4–6] In the case presented here, the patient experienced symptoms for over two decades before receiving an accurate diagnosis and has now received siltuximab therapy for more than 15 years – representing one of the longest treatment periods with the drug. All patient details relating to this case have been de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) safe harbor method. This report adheres to the CARE case report guidelines and an ethics approval waiver was granted by the US Oncology, Inc., Institutional Review Board (IRB).

Case presentation

The patient is a 63-year-old white male who initially presented with fatigue and night sweats in his late 20s. He reported that he had been experiencing these symptoms for nearly two decades and, over time, he got used to feeling unwell. In the 5 years prior to seeking medical care, he reported that his symptoms were getting progressively worse. The patient had a history of neuropathy and hypercholesterolemia. He went to see his primary care physician regarding his symptoms in 1999 and a chest X-ray showed lung nodules. A computed tomography (CT) scan of the chest showed several non-calcified pulmonary nodules with small lymph nodes in the hilum and the axilla. A 1.5 cm retroperitoneal lymph node adjacent to the celiac axis was observed. A transbronchial biopsy of the nodule was suggestive of sarcoidosis, and the patient's serum protein level was elevated. The erythrocyte sedimentation rate (ESR) in 2000 was high (39 mm/h, normal range <30 mm/h).

Shortly after, a bone marrow aspiration was performed, which showed no significant abnormalities. During this time, the patient's symptoms became worse. He was referred to see a local surgeon for an excisional biopsy of the palpable left inguinal lymph node. Pathology was consistent with Castleman disease, plasma cell type, as described by the angiofollicular hyperplasia on the pathology report from the local hospital in Ohio in 2005. Polymerase chain reaction testing revealed no human herpes virus-8 (HHV8) in the peripheral blood and the patient had negative human immunodeficiency virus (HIV) serology. As the patient did not display symptoms matching the diagnostic criteria for TAFRO [Thrombocytopenia, Ascites (anasarca) myeloFibrosis, Renal dysfunction, Organomegaly] syndrome, a diagnosis of iMCD-not otherwise specified (iMCD-NOS) was reached.[7] Bone marrow aspiration and biopsy showed normocellular marrow with normal maturation. There was no histological or flow cytometric evidence of malignant lymphoma or multiple myeloma. The patient tested negative for antinuclear antibodies and no reticulin fibrosis was present. Evaluation of the patient found no evidence of monoclonal gammopathy.

In 2005, the patient's levels of pro-inflammatory cytokine interleukin-6 (IL-6) were highly elevated (90.9 pg/ml, normal range $\leqslant 1.8$ pg/ml), as were his levels of its surrogate measure, C-reactive protein (CRP; 47.2 mg/dl, normal range $\leqslant 0.8$ mg/dl), confirming the presence of systemic inflammation

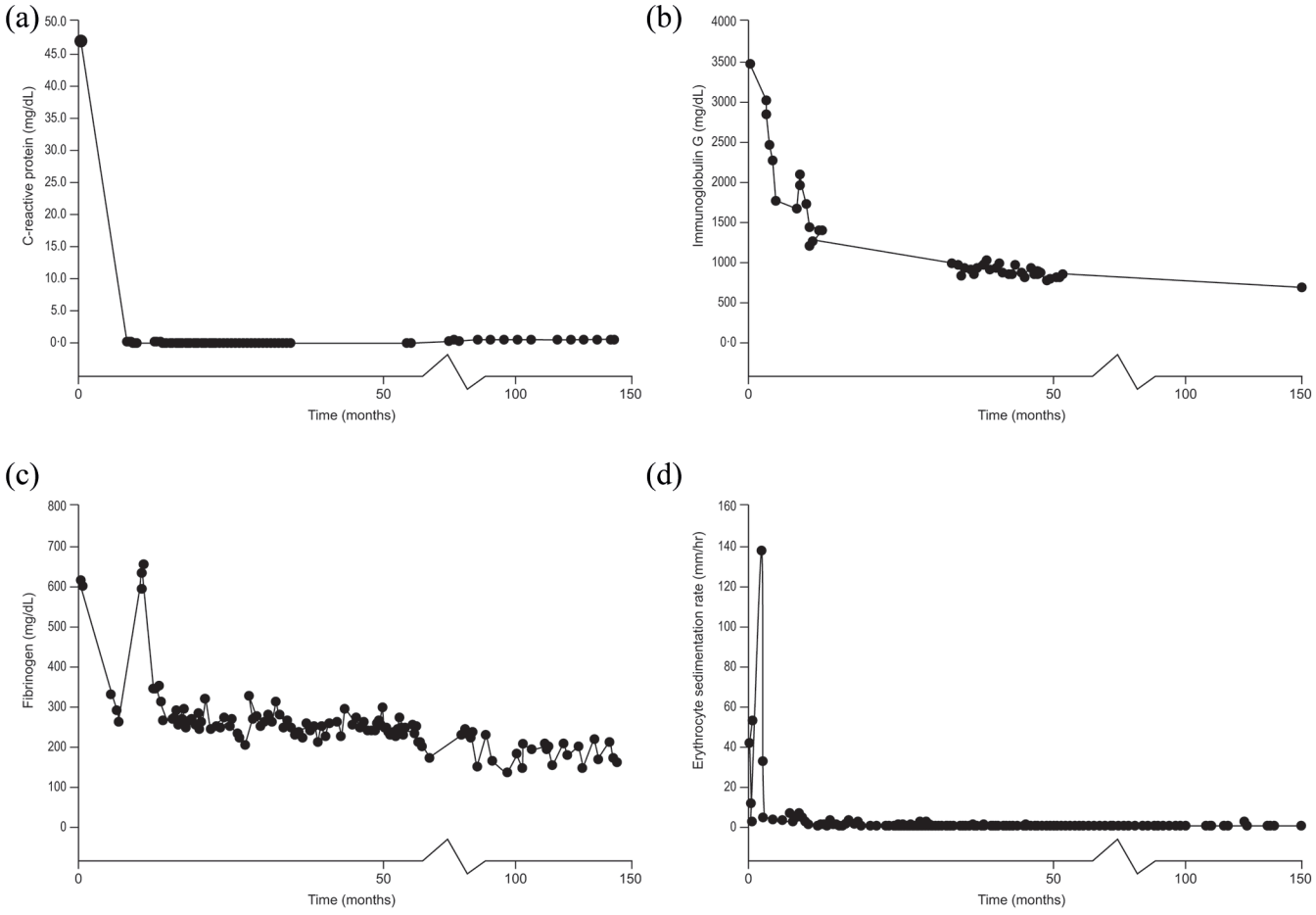

Figure 1. Individual laboratory measures for (a) C-reactive protein, (b) immunoglobulin G, (c) fibrinogen, and (d) ESR are shown at various monthly time points measured during the phase I and long-term safety extension studies. The first data points for (a) C-reactive protein and (b) immunoglobulin G represent the protein values prior to siltuximab administration, while the remaining values were measured after siltuximab administration. All values for (c) fibrinogen and (d) ESR were measured post siltuximab administration.

(Figure 1). The levels of immunoglobulin (Ig)G (3500 mg/dl, normal range 767–1590 mg/dl) and IgA (502 mg/dl, normal range 61–356 mg/dl) were elevated. Serum protein electrophoresis did not reveal the presence of monoclonal protein. The leukocyte count was normal (7700/mm^3, normal range 5000–10,000). Patient had normal levels of hemoglobin (13.6 g/dl, normal range 13.0–18.0 g/dl), platelets (407,000/µl, normal range 150,000–450,000/µl), and creatinine (0.8 mg/dl, normal range 0.7–1.3 mg/dl).

The patient was initially treated with methylprednisolone in 2005, after which his symptoms improved and CRP levels were markedly reduced. However, he developed progressive lymphadenopathy shortly after completion of the steroid treatment. He was thus treated with pulsed dexamethasone, at a dosage of 40 mg daily, after which his lymph nodes reduced in size. However, again after completion of the treatment, his lymphadenopathy recurred. After this treatment course, the patient had more difficulty tolerating further steroid therapy, developing increased fatigue and loss of appetite. He was administered dexamethasone for an additional 4 days; however, his IL-6 levels were abnormally high (79.4 pg/ml).

The patient provided informed consent to participate and be treated in the dose-finding phase I siltuximab study (NCT00412321) in 2005. His fluorodeoxyglucose positron emission tomography (FDG-PET) scan in 2005 showed multiple areas of increased metabolism, suggestive of

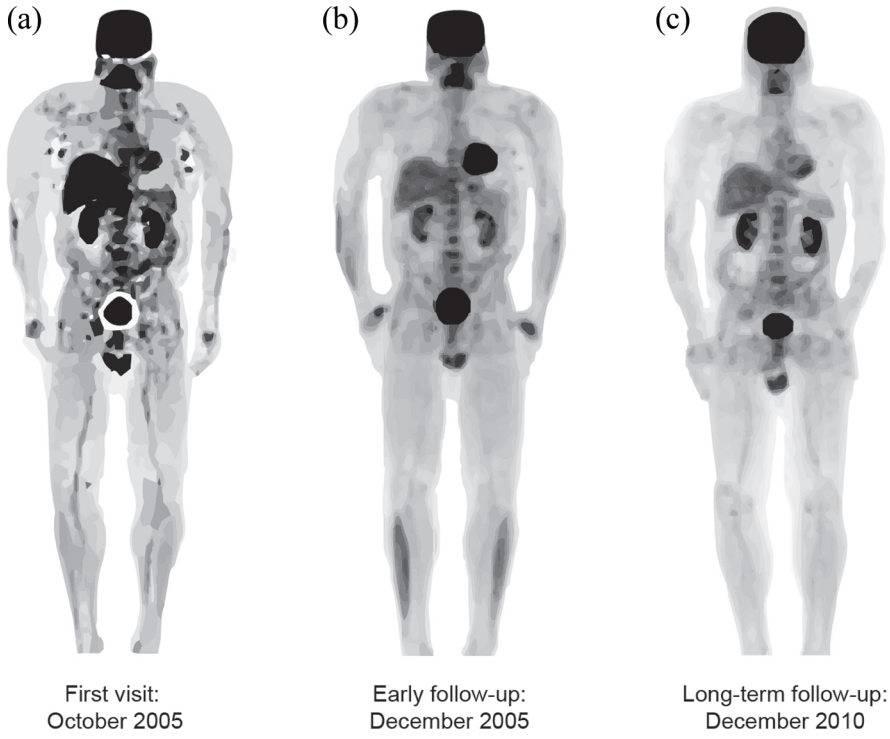

Figure 2. Whole-body FDG-PET early and long-term follow-up scans. (a) FDG-PET scan in 2005 shows multiple areas of increased metabolism suggestive of lymphadenopathy in the bilateral cervical, periclavicular, mediastinal, bilateral axillary, celiac axis, aortocaval, bilateral iliac, and bilateral groin regions. (b) FDG-PET scan 2 months later demonstrates the presence of persistent nodes in the right neck, bilateral axillae, bilateral inguinal, and celiac axis regions. However, the nodes had significantly decreased metabolism from the earlier scan and were described as stable to decrease in size. (c) FDG-PET scan in 2010 revealed multiple bilateral lung nodules, demonstrating no abnormal metabolic activity and described as benign. Based on the scan, there seemed to be no evidence of infection, no active focal bony lesions, and no evidence of extramedullary disease.

widespread lymphadenopathy (Figure 2). He received 95 doses of siltuximab. He tolerated the treatment well and achieved complete remission. His CRP levels were well controlled, indicative of sustained inhibition of IL-6 by siltuximab. IgG, ESR, and fibrinogen levels also normalized during siltuximab therapy (Figure 1).

The patient had short-term and long-term follow-up FDG-PET scans in 2005 and 2010. His hypermetabolic lymphadenopathy was resolved (Figure 2). The patient was subsequently enrolled on the long-term siltuximab safety study (NCT01400503) and was administered a further 100 doses of siltuximab at 11 mg/kg. The patient maintained his complete response throughout the study. He completed the safety study in 2017 and transitioned after US Food and Drug Administration (FDA) approval to commercial siltuximab, which he presently is still receiving at a dose of 11 mg/kg every 3 weeks. At the time of writing, the patient has received a total of 272 siltuximab doses. He is doing well on treatment and is essentially asymptomatic. At the last office visit, his examination was normal and there was no palpable lymphadenopathy.

Discussion

iMCD is a rare lymph node disorder that can be underdiagnosed. A major barrier to patients obtaining access to effective therapy is the time taken to receive the correct diagnosis. iMCD can be confused with other diseases that can cause similar histopathology and symptoms, for example autoimmune disorders (e.g. lupus), lymphoma, IgG4-related lymphadenopathy reactive due to viral etiology, sarcoidosis, etc. The Castleman Disease Collaborative Network (CDCN) diagnostic criteria stipulate that other

disorders which can give rise to Castleman-like histopathology require specific exclusion.[3]

Patients can have symptoms, including fever, sweats, splenomegaly, malaise, and abnormal laboratory results. IL-6 can be elevated in many cases and this patient was found to have very high IL-6 levels. He was quite symptomatic for many years and was initially treated with steroids, but responded poorly. Once enrolled in the siltuximab dose-finding phase I trial, he responded very well and achieved a complete symptomatic and tumor response that has been maintained throughout his therapy. He has been on maintenance therapy for 15 years, during which he has received nearly 300 infusions of the drug, with complete symptomatic control, resolution of lymphadenopathy, and excellent tolerance; this represents one of the longest treatment periods with siltuximab of any iMCD patient.

The phase I study was a dose-finding study in which patients who received the highest dose of siltuximab achieved the main efficacy endpoint of clinical benefit response.[4] No dose-related or cumulative toxicity was observed with the use of siltuximab during a long-term extension study.[5] A pivotal phase II trial confirmed the safety and efficacy of siltuximab across multiple sites.[5,6] In the treatment arm of the phase II study, 34% of patients achieved the primary endpoint of durable tumor and symptomatic response, compared with 0% in the placebo arm.[5] In addition, 57% achieved a symptomatic response and 38% had a tumor response, compared with 19% and 4% in the placebo arm, respectively.[5] In the long-term extension study, which included patients who had at least stable disease after receiving siltuximab in the randomized phase of the phase I and II studies, a disease control rate of 70% was observed in patients with follow-up of up to 6 years.[8] Of the 30% of patients in the study who discontinued, only four were due to progressive disease ($n=2$) or adverse events ($n=2$).[8] These data show that in those patients who do respond to siltuximab, long-term, sustainable responses are possible and treatment is well tolerated over long treatment periods without cumulative toxicity.

Currently, siltuximab is the only FDA-approved treatment for iMCD and is approved for all patients with multicentric Castleman disease that is HHV8 and HIV negative. As detailed in the CDCN treatment guidelines, where it is available, siltuximab is the recommended treatment choice.[2] This case highlights the importance of prompt diagnosis for iMCD patients, as effective therapy is available, as described in iMCD treatment guidelines.[2] Those who respond to siltuximab therapy may experience long-term disease control.

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Author contributions

Evan Lang: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Brenda Sande: Project administration; Writing – review & editing.

Samantha Brodkin: Project administration; Writing – review & editing.

Frits van Rhee: Data curation; Investigation; Methodology; Resources; Validation; Visualization; Writing – review & editing.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: E.L. received consultant fees from EUSA Pharma. F.v.R. received consultant fees from EUSA Pharma, GlaxoSmithKline, Karyopharm, Takeda, Sanofi, and the Castleman Disease Collaborative Network, and research funding from Janssen Pharmaceuticals and Bristol Myers Squibb. B.S. and S.B. are employees of EUSA Pharma.

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Ethics statement

Written informed consent was obtained from the patient for publication of this case report. Ethics

approval was not required for this case report and a waiver was granted by the US Oncology, Inc., Institutional Review Board (IRB).

ORCID iD

Evan Lang https://orcid.org/0000-0003-3926-0013

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