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Persistent Humoral Immunodeficiency with Rising Herpesvirus Loads Despite Successful IL-6 Blockade in a Patient with Idiopathic Multicentric Castleman Disease and IgM-λ Monoclonal Gammopathy

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Research Article

Keywords:

Posted Date: July 8th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10122651/v1

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Additional Declarations: No competing interests reported.

Abstract

Idiopathic multicentric Castleman disease (iMCD) typically presents with polyclonal hypergammaglobulinemia. We report a 25-year-old male with a 20-year history of generalized lymphadenopathy, found to have profoundly decreased serum IgG and IgA, markedly elevated IgM-λ monoclonal protein, and concurrent EBV, CMV, and HSV reactivation. Lymph node biopsy confirmed iMCD; bone marrow biopsy excluded Waldenström macroglobulinemia. The final diagnosis was iMCD with IgM-λ MGUS manifesting as a severe combined immunodeficiency-like syndrome. After three cycles of siltuximab, systemic inflammation resolved and lymphadenopathy regressed, yet hypogammaglobulinemia and the IgM clone persisted. This therapeutic uncoupling demonstrates that the humoral immunodeficiency and monoclonal B-cell proliferation are IL-6-independent. This case reveals a previously unrecognized iMCD endotype and underscores that control of inflammation does not equate to immune reconstitution. Lifelong immunoglobulin replacement, antiviral prophylaxis, and hematological surveillance are essential in such patients.

Introduction

Idiopathic multicentric Castleman disease (iMCD) is a rare and potentially life-threatening hematological disorder driven by interleukin-6 (IL-6), characterized by systemic inflammation, polyclonal lymphoproliferation, and multi-organ dysfunction[1]. The hallmark laboratory finding in iMCD is polyclonal hypergammaglobulinemia. Monoclonal immunoglobulin elevation with concurrent severe hypogammaglobulinemia and clinical immunodeficiency is exceptionally rare. We report a unique case of iMCD with IgM-λ monoclonal gammopathy manifesting as a severe combined immunodeficiency-like syndrome, in which IL-6 blockade paradoxically unmasked worsening viral replication.

Case Presentation

A 25-year-old male presented with a 20-year history of progressive, painless generalized lymphadenopathy involving the cervical, submandibular, axillary, and inguinal regions, accompanied by weight loss, chronic cough, chronic diarrhea, nasal congestion, and purulent rhinorrhea. His course was complicated by recurrent pneumonia, respiratory failure, and otitis media with progressive hearing loss. Repeated lymph node and bone marrow biopsies had been non-diagnostic.

On examination, he was cachectic with severe nasal congestion, purulent rhinorrhea, bilateral purulent otorrhea, and hearing loss. Generalized lymphadenopathy was palpable, with the largest node measuring 3 cm. Laboratory investigations revealed a paradoxical immunoglobulin profile: serum IgG < 0.33 g/L (reference: 7.51–15.6 g/L), IgA 0.07 g/L (reference: 0.82–4.53 g/L), and IgM 11.10 g/L (reference: 0.46–3.04 g/L). Serum immunofixation electrophoresis confirmed an IgM-λ monoclonal protein. Serum free light chain ratio, IgG4, antinuclear antibodies, and ANCA were negative. EBV-DNA was 189 copies/mL, CMV-DNA 1066 copies/mL, and HSV-DNA 787 copies/mL (reference: <50 copies/mL for all), confirming multiple herpesvirus reactivation. CT imaging demonstrated diffuse lymphadenopathy involving the

cervical, mediastinal, hilar, hepatic hilar, para-aortic, and hepatogastric regions, with right middle lobe bronchial occlusion and chronic pulmonary infectious changes.

Bone marrow biopsy revealed a hypercellular marrow with interstitial-to-nodular lymphoid aggregates. Flow cytometry showed no definitive monoclonal B-cell population. MYD88 L265P mutation testing was negative (wild-type). Lymph node excisional biopsy demonstrated follicular hyperplasia with regressed germinal centers, expanded mantle zones, and prominent follicular dendritic cell meshworks (CD21+, CD23+). Immunohistochemistry was as follows: CD20 (+), PAX5 (mostly+), CD79a (mostly+), BCL2 (+), BCL6 (germinal center+), CD10 (germinal center+), Ki-67 (~ 90% within follicles, ~ 20% elsewhere), SOX11 (−), CyclinD1 (−), kappa (−), lambda (−). EBER in situ hybridization was negative. HIV and HHV-8 testing were negative. These findings were consistent with iMCD, meeting the international consensus diagnostic criteria[1].

The final diagnosis was iMCD (HHV-8-negative) with IgM-λ monoclonal gammopathy of undetermined significance (MGUS), presenting as a severe combined immunodeficiency-like syndrome with multiple herpesvirus reactivation.

The patient received three cycles of siltuximab (11 mg/kg every 3 weeks).[2]After treatment, generalized lymphadenopathy regressed markedly. CRP decreased from 21.8 to 15.4 mg/L, and ESR normalized from 64 to 8 mm/h. However, cough, expectoration, purulent rhinorrhea, and otitis media showed no significant improvement. Immunoglobulin levels remained essentially unchanged. Notably, EBV-DNA rose from 189 to 431 copies/mL, CMV-DNA from 1066 to 3470 copies/mL, and HSV-DNA from 787 to 3093 copies/mL, indicating progressive viral replication (Table 1).

Table 1
Key laboratory parameters before and after siltuximab treatment

Parameter	Pre-treatment	Post-treatment	Reference range
IgA(g/L)	0.07	0.07	0.82–4.53
IgG(g/L)	<0.33	<0.33	7.51–15.6
IgM(g/L)	11.10	9.62	0.46–3.04
C3(g/L)	0.63	0.72	0.79–1.52
C4(g/L)	0.20	0.20	0.16–0.38
CRP(mg/L)	21.8	15.4	0–10
ESR(mm/h)	64	8	2–21
Immunofixation	IgM-λ positive	IgM-λ positive	Negative
EBV-DNA(Copies/ml)	189	431	<50
CMV-DNA(Copies/ml)	1066	3470	<50
HSV-DNA(Copies/ml)	787	3093	<50

Discussion

This case presents a unique iMCD phenotype that challenges the established paradigm of polyclonal hypergammaglobulinemia. The patient exhibited classic IL-6-driven systemic inflammation, yet simultaneously manifested profound IgG/IgA exhaustion, an isolated IgM-λ monoclonal protein, and multiple herpesvirus reactivation.

The severe hypogammaglobulinemia and viral infections necessitated differentiation from common variable immunodeficiency (CVID). However, the elevated IgM level and the presence of a monoclonal M protein excluded CVID, which typically features low-to-normal IgM and is a diagnosis of exclusion[3]. Bone marrow biopsy showing no lymphoplasmacytic infiltration and a wild-type MYD88 L265P mutation status excluded Waldenström macroglobulinemia. This case thus represents a distinct MCD-associated secondary immunodeficiency rather than a primary immunodeficiency disorder. As noted in the literature, severe secondary immunodeficiency can mimic primary immunodeficiency disorders, including susceptibility to multiple opportunistic viral infections[4].

The differential therapeutic response to siltuximab provides critical pathogenic insight. Systemic inflammation partially resolved (CRP decreased from 21.8 to 15.4 mg/L, ESR normalized from 64 to 8 mm/h, and lymphadenopathy regressed markedly), confirming that the iMCD component was IL-6-driven. However, the pan-hypogammaglobulinemia persisted, the IgM-λ clone was only slightly reduced (from 11.10 to 9.62 g/L), and—most strikingly—the viral loads of EBV, CMV, and HSV all increased substantially.

The worsening viral replication despite IL-6 blockade provides direct clinical evidence that the humoral immunodeficiency in this patient is completely independent of the IL-6 signaling pathway. Furthermore, given that IL-6 plays a recognized role in antiviral immune responses[5], the removal of residual IL-6-mediated antiviral signaling by siltuximab may have unmasked an even more profound underlying immunodeficiency, allowing unchecked viral replication.

This case delivers an actionable clinical message: for iMCD patients with monoclonal gammopathy and severe hypogammaglobulinemia, remission of inflammation does not equate to immune reconstitution, and IL-6 blockade may expose a deeper immunodeficiency by facilitating unchecked viral replication. Two independent, long-term management strategies are therefore required: (1) immunoglobulin replacement and antiviral therapy given the demonstrated risk of progressive viral replication, and (2) lifelong hematological surveillance for potential clonal evolution to symptomatic Waldenström macroglobulinemia[6]or EBV-associated lymphoproliferative disorders.

In conclusion, we report the first detailed characterization of an iMCD endotype defined by IL-6-independent humoral immunodeficiency and an autonomous IgM-λ clone, clinically complicated by rising herpesvirus loads during anti-IL-6 therapy. This expands the clinical spectrum of iMCD and imposes new requirements for the long-term, multi-dimensional management of affected patients.

Declarations

Ethics Statement

Written informed consent was obtained from the patient for the publication of this case report and any accompanying data.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contribution

Jirong Cheng contributed to the study conception, clinical data collection, literature review, and manuscript drafting. Yi Yang contributed to the study supervision, critical revision of the manuscript for

important intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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