LETTERS TO THE EDITOR
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Rapid relapse of idiopathic multicentric Castleman disease after siltuximab discontinuation in a case with complete remission for more than 10 years

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To the Editor,

Idiopathic multicentric Castleman disease (iMCD) is a rare lymphoproliferative disorder characterized by systemic inflammation, often associated with interleukin-6 (IL-6) overproduction (1). Siltuximab, an anti-IL-6 human-mouse chimeric monoclonal antibody, is recommended as first-line treatment for all cases of iMCD (2). Clinical trials have demonstrated durable disease responses in 42 (70%) patients treated with siltuximab for up to 6 years, maintaining disease control at their last on-study assessment (3-5). Furthermore, the longest recorded duration of siltuximab use in iMCD has surpassed 15 years, accompanied by sustained remission, underscoring its long-term efficacy and safety (6). However, the recommended 3-week siltuximab infusion intervals for an indefinite period pose significant burdens on both individuals and the healthcare system (2). Van Rhee et al. reported on 25 iMCD patients successfully transitioned from the standard 3-weekly dosing interval to an extended 6-weekly regimen, with only one case of suspected disease progression observed (3). Despite the lack of rigorous pharmacokinetic and pharmacodynamic analyses, the sustained disease control achieved with the extended dosing intervals prompts consideration of whether siltuximab discontinuation could be an option for patients who attain long-term complete remission (3).

We report a case of a 27-year-old Chinese male who initially presented with fever, fatigue, weight loss, and multiple enlarged lymph nodes. Laboratory tests revealed mild anemia, thrombocytosis, hypoalbuminemia, elevated CRP, and hypergammaglobulinemia. Biopsy of left supratrochlear lymph nodes confirmed the plasma cell subtype of Castleman disease. After ruling out diseases that mimic

iMCD, he was diagnosed with iMCD (1). Cyclophosphamide plus corticosteroids were initiated as first-line treatment in 2010, leading to marked symptom relief and lymph node regression. However, 20 months later, recurrent fever indicated disease progression. Consequently, siltuximab at 11 mg/kg every 3 weeks was administered, achieving complete remission as per Castleman Disease Collaborative Network criteria (2). From September 2017, his dosing intervals were extended to 6 weeks with sustained remission, and treatment ceased in September 2022 (Fig. 1-A, B1). Nevertheless, shortly after 5 months, his fever returned, accompanied by elevated CRP and newly enlarged lymph nodes on CT, indicating disease progression (Fig. 1-A, B2)(2). Oral sirolimus, administered as a third-line regimen, achieved partial remission after 8 months (7). With siltuximab being incorporated into China's medical insurance program in 2024, the patient resumed treatment (11 mg/kg every 3 weeks) and immediately achieved complete symptomatic and biochemical remission after two cycles. At the last follow-up, upon completing six cycles of siltuximab, the patient showed reduced lymph node size and achieved an overall complete response (Figures 1-A and B3)(2). During the administration of siltuximab, the patient did not report treatment-emergent adverse events, including hyperlipidemia and upper respiratory tract infection, which were the most commonly reported in the siltuximab extended dosing study.

In conclusion, three lessons are learned from this case. First, patients who respond favorably to siltuximab therapy may achieve long-term disease control through its continuous administration. Second, the infinite continuation of siltuximab in the management of iMCD is crucial, and any attempts to discontinue its use should be approached with caution and probably avoided. Thirdly, for patients who have exhibited a favorable response to siltuximab, its efficacy remains consistent upon re-administration, confirming the feasibility and efficacy of reusing the drug as a therapeutic approach in such cases.

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Ethics statement: The study was conducted in accordance with the principles outlined in the Declaration of Helsinki, with prior approval granted by the ethics committee of the local hospital (PUMCH; Beijing, China). Written informed consent was obtained from the individual for the publication.

Conflict of interest disclosures: The authors declare no competing financial interests.

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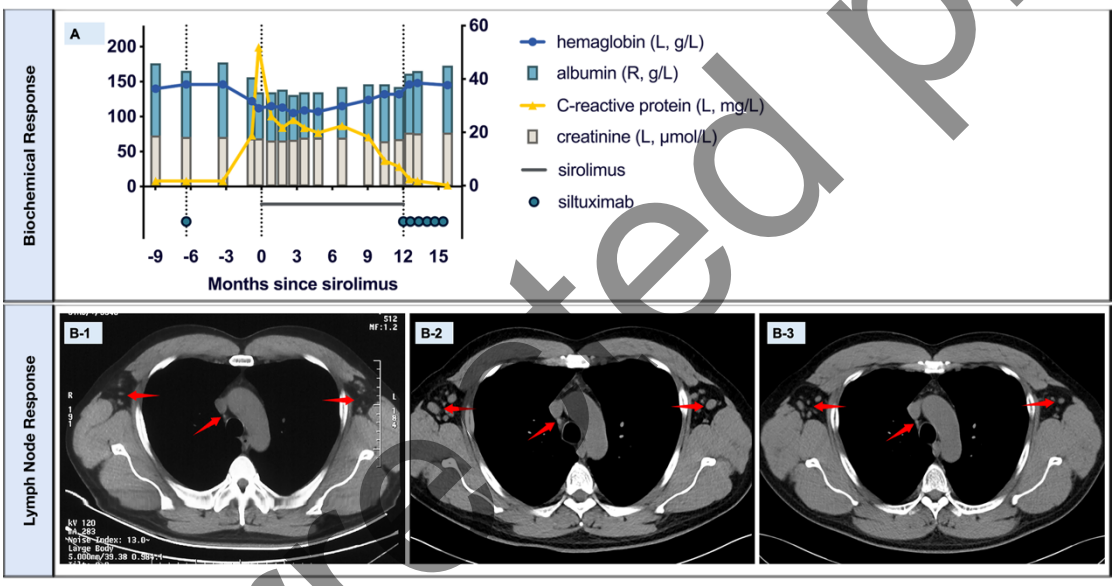

Figure 1. Individual laboratory measures at various time points (A). The three dashed lines represent the last administration of siltuximab in the initial phase, the first administration of sirolimus, and the first re-administration of siltuximab, respectively. The units and the corresponding Y axis are in notes at the right labels. R, right Y axis; L, left axis. Computed tomography (CT) shows the manifestations of lymph nodes 9 months prior to disease progression (B-1), during disease progression (B-2), and after six courses of siltuximab administration (B-3). At the last follow-up, the patient's lymph nodes had shrunk significantly, allowing for a full recovery of his physical fitness to the extent that he was capable of completing high-intensity fitness exercises, with a notable increase in his skeletal muscle mass evident in CT scans.