Turk J Hematol 2024;41:283-285

Rapid Relapse of Idiopathic Multicentric Castleman Disease After Siltuximab Discontinuation in a Case with Complete Remission for More Than 10 Years

On Yıldan Uzun Süredir Tam Remisyonda Olan İdiyopatik Multisentrik Castleman Hastalığı Olgusunda Siltuksimabın Kesilmesinden Sonra Hızlı Nüks

Yu-Han Gao, Jian Li, Lu Zhang

Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Department of Hematology, Beijing, China

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 [3,4,5]. 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. [3] reported on 25 iMCD patients who successfully transitioned from the standard 3-week dosing interval to an extended 6-week regimen, with only one case of suspected disease progression observed. 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.

We report the case of a 27-year-old Chinese man who initially presented with fever, fatigue, weight loss, and multiple enlarged lymph nodes. Laboratory tests revealed mild anemia, thrombocytosis, hypoalbuminemia, elevated C-reactive protein (CRP), and hypergammaglobulinemia. A biopsy of the 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 the criteria of the Castleman Disease Collaborative Network [2]. From September 2017, his dosing intervals were extended to 6 weeks with sustained remission, and treatment was ceased in September 2022 (Figures 1A and 1B-1). Nevertheless, shortly after 5 months, his fever returned, accompanied by elevated CRP and newly enlarged lymph nodes on computed tomography, indicating disease progression (Figures 1A and 1B-2) [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 1A and 1B-3) [2]. During the administration of siltuximab, the patient did not report treatment-emergent adverse events, including hyperlipidemia or upper respiratory tract infection, which were the most commonly reported in an extended dosing study of siltuximab [3].

In conclusion, three lessons can be 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

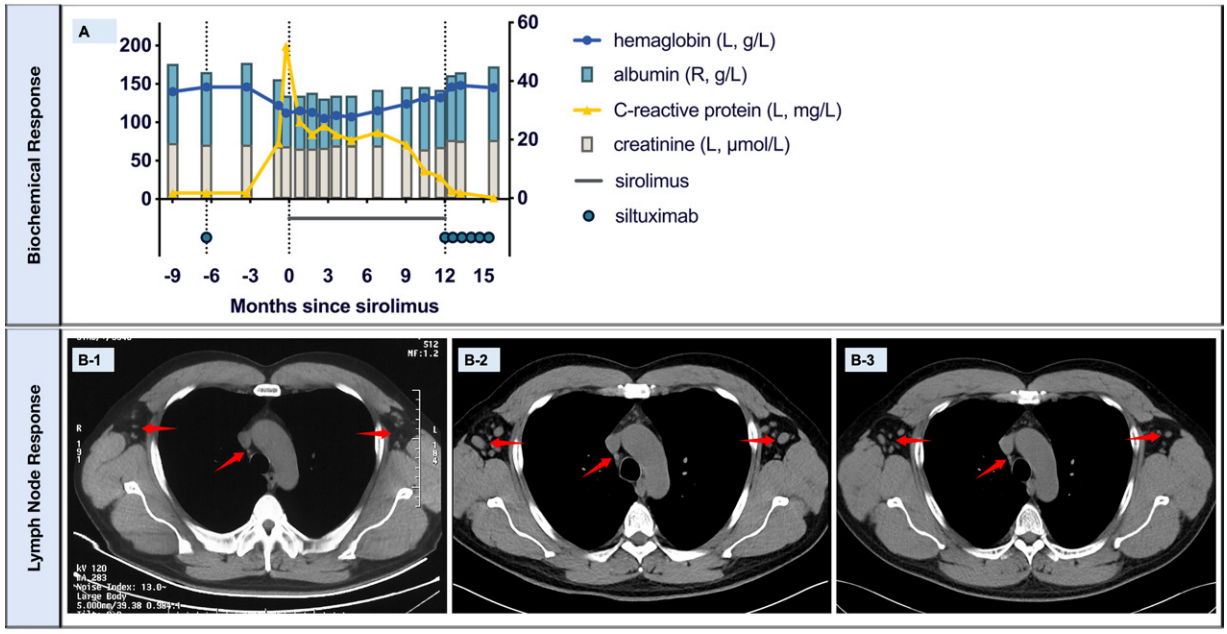

Figure 1. Individual laboratory measures at various time points (A). The three dashed lines represent the last administration of siltuximab in the initial phase, the first administration of sirolimus, and the first re-administration of siltuximab, respectively. The units and the corresponding Y-axis information are in notes to the right. R, Right Y-axis; L, left axis. Computed tomography (CT) showed manifestations in 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 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.

in the management of iMCD is crucial, and any attempts to discontinue its use should be approached with caution and probably avoided. Third, 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.

Keywords: Siltuximab, Idiopathic multicentric Castleman disease, Relapse, Discontinuation

Anahtar Sözcükler: Siltuksimab, İdiyopatik multisentrik Castleman hastalığı, Nüks, Sonlandırma

Ethics

Informed Consent: Written informed consent was obtained from the individual for the publication.

Acknowledgments

The authors thank the patient who kindly volunteered to participate in this study.

Footnotes

Authorship Contributions

Medical Practices: Y.H.G., J.L., L.Z.; Analysis or Interpretation: Y.H.G., J.L., L.Z.; Literature Search: Y.H.G, L.Z.; Writing: Y.H.G., L.Z.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This work was supported by the National High Level Hospital Clinical Research Funding (grant number 2022-PUMCH-A-021 to L.Z.) and the CAMS Innovation Fund for Medical Sciences (CIFMS) (grant number 2023-I2M-C&T-B-045 to L.Z.).

References

1. Fajgenbaum DC, Uldrick TS, Bagg A, Frank D, Wu D, Srkalovic G, Simpson D, Liu AY, Menke D, Chandrakasan S, Lechowicz MJ, Wong RS, Pierson S, Paessler M, Rossi JF, Ide M, Ruth J, Croglio M, Suarez A, Krymskaya V, Chadburn A, Colleoni G, Nasta S, Jayanthan R, Nabel CS, Casper C, Dispenzieri A, Fosså A, Kelleher D, Kurzrock R, Voorhees P, Dogan A, Yoshizaki K, van Rhee F, Oksenhendler E, Jaffe ES, Elenitoba-Johnson KS, Lim MS. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood. 2017;129:1646-1657.
2. van Rhee F, Voorhees P, Dispenzieri A, Fosså A, Srkalovic G, Ide M, Munshi N, Schey S, Streetly M, Pierson SK, Partridge HL, Mukherjee S, Shilling D, Stone K, Greenway A, Ruth J, Lechowicz MJ, Chandrakasan S, Jayanthan R, Jaffe ES, Leitch H, Pemmaraju N, Chadburn A, Lim MS, Elenitoba-Johnson KS, Krymskaya V, Goodman A, Hoffmann C, Zinzani PL, Ferrero S, Terriou L, Sato Y, Simpson D, Wong R, Rossi JF, Nasta S, Yoshizaki K, Kurzrock R, Uldrick TS, Casper C, Oksenhendler E, Fajgenbaum DC. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood. 2018;132:2115-2124.
3. van Rhee F, Casper C, Voorhees PM, Fayad LE, Gibson D, Kanhai K, Kurzrock R. Long-term safety of siltuximab in patients with idiopathic multicentric

Castleman disease: a prespecified, open-label, extension analysis of two trials. Lancet Haematol. 2020;7:e209-e217.

4. Kurzrock R, Voorhees PM, Casper C, Furman RR, Fayad L, Lonial S, Borghaei H, Jagannath S, Sokol L, Usmani SZ, van de Velde H, Qin X, Puchalski TA, Hall B, Reddy M, Qi M, van Rhee F. A phase I, open-label study of siltuximab, an anti-IL-6 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma, multiple myeloma, or Castleman disease. Clin Cancer Res. 2013;19:3659-3670.

5. van Rhee F, Wong RS, Munshi N, Rossi JF, Ke XY, Fosså A, Simpson D, Capra M, Liu T, Hsieh RK, Goh YT, Zhu J, Cho SG, Ren H, Cavet J, Bandekar R, Rothman M, Puchalski TA, Reddy M, van de Velde H, Vermeulen J, Casper C. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2014;15:966-974.

6. Lang E, Sande B, Brodkin S, van Rhee F. Idiopathic multicentric Castleman disease treated with siltuximab for 15 years: a case report. Ther Adv Hematol. 2022;13:20406207221082552.

7. Fajgenbaum DC, Langan RA, Japp AS, Partridge HL, Pierson SK, Singh A, Arenas DJ, Ruth JR, Nabel CS, Stone K, Okumura M, Schwarer A, Jose FF, Hamerschlak N, Wertheim GB, Jordan MB, Cohen AD, Krymskaya V, Rubenstein A, Betts MR, Kambayashi T, van Rhee F, Uldrick TS. Identifying and targeting pathogenic PI3K/AKT/mTOR signaling in IL-6-blockade-refractory idiopathic multicentric Castleman disease. J Clin Invest. 2019;129:4451-4463.

Address for Correspondence/Yazışma Adresi: Lu Zhang, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Department of Hematology, Beijing, China
E-mail : pumczhanglu@126.com ORCID: orcid.org/0000-0002-0860-9625

Received/Geliş tarihi: September 14, 2024
Accepted/Kabul tarihi: November 5, 2024

DOI: 10.4274/tjh.galenos.2024.2024.0339