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Case Report

Idiopathic Multicentric Castleman Disease following SARS-CoV-2 Vaccination

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Abstract

Idiopathic multicentric Castleman disease (iMCD) is a rare lymphoproliferative disorder. The preferred primary treatment for iMCD is siltuximab, an anti-interleukin-6 antibody (anti–IL-6). Chemotherapy is reserved for severe cases or when anti-IL-6 is unavailable. The increased IL-6 signaling in iMCD, increase in IL-6 after mRNA vaccines, and hyperactivation of IL-6 as a critical mediator in COVID-19 infection demonstrate a shared mechanism underlying inflammatory cytokine dysregulation. Herein, we present a case of iMCD after receiving a SARS-CoV-2 vaccination who was treated with traditional chemotherapy over the preferred siltuximab.

Keywords: Castleman disease, chemotherapy, SARS-CoV-2

Introduction

Castleman disease (CD) is a rare lymphoproliferative disorder with incidence and prevalence of 3.4 and 6.9 cases per million, respectively. The average age at diagnosis of multicentric CD patients is in the sixth decade of life.[1] The overproduction of interleukin-6 (IL-6) is a known driver in idiopathic multicentric CD (iMCD), and the primary treatment is siltuximab, an anti-IL-6 antibody. Previous studies have shown increased IL-6 levels after mRNA vaccines for SARS-CoV-2,[2] and that this may cause iMCD. In addition, IL-6 has been shown to play an important role in both vaccination and full-blown COVID-19 infection.[3]

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Case Report

A 40-year-old male with a history of asthma and hypertension presented with progressive symptoms of cough, dyspnea on exertion, and low-grade fever (<38°C) 3 months after an mRNA SARS-CoV-2 vaccine (Moderna). He had not tested positive for SARS-CoV-2 before this presentation. He reported no recent weight loss, night sweats, or fatigue. A chest X-ray showed left pleural effusion, and subsequent computed tomography (CT) examinations showed massive left pleural effusion and >1 cm mediastinal and retroperitoneal lymphadenopathies (including bilateral inguinal and iliac) with

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encasement of the great vessels [Figure 1a]. No organomegaly was noted. Pleural effusion cytology showed predominant lymphocytes and was negative for malignant cells. Pathology of the surgical excision of a 3 cm inguinal lymph node showed focal lymphoid hyperplasia and expansion of the interfollicular area filled with plasma cells. Expanded mantle zones were arranged in concentric rings around germinal centers ("onion skin"), and hyperplasia of high endothelial venules was also present [Figure 2]. These findings were consistent with multicentric CD, mixed/plasmacytic subtype. The results of human herpes virus-8, Treponema, light chain restriction, and Epstein–Barr virus-encoded small RNA were all negative. The ratio of immunoglobulin (Ig) G4 (+)/IgG (+) plasma cells was <40%. Laboratory tests were negative for autoimmune diseases, hepatitis B, and HIV. Complete blood count showed white blood cell count 5780/μL (lymphocyte 24.2%, neutrophil 63.9%), hemoglobin (Hb) 9.8 g/dl, and platelet count 365,000/μL. The C-reactive protein (CRP) level was 137 mg/L, lactate dehydrogenase (LDH) 215 U/L, β2-microglobulin 6768 μg/L, and albumin 2.3 g/dL. The serum IgG, IgA, and IgM values were 1730, 129, and 1750 mg/L, respectively. Polyclonal hypergammaglobulinemia was identified. The estimated glomerular filtration rate was 86 mL/min/1.73 m^2, liver function was normal, and there was no proteinuria. The patient's Eastern Cooperative Oncology Group status was 0. Taken together, this case was compatible with severe iMCD, not otherwise specified.

Due to the patient's financial preference, he received six cycles of cyclophosphamide, vincristine, doxorubicin, and prednisolone (CHOP). After the 6th cycle of CHOP, lymph nodes in the mediastinum, thoracic paraspinal region and retroperitoneum reduced to <1 cm. There was complete resolution of the left pleural effusion [Figure 1b] with improved laboratory data: Hb 12.3 g/dl, CRP 13.9 mg/L, IgG, IgA, and IgM 1037, 106, and 449 mg/dL, respectively. The patient achieved at least a partial response with symptom relief. He received a second mRNA SARS-CoV-2 (Moderna) vaccination 3 months after completing CHOP, and tested positive for SARS-CoV-2 2 months after the vaccination, during which he had recurrent constitutional symptoms for 1 month. He did not receive antiviral agents. CT showed a recurrence of multicentric CD with multiple retroperitoneal lymph node enlargements and bilateral iliac chain lymphadenopathies. He received cyclophosphamide, thalidomide, and dexamethasone as an alternative treatment, and was found to be clinically stable on CT after 3 months of this treatment.

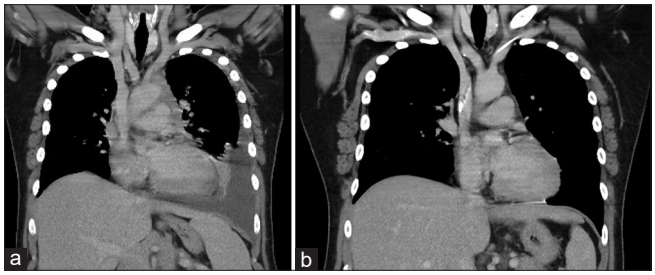

Figure 1: (a) Coronal computed tomography image at diagnosis, revealing mediastinal lymphadenopathies with encasement of the great vessels and left side pleural effusion. (b) Coronal computed tomography image after the 6th cycle of CHOP. CHOP: Cyclophosphamide, vincristine, doxorubicin, prednisolone

Discussion

According to the 2022 NCCN Guidelines, the preferred primary treatment for iMCD is siltuximab, an anti-IL-6 antibody. Overall, 34% of patients have been reported to have a durable symptomatic response to siltuximab, with a median time to response of 33 days.[4] Other recommended treatments include rituximab ± prednisone, or a combination of thalidomide, cyclophosphamide, and prednisone. If siltuximab is not available, tocilizumab may be used (category 2A) according to the CD Collaborative Network consensus guidelines on iMCD by an international working group.[5] The 2021 British Society for Haematology Guidelines also suggests a combination rituximab, cyclophosphamide, vincristine, prednisone or cyclophosphamide, vincristine, prednisone as an alternative.[6] Cytotoxic chemotherapies were reported to have a high response rate in the 2018 International Consensus pooled data analysis (78%, 102/131), but treatment failure with relapses was common (42%), and toxicities were significant. Compared to first-line anti-IL-6 treatment, the unsatisfactory response rate was ~ 50%, and the treatment failure rate was as high as 32%. Severe iMCD may not respond immediately to anti-IL-6 and high-dose steroids, which can take weeks to achieve a steady state concentration, and therefore aggressive intervention with multiagent chemotherapy should be considered.[5] Our patient had severe iMCD, and received six cycles of CHOP due to the unavailability of anti-IL-6 and his financial preference after shared decision-making. The

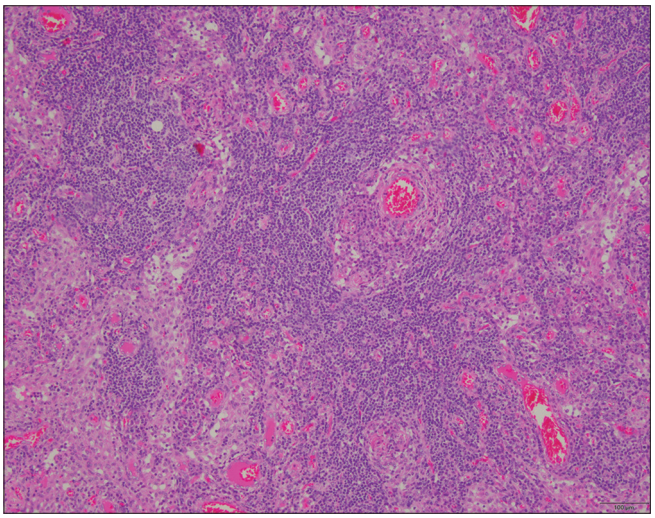

Figure 2: (Hematoxylin and eosin stain) Histologic change in Castleman disease, mixed/plasmacytic subtype (original magnification, ×100): Interfollicular areas are expanded by numerous mature plasma cells in groups and sheets, associated with variably prominent blood vessels. Follicles are small with regressive changes

subsequent management of patients with severe iMCD who fail to respond to anti-IL-6 or the first cytotoxic chemotherapy regimen, or those who relapse, is not well defined.[5] In recent years, there have been promising reports of the use of the mammalian target of rapamycin inhibitor sirolimus and the Janus kinase inhibitor ruxolitinib for refractory iMCD.[7] Our patient received 3 months of cyclophosphamide, thalidomide, and dexamethasone after relapse, and he was clinically stable. We will continue to evaluate the response.

Although rare, systemic inflammatory and immune-mediated adverse events have been reported following SARS-CoV-2 vaccination. The first case of iMCD associated with SARS-CoV-2 vaccination was reported by Hoffmann.[8] The significant increase in IL-6 with mRNA vaccines compared to adenovirus-vector-based vaccines[2] may be associated with the established pathogenesis of increased IL-6 signaling in iMCD.

The immunological profile of COVID-19 infection shows that hyperactivation of IL-6 is a critical mediator of respiratory failure. In a systematic review and meta-analysis, serum levels of IL-6 were significantly elevated in the setting of complicated COVID-19 disease.[3] Our patient was diagnosed with iMCD 3 months after the first SARS-CoV-2 vaccination, and he experienced disease progression after the second SARS-CoV-2 vaccination and infection. Although it is difficult to establish causality, a shared mechanism appears to underlie the inflammatory cytokine dysregulation in iMCD, post-SARS-CoV-2 vaccination, and infection.

Conclusion

Our case benefited from traditional chemotherapy as an alternative treatment which resulted in at least a partial response; however, severe iMCD is a potentially fatal disease that needs lifelong treatment. Further studies on the potential association between iMCD and SARS-CoV-2 vaccination and infection are needed. Further vaccinations should be scheduled cautiously with regard to the benefit and risks.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Mukherjee S, Martin R, Sande B, Paige JS, Fajgenbaum DC. Epidemiology and treatment patterns of idiopathic multicentric castleman disease in the era of IL-6-directed therapy. Blood Adv 2022;6:359-67.
2. Ostrowski SR, Søgaard OS, Tolstrup M, Stærke NB, Lundgren J, Østergaard L, *et al.* Inflammation and platelet activation after COVID-19 vaccines – Possible mechanisms behind vaccine-induced immune thrombocytopenia and thrombosis. Front Immunol 2021;12:779453.
3. Coomes EA, Haghbayan H. Interleukin-6 in COVID-19: A systematic review and meta-analysis. Rev Med Virol 2020;30:1-9.
4. van Rhee F, Wong RS, Munshi N, Rossi JF, Ke XY, Fosså A, *et al.* Siltuximab for multicentric Castleman's disease: A randomised, double-blind, placebo-controlled trial. Lancet Oncol 2014;15:966-74.
5. van Rhee F, Voorhees P, Dispenzieri A, Fosså A, Srkalovic G, Ide M, *et al.* International, evidence-based consensus treatment guidelines for idiopathic multicentric castleman disease. Blood 2018;132:2115-24.
6. Lomas OC, Streetly M, Pratt G, Cavet J, Royston D, Schey S, *et al.* The management of castleman disease. Br J Haematol 2021;195:328-37.
7. Hoffmann C, Hentrich M, Tiemann M, Rosenwald A, Weber F, Willenbacher W, *et al.* Recent advances in castleman disease. Oncol Res Treat 2022;45:693-704.
8. Hoffmann C, Wechselberger T, Drexel H, Dertinger S, Dirnhofer S, Pierson SK, *et al.* Idiopathic multicentric castleman disease occurring shortly after mRNA SARS-CoV-2 vaccine. Vaccines (Basel) 2022;10:1725.