LETTER TO THE EDITOR

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COVID-19 in a Patient with Autoimmune Scleritis on Triple Immunosuppression – An Immunological Perspective

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Dear Editor,

The ongoing COVID-19 pandemic can be vexing for uveitis specialists; especially when faced with a situation; wherein a follow-up patient on immunosuppressants; tests positive for SARS-CoV-2.

It was indeed extremely worrisome for us; when our patient; a 41-year-old diabetic lady with autoimmune posterior scleritis with a follow-up of about 8 months; on 12.5 mg/day of oral prednisolone, weekly subcutaneous 25 mg methotrexate and 3 monthly 750 mg pulsed intravenous cyclophosphamide tested positive for SARS-CoV-2 after having an episode of fever and body ache for 5 days; in June 2020. Increased predisposition to infection because of our immunosuppressive treatment and possible worse outcome was our logical concerns. This led us to study the interaction of the human immune system with SARS-CoV-2 and the implications that such an interaction would have; in a patient on immunomodulatory treatment.

Immune responses to SARS-CoV-2 include all arms of the immune system; tissue barriers, innate and adaptive cells, and mediators. The innate immune response is first activated mainly through pattern recognition receptors; resulting in release of Type 1 interferons and other inflammatory cytokines. In more severe infections, there is lymphopenia with reduced CD4+ T cells, CD8+ T cells, B cells, and natural killer cells and reduced monocytes, eosinophils, and basophils. The dreaded "cytokine storm" with excessive release of pro-inflammatory cytokines interleukin (IL)-6, IL-1β, IL-2, IL-8, IL-17, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, interferon gamma-induced protein-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, and tumor necrosis factor occurs in severe cases with resultant extensive tissue damage in lungs and other organs. Thus, an impaired initial adaptive immune response, followed by an uncontrolled activation of the innate immune response, causes severe disease.[1] An experimental coronavirus retinopathy model explains this biphasic nature of severe disease; a direct viral insult is at the basis of the initial infection which later on turns into a severe immune reaction, leading to potentially massive tissue damage.[2] Current best practice guidelines worldwide in relation to COVID-19 and immunosuppression in ophthalmology recommend the continuation of immunosuppressive treatment in patients who require them; with few exceptions.[3] The objective of continuation of immunosuppression is maintenance of remission on treatment, thus avoiding the need for possible high dose corticosteroid therapy in case of a relapse on an attempt to stop or taper these agents; which can be counterproductive.[3] In case of COVID-19 in a patient on these agents; data extrapolated from other specialties suggests reduction of oral prednisolone to <40 mg/day, temporarily withholding immunomodulatory treatments; while carefully monitoring COVID-19 disease and resumption of treatment once patient is asymptomatic.[4,5] This strategy was employed in the management of our patient; once she tested positive for COVID-19 with reverse transcription polymerase chain reaction.

Her chest CT scan showed several randomly distributed patchy areas of ground-glass opacification in bilateral lung parenchyma with predominant involvement of the right upper and lower lobes. Parenchymal involvement was between 5% and 25% in the right upper and both lower lobes and approximately 5% in the left upper and right middle lobe with a CT COVID score of 8. Her blood investigations showed a total leukocyte count of 5160/cmm; IL-6 level 26.9 pg/ml; serum lactate dehydrogenase level 269.2 U/L; C-reactive protein level 38.9 mg/l; D-dimer level 478.2 ng/ml; serum procalcitonin <0.05 ng/ml; and plasma fibrinogen-C level 358 mg/dl. In COVID ward; oral prednisolone at 12.5 mg/day was continued; but weekly subcutaneous methotrexate was withheld for 3 weeks till she became asymptomatic with no complications. At discharge, she had no breathlessness and maintained a SpO_2 of 99% both pre and post a 3 min walk test. Now at 16 weeks post-testing positive for COVID-19; and a total follow-up of 1 year with us; she remains asymptomatic from both respiratory and ophthalmic point of view and is on a tapered dose of 7.5 mg of oral prednisolone/day. She

maintains remission of autoimmune scleritis with a dose of 15 mg of oral methotrexate/week. To our extreme relief, not only was her stay in the COVID ward uneventful but she also remains completely comfortable and is able to carry out all her activities with ease at 15 weeks post-discharge from COVID ward.

This case was an eye opener for us, which led us to try to understand the immunology of COVID-19. The need to mitigate viral replication by an effective adaptive host immune response, which may possibly be impaired by use of immunosuppresses, requires withholding immunomodulatory treatment which we did in our patient during the period of 3 weeks after she tested positive for COVID-19. However, the distinct possibility that the "cytokine storm;" an uncontrolled activation of the innate immune response; that occurs in severe COVID-19 cases; may itself be moderated in our patients by prior use of "immunomodulatory" agents;[1] was and should be reassuring to an ophthalmologist and a uveitis specialist in these vexing times.

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