

Lockdown effects on a patient receiving immunosuppression for unilateral HLA- B27 associated uveitis during COVID-19 pandemic

Dear Editor,

A 35-year-old Asian Indian man was diagnosed with seronegative arthritis with negative HLA-B27 by immunofluorescence method initially in 2009 and 7 years later (2016) HLA-B27 positive by a polymerase chain reaction. He was referred to us in 2016 for recurrent unilateral eye pain and redness and was diagnosed as non-granulomatous anterior uveitis in the right eye (RE). He had a similar episode of redness in the left eye (LE) in 2012 and was treated elsewhere, the details were not available to us. He had been started on oral methotrexate 20 mg/week and sulphasalazine 1 g twice daily by the rheumatologist for his arthritis. He was prescribed topical steroids in the tapering dose and cycloplegic for this episode. He had three more episodes of acute anterior uveitis in the RE in 2017, which was treated with topical and systemic steroids along with sulphasalazine and methotrexate 20 mg/week.

He was lost to follow up for 2 years. In 2019, he had developed panuveitis with cystoid macular edema (CME) in the RE. Fundus fluorescein angiography showed flower petal pattern in macula, peripheral vascular leak, disc staining and leakage. He was on oral methotrexate 20 mg, tacrolimus 1 mg, and folvite 5 mg as prescribed by the rheumatologist when he consulted us again. He was restarted on topical and systemic steroids. Multiple immunosuppressives were started by the rheumatologist for his systemic condition. Tacrolimus was

added by the rheumatologist in the interim period 2017–19, the records of which were not available to us. When the patient consulted us, he was already on oral tacrolimus 1 mg twice daily. The exact indication for tacrolimus initiated in this patient by the rheumatologist was not known.

In consultation with the rheumatologist, the tacrolimus was stopped and was suggested injection adalimumab 40 mg subcutaneously for 3 months twice a month along with methotrexate 20 mg/week. Tacrolimus is known to cause maculopathy and hence the patient had been switched to adalimumab.^[1]

“Lockdown” was declared in India by the Government of India on 24th March 2020 for a period of 21 days, and then subsequently extended by 5 weeks.

Due to lockdown and non-availability of the drug, the patient stopped injection adalimumab in the month of April 2020 and he also stopped oral methotrexate on his own 2 months later (June 2020). He was apparently having no visual symptoms, hence did not feel the need to restart the medication or consult the specialist. He was off all medications for a month (June to July 2020).

He developed symptoms of fever, severe myalgia, loss of smell, and he was detected to be Coronavirus disease (COVID)-19 positive by reverse transcriptase-polymerase chain reaction (RT-PCR), 1 month (July 2020) after stopping the immunosuppression although this doesn't have any association. Unfortunately, his treatment details for COVID-19 were not accessible/available to us and according to the patient he was given oral antibiotics and multivitamins at the treating hospital.

He was discharged after a week of stay in the hospital and then presented to us with RE anterior and intermediate uveitis 3 weeks later. He had non-granulomatous keratic

precipitates, flare 3+, cells 3+, vitreous haze 2+, vitreous cells+, and the fundus was normal in the RE. He was restarted on topical and systemic steroids (35 mg) and referred back to the rheumatologist to restart oral methotrexate and injection adalimumab 40 mg subcutaneously and topical and systemic steroids were tapered over a month.

The patient was subjected to complete blood count, aspartate aminotransferase (AST or SGOT), and alanine aminotransferase (ALT or SGPT) 2–4 weeks once.

The points to ponder in this case were the role of his immunosuppression and the post-COVID-19 inflammation.

The evolving consensus on managing vitreo-retina and uvea practice in the post-COVID-19 pandemic era recommended that if a patient on immunosuppression, developed symptoms of COVID-19 infection, further management on the continuation of immunosuppression should be done in consultation with the infectious control disease specialist.^[2] Those who were confirmed COVID-19 infection or clinical signs of COVID-19 infection who are asymptomatic could continue with immunosuppressive agents along with monitoring of blood counts under the close monitoring of an infectious disease expert. Those symptomatic patients should temporarily stop immunosuppressive agents or biologics. Patients taking anti-tumor necrosis factor (TNF) agents like infliximab or adalimumab should omit their next dose until they fully recover. In such cases, local treatment options like intravitreal injection should be considered.^[2]

The International Uveitis Study Group jointly with the International Ocular Inflammation Society and the Foster Ocular Inflammation Society has similarly indicated the need to continue immunosuppression in patients without clinical signs of COVID-19 or confirmation of disease.^[3]

Our patient had stopped the immunosuppressives due to the non-availability of the medication. He developed COVID-19 symptoms a month later which may not be related to his cessation of use of immunosuppression. His treating specialist at the local hospital had advised him not to start any immunosuppression. He presented with a recurrence of unilateral anterior/intermediate uveitis 3 weeks after being diagnosed with COVID-19. Possibly the postviral inflammation was the cause for recurrence in our patient or the effect of immunosuppressive agents was not evident.

Thng *et al.* suggested that immunosuppressants with the exception of high-dose corticosteroids have a role in the treatment of COVID-19 disease and by extension, the immunosuppressed patient may paradoxically be conferred a protective effect or at the least, not be predisposed to a poorer clinical outcome as conventional wisdom may suggest. They also postulated that immunosuppression increasing the risk of patient getting infected with SARS-CoV-2 and developing severe complications may be slightly far fetched.^[4]

The viral envelope of the Severe acute respiratory syndrome- Corona Virus (SARS-CoV) has a spike glycoprotein (S protein) binds to the angiotensin-converting enzyme 2 (ACE2), on the surface of human cells.^[5,6] This is the possible mechanism of the pathogenesis in human cells after the binding. The affinity of SARS-CoV-2 S protein binding to ACE2 is 10 to 20 times higher than that of the SARS S protein, suggesting that SARS-CoV-2 might transmit more readily from person to person.^[7]

Virus replicating in human cells can cause host cell pyroptosis, which helps eradicate the virus. Subsequently, the immune response abates and patient recovery is possible. There are instances in which dysfunctional immune system causes unregulated production of cytokines like interleukin-6 (IL-6), IL-1 β , IFN- γ , MCP-1, IP-10, IL-4, and IL-10 leading to a downward spiral of immune-mediated end-organ damage.^[8,9]

COVID-19 might be just an association in uveitis. However, both in our experience and the published data, we firmly believe that the hyperinflammatory syndrome is a distinct possibility following viral infection. There is definitely a role of immunosuppression in treating Post COVID-19 patients with ocular hyperinflammatory status.^[9,10]

Patients with uveitis are asked to report immediately if they have any symptoms suggestive of upper respiratory tract infection, Fever, loss of taste or loss of smell, urinary tract infection, headache, nausea and skin rashes, and gastrointestinal upset.

Immunosuppressives may have a role in limiting this damage. IL-6 inhibitors specifically tocilizumab, a humanized monoclonal antibody, has been one of the leading agents studied due to the key role IL-6 plays in the late hyper-inflammatory phase of the disease and experience with this drug in the treatment of cytokine release syndrome caused by chimeric antigen receptors redirect T cells.^[11]

We have to consider if the risk of viral replication or the hyperinflammatory response is greater. There is no broad consensus on the timing, dose, and duration of immunosuppression to be considered in these scenarios.

Adalimumab (Humira (R), Abbott Laboratories) is the first fully human, recombinant IgG1 monoclonal antibody that specifically targets human TNF. Adalimumab blocks the interaction of TNF with the p55 and p75 cell surface TNF receptors, thereby neutralizing the activity of this cytokine.

Observational clinical data shows the possible role of anti-TNF therapy as a treatment for COVID-19. Anti TNF therapy has been used in many diseases.^[12]

Anti-TNF therapy in a set of 600 patients showed that either alone or in combination with other immunomodulatory drugs when compared with no disease-modifying antirheumatic drugs was associated with a lower rate of hospital admission for COVID-19.^[13]

In conclusion, we would never know in this particular patient had he continued his immunosuppression, would he have had a protective effect on the inflammatory effects of COVID-19. We also cannot confirm whether the relapse of uveitis was due to discontinuation of immunosuppressive agents or if COVID-19 infection had a role to play. Development of post-COVID-19 inflammation 3 weeks later necessitated resumption of his immunosuppressive medication.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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