COVID-19 vaccination and recurrent anterior uveitis

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A 35-year-old Asian Indian female previously diagnosed with bilateral anterior uveitis and on oral methotrexate developed bilateral anterior uveitis following first/second dose of coronavirus disease 2019 (COVID-19) vaccination. She had skipped her weekly dose of oral methotrexate following first dose of vaccination. Following the second dose, she reduced her oral methotrexate from 25 to 15 mg on her own, but did not stop like the previous occasion. She had extensive workup for her uveitis in the past with only positive severe acute respiratory syndrome coronavirus (SARS-CoV-2) antibodies. She developed unilateral anterior uveitis after she had COVID-19 in July 2022, which resolved with topical steroids and continuation of immunosuppression. This report illustrates that COVID-19 or its vaccination may presumably play a role in triggering the immune system and can cause recurrent ocular inflammation even in the absence of an extraocular inflammation.

Key words: Anterior uveitis, COVID-19, immunosuppression, Naranjo score, vaccination

Ocular adverse effects following COVID-19 vaccination have been increasingly reported in recent times. The reported ocular side effects include episcleritis, scleritis, uveitis, multifocal choroiditis, acute macular neuroretinopathy, Vogt–Koyanagi–Harada disease (VKH), central serous chorioretinopathy (CSCR), non-arteritic anterior ischemic optic neuropathy, herpes zoster reactivation, and acute retinal necrosis.[1-5] Occurrence of anterior uveitis following first or second dose of COVID-19 vaccination has been reported.[1,3]

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Case Report

A 35-year-old Asian Indian female had been previously diagnosed with bilateral anterior uveitis and was on oral methotrexate. She developed bilateral anterior uveitis following the first dose of COVID-19 vaccination and unilateral anterior uveitis following the second dose of COVID-19 vaccination.

The patient is a part of the study that was approved by the local ethics committee, vide approval number EC reference number C/2020/09/09 (virtual). All tenets of the Helsinki Declaration were adhered to. Informed written consent was obtained from the patient.

A patient with recurrent anterior uveitis with vitritis and no systemic clue except raised SARS-CoV-2 antibodies had been reported earlier.[6] The patient's ocular inflammation had been well controlled with weekly dose of oral methotrexate 25mg and oral sulfasalazine 1 g twice daily and folic acid 5 mg folic acid on days when methotrexate was not administered. She was administered the first dose of coronavirus vaccination (COVISHIELD™) on May 30, 2021, and she developed fever a day later with no eye symptoms. The fever resolved with oral paracetamol. She was advised to skip a dose of oral methotrexate following vaccination, based on the guidelines for immunosuppressive therapy and COVID-19 vaccination.[7] On June 29, 2021, she developed bilateral acute non-granulomatous anterior uveitis, with right eye (OD) anterior chamber showing flare 2+, cells 2+ [Fig. 1a, b] and left eye (OS) showing flare + cells + with no vitritis. She was restarted on topical steroid (prednisolone acetate 1%) and cycloplegic (homatropine 2%). During her consultation with the rheumatologist, the tests showed elevation of D-dimer to 0.560 µg/ml (<0.500) and C-reactive protein (CRP) to 12 mg/l (<5). The ocular inflammation in both eyes resolved in a month with topical steroids and resumption of oral methotrexate.

Subsequently, she took the second dose of the COVISHIELD™ on August 30, 2021 and developed non-granulomatous anterior uveitis in OD with the anterior chamber showing flare 2+, cells 2+ [Fig. 2a and b] without vitritis a week later. Her anti SARS-CoV-2 antibodies levels by (Serum/Chemiluminescent Immunometric Assay (CLIA) were raised to 11.78 (Normal <0.8). The patient, however, did not skip oral methotrexate, but reduced the dosage to 15 mg on her own. This time, the anterior uveitis occurred in a shorter time frame after COVISHIELD™ vaccine was administered and was unilateral. She was started on topical steroids (prednisolone acetate 1%), and oral methotrexate

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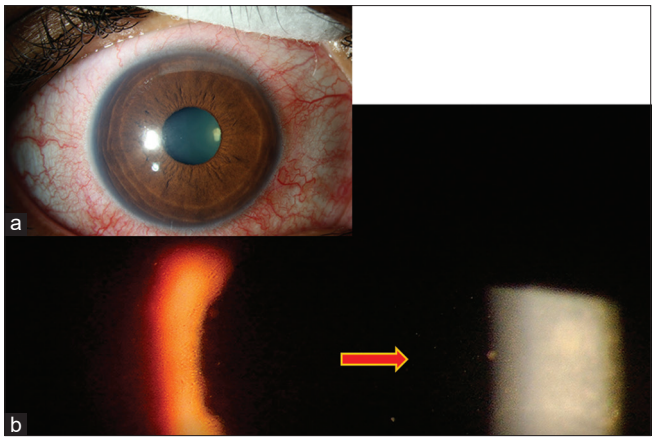

Figure 1: (a) Inset shows diffuse slit-lamp illumination of the right eye showing ciliary congestion. (b) Magnified beam using 1 mm × 1 mm using Standardized Uveitis Nomenclature for grading anterior chamber cells – shows 2+ cells (red arrow)

was increased to 25 mg weekly. Her symptoms resolved within a month.

She had couple of flare ups in both the eyes in December 2021 and February 2022, despite being on oral methotrexate 25 mg. Oral tacrolimus 0.5 mg twice daily was added in February 2022. She stopped all medications by the end of March 2022 as she developed vomiting and hair loss and also had leukopenia. She had been started on oral mycophenolate mofetil 500 mg twice daily in April 2022 and had no flare up till the first week of July 2022.

The patient developed COVID-19 with fever and myalgia in the first week of July 2022 and a week later, she had a flare up of her left eye anterior uveitis with flare 1+, cells1+, which was controlled with topical prednisolone acetate 1%, and the patient was continued on oral mycophenolate mofetil. The left eye anterior uveitis resolved by 3 weeks.

Discussion

This sequence of events points to the possible immune reactivation post-vaccination, resulting in anterior uveitis. This phenomenon of the post-vaccination flare of disease has been reported in several other autoimmune diseases as well.[8] It is difficult to speculate whether the vaccine triggered the inflammation or stopping a single dose or a reduced dose of methotrexate led to ocular inflammation.

The etiology of the occurrence of autoimmune diseases post-vaccination is unclear. However, molecular mimicry, bystander activation of the sequestered self-antigens, cytokine secretion from the macrophages, and genetic polymorphisms are the four possible mechanisms of the same. There are high chances that similar effects can trigger autoimmune response post-COVID-19 vaccination. This is also supported by the reported cases of other autoimmune conditions like Guillain–Barre syndrome and systemic lupus erythematosus post-vaccination.[9]

Recently, a case report of recurrent anterior uveitis following Pfizer COVID-19 vaccine in a 37-year-old healthy male was reported. Very similar to our patient, their patient had anterior uveitis after both doses, and also, the second episode of anterior uveitis was of earlier onset compared to the first dose.[10]

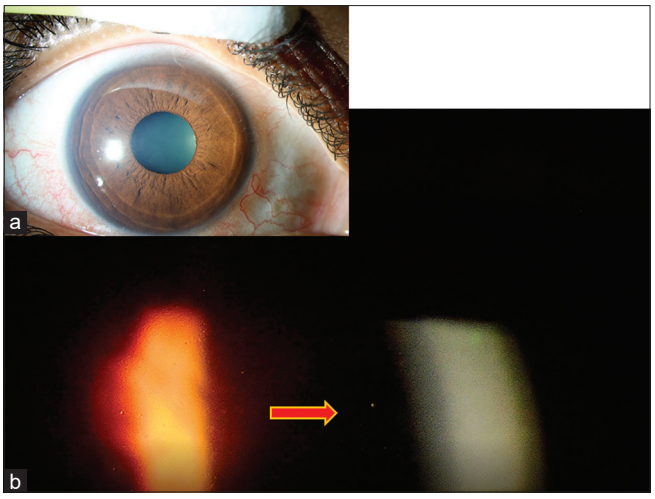

Figure 2: (a) Inset shows diffuse slit-lamp illumination of the right eye showing lesser ciliary congestion compared to the first episode. (b) Magnified beam using 1 mm × 1 mm using Standardized Uveitis Nomenclature for grading anterior chamber cells – shows 2+ cells (red arrow)

Table 1 gives a summary of anterior uveitis following COVID-19 vaccination.[11-18]

Some of the current non–mRNA-based COVID-19 vaccines contain polysorbate 80, including COVISHIELD™ (Serum Institute of India, Pune https://www.seruminstitute.com/pdf/covishield_ChAdOx1_nCoV19_corona_virus_vaccine_insert.pdf (accessed on April 18, 2022)).

COVISHIELD™ has the following excipients: l-histidine, l-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, sucrose, sodium chloride, and disodium edetate dihydrate (ethylenediaminetetraacetic acid [EDTA]), besides polysorbate 80. It is possible that the excipients might have triggered the immune response in our patient.

The Adverse Drug Reaction (ADR) Probability Scale was developed in 1991 by Naranjo and co-workers from the University of Toronto and is often referred to as the Naranjo Scale.[19] This scale was developed to help standardize assessment of causality for all adverse drug reactions and was not designed specifically for drug-induced liver injury. Our patient's Naranjo score was estimated as follows:

1. Are there previous conclusive reports on this reaction? +1
2. Did the adverse event appear after the suspected drug was administered? +2
3. Did the adverse event reappear when the drug was readministered? +2
4. Are there alternative causes that could on their own have caused the reaction? −1
5. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? +1

Our patient's score was 5. The interpretation is as below.

Total score 5–8 probable. The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.

Table 1: Summary of cases which presented as anterior uveitis after COVID-19 vaccination (as of April 29, 2022)

Author	Number of patients	Symptoms after vaccine	COVID vaccine type	First/second dose/ both (number of patients)	Type of anterior uveitis (number of patients)
Testi *et al.*[11]	41	1-14	*The Pfizer BioNTech (BNT162b2) COVID-19 vaccine *Astra Zeneca(R) *Moderna(R) *Sinopharm(R) *COVAXIN™	First dose (22)/ second dose (19)	*HLA-B27 (9) *Idiopathic AU (6) *Glaucomatocyclitic crisis (3) *Herpetic AU (2) *JIA-associated uveitis (1) *CMV AU (1) *SLE uveitis (1)
Rabinovitch *et al.*[12]	21			First dose (8), second dose (13)	
Ng *et al.*[13]	7	1 day-1 month	The Pfizer BioNTech (BNT162b2) COVID-19 vaccine or mRNA-1273	First/second	Non-granulomatous
Bolletta *et al.*[14]	5, 3 were HLA B-27 positive	1-30 days	The Pfizer BioNTech (BNT162b2) COVID-19 vaccine	First (2)/second dose (3)	Four non-granulomatous and one CMV AU
ElSheikh *et al.*[15]	1 ANA-positive oligoarticular JIA	5 days	Sinopharm(R)	Second dose	Non-granulomatous
Renisi *et al.*[16]	1	14 days	The Pfizer BioNTech (BNT162b2) COVID-19 vaccine	Second dose	Non-granulomatous
Alhamzani[17]	1	5 days after the first dose Earlier (days not mentioned) after the second dose	The Pfizer BioNTech (BNT162b2) COVID-19 vaccine	First and second doses	Non-granulomatous
Mahendradas[18]	1 JIA	1 week after both doses	COVAXIN™	First and second doses	Non-granulomatous
Present study	1	1 month after the first dose 1 week after the second dose 1 week after COVID-19	COVISHIELD™	First and second doses	Non-granulomatous

ANA=antinuclear antibody, CMV=cytomegalovirus, COVID-19=coronavirus disease 2019, HLA-B27=human leukocyte antigen B27, JIA=juvenile idiopathic arthritis, SLE=systemic lupus erythematosus, AU=Anterior uveitis

In patients who have had COVID-19, a dysfunctional immune system can cause unregulated production of cytokines like interleukin-6 (IL-6), IL-1b, interferon (IFN)-γ, Monocyte Chemoattractant Protein-1 (MCP-1), interferon γ-induced protein 10 kDa (IP-10), IL-4, and IL-10, leading to a downward spiral of immune-mediated end-organ damage.[20] This may also cause ocular manifestations like uveitis, which happened to our patient in July 2022, a week after COVID-19.

Conclusion

Our patient with previous history of idiopathic anterior uveitis with vitritis and raised COVID-19 antibodies developed anterior uveitis after both doses of vaccination. However, we should note that the immune reaction post-vaccination is transient and remission occurs with minor adjustments in immunomodulatory drugs, as seen in our patient. Vaccinations remain life-saving medications and should be taken by all patients with autoimmune disorders as per the existing guidelines.

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 anoymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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