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Severe panuveitis with iridis rubeosis activation and cystoid macular edema after BioNTech-Pfizer COVID-19 vaccination in a 17-year-old

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ABSTRACT

We report a case of severe uveitis flare-up with iridis rubeosis recurrence and cystoid macular edema early after the first BioNTech-Pfizer COVID-19 vaccination in a 17-year-old boy. We also performed a systematic literature review on ocular inflammation after COVID-19 vaccinations.

1. Introduction

The current global health crisis is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), a novel epidemic strain of *Betacoronavirus* responsible for the viral pandemic coronavirus disease 2019 (COVID-19). Within less than a year, several effective mRNA-based and viral vector-based vaccines were developed at an unprecedented speed and deployed via emergency use authorization for immunization to limit the spread of the disease and reduce its morbidity and mortality.[1] These COVID-19 vaccines were shown to induce potent immune responses, inducing SARS-CoV-2 neutralizing antibodies and eliciting strong Th1-biased $CD4^+$ responses.[2] Recent results from global COVID-19 vaccine trials with over 80,000 subjects showed a 95% efficacy for the mRNA vaccines. However, the COVID-19 vaccines may also disrupt immune regulation to cause systemic immune dysregulation and compromise ocular immune privilege and the patient's susceptibility for intraocular inflammation.[3,4]

2. Case report

A 17-year-old healthy boy was diagnosed with the first severe uveitis in his left eye in November 2016. In conjunction with anterior uveitis, he had suffered from retinal vein occlusion and iridis rubeosis. The diagnosis workup, chest x-ray and laboratory exams to rule out e.g., granulomatous and infectious inflammations and autoimmune diseases did not reveal any underlying etiology.

Methotrexate and TNF inhibitor adalimumab were initially used to prevent uveitis flare-up, until due to adverse effects they were changed to mycophenolate mofetil, which was also later ceased due to the same reason. Topical prednisolone acetate (10 mg/ml, b.i.d.) was prescribed to the left eye as preventive medication for uveitis. During the follow-up, complete resolution regarding retinal vein occlusion and rubeotic iris was observed.

The last anterior uveitis before COVID-19 vaccination was documented as mild in the patient's left eye in November 2020 and was treated with the routine protocol of topical steroids with a 5-week tapering down schedule. Thereafter, the patient was followed under regular quarterly visits and showed no signs of reactivation. Best-corrected visual acuity (BCVA) was 20/16 in his both eyes before the last uveitis episode and in the two consecutive follow-ups.

In June 2021, the patient had his first BioNTech-Pfizer (Comirnaty [BNT162b2]) COVID-19 vaccination. The following day, the patient contacted the ophthalmological unit with signs of severe uveitis and sudden visual loss in his left eye. BCVA was 20/16 in the right and 20/500 in the left eye. Corneal precipitates, aqueous cells (50 cells/slit), fibrin formation in the anterior chamber, widespread and prominent iridis rubeosis (Fig. 1), vitreous cells (16–25 cells/slit), and cystoid macular edema (Fig. 2) were observed. The patient was referred to a tertiary unit, University Hospital uveitis subspecialists.

Parabulbar triamcinolone (40 mg/ml; 1ml) was administered,

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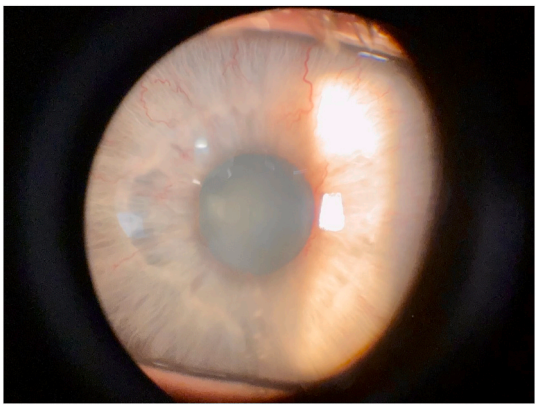

Fig. 1. Photograph of the left eye.

together with systemic prednisolone (starting from 60 mg and tapering down 10 mg every 2–3 days), topical prednisolone acetate eye drops (10 mg/ml, starting every hour when awake and tapering down every week as follows: every other hour, every third hour, q.i.d., b.i.d.), cyclopentolate eye drops (10 mg/ml, b.i.d for one week) and prednisolone eye gel (5 mg/ml, for the night for 3–4 weeks). At three weeks, due to dense aqueous (40 cells/slit) and vitreous cells (30–40 cells/slit) together with deteriorated BCVA (20/100) in the left eye parabulbar triamcinolone (40mg/ml; 1ml) was re-administered together with systemic prednisolone starting again from 60 mg and tapering down 20 mg every 3–4 days. Prednisolone acetate eye drops (starting every hour when awake and tapering down as above), cyclopentolate eye drops (b.i.d) and prednisolone eye gel (for the night) were administered to the left eye as well. One week after the second parabulbar triamcinolone, iritis (20 cells/slit) and vitritis (10 cells/slit) were recovering, visual acuity improved to 20/80 in the left eye. Systemic prednisolone (20 mg tapering down 5 mg every four days until 5 mg daily, and 5 mg daily thereafter until the next visit) and topical medication (as previously prescribed) were used. The patient was returned to the referring secondary ophthalmic unit.

At 2 months, aqueous (4 cells/slit) and vitreous (old cells and mild haze) were still recovering, whereas cystoid macular edema remained clinically significant and refractory. Visual acuity improved up to 20/50 in the left eye. Systemic prednisolone (5 mg daily), prednisolone acetate eye drops (every third hour when awake), tropicamide eye drops (once daily), and prednisolone eye gel (for the night) were used. Anti-VEGF injections for iridis rubeosis and cystoid macular edema were suggested, but not provided yet. Furthermore, the patient was advised to refrain from the previously scheduled second COVID-19 vaccine shot. He was referred back to the tertiary unit, University Hospital uveitis subspecialists.

At 4 months, the patient contacted the secondary ophthalmic unit with acute onset of symptoms. While tapering down topical and systemic steroids by the earlier schedule, the patient experienced a new recurrence of panuveitis. BCVA in the left eye was counting fingers (CF). Corneal precipitates, dense aqueous cells (40–50 cells/slit), fibrin formation in the anterior chamber, rubeosis in the iris and the angle, posterior synechiae, and opacities in the nucleus were observed obscuring fundus details. The patient was referred back to the tertiary unit, University Hospital uveitis subspecialists. He was provided with topical, systemic and intravitreal steroids. The last BCVA in the left eye was 20/100 and the biomicroscopy findings were mild corneal precipitates, aqueous cells (10–15 cells/slit), rubeosis in the iris and the angle, posterior synechiae, posterior subcapsular cataract, vitreous cells and cystoid macular edema without abnormalities in the optic nerve head, retinal vessels or periphery.

In the right eye, no signs of uveitis were observed and BCVA remained 20/16 thoughout the follow-up. In both eyes, intraocular pressure remained at the normal level throughout the follow-up.

3. Discussion

Vaccines, in general, do have rare serious adverse effects, including induction or reactivation of autoimmune diseases.[5] Vaccine-related uveitis is a rare adverse event. However, cases have been reported with many of the vaccines currently employed, including influenza, varicella-zoster, diphtheria-tetanus-pertussis, bacillus Calmette-Guérin (BCG), hepatitis A and B, brucella, human papilloma virus, pneumococcus, and measles-mumps-rubella vaccines.[6] Post-vaccine uveitis can manifest with a broad spectrum of ocular symptoms, ranging from eye redness, blurred vision and light sensitivity to the presence of floaters. Often, post-vaccine uveitis is anterior, mild, transient and responds promptly to topical corticosteroids. However, severe posterior and panuveitis including acute posterior multifocal placoid pigment epitheliopathy (AMPPE) and Vogt-Koyanagi-Harada (VKH) like syndromes, have also been reported following immunization.[7] The mechanism behind vaccine-related uveitis is unclear. Hypotheses have included molecular mimicry between vaccine peptide fragments and uveal self-peptides, immune complex deposition in delayed-type hypersensitivity, and other immune responses in response to vaccine adjuvants.[8]

Since February 2021, 46 reports of ocular side-effects linked to the COVID-19 vaccines have been reported to the Vaccine Adverse Event Reporting System (VAERS). Inflammation of the optic nerve, retina, uveal tract and anterior segment accounted for 9% of VAERS reports.[9] Twelve case reports of intraocular inflammation following COVID-19 vaccination were reviewed and included acute corneal graft rejection (n = 7, 7–21 days post vaccination), choroiditis (n = 1, 7 days post vaccination), uveitis (n = 4, 3–14 days post vaccination) and arteritic

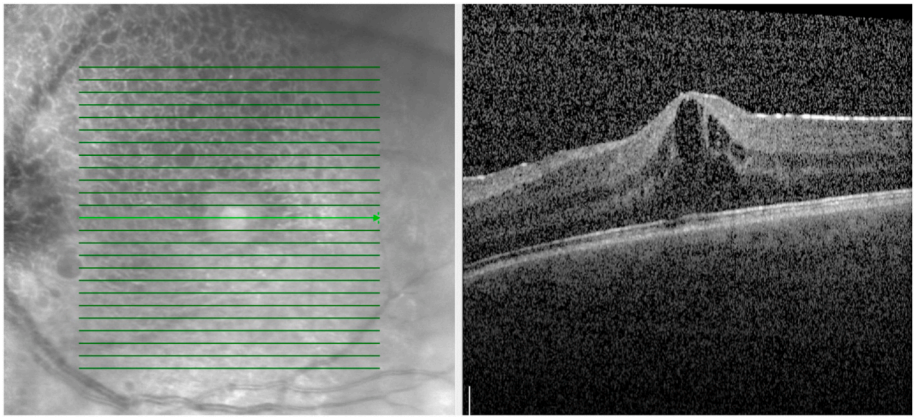

Fig. 2. Optical coherence tomography (OCT) scan of the left eye.

anterior ischemic optic neuropathy (n = 1, 2 days post vaccination).[10] A recent retrospective multicenter study reviewed all Comirnaty (BNT162b2) COVID-19 vaccination related-uveitis cases in Israel.[11] The study found that in twenty-three eyes of 21 patients (38% had a previous history of uveitis with a median of one year of inactivity before the flare-up) the mean time between vaccination and uveitis was 7.5 days (range 1–30).[11] The limitation in our Case Report is that fluorescein angiography (FA) and indocyanine green angiography (ICGA) were not documented in the patient's medical history to rule out differential disagnoses e.g., papillophlebitis and the posterior variant of Eales disease. Furthermore, these analyses would have been useful to clarify the presence, or not, of ischemic retina to explain the iris rubeosis.

Topical treatment with corticosteroids before and after vaccination may prevent flare-ups in patients susceptible to uveitis.[12] Clinicians should inquire about the patient's vaccination history and report temporal associations to the relevant agencies. Our patient received the Comirnaty (BNT162b2) vaccine, a lipid nanoparticle-formulated, nucleoside modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein.[1] Differently from the hepatitis B vaccine, which is most commonly associated with post-vaccine uveitis, Comirnaty (BNT162b2) does not contain aluminum salts as adjuvants in its formulation. However, both vaccines were developed utilizing genetic engineering and express genes in microbial cells from pathogens that encode surface antigens capable of inducing neutralizing antibodies in the pathogen-host. It has been speculated that mRNA vaccines induce strong activation of the cellular and humoral immune responses, resulting in molecular mimicry that may lead to immune cross-reactivity, triggering an autoimmune disease like anterior uveitis.[13] The original uveitis and its recurrence were relatively unusual and severe for uveitis as is the association with CRVO and rubeosis. The patient was advised to refrain from the previously scheduled second COVID-19 vaccine shot. Notably, a different vaccine formulation or local prophylactic treatment with re-immunization could have been considered as the risk of contracting COVID-19 also carries morbidity.

4. Conclusions

Ophthalmologists should be aware, and patients need to be educated to follow-up immediately if they notice any changes like discomfort, redness, or blurred vision after vaccination. The findings in this report should not deter the administration of the COVID-19 vaccination because early recognition and prompt treatment of uveitis most often yields positive outcomes. The minimal risks of uveitis following vaccination do not outweigh the benefits of COVID-19 vaccination. Nevertheless, patients with suspected ocular adverse events such as uveitis after the first vaccination should discuss with their physicians and balance between the potential benefits and risks regarding the second COVID-19 vaccine injection.

Patient consent

Consent to publish personal information and case details has been obtained from the patient.

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