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Ophthalmic manifestations of COVID-19 vaccines: Our experience

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Abstract---Several COVID-19 vaccines have been developed and approved for use around the world from December 2020, to combat the pandemic caused by the novel SARS-CoV-2 virus. Several ophthalmic manifestations of the COVID-19 vaccines have been reported by ophthalmologists. This review was undertaken to recognize, encourage active reporting and determine the pathogenesis and time of appearance for better awareness and understanding of the ophthalmic manifestations of COVID-19 vaccines. A literature search was performed for publications on the ophthalmic manifestations of COVID-19 vaccines between January 1, 2021 and November 7, 2021. 23 case reports, 17 letters to editors, 3 ophthalmic images, 4 brief communications, 4 retrospective cohort studies and 2 case control studies were included. Posterior segment, including the uvea, choroid and retinal vasculature, was most commonly affected and the reported clinical features developed at a median of four days from the time of vaccination. The possible mechanisms include molecular mimicry of the vaccine components with host ocular tissues, antigen-specific cell and antibody-mediated hypersensitivity reactions to viral antigens and adjuvants present in the vaccines. The causal relationship of the ocular signs and symptoms and COVID-19 vaccines has not been established and requires long-term and large multicentre data. Most of the reported manifestations are mild, transient and adequately treated when diagnosed and managed early. The benefits of COVID-19 vaccination outweighs the reported rare adverse events and should not be a deterrent to vaccination.

Keywords---corneal graft rejection, COVID-19 vaccine, COVID-19, inactivated vaccine, mRNA vaccine, ophthalmic manifestations, SARS-CoV-2, vascular occlusion, vector based vaccine.

Introduction

The year 2020 was unlike any other, a year of uncertainty, distancing, and loss. Man has always found his way through obstacles and challenges; David must come to fell Goliath. The best minds around the world worked at an unprecedented pace to develop vaccines against the novel SARS-CoV-2 virus. By December 2020, vaccines against COVID-19 were authorized for emergency use through expedited clinical trials. Like any change, any revolution, it too faced trials and tribulations, hype and hysteria, media and political might. As we enter the last quarter of 2021, it may be safe to say that the vaccines have “lived and let live.” A large population has been vaccinated, 7,027,377,238 vaccine doses, to be exact, as of November 7, 2021, have been administered, lockdowns are being lifted and gradually life seems to be returning to normal, albeit a new one.^[1]

The main vaccines approved for use around the world are the nucleoside-modified RNA vaccine (BNT162b2) by Pfizer-BioNTech, the recombinant adenoviral vector encoding SARS-CoV-2 spike (S) glycoprotein (ChAdOx1 nCoV-19 Coronavirus vaccine Recombinant COVISHIELD by Serum Institute of India based on the Oxford AstraZeneca Chimpanzee Adenovirus Vected Vaccine (AZD1222)), and the inactivated SARS-CoV-2 vaccine (BBIBP-CorV, Sinopharm). Additionally, there are other vaccines including Sputnik V, Russia, mRNA-1273 Moderna, Janssen, Johnson and Johnson COVAXIN by Bharat Biotech, India, and CoronaVac from China. The vaccines have been found to be 94%–95% effective.^[2-4] The common side effects of these vaccines are mild to moderate pain, swelling, and erythema at the injection site, chills, fatigue, malaise, headache, and fever. Diarrhea, nausea, vomiting, and dermatitis are less frequent side effects documented. These usually start within 24–48 hours of the inoculation and last for 1–2 days. ^[2-5]

Methods

A literature search was performed on PubMed with search words, COVID-19 vaccine, ophthalmology, eye, adverse effects, SARS-CoV-2, ocular manifestations, graft rejection, retina, vitreous, orbit, facial palsy, uveitis, nerve palsies, choroiditis, retinal vascular occlusion, mRNA vaccine, adenovirus vector vaccine, and inactivated vaccine. The articles included in this December 2021 Sen and Honavar: After the storm review are in English language, published between January 2021 and November 7, 2021. It is not an exhaustive review, but the authors have tried to include all the important reports with 23 case reports, 17 letters to editors, 3 image-based reports, 4 brief clinical communications, 4 retrospective cohort, and 2 casecontrol studies.

Eyelid, Ocular Surface and Anterior Segment Manifestations of COVID-19 Vaccine

The eyelid, ocular surface, and cornea are easily observable by patients and, therefore, present as soon as the symptoms develop. Eighteen cases of ocular adnexal and anterior segment manifestations have been reported.^[7-16] The mean age of the patients was 57.5 ± 15.6 (median 62.5) years, and there were 9 females and 6 males (3 gender unspecified). The Pfizer-BioNTech mRNA vaccine was the most common vaccine, used in 13 patients, two had received the viral vector-based Covishield, and three had received the inactivated Sinopharm vaccine. The majority of the symptoms were after the first dose,^[11] whereas four patients presented after the second dose. The median interval from vaccination to development of symptoms was 7 (mean 9.8 ± 8) days.

Eyelid

The eyelid involvement was transient in all cases limited to unilateral erythematous edema and bilateral purpuric rash. All cases were after the Pfizer-BioNTech mRNA vaccine. The three cases of acute onset eyelid edema reported by Austria *et al.*^[7] resolved with observation, antihistamine, and oral corticosteroids, respectively, within 1–2 days. The purpuric rash observed in three patients developed at a median of 18 days and resolved spontaneously within 10–15 days. The coagulation profile was normal in all three.^[8] Eyelid edema can be a part of an anaphylactic reaction, but none of the patients reported any systemic adverse effects. Periorbital swelling is seen in ocular vaccinia after the smallpox vaccine, and ocular respiratory syndrome is reported with the influenza vaccine.^[8] The mechanisms proposed after COVID-19 vaccination include complement-induced reaction and molecular mimicry with an autoimmune response.

Cornea

Corneal graft rejection was the most common anterior segment manifestation of the COVID-19 vaccine. Seven of the nine cases were following the Pfizer-BioNTech mRNA vaccine at a median duration of 7 (mean 10.3 ± 7.2) days. The remaining two received the viral vector-based Covishield vaccine. Four patients had undergone penetrating keratoplasty, whereas the rest had undergone lamellar keratoplasty. Five of eight patients were on topical corticosteroids at the time of vaccination. In the case reported by Phylactou *et al.*, the patient also had a retroviral infection and was on treatment for the same.^[11] Three patients had bilateral corneal transplants and of these, one patient developed rejection in only one eye. Five eyes had undergone repeat transplants following prior failures. Only one patient developed systemic symptoms, moderate chills, and myalgia following the vaccination.^[9] The symptoms and signs were typical of endothelial graft rejection with acute onset of diminution of vision, redness, photophobia with or without pain, graft edema, Descemet's folds, and anterior chamber (AC) reaction. [Figs. 2 and 3] Treatment was with frequent (1–2 hourly) administration of topical corticosteroids with or without oral steroids. Acyclovir/Valacyclovir was started in

two patients to counter a possible viral infection.^[9,14] All the patients recovered within 1–4 weeks.

The cornea is an immunoprivileged organ, and corneal transplantation has the highest rate of success. Lamellar keratoplasty has ensured further protection of the graft. Graft rejection can follow the breakdown of the blood–ocular barrier following intraocular inflammation or recurrent viral infection.^[11] Corneal graft rejection after immunization has been reported with influenza, hepatitis B, tetanus, and yellow fever vaccines.^[10,11] Bilateral graft failure in two of three patients with transplants in both eyes, and the temporal sequence of events points towards the role of the COVID–19 vaccine. The suggested mechanisms of graft failure are the vaccine–induced immune enhancement and cross–reactivity of virus antigen–specific T–cells with HLA antigen–disparate corneal allograft endothelial cells, increased vascular permeability after the vaccination, and presence of mRNA in the aqueous following a prior COVID–19 infection.^[14] The COVID–19 vaccine induces a strong antibody response with CD4 + Th1 cells, which are also mediators of corneal graft rejection.^[10] Systemic reactogenicity would be more likely after the second dose of vaccination than the first one, but seven of the nine patients developed rejection after the first dose itself. Also, none of the patients were reported to have had prior COVID–19 infection, but one cannot rule out mild, asymptomatic infection. Nevertheless, the possibility of graft rejection following immunization necessitates considering deferral of elective corneal transplants by 3–6 months after the final dose of COVID–19 vaccine and initiating corneal transplant patients on topical corticosteroids before the first dose of vaccine and continuing for a month after the second dose.^[10] Patients with repeat grafts and immunocompromised state are at a higher risk of rejection and should be forewarned. While all patients recovered, it must be borne in mind that endothelial cell loss following graft rejection is irreplaceable.

Ocular Surface and Sclera

Pichi *et al.* reported a case series of seven patients with a mean age of 41.4 years who developed ocular complaints following the first dose of the inactivated Sinopharm vaccine.^[16] Four eyes of three patients developed episcleritis and scleritis at a mean of 5.2 days. One patient had a history of rheumatoid arthritis, was on sulfasalazine and presented with scleritis. Tapering doses of topical corticosteroid were prescribed, and the inflammation resolved in all the cases. Scleritis and episcleritis have been reported after the administration of live attenuated vaccines as well as post–COVID–19 infection.^[6,17]

Uvea

Vogt–Koyanagi–Harada Syndrome (VKH)

The three cases of VKH following COVID–19 vaccination were characterized by the typical acute onset of bilateral painless loss of vision, anterior chamber granulomatous inflammation, and exudative retinal detachment . Papasavvas reported a case of a 43–year–old female who had a past history of VKH, on infliximab and without inflammation for 6 years. There was a reactivation 42 days after the second dose of the mRNA vaccine.^[20] Two of the three cases were

following the mRNA Pfizer–BioNTech vaccine. All the cases were treated with systemic corticosteroids and resolved. VKH is a T-cell-mediated multisystem autoimmune disease against melanocytes with ocular, neurological, audiovestibular, and dermatological manifestations. Viral infections have been known to trigger VKH with cytomegalovirus (CMV), influenza A, hepatitis C being implicated.^[18] Antigenic cross-reactivity, HLA-DR4 status of patient (with influenza A), and interferon have been the mechanisms suggested in relation to viral infections causing VKH. Bacillus Calmette–Guerin (BCG) vaccine, influenza, hepatitis B, and yellow fever vaccinations have all been reported to cause cases of VKH, the onset ranging from 3 days to 4 weeks.^[18] VKH after COVID-19 vaccination may be a result of T- and B-cell-induced hypersensitivity reaction, an inflammatory reaction to adjuvants in a vaccine, or sensitization to melanocytic antigens by viral antigens. mRNA-based vaccines do not have any viral antigens or adjuvants but induce humoral immunity, T helper (CD4 + cells) and cytotoxic T cell response which could potentially trigger the inflammatory response.^[19]

Choroid Choroiditis

In multifocal choroiditis, the pathological process lies in the retinal pigment epithelium (RPE). Two cases of bilateral choroiditis presenting 4–5 days after vaccination have been published. The case from India was in a healthy male who developed symptoms after the second dose of the viralvector-based vaccine, Covishield. The patient had systemic symptoms of headache, ocular pain, and pain at the injection site for 2 days after both doses of the vaccine.^[27] The second case from China was following the first dose of the inactivated vaccine.^[28] Both patients responded to corticosteroids.

Central serous chorioretinopathy (CSCR)

In January 2021, Fowler *et al.* reported the only case of central serous chorioretinopathy in a 33-year-old healthy male after 3 days of the first dose of the mRNA vaccine.^[29] The OCT and fluorescein angiography (FA) showed the typical features of CSCR. The patient was initiated on spironolactone, and it resolved in 3 months. In the absence of any other risk factor for CSCR, (space)like the use of corticosteroids or type A personality, the authors attributed it to the vaccine.^[29] A second case of forme fruste CSCR has been reported by Pichi *et al.* after the Sinopharm inactivated COVID-19 vaccine.^[16] Rare cases of CSCR after influenza, yellow fever, anthrax, and small pox vaccines have been described. mRNA-induced endogenous glucocorticoid release and increased permeability of endothelial cells and leaky choriocapillaris on exposure to extracellular naked RNA are the possible pathological mechanisms for the development of CSCR after COVID-19 vaccination.^[29]

Retinal vascular occlusions

Central and hemi- retinal vein occlusion

Bialasiewicz *et al.* and Endo *et al.* reported a case of central retinal vein occlusion (CRVO) each from Qatar and Colombia, respectively.^[30,31] Systemic vascular events

have been reported following the adenoviral vector-based vaccines, but these are rare with mRNA vaccines with isolated cases being reported of deep vein thrombosis and thrombocytopenia.^[43,44] In the eye, both were following the Pfizer-BNT mRNA vaccine. One patient, with atopic dermatitis developed acute onset of pain, redness, and reduction of vision within a few minutes of administration of the second dose of the vaccine. Fundus examination showed a hemorrhagic CRVO and was treated with monthly intravitreal aflibercept injections and low dose acetylsalicylic acid as an antithrombotic measure. The retinal findings improved, and the patient is still under active treatment.^[30] The second case was of a healthy 52-year-old male who developed nonischemic CRVO after 15 days of the first dose of the vaccine. He was treated with intravitreal corticosteroid injection initially, and intravitreal bevacizumab was added later along with oral apixaban.^[31] This issue of Indian Journal of Ophthalmology (IJO) has a case of hemiretinal vein occlusion (HRVO) reported in a young healthy male following the second dose of Sputnik V vaccine.^[32] The patient's blood work-up, inflammatory markers, and coagulation profile were unremarkable as was the history for any systemic diseases increasing the risk of vascular occlusive events. The patient had strongly positive antibodies IgG to the vaccine and may represent an unusually enhanced immune and possible inflammatory response to the vaccine.^[32] The development of retinal vascular occlusions in patients with no other systemic risk factors suggests a possible association of the vaccine to the event.

Retina

Acute retinal necrosis (ARN)

Mishra *et al.* reported the only case of ARN following the viral vector-based vaccine, Covishield, with reactivation of varicella-zoster infection in an immunocompetent male with a history of chickenpox 25 years ago. It was preceded by fever and myalgia after the vaccination.^[41] ARN has been reported after the influenza vaccine and SARS-CoV-2 infection. A case series of seven adults developing varicella zoster virus (VZV) reactivation after COVID-19 vaccination has been published and involves a T-cell-mediated immune mechanism.^[47] ARN may resolve spontaneously in immunocompetent patients. In the case of ARN reported, the anti-SARS-CoV-2 spike protein antibodies following vaccination were inadequate, and he was treated with valacyclovir, topical corticosteroids, cycloplegic, intravitreal ganciclovir, and oral corticosteroids. Firstly, it could be immunosenescence, and reduced thymic production of T-cells, which after vaccination caused a relative paucity of T-cell-mediated immunity at the site of VZV infection and its intraocular spread via long ciliary nerves. Secondly, an exhaustion of T-cells following vaccination could lead to a reactivation of VZV, leading to acute retinal necrosis. The third possibility could be a cross-reaction between COVID-19 anti-spike antibodies with varicella zoster spike glycoprotein amino acids amounting to anergy of T-cell-mediated immunity and subsequent reactivation of VZV.^[41]

Acute zonal occult outer retinopathy (AZOOR)

A single case of bilateral AZOOR was documented by Maleki *et al.* in a healthy woman 10 days after vaccination with the Moderna mRNA-1273 vaccine.^[42] There was a nasal visual field defect in the left eye, and multifocal electroretinography (ERG) showed defective areas in inferotemporal macula in the right eye and temporal macula in the left eye. OCT showed characteristic disruption of the outer retinal layers. The patient was treated with an intravitreal dexamethasone implant in the left eye. Elevated erythrocyte sedimentation rate (ESR) indicated the inflammatory nature of the pathology. T helper cells and cross-reacting antibodies against the outer retinal layers and retinal pigment epithelial cells were most likely involved in the pathogenesis.

Orbital Manifestations of COVID 19 Vaccine

Orbital complications are uncommon, and there are four published reports to date.^[65,68] The mean age affected was 44.6 ± 11.3 (median 47.5) years with 3 females. There was one case each following the two mRNA vaccines from Pfizer and Moderna. Both cases of superior ophthalmic vein thrombosis (SOVT) were following vaccination with ChAdOx1 nCoV19 vaccine.^[67,68] Information about the vaccine dose was available for three patients, two of them were following the first dose and one after the second dose. The onset of symptoms was at a median of 6 (mean 6.3 ± 3) days from the time of vaccination.

Thyroid eye disease

Rubinstein *et al.* reported a case of thyroid eye disease in a patient with a history of Graves' disease for 11 years but without any ophthalmic involvement.^[65] The onset of eyelid edema, proptosis, ptosis, and diplopia were within 3 days of the second dose of vaccine. Thyroid ophthalmopathy was confirmed on clinical examination (CAS 5), computed tomography (CT) scan, and elevated serum thyroid stimulating immunoglobulin. The patient responded to teprotumumab.

Tolosa Hunt syndrome

Chuang *et al.* reported a case of Tolosa Hunt syndrome following vaccination.^[66] A granulomatous inflammatory process involving the cavernous sinus remains a diagnosis of exclusion and responds to corticosteroids. Spontaneous remission has been reported.

Superior ophthalmic vein thrombosis

Patients with SOVT present with headache, proptosis, ophthalmoplegia, diplopia, and diminished vision and filling defect on CEMRI with a dilated SOV confirms the diagnosis. Two cases of superior ophthalmic vein thrombosis after the viral vector-based vaccine ChAdOx1 nCov19 vaccine have been published. In the report by Panovska-Stavridis *et al.*, the patient had thrombocytopenia, high D-dimer levels, and platelet factor 4 antibodies.^[68] She was treated with intravenous immunoglobulin (IVIG) and tapering doses of oral corticosteroids. The

second patient was an older female, fifty-five-year-old with features suggestive of secondary immune thrombocytopenia. She was treated with heparin but developed ischemic stroke.^[67]

As discussed in the previous section, cases of CSVT after the adenoviral vector vaccines have been described and are amongst the most serious adverse effects. Thrombotic thrombocytopenia is an immune mediated post vaccination complication. A multicentric cohort study by Perry et al found that patients with VITT related CSVT were more likely to have received the ChAdOx1 vaccine, younger, without systemic risk factors, had more extensive venous thrombosis, intracranial hemorrhage and more concurrent extracranial and arterial thrombosis with worse outcome as compared to patients without VITT associated CSVT. The outcome improved with use of IVIG and nonheparin anticoagulants.^[69] Ophthalmologists should be aware of the occurrence of such thrombotic events. Frequently, they may be the ones to diagnose the condition which may preempt fatal cerebral ischemia. Patients with underlying thyroid disease should undergo a baseline ophthalmic examination before vaccination and be informed about the possibility of thyroid eye disease flaring.

Discussion

Ocular manifestations of the COVID19 vaccine are not uncommon but relatively mild and transient except for cases of retinal and ophthalmic vascular occlusions and graft rejections. In a cross-sectional study based on an online survey questionnaire, Kadali et al. found that of the 803 healthcare workers who received the BNT162b2 mRNA vaccine, very few had nonspecific ocular symptoms of blurred vision (4/803, 0.5%), eye pain (7/803, 0.87%), and flashes (2/803, 0.25%).^[70] A similar study on 432 healthcare workers who received the mRNA1273 vaccine showed that frequency of ophthalmic side effects was rare (eye pain: 15/432, 3.47%), to extremely rare (blurring of vision: 4/432, 0.93%; flashing lights: 3/432, 0.69%).^[71] The posterior segment, the retinal vasculature, and the uvea are most frequently affected. Comparison by age shows that patients with posterior segment manifestation were relatively younger (mean age 43.6 years) as compared to patients with neuro ophthalmic lesions (mean age 58.3 years) and corneal graft rejections (mean 65 years). The median time for the development of ocular signs and symptoms was 7 days for eyelid, ocular surface, and anterior segment, 6 days for orbit and 4 days for the posterior segment and neuro ophthalmological cases. These details are important to follow up high risk patients in the ophthalmic clinic. Patients with corneal grafts should be followed within a week, whereas those with JIA or prior history of uveitis need to be called in earlier.

The vaccines have been found to be safe before receiving approval from the appropriate authority. Adverse effects following vaccination are infrequent, benign, transient, and treatable. Serious adverse effects including anaphylaxis and thrombocytopenia are rare. The ocular manifestations have been attributed to molecular mimicry (similarities in the structure of SARS CoV 2, human or chimpanzee adenoviral components), antigen specific cell, and antibody mediated hypersensitivity reactions to spike antigen, or other viral antigens and adjuvants present in the vaccines that enhance immunogenic activity. The mechanisms are similar to those seen with various other vaccines that have been used for

several years including influenza, MMR, hepatitis A and B, yellow fever, BCG, DPT, and HPV. Almost all the manifestations have been managed conservatively or with steroidal and nonsteroidal immunosuppressants. That being said, it is important to report all manifestations to improve the knowledge base of physicians and patients. For ophthalmologists, this awareness is necessary to be able to counsel patients for vaccination, informing them of the possible symptoms for early presentation, diagnosis, and initiation of treatment. Patients with corneal grafts can be started on frequent topical corticosteroids a week before vaccination, and this can be tapered slowly after the second dose. Those who require non-urgent corneal transplantation may be scheduled after 4–6 months of the completion of all doses of vaccination. Patients with a history of inflammatory eye diseases should be warned of possible reactivation or recurrence and educated about early symptoms. Knowledge about the adverse effects is also important to encourage patients for vaccination and counter false information.

Conclusion

As further information is acquired and shared, the long term implications of the vaccines will become more clear. Patients who developed the signs after the first dose need to be followed up after the second dose to document if they had a similar reaction or not. This will throw further light on the true association of the vaccines with the ocular events as well as the risk factors for the same. It may also be prudent to classify the associations as possible, probable, definite, or unrelated as more cases come to light. Corneal graft rejection after the first dose raises the question of the timing of the second dose. The permanent or residual effects of the manifestations are also to be determined.^[72]

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Conflicts of interest

There are no conflicts of interest.

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