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Association of Ocular Adverse Events With Inactivated COVID-19 Vaccination in Patients in Abu Dhabi

Francesco Pichi, MD; Shaikha Aljneibi, MD; Piergiorgio Neri, MD, PhD; Steven Hay, COT; Christine Dackiw, MD; Nicola G. Ghazi, MD

IMPORTANCE As vaccinations against COVID-19 continue, potential ocular adverse events should be reported in detail to increase awareness among the medical community, although typically, a causal relationship cannot be established definitively.

OBJECTIVE To describe ocular adverse events that occur soon after receiving an inactivated COVID-19 vaccination (Sinopharm).

DESIGN, SETTING, AND PARTICIPANTS This case series took place from September 2020 to January 2021 at Cleveland Clinic Abu Dhabi, a tertiary referral center. Patients who reported ocular adverse events and presented within 15 days from the first of 2 doses of an inactivated COVID-19 vaccine were analyzed.

MAIN OUTCOMES AND MEASURES Each patient underwent Snellen best-corrected visual acuity that was then converted to logMAR, applanation tonometry, and biomicroscopic examination with indirect ophthalmoscopy. Color fundus photography was obtained with a conventional 9-field fundus photography camera or with a widefield fundus photography system. Optical coherence tomography and optical coherence tomographic angiography images were obtained. Sex, race, age, and clinical data were self-reported.

RESULTS Nine eyes of 7 patients (3 male individuals) presenting with ocular complaints following COVID-19 vaccine were included in the study. The mean (SD) age was 41.4 (9.3) years (range, 30-55 years); the mean best-corrected visual acuity was 0.23 logMAR (range, 0-1 logMAR; approximate Snellen equivalent, 20/32). The mean time of ocular adverse event manifestations was 5.2 days (range, 1-10 days). One patient was diagnosed with episcleritis, 2 with anterior scleritis, 2 with acute macular neuroretinopathy, 1 with paracentral acute middle maculopathy, and 1 with subretinal fluid.

CONCLUSIONS AND RELEVANCE In this case series study of 7 patients, the timing of transient and ocular complications 5.2 days after vaccination with an inactivated COVID-19 vaccine supported an association with the ocular findings, but a causal relationship cannot be established from this study design.

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Invited Commentary
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Author Affiliations: Eye Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates (Pichi, Aljneibi, Neri, Hay, Dackiw, Ghazi); Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, Ohio (Pichi, Neri).

Corresponding Author: Francesco Pichi, MD, Eye Institute, Cleveland Clinic Abu Dhabi, PO Box 112412, Al Maryah Island, Abu Dhabi, United Arab Emirates (ilmiticopicchio@gmail.com).

As of March 2021, the COVID-19 pandemic has caused 35 million infections and more than 1 million deaths worldwide, leading to the urgent demand for a vaccine.[1] To date, 2 inactivated vaccine candidates have been reported to protect against SARS-CoV-2. The inactivated COVID-19 vaccine by Sinopharm's China National Biotec Group is mixed with aluminum-based adjuvant and has been found tolerable and immunogenic in healthy people with 2 doses administered 21 days apart.[2] As of March 2021, the United Arab Emirates Ministry of Health and Prevention announced that the United Arab Emirates had crossed 2 million doses of the Sinopharm inactivated vaccine (20% of the population). We hereby present a case series of ocular adverse events presenting at Cleveland Clinic Abu Dhabi in the United Arab Emirates after receiving the Sinopharm COVID-19 vaccine.

Methods

Retrospective consecutive case series, adherent to the reporting guidelines,[3] of patients presenting at the retina and uveitis service from September 2020 to January 2021 were performed in accordance with the ethical standards of the Declaration of Helsinki.[4] The institutional review board of Cleveland Clinic Abu Dhabi waived the need for approval of a case series of fewer than 10 patients. Written informed consent was obtained from all enrolled individuals.

The main inclusion criterion was the development of ocular symptoms within 15 days from the first dose of the COVID-19 vaccine. Each patient underwent Snellen best-corrected visual acuity (BCVA) that was then converted to logMAR and bio-

microscopic examination. Color fundus photography was obtained with a 9-field fundus photography (Carl Zeiss Meditec) camera. Optical coherence tomography (OCT) was obtained with a spectral-domain machine (Spectralis HRA OCT; Heidelberg Engineering) and swept-source PLEX Elite 9000 (Carl Zeiss Meditec) was used for OCT angiography images.

Sex, race, age, and clinical data were self-reported and collected, and patient data were deidentified. None of the included patients were previously reported in any other publication.

Key Points

Question Can ocular adverse events present after inactivated COVID-19 vaccine?

Findings In a retrospective case series, 9 patients presented with ocular complaints 5.2 days after administration of an inactivated COVID-19 vaccine. One patient was diagnosed with episcleritis, 2 with anterior scleritis, 2 with acute macular neuroretinopathy, 1 with paracentral acute middle maculopathy, and 1 with subretinal fluid.

Meaning Mild, reversible ocular adverse events, both in the anterior and posterior segment, were noted after patients received the inactivated COVID-19 vaccine, although a causal relationship cannot be established from this case series.

Results

Nine eyes of 7 patients (3 male individuals) presenting with ocular complaints following COVID-19 vaccine were included in the study. The mean (SD) age was 41.4 (9.3) years (range, 30-55 years); the mean BCVA was 0.23 logMAR (approximate Snellen equivalent, 20/32) with a range of 0 to 1 (20/20 to 20/200). The mean time of ocular adverse events was 5.2 days (range, 1-10 days).

Patients were diagnosed with episcleritis (case 1), anterior scleritis (case 2 and case 5), acute macular neuroretinopathy (AMN) (case 3 and case 4), paracentral acute middle maculopathy (PAMM) (case 7), and subretinal fluid (case 6).

Selected Cases

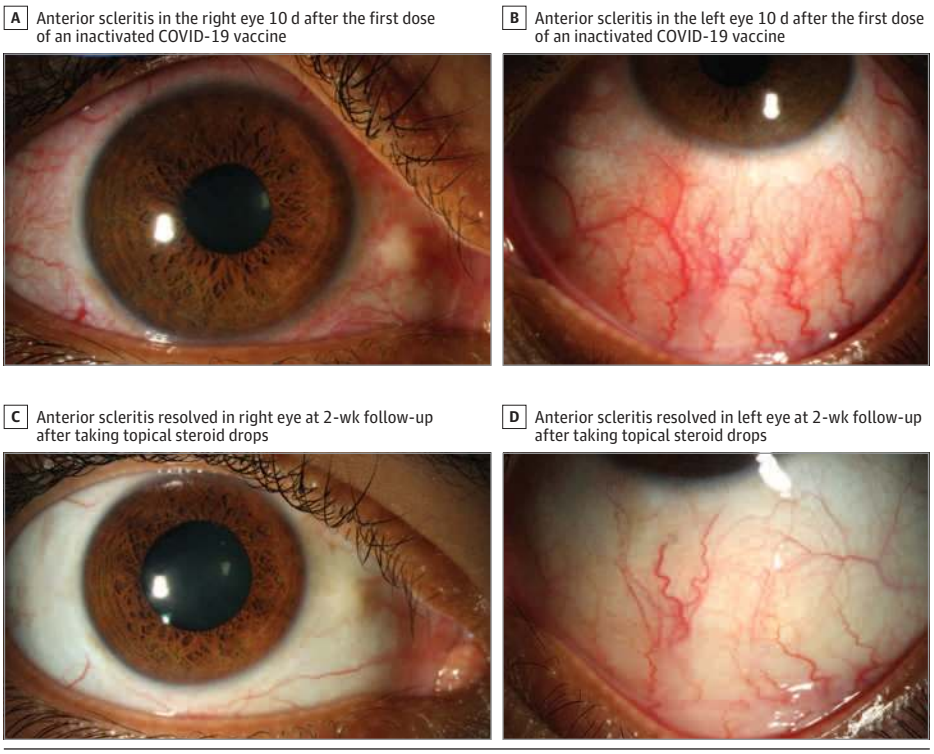
Case 2

Patient 2 presented to our uveitis clinic with redness and pain in both eyes 1 week after receiving an inactivated COVID-19 vaccine. The patient's medical history was remarkable for rheumatoid arthritis, well controlled with sulfasalazine. Visual acuity at baseline was 20/20 OU with an intraocular pressure of 18 mm Hg. Slitlamp examination showed more than 2 diffuse scleral hyperemia (**Figure 1**A and B) with positive phenylephrine test results. No cells and flare were noticed in the anterior chamber and no further signs of inflammation were seen. The patient started receiving a tapering dose of topical steroid to control the episode; on 1-week follow-up, the scleritis had resolved (Figure 1C and D).

Case 3

Patient 3 had an ocular history of central serous chorioretinopathy in both eyes with a chronic serous pigment epithelial detachment in the left eye (**Figure 2**A) and a BCVA of 20/25

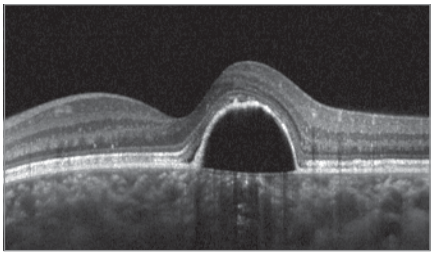
Figure 1. Scleritis Associated With Inactivated COVID-19 Vaccine



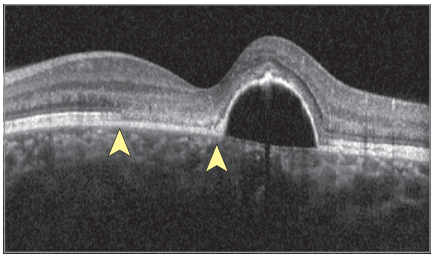
A and B, Right and left eye of a patient who presented with bilateral anterior scleritis 10 days after receiving the first dose of an inactivated COVID-19 vaccine (Sinopharm). The patient started taking topical steroid drops, and the bilateral episode completely resolved at 2-week follow-up (C and D).

Figure 2. Acute Macular Neuroretinopathy After Inactivated COVID-19 Vaccine

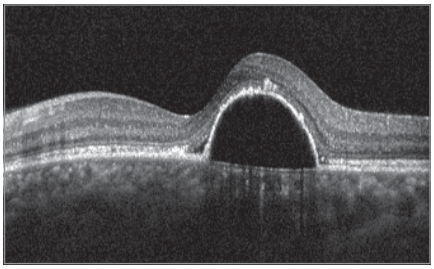
A Left eye showing central serous chorioretinopathy, serous pigment epithelial detachment, and a thick choroid



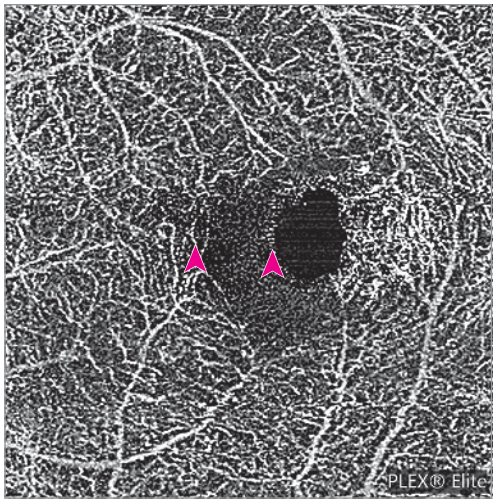
B 1 wk After inactivated COVID-19 vaccine hyperreflectivity of the outer plexiform layer, Henle fiber layer, and outer nuclear layer with attenuation of the photoreceptors



C Tomographic picture resolved at 2-mo follow-up



D A semilunar area of signal absence corresponding to the hyperreflective deep lesion



A patient with an ocular history of central serous chorioretinopathy, in the left eye visible (A) with a serous pigment epithelial detachment and a thick choroid presented with profound loss of central vision 1 week after receiving the inactivated COVID-19 vaccine (Sinopharm). Spectral-domain optical coherence tomography showed hyperreflectivity of the outer plexiform layer, Henle fiber layer, and outer nuclear layer with attenuation of the photoreceptors (B, yellow arrowheads), compatible with acute macular neuroretinopathy. Swept-source optical coherence tomographic angiography at the level of the deep capillary plexus (C) showed a semilunar area of signal absence (pink arrowheads) corresponding with the hyperreflective deep spectral-domain optical coherence tomography lesion that may be a sign of slower deep capillary flow or an artifact from the outer retina changes. The patient was closely observed and at 2-month follow-up the tomographic picture had resolved (D).

at previous visits. The patient presented to our emergency department with an acute vision loss in the left eye 5 days after receiving the inactivated COVID-19 vaccine (Sinopharm). Vital parameters were within normal limits, but the BCVA in the left eye had dropped to 20/400. Spectral-domain OCT showed hyperreflectivity of the outer plexiform layer, Henle fiber layer, and outer nuclear layer (Figure 2B, yellow arrowheads) nasal to the unchanged pigment epithelium detachment. Ellipsoid and interdigitation zones were attenuated. The tomographic picture was consistent with AMN. Swept-source OCT angiography at the level of the deep capillary plexus showed a semilunar area of flow void (Figure 2D, pink arrowheads) corresponding with the hyperreflective deep spectral-domain OCT lesion. The patient was closely observed, and at 2-month follow-up, the tomographic picture had resolved (Figure 2C) and BCVA was back to 20/30.

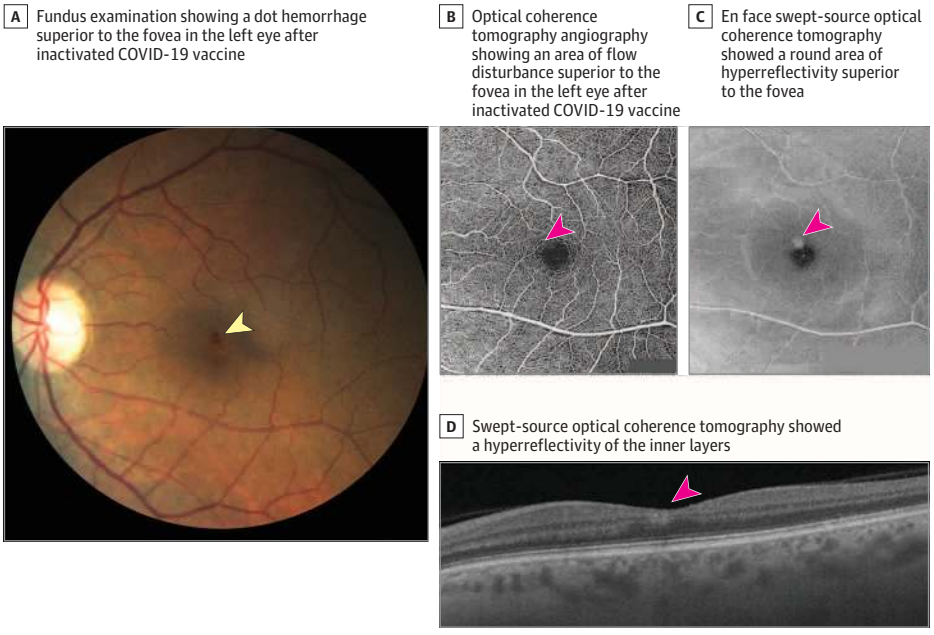
Case 7

Patient 7 presented to the retina clinic in January 2021 with blurry vision in the left eye and headache. Ocular and medical history were unremarkable. However, the patient reported that 20 minutes after receiving COVID-19 vaccine (Sinopharm), they developed persistent tachycardia and raised systolic blood pressure, recorded at 210 mm Hg, and was nonresponsive to treatment for 3 weeks. Simultaneously, the patient started noticing an inferior scotoma in the left eye. BCVA at presentation was 20/30 OS, and dilated fundus examination revealed a dot hemorrhage superior to the fovea (**Figure 3**A). OCT angiography revealed a superior enlargement of the foveal avascular zone (Figure 3B). This fundus and OCT angiography finding corresponded with a round area of hyperreflectivity superior to the fovea on en face SS-OCT (Figure 3C) that on B-scan SS-OCT presented as an opacification of the inner layer (Figure 3D).

Discussion

In the current case series, we report 9 eyes presenting with ocular adverse events after the first inoculation of in-

Figure 3. Paracentral Acute Middle Maculopathy in a Patient Receiving Inactivated COVID-19 Vaccine



One patient developed a sudden paracentral scotoma in the left eye after receiving the inactivated COVID-19 vaccine (Sinopharm). The patient's fundus examination revealed a dot hemorrhage superior to the fovea (A). Optical coherence tomography angiography revealed a superior enlargement of the foveal avascular zone (B). This fundus and optical coherence tomographic angiography finding corresponded with a round area of hyperreflectivity superior to the fovea on en face swept-source optical coherence tomography (C) that on B-scan swept-source optical coherence tomography presented as an opacification of the inner layers (D). These imaging features may be consistent with paracentral acute middle maculopathy or be secondary to intraretinal hemorrhage.

activated COVID-19 vaccine (Sinopharm), although a causal relationship cannot be established from this study design. Only 1 patient (case 7) presented associated systemic signs of vaccine reaction in the form of uncontrollable hypertension.

At a mean of 6 days after the first inoculation, 2 of 9 eyes in the present series presented with acute unilateral vision loss associated with AMN and 1 of 9 eyes with PAMM. PAMM[5] and AMN[6] have been reported after H1N1 vaccination. Furthermore, Virgo and Mohamed[7] reported 2 patients with new paracentral scotoma secondary to AMN and PAMM 16 days after confirmed COVID-19 infections.

One patient presented with bilateral, shallow areas of subretinal fluid with no thickening of the underlying choroid and an associated hypertrophy of the photoreceptor overlying the fluid. This picture was suggestive of a forme fruste of central serous chorioretinopathy that has previously been documented after smallpox[8] and anthrax vaccination.[9]

Scleritis and episcleritis was reported in 4 of 9 cases at a mean of 5 days after the first dose of the vaccine. Although uncommon, there are few reports of episcleritis and scleritis following administration of live, attenuated viruses.[10] Consistent with the reported literature, the present cases of scleritis noted soon after vaccination were mild. Of note, Méndez-Mangana et al[11] reported a patient with episcleritis 7 days after confirmation of COVID-19 infection.

The theoretic pathogenesis of an inactivated COVID-19–associated ocular inflammation is not known. Commonly proposed mechanisms have included both molecular mimicry and antigen-specific cell and antibody-mediated hypersensitivity reactions.[12-14]

Limitations

The timing of complications 5.2 days after vaccination points toward an association between inactivated COVID-19 vaccination (Sinopharm) and the ocular findings. During the study period, no additional cases of AMN or PAMM were identified in our tertiary center, while cases of scleritis, episcleritis, and subretinal fluid were common.

Conclusions

As the urge for a vaccine against COVID-19 continues, we expect to see an increasing number of ocular adverse events from the various candidates.

ARTICLE INFORMATION

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Concept and design: Pichi, Neri, Ghazi.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Pichi, Aljneibi, Neri, Hay.
Critical revision of the manuscript for important intellectual content: Neri, Dackiw, Ghazi.
Statistical analysis: Pichi, Neri.
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Invited Commentary

COVID-19, COVID-19 Vaccinations, and Subsequent Abnormalities in the Retina
Causation or Coincidence?

Lee M. Jampol, MD; Robert Tauscher, MD; Hans Peter Schwarz, MD

Pichi and colleagues[1] in this issue of *JAMA Ophthalmology* describe ocular adverse events after Sinopharm COVID-19 vaccination, including 4 retinal events. Little is known about this vaccine.[2] Despite the large number of doses of vaccine having been administered worldwide, its adverse systemic events remain uncertain. We will review the evidence regarding associations of COVID-19 infection or COVID-19 vaccination with subsequent ocular adverse events, in particular retinal problems, to consider whether these abnormalities are causally associated or just coincidental. COVID-19 infection causes widespread damage to multiple organs. Proinflammatory cytokines are released and are strong inducers of a procoagulant/prothrombotic reaction,[3] resulting in intravascular coagulopathies and endothelial injury. In regard to the retina, COVID-19 infection can be associated with anemia, hypertension or hypotension, hypoxia, and other systemic morbidities, which can contribute to retinal findings such as nerve fiber layer infarcts, hemorrhages, or microaneurysms. Vasculitis and thromboembolism also can contribute to retinal ischemia. Thus, we are not surprised to see reports of retinal hemorrhages, dilated and tortuous retinal veins, central retinal vein occlusion, central retinal artery occlusion, acute macular neuroretinopathy (AMN), paracentral acute middle maculopathy, acute retinal necrosis, endophthalmitis, optic neuritis, and others. These may not be due to the virus, but due to the systemic complications that this virus can cause. In the hundreds of millions of cases of COVID-19 infection seen worldwide, findings supporting direct retinal damage (other than vascular damage) from the virus have not been described. Retinal macro- and microvascular damage[4] seen in patients with COVID-19 could be related to systemic thromboembolism, other systemic morbidities, or to the effect of the virus on retinal vessels. COVID-19 infection is also associated with a massive dysregulation of the humoral immune system characterized by the appearance of potent autoantibodies reacting against a wide range of soluble and tissue-specific proteins, which also might contribute to ocular disease.

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What about COVID-19 vaccination and the retina? There have been anecdotal cases of adverse retinal ischemic events presented at conferences and undoubtedly awaiting publication. For example, we recently saw a middle-aged woman with diabetes and hypertension with a remote branch retinal artery occlusion in the left eye. Optical coherence tomography on the right showed AMN. Two weeks prior, she had received a Johnson & Johnson COVID-19 vaccination. Is the AMN from the vaccination or related to her systemic vasculopathy? When rare retinal findings (eg, AMN) are noted in association with a more common event (in this case COVID-19 vaccination), the findings may be unrelated. However, there are situations where one can suspect the associations have a real cause-and-effect relationship. Post–adenovirus vector vaccination (Johnson & Johnson, AstraZeneca), patients can have potentially life-threatening cerebral venous sinus thrombosis (CVST).[5] These patients often have thrombocytopenia, which is very rarely associated with thrombosis. While CVST and thrombocytopenia after COVID-19 vaccination are extremely rare, it is much more common than in the general population. In these patients with CVST, the presence of platelet-activating autoantibodies against platelet factor 4 causes multicellular activation of coagulation. It mimics autoimmune heparin-induced thrombocytopenia. This syndrome is now called vaccine-induced immune thrombotic thrombocytopenia. It usually occurs within the first 3 weeks following vaccination, mostly in younger women. Anti–platelet factor 4 antibodies are pathognomonic for vaccine-induced immune thrombotic thrombocytopenia. As of April 4, 2021, 169 cases of CVST were reported in 34 million individuals vaccinated with AstraZeneca in the European Union and UK, corresponding to a reporting rate of 5 cases per million vacci-