Case Report: Acute Posterior Multifocal Placoid Pigment Epitheliopathy after SARS-CoV-2 Vaccination

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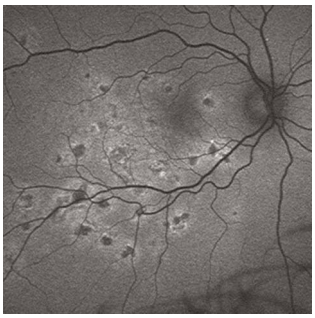
SIGNIFICANCE: Acute posterior multifocal placoid pigment epitheliopathy is an uncommon inflammatory chorioretinopathy that has been reported after vaccination. This is the first reported case, to our knowledge, after vaccination for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a healthy adolescent boy.

PURPOSE: This report aimed to inform the eye care community about a possible ocular sequela of SARS-CoV-2 vaccination.

CASE REPORT: A 17-year-old boy presented to a clinic for a second opinion after sudden-onset blind spots in his right eye. His medical history was remarkable for receiving the first dose of the Pfizer-BioNTech SARS-CoV-2 vaccine 2 weeks before symptom onset. He had no history of ocular inflammation, autoimmune disease, or systemic infection. A diagnosis of unilateral acute posterior multifocal placoid pigment epitheliopathy was made based on the presence of typical fundus lesions and noninvasive imaging with fundus autofluorescence, retinal optical coherence tomography, and optical coherence tomography angiography. The diagnosis was further confirmed with fluorescein angiography. The patient developed an anterior vitritis in the right eye 42 days after initial symptom onset. His unilateral intraocular inflammation resolved after a 5-week course of prednisone.

CONCLUSIONS: Acute posterior multifocal placoid pigment epitheliopathy is a self-limited inflammatory condition of the outer retina that usually affects young adults and often does not require treatment. It has been reported to occur after vaccination for influenza, polio, hepatitis B, meningococcus C, and varicella zoster virus. This is the first known case to occur after SARS-CoV-2 vaccination in a healthy adolescent boy.



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Acute posterior multifocal placoid pigment epitheliopathy is an uncommon idiopathic inflammatory chorioretinopathy characterized by multiple creamy subretinal lesions. It typically occurs in young adults between the ages of 20 and 40 years with equal predilection for sex and race.[1–4] Although the incidence of the disease is unclear, it has been reported to occur in 0.15 individuals per 100,000, and there may be an increased risk in individuals possessing the human leukocyte antigens B27 and DR2.[5] No definitive cause has been confirmed, but the condition has been reported to follow a viral illness or occur after vaccination, indicating an immune-mediated reaction to a viral antigen.[3] Although treatment is often unnecessary because the disease is self-limiting, some patients may benefit from oral steroids, particularly if macular lesions are present.[3,4] Although the presentation is typically bilateral in 75% of patients, acute posterior multifocal placoid pigment epitheliopathy may initially begin in one eye, with the fellow eye demonstrating lesions days to weeks after the first eye is affected.[6] This case is unique for its unilateral presentation that occurred 2 weeks after administration of the first dose of the Pfizer-BioNTech (Pfizer, New York, NY; BioNTech, Mainz, Germany) vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a healthy adolescent boy without a history of the novel coronavirus disease (COVID-19) infection that was discovered in December 2019. The typical fundus lesions along with a mild vitritis that developed during the disease are most consistent with the diagnosis of acute posterior multifocal placoid pigment epitheliopathy.[1–4] The authors strive to bring awareness about this possible ocular sequela of the novel SARS-CoV-2 messenger RNA (mRNA) vaccine to the eye care community.

CASE REPORT

A 17-year-old healthy boy presented to a clinic for a second opinion of his ocular condition. He was initially seen at the emergency department 2 weeks before presentation for an acute visual disturbance in the right eye that was described as "blind spots" in his vision. He was examined by an attending optometrist who diagnosed the patient with right acute posterior multifocal pigment epitheliopathy (Fig. 1). He presented to our clinic 6 days later for a second opinion. On examination, his uncorrected Snellen visual acuity was 20/20 in the right and left eyes. Extraocular motilities were full and smooth in both eyes. Pupils were equal and briskly reactive to light without an afferent pupillary defect in both eyes. Confrontation visual fields were full in both eyes. Slit-lamp examination showed a normal result in both eyes. Goldmann applanation tonometry was 18 mmHg in the right eye and 17 mmHg in the left eye. A dilated fundus examination revealed clear vitreous in both eyes. Both optic nerves were well perfused with distinct margins. Cup-to-disc ratio was 0.35 in both eyes, and the retinal vasculature was normal caliber in both eyes. There were multiple flat, creamy-white placoid subretinal lesions within the posterior pole and temporal

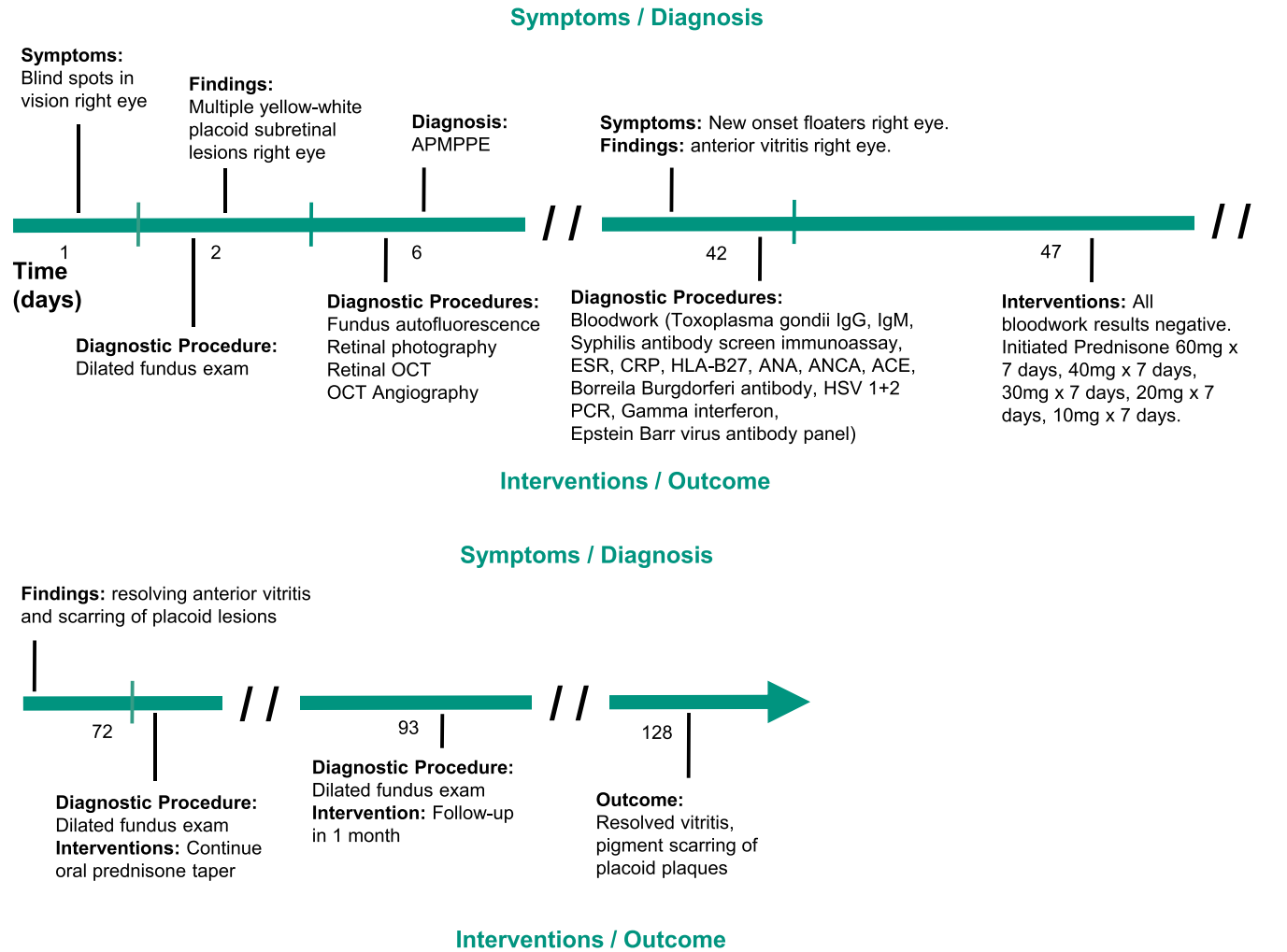

FIGURE 1. Clinical timeline. A 17-year-old Latino boy was diagnosed with unilateral acute posterior multifocal placoid pigment epitheliopathy 2 weeks after receiving the Pfizer-BioNTech COVID-19 vaccine. The patient developed an anterior vitritis 42 days after initial symptom onset. After a negative blood work panel, he was started on oral corticosteroids. ACE = angiotensin-converting enzyme; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; APMPPE = acute posterior multifocal placoid pigment epitheliopathy; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HLA = human leukocyte antigen; HSV = herpes simplex virus; OCT = optical coherence tomography; PCR = polymerase chain reaction.

midperipheral retina of the right eye, which are demonstrated in Fig. 2. The retinal fundus of the left eye was unremarkable.

Fundus autofluorescence (Fig. 3) and optical coherence tomography angiography (Fig. 4) confirmed a diagnosis of acute posterior multifocal placoid pigment epitheliopathy in the right eye. Fundus autofluorescence of the right eye demonstrated multiple hypoautofluorescent placoid lesions in the posterior pole and midperiphery with hyperautofluorescent borders, which is consistent with the acute phase of the disease because of the proposed masking of the underlying retinal pigment epithelium by swollen retinal cells.[5–7] Fundus autofluorescence of the left eye was unremarkable. Optical coherence tomography angiography of the right eye demonstrated hypoperfusion of the choriocapillaris in a placoid pattern that was more extensive than the clinically observed creamy-white lesions. Optical coherence tomography angiography of the left eye showed a normal result. Optical coherence tomography of the right eye (Fig. 5A) demonstrated focal areas of disruption of the ellipsoid layer, outer retina, and retinal pigment epithelium, whereas optical coherence tomography of the left eye (Fig. 5B) was unremarkable. The patient was seen by an ophthalmologist 2 days later for fluorescein angiography, which further confirmed a diagnosis of unilateral acute posterior multifocal placoid pigment epitheliopathy in the right eye by demonstrating early hypofluorescence and late staining of the placoid lesions in the right eye. Fluorescein angiography of the left eye was unremarkable.

The patient was observed without any intervention until he developed a mild anterior vitritis in the right eye 42 days after initial presentation. A laboratory evaluation was ordered for the patient, which included the following panel: *Toxoplasma gondii* immunoglobulins G and M, syphilis antibody screen immunoassay, erythrocyte sedimentation rate, C-reactive protein, human leukocyte antigen B27, antinuclear antibody, antineutrophil cytoplasmic antibody, angiotensin-converting enzyme, *Borrelia burgdorferi* antibody, herpes simplex virus 1 and 2 polymerase chain reaction, γ-interferon, and Epstein-Barr virus antibody panel. The laboratory evaluation revealed negative results for a systemic infectious and autoimmune etiology, and the patient was subsequently started on a course of oral

FIGURE 2. Ocular findings at presentation. (A) Fundus photography demonstrates multiple flat yellow-white placoid lesions in the posterior pole and temporal midperiphery of the right eye with sparing of the fovea, indicating active disruption of the retinal pigmented epithelium and outer retina. Several healing lesions (white arrows) can be visualized temporal to the macula. (B) Fundus photography of the left eye demonstrates normal findings.

prednisone that was tapered for 5 weeks. Four months after initial symptom onset, the placoid lesions were replaced by pigmented scars, and the anterior vitritis was completely resolved. During this time, the left eye remained unaffected. The patient's Snellen visual acuity remained at 20/20 in the right and left eyes. The complete timeline of the patient's ocular events is outlined in Fig. 1.

DISCUSSION

This case report highlights the clinical presentation of acute posterior multifocal placoid pigment epitheliopathy after administration of the first dose of the mRNA SARS-CoV-2 vaccine in a healthy 17-year-old boy. On March 11, 2020, the World Health Organization declared a global pandemic as a result of the rapidly spreading SARS-CoV-2 virus responsible for COVID-19. The Pfizer-BioNTech COVID-19 mRNA vaccine became available under the Emergency Use Authorization on December 11, 2020, for individuals 16 years and older.[8] The close temporal correlation of symptom onset to vaccine administration without any preceding viral illness provides a clinical presumption that the patient's acute posterior multifocal placoid pigment epitheliopathy was triggered by the COVID-19 mRNA vaccine.

The Pfizer-BioNTech mRNA vaccine uses a lipid nanoparticle–encapsulated mRNA that encodes a stabilized prefusion form of the SARS-CoV-2 glycoprotein trimer.[9,10] The vaccine produces high levels of neutralizing antibodies that target the spike proteins in the virus.[9,11] The advantage of an mRNA vaccine is that it is noninfectious, does not integrate into the host genome, and does not induce vector-specific responses.[10] However, it may result in potential ocular inflammatory events due to aberrant activation of the innate and acquired immune systems due to similarities between the SARS-CoV-2 spike glycoprotein and human proteins.[11–13] Stimulation of a strong T-cell response by the vaccine can thus induce autoimmune manifestations because of a close resemblance between vaccine peptide fragments and uveal self-peptides. It has been postulated that neutralizing antibodies against SARS-CoV-2 spike proteins and activated T-helper-1 cells can cross-react with proteins and antigens in large arteries, outer retinal layers, and retinal pigment epithelial cells.[9,11] Another potential cause of retinal inflammatory reactions is inflammatory damage caused by vaccine adjuvants that are found in mRNA vaccines whose role is to potentiate immunogenic activity.[12,14] Various ocular sequelae after COVID-19 mRNA vaccination have been reported in the literature, including acute anterior uveitis, multifocal choroiditis, acute zonal occult outer retinopathy, reactivation of Vogt-Kayanagi-Harada disease, multiple evanescent white dot syndrome, and acute macular neuroretinopathy.[11,13,14]

The clinical features of white lesions in the choroid, the sensory retina, and/or the retinal pigment epithelium fall under the subgroup of posterior segment conditions known as white dot syndromes. Each white dot syndrome has specific characteristics that aid in the differential diagnosis. It is important to differentiate correctly between the various syndromes because the clinical course, treatment, and outcomes vary by each condition. The acute onset of symptoms and fundus appearance of multiple large placoid, cream-colored, flat lesions in the posterior pole of the right eye were consistent with a diagnosis of acute posterior multifocal placoid pigment epitheliopathy. The development of a mild anterior vitritis in the affected eye 42 days after symptom onset was also consistent with a diagnosis of acute posterior multifocal placoid pigment epitheliopathy because this condition has been associated with anterior uveitis and vitritis.[1,2] The development of vitritis is likely due to delayed-onset inflammation that can affect other parts of the eye during the healing phase of the disease.[15]

The pathophysiology of acute posterior multifocal placoid pigment epitheliopathy is poorly understood but is believed to be a result of a hypersensitivity-induced or cell-mediated immunity to a viral antigen.[2,16] The immune reaction is thought to cause an occlusive choroidal vasculitis that leads to ischemic injury of the overlying retinal pigment epithelium and photoreceptor layers, thereby producing the characteristic fundus appearance of deep yellow-white placoid lesions.[6,7,17] The primary insult appears to be at the level of the choriocapillaris, with outer retinal changes occurring secondary to the choroidopathy. This proposed pathophysiology is supported by multimodal imaging that demonstrates reversible choroidal hypoperfusion.[7] Optical coherence tomography angiography clearly demonstrates choriocapillaris hypoperfusion in acute phases of the disease

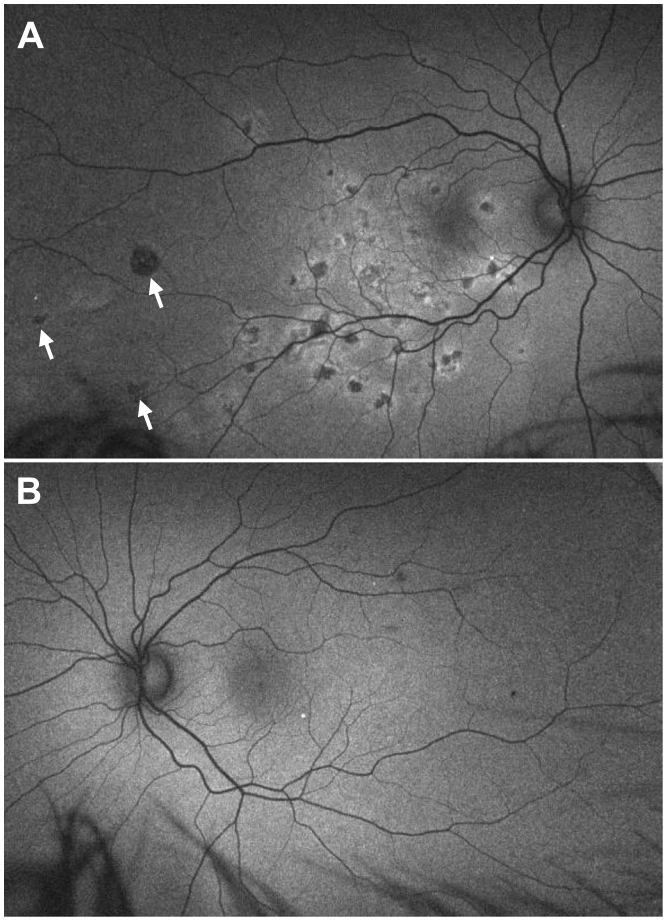

FIGURE 3. Fundus autofluorescence at presentation. (A) The right eye has multiple well-defined hypoautofluorescent lesions surrounded by hyperautofluorescent borders in the posterior pole corresponding to the placoid lesions seen on clinical examination. Inactive lesions in the temporal midperiphery are entirely hypoautofluorescent (white arrows). (B) The left eye is normal. Scattered artifacts are present.

that extends beyond areas of clinically visible creamy placoid lesions, further suggesting that the choriocapillaris is the primary site of inflammation in this disorder.[17] Because of mounting evidence that acute posterior multifocal placoid pigment epitheliopathy is most likely a primary choroidopathy, some authors have suggested renaming the condition to multifocal ischemic choroidopathy.[4,6,7]

There are four proposed phases of acute posterior multifocal placoid pigment epitheliopathy that are described in the literature.[7] Phase 1 (choroidal) is caused by hypoperfusion of the choriocapillaris that is detected with optical coherence tomography angiography and confirmed with hypocyanescence on indocyanine green angiography and early fluorescein angiography. Optical coherence tomography and fundus autofluorescence results are normal in this stage. Stage 1 lesions can resolve spontaneously and reverse to normal optical coherence tomography angiography findings, or they can evolve to phase 2. Phase 2 (chorioretinal) demonstrates classic active lesions on fluorescein angiography with early hypofluorescence and late staining, persistent hypocyanescence on indocyanine green angiography, and choroidal hypoperfusion on optical coherence tomography angiography. Loss of structural integrity and hyperreflectivity of outer retinal layers is seen on optical coherence tomography. Fundus autofluorescence demonstrates hypoautofluorescent lesions, presumably due to a masking effect by swollen retinal cells, with a typical hyperautofluorescent ring indicating increased lipofuscin accumulation due to a stressed retinal pigment epithelium. Phase 3 (transitional) demonstrates thinning and disruption of outer retinal layers on optical coherence tomography, persistent hypoperfusion of choriocapillaris on optical coherence tomography angiography, and progressive central hyperautofluorescence on fundus autofluorescence because of loss of structural integrity of the retinal pigment epithelium. Phase 4 (resolution) demonstrates persistent thinning of the outer retina on optical coherence tomography with hyporeflectivity at the level of the retinal pigment epithelium, hypoautofluorescent changes on fundus autofluorescence, and normalized choriocapillaris on optical coherence tomography angiography.

Although many cases of acute posterior multifocal placoid pigment epitheliopathy are presumed to be idiopathic, they have also been reported in patients with a history of recent vaccination against influenza, hepatitis A, hepatitis B, meningococcus C, varicella zoster virus, and yellow fever.[8,12] Signs of acute posterior multifocal placoid pigment epitheliopathy typically occur bilaterally in 75% of patients at presentation or occur sequentially between the two eyes within days to weeks in young, healthy individuals without sex or racial predilection.[1,2,6] In rare cases of unilateral presentations of the disorder, it has been reported that swept-source optical coherence tomography will reveal subfoveal choroidal thickening in seemingly unaffected fellow eyes, many of which will eventually develop some signs of disease activity in the future and should therefore be monitored carefully for development of bilateral disease.[3] Truly unilateral presentations may coincide with other atypical features of the disease, and systemic treatment may be indicated more frequently than in classically bilateral presentations.[3] In most cases, patients present with photopsia, blurred vision, and paracentral scotomas.[1,2] In some cases, patients may present with meningeal symptoms including headaches, photophobia, stiff neck, malaise, or central nervous system vasculitis.[14] If the patient in this case exhibited any neurological symptoms, a brain MRI and lumbar puncture would have been indicated to rule out central nervous system involvement.

Ancillary testing with optical coherence tomography angiography and fundus autofluorescence demonstrated results that were consistent with a diagnosis of acute posterior multifocal placoid pigment epitheliopathy. The multimodal imaging confirmed key anatomic and clinical features of this disorder. The optical coherence tomography scans of the areas with placoid lesions demonstrated loss and disruption of the inner segment–outer segment ellipsoid zone, external limiting membrane, and retinal pigment epithelium that are typical of acute posterior multifocal placoid pigment epitheliopathy lesions. Optical coherence tomography angiography provided a noninvasive angiographic study of the retina and choroid, revealing hypoperfusion of the choriocapillaris that extended beyond areas of creamy-white retinal lesions observed on the fundus examination.

Fundus autofluorescence was very useful in differentiating acute posterior multifocal placoid pigment epitheliopathy from other white dot syndromes. Hyperautofluorescence results from an accumulation of lipofuscin in macrophages that are responsible for removing damaged retinal pigment epithelium, whereas hypoautofluorescence is typically caused by disruption or death of retinal pigment epithelial cells.[18] In active stages of acute posterior multifocal placoid pigment epitheliopathy, fundus autofluorescence demonstrates hypoautofluorescent lesions due to the masking effect of the retinal

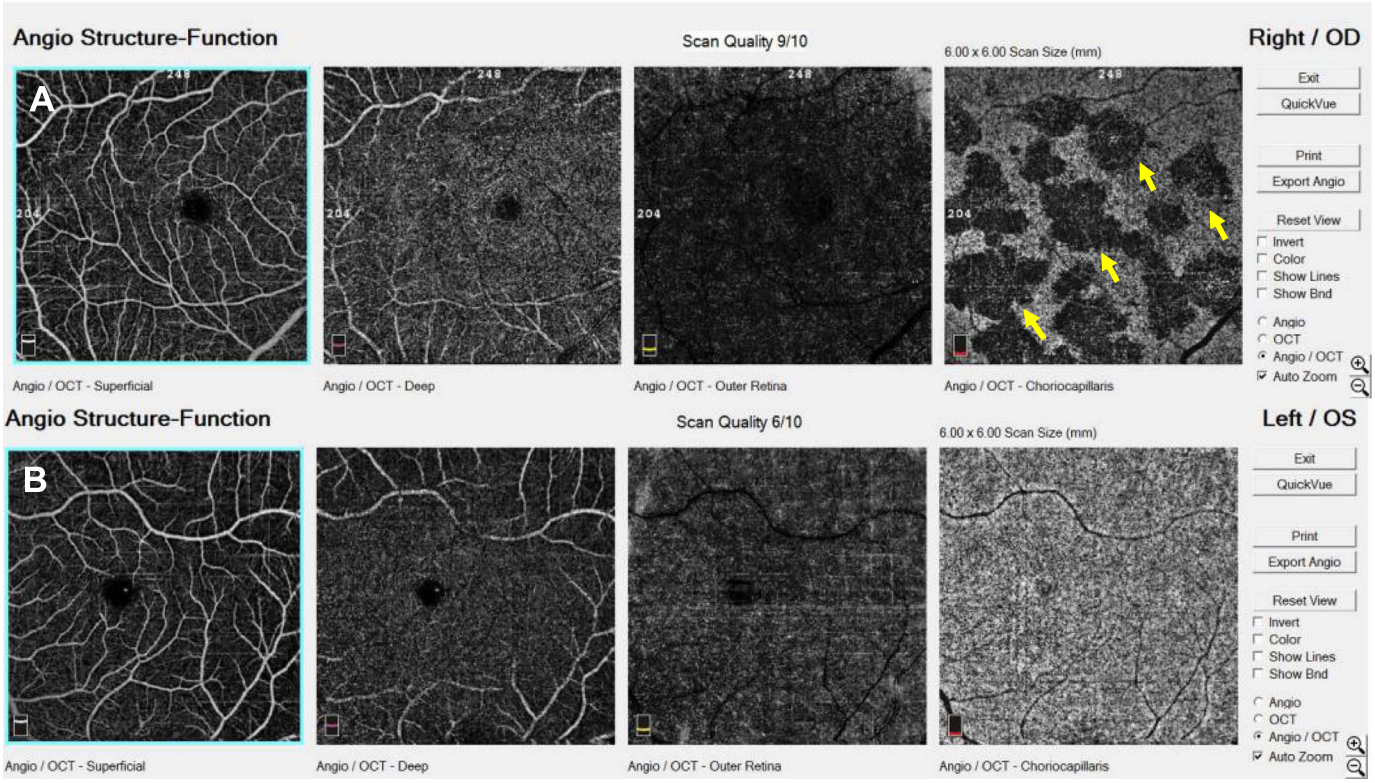

FIGURE 4. Optical coherence tomography angiography at presentation. (A) The right eye demonstrates normal superficial and deep retinal capillary plexus. There is significant hypoperfusion of the right choriocapillaris in a placoid pattern (yellow arrows), which are far more numerous than the areas of creamy placoid lesions observed on clinical examination. (B) Optical coherence tomography angiography of the left eye shows a normal result for deep and superficial retinal layers and the choriocapillaris.

pigment epithelium by overlying swollen retinal cells. The areas of hypoautofluorescence are surrounded by hyperautofluorescent borders that result from visualization of a stressed retinal pigment epithelium that surrounds the placoid lesions.[5] This pattern of hypoautofluorescent placoid lesions with hyperautofluorescent borders was clearly evident in our patient's imaging results. This case highlights the use of noninvasive multimodal imaging to differentiate acute posterior multifocal placoid pigment epitheliopathy from other white dot syndromes, including serpiginous choroidopathy, birdshot chorioretinopathy, and unilateral acute idiopathic maculopathy. Although serpiginous choroidopathy has similar findings on fundus autofluorescence, it is more commonly seen in older patients and presents with lesions emanating from the peripapillary region, which was not seen in this patient.[19] The fundus autofluorescence lesions in birdshot chorioretinopathy demonstrate hypoautofluorescence without the hyperautofluorescent borders that are seen in acute posterior multifocal placoid pigment epitheliopathy.[19] Lastly, acute idiopathic maculopathy lesions will not demonstrate the hyperfluorescent halo pattern on fundus autofluorescence that is seen in acute posterior multifocal placoid pigment epitheliopathy.[19]

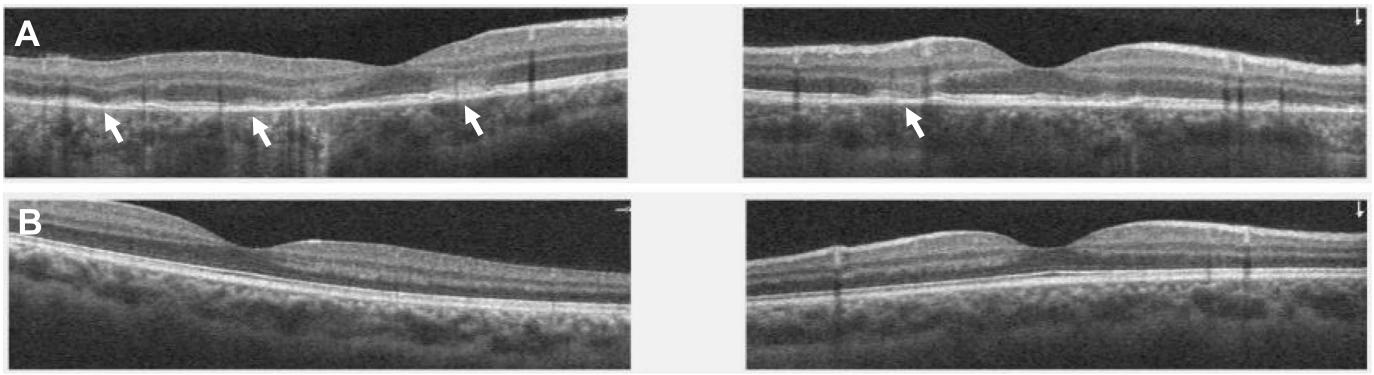

FIGURE 5. Optical coherence tomography at presentation. (A) The right eye has disruption of the retinal pigment epithelium and photoreceptor inner-segment/outer-segment layers (white arrows). (B) The left eye has intact retinal pigment epithelium and outer retinal layers.

Patients with acute posterior multifocal placoid pigment epitheliopathy typically have a good visual outcome with a monophasic, nonrecurring clinical course, although full recovery can take weeks to months.[1] Although this disorder is typically self-limiting and usually does not necessitate treatment, steroids may be considered if there is macular involvement or if vitritis is present, as was the case with the patient in this report.[3,4] However, there is no clear information regarding the use of oral steroids aside from suggesting that systemic treatment may be beneficial if foveal involvement is present, and most patients can be observed without any intervention.[3,4]

CONCLUSIONS

This case underscores the potential for SARS-CoV-2 vaccine–related ocular sequelae because this is the first reported case of acute posterior multifocal placoid pigment epitheliopathy after an mRNA vaccine, to the authors' knowledge. The authors recommend that the eye care community monitors patients for acute symptoms of paracentral scotomas with or without reduced visual acuity after vaccination for SARS-CoV-2.

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