COVID-19 VACCINE–INDUCED ACUTE EXUDATIVE POLYMORPHOUS VITELLIFORM MACULOPATHY: CASE REPORTS

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Background: Acute exudative polymorphous vitelliform maculopathy is a presumed retinal pigment epithelium abnormality that has been reported in patients with neoplasms and under certain classes of drugs. The pathophysiology remains unclear, despite the typical clinical features.

Purpose: To report two cases of acute exudative polymorphous vitelliform maculopathy occurring after vaccination with a COVID-19 vaccine.

Case Reports: Two adult patients presented with visual disturbance after inoculation with a COVID-19 vaccine. The patients were otherwise healthy and have no family history of retinal dystrophies. Both cases exhibited the following features on multimodal imaging: multifocal hyporeflective lesions involving the macula, elongated photoreceptors, accumulated vitelliform material exhibiting autofluorescence, and lack of fluorescein dye leakage. Evidence of retinal pigment epithelium dysfunction was confirmed by electrooculography.

Conclusion: Two cases of acute exudative polymorphous vitelliform maculopathy occurring after COVID-19 vaccination were reported. A relationship between the vaccine and the retinal pigment epithelial abnormality development that led to acute exudative polymorphous vitelliform maculopathy was postulate, possibly through autoantibodies against the severe acute respiratory syndrome coronavirus 2 virus structural surface glycoprotein antigens that cross react with the normal retinal pigment epithelial cells.

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Acute exudative polymorphous vitelliform maculopathy (AEPVM) is a rare and poorly understood condition that was first described by Gass[1] in 1988. It is typically characterized by acute multifocal exudative macular detachment followed by the formation of polymorphous vitelliform deposits. The ocular signs are usually associated with blurring of vision. The term "vitelliform" was derived from the Latin word vitellum (which means egg yolk). Such deposits are more commonly seen in Best vitelliform macular dystrophy and other bestrophinopathies with underlying mutations in Bestrophin-1 gene (*BEST1* gene) and are believed to develop from poor RPE function and RPE–retina apposition.[2] A similar abnormality is believed to occur in AEPVM.[3]

The safety and efficacy profile of the Oxford–AstraZeneca chimpanzee replication-deficient adenovirus–vectored vaccine ChAdOx1 nCoV-19 (AZD1222) against severe acute respiratory syndrome coronavirus 2 was published in the Lancet in early 2020.[4] The vaccine was authorized for public use by the European Medicines Agency in February 2020. Emerging ocular adverse events that are temporally related to COVID-19 vaccination have been reported.[5]

In this report, we present 2 cases with a picture consistent with AEPVM after administering the AZD1222 vaccine and describe the findings on

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multimodal imaging. To our knowledge, no previous reports have indicated that severe acute respiratory syndrome coronavirus 2 infection or any of its vaccines may be related to AEPVM.

Case Reports

Case 1

A 34-year-old male patient presented with bilateral blurring of vision 14 days after administration of the AZD1222 vaccine. Best-corrected visual acuity was 20/30 in both eyes. Anterior segment examination was unremarkable. Dilated fundus examination showed symmetric multifocal pockets of subretinal fluid in the fovea in both eyes, which was confirmed on optical coherence tomography. One week later, numerous smaller blister-like lesions developed surrounding the macula. The photoreceptor outer segments appeared diffusely elongated on optical coherence tomography B-scans. None of the lesions demonstrated hyperfluorescence on fluorescein angiography. The Arden ratio was found to be subnormal at 1.7 in the right eye and borderline at 1.8 in the left eye on electrooculogram (EOG), denoting the underlying RPE abnormality (Figure 1).

Based on the clinical picture, the patient was tentatively diagnosed as AEPVM and had a pending oncology screening to exclude the possibility of a paraneoplastic element. After a thorough assessment by an oncologist and a positron emission tomography/computed tomography (PET/CT) image, an underlying malignancy was ruled out. Oral prednisolone therapy was initiated at 60 mg daily dose, and the patient was advised against administering the second dose of the vaccine. Subsequently, the intraretinal fluid subsided, but the hyporeflective subretinal spaces persisted in the fovea and around the arcades, demonstrating newly formed hyperreflective vitelliform material in the dependent part and along the edges of each space. The findings were best visualized on blue fundus autofluorescence (FAF). After 4 weeks, vision progressively improved to 20/20 in both eyes, and systemic steroids were gradually tapered. Few of the parafoveal lesions showed resorbed subretinal material with restored photoreceptor–RPE anatomical apposition (Figure 1).

Case 2

A 39-year-old female patient was referred for assessment of submacular fluid developing 10 days after the administration of AZD1222 vaccine. The best-corrected visual acuity was 20/20 in both eyes. Optical coherence tomography revealed sensory elevation of the fovea in both eyes. The left eye showed few satellite lesions. The lesions, which appeared hyperautofluorescent on FAF, flattened on follow-up after 2 weeks and progressed into amassed hyperreflective vitelliform material associated with markedly thickened photoreceptor outer segments. Electrooculogram revealed a reduced Arden ratio of 1 in the right eye and 1.2 in the left eye, denoting marked RPE affection. No systemic therapy was administered, and the patient did not receive the second dose of the vaccine (Figure 2).

Discussion

In this report, we present 2 cases of AEPVM occurring after a single dose of AZD1222 vaccine. AEPVM is a rare and bilateral disorder of the RPE, and its pathologic findings remain poorly understood to date; however, an autoimmune reaction is postulated.[3] Histopathological studies of the eye of a patient diagnosed with polymorphous paraneoplastic retinopathy and multiple vitelliform lesions demonstrated significant retinal edema and atrophy of the inner nuclear layer extending to the outer plexiform layer and outer nuclear layers, brought on by cross-reacting autoantibodies against the malignancy, which affect the normal retinal antigens.[6] On a similar note, AZD1222 vaccine has also been associated with an autoimmune response in the body, most probably through increasing circulating interferons.[7] A similar cascade is known to occur in severe acute respiratory syndrome coronavirus 2 infections. Based on the above, whether there is a common pathophysiology between AEPVM and the autoimmune reactions of AZD1222 is unknown.

It has been well documented that RPE dysfunction is the cornerstone of AEPVM. In the earlier stages of its discovery, the disease was believed to be exclusively paraneoplastic; however, it has since been reported with melanomas[8] as well as viral diseases.[9] It is typically characterized by transient visual symptoms and headache followed by multifocal exudative lesions, elongated photoreceptor outer segments, and subsequent formation of vitelliform deposits. Continuous RPE failure leads to lipofuscin accumulation and the emergence of yellow deposits that appear hyperautofluorescent on FAF.[3] An inner choroid–RPE dysfunction is demonstrated on ICGA and is believed to be responsible for fluid accumulation.[4] Regaining RPE function leads to resorption of the amassed deposits and subsequent restoration of anatomical RPE–photoreceptor apposition. Electrooculogram remains subnormal despite near complete resolution of deposits, denoting a persistent RPE abnormality as demonstrated in both cases.

Numerous retinochoroidal morbidities after COVID vaccination are reported.[5] Saraceno et al[10] also demonstrated a picture of Vogt–Koyanagi–Harada disease developing 48 hours after AZD1222 administration in a 62-year-old female patient. Unlike the previous report, both our patients did not show classic signs of ocular inflammation on slit-lamp examination and their best-corrected visual acuity remained mildly affected throughout the follow-up period.

Based on the above, the causation between AZD1222 immunization and the development of AEVPM is highly plausible for various reasons, the short interval between inoculation and presentation, the lack of history of systemic illness, medications or malignancies in our subjects that correlate with the

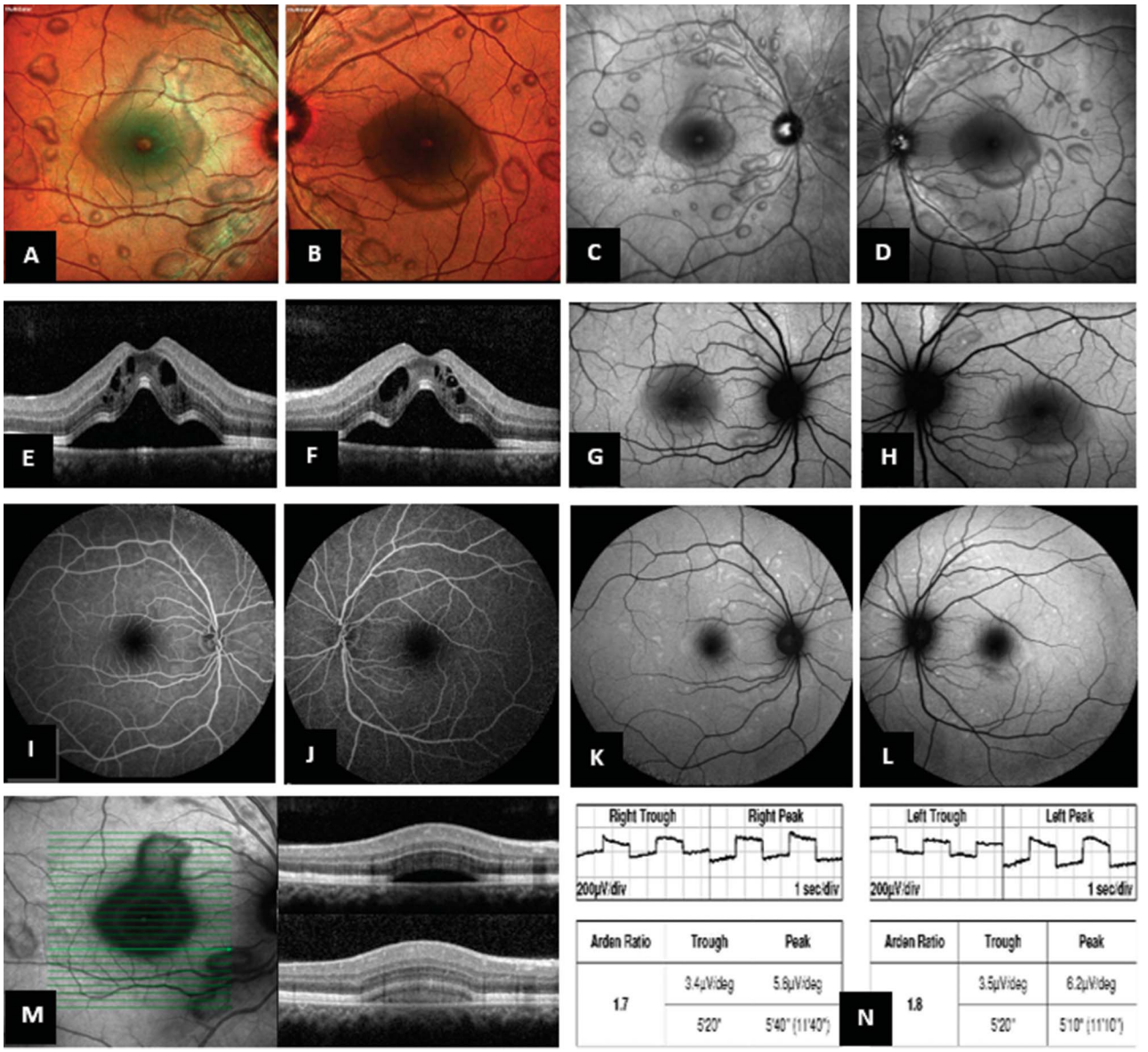

Fig. 1. Multimodal imaging of Case 1. **A** and **B.** Multicolor images of the right (**A**) and left (**B**) eyes at presentation show the multifocal lesions in the posterior pole. **C** and **D.** Infrared montage images of the right (**C**) and left (**D**) eyes showing the extent of the lesions. **E** and **F.** Optical coherence tomography scans through the fovea show the main lesion with subretinal and intraretinal fluid in the right (**E**) and left (**F**) eyes. **G** and **H.** Fundus autofluorescence of the right (**G**) and left (**H**) maculae demonstrate the presence of hyperautofluorescent vitelliform material at the edges of the lesions and lower (dependent) part of the macular sensory detachment. **I** and **J.** Fluorescein angiography of the right (**I**) and left (**J**) eyes confirm the absence of leakage. **K** and **L.** Fundus autofluorescence of the posterior pole demonstrate the hyperautofluorescent lesions beyond the arcades. **M.** Registered follow-up optical coherence tomography B scans of the right eye showing the progressive accumulation of vitelliform material in the dependent part of the subretinal space and elongation of photoreceptors 1 week after presentation (lower panel). **N.** Electrooculogram showing subnormal Arden ratio in the right eye and borderline in the left eye.

clinical findings, and the absence of any family history of a vitelliform retinal dystrophy.

In conclusion, our cases demonstrate the triggering of AEVPM with multifocal exudation and vitelliform material shortly after AZD1222 vaccination. We postulate that this may have been a result of autoantibodies against any of the structural surface glycoprotein antigens of the live-attenuated severe acute respiratory syndrome coronavirus 2 virus that cross-react with the normal RPE cells, leading to the development of the earlier pockets of subretinal fluid and later vitelliform deposits. The final clinical picture was not altered by systemic corticosteroids, and hence, we cannot draw a conclusion on their impact on AEVPM. In the era of a global pandemic and a widespread vaccination movement, we may continue

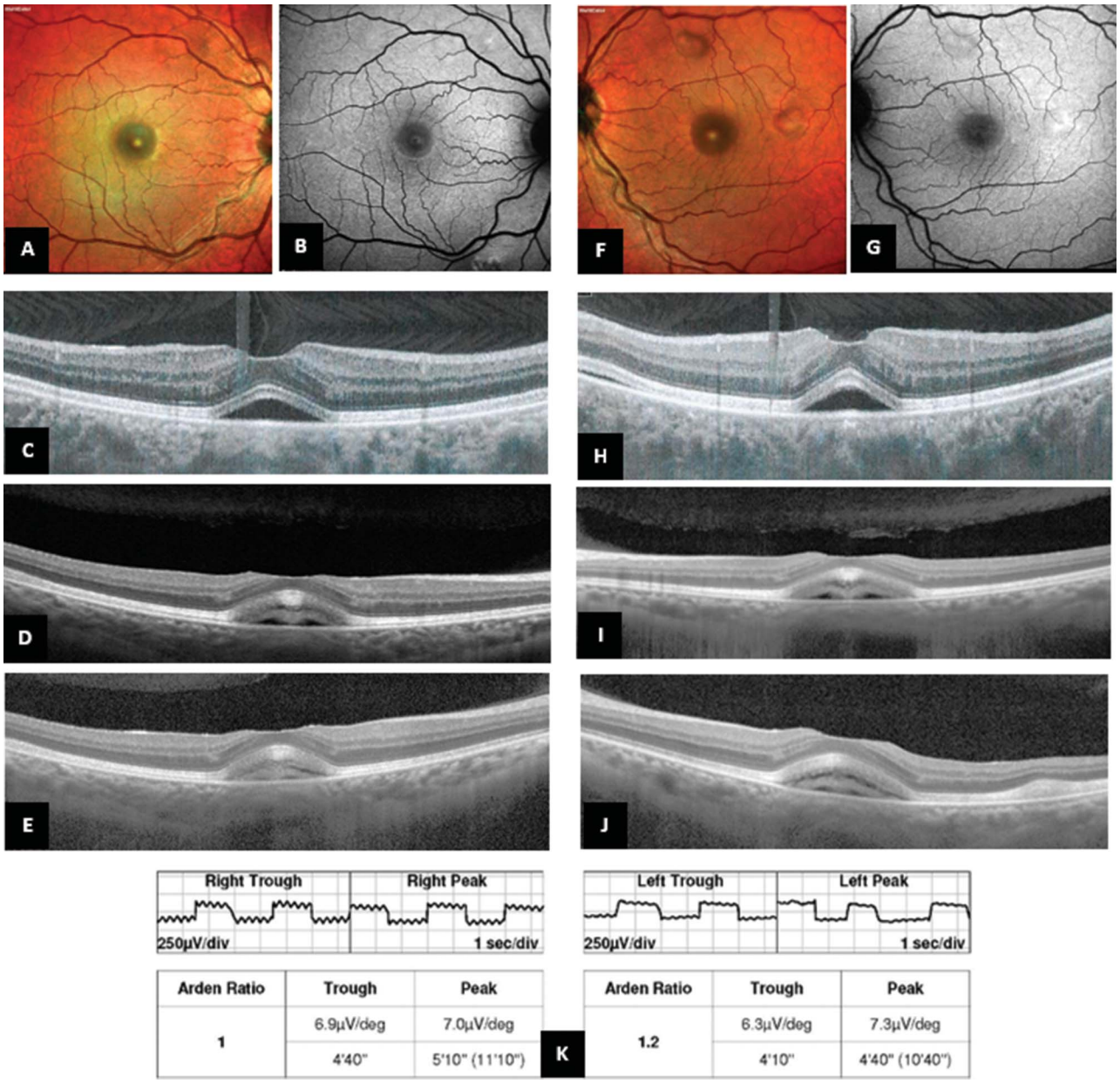

Fig. 2. Multimodal imaging of Case 2. **A** and **B.** Multicolour images (**A**) and FAF (**B**) of the right eye shows the exudative macular lesions. **F** and **G.** Multicolour images (**F**) and FAF (**G**) of the left eye show blister-like lesions surrounding the center. **C** and **H.** Optical coherence tomography Bscans of the right eye (**C**) and the left eye (**H**) confirming the lesions at presentation. Optical coherence tomography Bscans show the evolution of vitelliform material in the fovea and photoreceptor changes after 2 weeks in the right eye (**D**) and the left eye (**I**) and after 4 weeks in the right eye (**E**) and the left eye (**J**). Electrooculogram (**K**) demonstrating a reduced Arden ratio in both eyes.

to observe more abnormal side effects of COVID-19 vaccination.

Key words: COVID, vaccine, vitelliform, maculopathy, polymorphous.

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