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Case Report

A Case of Bilateral Frosted Branch Angiitis after mRNA COVID-19 Vaccination

Mai Kitaoka Takako Ohnishi Satoshi Sugaya Harumasa Yokota
Taiji Nagaoka Satoru Yamagami

Division of Ophthalmology, Department of Visual Sciences/Nihon University School of Medicine/Itabashi, Tokyo, Japan

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Abstract
We report a case of bilateral frosted branch angiitis (FBA) following mRNA-1273 COVID-19 vaccination. A 79-year-old male was referred to our hospital with a sudden onset of blurred vision in the right eye, which occurred during his return home after receiving the third dose of a messenger RNA (mRNA) COVID-19 vaccine. Fundoscopy revealed severe retinal vasculitis with sheathing of the artery and vein in the right eye more so than in the left eye, suggestive of bilateral FBA. Optical coherence tomography showed significant macular edema and serous retinal detachment in the right eye. Polymerase chain reaction assay detected Epstein-Barr virus (EBV) in the aqueous humor, and antibody against the EBV viral capsid antigen was positive for IgM. The next day, best-corrected visual acuity (BCVA) worsened to 0.08 due to macular edema in the left eye. After 2 courses of pulse steroid therapy and intravenous infusion of acyclovir, macular edema had disappeared and sheathing of retinal vessels was improving. At 5 months after the mRNA COVID-19 vaccination, BCVA was maintained 0.15 in the right eye and 0.7 in the left eye. Severe uveitis, such as FBA, can occur after mRNA COVID-19 vaccination.

Introduction

With the widespread implementation of vaccination campaigns during the COVID-19 pandemic, many reports of vaccine-related uveitis have emerged. Frosted branch angiitis (FBA), first reported by Ito et al. [1] in Japan in 1976 as a form of pediatric uveitis, is a rare form of acute uveitis with severe vasculitis in which sheathing of the vessels looks like frosted

Correspondence to:
Takako Ohnishi, oonishi.takako@nihon-u.ac.jp

branches of a tree. While the primary cause of FBA is unknown, some viral infections, toxoplasmosis, and Behçet's disease have been reported to be associated with the pathogenesis of FBA [2–6].

Case Report

A 79-year-old male was referred to our hospital on the day after receiving the third dose of a messenger RNA (mRNA) COVID-19 vaccine. He first noticed blurred vision with floaters in the right eye during his return home immediately after vaccination.

At the initial examination, best-corrected visual acuity (BCVA) was 0.03 in the right eye and 1.0 in the left eye. Intraocular pressure was 13 mm Hg in the right eye and 17 mm Hg in the left eye. The patient reported no flu-like symptoms (e.g., fever, sore throat) and no COVID-19-specific symptoms (e.g., loss of taste). He was taking an anticoagulant due to atrial fibrillation. Past medical history included bronchial asthma. His vaccination history included the first and second doses of the BNT162b2 (Pfizer-BioNTech) mRNA COVID-19 vaccine and the third dose of the mRNA-1273 (Moderna TX, Inc.) mRNA COVID-19 vaccine.

Slit-lamp examination revealed the presence of inflammation, seen as cells, grade 2+ in the right eye and 1+ in the left eye and flare grade 1+ in both eyes, with mild, fine keratic precipitates in the anterior chamber. Funduscopic examination revealed grade 1+ vitreous haze and severe retinal vasculitis, with sheathing of the artery and vein in both eyes (Fig. 1a), suggestive of FBA. In addition, significant blot hemorrhages were found on the entire retina. Fluorescein angiography revealed dye staining and slight leakage from the retinal veins in both eyes (Fig. 1b). Optical coherence tomography of the macula showed retinal edema and retinal detachment in the right eye (Fig. 1c).

To exclude retinal vasculitis related to autoimmune disease or typical viral infection, medical examination and PCR assays of the aqueous humor were performed. There were no abnormal findings indicative of autoimmune disease. Tests for various viruses commonly associated with uveitis, i.e., cytomegalovirus, herpes simplex virus, varicella-zoster virus, human immunodeficiency virus, tuberculosis, and toxoplasmosis, were negative. PCR assay of the aqueous humor detected Epstein-Barr virus (EBV), and antibody against the EBV viral capsid antigen was positive for IgM. We were able to detect EBV in the aqueous humor, but our laboratory equipment was not able to quantify it.

The day after the initial visit, the patient complained of blurred vision in the left eye, and BCVA in the left eye worsened to 0.08. Funduscopic findings revealed expanded retinal vasculitis and development of macular edema in the left eye (Fig. 2). Pulse steroid therapy (methylprednisolone 1,000 mg/day for 3 days) and intravenous infusion of acyclovir (1,500 mg/day) were started immediately. The first course of pulse steroid therapy did not have an adequate therapeutic effect, so a second course was started 4 days after the first. The second course was successful, and the funduscopic findings improved (Fig. 3). Although the BCVA also gradually improved to 0.15 in the right eye and 0.6 in the left eye, irreversible damage remained in the right eye, which had severe macular edema. Fluorescein angiography was repeated 14 days later and showed both decreasing inflammation in the retinal vessels and ischemia in the periretinal area. At the time of this report (5 months after the COVID-19 vaccination), BCVA was maintained 0.15 in the right eye and 0.7 in the left eye. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530794).

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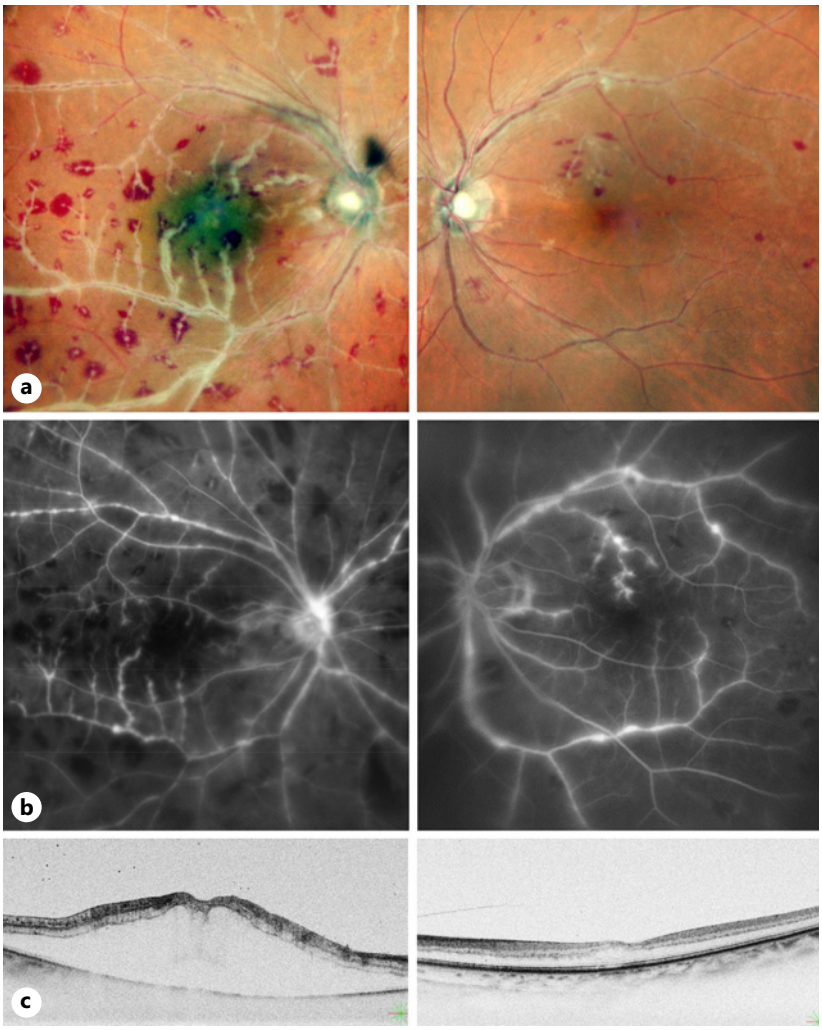

Fig. 1. Findings at the initial examination (the day after vaccination). BCVA was 0.03 in the right eye and 1.0 in the left eye. Color fundus photographs showed retinal vasculitis with sheathing of the arteries and veins (suggestive of FBA), retinal blot hemorrhages, and vitreous haze grade 1+ in both eyes (**a**). Fluorescein angiography revealed dye staining and slight leakage from retinal veins, with leakage of the optic disc and a non-perfusion area in the peripheral fundus in the right eye (**b**). Optical coherence tomography of the macula showed retinal edema and retinal detachment in the right eye (**c**).

Discussion

Reports of uveitis after COVID-19 vaccination in Israel, where the majority of the population was vaccinated early in the COVID-19 pandemic, indicated that most cases of vaccine-related uveitis involved mild anterior uveitis and all cases responded well to topical corticosteroid eye drops [6]. In addition to the more prevalent reports of cases with favorable prognosis, however, there also are sporadic reports of cases with severe forms of posterior uveitis, such as Vogt-Koyanagi-Harada disease, multiple evanescent white dot syndrome, acute macular neuroretinopathy, and acute retinal necrosis [7–10].

Although EBV DNA has been detected in healthy people [11], a large viral load may lead to inflammatory conditions of the eye, such as uveitis. Recent reports describe the involvement of EBV in both acute retinal necrosis and FBA [12, 13]. A limitation of this study is that our

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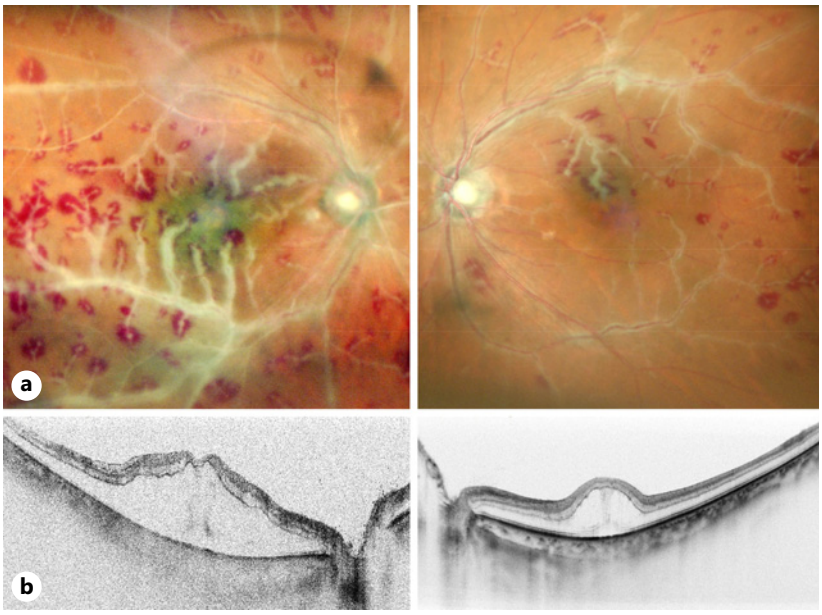

Fig. 2. Findings at 1 day after the initial visit (2 days after the patient had received the third dose of the COVID-19 vaccine). BCVA was 0.03 in the right eye and 0.08 in the left eye. Color fundus photographs showed worsening retinal vasculitis in both eyes but especially in the left eye (**a**). Retinal edema also had developed in the left eye (**b**).

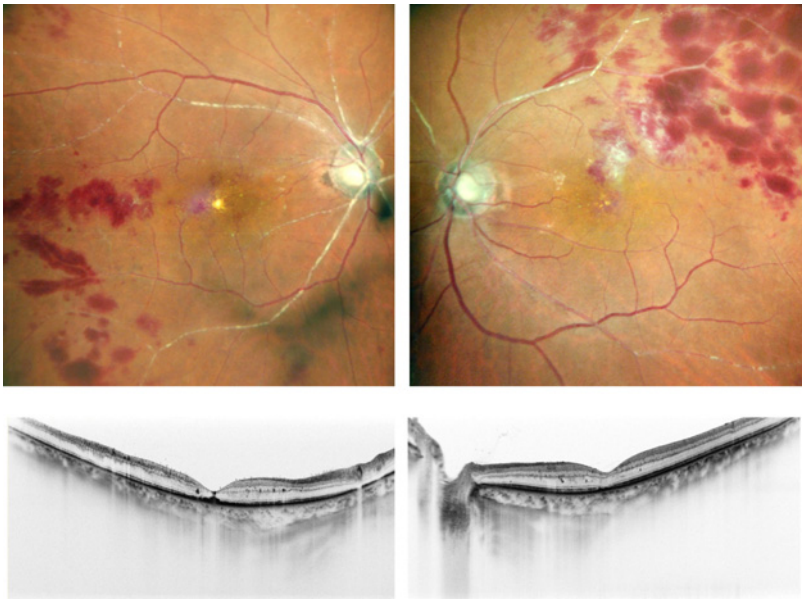

Fig. 3. Findings after 2 courses of pulse steroid therapy and intravenous infusion of acyclovir (20 days after COVID-19 vaccination). BCVA was 0.15 in the right eye and 0.6 in the left eye. Color fundus photographs showed that sheathing of retinal vessels was improving, and macular edema had disappeared. FBA after mRNA COVID-19 vaccination.

laboratory equipment was not able to quantify EBV. In this patient, EBV DNA was detected from serum and aqueous humor, indicating that EBV may be associated with the development of FBA in this case.

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Interestingly, reports of increased incidence of shingles after COVID-19 vaccination suggest that reactivation of herpes viruses may be accelerated following vaccination [14]. Although the mechanism of vaccine-related uveitis is unclear, it is possible that inflammation can be induced by the adjuvants used in inactivated or subunit vaccines to enhance viral immunogenicity.

Conclusion

We have presented a case involving a 79-year-old Japanese male who developed severe FBA after receiving mRNA COVID-19 vaccination. As COVID-19 vaccination continues to be necessary, postvaccination ocular symptoms should be taken seriously due to the possibility of severe uveitis, which can cause irreversible vision loss.

Acknowledgment

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Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. In accordance with local and national guidelines, ethical approval was not required for this study.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

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Author Contributions

M.K. conceptualized the study and collected the data. T.O. evaluated the results and drafted the manuscript. T.O. and S.S. collected and reviewed the data. H.Y. and T.N. participated in the design of the study and critically reviewed the results and manuscript. S.Y. supervised the manuscript. All the authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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