Acute Retinal Pigment Epitheliitis following Vaccination

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Keywords
Acute retinal pigment epitheliitis · Coronavirus disease 2019/influenza vaccinations · EZ disruption · IZ disruption · Optical coherence tomography

Abstract
We present a rare case of acute retinal pigment epitheliitis (ARPE) following vaccination. An 18-year-old Japanese man visited our hospital with a 5-day history of a central scotoma in the right eye. He had received the second dose of coronavirus disease 2019 vaccination (BNT162b2 mRNA, Pfizer-BioNTech) 1 month prior, following which he developed a low-grade fever of 37.3–37.5°C for 2 days accompanied by joint pain. Although he had received influenza vaccination 5 days prior to this presentation, no systemic symptoms other than injection site pain were observed. Blood test results were unremarkable. Ophthalmological examination revealed a decimal best-corrected visual acuity (BCVA) of 0.8 and 1.2 in the right and left eyes, respectively. Intraocular pressure was 15 mm Hg in both eyes. Intraocular inflammation was not observed. Fundus examination revealed a localized lesion of pigment stippling associated with yellowish hypopigmentation in the fovea. Fluorescein angiography revealed slight transmission hyperfluorescence without leakage. Optical coherence tomography (OCT) revealed disruption of the external limiting membrane (ELM), ellipsoid zone (EZ), and interdigitation zone (IZ). We diagnosed the patient with ARPE in the right eye. The patient was followed up without treatment. Five weeks after onset, the central scotoma in the right eye disappeared, and patient's BCVA improved to 1.5. OCT showed improvement in ELM and EZ continuity in the right eye, but IZ remained disruptive. Although the exact pathophysiology of the association between ARPE and these vaccinations is unclear, ARPE may develop after the vaccination.

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Introduction

Acute retinal pigment epitheliitis (ARPE) was first described by Krill and Deutman [1] in 1972 as an abnormality of the retinal pigment epithelium (RPE). ARPE is a rare disease and is characterized by an acute blurred vision or a central scotoma, which usually resolves with good visual acuity (VA) within a few months without treatment [1-5]. Generally, ARPE affects young healthy individuals [1-5]. Although bilateral cases have been reported [3], most patients are affected unilaterally [6]. Additionally, some cases are infrequently recurrent [3]. The diagnosis of ARPE depends on the presence of fine pigment stippling surrounded by yellowish hypopigmented halos in the macula [1-5].

Optical coherence tomography (OCT) is also a useful tool for the diagnosis of ARPE and identification of the primary site of inflammation in ARPE [7-13]. Currently, rather than the RPE, the outer retinal layer, especially including the interdigitation zone (IZ), ellipsoid zone (EZ), and external limiting membrane (ELM), is considered the mainstay of inflammation in ARPE [7-13].

Although the exact pathophysiology of the disease is not fully understood, the acute occurrence of ARPE following flu-like symptoms has been suggested to be the origin of viral infections [2, 12, 14]. However, to the best of our knowledge, no report has described ARPE following the coronavirus disease 2019 (COVID-19) and influenza vaccinations, to date. Herein, we present a rare case of ARPE after these vaccinations.

Case Report

An 18-year-old Japanese man with a 5-day history of a central scotoma in the right eye was referred from another hospital. He had received the second dose of COVID-19 vaccination (BNT162b2 mRNA, Pfizer-BioNTech) 31 days prior to the presentation. The patient’s medical history was unremarkable. Prior to this presentation, the patient was in good health and had no history of viral infection. In addition, he did not develop fever or other systemic symptoms after the first dose of COVID-19 vaccination (BNT162b2 mRNA, Pfizer-BioNTech). However, following the second COVID-19 vaccination dose, he developed a low-grade fever of 37.3–37.5°C for 2 days accompanied by joint pain. Oral antipyretic analgesics were not administered during the symptomatic period. Additionally, he had received influenza vaccination 5 days prior to this presentation. In other words, the influenza vaccine was administered 26 days after he received the second dose of COVID-19 vaccination. No systemic symptoms other than injection site pain were observed. Blood test results revealed no abnormalities.

Ophthalmological examination revealed a decimal best-corrected VA (BCVA) of 0.8 and 1.2 in the right and left eyes, respectively. Intraocular pressure was 15 mm Hg in both eyes. Intraocular inflammation was not observed in any eye. Fundus examination revealed a localized lesion of pigment stippling associated with yellowish hypopigmentation in the fovea (shown in Fig. 1a, b). Fluorescein angiography showed slight transmission hyperfluorescence without leakage (shown in Fig. 1c, d). OCT revealed disruption of the ELM, EZ, and IZ (shown in Fig. 2a). Based on these findings and previously reported diagnostic criteria [12], we diagnosed ARPE in the right eye of the patient. His left eye was normal.

The patient was followed up without any treatment. Nine days after the onset, the central scotoma in the right eye tended to improve, and his BCVA in the right eye improved to 1.0. The ELM continuity improved on OCT images of the right eye, but the EZ and IZ remained disruptive (shown in Fig. 2b). Five weeks after the onset, the central scotoma in the right eye disappeared, and his BCVA in the right eye improved to 1.5. ELM and EZ continuity improved
on OCT images of the right eye, but the IZ remained disruptive (shown in Fig. 2c). After the last visit, the patient was referred to a referral hospital.

**Discussion**

We present for the first time a rare case of ARPE that may have been associated with both COVID-19 and influenza vaccinations. ARPE is a self-limiting, inflammatory retinal disorder. Lu et al. [13] evaluated the process of recovery of the outer retinal structures using OCT and its correlation with VA. They reported that recovery occurred in a sequence of ELM, EZ, and IZ restoration, and VA improved when the IZ was restored [13]. They also suggested that the IZ is the primary site of inflammation in ARPE [13]. In our patient, a similar process of recovery was observed [13], and the outer retinal layers, as well as VA, showed improvement.
The etiology of ARPE has been suggested to be a viral infection [2, 12, 14]. The acute onset and rapid course to resolution suggest an inflammatory event. However, the patient had no history of viral infection. Meanwhile, he developed low-grade fever with joint pain following the second dose of COVID-19 vaccination. The time interval from the administration of the second COVID-19 vaccination to the onset of ARPE was 31 days. Bolletta et al. [15] reported cases of nongranulomatous anterior uveitis, panuveitis in new-onset Behçet’s disease, and multiple evanescent white dot syndrome (MEWDS) following COVID-19 vaccination with time intervals of 30, 30, and 28 days, respectively. Considering the development of fever following the second COVID-19 vaccination in our patient, the timing of onset of previously reported ophthalmic adverse effects after COVID-19 vaccination [15], and the fact that COVID-19 vaccinations can cause an inflammatory reaction, we speculate that COVID-19 vaccination may trigger ARPE.

Furthermore, our patient had received an influenza vaccination 5 days prior to ARPE presentation. One report described the occurrence of ARPE after influenza infection [14], but no cases of ARPE following influenza vaccination have been reported. After influenza vaccination, no systemic symptoms other than injection site pain were observed; however, the possibility that this may have contributed to the onset of ARPE cannot be ruled out.

Differential diagnosis for ARPE includes MEWDS, acute posterior multiple placoid pigment epitheliopathy (APMPPE), acute foveitis, acute macular neuroretinopathy, and acute zonal occult outer retinopathy (AZOOR). MEWDS typically shows an extensive retinal involvement where multiple whitish dots at the level of the outer retina can be seen not only in the paramacular area but also in the midperipheral fundus [16], which is not consistent with
the present case. Similarly, classical fundus findings in APMPPE are yellow-white placoid lesions at the level of the RPE in the posterior pole [17]. Fluorescein angiography in APMPPE shows early hypofluorescence corresponding to the placoid lesion followed by late, irregular hyperfluorescent staining, which is not consistent with the present case. Acute fovealitis shows yellow-white punctate opacities in the central fovea and acute alterations in the outer retinal layers in the absence of RPE, accompanied by hyperreflective foveal material [18]. The present case is considered typical ARPE rather than acute fovealitis. Acute macular neuroretinopathy could be ruled out because it is defined by the presence of intraretinal, reddish-brown, wedge-shaped lesions around the fovea, and OCT shows hyperreflectivity in the outer plexiform and outer nuclear layers and EZ disruption [19]. AZOOR is characterized by acute loss of one or more zones of outer retinal function [20]. Fundus photograph in AZOOR is almost normal, which is not consistent with the present case.

This report has a major limitation in that it includes only 1 case suggesting that vaccination could cause ARPE. Although establishing a causal relationship between these vaccinations and the occurrence of ARPE is challenging, accumulation of similar cases is warranted to elucidate the pathophysiology of ARPE. In conclusion, both COVID-19 and influenza vaccinations can potentially trigger this peculiar macular disease.

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Statement of Ethics

The Ethics Committee of Shinseikai Toyama Hospital waived the need for approval for this report as it involved a retrospective review of medical records. This report adhered to the tenets of the Declaration of Helsinki 1964. This report is in conformance with the CARE checklist (online suppl. file; see www.karger.com/doi/10.1159/000527598 for all online suppl. material). Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Hirofumi Sasajima, Akari Aoyagi, and Takafumi Suzuki collected clinical data. Hirofumi Sasajima, Masahiro Zako, and Yoshiki Ueta analyzed the findings and provided critical suggestions. Hirofumi Sasajima contributed to the preparation of the original draft. Masahiro Zako reviewed and edited the manuscript. Hirofumi Sasajima, Masahiro Zako, Akari Aoyagi,
Yoshiki Ueta, and Takafumi Suzuki agreed to be accountable for all aspects of this work and approved the final version of this manuscript for publication.

**Data Availability Statement**

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

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