

COVID-19 mRNA Vaccine-Associated Uveitis Leading to Diagnosis of Sarcoidosis: Case Report and Review of Literature

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Abstract

A 34-year-old Japanese person with male gender identity who had been taking intramuscular injection of methyltestosterone depot for 11 years after bilateral mastectomy noticed blurred vision 5 days after the second vaccination for COVID-19 (Tozinameran; Pfizer-BioNTech) in the interval of 3 weeks following the first vaccination. The patient was diagnosed as granulomatous iritis with mutton-fat keratic precipitates and small iris nodules at the pupillary margin in the right eye and began to have 0.1% betamethasone eye drops with good response. The patient, however, continued to have fever and malaise and showed a high level of serum soluble interleukin-2 receptor (sIL-2R) even 4 weeks after the second vaccination. Computed tomographic scan disclosed mediastinal and bilateral hilar small lymphadenopathy together with limited granular lesion in the right lung. Gallium-67 scintigraphy demonstrated high uptake not only in mediastinal and hilar lymph nodes but also in bilateral parotid glands. Right parotid gland biopsy revealed noncaseating granulomas and proved pathological diagnosis of sarcoidosis. The systemic symptoms were relieved by oral prednisolone 20 mg daily. Even though the causal relationship remains undetermined, this case is unique at the point that vaccine-associated uveitis led to the detection of pulmonary lesions and lymphadenopathy, resulting in clinical and pathological diagnosis of sarcoidosis. In literature review, 3 patients showed sarcoidosis-like diseases after COVID-19 vaccination: 2 patients were diagnosed clinically as Lofgren syndrome with acute onset of erythema nodosum and ankle swelling, with or without mediastinal and hilar lymphadenopathy, whereas 1 patient with mediastinal lymphadenopathy but no uveitis was diagnosed pathologically by biopsy as sarcoidosis.

Keywords

COVID-19 vaccination, vaccine-associated uveitis, granulomatous iritis, sarcoidosis, parotid gland biopsy, lymphadenopathy, soluble interleukin-2 receptor (sIL-2R), literature review, noncaseating granuloma, gallium scintigraphy (gallium scan)

Background

Uveitis is the state of intraocular inflammation and occurs either in association with systemic inflammatory diseases or in isolation only involving the unilateral eye or both eyes. Well-known systemic diseases which frequently develop uveitis are sarcoidosis,^{1,2} Behcet disease,³ Vogt-Koyanagi-Harada disease, tubulointerstitial nephritis,⁴ and inflammatory bowel disease.⁵ Furthermore, diabetes mellitus, as a common disease, is sometimes diagnosed at first by the onset of iritis called diabetic iritis. Based on the main location of inflammation in the eye tissue, uveitis is classified into anterior uveitis (iritis or iridocyclitis) and posterior uveitis (retinitis or choroiditis) and their combination called panuveitis. Based on the nature of inflammation, uveitis is

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also classified as granulomatous and non-granulomatous uveitis. Sarcoidosis is a most frequent cause for granulomatous uveitis.

Vaccine-associated uveitis is a key phrase in the list of differential diagnosis of uveitis and has been reported to occur after vaccinations for different disease targets.⁶⁻⁸ Recently, tens of millions of people even in Japan have undergone newly developed vaccines for coronavirus disease 2019 (COVID-19) which is caused by an infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).⁹ Uveitis and conjunctivitis are noted as eye manifestations of COVID-19,¹⁰ but has not been listed as a major adverse event in series of clinical trials for COVID-19 vaccines.^{11,12} Later, vaccine-associated uveitis has been suggested to occur after COVID-19 vaccination by many case reports.¹³⁻²² Summary of preceding cases in the literature is given as tables in some reports^{13,14} and large series of patients with uveitis after COVID-19 vaccination were described in most recent articles.²⁰⁻²² In this study, we described a Japanese patient with COVID-19 mRNA vaccine-associated uveitis who showed persistent fever with malaise and was diagnosed clinically and pathologically as sarcoidosis by parotid gland biopsy.

Case Report

A 34-year-old Japanese person with male gender identity had fever up to 38.6°C next day after the second vaccination for COVID-19 (Tozinameran; Pfizer-BioNTech, New York, NY, USA) in the interval of 3 weeks following the first vaccination. On day 2, the patient had persistent fever and visited a local hospital. The chest plain x-ray film showed nothing particular and blood examination was within normal limits. Nasopharyngeal SARS-CoV-2/influenza virus antigen test was negative. On day 5, the patient began to have a blurred vision and injection in the right eye, together with fever, malaise, and appetite loss and continued to have eye and systemic symptoms until day 20 when the patient visited a local eye doctor. The patient was pointed to have bilateral iritis and referred to Okayama University Hospital.

On the first visit, the best-corrected visual acuity in decimals was 1.0 in the right eye and 1.2 in the left eye. The intraocular pressure was 8 mm Hg in the right eye and 9 mm Hg in the left eye. The right eye had 2+ mutton-fat keratic precipitates, together with synechia iris posterior with small iris nodules in the lower half of the pupillary margin but no aqueous cells (Figure 1A and 1B). Gonioscopy revealed several small peripheral anterior synechiae in the right eye. The left eye had a few keratic precipitates and no aqueous cells (Figure 1C). The retina and optic disks in both eyes were normal (Figure 1D-1G). Physical examinations detected no particular findings, including no skin rashes. Repeated test for SARS-CoV-2 was negative by polymerase chain reaction of the nasopharyngeal swab. Soluble interleukin-2 receptor (sIL-2R) was elevated to 691.7 U/mL while blood angiotensin-converting

enzyme activity was within the normal range at 14.1 U/L. Serological tests for syphilis, including rapid plasma reagent test and treponemal pallidum latex agglutination, were both negative. Interferon- γ -releasing assay with T-SPOT (Oxford Immunotec, Ltd., Oxfordshire, UK) was negative as well. In the past history, the patient had undergone bilateral mastectomy for gender identity disorder at the age of 23 years, and since then, had been taking intramuscular injection of methyltestosterone depot 125 mg every 3 weeks.

Eye drops the patient used was changed from 0.1% fluorometholone 4 times daily in the right eye to 0.1% betamethasone 6 times daily in the right eye and twice daily in the left eye. In a week, iritis in the right eye became milder but the patient continued to have fever, malaise, and lumbago. Chest to abdominal computed tomographic scan disclosed mild enlargement of mediastinal and bilateral hilar lymph nodes (Figure 2B), together with lobular granular shadows in right upper and lower lobes (Figure 2A). Serum sIL-2R was further elevated to 1426.5 U/mL while serum level of IgG4 remained with normal range at 12.5 mg/dL. Because of persistent fever and malaise in the following 2 weeks, the patient was hospitalized for systemic investigation. After admission, the patient underwent gallium-67 scintigraphy which showed high uptake in bilateral parotid glands (Figure 2D), together with mild uptake in the mediastinal and bilateral hilar lymph nodes (Figure 2C). Right parotid gland needle biopsy demonstrated noncaseating granulomas (Figure 2E, 2F), leading to the diagnosis of sarcoidosis. The patient began to take oral prednisolone 20 mg daily, leading to the subsidence of fever and malaise. The patient continued to use 0.1% betamethasone eye drops and had no iritis anymore in the right eye in a month.

Discussion

The present patient noticed blurred vision in the right eye about 5 days after the second intramuscular inoculation of mRNA vaccine for COVID-19 and was diagnosed clinically to have uveitis about 3 weeks after the inoculation. The right eye was mainly involved with uveitis, and the nature of intraocular inflammation was called more precisely as granulomatous iritis which presented mutton-fat keratic precipitates and small iris nodules with synechia iris posterior at the pupillary margin. Uveitis responded well to corticosteroid eye drops. However, the patient continued to have fever and malaise even in 4 weeks after the second inoculation, and systemic examinations successfully led to the diagnosis of sarcoidosis.

The present patient fulfilled the diagnostic criteria for sarcoidosis: 2 or more organs (eye and lung) with typical signs are involved clinically and noncaseating granulomas were pathologically proven by needle biopsy at the parotid gland.^{23,24} Based on the time sequence of event, sarcoidosis in this patient would be induced by COVID-19 mRNA vaccine inoculation. At least, we assume that this patient might have a predisposing factor for the development of sarcoidosis and that

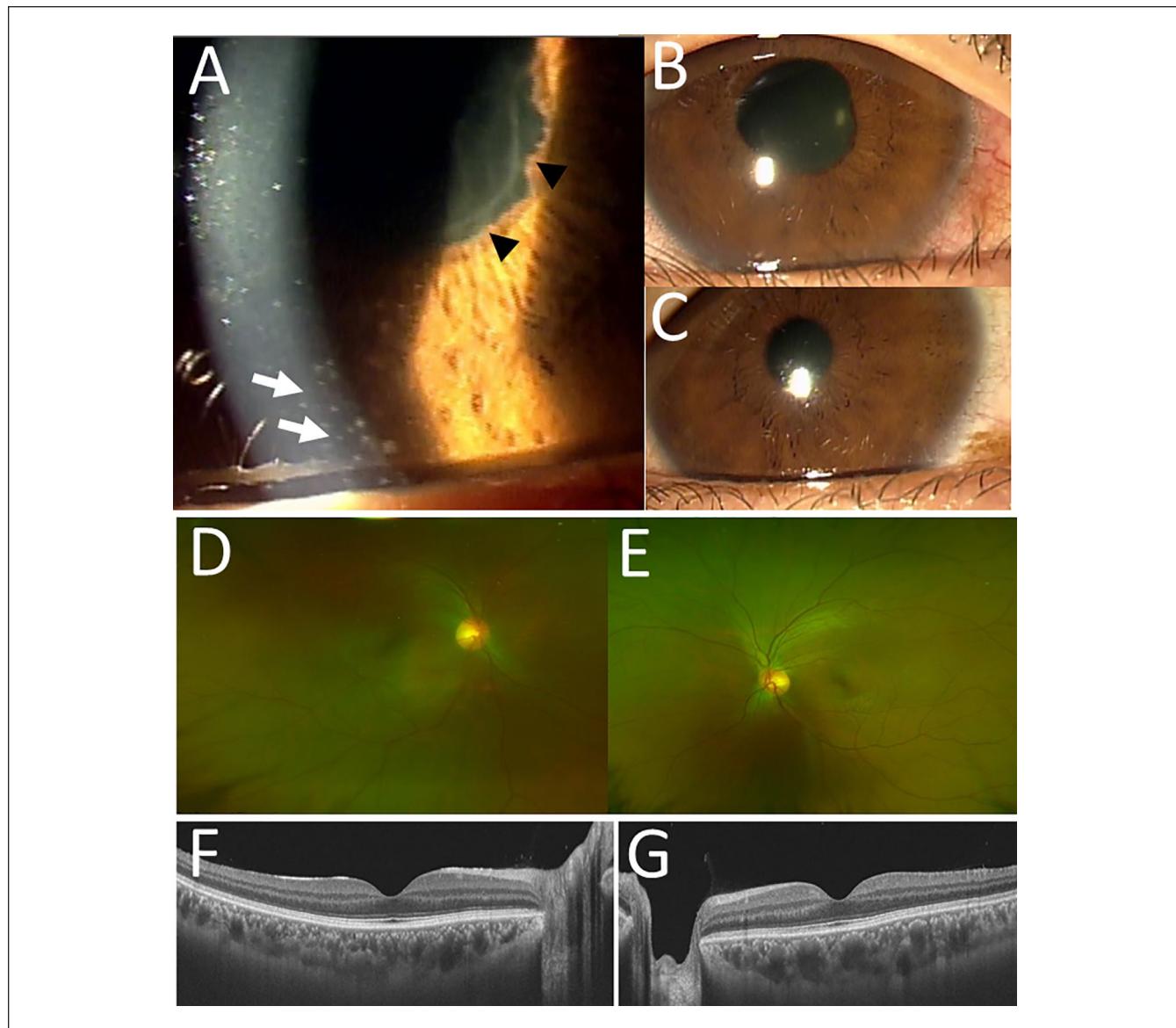


Figure 1. Slit-lamp biomicroscopy at the initial visit. Note mutton-fat keratic precipitates (white arrows, A) and fibrin deposition (black arrowheads, A) on the lens surface with synechia iris posterior and small iris nodules at the pupillary margin in the right eye. Also note ciliary injection in the right eye (B) in contrast with the normally appearing left eye (C). The retina appears normal in the right eye (D) and the left eye (E). Optical coherence tomography shows normal macula in the right eye (F) and the left eye (G).

the inflammation induced by the vaccination may have led to systemic sarcoidosis. Reactivation of uveitis by COVID-19 mRNA vaccination has been indeed reported as a case report.²⁵

From the viewpoint of eye manifestations, it should be noted that the patient only presented so-called anterior segment inflammation (anterior uveitis) as granulomatous iritis but did not show posterior segment inflammation (posterior uveitis) such as retinal segmental periphlebitis and snowball-like vitreous opacity, which are characteristic to sarcoidosis.²³ As COVID-19 vaccine-associated retinal manifestations have been reported so far,²⁶⁻³⁰ fundus imaging with optical coherence tomography in this patient was performed but did not detect any abnormalities in the retina

and choroid. In this patient, we might be simply looking at the early phase of intraocular inflammation caused by sarcoidosis. The presumed early phase of sarcoidosis in this patient would be also supported by limited lung-field lesions and small hilar and mediastinal lymphadenopathy. In addition, bilateral parotid glands were not enlarged to be detected clinically. The patient also did not show skin manifestations. Under the circumstances without an indicative clue, gallium-67 scintigraphy was a key diagnostic procedure which led to parotid gland biopsy.

Based on the rationale presented above, the early phase of sarcoidosis, involving at least the eyes, right lung field, hilar and mediastinal lymph nodes, and parotid glands, would be

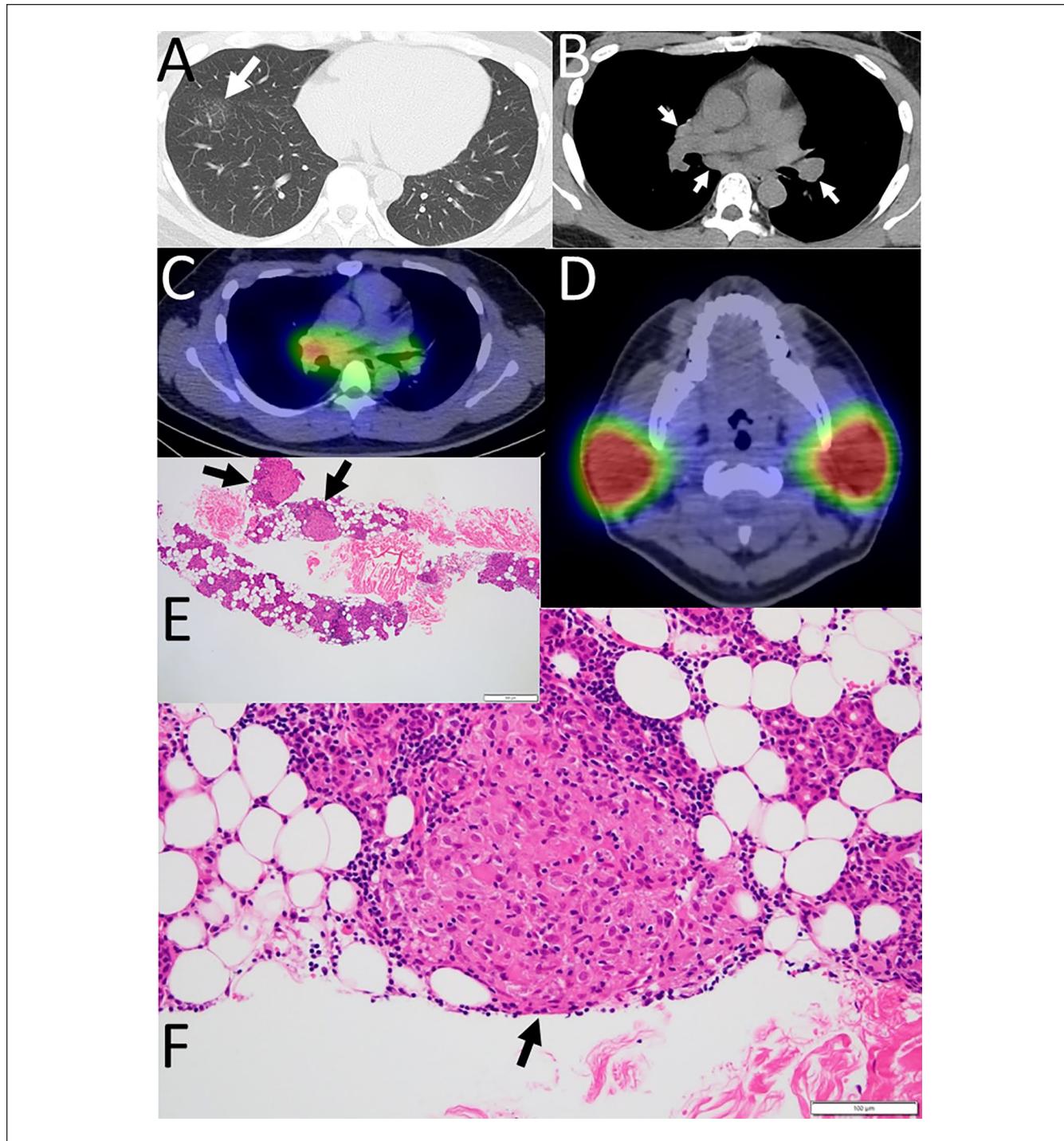


Figure 2. Chest computed tomography performed 10 days after the initial visit, showing ground-glass opacity lesions in the right lung (arrow, A) and mild bilateral hilar lymph nodes enlargement (arrows, B). Gallium-67 scintigraphy further investigated 2 weeks after the computed tomography, showing abnormal uptakes in bilateral hilar lymphadenopathy (C) and bilateral parotid glands (D). Needle biopsy in the right parotid gland, showing noncaseating granulomas (arrows in E and F). Hematoxylin-eosin stain. White scale bar = 500 µm in E and 100 µm in F.

considered as the sequelae of the COVID-19 mRNA vaccine inoculation. To the best of our knowledge, 2 cases have been reported to develop Lofgren syndrome after the COVID-19

vaccination (Table 1).³¹ These 2 patients showed erythema nodosum and bilateral ankle swelling in common, and with or without hilar and mediastinal lymphadenopathy, and was

Table I. Review of 4 Patients With COVID-19 Vaccine-Associated Lofgren Syndrome and Pathologically Proven Sarcoidosis Including the Present Patient.

Case no. / gender/age at onset	Vaccine (name, company)	Initial signs and symptoms	Timing of initial signs and symptoms	Imaging findings (examination)	Blood ACE, U/L	Serum sIL-2R, U/mL	Pathological diagnosis of noncaseating granulomas	Therapy	Diagnosis	Author
1/Male/44	mRNA vaccine (Tozinameran; Pfizer-BioNTech)	None	One day after second vaccination	Mediastinal lymphadenopathy (FDG-PET)	Not described	Not described	Transbronchial needle biopsy of mediastinal lymph node	None	Sarcoidosis	Baucknecht et al ³⁵
2/Female/21	Adenoviral vector vaccine (Vaxzevria, AstraZeneca) 12 weeks earlier mRNA vaccine (Elasomeraan, Moderna)	Erythema nodosum Ankle swelling Fever, Malaise	3 days after second vaccination	None	Normal	Not described	Not done	Oral prednisolone 20 mg daily and tapering	Lofgren syndrome	Rademacher et al ³¹ (Case 1)
3/Male/27	Adenoviral vector vaccine (Vaxzevria, AstraZeneca)	Erythema nodosum Ankle swelling Fever, Malaise	7 weeks later	Bilateral hilar and mediastinal lymphadenopathy Fine nodular lung lesions (CT)	Normal	854	Not done	Oral prednisolone 20 mg daily	Lofgren syndrome	Rademacher et al ³¹ (Case 2)
4/Female ^a /34	mRNA vaccine (Tozinameran; Pfizer-BioNTech)	Blurred vision with granulomatous iris Persistent fever Malaise, lumbago	5 days after second vaccination	Bilateral hilar and mediastinal lymphadenopathy Right lung granular lesions (CT)	14.1	691.7	Right parotid gland biopsy, based on high uptake in gallium scan	Topical 0.1% beamethasone Oral prednisolone 20 mg daily and tapering	Sarcoidosis	This case

Abbreviations: ACE, angiotensin-converting enzyme activity; sIL-2R, soluble interleukin-2 receptor; FDG-PET, [¹⁸F] fluorodeoxyglucose-positron emission tomography; CT, computed tomography

^aMale gender identity.

diagnosed as Lofgren syndrome without performing biopsy.³¹ Lofgren syndrome is considered as an acute type of sarcoidosis-like disease and is characterized by mediastinal and hilar lymphadenopathy, ankle swelling, and skin rashes as erythema nodosum.^{32,33} A case of Lofgren syndrome has been also reported to occur in close temporal association with COVID-19.³⁴ The other report of a patient with mediastinal lymphadenopathy proven by biopsy as sarcoidosis (Table 1) has emphasized that care must be taken to read the results of fluorodeoxyglucose positron emission tomography after the COVID-19 vaccination.³⁵ Furthermore, sarcoidosis-associated uveitis was reported to develop after influenza vaccination³⁶ and varicella-zoster virus vaccination (Shingrix, GlaxoSmithKline, Brentford, UK).³⁷

The accumulation of cases with sarcoidosis sequel to vaccination will lead to understanding of the unknown pathogenesis of sarcoidosis. Old literatures suggested that BCG (Bacillus Calmette-Guerin) vaccination would be linked to the onset of sarcoidosis.³⁸ More recently, juvenile sarcoidosis, which is now designated as Blau syndrome in the entity of autoinflammatory diseases,³⁹ has been reported to develop after BCG vaccination.^{40,41} In the light of the present case with presumed COVID-19 mRNA vaccine-associated sarcoidosis, immunological perturbation as a result of vaccination might underlay the onset of sarcoidosis. As the specific entity of uveitis, Vogt-Koyanagi-Harada disease has been reported to develop after COVID-19 vaccination.⁴² The manifestations of Vogt-Koyanagi-Harada disease-like uveitis have been known to be induced by immune checkpoint inhibitors as well.⁴³ COVID-19 vaccination would lead to abnormal regulation of the immune system to develop different kinds of uveitis such as sarcoidosis and Vogt-Koyanagi-Harada disease.

In conclusion, the present patient was unique at the point that presumed COVID-19 mRNA vaccine-associated uveitis led to the diagnosis of sarcoidosis which fulfilled the clinical and pathological diagnostic criteria for sarcoidosis. It remains to be determined whether COVID-19 vaccination and the onset of sarcoidosis in the present patient would be just a coincidence in the time course of the disease or would have a causal relationship.

Authors' Note

Data are available upon reasonable request to the corresponding author.

Author Contributions

TM and MK as ophthalmologists, HH and HH as internists followed and treated the patient, KU as an otolaryngologist did parotid gland biopsy, and TT as a pathologist made pathological diagnosis. TM wrote the manuscript, and HH, TT, KU, MK, and HH did critical review of the manuscript, and all authors approved the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

Ethics committee review was not applicable due to the case report design, based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects, issued by the Government of Japan.

Informed Consent Statement

Verbal informed consent was obtained from the patient for the anonymized information to be published in this article.

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