Int Ophthalmol
https://doi.org/10.1007/s10792-023-02684-4

CASE REPORT

# Intraocular inflammation following COVID-19 vaccination: the clinical presentations

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Received: 4 October 2022 / Accepted: 4 March 2023


**Abstract**
*Purpose* The purpose of the study was to describe the cases of intraocular inflammation following COVID-19 vaccination (Comirnaty mRNA vaccine and CoronaVac vaccine) in Hong Kong.
*Methods* This was a retrospective case series.
*Results* This series includes 16 eyes among 10 female patients, with a mean age of 49.4 ± 17.4 years. Eight patients (80%) received the Pfizer-BioNTech mRNA vaccination. Anterior uveitis was the most common presentation of postvaccination uveitis (50%) observed in our series, followed by intermediate uveitis (30%) and posterior uveitis (20%), respectively. A case of retinal vasculitis in the form of frosted branch angiitis, previously only reported following COVID-19 infection, was observed following COVID-19 vaccination. The median time from vaccination to uveitis onset was 15.2 days (range: 0–6 weeks). Inflammation in 11 out 16 eyes (68.75%) was completely resolved with topical steroids.
*Conclusion* Anterior uveitis was the predominant presentations of uveitis flare-ups following COVID-19 in our case series, followed by intermediate uveitis. Aligning with the current global literature concerning this issue, most of the uveitis attacks presented as anterior uveitis and were completely resolved with topical steroids. Consequently, the risk of uveitis flare-ups should not deter the public from receiving COVID-19 vaccines.

**Keywords** COVID-19 vaccines · Postvaccination uveitis · BioNTech mRNA vaccine · CoronaVac vaccine · Ocular inflammation

## Introduction

The COVID-19 pandemic caused by the SARS-CoV-2 has had devastating impacts worldwide. COVID-19 vaccines have offered much needed hope in tackling the pandemic, remaining the mainstay of disease prevention efforts. In the local setting of the Hong Kong Special Administrative Region (HKSAR), the government approved the emergency use of COVID-19 vaccines in early 2021, including the Comirnaty (BNT162b2) messenger RNA (mRNA) vaccine supplied by Fosun Pharma and BioNTech (equivalent to the Pfizer-BioNTech vaccine

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Published online: 31 March 2023

distributed elsewhere) [1], alongside the CoronaVac inactivated virus vaccine developed by Sinovac Biotech [2].

Vaccination has previously been observed to associate with immune-related ocular phenomena. Before COVID-19, uveitis was reported to associate with various antiviral vaccines, including the hepatitis B vaccine [3, 4], the varicella vaccine [5], the herpes zoster vaccine [6], the bacille Calmette–Guérin (BCG) vaccine [7], and the human papillomavirus (HPV) vaccine [8]. Given public concerns regarding the safety of COVID-19 vaccines, vaccination data are much needed for the monitoring and surveillance of potential adverse ocular effects.

The most common ocular manifestations of COVID-19 include conjunctivitis, keratitis, keratoconjunctivitis, episcleritis, uveitis, posterior ischemic optic neuropathy, and other conditions involving the retinal vasculature [9–11]. In particular, intraocular inflammation and retinal vascular involvement have been described among patients infected with COVID-19 [11, 12]. It remains uncertain whether vaccination against COVID-19 can produce potentially vision-threatening inflammatory responses similar to COVID-19 infection. This study reports a case series describing the clinical spectrum of ocular inflammatory events related to COVID-19 vaccination observed locally in Hong Kong.

## Methods

Case series data were obtained from the medical records for patients at the Eye Clinic for Prince of Wales Hospital who were consecutively diagnosed with uveitis shortly after receiving COVID-19 vaccines in Hong Kong (either the Comirnaty or CoronaVac vaccine) between March and October 2021. All patients were diagnosed with uveitis resulting from COVID-19 vaccination after ruling out alternative causes for uveitis. The causality between vaccination events and the onset of uveitis was evaluated using the World Health Organization Adverse Reaction Terminology (WHO-ART) [13]. Uveitis presentations were described using the classification developed by the Standardization of Uveitis Nomenclature (SUN) Working Group. Additional demographic and clinical data were also obtained from medical records, including patient age, gender, past medical and ocular history, dates of receiving the first and second doses of COVID-19 vaccines, vaccine type, presenting symptoms, visual acuity, other ocular findings, treatment, and clinical outcomes.

Serology and viral polymerase chain reaction (PCR) and real-time polymerase chain reaction (RT-PCR (SARS-CoV-2)) testing were performed for patients on an individual basis. Administered serology tests included those for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), C3 protein, C4 protein, rheumatoid factors, syphilis, and human leukocyte antigen B27 (HLA-B27). PCR testing methods included anterior chamber tapping and vitreous fluid tapping.

This study was conducted in accordance with the tenets of the Declaration of Helsinki, with the approval from the joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee (CREC NTEC 2020.349).

## Results

Our case series includes 16 eyes from ten female patients. Their mean age was $49.4 \pm 17.4$ years (range: 15–79 years). Eight patients (80%) had received the Comirnaty vaccine, while the other two (20%) had received the CoronaVac vaccine. Nine (90%) developed postvaccination uveitis after their second vaccine dose, while one (10%) developed it after her first dose. Among the occurrences of postvaccination uveitis observed in the case series, anterior uveitis was the most prevalent type (five patients; 50%), followed by intermediate uveitis (three patients; 30%) and posterior uveitis (two patients; 20%), respectively. The median time from vaccination to uveitis onset was 15.2 days (range: 0–6 weeks). Regarding treatment outcomes, topical steroids resulted in complete resolution of uveitis for 11 out of 16 eyes (68.75%). Table 1 summarizes the clinical information for the case series.

### Anterior uveitis

Among the five cases (1, 2, 5, 6, and 8) presenting with anterior uveitis, the first four had a previous history of anterior uveitis. The disease had been

**Table 1** Case summaries

| # | Age | Systemic diseases | Uveitis history | Disease quiescence prevaccination | Inflammation postvaccination | Symptoms postvaccination | Baseline VA | VA at presentation | Onset interval | Vaccine (dose) | Inflammation grade and disease patterns | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 68 | AS | LE: AU | 4 mos | BE: AU | BV, redness | BE: 20/30 | LE: 20/30; RE: HM | 7 days | Comirnaty (2nd) | BE: grade 2+; AC cells Fine KPs | Topical steroids |
| 2 | 41 | Nil | LE: AU | 2 yrs | BE: AU | BV, redness | BE: 20/20 | LE: 20/60; RE: 2/80 | 4 days | Comirnaty (2nd) | LE: grade 2+; AC cells RE: grade 4+w/hypopyon; mutton fat KPs; extensive 270-degree PS | Topical steroids |
| 3 | 55 | Nil | RE: IU | 9 mos | RE: IU | Floaters, redness | BE: 20/20 | LE: 20/20; RE: 20/30 | 2 wks | Comirnaty (1st) | RE: grade 1+; VH; fine KPs | Topical steroids |
| 4 | 58 | Nil | Nil | N/A | BE: IU | BV, redness | BE: 20/40 | LE: 20/80; RE: 20/60 | 3 wks | Comirnaty (2nd) | BE: grade 1+; VH | Topical steroids |
| 5 | 43 | AS | RE: AU | 13 mos | RE: AU | BV, redness | BE: 20/16 | LE 20/16; RE 20/30 | 2 wks | Comirnaty ($1^{st}$) | RE: grade 1+AC cells (Fig. 1) | Topical steroids |
| 6 | 43 | Nil | LE: AU | 10 yrs | LE: AU | BV, redness | LE: 20/30 | LE: HM | 3 wks | Comirnaty (2nd) | LE: grade 4+; AC cells w/ fibrin and hypopyon; pigmented KPs, limited PS | Topical steroids |
| 7 | 41 | Nil | Nil | N/A | BE: PU | BV, flashes | BE: 20/20 | LE 8/200; RE 20/100 | 6 wks | CoronaVac (2nd) | BE: diffuse vasculitis (frosted branch angiitis); choroiditis (Fig. 2) | IV PMP; oral steroids |
| 8 | 51 | Nil | Nil | N/A | BE: AU and SU | Redness | BE: 20/16 | BE: 20/40 | 1 day | CoronaVac (1st) | BE: grade 2+; AC cells; fine KPs, limited PS | Topical steroids |
| 9 | 79 | Nil | Nil | N/A | LE: MFC w/o vitritis | BV | LE: 20/40 | LE: 20/80 | 2 wks | Comirnaty (2nd) | LE: MEWDS (Fig. 3) | Oral steroids |
| 10 | 15 | Nil | Nil | N/A | BE: IU | BV | BE: 20/20 | LE 20/30; RE 20/40 | 2 wks | Comirnaty (2nd) | BE: grade 2; VH w/ CME | Oral steroids; MTX |

*AC* anterior chamber, *AS* ankylosing spondylitis, *AU* anterior uveitis, *BE* both eyes, *BV* blurred vision, *CME* cystoid macular edema, *HM* hand movement, *IU* intermediate uveitis, *IV PMP* intravenous pulse methylprednisolone, *KP* keratic precipitates, *LE* left eye, *MEWDS* multiple evanescent white dot syndrome, *MFC* multifocal choroiditis, *MTX* methotrexate, *PS* posterior synechiae, *PU* posterior uveitis, *RE* right eye, *SU* scleral uveitis, *VA* visual acuity, *VH* vitreous haze

quiescent for a period between 4 months and 10 years before these four patients received COVID-19 vaccines. Severity of anterior uveitis and associated features including the presence of keratic precipitates, posterior synechiae, and Busacca and Koeppe's nodules are reported in Table 1. The presence of keratic precipitates and posterior synechiae were commonly observed in our cases of AU; however, associated granulomatous inflammatory features such as Busacca or Koeppe's nodules were not observed. Moreover, two cases (1 and 5) had ankylosing spondylitis (AS) as a comorbidity, testing positive for HLA-B27. In particular, Case 5, who developed a right anterior uveitis flare-up after their first dose of the Comirnaty vaccine, had a strong family history of AS. Only she had been receiving long-term immunomodulating therapy (methotrexate) to control their AS; the other four patients were not taking any immunosuppressive medications for systemic diseases at diagnosis. Case 5 was shown in Fig. 1.

All patients in this group presented with redness in the eye and blurred vision within 1–14 days of receiving a dose of the Comirnaty vaccine. The median duration between vaccination administration and uveitis flare-up was $15.2 \pm 11.4$ days. No case exhibited sustained elevation in intraocular pressure. All were treated using a course each of topical steroids and cycloplegic eye drops, which sufficed to resolve all signs and symptoms of anterior uveitis.

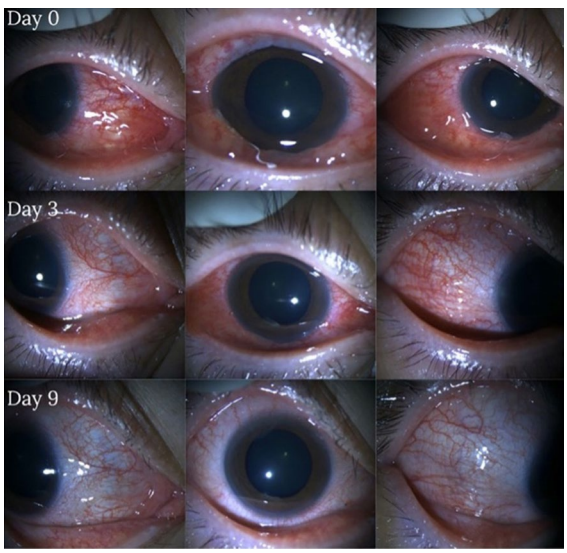


**Fig. 1** Slit-lamp photographs showing diffuse anterior scleritis and anterior uveitis. This patient presented shortly after receiving the second dose of the Comirnaty mRNA vaccine. Interval improvements were observed at 3 and 9 days after the initiation of treatments using topical corticosteroids and cycloplegic eye drops

### Intermediate uveitis

Among the three cases (3, 4, and 10) presenting intermediate uveitis flare-ups, one (Case 3) had a background history of intermediate uveitis; the disease had been quiescent for 9 months before she received the first dose of the Comirnaty vaccine. Case 4 saw a relapse of unilateral uveitis after the second dose of Comirnaty, while Case 10 saw new-onset intermediate uveitis develop bilaterally 3 weeks after the second dose of Comirnaty. For the latter two patients, their ocular inflammation and visual symptoms were completely resolved after being administered a course each of topical steroids and cycloplegic eye drops.

### Retinal vasculitis

The two cases of postvaccination posterior uveitis include one presenting sinister ocular inflammation (Case 7) and another presenting severe retinal vasculitis (Case 9). For Case 7, the patient presented with fever, headaches, and blurred vision 2 weeks after receiving the second dose of the CoronaVac vaccine. Visual examinations discovered bilateral frosted branch angiitis with widespread vascular sheathing and multiple dots, the latter indicating retinitis (Fig. 2). Optical coherence tomography (OCT) revealed multiple pockets of subretinal fluid with evidence of retinal pigment epitheliitis and outer retinitis. Moreover, fluorescein angiography uncovered evidence of perivascular leakage with limited capillary dropout. However, indocyanine green angiography (ICG) observed no hypercyanescence.

Prior to PCR and serological testing, the patient of Case 7 received an intravitreal injection of empirical foscarnet (2.4 mg). Following anterior chamber paracentesis, she tested negative on PCR tests for the varicella zoster, cytomegalovirus, and herpes simplex viruses. She also received negative results for her serology workup, including tests for autoimmune markers, complete blood count, toxoplasmosis, HIV, syphilis, and tuberculosis. After all infectious causes were excluded, the patient was treated using

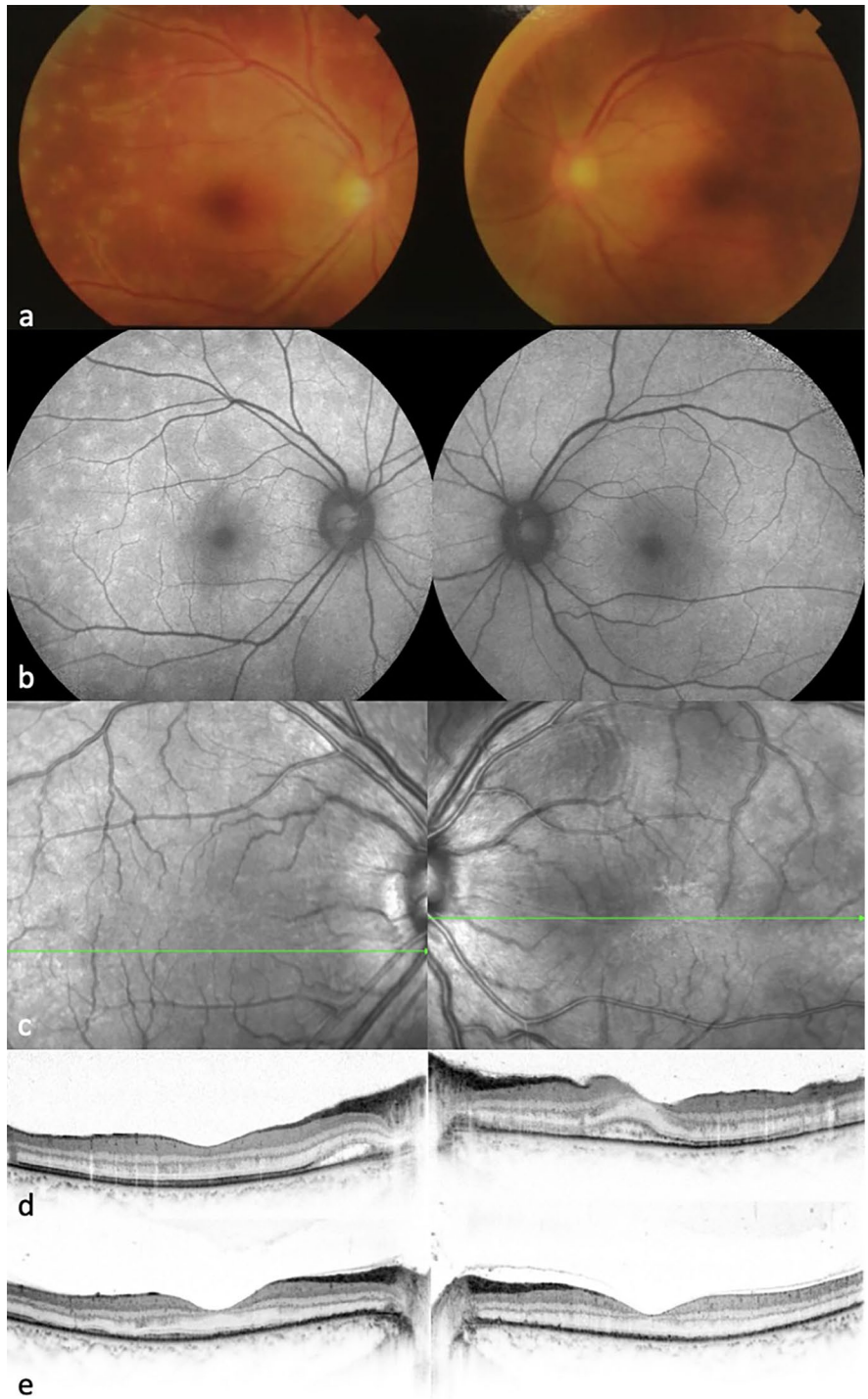


**Fig. 2** From top, **a** fundus photographs of a female (Case 7) who developed a mixed picture of combined frosted branch angiitis, choroiditis, and outer retinal inflammation at 2 weeks after receiving the second dose of the CoronaVac inactivated COVID-19 vaccination. **b** Fundus autofluorescence images with extensive multifocal gray–white chorioretinal hyperautofluorescence spots. **c** Red-free images at the acute phase. **d** Optical coherence tomography (OCT) scans of the images in (**c**). These two sets of images indicate a good response to intravenous pulse steroids after excluding infectious causes, with visual acuity recovering to 1.0 three months after disease the onset (presenting bilateral visual acuity was 0.1). **e** Resolution of subretinal fluids after systemic steroid treatment, with areas of remaining inner segment/outer segment disruption observed bilaterally

an infusion of intravenous pulse methylprednisolone, followed by oral steroids. Ocular inflammation subsided quickly following treatment.

## Discussion

Despite reports on the ocular effects of COVID-19 vaccination being limited until now, certain studies

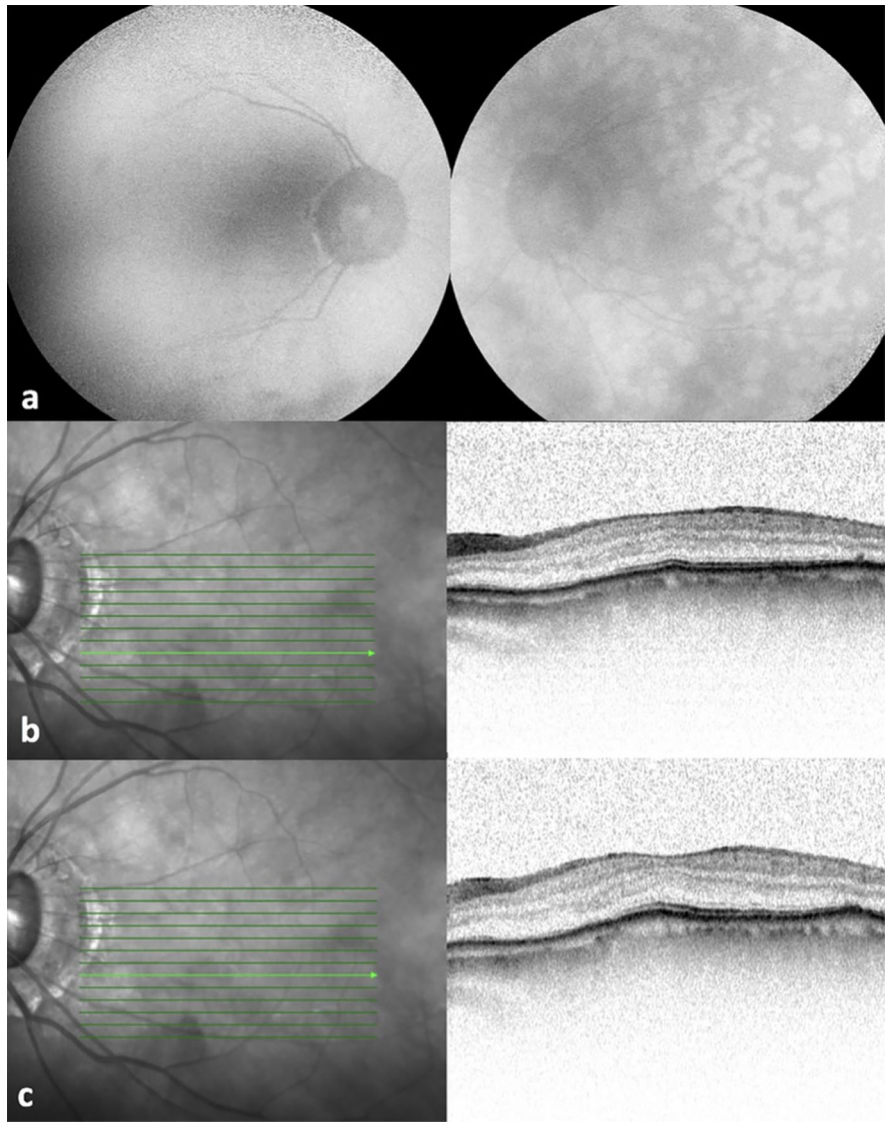


**Fig. 3** An elderly female (Case 9) presented with unilateral multiple evanescent white dot syndrome (MEWDS) in her left eye **a** after receiving the second dose of the Comirnaty mRNA vaccine. Her case represents an occurrence of MEWDS in a patient older than the typical age range (15–50 years). Fundus autofluorescence images **b**, **c** show pattern hyperautofluorescence typical of MEWDS in her left eye. The patient responded well to combined treatments with oral steroids and intravitreal Ozurdex injections

have observed diverse manifestations of ocular phenomena following COVID-19 vaccination. These studies cover a wide range of presentations, including anterior uveitis [14, 15], posterior uveitis [16], multifocal choroiditis [17], panuveitis, Vogt–Koyanagi–Harada syndrome (VKH) [18], and white dot syndromes[19] (Table 2). Nevertheless, most reports have insufficient evidence other than the temporal association to prove the causality between the described ocular inflammation and COVID-19 vaccination. Presumed cases of uveitis related to COVID-19 vaccination reported in the literature include new presentations of onset bilateral juvenile idiopathic arthritis (JIA)-associated anterior uveitis, unilateral anterior uveitis, bilateral choroiditis, and bilateral panuveitis, in addition to the recurrence of VKH syndrome [14–17].

## Clinical presentations of vaccine-associated uveitis

Among the literature describing ocular inflammatory events following COVID-19 vaccination, most reports noted the occurrence of anterior segment inflammation. Recently, a large-scale study including 1094 cases of vaccine-associated uveitis from different countries was reported, summarizing the

**Table 2** Summary of the literature studies

| Study title | Summary | Vaccine(s) | Doses | Time to onset (days) |
|---|---|---|---|---|
| Acute uveitis following COVID-19 vaccination [15] | Case report of juvenile idiopathic arthritis-associated anterior uveitis postvaccination | BBIBP-CorV | 2 | 5 |
| Bilateral multifocal choroiditis following COVID-19 vaccination [17] | Case report of bilateral multifocal choroiditis postvaccination | AstraZeneca | 2 | 9 |
| Panuveitis following vaccination for COVID-19 [20] | Case report of panuveitis postvaccination | Pfizer | 2 | 3 |
| Anterior uveitis onset after BNT162b2 vaccination [14] | Case report of unilateral anterior uveitis postvaccination | Pfizer | 2 | 14 |
| Acute reduction of visual acuity and visual field after Pfizer-BioNTech COVID-19 vaccine 2nd dose: a case report [21] | Case report of possible uveitis postvaccination | Pfizer | 2 | 3 |
| Uveitis following the BNT162b2 mRNA vaccination against SARS-CoV-2 infection [22] | Multicenter retrospective study describing vaccine-related uveitis and multiple evanescent white dot syndrome postvaccination | Pfizer | 1,2 | 1–30 |
| Bilateral uveitis after inoculation with COVID-19 vaccine: a case report [16] | Case report of bilateral posterior uveitis postvaccination | Inactivated[#] | 1 | 5 |
| Vogt–Koyanagi–Harada syndrome following COVID-19 and ChAdOx1 nCoV-19 (AZD1222) vaccine [18] | Case report of complete VKH postvaccination | AstraZeneca | 2 | 4 |
| COVID-19 recombinant mRNA vaccines and serious ocular inflammatory side effects: real or coincidence? [19] | One case of bilateral arteritic anterior ischemic optic neuropathy postvaccination; one case of bilateral acute zonal occult outer retinopathy postvaccination | Pfizer; Moderna | 2 | 2; 10 |
| Ocular inflammatory events following COVID-19 vaccination: a multinational case series[10] | Seventy patients presented with ocular inflammatory events within 14 following COVID-19 vaccination, of which 58.6% presented with anterior uveitis | Pfizer, AstraZeneca, Moderna, Sinopharm, Covaxin | 2 | < 14 |

mRNA vaccines (BNT162b2, Pfizer-BioNTech; mRNA-1273, Moderna); protein subunit vaccines (NVX-CoV2373, Novavax); vector vaccines (Ad26.COV2, Janssen Johnson & Johnson; ChAdOx1 nCoV-19/AZD1222, Oxford-AstraZeneca); whole-virus vaccines (CoronaVac, Sinovac; BBIBP-CorV, Sinopharm)

[#]One of the several inactivated vaccines developed in China; the exact name was not reported

results from adverse event reporting system; anterior uveitis remained as the most common observed vaccine-associated uveitis (VAU) [23]. Similar to our report, a female predominance was observed in the reported VAU cases. Another large case series for anterior segment inflammation was reported by Testi et al. in a multicenter study of 70 patients. In this series, the most common postvaccination inflammatory events were anterior uveitis (58.6%), followed by posterior uveitis (12.9%) and scleritis (10%). Most patients were managed with topical corticosteroids, with vision remaining the same for 92.9% of cases [24].

## Posterior segment involvements in vaccine-associated uveitis

On the other hand, a few reports revealed potential retinal layer or posterior segment involvement following COVID-19 vaccination, suggesting neurological tissue inflammation. In Israel, Rabinovitch et al. reported 21 cases of uveitis following COVID-19 vaccination, of which two cases also developed multiple evanescent white dot syndrome (MEWDS) affecting the retina [22]. Pichi et al. described seven patients presenting with uveitis, along with two instances of rare clinical entities, namely, acute macular neuroretinopathy (AMN) and paracentral middle maculopathy (PAMM) [25]. Similar to the multicenter report by Testi et al. [24], most of the ocular inflammatory events observed by Pichi et al. occurred after patients received the Pfizer-BioNTech vaccine.

Several mechanisms have been suggested to explain ocular inflammatory responses following COVID-19 vaccination. Among them, the most generally accepted theories include the activation of antigens generated secondary to molecular mimicry resulting from similarities between vaccine and uveal peptides, type III hypersensitivity reactions, and other innate immune reactions induced by vaccination [26, 27]. In sum, our study reported the temporality of COVID-19 vaccination and the onset of ocular inflammatory events, observing relatively short intervals between these two events. Causality is possible given current understanding of uveitis events following other vaccinations, as well as generally accepted proposals for biological responses following vaccination.

## Newly observed uveitis entities in our series

In our case series, we also report a new entity of frosted branch angiitis, choroiditis, and outer retinal inflammation, which mimics a mixed picture of widespread retinal vasculitis and choroiditis, following the administration the CoronaVac inactivated whole-virus vaccine. Formulating from harvested, inactivated, and purified whole particles of the SARS-CoV-2, the CoronaVac vaccine is generally expected to induce a broader immune response compared to mRNA vaccines that only target spike proteins [28, 29]. Neutralizing antibodies and/or activated T-helper cells may cross-react with proteins and antigens in multiple ocular tissue layers, including parts of the retinal vessels, outer retinal layers, retinal pigment epithelial cells, and the choroid. So far, retinal vasculitis has only been reported following COVID-19 infection [30]. This case in our series illustrated the potential for COVID-19 vaccines to induce similar vascular inflammatory events, albeit to a milder extent than infection.

In our series, most patients presenting with anterior uveitis (six out of seven patients) experienced uveitis attacks after receiving the Comirnaty vaccine, whereas only one patient developed ocular inflammation involving multiple layers of chorioretinal tissue after receiving the CoronaVac vaccine. The differences in the technologies used by both vaccines may imply distinct immunogenicity mechanisms specific to each vaccine platform. Considering the low occurrence rates of vaccine-related uveitis, continued data collection and future research are warranted to evaluate the safety profiles of each vaccine, including ocular side effects. Nevertheless, given that nearly all uveitis cases following vaccination with the Comirnaty vaccine could be resolved rapidly and completely following a short course of topical steroids, the benefits of vaccination still far outweigh the potential risk of ocular adverse events.

## Clinical course of the available VAU case series

Within the current literature, anterior uveitis is the most prevalent presentation of uveitis flare-ups after various vaccination regimens, followed by intermediate uveitis. The literature also observes that most reported cases resolve rapidly following one course of topical steroids. In the most comprehensive review

of vaccine-induced uveitis yet, Benage and Fraufelder identify a median time range from vaccination to uveitis onset of 16 days (range: 1 day–6 years) [4]. For our case series, the median date of anterior and intermediate uveitis presentations was 15 days (range: 0–6 weeks) following vaccination with the Comirnaty vaccine. Our series did not include specific antibody tests and titrations for the SARS-CoV-2. Nevertheless, factors including the temporal sequence of vaccination and disease events, the absence of identifiable alternative causes from accessory examinations, the transience of severe ocular inflammation symptoms, and good treatment responses to steroids all strongly suggest that uveitis can be a vaccine-induced immune response.

### Potential mechanisms for vaccine-associated uveitis

Of the two available vaccines in Hong Kong, the Comirnaty mRNA vaccine uses lipid nanoparticle encapsulated mRNA to encode a full-length spike protein of the SARS-CoV-2, which is also locked down by two proline mutations to avoid integration into the host cell genome [31]. This vaccine induces strong activation of the cellular and humoral immune responses, exhibiting dose-dependent side effects [32]. Because of the similarities between the SARS-CoV-2 spike protein and proteins in uveal tissues, molecular mimicry may cause immune cross-reactivity, triggering autoimmune diseases such as anterior uveitis [31, 33]. In accordance with available reports, most cases in our series developed uveitis following the second dose of COVID-19 vaccines, potentially because of greater, and possibly dose-dependent, reactogenicity.

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Potential role of vaccines in creating inflammatory reaction less than the extent of cytokine storms by SARS-CoV-2 may provide us an insight into the potential mechanisms of vaccine-associated uveitis. Coronavirus-2 (SARS-CoV-2) causes acute respiratory distress syndrome (ARDS) in 15% of COVID-19 cases. ARDS is mainly triggered by elevated levels of pro-inflammatory cytokines, referred to as cytokine storm which is induced by an excessive immune response rather than the viral load. Cytokine storm is defined as acute overproduction and uncontrolled release of pro-inflammatory markers systemically, as well as reduced macrophages functions and peripheral lymphopenia [34, 35].

Besides, recent studies suggest that excessive production of some cytokines, such as interleukin-6, interleukin-1, interleukin-17, and tumor necrosis factor-alpha, may be the leading cause of inflammatory response in COVID-19-related cytokine storms [36]. We understand that these interleukins and inflammatory factors play a crucial role in many ocular inflammatory events. Also, SARS-CoV-2 has a predilection target at organs expressing ACE2 receptor, which is abundantly expressed in the pulmonary system, and to a lesser extent, in the eye and brain. Thus, ocular tissue is also highly suspectable to SARS-CoV-2 entry and replication. These two factors may shed a light into the phenomenon of vaccine-associated uveitis.

## Conclusion

This study reported a case series of intraocular inflammation events following COVID-19 vaccination, covering a broad disease spectrum. Anterior uveitis is most prevalent presentation in the series, followed by intermediate uveitis. Because early treatment of uveitis often results in rapid and complete resolution, uveitis flare-ups should not deter people from receiving COVID-19 vaccines. Nevertheless, the general public should be made aware about the potential risk of uveitis attacks and possible ocular symptoms following vaccination.

**Acknowledgements** Not applicable.

**Authors' contribution** All authors listed here are qualified for authorships. This is to certify all the authors gained credit by fulfilling substantial contributions to conception and design, acquisition and analysis of data, drafting and revising the article, and approval of the version to be published.

**Funding** This research did not receive any funding and sponsorships. The authors have no relevant financial or non-financial interests to disclose.

**Data availability** Not applicable.

**Declarations**

**Conflict of interest** The authors have no conflicts of interest to declare that are relevant to the content of this article.

**Ethics approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Consent to participate** This is a retrospective study that does not contain medical information or clinical photos of identifiable living individuals.

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