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Uveitis following COVID-19 vaccination: a literature review for Canadian ophthalmologists

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INTRODUCTION

The advent of SARS-CoV-2 (COVID-19) vaccines markedly reduced adverse outcomes associated with COVID-19 infection. With over 12 billion doses of COVID-19 vaccines administered globally as of June 2022, reports have emerged of ocular sequelae following immunization.¹ Vaccination remains the most effective way to reduce the risk of COVID-19-related morbidity and mortality. However, it is important for ophthalmologists to understand the potential adverse events related to SARS-CoV-2 vaccination to provide opportunity for appropriate patient counselling and diagnosis. This review outlines the reported associations between COVID-19 vaccination and uveitis, including proposed mechanisms and recommendations for treating ophthalmologists.

REVIEW OF VACCINE TECHNOLOGY

In Canada, the most widely available vaccines against SARS-CoV-2 infection include the Moderna Spikevax (mRNA-1272) and Pfizer-BioNTech Comirnaty (BNT162b2) mRNA vaccines, as well as the AstraZeneca Vaxzevria (formerly Covishield, ChAdOx1nCoV-19/AZD1222) and Janssen Jcovden (Ad26.COVS.S) viral vector vaccines. Inactivated viral vaccines are also widely used in other countries. mRNA vaccines deliver an antigen derived from the SARS-CoV-2 spike glycoprotein to the host deltoid muscle cell. Viral vector vaccines carry DNA that encodes for the SARS-CoV-2 spike glycoprotein within an adenovirus vector. Both vaccines trigger innate immune responses by toll-like receptors, inflammasomes, and other immune sensors, leading to the release of inflammatory cytokines.^{2,3} B-cell response includes formation of antibody-secreting plasma and memory B cells.^{2,3} T-cell response predominantly features production of T-helper 1 cytokines, including interferon gamma, interleukin-2, and tumour-necrosis factor. A second vaccine dose is required for both mRNA and viral vector vaccines to amplify the production of adaptive immune cells.

REPORTED UVEITIC COMPLICATIONS

Anterior Uveitis

Anterior uveitis (AU) is the most common site of ocular inflammation following inoculation with any COVID-19 vaccine. Over 200 cases of AU have been published to date.^{4,5,7} Most cases are idiopathic, unilateral, and occur within 14-21 days of vaccination.^{4,5} There does not appear to be a clear association with first or second dose of vaccine, or association with gender.^{4,5} Treatment with topical or periocular steroids over one month typically resolves inflammation with preservation of baseline visual acuity.^{5,7}

At our centre, we report a healthy 54-year-old man with new onset bilateral, chronic AU following vaccination with the BNT162b2 Pfizer-BioNTech booster dose. The patient's previous vaccine doses did not trigger any adverse events. Two days following his booster inoculation, the patient developed bilateral non-granulomatous AU (**Figure 1**).

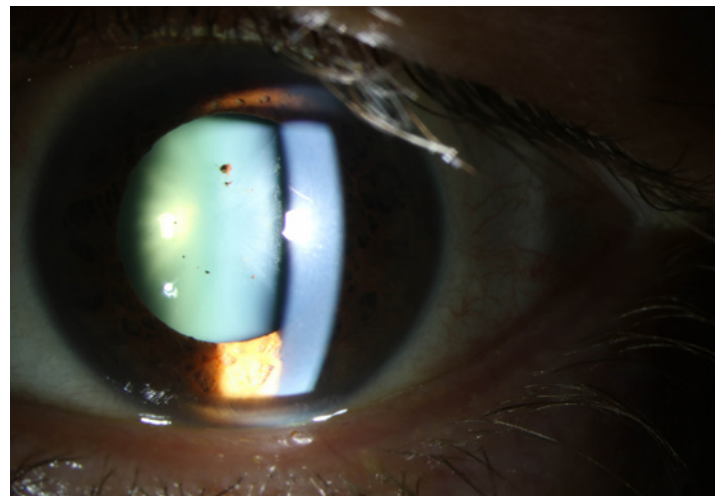


Figure 1: Slit lamp photograph of the left eye demonstrating residual fine keratic precipitates and anterior lens pigmentation following posterior synechiae, associated with non-granulomatous anterior uveitis 2 days after Pfizer booster inoculation; patient photos courtesy of Derzko-Dzulynsky, MD, Emami, MD and Pereira, MD

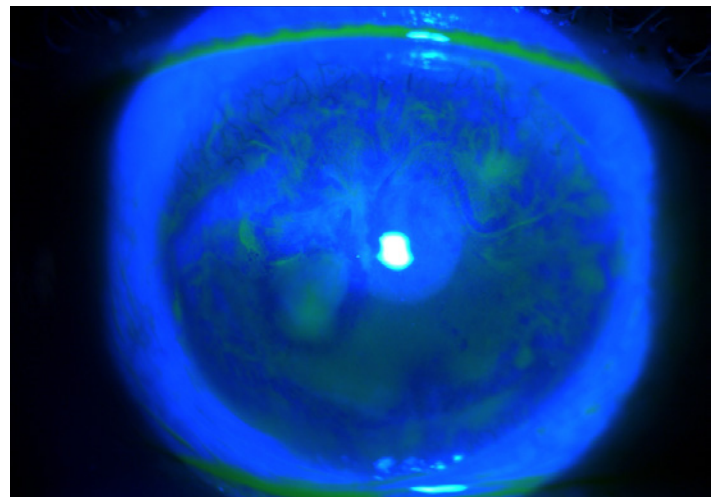
Topical steroid therapy was initiated and treatment was required for over six months. Investigations for infectious and inflammatory etiologies were negative and the patient's vision was preserved at 20/25 in both eyes. Among patients who experience a relapse of AU following COVID-19 vaccination, the vast majority of cases resolve with a short course of topical steroid drops; however, researchers have reported two patients who required escalation of baseline immunomodulatory therapy (IMT) to achieve AU remission, with good visual outcomes.⁶

Reactivation of HLA-B27 and herpetic AU have been reported by several groups.^{7,8} We report a 30-year-old female with recurrent HLA-B27-positive AU, previously controlled with one drop of topical prednisolone acetate 1% per week, who presented with eye pain two days following her COVID-19 mRNA booster vaccination. The patient's slit lamp examination revealed 0.5+ cells OS, consistent with AU. Topical steroids were increased to six times daily and tapered over 3 months, with complete resolution of AU and preserved visual acuity of 20/25. In addition, we evaluated an 81-year-old female with well-controlled herpes simplex virus (HSV) keratitis on prophylactic acyclovir 400 mg PO b.i.d.. She presented with decreased vision two weeks following her second dose of Pfizer-BioNTech. Her examination revealed moderate corneal edema, acute stromal haze and 1+ anterior chamber cell OS. She required one month of treatment with topical dexamethasone 0.1% and acyclovir 400 mg PO five times per day. Despite resolution of the keratouveitis, her limbal stem cell deficiency progressed as a result of this vaccine-associated flare (**Figure 2**).

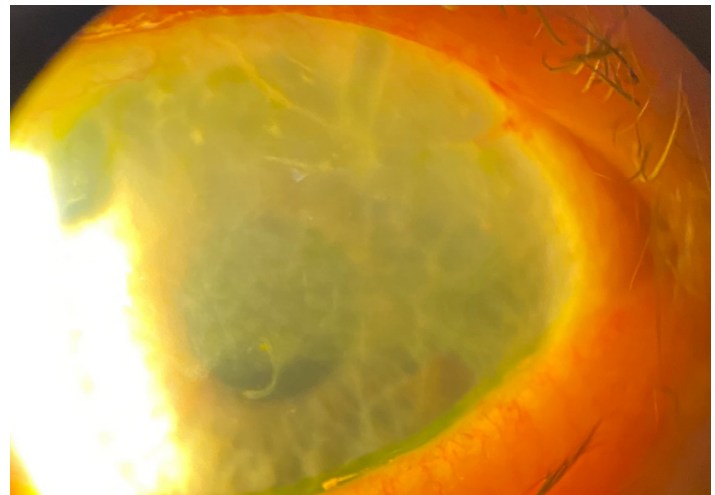
COVID-19 vaccine-associated AU typically presents with mild blurred vision, photophobia, and mild-to-moderate anterior chamber reaction; keratic precipitates and posterior synechiae may also be present. In 2022, researchers reported a case of hypopyon-associated unilateral idiopathic AU in a healthy 21-year-old female two days following her second dose of the BNT162b2 Pfizer-BioNTech vaccine.⁹ Despite its rapid onset, the patient regained 20/20 vision and achieved quiescence within one month of treatment with topical and oral steroids. These cases in the literature, and our single centre experience, demonstrate the heterogeneity of AU presentation following COVID-19 vaccine administration. Importantly, no cases of permanent vision loss have been reported secondary to vaccine-associated AU. Patients with AU following COVID-19 inoculation have uniformly responded rapidly to local and systemic therapy and demonstrated complete resolution of symptoms.^{6,7,9}

Non-Anterior Uveitis

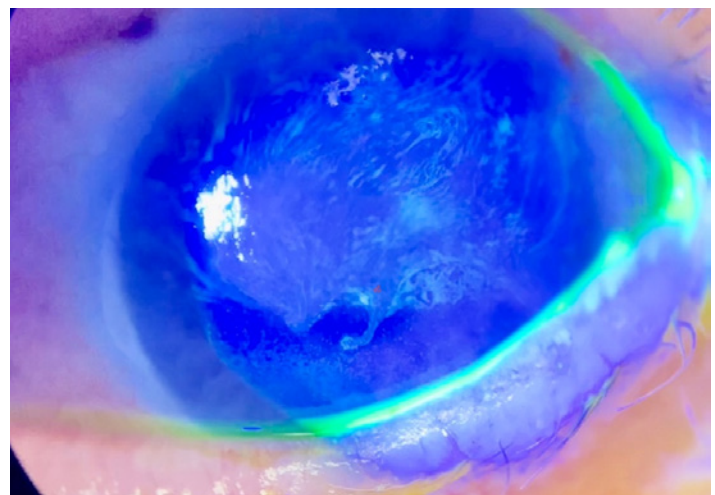
Non-AU (intermediate, posterior and panuveitis) occurs much less commonly than AU following COVID-19 vaccination and more often presents with severe vision loss requiring more intensive treatment. In 2021, a single case of idiopathic unilateral panuveitis, which occurred three days following the second dose of the Pfizer-BioNTech vaccine, and involved a 43-year-old female presenting with 20/500 vision, 2-3+ vitreous cells and peripheral retinal



A



B



C

Figure 2: Left eye slit lamp photos (A) Baseline with moderate limbal stem cell deficiency (note the whorl pattern of "late" fluorescein staining) with best corrected Snellen vision of 20/50. (B) 1 month following treatment of HSV immune stromal keratitis and uveitis which flared up 2 weeks after second dose of the Pfizer vaccine. (C) Slit lamp photograph with inactive herpetic disease but extensive advancement of the whorl pattern of "late" fluorescein staining indicating progression of limbal stem cell deficiency; patient photos courtesy of Clara C. Chan, MD

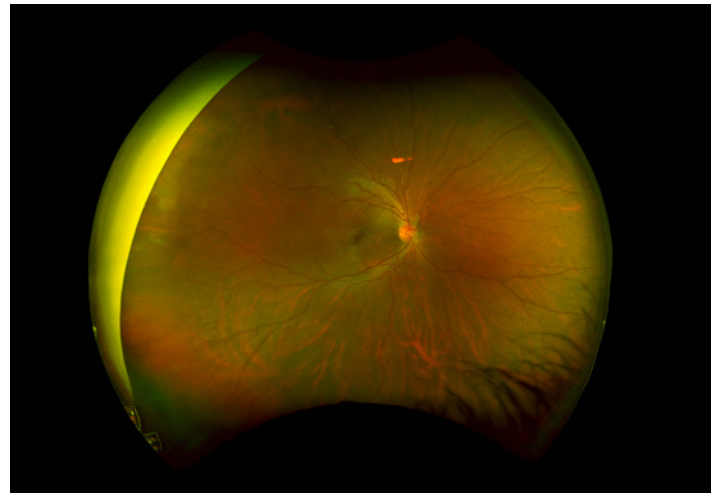
vascular leakage was reported.¹⁰ This case was treated with 50 mg oral prednisone daily with subsequent steroid taper, leading to an excellent visual outcome. Another group reported 6 cases of recurrent non-infectious panuveitis, intermediate or posterior uveitis following mRNA vaccination in patients with uveitis controlled with oral steroids or IMT.⁶ All cases were managed with local ophthalmic and/or systemic steroids, or escalation of baseline IMT, without lasting complications.⁶ In a review of almost 2.5 million Pfizer-BioNTech vaccinations in Israel, researchers identified 17 cases of intermediate, posterior, or panuveitis occurring within 3 weeks of inoculation.⁴ Although no treatment outcomes were reported, the study highlights the rare nature of vaccine-associated posterior uveitis.

There have been more than ten reported cases of Vogt-Koyanagi-Harada (VKH) onset or relapse following administration of all COVID-19 vaccine types, occurring within 1 day to six weeks after vaccination.^{7,11,12} This bilateral exudative panuveitis typically requires treatment with high-dose systemic steroids and/or IMT to achieve quiescence, though permanent vision loss can occur due to damage of the retinal pigment epithelium (RPE) and choroid.¹³ VKH is believed to be caused by T-cell mediated autoimmune reaction against melanocytes in the uvea and other target organs. Molecular mimicry, whereby vaccine epitopes resemble host epitopes and thereby trigger innate immune activation, is one of the hypothesized mechanisms of VKH activation following inoculation.¹² Despite a relatively prolonged treatment course requiring systemic corticosteroids and occasionally IMT, most patients with vaccine-related VKH achieve resolution of subretinal exudation and excellent visual acuity.^{12,13,14}

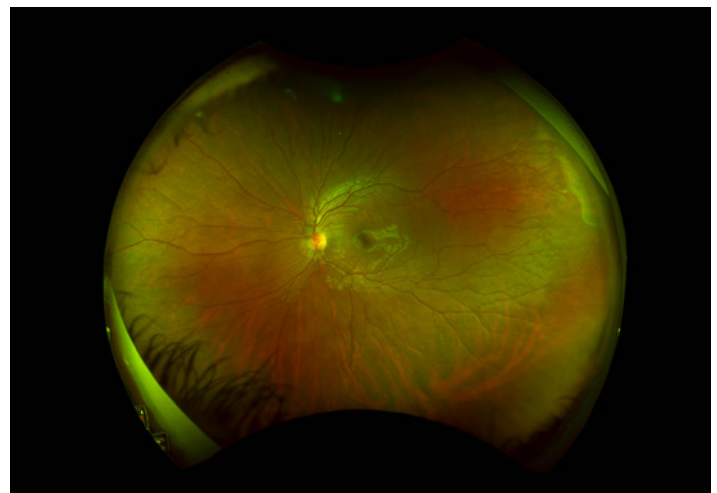
Similar to other reports of post-vaccination uveitis, white dot syndromes have been associated with COVID-19 vaccination. There was a reported case of unilateral acute posterior multifocal placoid pigment epitheliopathy 2 weeks following administration of the second dose of Pfizer-BioNTech vaccine in a healthy adolescent male.¹⁵ Oral steroids were initiated to treat mild vitreous cell, and the disease became inactive after several weeks. Visual acuity returned to baseline; however, RPE scarring remained. Multiple evanescent white dot syndrome (MEWDS) is a self-limited autoimmune chorioretinitis that typically affects young, myopic females and may be associated with a viral prodrome. Over ten cases of MEWDS have been reported following COVID-19 mRNA vaccination,^{7,16,17} inactivated,^{18,19} and protein subunit vaccines.²⁰ All cases resolved within several weeks.

We report one case of unilateral panuveitis with retinal vasculitis at our centre. A 29-year-old male, previously known for well-controlled idiopathic AU, presented with blurred vision 20 days after administration of his second mRNA vaccine dose. Moderate anterior chamber cell and flare, optic disc edema, and cystoid macular edema were noted OU (**Figures 3a-b**). Fluorescein angiography demonstrated cystoid macular edema and peripheral vascular leakage in both eyes (**Figures 3c-d**).

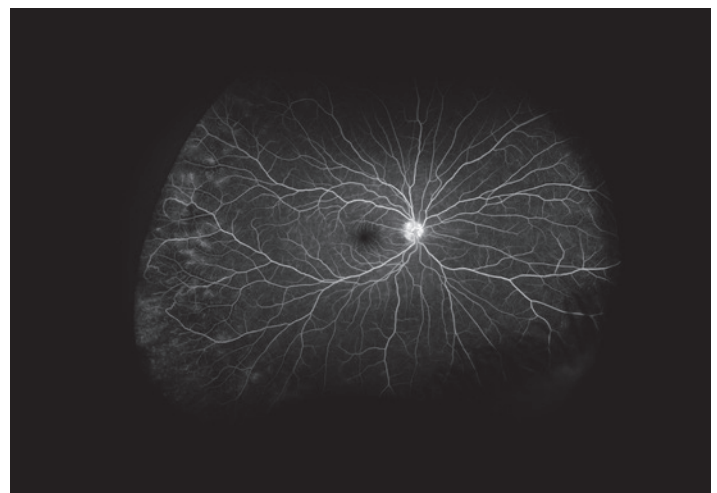
The intraocular inflammation and vasculitis initially resolved with the use of high dose oral prednisone (1mg/kg); however, retinal vasculitis recurred as steroids were tapered and methotrexate was initiated. Given the patient's history of uveitis prior to his vaccination, the relationship between COVID-19 vaccination and retinal vasculitis remains unclear.



A



B



C



D

Figure 3: Optos colour widefield photograph (Optos California) of the (A) right eye and (B) left eye demonstrating peripheral vascular sheathing and blunted foveal reflex (due to cystoid macular edema). Intravenous fluorescein angiography late phase images (Optos) of the (C) right eye and (D) left eye demonstrating leakage in macula and retinal periphery demonstrating cystoid macular edema and peripheral retinal vasculitis; patient photos courtesy of Derzko-Dzulynsky, MD, Emami, MD and Pereira, MD

Infectious posterior uveitis has also been reported following COVID-19 immunization. In 2021 researchers reported a single case of the development of unilateral varicella zoster virus acute necrotising retinitis (ARN) three days after receiving an adenovirus vector vaccine.²¹ The aqueous humour at presentation was positive for varicella zoster virus by qualitative polymerase chain reaction test. The patient had a history of diabetes mellitus. Despite appropriate systemic antiviral treatment and resolution of the active retinitis over several months, the patient's final visual acuity was impaired at 20/50 at final follow-up. Of note, the patient did not demonstrate antibodies to the SARS-CoV-2 spike glycoprotein on serologic testing despite previous vaccination, suggesting impaired immune function that may have contributed to development of ARN.²¹

PROPOSED MECHANISMS OF UVEITIS FOLLOWING SARS-COV-2 VACCINATION

Vaccine-associated uveitis is not a new phenomenon. In fact, uveitis flares have been reported following most widely-administered inoculations, most frequently for hepatitis B, human papilloma virus, Bacille Calmette-Guerin, influenza, and varicella zoster virus vaccines.^{22,23} Most cases of uveitis in this context are mild, short-lived, and resolve with observation or minimal intervention.²²

Multiple mechanisms may link COVID-19 vaccination and uveitis flares. Several explanations have been proposed, including: (1) molecular mimicry, whereby the vaccine antigen may resemble self-antigens (often uveal self-peptides) that activate adaptive immunity; (2) activation of sequestered self-antigens by innate and adaptive immune cells triggered by recent vaccination; and (3) over-secretion of inflammatory cytokines in the setting of vaccination that

cause additional recruitment of T-helper cells.²⁴ Molecular mimicry, in particular, has been implicated in HLA-B27-associated diseases. HLA-B27-expressing immune cells, including macrophages, have molecular similarity to certain bacterial and viral antigens. Peptides originating from viruses, bacteria, or other pathogens may therefore cross-react with HLA-B27 expressing immune cells due to antigen mimicry, initiating an inflammatory response.²⁵ This molecular pathway may explain relapses of HLA-B27 uveitis following COVID-19 vaccination. Some studies further suggest that the release of type 1 interferon induced by mRNA vaccines could initiate autoimmune activity resulting in uveitis.⁵ In addition, reports from the dermatology literature postulate that the large-scale shift of naïve CD8+ cells induced by vaccination may temporarily exacerbate T-cell mediated autoimmune conditions such as herpes zoster virus.^{26,27} It is possible that relapses of VKH and other cell-mediated uveitis conditions may be derived from a similar immunologic reaction post-vaccination.

RECOMMENDATIONS FOR OPHTHALMOLOGISTS

This literature review highlights the ocular inflammatory events associated with SARS-CoV-2 vaccination. It is reassuring that the vast majority of vaccine-associated uveitis cases are mild, anterior, of short duration, treated adequately with topical steroid drops, and have not been associated with permanent vision loss. Non-anterior uveitis occurs less frequently following COVID-19 vaccination and may require treatment with oral steroids or systemic immunosuppression. Pre-existing uveitis can be reactivated by COVID-19 vaccination, if not previously well-controlled. The onset of uveitis following COVID-19 vaccination ranges between 2 days to 3 weeks following vaccination.

In a study of approximately 2.5 million doses of administered Pfizer-BioNTech vaccine, an attributable risk of only one case of non-infectious uveitis per 1,000 vaccinated people among patients with a pre-existing history of uveitis was demonstrated.⁴ In contrast, the lack of vaccination carries considerable risk of COVID-19-related morbidity and mortality. Unvaccinated patients with a pre-existing history of non-infectious uveitis have been shown to be at higher risk of COVID-19 infection if taking systemic corticosteroids or tumour necrosis factor-alpha agents, and may be at higher risk of COVID-19-related hospitalization and death if taking systemic corticosteroids.²⁸

There is currently insufficient evidence to recommend universal monitoring for uveitis flares in patients who receive COVID-19 vaccination. However, chronic uveitis should be well-controlled prior to COVID-19 vaccination. Ophthalmologists may wish to counsel patients with a history of uveitis about the small, increased risk of uveitis exacerbation following COVID-19 immunization and consider following patients more closely after COVID-19 vaccination.

Ophthalmologists may consider increasing topical steroid medications prior to COVID-19 vaccinations in patients with a history of AU. This approach should not reduce the

immunogenicity of vaccination and may blunt the severity of potential ocular inflammation. We recommend that ophthalmologists collaborate with cross-disciplinary specialists to optimize the timing of IMT relative to COVID-19 vaccination to maximize vaccine immunogenicity.²⁹

Finally, we encourage all healthcare providers who suspect ocular adverse events following COVID-19 immunization to report their findings to local and national vaccine surveillance bodies to facilitate early identification of potential safety concerns.^{30,31}

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