Case Report

Unilateral macular branch retinal vein occlusion in a healthy Indian woman following coronavirus disease vaccination: a case report and comprehensive literature review

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ABSTRACT

Background: The coronavirus disease (COVID-19) vaccines exert ocular adverse effects, including episcleritis, scleritis, anterior and recurrent uveitis, acute macular neuroretinopathy, paracentral acute middle maculopathy, ophthalmic vein thrombosis, Graves' disease, arteritic anterior ischemic optic neuropathy, non-arteritic anterior ischemic optic neuropathy, central serous chorioretinopathy, Vogt-Koyanagi-Harada disease, multifocal choroiditis, cranial nerve palsies such as facial or abducens nerve palsy, acute zonal occult outer retinopathy, acute zoster ophthalmicus following re-activation of the varicella-zoster virus, acute retinal necrosis, and multiple evanescent white dot syndrome. In this case report, we explored the possibility of macular branch retinal vein occlusion and its association with COVID-19 vaccination.

Case Presentation: A 44-year-old healthy woman presented with unilateral non-progressive blurring of vision in the right eye (OD). Her best-corrected distance visual acuity (BCDVA) in OD was 20 / 40. The anterior-segment evaluation was normal. Fundus evaluation of the OD revealed macular branch vein occlusion. She had a history of COVID-19 vaccination within 1 month. The interleukin-6 level was elevated six folds to 30.5 pg / mL. However, COVID-19 immunoglobulin G (IgG) antibodies were negative. Infective etiologies, such as tuberculosis and dengue, were ruled out. Spectral-domain optical coherence tomography (SD-OCT) of the OD showed hyperreflective dots in the posterior vitreous, inner retinal swelling, and cystoid changes in the macula. The maximum central macular thickness was 486 µm. A single dose of bevacizumab was administered at OD intravitreally. At the final follow-up 2.5 months later, her BCDVA had improved to 20 / 20 OD. Fundus evaluation revealed fewer retinal hemorrhages and cotton wool spots. SD-OCT of the OD showed a normal foveal contour and absence of cystoid spaces. Her maximum central macular thickness was 236 µm.

Conclusions: A temporal effect of vein occlusion secondary to COVISHIELD™ vaccination may occur in the absence of systemic risk factors. The interleukin-6 level was elevated, and the remaining blood test results were within normal limits. Since this is a case report, it is limited by the absence of strong evidence to prove this causal relationship between macular branch retinal vein occlusion and the specific brand of COVID-19 vaccination.

KEYWORDS

COVID-19 virus vaccines, ChAdOx1 nCoV 19, COVISHIELD™, macula, retinal branch vein occlusion, cystoid macular edema, avastin™, intravitreal injection

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INTRODUCTION

Various adverse ocular effects, including vascular insults, have been observed with coronavirus disease (COVID-19) vaccines [1]. Neuro-ophthalmological complications [2] include arteritic anterior ischemic optic neuropathy [3], non-arteritic anterior ischemic optic neuropathy (NA-AION) [4], and multiple cranial nerve palsies, such as facial or abducens nerve palsy [5-8].

Likewise, orbital, eyelid, and anterior segment manifestations include swelling and severe allergic reaction or purpuric lesions of the eyelids [9, 10], Graves' disease [6, 11], episcleritis, scleritis [12, 13], corneal graft rejection [6], anterior and recurrent uveitis [14-16], acute herpes zoster ophthalmicus following re-activation of the varicella-zoster virus [17], and ocular manifestations of juvenile idiopathic arthritis [18].

Several reports reveal posterior segment and retinal complications, such as acute retinal necrosis with re-activation of the varicella-zoster virus [19], multiple evanescent white dot syndrome [6, 20], acute macular neuroretinopathy [6, 13, 21, 22], paracentral acute middle maculopathy [13, 23], subretinal fluid [13], ophthalmic vein thrombosis [6], retinal vein occlusions [24, 25], central serous chorioretinopathy [26],Vogt-Koyanagi-Harada disease and relapse [27-29], multifocal choroiditis [30], and acute zonal occult outer retinopathy [3, 6].

Here, we report a case of unilateral macular branch retinal vein occlusion (BRVO) following COVID-19 vaccination and its successful resolution after a single dose of an intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection.

CASE PRESENTATION

A 44- year old Asian Indian woman presented with a history of non-progressive blurring of vision in her right eye (OD). She had received the first dose of COVISHIELD™ (ChAdOx1 nCoV 19 manufactured by Serum Institute of India Limited, Pune) vaccination less than 1 month earlier. She had no known systemic history, including COVID-19 infection.

On ocular examination, her best-corrected distance visual acuity (BCDVA) values using Snellen chart (Snellen chart, Nidek automatic chart projector CP 670; Nidek Co., Ltd., Gamagori, Japan) were 20 / 40 and 20 / 20 in the OD and left eye (OS), respectively. The bilateral anterior-segment evaluation using a slit lamp (Haag Streit, Mason, OH, USA) was normal. Intraocular pressure measurements in both eyes using a Goldmann applanation tonometer (AT-900; Haag-Streit AG, Koniz, Switzerland) mounted on a slit-lamp microscope were normal.

Fundus evaluation was performed using indirect binocular ophthalmoscopy (Keeler Instruments, Inc., PA, USA) and a + 20-diopter non-contact ancillary lens (VOLK Optical Inc., Mentor, OH, USA). Fundus evaluation of the OD showed a cup-disc ratio (CDR) of 0.7 with multiple cotton wool spots (CWSs) and retinal hemorrhages in the superotemporal quadrant confined within the vascular arcade and associated with macular edema (Figure 1). OS showed a CDR of 0.7 with normal retina. Superior branch macular vein occlusion with secondary macular edema was diagnosed in OD. Initially, systemic evaluation by a rheumatologist for autoimmune conditions yielded negative results.

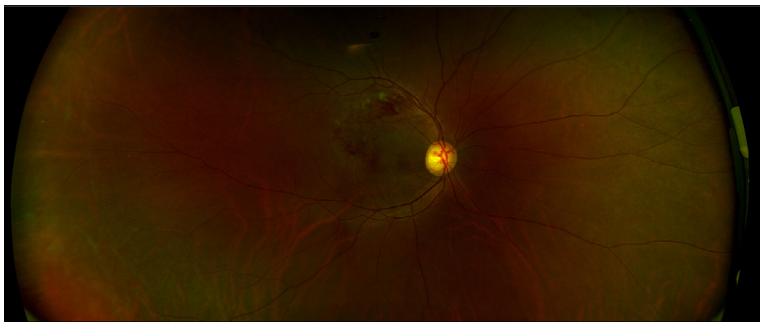

Figure 1. Ultrawide colour fundus photograph of the right eye with optos™ (Optos P200DTx icg, Optos, Marlborough, MA, USA) showing multiple flame-shaped, dot and blot haemorrhages with yellow fluffy areas representing cotton wool spots in the superotemporal quadrant confined within the vascular arcade with secondary macular edema. The cup-disc-ratio of the optic nerve is 0.7 with temporal thinning of the neuroretinal rim.

Ocular investigations were conducted. Spectral-domain optical coherence tomography (SD-OCT; Heidelberg Retinal SD-OCT; Heidelberg Engineering, Inc., Dossenheim, Germany) of the OD revealed hyperreflective dots in the posterior vitreous, inner retinal swelling, and cystoid changes in the macula (Figure 2A). Her maximum central macular thickness was 486 μm. Multicolor imaging (MCI; Figure 3A-D) performed with Spectralis™ (Heidelberg Retinal Angiography; Heidelberg Engineering, Inc., Dossenheim, Germany) showed predominant changes in blue (Figure 3B) and green (Figure 3C) reflectance showing brighter areas depicting CWS. Darker areas on the infrared reflectance were due to the shadow effect of the inner layers of the retina (Figure 3D).

Further systemic investigations revealed normal prothrombin and activated partial thromboplastin times, and a peripheral blood smear showed a normochromic normocytic picture with absolute neutrophilia. C-reactive protein, D-dimer, serum ferritin, lactate dehydrogenase, and fibrinogen levels were within normal limits. COVID-19 immunoglobulin G (IgG) antibodies were negative. Infective etiologies, such as tuberculosis and dengue, were ruled out.

Serum homocysteine levels were mildly raised to 21.19 mmol / L (normal range: 5 – 15 mmol / L), and the erythrocyte sedimentation rate was 35 mm / hour. The interleukin-6 level was elevated six-folds to 30.5 pg / mL (normal range: 0.3 – 5 pg / mL). Repeat serum homocysteine levels 1 week later in another laboratory were within normal limits.

As the IL-6 level was elevated, the patient was referred to a rheumatologist who performed a systemic evaluation and advised an autoimmune work-up, which included anti-cyclic citrullinated peptide, anti-nuclear antibody profile, anti-neutrophilic cytoplasmic antibody, anti-phospholipid antibodies IgM / IgG, and beta-glycoprotein IgM / IgG, all of which were negative. The patient did not agree to undergo further haematological investigations, such as thrombophilia screening, owing to financial constraints.

We advised her for treating macular edema secondary to BRVO. Following her consent, she was provided with a single dose of the intravitreal bevacizumab (Avastin™, Genentech, Inc., Roche, Basel, Switzerland) injection 0.5 mg / 0.05 mL to OD [31]. At the final follow-up 2.5 months later, her BCDVA was 20 / 20 in both eyes. Fundus evaluation of the OD showed fewer CWS and fewer hemorrhages, with no evidence of macular edema.

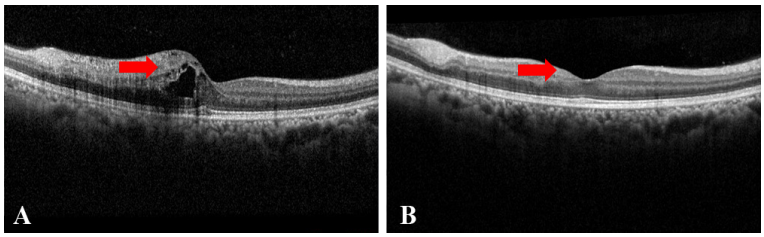

Figure 2. (A) The spectral-domain optical coherence tomography (SD-OCT) image (Heidelberg Retinal SD-OCT; Heidelberg Engineering, Inc., Dossenheim, Germany) of OD macula shows intraretinal cystoid spaces with neurosensory detachment at presentation (red arrow). (B) The SD-OCT image of OD macula shows complete resolution of macular edema (red arrow) 2.5 months after a single dose of the bevacizumab anti-vascular endothelial growth factor (Avastin™, Genentech, Inc., Roche, Basel, Switzerland) injected intravitreally (0.5 mg / 0.05 mL).

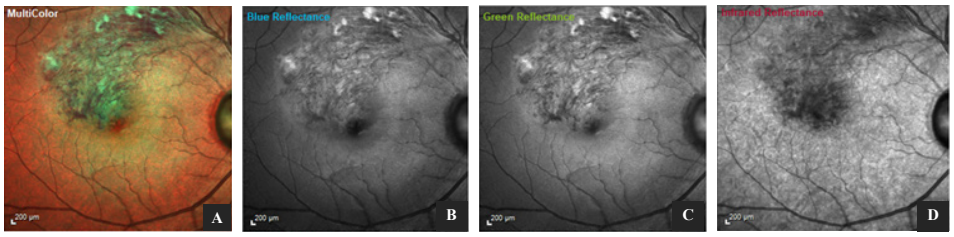

Figure 3. Multicolour imaging was performed with Spectralis™ (Heidelberg Retinal Angiography; Heidelberg Engineering, Inc., Dossenheim, Germany). (A) The pseudocolor image showing greenish whitish areas in the superior macula interspersed with hemorrhages. (B) The blue and (C) green reflectance show bright and dark areas corresponding to cotton wool spots and hemorrhages, respectively, and indicating involvement of the inner and middle retinal layers. (D) At the level of the retinal pigment layer, infrared reflectance shows dark areas due to the shadowing effect of the inner and middle layers .

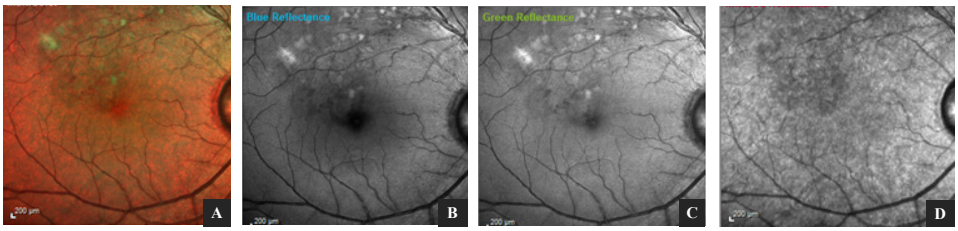

Figure 4. Multicolour imaging was performed with Spectralis™ (Heidelberg Retinal Angiography; Heidelberg Engineering, Inc., Dossenheim, Germany). (A) The pseudocolor image shows reduction in the green areas indicating resolution. (B) The blue and (C) green reflectance show fewer darker areas signifying reduction in hemorrhages. Bright spots, although reduced, have not disappeared completely. (D) The infrared reflectance shows a lesser effect of shadowing.

At the 2.5-month follow-up, SD-OCT of the OD showed a normal foveal contour and the absence of cystoid spaces (Figure 2B). Her maximum central macular thickness was 236 μm. MCI (Figure 4A-D) show reduced brighter areas on blue (Figure 4B) and green (Figure 4C) reflectance, with better delineation of retinal vessels. Darker areas of infrared reflectance were also reduced (Figure 4D). Fundus fluorescein angiography, which is an invasive test, was not performed because the patient refused.

The study protocol was approved by the Narayana Nethralaya Ethics Committee, Vide approval number EC reference NO C/2020/09/09 (virtual). All tenets of the Declaration of Helsinki were adhered to. Written informed consent was obtained from the patient for inclusion in this study.

DISCUSSION

Our patient was successfully managed with a single dose of the intravitreal anti-VEGF injection for superior branch macular vein occlusion and secondary macular edema in the OD and had a history of COVID-19 vaccination less than 1 month earlier.

Retinal vein occlusion can occur owing to various causes. They include hypertension, hyperlipidaemia, diabetes, and hypercoagulable states [32, 33]. Rarer causes such as dengue fever [34], Factor V Leiden mutations [35], and systemic malignancies such as hepatocellular carcinoma with antecedent medications or stopping them can cause vein occlusions [36]. Our patient had no predisposing disease.

A wide range of thromboembolic events after COVD-19 vaccinations with adenovirus vector-based vaccines have been reported [37] and are associated with systemic inflammation and platelet and endothelial dysfunction [38, 39]. Some cases of blood clots in the brain prompted European countries to halt the Oxford-AstraZeneca vaccine, which has since been resumed after allaying fears [40]. In India, the Oxford AstraZeneca vaccine is marketed as COVISHIELD™ [41]. Women may have a preponderance to clotting along with thrombocytopenia, which may be autoimmune [42].

Summaries of spontaneous reports of suspected adverse drug reactions (ADRs) (Yellow Cards) to COVID-19 vaccines by the UK Medicines and Healthcare Products Regulatory Agency are frequently published. Similar data have been published in the European Economic Area EudraVigilance database [43]. Approximately 4814 Yellow Card reports per million doses of AstraZeneca (ChAdOx1 nCoV-19) with 23 fatal and 2890 per million doses of tozinameran (Pfizer/BioNTech) with 13 fatal cases have been reported. Reported cases of retinal vein occlusion and thrombosis in Europe increased from 0 to 168 with AstraZeneca, of which four cases were associated with thrombocytopenia and increased from 1 to 220 with tozinameran [43].

A study from the Montefiore Sickle Cell Center for Adults examined acute care usage for vaso-occlusive crises and the frequency and severity of side effects following COVID-19 vaccination among their patients [44]. As part of regular care, patients were asked if they had received the COVID-19 vaccination, and any side effects were noted. Electronic medical records were reviewed for the type of vaccine, dates received, episodes of vaso-occlusive crises within 7 days of administration, and side effects. The risk of average hospital utilization per week in 2019 was used as baseline. They found that less than one in 10 patients presented to the hospital within 1 week of vaccination, with a similar risk of hospital utilization in 1 week in 2019 [44].

Retinal vein occlusions have been reported in association with COVID-19 vaccines [24, 25, 45-48]. A systematic review of 49 studies of ocular vascular events involved 130 patients. The most common event was venous occlusion (54.3%), followed by the first dose (46.2%), and within the first 5 days after vaccination (46.2%). Pfizer and AstraZeneca vaccines were the most common causes of vascular events (81.6%), which mostly occurred unilaterally (73.8%). The most common treatment was intravitreal anti-VEGF administered

to 39 (30.4%) patients, with documented improvement or persistence in the final best-corrected visual acuity in 91.3% of patients [45]. Similarly, Girbardt et al. reported six cases of retinal vascular events shortly after receiving COVID-19 vaccines: AstraZeneca, Pfizer-BioNTech, and Moderna mRNA vaccines. Two patients with retinal vascular occlusions, one with venous stasis retinopathy, one with NA-AION, one with a singular parapapillary cotton-wool spot, and one with bilateral acute macular neuroretinopathy were managed individually [46].

Sonawane et al. [24] reported unilateral central retinal vein occlusion (CRVO) with cystoid macular edema in a 50-year-old man with diabetes 4 days after receiving the second dose of the COVISHIELD™ vaccine. The other eye had mild nonproliferative diabetic retinopathy. This patient had uncontrolled diabetes with a glycated hemoglobin of 13.2% and a deranged renal profile, which could be a possible independent risk factor. The second patient was a 43-year-old woman who developed impending CRVO with no cystoid macular edema 3 days after receiving the second dose of the COVISHIELD™ vaccine who managed with a closed follow-up [24].

Another study reported retinal venous occlusion following the third dose of the AstraZeneca/COVISHIELD™ vaccine [25]. He received the third dose of the vaccine 2 months after the second dose and developed blurring of vision 25 days after the third dose. However, the laboratory investigations were inconclusive. He was managed with pulse corticosteroids and tapered doses of oral corticosteroids without intravitreal injections [25]. Similar to these reports [24, 25] our patient had a history of receiving the COVISHIELD™ vaccine and her BCDVA improved to 20 / 20 in the OD after a single dose of intraviral Avastin™.

CRVO after an mRNA-based COVID-19 vaccine has also been reported [47, 48]. A 50-year-old healthy, non-obese, non-smoking man developed CRVO immediately after receiving the second dose of an mRNA-based vaccine. Hematological workup and D-dimer levels were within normal limits. The patient was started on low-dose acetylsalicylic acid (100 mg / day), administered with multiple aflibercept intravitreal injections, and experienced a rapid decrease in macular edema with recovery [47]. A 52-year-old man developed CRVO 15 days after receiving the first dose of the COVID-19 vaccine. Systemic work-up was negative, and the authors concluded that this patient had no previous risk factors; however, a positive response to intravitreal steroids, antiangiogenics, and systemic anticoagulation may suggest a correlation between the COVID-19 vaccine and the event [48]. Likewise, our patient had no known systemic history, including COVID-19 infection and her systemic work-up was negative for any predisposing disease.

Our case belongs to the category of possible adverse drug reactions (total score, 1 – 4) according to the Naranjo Algorithm-ADR Probability Scale [49]. This is similar to other case reports in which a myriad of retinal vascular insults had been noted earlier. Since this is a case report, it is limited by the absence of strong evidence to prove this causal relationship between macular branch retinal vein occlusion and the specific brand of COVID-19 vaccination. The incidence of retinal vascular occlusions in the preceding years and those following COVID-19 or its vaccination would provide clues as to whether or not there was any role of the virus, its antigen, or vaccination in causation.

CONCLUSIONS

This case report highlights branch retinal vein occlusion with macular edema in a healthy woman following COVID-19 vaccination. It did not attribute the causes or effects of vaccination or retinal events. The IL-6 level was elevated, and the remaining blood test results were within normal limits. The rheumatologist did not suggest any further treatment, as the patient had no systemic disease. Thrombophilia screening in this patient, including protein C, protein S, anti-thrombin, and Leiden V mutations, would have added value to this report.

ETHICAL DECLARATIONS

Ethical approval: The study protocol was approved by the Narayana Nethralaya Ethics Committee, Vide approval number EC reference NO C/2020/09/09 (virtual). All tenets of the Declaration of Helsinki were adhered to. Written informed consent was obtained from the patient for inclusion in this study.
Conflict of interests: None

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