

Retinal venous occlusion following COVID-19 vaccination: Report of a case after third dose and review of the literature

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A 28-year-old, healthy male presented with blurring of vision in the right eye following third dose of the AstraZeneca/COVISHIELD vaccine. Further examination revealed ischemic central retinal vein occlusion, and subsequent laboratory investigations were inconclusive for his eye disease. He responded to pulse corticosteroid and tapering doses of oral corticosteroids without requiring any intra-vitreous injection. Twelve articles were identified with the help of a PubMed literature search, and a short review of these patients was performed. Retinal vein occlusion can occur because of inflammation-induced thrombosis after coronavirus disease 2019 vaccination and may respond to anti-inflammatory therapy.

Key words: Anti-inflammatory therapy, COVID-19, COVID-19 vaccine, retinal vein occlusion

Several vaccines have been developed to alleviate the morbidity or mortality associated with the coronavirus disease 2019 (COVID-19). These vaccines have been proved to be a boon for humankind, and in the past 1 year, more than 10.7 billion doses have been administered across 184 countries. However, there are reports of mild systemic adverse reactions in some patients, including a few isolated cases of ocular inflammatory events following COVID-19 vaccination. Re-activation of various uveitic entities and new onset of various uveitic entities were proclaimed to be related to COVID-19 vaccination in some patients. On the other hand, a few potentially life-threatening thrombotic episodes have been reported in patients receiving COVID-19 vaccines, especially AstraZeneca, and a similar phenomenon has been observed in the eyes as well.^[1] There

has been an increase in the report of retinal venous occlusion (RVO) following vaccination for COVID-19 in the past 1 year.^[2-8] Many such associations could be anecdotal, but one should not ignore the cause-and-effect hypothesis associated with these cases.^[1] We report a case of central retinal vein occlusion (CRVO) and reviewed the literature on RVO following COVID-19 vaccination.

Case Report

A 28-year-old, apparently healthy male presented to our clinic with a history of sudden onset painless loss of vision in the right eye. He completed two doses of the AstraZeneca vaccine (the SII/COVISHIELD and AstraZeneca/AZD1222 vaccines) in Oman and took the third dose of the AstraZeneca vaccine in India. The gap between the second and third doses of vaccine was 2 months. He developed blurring of vision after 25 days of the third dose of vaccination.

On examination, Snellen visual acuity was 2/60 in the right eye and 6/6 in the left eye. Slit-lamp examination showed a quiet anterior chamber, occasional cells in the anterior vitreous, and a clear lens in the right eye. His pupils were reactive and did not show any relative afferent papillary defect. Fundus examination of the right eye showed a swollen disc, tortuous and dilated retinal vessels, flame-shaped and dot blot retinal hemorrhages, and extensive cotton wool spots scattered around the posterior pole [Fig. 1a]. Slit-lamp examination and fundus examination of the left eye were unremarkable. Fundus fluorescein angiography (FFA) of the right eye showed hypofluorescence with delay in venous filling (arterio-venous transit time 42 seconds) in the early phase of the angiogram and blocked fluorescence corresponding to the areas of hemorrhages [Fig. 2]. Swept-source optical coherence tomography (SS-OCT) of the right eye revealed macular edema (ME) with sub-retinal fluid with a foveal thickness of 823 microns [Fig. 3a]. He was extensively investigated to rule out other causes, and his complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, blood urea nitrogen, creatinine, angiotensin-converting enzyme, lysozyme, prothrombin time, partial thromboplastin time, D-dimer, serum homocysteine, and fibrinogen levels were within normal limits. The results of the work-up for hyper-coagulability, HLA B-51 anti-dsDNA, anti-nuclear antibodies, and rheumatoid factor were in the normal range. The results from a focused work-up for infectious etiologies, such as Venereal Disease Research Laboratory, treponemal antibodies, Mantoux test, QuantiFERON gold, and human immunodeficiency virus antibodies, were unrevealing. His carotid Doppler was within normal limits, and opinions

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Figure 1: Fundus photographs of the right eye (a) At presentation, (b) After pulse corticosteroid (3 days) therapy, and (c) after a month

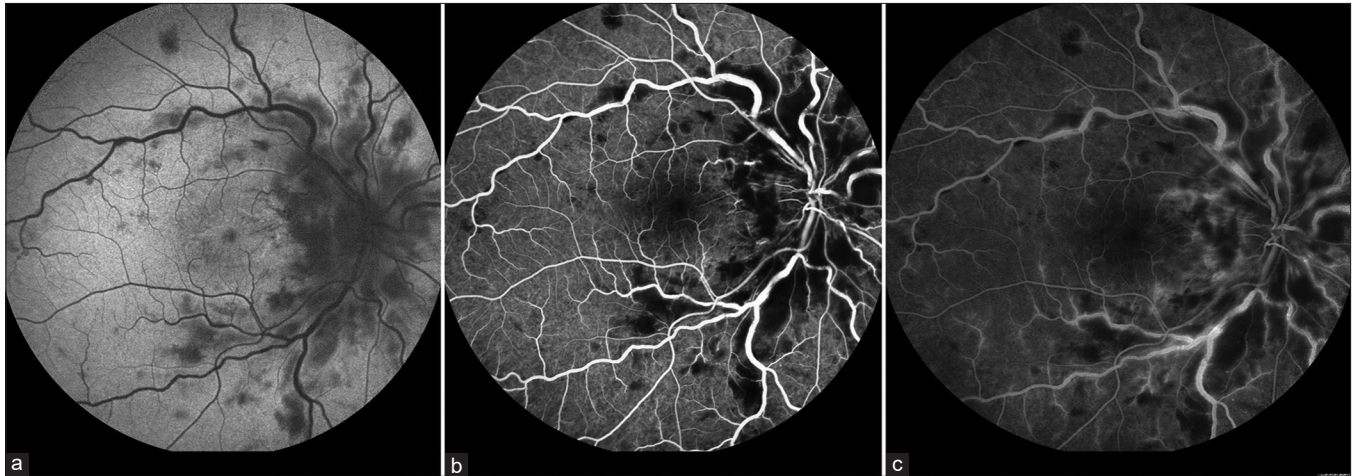


Figure 2: Fundus fluorescein angiography (FFA) of the right eye showing hypofluorescence with delay in venous filling in the early phase of the angiogram and blocked fluorescence corresponding to areas of hemorrhages

from cardiologist and rheumatologist revealed no evidence of any systemic disease. He was administered pulse corticosteroid (intravenous methylprednisolone, IVMP) 1 gram for 3 days. After three doses of the pulse corticosteroid, his visual acuity improved to 6/45, and we observed a considerable reduction in hemorrhages, cotton-wool spots, and disc edema [Fig. 1b]. SS-OCT of the right eye showed a reduction of macular edema, and foveal thickness reduced to 257 microns [Fig. 3b]. He was started on oral corticosteroid 1 gm/kg/body weight in tapering doses and advised to come after a month.

After 1 month, the visual acuity in his right eye had improved to 6/9. Slit-lamp examination of both eyes was unremarkable. Fundus examination of the right eye revealed the resolution of most of the hemorrhages and cotton-wool spots and a few resolving hard exudates perifoveally with complete resolution of the disc edema [Fig. 1c]. OCT confirmed the resolution of macular edema; the foveal thickness had reduced to 166 microns [Fig. 3c].

Discussion

We reported a case of CRVO following third dose of AstraZeneca vaccine. RVO after the third dose of COVID-19 vaccination has not been reported before. However, there are several reports of RVO following AstraZeneca vaccinations.^[9] The AstraZeneca vaccine is an adenovirus vector vaccine, where S protein has not been modified to stabilize, and the expression of S protein in the circulation after vaccination is believed to

induce a pro-inflammatory or pro-coagulant response.^[1] We believe that our patient showed an inflammatory response following vaccination and responded well to anti-inflammatory treatment. Our patient was a young man without any predisposing comorbidities that can be attributed to the development of RVO, and all the laboratory parameters to rule out other inflammatory and infectious etiologies were normal. Intra-vitreous injection of the anti-vascular endothelial growth factor (VEGF) or steroids was deferred in view of good reduction of cystoid macular edema (CME) with the pulse corticosteroid and the concern regarding sub-foveal migration of hard exudates with sudden reduction of CME.

Using the terminologies 'Retinal Vein Occlusions' and 'Covid-19 Vaccine', we found 12 articles that reported 19 patients with venous occlusions. Table 1 highlights the details of these 20 patients, including our patient. Among these 20 patients, two patients had a previous history of RVO.^[10] Three patients developed combined central retinal artery occlusion and CRVO, and hemispheric or hemi-retinal RVO was reported in two patients. CRVO was reported in five patients, including the index case, and six patients developed branch retinal vein occlusion (BRVO). Impending CRVO and venous stasis retinopathy were reported in one patient each. Thirteen patients had received messenger RNA (mRNA) vaccines from Pfizer-BioNTech, and one patient took the mRNA vaccine (Moderna). Six patients, including ours, developed RVO following Oxford-AstraZeneca vaccinations. The interval between

Table 1: Review of the literature of patients who developed retinal vein occlusion following COVID-19 Vaccinations

Author	Age/ Sex	Name of the Vaccine, Dose No	Time interval between the vaccine and onset of symptoms	Venous Occlusion	Management
Bialasiewicz <i>et al.</i> ^[2]	50 y/M	Pfizer*, Second dose	Immediately	Hemorrhagic CRVO with ischemic areas in the left eye	Aspirin 100 mg/day, IVit afibercept monthly
Pur <i>et al.</i> ^[3]	34 y/M	Pfizer*, First dose	2 days	Superior nasal BRVO of the right eye	Conservative
Endo <i>et al.</i> ^[4]	52 y/M	Pfizer*, First dose	15 days	Non-ischemic CRVO of the left eye	IVit dexamethasone 0.4 mg/0.1 ml, IVit Bevacizumab, Oral apixaban
Lee <i>et al.</i> ^[5]	34 y/M	Pfizer*, Second dose	10-12 days	Combined CRAO and CRVO of the left eye	Hyperbaric oxygen, IVit afibercept, Cocktail of Dexamethasone, Bromfenac, and Acetazolamide, Oral steroid, LMWH, Apixaban, Pulse steroid, Pentoxifylline
Tanaka <i>et al.</i> ^[10]	71 y/F	Pfizer*, Second dose	1 day	Superior temporal BRVO with ME (old patient of inferior temporal BRVO) in the left eye	IVit aflibercept
	74/M	Pfizer*, First dose	1 day	Temporal superior BRVO with ME in the right eye (recurrence)	Two doses of IVit ranibizumab
Sacconi <i>et al.</i> ^[12]	74/M	Moderna**, Second dose	2 days	Hemispheric retinal vein occlusion	oral anti-coagulation therapy.
Girbardt <i>et al.</i> ^[7]	81/F	Pfizer*, Second dose	12 days	Combined CRAO and CRVO	IVit anti-VEGF
	40/M	Pfizer*, First dose	5 days	Venous stasis retinopathy	NA
Peters <i>et al.</i> ^[6]	71/M	AstraZeneca*, First dose	48 hours	Inferior macula BRVO with ME	IVit Bevacizumab monthly
	58/M	AstraZeneca*, First dose	72 hours	Hemi-retinal RVO with ME	IVit Bevacizumab monthly
	73/F	AstraZeneca*, First dose	72 hours	Infero-temporal BRVO with ME	IVit Aflibercept
	47/F	Pfizer*, First dose	5 Days	Supero-temporal BRVO with ME	IVit Bevacizumab monthly
	36/M	Pfizer*, second dose	24-72 hours	Non-ischemic CRVO with ME	IVit Aflibercept
Sugihara <i>et al.</i> ^[11]	38/M	Pfizer*, Second dose	15 Days	BRVO with ME	IVit Aflibercept
Sonawane <i>et al.</i> ^[9]	50/M	AstraZeneca*, Second dose	4 Days	CRVO with ME	IVit anti-VEGF
	43/F	AstraZeneca*, Second dose	3 days	Impending CRVO	Conservative
Shah <i>et al.</i> ^[8]	27/F	Pfizer*, First dose	10 days	CRVO	IVit Ranibizumab
Ikegami <i>et al.</i> ^[13]	54/F	Pfizer*, Second dose	8 Days	Combined CRAO + CRVO	NA
The present case	28/M	AstraZeneca*, Third dose	25 days	Ischemic CRVO with ME	Pulse corticosteroid, followed by Oral corticosteroid

[*The Pfizer/BioNTech Comirnaty vaccine; *The SII/COVISHIELD and AstraZeneca/AZD1222 vaccine; **The Moderna COVID-19 vaccine (mRNA 1273)],
CRVO - Central retinal vein occlusion, BRVO - Branch retinal vein occlusion, CRAO - Central retinal artery occlusion, ME - Maculae edema, IVit - Intravitreal
injection, LMWH - Low-molecular weight heparin, VEGF - Vascular endothelial growth factor

vaccination and symptom onset remained highly variable in these patients. Only one patient developed ocular symptoms immediately after the vaccination.^[2] The predominant complaint in these patients was blurring or diminution of vision, and some patients complained of associated photopsia,^[3]

central scotoma,^[7] headache, and tinnitus.^[8] A few patients developed milder symptoms after vaccinations, which they ignored initially until they suffered a gross diminution of vision.^[3,11] Similarly, a few patients initially presented with a relatively milder clinical picture and later developed RVO.

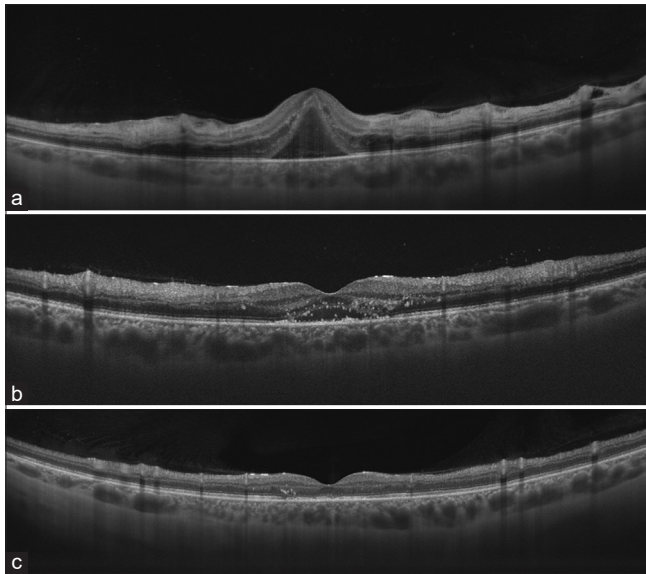


Figure 3: SS-OCT of the right eye (a) At presentation showing macular edema with sub-retinal fluid with a foveal thickness of 823 microns, (b) After 3 days of the pulse corticosteroid (intravenous methylprednisolone 1 gram daily) showing reduction of macular edema with a foveal thickness of 257 microns, and (c) At 1 month follow-up with a foveal thickness of 166 microns

A 34-year-old male developed blurring of vision 10–12 days after the second dose of the Pfizer-BioNTech vaccine and was diagnosed as early or impending vein occlusion.^[5] He was started on low-dose aspirin, but the next day, his vision reduced to counting fingers because of combined occlusion.

Seven patients were young and below the age of 40 years. The majority of these patients were healthy and without any systemic comorbidities. A 27-year-old female with a history of idiopathic intra-cranial hypertension developed CRVO 10 days after the first dose of the Pfizer-BioNTech vaccine.^[8] There was further deterioration of her visual acuity when she took the second dose of the vaccine.^[8] Worsening of pre-existing RVO with vaccination has been reported after vaccinations.^[10] Among the patients >40 years, two patients had a history of hypertension, one had diabetes with features of non-proliferative diabetic retinopathy in the eyes, and another patient was a breast cancer survivor with a history of heart disease. Most of these patients were treated with intra-vitreous anti-VEGF injection, and many of them required more than one injection.

Conclusion

To our knowledge, this is the first report of RVO following the third dose of the COVID-19 vaccine, managed effectively with systemic steroid and without intravitreal anti-VEGF agent. This report also highlighted the role of anti-inflammatory therapy in managing RVO following vaccinations, thereby supporting

the hypothesis of inflammation-induced thrombosis in such cases. In addition, the significant response to pulse corticosteroid therapy and the subsequent oral corticosteroid in our case suggests that prompt diagnosis and aggressive anti-inflammatory therapy can be sight-saving in such a case of adverse reaction to COVID-19 vaccination.

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Conflicts of interest

There are no conflicts of interest.

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