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

Parthopratim Dutta Majumder, Vadivelu Jaya Prakash

A 28-year-old, healthy male presented with blurring of vision in the right eye following third dose of the AstraZeneca/COVISHEILD 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-vitreal 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.[3] There has been an increase in the report of retinal venous occlusion (RVO) following vaccination for COVID-19 in the past 1 year. Many such associations could be anecdotal, but one should not ignore the cause-and-effect hypothesis associated with these cases.[4] 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/COVISHEILD 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 bot 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

Medical and Vision Research Foundations, Sankara Nethralaya, Sankara Nethralaya, Chennai, Tamil Nadu, 'Department of Vitreoretina, Medical and Vision Research Foundations, Sankara Nethralaya, Sankara Nethralaya, Chennai, Tamil Nadu, India

Correspondence to: Dr. Parthopratim Dutta Majumder, Department of Uvea, Sankara Nethralaya, 18, College Road, Nungambakkam, Chennai, Tamil Nadu - 600 006, India. E-mail: drparthopratim@gmail.com

Received: 05-Mar-2022  Revision: 30-Mar-2022
Accepted: 12-Apr-2022  Published: 31-May-2022

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

Cite this article as: Dutta Majumder P, Prakash VJ. Retinal venous occlusion following COVID-19 vaccination: Report of a case after third dose and review of the literature. Indian J Ophthalmol 2022;70:2191-4.
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-vitreal 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. 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

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. 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. 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-vitreal 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.
vaccination and symptom onset remained highly variable in these patients. Only one patient developed ocular symptoms immediately after the vaccination. The predominant complaint in these patients was blurring or diminution of vision, and some patients complained of associated photopsia, central scotoma, headache, and tinnitus. A few patients developed milder symptoms after vaccinations, which they ignored initially until they suffered a gross diminution of vision. Similarly, a few patients initially presented with a relatively milder clinical picture and later developed RVO.

### 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 et al. | 50 y/M   | Pfizer*, Second dose        | Immediately                                              | Hemorrhagic CRVO with ischemic areas in the left eye          | Aspirin 100 mg/day, IVit aflibercept monthly                              |
| Pur et al. [3]  | 34 y/M   | Pfizer*, First dose         | 2 days                                                   | Superior nasal BRVO of the right eye                          | Conservative                                                             |
| Endo et al. [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 et al. [5]  | 34 y/M   | Pfizer*, Second dose        | 10-12 days                                               | Combined CRAO and CRVO of the left eye                        | Hyperbaric oxygen, IVit aflibercept, Cocktail of Dexamethasone, Bromfenac, Oral steroid, LMWH, Apixaban, Pulse steroid, Pentoxifylline |
| Tanaka et al. [10] | 71 y/F   | Pfizer*, Second dose        | 1 day                                                    | Superior temporal BRVO with ME (old patient of inferior temporal BRVO) in the left eye | Two doses of IVit ranibizumab                                               |
| 74/M            | Pfizer*, First dose         | 1 day                                                    | Temporal superior BRVO with ME in the right eye (recurrence) | Two doses of IVit ranibizumab                                   |
| Sacconi et al. [12] | 74/M     | Moderna**, Second dose      | 2 days                                                   | Hemispheric retinal vein occlusion                            | Oral anti-coagulation therapy.                                             |
| Girhardt et al. [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 et al. [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 et al. [11]          | 38/M     | Pfizer*, Second dose        | 15 Days                                                  | BRVO with ME                                                   | IVit Aflibercept                                                          |
| Soniwane et al. [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 et al. [8]  | 27/F     | Pfizer*, First dose         | 10 days                                                  | CRVO                                                         | IVit Ranibizumab                                                          |
| 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
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. 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. There was further deterioration of her visual acuity when she took the second dose of the vaccine. Worsening of pre-existing RVO with vaccination has been reported after vaccinations. 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-vitreal 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.

References

1. Jampol LM, Tauscher R, Schwarz HP. COVID-19, COVID-19 vaccinations, and subsequent abnormalities in the retina: Causation or coincidence? JAMA Ophthalmol 2021;139:1135-6.
2. Bialasiewicz AA, Farah-Diab MS, Mekbarki HT. Central retinal vein occlusion occurring immediately after 2nd dose of mRNA SARS-CoV-2 vaccine. Int Ophthalmol 2021;41:3889-92.
3. Pur DR, Catherine Danielle Bursztyn LL, Iordanous Y. Branch retinal vein occlusion in a healthy young man following mRNA COVID-19 vaccination. Am J Ophthalmol Case Rep 2022;26:101445.
4. Endo B, Bahamon S, Martinez-Pulgarin DF. Central retinal vein occlusion after mRNA SARS-CoV-2 vaccination: A case report. Indian J Ophthalmol 2021;69:2865-6.
5. Lee S, Sankhala KK, Bose S, Gallemore RP. Combined central retinal artery and vein occlusion with ischemic optic neuropathy after COVID-19 vaccination. Int Med Case Rep J 2022;15:7-14.
6. Peters MC, Cheng SS, Sharma A, Moloney TP. Retinal vein occlusion following COVID-19 vaccination. Clin Exp Ophthalmol 2022. doi: 10.1111/ceo.14056.
7. Girbardt C, Busch C, Al-Sheikh M, Gunzinger JM, Invernizzi A, Xhepa A, et al. Retinal vascular events after mRNA and adenoviral-vectorized COVID-19 vaccines-A case series. Vaccines (Basel) 2021;9:1349.
8. Shah PP, Gelnick S, Jonisch J, Verma R. Central retinal vein occlusion following BNT162b2 (Pfizer-BioNTech) COVID-19 messenger RNA vaccine. Retin Cases Brief Rep 2021. doi: 10.1097/ICB.0000000000001214.
9. Sonawane NJ, Yadav D, Kota AR, Singh HV. Central retinal vein occlusion post-COVID-19 vaccination. Indian J Ophthalmol 2022;70:308-9.
10. Tanaka H, Nagasato D, Nakakura S, Tanabe H, Nagasawa T, Wakuda H, et al. Exacerbation of branch retinal vein occlusion post SARS-CoV-2 vaccination: Case reports. Medicine (Baltimore) 2021;100:e28236.
11. Sugihara K, Kono M, Tanito M. Branch retinal vein occlusion after messenger RNA-Based COVID-19 vaccine. Case Rep Ophthalmol 2022;13:28-32.
12. Sacconi R, Simona F, Forte P, Querques G. Retinal vein occlusion following two doses of mRNA-1227 (Moderna) immunization for SARS-CoV-2: A case report. Ophthalmol Ther 2022;11:453-8.
13. Ikegami Y, Numaga J, Okano N, Fukuda S, Yamamoto H, Terada Y. Combined central retinal artery and vein occlusion shortly after mRNA-SARS-CoV-2 vaccination. QJM Int J Med 2022;114:884-5.