Central retinal vein occlusion post-COVID-19 vaccination

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Coronavirus disease 2019 (COVID-19) is known to cause thromboembolic episodes apart from acute respiratory distress syndrome (ARDS). With large vaccine drives all across the world, there are a few case reports on post-vaccine thrombotic events seen with the AZD1222, ChAdO × 1 vaccine. Here, we present two cases of central retinal vein occlusion presenting immediately after receiving the second dose of the Covishield vaccine. Although the causal relationship cannot be drawn, the ophthalmologist should be aware of this adverse reaction.

Key words: COVID-19, Covishield, CRVO

Coronavirus disease 2019 (COVID-19) has caused a widespread impact on health, including mortality, not only among older adults but also among those with pre-existing health conditions. With its mutating strains, it has caused more distress in the second wave affecting the young population including children. Mass vaccination drives could play an important role in achieving herd immunity, preventing severe diseases, and controlling the ongoing health crisis. We report two cases of central retinal vein occlusion developed post second dose of AZD1222 (Covishield) vaccination.

Case Reports

Case 1

A 50-year-old diabetic male came with right eye diminution of vision 4 days after receiving the second dose of vaccination (Covishield, AZD1222, ChAdOX 1). The best-corrected visual acuity was OD 6/60 and OS 6/6. The anterior segment examination and intraocular pressure were within normal limits in both eyes. The fundus examination revealed disk edema, dilated and tortuous veins, diffuse retinal hemorrhages with macular edema, suggestive of central retinal vein occlusion [Fig. 1a]. The left eye fundus showed mild non-proliferative diabetic retinopathy changes. The optical coherence tomography showed cystoid macular edema with a central foveal thickness of 571 um in the right eye [Fig. 1b]. The lab reports revealed uncontrolled diabetes with HbA1C of 13.2 with deranged renal profile (blood urea: 80 mg/dL, creatinine: 1.9 mg/dL), normal C-reactive protein (CRP) 1.9 mg/L (*n*: <5), d-dimer 233 ng/mL, (*n*: <500), PT/ activated partial thromboplastin time (APTT), differential leukocyte count (N60, L38, E2), complete blood count (CBC), basic coagulation profile, lipid profile, cardiac echography, and negative reverse transcriptase polymerase chain reaction (RT-PCR) for COVID-19. He was given intravitreal injection anti-vascular endothelial growth factor (VEGF) for cystoid macular edema.

Case 2

A 43-year-old female with unremarkable systemic history presented with right eye sudden-onset diminution of vision 3 days after receiving the second dose of vaccination (Covishield, AZD1222, ChAdOX 1). Her best-corrected visual acuity was OD 5/60 and OS 6/12. The anterior segment examination showed an immature senile cataract in both eyes and dense central posterior subcapsular in right eye (OD). The intraocular pressure was within normal limits in both eyes. The fundus examination of the right eye showed hyperemic and edematous disk, tortuous veins, and intraretinal hemorrhages in all quadrants suggestive of impending central retinal vein occlusion [Fig. 1c and d]. The left eye fundus was unremarkable. The blood investigations revealed raised erythrocyte sedimentation rate (ESR): 49, CRP 14.6 (*n*: <5), rheumatoid factor (RF) 11 (*n*: <8) and d-dimer 6077.4 ng/mL, (*n*: <500). The differential leukocyte count was N65, L23, E12, HBA1C 4.6, with normal CBC, peripheral smear, serum angiotensin converting enzyme (ACE), bleeding and clotting time, renal function tests, lipid profile, PT/APTT. RT-PCR of oral/nasal swab for COVID-19 was negative. The optical coherence tomography (OCT) revealed no cystoid macular edema (CME), and fundus fluorescein angiography (FFA) could not be done as the patient was not willing for an invasive procedure, so she was closely followed up.

Discussion

COVID-19 has led to a global-scale pandemic creating an unprecedented burden on human health and public health processes. Although the acute respiratory distress syndrome (ARDS) represents the hallmark of COVID-19-associated clinical manifestations, thromboembolic events are catastrophic in patients with severe COVID-19 and have been linked to cause morbidity and mortality in patients infected with SARS-CoV-2, owing to hyperinflammation and pre-existing cardiovascular disease.

The coronaviruses are enveloped; positive sense single stranded ribonucleic acid (RNA) viruses with a glycoprotein spike, mediating receptor binding and cell entry during

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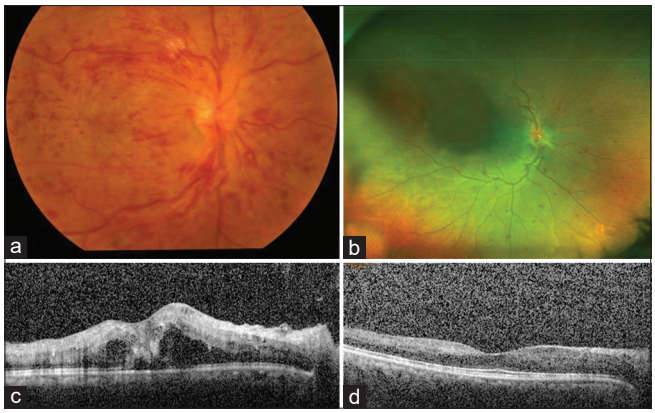

Figure 1: (a) Fundus photo showing disk edema, tortuous veins, and retinal hemorrhages in case 1, (b) OCT showing cystoid macular edema with subretinal fluid in case 1, (c) Fundus photo showing disk edema, tortuous veins, and retinal hemorrhages in case 2, (d) OCT showing hyperreflectivity of the inner retinal layers in case 2

infection. The roles of the spike protein in receptor binding and membrane fusion make it an attractive vaccine antigen.[1] With many vaccines under trial, India is running the largest vaccination campaign with mainly Covishield (AZD1222) and Covaxin (BBV152) in circulation. The ChAdOx1 nCoV-19 vaccine (AZD1222) was developed at Oxford University and consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the full-length structural surface glycoprotein (spike protein) of SARS-CoV-2, with a tissue plasminogen activator leader sequence.[1]

Lately, there are reports of vascular thromboembolic catastrophes post-vaccination, especially with ChAdOX 1.

A Scottish national population-based analysis among 2.53 million people who received their first dose of SARS-CoV-2 vaccines revealed a potential association between receiving a first-dose ChAdOx1 vaccination and occurrence of immune thrombocytopenic purpura (ITP), arterial thromboembolic, and hemorrhagic events with an incidence of 1.13 cases per 100,000 vaccinations. Also, the adverse events with ChAdOX 1 were more after the first dose of ChAdOX 1 compared to BNT162b2 (Pfizer).[2]

Another study involving people aged 18–65 years who received the ChAdOx1 vaccine in Denmark and Norway observed increased rates of venous thromboembolic events, including cerebral venous thrombosis (standardized morbidity ratio of 1.97 and 95% CI 1.50–2.54) and intracerebral hemorrhage (standardized morbidity ratio of 2.33 and 95% CI 1.01–4.59).[3] There are a few reports of thrombotic events after Covishield in India too.[4,5]

Greinacher *et al*.[6] suggested that the interactions between the vaccine and platelets or between the vaccine and PF4 (platelet factor 4) could play a role in pathogenesis. The proposed mechanisms include the formation of autoantibodies against PF4, antibodies induced by the free deoxyribonucleic acid (DNA) in the vaccine that cross-reacts with PF4, platelets, and adenovirus binds to the platelets causing platelet activation. Since vaccination of millions of people will be complicated by a background of thrombotic events unrelated to the vaccination, they suggested a PF4-dependent enzyme-linked immunoassay (ELISA) or a PF4-enhanced platelet-activation assay to confirm the diagnosis of vaccine-induced immune thrombotic thrombocytopenia through this novel mechanism of post-vaccine formation of platelet-activating antibodies against PF4 and also naming this novel entity vaccine-induced immune thrombotic thrombocytopenia (VITT) to avoid confusion with the heparin-induced thrombocytopenia.

Apart from the thrombotic events, a few cases of neurological adverse effects have also been reported post-vaccination. Román *et al*.[7] reported the occurrence of three acute transverse myelitis among 11,636 participants in the AZD1222 vaccine.

To the best of our knowledge, there are no previous reports of retinal venous occlusion following the AZD1222 vaccination. However, considering the rarity of such events, the potential risks of such events should be interpreted in light of the proven beneficial effects of the vaccine.

Conclusion

Herein, we report two cases of central retinal vein occlusion (CRVO) following the Covishield vaccination with the purpose of generating awareness among the ophthalmologists regarding the rare adverse event and unfurling the possible pathophysiology behind it. At this juncture, it would be premature to draw a causal relationship between the COVID-19 vaccine and CRVO. These reports should never discourage the vaccine rollout, but monitoring of the evolving data should be carried on by manufacturers and independent authorities before coming to a definitive conclusion.

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Conflicts of interest

There are no conflicts of interest.

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