Retinal hemorrhage of late post COVID-19 and post vaccine related pathogenic mechanisms: A new challenge for ophthalmologist in COVID era

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Abstract

COVID-19 infection results in extensive organ dysfunction. Thrombotic problems linked to COVID–19 disease is common and can affect the retina. We will report a case of retina hemorrhage with possibility of linkage between COVID-19 infection or immunization to determine whether these abnormalities are causal or coincidental.

Introduction:

COVID-19 is a highly contagious that spreads from person to person primarily by affected person’s respiratory droplets and contamination objects or bodily limbs via the nostrils, mouth, and ocular route (1, 2). COVID-19 may affects multiple organ system (cardiovascular diseases, respiratory failure, renal failure, liver damage, ocular adverse effect) but it is difficult to monitor all the system (3). The nasolacrimal system allows pulmonary virus spreads through the eye. As a result, virus-infected nanoparticles interacted with the ocular surface and can then infiltrate the lung tissue through the nasolacrimal channel. The angiotensin converting enzyme 2 (ACE2) binding site is present in the retina as a facilitator for virus entry into human host which may leads to retinal involvement by SARS-CoV-2 (4-6). Conjunctivitis, conjunctival erythema, chemosis, epiphora, cotton wool spots (CWS), and microhemorrhages have been confirmed on fundus assessment. Hyperreflective abnormalities at the point of the ganglion cell and internal plexiform layer at the papillomacular region can be detected through spectral-domain optical coherence tomography (SD-OCT)(7, 8). In Germany, SARS-CoV-2 virus RNA was found in the retinas where three of the 14 number COVID-19 patients who died (4) and another study conducted in Italy found additional papillary focal retinal hemorrhage in the post-COVID-19 group(9). Severe capillary lesions such as cotton wool spots, retinal hemorrhages, sectoral retinal infarction have subsequently been reported in admitted, severe COVID-19 patients which suggests a new SARS-CoV-2 association (10). The generation of cytokines, which are responsible for the activation of a procoagulant prothrombotic response, is causing concern about these retinal microvascular observations, which could be a symptom of COVID-19’s intravascular coagulopathies and endothelial damage (11). As COVID-19 vaccinations become more common, the might be a increases concern of ophthalmic consequence due to vaccination (12), however a microvascular anomaly in the deep capillary plexus of the retina is suspected, the pathogenesis is unexplained (13, 14). In one case series, eye adverse events take place immediately after getting an inactivated COVID-19 vaccination were observed (12) and according to an interim analysis of four randomized controlled studies based on vaccine safety data, ocular consequences are uncommon with
Live-virus vaccinations (AstraZeneca vaccine) (15, 16). In this report, we present a patient with secondary retinal hemorrhage who had recovered back from COVID-19 and had also received COVID-19 vaccination.

Case Report:
A male patient aged 41-years felt a mild cough followed by fever and also anosmia on October 14, 2020. He had previous contact with a COVID-19 family member with whom he was staying, but no prior history of traveling outside of the country prior to this occurrence. As his family history was positive, he went for RT-PCR testing for SARS-CoV-2 and became positive as COVID-19 on 16th October, 2020 and was in isolation at home. On the next day, 17th October, he had fever with dry cough constantly, sore throat followed by fatigue. His temperature was 104 °F, blood pressure 130/70 mmHg, pulse rate 98 bpm (regular) and oxygen saturation on pulse-oximetry was 98-99 % without oxygen. Routine blood tests or chest X-ray was not done on that time. The patient started medications from October 17, 2020 (Table 1). On 22th October 2020, physical examination indicated normal vital signs. Throughout this time, he had a mild covid symptom and was self-medicating at home, with no need for hospitalization. On 10th November 2020, the patient went for COVID-19 test that was negative and was completely stable without any complication. After the symptom free from Covid-19, December 2020, he was diagnosed as systemic hypertensive and started medication (Table 1) as recently six months diagnosed as hypertension without no other history of any significant co-morbidities. Later on, he gave his 1st dose of COVID-19 vaccine which was Live-virus vectored based vaccine (COVISHIELD vaccine-AstraZeneca) on 16 February 2021. He completed his 2nd dose of vaccine on 17 April 2021. From 1st dose of vaccine up to completing date of 2nd dose of vaccine he had no complication arises. Although the patient complaints of fatigue that last for 4 months after acute COVID-19. He had no history of diabetic and no history of Rheumatoid arthritis or no trauma of history on eye previously. He noticed 3-4 number floaters in his right eye on June 1, 2021, which changed or grew dramatically. Other complaints were light flashes, a curtain moving into and obstructing his vision, and diminished vision in his right eye and became red in colour on right eye. He had no complaints of watering of eye, headache, eye ache, eyelid swelling, any foreign body sensation. He had no other history of any trauma on eye or previous eye operations. On, 7th June, 2021, he went to ophthalmologist of the Ispahani Islamia Eye Institute and Hospital, Dhaka for this complication. Details of eye examination finding are given in (Table 2) and fundus of R/E: Total vitreous hemorrhage shows in figure 1 and other blood investigation (Table 1) was also done and on same day he had immediately underwent Yag Laser Hyalodotomy as outdoor base case. He was discharged on same day and advised with medication (Table 2). On, 19 June, 2021 and 26 June, 2021 two outdoor follow up done with medication (Table 2) as continue treatment. Then, on July 28, 2021, it appeared to be clearing in some stages, but it was still a nonrevolving vitreous haemorrhage. Following that, he was scheduled to undergo Pars plana vitrectomy (PPV) with endolaser and anti-vascular endothelial growth factor (anti-VEGF) medications by an ophthalmologist at the Ispahani Islamia Eye Institute and Hospital in Dhaka. On, 29 July, 2021 he went to india for further follow-up and visited Sankara Nethralaya eye hospital, Chennai, India and done Ultrasound biomicroscopy (UBM) on 31 July, 2021 (Figure 2) and found on the right eye, there was a retinal detachment as well as a complete posterior vitreous detachment, and the vitreous displayed a large number of low reflective dot mobile echoes. On, 3rd August 2021, he again consults with doctor and advise to do OPTOS Retinal Exam and examination revealed plenty of low reflective dot and clump echos on right eye (Table 3). He continues his eye drop medication. For further better management, he planned to go LV Prasad eye institute, Hydarabed on 11th August 2021. As recommended by an ophthalmologist, the operation was conducted properly and he was discharged from the hospital that day in a stable condition with medicine. Procedure done successfully and discharged from hospital in a stable condition on same day with medication. On follow-up, 16 August, 2021, eye examination, On right eye examination: eyelids edematous, conjunctiva chemosis, cornea clear (Table 3). During the whole period scenario, physician not found any significant cause of this retinal haemorrhage except may be complication of post COVID or vaccine related retinal complication. Last follow up in Bangladesh on 6 October 2021, VAR:6/6 and VAL:6/6.

In summary, this patient was diagnosed COVID-19 on 16 October, 2020 (RT-PCR positive) and nasopharyngeal swab for SARS-CoV-2 was negative on 10th November 2020. The patient took first dose of COVID-19
vaccine (Live-virus vectored based vaccine, COVISHIELD vaccine-AstraZeneca) on the 16th February 2021 and 2nd dose on 17th April 2021. Retinal hemorrhage was seen on 1st June, 2021 and underwent Yag Laser Hyalodotomy and medication in Dhaka on 7 June, 2021. Then he went to Chennai eye hospital, India and go through further investigation. Later on, again he admitted into the Hydarabed hospital on 12th August 2021 for right sided Pars plana vitrectomy (PPV) and later was discharged on same day. His blood pressure and random blood sugar levels were both normal at the time of ocular manifestation. During follow-up in Bangladesh on 6 October 2021, visual acuity 6/6, indicating that his eye clinical condition had improved. There was no further occurrence of hemorrhage after this follow-up.

Discussion:

According to our knowledge this might be first cases in Bangladesh presented with this rare condition of post-COVID-19 retinal hemorrhage. Though a straightforward clear correlation could not be established regarding study configuration, as male patient may develop ocular consequences that may have influenced retinal changes as a result of post-Covid consequences or 43 days after receiving a Live-virus vectored based COVID-19 vaccine (AstraZeneca vaccine). Theoretical pathophysiology of COVID-19 inactivation-related ocular inflammation is unknown. Respectively molecular mimicry and antigen-specific cellular and antibody-mediated immune system disorders have been suggested as possibilities (17-19). The discovery of COVID-19 viral RNA in the retina is significant. In addition, a new host cell entrance route involving the receptor CD147 has been identified (20), CD147 is present at moderate-to-high levels throughout all cell types of the human retina, particularly in retinal ganglion cells (GCs), in contrast to ACE2 (21). Furthermore, positive RT-PCR findings have been published in human retinal biopsies, implying that the viral proteins is invading retinal nerves specifically (4). Certain coronavirus variants can invade retinal cells in other vertebrate species both in situ and in retinal cultured cells (22) and in vivo following viral proteins were injected intravitreally(23) producing experimental coronavirus retinopathy(ECOR)(24, 25). Three out of 14, RB samples were positive for SARS-CoV-2 RdRp-gene, E-gene, and Orf nCoV-gene-specific sequences in the retina in one research in Germany (4). Most notably, retinal microangiopathy exhibited as cotton wool patches (diagnostic and therapeutic sign related with nerve fiber ischaemia) was seen in 6 out of 27 outpatients evaluated by retinal fundoscopic, B-scan OCT(Optical Coherence Tomography), and Optical Coherence Tomography Angiography angiography (OCT-A) at a mean of 43 days following COVID-19 disease onset in Spain (26). Retinal hemorrhages were identified in 9% of COVID-19 victims even during acute phase of infection, cotton wool patches in 7%, dilated veins in 28%, and twisted vessels in 13% in a study in Italy (27). With no complaints or indicators of intraocular inflammation, four patients out of 12 patients showed with mild cotton wool patches and microhemorrhages across the retinal apartment(7). In terms of our own experience, we had a similar case of retinal hemorrhage. There is no intraocular inflammation or discomfort in the eyes. In COVID-19 individuals, there are at minimum two basic ways that vascular injury can occur: The first is a prothrombotic state, similar to disseminated intravascular coagulation (DIC)(28) and secondly, due to spontaneous viral infection of the vascular endothelium and widespread endothelial dysfunction, a vasculitis-like reaction starts(29). Retinal hemorrhages that represent the outcomes in retinopathy related to blood dyscrasias may be a connection with SARS-CoV-2 in the perspective of a coagulopathy evoked by the pathogen in the utter lack of arterial hypertension, no symbols of diabetic retinopathy, and the total lack of other cardiovascular risk, as well as the improvement after the COVID-19 regimen, as well as betterment after the COVID-19 medical therapy. Retinal hemorrhages (subretinal, subhyaloid, or intraretinal), capillary tortuosity, and cotton balls patches are all ophthalmic symptoms of blood dyscrasia. Hype viscosity and prolonged arteriovenous passage time are assumed to be the reasons(30). Our case was a subhyaloid subtype of retinal hemorrhage. In, Abu Dhabi(12), Scleritis and episcleritis were detected in 4 of 9 instances, on average 5 days after the first dose of the vaccination. After compiling all of the data from our report and the other assessment research, we discovered that several clinical findings are in accordance across all of these patients, such as the nature of the retinal hemorrhage or abnormalities pertaining to the covid19 complication and vaccination, but our case was unique in that it was post covid retinal hemorrhage or late COVID-19 vaccine induced retinal hemorrhage. The baseline retina record from validated COVID-19 patients who had been immunized for COVID-19 and were later admitted for ocular
treatment of extreme and urgent condition was a major strength of our study. Patients with subhyaloid hemorrhage were more likely to show with systemic hypercoagulopathy and cytokine storm during retina evaluation. There are certain limitations to our research. First, our case only included young, healthy men, limiting the generalizability of our findings. Second, complications occur at different/long times and we don’t obtain a definitive answer, whether it’s for post COVID-19 or vaccine-related issues. Third, no supplemental hematological and biochemical analyses/studies, such as D-dimer and prothrombin time, bleeding time, clotting time would be suitable to alternative way of COVID-19 hyper-coagulopathy as a biological process for the retinal signboards, as well as laboratory levels of serum, such as C reactive protein, to link the retinal outcomes to correlating systemic inflammation. Also, while there was no massive distinction between patients with and without increased blood pressure, it could still be a significant contributor.

**Conclusion:**

As COVID-19 becomes more endemic, a dedicated international registry for tracking unusual ocular consequence following COVID-19 vaccination could help us better understand the disease. It might be useful to figure out which people have a high risk of suffering ocular consequence as a result of post COVID-19 infection or immunization. Our findings point to a possible retinal haemorrhage with an unusual trajectory, highlighting the complexities of diagnosing and treating this event with the Covid19 vaccination. As a result of the inflammatory cytokines and hypercoagulable conditions produced by infection with SARS-CoV-2, ophthalmologists must be cautious of ocular vascular disorders. As the investigation for a post covid and COVID-19 vaccine continues, we should expect higher incidence in the frequency of ophthalmic consequence from the various possibilities.

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**Declaration of competing interest**

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Author contributions**

The article's first draft was written by MAA and MDH. MAA, SN, SA and TAD contributed to the literature review and manuscript preparation. All authors contributed to the final version by critically reviewing and editing drafts.

**Ethical approval**

The article is about a case study. As a result, our Ethics Committee’s consent was not required.

**Consent**

The patient’s written informed consent for publishing of this case report, as well as images, was acquired.


Table and figure

Table 1. Laboratory parameters of the cases

<table>
<thead>
<tr>
<th>Investigation</th>
<th>7th June 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Creatine</td>
<td>0.91 mg/dl</td>
</tr>
<tr>
<td>S. ALT</td>
<td>49 U/L</td>
</tr>
<tr>
<td>Lipid Profile</td>
<td></td>
</tr>
<tr>
<td>S. Cholesterol</td>
<td>151 mg/dl</td>
</tr>
<tr>
<td>S. Triglyceride</td>
<td>291 mg/dl</td>
</tr>
<tr>
<td>S.HDL</td>
<td>27 mg/dl</td>
</tr>
<tr>
<td>Non-HDL Cholesterol</td>
<td>124 mg/dl</td>
</tr>
<tr>
<td>T. Cholesterol-HDL Ratio</td>
<td>5.59</td>
</tr>
<tr>
<td>ACR</td>
<td></td>
</tr>
<tr>
<td>Urine Micro-Albumin</td>
<td>19.10 mg/L</td>
</tr>
<tr>
<td>Urine Creatinine</td>
<td>4.42 gm/L</td>
</tr>
<tr>
<td>Micro-Albumin Creatinine Ration</td>
<td>4.32 mg/gm</td>
</tr>
<tr>
<td>Platelet count Creatinine Ration</td>
<td>210000 per microliter of blood.</td>
</tr>
</tbody>
</table>

Table 2. Medication list

<table>
<thead>
<tr>
<th>Date</th>
<th>Medication received</th>
</tr>
</thead>
<tbody>
<tr>
<td>On, 17th October, 2020</td>
<td>Paracetamol 500mg 1tab 8hourly, Azithromycin 500mg once at night, Losartan potassium 50mg at night and Bisoprolol 2.5mg at morning</td>
</tr>
<tr>
<td>On, 1st December 2020</td>
<td>Tranexenic acid 500mg and Moxifloxacin eye on right 6hourly to continue treatment</td>
</tr>
<tr>
<td>On, 7th June, 2021</td>
<td>Tranexenic acid 500mg and Moxifloxacin eye on right 6hourly to continue treatment</td>
</tr>
<tr>
<td>19 June, 2021 and 26 June, 2021 two outdoor follow up</td>
<td>Tranexenic acid 500mg and Moxifloxacin eye on right 6hourly to continue treatment</td>
</tr>
</tbody>
</table>
### Table 3. Eye examination

<table>
<thead>
<tr>
<th>Date and institute</th>
<th>Examination finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>On, 7th June, 2021, Ispahani Islamia Eye Institute and Hospital, Dhaka</td>
<td>On eye examination finding, VAR (Right visual acuity)</td>
</tr>
<tr>
<td>On, 3rd August 2021, Sankara Nethralaya eye hospital, Chennai, India.</td>
<td>Examination revealed attached retina with plenty of low reflective dot and clump echos and cornea and conjunctiva of both eyes were normal</td>
</tr>
<tr>
<td>On, 16th August 2021, Sankara Nethralaya eye hospital, Chennai, India.</td>
<td>Eye examination on right eye, eyelids edematous</td>
</tr>
</tbody>
</table>

Total vitreous hemorrhage

IOP: 14 mm hg and Left eye (L/E): Intra ocular pressure (IOP): 11 mm hg
Figure 1. Fundoscopy shows retinal haemorrhage

Figure 2. Ultrasound biomicroscopy (UBM) which showed retinal detachment as well as complete posterior vitreous detachment and vitreous shows multiple number of low reflective dot mobile echoes on right eye.