

# 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 are common and can affect the retina. We will report a case of retina hemorrhage with possibility of linkage between COVID-19 infection and immunization to determine whether these abnormalities are causal or coincidental.

## KEY WORDS

Bangladesh, COVID-19, ocular effect, retinal hemorrhage, vaccine

## 1 | 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.<sup>1,2</sup> COVID-19 may affects multiple organ system (cardiovascular diseases, respiratory failure, renal failure, liver damage, and ocular

adverse effect) but it is difficult to monitor all the system.<sup>3</sup> 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

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SARS-CoV-2.<sup>4–6</sup> 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).<sup>7,8</sup> In Germany, SARS-CoV-2 virus RNA was found in the retinas where three of the 14 number COVID-19 patients who died<sup>4</sup> and another study conducted in Italy found additional papillary focal retinal hemorrhage in the post-COVID-19 group.<sup>9</sup> Severe capillary lesions, such as cotton wool spots, retinal hemorrhages, and sectoral retinal infarction, have subsequently been reported in admitted, severe COVID-19 patients which suggests a new SARS-CoV-2 association.<sup>10</sup> 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.<sup>11</sup> As COVID-19 vaccinations become more common, the might be a increases concern of ophthalmic consequence due to vaccination<sup>12</sup>; however, a microvascular anomaly in the deep capillary plexus of the retina is suspected, the pathogenesis is unexplained.<sup>13,14</sup> In one case series, eye adverse events take place immediately after getting an inactivated COVID-19 vaccination were observed<sup>12</sup> 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).<sup>15,16</sup> 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.

## 2 | 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 October 16, 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, and 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 on October 17, 2020 (Table 1). On October 22, 2020, physical examination indicated normal vital

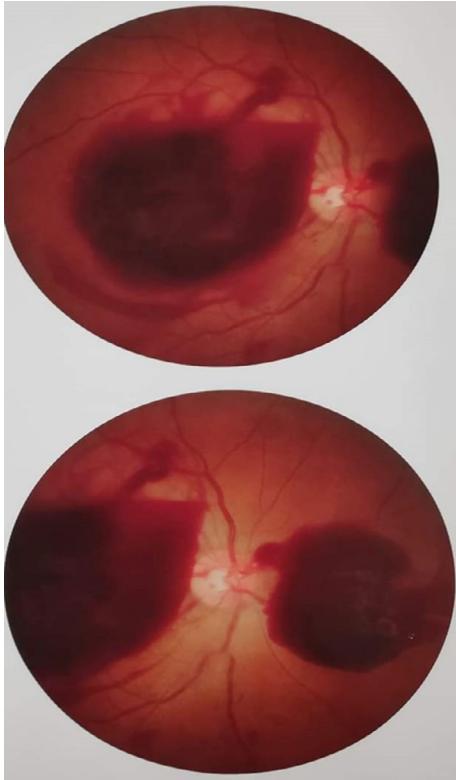
TABLE 1 Laboratory parameters of the cases

Investigation	7 <sup>th</sup> June 2021
S. Creatine	0.91 mg/dl
S. ALT	49 U/L
Lipid Profile	
S. Cholesterol	151 mg/dl
S. Triglyceride	291 mg/dl
S.HDL	27 mg/dl
Non-HDL Cholesterol	124 mg/dl
T. Cholestero-HDL Ratio	5.59
ACR	
Urine Micro-Albumin	19.10 mg/L
Urine Creatinine	4.42 gm/L
Micro-Albumin Creatinine Ratio	4.32 mg/g
Platelet count	210,000 per microliter of blood

signs. Throughout this time, he had a mild COVID symptom and was self-medicating at home, with no need for hospitalization. On November 10, 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 February 16, 2021. He completed his 2nd dose of vaccine on April 17, 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 color on right eye. He had no complaints of watering of eye, headache, eye ache, eyelid swelling, and any foreign body sensation. He had no other history of any trauma on eye or previous eye operations. On, June 7, 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 Hyalodototomy as outdoor base case. He was discharged on same day and advised with medication

**TABLE 2** Medication list

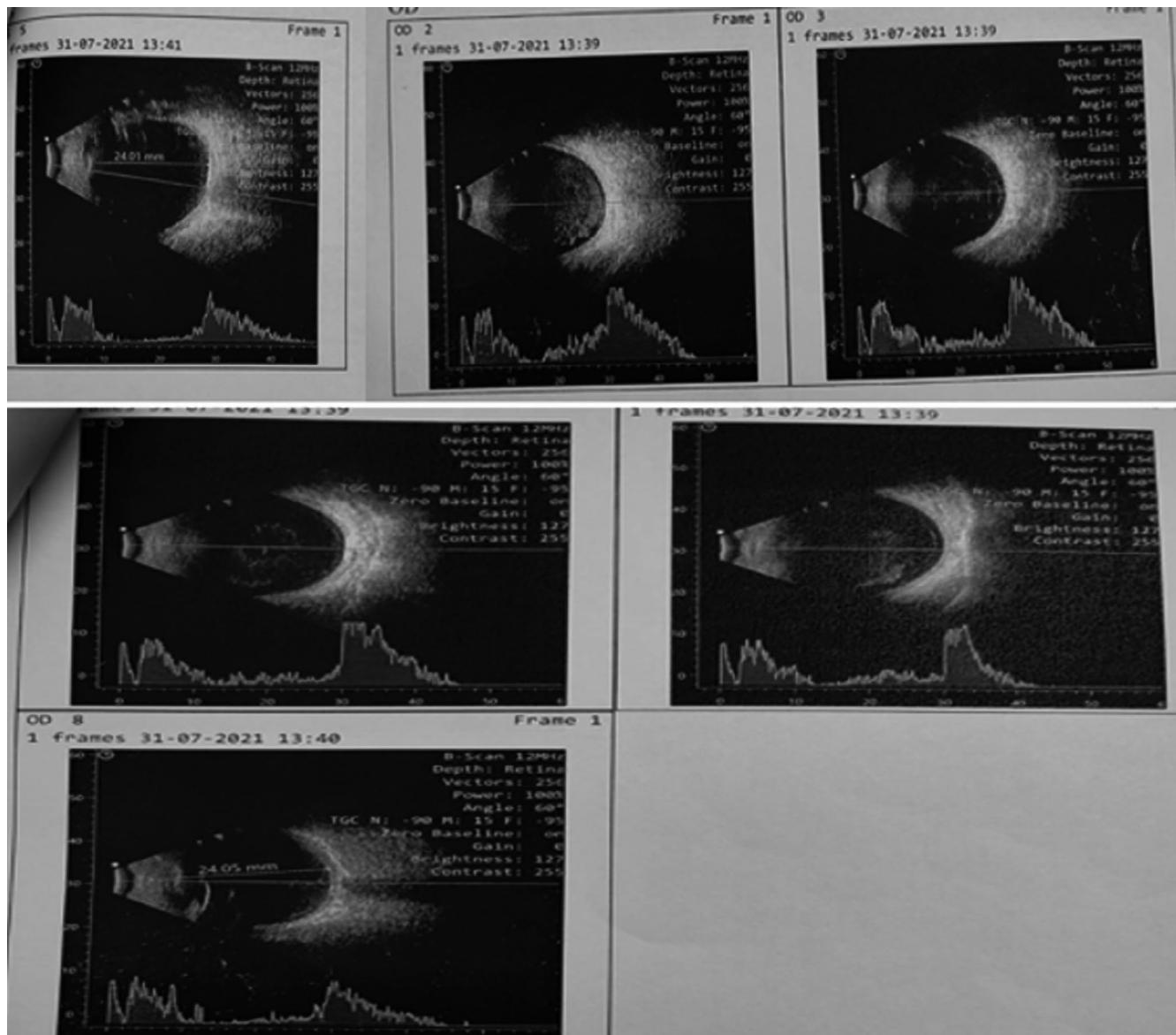
Date	Medication received
On October 17, 2020	Paracetamol 500 mg 1 tab 8 hourly, Azithromycin 500 mg once at night for 5 days, Deflazacort 24 mg 12 hourly for 5 days, and Enoxaparin sodium 60 mg once daily 5 days
On December 1, 2020	losartan potassium 50 mg at night and bisoprolol 2.5 mg at morning
On June 7, 2021	Tranexamic acid 500 mg and Moxifloxacin eye on right 6 hourly to continue for 7 days
June 19, 2021 and June 26, 2021 two outdoor follow-up	Moxifloxacin eye on right 6 hourly and Nepafenac eye drop on right eye 12 hourly eye drop as continue treatment

**FIGURE 1** Fundoscopy shows retinal hemorrhage

(Table 2). On June 19, 2021 and June 26, 2021, two outdoor follow-ups 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 hemorrhage. 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 July 29, 2021, he went to India for further follow-up and visited Sankara Nethralaya eye hospital, Chennai, India and done ultrasound biomicroscopy (UBM) on July 31, 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 August 3, 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, Hyderabad on August 11, 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. During follow-up of eye examination on August 16, 2021; eyelids were edematous, there was chemosis in conjunctive, but cornea was clear (Table 3). During the whole period scenario, physician did not find any significant cause of this retinal hemorrhage except may be complication of post-COVID or vaccine-related retinal complication. Last follow-up in Bangladesh on October 6, 2021, VAR:6/6 and VAL:6/6.

In summary, this patient was diagnosed COVID-19 on October 16, 2020 (RT-PCR positive) and nasopharyngeal swab for SARS-CoV-2 was negative on November 10, 2020. The patient took first dose of COVID-19 vaccine (Live-virus vectored based vaccine, COVISHIELD vaccine-AstraZeneca) on February 16, 2021 and 2nd dose on April 17, 2021. Retinal hemorrhage was seen on June 1, 2021 and underwent Yag Laser Hyalodotometry and medication in Dhaka on June 7, 2021. Then, he went to Chennai eye hospital, India and go through further investigation. Later on, again he was admitted into the Hyderabad hospital on August 12, 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 October 6, 2021, the visual acuity was 6/6. indicating that clinical condition of his eye clinical had improved. There was no further occurrence of hemorrhage after this follow-up.



**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

### 3 | DISCUSSION

According to our knowledge, this might be first case 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.<sup>17-19</sup> 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,<sup>20</sup> 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.<sup>21</sup> Furthermore, positive RT-PCR findings have been published in human retinal biopsies, implying that the viral proteins are invading retinal nerves specifically.<sup>4</sup> Certain coronavirus variants can invade retinal cells in other vertebrate species both *in situ* and in retinal cultured cells<sup>22</sup> and *in vivo* following viral proteins were injected intravitreally<sup>23</sup> producing experimental coronavirus retinopathy(ECOR).<sup>24,25</sup> 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

TABLE 3 Eye examination

Date and Institute	Examination finding
On June 7, 2021, Ispahani Islamia Eye Institute and Hospital, Dhaka	On eye examination finding, VAR (Right visual acuity)- Counting Fingers (CF) 3 feet without and VAL (Left visual acuity)- 6/9 without, Anterior Segment of Right eye (R/E): Intraocular pressure (IOP):14 mm hg and Left eye (L/E): Intraocular pressure (IOP):11 mm hg and fundus of R/E: Total vitreous hemorrhage
On August 3, 2021, Sankara Nethralaya eye hospital, Chennai, India	Examination revealed attached retina with plenty of low reflective dot and clump echos and cornea and conjunctiva of both eyes were normal
On August 16, 2021, Sankara Nethralaya eye hospital, Chennai, India	Eye examination on the right eye, eyelids edematous, conjunctiva chemosis at 6 o clock and 10 o clock, sclera mild congestion, cornea clear, anterior chamber- deep, iris- normal color and pattern, pupil- dilated and fixed, post-dilated examination, pupil of R/E -7 mm, lens clear and L/E- 3 mm undilated and leans clear, fundus examination R/E – Media clear, optic disc size- medium size disc, optic disc -normal, blood vessel- normal, macula-normal, Cup/Disc ratio-0.3, Fundus- retina ON. During the whole period scenario, physician did not find any significant cause of this retinal hemorrhage

research in Germany.<sup>4</sup> Most notably, retinal microangiopathy exhibited as cotton wool patches (diagnostic and therapeutic sign related to nerve fiber ischemia) was seen in 6 out of 27 outpatients evaluated by retinal fundoscopic, B-scan OCT(Optical Coherence Tomography), and optical coherence tomography angiography (OCT-A) at a mean of 43 days following COVID-19 disease onset in Spain.<sup>26</sup> 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.<sup>27</sup> 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.<sup>7</sup> 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),<sup>28</sup> and secondly, due to spontaneous viral infection of the vascular endothelium and widespread endothelial dysfunction, a vasculitis-like reaction starts.<sup>29</sup> 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 the 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.<sup>30</sup> Our case was a subhyaloid subtype of retinal hemorrhage. In, Abu Dhabi,<sup>12</sup> 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 COVID-19 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 do not 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 hypercoagulopathy 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.

#### 4 | 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 hemorrhage with an unusual trajectory, highlighting the complexities of diagnosing and treating this event with the COVID-19 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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## CONFLICT OF 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

MAA and MDH wrote the first draft of the article. 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.

## DATA AVAILABILITY STATEMENT

Data can be shared based on the reader's reasonable request and priority base and some restrictions will apply.

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