

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

Mohammad Ashraful Amin¹, Sabrina Nahin², Taslima Ahmed Dola³, Sadia Afrin¹, and Mohammad Delwer Hossain Hawlader¹

¹North South University

²Green Life Medical College and Hospital

³East West Medical College and Hospital

January 28, 2022

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, Hyderabad 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 Hyderabad 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 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 (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.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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.

1. Ahmed MS, Kabir MS, Bhuiyan MH. COVID-19: Effects on Eye in Bangladesh. *Bangladesh Medical Journal*. 2020;49(2):14-8.
2. Park SH. Personal protective equipment for healthcare workers during the COVID-19 pandemic. *Infection & chemotherapy*. 2020;52(2):165.
3. Bansal R, Markan A, Gautam N, Guru RR, Lakshmi P, Katoch D, et al. Retinal involvement in COVID-19: Results from a prospective retina screening program in the acute and convalescent phase. *Frontiers in medicine*. 2021;8.
4. Casagrande M, Fitzek A, Puschel K, Aleshcheva G, Schultheiss H-P, Berneking L, et al. Detection of

- SARS-CoV-2 in human retinal biopsies of deceased COVID-19 patients. *Ocular immunology and inflammation*. 2020;28(5):721-5.
5. Li Y-P, Ma Y, Wang N, Jin Z-B. Eyes on coronavirus. *Stem Cell Research*. 2021;51:102200.
6. Pedersen NC. A review of feline infectious peritonitis virus infection: 1963–2008. *Journal of feline medicine and surgery*. 2009;11(4):225-58.
7. Marinho PM, Marcos AA, Romano AC, Nascimento H, Belfort R. Retinal findings in patients with COVID-19. *The Lancet*. 2020;395(10237):1610.
8. Rim JH, Lee S-T, Gee HY, Lee BJ, Choi JR, Park HW, et al. Accuracy of next-generation sequencing for molecular diagnosis in patients with infantile nystagmus syndrome. *JAMA ophthalmology*. 2017;135(12):1376-85.
9. Savastano MC, Gambini G, Cozzupoli GM, Crincoli E, Savastano A, De Vico U, et al. Retinal capillary involvement in early post-COVID-19 patients: a healthy controlled study. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2021:1-9.
10. Pereira L, Soares L, Nascimento P. Retinal findings in hospitalised patients with severe COVID-19 [published online ahead of print October 16, 2020]. *Br J Ophthalmol* doi.10.
11. Vavvas DG, Sarraf D, Sadda SR, Elliott D, Ehlers JP, Waheed NK, et al. Concerns about the interpretation of OCT and fundus findings in COVID-19 patients in recent Lancet publication. *Nature Publishing Group*; 2020.
12. Pichi F, Aljneibi S, Neri P, Hay S, Dackiw C, Ghazi NG. Association of ocular adverse events with inactivated COVID-19 vaccination in patients in Abu Dhabi. *JAMA ophthalmology*. 2021;139(10):1131-5.
13. Bhavsar KV, Lin S, Rahimy E, Joseph A, Freund KB, Sarraf D, et al. Acute macular neuroretinopathy: a comprehensive review of the literature. *Survey of ophthalmology*. 2016;61(5):538-65.
14. Hwang CK, Sen HN. Concurrent vascular flow defects at the deep capillary plexus and choriocapillaris layers in acute macular neuroretinopathy on multimodal imaging: A case series. *American Journal of Ophthalmology Case Reports*. 2020;20:100866.
15. Ng XL, Betzler BK, Testi I, Ho SL, Tien M, Ngo WK, et al. Ocular adverse events after COVID-19 vaccination. *Ocular immunology and inflammation*. 2021:1-9.
16. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet*. 2021;397(10269):99-111.
17. Agarwal M, Majumder PD, Babu K, Konana VK, Goyal M, Touhami S, et al. Drug-induced uveitis: A review. *Indian Journal of Ophthalmology*. 2020;68(9):1799.
18. Cunningham Jr ET, Moorthy RS. Vaccine-associated posterior uveitis. *LWW*; 2020.
19. Cunningham Jr ET, Moorthy RS, Fraunfelder FW, Zierhut M. Vaccine-associated uveitis. *Taylor & Francis*; 2019.
20. Wang K, Chen W, Zhou Y-S, Lian J-Q, Zhang Z, Du P, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. *BioRxiv*. 2020.
21. Hamashima K, Gautam P, Lau KA, Khiong CW, Blenkinsop TA, Li H, et al. Potential modes of COVID-19 transmission from human eye revealed by single-cell atlas. *BioRxiv*. 2020.
22. Wang Y, Detrick B, Hooks JJ. Coronavirus (JHM) replication within the retina: analysis of cell tropism in mouse retinal cell cultures. *Virology*. 1993;193(1):124-37.

23. Robbins S, Hamel C, Detrick B, Hooks J. Murine coronavirus induces an acute and long-lasting disease of the retina. *Laboratory investigation; a journal of technical methods and pathology*. 1990;62(4):417-26.
24. Chin MS, Hooper LC, Hooks JJ, Detrick B. Identification of α -fodrin as an autoantigen in experimental coronavirus retinopathy (ECOR). *Journal of neuroimmunology*. 2014;272(1-2):42-50.
25. Detrick B, Lee MT, Chin MS, Hooper LC, Chan C-C, Hooks JJ. Experimental coronavirus retinopathy (ECOR): retinal degeneration susceptible mice have an augmented interferon and chemokine (CXCL9, CXCL10) response early after virus infection. *Journal of neuroimmunology*. 2008;193(1-2):28-37.
26. Landecho M, Yuste J, Gándara E, Sunsundegui P, Quiroga J, Alcaide A, et al. COVID-19 retinal microangiopathy as an in vivo biomarker of systemic vascular disease? *Journal of internal medicine*. 2021;289(1):116-20.
27. Invernizzi A, Torre A, Parrulli S, Zicarelli F, Schiuma M, Colombo V, et al. Retinal findings in patients with COVID-19: Results from the SERPICO-19 study. *EClinicalMedicine*. 2020;27:100550.
28. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of thrombosis and haemostasis*. 2020;18(4):844-7.
29. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *The Lancet*. 2020;395(10234):1417-8.
30. Monferrer-Adsuara C, Castro-Navarro V, Gonzalez-Giron N, Remoli-Sargues L, Ortiz-Salvador M, Montero-Hernandez J, et al. A case of bilateral unusual retinal hemorrhages in a COVID-19 patient. *European Journal of Ophthalmology*. 2020;1120672120984381.

Table and figure

Table 1. Laboratory parameters of the cases

Investigation	7 th 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 Ration	4.32 mg/gm
Platelet count	210000 per microliter of blood.

Table 2. Medication list

Date	Medication received
On, 17 th October, 2020	Paracetamol 500mg 1tab 8hourly, Azithromycin 500mg once at night
On, 1 st December 2020	losartan potassium 50mg at night and bisoprolol 2.5mg at morning
On, 7 th June, 2021	Tranexenic acid 500mg and Moxifloxacin eye on right 6hourly to clear
19 June, 2021 and 26 June, 2021 two outdoor follow up	Moxifloxacin eye on right 6 hourly and Nepafenac eye drop on right

Table 3. Eye examination

Date and institute	Examination finding
On, 7 th June, 2021, Ispahani Islamia Eye Institute and Hospital, Dhaka	On eye examination finding, VAR (Right visual
On, 3rd August 2021, Sankara Nethralaya eye hospital, Chennai, India.	Examination revealed attached retina with plenty
On, 16th August 2021, Sankara Nethralaya eye hospital, Chennai, India.	Eye examination on right eye, eyelids edematous

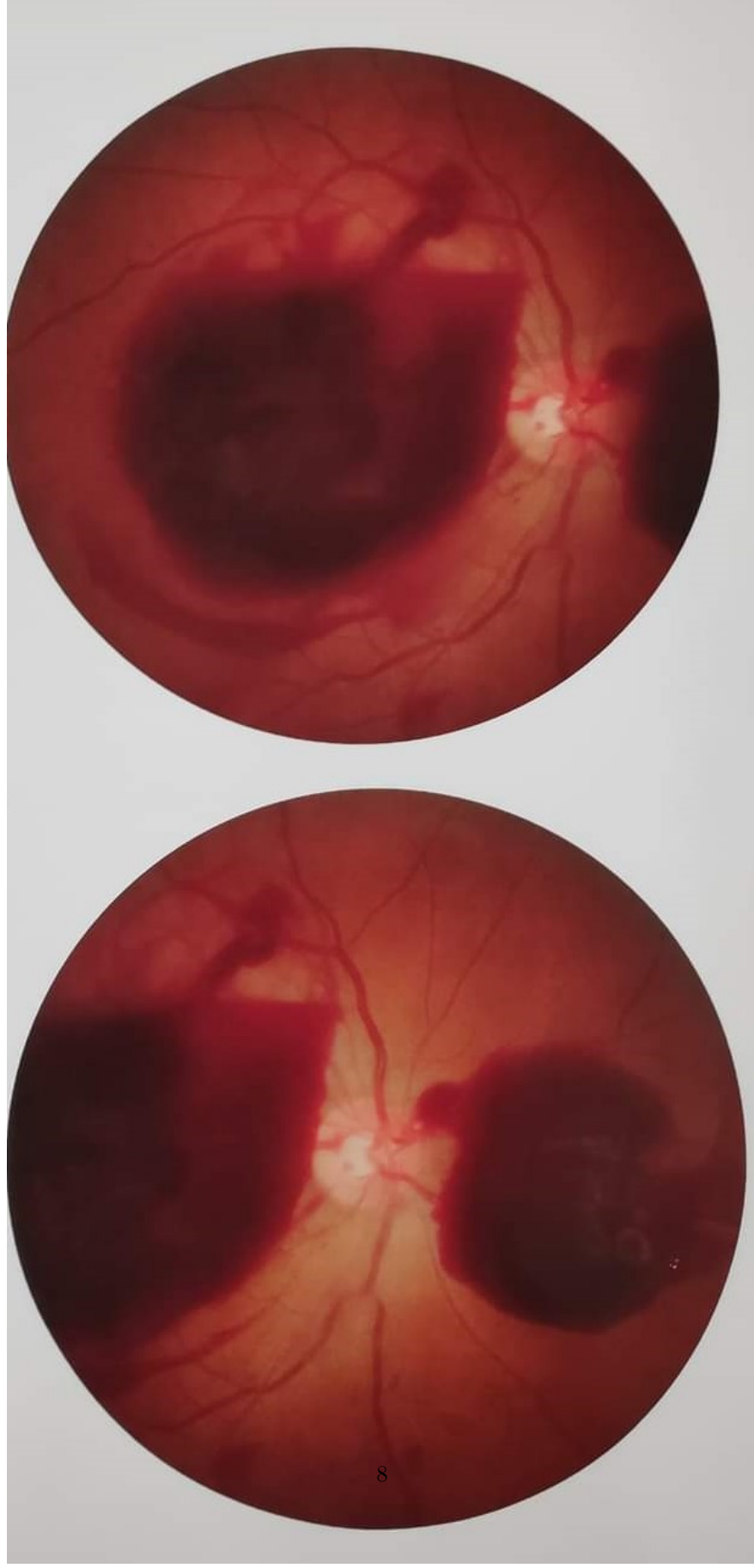


Figure 1. Fundoscopy shows retinal haemorrhage

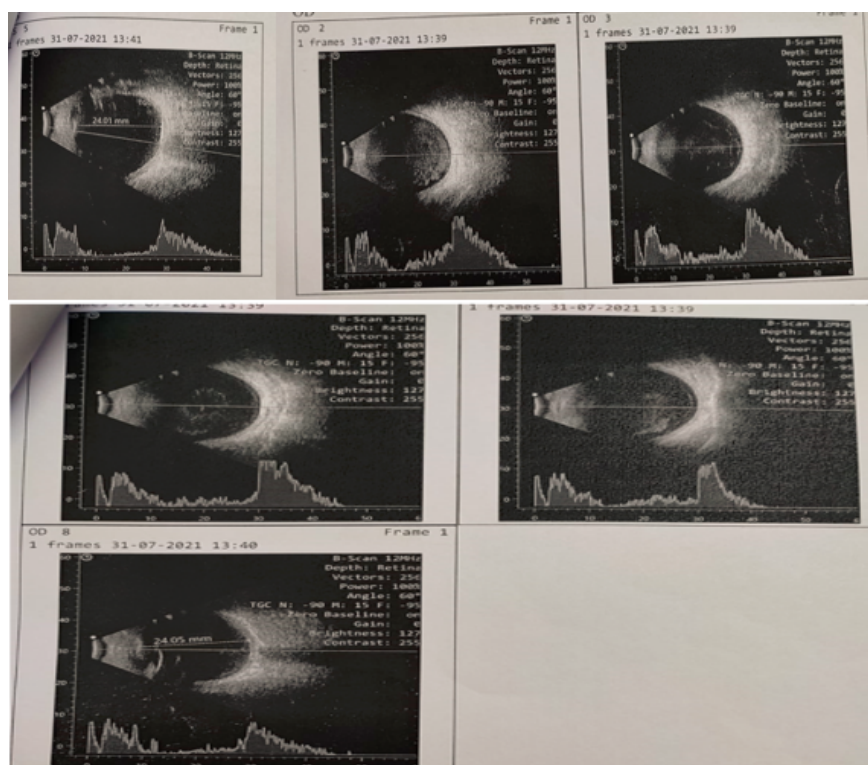


Figure 2. Ultrasound biomicroscopy (UBM) which showed retinal detachment as well as complete posterior vitreous detachment and vitreous shows multiple number of low reflective dot mobile echoes on right eye.

