

A case of bilateral unusual retinal hemorrhages in a COVID-19 patient

Clara Monferrer-Adsuara¹ , Verónica Castro-Navarro^{1,2},
Nuria González-Girón¹, Lidia Remolí-Sargues¹ ,
Miguel Ortiz-Salvador¹, Javier Montero-Hernández^{1,2}
and Enrique Cervera-Taulet^{1,2}

European Journal of Ophthalmology
2022, Vol. 32(2) NP123–NP127

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DOI: 10.1177/1120672120984381

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Abstract

Purpose: There have been anecdotal reports of ocular manifestations in the Coronavirus Disease 2019 (COVID-19). As the pandemic is spreading and the whole picture is yet unknown, ophthalmologists should be aware of unusual ocular presentations of COVID-19 since they could precede the development of severe respiratory distress.

Methods: We report here the first case of a patient with bilateral unusual dot-blot retinal hemorrhages and retinal venous dilation who presented shortly thereafter a PCR-proven COVID-19.

Case report: A 59-year-old woman presented with a 7 days history of blurred vision in both eyes. Fundus examination revealed bilateral venous stasis and dot and blot intra-retinal hemorrhages preceding the diagnosis of COVID-19 in a patient with mild respiratory symptoms that progressed within a few days to a severe respiratory distress. After 1 month of the COVID-19 treatment, fundus examination improved and fluorescein angiography demonstrated no diabetic retinopathy signs, no retinal vasculitis and no significant delay in arterial or venous filling.

Conclusion: Intraretinal hemorrhages similar to those found in the retinopathy associated to blood dyscrasias could be an association with SARS-CoV-2 in the context of a coagulopathy induced by the infection.

Keywords

COVID-19, intraretinal hemorrhages, novel coronavirus, ophthalmology, SARS-CoV-2

Date received: 4 September 2020; accepted: 8 December 2020

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus strain, was detected in late December 2019 in Wuhan, the capital of Central China's Hubei Province, and has promptly propagated raising major global concerns. Its human infection has been designated as Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) and is currently considered a global pandemic posing a global threat to public health.^{1,2}

COVID-19 has the lungs as the target organ inducing an acute lung inflammation which can evolve to respiratory and multiorgan failure. The complete spectrum of presentations is not fully elucidated as the pandemic is still in progression but, interestingly, thrombotic alterations seem to emanate as important issues in these patients.³

In line with current reports, SARS-CoV-2 can induce a mild follicular conjunctivitis (0.8%),^{2,4,5} other sight-threatening ocular complications as anterior uveitis, optic

neuritis, and retinitis have been exclusively evidenced in animal models.⁶ As far as we know, we report here the first patient with bilateral unusual dot-blot retinal hemorrhages and retinal venous dilation who was diagnosed shortly thereafter with COVID-19.

Case report

A 59-year-old woman presented on March 3rd with a 7-days history of bilateral blurred vision. Her medical history

¹Hospital General Universitario de Valencia, Valencia, Spain

²Facultad de Medicina, Universidad Católica de Valencia 'San Vicente Mártir', Valencia, Spain

Corresponding author:

Clara Monferrer Adsuara, Hospital General Universitario de Valencia, 2 Tres Creus Avenue, Valencia, Comunitat Valenciana 46014, Spain.

Email: Clara_cma@hotmail.com

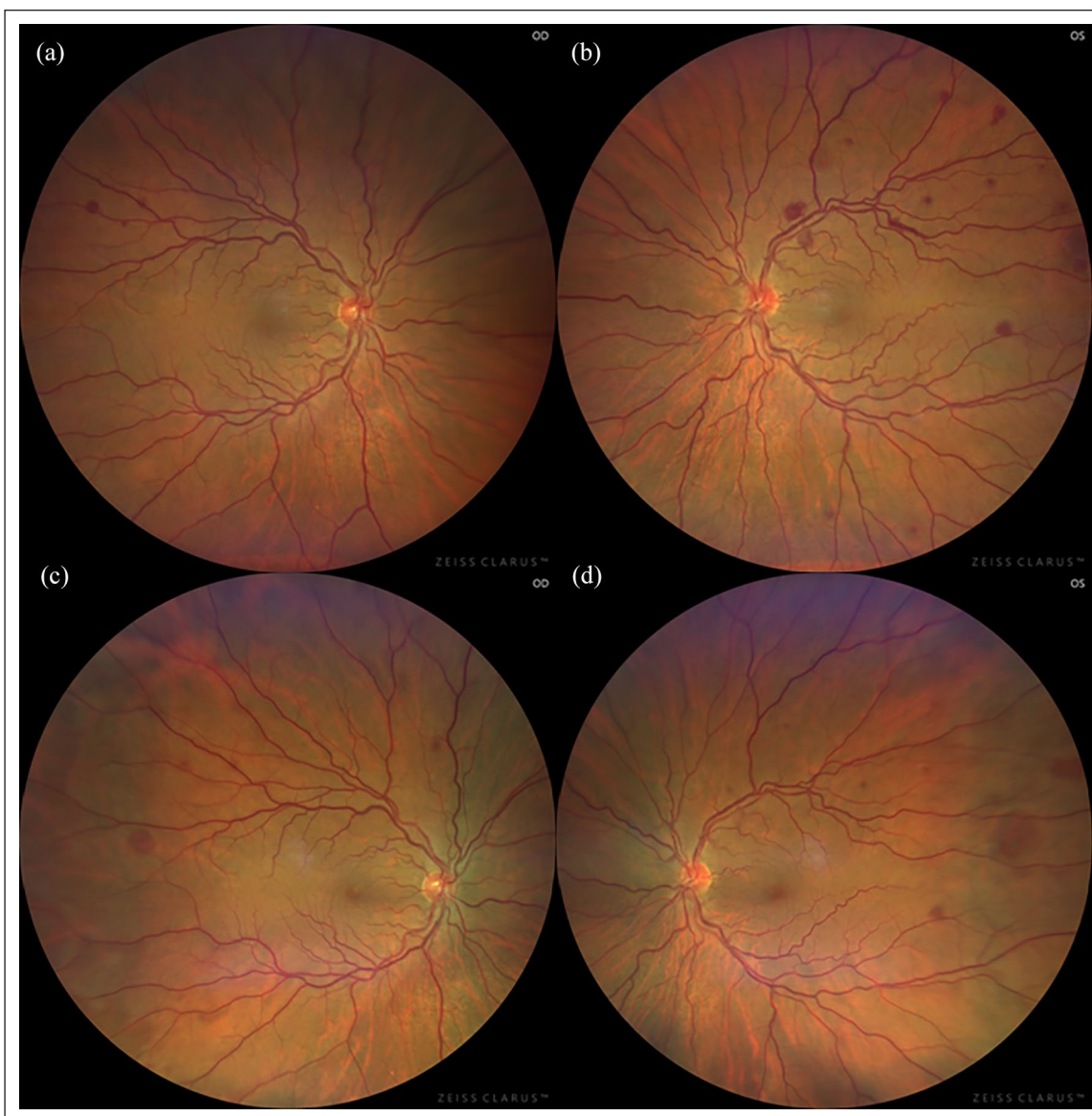


Figure 1. Ultra-widefield retinal imaging (CLARUS 500, Carl Zeiss Meditec Inc., Dublin, CA, USA) showing right (OD) (a) and left eye (OS) (b) venous dilation and mild tortuosity, with scattered large dot blot retinal hemorrhages; the latter were significantly more pronounced in the OS (b). After 1 month of the COVID-19 treatment, improvement of the retinal hemorrhages in the OD (c) and OS (d).

included a 3-year history of Type 2 diabetes (HbA1c value of 6.5% on January 2020) without any secondary vascular complications, treated with 850mg metformin hydrochloride once daily. At that time, the patient was receiving empiric oral antibiotic and corticosteroids prescribed by her general practitioner because of a 1-week long clinical picture of dyspnea and painless bilateral lower limb edema.

At presentation, best-corrected visual acuity (BCVA) Snellen equivalent was 20/25 in her right eye (RE) and 20/32 in her left eye (LE). Her refractive status was +0.25/+0.25 axis 90 in her RE and +0.00/+0.50 axis 85 in her LE. Anterior segment exploration was unremarkable. Fundus examination evidenced retinal vascular

tortuosity and intraretinal dot-and-blot hemorrhages along the vascular arcades in both eyes (OU) (Figure 1(a) and (b)); both optic discs were slightly hyperemic with a subtle effacement of the nasal border. There were no signs of diabetic/hypertensive retinopathy and no vitritis or chorioretinal inflammation signs were observed. Optical coherence tomography (OCT) excluded macular edema (Figure 2(a) and (b)) and displayed a retinal nerve fiber layer thickness (RNFL) of 112 μm RE and 117 μm LE. At this point, the patient refused the fluorescein angiography as she was experiencing dyspnea of an unknown cause so a month follow-up examination was decided for a close monitoring.

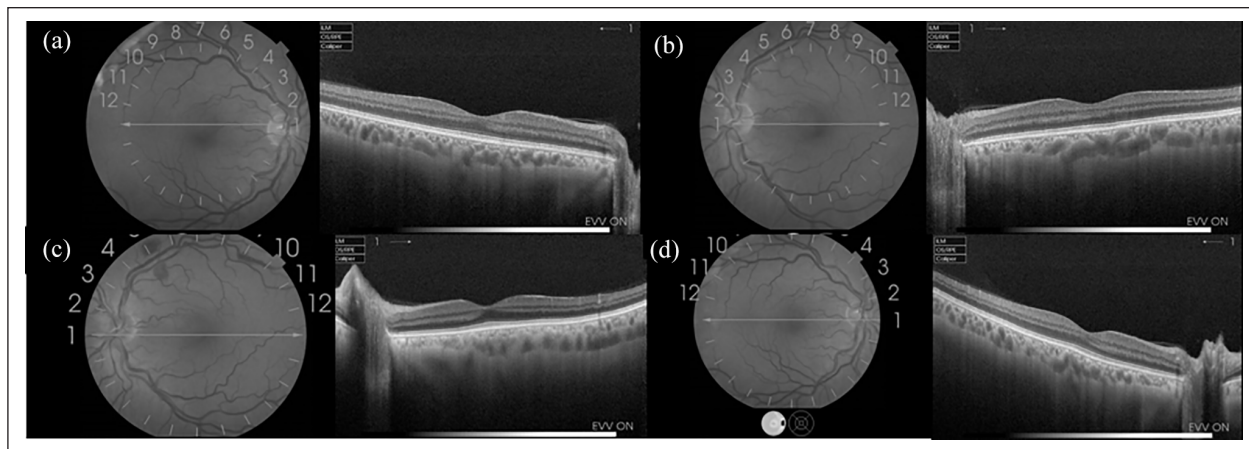


Figure 2. Note the registered swept-source optical coherence tomography (Triton DRI OCT; Topcon Corp, Tokyo, Japan) showing normal features of the macula at presentation in the right (a) and left (b) eye and after 1 month of the COVID-19 treatment in the right (c) and left (d) eye.

On March 17, the patient returned to the emergency department with a significant worsening of her dyspnea. A chest X-ray was performed, images of which reported a basal right pulmonary infiltrate. She was empirically started on levofloxacin 500 mg/day and she was admitted to hospital. Antigen tests for influenza A and B were reported back as negative and, on March 21st, an oropharyngeal swab test of SARS-CoV-2 by qualitative real time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay resulted positive.

During admission, lab studies evidenced abnormal coagulation tests consisting in thrombocytopenia ($126 \times 10^9/L$) and elevation of D-dimer (353 ng/mL). Her respiratory symptoms improved after antimicrobial therapy (lopinavir-ritonavir 400/100 mg BID, interferon Beta-1B 250 mcg every 48 h, hydroxychloroquine 200 mg BID oral and prophylactic low molecular weight heparin) and symptomatic treatment and the dynamics of the chest X-ray showed progressive absorption of the lung infiltrates. On March 31, the patient was discharged and guided to quarantine at home.

One month after admission, an ophthalmological examination revealed improvement of the bilateral hemorrhages although venous dilation persisted (Figure 1(c) and (d)) with some faint hemorrhages that were not apparent on the initial examination, suggesting that the pathophysiological process is dynamic and ongoing, at least to some extent; best-corrected visual acuity (BCVA) Snellen equivalent was 20/20 in her right eye and 20/25 in her left eye (LE). Macular OCT remained unremarkable (Figure 2(c) and (d)) and RNFL thickness showed a minimal change, 109 μm RE and 110 μm LE. Fluorescein angiography demonstrated no diabetic retinopathy signs, no retinal vasculitis and no significant delay in arterial/venous filling; no retinal ischemia or neovascularization was observed (Figure 3(a) and (b)).

Discussion

There are several potential causes of bilateral venous stasis retinopathy with bilateral intraretinal hemorrhages including: inflammatory infectious, vascular/hematologic causes, compressive lesion, and medications. Although the most frequent differential diagnoses comprise vascular/hematologic etiologies (hypertensive, chronic ocular ischemia, diabetes carotid artery occlusion, dysproteinemias, blood dyscrasias and anemia), other less prevalent diseases such as infections or inflammatory/autoimmune conditions, among other, need to be considered.

At present, a SARS-CoV-2 epidemic has rapidly raised from Wuhan and the WHO has stated a public health emergency of international concern.² This new strain is extremely transmissible and the clinical picture ranges from asymptomatic to severe illness, sepsis and death.⁷ COVID-19's signs and symptoms comprise fever (>80%), cough (>60%), myalgia, fatigue (>40%), sputum production and headache.^{2,8} Complications in critical cases encompasses pneumonia, cardiomyopathy, renal failure, encephalopathy and stroke.²

Severe COVID-19 is responsible for excessive coagulation activation leading to thrombotic complications and massive fibrin formation. In this SARS-CoV-2's procoagulant effect, the activation/interactions between monocytes, macrophages, platelets, endothelial cells, and lymphocytes play a crucial role, leading to fibrin deposition in alveolus and interstitial lung tissue that, together with microcirculation thrombosis, play a part in worsening respiratory failure leading to poor outlook and death. Additionally, other serious venous thromboembolic complications and arterial events (e.g. acute myocardial infarction) have been described and are probably being largely underestimated.³

An endotheliopathy appears to contribute to the pathophysiology of microcirculatory changes in SARS-COV-2

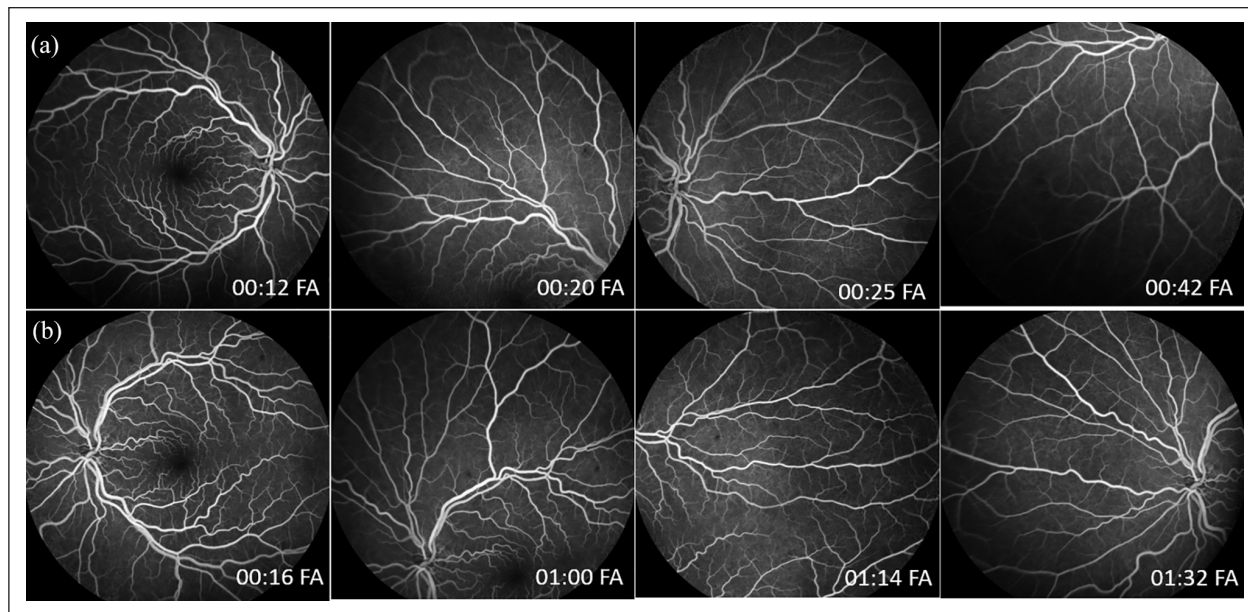


Figure 3. Note the right (a) and left eye (b) fluorescein angiography (Heidelberg Spectralis. HRA + OCT, Heidelberg Engineering, Heidelberg, Germany) were no signs of diabetic retinopathy, retinal vasculitis or retinal vein/arterial occlusion signs were observed.

infections as the receptor for viral adhesion is the angiotensin-converting enzyme 2 (ACE2) receptor on endothelial cells, with viral replication causing inflammatory cell infiltration, endothelial cell apoptosis, and microvascular prothrombotic effects. As a result, a thrombotic microangiopathy may occur explaining reports of cerebrovascular complications in younger patients, myocardial ischemia, and increasing reports of both micro and microcirculatory thromboembolic complications.⁹

Initial reports on COVID-19 cases laboratory and clinical findings comprise D-dimer elevation, thrombocytopenia, prothrombin time prolongation, and disseminated intravascular coagulopathy. Elevated D-dimer (46.6%) and thrombocytopenia (36.2%) are commonly developed being these ratios even greater in serious COVID-19 (59.6% and 57.7%, respectively).¹⁻³

Since COVID-19 emergence, there have been anecdotal papers related to ophthalmic infection. According to current literature, COVID-19 patients can suffer a mild follicular conjunctivitis otherwise indistinguishable from different viral causes.⁶ In a large report consisting of 1099 cases, congested conjunctiva was observed in 0.8% of the patients⁷ and in one study, 31.6% presented ocular signs similar to conjunctivitis (epiphora, chemosis, conjunctival hyperemia, or increased secretions), a rather high rate compared with other reports.⁶ Ocular symptoms have been described more frequently in the middle phase of COVID-19 and in cases with serious pneumonia; whether ophthalmic secretions could be contagious is still controversial.^{5,7}

Interestingly, in our case report, ocular manifestations consisted in blurred vision and ocular findings included bilateral venous stasis and dot-and-blot intraretinal hemorrhages preceding the diagnosis of SARS-CoV-2

infection in a patient with mild respiratory manifestations, that we believed were related to an undiagnosed COVID-19, that worsened within a few days to a severe respiratory distress. In the absence of arterial hypertension, no signs of diabetic retinopathy and the absence of other cardiovascular risk factors, as well as the improvement after the COVID-19 treatment, intraretinal hemorrhages that resemble the findings in retinopathy associated to blood dyscrasias could be an association with SARS-CoV-2 in the context of a coagulopathy induced by the infection. Ophthalmic features present in blood dyscrasia include retinal hemorrhages (subretinal, subhyaloid or intraretinal), vascular tortuosity and cotton wool spots and hyperviscosity and increased arteriovenous passage time are thought to be the causes. Other diseases resulting in hypercoagulability, such as factor V Leiden, Protein C or S and antithrombin III deficiencies, essential thrombocythemia, and disseminated intravascular coagulation, may also debut with vascular occlusions, cotton-wool spots and retinal hemorrhages.

To our knowledge, this is the first described case of venous stasis and dot-and-blot intraretinal hemorrhages as the ophthalmological manifestation in COVID-19. The patient consulted initially to the ophthalmology department with this retinopathy and mild respiratory symptoms, but no fever; thus, these findings could represent an early manifestation of COVID-19.

In conclusion, this report highlights the importance for ophthalmologists to remain vigilant and take into consideration COVID-19 as a possible etiology of retinopathy associated to blood dyscrasias and vascular tortuosity. As the pandemic is still in process and the whole picture remains unknown, eye care professionals should be aware of these

unusual ophthalmological presentations since they could precede the progression to a severe respiratory distress.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

The patient provided written informed consent for the publication of medical information and images.

ORCID iDs

Clara Monferrer-Adsuara  <https://orcid.org/0000-0003-0399-0903>

Lidia Remolí-Sargues  <https://orcid.org/0000-0002-7919-0462>

References

1. Salata C, Calistri A, Parolin C, et al. Coronaviruses: a paradigm of new emerging zoonotic diseases. *Pathog Dis* 2019; 77(9): ftaa006.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395(10223): 497–506.
3. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. *Thromb Haemost* 2020; 120(6): 998–1000.
4. Yu A-Y, Tu R, Shao X, et al. A comprehensive Chinese experience against SARS-CoV-2 in ophthalmology. *Eye Vis (Lond)* 2020; 7: 19.
5. Chen M-J, Chang K-J, Hsu C-C, et al. Precaution and prevention of Coronavirus Disease 2019 (COVID-19) infection in the eye. *J Chin Med Assoc* 2020; 83(7): 648–650.
6. Seah I and Agrawal R. Can the Coronavirus Disease 2019 (COVID-19) affect the eyes? A Review of Coronaviruses and Ocular Implications in Humans and Animals. *Ocul Immunol Inflamm* 2020; 28(3): 391–395.
7. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; 382: 1708–1720.
8. Cheema M, Aghazadeh H, Nazarali S, et al. Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19). *Can J Ophthalmol* 2020; 55(4): e125–e129.
9. Connors JM and Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020; 135(23): 2033–2040.