Case report

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Focal superior quadrant haemorrhages in post COVID-19 patient: A target for personalized medicine

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Abstract

Purpose: To report a case of multiple superior quadrant intraretinal haemorrhages in post-COVID-19 patient.

Case description: A 58-year-old male with a history of coronary artery disease and hypertension, presented with multiple superior quadrant intraretinal haemorrhages in the superonasal quadrant of the left eye 1 month after hospitalization for COVID-19. The right eye was normal. During his 10-day stay, he was treated with hydroxychloroquine, lopinavir + ritonavir, ceftriaxone, and his pre-existing antiplatelet therapy. During hospitalization, a complete medical work up showed an anomalous increase in D-dimer. He did not require intensive care support.

Conclusions: In this report, we focused on the origin of retinal bleeding in a post COVID-19 patient, likely due to a focal occlusion of a vessel. Considering the nature of SARS-CoV-2 infection, we hypothesize that retinal haemorrhages were caused by a combination of factors including the patient's antiplatelet therapy and the thrombotic microvascular injury caused by the virus.

Keywords

Antiplatelet therapy, arterial occlusion, coagulopathy, COVID-19, sub-internal limiting membrane haemorrhage

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), has already infected more than 57 million people and caused over 1,300,000 deaths to date, representing a major global health crisis.[1]

Although our knowledge about the pathogenesis of COVID-19 is still incomplete, multiple studies have demonstrated that severe cases are associated with haemostatic abnormalities and vascular complications ranging from thrombotic microangiopathy to dramatic disseminated intravascular coagulations (DIC). These events have a high risk of morbidity and mortality due to acute respiratory distress syndrome (ARDS), shock and multiple organ failure (MOF).[2]

Autopsies have also confirmed the presence of platelet-rich thrombotic accumulations in the microcirculation of several organs, primarily the lungs, in most complex COVID-19 cases. This seems to be related both to severe systemic activation of the complement pathways and to direct viral damage.[2] According to previous studies, the occurrence of thromboembolic complications ranges from 7.7% to 49%[3] and it is interesting to consider that arterial thrombosis is not so frequent in sepsis or infection but is unexpectedly prominent in COVID-19.[2]

Therefore, the administration of heparin has been recommended for routine patient care, although the optimal

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dosage remains highly debated. Guidelines[2] also suggest that a less potent antiplatelet agent (such as clopidogrel) should be considered for patients with high bleeding risk, but it is not clear whether antiplatelet therapy is as effective as anticoagulant therapy.

In this study, we describe a case of a post-COVID-19 patient with intraretinal haemorrhages, who was in treatment with antiplatelet therapy for previous cardiopathic ischaemia. Our clinical evidence suggests a possible vasculopathic effect of SARS-COVID-2 infection even in the absence of extensive systemic involvement.

Case description

After two negative consecutive nasopharyngeal swabs and detection of anti-SARS-CoV-2 IgGs in blood samples, a 58-year-old male patient, hospitalized for moderate COVID-19, was discharged after a 10-day hospital stay. At 30 days, an ophthalmological consult was requested to evaluate the presence of abnormalities of the retinal vessels and ocular surface by the Gemelli Against COVID Post-Acute Care Study Group.[4]

The medical history of the patient was notable for the presence of coronary artery disease, hypertension, and chronic hyperuricemia. He suffered a myocardial infarct 14 months before this study and was treated with dual antiplatelet therapy (ticagrelor 90 mg once daily; ASA 100 mg once daily), beta blocker (bisoprolol fumarate 3.75 mg once daily), angiotensin receptor blocker (telmisartan 80 mg per day), and atorvastatin (40 mg per day).

During SARS-CoV-2 infection, the patient was hospitalized due to febrility and tachypnoea but did not require intensive care as he was only slightly hypoxemic. At the time of hospital admission, the general laboratory examination showed mild lymphocytopenia and neutropenia, elevation in fibrinogen (433 mg/dL, normal value: 200–400 mg/dL), serum levels of lactate dehydrogenase LDH (371 U/L, normal value: $<$250 U/L), and PCR (12 mg/dL, normal value: $<$0.500 mg/dL). He was treated with hydroxychloroquine, lopinavir + ritonavir 800/200 mg per day, ceftriaxone, and his pre-existing antiplatelet therapy.

During our ophthalmological examination, visual acuity was 55/55 in both eyes, with the anterior segment and intraocular pressure within normal limits. Indirect ophthalmoscopy of the left eye showed multiple para-papillary intraretinal haemorrhages in the superonasal quadrant (Figure 1). The closest to the optic disc developed with a perivascular cuff-like appearance around the affected artery and was associated with a larger flame-shaped retinal haemorrhage in the midperiphery, along the temporal branch originating from the same vessel.

Using spectral domain Zeiss Cirrus 5000-HD-OCT Angioplex (version 10.0, Carl Zeiss, Meditec Inc., Dublin, CA, USA), it was possible to determine the location of the haemorrhages involving the inner retinal layers under the internal limiting membrane (ILM). The presence of a vitreous tuft was also detected above the affected artery, while the posterior pole appeared free of haemorrhages. Optical coherence tomography angiography showed a blood masking effect that reduced visualization of perivasal anatomical details. Flow reduction downstream of the occluded site was demonstrated by the disappearance of the usual arterial capillary network (Figure 2).

A complete medical check-up including blood count and coagulation tests was performed, showing an anomalous increase in D-dimer (852 ng/ml); normal values are generally not superior to 500 ng/ml. Coombs test, anti-cardiolipin antibodies and anti-nuclear antibodies were all negative.

We tested the patient again after 1-week and funduscopic examination showed bleeding persistence with no enlargement. We decided to perform a fluorescein angiography (FA), which showed in the left eye marked hypo-fluorescence around the artery involved in the bleeding and no signs of peripheral ischaemia (Figure 3). Visual acuity was preserved and the patient did not report any symptoms. No intervention or change in therapy was performed.

A written informed consent was obtained for publication of this case report.

Conclusions

In this case report, we analysed a post discharge COVID-19 patient who underwent antiviral therapy with no heparin administration, while continuing his previous antiplatelet therapy. Our attention was focused on the origin of his retinal bleeding, which seemed likely due to a focal occlusion of the vessel.

As recently described,[2] COVID-19 may be associated with thrombotic events as a possible consequence of hypoxia secondary to ARDS, hyper-inflammation, platelet activation or endothelial dysfunction.

In addition, we must consider that bed rest and mechanical ventilation increase the risk of venous thromboembolism and are more prolonged in critically ill patients. Thus, the use of antithrombotic prophylaxis with low-molecular-weight heparin has been recommended by the International Society on Thrombosis and Haemostasis for all admitted patients without contraindications. Additionally, heparin revealed a useful anti-inflammatory action representing, nowadays, a cornerstone of treatment. However, discussion over the correct dosage of the drug is still ongoing.[2]

Although we present a patient with pre-existing heart disease, SARS-CoV2 could be involved in the mild occlusion of the peripheral circulation, as in our case, but also in more severe complications as reported by Yahalomi et al.[5]

According to COVID-19 guidelines, antiplatelet therapy should be continued in patients with acute coronary syndrome and acute stroke,[6] although there is insufficient evidence on the efficacy of antiplatelet therapy alone compared to heparin therapy.

Currently, the use of antiplatelet agents in COVID-19 is considered a potential alternative to anticoagulation and

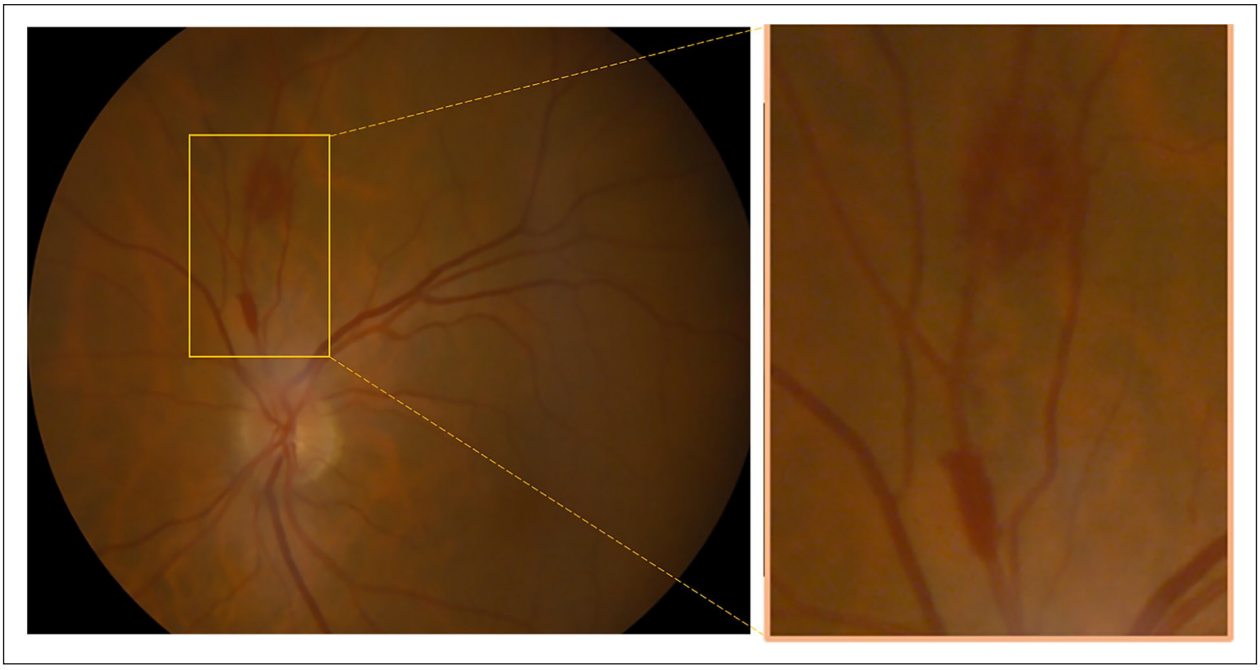

Figure 1. Colour fundus photography (Cobra HD Fundus Camera, CSO, Florence, Italy) of the left patient's eye at initial presentation. Multiple parapapillary intraretinal haemorrhages involving the superonasal quadrant observed on fundus examination and herewith showed in.

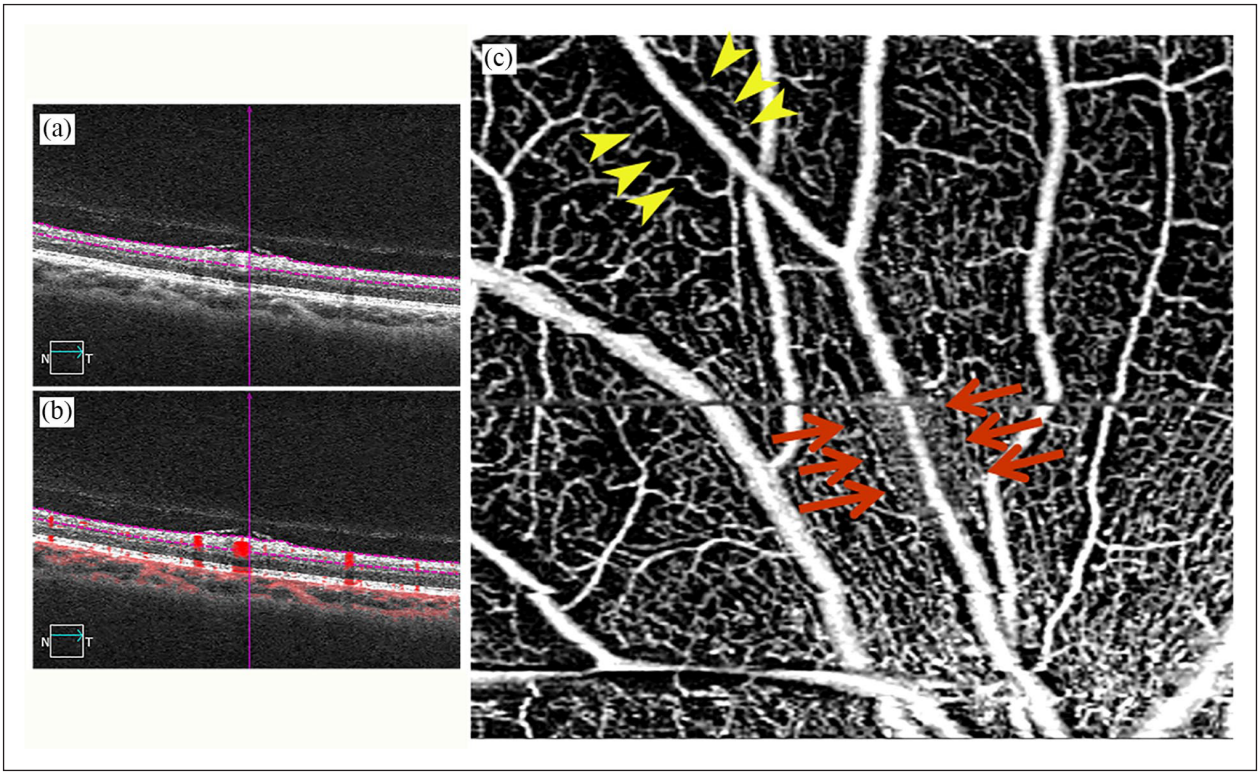

Figure 2. (a) OCT B-scan shows a sub-inner limiting membrane haemorrhage. A focal elevation of the ILM (internal limiting membrane) can be seen above the arterial vessel, (b) corresponding B-scan with the addition of flow details (red) to the OCT structural image, and (c) optical coherence tomography angiography details of the arterial focal occlusion 1-month COVID-19 after discharge. The image shows a perivascular haemorrhage (orange arrows) with reduced visualization of peri-vasal anatomical details and local narrowing of the vessel caliber. Beyond the retinal periarterial capillary free zone, which is a normal variant, we can note a pathological depletion of small-caliber vessels (yellow arrowheads) around the branch not responsible for bleeding, due to its blood flow reduction (Zeiss Cirrus 5000-HD-OCT Angioplex, sw version 10.0, Carl Zeiss, Meditec, Inc., Dublin, CA, USA).

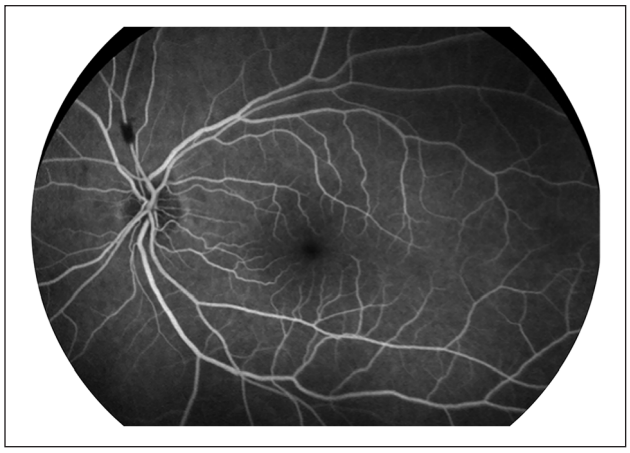

Figure 3. Fluorescein angiogram performed at 1-week follow-up visit showing a shadow effect secondary to the haemorrhage. No evidence of areas of ischaemia or vasculitis were observed.

an Italian study by Ranucci et al.[7] showed normalization of coagulation using a combination of heparin, clopidogrel, and antithrombin.

The role of dual antiplatelet therapy is a key factor in acute coronary syndrome, representing the current standard-of-care. In patients with STEMI (ST-Elevation Myocardial Infarction), the updated ESC (European Society of Cardiology) guidelines[8] recommend the administration of a P2Y12-receptor antagonist such as clopidogrel, prasugrel, or ticagrelor (loading dose 180 mg followed by 90 mg bid) in combination with ASA for 12 months. This therapy may be continued beyond 12 months in all patients with moderate to high risk of ischaemic events reducing the dose of the first drug (e.g. 60 mg bid of ticagrelor in combination with ASA).

Based on this indication, our patient fell into the moderate to high-risk category and was treated with prolonged dual antiplatelet therapy including aspirin and ticagrelor. This aspect is particularly important to our analysis because the combination of ticagrelor and low-dose aspirin reduced the occurrence of cardiovascular death but was associated with significantly more bleeding compared with placebo administration.

However, the scientific literature is divided regarding whether the risk of increased retinal or subretinal bleeding and the prevalence of ocular haemorrhage with anticoagulant therapy (about 8%) is higher than with antiplatelet drugs (dabigatran [1.9%] and ticagrelor [2.7%]).[9] We hypothesize that the retinal haemorrhages were caused not only by a combination of pre-existing factors including dual antiplatelet therapy but also for the generalized thrombotic microvascular effect by SARS-CoV-2.

We would like to emphasize that the patient showed additionally an increase in D-dimer (852 ng/ml) during the medical work-up, which is an important parameter to monitor the onset of a pro-thrombotic state in COVID-19 patients, although the considered predictive value of thromboembolism risk corresponded to 1000 ng/ml.

Recently, we described a potential peripapillary impairment in post-infectious patients likely due to the action of SARS-CoV-2 on retinal capillary microcirculation. Analysing OCT-A imaging, a reduction of RPCP-PD (radial peripapillary capillary plexus perfusion density) in a post-COVID-19 group compared to the control group was detected. This vascular impairment was found with greater frequency in hypertensive patients and in patients treated with antiplatelet therapy or lopinavir + ritonavir.[4]

Therefore, drug–to-drug interactions with anti-IL-6 (tocilizumab) and anti-viral (lopinavir, ritonavir, or darunavir) should also be considered. Ticagrelor is a substrate of CYP3A and the use of ticagrelor with strong CYP3A4 inhibitors (e.g. ritonavir) can increase the ticagrelor C_{max} and AUC leading to an increased risk of bleeding.[10]

More studies are needed to evaluate the presence of systemic vascular impairments involving multiple organs in patients who recovered from SARS-CoV-2 infection and to analyse the potential correlation between viral damage and unexpected haemorrhages. A question that opens new future observations could be whether the haemorrhages detected are those of an improving condition of possible larger retinal haemorrhages, which occurred in the acute phase of hospitalization.

Ophthalmologists should carefully investigate early signs of microvascular injury to understand the degree of retinal vascular involvement due to COVID-19 and to evaluate a possible regression of its manifestation.

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