Central Retinal Vein Occlusion After Discontinuation of Rivaroxaban Therapy in a Young Patient with COVID-19 Pulmonary Embolism: A Case Report

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Patient: Male, 38-year-old
Final Diagnosis: Central retinal vein occlusion
Symptoms: Visual acuity worsening
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases • Ophthalmology • Pulmonology

Objective: Unusual clinical course
Background: We present the report of the first case, to the best of our knowledge, of central retinal vein occlusion (CRVO) that occurred 3 days after anticoagulation discontinuation in a patient with a history of pulmonary embolism in the course of COVID-19.

Case Report: A previously healthy 38-year-old man was hospitalized in April 2021 with severe COVID-19 pneumonia, complicated by segmental and subsegmental pulmonary embolism. The patient was treated with a concurrent combination of remdesivir, dexamethasone, therapeutic enoxaparin, ceftriaxone, passive oxygen therapy, and convalescent plasma therapy, which led to pulmonary improvement. The treatment with therapeutic enoxaparin (80 mg/0.8 mL twice a day) was continued for 1 month after discharge, followed by 15 mg of rivaroxaban twice a day for 3 weeks and 20 mg of rivaroxaban once a day for 11 weeks. Within 3 days after rivaroxaban discontinuation, the patient experienced a decrease in visual acuity in his right eye, to the level of 5/25. Nonischemic CRVO with cystoid macular edema was diagnosed and an intravitreal injection of ranibizumab was performed. Common identifiable factors contributing to CRVO were excluded, and the treatment with prophylactic enoxaparin was initiated. Two weeks later, macular edema decreased significantly and visual acuity improved to 20/20. The treatment with enoxaparin was discontinued.

Conclusions: Rebound hypercoagulability after discontinuation of rivaroxaban therapy can manifest as CRVO in a young patient with a history of COVID-19 pulmonary embolism. It was successfully treated with an intravitreal injection of ranibizumab.

Keywords: COVID-19 • Retinal Vein Occlusion • Rivaroxaban

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Background

Central retinal vein occlusion (CRVO), one of the most prevalent retinal vascular diseases, is manifested by sudden, painless, unilateral deterioration in visual acuity. CRVO rarely affects patients at a young age. Age-related changes in the cardiovascular system are a leading factor in the development of CRVO. This ophthalmic disease is most often diagnosed in patients over the age of 60 years who have atherosclerosis, arterial hypertension, lipid disorders, obesity, or diabetes mellitus [1]. Typical risk factors may not be as important in patients younger than 40 years as in the elderly, except for hyperlipidemia. Moreover, hypercoagulable states, chronic venous inflammation, glaucoma, and the presence of an orbital tumor can play a role in the pathogenesis of CRVO in younger patients [2].

Changes in the human organism triggered by the presence of SARS-CoV-2 are associated with a high risk of thromboembolic events, leading to multi-directional failure of the organism [3,4]. Increased inflammation that is followed by the immune response of a cytokine storm leading to blood hypercoagulability and disseminated intravascular coagulation also affects the eyes. Because COVID-19 disease was not previously known, there were no guidelines available for the treatment of patients with COVID-19. Therefore, the disease itself and the medications used to treat patients with COVID-19 may have contributed to the occurrence of complications. We present the report of the first case, to the best of our knowledge, of CRVO that took place 3 days after rivaroxaban discontinuation in a patient who had a history of pulmonary embolism (PE) in the course of COVID-19.

Case Report

In October 2021, a 38-year-old man was referred for ophthalmological evaluation for decreased visual acuity in his right eye for the last 2 weeks. In April 2021, the patient was hospitalized for 17 days in the Department of Infectious Disease for severe COVID-19 pneumonia, confirmed with a real-time reverse transcription-polymerase chain reaction (RT-PCR) from a nasopharyngeal swab. The patient’s oxygen saturation on room air was 87%. His course was complicated by segmental and subsegmental PE, which was diagnosed by computed tomography with pulmonary angiography (CTPA) [5]. His previous medical history was negative, and he did not use any regular medication. The patient denied cigarette smoking, alcohol abuse, and drug use. His family history was negative for malignancy, blood clotting disorder, or venous thromboembolism. In the Department of Infectious Disease, the patient was treated with a concurrent combination of remdesivir, dexamethasone, therapeutic enoxaparin, ceftriaxone, passive oxygen therapy, and convalescent plasma therapy, which led to pulmonary improvement. The treatment with therapeutic enoxaparin (80 mg/0.8 mL twice a day) was continued for 1 month after discharge, followed by 15 mg of rivaroxaban twice a day for 3 weeks and 20 mg of rivaroxaban once a day for 11 weeks.

In September 2021, the patient was without symptoms and there were no radiological features of PE in the control CTPA; therefore, the treatment with rivaroxaban was discontinued. Within 3 days, the patient experienced a sudden, painless decline in visual acuity in his right eye and denied other symptoms. His past ocular history was negative, except for mild myopia. On initial presentation, his best corrected visual acuity was 5/25 in the right eye (RE) and 20/20 in the left eye (LE). The pupils were equally round and reactive to light and accommodation; relative afferent pupillary defect was absent. Intraocular pressure was 20 mm Hg in the RE and 16 mm Hg in the LE. Anterior segment examination was within normal limits in both eyes. Dilated fundus examination of the RE revealed a tortuosity and dilatation of all branches of the central retinal vein, with dot, blot, and flame hemorrhages in all quadrants. Mild optic disc edema, cotton-wool spots, and macular edema were also observed in the RE (Figure 1A). A fundus examination of the LE was normal. Swept-source optical coherence tomography of the RE demonstrated cystoid macular edema (CME), with a central retinal thickness of 459 μm (Figure 1B). Fluorescein angiography showed delayed arteriovenous transit time without areas of non-perfusion or neovascularization (Figure 2A, 2B). Nonischemic CRVO with CMO was diagnosed, and an intravitreal injection of ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland; Genentech Inc., South San Francisco, CA, USA) was performed 5 days after presentation.

The patient was immediately seen by a physician from the Internal Medicine Department, who found no abnormalities on physical examination. Due to the past medical history of PE after COVID-19 and recently discontinued anticoagulation, the internal medicine physician recommended treatment with prophylactic enoxaparin (40 mg/0.4 mL twice a day). Except for elevated blood cholesterol (243 mg/dL; reference range 115-190 mg/dL) and D-dimer (543 ug/L; reference range <500 ug/L) levels, all results from the following tests were unremarkable: diagnostic workup, including blood pressure, electrocardiography, complete blood count, glucose level, prothrombin time, international normalized ratio, activated partial thromboplastin time, C-reactive protein, erythrocyte sedimentation rate, antithrombin-III, protein C activity, protein S antigen, lupus anticoagulant, fibrinogen, anti-β-2-glycoprotein-1 antibodies, anti-cardiolipin antibodies, angiotensin-converting enzyme, QuantiFeron Gold, anti nuclear antibodies, anti-double stranded deoxyribonucleic acid antibodies, anti-tpo-pnema IgG and IgM, magnetic resonance imaging of the brain and orbits, and CTPA. RT-PCR for SARS-CoV-2 from the nasopharyngeal swab was negative. The treatment with enoxaparin...
was discontinued after 2 weeks because there was persistent bleeding from the wound of the lower limb after mild trauma.

At initial follow-up, 2 weeks after intravitreal injection of ranibizumab, macular edema decreased significantly and the RE visual acuity improved to 20/20 (Figure 3A, 3B). Within 3 months, hemorrhages and most cotton-wool spots resolved, and the patient denied any systemic and ophthalmological symptoms (Figure 4).

**Discussion**

We observed CRVO in our patient 3 days after discontinuation of the treatment with rivaroxaban for COVID-19-associated PE. We found no case report of CRVO after the cessation of rivaroxaban treatment or in the long interval after SARS-CoV-2 infection. The management of patients with COVID-19 and coagulation abnormalities can be challenging owing to the limited data. PE is the standard indication for full-dose anticoagulation, unless there is a contraindication to the therapy (including active bleeding) or to the use of heparin (history of heparin-induced thrombocytopenia). All patients with COVID-19 and documented PE should receive anticoagulation similar to individuals without COVID-19, and the treatment should be continued for 3 months. If the patient has recovered from COVID-19 and has no ongoing risk factors for venous thromboembolism, therapeutic anticoagulation could be discontinued [6-8]. While deciding on the duration of therapy, it is advised to balance the risk of thrombosis and bleeding.

In clinical practice, temporary interruption of treatment with rivaroxaban is common. There are only a few reported cases of “rebound thrombosis” after cessation of anticoagulation. Nagasayi et al described a patient with a permanent pacemaker and atrial fibrillation treated with rivaroxaban in whom
the treatment was discontinued due to traumatic acute subdural hematoma. Cessation of treatment resulted in an upper extremity deep vein thrombosis, which resolved after the reintroduction of the rivaroxaban [9]. Another reason for discontinuing rivaroxaban therapy was a parotid surgery in a 58-year-old male patient with atrial fibrillation. It resulted in PE within 4 days after drug discontinuation [10]. The drug was also withdrawn by patients without consulting their physician. In a review of reported complications following discontinuation of rivaroxaban therapy, the majority were stroke (23/31), followed by deep vein thrombosis, transient ischemic attack, and PE. Two patients who discontinued rivaroxaban without consulting their physician died after stopping therapy due to stroke and PE [11].

As mentioned above, PE provoked by a reversible risk factor has a low risk of recurrence and is usually treated for 3 months. However, premature discontinuation of rivaroxaban increases the risk of thrombotic events. Our patient received anticoagulation treatment for almost 5 months, and CRVO occurred 3 days after discontinuation of the therapy; no additional risk factors for thromboembolic events were identified. It is unknown how long the hypercoagulable state persists after SARS-CoV-2 infection and whether hypercoagulability is a reversible risk factor. There was a report of postoperative acute PE 6 weeks after a mild course of COVID-19 [12]. The pathogenesis of hypercoagulability in COVID-19 is not completely understood. There is evidence of direct endothelial injury, microvascular inflammation, and documented changes in prothrombin factors in patients with severe COVID-19 [13-16]. Post-COVID syndrome can occur up to 7 months in the postacute phase, and the mechanism of this complication is not completely understood. Organ injury and the chronic inflammatory process, as well as adverse effects of taken medicines, can lead to dyspnea, fatigue, neurological dysfunction, and many other symptoms after the acute phase of COVID-19 [17,18].

There are known reports of patients who experienced symptoms of CRVO in the acute phase of SARS-CoV-2 infection [19-22]. The treatment of the complications of CRVO includes systemic management, treatment of macular edema, and neovascularization [3]. In our patient, systemic assessment ruled out all common causes of a hypercoagulable state. Before the exclusion of venous thromboembolism and the occurrence of bleeding, the patient was treated with prophylactic enoxaparin for 2 weeks. Macular edema decreased and visual acuity improved after 1 injection of ranibizumab in our patient, and the treatment was discontinued. Previous case reports of CRVO with CMO following SARS-CoV-2 infection were treated with intravitreal injections of ranibizumab [22] and bevacizumab [20]. Oral methylprednisolone (40 mg/day) [22] and oral aspirin (150 mg/day) [19] have been used in therapy. Untreated CRVO without CMO also resulted in the complete resolution of symptoms [22].

From our patient’s perspective, the treatment of CRVO itself was not demanding, and his visual acuity improved rapidly to a pre-disease level. During the treatment with prophylactic enoxaparin, persistent bleeding from the wound of the lower limb occurred and the patient had difficulty walking. After excluding deep vein thrombosis, the decision was made to discontinue enoxaparin treatment. The patient remained asymptomatic for a further follow-up period, until June 2022.
Figure 3. (A) Color fundus photography of the right eye 2 weeks after intravitreal injection of ranibizumab. Significant reduction of vascular changes, hemorrhages, and cotton-wool spots. No macular and disc edema was visualized. (B) Swept source optical coherence tomography of the right eye 2 weeks after intravitreal injection of ranibizumab.

Figure 4. Color fundus photography of the right eye 2 months after intravitreal injection of ranibizumab. A small amount of cotton-wool spots remained.

A limitation of this case report is that the patient was treated in different hospitals; we based our description of the period associated with hospitalization due to SARS-CoV-2 infection on the medical record and consultation with the Department of Infectious Disease. Another limitation of the study is that it was not possible to identify the specific factor that influences the occurrence of CRVO. However, we have presented the possible pathomechanism and coincidence in time with the hypercoagulable state and discontinuation of rivaroxaban treatment in the discussion. The strength of the report is the exclusion of other most common identifiable factors contributing to the CRVO and the unique course of the disease. We found no case report of CRVO after rivaroxaban discontinuation due to any cause, especially in a young, previously healthy patient with a history of PE in the course of COVID-19.
Conclusions

Rebound hypercoagulability can occur after discontinuation of anticoagulant therapy in a young patient with COVID-19-associated PE. It can manifest as CRVO complicated by CMO, which can be successfully treated with an intravitreal injection of ranibizumab. However, it is not known when the treatment of the disease can be considered complete.

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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