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Acute ophthalmic artery occlusion in a COVID-19 patient on apixaban

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We report a case of ophthalmic artery occlusion (OAO) in a young patient with COVID-19 infection that was on therapeutic anticoagulation with apixaban for deep venous thrombosis (DVT).

A 48-year-old man with obesity was hospitalized with a severe form of COVID-19 infection, complicated with acute respiratory failure, septic shock, dilated cardiomyopathy and fungemia. Despite treatment with prophylactic enoxaparin (initial D-Dimer 1.14 μg/ml FEU (normal < 0.05 μg/ml FEU), D-Dimer increased to above 20 μg/ml FEU and patient continued to spike high fevers. This prompted further investigations and upper and lower extremities DVTs were confirmed and managed with enoxaparin 1 mg/kg twice daily. D-dimer level decreased to 4.98 μg/ml FEU while on therapeutic anticoagulation. Three weeks later pending hospital discharge, the anticoagulation was switched to oral apixaban 10 mg twice daily. Patient developed acute severe right eye visual loss of no light perception and was diagnosed with incomplete OAO. D-Dimer was elevated at 2.13 μg/ml FEU. Stroke etiological work-up found no embolic sources, resolution of the dilated cardiomyopathy and negative antiphospholipid antibodies. Treatment was changed to enoxaparin and no thrombotic events were encountered to date.

Ocular vascular complications have not yet been reported in COVID-19. Controversy exists on the best management algorithm for the hypercoagulable state associated to COVID-19 Either direct oral anticoagulants or low-molecular-weight-heparin are considered appropriate at discharge for patients with venous thromboembolism. The optimum regimen for ischemic stroke prevention and the significance of D-Dimer for anticoagulation monitoring in COVID-19 remain unclear.

Keywords: Ophthalmic artery occlusion—COVID-19—Stroke—Anticoagulation

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Ischemic stroke is a rising neurological complication of COVID-19 infection.[1–3] Previously reported ophthalmic findings in COVID-19 patients are mainly ocular surface disorders [4,5] and ocular vascular complications have not yet been reported. Ophthalmic artery occlusion (OAO) is a carotid circulation ischemic stroke syndrome. We report a case of acute OAO in a young patient with a severe form of COVID-19 infection that was on therapeutic anticoagulation with apixaban for deep venous thrombosis (DVT).

A 48-year-old man with a history of obesity (BMI 41 kg/m^2) and sleep-disordered breathing presented with fever, cough, and progressive dyspnea following a business trip to Florida two weeks before. The chest X-ray showed bilateral patchy middle and lower field pulmonary infiltrates. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA Reverse Transcriptase-PCR from the nasopharynx was positive. He was intubated

two days later for acute hypoxemic respiratory failure. Baseline D-Dimer was 1.14 μg/ml FEU (normal ≤ 0.05 μg/ml FEU). He was treated with hydroxychloroquine, tocilizumab and prophylactic enoxaparin 40 mg subcutaneous injections daily. Patient's hospital stay was complicated with septic shock treated with broad-spectrum antibiotics, dilated cardiomyopathy, acute renal injury and Candida albicans fungemia. Two weeks post-intubation on a surveillance check, D-Dimer value had increased to above 20 μg/ml FEU. This markedly elevated value and persistent fevers despite antimicrobials prompted venous duplex ultrasound that confirmed bilateral upper and lower extremities DVTs, and enoxaparin 150 mg (1 mg/kg) twice daily was started. Two days after the therapeutic dose of enoxaparin was started, D-Dimer value had decreased, however remained mildly elevated at 4.98 μg/ml FEU. Three weeks later pending discharge, decision was made to transition to oral apixaban 10 mg twice daily. Thirty-seven hours after the last dose of enoxaparin and twenty-four hours after apixaban was started, the patient developed sudden-onset painless right eye vision loss. Immediate ophthalmological examination showed visual acuity of no light perception in the right eye and 20/20 in the left eye. Anterior segment and motility examination were normal, and there was a right dense relative afferent pupillary defect. Dilated funduscopic examination showed mild optic disc edema, retinal whitening consistent with retinal edema, and mildly attenuated retinal vessels. No peripheral retinal hemorrhages or emboli were noted. 96 h later, the funduscopic examination showed more diffuse retinal and optic disc edema, with an intact area of retinal perfusion in the infero-temporal peripapillary region, retinal exudates, severely attenuated retinal vessels, and absent macular cherry-red spot, confirming a diagnosis of incomplete OAO. The funduscopic examination of the left eye was normal.

Laboratory work-up after the onset of visual symptoms revealed mildly elevated D-Dimer (2.13 μg/ml FEU), fibrinogen (608 mg/dl; normal range 200−400 mg/dl), prothrombin time (16.8 s; normal range 11.9−14.4 s), international normalized ratio (1.4; reference range 0.8−1.3), partial thromboplastin time (37 s; normal range 22−37 s), pro-calcitonin (0.13 ng/ml; normal ≤ 0.07 ng/ml), ferritin (718.73 ng/ml; normal range 21.81−274.66 ng/ml), mild lymphopenia (0.86 × 1000 μl/), bandemia (12 × 1000 μl/), thrombocytosis (511 × 1000 μl/)) and normal C-reactive protein (4.3 mg/l; normal ≤ 5 mg/l). Anticardiolipin and beta-2 glycoprotein IgA, IgM and IgG titers were not elevated. Lupus anticoagulant was not detected. MRI of the brain and orbits and CT angiogram head and neck were normal. Transthoracic echocardiogram was unremarkable. Patient was not on medications that could potentially affect apixaban metabolism (e.g. P-glycoprotein and strong CYP3A4 inducers). The anticoagulant regimen was changed to enoxaparin 1 mg/kg twice daily and the patient has had no further thrombotic events to date.

The incidence of thrombotic complications in patients with COVID-19 infection is elevated due to multiple factors and is associated with poorer outcomes.[6,7] In this case, a cardioembolic etiology of the OAO was unlikely. Although multifactorial cardiomyopathy was described in COVID-19,[8] and our patient had developed right ventricle dilatation initially, the repeat echocardiogram at the time of the OAO showed normal cardiac chambers' sizes, valves and myocardial motility. Telemetry monitoring did not show arrhythmias and transcranial doppler ultrasound with bubble study demonstrated no cardiac shunt. Antiphospholipid antibodies in association with multiple cerebral and systemic infarctions was recently described in 3 COVID-19 patients,[9] however our patient had negative titers of these antibodies. In a recent report of 5 young patients with ischemic strokes and large vessels occlusion, the presumed mechanisms were coagulopathy and vascular endothelial dysfunction and either antiplatelets or apixaban were begun.[3] The coagulopathy that COVID-19 patients develop may be unique and different from other virus-induced or sepsis related coagulopathy and considerable investigation remains to be done. Evidence of venous and arterial thromboembolic events in these patients suggest that pharmacologic anticoagulation prophylaxis for all hospitalized patients with confirmed or highly suspected COVID-19, regardless of venous thromboembolism (VTE) risk should be considered; such prophylaxis is recommended by major societies[10,11] (e.g. American Society of Hematology, International Society of Hemostasis and Thrombosis, Anticoagulation Forum). A systematic review of 26 consecutive patients with severe COVID-19 who were screened for VTE showed 100% rate of VTE in patients who received prophylactic anticoagulation when compared to 56% rate of VTE in patients receiving therapeutic anticoagulation.[7] Our patient also had evidence of VTE early in the infectious disease process and was treated with a therapeutic dose of low-molecular-weight-heparin (LMWH). One day after switching to therapeutic apixaban, he developed an arterial thrombotic event. D-Dimer was noted to remain mildly elevated despite therapeutic anticoagulation. While D-Dimer elevation have been associated with worse outcomes in patients with COVID-19,[6] it is unknown if intensification of anticoagulant therapy based on D-Dimer thresholds alone improve patient outcomes.[11] Current guidelines do not recommend monitoring D-Dimer for the purpose of guiding anticoagulant therapy,[11] even so in our case it provided meaningful information.

Controversy exists on the best management algorithm for the hypercoagulable state associated to COVID-19.[12] Prior reports support anti-inflammatory properties of heparin in other medical conditions,[13] and current anticoagulation guidelines endorse either direct oral anticoagulants or LMWH for COVID-19 patients with VTE at

hospital discharge.[10,11] Hence, the optimum regimen for ischemic stroke prevention in COVID-19 and the significance of D-Dimer for anticoagulation monitoring remain unclear and warrant further investigation.

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