CLINICAL VIGNETTE

Delayed Pulmonary Embolism after Mild COVID-19 Illness

Aldo Ilarde, MD and May-Lin Wilgus, MD

Clinical History

We present a 63-year-old male with active medical problems including Asthma, Ulcerative colitis, Depression, Hypogonadism, and Laryngopharyngeal reflux. The patient had a prior DVT involving the saphenous vein treated with several months of anticoagulation. He is a former smoker and uses recreational marijuana. Family history is pertinent for thromboembolism in his sister, and CAD and CVA in his father and paternal grandfather. His father also had penile and anal cancer while his maternal grandmother had pancreatic and lung cancers. His current medications include Testosterone gel, Sildenafil, Mesalamine, Sertraline, Zolpidem, Lansoprazole and scheduled infusions of vedolizumab.

The patient developed COVID-19 four months prior to presentation. Symptoms were mild and lasted one week. He was treated conservatively with supportive care and did not require hospitalization. After his COVID-19 infection he noted a progressive cough, shortness of breath and fatigue. He was treated for asthmas exacerbation with Doxycycline and glucocorticoids but did not improve. On exam he had exertional desaturation and positive D-dimer. Chest CT angiogram revealed bilateral pulmonary emboli, with no right ventricular strain. He was admitted and treated with apixaban and his asthma improved with inhaled fluticasone/umeclidin/vilanterol. Hypercoagulable evaluation was unrevealing. Hematology recommended lifetime anticoagulation and additional evaluation to rule out occult malignancy.

Discussion

Coronavirus disease 2019 (COVID-19) hit the world with such ferocity that we are continuing to grapple with this disease and its myriad effects on the human body and society. We were ill-prepared to deal with this global pandemic. Modern technology and medical science did not foresee the societal effects, challenging our health, political, cultural, and religious institutions. We have persevered but the challenge to conquer this virus continues.

COVID-19 infection, while predominantly respiratory, is now known to potentially impact multiple organ systems. One organ system adversely affected is the hematologic system and in particular the coagulation system. The pathogenesis of thromboembolism related to COVID-19 infection is likely multifactorial including endothelial injury from direct invasion of endothelial cells by SARS-CoV-2, complement activation, platelet activation, and an elevation of proinflammatory cytokines.[1] In acute illness, elevated D-dimer levels are associated with worse disease severity.[2]

Venous thromboembolism, including extensive deep venous thrombosis (DVT) and pulmonary embolism (PE), was very common in acutely ill patients with COVID-19 early in the pandemic, seen in up to one-third of patients in the intensive care unit (ICU) even when prophylactic anticoagulation was used.[3-5]

Arterial occlusion stroke, myocardial infarction, and limb ischemia have also been reported with COVID-19 infection. Microvascular thrombosis in autopsied lungs have been documented with unclear mechanism. Bleeding is less common even in patients receiving anticoagulation or those with thrombocytopenia.[6]

Patients hospitalized for COVID-19 without critical illness have lower incidence of VTE, estimated at 3%.[7] Thrombotic events have been observed in COVID-19 patients who were not admitted to the hospital but appear to be rare. Incidence of VTE in outpatients within 30 days after COVID-19 diagnosis was reported at 1.4% vs 1.3% in controls,[8] and the ACTIV-4B trial, a randomized trial of outpatient thromboprophylaxis, reported only a single VTE among 558 participants (0.2%), with no thromboembolic events.[7] Nevertheless, other studies, detected an association between mild COVID-19 illness and VTE. A large Danish cohort study of post-acute effects of COVID-19 in non-hospitalized patients, reported a significantly higher rate of VTE in COVID patients (0.2%) vs controls (0.1%), with RR 1.77 (1.09-2.86).[9] A smaller case control study of VTE incidence 3 months post mild COVID-19 illness, Clavijo et al reported a significantly higher rate of VTE in the COVID patients vs controls, even after adjusting for risk factors including prior VTE and cancer.[10]

The observed association between COVID-19 infection and VTE led to the incorporation of anticoagulation into many early treatment protocols. Subsequent data has shown that use of empiric therapeutic anticoagulation for critically ill COVID patients is not superior to standard dose prophylaxis.[11] The use of empiric therapeutic anticoagulation for hospitalized but not critically ill COVID-19 patients may have benefit over prophylactic anticoagulation.[12] In contrast, use of therapeutic or prophylactic anticoagulation for management of outpatients

with COVID-19 has not been proven beneficial. The ACTIV-4B trial comparing therapeutic dose apixaban, prophylactic dose apixaban, low dose aspirin, and placebo was stopped early due to low rates of VTE and showed no difference in outcome between the groups.[13]

Conclusion

COVID-19 illness is associated with increased risk for VTE, and this risk likely extends to outpatients with mild COVID-19 disease. Our patient may have unidentified heritable risk factors for VTE, but the trigger for his pulmonary embolism appears to be COVID-19 infection. The duration of inflammatory activation post COVID-19 illness is uncertain, and thromboembolism should be considered in patients with even a subacute history of COVID who present with dyspnea, particularly in those patients who have additional risk factors for VTE. VTE may be part of the spectrum of long COVID.[14] Our patient is being evaluated and treated for other features of long COVID including fatigue. He remains on lifelong anticoagulation and will undergo further testing to exclude chronic thromboembolism.

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