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Extensive Peripheral Arterial Thrombosis in a Patient with SARS-CoV-2 Infection

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Abstract Thrombosis is one of the major underlying pathogenetic mechanisms leading to increased morbidity and mortality among COVID-19 patients. Thromboembolic events as well as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are the major causes of death in this continued pandemic. While elevated D-dimer level suggests worse thrombotic outcomes, levels at which benefits of anticoagulation outweigh the bleeding risk is yet to be determined. In this report, we present a case of a 72-year-old man with COVID-19 presented with confusion and subsequently developed acute hypoxic respiratory failure. On hospital day 7, patient developed extensive peripheral arterial thrombosis with acute rise of D-dimer from 800 to 14,899 ng/ml. He was treated with heparin drip and underwent urgent brachial, radial and ulnar embolectomy under general anesthesia. In this report, we also discuss the pathogenetic mechanisms and management of thromboembolism in COVID-19 patients, highlighting the role of early detection and aggressive therapeutic interventions that could be life and / or limb saving strategy.

Keywords: *COVID-19, limb ischemia, arterial thrombosis, point-of-care ultrasound, D-dimer*

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1. Introduction

Since the first detected case of Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in December 2019, the virus has spread at a formidable pace to infect more than 11.3 million individuals globally, claiming over 532,000 lives by July 2020. Our understanding of this devastating disease is growing exponentially. To date, there is an increasing concern of thrombosis, coagulopathy and thromboembolic events in patients with SARS-CoV-2 infection [1]. Increased rate of venous thrombosis and acute ischemic cerebrovascular accidents were reported in patients requiring critical care in Netherlands despite at least standard doses of thromboprophylaxis [2]. Increasing rate of both disseminated intravascular coagulation (DIC) and cerebrovascular accidents attributed to arterial thrombosis has been reported [3]. Increased risk of mortality in patients with COVID-19 was associated with coagulopathy reflected in increased levels of D-dimer, fibrinogen degradation products and prolonged thromboplastin time [4]. Higher rate of mortality was also noted in COVID-19 patients with D-dimer levels greater than 1,500 ng/mL when compared to those with lower values [5]. Therapeutic anticoagulation in COVID-19 patients, who demonstrate greater than 6-fold increase in D-dimer, was associated with a 20% reduction in mortality in a series of 449 Chinese patients [6]. Locally, central arterial thrombosis of the cerebral and coronary circulation were reported in New York City [7]. All patients had an elevated level of D-dimer, suggesting that SARS-CoV-2 induced coagulopathy may be a significant culprit in these cases. This suspicion was confirmed in autopsies study in COVID-19 patients, showing that peripheral parenchyma exhibited aggregates of thrombosed vessels and significant hemorrhage [8]. Despite numerous cases of coagulopathy, acute limb ischemia has rarely been reported, we present a case of acute limb ischemia in a patient infected with SARS-CoV-2.

2. History of Presenting Illness

A 75-year-old male was brought in by EMS to the hospital after his daughter found him confused on the morning of presentation. The daughter reported that her father had become increasingly weak over the past week and had been complaining of cough and fever. On presentation, he was found to be febrile to 101.3^{0}F, tachycardiac to 104 beats per minute, with a blood pressure of 143/81 mmHg and saturation of 91% on room air, breathing 18 times a minute. Examination revealed an elderly man in mild respiratory distress who was disoriented to time and person. He had labored breathing with use of accessory muscles of respiration and scattered coarse crackles in bilateral lung fields. Cardiovascular examination did not elicit abnormal jugular venous distension, cardiac murmurs or peripheral edema. His extremities were warm and distal pulses palpable and symmetrical in all four extremities.

He had a history of hypertension, coronary artery disease (quadruple coronary artery bypass surgery in 2006), smoking (20 pack years) and mild dementia. His medications included aspirin 81 mg, clopidogrel 75 mg, metoprolol succinate 50 mg, enalapril 5 mg and rosuvastatin 20 mg.

The differential diagnosis include community acquired pneumonia and atypical pneumonia from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.

His hemoglobin was 12.6 gm/dl, WBC count 8.6 x 10^3 cell/uL (3% lymphocytes) and platelet count 172 x 10^3 cells/mm^3. He had a sodium of 138 mEq/L, potassium of 4.4 mEq/L, chloride of 106 mEq/L, bicarbonate of 22 mEq/L, BUN of 35 mg/dL, creatinine of 1.7 mg/dL, ferritin of 1650 ng/mL, CRP of 20 mg/L and D-dimer of 1,222 ng/ml. Troponin-I was 0.083 mg/mL. Electrocardiogram revealed normal sinus rhythm, Q waves in the inferior leads and a QT_c duration of 394 milliseconds. Chest x-ray showed bilateral patchy opacities in the mid to low lung fields. Nucleic acid amplification test for SARS-CoV-2 was positive.

Therapy was initiated with hydroxychloroquine 400 mg BID and azithromycin 500 mg. This was followed by hydroxychloroquine 200 mg BID for 7 days, azithromycin 250 mg QD for 5 days and subcutaneous heparin injections for VTE prophylaxis.

Over the next 2 days, the patient's hypoxic respiratory failure worsened and his oxygen requirements progressively increased requiring a 50% FiO_2 Venturi-mask. Chest x-ray demonstrated worsening bilateral patchy infiltrates and areas of consolidation (Figure 1). He was transferred to the MICU on day 3, placed on a non-rebreather and started on methyl prednisolone and ceftriaxone.

The patient had a mid-line catheter placed into his right antecubital vein on day 4. No arterial line was placed and he had one radial arterial blood gas sampling on day 3. His respiratory status stabilized with the above treatment. On the morning of day 7, his D-dimer was noted to have risen sharply (Figure 2) and the dose of low molecular weight heparin was doubled. In the afternoon of day 7, he complained of new sharp pain in his right hand. On examination, his right hand was cool to the touch and no brachial or radial pulse could be palpated. Point-of-care ultrasound was consistent with flow obstruction in the territory supplied by the right brachial artery (Figure 3). Heparin drip was initiated and he underwent urgent brachial, radial and ulnar embolectomy under general anesthesia. Cylindrical thrombi measuring 0.3 cm to 8.5 cm in length and 0.2 cm to 0.4 cm in diameter were extracted (Figure 4). Post-operatively, right brachial and radial pulses and strong palmar doppler arch signals were appreciated. He was subsequently successfully extubated and transitioned to enoxaparin (1mg/kg BID). Two-dimensional echocardiography did not reveal a cardioembolic source for the thrombus. No underlying hypercoagulable disorder or DIC was identified.

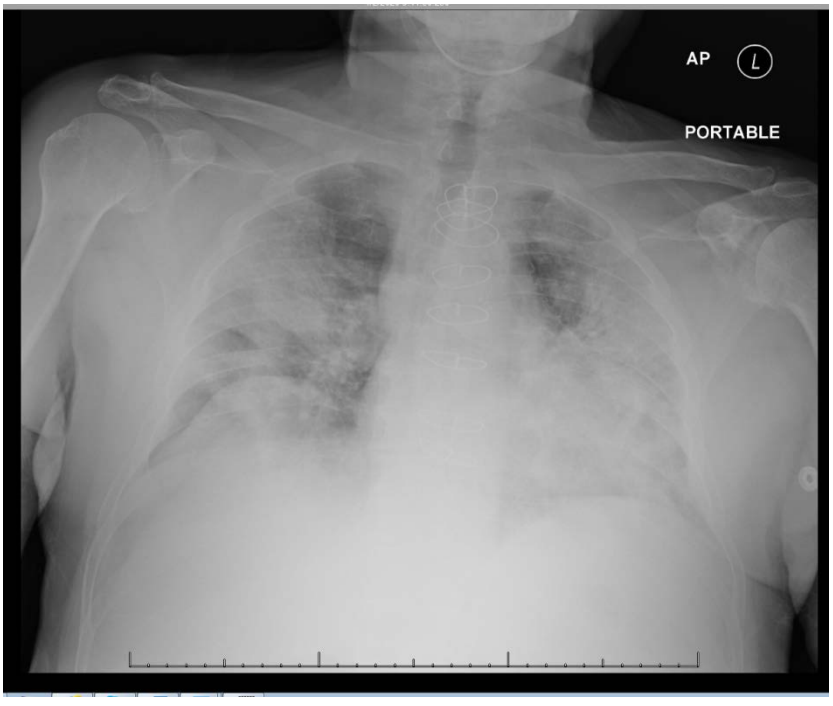

Figure 1. Chest x-ray demonstrated worsening bilateral patchy infiltrates and areas of consolidation

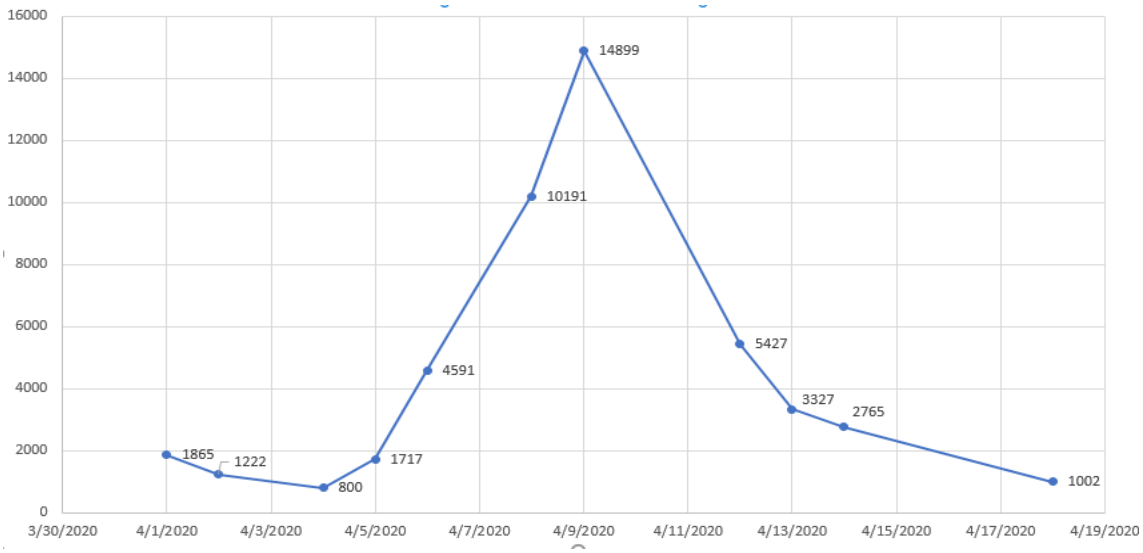

Figure 2. Demonstrates sharp rise in D-dimer level from 800 to 14,899 ng/ml associated with extensive thrombosis

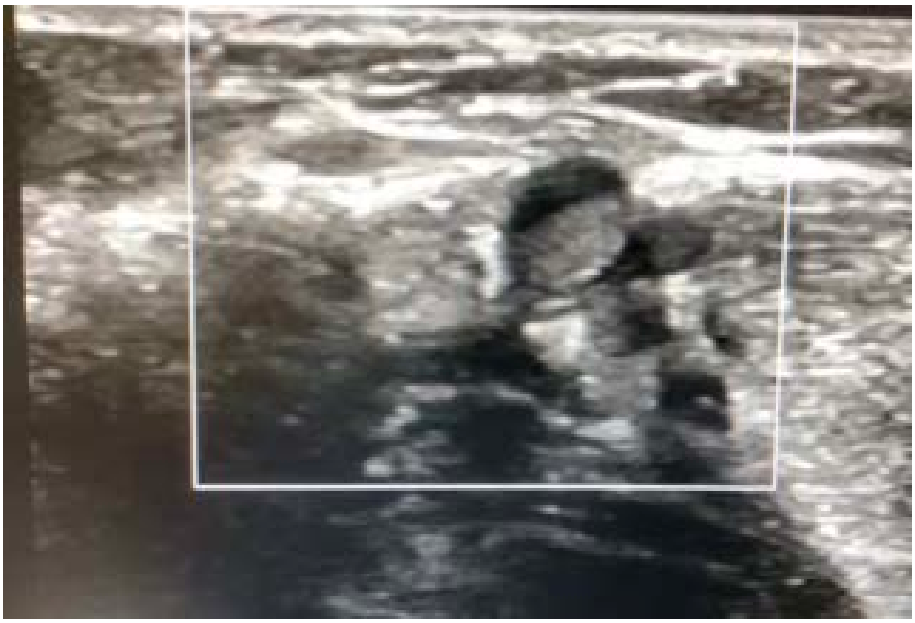

Figure 3. Flow-limiting right brachial arterial thrombus on point-of-care vascular ultrasound

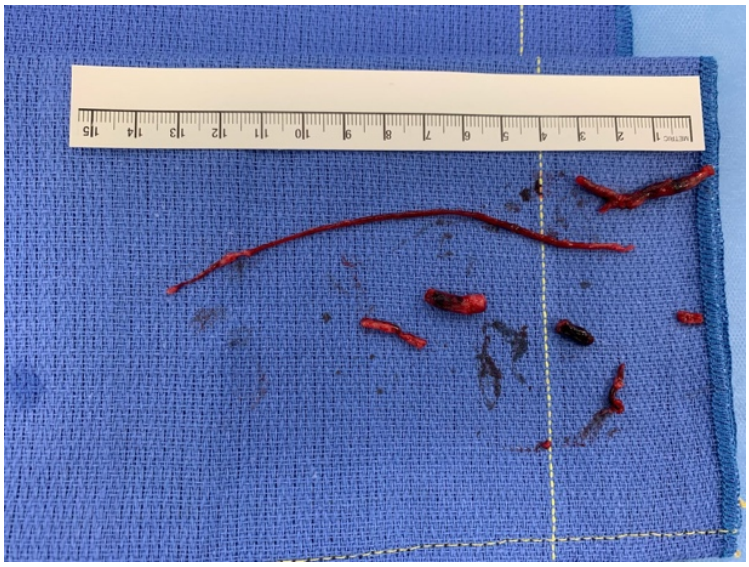

Figure 4. Cylindrical thrombi measuring 0.3 cm to 8.5 cm in length and 0.2 cm to 0.4 cm in diameter were extracted via brachial, radial and ulnar embolectomy under general anesthesia

3. Discussion

Since the first detected case of SARS-CoV-2 in December 2019, the virus has spread at a formidable pace to infect more than 2 million individuals globally, claiming close to 140,000 lives by mid-April 2020. There is a growing body of evidence that suggests that patients with SARS-CoV-2 infection are at increased risk of thrombosis, coagulopathy and thromboembolic events [1]. A recent study from Netherlands reported a 31% incidence of thrombosis in 184 patients admitted to the ICU [2]. Chen *et al* attributed 19 of the 133 deaths in a Chinese patient cohort to DIC [3]. Coagulopathy manifesting in increased D-dimer, fibrinogen degradation products and prolonged thromboplastin time were associated with increased risk of mortality in a cohort of 183 Chinese patients [4]. A retrospective analysis from 2 hospitals in China confirmed that patients with D-dimer levels greater than 1,500 had higher mortality when compared to patients with lower values [9]. Anticoagulation with heparin or enoxaparin in SARS-CoV-2 infected patients who demonstrate greater than 6-fold increase in D-dimer, was associated with a 20% decrease in mortality in a series of 449 Chinese patients [6]. In a recent series from New York city of 18 SARS-CoV-2 infected patients evaluated for ST-elevation myocardial infarction, 2/3rd patients who underwent coronary angiography were found to have obstructive coronary disease. All patients had elevation of D-dimer, suggesting that SARS-CoV-2 induced coagulopathy may be a significant culprit in these cases [7].

The results of a series of autopsies conducted on SARS-CoV-2 infected patients showed that although the pulmonary arteries at the hilum were free of thrombus, peripheral parenchyma exhibited aggregates of thrombosed vessels and significant hemorrhage [8].

It appears that hypoxia from pulmonary involvement, an inflammatory response to viremia, prolonged immobilization and diffuse intravascular coagulation all possibly contribute to the pro-thrombotic state associated with SARS-CoV-2 infections [9,10]. The virus predisposes infected patients to both venous and arterial thrombosis [3]. In light of such reports, many institutions have adopted an approach to anticoagulate at therapeutic doses for VTE based on their absolute D-dimer levels. Yin *et al* demonstrated an improved prognosis with the use of enoxaparin in severe SARS-CoV-2 infection and D-dimer levels greater than six times the upper limit of normal [4].

Acute arterial occlusion can lead to life or limb threatening ischemia and is a vascular emergency. It is more common in the lower extremities and most frequently affects patients with a history of peripheral arterial disease. Other causes include embolism from the heart, aorta or iliac arteries and blunt penetrating trauma [11]. We are reporting a case of extensive upper extremity arterial thrombosis attributed to infection with SARS-CoV-2.

Our patient had a D-dimer of 1,222 ng/ml, which was less than six times the upper limit of normal. Despite being on prophylactic doses of heparin to prevent VTE, with no identifiable risk factors for hypercoagulability and no source of thromboembolism, he suffered from extensive limb threatening thrombosis.

While elevated D-dimer seems to suggest worse outcomes, it is challenging to define a level at which initiating therapeutic anticoagulation may be beneficial. Individual patients may have different levels at which systemic thrombosis occurs based on underlying comorbidities.

The patient continues to be treated for his hypoxic respiratory failure with high flow nasal cannula.

4. Conclusion

This is one of the first few reported cases of extensive peripheral arterial thrombosis with SARS-CoV-2 infection. Our case highlights the urgent need for retrospective analysis and clinical trials to define the value of D-dimer at which initiating therapeutic anticoagulation to prevent life-threatening thrombosis would be beneficial.

Patients with SARS-CoV-2 infection have high incidence of both arterial and venous thromboses. Our case emphasizes the need for a robust vascular examination on SARS-CoV-2 infected patients and consideration of early anticoagulation.

Abbreviation List

VTE: Venous thromboembolism
DIC: Disseminated intra-vascular coagulation

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