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Bilateral upper extremity thrombosis associated with protein C deficiency in a COVID-19 patient; a case report

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Abstract

The coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has affected different communities all over the world. A wide spectrum of complications has been reported due to COVID-19 infection, among which a hypercoagulability state is one of the most significant. The patient was a 44-year-old obese woman with a history of diabetes, hypothyroidism, cigarette smoking and opium addiction, who had recently been diagnosed with COVID-19 and had undergone cardiac surgery due to right atrial thrombosis. The patient was also affected by bilateral upper extremity thrombosis 20 days after surgery. Protein C deficiency was diagnosed by measuring serum levels and she was discharged from the hospital with apixaban instead of warfarin due to protein c deficiency.

Keywords: COVID-19, SARS-CoV-2, Thrombus, Protein C deficiency, Anticoagulation

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Introduction

Coronavirus disease 2019 (COVID-19) disease can be a critical illness with multi-organ involvement. Thrombosis formation, in these patients can be associated with increased mortality and morbidity (1,2).

Pulmonary embolism (3), stroke, venous thrombosis (4) and ischemic heart disease have been reported as thrombotic complications (1,2). We present an interesting case of protein C deficiency which was diagnosed after COVID-19 infection and manifested with different vascular complications.

Case Report

A 44-year-old female patient with a history of diabetes, opium addiction, cigarettes smoking and hypothyroidism, who had undergone heart surgery, was admitted to the emergency department for sudden onset severe acute pain in both upper extremities, three weeks after cardiac surgery. She had a history of hospitalization and treatment for COVID-19 (in December-2020) with remdesivir and corticosteroids. Cardiac surgery had been performed in order to remove multiple mobile masses in the right atrium (3×4 cm) and in the inferior vena cava (1.5×1.5 cm), which were confirmed to be clots by histopathologic study. The patient was discharged with low-dose anticoagulation and

an international normalized ratio (INR) of around 2.5, normal peripheral pulses and normal echocardiography without complications.

Three weeks later, the patient was readmitted to the intensive care unit based on clinically suspicious arterial thrombosis. On physical examination, blood pressure was 140/80 mm Hg, the pulse rate was 88 beats per minute and the respiratory rate was 16 per minute with mild dyspnea. Examination of the extremities in the emergency department revealed pain, discoloration, coldness with decreased sensation in bilateral upper limbs predominantly on the right side. The peripheral pulses of the upper extremities were not easily detected (1+).

Echocardiography demonstrated a left ventricular ejection fraction of 55%, moderate tricuspid regurgitation and high pulmonary artery pressure. Doppler ultrasonography and computed tomography angiography of upper extremity vessels were performed. Thrombosis of the right radial, left ulnar and lower two thirds of the brachial arteries, right cephalic, basilic and internal jugular veins were reported by Doppler ultrasonography. The computed tomography angiography report showed that the right innominate, subclavian, brachial, ulnar and interosseous arteries were normal. The right radial artery was occluded. The proximal to mid part of the

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■ Implication for health policy/practice/research/medical education

A wide spectrum of complications has been reported due to COVID-19 infection. There is still concern about the increased risk of acute thrombosis and hypercoagulation in COVID-19 patients, but this risk seems to be higher in patients with protein C deficiency.

left ulnar artery was occluded and no contrast filling was seen in it. The left radial artery was patent along its entire course down to the palmar arch. Pulmonary computed tomography (CT) angiography was conducted to detect a possible embolism of the pulmonary arteries. The computed tomography angiography of pulmonary arteries showed signs of acute embolism in the segmental branches of the right pulmonary artery. Spiral CT scan of the chest without contrast showed pulmonary edema and barely visible patches of ground glass opacity at the basal segments of the left lower lobe which was an indeterminate for COVID-19 infection. Laboratory tests revealed decreased platelet levels ($120\,000/\text{mm}^3$), leukocytosis (white blood cell= $13\,800/\text{mm}^3$ and neutrophil count = 87.4%) and an international normalized ratio (INR) of 2.2. We found that the patient had a history of protein C deficiency based on laboratory tests.

In order to exclude other sites of thrombosis, systematic vascular ultra sound assessment of the lower extremities was undertaken. No signs of systemic thrombosis were detected. The medical team decided to start therapeutic anticoagulation with intravenous unfractionated heparin with an initial bolus dose of 8000 units followed by a constant maintenance infusion of 1500 units per hour. Laboratory monitoring was conducted by checking activated heparin time and INR. On the fifth day after starting the anticoagulant, her pain resolved and the color of the upper limbs improved and on the tenth day, she made a full recovery. Aspirin (80 mg daily) was added to the anticoagulation treatment in addition to insulin, levothyroxine, methadone, furosemide, losartan and ceftriaxone.

After the discontinuation of heparin and warfarin due to protein C deficiency, apixaban was prescribed instead of warfarin. On day 12, the patient was discharged from hospital in a stable condition.

A 3-month follow-up showed normalization of the patient's condition without the recurrence of symptoms. Protein C was tested again after three months and was still low.

Discussion

Based on the evidence, cardiovascular involvement during COVID-19 disease may play a major role in the prognosis. COVID-19 has been associated with increased cardiovascular complications including myocarditis, arrhythmias and pulmonary embolism (2,5).

Furthermore, COVID-19 infection has been

accompanied by inflammation and thrombosis, which have mutual interaction and the inflammatory state of the infection can lead to hypercoagulability (6).

Intra cardiac thrombosis has rarely been reported in COVID-19 patients (7,8). Right heart thrombus formations a critical condition which can lead to pulmonary embolism (2,9). In some studies, inherited thrombophilia has been reported to increase the risk of thrombosis in COVID-19 patients (10). Congenital protein C deficiency is a rare autosomal dominant disease with homozygous and heterozygous types and is associated with an increased risk of abnormal clot formation (11,12). The acquired type of the disease has been reported in some cases, such as the use of vitamin K antagonist, sepsis and disseminated intra vascular coagulation (9).

The role of protein C deficiency in venous thromboembolism has been discussed in different studies; however, there is a relatively low-incidence of arterial thrombosis in this setting (11,13). Arterial thrombosis in our patients also rare in this regard.

Activated protein C has been known to have a pivotal anti-inflammatory and anti-coagulation role. It has been established that on admission level of protein C in COVID-19 has been associated with short term mortality (13).

Our patient had a history of a COVID-19 infection coupled with protein C deficiency and both of these two conditions appear to be effective in the formation of thrombotic masses in the heart as well as in the arteries of the upper extremities. Surgery was performed to remove the thrombotic mass in the right atrium and the upper limb thromboses were treated medically, and these measures were effective in stabilizing the patient. Use of novel oral anticoagulants (NOACs) in protein C deficiency is recommended due to absence of a decrease in the levels of protein C and S with their consumption (11).

Conclusion

There is still concern about the increased risk of acute thrombosis and hypercoagulation in COVID-19 patients, but this risk seems to be higher in patients with protein C deficiency. Therefore, careful examination of patients in combination with appropriate anticoagulation therapy can play an important role in treating these patients.

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Authors' contribution

Conceptualization: ZAA; Methodology: SJ; Validation: ZAA; Formal Analysis: SMM; Investigation: HG; Resources: SJ; Data Curation: SAM; Writing—Original Draft Preparation: SMM; Writing—Review and Editing: HG; Visualization: SAM; Supervision: SMM; Project Administration: ZAA; Funding Acquisition: SJ.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. Written informed consent was obtained from the patient for publication of this report.

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