



Case report

Sudden development of the upper and lower limb ischemia as the first manifestation of COVID-19 infection

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ABSTRACT

Introduction and importance: Atherosclerosis is the most common cause of peripheral vascular disease, and common predisposing causes are inflammation and diabetes. It is over two year that the COVID-19 pandemic has impacted the world and costed millions of lives.

Case presentation: The patient was a case of COVID-19 infection presenting as acute arterial occlusion in the upper and lower limb.

Clinical discussion: Hyper coagulopathy is one of the COVID-19 outcomes that may develop PAD following the involvement of vascular endothelium in the cytokine storm phase. Endothelial damage following COVID-19, especially in those with underlying diseases such as diabetes mellitus or inflammatory diseases with vascular involvement, can cause acute vascular events.

Conclusion: Patients with inflammatory diseases and diabetes are prone to the uncommon symptoms of COVID-19 and more vulnerable to peripheral vascular occlusion, especially when the underlying disease remains uncontrolled, so anticoagulation with therapeutic doses is recommended for their treatment. Inflammation as a pre-disposing factor for PAD should be controlled using plasmapheresis or anti-inflammatory drugs depending on the patient's condition.

1. Introduction

Peripheral arterial disease (PAD) is a slowly progressive condition caused by atherosclerotic changes in the artery wall, gradually leading to the narrowed arterial lumen and decreased blood flow. In 2018, PAD affected about 118 million people worldwide [1]. There are two etiologies for PAD: atherosclerotic and non-atherosclerotic. In atherosclerotic lesions, occurring in 85 % of population aged above 65, thrombosis blocks pre-narrowed arteries and causes severe stenosis [2]. In non-atherosclerotic lesions, accounting for 10 to 15 % of the cases, thromboembolism occurs when a blood clot travels from another region, such as the heart or aneurysmal arteries, and causes an arterial blockage [3]. In other specific conditions, such as paradoxical embolism or phlegmasia cerulea dolens, the resulting embolism has a venous origin [4].

The incidence of thromboembolism in the lower extremities is four times higher than that of the upper extremities [5]. Thrombosis of the upper extremity resulting from atherosclerosis usually requires bypass

surgery and thromboembolectomy and is very uncommon. The risk factors of thrombosis of the upper extremity include age, hypertension, diabetes, heart failure, and trauma, as well as iatrogenic factors, such as catheterization [6].

In December 2019, pneumonia caused by severe acute respiratory syndrome Coronavirus-2 (SARS-CoV2) emerged from Wuhan, China, called Coronavirus disease 2019 (COVID-19) [7]. The early manifestations of the disease include fever, cough, shortness of breath, fatigue, nausea and vomiting, anorexia, diarrhea, and abdominal pain [8]. Numerous reports highlighted coagulation disorders in patients with COVID-19, and laboratory test results indicate such complications in 20 to 50 % of patients admitted to hospital with COVID-19 (i.e., high serum D-dimer levels, thrombocytopenia, decreased serum fibrinogen levels) [9].

This report presents a case of Rheumatoid Arthritis and type 2 diabetes mellitus presenting with symptoms of ischemia in the upper and lower limbs and underwent thromboembolectomy and endarterectomy,

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and was diagnosed with COVID-19 infection afterward.

2. Case presentation

The case was a 47-year-old female patient referring to the emergency department following pain, swelling, and sudden coldness in the left hand and right foot. The symptoms started the evening of the attending day with numbness in the left-hand fingers; she was transferred to the hospital following the exacerbation of numbness, coldness, and swelling in the left hand. She reported similar symptoms in the right foot during transfer. Her vital signs on arrival were as follows: blood pressure 90/60 mmHg with sinus tachycardia of 100 bpm and a respiratory rate of 20 beat/min, a body temperature of 36.8 °C, and an oxygen saturation level of 98 %. She did not report a history of claudication. She had a past history of rheumatoid arthritis (RA), type 2 diabetes mellitus (DM), dyslipidemia, and no psychosocial history. She was taking prednisolone 5 mg every 12 h, glibenclamide 5 mg daily, as well as metformin 500 mg daily was taken to control diabetes. On physical examination, the left upper extremity was cold, cyanotic and had non-fixed mottling with slow capillary refill (>4 s), paresthesia was evident, and a muscle force of 0 out of 4 was reported; in addition, brachial, ulnar, and radial pulses were impalpable. Musculoskeletal examination of the upper extremities indicated ulnar deviation of the wrists, MTP joint swelling, and reduced ROM, along with tenderness in joints. In the right lower extremities, the limb was cold, cyanotic and non-fixed mottling was detectable, paresthesia and a muscle force of 2 out of 4 was reported; in addition, dorsalis pedis, posterior tibial and popliteal pulses were impalpable, and water hammer pulse was palpated in the femoral artery. The patient also had grade 2 diabetic foot ulcers based on the Wegener classification on the palmar surface of her right toe. There was no active arthritis in the lower extremities.

With the clinical examination findings in favor of ischemia, treatment with bolus intravenous dose of heparin 5000 unit continued with infusion of 1000 unit per hour of heparin and aspirin tablet 300 mg stat and 80 mg per os daily plus atorvastatin tablet 80 mg stat and 40 mg daily per os was immediately started.

Arterial color Doppler ultrasound was performed, and echogenic thrombosis was detected in the brachial artery; and, blood flow in the brachial, ulnar, and radial arteries was absent. Color Doppler ultrasound on the right lower extremities did not show a clear blood flow in the dorsalis pedis and posterior tibial arteries. According to the patient's lymphopenia and Computed Tomography (CT) scan findings (Fig. 1), a Polymerase Chain Reaction (PCR) was performed on nasopharyngeal and oropharyngeal swabs, in order to confirm the diagnosis of COVID-19 infection.

According to the Rutherford classification, grade IIb (immediately threatened) in the left hand and IIa (marginally threatened) in the right foot were raised. The patient was immediately transferred to the

operating room and thrombectomy of the right lower limbs was performed in femoral and for the left upper limbs in the brachial, radial, and ulnar arteries.

In paraclinical practices, the laboratory test results were as follows:

Hemoglobin 8.4 g/dl (12–16), mean corpuscular volume 79 fl (80–96), total leucocyte count 8600 cu/mm (4000–10,000), absolute neutrophil count 7052 cu/mm (1500–8000), absolute lymphocyte count 902 cu/mm (1500–4500), platelets 363,000 (150,000–450,000), urea 61 mg/dl (15–45), serum creatinine 2.2 mg/dl (0.5–1.4), prothrombin time 15.9 s (9.9–13), international normalized ratio 1.5 (1–1.4), partial thromboplastin time 30 s (60–45), lactate dehydrogenase 2751 U/l (0–500), C-reactive protein 3+ (negative), ferritin level 360 ng/ml (4.6–204), rheumatoid factor 3+ (negative), albumin 2.7 g/dl (3.5–5.5), aspartate aminotransferase 445 u/l (5–40 u/l), alanine aminotransferase 41 u/l (5–40 u/l), alkaline phosphatase 212 u/l (64–306), beta-2 glycoprotein IgM and IgG negative, anti-cardiolipin IgM and IgG negative, C3 77 mg/dl (75–165), C4 12.4 mg/dl (10–40), CH50 80 U (70–150), blood sugar 263 mg/dl (70–140).

Echocardiography showed normal functioning left and right ventricles and normal valves. Ejection fraction was 50 %. No clots and vegetations were reported.

The patient had palpable pulses in the right lower extremity and adequate capillary filling after the thrombectomy, and the limb was warm. The left upper extremities were warm to the wrist, but the radial and ulnar pulses were still impalpable; however, blood flow was detectable on pen Doppler ultrasound, and the pulse oximetry revealed a SatO₂ of 98 %, similar to the opposite hand. At the dorsal side of the left hand, two 2 × 2 cm ischemic lesions were detected. The left hand was swollen and cyanotic.

On the 3rd day of hospitalization, the patient was transferred to the COVID-19 ICU based on the positive result of PCR. Following the exacerbation of the patient's condition she faced a decrease in consciousness and metabolic acidosis. Unfortunately, on the 5th day of hospitalization, cardiac and respiratory arrest occurred, and she did not survive despite clinician's attempt. The work has been reported in line with the SCARE 2020 criteria [10].

3. Discussion

Ischemia in the upper extremities accounts for <5 % of extremity ischemia cases, and embolism is the most common cause. Blockage due to embolism usually occurs at the separation site of the radial and ulnar arteries from the brachial [11,12].

Peripheral vascular disease is one of the most common diseases in patients with diabetes, and a large population of these patients undergoes amputation every year [13]. Diabetes is a major risk factor for atherosclerosis and increases the risk of PAD as reported in many studies [14]. Also, there is a direct relationship between the risk of PAD and the

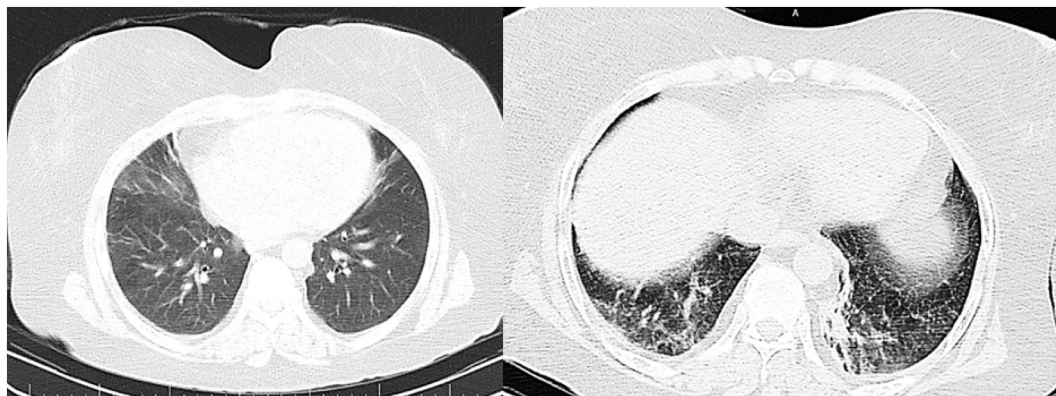


Fig. 1. Chest CT scan of the patient in pulmonary window: mild ground glass opacity was seen at the base of both lungs.

duration of diabetes [15]. Inflammation is one of the risk factors for atherothrombosis; CRP is one of the inflammatory factors affecting PAD development in diabetic patients [16]. In addition to platelet dysfunction, diabetic patients experience overexpression of platelet receptors in peripheral arteries. Moreover, uncontrolled diabetes increases the risk of coagulation disorders in peripheral arteries [17].

Rheumatoid vasculitis has been reported in 10 %–15 % of patients with RA. In a study by Yamamoto et al., on 193 patients with vasculitis in connective tissue disease undergoing surgery for the management of limb ischemia, three matched by age and disease duration (20 years) had RA and all lost their limbs within three years, despite surgery [18]. The results of studies on the increased risk of PAD by RA were controversial. Some suggest RA as a risk factor for PAD and some consider the risk of PAD in patients with RA similar to that of healthy individuals [19]. But it is evident that RA increases the risk of vascular atherosclerosis [20].

Hyper coagulopathy is one of the COVID-19 outcomes that may develop PAD following the involvement of vascular endothelium in the cytokine storm phase [21]. Endothelial damage following COVID-19, especially in those with underlying diseases (such as diabetes mellitus or inflammatory diseases such as RA) that have vascular disorders, can cause acute vascular events.

In a study by M. Bae et al., on 35 patients with acute and chronic upper extremity ischemia, including 15 with hypertension, three with diabetes, and two with RA, the most common site of occlusion was the brachial artery (48.6 %), and in two of them, acute renal failure was reported as the adverse effect of treatment. In their study, patients with high LDH levels and longer symptom onset had greater functional problems [22].

In a study by Willenberg et al., on 2783 patients continuously taking corticosteroids for more than five years, the results suggested an increased risk of ischemia in extremities in those taking corticosteroids for the management of inflammatory diseases in long-run [23].

Here we reported a 47-year-old female patient presenting with acute ischemia in the left hand and right foot. The patient, who had diabetes and RA and was taking corticosteroids for a long time, referred to the hospital with atypical complications of COVID-19. Simultaneous development of ischemia in the upper and lower extremities is rare and has a poor prognosis [21]. In addition, the patient did not complain of shortness of breath and decreased oxygen saturation throughout the treatment course, atypical manifestations of COVID-19, which might be the adverse outcome of long-term use of corticosteroids or an uncontrolled underlying inflammatory disease.

Due to the emergence of COVID-19 and the lack of a definitive treatment, especially in those with uncontrolled rheumatic diseases on immunosuppressive drugs, care givers should always be aware of atypical presentations of COVID-19 infection. Furthermore, administration of therapeutic doses of anticoagulant agents and taking measures such as plasmapheresis or the use of anti-inflammatory drugs to diminish inflammation, along with supportive cares, may prevent unpredictable complications.

4. Conclusion

We reported a case that developed ischemia in the upper and lower extremities following the atypical symptom of COVID-19. Patients with inflammatory diseases and diabetes are prone to the uncommon symptoms of COVID-19 and more vulnerable to peripheral vascular occlusion, especially when the underlying disease remains uncontrolled, so anticoagulation with therapeutic doses is recommended for their treatment. Inflammation as a predisposing factor for PAD should be controlled using plasmapheresis or anti-inflammatory drugs depending on the patient's condition.

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Ethical approval

This study was approved by the Ethical Committee of Ardebil University of Medical Sciences. Reference number: IR.ARUMS.REC.1400.149.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Shafagh Aliasgarzadeh: Data collection and analysis; AmirAhmad Arabzadeh: Study concept, design, and supervision; Sepideh Fathibitaraf: Drafting the manuscript; Mohammad Negaresh: Drafting and revision of the manuscript.

Registration of research studies

Not applicable.

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Declaration of competing interest

The authors have declared no conflict of interest.

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