SMJ Singapore Medical Journal

Delayed acute upper limb ischaemia manifesting months after COVID-19 infection

Chuan Han Ang[1], MBBS, MRCS, Derek Ho[1], MBBS, FRCS

[1]Department of General Surgery, Changi General Hospital, Singapore

Correspondence: Dr Ang Chuan Han, Resident, Department of General Surgery, Changi General Hospital, 2 Simei Street 3, Singapore 529889. angchuanhan@gmail.com

Singapore Med J 2021, 1–11
https://doi.org/10.11622/smedj.2021194
Published ahead of print: 31 October 2021

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global pandemic presenting with a wide spectrum of clinical manifestations from asymptomatic to respiratory, cardiovascular, neurological, gastrointestinal symptoms, to acute respiratory distress syndrome and multiple organ failure. Although respiratory symptoms predominate, thrombotic complications including myocardial infarction, ischemic stroke and venous thromboembolism secondary to a hypercoagulable state have been reported in severe COVID-19 infections. Arterial thrombosis of aorta, brachial artery, radial artery, superior mesenteric artery, iliac artery and prosthetic vascular grafts have also been reported.[1] The relationship between COVID-19 and a hypercoagulable state has been observed in earlier studies.[2] But the true prevalence of thrombosis in patients with COVID-19 has not been fully established as most patients with thrombosis have poor premorbid conditions which already predispose to them acquiring thrombosis in the intensive care unit.[3] We present a delayed presentation of acute upper limb ischemia (Rutherford Class IIb) in a young and healthy patient with asymptomatic COVID-19 infection 7 months ago, and discuss the acute management, duration of anticoagulation and clinical implications.

CASE DESCRIPTION

A 30-year-old Indian male with a previous COVID-19 infection 7 months ago presented with acute right hand pain for 1 week. He was part of the migrant worker community in Singapore who were all screened for COVID-19. He was asymptomatic and had no respiratory symptoms. There was a surge in COVID-19 among the migrant workers, hence they were routinely screened regardless of their symptoms. This was conducted with the intention to isolate and treat them effectively, with the symptomatic patients nursed in hospitals. He has been working in Singapore for the past 11 years as a cleaner and denies carrying heavy loads. He is a non-smoker, had no recent history of trauma, denied ingestion of traditional medication or illicit

drugs, and had no family history of pro-thrombotic or autoimmune disease, stroke and deep venous thrombosis. On the day of admission, the patient had worsening pain of his right hand, numbness over all fingers and decreased grip strength. He was afebrile with a respiratory rate of 19/minute and saturation of SpO_2 99% on room air, but he was tachycardic with heart rate of 95/minute and blood pressure of 181/123 mmHg. On examination, his right hand was pale and cool to touch, brachial pulse was 2+ but radial and ulnar pulses were not palpable without any Doppler signal. His initial laboratory investigations were mostly normal with a normal coagulation profile (PT 10.3s, aPTT 24.5s, INR 0.95) but his white cell count was elevated at $18.3x10^9$/L (Hb 18 g/dL, Plt 356 10^9/L). A computed tomography peripheral angiogram of his right upper limb revealed a partially obstructing thrombus in the right proximal subclavian artery (Figure 1), embolus in the right brachial artery just before the bifurcation (Figure 2), trickle of contrast in the radial artery, but no flow in the ulnar artery and palmar arches.

Despite having no respiratory symptoms, and a normal chest x-ray, the patient was isolated while awaiting repeat COVID-19 swab tests. Decision was made for an embolectomy due to 2 separate sites of thrombosis at the subclavian and brachial arteries, making catheter-directed thrombolysis impossible. Furthermore, he was a young and healthy male with pre-morbidly normal arteries, hence embolectomy will have the best chance of removing the most clot burden. He underwent a right upper limb brachial open embolectomy and bovine patch repair on the same day. The subclavian thrombus was removed via retrograde embolectomy through the brachial arteriotomy with a fogarty catheter. Clearance of thrombus was confirmed with a strong forward bleed, and angiogram done via a Berenstein catheter placed at the innominate artery. All clots were cleared from the interossei and ulnar arteries but the fogarty catheter was unable to pass into the radial artery due to chronic occlusion. He was started on subcutaneous enoxaparin twice a day and aspirin daily. Post-operatively, his pain and strength improved, but had residual numbness over second to fourth fingertips. Doppler revealed

biphasic ulnar artery but no signal over radial artery. The following day, his COVID-19 swab tests were negative and he was de-isolated. Ultrasound arterial occlusion scan showed triphasic flow in the subclavian, axillary and brachial arteries, no flow in the radial artery, monophasic flow in the proximal ulnar artery, and re-occlusion of the distal ulnar artery. Although there was clinical improvement of strength and sensation, the distal perfusion to fingers was still poor, possible due to the remnant chronic layered clots distally. The patient underwent a right upper limb open thrombectomy and catheter-directed thrombolysis through a direct puncture on the brachial artery patch with a 5FR sheath anchored to the skin and temporary closure of the antecubital fossa incision. All fresh thrombus were removed and angiogram showed patent ulnar and palmar arteries. In view of early re-thrombosis in a young patient's dominant hand, overnight thrombolysis with urokinase was administered to achieve the best possible outcome. A 4FR 10cm Cragg-McNamara catheter was placed in the distal ulnar artery with intra-arterial urokinase for 24-hours, and intravenous heparin infusion was started. On the third day, the patient underwent a right upper limb diagnostic angiogram, removal of thrombolysis catheter and secondary closure of the antecubital fossa incision. Angiogram showed run-off via ulnar artery to the palmar arch with reconstitution of the occluded radial artery (Figure 3). Thrombus sent for histology revealed blood clot without evidence of granuloma, malignancy or fungal elements, and culture was negative for bacterial growth.

Postoperatively, the patient had no more pain, numbness resolved and strength returned to baseline. Radial and ulnar pulses were 1+ and Doppler signals were biphasic. Heparin infusion was halted on the fifth day and enoxaparin was restarted. The haematologist's impression was that of acute extensive arterial thrombosis contributed by history of COVID-19 infection. His cardiovascular risk factors were normal with a normal lipid panel, HbA1c and fasting glucose. His pro-thrombotic investigations were also negative, other than a borderline lupus anticoagulant antibody. JAK2 mutation, anti-cardiolipin IgM and IgG, anti-beta 2

glycoprotein IgM, anti-myeloperoxidase antibody, anti-proteinase 3 antibody, anti-neutrophil cytoplasmic antibody, antinuclear antibody, anti-double-stranded DNA antibody, smith antibody, ribonucleoprotein antibody, Ro, La, Scl 70, Jo-1, anti-extractable nuclear antigen antibodies were negative. Echocardiogram showed a normal ejection fraction without any valvular abnormalities, no intra-cardiac thrombus and negative agitated saline study. 24h Holter monitoring was normal. Computed tomography aortogram showed no focal plaque in the thoracic aorta, normal calibre thoracic aorta, no filling defect in the subclavian artery, no suggestion of thoracic outlet syndrome and accessory ribs. Enoxaparin was converted to rivaroxaban on the seventh day and he was discharged with 3 months of rivaroxaban and lifelong aspirin. When the patient was reviewed in clinic after 3 months, his neurological status has recovered completely.

DISCUSSION

The largest case series of COVID-related acute limb ischemia come from Italy and New York. Bellosta[4] et al discussed their series of 20 patients with acute limb ischemia over 3 months and demonstrated a five-fold increase in acute limb ischemia compared to the same period in 2019, and concluded that successful revascularisation was lower than expected due to a virus-related hypercoagulable state. Etkin et al[5] documented 49 COVID-19 patients with arterial thromboembolism over 11 weeks in New York, with a high limb loss and mortality. Xiong et al[6] conducted a meta-analysis which demonstrated that D-dimer levels and prothrombin time were higher in patients with severe COVID-19 infection. The prognosis for patients who develop thrombosis on a background of severe COVID-19 infection is bleak, as it is a reflection of the aggressive disease progression contributed by sepsis induced coagulopathy. Autopsy findings[7] of microthrombi in multiple organs suggest that thrombosis may have contributed to multiple organ failure in severe COVID-19 infection. There are few reports of acute limb

ischemia in COVID-19 patients with varying severity and corresponding different management. Veerasuri[1] et al presented a case with mild COVID-19 symptoms with Rutherford Class I acute limb ischemia which was managed conservatively. Muhammad et al[(8)] presented another case who underwent catheter-directed thrombolysis for 48-hours and achieved successful revascularisation. Apart from the method of thrombectomy and thrombolysis, the use of postoperative heparin infusion improves limb salvage and overall survival rates.[(4)] Little is known about the persistence of vasculitis in the recovery phase of COVID-19 infection. Fan et al[(9)] described four cases of delayed arterial thrombosis who presented at a median of 78 days after positive SARS-CoV-2 total antibody positivity. These patients presented with strokes, acute myocardial infarction and acute lower limb ischemia despite a previous mild or asymptomatic COVID-19 infection. The sustained prothrombotic changes in COVID-19 patients were demonstrated by Von Meijenfeldt et al[(10)] who found enhanced thrombin generation, decreased plasma fibrinolysis, elevated factor VIII, von Willebrand factor and plasminogen activator inhibitor-1 levels on admission and four months after discharge, suggestive of platelet activation and ongoing intravascular coagulation.

Various mechanisms have been proposed to explain the pathophysiology of COVID-19 and hypercoagulopathy. Firstly, viral invasion using angiotensin-converting enzyme 2 receptors on the vascular endothelial cells leads to endothelial dysfunction, and viral-induced luminal expression of tissue factor.[(11)] Secondly, severe COVID-19 infection has been associated with a cytokine storm characterised by increased production of interleukin-1, interleukin-2, interleukin-6 and tumour necrosis factor-alpha, and the resultant systemic inflammatory response syndrome activates the endothelium, neutrophils and platelets, resulting in systemic thrombosis.[(12)] Thirdly, activated monocytes in severe COVID-19 infection upregulate tissue factor, which in turn activates the coagulation cascade and thrombosis.[(13)] The excessive complement activation in COVID-19 leads to diffuse thrombotic macroangiopathy

and end-organ dysfunction. Fourthly, as most severe COVID-19 patients are in intensive care units, the immobilisation further results in stasis and hypercoagulability. As our patient was clinically stable and had an infection 7 months ago, this case highlights that prolonged endothelial damage from COVID-19 plays a major role in the development of subsequent thrombosis.

The classic Virchow's triad for thrombosis consists of stasis, endothelial injury and a hypercoagulable state, with endothelial dysfunction being the key contributor in post COVID-19 thrombosis. This is triggered by the cytotoxic effects of COVID-19 infection and an overactive immune response causing prolonged vasculitis.[14] The breach in endothelial barrier exposes tissue factors and procoagulant cytokines which initiate the extrinsic coagulation pathway and predispose recovered individuals to thrombosis. The persistence of endothelial dysfunction is demonstrated by the increased numbers of circulating endothelial cells (biomarkers for vascular injury) and increased expression of endothelial activation markers (intercellular adhesion molecule 1, P-selectin) in convalescent COVID-19 patients compared with healthy non COVID-19 individuals. Chioh et al[15] also confirmed that proinflammatory cytokine production remained heightened post-infection, suggesting that the prolonged overactive state of the immune system is implicated in endothelial dysfunction.

The International Society on Thrombosis and Haemostasis[16] and American Society of Haematology recommend that all hospitalised patients with severe COVID-19 receive pharmacologic thromboprophylaxis with low molecular weight heparin in the absence of bleeding. Therapeutic anticoagulation is not required unless venous thromboembolism is confirmed. There is currently no consensus on anticoagulating patients with COVID-19 prophylactically to prevent arterial thrombotic events, but the current guidelines have been applied to arterial thrombotic prophylaxis.[12] Oral anticoagulation is an established therapy following intervention for acute limb ischemia with subsequent reduction in recurrent ischemic

limb events and amputation.[17] The combination of rivaroxaban and aspirin has overall benefit in patients with peripheral arterial disease in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial,[18] and a subgroup who had acute limb ischemia also had a reduction in amputation and mortality rate. However data specific to post procedural anticoagulation in patients with COVID-19 are sparse. We continued anticoagulation for this young and healthy patient for 3 months, as there is an attributable cause for the hypercoagulable state without any other risk factors. Some authors choose to treat their patients with a longer period of anticoagulation up to 1 year.[19] There is no guideline for the duration of anticoagulation in patients with cryptogenic or post COVID-19 acute limb ischaemia, and the efficacy and safety of prolonged thromboprophylaxis in post COVID-19 survivors require further clinical trials.

Our report emphasises that physicians need to consider a recent COVID-19 infection (up to 7 months as our case demonstrated) as a risk factor for acute thrombosis, in order to initiate treatment promptly. However, this is compounded by the fact that some patients are asymptomatic, and might not be tested for it initially.

In conclusion, it is reassuring that COVID-19 vaccinations have begun production and usage, but for the population who has ever been infected with COVID-19, the pro-thrombotic state may last a few months. It is also comforting that the treatment for acute limb ischemia in a patient who was previously infected with COVID-19 is the same, and the outcome is good if treatment is started promptly. In summary, we present a case of delayed acute limb ischemia 7 months from previous COVID-19 infection. Endothelial damage from previous COVID-19 infection predisposes to thrombosis even after the acute phase of infection. The duration of anticoagulation should be customised according to the patient's risk profile.

ACKNOWLEDGEMENT

Informed consent was obtained from the patient for publication of this article and the accompanying images.

REFERENCES

1. Veerasuri S, Kulkarni SR, Wilson WR, Paravastu SCV. Bilateral acute lower limb ischemia secondary to COVID-19. Vasc Endovascular Surg 2021; 55:196-9.
2. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med 2020; 58:1116-20.
3. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020; 18:1421-4.
4. Bellosta R, Luzzani L, Natalini G, et al. Acute limb ischemia in patients with COVID-19 pneumonia. J Vasc Surg 2020; 72:1864-72.
5. Etkin Y, Conway AM, Silpe J, et al. Acute arterial thromboembolism in patients with COVID-19 in the New York City area. Ann Vasc Surg 2021; 70:290-4.
6. Xiong M, Liang X, Wei YD. Changes in blood coagulation in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Br J Haematol 2020; 189:1050-2.
7. Fox SE, Akmatbekov A, Harbert J, et al. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med 2020; 8:681-6.
8. Muhammad K, Tantawy TG, Makar RR, Olojugba O. Successful catheter-directed thrombolysis for acute lower limb ischemia secondary to COVID-19 infection. Ann Vasc Surg 2021; 71:103-11.
9. Fan BE, Umapathi T, Chua K, et al. Delayed catastrophic thrombotic events in young and asymptomatic post COVID-19 patients. J Thromb Thrombolysis 2021; 51:971-7.

10. Von Meijenfeldt FA, Havervall S, Adelmeijer J, et al. Sustained prothrombotic changes in COVID-19 patients 4 months after hospital discharge. Blood Adv 2021; 5:756-9.
11. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020; 395:1417-8.
12. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020; 75:2950-73.
13. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: incidence, pathophysiology, and management. Thromb Res 2020; 194:101-15.
14. Fan BE, Cheung C. Post COVID-19 arterial thromboembolism: a clear and present danger. Semin Thromb Hemost 2021 Apr 15. http://doi.org/10.1055/s-0041-1728717. [Epub ahead of print]
15. Chioh FW, Fong SW, Young BE, et al. Convalescent COVID-19 patients are susceptible to endothelial dysfunction due to persistent immune activation. Elife 2021; 10:e64909.
16. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020; 18:1859-65.
17. Campbell WB, Ridler BM, Szymanska TH. Two-year follow-up after acute thromboembolic limb ischaemia: the importance of anticoagulation. Eur J Vasc Endovasc Surg 2000; 19:169-73.
18. Anand SS, Caron F, Eikelboom JW, et al. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS trial. J Am Coll Cardiol 2018; 71:2306-15.

19. Costa VO, de Almeida GBC, Nicolini EM, et al. Acute arterial occlusion of the lower limb as the main clinical manifestation in a patient with Covid-19 - case report. Int J Surg Case Rep 2020; 77:454-8.

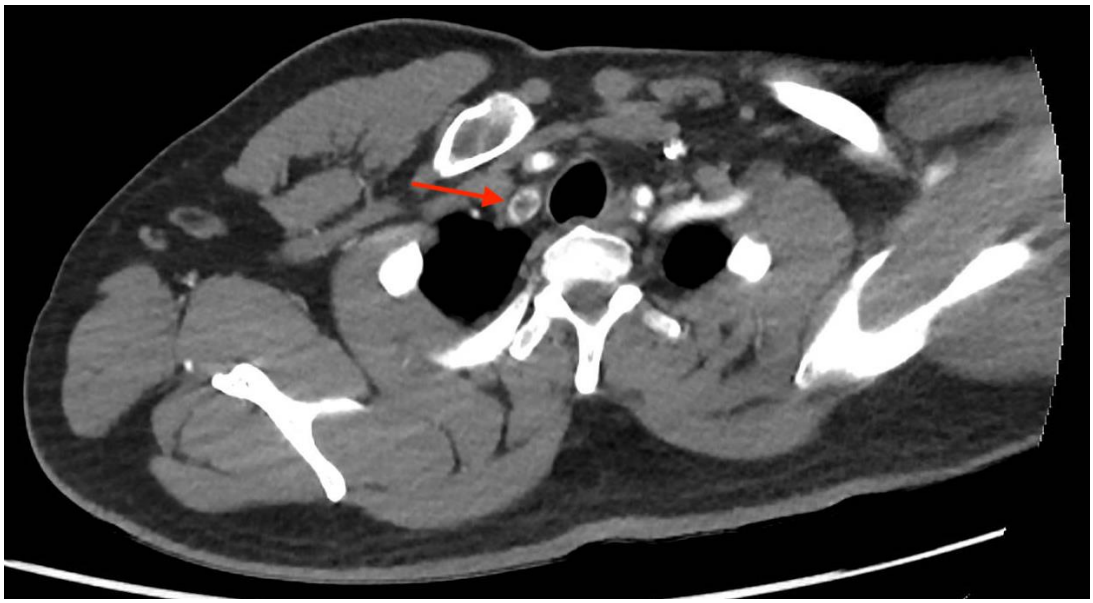

Figure 1: Partially obstructing thrombus in the right proximal subclavian artery.

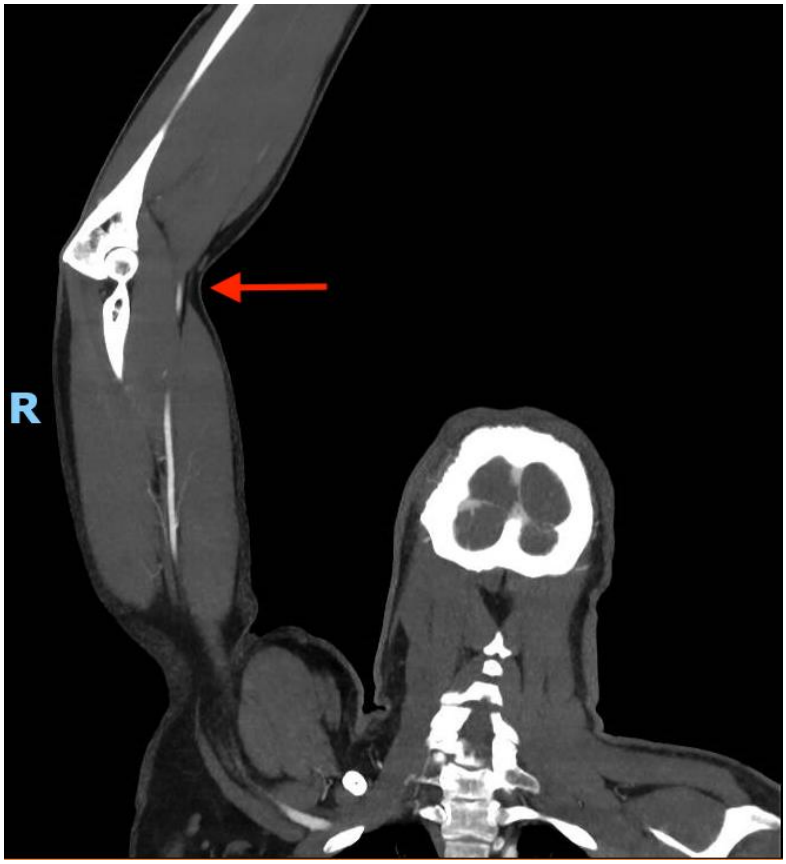

Figure 2: Cut-off of opacification in the distal right brachial artery just before the bifurcation suspicious for an embolus.

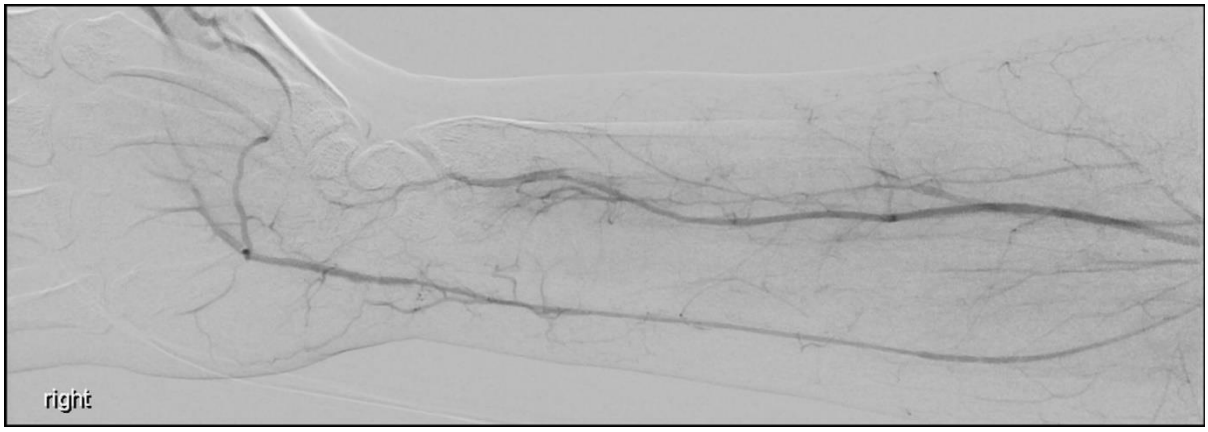

Figure 3: Intra-operative angiogram showing run-off via ulnar artery to the palmar arch with reconstitution of the occluded radial artery.