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LETTER TO THE EDITOR

Delayed catastrophic thrombotic events in young and asymptomatic post COVID-19 patients

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We read with interest the editorial "Anticipating the long-term cardiovascular effects of COVID-19 [1]" which featured COVID-19 end-organ thrombotic complications. COVID-19 associated hypercoagulability [2] and increased thromboembolism in COVID-19 has been well described [3]. While the editorial raised the key question about "*potential* long-term cardiovascular effects (of COVID-19)", little is known about the post COVID-19 vascular complications. In response, we would like to highlight a series of catastrophic arterial events observed in post COVID-19 patients (Table 1), echoing the Editor's concerns of post-infectious vasculopathy.

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During the months of April 2020 to July 2020, Singapore experienced a surge in COVID-19 cases amongst our migrant workers. Subsequently, in July 2020 to September 2020, 4 young healthy migrant workers presented with catastrophic, large arterial thromboses. They were detected to have COVID-19 during routine screening of affected migrant workers' dormitories. They had raised Immunoglobulin G for SARS-CoV-2 (Roche Elecsys Anti-SARS-CoV-2) indicative of COVID-19 seroconversion. They were asymptomatic and did not meet criteria necessitating hospitalization nor thromboprophylaxis and were quarantined at isolation facilities. Subsequently, they presented with a sentinel thrombotic event at a median of 78 days from seroconversion. Their median age was 38.5 years, and they were of South Asian ethnicity. Cardiovascular risk factors screening showed that one had recently diagnosed diabetes mellitus with a HbA1c of 6.7% whilst the others did not have any risk factors.

Two patients suffered from severe large vessel ischaemic strokes (Fig. 1a–d), one had an acute ischaemic limb (Fig. 2a) due to emboli from an aortic thrombosis (Fig. 2b), and one had anterolateral ST-Elevation Myocardial Infarction (Fig. 3a–c). No features of overt arteriosclerotic disease were found during neuroimaging, CT angiography and coronary angiography. Thrombophilia screen and stroke evaluation inclusive of carotid imaging, echocardiography, 24-h holter monitoring were normal.

The remarkable features of these cases include young age without preexisting cardiovascular risk factors, asymptomatic SARS-CoV-2 infection and the long latency between initial positive serology and their catastrophic vascular event. Firstly, two patients had an unusual site of thrombosis, with mobile aortic thromboses discovered on CT imaging. Aortic thrombosis is rare in young patients without a significant thromboembolic risk factors or pre-existing arteriosclerosis. The SARS-CoV-2 virus is

Table 1 Four cases of post COVID-19 acute arterial thromboses

No	Age	Ethnic group	Sex	Presentation	Arterial events and co-morbidities	Imaging	SARS-CoV total antibody	SARS-CoV PCR	Date of arterial event	Days from positive serology to thrombosis	Treatment	Initial haemostatic assessment	Repeat haemostatic assessment	Current status
1	38	Indian	M	Fall with Acute right sided weakness Global aphasia NIHSS: 23	Acute left MCA infarct No comorbidities	MRI brain Diffuse loss of grey-white differentiation and restricted diffusion involving the left fronto-parieto-temporal lobes and left basal ganglia	Positive × 1 27 May	Not tested	7 July	41 days	1.IV rtPA 2.Endovascular therapy 3. Aspirin	PT 13.5 APTT 26.4 D-dimer 3.20 Fibrinogen 2.7 vWF 260% Factor VIII NA Platelets 227	22 July > 3 Aug > 7 Oct PT 14.3 > 13.5 > 13.3 APTT 28.8 > 31.1 > 27.1 D-dimer 3.39 > 1.22 > 0.46 Fibrinogen 7.5 > 5.6 > 3.3 vWF 272% > 240% > 186% Factor VIII 208% (7 Oct) Platelets 583 > 369 > 256	71 days in Rehabilitation

Table 1 (continued)

No	Age	Ethnic group	Sex	Presentation	Arterial events and co-morbidities	Imaging	SARS-CoV total antibody	SARS-CoV PCR	Date of arterial event	Days from positive serology to thrombosis	Treatment	Initial haemostatic assessment	Repeat haemostatic assessment	Current status
2	39	Indian	M	Acute right sided weakness Global aphasia NIHSS: 25	Left MCA and PCA infarct Pulmonary Embolism Infrarenal aortic thrombus Newly diagnosed DM	MRI brain Large area of restricted diffusion is noted in the left fronto-parieto-temporal lobes, the left occipital and posterior medial temporal lobes CT pulmonary angiogram Thrombi seen in the right lower lobe, left upper lobe, left lower lobar, segmental and segmental branches. The main pulmonary arteries have no filling defects seen CT abdomen/pelvis Eccentric mural thrombus in the infrarenal aorta	Positive×2 21 May 14 Aug	Negative×2 20 Aug 21 Aug	5 Aug	76 days	1.Thrombectomy 2.Craniectomy 3.Low molecular weight heparin with bridging to warfarin	PT 13.7 APTT 26.6 D-dimer 3.55 Fibrinogen 5.8 vWF 226% Factor VIII 238% Platelets 301	30 Sept PT 30.9 APTT 38.4 Fibrinogen 4.7 vWF 153% Factor VIII 217% Platelets 256	30 days in Rehabilitation

Table 1 (continued)

No	Age	Ethnic group	Sex	Presentation	Arterial events and co-morbidities	Imaging	SARS-CoV total antibody	SARS-CoV PCR	Date of arterial event	Days from positive serology to thrombosis	Treatment	Initial haemostatic assessment	Repeat haemostatic assessment	Current status
3	49	Indian	M	Left acute painful lower limb	Left acute ischaemic limb Infrarenal aortic thrombus No comorbidities	CT angiography Occlusion of the left popliteal artery extending to tibioperoneal trunk and into the origins of the ATA, PTA and peroneal arteries. Aetiology is likely an embolus from the distal aorta/left common iliac artery	Positive × 1 3 June	Negative × 3 12 May 21 May 2 Sept	2 Sept	91 days	1.Thrombectomy 2.IV Heparin followed by Rivaroxaban	PT 13.1 APTT 26.7 D-dimer 0.42 Fibrinogen NA Factor VIII 216% vWF 161% Platelets 256	Not assessed yet as thrombotic event was recent	Discharged Home Well
4	38	Indian	M	Chest pain and sudden collapse	ST-Elevation myocardial infarction No comorbidities	Coronary angiogram 1. Dominance—Right-dominant 2. LM—Free of significant disease 3. LAD—Ostial LAD occluded 4. LCx—Normal 5. Ramus intermedius (RI)—Normal 6. RCA – Normal	Positive × 1 9 July Negative × 1 29 May	Negative × 4 24 June 27 Sept 28 Sept 3 Oct	27 Sept	80 days	1.PCI with drug eluting stent to LAD 2. Intraaortic balloon pump 3. Heparin 4. Aspirin 5. Ticagrelor	PT 15.7 APTT 31.8 D-dimer 4.11 Fibrinogen 5.2 vWF 374% Platelets 156	Not assessed yet as thrombotic event was recent	Admitted to cardiac intensive care unit

NIHSS National Institutes of Health Stroke Scale, *MCA* middle cerebral artery, *PCA* posterior cerebral artery, *MRI* magnetic resonance imaging, *IV rTPA* intravenous recombinant tissue plasminogen activator, *CT* computer tomography, *DM* diabetes mellitus, *LM* left main, *LAD* left anterior descending artery, *LCx* left circumflex artery, *RCA* right coronary artery, *PCI* percutaneous coronary intervention, *NA* not available

Prothrombin Time (PT): 11.7–14.0 s. Activated partial thromboplastin time (aPTT): 27.0–37.0 s. Fibrinogen: 1.8–4.5 g/L. D-Dimer: < 0.5 µg/ml. Platelets: 150–360 × 10^9/L. Factor VIII: 60–150%. Von Willebrand Factor (vWF): 56–160%

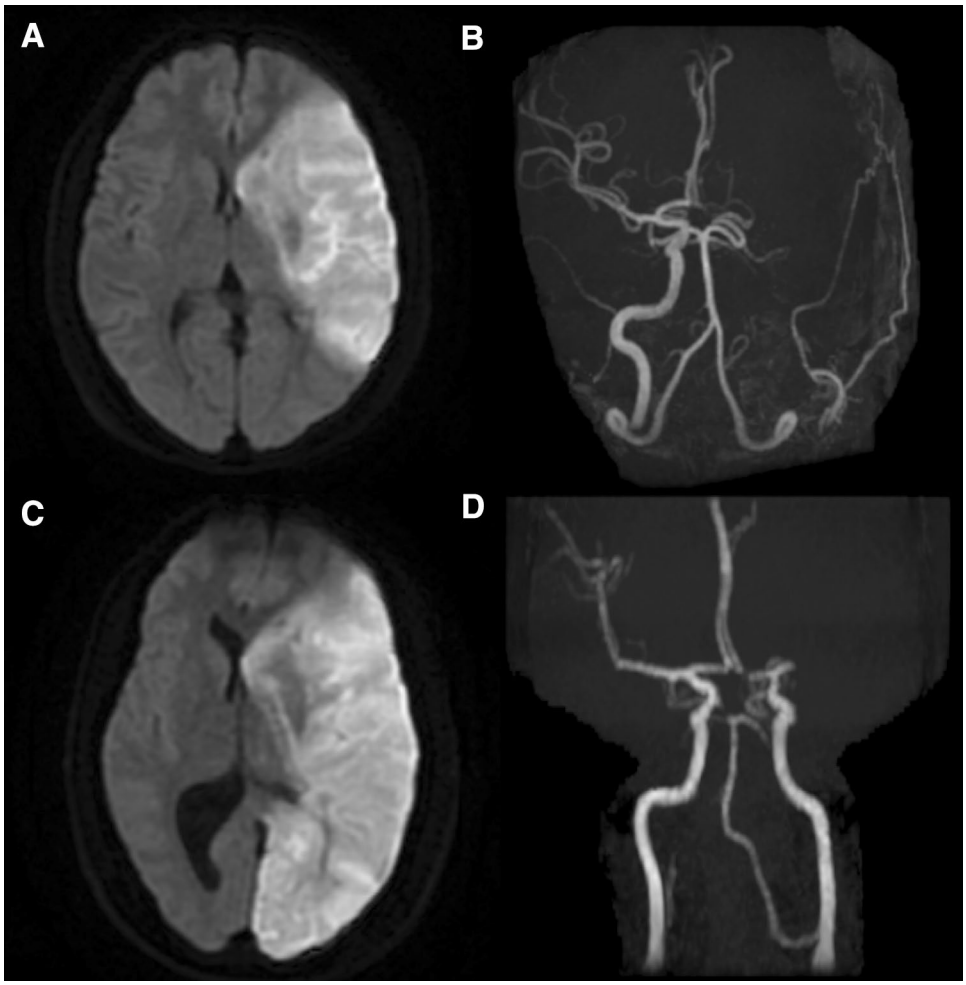

Fig. 1 **a-d** Acute magnetic resonance brain images of the 2 patients with large vessel ischaemic stroke. They show large areas of restricted diffusion in left middle cerebral, and middle cerebral, posterior cerebral artery territories, respectively. Adjoining intracranial magnetic resonance angiograms show loss of normal flow void in the left internal carotid and middle cerebral arteries in the first patient (**a**, **b**), and M1 segment of left middle cerebral artery in the second patient (**c**, **d**)

known to cause endothelial damage during acute infection [4, 5] and cases of COVID-19 associated acute ischaemic limb secondary to embolism from aortic thrombosis have been described [6, 7]. However, less is known about persistence of endotheliitis in the convalescent phase of illness. We postulate that post SARS-CoV-2 infection, a state of endothelial activation with downstream signaling pathways of low-grade inflammation and thrombosis may persist [8]. Similar mural thrombosis has been described in patients on chemotherapy and has been attributed to trauma to vascular endothelium and a hypercoagulable state [9]. However, our patients did not consume any medications and did not have any endovascular lines. The aortic thrombosis in COVID-19 could be a consequence of persistent endothelial dysfunction due to viral inclusion bodies at specific sites (this has been reported in Chilblains ('COVID toes') in children and young adults [10]) Secondly, haemostatic assessment of the 4 patients at time of acute thrombosis highly suggested a hypercoagulable state, with a markedly raised Factor VIII, elevated von Willebrand factor antigen, increased D-dimer levels and hyperfibrinogenaemia. Both endothelial dysfunction and hypercoagulability are 2 key factors in Virchow's triad for thrombosis. The post-thrombosis evaluation of the haemostatic profile in 2 of our patients with ischaemic stroke at a 2 to 3-month window from onset of acute stroke revealed declining but persistently raised von Willebrand factor antigen, Factor VIII, and fibrinogen levels. A persistently raised von Willebrand factor may reflect chronic endothelial activation and dysfunction [11], as well as ongoing platelet hyperactivation [12]. Thirdly, for the young patient with cardiac arrest and acute myocardial infarction, COVID-19 may have induced an 'accelerated atherosclerosis' and precipitated a coronary event during his convalescence. There was complete occlusion of left anterior descending (LAD) artery (Fig. 3a). This is suggested by findings from Intravascular ultrasound (Volcano Eagle Eye catheter) which was used to interrogate the LAD artery. Small amount of clot was retrieved using thrombectomy device. It showed a focal heavily fibrous plaque burden of 59% and minimal lumen diameter of 2.1 mm in the ostial LAD (Fig. 3c), with a plaque burden of more than 70% and

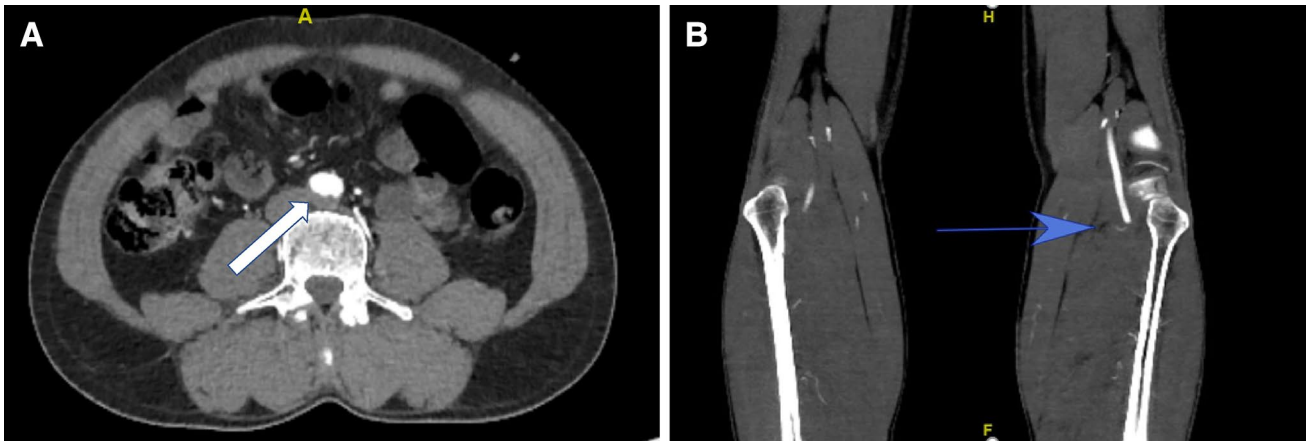

Fig. 2 **a** An eccentric thrombus (white arrow) is present in the distal aorta just before its bifurcation. **b** An abrupt cut off of the left popliteal artery (blue arrow)

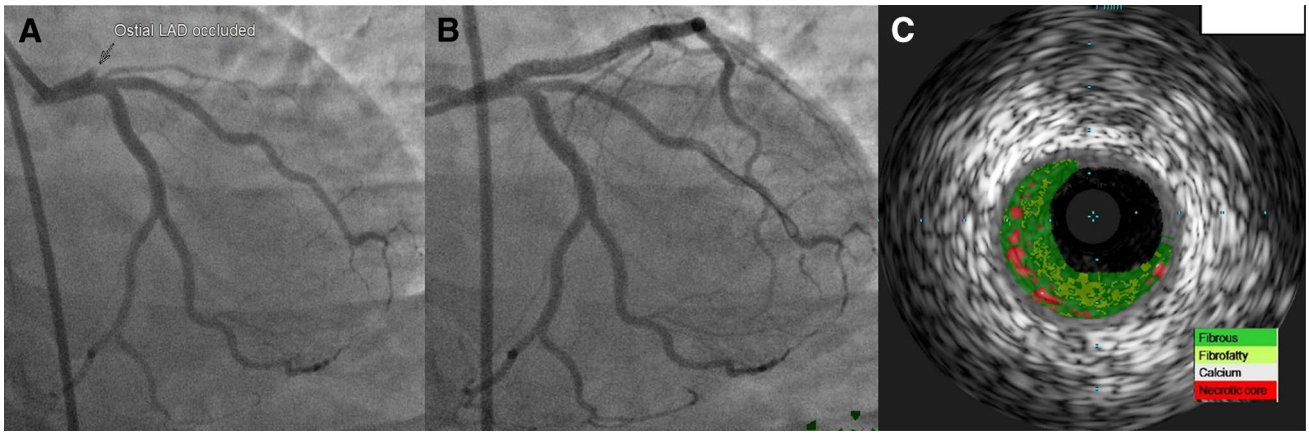

Fig. 3 **a** Coronary angiogram showed complete occlusion of ostial left anterior descending artery (LAD). Left circumflex artery and ramus intermedius branch are normal. **b** Restoration of flow in the LAD after implantation of drug eluting stent. **c** Intravascular ultrasound (virtual histology) showed predominantly fibrotic plaque with minimal necrotic core in the ostial LAD

minimal lumen area of less than 4mm^2 being independent predictors of major adverse cardiovascular events [13]. This is unusual as fibrotic lesions are usually deprived from lipid and inflammatory cells and hence less likely to rupture and generate thrombosis [14].

COVID-19 is known to cause cardiac complications with a case series from China reporting a high percentage (19.7%) of COVID 19 patients having evidence of myocardial injury with 51% in-hospital mortality compared with 4.5% without raised troponin [15]. Potential mechanisms that explain cardiac injury during acute infection include (i) imbalance in myocardial demand and supply due to tachycardia and hypotension from type 2 myocardial infarction; (ii) acute atherothrombosis in a virally induced thrombotic and inflammatory milieu; (iii) microvascular dysfunction from microthrombi or endothelial injury; (iv) stress-related cardiomyopathy (Takotsubo) and (v) direct cardiomyocyte toxicity and myocarditis, of which artherothrombosis as well as direct cardiomyocyte toxicity may cause sustained long-term damage to the coronary vessels and the myocardium, with 10 patients in Germany critically ill with COVID-19 demonstrating low to no detectable virus in myocardial tissues despite multiple microemboli in the heart [16]. These observations suggest that the SARS-CoV-2 virus poses significant and chronic immuno-thrombogenicity which may cumulate eventually in a major thrombotic event.

Although small, our case series suggests that catastrophic vascular events can occur unexpectedly in fit patients with mild or asymptomatic COVID-19 infection and may unpredictably happen many weeks later.

The COVID-19 pandemic has a prolonged and serious impact on the cardiovascular health of patients. Hence for

convalescent patients, regardless of the severity of infection and the absence of co-morbidities, clinicians should remain vigilant for post-infective thrombotic sequelae as well as consider screening for and closely managing cardiovascular risk factors. Multi-disciplinary collaboration into the epidemiology, pathogenesis and treatment of COVID-19 associated thrombosis and in evaluating the utility of extended thromboprophylaxis for COVID-19 patients should be strongly considered.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval A waiver of informed consent was provided by the Ministry of Health (Singapore), under the provisions of the Infectious Diseases Act.

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