ST-segment elevation myocardial infarction in post-COVID-19 patients: A case series
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ABSTRACT
Coronavirus disease 2019 (COVID-19) is associated with an increased risk of thromboembolic events in the acute setting. However, the abnormal thrombotic diathesis is not known to persist into the recovery phase of COVID-19 infection.

We described 3 cases of ST-segment elevation myocardial infarction in healthy male patients who recovered from COVID-19 with no prior cardiovascular risk factors. They shared features of elevated von Willebrand factor antigen, factor VIII and D-dimer level. One patient had a borderline positive lupus anticoagulant. Intravascular ultrasound of culprit vessels revealed predominantly fibrotic plaque with minimal necrotic core. Clot waveform analysis showed parameters of hypercoagulability. They were treated with dual antiplatelet therapy, angiotensin-converting-enzyme inhibitor, beta blocker and statin. These cases highlight the strong thrombogenic nature of COVID-19 that persisted among patients who recovered from infection. Several suspected mechanisms could explain the association between vascular thrombosis in the convalescent period (endothelial dysfunction, hypercoagulability, systemic inflammatory response and vasculopathy). Additional studies on “long COVID” are essential for identifying endotheliopathy and thrombotic sequelae.

Keywords: Coronary artery disease, hypercoagulability, pandemic, thrombosis

Coronavirus disease 2019 (COVID-19) has been associated with thromboembolic phenomenon in the early phase of disease. Growing evidence suggests a hypercoagulable state as well as abnormal platelet activation, impaired fibrinolysis, and endothelial dysfunction in COVID-19 patients, resulting in thrombosis. The lungs are thought to be the epicentre of thrombosis, where thrombosis may manifest as in situ pulmonary thrombosis, as well as systemic micro- and macrovascular thrombosis. Little is known about post-COVID-19 thrombotic complications.

Singapore adopted a mass screening strategy for its foreign workers after COVID-19 clusters were discovered in their dormitories. We report 3 cases of healthy male foreign workers who presented with massive acute myocardial infarction (AMI) after recovery from COVID-19. All 3 had raised immunoglobulin G levels for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that is indicative of seroconversion (Table 1). Prior to their AMI presentation, the cases were asymptomatic and belonged to a low-risk group. They did not require hospital admission nor thromboprophylaxis and were quarantined at isolation facilities.

Case 1. A 38-year-old man, with no significant cardiovascular risk factors, was admitted to the emergency department with an out-of-hospital ventricular fibrillation (VF) cardiac arrest. He presented 80 days after his positive SARS-CoV-2 antibody serology on 9 July 2020. He was successfully resuscitated, and a subsequent electrocardiogram (ECG) showed ST-segment elevation in anterior leads. He was intubated for airway protection and started on vasopressor support for cardiogenic shock. Urgent coronary angiogram showed single vessel coronary artery disease with a complete occlusion of the left anterior descending artery (LAD) (Fig. 1A). Intravascular ultrasound (IVUS) with Eagle Eye IVUS Catheter (Philips Healthcare, Ann Acad Med Singap 2021;50:425-30

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Cambridge, US) revealed a minimal amount of clot, which was retrieved using a thrombectomy device. Virtual histology (via IVUS) showed a focal, heavily fibrous plaque burden of 59% with minimal necrotic core and minimal lumen diameter of 2.1mm in the ostial LAD (Fig. 1B). A drug-eluting stent (3.8x40mm) was subsequently implanted in the LAD with optimal result and an intraaortic balloon catheter was inserted for mechanical circulatory support.

The patient was initiated on our protocolised post-cardiac arrest care bundle including targeted temperature management at 33 degrees Celsius in the cardiac intensive care unit. Chest X-ray revealed mild pulmonary congestion with no evidence of consolidation. His reverse transcription-polymerase chain reaction (RT-PCR) results for COVID-19 was negative. Transthoracic echocardiography (TTE) revealed moderate left ventricular systolic dysfunction (left ventricular ejection fraction 40%) with hypokinesia in the LAD territory. Laboratory results showed elevated von Willebrand factor (VWF) antigen of 366%, factor VIII 273%, elevated D-dimer 2.98 μg/mL, and borderline

| Case 1 | Case 2 | Case 3 |
|--------|--------|--------|
| Age, years | 38 | 50 | 36 |
| Sex | Male | Male | Male |
| Cardiovascular risk factors | None | None | None |
| SARS-CoV-2 RT-PCR results and dates | Negative 24 Jun, 27 Sep, 28 Sep, 3 Oct 2020 | Positive 4 Jun 2020 | Negative 6 Jun, 14 Jul, 30 Nov 2020 |
| SARS-CoV-2 total antibody result and date | Positive 9 Jul 2020 | Positive 8 Jun 2020 | Positive 18 Jun 2020 |
| Arterial event | VF arrest, myocardial infarction, occlusion of LAD | VF arrest, myocardial infarction, occlusion of proximal LAD | Myocardial infarction, occlusion of LAD |
| No. of days from positive serology to thrombosis | 80 | 174 | 165 |
| D-dimer, μg/mL (reference range <0.5 μg/mL) | >4 | 1.02 | 0.43 |
| Fibrinogen, g/L (reference range 1.8–4.5 g/L) | 5.2 | 5.7 | 3.6 |
| Activated partial thromboplastin time, s (reference range 27–37s) | 31.8 | 26.5 | 28.8 |
| Prothrombin time, s (reference range 11–14s) | 15.7 | 13.7 | 12.7 |
| Lupus anticoagulant | Weakly present | Absent | Absent |
| VWF antigen, % (reference range 56–160%) | 366 | 215 | 92 |
| Factor VIII, % (reference range 60–150%) | 273 | 338 | 162 |
| Treatment | Aspirin, ticagrelor, drug eluting stent implantation | Dual antiplatelet therapy, drug eluting stent implantation, glycoprotein IIb/IIIa inhibitor | Dual antiplatelet therapy, drug eluting stent implantation |
| Follow-up and outcome | Successful treatment, undergoing rehabilitation | Successful treatment, discharge on day 12 | Successful treatment, discharge on day 6 |

LAD: left anterior descending artery; RT-PCR: reverse transcription-polymerase chain reaction; VF: ventricular fibrillation; VWF: von Willebrand factor.
positive lupus anticoagulant. A further workup did not reveal any evidence of hyperlipidaemia, diabetes mellitus, thyroid disorder or metabolic syndrome.

The patient’s hospitalisation was complicated by lower limb compartment syndrome, which was treated with fasciotomy; acute kidney injury; and critical illness neuromyopathy. Tracheostomy was performed in view of prolonged mechanical ventilation and myopathy. He is currently undergoing intensive rehabilitation in our institution.

**Case 2.** A 50-year-old man presented to the emergency department for worsening chest pain. Initial physical examination revealed his blood pressure as 116/93mmHg; a heart rate of 120 beats per minute; and oxygen saturation 100% (on 2 litres of supplementary oxygen). Heart sounds were normal without murmurs and there were no abnormalities detected on lung auscultation. The man presented 174 days after his positive SARS-CoV-2 antibody test result on 8 June 2020. He developed a VF arrest while waiting for an ECG, where immediate resuscitation and defibrillation were carried out successfully. The ECG post-defibrillation showed ST-segment elevation in the anterior leads. The patient was subsequently intubated and transferred to the cardiac catheterisation laboratory. Coronary angiogram revealed acute thrombotic occlusion of the ostial segment of LAD. Virtual histology (via IVUS) revealed a predominantly fibrous plaque (31% burden) that was successfully treated through thrombectomy, followed by stent implantation (Figs. 1C and 1D). Given the thrombus burden, he was treated with glycoprotein IIb/IIIa inhibitor (eptifibatide) infusion. TTE showed mild left ventricular systolic dysfunction (left ventricular ejection fraction 45%) with hypokinesia in the apex and anterior wall.

The patient had a high fibrinogen level of 5.7g/L (1.8–4.5g/L); elevated VWF level of 215% (56–160%); factor VIII level of 338%; and a raised D-dimer level of 1.02 μg/mL (<0.5 μg/mL). His cardiovascular risk factor screening panel and SARS-CoV-2 RT-PCR results were negative. Clot waveform analysis (CWA) through activated partial thromboplastin time using automated blood coagulation analyser CN-6000 (Sysmex Corp, Kobe, Japan) found a markedly elevated median maximum velocity (Min1) of 8.007%/s (reference range 2.86–6.78/s), elevated median maximum acceleration (Min2) of 1.341 (reference range 0.46–1.10), and a high median delta change of 68.6%/s (reference range 25.21–63.09) (Fig. 2).

The patient’s clinical and haemodynamic condition improved gradually. He was extubated and discharged after 12 days of hospitalisation.
Case 3. A 36-year-old man was admitted to our hospital with a persistent chest pain of 3 hours. On admission, his blood pressure and heart rate were 120/88 mmHg and 88 beats per minute, respectively. Oxygen saturation was 100% on room air with normal lung auscultation. ECG showed hyperacute T waves in the anterior leads and his RT-PCR results for COVID-19 was negative. He presented 165 days after his positive SARS-CoV-2 antibody serology on 18 June 2020. He demonstrated a raised factor VIII level of 162% and a VWF level of 92%. Coronary angiogram revealed an acute mid-LAD occlusion, for which he underwent angioplasty with successful implantation of a drug-eluting stent (Fig. 3). After percutaneous coronary intervention, the chest pain and ST-segment deviation resolved. The patient was discharged well on day 6 of his hospitalisation.

While it is known that approximately 30% of myocardial infarctions are preceded by an upper respiratory infection, in particular influenza; less is known about the thrombotic sequelae in COVID-19 during the convalescent period.\textsuperscript{7,8} We described 3 cases of COVID-19 recovered patients who presented with AMI. The remarkable characteristics of these cases included their relatively young age without preexisting cardiovascular risk factors, preceding asymptomatic SARS-CoV-2 infection, and the presence of a long latency period between initial positive SARS-CoV-2 serology and their AMI.

Thrombosis has been classically associated with Virchow’s triad of blood stasis, endothelial activation, and hypercoagulable state. However, in the convalescent phase after a COVID-19 infection, studies have described a waning hypercoagulable state with possible persistence of endothelial dysfunction in patients. This has been well described in children during their recovery from COVID-19.

Multisystem inflammatory syndrome in children (MIS-C) is a newly defined post-viral myocarditis and inflammatory vasculopathy of children following COVID-19 infection. MIS-C is likely due to viral tropism of myocardial and endothelial cells by the...
coronavirus. The best evidence supporting MIS-C have been demonstrated in paediatric cases presenting with self-limited, chilblain-like acral purpuric lesion.9 The children remain otherwise asymptomatic, and interestingly, often test negative for SARS-CoV-2 in nasopharyngeal samples. Some acute viral infections are associated with transiently elevated lupus anticoagulant, but they can persist and lead to thromboembolic complications by various mechanisms, including the release of microparticles and exposure of prothrombotic phospholipids.10 Although the significance of these antibodies is not well established yet, COVID-19-induced lupus anticoagulant could favour the occurrence of thromboembolic events in children populations and hence should be systematically tested for.

Virtual histology via IVUS revealed heavily fibrous plaques in the coronary arteries of the cases described. This is unusual as fibrotic lesions are usually deprived of lipid and inflammatory cells, and hence less likely to rupture and generate thrombosis.11 A fibrotic plaque consists mainly of fibrous tissue without a necrotic core or calcium.12,13 This type of plaque is mostly indolent and stable in comparison with thin cap fibroatheroma, the main culprit in acute coronary syndrome. Interestingly, in the current cases described, delayed thrombotic arterial events occurred 80–174 days from the onset of positive SARS-CoV-2 serology. Laboratory evaluation of the haemostatic profiles with raised factor VIII, VWF and D-dimer supported an ongoing vasculopathy. The CWA, a global haemostatic test that was performed on case 2, demonstrated parameters of hypercoagulability. There were increased (1) clot Min1 "thrombin burst"; (2) peak of second derivative curve; (3) clot maximum deceleration; and (4) delta change (decreased light transmission reflective of increased clot thickness) as demonstrated by Fan et al.14 In addition, autopsy series demonstrated the presence of cardiac microemboli despite the absence of viral particles in the myocardium.15

Our case series suggest that life-threatening myocardial infarction can occur unexpectedly in otherwise healthy patients with asymptomatic COVID-19 infection. Physicians should have a high index of suspicion in managing patients in the convalescent phase. Screening for and strict management of cardiovascular risk factors are of utmost importance post COVID-19. Further longitudinal studies in patients with “long COVID” should be performed to look for post-COVID-19 associated endotheliopathy and thrombotic sequelae, where there may be a role for thromboprophylaxis in high-risk groups.

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