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Article Summary: STEMI can be the presenting diagnosis in adults with COVID-19. Presented, is a case of a 15-year-old female with coronary thrombosis-induced STEMI associated with COVID-19.

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Drs. Persson and Kim (a) provided substantial contribution to conception and design of the manuscript and (b) drafted the article and revised it critically for important intellectual content. Drs. Shorofsky, Leahy, Friesen, Khanna, and Cole (a) provided substantial contribution to conception and design, (b) revised the article critically for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abbreviations: ST-elevation myocardial infarction (STEMI), myocardial infarction (MI), severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), coronavirus disease 2019 (COVID-19), multisystem inflammatory syndrome in children (MIS-C)

Keywords: COVID-19, STEMI, thrombosis
Abstract

ST-elevation myocardial infarction (STEMI) is an identified presentation of COVID-19 in adults but has not been reported in children. We present a case of a 15-year-old female with a coronary thrombosis-induced STEMI in the setting of acute SARS-CoV-2 infection, not associated with multisystem inflammatory syndrome in children (MIS-C). The patient presented with chest pain, ST-elevation, and myocardial dysfunction. Coronary angiography identified thrombosis treated with anticoagulation and antiplatelet therapy. Myocardial infarction must be considered in children who present with COVID-19-associated myocardial dysfunction.

Introduction

Transmural myocardial ischemia and ST-elevation myocardial infarction (STEMI) have been associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in adults. Myocardial infarctions in acute SARS-CoV-2 infection have occurred as the primary presentation\(^1\) of COVID-19, as well as a secondary thrombotic complication of the acute disease. In children, coronary ischemia is associated with multisystem inflammatory syndrome in children (MIS-C)\(^2,3\) but there are no reports describing myocardial infarction (MI) with acute COVID-19. Nevertheless, thrombosis is commonly associated with COVID-19 across the lifespan.\(^4,5\)

Patient Presentation

A previously healthy 15-year-old, 49-kg, female presented to the emergency department with a one-day history of acute onset, severe chest pain with left shoulder radiation, nausea, and vomiting. She was in her usual state of health until one week prior to presentation, when she developed dyspnea. She developed anosmia four days prior to presentation. The patient’s sister
had a positive SARS-CoV-2 polymerase chain reaction (PCR) on the day prior to the patient’s presentation and another close contact had an upper respiratory infection the week prior to the patient’s symptom onset but did not have SARS-CoV-2 testing. The patient had no significant past medical history, did not smoke, and took no medications.

On initial presentation, the patient was afebrile but ill-appearing with mild tachypnea, normal heart rate, blood pressure, and oxygen saturation in room air. Physical examination revealed no dyspnea, murmur, gallop, conjunctivitis, rash, or calf tenderness. Chest radiography was normal.

Electrocardiography demonstrated ST-elevation in anterolateral leads (V3-V6, I, and aVL), ST depression in leads V1 and V2, and T wave inversion in lead III (Figure 1). She was given aspirin 325 mg.

Initial laboratory evaluation was notable for elevated troponin (0.579 ng/mL; upper limit of normal (ULN) 0.119 ng/mL) and D-dimer (0.92 mg/L; ULN 0.5 mg/L). SARS-CoV-2 PCR on nasopharyngeal swab was positive. There was neutrophilic leukocytosis (15,000/mcL) with lymphopenia (absolute lymphocyte count 790/mcL). C-reactive protein, procalcitonin, erythrocyte sedimentation rate, platelet count, and ferritin were all normal. Urine pregnancy test was negative.
Given the concern for cardiac chest pain, with the differential diagnosis including STEMI, myocarditis, and MIS-C, the patient was transferred to a pediatric quaternary care center for further evaluation and management. Repeat laboratory evaluation upon arrival at the pediatric referral center (four hours after initial presentation) demonstrated rising troponin (13.7 ng/mL) and D-dimer (1.23 mg/L) and elevated serum NT-pro BNP (676 pg/mL; ULN 125 pg/mL). She received one dose of intravenous immunoglobulin (IVIG) 2 g/kg given concern for myocarditis and/or MIS-C. Transthoracic echocardiogram demonstrated akinesis of the left ventricular (LV) apex with normal function of the basal and mid-wall segments and a resultant ejection fraction of 54% (Supplemental Video 1 and 2). Right ventricular function was normal and coronary arteries were normal in origin and size. For the diagnosis of STEMI, she was taken emergently to the cardiac catheterization laboratory for coronary angiography under general anesthesia.

In the catheterization laboratory, LV end diastolic pressure was elevated (11 mmHg). Coronary angiography demonstrated a thrombus in the distal ramus branch of the left coronary artery with abrupt cessation of flow in the distal left anterior descending coronary artery, consistent with complete occlusion near the LV apex (Figure 2 and Supplemental Video 3). The right coronary arteries were patent. Given the time to catheterization, distal nature of the thrombosis, and small coronary artery size, percutaneous coronary intervention (PCI) and/or thrombectomy were not performed. A bolus of unfractionated heparin (100 units/kg) was given, followed by a continuous infusion (goal anti-Factor Xa level 0.5 -0.7 units/mL). For antiplatelet therapy, two boluses and 24-hour continuous infusion of eptifibatide (glycoprotein IIb/IIIa inhibitor) were administered, followed by dual antiplatelet therapy (DAPT) with clopidogrel and aspirin.
She was admitted to the pediatric cardiac intensive care unit and treated for acute COVID-19 with five-day course of remdesivir. Corticosteroids were not prescribed given lack of hypoxemia. No additional IVIG nor other immunomodulatory medications were prescribed, as her clinical picture was not consistent with MIS-C.

Ultrasonography revealed no deep vein thromboses. Agitated saline echocardiography revealed no patent foramen ovale. She had no personal history of thrombosis. Family history revealed miscarriages in the patient’s mother and sister, but no family history of atherosclerosis or myocardial infarction at a young age. Standard coagulation tests were normal. Targeted thrombophilia testing demonstrated normal protein C, protein S, antithrombin III levels, with negative prothrombin mutation and lupus anticoagulant. Beta-2 glycoprotein and anti-cardiolipin antibodies were negative, aside from an elevated anti-cardiolipin IgG of 56.4 CU (ULN < 20.0 CU). Lipid profile revealed a low HDL at 27.7 mg/dL.

After peak to 20 ng/dL, serum troponin declined after initiation of antithrombotic therapy. D-dimer declined at 24 hours. At discharge, DAPT, apixaban, atorvastatin, and metoprolol succinate were prescribed.

Upon discharge, the patient established coordinated care with an adult cardiologist in her hometown and a pediatric cardiologist at the pediatric hospital from which she was discharged. She developed small LV thrombi in the setting of apical akinesis and anticoagulation non-
compliance. The patient’s medications were resumed and close outpatient follow-up with her cardiologist planned.

**Discussion**

We present the first reported case of an adolescent with STEMI in the setting of acute SARS-CoV-2 infection. Hypercoagulability and thrombotic disease in COVID-19 is thought to be related to microcirculatory inflammation and platelet activation resulting in vascular thromboses. Inflammatory platelet activation is thought to play a role in MI due to COVID-19 in adults and STEMI may be the first presenting clinical manifestation, as it was in this pediatric case. Additionally, with the COVID-19 pandemic, multisystem inflammatory syndrome in children (MIS-C) has emerged. Coronary artery ectasia in MIS-C is quite common and coronary pathology similar to that seen in Kawasaki disease is associated with myocardial ischemia and infarction. The association between MI and COVID-19 in children has been anticipated but not yet reported.

There is risk of thromboembolic events in patients with COVID-19. The pathogenesis, while incompletely understood, is likely related to Virchow’s triad of endothelial injury, hypercoagulable state, and blood flow stasis. Endothelial dysfunction is thought to be caused by direct invasion of the endothelial cells by SARS-CoV-2. COVID-19 has been associated with a hypercoagulable state induced by increased prothrombotic factors. Interestingly, our patient exhibited no elevated inflammatory markers. Though pre-existing prothrombotic conditions and family history of thrombosis may pose additional thrombosis risk associated with SARS-CoV-2 infection, the evidence for thrombophilia testing in adults varies widely. Some
literature surmises that COVID-19 disease, itself, suffices as a primary cause of thrombosis and recommends no additional testing, while others suggest extensive testing.\textsuperscript{13,14} It is unknown how to apply this range of recommendations to a child with MI. In this case, the patient’s only finding on thrombophilia testing was elevated anti-cardiolipin IgG. The patient may have developed antiphospholipid syndrome as a result of COVID-19, however, follow up testing at 12 weeks will be needed to confirm this diagnosis.\textsuperscript{15,16} Finally, the patient was not overweight and lipid panel revealed merely a low HDL; this was not thought to be a strong risk factor in a healthy 15-year-old. Nevertheless, the patient was prescribed atorvastatin for post-MI management for the hypothesized beneficial pleotropic effects, including decreased inflammation, inhibition of platelet aggregation, improved endothelial function, stimulation of endothelial progenitor cells, and increased plaque stability.\textsuperscript{17,18}

Left ventricular dysfunction by echocardiography should prompt consideration of COVID-19-associated myocarditis. In this case, an empiric dose of IVIG was given for the potential of myocarditis and MIS-C. When ST-segment elevation is noted in a child presenting with COVID-19, myopericarditis should also be considered. Further, the differential diagnosis of ST-elevation is broad and can be divided into ischemic and non-ischemic etiologies. Non-ischemic etiologies include pericarditis, early repolarization, bundle-branch blocks, and LV hypertrophy with strain.\textsuperscript{17} Although the majority of adults who present with acute chest pain, ST-elevation, and ischemia have had atherosclerotic plaque rupture, it is important to consider alternative causes of ischemia, particularly in young people.\textsuperscript{18,19}
The standard of care for adults is door-to-PCI time within 90 minutes.\textsuperscript{16,20} This standard has been reinforced during the COVID-19 pandemic.\textsuperscript{21} Additionally, if PCI is not feasible, transfer to a primary PCI center with intervention within 120 minutes is recommended.\textsuperscript{17,20}

Treatment strategies for adolescents with STEMI will need to be extrapolated from the adult recommendations.\textsuperscript{17,20} Primary stenting, balloon angioplasty, and manual aspiration thrombectomy were considered in this patient. However, intervention was not attempted due to the small vessel size, evidence of flow around the thrombus, and risk of dissection. Rather, systemic anti-thrombotic therapies were employed. Alternatively, intra-coronary or systemic fibrinolytic therapy, both described in coronary thrombosis due to Kawasaki disease, might be considered in COVID-19-associated STEMI in children.\textsuperscript{8}

This case presents an adolescent requiring emergent PCI for COVID-19-associated STEMI. Centers without pediatric interventional cardiology expertise should consider whether the age and/or weight threshold should be lowered to include the care of a child requiring PCI for STEMI. The unusual presentation of STEMI in an adolescent, as well as the potential reluctance of adult centers to care for a child requiring PCI, contributed to the delay in this patient’s evaluation. Systemic fibrinolytic therapy might be considered if a delay to PCI is projected.\textsuperscript{17,20} Transfer from an adult PCI center to a pediatric center poses challenges. Most pediatric centers are not staffed for emergent PCI. Adult STEMI evaluations can often be done without general anesthesia; however, this may not be feasible in a child. SARS-CoV-2 infection posed an additional issue in this patient who received general anesthesia with endotracheal intubation.
In summary, this case describes a 15-year-old with acute coronary artery thrombosis-induced STEMI secondary to COVID-19. Coronary artery thrombosis was not a consequence of MIS-C. This patient was treated with systemic anticoagulation and DAPT. Though pediatric MI is exceedingly rare, the hyperinflammatory and hypercoagulable state caused by COVID-19 may be a novel cause of pediatric MI. In addition to myopericarditis, the potential for acute coronary artery thrombosis must be considered in children with COVID-19 presenting with chest pain. PCI centers should reconsider age and weight thresholds for intervention in children. Pediatric centers should consider the need for emergent PCI in a child presenting with MI. Nevertheless, further study of this disease entity is needed and its distinction from MIS-C must be made.

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Figure 1: Initial electrocardiogram: There is ST-elevation in the anterolateral leads (V3-V6, I, and aVL) with ST depression in leads V1-V2 and T wave inversion in lead III. An ectopic atrial rhythm is also noted.
Figure 2: Left coronary artery angiogram: The left main coronary artery and branching pattern is normal. There is a well-organized filling defect in the distal ramus branch of the left coronary artery, where the vessel measures approximately 1.3 mm. There is flow visualized around the filling defect. Additionally, the distal left anterior descending coronary artery terminates abruptly suggesting distal occlusive thrombus.
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