Left ventricular thrombus in the multisystem inflammatory syndrome in children associated with COVID-19

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ABSTRACT

A 3-year-old girl presenting with fever, mucocutaneous inflammation, and acute gastrointestinal symptoms met criteria for the multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C). Echocardiography showed severely decreased left ventricular (LV) function with an apical mass. After treatment with intravenous (IV) immunoglobulin, IV steroids, anakinra, milrinone, and systemic anticoagulation, her LV function rapidly improved and the mass became increasingly mobile. Given the risk of systemic embolization, the mass was excised through left ventriculotomy and pathology confirmed a thrombus.

Keywords: Left ventricular thrombus, multisystem inflammatory syndrome in children, severe acute respiratory syndrome coronavirus 2, surgery

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) represents a rare and often severe disease process related to COVID-19 infection. The incidence of pulmonary embolism and arterial thrombosis (stroke and myocardial infarction) is markedly increased in severe adult COIVD-19 infection.[1] Although thrombotic complications are less frequent in children, pulmonary embolism and thrombotic microangiopathy have been reported in MIS-C.[2,3] MIS-C is associated with myocardial dysfunction increasing the milieu for thrombus formation.[4] We present the case of an intracardiac thrombus associated with MIS-C.

CASE REPORT

A previously healthy 3-year-old girl was admitted to a community hospital reporting 5–6 days of fever and 48 h of nausea, vomiting, diarrhea, and body stiffness. Laboratory evaluation showed microcytic anemia, hyponatremia, normal white blood cell count with low absolute lymphocyte count, and elevated blood urea nitrogen (BUN), and creatinine [Table 1 for full laboratory results]. Inflammatory markers were elevated (erythrocyte sedimentation rate [ESR] 37 mm/h, C-reactive protein [CRP] 24.2 mg/dL, and ferritin 493 ng/mL). She tested positive for rhinovirus and group A Streptococcus and negative for COVID-19 by polymerase chain reaction.

Shortly after admission, her fever increased to 39.4 degrees, oxygen saturation dropped to 84%, and she became hypotensive. Evaluation for MIS-C revealed elevations in B-type natriuretic peptide (BNP, 9786 pg/mL), troponin I (0.11 ng/mL), and D-dimer (5.13 mcg FEU/mL). Severe

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Table 1: Laboratory values

Laboratory study	Result	Reference range
General evaluation		
Hemoglobin (g/dL)	**11.0**	11.5-13.5
Mean corpuscular volume (fL)	**71.0**	75.0-87.0
White blood cell count (K/mcL)	9.3	6.0-17.0
Absolute lymphocyte count (K/mcL)	**1.6**	4.0-10.5
Blood urea nitrogen (mg/dL)	**45**	9-22
Creatinine (mg/dL)	**0.74**	0.18-0.55
Erythrocyte sedimentation rate (mm/h)	**37**	0-9
C-reactive protein (mg/dL)	**24.2**	0-0.7
MIS-C evaluation		
Ferritin (ng/mL)	**493**	5-100
B-type natriuretic peptide (pg/mL)	**9786**	0-100
Troponin I (ng/mL)	**0.11**	0.00-0.04
D-dimer (mcg FEU/mL)	**5.13**	0.00-0.50
SARS-CoV-2 IgG antibody index	**5.9**	<1.4
Cytokine panel		
Soluble interleukin 2 receptor	**5650.6**	175.3-858.2
Interleukin 10 (pg/mL)	**42.0**	≤2.8
Interleukin 13 (pg/mL)	**14.5**	≤2.3
Interleukin 17 (pg/mL)	**7.8**	≤1.4
Interleukin 6 (pg/mL)	**21.6**	≤2.0
Thrombophilia evaluation		
Total homocysteine level (umol/L)	<3	0-15
Functional protein C level (%)	**117**	40-92
Free protein S antigen (%)	89	62-120
Enzymatic antithrombin activity (%)	106	82-139
Activated protein C resistance	4.3	≥2.00
Prothrombin time (s)	**18.2**	12.0-15.5
Prothrombin G20210A variant	Negative	Negative
Antiphospholipid antibody evaluation		
B2Glycoprotein 1, IgG antibody (SGU)	0	0-20
B2Glycoprotein 1, IgM antibody (SMU)	6	0-20
Cardiolipin antibody IgG (GPL)	3	0-14
Cardiolipin antibody IgM (MPL)	0	0-12
Prothrombin Antibody, IgG (units)	10	0-19
Phosphatidylserine antibody IgG (U/mL)	8	0-10
Phosphatidylserine antibody IgM (U/mL)	18	0-24
Phosphatidylserine and prothrombin IgG (units)	10	0-30
Phosphatidylserine and prothrombin IgM (units)	16	0-30

Bold indicates a value outside the reference range. MIS-C: Multisystem inflammatory syndrome in children, IgG: Immunoglobulin-G, IgM: Immunoglobulin-M, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

acute respiratory syndrome coronavirus 2 IgG antibody testing was positive. She was transferred to a tertiary pediatric intensive care unit for the treatment of MIS-C.

On arrival, she was agitated and had tachycardia, an S3, hepatomegaly, and cardiomegaly on chest x-ray. Echocardiography demonstrated moderate tricuspid and mild mitral valve regurgitation, normal coronary artery dimensions, severely reduced left ventricular (LV) ejection fraction (31%), and a sessile mass in the LV apex [Figure 1a and Video 1, online]. Blood cultures returned negative. Evaluation for causes of myocarditis demonstrated no evidence of acute infection with influenza, cytomegalovirus, Epstein-Barr virus, enterovirus, human herpesvirus 6, human immunodeficiency virus, herpes simplex virus, parvovirus B19, adenovirus, varicella-zoster virus, or hepatitis A, B, or C. Due to hypoxia and suspected MIS-C, there was a concern for a pulmonary embolism and the decision was made to proceed with chest/abdominal computed tomography angiography despite the patient's renal dysfunction. This was negative for arterial or venous thrombus. She was started on therapeutic heparin for thrombus, oxygen, epinephrine, and milrinone and treated for MIS-C with intravenous immunoglobulin and methylprednisolone.

Within 24 h of treatment, her hypotension resolved and laboratory markers improved (BNP 2,994 pg/mL, BUN 18 mg/dL, and creatinine 0.53 mg/dL). Due to an initial decrease followed by a rise in CRP (22.3 mg/dL), anakinra was added and inflammatory markers subsequently decreased.

Repeat echocardiography within 24 h of anti-inflammatory therapy showed improved LV shortening and ejection fractions (23% and 47%, respectively) which normalized by hospitalization day 3. As LV function improved, the mass appeared increasingly mobile and more pedunculated [Figure 1b and Video 2, online] increasing the risk of embolization. She was taken to the operating room for mass resection.

Based on the location of the thrombus, a transmitral or transaortic approach was believed to be insufficient for complete thrombus removal, therefore a left ventriculotomy was planned. Cannulation strategy consisted of a single venous cannula and her heart was arrested with antegrade cardioplegia with the placement of an LV vent. A fish-mouth incision was made 2-3 cm lateral and parallel to the left anterior descending artery [Figure 2a]. A 2 × 2 gauze was placed into the LV cavity to collect any debris during excision. On surgical inspection, the mass had a friable, pedunculated portion with central liquefaction at the end of a stalk. It emanated from a broad base of thrombus incorporated within trabeculated muscle bands and was very adherent to the myocardium. The thrombus measured 1.9 cm × 1.5 cm × 0.6 cm and was completely excised [Figure 2b]. A series of felt strips were employed to assist in the closure of the left ventriculotomy, which was performed in two layers with a running 5-0 polypropylene suture [Figure 2c]. Cardiopulmonary bypass time and arrest time were 60 and 30 min, respectively. No residual mass was seen on postoperative transesophageal echocardiography. Pathology confirmed a thrombus with no fungal and bacterial organisms.

An extensive thrombophilia workup was negative for antiphospholipid antibodies and did not identify any thrombotic predisposition. Postoperative echocardiography demonstrated ongoing normal function with some echo bright areas at the LV apex, but no evidence of LV thrombus. By the second postoperative day, the patient developed decreased right arm movement a vascular ultrasound was obtained and demonstrated a nonocclusive thrombus associated with a peripherally inserted central catheter in the right subclavian vein. The patient was re-started on a heparin infusion. A persistent left gaze preference was then noted, and magnetic resonance imaging of the brain identified an arterial ischemic stroke involving the left middle cerebral artery posteriorly with a small thrombus in a left M2 segment vessel. The heparin infusion was transitioned to enoxaparin three days after initiation with a planned 3-month course of anticoagulation targeting an anti-Xa level of 0.5-1.0 IU/mL. Low-dose aspirin was also started on postoperative day 10 with a planned 3-month course. The patient demonstrated steady neurologic improvement with no persistent weakness or gaze preference but required supplemental nasogastric feedings and ongoing aspirin and enoxaparin at the time of discharge.

DISCUSSION

Endothelial injury and inflammation in MIS-C present a procoagulant state. In addition, decreased systolic ventricular function is common in MIS-C but there is the potential for rapid recovery.[4] This combination may predispose MIS-C patients to the development of intracardiac thrombi and increase the risk of embolization. The quick recovery of LV function may increase the risk of embolization. In adults with LV thrombi following myocardial infarction (MI), the risk of embolization was 10-15% if untreated,[5] and even higher if the thrombus was mobile or protruded into the LV cavity.[6] Given her rapid recovery of function, we considered our patient's risk of embolization to be higher than the risk after MI in adults. Since she still suffered a stroke, surgery did not completely eradicate the risk of embolization, though the risk of a catastrophic event was mitigated.

Intracardiac thrombi have been reported in acute COVID-19[7,8] but we were only able to identify one report

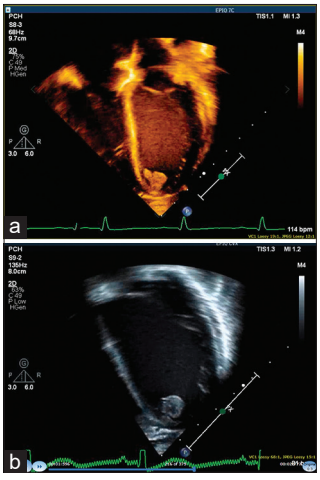

Figure 1: (a) Sessile mass in the left ventricular apex. (b) Mobile mass attached by a pedunculated portion to a broad base

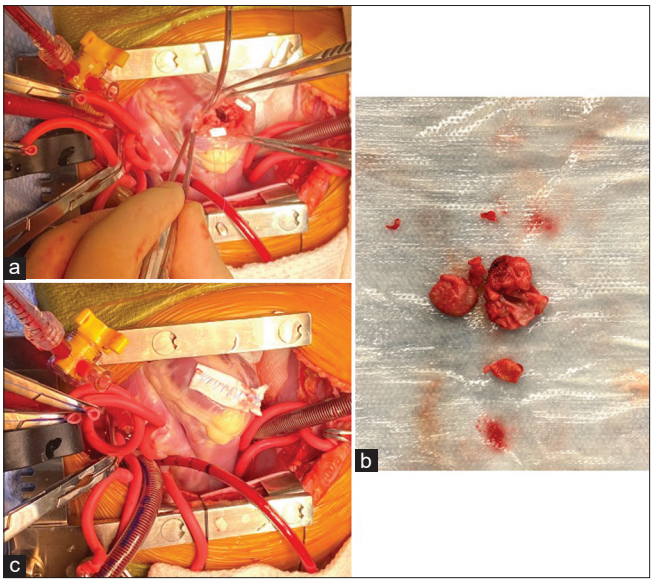

Figure 2: (a) Left ventriculotomy used to access the mass. (b) Mass following complete resection. (c) Ventriculotomy closure using felt strips

of intracardiac thrombus in MIS-C.[9] To some extent, the inflammatory state associated with acute COVID-19 in adults may mirror that seen in children affected by MIS-C. Anticoagulation in acute COVID-19 and MIS-C is controversial; however, recent expert consensus-based guidelines recommend prophylactic anticoagulation in children with acute COVID-19 or MIS-C, particularly if there is markedly elevated D-dimer or other risk factors for venous thromboembolism.[10] It is unclear if our patient would have benefited from earlier recognition of MIS-C with subsequent prophylactic anticoagulation.

This patient's presentation highlights the importance of a high index of suspicion for thrombi in MIS-C as well as the importance of serial echocardiographic evaluation and a potential need for aggressive surgical planning toward excision. In the case of an LV thrombus, a left ventriculotomy, although uncommonly used in cardiac surgery, may provide for a useful approach toward resection.

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Conflicts of interest

There are no conflicts of interest.

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