

Letter to the Editor**Intracardiac Thrombosis in the Three-Year-Old Boy with Normal Left Ventricle Systolic Function in MIS-C Associated with COVID-19****Keywords:** Intracardiac thrombosis, MIS-C, COVID-19.**Published:** March 1, 2022**Received:** December 15, 2021**Accepted:** February 12, 2022**Citation:** Krasic S., Popovic S., Kravljanac R., Prijic S., Vukomanovic V. Intracardiac thrombosis in the three-year-old boy with normal left ventricle systolic function in MIS-C associated with COVID-19. *Mediterr J Hematol Infect Dis* 2022, 14(1): e2022028, DOI: <http://dx.doi.org/10.4084/MJHID.2022.028>This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**To the editor.**

A multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, a newly described condition, is a hypercoagulable state caused by hyperinflammation and cytokine storm.¹⁻⁴ Although more than half of the patients with MIS-C (76%) have biochemical evidence of coagulopathy, the prevalence of deep vein thrombosis or pulmonary emboli is low (8%). On the other hand, the most extensive published MIS-C case series have not reported thrombotic complications.¹⁻⁴

Intracardiac thrombus is not a common condition in otherwise healthy children, and the most common location is the right-sided chambers. A left-sided intracardiac thrombus is almost always associated with left ventricular (LV) dysfunction or arrhythmia.⁵

We presented a left ventricle thrombus in a three-year-old boy with the normal systolic function of the left ventricle in MIS-C associated with COVID-19.

Clinical-Description. A three-year-old boy with a history of previous COVID-19 was admitted to the hospital due to a seven-day high fever (40,3°C), macular erythematous rash, bilateral nonexudative conjunctivitis, palmar-plantar edema, diarrhea, and

vomiting. He was initially treated with oral antibiotics. At the admission, he was febrile (38,6°C) with normal vital signs (heart rate 150/min, blood pressure 90/48 mmHg, respiratory rate 20/min). The physical examination revealed mucocutaneous (strawberry tongue and rash) and conjunctival changes. Laboratory findings showed mild anemia, hypoalbuminemia, hyponatremia, elevated C-reactive protein (CRP), pro-BNP, and mildly elevated liver enzymes D-dimers (**Table 1**). Routine urine examination showed sterile pyuria. The antibodies IgM and IgG classes against SARS-CoV-2 were detected in the blood sample by ELISA technique. ECG and thoracic X-ray were normal. Echocardiographic finding pointed out a normal systolic and diastolic function of the LV. The dimension of the proximal coronary arteries was average. According to physical examination and the results of the performed analysis, diagnosis of MIS-C associated with COVID-19 was made. Three pulses of intravenous methylprednisolone were administered at a 24 hours interval. The patient became afebrile after the first IVMP. Control laboratory parameters were in the reference range, and after 7 days of in-hospital stay, the discharge was planned.

Table 1. Laboratory finding of our patient during the in-hospital stay.

	admission	day of intracardiac thrombosis	discharge
Thrombocytes 10 ⁹ /L	218	252	322
CRP (mg/L)	81.4	1.4	0.3
Fibrinogen (g/L)	4.4	2.2	2.4
D-dimers (ng/mL)	720	642	38
Sodium (mmol/L)	128	135	141
Albumin (g/L)	28	33	38
Pro-BNP (pg/mL)	2088	144	65
Troponin I (ng/mL)	< 0.05	< 0.05	< 0.05
EF (%)	63	65	63
EDD (mm)	35	33	32
MR (+)	1	1	1



Figure 1. Echocardiography examination of our patient. A pedunculated bifid mobile 14x10 mm mass at the apex of the left ventricle.

Before the planned discharge, control echocardiography was performed. The echocardiogram showed no valvular abnormalities, normal LV systolic function with an ejection fraction of 65%, and a pedunculated bifid mobile 14x10 mm mass at the apex of the LV (**Figure 1**). He was immediately transferred to the pediatric intensive care unit. Anticoagulation and anti-aggregating drugs were administered. Laboratory findings pointed out the normal range of D-dimer, fibrinogen and platelets (**Table 1**). Additional hematology evaluation found elevated coagulation factor VIII (FVIII) (280,5%, reference range 50-150%), and XII (FXII) (209,8%, reference range 50-150%), while protein S and protein C activity levels were in the normal range. Anti-cardiolipin IgG and IgM antibodies were within normal limits. Factor V Leiden and FII gene mutations were not present. After 36 hours of verified intracardiac thrombosis, he became febrile again and developed right-sided hemiplegia and facial palsy associated with eye deviation (Prévost's sign) toward the left side, and aphasia. The same evening, in the control echocardiographic finding floating, LV mass was not observed. Urgent endocranial computerized tomography (CT) angiography was performed and, a perfusion defect of the M2 segment of the left middle cerebral artery (MCA) was described. Brain magnetic resonance imaging (MRI) and MRI angiography showed a sizeable ischemic zone without signs of hemorrhage due to lack of perfusion in the MCA territory, especially in its terminal branches (**Figure 2**). Electroencephalogram (EEG) was done within 8 hours from the appearance of neurological signs and showed asymmetric background activity with slow theta activity above the left side without epileptic discharges (**Supplement 1**). Due to the multi-day of fraxiparine

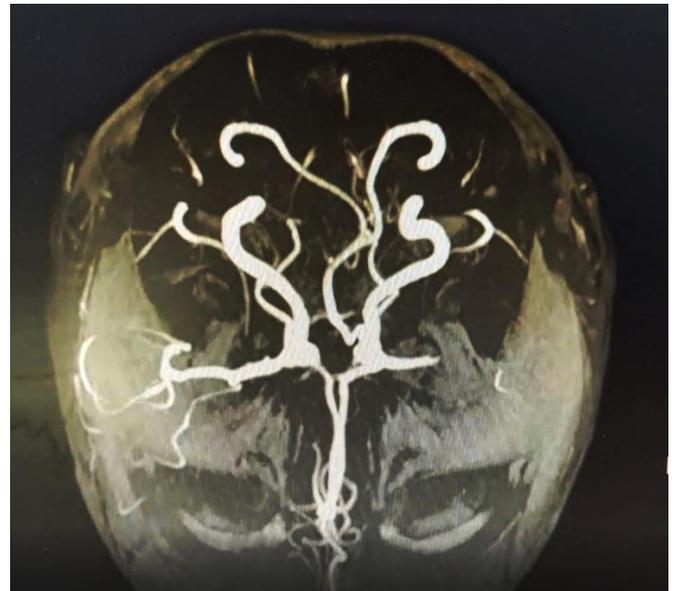


Figure 2. MRI angiography examination of our patient. The perfusion defect in the MCA territory, especially in its terminal branches.

management, thrombolysis was contraindicated, and the physician's council decided to continue anticoagulant and antiplatelet therapy, along with other symptomatic and supportive measures. During the one month in-hospital stay, the general condition improved, while neurological recovery lasted for a long time, and the boy was discharged with significant hemiplegia with improvement in speech and facial palsy. The control brain MRI showed cortico-subcortical atrophy of the basal ganglia limited zones of cytotoxic edema in the left parietal cortex with secondary ventriculomegaly one month after acute cerebral stroke. A significant reduction of ramification and flow in the terminal branches of the left MCA was described.

Discussion. We presented the left ventricle thrombus in the three-year-old boy with the normal systolic function of the LV in MIS-C associated with COVID-19. Namely, the occurrence of one or more Virchow triad components predisposes intravascular or intracardiac thrombosis. Bigdelian et al. presented three patients with acute intracardiac thrombosis during COVID-19; all of those children had preserved EF. In comparison to patients with COVID-19 (2.1%, 95% CI, 1% to 4%) and asymptomatic SARS-CoV-2 infection (0.7%, 95% CI, 0.1% to 2.4%), patients with MIS-C had the highest incidence at 6.5% (95% CI, 3% to 12%) of thrombotic events.⁶ Among patients with thrombotic events (20 pts) only 3 had intracardiac thrombosis and associated comorbidities - two with acute COVID-19 and cancer, and one with MIS-C and obesity. All of those patients had catheter-related thrombosis.⁶ Schroder J et al. presented a healthy 17-years-old boy with systolic dysfunction of LV and a mural thrombus near the posteromedial papillary muscle in the LV apex.⁷ Our patient had normal LV systolic function, but despite this, LV thrombus was developed at the time of intended discharge.

In SARS-CoV-2 infection, increased acute-phase reactants such as fibrinogen and CRP may contribute to the hypercoagulable state.¹⁻⁴ Our patient had normal coagulation status, including fibrinogen and D-dimers, but markedly elevated FVIII and FXII. Factor VIII and von Willebrand (VWF) have previously been described as acute phase reactants.^{8,9} Strong independent associations have been proved between elevated FVIII and an increased risk of arterial thrombosis.^{8,9} Although

endothelial cells produce FVIII and VWF, SARS-CoV-2 might induce their accelerated synthesis acting on endothelial ACE-2 receptors. Coagulation factor XII (FXII, Hageman factor) is a plasma protease that initiates the procoagulant and proinflammatory contact system. In addition to its role in thrombosis, FXIIa contributes to inflammation by activating the inflammatory bradykinin-producing kallikrein-kinin system.¹⁰ SARS-CoV-2 induced endothelial dysfunction leads to activation of the external coagulation pathway.¹⁻⁴

On the other hand, increased IL-6 and other cytokines establish a prothrombotic state by disabling the natural anticoagulants.⁸ Consequently, our patient had a transient hypercoagulable state, likely secondary to the recent SARS-CoV-2 infection. To the best of our knowledge, that is the first case of a three-year-old boy with intracardiac thrombosis in LV with normal systolic function during MIS-C associated with COVID-19.

Conclusions. Floating intracardiac thrombus in children with normal LV systolic function is hazardous with excellent potential for thromboembolic complications. The hypercoagulable state might be one of the most critical risk factors for intracardiac thrombosis event. Systolic function of LV is preserved. Recent SARS-CoV-2 infection leads to coagulopathy and hypercoagulable condition with increased risk of vessels thrombosis and embolism; pharmacological thromboprophylaxis in MIS-C should be highly recommended.

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Competing interests: The authors declare no conflict of Interest.

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Supplement 1. EEG findings in our patient (longitudinal montage, 70 -100 mcV/cm sensitivity, 30 mm/cm speed, frequency filters: low-pass 70 Hz, high-pass 1 Hz)



An asymmetric basic activity between left and right hemisphere