

## Case Report

# Infective Endocarditis in a Previously Healthy Adolescent Masquerading as Systemic Lupus Erythematosus in the COVID-19 Era

**Background:** Multisystem inflammatory syndrome of children (MIS-C) has emerged as a serious systemic inflammatory disorder complicating COVID-19 infection in children. Arterial and venous thrombosis have been reported complicating COVID-19 infection but not infective endocarditis (IE). **Case presentation:** Herein, we describe a 12-year-old girl initially presented with picture of MIS-C with echocardiography (ECHO) revealing only pericardial effusion, for which she has received single dose of pulsed methylprednisolone with no improvement, her blood picture was significant for anemia and thrombocytopenia, with increased acute phase reactants (APRs) including serum ferritin and IL-6. She was found to have as well oral ulcers, polyarthritits, vascular purpura, and exaggerated deep tendon reflexes. She had history of low-grade fever, gastrointestinal illness, together with myalgia and easily fatigability during the last month before presentation, symptoms suggestive of viral infection most probably SARS-CoV-2 infection with positive COVID-19 IgG. The girl was considered as probable systemic lupus erythematosus (SLE) in face of negative immunological evaluation for SLE except for moderately positive anti-cardiolipin IgM. Initially, the girl has responded to intravenous steroids but ten days later, she came back toxic with marked increase in APRs and ECHO revealed left atrial mural highly mobile floating mass, blood culture was positive for staphylococcus coagulase negative organism, steroids were gradually withdrawn, and complete resolution of the IE was achieved after six weeks of parenteral antibiotics. **Conclusion:** COVID-19 infection can result in subclinical cardiac affection making the heart vulnerable to colonization with even mild bacteremia. Although autoimmune features of IE are uncommon but can confuse the presentation especially when the vegetations could not initially be detected by ECHO.

**Key words:** Infective endocarditis, Autoimmune diseases, Systemic lupus erythematosus, COVID19, MIS-C

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## INTRODUCTION

In recent times, infective endocarditis (IE) has resurfaced as a major clinical challenge, with profound implications. This alarming trend is particularly concerning as it affects younger patient populations, highlighting the pressing need for comprehensive strategies to address this evolving challenge.<sup>1</sup> The intricate nature of the disease necessitates precise diagnosis and promotes effective treatment.<sup>2</sup> While pre-existing heart conditions remain the primary predisposing factor for pediatric IE, a new era has emerged: IE in children with structurally normal hearts which has become an apparent entity.<sup>3</sup>

Roughly, 8–10% of pediatric IE cases arise in the absence of pre-existing heart conditions, yet other risk factors come into play. These

include immunodeficiency, prolonged parenteral nutrition, and the presence of central venous catheters, especially those near the heart or tunnelled central venous catheters. This in addition to the recently reported infection with SARS-CoV-2 virus.<sup>4</sup>

COVID-19 triggers a prothrombotic state, heightening the risk of microvascular, venous and/or arterial thrombosis which plays a pivotal role in COVID-19 related cardiovascular complications.<sup>5</sup> The underlying mechanisms of thrombus formation in the COVID-19 infection may be attributed to the hypercoagulation and inflammatory state of the disease incurred by the SARS-CoV-2 virus infection.<sup>6</sup>

Occasional reports have associated IE with complications stemming from SARS-CoV-2 infections.<sup>7</sup> However, the precise mechanisms by which COVID-19 predisposes to IE are yet

to be fully elucidated.<sup>8</sup> Clinically, IE may present with a myriad of highly variable symptoms and signs, some of which may point the clinician toward an autoimmune disorder instead of an underlying infection particularly in the absence of classic IE manifestations.<sup>9</sup>

We present a 12-year-old previously healthy girl whose initial presentation of IE mimicked lupus that possibly complicated COVID-19 infection.

### CASE PRESENTATION

A 12-year-old previously healthy girl, whose illness started with high grade persistent fever (39 °C), bony aches, anorexia, and malaise up to secondary inability to walk. Ten days before her illness, the girl had brief episodes of expressive aphasia, which had been considered psychological stress by her parents. The girl was then admitted at hospital because of severe persistent headache associated with blurring of vision, vomiting and dizziness. Shortly after, a vasculitic purpura developed on her palms and soles together with oral ulcers and mucositis. Her routine laboratory workup revealed thrombocytopenia (platelets:  $75 \times 10^9/L$ ), with mildly elevated total leukocytic count (TLC) of  $11 \times 10^9/L$  and normal haemoglobin (Hb) level of 12 gm/dl, C-reactive protein (CRP) was markedly elevated 154 mg/L while the erythrocyte sedimentation rate (ESR) was 17 mm/hour. Total creatine phosphokinase (CK-Total) was mildly elevated 256 U/L (N: 30-145 U/L), CK-MB 11.5 U/L (N: 5-25 U/L) and troponin 0.15 ng/ml (N: 0-0.04 ng/ml). Serum ferritin level of 657 ng/ml (N: 7-140 ng/ml), IL-6 level of 1176 pg/mL (N: <7 pg/ml) and D-dimer 0.98 mg/L (N: <0.50 mg/L). Plain chest x-ray revealed mild cardiomegaly and her echocardiogram (ECHO) was significant for mild circumferential pericardial effusion, mild mitral regurge, tricuspid regurge, mildly dilated left ventricle and good systolic function. The patient was initially treated as multisystem inflammatory syndrome in children (MIS-C)-COVID-19 related as has been described in the medical report based on clinical and laboratory features with positive COVID-19 IgG. She received single dose of intravenous pulsed

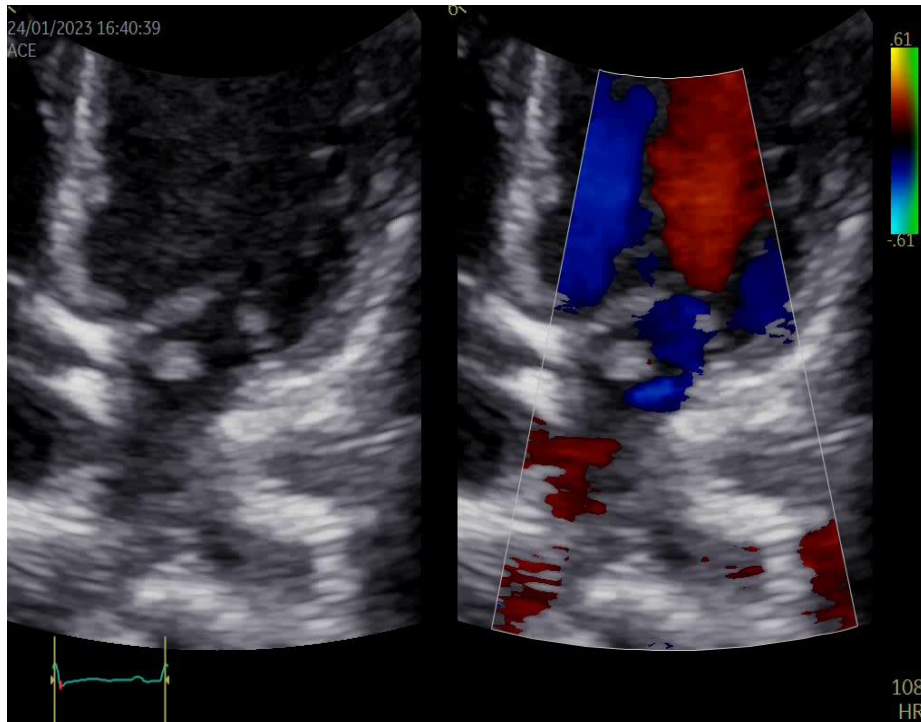
methylprednisolone at a dose of 30 mg/kg and referred to the Pediatric Allergy, Immunology and Rheumatology Unit, Children's Hospital, Ain Shams University for further evaluation and management. On presentation, the girl looked ill, temperature was 39 °C, her heart rate was 140/minute, regular and her blood pressure was 120/80 mmHg. There were oral ulcers, malar rash (figure 1) and vasculitic purpura on her hand and feet. She had as well bilateral knee and ankle arthritis in addition to the left first metatarsophalangeal arthritis. Cardiac examination did not reveal abnormality apart from regular tachycardia. Neurological examination was positive for bilateral exaggerated deep tendon reflexes of the lower limbs with patellar and adductor reflexes as well as bilateral positive Babinski sign. Otherwise, no other additional clinical features. Laboratory studies showed normal TLC  $5 \times 10^9/L$ , Hb level of 11.4 gm/dl, and a platelet count of  $49 \times 10^9/L$ . The ESR and CRP level were elevated at 40 mm/h and 255 mg/L, respectively. Her immunological evaluation was negative for anti-nuclear and anti-double stranded deoxyribonucleic acid antibodies with normal serum complement 3 (C3), but with mildly positive cytoplasmic antineutrophil cytoplasmic antibody titer (c-ANCA). The antiphospholipid antibodies were positive only for anti-cardiolipin (ACL) IgM level (56 MPL U/mL). She had mildly elevated triglycerides but normal fibrinogen, ferritin was still elevated (500 ng/dl). Magnetic resonance imaging (MRI) of the brain showed left sided central gyrus and juxta cortical white matter recent infraction exhibiting diffusion restriction with high signal at FLAIR sequence. Audiometry was done showing right severe sensory neural hearing loss with no speech discrimination. Right mild field changes were found on visual evoked potential done. ECHO revealed only pericardial effusion. Based on the patients' clinical presentation, laboratory and imaging features, the girl was considered as a probable case of systemic lupus erythematosus (SLE), the highly elevated CRP was interpreted in the context of possible associated infections, macrophage activation syndrome in addition to the underlying serositis and arthritis. Initially

the patient was placed on broad spectrum antibiotics and intravenous dexamethasone at moderate dose for 48 hours with resolution of fever and mild improvement of the other constitutional symptoms and the blood picture as well as APRs. Dexamethasone was replaced by intravenous methylprednisolone at a dose of 30 mg/kg/day for 3 days, the patient was also placed on low dose aspirin 3 mg/kg/day because of high ACL IgM with evidence of cerebral small vessel vasculitis. The patient showed very good response with normalization of blood picture as well as APRs and was discharged on full dose oral steroids (60 mg/day) to come after 2 weeks for follow up. However, ten days later after discharge, patient again presented with high grade fever (39 °C) associated with generalized bony aches and malaise. The girl looked toxic, her vital data were as follow: heart rate was 130/min, blood pressure: 110/70, and respiratory rate: 28/min. Her general and systems examination were otherwise free. Her blood picture was significant for moderate microcytic hypochromic anaemia where TLC was  $11.2 \times 10^9/L$ , a haemoglobin level of 8 gm/dl, a platelet count of  $338 \times 10^9/L$ , an elevated CRP

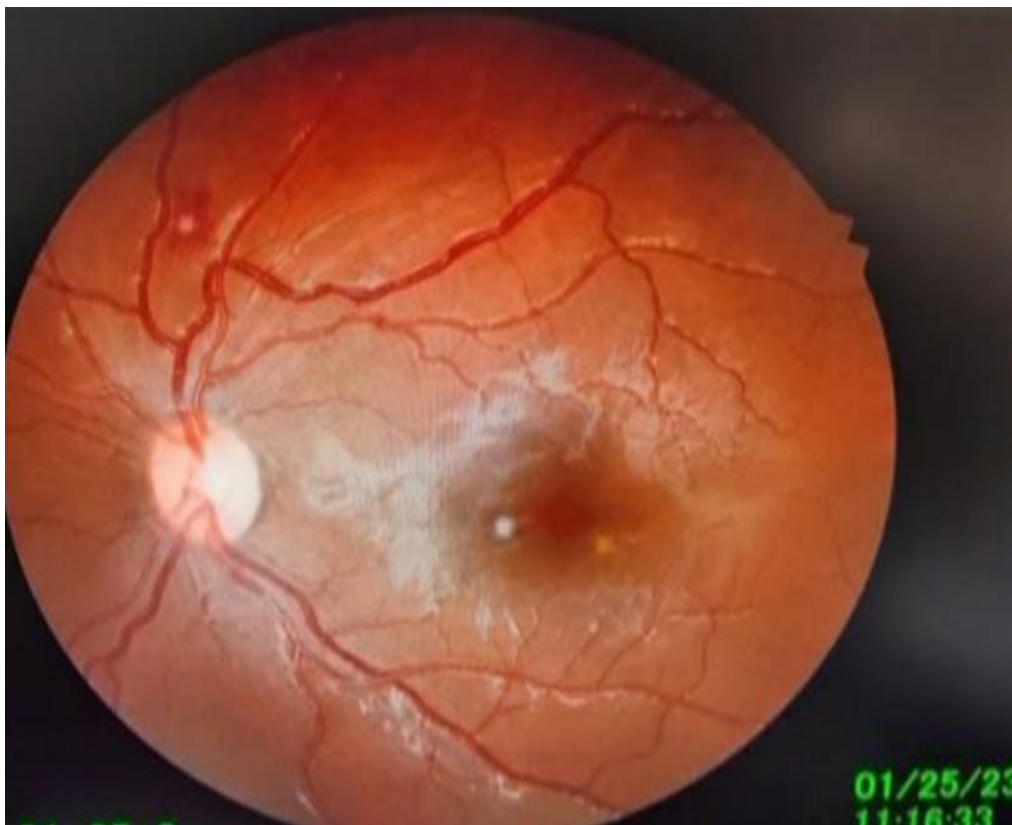
level of 134 mg/L, and an ESR of 75 mm/hour. Echocardiogram at this time of presentation showed left atrial mural highly mobile floating mass related to the posterior mitral leaflet, measuring 11×18 mm with moderate mitral regurgitation (figure 2), mild tricuspid regurgitation, with estimated RVSP= 35 mmHg and ejection fraction of 61%. The results of the three successive blood cultures were positive for *Staphylococcus coagulase* negative organism. Fundus examination revealed Roth spots (figure 3). Therefore, the girl was diagnosed with as a definite case of infective endocarditis (IE) initially presented with autoimmune features. Broad spectrum antibiotics namely vancomycin and meropenem were initiated and planned to be continued for 6 weeks in addition to gradual withdrawal of oral prednisolone till stopped after 3 weeks. The patient was continued to improve clinically with normalization of her blood picture and APRs. Serial echocardiographic studies revealed gradual reduction in the left atrial mass size together with improvement of mitral regurgitation severity. Complete resolution of her echocardiographic findings was accomplished by week 10 of presentation.



**Figure 1.** An erythematous non itchy patches with some papules sparing the nasolabial fold (resembling malar rash)



**Figure 2.** Echocardiography examination of our patient showing left atrial mural highly mobile floating mass related to the posterior mitral leaflet measuring 11×18 mm.



**Figure 3.** Fundus examination showing Roth spots.

## **DISCUSSION**

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 dysfunction or arrhythmia.<sup>10</sup> The emergence of COVID-19 has spotlighted the critical role of inflammation in fostering intra-myocardial microthrombosis, a reciprocally, synergistic, and complex interplay between the body's innate immune defences and the coagulation system, designed to combat pathogens. This thromboinflammatory phenomenon, while a natural protective response, can spiral into a problematic state known as dysregulated immunothrombosis, particularly evident in MIS-C cases.<sup>11</sup>

In 2021, Blagova et al, reported that endocarditis was found in 28% of patients with post-COVID myocarditis (one case of IE and four nonbacterial thromboendocarditis (NBTE)).<sup>12</sup>

In our study, the blood culture unveiled the presence of coagulase-negative staphylococci, a microorganism typically colonizes the skin and mucous membranes, known for its relatively low virulence and only seldom causes native valve or mural endocarditis. Hence, we suggested that MIS-C induced immunothrombosis may be the catalyst for underlying endothelial damage, setting the stage for this organism to instigate left-sided IE in a structurally intact heart.

In 2022, Kukhtinova and Ivanov highlighted a rare occurrence of an acute right atrial mural non-floating thrombus in a 6-year-old child with COVID-19.<sup>13</sup> Some other previous reports documented the occurrence of left sided thrombosis post COVID-19 in children, where Barfuss and colleagues reported a left ventricular thrombus in a 3-year-old girl, diagnosed with MIS-C COVID-19, secondary to left ventricular myocardial dysfunction.<sup>14</sup> Also, Krasic et al. reported a 3-year-old boy with MIS-C associated with COVID-19 who intriguingly, exhibited intracardiac thrombosis despite maintaining normal left ventricular systolic function,<sup>10</sup> a report that challenges our

understanding of the virus's cardiac implications.

Our reported case was a previously healthy adolescent with positive COVID-19 serology, who presented with autoimmune features suggestive of probable SLE and was found to have left-sided intracardiac mass complicating coagulase-negative endocarditis. Remarkably, this occurred in the absence of traditional risk factors and with preserved left ventricular function, marking a unique intersection of conditions in medical literature. IE is not a common but remains a highly serious condition which may present with multisystem disturbances mimicking a broad range of systemic autoimmune diseases as ANCA associated vasculitis (AAV), SLE, and systemic onset juvenile idiopathic arthritis (sJIA).<sup>15</sup> Rheumatic manifestations may be prevalent in nearly 30% of patients with IE, but often predating this diagnosis by several months.<sup>16</sup>

Although our patient presented with cutaneous vasculitis and arthritis, alongside elevated inflammatory markers (ESR and CRP) with ANCA positivity. However, she did not satisfy the diagnostic criteria for AAV. Adding to the diagnostic complexity, the presence of thrombocytopenia, normal blood pressure, no evidence of arterial aneurysms or stenosis in brain MR imaging make AAV unlikely possible. In the dynamic interplay between infections and autoimmune responses, transient ANCA positivity can be seen during infections. In IE, the sustained bacterial infection causes vascular damage which may activate the expression of cytoplasmic enzymes (proteinase 3 and myeloperoxidase in the endothelial cells and polymorphnuclear giant cells), thus producing a low titre of ANCA.<sup>17</sup> Remarkably, ANCA has been detected in 18% to 33% of patients with IE, illustrating the antibody's association with infectious processes beyond its well-documented link to autoimmune vasculitides. The presence of ANCA in these cases is not permanent; it gradually diminishes and eventually turns negative following the clearance of the pathogen. This resolution reflects the restoration of autoantigen tolerance, which had been temporarily disrupted by the

infection.<sup>18</sup> In our case, SLE was the best fit clinical diagnosis guided by a constellation of clinical manifestations and laboratory findings. These included patients' clinical presentation of constitutional symptoms, the presence of oral ulcers, vasculitic purpura and arthritis together with the laboratory evidence of thrombocytopenia, elevated ESR and positivity of anti-cardiolipin antibody, as well as the reported pericardial effusion on echocardiogram done. Furthermore, both the clinical assessments and the radiological evidence pointed towards CNS involvement, reinforcing the suspicion of SLE. Despite these significant indicators leaning towards an SLE diagnosis, the patient's toxic appearance, the unexplained highly elevated CRP, and the lack of specific immunological markers were still questionable in our patient till repeating the ECHO for the third time uncover the left mural mass establishing the diagnosis of IE.

This case reiterates the need to consider infectious mimickers of autoimmune disease. In the course of IE, the presentation with immune mediated manifestations places the clinicians at a crossroads, navigating the complexities of accurately diagnosing and effectively treating the condition.

## CONCLUSION

IE may present with immune mediated clinical features shared with pediatric rheumatic diseases. However, when such symptoms are accompanied by underlying structurally abnormal heart disease, IE emerges as the most probable diagnosis, particularly in patients presenting with fever. Diagnosis is challenging when IE presents with autoimmune manifestations in a in previously healthy adolescent, where the clinical picture may closely resemble SLE. However, the significant toxic symptoms with persistently elevated CRP and lack of specific antinuclear antibodies should raise suspicion to search for hidden infections including IE. Whether the predominance of autoimmune manifestations of IE is related to previous COVID-19 infection, this remains to be elucidated. Adherence to the basic evaluation of a patient with toxemia

irrespective of the other associated features will help to reach the correct diagnosis of underlying hidden infection with IE among the most common causes.

## CONFLICTS OF INTEREST

Authors declare they have no conflicts of interest.

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