

Can MIS-C develop beyond 16 weeks?

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An otherwise healthy, 36-month-old girl presented to the local hospital two days before admission to our hospital due to symptoms of fever and abdominal pain. Based on examination findings, high C-reactive protein (CRP, 152 mg/L) and pericardial effusion were observed and she was referred to our tertiary center with the suspicion of multisystem inflammatory syndrome in children (MIS-C).

In her medical history, the fever exceeded 39 degrees, despite antipyretics. Vomiting was added to her complaints on the day of admission (Date: 15.01.2021). Her family history revealed that her parents had novel coronavirus disease-2019 (COVID-19) in September 2020. Her real-time reverse transcription polymerase chain reaction (RT-PCR) result was positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), even asymptomatic about 19 weeks ago before the application to our hospital (Date: 07.09.2020).

On physical examination, the fever was 39.5°C, tachycardia with a pulse was 120/min with normotensive. The mouth and throat examination were normal, except for hyperemia of the lips which was evident. The pulmonary,

neurological, abdominal musculoskeletal, and lymph node examinations were unremarkable. Serum biochemistry showed high inflammation markers, including procalcitonin, CRP, ferritin, D-dimer, and fibrinogen (20.61 µg/L, 364 mg/L, 334 µg/L, 3340 µg/L, 768 mg/d, respectively) with hypoalbuminemia (3 g/dL). In the cardiac markers, B-type natriuretic peptide was 61 ng/L (normal range, 2 to 100 ng/L) and troponin I 34 ng/L (normal range, 2.5 to 46 ng/L). The RT-PCR tests for SARS-CoV-2 were negative within 48-h apart, and the SARS-CoV-2 immunoglobulin G result was positive (Abbott Diagnostics; value: 4.27, range 0 to 1.3) and immunoglobulin M (IgM) result was negative. The nasopharyngeal swab was tested via RT-PCR for common respiratory agents, and the result was negative.

Cefotaxime and vancomycin were initiated after the throat, blood, and urine cultures were taken from the patient who appeared ill and was in the sepsis clinic. Echocardiography was performed on admission with normal results. Serological tests for Epstein-Barr virus, cytomegalovirus, parvovirus B19, and human immunodeficiency virus (HIV) were negative. The presence of

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gastrointestinal findings, lymphopenia suggestive of hematological involvement, high D-dimers, and acute phase reactions and tachycardia suggestive of cardiac involvement, and the presence of echocardiographic findings in the external center and excessive sick appearance of the patient were suggestive of MIS-C. Intravenous immunoglobulin (IVIg) (1 g/kg, two days) and 2 mg/kg/day intravenous methylprednisolone treatment was started at 10 h of the treatment. In addition, enoxaparin was administered at a prophylactic dose. On the second day of the hospitalization, fever decreased, oral intake increased, and acute phase reactants decreased. However, the lymphocyte count decreased by 400 mm³/cell. All culture results were negative. No pathological findings were detected in repeated echocardiography. The patient was discharged with orally taken steroid and low-dose enoxaparin on Day 7 of the hospitalization. She has been under follow-up in the cardiology, rheumatology, and infectious diseases clinics. A written informed consent was obtained from the parents of the patient.

Multisystem inflammatory syndrome in children is a hyperinflammatory disorder and usually develops four to six weeks after SARS-CoV-2 infection and is likely initiated by an adaptive immune response.^{1,2} It has been investigated that children also suffer from SARS-CoV-2 infection with milder symptoms than adults, although the reasons for this have not been elucidated yet. However, several theories have been discussed involving differences in the immune system, such as thymic function difference, cross-reactive immunity against other coronaviruses, and differences in the expression of the angiotensin-converting enzyme 2 (ACE2) receptor used by the virus to enter the cell.³ In the Weisberg et al.'s⁴ study, cases with a diagnosis of MIS-C showed ineffective and reduced neutralizing antibody activity against SARS-CoV-2, compared to adults who had severe COVID-19 and recovered.

A review by Haslak et al.⁵ and a more recent study⁶ showed that MIS-C occurred primarily in school-aged children and adolescents and cases were reported to occur less frequently at younger ages, as in our patient. In the largest series related to the MIS-C, the median age of the patients was eight years (interquartile

range, 4 to 12 years) and the youngest case was two-week-old.⁶

The Centers for Disease Control and Prevention's (CDC) case definition for MIS-C includes a positive RT-PCR, serology, or antigen test for SARS-CoV-2; or COVID-19 exposure within the four weeks before the onset of symptoms.¹ However, according to the World Health Organization (WHO), case definition for MIS-C does not include a four-week period, although it includes similar test results.⁷ In the literature, MIS-C has been described as presenting within two to six weeks, typically within 21 to 25 days, of an illness compatible with acute COVID-19.⁸ Cirks et al.⁹ reported a case that was diagnosed with MIS-C after 16 weeks period of COVID-19. Our case demonstrates a 131-day interval between acute COVID-19 and MIS-C diagnosis; this period is the longest in the literature. Future reports should continue to highlight this period to better define the expected lag period between COVID-19 and MIS-C.

The underlying mechanism of MIS-C is still unknown and children usually have asymptomatic COVID-19 and, thus, it is unpredictable which child would develop MIS-C after COVID-19. Therefore, serial RT-PCR and antibody monitoring are practically futile in children with COVID-19. Further studies are needed to clarify the pathophysiology and genetic background of MIS-C. Our patient had laboratory-confirmed COVID-19 disease about 19 weeks ago. She had no symptoms during both COVID-19 disease and the period of 19 weeks. Did hyperinflammation occur in our patient only after 19 weeks, or did the patient develop SARS-CoV-2 asymptotically again during this period? Further studies that uncover the pathophysiology of MIS-C disease are needed to show which of these confounding results is correct.

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