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Clinical Notes

First case of COVID-19 L452R-induced multisystem inflammatory syndrome in a child in Japan

Shiho Fukuzawa, Jun Kubota, Wataru Murasaki, Ryota Saito and Noriko Takahata
Department of Pediatrics, The Jikei University School of Medicine, Tokyo, Japan

Key words COVID-19, L452R, multisystem inflammatory syndrome.

The prevalence of coronavirus disease 2019 (COVID-19) is low in children, and the symptoms of the disease are generally milder in children than in adults.[1] However, since 2020 there have been increasing reports from Europe and the USA describing COVID-19-associated multisystem inflammatory syndrome in children (MIS-C), which appears to develop after infection rather than during the acute phase of COVID-19. The clinical features of MIS-C are similar to those of Kawasaki disease.[1] There are fewer reports of MIS-C in Asia[2]; however, we encountered the case of a school-aged child with MIS-C in Japan.

An 8-year-old male patient was referred to our institution because of a fever lasting for 4 days, with associated right cervical lymphadenopathy, bilateral conjunctival injection, inflamed lips, abdominal pain, vomiting and diarrhea. Twenty-four days earlier he had been diagnosed with COVID-19 infection. Laboratory tests detected the L452R strain. During consultation, he exhibited Kawasaki-like symptoms and concurrent gastrointestinal manifestations. No abnormal neurological findings were noticed. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test performed using a nasopharyngeal swab was negative; however, the antibody level for SARS-CoV-2 was elevated to 256 U/mL. Blood test findings on admission were as follows: white blood cells, 10.7 × 10^3/μL; D-dimer, 26.7 μg/mL; aspartate aminotransferase, 124 IU/L; sodium, 127 mmol/L; erythrocyte sedimentation rate, 18 mm/h; procalcitonin, 5.08 ng/mL; brain natriuretic peptide, 42.8 g/mL; ferritin, 1802 ng/mL; and C-reactive protein, 9.26 mg/dL. Echocardiography indicated an ejection fraction of 75.1%: the diameter of the left main trunk (LMT), left anterior descending coronary artery (LAD), and right coronary artery (RCA) was 2.9 mm (Z score 0.93), 2.0 mm (Z score −0.17), and 2.7 mm (Z score 1.22), respectively. Abdominal ultrasonography showed no evidence of gastrointestinal wall thickening, ascites storage or hepatosplenomegaly. The levels of the cytokines interleukin-6 (IL-6), soluble tumor necrosis factor receptor I (sTNF-R) and sTNF-RII were 200 pg/mL, 4,200 pg/mL and 22 700 pg/mL, respectively. Based on the diagnostic criteria proposed by the World Health Organization, the patient was diagnosed with MIS-C.[3] Therapy with i.v. immunoglobulin (IVIG) (2 g/kg/day), prednisolone (2 mg/kg/day) and aspirin (30 mg/kg/day) was initiated. On the third day of hospitalization the patient was still febrile with a temperature of 38°C, with persisting cervical lymphadenopathy, conjunctival injections and lip inflammation. Echocardiography showed an increase in echogenicity of the coronary arteries and a tendency of the diameter to expand (LMT 3.2 mm [Z score 1.51], LAD 2.7 mm [Z score 1.46], and RCA 3.1 mm [Z score 1.96]). Furthermore, abdominal ultrasonography showed evidence of ascites and intestinal edema. Following another IVIG infusion cycle at 2 g/kg/day, the patient became afebrile. Lip inflammation and cervical lymphadenopathy resolved on the fourth day. Conjunctival injections were resolved on the fifth day of hospitalization. No recurrence of symptoms was observed. Repeat blood tests, echocardiography, and abdominal ultrasonography showed improvement from baseline results. Aspirin dosage was decreased to 5 mg/kg/day, and prednisolone was tapered gradually. Cytokine levels on the 11th day of hospitalization decreased: IL-6 was <3 pg/mL, sTNF-RI was 1030 pg/mL and sTNF-RII was 6040 pg/mL. The patient was discharged on the 24th day with no noted sequelae (Fig. 1).

This case is consistent with a previous study reporting that MIS-C is commonly encountered in school-aged children.[4] In the present study gastrointestinal tract symptoms were observed, but no cardiac dysfunction or neurological symptoms were noted, which are typically present in 50–85%, 60%, and 40% of children with MIS-C, respectively.[1] Although the mechanism of MIS-C is unknown, IL-6 and TNFα have been shown to play an important role.[1] In the present case, cytokine levels improved after treatment; however, in 41% of treatments with IVIG and steroids, IVIG treatment has had to be repeated.[5] If IVIG and steroid treatment show no significant

Correspondence: Shiho Fukuzawa, MD, Department of Pediatrics, The Jikei University Katsushika Medical Center, 6-41-2, Aoto, Katsushika-ku, Tokyo 125-8506, Japan.
Email: sfukuzawa2@gmai.com

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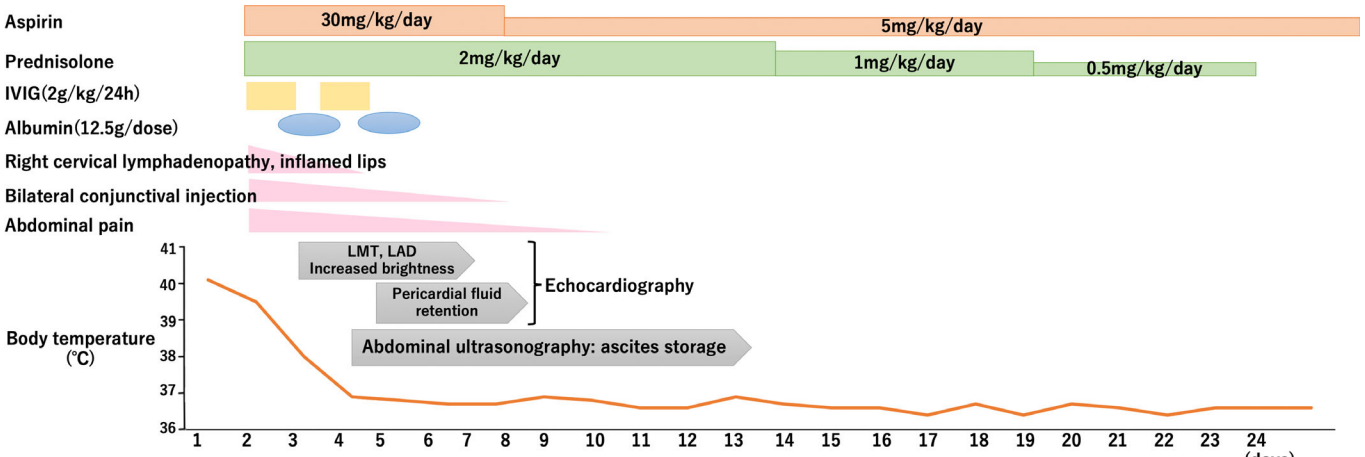

AST (IU/L)	124	89			43				57				37						24				
Alb(g/dL)	3.4	2.5			2.4				3.3				3.6						3.7				
Sodium(mmol/L)	127	132			133				134				135						140				
CRP(mg/dL)	9.26	7.79			1.49				0.39				0.1						0.04				
WBC($\times 10^3/\mu L$)	10.7	8.1			6.7				15.6				15.1						14.1				
D-dimer(μg/mL)	26.7	7.1			2.4				1.8				0.9						0.6				
BNP(g/mL)	42.8				114.6				32.7										6.6				
IL-6(pg/mL)	200				14								<3										
sTNFR-I(pg/mL)	4200				3450								1030										
sTNFR-II(pg/mL)	22700				23400								6040										

Fig. 1 Clinical course. Alb, albumin; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CRP, C-reactive protein; IL-6, interleukin-6; IVIG, i.v. immunoglobulin; LAD, left anterior descending coronary artery; LMT, left main trunk; sTNF-RI, soluble tumor necrosis factor receptor I; sTNF-RII, soluble tumor necrosis factor receptor II; WBC, white blood cells.

improvement, IL-6 or TNFα inhibitors have been shown to be effective in refractory cases based on the presumed mechanism of MIS-C.[1,4,5]

To the best of our knowledge, this is the first case of MIS-C associated with the L452R strain. There are no studies reporting a change in the incidence of MIS-C compared with the past after the appearance of L452R; hence, future research clarifying this is needed. Pediatricians should consider a diagnosis of MIS-C in children presenting with Kawasaki-like symptoms after COVID-19 infection, with multi-organ abnormalities such as gastrointestinal tract symptoms.

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Disclosure

The authors declare no conflict of interest.

Ethics approval

This study was approved by the Institutional Review Board of The Jikei University School of Medicine (33-316(10939)).

Informed consent

Informed consent for publication of this report was obtained from the patient's parents.

Author contributions

WM initially evaluated the patient; SF, JK, WM and RS were responsible for the diagnosis and treatment; S.F. wrote the manuscript; J.K. assisted in the preparation of the manuscript; and N.T. supervised the patient management. All co-authors have read and approved the final manuscript.

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