Case report

A young child with pediatric multisystem inflammatory syndrome successfully treated with high-dose immunoglobulin therapy

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\textbf{A B S T R A C T}

Pediatric multisystem inflammatory syndrome (MIS-C) is a disease that presents mainly in older children after coronavirus disease 2019 (COVID-19) and is associated with Kawasaki-like symptoms and multiple-organ failure. The number of cases of MIS-C has increased since April 2020, with reports mainly from Europe and the United States. The reason is unclear, but few cases of MIS-C have been reported in Asian countries, including Japan. No treatment has been established for MIS-C. In this study, we report the case of a young boy treated with IVIg for MIS-C by measuring the cytokine profile over time. A 4-year-old boy presented with Kawasaki disease-like symptoms 28 days after a positive result from polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), meeting the World Health Organization criteria for MIS-C diagnosis. Blood tests showed lower levels of C-reactive protein and ferritin, and no decrease in lymphocyte count (<1000/μL) or more increase in fibrinogen than those reported in Japan for MIS-C in school-aged children and older. Neopterin, interleukin (IL)-6, IL-1β, soluble tumor necrosis factor receptor (sTNF-R)I and sTNF-RII were all high at disease onset, but neopterin, IL-6, and sTNF-RII rapidly decreased with fever resolution after the second dose of IVIg, while IL-18 and sTNF-RII decreased bimodally. As far as we can determine, this case represents the youngest identified in Japan. The key point of difference between MIS-C and Kawasaki disease is older age in MIS-C, but attention is also needed in infants.

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Introduction

COVID-19 in children is less common and less severe than that in adults. However, eight cases of children with severe illness after SARS-CoV-2 infection and symptoms similar to atypical Kawasaki disease. Kawasaki disease shock syndrome, macrophage activation syndrome, and toxic shock syndrome were reported in the United Kingdom in April 2020 [1]. Subsequently, similar cases were reported from Europe and the United States, and the inflammatory condition associated with COVID-19 in children was then defined as multisystem inflammatory syndrome in children (MIS-C) in the United States and as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS) in the United Kingdom. In Japan, the Japanese Society of Pediatrics, the Japanese Society of Pediatric Infectious Diseases, the Japanese Society of Pediatric Rheumatology, the Japanese Society of Pediatric Cardiology, and the Japanese Society of Intensive Care Medicine jointly developed the “Consensus Statement on Pediatric COVID-19 Associated Multisystem Inflammatory Syndrome (MIS-C/PIMS)” in May 2021 [2]. Differentiating MIS-C/PIMS from Kawasaki disease is important. Kawasaki disease was reported for the first time in Japan in 1967, and is common in East Asia, with a predilection for children under 4 years old [3]. On the other hand, MIS-C/PIMS appears more common among blacks and Hispanics, and the median age of onset is 9 years, with Kawasaki-like symptoms and severe inflammation of multiple organs [4]. Our patient, who was 4 years younger than the age at which MIS-C/PIMS is most likely to occur, showed multiple organ involvement including pericardial effusion, mild mitral regurgitation, pleural effusion, ascites, hepatosplenomegaly, gallbladder wall thickening, and intestinal edema. However, the multi-organ damage improved with IVIg, including supportive care such as diuretics and...
albumin preparation and additional administration of IVlg. As cytokine profiles were measured over time in our patient, we report the outcomes along with these changes.

**Case report**

A 4-year-old boy presented to the previous doctor with abdominal pain and vomiting and a 5-day history of high fever (>39 °C). He was referred to our hospital for further investigation and treatment. Erythema appeared on the abdomen and lower legs on the third day of fever, and bilateral bulbar conjunctival injection, cracking of the lips, and edema of the tips of the fingers and toes were observed the following day. In terms of family history, the boy’s parents had returned positive PCR results for SARS-CoV-2 29 days before the onset of fever, and the boy tested positive the next day, although he was asymptomatic. He had been born at full term with a birth weight of 2658 g, and no perinatal abnormalities. Medical history included febrile convulsion, and he was not on any regular medications.

On physical examination at the time of admission, he was febrile (39.8 °C). Blood pressure was 108/56 mmHg, heart rate was 146 beats/min, respiratory rate was 30 breaths/min with an O2 saturation of 98% on room air. Examination of the face and oropharynx showed bilateral conjunctival congestion, cracking of the lips, strawberry tongue, and diffuse injection of the oral and pharyngeal mucosa. Head and neck examinations revealed right cervical lymphadenopathy (diameter, 1.5 cm) with tenderness. Cardiovascular examination showed no abnormalities, the lungs were clear on auscultation, and abdominal examination was unremarkable with no hepatosplenomegaly. Neurological examination was completely unremarkable. Polymorphous exanthema were seen on the abdomen and both lower legs, with no erythema at the BCG vaccination site. His extremities appeared flushed and edematous.

On admission, initial blood tests revealed significant neutrophilia, thrombocytopenia, hyponatremia, hepatic dysfunction, and mildly elevated CRP (Fig. 1). Echocardiography showed mild mitral regurgitation and pericardial effusion, but good left ventricular contractility and no coronary dilation (#1: 1.5 mm [Z-score: −1.2]; #5: 2.2 mm [Z-score: −0.5]; #6: 1.9 mm [Z-score 0.2]; #11: 1.8 mm). A nasal SARS-CoV-2 rapid antigen test (immunochromatographic method; Mizuhomedy Co., Saga, Japan) yielded a negative result. In addition, a nasal rapid antigen test (for RS virus and adenovirus; immunochromatographic method; Sekisui medical Co., Tokyo, Japan), pharyngeal rapid antigen test (for streptococci; immunochromatographic method; Tauns Co., Shizuoka, Japan), and fecal rapid virus antigen test (norovirus, rotavirus, and adenovirus; immunochromatographic method; Mizuhomedy Co., Saga, Japan) were all negative. Stool and blood cultures showed no significant growth of bacteria. An anti-SARS-CoV-2 (N protein) antibody test (electrochemiluminescence immunoassay; Roche Diagnostics, Tokyo, Japan) showed a cutoff index of 106 and elevated antibody titer on day 5.

At the time of admission on day 5 of fever, all six principal clinical features of Kawasaki disease were present. MIS-C/PIMS was therefore diagnosed according to both Centers for Disease Control and Prevention criteria and World Health Organization criteria, based on age, duration of fever, multisystem symptoms, laboratory data of inflammatory findings, involvement of SARS-CoV-2 infection, and exclusion of other diseases such as infections other than SARS-CoV-2 and sepsis. Kobayashi score for the IVlg refractory risk group of Kawasaki disease was 3 in this case, which did not meet the indications for starting prednisolone (PSL) as described in the RAISE study (score >5), because the serum sodium level was 126 mEq/L (<133 mEq/L) and the platelet count was 10.7 × 10^9/μL (<30.0 × 10^9/μL) [3]. The patient started IVlg (2 g/kg/dose) and aspirin (30 mg/kg/day) the same day in accordance with Japanese Society of Pediatric Cardiology Guidelines for the Acute Treatment of Kawasaki Disease (as revised in 2020) and MIS-C/PIMS Clinical Consensus Statement [2,3]. However, fever continued and the clinical features of Kawasaki disease did not improve, so he was treated with IVlg (2 g/kg/dose) again on day 4 of hospitalization. The day after this second IVlg administration, the fever broke, abdominal symptoms such as abdominal pain and nausea disappeared, and blood tests showed a high erythrocyte sedimentation rate, and levels of d-dimer and BNP, indicating hypoalbuminemia (Table 1). Abdominal ultrasonography showed hepatosplenomegaly, gallbladder wall thickening, intestinal edema, and ascites effusion, and chest X-ray revealed right interlobar pleural effusion with a cardiothoracic ratio of 0.53. Due to edema of the face and lower legs and decreased urine output, intravenous administration of 25% albumin (0.75 g/kg/day) and furosemide (1.4 mg/kg/day) was started on day 6 of hospitalization. Serum albumin levels improved the day after albumin administration, and furthermore, edema decreased and urine output improved the next day, so furosemide administration was terminated. On the 9th hospital day, blood tests showed improvement in CRP and BNP levels, and a chest X-ray confirmed the disappearance of pleural effusion. No coronary artery lesions or abnormalities in left ventricular diastolic function were observed by echocardiography during the disease course, and the mild mitral regurgitation and pericardial effusion that had been observed at the time of initial examination also disappeared on day 13 of hospitalization. Echocardiography on day 9 of hospitalization showed sinus rhythm with no abnormal Q waves or ST-T changes. Abdominal ultrasonography on day 12 of hospitalization showed that hepatosplenomegaly, ascites, and gallbladder wall thickening had disappeared, and general condition improved. Membranous desquamation was observed next day, and ASA was reduced to 5 mg/kg/day the day after that. The patient was discharged after 14 days in the hospital. Outpatient follow-up was continued, and no flare-up of symptoms or abnormality in echocardiography had been observed as of 5 months after disease onset.

**Discussion**

We initially suspected Kawasaki disease because the patient was 4 years old, the age at which Kawasaki disease is most likely to occur, and had all the principal clinical features. Previous reports from a meta-analysis of 1132 patients with Kawasaki disease have shown median hematological findings of: CRP, 6.7 mg/dL; lymphocyte count, 2800/μL; platelet count, 36.5 × 10^9/μL; ferritin, 200 mg/dL; d-dimer, 1.65 μg/mL; and ESR, ≥ 80 mm/h. Median values reported from a study of MIS-C/PIMS patients were: CRP, 24.9 mg/dL; lymphocyte count, 831/μL; platelet count, 15.5 × 10^9/μL; ferritin, 910 mg/dL; d-dimer, 3.75 μg/mL; and ESR, 60–75 mm/h [2,4,5]. Compared with MIS-C/PIMS, CRP, lymphocyte count, and ferritin were lower and platelet count and hemoglobin precipitation were higher in Kawasaki disease, and the blood test results in this case were closer to those in Kawasaki disease (Table 1). However, the presence of abdominal symptoms and multiple-organ dysfunction, the history of SARS-CoV-2 infection, and the positive results from the new coronavirus antibody test made the diagnosis of MIS-C/PIMS possible.

The number of reports of MIS-C/PIMS has been increasing since 2020, mainly from Europe and the United States, and although the reason for this is unclear, few reports have been made from Japan and other Asian countries [6]. As of February 2022, seven cases appear to have been reported in Japan, all in schoolchildren ≥9 years old, as in overseas reports [7–12]. Our case represents the youngest reported in Japan to date. Although overseas reports have described cases in infants after 3 months old, only a few cases in such young individuals have been reported [5]. We therefore compared the clinical characteristics and hematological findings of the present case with those of seven cases reported in Japan (Table 2) [7–12]. CRP and ferritin levels were lower than those reported in Japan, and
closer to those results reported by Zhao et al. [13]. They reported that levels in the MIS-C/PIMS group under 5 years of age were significantly lower than those in other age groups. In Kawasaki disease, 79% of patients show the five major symptoms, and 50% have cervical lymphadenopathy, the least common of the six major symptoms [14, 15]. On the other hand, among overseas MIS-C/PIMS reports, 23% of patients had at least five of the principal clinical features of Kawasaki disease, and only 6% had all six features [5]. Polymorphous exanthema occurred in 52–55% of cases, edema of hands or feet in 13–16%, strawberry tongue in 4%, diffuse injection of oral and pharyngeal mucosae in 23–29%, and cervical lymphadenopathy in 4–16% [4, 16]. In the present study in Japan, more than 5 major symptoms were observed in seven cases (88%), including the present case. The difference in the frequency of principal clinical features of Kawasaki disease between Japan and overseas in MIS-C/PIMS may be due to racial differences between Japanese and the African and Caribbean Hispanic populations that account for most of the overseas cases [4]. Acute abdomen was observed in 4.6% of patients with Kawasaki disease, gastrointestinal symptoms were observed in more than 80% of patients with MIS-C/PIMS, and abdominal findings were also observed in all cases in Japan [5, 17]. The presence of abdominal symptoms is important in differentiating Kawasaki disease from MIS-C/PIMS.

MIS-C/PIMS has been postulated to develop as a result of secondary immune-mediated damage 4–6 weeks after SARS-CoV-2 infection, and cytokine storm due to activation of macrophages and T cells may also be involved in the pathogenesis, although the details remain unclear. Cytokines such as IL-1, IL-6, IL-8, IL-10, and TNF-α are elevated in MIS-C/PIMS, similar to Kawasaki disease [7, 18]. In our case, neopterin, IL-6, and sTNF-RII decreased rapidly with fever resolution after the second IVlg administration, and IL-18 and sTNF-RI showed bimodal decreases (Fig. 1). Takasago et al. examined 71 cytokines and reported that cytokines showed five patterns of behavior, including IL-6, IL-10, IL-17, and IL-8 decreasing rapidly after
treatment, and IL-18, IL-1β, IL-12, and TNF-α decreasing bimodally [7]. The same was observed in our case. In this case, CRP and ferritin were not elevated, but IL-6 was elevated, suggesting the utility of confirming elevated ESR and D-dimer and measuring IL-6 as indicators of inflammatory markers in infants with MIS-C/PIMS. However, since the number of facilities that can submit cytokine profiles is limited, further studies are needed.

The MIS-C/PIMS Practice Consensus Statement recommends glucocorticoids for patients who are refractory to IVIg or in shock. Previous reports have shown that the response rate to treatment was higher with combined IVIg and glucocorticoids than with IVIg alone, and additional treatment was significantly less necessary with the combination [19]. Furthermore, a study of 518 MIS-C/PIMS patients found no difference in treatment response rate between IVIg alone and the combination of IVIg and glucocorticoids, but the risk of new or persistent cardiovascular events was lower in the latter group than in the former [20]. As far as we could find, no reports have examined differences in efficacy of treatment according to age or stratification of treatment methods in MIS-C/PIMS. Whether the Kobayashi score is useful in MIS-C/PIMS, and whether combined IVIg and PSL is better in the initial treatment requires further investigation.

| Table 1 |
| --- |
| Blood analyses of Kawasaki disease on day 9 WBC: white blood cell count; RBC: red blood cell count; PT-INR: international normalized ratio of prothrombin time; APTT: activated partial thromboplastin time; ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; ALAT: alanine aminotransferase; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; CRP: C-reactive protein; BNP: brain natriuretic peptide; IL: interleukin; sTNF-RI: soluble tumor necrosis factor receptor I; sTNF-R2: soluble tumor necrosis factor receptor II. |
| Laboratory tests | Result | Conventional units |
| --- | --- | --- |
| WBC | 4700 | /μL |
| Neutrophil | 55.1 | % |
| Eosinophil | 7.4 | % |
| Basophil | 0.0 | % |
| Monocyte | 2.5 | % |
| Lymphocyte | 35.0 | % |
| RBC | 3.76 × 10⁶ | /μL |
| Hb | 10.0 | g/dL |
| MCV | 80.3 | fl |
| HCT | 30.2 | % |
| WBC | 6.9 | g/dL |
| ALb | 1.8 | g/dL |
| AST | 34 | U/L |
| ALT | 21 | U/L |
| LD | 239 | U/L |
| ALP | 69 | U/L |
| BUN | 15.2 | mg/dL |
| Cre | 0.39 | mg/dL |
| Na | 139 | mEq/L |
| K | 4.0 | mEq/L |
| Cl | 109 | mEq/L |
| Ferritin | 173 | ng/ml |
| CRP | 2.79 | mg/dL |
| Glu | 85 | mg/dL |
| ESR | 95 | mm/h |
| PT | 9.7 | S |
| APTT | 0.87 | |
| Fibrinogen | 298 | mg/dL |
| Neutrophil | 55.1 | % |
| BNP | 128.1 | pg/mL |
| ESR | 95 | mm/h |
| PT-INR | 32.4 | S |
| IL-6 | 18.0 | μg/mL |
| D-dimer | 111 | nmol/L |
| sTNF-R1 | 3100 | pg/mL |
| sTNF-R2 | 13,200 | pg/mL |

| Table 2 |
| --- |
| Comparison of clinical course and laboratory findings between domestic MIS-C reports and our case Percentage s are rounded to the first decimal place (except for neutrophil | lymphocyte count, platelet count, serum Na concentration) seen during the course of the study, taken from the following sources [7–12]. |
| Takasago et al.[7] | Uchida et al.[8] | Fukuda et al.[9] | Baba et al.[10] | Wakamori et al.[11] | Kudo et al. | Yamaguchi et al.[12] | Mean | Case |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Age | 9 | 16 | 9 | 10 | 12 | 11 | 15 | 12 | 4 |
| Male | F | M | M | M | M | M | M | 5 | M |
| Kawasaki disease sign (6/6) | 6/6 | 3/6 | 6/6 | 6/6 | 5/6 | 6/6 | 6/6 | 6/6 | 6/6 |
| Abdominal symptoms | abdominal pain, vomiting | abdominal pain | diarrhea | abdominal pain, diarrhea | nausea | vomiting | diarrhea | abdominal pain, vomiting | |
| Kobayashi score (> 5) | 5 | 6 | 5 | 4 | 5 | 5 | 5 | 5 | 3 |
| IVIg | effective | effective | effective | effective | refractory | Refractory | refractory | effective | added |
| PSL | 2 mg/kg/d | – | – | 2 mg/kg/d | 60 mg/d | – | 60 mg/d | 7 | |
| CRP (mg/dL) | 22.05 | 20.6 | 22.6 | 21.9 | 15.3 | 13.2 | 10.22 | 17.98 | 2.79 |
| Neutrophils (%) | 90% | 93.1% | 93.6% | 91% | 72.5% | 89% | 95% | 89.2% | 79.7% |
| Lymphocytes (μL) | 470 | 359 | 512 | N.D. | 470 | 325 | 300 | 406 | 1554 |
| Platelets (<10⁸/μL) | 15.8 | 13 | 31.5 | 7.2 | 9.1 | 15.1 | 4.9 | 13.8 | 10.7 |
| Sodium (mEq/L) | 126 | 132 | 129 | 131 | 132 | 133 | 130 | 130.4 | 126 |
| Procalcitonin (ng/mL) | 25.6 | 5.38 | 1.8 | N.D. | 1.6 | N.D. | N.D | N.D | N.D |
| Ferritin (ng/mL) | 987 | 294 | 831 | 3685 | N.D. | 570 | 11,404 | 2961 | 173 |
| ESR (mm/h) | 54 | N.D | 79 | N.D | 33 | N.D | 69 | N.D | 95 |
| D-dimer (μg/mL) | 4.9 | 5.0 | 3.6 | 28 | 6.7 | 5.4 | 13.0 | 9.5 | 19.4 |
| Fibrinogen (mg/dL) | 691 | 606 | 758 | 605 | 593 | 447 | 412 | 587 | 330 |
| IL-6 (pg/mL) > 500 | N.D. | 412 | N.D. | N.D | 136 | N.D | N.D | N.D | 157 |
| Interval of SARS-CoV-2-positive infection | 31 | 23 | 30 | N.D | 45 | 46 | 27 | 34 | 28 |
We encountered a case involving a 4-year-old boy who presented with Kawasaki-like symptoms 28 days after a positive SARS-CoV-2 PCR test and was diagnosed with MIS-C/PIMS. MIS-C/PIMS is most common among children of school age and older, but can also occur in young children and is a serious disease. It is important to keep this disease in mind when Kawasaki-like symptoms are observed in infants.

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**Authorship statement**

Each author attests to the integrity of the work, and has given their approval for this version to be published. Furthermore, each author certifies that this material has not been and will not be submitted to or published in any other publication before a decision is received from this journal.

**Consent**

Informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal request.

**Author contributions**

All authors also provided final approval of the manuscript for publication.

**Declarations of Competing Interest**

We declare no conflicts of interest.

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