

Case Report



A Case of Multisystem Inflammatory Syndrome in Children (MIS-C) with Acute Myocarditis

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ABSTRACT

After initial reports of multisystem inflammatory syndrome in children (MIS-C) in April 2020 in Europe, this disease has been known to occur in children with recent history of coronavirus disease 2019 (COVID-19) and most cases have been reported in Europe and the United States of America. We report a case of a 14-year-old girl who was diagnosed with MIS-C with acute myocarditis and successfully treated with intravenous immunoglobulin (IVIG), methylprednisolone, and anakinra. At initial presentation, she had persistent high fever, generalized rash, generalized swelling, abdominal pain, and low blood pressure. She showed a remarkably elevated level of inflammation and cardiac enzyme markers and had a previous history of COVID-19 5 weeks before the initial presentation. After extensive work up, other infectious and non-infectious causes were excluded. She was diagnosed with MIS-C and initially treated with IVIG and high-dose methylprednisolone; however, despite treatment, her heart function deteriorated and coronary artery dilatation progressed. Therefore, anakinra, an interleukin-1 receptor antagonist, was administered on hospital day 6, after which her cardiac function exhibited improvement. She was discharged on hospital day 19 without any symptoms, and follow-up echocardiography after 1 month revealed fully recovered heart function with normal coronary arteries.

Keywords: COVID-19; SARS-CoV-2; Pediatric multisystem inflammatory disease, COVID-19 related; Myocarditis

INTRODUCTION

Since December 2019 coronavirus disease 2019 (COVID-19) has been continuously spreading worldwide. By August 25, 2021, the cumulative number of confirmed COVID-19 cases in Korea exceeded 240,000 and the case fatality rate was 0.9%. In contrast, no fatal cases have been reported among individuals under 20 years of age in Korea, which reflects a better prognosis than in adults. Reports throughout the world also show relatively better prognosis in children than in adults.^{1,2)}

Early during the pandemic, in April 2020, a number of pediatric patients suffering from fever, rash, shock, and multi-organ failure were reported in London,³⁾ and similar cases were

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: Choi S, Lee H; Data curation: Lim JG, Oh KJ, Lee H; Investigation: Lim JG, Lee DH, Oh KJ, Lee H; Project administration: Lee H; Supervision: Lee DH; Visualization: Lim JG; Writing - original draft: Lim JG, Lee H; Writing - review & editing: Lim JG, Choi S, Song YH, Lee J, Lee H.

subsequently reported in other countries.⁴⁾ These conditions were found to occur 2–6 weeks after COVID-19 and were acknowledged as multisystem inflammatory syndrome in children (MIS-C). MIS-C is characterized by systemic hyperinflammation with multi-organ failure in children who have previously suffered from COVID-19. MIS-C cases have been reported worldwide, mostly in Europe and America, but only a few have been reported in Asia. Herein, we report a case of MIS-C with acute myocarditis who was successfully treated with immunomodulatory agents.

CASE

A 14-year-old girl was transferred to our hospital with 4 days of high-grade fever, generalized rash, bilateral conjunctival injection, generalized swelling, general weakness, and hypotension. Six weeks before visiting our hospital, her father was diagnosed with COVID-19, and subsequently, she was also confirmed positive by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR). At that time, she had no symptoms except anosmia and received no further SARS-CoV-2 PCR tests. Five weeks after being diagnosed with COVID-19, she had a high fever up to 39°C and visited the emergency room (ER) of a local hospital. In the ER, she underwent a SARS-CoV-2 PCR test, which came out to be positive. However chest radiography was normal and she did not have any respiratory symptoms; therefore, the positive SARS-CoV-2 PCR result was thought to be from a previous infection rather than re-infection. Two days later, she experienced abdominal pain and was admitted to a local hospital. The day before she visited our hospital, hypotension (blood pressure 90/60 mmHg) was detected and antibiotics (piperacillin/tazobactam) were administered under the suspicion of septic shock. The following day, she developed a rash and bilateral conjunctival injection and was transferred to our hospital for further evaluation.

Upon presentation, she reported fever up to 39°C, headache, mild dyspnea, generalized swelling, abdominal pain, and general weakness. Physical examination showed hypotension (blood pressure 91/44 mmHg), dehydrated lips and tongue, bilateral conjunctival injection, a macular amorphous rash covering the whole body (**Fig. 1A and B**), abdominal tenderness in the right upper quadrant and generalized swelling. Vital signs included mild tachypnea (28 breaths/min), tachycardia (133 beats/min), and persistent high fever regardless of antipyretics. Her usual weight and height were 55 kg and 167 cm, respectively (body mass index: 19.72 kg/m²), but she had gained 5 kg and was 60 kg on initial presentation.

Initial laboratory results showed a high white blood cell count of 14.9×10^3 /uL with dominance of segmented neutrophils (92.9%), and mild grade thrombocytopenia of 117×10^3 /mL. Serum creatinine levels were elevated up to 1.02 mg/dL and C-reactive protein (CRP) levels were high (27.25 mg/dL). Creatine kinase MB isoenzyme and troponin I were initially within the normal range; however, pro B-type natriuretic peptide levels were elevated (3,029.1 pg/mL). SARS-CoV-2 PCR results from both nasopharyngeal and oropharyngeal swab were negative. Blood, urine, and stool cultures tested negative. All other microbiological tests, including respiratory virus PCR, Epstein Barr virus viral capsid antigen immunoglobulin M (IgM) antibody, group A streptococcus antigen (throat swab), cytomegalovirus IgM, tsutsugamushi antibody, and leptospira antibody tests, were negative. Initial chest radiography revealed bilateral pleural effusion. Abdominal sonography showed signs of hepatic parenchymal disease, gall bladder wall thickening, pancreatitis, pelvic ascites, and

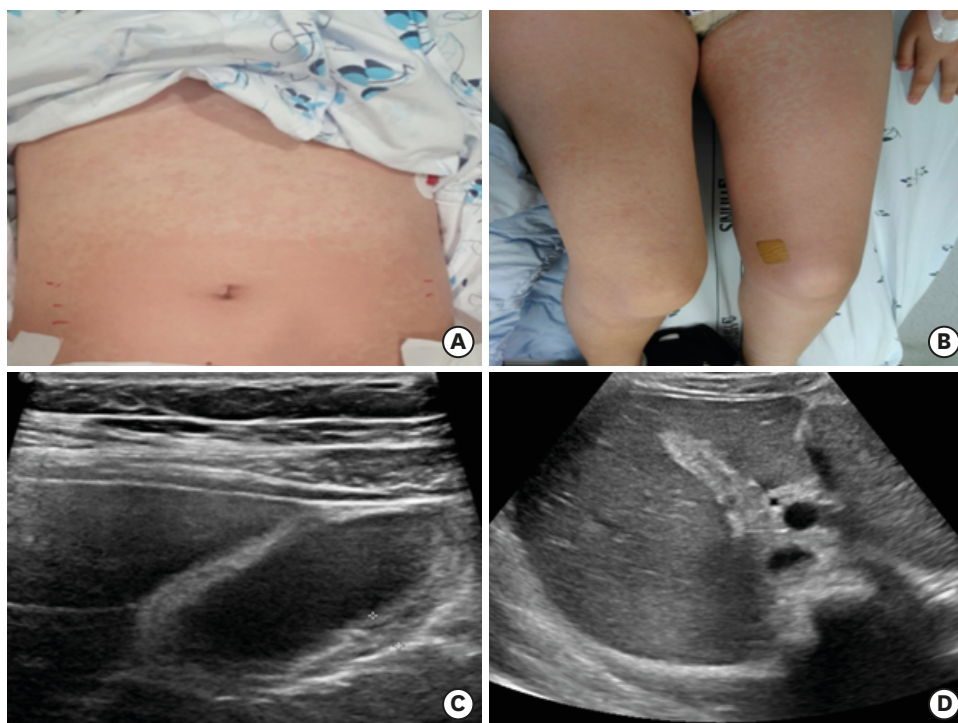


Fig. 1. (A, B) There is amorphous erythematous skin rash on whole body. (C, D) Initial abdomen sonography revealed thickened gall bladder wall and increased echogenicity of liver parenchyme, indicating the possibility of hepatic parenchymal disease.

paralytic ileus (**Fig. 1C and D**). Initial echocardiography (EchoCG) revealed normal ventricular function, with a normal coronary artery and ejection fraction (EF) of 67.4%.

As she was under 19 years of age, had persistent fever, had multi organ damage with previous history of COVID-19 and no any evidence of other microbial infections, MIS-C was strongly suspected based on the diagnostic criteria for MIS-C.⁵⁾ With supportive care including inotropic agents (dopamine, dobutamine, norepinephrine) and empirical antibiotics (ceftriaxone) for potential risk of infection, intravenous immunoglobulin (IVIG) 2 g/kg was administered on the first day of hospitalization, based on the clinical guidance for MIS-C developed by the American College of Rheumatology.⁶⁾

On hospital day 2, fever, tachypnea, and tachycardia persisted. CRP levels and leukocytosis were aggravated, and symptoms such as abdominal pain, rash, and dyspnea did not improve. EchoCG showed a decrease in left ventricle (LV) function compared to that on day 1, and levels of troponin-I were markedly elevated (0.892 ng/dL). Therefore, high-dose intravenous methylprednisolone pulse therapy (30 mg/kg/day) for 3 days was initiated. On hospital day 3, an echocardiogram showed ST elevation on the lateral and anterior walls (**Fig. 2A**). EchoCG revealed marked LV dysfunction, with a decreased EF of 43.0%. CRP elevation and leukocytosis persisted, and troponin I levels were extremely elevated up to 14.388 ng/dL, therefore a 2nd dose of IVIG (1 g/kg) was administered. On hospital day 4, thrombocytopenia was aggravated (50×10^3 /mL), and dyspnea and lung haziness due to pulmonary edema on chest radiography progressed (**Fig. 2B**); accordingly, a high-flow nasal cannula was applied. EF dropped to 39% on hospital day 5, and the left main coronary artery (LMCA) diameter was dilated (z-score 4.26) on hospital day 6 (**Fig. 2C and D**). Fever and tachycardia persisted;

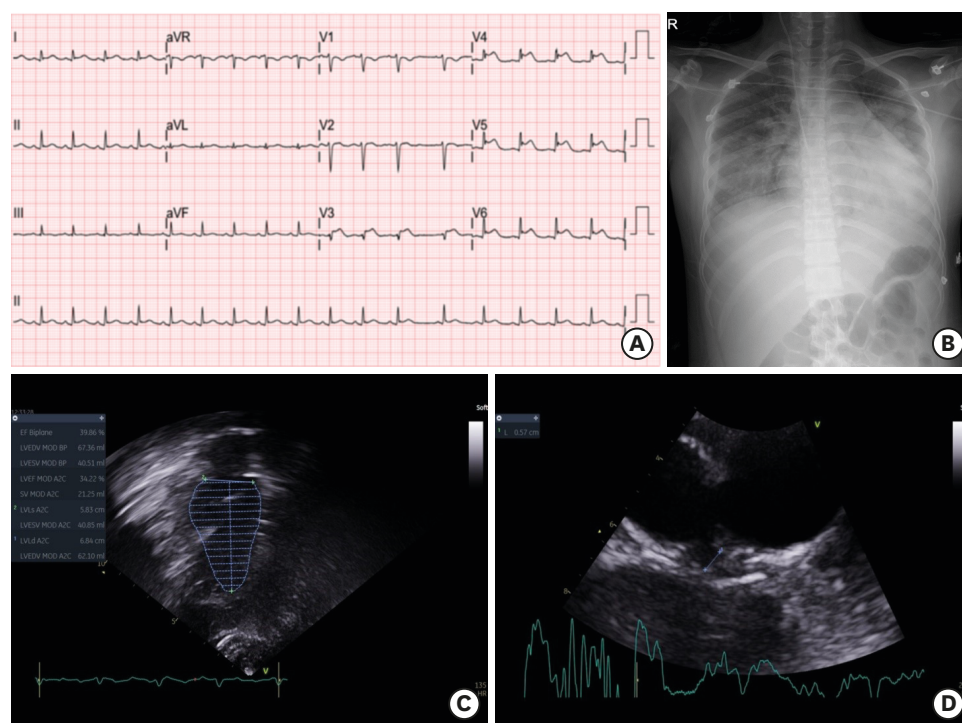


Fig. 2. (A) ST elevation on leads V3–6 was detected on echocardiogram at first on hospital day 3. (B) In chest X-ray, cardiomegaly with marked pulmonary edema was shown on hospital day 4. (C) Echocardiography revealed marked left ventricle dysfunction and ejection fraction was checked 39% in biplane on hospital day 5. (D) Left main coronary artery dilatation of 5.7 mm (z-score 4.26) was detected on hospital day 6.

therefore, anakinra, an interleukin (IL)-1 antagonist, was started on hospital day 6 (100 mg bid) and the dose was increased the next day (200 mg bid).

On hospital day 7, fever and tachycardia improved slightly. Platelet levels also increased to 83×10^3 /mL, so with the improvement of thrombocytopenia, aspirin was initiated for coronary artery dilatation. Symptoms, including rash, fever, abdominal pain and respiratory difficulty, improved, and blood pressure was stable without inotropic agents. Anakinra was tapered and discontinued on day 16 of hospitalization (**Fig. 3**). Follow-up EchoCG on hospital day 12 showed normalized LV function with a mild improved state of LMCA dilatation (z-score 3.17). The patient was discharged on hospital day 19, and EchoCG after 1 month showed normal heart function with normal coronary arteries.

This study was approved by the International Review Board (IRB) of Seoul National University Bundang Hospital (IRB number: B-2109-707-702).

DISCUSSION

With a marked increase in the number of patients showing systemic hyperinflammation shortly after COVID-19, a definition and diagnostic criteria for this condition have been proposed globally by several organizations. Korean version of MIS-C case definition was also published by Korea Disease Control and Prevention Agency (KDCA) in June 2020 and a surveillance system was developed accordingly.^{5,7)} The common conditions of diagnostic criteria from the organizations including World Health Organization, Royal College of

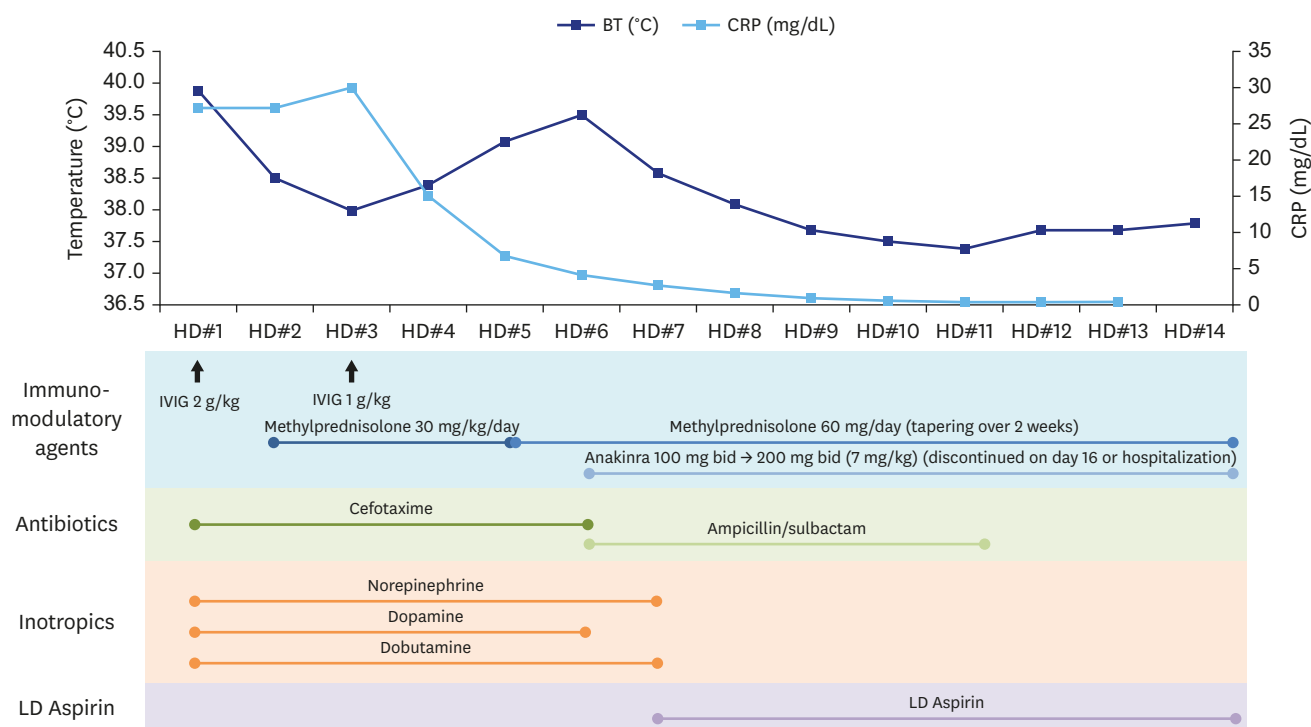


Fig. 3. It shows the use of immunomodulatory agents (IVIG, methylprednisolone, and anakinra), antibiotics, inotropics, and low dose aspirin during hospital course. Abbreviations: BT, body temperature; CRP, C-reactive protein; HD, hospitalization day; IVIG, intravenous immunoglobulin; LD, low dose.

Paediatrics and Child Health, Centers for Disease Control and Prevention, and KDCA were young age (under 19 years), persistent fever with evidence of inflammation, multiple organ damage, and evidence of SARS-CoV-2 infection without other microbial cause.^{5,7-9)} Our patient was 14 years old, had a history of COVID-19, and presented with persistent high fever with multi-organ failure and extremely elevated inflammation marker levels without evidence of other infection; thus, she met the diagnostic criteria of MIS-C. A There were only few patients diagnosed with MIS-C in Korea, and the first patient was reported in November 2020.¹⁰⁾

MIS-C is a rare complication of COVID-19 and usually occurs approximately 2 to 6 weeks after COVID-19.¹¹⁾ As the number of COVID-19 patients is on the rise, cases with MIS-C may also increase subsequently. In addition, symptoms of MIS-C vary and patients with life-threatening manifestations may be seen infrequently. Therefore, clinical suspicion and appropriate management are important. The gastrointestinal system is the most commonly affected, followed by cardiovascular, hematologic, mucocutaneous, and respiratory systems.¹²⁾ Symptoms may be nonspecific and can be difficult to distinguish from other infectious diseases or non-infectious diseases such as cancer or Kawasaki disease. Therefore, if the patient has various organ-related symptoms with high fever and a history of COVID-19, MIS-C should be suspected early and a proper assessment is essential for differential diagnosis.

In patients with MIS-C, cardiovascular involvement is common and can lead to severe conditions such as low blood pressure, coronary artery aneurysm, or myocardial dysfunction.¹²⁾ Our patient showed symptoms of multi-organ involvement, with prominent features of acute myocarditis, demonstrated with hypotension, significant elevation of cardiac marker levels, LV dysfunction and coronary artery dilatation above a z-score of 2. Cardiovascular involvement has been reported in up to 80% of patients with MIS-C.¹²⁾

A previous study that analyzed only MIS-C patients with acute LV dysfunction reported that 80% of patients showed cardiogenic shock, which required treatment with inotropic agents, and coronary artery dilatation above a z-score of 2 was observed in 17% of patients.¹³⁾ Therefore, patients suspected of MIS-C should need a detailed evaluation of heart function and coronary artery.

Currently, the pathogenesis of MIS-C is not well defined. MIS-C seems to occur in the post-infectious period, and the fact that cases of MIS-C increased within weeks after the surge of COVID-19 supports this hypothesis.¹⁴⁾ A systemic review of MIS-C also noted that the proportion of subjects with positive SARS-CoV-2 serology was much higher than that of positive SARS-CoV-2 PCR results, which suggests that MIS-C is more associated with post-infection conditions than with current infection.¹⁵⁾ Another recent study analyzed the immune profile in the blood of MIS-C patients, and identified extreme elevation of various cytokines including IL-17A and IL-6, and CD40.¹⁶⁾ These findings indicate that in the post-infection period, various cytokines are released into the bloodstream, resulting in systemic hyperinflammation with multi-organ damage. These findings correlate with the results from our patient (negative SARS-CoV-2 PCR at presentation, but a positive result 5 weeks ago). Serologic tests for SARS-CoV-2 showed positive antibodies by enzyme-linked immunosorbent assays and immunofluorescence assays, and positive neutralizing antibodies were also detected. As MIS-C may increase with an increase in COVID-19 cases, further studies on its pathogenesis are warranted to guide proper management of this syndrome.

MIS-C causes a hyperinflammatory reaction in various systems; therefore, treatment aims to reduce inflammation and prevent organ failure. In our patient, IVIG was administered on the first day, and high-dose methylprednisolone pulse therapy was started the next day due to persistent symptoms. IVIG and glucocorticoids are the most widely used and proposed as the 1st line agents for treating MIS-C, based on previous experience using IVIG in similar diseases such as Kawasaki disease or myocarditis.^{11,17)} Our patient received a second dose of IVIG due to the refractory response, and based on previous experience with Kawasaki disease and available treatment guidelines at that time.⁶⁾ Currently, administration of a second dose of IVIG to patients with refractory MIS-C is not recommended due to the potential side effects of IVIG, such as volume overload or hemolytic anemia,¹¹⁾ however, simultaneous use of glucocorticoid and IVIG may be considered. According to recent reports, concurrent use of IVIG and glucocorticoid was found to reduce the risk of cardiovascular dysfunction compared with IVIG alone,¹⁸⁾ and another retrospective study of patients with MIS-C noted that treatment with IVIG alone had a higher risk of treatment failure than combined treatment with IVIG and glucocorticoid.¹⁹⁾

Anakinra was administered to our patient from hospital day 6 due to persistent symptoms such as fever, dyspnea, rash, coronary artery dilatation and deteriorating LV function despite IVIG and high-dose methylprednisolone. Anakinra, being an IL-1 receptor antagonist and a relatively safe and effective medication for refractory Kawasaki disease, was the most frequently considered biological agent for treatment of MIS-C refractory to IVIG and glucocorticoid. In MIS-C the recommended dose is more than 4 mg/kg/day.^{11,20)} So far there are limited data on the efficacy of other biological agents for MIS-C, however, there are some reports on the use of tocilizumab or infliximab.^{12,14)} In this case, anakinra was used safely and resulted in clinical improvement shortly after initiation, including a marked improvement in LV dysfunction. Follow-up EchoCG 1 month after discharge showed fully recovered LV function and normal coronary artery dimensions.

In conclusion, we report a case of MIS-C with acute myocarditis that was successfully treated with IVIG, high-dose methylprednisolone, and anakinra. MIS-C is a recently newly defined disease entity which occurs after COVID-19. Since there were only few case reports on MIS-C in Korea, many clinicians may not be familiar with MIS-C. However, considering the rapid progression and severe manifestations of MIS-C, awareness of the clinical manifestations and treatment modalities in MIS-C is important. In addition, further research on the characteristics and pathogenesis of MIS-C will be needed for proper management.

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요약

2020년 4월에 유럽에서 처음으로 소아 다기관 염증 증후군(multisystem inflammatory syndrome in children; MIS-C)이 확인된 이후, MIS-C는 코로나바이러스감염증-19(COVID-19)의 병력이 있는 소아들에게서 발병하는 것으로 알려졌고 대부분의 환자들은 유럽과 미국에서 보고되었다. 이에 국내에서 진단된 MIS-C 사례로, 급성 심근염이 동반되고 정맥내 면역글로불린(intravenous immunoglobulin; IVIG), 스테로이드 및 anakinra로 효과적으로 치료한 증례를 보고하고자 한다. 내원 5주 전 COVID-19 진단받은 병력이 있는 14세 여아가 지속되는 고열, 전신 발진 및 부종, 복통, 그리고 저혈압을 주소로 내원하였다. 혈액검사에서 염증수치 및 심장효소수치 상승을 보였고 감염질환을 비롯하여 다른 질환이 배제되었다. 환자는 MIS-C 진단 하에 IVIG와 고용량 메틸프레드니솔론(methylprednisolone) 요법으로 치료하였으나 심기능이 점차 악화되고 관상동맥 확장증이 확인되었다. 이에 제6병일부터 인터루킨-1 수용체 길항제인 anakinra를 투여하였고 이후 점차 환자의 심기능이 호전되었다. 환자는 제19병일에 퇴원하였고 1개월 후 시행한 심초음파상 심기능 및 관상동맥이 정상화되었다.