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Case Report

A Case of 1-Month Fever Caused by CMV Infection in a Patient With MIS-C Treated With IVIG, Infliximab, and High-Dose Methylprednisolone

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is a rare complication of coronavirus disease 2019 (COVID-19), causing multi-organ damage affecting the heart, lungs, kidneys, digestive tract, and nervous system. As the cases of MIS-C have been increasing following the COVID-19 pandemic, the importance of appropriate management for MIS-C is becoming increasingly apparent. Immunomodulating agents such as anakinra, infliximab, and steroids are regarded as supplementary therapy to the first-line treatment with intravenous immunoglobulin. However, these immunomodulating therapies can potentially precipitate opportunistic infections, including those caused by cytomegalovirus (CMV), Epstein-Barr virus, and tuberculosis, or increase the risk of co-infections. Herein, we report a case of a 3-year-old boy who was treated with immunoglobulin, infliximab, and high-dose methylprednisolone for MIS-C, and subsequently developed a persistent fever lasting 32 days caused by a CMV infection.

Keywords: Cytomegalovirus infection; COVID-19; Infliximab; Methylprednisolone; Pediatric multisystem inflammatory disease, COVID-19 related

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory, multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a rare disease that occurs in 2 per 100,000 after the coronavirus disease 2019 (COVID-19).[1,2] Despite various differences between MIS-C and Kawasaki disease (KD), similar characteristics and coronary arteries complications exist.[3] If left untreated, MIS-C can cause serious complications, including death, because of multi-organ failure, especially involving the cardiovascular system.[4] To reduce these complications, immunoglobulin therapy is recommended as the first-line treatment.[5] In refractory cases, additional therapy with steroid and biological agents, including tumor necrosis factor (TNF) receptor inhibitors and interleukin inhibitors such as infliximab, anakinra, and tocilizumab, are recommended as secondary treatment for MIS-C.[5] Nevertheless, TNF receptor inhibitors and interleukin inhibitors have adverse effects that can cause immunosuppression, which may lead to secondary infections.[6-8] Herein, we report a case of a 3-year-old boy who was treated with immunoglobulin, infliximab, and high-dose methylprednisolone for MIS-C, and

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

Author Contributions
Conceptualization: You J; Data curation: Jeong G; Formal analysis: Jeong G; Funding acquisition: You J; Investigation: Jeong G; Validation: Jeong G; Visualization: Jeong G; Writing - original draft: Jeong G; Writing - review & editing: Jeong G, You J.

subsequently developed a persistent fever lasting 32 days caused by a cytomegalovirus (CMV) infection (**Fig. 1**).

CASE

A 3-year-old boy, who had a history of COVID-19 diagnosed 4 months prior, visited the outpatient clinic complaining of fever lasting 5 days. One day after the onset of the fever, he had diarrhea and generalized rashes. His blood pressure and respiratory rate were normal (118/72 mmHg, 26 /min), whereas his pulse rate and body temperature were elevated (130/min, 38.2°C). His height was 100 cm (90th percentile), and his weight was 17.1 kg (70th percentile), and these were within the normal growth range. On physical examination, features of KD were observed, including red lips, conjunctival injection, palpable cervical lymph nodes in both upper jugular areas, and generalized rashes, with the exception of hand and foot edema. He had no past medical history other than COVID-19 and no family history of KD.

Initial laboratory test results are shown in **Table 1**. Complete blood cell count (CBC) revealed neutrophil-dominant leukocytosis of 14,590 /μL (neutrophil, 93%; lymphocyte, 2.3%). Elevated aspartate transaminase (227 U/L), alanine transferase (173 U/L), and elevated creatinine (0.69 mg/dL) were detected in the biochemical analysis. The coagulation test revealed prothrombin time prolongation (international normalized ratio, 1.41) and D-dimer elevation (0.582 mg/L). Pro-brain natriuretic peptide was elevated at 2,409 pg/mL, although troponin-T, a cardiac marker, was within the normal range (13 ng/L). The initial radiograph and electrocardiogram showed no abnormalities. During the initial echocardiography (**Table 2**), we observed mild coronary artery dilatation with an left main coronary artery (LMCA) z score of 2.35, calculated using the method described by Kobayashi et al.[9] Furthermore, the left ventricular

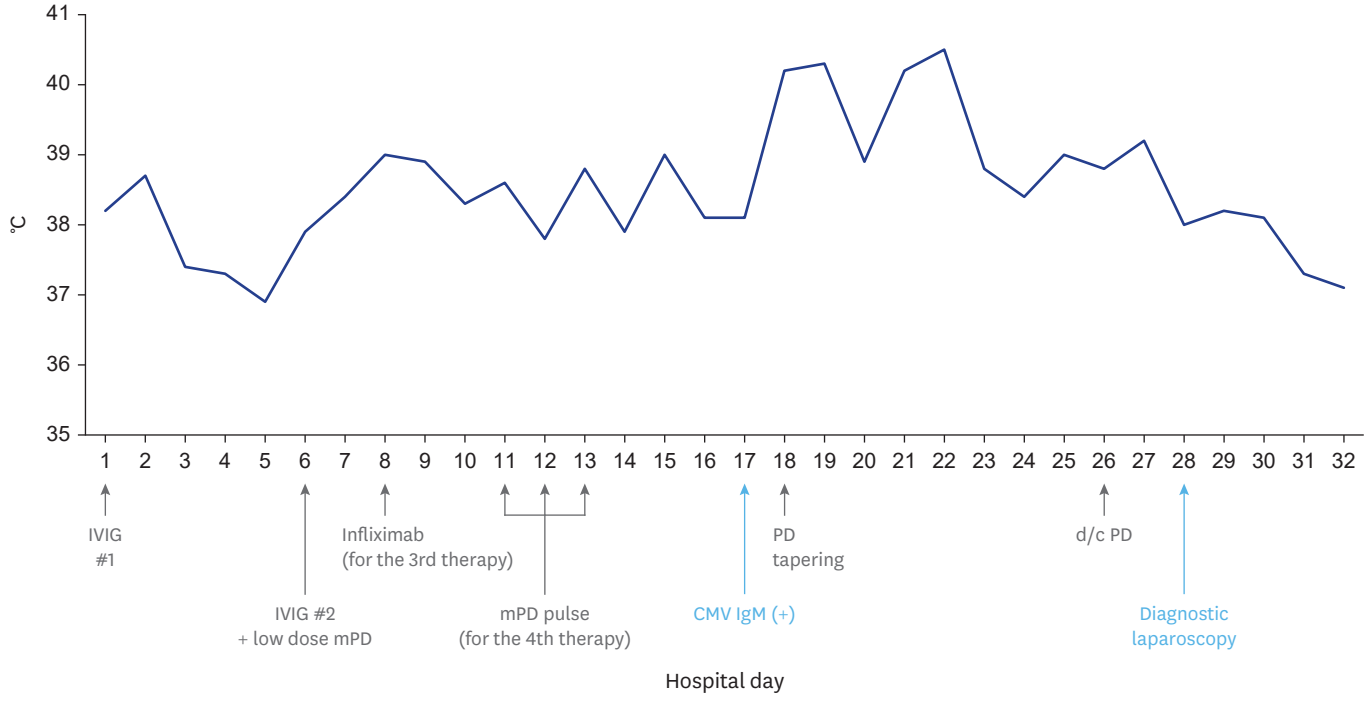

Fig. 1. The highest body temperature of the patient during the hospital course.
Abbreviations: IVIG, intravenous immunoglobulin; mPD, methylprednisolone; CMV, cytomegalovirus; IgM, immunoglobulin M; d/c, discontinued; PD, prednisolone.

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Table 1. Laboratory findings of the patient on the timeline of treatment

Laboratory findings	HD #1	HD #5	HD #8	HD #10	HD #17
WBC (/μL)	14.59×10^3	16.71×10^3	19.22×10^3	24.88×10^3	19.22×10^3
Neutrophil (%)	93.0	76.6	78.7	55.2	79.7
Lymphocyte (%)	2.3	10.6	14.5	29.9	14.5
Hemoglobin (g/dL)	11.0	11.5	11.0	11.2	11.0
Platelet (/μL)	498×10^3	219×10^3	336×10^3	498×10^3	498×10^3
Na (mmol/L)	136	132	134	135	134
K (mmol/L)	4.5	4.3	5.1	4.8	5.1
Cl (mmol/L)	98	97	98	101	98
Protein (g/dL)	5.1	7.2	8.7	8.4	6.8
Albumin (g/dL)	3.4	2.9	3.3	3.4	2.8
BUN (mg/dL)	17	7	9	9	13
Cr (mg/dL)	0.69	0.32	0.42	0.49	0.31
AST (U/L)	227	17	24	23	17
ALT (U/L)	173	22	15	11	8
CRP (mg/L)	46.09	6.65	36.97	18.06	5.18
Pro-BNP (pg/mL)	2,409	365.3			<50

Abbreviations: HD, hospitalization day; WBC, white blood cell; Na, sodium; K, potassium; Cl, chloride; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein, Pro-BNP, pro-brain natriuretic peptide.

Table 2. The echocardiographic findings of the patient on the timeline of treatment

Echocardiographic findings	HD #1	HD #8	HD #14	One month after discharge
Ejection fraction (%)	59.6	61.3	79	68.6
Global Longitudinal strain (%)	−14	−16	−23	−20
LMCA (mm) (z score)	3.14 (2.35)	3.36 (2.96)	3.09 (2.33)	3.08 (2.20)
LAD (mm) (z score)	2.43 (1.55)	2.43 (1.82)	2.09 (0.78)	1.92 (0.24)
LCx (mm) (z score)	1.78 (0.44)	2.11 (1.31)	1.94 (0.89)	2.17 (1.38)
RCA (mm) (z score)	2.72 (2.09)	2.72 (1.89)	2.16 (0.76)	1.73 (0.61)

The z score was calculated based on the study of Kobayashi et al.[9]
Abbreviations: HD, hospitalization day; LMCA, left main coronary artery; LAD, left anterior descending; LCx, left circumference artery; RCA, right coronary artery.

ejection fraction was 59.6%, and an absolute negative strain value of 14%. After the patient was diagnosed with MIS-C and KD based on the World Health Organization (WHO) criteria, intravenous immunoglobulin (IVIG; 2 g/kg) and aspirin were promptly administered. Later, the fever subsided, and he was discharged from the hospital on day 4.

The patient revisited our clinic complaining of fever 1 day after discharge. Given the brief interval between the patient's initial and subsequent hospital admissions, the duration of his hospital stay will be documented continuously. On the 5th day of hospitalization, as the only apparent symptom was fever, a newly contracted viral infection was our primary diagnosis. However, the fever persisted, and laboratory findings showed typical MIS-C findings such as neutrophil-dominant leukocytosis, hyponatremia, hypoalbuminemia, and elevated C-reactive protein (**Table 1**). On the 5th day of hospitalization, second-line treatment with IVIG (2 g/kg) and low-dose intravenous methylprednisolone (1 mg/kg/day) was administered, considering IVIG-refractory MIS-C. Even after second-line treatment, the fever persisted. Furthermore, dilated coronary arteries (LMCA z score of 2.96) were identified on echocardiography on the 8th day of hospitalization (**Table 2**). Therefore, we decided to administer an additional immunomodulating drug, infliximab, to treat MIS-C on the 8th day, according to the American College of Rheumatology guidelines.[10] Nevertheless, even after administering infliximab, the fever did not subside. On the 11th day of hospitalization, we administered a pulse dose of methylprednisolone (30 mg/kg/day) and subsequently changed it to oral (PO) prednisolone (1 mg/kg/day). However, the fever persisted (**Fig. 1**).

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Although we considered the possibility of viral infection due to the immunosuppressants and autoimmune diseases, only the parainfluenza virus was detected, and it has been present since the initial onset of the disease. In the evaluation of autoimmune disease, both rheumatoid factor and fluorescent antinuclear antibody screening tests showed negative results. With aggressive treatment for MIS-C, inflammatory markers returned to the normal range on the 10th day of hospitalization (**Table 1**), and there was an improvement in coronary artery dilatation by the 14th day (**Table 2**), although the fever persisted for 17 more days. Furthermore, on the 16th day, the patient developed a new-onset abdominal pain and hepatomegaly measuring 2 finger breadths. Therefore, we repeated laboratory tests to investigate secondary or concealed infections and performed imaging studies, including chest and abdomen computed tomography (CT). The serologic test revealed the presence of CMV immunoglobulin M (IgM) and a positive qualitative test result of blood CMV polymerase chain reaction (PCR) on the 25th day. Multiple lymphadenopathies in the mesenteric area, terminal ileitis, and hepatomegaly were identified on abdominal CT and positron emission tomography-CT on the 18th day (**Fig. 2A and B**). A surgical biopsy, performed on the 28th day, showed only reactive changes in the lymph node, with negative staining for CD1a, S-100, CD123, Epstein-Barr virus-encoded small ribonucleic acid, and CMV. (**Fig. 2C**). No evidence of a malignancy was found.

In conclusion, the patient was diagnosed with CMV infection while on infliximab and methylprednisolone pulse therapy for MIS-C treatment. PO prednisolone was gradually reduced and discontinued on the 26th day of hospitalization. The fever subsided 4 days after discontinuing steroids. By the 30th day of hospitalization, clinical symptoms, including abdominal pain and hepatosplenomegaly, had significantly improved. Therefore, additional tests for CMV infection were not performed before discharge. During the one-month follow-up at the outpatient clinic, the patient had no fever, and the CMV IgM serology and CMV quantitative tests revealed negative results. Coronary artery dilatation persisted on follow-up echocardiography (**Table 2**), and aspirin was continued.

The Institutional Review Board (IRB) of Jeonbuk National University Hospital approved this study (IRB No. 2022-11-012). The need for informed consent was waived because it is a retrospective study.

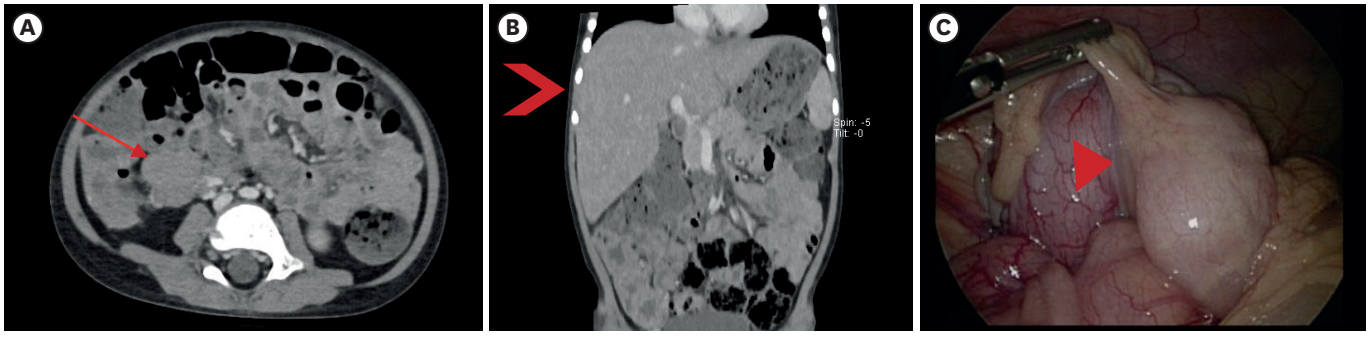

Fig. 2. Abdominal CT and laparoscopic finding of the patient.
(A) Red arrow shows enlarged LN in abdominal CT. (B) Hepatomegaly is shown in abdominal CT with a red arrow without a line. (C) Red arrowhead indicates enlarged LN in laparoscopic findings.
Abbreviations: CT, computed tomography; LN, lymph node.

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DISCUSSION

To the best of our knowledge, this is the first case of MIS-C with persistent fever for one month because of CMV infection. In this study, we report a case of concurrent CMV infection in a patient treated with immunomodulating therapy for MIS-C, although the causal relationship between these conditions remains unclear. There are reports of CMV infection after administering infliximab in patients with ulcerative colitis.[6] Given the limited number of reports on infections concurrent with MIS-C, our case report underscores the importance of maintaining vigilance and conducting comprehensive investigations to detect and better understand such associated infections.

After the first patient in Korea was reported in October 2020,[11] several cases of MIS-C were registered by the Korean Disease Control and Prevention Agency. In a Korean national survey reported in September 2022, 57.65% of the general population had positive nucleocapsid (N) antigen SARS-CoV-2 antibody test. In the pediatric population, about 80% of those aged 5–9 years had already experienced COVID-19.[12] As COVID-19 is predicted to remain, MIS-C occurrence is expected to continue. Hence, the complications after treatment should be reported in detail.

In our case report, the patient was initially diagnosed as having MIS-C based on the WHO criteria and CDC case definition because he was under 20 years old and had fever with elevated inflammatory markers, multi-organ involvement, including mucocutaneous infection, gastrointestinal problems, features of myocardial dysfunction, elevated creatinine levels, and a history of COVID-19 along with positive SARS-CoV-2 antibody for N and spike proteins.[13,14] Although the patient had characteristic Kawasaki features, including red lips, conjunctival injection, palpable cervical lymph nodes, and generalized rashes, he differed from typical KD patients in that he had decreased ventricular function indicated by an absolute strain and an increased creatinine level. Since MIS-C and KD are often indistinguishable, and 40–50% of MIS-C satisfy the diagnostic criteria for complete or incomplete KD, it is difficult to completely differentiate between the 2 diseases.[15] When the patient revisited our clinic due to fever, we suspected infection because he complained only of fever. After readmission, the fever relapses occurred more frequently with shorter intervals. Laboratory findings showed typical MIS-C findings, including hypoalbuminemia, hyponatremia, neutrophilia, and lymphocytopenia. Hence, refractory MIS-C and KD were diagnosed. After the treatments with infliximab and methylprednisolone pulse therapy, he developed abdominal discomfort and hepatomegaly. The origin of fever was confirmed as CMV infection using a blood CMV PCR test. Since the baseline CMV IgM level is unknown, it is unclear whether it is a primary infection or a reactivation. However, since both IgM and immunoglobulin G (IgG) at the time of fever were reactive and PCR was positive, both possibilities were considered. CMV infection may have developed after the 4th treatment with methylprednisolone pulse therapy because the fever seemed to subside only during that period.

In one study in Korea involving 11,584 patients from 1995 to 2015, about 81.7% of patients under the age of 10 were CMV IgG-positive.[16] In CMV infection, IgM is an indicator of acute infection, and IgG indicates a past infection.[17] Since it is difficult to infer the exact time of infection with only one indicator, it is recommended to check both IgM and IgG when CMV infection is suspected. In our patient, IgM was positive, and IgG was reactive at 144.4 AU/mL, suggesting a relatively recent infection. Steroid tapering was initiated to address the possible cause of the CMV infection, such as the administration of immunosuppressants.

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In the treatment of MIS-C, the first-line approach using IVIG and concurrent steroid use is recommended for hemodynamically unstable patients.[10] If the primary treatment fails, high-dose steroids or immunomodulatory, such as anakinra and infliximab, can be considered as additional treatment because the pathophysiology of MIS-C involves hyper-immune reactivation against previous COVID-19.[18,19] Although these biological agents are highly effective in managing various chronic inflammatory diseases, their effect on the immune system can increase the risk of opportunistic infections such as tuberculosis and cytomegalovirus.[7,20]

If other infections are suspected in patients receiving immunomodulating agents for MIS-C, a rapid diagnostic method using techniques such as CT and biopsy is required. Although the patient's fever persisted, his inflammatory markers decreased, and there was an improvement in coronary artery dilatation. However, the aggravation of only hepatomegaly and abdominal pain raised suspicion of a fever caused by another viral infection rather than a worsening of MIS-C. Hence, when evaluating the patient's condition, we considered symptoms, physical examination, laboratory findings, and imaging results.

Concurrent or opportunistic infection should be considered when steroids and biological agents, used to treat MIS-C, weaken patients' immune systems and cause persistent fever. Rapid diagnostic tools should be utilized when the fever persists. Laboratory and echocardiographic findings can indicate the fever's origin.

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요약

소아 다기관 염증 증후군(multisystem inflammatory syndrome in children, MIS-C)은 코로나바이러스감염증-19 (코로나19; coronavirus disease 2019, COVID-19)의 드문 합병증으로 심장, 폐, 신장, 소화관 및 신경계를 포함한 다기관 손상을 일으킨다. 코로나19 팬데믹 이후 MIS-C 사례가 증가함에 따라 MIS-C에 대한 적절한 치료의 중요성이 강조되고 있다. anakinra, infliximab, 스테로이드와 같은 면역 조절제는 MIS-C에 대한 intravenous immunoglobulin (IVIG)의 1차 치료에 대한 추가 요법으로 고려되지만 cytomegalovirus (CMV), Epstein-Barr 바이러스 및 결핵과 같은 2차 감염을 유발할 소지가 있다. 저자들 MIS-C로 IVIG, steroid 및 infliximab을 투여한 환자에서 동반된 CMV 감염으로 인하여 약 한달간 지속되는 발열이 발생한 3세 남아의 증례 1례를 처음으로 보고하였다.