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Case Report

Severe SARS-CoV-2 Infection With Multiorgan Involvement Followed by MIS-C in an Adolescent

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

ABSTRACT

Children and adolescents with coronavirus disease 2019 (COVID-19) generally have mild symptoms. Severe infection due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) involving multiorgan dysfunction is rare in this population. Herein, we present an unusual case of severe SARS-CoV-2 infection with multiorgan involvement followed by multisystem inflammatory syndrome in children (MIS-C) in a vaccinated 16-year-old boy. The patient was unconscious on initial presentation, and had severe paralytic ileus. On laboratory examination, there was severe metabolic acidosis, lymphocytopenia, thrombocytopenia, elevated inflammatory markers, elevated liver enzymes, and evidence of acute kidney injury with proteinuria and hematuria. His symptoms improved with the administration of remdesivir and dexamethasone. The patient briefly experienced MIS-C 2 weeks after the diagnosis of COVID-19, but the patient was discharged without any complications.

Keywords: COVID-19; MIS-C associated with COVID-19; SARS-CoV-2; Children

INTRODUCTION

Since the declaration of coronavirus disease 2019 (COVID-19) as a global pandemic by the World Health Organization in March 2020, many children worldwide have been affected by the disease. Current knowledge suggests that most children with COVID-19 have mild symptoms.[1,2] However, some children may experience severe disease, especially if they have underlying medical conditions, such as type 1 diabetes, congenital heart disease, or obesity.[3] Severe COVID-19 in children primarily manifests as pneumonia requiring noninvasive respiratory support or invasive mechanical ventilation.[4] Although rare, some children may develop multiorgan failure involving the heart, kidney, and gastrointestinal tract.[5] Herein, we report a case of an adolescent with COVID-19 who experienced severe infection with multiorgan involvement followed by multisystem inflammatory syndrome in children (MIS-C).

Author Contributions

Conceptualization: Han MS; Data curation: Lim B; Formal analysis: Lim B; Investigation: Lim B, Shin SM; Supervision: Han MS; Visualization: Shin SM, Han MS; Writing - original draft: Lim B; Writing - review & editing: Shin SM, Han MS.

CASE

A 16-year-old boy was referred to the emergency department (ED) on December 21, 2021, because of an altered mental status. The patient, who was raised in an orphanage, was diagnosed with schizophrenia at the age of 9 and has been on medication since. He was frequently admitted to a community hospital for psychosocial rehabilitation, psychotherapy, and social skill training. The patient was able to communicate in everyday life and complain of discomfort and pain. He had been admitted to the community hospital at the time an outbreak of COVID-19 occurred in that hospital (4 days prior to the visit), but because the patient did not have any symptoms and because the COVID-19 polymerase chain reaction (PCR) result was negative, he was discharged to the orphanage the following day. The day before the visit, he complained of slight abdominal discomfort, but his general condition was good and oral intake was not decreased. One hour prior to admission, at around 8 o'clock in the morning, an orphanage staff member found the patient unconscious in his bedroom and breathing abnormally. Therefore, the patient was transferred to the ED. The patient had received a second dose of a COVID-19 mRNA vaccine (Pfizer-BioNTech) 18 days before the visit.

On initial examination, the patient had hyperpnea, and his blood pressure was unmeasurable. His Glasgow Coma Scale score was 5. The patient was not obese, and his body mass index was 17.89 kg/m^2. He was immediately intubated, and mechanical ventilation was initiated. Initial arterial blood gas analysis revealed severe metabolic acidosis (pH, 7.065; pCO_2, 31.5 mmHg; pO_2, 320.9 mmHg; HCO_3, 8.8 mEq/L; lactate, 8.57 mmol/L). His initial white blood cell count was 9,550/μL and C-reactive protein (CRP) level was 17.28 mg/dL. His creatinine level was 1.84 mg/dL, and fractional excretion of sodium was 0.1%, suggesting prerenal acute kidney injury. Proteinuria and hematuria were observed on urinalysis. The troponin I level was normal, and the inferior vena cava was collapsed on bedside echocardiography. Intravenous bicarbonate therapy and fluid resuscitation were performed. Inotropics and broad-spectrum antibiotics were administered. The patient's mental status recovered fully after 7 hours of emergency management. His abdomen was distended, bowel sounds were hypoactive, and tenderness was observed over the entire abdomen. Abdominal radiography and computed tomography (CT) revealed severe paralytic ileus with multifocal hypoenhancing areas in the liver and spleen (**Fig. 1**). A Levin tube was inserted, and oral feeding was discontinued. Although the patient did not have fever or respiratory symptoms, his COVID-19 PCR result was positive (Ct value: E gene, 14.07 and RdRP gene, 12.17). Accordingly, he was started on remdesivir and dexamethasone (6 mg every 24 hours). He was weaned off ventilator support after 11 hours and received respiratory support via a nasal cannula in the ED, and he was admitted to the isolation ward for further management.

During the first 4 days of hospital admission, the absolute lymphocyte count (ALC) and platelet count decreased to 173/μL and 49,000/μL, respectively. Aspartate aminotransferase and alanine aminotransferase levels increased to 447 IU/L and 188 IU/L, respectively, and total bilirubin level increased to 1.8 mg/dL. His serum albumin level was as low as 2.1 g/dL and the CRP level peaked at 33.87 mg/dL. On hospital day 4, the patient started passing loose mucoid stool 7 times per day and had persistent diffuse tenderness over the distended abdomen. These abdominal symptoms and abnormal laboratory findings gradually improved, the Levin tube was removed, and oral feeding was carefully started on hospital day 7. Remdesivir was administered for 5 days and dexamethasone was administered for 10 days and was discontinued without tapering. No organisms were isolated in blood and stool cultures.

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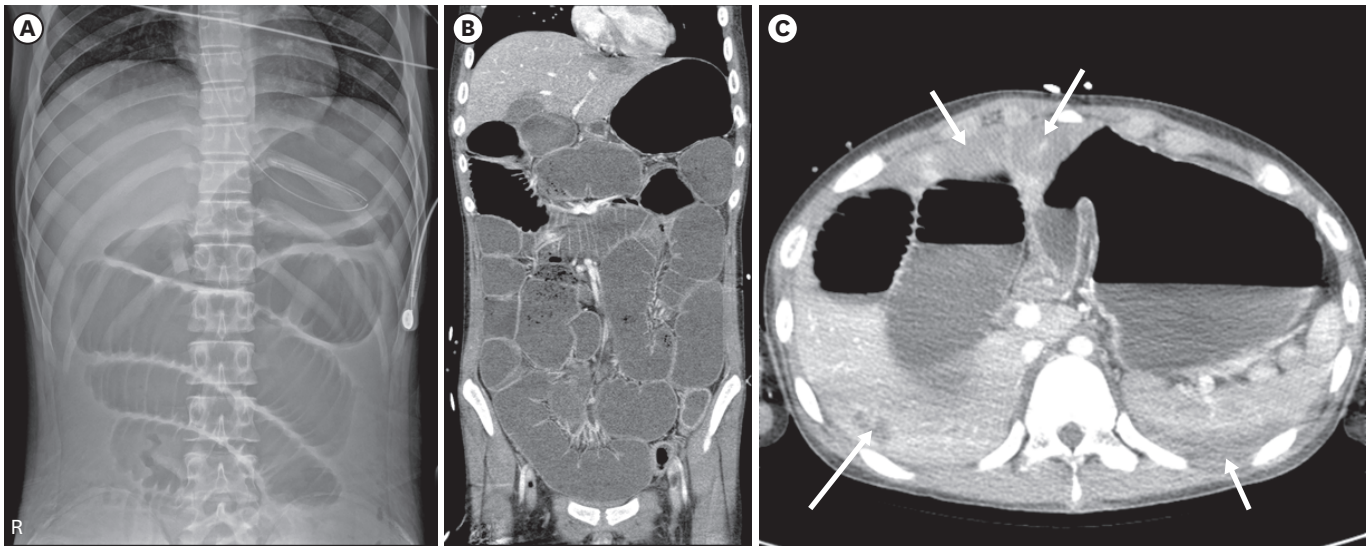

Fig. 1. (A) Supine abdominal radiography shows diffuse gaseous-dilated small bowel loops in the central abdomen. Coronal (B) and axial (C) abdominal computed tomography scans show diffuse gas- and fluid-filled dilatation of entire hollow viscus, suggesting severe paralytic ileus, and multifocal hypoenhancing areas (arrows in C) in the liver and spleen, possible ischemic change due to mass effects.

On hospital day 15, the patient suddenly developed fever of up to 39.3°C and started having watery diarrhea 6 times per day. The following day, his blood pressure suddenly dropped to 87/50 mmHg and heart rate rose to 103 bpm; hence, he was started on continuous infusion of norepinephrine. The patient did not have rash or conjunctival injection. On laboratory examination, his ALC had decreased again to 265/μL; the sodium and albumin levels had decreased to 130.9 mmol/L and 2.8 g/dL, respectively; and the CRP level had increased to 13.61 mg/dL. The prothrombin time and activated partial thromboplastin time were 1.13 INR and 28.8 sec, respectively, and the D-dimer level was 1.44 mg/L. The N-terminal pro-brain natriuretic peptide level was 286.1 pg/mL, while creatine kinase-MB and troponin I were normal, and no abnormality was observed on electrocardiography. No organisms were isolated in blood, stool, and urine cultures. He was diagnosed as having MIS-C according to the criteria of the Centers for Disease Control and Prevention.[6] On hospital day 17, fever and diarrhea improved without the administration of immunosuppressants, and norepinephrine was discontinued as his vital signs stabilized. Laboratory values also gradually improved to normal. The patient was discharged on hospital day 24 without any complications. The patient remained healthy at the 1-week follow-up. The overall clinical course of the patient is shown in **Fig. 2**.

This study was approved by the Institutional Review Board of Seoul Metropolitan Government-Seoul National University Boramae Medical Center, and written informed consent was waived (IRB No: 20-2022-33).

DISCUSSION

The patient presented in this study was a 16-year-old adolescent with schizophrenia who was admitted to the ED because of an altered mental status. His initial blood pressure was unmeasurable, his abdomen was distended, and tenderness was observed over the entire abdomen. Abdominal radiography and CT revealed severe paralytic ileus. Laboratory

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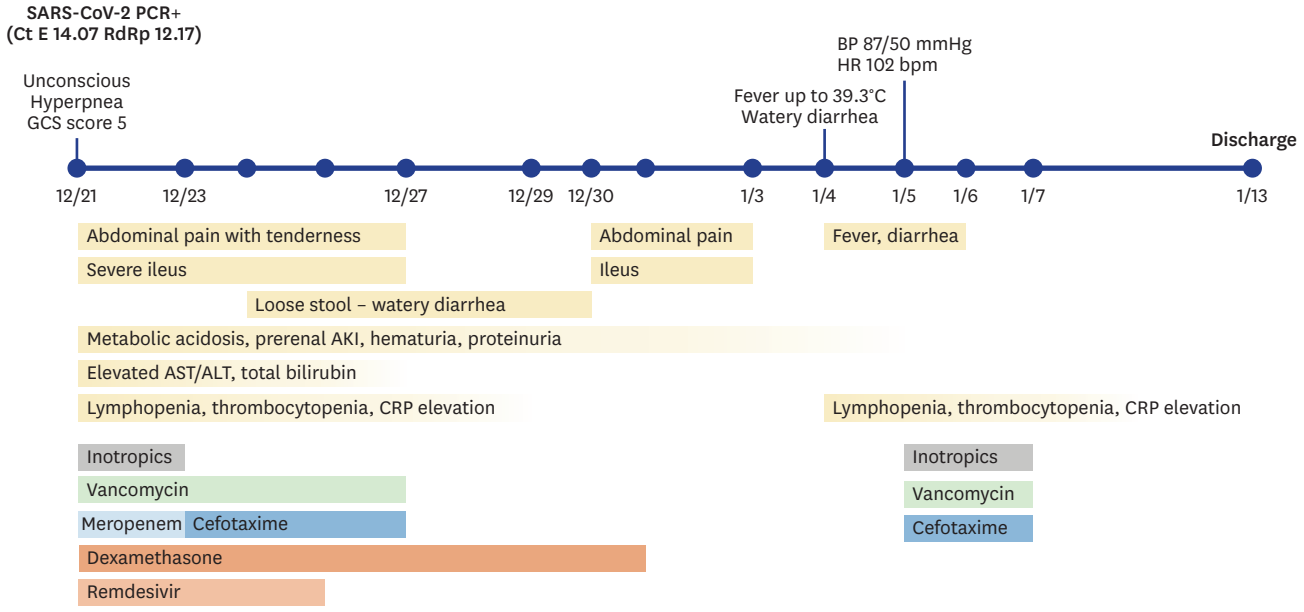

Fig. 2. Diagram of the clinical course of a 16-year-old adolescent with severe coronavirus disease 2019 with multiorgan involvement followed by multisystem inflammatory syndrome in children.
Abbreviations: SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; PCR, polymerase chain reaction; Ct, cycle threshold; GCS, Glasgow Coma Scale; BP, blood pressure; HR, heart rate; AKI, acute kidney injury; AST/ALT, aspartate aminotransferase/alanine transaminase; CRP, C-reactive protein.

examination revealed severe metabolic acidosis and evidence of acute kidney injury with proteinuria and hematuria. A history of exposure to a COVID-19 outbreak prompted an evaluation for COVID-19, and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR result was positive with low Ct values. During the hospital course, lymphocytopenia, thrombocytopenia, elevated inflammatory marker levels, and elevated liver enzyme levels were also observed. His symptoms improved with the administration of remdesivir and dexamethasone. The patient briefly experienced MIS-C 2 weeks after the diagnosis of COVID-19 but was discharged without any complications.

Although most children with COVID-19 experience mild symptoms, some children—especially those with underlying medical conditions—may develop severe infection involving multiple organs, apart from the lungs. Previously published reports have demonstrated that myocarditis, neuritis, or acute kidney injury can occur during the acute stage of SARS-CoV-2 infection in children.[7-9] The development of septic shock or cardiogenic shock independent of lung disease has also been described.[10,11]

Current knowledge suggests that COVID-19 is a systemic disease.[12] SARS-CoV-2 can affect multiple organs by entering host cells via its unique mode of entry. To enter the host cell, the spike protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) and uses the cellular protease transmembrane serine protease 2 (TMPRSS2) for priming.[13] Thus, co-expression of both ACE2 and TMPRSS2 on the cell surface is required for SARS-CoV-2 to enter the target cells. ACE2 and TMPRSS2 are co-expressed not only in lung cells but also in renal, myocardial, neural, and gastrointestinal tissues.[12] Therefore, SARS-CoV-2 can directly damage these tissues, leading to multiorgan injury. In addition, the overactivation of innate immunity and dysregulation of the immune response may contribute to severe COVID-19. Although the overall magnitude of immune dysregulation and cytokine-release syndrome seems smaller in children than in adults, signaling by interferons and inflammasomes,

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activated SARS-CoV-2-specific T cells, and robust humoral responses may still be observed in children with severe COVID-19, as in the present case.[14]

Schizophrenia is a known risk factor for increased mortality in adults with COVID-19.[15] Although the underlying mechanism remains unclear, a difference might exist in the immune response to COVID-19 owing to the genetic variation in the major histocompatibility complex class I genes in patients with schizophrenia.[16] Moreover, patients with schizophrenia have dysfunctional T-cell immune responses, which is a major characteristic of severe infection.[17] Additionally, antipsychotic medications for schizophrenia, especially clozapine, are known to be associated with an increased risk of broad pneumonia and sudden death.[18] Our patient might have been susceptible to severe COVID-19 because of these multiple biological factors related to his medical illness.

The patient presented in this case experienced MIS-C 2 weeks after the diagnosis of COVID-19. The symptoms of MIS-C improved rapidly without the administration of immunosuppressants. Although MIS-C is relatively rare, it is a significant complication of COVID-19 in children. Postinfectious immune reactions seem to account for this recently recognized novel pediatric illness, as it is often noticed 2–4 weeks after the diagnosis of or exposure to COVID-19.[19] Clinical features of MIS-C are diverse, ranging from mild to critical and necessitate intensive care.[20] Almost all patients with MIS-C present with fever, and common symptoms include gastrointestinal symptoms, cardiovascular symptoms, and rashes. Some patients present with MIS-C without the features of Kawasaki disease, while others have overlapping features. Clinical suspicion is key to the diagnosis and prompt management of MIS-C.

To the best of our knowledge, this is the first reported case of an adolescent experiencing severe COVID-19 with multiorgan dysfunction followed by MIS-C in Korea. This case emphasizes the need to carefully monitor and promptly manage the serious extrapulmonary manifestations of COVID-19, even in children.

REFERENCES

1. Cui X, Zhao Z, Zhang T, Guo W, Guo W, Zheng J, et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). J Med Virol 2021;93:1057-69.
PUBMED | CROSSREF
2. Irfan O, Muttalib F, Tang K, Jiang L, Lassi ZS, Bhutta Z. Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis. Arch Dis Child 2021;106:440-8.
PUBMED | CROSSREF
3. Kompaniyets L, Agathis NT, Nelson JM, Preston LE, Ko JY, Belay B, et al. Underlying medical conditions associated with severe COVID-19 illness among children. JAMA Netw Open 2021;4:e2111182.
PUBMED | CROSSREF
4. Fernandes DM, Oliveira CR, Guerguis S, Eisenberg R, Choi J, Kim M, et al. Severe acute respiratory syndrome coronavirus 2 clinical syndromes and predictors of disease severity in hospitalized children and youth. J Pediatr 2021;230:23-31.e10.
PUBMED | CROSSREF
5. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr 2020;174:868-73.
PUBMED | CROSSREF
6. Centers for Disease Control and Prevention. CDCHAN-00432, May 14, 2020. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19) [Internet]. Atlanta:

Centers for Disease Control and Prevention; 2020 [cited 2022 May 24]. Available from: https://emergency.cdc.gov/han/2020/han00432.asp.

7. Lindan CE, Mankad K, Ram D, Kociolek LK, Silvera VM, Boddaert N, et al. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. Lancet Child Adolesc Health 2021;5:167-77.
PUBMED | CROSSREF
8. Beaudry JT, Dietrick B, Lammert DB, Constas A, McCaw J, Hammond J, et al. Fatal SARS-CoV-2 inflammatory syndrome and myocarditis in an adolescent: a case report. Pediatr Infect Dis J 2021;40:e72-6.
PUBMED | CROSSREF
9. Bjornstad EC, Seifert ME, Sanderson K, Feig DI. Kidney implications of SARS-CoV2 infection in children. Pediatr Nephrol 2022;37:1453-67.
PUBMED | CROSSREF
10. Dallan C, Romano F, Siebert J, Politi S, Lacroix L, Sahyoun C. Septic shock presentation in adolescents with COVID-19. Lancet Child Adolesc Health 2020;4:e21-3.
PUBMED | CROSSREF
11. Joshi K, Kaplan D, Bakar A, Jennings JF, Hayes DA, Mahajan S, et al. Cardiac dysfunction and shock in pediatric patients with COVID-19. JACC Case Rep 2020;2:1267-70.
PUBMED | CROSSREF
12. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020;26:1017-32.
PUBMED | CROSSREF
13. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-280.e8.
PUBMED | CROSSREF
14. Chou J, Thomas PG, Randolph AG. Immunology of SARS-CoV-2 infection in children. Nat Immunol 2022;23:177-85.
PUBMED | CROSSREF
15. Nemani K, Li C, Olfson M, Blessing EM, Razavian N, Chen J, et al. Association of psychiatric disorders with mortality among patients with COVID-19. JAMA Psychiatry 2021;78:380-6.
PUBMED | CROSSREF
16. Mokhtari R, Lachman HM. The major histocompatibility complex (MHC) in schizophrenia: a review. J Clin Cell Immunol 2016;7:479.
PUBMED | CROSSREF
17. Steiner J, Jacobs R, Panteli B, Brauner M, Schiltz K, Bahn S, et al. Acute schizophrenia is accompanied by reduced T cell and increased B cell immunity. Eur Arch Psychiatry Clin Neurosci 2010;260:509-18.
PUBMED | CROSSREF
18. De Leon J, Sanz EJ, De Las Cuevas C. Data from the World Health Organization's pharmacovigilance database supports the prominent role of pneumonia in mortality associated with clozapine adverse drug reactions. Schizophr Bull 2020;46:1-3.
PUBMED | CROSSREF
19. Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C) [Internet]. Atlanta: Centers for Disease Control and Prevention; 2021 [cited 2022 May 24]. Available from: https://www.cdc.gov/mis-c/hcp/.
20. Kaushik A, Gupta S, Sood M, Sharma S, Verma S. A systematic review of multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. Pediatr Infect Dis J 2020;39:e340-6.
PUBMED | CROSSREF

요약

코로나19로 확진된 소아와 청소년은 대개 경한 증상을 나타내며 SARS-CoV-2 감염으로 인한 다기관 기능부전은 매우 드물다. 저자들은 코로나19 예방접종을 완료한 16세 청소년에게서 발생한 다기관을 침범한 심한 SARS-CoV-2 감염에 대해 보고하고자 한다. 환자는 내원 당시 의식이 없었으며 심한 마비성장폐색증이 있었다. 혈액검사 상 심한 대사성 산증과 함께 림프구감소증, 혈소판감소증, 염증 수치 상승, 간수치 상승, 단백뇨와 혈뇨가 동반된 급성 신손상의 증거가 있었다. 환자의 상태는 렘데시비르와 덱사메타손 투여와 함께 점차 호전되었다. 코로나19 확진 2주 후에 환자는 다기관염증증후군을 짧게 경험하였으나 특별한 합병증 없이 퇴원하였다.