A Suspected Case of Multisystem Inflammatory Disease in Children Following COVID-19 Vaccination: A Case Report and Systematic Literature Review

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Abstract: Multisystem inflammatory syndrome in children (MIS-C) is rare but can be a potentially serious complication following SARS-CoV-2 infection in children.[1] Introduction of coronavirus disease 2019 (COVID-19) vaccines are effective in lowering the burden due to SARS-CoV-2. However, there have been reports of MIS occurrence following COVID-19 vaccination in adults.[2] The potential public health implication of MIS-C following COVID-19 vaccination is not clear in children. Our objective is to describe the spectrum of clinical disease, therapy, and outcomes of MIS-C following COVID-19 vaccination in children.

Keywords: multisystem inflammatory, MIS-C, PIM-TS, systematic review

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INTRODUCTION

A 15-year-old female patient with no medical history other than allergic rhinitis received the second dose of BNT162b2 mRNA SARS-CoV-2 vaccine in December 2021. Fever and headache started 2 days after the vaccination, and after 5 days, sore throat and abdominal pain developed. On day 6 after vaccination, conjunctival injection was noted and an atypical rash all over the body appeared, prompting her to seek evaluation at the emergency room of Korea University Anam Hospital. In the emergency room, her mental status was alert, body temperature was 40.3°C, and her vital signs were stable (heart rate 130 beats/min, blood pressure 98/41 mm Hg). On physical examination, nonpurulent conjunctival injection and rashes on the trunk and extremities were observed (Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E800). She complained of mild abdominal discomfort. Initial laboratory findings included: hemoglobin 13.3 g/dL, white blood cell count (WBC) 12,300/mL (neutrophil 92.1%, lymphocyte 2.6%, eosinophil 2.6%), platelet count 59,000/mL, BUN/Cr 30.1/1.18 mg/dL, aspartate transaminase (AST)/alanine aminotransferase (ALT) 52/51 IU/L (normal range: ≤45 IU/L), C-reactive protein (CRP) 172 mg/L (normal range: ≤5.0 mg/L), procalcitonin 3.57 ng/mL (normal range: ≤0.046 ng/mL), lactic acid 4.1 mmol/L (normal range: 0.5–2.2 mmol/L), lactate dehydrogenase (LDH) 626 IU/L (normal range: 238–422 IU/L), troponin T 0.048 ng/mL (normal range: ≤0.014 ng/mL), N terminal brain natriuretic peptides (NT-ProBNP) 1,345 pg/mL (normal range: ≤125 pg/mL), creatine kinase (CPK) 33 IU/L (normal range: 38–185 IU/L), D-dimer 11.38 μg/mL (normal range: ≤0.5 μg/mL), fibrinogen 238 mg/dL (normal range: 225–457 mg/dL). There were no findings on chest radiograph; computed tomography (CT) of her chest, abdomen, and pelvis showed lymph node enlargement in the left axillary area and a small amount of ascites in the pelvic cavity. Three hours after presentation, the patient's blood pressure dropped to 76/32 mm Hg, and she was admitted to the intensive care unit (ICU). Initially, on suspicion of septic shock, ceftriaxone, azithromycin, and clindamycin were started, and norepinephrine was used to control blood pressure (Figure 1). However, the fever persisted through the third day of hospitalization and there was no improvement in symptoms. On day 3 after hospitalization, chest radiograph showed pleural effusion and pulmonary edema, and echocardiography showed normal ventricular function under norepinephrine infusion state and no coronary artery dilatation, but trivial mitral regurgitation and scanty pericardial effusion were observed. Intravenous immunoglobulin (IVIG) at 2 g/kg over 48 hours and moderate dose aspirin (30 mg/kg/d) were administered. Fever resolved 2 days after IVIG administration and blood pressure normalized (Figure 1). The patient was discharged 2 days later. At the outpatient visit 1 month later, the patient's general condition was good, and laboratory findings included: hemoglobin 12.0 g/dL, WBC 5,070/mL (neutrophil 49.4%, lymphocyte 42.0%, eosinophil 1.7%), platelet count 273,000/mL, AST/ ALT 26/16 IU/L, C-reactive protein (CRP) 1.0 mg/L. On echocardiography, there was no coronary artery change, and trivial mitral regurgitation and scanty pericardial effusion were also improved.

In Korea, suspected MIS-C cases are reported to the national surveillance system, where the experts assess whether the case meets the criteria for MIS-C case definition, as described previously.[3] The serological assays for SARS-CoV-2 are conducted including plaque reduction neutralizing antibody test (PRNT) and the EUROIMMUN anti-SARS-CoV-2 IgG for all reported cases.

The present case was assessed by the national surveillance system and was at level 1 of diagnostic certainty according to the Brighton Collaboration Case Definition.[4] The conclusion was that the case partly met the case criteria for multisystem inflammatory syndrome but did not have exposure history and had temporal association with COVID-19 vaccination. The PRNT result was positive at 1:548 (limit: >1:10); and the ELISA positive at 61.8% (limit: >30%).

MATERIALS AND METHODS

We searched PubMed for eligible clinical reports and surveillance data on MIS-V through March 6, 2022. Titles, abstracts, and full-length texts in English were screened for eligible articles using "multisystem inflammatory syndrome" as a MeSH search term OR "pediatric inflammatory multisystem syndrome" OR "paediatric inflammatory multisystem syndrome" OR "MIS-C" OR "PIMS-TS" AND "vaccine" OR "vaccination" OR "immunization" OR "immunisation" in all search fields. We excluded adult-onset cases (defined as >18 years of age), duplicate and nonclinical publications. We extracted and collated relevant data in accordance with Preferred Reporting Items for Systematic Reviews and

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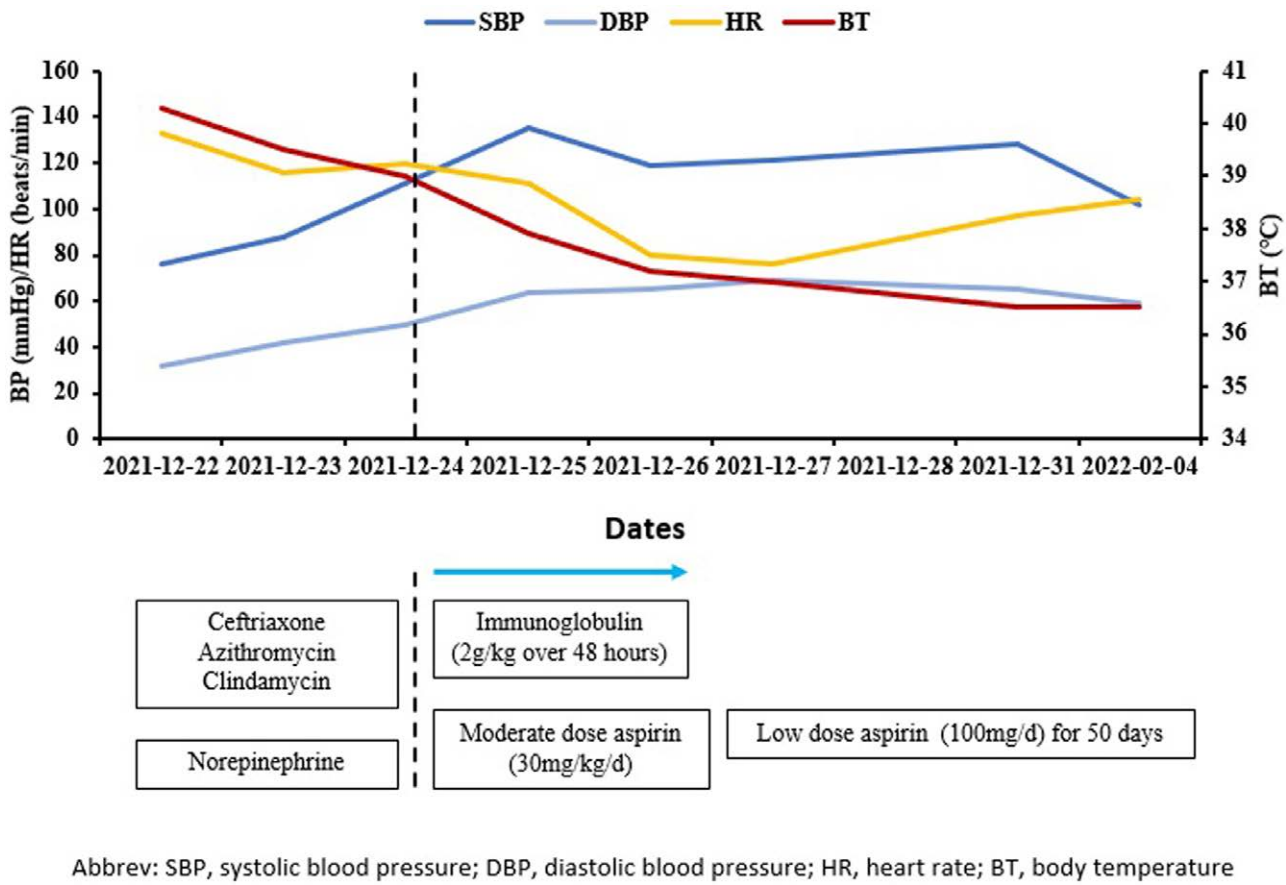

FIGURE 1. Clinical course of the case-patient of multisystem inflammatory syndrome in children following COVID-19 vaccination.

Meta-Analyses (PRISMA) guidelines. Specifically, we recorded age, sex, month and year of onset, type, doses of COVID-19 vaccines, interval since vaccination, geographic site of report, comorbidities, symptoms and signs, treatment regimen, and outcome. For case ascertainment, we used the Brighton Collaboration Case Definition to assess each case with available clinical and laboratory information reported.[4]

RESULTS

We identified 9 reports that met the inclusion criteria (Figure 2). The publications included 7 case reports,[5–11] 1 surveillance report,[12] and 1 case-control study.[13] Among 8 cases of MIS-C following COVID-19 vaccination including our case, 6 were males, and 4 had underlying comorbidities (Table 1). The broad geographic distribution of cases included 2 patients identified in United States,[8,10] 2 in Europe,[6,7] 2 in Middle East,[5,10] 1 in New Zealand,[9] and 1 in South Korea. Six case-patients had symptom onset after their second dose of COVID-19 vaccines, which were mostly BNT162b2 vaccine except for one case-patient had received mRNA1273 vaccine. The interval between vaccination and onset of symptom ranged from 2 days to 10 weeks. None of the case-patients had exposure history or positive PCR of SARS-CoV-2; and 6 case-patients had positive antibody against SARS-CoV-2. All case-patients exhibited fevers and symptoms meeting criteria of MIS-C, and 4 case-patient had echocardiographic evidence of myocarditis or pericarditis. Seven case-patients received immunomodulatory therapy including IVIG or steroids, and all cases have recovered without significant sequelae or complications. All of the reported cases met level 1 of diagnostic certainty according to the Brighton Collaboration Case Definition, except for 1 case with Level 2b.

In the United States between December 2020 and August 2021, 21 children and adolescents with MIS-C after COVID-19 vaccination were identified[12]; in France between September and October 2021, among 107 children with MIS-C hospitalized, 7 had received one dose vaccination[13] (not in table).

DISCUSSION

Potentially significant MIS-C temporally associated with COVID-19 vaccines, although rare, may pose substantial diagnostic and therapeutic challenges. Our systematic review of the literature identified MIS-C followed by vaccination in only 36 pediatric case-patients, including the present case, across the globe. All cases had negative PCR tests, whereas most (7/8) had positive serological markers. All cases have had fevers and multi system involvement of clinical syndromes, and a sizeable proportion (50%) had myocarditis/pericarditis involvement, which emphasizes the importance of assessing the heart in pediatric patients with postvaccination MIS-C-like symptoms. All case-patients improved after 5–14 days of hospitalization.[14] Moreover, given the incidence of MIS-C is estimated approximately 200 per one million children after having SARS-CoV-2 infection; the estimated incidence of MIS-C temporally associated with COVID-19 vaccination is notably low at 1.0 case per one million children after receiving vaccines.[15,16]

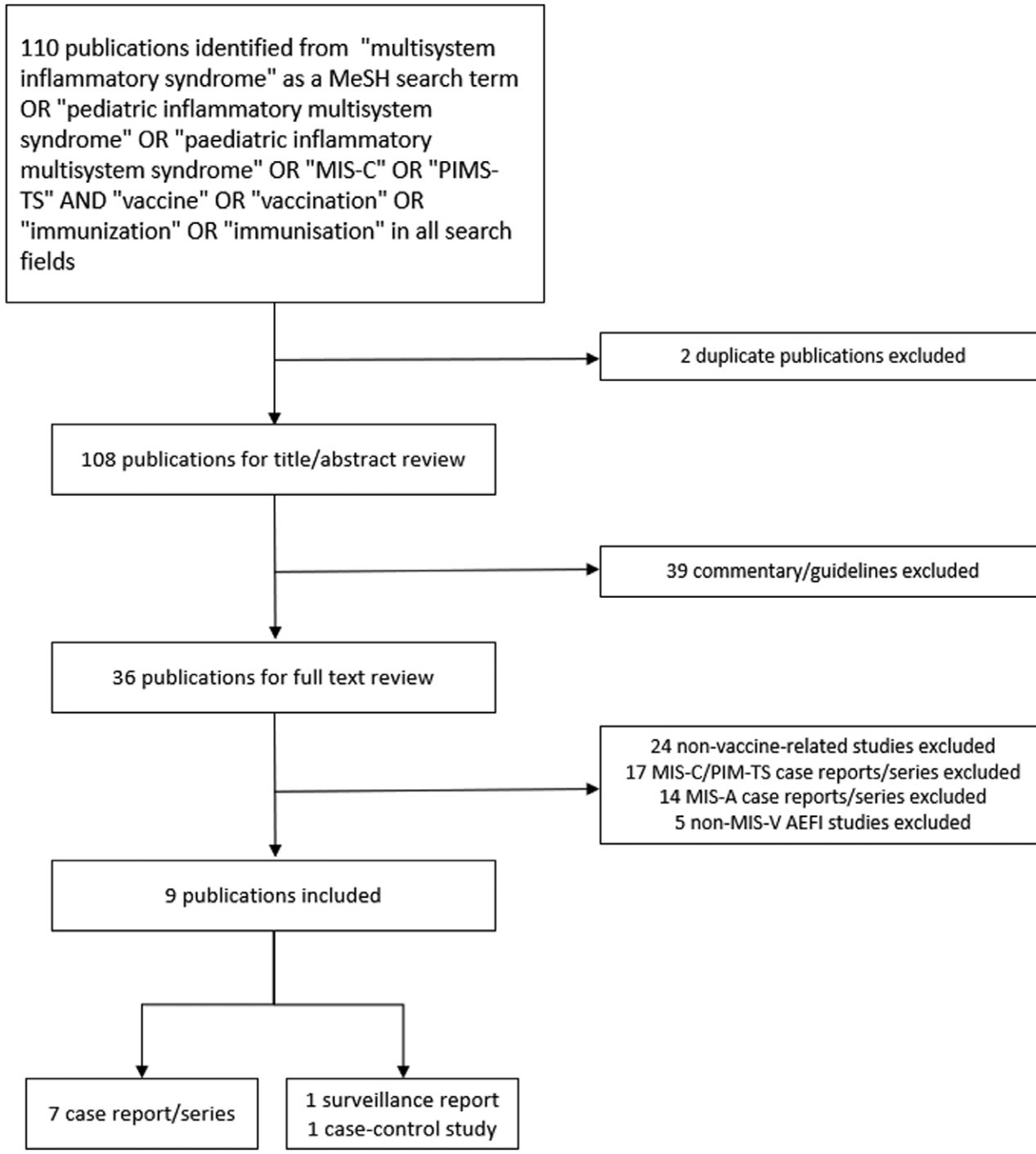

FIGURE 2. Results of literature search and identification of studies according to the PRISMA. PRISMA indicates Preferred Reporting Items of Systematic Reviews and Meta-Analyses.

No evidence-based guidelines for treatment of MIS-C following COVID-19 vaccination exist because there are only handful of case reports as of this point, and no randomized controlled trials have been conducted to optimize choice of immunomodulators or duration of therapy. Most cases had followed either World Health Organization or American College of Rheumatology guidelines for MIS-C,[17] and have described rapid improvement of symptoms and signs following initiation of the therapy.

Our findings are subject to number of limitations. First, SARS-CoV-2 exposure history of each case remains uncertain, as in the case we presented. Second, given the vaccines were prioritized to high-risk pediatric patients, the background population between MIS-C following SARS-CoV-2 infection versus vaccination differs; therefore, the results should be interpreted cautiously. There are atypical features of the reported patients in comparison to typical clinical features of MIS-C cases. For instance, 2 cases have

TABLE 1. Systematic Review of Reported Cases of Multisystem Inflammatory Syndrome in Children Following COVID-19 Vaccination

	Case-patient				Vaccination				SARS-CoV-2			Clinical findings				
Ref.	Age	Sex	Comorbidity	Country	Type	Dose	Month/ year	Interval	h/o exposure	PCR	SARS-CoV-2 Ab	Initial symptoms and signs	Presence of myocarditis	Hospital course	Outcome	BCCD
Hugh McGann et al[9]	16	Male	h/o septic arthritis, aortic regurgitation	New Zealand	BNT162b2	First	September 2021	12 days	Not reported	Negative	Positive IgM and IgG anti-spike antibodies	Fever, upper abdominal pain, respiratory distress, rash	None	IVIG, steroids, ventilatory/ ICU care	Improved, discharged home 14 days after admission having made an excellent recovery	Level 1
Poussaint et al[10]	12	Male	Recent Lyme disease	United States	BNT162b2	Second	Not reported	2 days	Unidentified	Negative	(S protein) 19.83 IV	Fever, headache, vomiting, diarrhea, erythema migrans	Present	No specific immunomodulatories	Improved, discharged on hospital day 5	Level 2b
Yalçinkaya et al[11]	12	Male	None	Turkey	BNT162b2	First	Not reported	27 days	Unidentified	Negative	(S protein) >257 BAU/mL	Fever, eye redness, diarrhea, neck pain/swelling	Not reported	IVIG, Steroids	Improved, discharged 5 days with no sequela or complication	Level 1
DeJong et al[8]	14	Female	Sickle cell disease on hydroxyurea	USA	BNT162b2	Second	Not reported	2 months	Unidentified	Negative	Not reported	Fever, malaise, abdominal symptoms	None	IVIG, Steroids, ICU care	Improved, discharged home in good condition after 7 days	Level 1
Abdelgalil et al[5]	12	Male	None	Saudi Arabia	BNT/162b2 and mRNA1273	Second	Not reported	5 weeks	Not reported	Negative	(S protein) >65680 IU/mL	Fever, eyes redness, rash, fatigue, abdominal pain	Present	IVIG, ASA	Improved, returned to premorbid baseline except mild fatigue	Level 1
Buchhorn et al[6]	18	Male	h/o HIE, epilepsy on AEDs	Germany	BNT162b2	Second	February 2021	10 weeks	Not reported	Negative	Positive	fever, hypotension	Present	IVIG, colchicine, ibuprofen	Improved, no effusions in EchoCG	Level 1
Chai et al[7]	17	Male	None	Denmark	BNT162b2	Second	Not reported	5 days	Not reported	Negative	Not reported	Fever, vomiting, myalgia and chest pain	Present	IVIG, Steroids, ICU care	Improved, with no obvious clinical sequelae	Level 1
Case	15	Female	None	South Korea	BNT162b2	Second	December 2021	5 days	Unidentified	Negative	Positive	fever, headache, sore throat, abdominal pain	None	IVIG	Improved	Level 1

AED indicates antiepileptic drug; ASA, acetylsalicylic acid; BCCD, Brighton Collaboration Case Definition; EchoCG, echocardiography; h/o, history of; HIE, hypoxic ischemic encephalitis; ICU, intensive care unit; IVIG, intravenous immunoglobulin.

underlying comorbidities and only half of these reported patients have echocardiographic evidence of myocarditis or pericarditis, which are unusual in typical MIS-C cases. More importantly, all cases reported here only have temporal association between vaccine and the event; therefore, the result should not hinder the intention to vaccinate children against SARS-CoV-2, especially in the high-risk children. The serologic results do not distinguish between SARS-CoV-2 infection and COVID-19 vaccination and thus adds nothing to the causality assessment in each case. There may be some cases are not true cases of MIS-C or where post-SARS-CoV-2 infection or exposure cannot be completely ruled out.

In conclusion, clinical and serological diagnosis, assessment of cardiac involvement, and prompt initiation of effective therapy are critical to provide optimal care for patients with rare MIS-C following COVID-19 vaccination in children.

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