

# Multisystem Inflammatory Syndrome after COVID-19 Vaccination (MIS-V) Presenting with Retropharyngeal Phlegmon in a 15-year-old Boy in Japan

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**Abstract** Our case report presents a young patient vaccinated for coronavirus disease 2019 (COVID-19) who developed multisystem inflammatory syndrome in children (MIS-C), which was later confirmed to be multisystem inflammatory syndrome after vaccination (MIS-V). 15-year-old boy previously infected by COVID-19 who received the first dose of COVID-19 vaccine 50 days later and developed fever, lethargy, headache, diarrhea, nausea, lip swelling, neck pain, and dysphagia. Contrast-enhanced computed tomography revealed a low absorption area with no contrast effect was observed in the posterior pharyngeal gap suggesting retropharyngeal phlegmon. He was diagnosed to be MIS-V level 2 based on the Brighton Collaboration Case Definition and improved by Intravenous immunoglobulin (IVIG). The frequency of neck symptoms in MIS-V is higher than in other febrile diseases, and many cases of retropharyngeal phlegmon are observed. In addition, pediatric COVID-19 is mostly asymptomatic or mild; therefore, it is predicted that children who are unaware of their history of COVID-19 before vaccination are not rare. Therefore, after vaccination, extra care should be required to development of MIS-V in children.

**Keywords:** COVID-19, vaccine, MIS-C, neck pain, dysphagia, adverse event following immunization, child

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## 1. Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a disease that causes severe systemic inflammation across multiple organ systems, which appears 2-6 weeks after contracting coronavirus disease 2019 (COVID-19) [1,2]. The Centers for Disease Control and Prevention (CDC) [3] and World Health Organization (WHO) [4] have defined the trigger for the onset of MIS-C as previous infection of, or close contact with, COVID-19. With the recent widespread use of COVID-19 vaccines for individuals aged 12 years and older, some cases of MIS-C have developed after vaccination and are reported as multisystem inflammatory syndrome after vaccination (MIS-V) [5,6,7]. However, it is currently unclear whether MIS-C develops after COVID-19 vaccination. Hence, it is necessary to evaluate and analyze MIS-C cases with unified criteria.

Some MIS-C patients present with retropharyngeal phlegmon, which is found in inflammatory diseases such as Kawasaki disease [8,9,10]. This presentation is thought to be a symptom of systemic inflammatory diseases; however, we recently encountered a pediatric case of

MIS-V accompanied by retropharyngeal phlegmon. Based on our experience with this case and the discussion in this report, we propose that retropharyngeal phlegmon can be considered as one of the symptoms of MIS-V.

## 2. Case Presentation

Our patient was a 15-year-old boy previously infected by COVID-19. He initially presented with fever and a mild sore throat. His COVID-19 infection was confirmed as positive by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) real-time reverse transcriptase-polymerase chain reaction test from a nasopharyngeal swab. The symptoms resolved spontaneously in a few days without exacerbation. He received the first dose of COVID-19 messenger RNA vaccine (Moderna) 50 days later. Vaccination was administered on the left upper arm; immediately after administration, the patient felt pain at the vaccination site.

On post-vaccination day 1, the patient developed fever (temperature 39°C), lethargy, headache, diarrhea, nausea, lip swelling, and right neck pain. On post-vaccination day 4, he sought medical consultation because his systemic conditions were exacerbated, his fever continued with a

temperature of 39.8°C, no symptom improvement occurred, and he experienced a loss of appetite.

On admission, the patient's temperature was 39.6°C, heart rate was 96 beats/minute, blood pressure was 103/50 mmHg, respiratory rate was 18 breaths/minute, and oxygen saturation was 98% on room air. Bilateral conjunctival hyperemia, lip swelling, dysphagia, right neck pain, and right cervical lymphadenopathy were observed; however, redness at the Bacillus Calmette-Guérin vaccination scar and distal lower and upper limb edema were not observed. Chest auscultation revealed no abnormal breath sounds bilaterally and no heart murmur. The abdomen was flat and soft without spontaneous pain or tenderness, and no splenohepatomegaly was detected.

On examination, the white blood cell count was 4440/ $\mu$ L; neutrophil count was 3472 / $\mu$ L; lymphocyte count decreased to 648/ $\mu$ L; C-reactive protein (CRP) and erythrocyte sedimentation rate (in 1 hour) increased to 7.83 mg/dL and 60 mm, respectively; procalcitonin was 0.20 ng/mL; ferritin was 239 ng/mL; and interleukin 6 was 36.7 pg/mL. Prolongations were noted in activated partial thromboplastin time of 39.4 sec, partial thromboplastin time of 14.7 sec, and prothrombin time-international normalized ratio of 1.23. Also, fibrinogen was increased to 506 mg/dL, and d-dimer was increased to 1.72  $\mu$ g/mL. No liver dysfunction and renal dysfunction were observed. No abnormalities were noted in echocardiogram and electrocardiogram, and N-terminal pro-brain natriuretic peptide was 18 pg/mL, with no increase observed. Reverse transcription polymerase chain reaction detection of SARS-CoV-2 from a nasopharyngeal swab was negative on admission, and the patient had both positive nucleocapsid SARS-CoV-2 immunoglobulin G and spike glycoprotein immunoglobulin G (>1160 IU/ml) later.



**Figure 1.** A low absorption area with no contrast effect was observed in the posterior pharyngeal gap

On admission, considering the possibilities of MIS-C, Kawasaki disease, and bacterial infection, cefotaxime was initiated at 2 g/day. On hospital day 3, the patient's right

neck pain and dysphagia, and neck contrast-enhanced computed tomography was performed. A low absorption area with no contrast effect was observed in the posterior pharyngeal gap (Figure 1). Treatment response to cefotaxime was poor, with white blood cell count of 3590/ $\mu$ L and CRP of 7.64 mg/dL. However, as at the patient's initial presentation, rash and distal lower and upper limb edema were not observed. Kawasaki disease was not diagnosed, and the patient was subsequently diagnosed with MIS-C.

Intravenous immunoglobulin (IVIG) was initiated at 1 g/kg/day, and oral aspirin was started at 200 mg (3 mg/kg/day). By hospital day 4, the patient's fever had subsided, and the inflammatory response was decreasing; hence, no additional IVIG was administered. The patient subsequently recovered without relapse. On hospital day 8, blood tests showed that inflammatory response was almost negative (CRP 0.51 mg/dL). On hospital day 9, an echocardiogram revealed no coronary artery dilatation and no pericardial effusion. In addition, blood culture and throat culture were negative. Therefore, the patient was discharged on hospital day 10. Only the oral aspirin was continued as an outpatient medication. Follow-up echocardiograms also showed no coronary artery dilatation and pericardial effusion.

### 3. Discussion

The term MIS-V describes MIS-C that develops after COVID-19 vaccination. The Brighton Collaboration Case Definition has established parameters for case definition and diagnostic certainty to evaluate MIS-C based on unified criteria. According to these criteria, cases with fever persisting for 3 days or more, two or more clinical symptoms (mucocutaneous, gastrointestinal, shock/hypotension, and neurologic), inflammatory test findings, two or more findings of disease activity, and history of exposure to COVID-19 or history of COVID-19 vaccination are defined to be a definitive case, categorized as MIS-C level 1. Based on combined findings, the MIS-C levels 2-5 are defined as follows: level 2 is a probable case, level 3 is a possible case, level 4 is insufficient evidence, and level 5 is not a case of MIS-C. The current case was considered to be a probable case, level 2. These criteria do not consider the timing of COVID-19 vaccination and MIS-C onset. Similar to previous infection, MIS-V is predicted to develop within 4-6 weeks after vaccination [11].

Currently, MIS-C occurring after vaccination has been reported as MIS-V, and seven cases of MIS-V, including the current case, have been reported to date [5,6,12,13] (Table 1). The patient age of onset ranged from 15 to 40 years; most patients were young, with four cases involving patients in teens. Time to onset was a median of 12 days (1-70 days), which is shorter when compared with previous infection. With regard to the onset trigger, COVID-19 infection preceded MIS-V onset in three cases, including the current case. Four patients developed it after the first dose of vaccine, and three developed it after the second dose of vaccine.

**Table 1. Cases of Multisystem inflammatory syndrome after vaccination (MIS-V)**

Age	Sex	Symptoms	Previous COVID-19	First vaccine	Second vaccine	RT-PCR	Plasma IgG antibody
44yr [13]	F	Fever, chest pain, bilious vomiting, loose stools, rash	NA	2 d before	NA	Negative	Negative
40yr [6]	M	Fever, headache, neck pain, malaise, diarrhea, lethargy	34 d before	42 d before	4 d before	Positive	Positive*
20yr [6]	F	Fever, rash, diarrhea, vomiting, cardiogenic shock, acute renal failure	NA	12 d before	NA	Positive	Positive*
18yr [6]	M	Fever, headache, abdominal pain, diarrhea, vomiting	43 d before	19 d before	NA	Negative	Positive*
18yr [5]	M	Fever, hypotension	NA	NA	10w before	Negative	Positive
17yr [12]	M	Fever, headache, lethargy, diarrhea, vomiting, myalgias, rash, cardiogenic shock, acute renal failure	NA	NA	5 d before	Negative	Positive <sup>†</sup>
15yr (Current)	M	Fever, headache, lethargy, neck pain, dysphagia, diarrhea, vomiting	50 d before	1 d before	NA	Negative	Positive* <sup>†</sup>

\*Nucleocapsid SARS-CoV-2 immunoglobulin G, <sup>†</sup>spike glycoprotein immunoglobulin G, NA, not applicable.

Recently, MIS-V has caught much attention as an adverse event following immunization (AEFI) [11]. It has been pointed out that mild to moderate symptoms similar to those of influenza and COVID-19 may develop within a few days in 1 of 15 individuals after COVID-19 vaccination [14]. The frequency of systemic symptoms caused by the first dose of the COVID-19 vaccine was 2-9 times higher in individuals previously infected by COVID-19 than in individuals with no previous infection, and the frequency tended to be higher in women and young people [15,16].

In previously infected individuals, spike glycoprotein immunoglobulin G antibody titers after the first dose of COVID-19 vaccine were significantly higher than those who had not been previously infected, and one dose of vaccine could maintain antibody titers equivalent to those produced after the second dose of vaccine [17,18,19]. Based on these findings, it has been pointed out that the increase in reactivity may be related to the increase in immunogenicity [15]. Furthermore, it is believed that the cytokine storm associated with immune dysregulation caused by the preceding asymptomatic or symptomatic COVID-19 infection, as well as overreaction of the immune system, may cause multiple organ failure [6]. The current case was confirmed to be positive for nucleocapsid SARS-CoV-2 immunoglobulin G and to have previously been previously infected; in addition, the spike glycoprotein immunoglobulin G titer increased (>1160 IU/ml) after the first dose of vaccine. Also, the patient was young (age 15 years), which is also considered to be a risk factor.

The clinical symptoms of MIS-V are similar to those of MIS-C, namely fever, mucocutaneous, gastrointestinal, shock/hypotension, and neurologic symptoms (Table 1) [3,4]. No cases of MIS-C after previous infection presented with retropharyngeal phlegmon accompanied by neck pain and dysphagia, which were found in the current case. With regard to retropharyngeal lesions, 39 of 137 individuals (28.5%) diagnosed with MIS-C reported neck symptoms, whereas diagnosis on imaging by computed tomography or magnetic resonance imaging revealed retropharyngeal phlegmon in four individuals [8]. In addition, in a study comparing patients with febrile illnesses, such as gastroenteritis and upper respiratory tract inflammation, and MIS-C, the frequency of neck pain was significantly higher in the MIS-C group than in the febrile illness group (OR 536.5, 95%CI [2.23-129,029]) [20]. The pathophysiology has not been elucidated yet; however, it is believed that enhanced vascular permeability associated with excessively produced inflammatory cytokines and the activation of lymphoid cells thickens the soft tissues of the

posterior pharynx [21,22]. In MIS-C, the frequency of neck-associated symptoms is high, and these symptoms may be accompanied by retropharyngeal phlegmon; notably, these symptoms may also be observed in MIS-V. As far as we have investigated, there is no case of MIS-V with retropharyngeal phlegmon to the best of our knowledge, and our report is the first.

If the target age range for COVID-19 vaccination is extended in the future to include children aged 5 years, it is necessary to watch the trend of the onset of MIS-V in children. Pediatric COVID-19 is mostly asymptomatic or mild; therefore, it is predicted that children who are unaware of their history of COVID-19, which is an onset risk for MIS-V, before vaccination are not rare. In addition, it is expected that MIS-V will be considered an AEFI; thus, it is necessary to evaluate symptoms that appear after COVID-19 vaccination based on unified criteria and to avoid refraining from vaccination.

## 4. Conclusion

This case report describes our experience with a pediatric patient who developed MIS-V with retropharyngeal phlegmon after previously contracting COVID-19. It is anticipated that our report will play an important role in identifying the clinical characteristics of MIS-V and that it can contribute to establishing appropriate diagnosis and treatment methods.

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