

SARS-CoV-2 infection may not be a prerequisite for developing multisystem inflammatory syndrome in children

Sirs,

While reviewing the literature on multisystem inflammatory syndrome in children (MIS-C), the most serious paediatric disease related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1, 2), we found an interesting case report by Song *et al.* (3). The authors reported a 5-year-old girl with Kawasaki disease (KD) shock syndrome who showed lung consolidation with pleural effusion and abdominal pain mimicking appendicitis. It would have been difficult to diagnose and treat the patient, because the co-occurrence of respiratory and gastrointestinal manifestations is uncommon in KD or KD shock syndrome (2, 3). Here, we wish to make some comments on the importance of SARS-CoV-2 in the development of MIS-C by presenting our own experience.

An 11-year-old boy was hospitalised with a 4-day history of fever and abdominal pain. Abdominal computed tomography (CT) ruled out appendicitis, but blood tests showed elevated C-reactive protein and procalcitonin levels. The patient was given empiric antibiotics for 3 days. However, his symptoms persisted and he suddenly developed hypotension. Suspected of septic shock, he was transferred to the intensive care unit. The next day, typical symptoms of KD appeared, such as conjunctivitis, cracked lips, and strawberry tongue. At that point, MIS-C could be included in the diagnostic considerations. Comparing the clinical characteristics of our patient with those of Song *et al.*'s patient, there are interesting similarities and differences (Table I). Both patients showed KD-like features, hypotension, myocardial dysfunction with coronary abnormalities, coagulopathy, and gastrointestinal problems. Lung consolidation and pleural effusion were confirmed on chest CT of both patients. For treatment, our patient received one dose of intravenous immunoglobulin (IVIG), and Song *et al.*'s patient received two doses of IVIG and corticosteroids. Our patient was confirmed to be infected with SARS-CoV-2 and was reported as the first case of MIS-C in the Republic of Korea (4). Song *et al.*'s patient fully met the case definitions of MIS-C, with

Table I. Comparison of clinical characteristics between Song *et al.*'s patient and our patient.

	Song <i>et al.</i> 's patient	Our patient
WHO case definitions for MIS-C		
Patients 0-19 years old, AND ≥2/5 following:	5-year-old girl	11-year-old boy
i) KD-like features*	+	+
ii) Hypotension or shock (BP, mmHg)	+(70/30)	+(66/36)
iii) Myocardial dysfunction (pro-BNP, ng/L)	+(2,464)	+(3,131)
Coronary abnormalities (LAD, mm)	+(3.7)	+(3.8)
iv) Evidence of coagulopathy	+	+
v) Gastrointestinal problems [†]	+	+
AND Elevated markers of inflammation	+	+
AND No other obvious microbial cause	+	+
AND Evidence of SARS-CoV-2 infection	NA	+
Other important findings		
Chest CT (consolidation and pleural effusion)	+	+
Hemodynamic support	+	+
IVIG and aspirin therapy	+	+
Corticosteroid therapy	+	-
When the case was reported	Before COVID-19 outbreak	After COVID-19 outbreak

WHO: World Health Organization; MIS-C: multisystem inflammatory syndrome in children; KD: Kawasaki disease; BP: blood pressure; pro-BNP: prohormone of brain natriuretic peptide; LAD: left anterior descending coronary artery; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; NA: not available; CT: computed tomography; IVIG: intravenous immunoglobulin; COVID-19: coronavirus disease 2019.

*Fever, conjunctivitis, oropharyngeal inflammation, skin rash, changes of the extremities, or cervical lymphadenopathy. [†]Both patients underwent abdominal CT to rule out appendicitis.

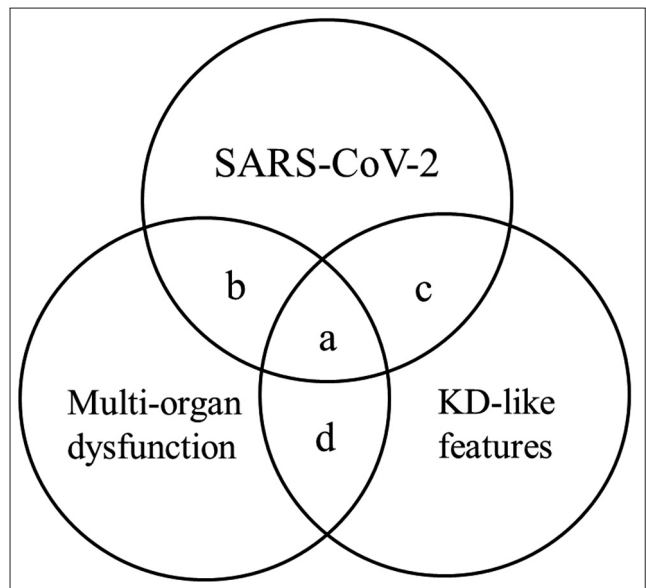
$$a. \text{ SARS-CoV-2 } \times \left(\text{Inflammatory response} + \text{Host susceptibility} \right) = \text{COVID-19}$$

$$b. \left(\text{SARS-CoV-2} + \text{Inflammatory response} \right) \times \text{Host susceptibility} = \text{MIS-C}$$

Fig. 1. Importance of SARS-CoV-2 and host susceptibility in the pathogenesis of clinical syndromes. a. COVID-19 does not occur without SARS-CoV-2, but can occur without host susceptibility; b. MIS-C does not occur without host susceptibility, but could occur without SARS-CoV-2.

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 2019; MIS-C: multisystem inflammatory syndrome in children.

Fig. 2. Potential MIS-C phenotypes determined by the combination of SARS-CoV-2, KD-like features, and multi-organ dysfunction. a. SARS-CoV-2 (+), multi-organ dysfunction (+), KD-like features (+); b. SARS-CoV-2 (+), multi-organ dysfunction (+), KD-like features (-); c. SARS-CoV-2 (+), multi-organ dysfunction (-), KD-like features (+); d. SARS-CoV-2 (-), multi-organ dysfunction (+), KD-like features (+). MIS-C: multisystem inflammatory syndrome in children; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; KD: Kawasaki disease.



the exception of the evidence of SARS-CoV-2 infection. The most important difference between the two cases was when the case was reported. Song *et al.*'s patient was reported prior to the coronavirus disease 2019 (COVID-19) outbreak,

but our patient was reported after the outbreak.

The causal relationship between SARS-CoV-2 infection and MIS-C remains uncertain (5). However, most experts agree that MIS-C can be developed when the

immune system of genetically susceptible hosts is triggered by SARS-CoV-2 (1, 6). The importance of SARS-CoV-2 and host susceptibility in the pathogenesis of COVID-19 may differ from that of MIS-C. COVID-19 does not occur without SARS-CoV-2, but can occur without host susceptibility (Fig. 1a). Conversely, MIS-C does not occur without host susceptibility, but could occur without SARS-CoV-2 (Fig. 1b). In practice, pathogens other than SARS-CoV-2 have been identified in patients with clinical features of MIS-C (7, 8). In other words, SARS-CoV-2 infection may not be a prerequisite for developing MIS-C.

MIS-C is a syndrome complex with a wide spectrum of phenotypes (6). The MIS-C phenotype is determined by a combination of SARS-CoV-2, KD-like features, and multi-organ dysfunction (5). There are two types of MIS-C related to SARS-CoV-2 (9). One meets the criteria for both MIS-C and KD (Fig. 2a), and the other meets the criteria for MIS-C but not the criteria for KD (Fig. 2b). The clinical manifestations of Fig. 2c can be aggravated to those of Fig. 2a. With the exception of evidence of SARS-CoV-2 infection, the clinical manifestations of Fig. 2d (Song *et al.*'s patient) are the same as those of Fig. 2a (our patient). It is important to confirm the presence of SARS-CoV-2 in patients with KD-like features or in those with multi-organ dysfunction. However, therapeutic agents for MIS-C such as IVIG, corticosteroids, or biologics, should be determined based

on the severity of inflammation rather than the presence of SARS-CoV-2 (10). MIS-C unrelated to SARS-CoV-2 was reported before the COVID-19 outbreak and has been identified during the COVID-19 pandemic. Therefore, it is necessary to monitor whether MIS-C persists after the COVID-19 pandemic is over. Understanding the relationship between SARS-CoV-2 and MIS-C will provide useful clues for studying the pathogenesis of KD as well as MIS-C.

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