Should multisystem inflammatory syndrome in children be considered occult macrophage activation syndrome?

Sir,

Although the pandemic has officially ended, sporadic outbreaks of COVID-19 continue to occur, and paediatricians may still encounter multisystem inflammatory syndrome (MIS-C) in children (1-3). MIS-C is a serious complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, characterised by systemic inflammation, organ dysfunction, and an infectious trigger (4-6). Interestingly, many patients with MIS-C exhibit 'Kawasaki disease (KD)-like symptoms', including rash, conjunctivitis, and mucositis (6). However, these symptoms sometimes lead to diagnostic confusion. For example, it can be difficult to distinguish MIS-C from other hyperinflammatory diseases with KD-like symptoms, such as atypical KD, Kawasaki disease shock syndrome (KDSS), or Kawasaki disease complicated by macrophage activation syndrome (KD/MAS) (7-10). Among the KD-like hyperinflammatory diseases, including MIS-C, KD/MAS is considered the most severe in terms of systemic inflammation and organ dysfunction (2, 8).

In children, the most common cause of macrophage activation syndrome (MAS) is systemic juvenile idiopathic arthritis (SJIA) (11). MAS also occurs in other autoimmune or autoinflammatory diseases, including systemic lupus erythematosus (SLE) and KD (12, 13). During the COVID-19 pandemic, MIS-C has emerged as an important cause of paediatric MAS (4, 5). Early diagnosis and timely treatment of MAS in MIS-C patients are crucial because the clinical course of MIS-C with MAS is more severe than that of MIS-C without MAS (3). This brief report aims to compare the characteristics of MIS-C with and without MAS to identify clinical clues for early recognition of MAS in patients with MIS-C. It also explores the similarities and differences between KD, MIS-C, KDSS, and KD/MAS.

This retrospective study reviewed the medical records of 22 patients hospitalised with MIS-C from January 2020 to December 2022 at four hospitals in Korea (9). MIS-C was diagnosed using the case definition of the Council of State and Territorial Epidemiologists/Centres for Disease Control and Prevention (CSTE/CDC) (6). Diagnosis of MAS was based on the 2016 classification criteria for MAS secondary to SJIA (SJIA/MAS) (2, 8). During hospitalisation, all patients underwent baseline testing for MIS-C (*e.g.*, blood, echocardiography, or SARS-CoV-2) and were treated with one or more immunomodulators (*e.g.*, intravenous immunoglobulin [IVIG] or steroids).

Table I. Comparison of characteristics between MIS-C with MAS group and MIS-C without MAS group.

	MIS-C with MAS (n=11)	MIS-C without MAS (n=11)	*p* value*
Clinical findings			
Sex, male	5 (45.5)	6 (54.5)	1.000
Age, years	9.1 (4.1–16.0)	9.5 (0.9–12.0)	0.699
Fever duration, days	5.0 (3.0–15.0)	5.0 (3.0–10.0)	0.917
KD-like features: rash, conjunctivitis, or mucositis	9 (81.8)	9 (81.8)	1.000
Splenomegaly ± hepatomegaly	6 (54.5)	1 (9.1)	0.063
IVIG resistance (*i.e.*, initial treatment failure)	5 (45.5)	2 (18.2)	0.361
Laboratory findings			
CRP, mg/dL	13.8 (3.2–25.5)	5.1 (3.3–9.4)	0.130
Albumin, g/dL	2.8 (2.5–3.2)	3.4 (2.3–4.1)	0.048
Ferritin, ng/mL	1,145 (690–10,364)	286 (148–443)	<0.001
Platelet count, $10^3/\mu L$	103 (62–431)	181 (103–389)	0.010
AST, U/L	52 (40–579)	57 (33–94)	0.843
Hypertriglyceridemia or hypofibrinogenemia	8 (72.7)	9 (81.8)	1.000
Organ dysfunction			
Cardiac: EF < 55%, CAAs, or elevated Tn	8 (72.7)	4 (36.4)	0.198
Shock or hypotension	6 (54.5)	0 (0.0)	0.012
Gastrointestinal involvement	11 (100.0)	9 (81.8)	0.476
Haematology: thrombocytopenia or lymphopenia	10 (90.9)	7 (63.6)	0.311
Other organs: neurologic, renal, or musculoskeletal	6 (54.5)	0 (0.0)	0.012
Evidence of SARS-CoV-2 infection	11 (100.0)	11 (100.0)	1.000

Data are presented as frequency (%) or median (range).
MIS-C: multisystem inflammatory syndrome in children; MAS: macrophage activation syndrome; KD: Kawasaki disease; IVIG: intravenous immunoglobulin; CRP: C-reactive protein; AST: aspartate transaminase; EF: ejection fraction; CAA: coronary artery abnormalities; Tn: troponin; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
*Fisher's exact test was used to compare categorical variables, and the Mann-Whitney *U* test was used to compare continuous variables.

Of the patients with MIS-C, 50% (11/22) met the 2016 MAS criteria. Table I compares the characteristics of the MIS-C with MAS group (n=11) and those of the MIS-C without MAS group (n=11). Male proportion and median age did not differ between the two groups. All patients in both groups showed persistent fever, and most patients (82%) had KD-like symptoms. Splenomegaly (p=0.063) and IVIG resistance (p=0.361) were more common in the MIS-C with MAS group than in the MIS-C without MAS group. Laboratory abnormalities observed in both groups included anaemia, lymphopenia, elevated C-reactive protein, increased hepatic transaminase levels, hypertriglyceridemia, and hypofibrinogenemia. Compared to the MIS-C without MAS group, the MIS-C with MAS group had higher ferritin levels (p<0.001) and lower platelet counts (p=0.010) and albumin levels (p=0.048). All patients in the two groups presented with multi-organ dysfunction, such as cardiac, gastrointestinal, or hematologic involvement. Shock (p=0.012) and other organ involvement (p=0.012) were more common in the MIS-C with MAS group than in the MIS-C without MAS group. Evidence of SARS-CoV-2 infection was demonstrated in all patients in the two groups according to the CSTE/CDC definition (6). There were no deaths observed in either group.

In April 2020, Verdoni *et al*. (14) reported the first case series of MIS-C. They found that 50% (5/10) of patients met the 2016 MAS criteria and had more severe clinical and laboratory features than MIS-C patients who did not meet the criteria, which is very similar to the results of the present study. A recent study by Gámez-González *et al*. (3) showed that a considerable number of MIS-C patients (17%, 212/1238) presented with MAS-like features and fulfilled the 2016 MAS criteria. One possible explanation for the unexpectedly high frequency of MAS in MIS-C is that MIS-C and MAS may share not only clinical phenotypes but also underlying pathogenic mechanisms (8). According to immunologic analysis (15), interferon-gamma (IFN-γ) and IFN-γ-related cytokines, which play a central role in the pathogenesis of MAS,

	KD	MIS-C	KDSS	KD/MAS
Persistent fever	100%	100%	100%	100%
KD-like symptoms (e.g., rash or conjunctivitis)	100%	82%	100%	100%
Systemic inflammation (CRP ≥ 3.0 mg/dL)	81%	100%	100%	100%
Splenomegaly ± hepatomegaly	2%	32%	(Possible)	69%
Hyperferritinemia (> 684 ng/mL)	5%	50%	(Possible)	92%
Cardiac involvement, including CAAs	20%	54%	73%	46%
Shock or hypotension	1%	27%	100%	(Possible)
Gastrointestinal involvement	26%	91%	75%	(Possible)
Hematology (e.g., thrombocytopenia)	2%	77%	80%	87%
Evidence of SARS-CoV-2 infection	0%	100%	0%	0%
Mortality rate	0%	0%	7%	13%

Fig. 1. Comparative frequency of characteristics of KD-like hyperinflammatory diseases: KD (13), MIS-C (this study), KDSS (10), and KD/MAS (12).
KD: Kawasaki disease; MIS-C: multisystem inflammatory syndrome in children; KDSS: Kawasaki disease shock syndrome; KD/MAS: Kawasaki disease complicated by macrophage activation syndrome; CRP: C-reactive protein; CAAs: coronary artery abnormalities; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

were also the main drivers of the inflammatory response in MIS-C, and the levels of IFN-γ and cytokines increased proportionally with severity of MIS-C.

The concept of occult MAS is useful for early recognition of MIS-C complicated by MAS (MIS-C/MAS) (2). Occult MAS refers to an inflammatory state that does not fully meet the criteria for MAS but may progress to fulminant MAS (16). For example, if a patient with SJIA shows unexpected exacerbations despite appropriate management (*i.e.*, active SJIA), the patient should be considered to have occult MAS (11). Similarly, if a patient with KD develops IVIG resistance (*i.e.*, refractory KD), the patient should also be considered to have occult MAS (13). In fact, approximately 30% of active SJIA and about 7% of refractory KD cases progress to fulminant MAS (11, 13). MIS-C itself is a severe hyperinflammatory disease and the incidence of MAS in MIS-C has been reported to be 17% to 50% (3, 14), which is much higher than in other paediatric diseases such as SJIA (~10%), SLE (~5%), or KD (~2%) (9). Therefore, it is reasonable to consider MIS-C as occult MAS, similar to active SJIA and refractory KD.

Figure 1 illustrates the characteristics of KD-like hyperinflammatory diseases: KD (13), MIS-C (this study), KDSS (10), and KD/MAS (12). Approximately 7% of KD patients may experience shock, a form of organ dysfunction, and are diagnosed with KDSS (10). MIS-C is diagnosed when multi-organ dysfunction and SARS-CoV-2 infection are present in patients with systemic inflammation (6). KD/MAS is diagnosed when severe inflammation that meets the 2016 MAS criteria, including hyperferritinemia, is identified in patients with KD or KDSS (12). Similarly, MIS-C/MAS is diagnosed when severe inflammation that meets the 2016 MAS criteria is identified in patients with multi-organ dysfunction and SARS-CoV-2 infection (7). Understanding the relationship among these four diseases will be helpful in studying the pathogenesis and therapeutic strategies for KD-like hyperinflammatory diseases, including MIS-C. This study is limited by its retrospective design, small sample size, and lack of immunologic data. However, half of MIS-C patients met the 2016 MAS criteria, and some findings (*e.g.*, hyperferritinemia or shock) could be used as clues to detect MAS in MIS-C patients. To avoid overlooking MAS, we suggest that it is necessary to consider MIS-C as occult MAS.

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This study was approved by the Institutional Review Board of Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea (approval number: HC24RASI0025).

Competing interests: None declared.

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