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Review Article

Macrophage activation syndrome in Kawasaki disease: a literature review of Korean studies

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Macrophage activation syndrome (MAS) is a rare but potentially life-threatening complication of Kawasaki disease (KD). In Korea, many studies on KD have been reported, but there are only a few studies on MAS complicating KD (MAS-KD). This study was conducted to provide the characteristics of MAS-KD patients in Korea through a literature review. A total of 23 Korean patients with MAS-KD from 10 papers were included in this study. All MAS-KD patients met the hemophagocytic lymphohistiocytosis (HLH)-2004 criteria and/or the 2016 MAS criteria. The incidence of MAS-KD in Korean children was 0.8%~1.1%, which is relatively low compared to North America (1.9%). MAS-KD patients had lower rates of KD-related features and higher rates of incomplete KD, coronary artery abnormalities, and intravenous immunoglobulin resistance than patients with KD without MAS. Notable laboratory abnormalities in MAS-KD include anemia, neutropenia, thrombocytopenia, hypoalbuminemia, increased hepatic transaminase levels, and hyperferritinemia. For treatment of MAS-KD, the HLH-2004 protocol (i.e., 40 weeks of complex chemotherapy) was applied to 15 patients (65%), which is a significantly greater than those treated with this protocol in other countries (35%). Two patients (9%) died during the HLH-2004 protocol. In actual practice, MAS may be underrecognized in patients with KD. Clinical suspicion is paramount for early diagnosis and timely treatment.

Keywords: Macrophage activation syndrome, Kawasaki disease, Korea, Child

INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis of childhood, characterized by fever, conjunctivitis, oropharyngeal inflammation, skin rash, changes in the extremities, and cervical lymphadenopathy [1-3]. KD is the leading cause of acquired heart disease in children in developed countries and can lead to cardiovascular complications, including coronary artery abnormalities (CAAs) [4]. Fortunately, high-dose intravenous immunoglobulin (IVIG) administration in the acute phase of KD has been shown to achieve good results in reducing the prevalence of CAAs and controlling systemic inflammation [5,6]. However, 10%~20% of patients with KD do not respond to initial IVIG treatment and are at high risk of developing CAAs [7,8].

Although rare, KD patients may develop another important complication called macrophage activation syndrome (MAS) [9-11]. MAS, part of the spectrum of hemophagocytic lymphohistiocytosis (HLH), is a hyperinflammatory phenomenon characterized by fever, splenomegaly, cytopenia, and multi-organ dysfunction [12-15]. The term MAS was first used to describe a clinical syndrome of hemorrhagic, hepatic, and neurologic abnormalities in seven patients with systemic juvenile idiopathic arthritis (SJIA) [12]. Systemic lupus erythematosus is another important cause of MAS in children [13]. In recent studies, MAS has been increasingly reported in patients with KD, which has become the third most common cause of MAS in children [14].

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It is well known that KD occurs more frequently in East Asian countries, including Korea, Japan, and China, than in North America and Europe [3,4]. Therefore, the incidence of MAS complicating KD (MAS-KD) is expected to be high in East Asia proportional to the incidence of KD. However, there are only a few studies on MAS-KD in East Asia, especially Korea.

The purpose of this study was to conduct a literature review of Korean studies on MAS-KD and to describe the epidemiology, clinical manifestations, diagnosis, and treatment of these patients. Useful clues for early recognition of MAS-KD are also provided.

MAIN SUBJECTS

Literature review

A literature search was performed using keywords as follows: (hemophagocytic syndrome, hemophagocytic lymphohistiocytosis, or macrophage activation syndrome) AND (Kawasaki disease or mucocutaneous lymph node syndrome) AND (Korea, South Korea, or Republic of Korea). The databases searched were PubMed, KoreaMed, and Google Scholar. A total of 10 Korean studies, including 5 original articles and 5 case reports, was found [16-25]. A careful review of the 10 papers revealed

Table 1. MAS-related features, treatment, and outcomes of the 23 Korean patients with MAS-KD

Case no.*	Sex/age (yr)	Fever (day)	Splenomegaly	Hb/WBC/PLT†	TG↑ or FIB↓	Ferritin (ng/mL)	HPC	Treatment‡	Recovery
1	M/2	Y (18)	Y	Y/Y/Y	Y	463	Y	CS, VP-16	Y
2	M/4	Y (18)	Y	Y/-/-	-	2,831	Y	HLH-2004	Y
3	F/8	Y (8)	Y	-/-/Y	Y	3,632	Y	HLH-2004	-
4	M/6	Y (18)	Y	-/-/-	-	768	Y	HLH-2004	Y
5	F/14	Y (22)	Y	Y/Y/Y	Y	43,216	Y	HLH-2004	-
6	M/8	Y (7)	Y	-/-/-	Y	3,490	Y	HLH-2004	Y
7	M/3	Y (22)	-	Y/-/Y	-	20,000	Y	CS	Y
8	M/7	Y (3)	-	-/Y/Y	Y	3,200	Y	CS	Y
9	F/9	Y (8)	Y	-/-/Y	Y	20,000	Y	HLH-2004	Y
10	M/17	Y (20)	-	-/Y/-	Y	1,178	Y	HLH-2004	Y
11	M/1	Y (20)	Y	Y/Y/-	Y	3,946	-	HLH-2004	Y
12	F/3	Y (14)	Y	Y/Y/Y	-	6,647	Y	HLH-2004	Y
13	M/2	Y (7)	-	Y/-/Y	Y	463	Y	HLH-2004	Y
14	M/2	Y (20)	-	-/-/-	Y	590	Y	CS, IFX	Y
15	F/5	Y (11)	-	-/Y/Y	Y	2,329	Y	HLH-2004	Y
16	F/4	Y (25)	Y	-/-/-	Y	12,411	Y	HLH-2004	Y
17	M/0	Y (13)	Y	Y/-/-	Y	16,500	Y	HLH-2004	Y
18	F/0	Y (18)	-	-/Y/Y	Y	1,051	-	CS, 2nd IVIG	Y
19	M/2	Y (10)	Y	-/-/-	Y	5,310	Y	CS	Y
20	F/2	Y (12)	Y	Y/-/Y	Y	57,100	Y	CS, CSA	Y
21	M/7	Y (14)	Y	Y/Y/Y	Y	1,420	-	HLH-2004	Y
22	M13	Y (12)	Y	-/Y/Y	Y	790	NA	CS, 2nd IVIG	Y
23	F/1	Y (14)	Y	Y/Y/Y	Y	21,900	-	HLH-2004	Y

MAS: macrophage activation syndrome, MAS-KD: macrophage activation syndrome complicating Kawasaki disease, Hb: anemia, WBC: leukopenia or neutropenia, PLT: thrombocytopenia, TG↑ or FIB↓: hypertriglyceridemia (>156 mg/dL) or hypofibrinogenemia (≤360 mg/dL), HPC: hemophagocytosis, M: male, F: female, Y: yes or present, -: no or absent, NA: not available or not tested, CS: corticosteroids, VP-16: etoposide, HLH: hemophagocytic lymphohistiocytosis, IFX: infliximab, IVIG: intravenous immunoglobulin, CSA: cyclosporine A. *Data sources: case 1; Data from the article of Yun et al. (J Korean Pediatr Soc 2002;45:664-8) [16], cases 2~6; Kim et al. (Pediatr Hematol Oncol 2011;28:230-6) [18], cases 7~13; Kang et al. (Blood Res 2013;48:254-7) [19], cases 14~18; Roh et al. (Children (Basel) 2021;8:269) [22], cases 19~22; Rhee et al. (Children (Basel) 2022;9:1588) [23], and case 23; Lee et al. (Kawasaki Dis 2024;2:e4) [25]. †Cytopenia is defined as hemoglobulin <10.0 g/dL, leukocyte count <5.0×10^3/μL or neutrophil count <1.0×10^3/μL, and platelet count <110×10^3/μL. ‡Additional treatments other than initial IVIG and aspirin. The HLH-2004 protocol involves 40 weeks of complex chemotherapy, including CS, CSA, and VP-16.

that some patients were reported in both the original and case studies. After filtering out duplicate cases based on demographics and laboratory results (e.g., age or ferritin levels), 23 patients with MAS-KD were selected from the 10 papers and included in this study (data sources: case 1 [16], cases 2~6 [18], cases 7~13 [19], cases 14~18 [22], 19~22 from [23], and case 23 [25]). A Korean nationwide study on KD (n=14,916) [4] was used to compare data between MAS-KD and KD without MAS (i.e., typical KD). A systematic review of MAS-KD (n=69) by García-Pavón et al. [10] was used to compare data between Korea and other countries.

Epidemiology

Among the 23 MAS-KD patients analyzed, the median age was 4.0 (interquartile range, 0.4~8.0) years, and the male-to-female ratio was 1.6 (14/9). All patients met the diagnostic criteria for both KD [3] and MAS [26-28]. Two studies reported incidence rates of MAS in KD as follows: 0.8% (4/468) in Rhee et al. [23] and 3.2% (5/158) in Roh et al. [22]. Roh et al. [22] found that the incidence of MAS-KD was exceptionally high (3.2%) because their prospective study included only severe cases in which ferritin levels were tested. When severity was adjusted based on the rate of refractory KD, the incidence of MAS-KD was approximately 1.1%.

According to our investigation, the incidence of MAS-KD in Korea (0.8%~1.1%) is similar to that in China (1.1%, 8/719) [29] and low compared to that in North America (1.9%, 12/638) [30]. This difference in MAS-KD incidence may be due to racial differences; for example, in contrast to typical KD (i.e., KD without MAS), hyperinflammatory diseases with KD-related features, such as Kawasaki disease shock syndrome (KDSS) or coronavirus disease 2019 (COVID-19)-associated multisystem inflammatory syndrome in children (MIS-C), have been reported to be more common in North America and Europe than in East Asia [31-33]. Another explanation for the observed relatively low incidence of MAS-KD is the possibility that MAS is underrecognized in Korean KD patients. This may occur due to (1) the similar clinical and laboratory features between MAS and severe KD, (2) the absence of specific diagnostic criteria for MAS-KD, and (3) a lack of clinical suspicion for MAS-KD [29,34].

Clinical manifestations

Table 1 shows MAS-related features (e.g., fever, splenomegaly, cytopenia, hyperferritinemia, or hemophagocytosis), treatment, and outcomes of the 23 Korean patients with MAS-KD. All patients (100%) experienced persistent fever, and the median duration of fever before MAS-KD diagnosis was 14 (interquartile range, 10~20) days. Splenomegaly was present in approximately two-thirds (16/23) of patients, and bicytopenia or pancytopenia was observed in 56% (13/23). Thrombocytopenia (61%, 14/23) was the most frequently observed cytopenia. Hypertriglyceridemia or hypofibrinogenemia was present in 83% of patients (19/23). Most patients (91%, 21/23) showed hyperferritinemia and hemophagocytosis was seen in 78% (18/23).

Table 2 presents the clinical findings of MAS-KD (this study) and KD without MAS (the Korean nationwide study). Among the five KD-related features, skin rash (81%, 13/16) was the most frequent, and extremity changes (37%, 6/16) were the least frequent. Half (8/16) of the MAS-KD patients presented with incomplete KD. One-quarter (4/16) had CAAs, and all (16/16) had IVIG resistance. Compared to patients with KD without MAS, MAS-KD patients demonstrated a lower proportion of KD-related features and higher proportions of incomplete KD, CAAs, and IVIG resistance. Table 3 shows the MAS-KD laboratory findings from Korea (this study) and other countries (the systematic review). Both studies provide very similar laboratory results: anemia, leukopenia or neutropenia, thrombocytopenia, hypoalbuminemia, increased C-reactive protein and hepatic transaminase levels, and hyperferritinemia.

Although organ dysfunction is not included in the diagnostic criteria for MAS, it is a principal feature. For example, a study of MAS complicating SJIA (MAS-SJIA) [13] reported that more

Table 2. Clinical findings of MAS-KD (this study) and KD without MAS (the Korean nationwide study [4])

	MAS-KD (%)	KD without MAS (%)
Conjunctivitis	69	89
Oropharyngeal inflammation	50	83
Skin rash	81	83
Changes in extremities	37	65
Cervical lymphadenopathy	69	59
Incomplete KD	50	33
CAAs	25	11
IVIG resistance	100	12

MAS-KD: macrophage activation syndrome complicating Kawasaki disease, KD: Kawasaki disease, MAS: macrophage activation syndrome, CAAs: coronary artery abnormalities, IVIG: intravenous immunoglobulin.

Table 3. MAS-KD laboratory findings of Korea (this study) and other countries (the systematic review [10])

	MAS-KD in Korea	MAS-KD in other countries
Hemoglobin (g/dL)	10.3 (8.2~11.3)	8.7 (7.0~10.6)
Leukocyte count ($10^3/\mu L$)	12.1 (3.9~13.4)	4.4 (2.1~12.2)
Absolute neutrophil count ($10^3/\mu L$)	2.2 (1.3~3.7)	1.8 (1.0~4.1)
Platelet count ($10^3/\mu L$)	106 (69~212)	85 (60~115)
ESR (mm/h)	35 (10~35)	64 (35~88)
CRP (mg/dL)	18.4 (12.0~20.2)	7.3 (1.3~12.4)
Albumin (g/dL)	2.8 (2.7~3.4)	2.4 (1.8~2.7)
AST (U/L)	282 (72~544)	225 (105~626)
ALT (U/L)	230 (26~397)	318 (83~420)
Triglycerides (mg/dL)	197 (135~253)	236 (146~314)
Fibrinogen (mg/dL)	198 (108~198)	191 (105~268)
Ferritin (ng/mL)	3,490 (1,051~16,500)	3,490 (975~13,979)

Values are presented as median (interquartile range, 25th~75th percentile). MAS-KD: macrophage activation syndrome complicating Kawasaki disease, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

than 30% of patients had neurologic abnormalities, while approximately 20% experienced hemorrhagic problems. In the present study, data on organ dysfunction were available for only 6 of the 23 patients. Of these, 5 (83%, 5/6) suffered a form of organ dysfunction, such as coagulopathy, seizure, shock, arthritis, or skin necrosis [16,23,25]. The systematic review found that 46% of patients had cardiac dysfunction, 13% had neurologic dysfunction, and 9% had respiratory dysfunction. The extent of organ dysfunction observed in MAS-KD patients is of great importance as it directly affects the disease course and prognosis [33,35].

Diagnosis

Because there are no specific diagnostic criteria for MAS-KD, HLH or MAS criteria designed for diseases other than KD have been used (Table 4) [26-28]. Among these, the HLH-2004 criteria have been the most widely used for diagnosing MAS-KD in both Korea and other countries [11]. In this study, 78% (18/23) patients met the HLH-2004 criteria and 82% (19/23) met the 2016 MAS criteria. Similarly, the systematic review also reported similar results that 78% of patients met the HLH-2004 criteria and 74% met the 2016 MAS criteria.

In practice, the HLH-2004 criteria are diagnostically useful. However, they are not sensitive for diagnosing MAS-KD because they were originally developed for primary HLH, which is an autosomal-recessive genetic disorder [26]. In addition, assays for sCD25 levels or natural killer cell functions are not readily available to many institutions [15]. To address these limitations, the Paediatric Rheumatology International Trials Organisation (PRINTO) proposed the 2016 classification criteria for MAS in patients with SJIA [27]. Compared with the HLH-2004 criteria, the 2016 MAS criteria are more sensitive for diagnosing MAS in KD as well as in SJIA [36]. Fardet et al. [28] proposed the hemophagocytic syndrome diagnostic score (HScore) to diagnose MAS or secondary HLH. During the COVID-19 pandemic, the HScore was often used to diagnose MIS-C and other COVID-19-associated cytokine storm or hyperinflammatory conditions [37-39]. Because these diagnostic methods are complementary rather than competitive, more than one method may be used to diagnose MAS-KD depending on the clinical situation [14,40]. Multicenter clinical studies are necessary to evaluate universally applicable diagnostic methods and develop specific diagnostic criteria for MAS-KD.

Treatment

Unfortunately, no controlled trials have been conducted on the treatment of pediatric MAS, including MAS-SJIA and MAS-KD [34]. Therefore, the treatment of MAS-KD is based on knowledge of primary HLH and experience with previous MAS case series [13,15]. In this study, all 23 patients received standard treatment for KD (i.e., initial IVIG and aspirin). However, because fever was uncontrolled, all patients received additional

Table 4. MAS diagnostic criteria: HLH-2004 [26], 2016 MAS classification [27], and HScore [28]

HLH-2004*	2016 MAS Classification†	HScore (points)‡
Fever	-	Fever 38.4°C~39.4°C (33), >39.4°C (49)
Splenomegaly	Any two of the four criteria	Hepatomegaly or splenomegaly (23), both (38)
Cytopenia ≥2 cell lines	Platelet counts ≤181×10^3/μL	Cytopenia 2 cell lines (24), 3 cell lines (34)
-	AST >48 U/L	AST ≥30 U/L (19)
Triglycerides ≥265 mg/dL	Triglycerides >156 mg/dL	Triglycerides 133~354 mg/dL (44), >354 mg/dL (64)
or fibrinogen ≤150 mg/dL	Fibrinogen ≤360 mg/dL	Fibrinogen ≤250 mg/dL (30)
Ferritin ≥500 ng/mL	Ferritin >684 ng/mL (essential)	Ferritin 2,000~6,000 ng/mL (35), >6,000 ng/mL (50)
sCD25 (sIL-2R) ≥2,400 U/mL	-	-
Low NK cell function	-	-
Hemophagocytosis in BM, liver, or LN	-	Hemophagocytosis (35)
-	-	Known immunosuppression (18)

MAS: macrophage activation syndrome, HLH: hemophagocytic lymphohistiocytosis, HScore: hemophagocytic syndrome diagnostic score, -: not applicable, AST: aspartate aminotransferase, sIL-2R: soluble interleukin-2 receptor, NK: natural killer, BM: bone marrow, LN: lymph node. MAS is diagnosed when *≥5/8 criteria, †≥2/4 criteria plus hyperferritinemia, or ‡sum of points ≥169.

treatment. Therapeutic approaches for MAS-KD varied, with corticosteroids (CS) administered to 100% (23/23), cyclosporine A (CSA) administered to 74% (17/23), etoposide (VP-16) administered to 70% (16/23), and infliximab administered to 4% (1/23) of patients (Table 1). Almost two-thirds of patients (65%, 15/23) received 40 weeks of complex chemotherapy according to the HLH-2004 protocol [26], which is significantly greater than the number in the systematic review to receive this treatment (35%, 24/69). Two patients died (9%, 2/23) under the HLH-2004 protocol.

Many patients with MAS recover successfully with short-term (~8 weeks) simple immunomodulators instead of long-term (~40 weeks) complex chemotherapy [41,42]. However, patients who meet the diagnostic criteria for MAS are at risk of receiving longer and more complex treatments than necessary due to overwhelming clinical manifestations [43]. Therefore, careful monitoring of the therapeutic response is essential to avoid overtreatment [41-43]. Recently, cytokine-specific biologics such as anakinra have been preferred over traditional immunosuppressants such as VP-16 or CSA as initial combination therapy with CS or as second-line therapy for refractory MAS [44-47].

Clues for early recognition

As shown in Tables 2 and 3, MAS-KD cases present more severe clinical and laboratory findings than cases of KD without MAS. However, these findings are observed not only in MAS-KD, but also in severe KD, which can delay the diagnosis of MAS in patients with KD [11,13]. Figure 1 summarizes useful clues for early recognition of MAS-KD. First, it is necessary to consider refractory KD as occult or impending MAS that can progress to overt MAS. In this study, all 23 patients had persistent fever despite initial IVIG treatment (i.e., refractory KD). In practice, MAS usually occurs when refractory KD worsens [48,49]. Rhee et al. [23] reported that most (45/46) MAS-KD patients did not respond to initial IVIG treatment, and that MAS was much more common in refractory KD (6.3%~12.5%) than in typical KD (0.4%~1.9%). Therefore, they suggested that MAS screening should be included in the routine laboratory tests performed for refractory KD.

Second, if KD patients have splenomegaly, thrombocytopenia, or hyperferritinemia, the possibility of developing MAS-KD should be considered. Splenomegaly is uncommon in KD patients without MAS but occurs in two-thirds of MAS-KD patients [29,50]. However, splenomegaly itself simply indicates the presence of severe inflammation and may be observed in other severe forms of KD [51]. Whereas thrombocytosis is a key laboratory finding in KD without MAS, thrombocytopenia is the earliest laboratory abnormality in MAS-KD [3,39]. Hyperferritinemia is the most prominent laboratory finding in MAS-KD [22,52]. In this study, approximately 80% (18/23) of patients had ferritin levels >1,000 ng/mL, and 30% (7/23) had ferritin levels >10,000 ng/mL. Hyperferritinemia >10,000 ng/mL is well known to be highly specific for MAS in patients with SJIA or

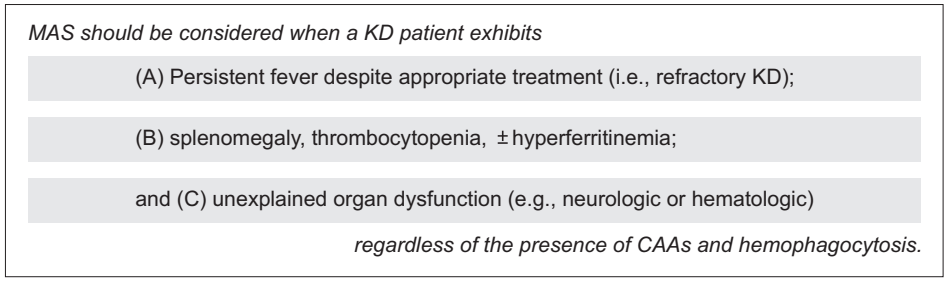

Figure 1. Clues for early recognition of MAS in children with KD. MAS: macrophage activation syndrome, KD: Kawasaki disease, CAAs: coronary artery abnormalities.

KD [53,54]. In addition, ferritin levels relative to erythrocyte sedimentation rate (ESR) (i.e., ferritin/ESR ratio) are considered a useful diagnostic clue for MAS, because a drop in ESR due to fibrinogen depletion is often seen in patients with MAS [14,43].

Third, when unexplained organ dysfunction is observed in KD patients, MAS-KD should be included in the differential diagnosis [31,32]. Organ dysfunction is uncommon in KD without MAS but is a shared feature of KD-related hyperinflammatory diseases like MAS-KD, KDSS, and MIS-C [33,34]. Patients with MAS-KD present with various types of organ dysfunction, such as cardiac, neurologic, respiratory, hematologic, renal, or gastrointestinal problems [10,11]. When clinicians encounter patients with fever and organ dysfunction, the first thing that comes to mind is severe sepsis. However, some patients with fever and organ dysfunction may require simple immunomodulators such as IVIG or CS rather than complex antibiotics such as vancomycin or meropenem [55,56]. It should also be noted that so-called pathognomonic findings, such as CAAs or hemophagocytosis, are neither necessary nor sufficient for diagnosis of KD and/or MAS and may be present in other diseases that cause severe inflammation [57-59]. Therefore, the diagnosis and treatment of MAS-KD should not be delayed due to the presence or absence of CAAs or hemophagocytosis [60].

Limitations of this study

This study is a literature review of MAS-KD studies conducted in Korea, not a systematic review. The data were described arithmetically without statistical analysis, and some Korean data may not have been included in this study. One of the important findings of this study is that the incidence of MAS-KD in Korea is relatively low compared to other countries. The low incidence of MAS-KD in Korea is thought to be due to racial differences, similar to the low incidence of KDSS and MIS-C in Korea [31-33]. However, the limitations of this study may have influenced the differences in the incidence of MAS-KD, suggesting the need for nationwide and/or multinational studies on MAS-KD.

CONCLUSION

The incidence of MAS-KD was lower in Korea (0.8%~1.1%) than in North America (1.9%). Similar to MAS-KD patients in other countries, Korean MAS-KD patients exhibit more severe clinical manifestations compared to KD patients without MAS. However, these findings in MAS-KD can also be observed in exacerbations of KD, which sometimes leads to diagnostic confusion. Because there are no established guidelines for MAS-KD, patients have been diagnosed using criteria for diseases other than KD, such as the HLH-2004 criteria and the 2016 MAS criteria, and have received treatment based on the HLH-2004 protocol and expert opinion. For early recognition of MAS-KD, it is necessary to consider MAS in KD patients with persistent fever (i.e., refractory KD), thrombocytopenia or hyperferritinemia, and unexplained organ dysfunction.

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CONFLICT OF INTEREST

SYL has been an editorial board member since May 2024, but

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AUTHOR CONTRIBUTIONS

Conceptualization: S.Y.L. Data curation: D.C.J. and S.Y.L. Formal analysis: D.C.J. Writing-original draft: S.Y.L. Writing-review & editing: D.C.J. and S.Y.L. Both authors approved the final manuscript.

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