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CASE REPORT

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A Ukrainian infant with giant coronary aneurysms: A case report and literature review

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Key Clinical Message: COVID may manifest multisystem inflammatory syndrome in children (MIS-C) which mimics Kawasaki disease (KD). Differentiating KD and MIS-C is difficult. Immunomodulatory treatment should be initiated promptly without accurate diagnosis.

Abstract: A febrile Ukrainian infant developed giant aneurysms in coronary arteries. Differentiating between Kawasaki disease and multisystem inflammatory syndrome in children was difficult. In both illnesses, coronary aneurysm may develop unless treated promptly. Therefore, guidelines should synthesize these clinical entities so that treatment can be initiated before rigorous diagnosis.

KEYWORDS

COVID-19, Kawasaki disease, mucocutaneous lymph node syndrome, multisystem inflammatory syndrome in children, SARS-CoV-2

1 | INTRODUCTION

Kawasaki disease (KD) is a systemic vasculitis in children characterized by fever and mucocutaneous manifestations. As many as 40% of KD patients develop transient or permanent dilatation of the coronary artery(s).[1] Prompt diagnosis and treatment with intravenous immunoglobulin (IVIG) and aspirin,[2–4] augmented by adjunct therapies,[5–8] has decreased the rate of coronary complications in resource-rich countries.[9] However, the rate of severe coronary sequelae remains high in resource-limited regions due to delayed diagnosis and insufficient treatment. Meanwhile, SARS-CoV-2 infection in children can cause an illness that mimics the symptoms of KD. This state was named multisystem inflammatory syndrome in children (and adolescence) (MIS-C) by the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO),[10,11] and pediatric multisystem

inflammatory syndrome temporally associated with COVID-19 (PIMS) by Royal College of Pediatrics and Child Health.[12]

2 | CASE HISTORY/EXAMINATION

A 4-month-old female Ukrainian infant of Caucasian ethnicity developed a fever of 39.4°C in June 2022 (Day 1). She coughed vehemently and had watery diarrhea, and her abdomen was distended. She was admitted to Saint Nicholas Hospital in Lviv and started on ceftriaxone on Day 2. She developed maculopapular rashes on Day 3. Although the antibiotics were changed to tobramycin and clarithromycin, the rashes persisted. Her erythrocyte sedimentation rate (ESR) was high (Figure 1A). SARS-CoV-2 antibody test (EQUI, Kyiv) showed a positive IgG level of 2.7 (reference range: <1.1), and a negative IgM of 0.4 (<0.9). D-dimer was high at 4780 μg/L (normal: <1000 μg/L) on Day 6. Accordingly, she was diagnosed with MIS-C based on the diagnostic criteria of the CDC (Table S1).[10] However, her mother later reported that she had contracted SARS-CoV-2 at the 4th month in her pregnancy. In addition, the antibody tests conducted for the patient in January 2023 were negative for IgG and IgM. Therefore, in hindsight, the positive IgG on the admission may have been passively transferred from her mother.

On Day 6, 2 g/kg of IVIG (Bioven Mono®) and aspirin (50 mg/kg/day) were given, while dexamethasone (1 mg/kg/day) was initiated based on the recommendations for the treatment of MIS-C (Table S2).[13,14] The fever subsided on Day 7. After dexamethasone was stopped, however, the fever recurred. She was remarkably anemic on Day 10 (Figure 1B). Therefore, the possibility of macrophage activation syndrome (MAS) was considered, and

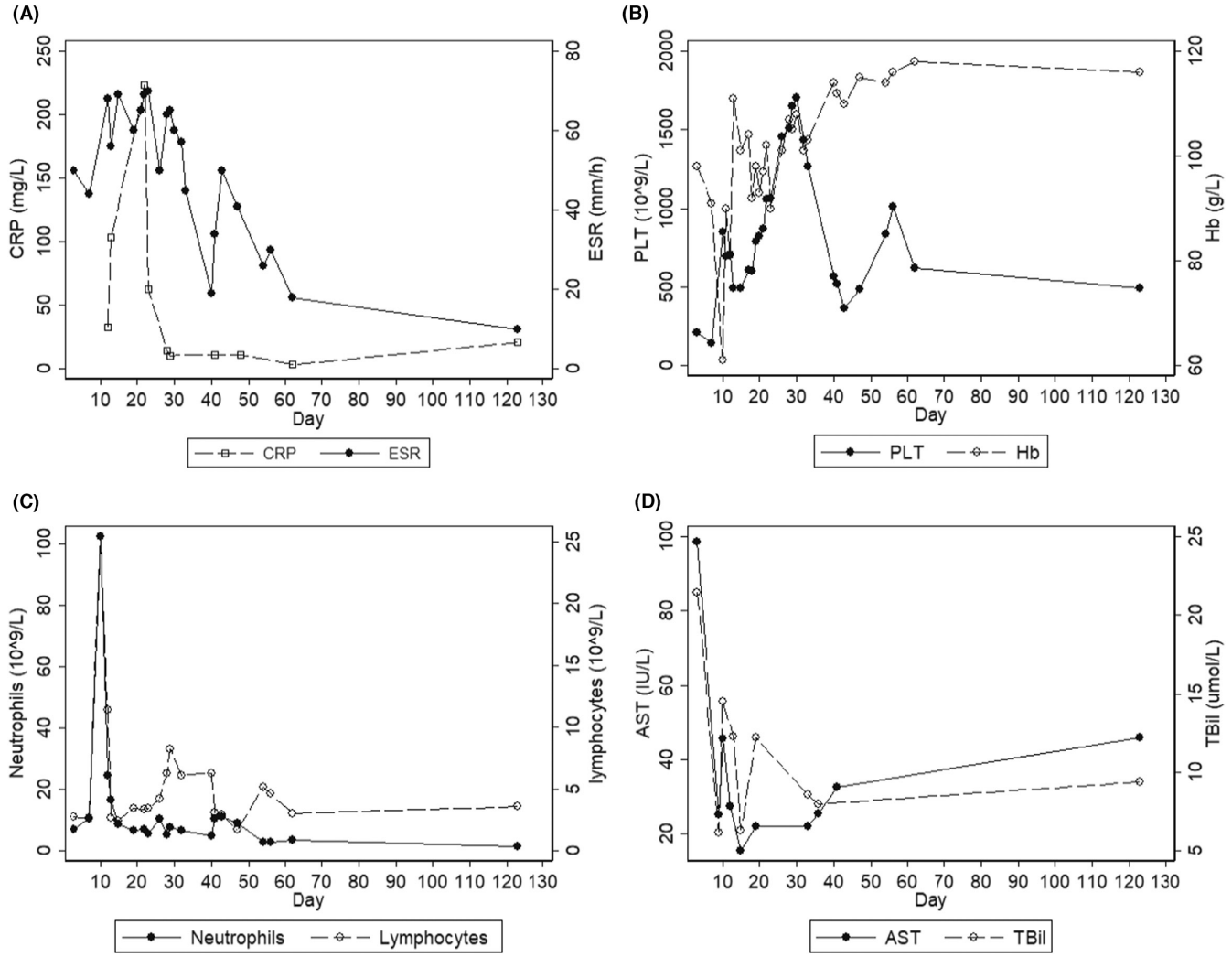

FIGURE 1 Longitudinal changes in the biomarkers for KD and MIS-C. (A) C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). (B) Platelet count (PLT) and hemoglobin (Hb). (C) Counts of neutrophils and lymphocytes. (D) Aspartate aminotransferase (AST) and total bilirubin (TBil).

she was transferred to the Western Ukrainian Specialized Children's Medical Centre (WUSCMC) in Lviv. Upon her arrival at WUSCMC, the patient's D-dimer was 5070 μg/L (normal: <1000 μg/L) and procalcitonin was 6.07 ng/mL (<0.05 ng/mL), indicating intense inflammation. In addition, a chest X-ray showed right-sided pneumonia. On Day 14, neither the ferritin level of 475 ng/mL (>684 ng/mL in MAS) nor the platelet count (PLT) of 492×10^9/L (<181×10^9/L in MAS) fulfilled the MAS criteria.[15] On Days 19–20, her palms and soles were edematous, while conjunctivitis and cheilitis were noted.

Cardiological imagery studies—that is, high-resolution contrast-enhanced computer tomography (CE-CT) and echocardiography—were suspended in Lviv due to the war's disruption of human movement and material supplies. Therefore, on Day 22, we conducted conventional resolution contrast-enhanced computer tomography (CE-CT), with a resolution insufficient for cardiological study. This CE-CT suggested the development of cardiac aneurysms in the right coronary artery (RCA), the left main trunk of the coronary artery (LMT), and the left anterior descending artery (LAD; Figure S1). Subsequently, an echocardiologist with expertise in infantile patients was dispatched from Kyiv to Lviv. The echocardiography on Day 29 confirmed the giant coronary aneurysms, defined as a Z score > 10 standard deviations (SDs) (Figures 2A and 3A).

Because coronary giant aneurysms coexisting with mucocutaneous manifestations are known to be more frequently associated with KD than with MIS-C,[16–18] we considered the possibility of KD. This patient satisfied the diagnostic criteria for all of KD, MIS-C, and PIMS (Table S1).[10,12,19] All the scores of Kobayashi, Egami, and Sano indicated high probabilities of unresponsiveness to the first IVIG (Table S3).[20–22] Mitral regurgitation which was identified on Day 29 (Video S1) was known to be a predictor for poor cardiac prognosis.[23]

The patient had defervesced. However, increase in C-reactive protein (CRP) (Figure 1A) and elevation in liver enzymes (Figure 1D) suggested that the hyperinflammatory state recurred by Day 20.[22,24] We did not receive this information until Day 29 due to the disruption of laboratory test services. On this day, the patient was given IVIG 2 g/kg, and aspirin 50 mg/kg/day, while dexamethasone 2 mg/kg/day were commenced. On Day 30, we started high-molecular-weight heparin to prevent thrombus

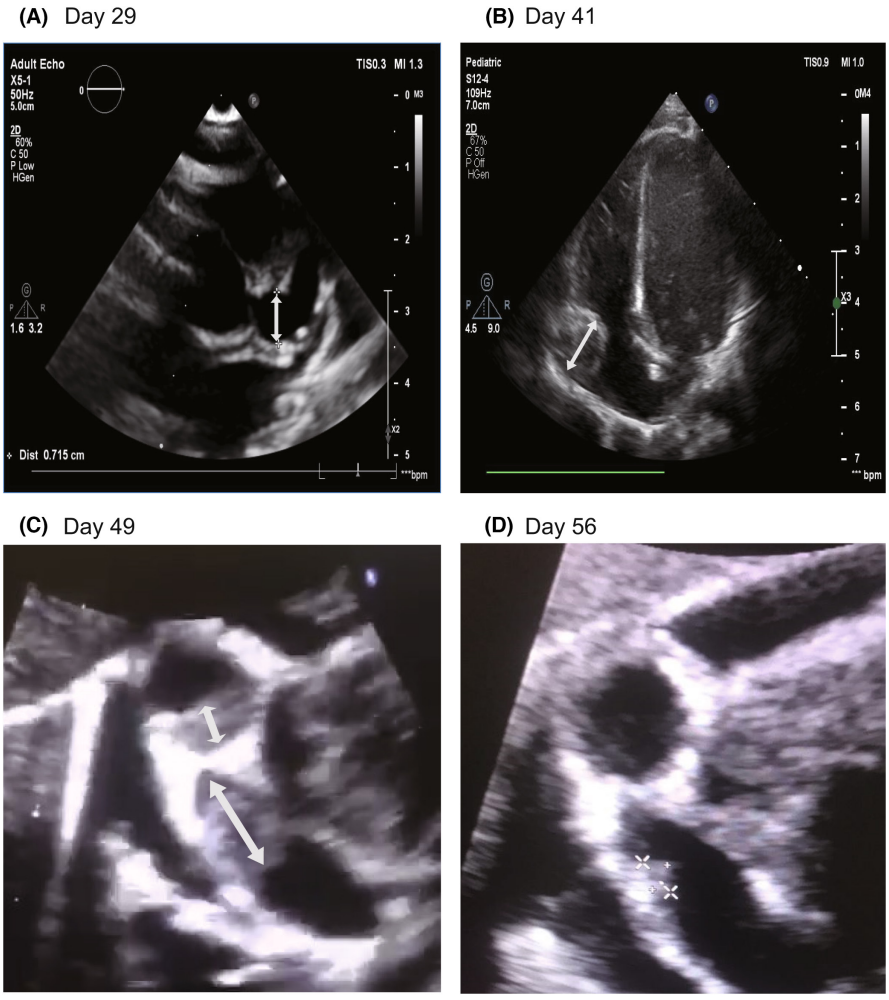

FIGURE 2 Temporal changes in the echocardiography. (A) Aneurysms were identified on Day 29 (the two-pointed arrow indicates the aneurysm in the LMT). (B) RCA was found to be obstructed by a thrombus (two-pointed arrow) on Day 41. (C) The thrombi (two-pointed arrows) gradually decreased in size (D) and almost disappeared by Day 56.

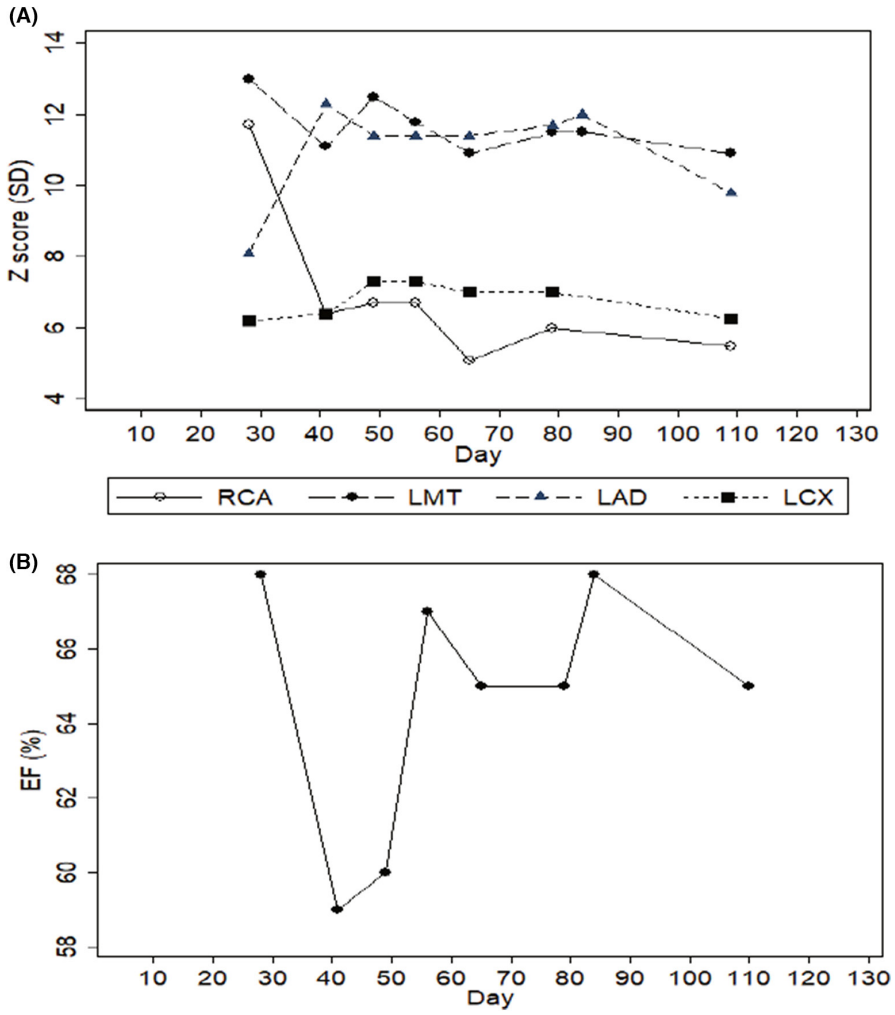

FIGURE 3 Sizes of coronary aneurysms and cardiac contractility. (A) The sizes of coronary arteries are expressed in *Z*-scores, and (B) the contractility is represented by the ejection fraction (EF).

formation.[25] The dose of heparin was continuously adjusted based on the activated coagulation time (ACT). The ACT was initially unstable but gradually stabilized.

However, electrocardiograms conducted on Day 41 showed elevated ST segments and an abnormal Q wave. The troponin I level was elevated to 5.78 ng/mL (normal: <0.16 ng/mL). The echocardiography identified a thrombus obstructing the RCA (Figure 2B). The ejection fraction (EF) decreased from 68% (Day 28) to 59% (Day 41) (Figure 3B). Collectively, we diagnosed myocardial infarction. Therefore, we started a combination of aspirin 5 mg/kg/day and warfarin.[26]

The indicators representing hyperinflammation (i.e., CRP, ESR, anemia, leucocytosis, and the elevated liver enzymes) normalized by Day 62 (Figure 1). The echocardiographies conducted longitudinally found that the thrombus in the RCA decreased in size and disappeared (Figure 2C,D). In accordance, the cardiac contractility normalized (Figure 3B). The patient was discharged on Day 72.

We suggested that the parents bring the patient to Kyiv for high-resolution CE-CT. They initially hesitated to visit Kyiv, fearing the repeated aerial attacks there. The patient underwent high-resolution CE-CT in the Ukrainian Children's Cardiac Center (UCCC), Kyiv, on Day 84. This high-resolution CE-CT identified aneurysms in the RCA,

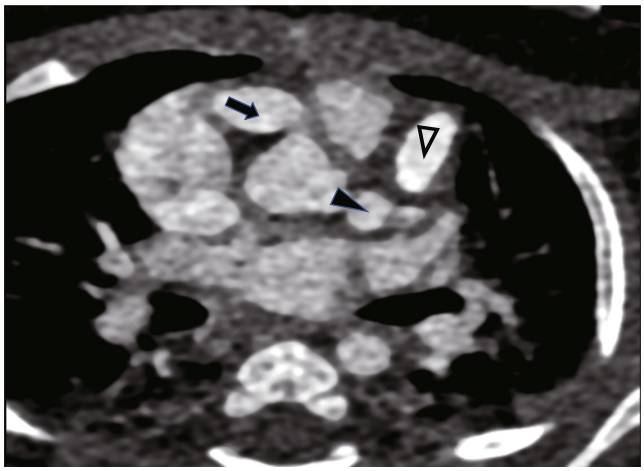

FIGURE 4 High-resolution CE-CT on Day 84. Spindle-shaped aneurysms are remarkable in the coronary arteries of RCA (arrow), LMT (filled arrow head), and LAD (open arrow head).

TABLE 1 Godfred-Cato's score to differentiate KD and MIS-C, applied to our patient.

Criteria	Score	Day 7	Day 20
PLT $<150\times10^9$/μL	2	144×10^9/μL (2 scores)	826×10^9/μL (0 scores)
Abdominal pain	1	Possibly present (1 score)	Unknown (0 score)
Headache	1	Unknown (0 score)	Unknown (0 score)
Pericardial effusion	1	Unknown (0 score)	Unknown (0 score)
CRP >100 mg/L	1	<100 mg/L (1 score)	103 mg/L (1 score)
Rash	−1	Present (−1 score)	Present (−1 score)
Mucocutaneous lesions	−2	Absent (0 score)	Present (−2 scores)
Total (Probability of MIS-C)		3 scores (MIS-C: 97%)	−2 scores (MIS-C: 8%)

LMT, and LAD (Figure 4). In the latest echocardiography on Day 110, a giant aneurysm (>10 SDs) remained in the LMT, and large aneurysms (>5 SD) persisted in the RCA, LAD, and left circumflex artery (LCX) (Figure 3A).

Echocardiography with an interval of 3–6 months is recommended for this patient; assessment of inducible myocardial ischemia and imagery studies (e.g., CT, MRI, or coronary angiography) should be conducted with an interval which depends on the regression of the coronary aneurysms.[25,26] However, conducting these studies regularly is increasingly difficult in Ukraine.

3 | DISCUSSION

In the greater Kyiv region, between 2020 and 2021, 57 patients were diagnosed with MIS-C (mean age: 9.5 years) and 48 with KD (6.1 years). The mean age of MIS-C diagnosis in this region was consistent with reports from other countries.[18,27] However, the mean or median ages of KD patients have been below 3 years in almost all the countries/regions that reported the epidemiology of KD,[9,18,26,28,29] including Ukraine.[30] Therefore, the ages of KD patients reported in the Kyiv region during the COVID-19 pandemic were exceptionally high. Using a simple calculation, we estimated that half of the KD cases reported during the COVID-19 outbreak were in fact MIS-C (Text S1). This illustrates the inherent difficulty in differentiating MIS-C from conventional KD.

Initially, we made a diagnosis of MIS-C based on her anti-SARS-CoV-2 IgG-positive and IgM-negative status.[31] However, in hindsight, the positive IgG may have been due to passive transfer of the maternal antibody. Godfred-Cato et al. proposed a scoring system to differentiate between MIS-C and KD.[17] The Godfred-Cato score predicted that our patient had MIS-C with a probability of 97% on Day 7, and of 8% on Day 20 (Table 1). However, abdominal pain and headache in this scoring system could not be assessed in our patient. Apart from the items in this scoring system, many characteristics were consistent with KD (Table 2).[27,32,33] Therefore, we could not differentiate MIS-C and KD at the moment of acute phase.

TABLE 2 Characteristics that were not included in Table 1 are applied to our patient to differentiate KD and MIS-C.

Findings that support KD	Value in our patient
Young age	4 months old
Giant aneurysms	Present in multiple branches
Onset less than 2 weeks after a fever	No prior febrile episodes within 6 weeks
Absence of lymphopenia	Minimum lymphocytes: 1.74×10^9/L
Absence of acute kidney injury	Maximum creatinine: 60 μmol/L
Thrombocytosis in convalescence	Maximum PLT in convalescence: 1707×10^9/L
Neutrophilia	Maximum Neutrophils: 102×10^9/L
Findings that support MIS-C	**Value in our patient**
IgG (+) and IgM (−) against SARS-CoV-2	IgG 2.7, IgM 0.4
Presence of neutrophilia	Maximum neutrophils: 102×10^9/L
Mitral valve lesion	Mitral valve regurgitation
Respiratory distress and/or pneumonia	Pneumonia was present

To identify the risk factors for giant aneurysms in MIS-C/PIMS, we searched PubMed by using a search term ("multisystem inflammatory syndrome" AND "giant") on January 20, 2023. We read all 18 literatures hit by this search, and selected 9 case reports which described the acute phase of 11 patients (Table 3).[34–42] Among the patients in Table 3, all but one patient received the first IVIG on Day 5 or later. However, IVIG has been administered increasingly earlier for the KD patients in resource-rich countries: for example, 40% of the KD patients receive the first IVIG on Day 4 or earlier in Japan.[43] Therefore, earlier

TABLE 3 Cases with giant coronary aneurysms from MIS-C/PIMS identified in our literature search.

First author and reference	Country (ethnicity)	Age	Sex	Day of 1st IVIG	IVIG dose	Adjunct therapy[a]	CRP (mg/L)100–260[b]	D-dimer (μg/L)1200–4400[b]	Ferritin (ng/mL)225–911[b]
Our patient	Ukraine	4 m	F	6	2	Dx	223	**5070**	475
Zaki[34]	UAE (Indian)	6 m	M	4	2	mPSL, IVMP, IFX	202		213
Richardson[39]	UK	5 m	F	5	1	mPSL, ANK, IFX	73	**6692**	**937**
Villacis-Nunez[36]	USA (African)	4 m	M	6	1	IVMP, Dx, IFX, PSL	56	1359	76
	USA (African)	2 y	M	5	1	IVMP, ANK, IFX, PSL	157	4211	514
	USA (Hispanic)	12 y	F	5	2	IVMP, ANK, TOC	>200	1749	567
Manchola Narvaez[35]	Columbia	4 m	F	15	1		136	4153	194
Drury[38]	USA	3 m	F	26	1	IFX	**278**	**5500**	
Shahbaznejad[42]	Iran	14 m	M	6	2	PSL, IFX	38		
Tracewski[37]	Poland	2 y	M	10	1		78		97
Hasan[40]	Qatar	1 y	M		2		143	3060	621
Ghatasheh[41]	UAE (Asian)	9 m	M	14	1		110		

[a]Abbreviations for adjunct immunomodulatory therapies: ANK, anakinra; Dx, dexamethasone; IFX, infliximab; IVMP, intravenous methylprednisolone pulse; mPSL, methylprednisolone (other than pulse); PSL, prednisolone; TOC, tocilizumab.

[b]For the laboratory items, the maximum value in the acute phase is presented for C-reactive protein (CRP), D-dimer, and ferritin, while the minimum value is presented for platelets (PLT). Interquartile rage (IQR), derived from all MIS-C patients in the ref. [44] is presented. Values exceeding the IQR are shown in bold.

initiation of IVIG for MIS-C/PIMS might decrease the incidence of giant aneurysms. In addition, among the patients with giant aneurysms in Table 3, only a limited number of patients showed high values of CRP, ferritin, or D-dimer which were associated with an elevated risk for cardiac sequelae.[44] This finding suggests that predicting emergence of giant aneurysms based upon biomarkers is difficult.

Considering the current ubiquity of SARS-CoV-2, history of exposure to this virus and/or a positive result(s) from virological/serological test would not definitively exclude KD. However, there are important discrepancies in the management for these illnesses (Table S2). For example, the second IVIG treatment is not recommended for a refractory MIS-C patient,[14] while the second IVIG is frequently given to reoccurring KD cases.[26,45] As a result, Infliximab and Anakinra are given a greater role in the treatment of MIS-C than that in KD.[14] Tocilizumab is recommended for MIS-C,[14] but is avoided for KD.[26,45,46] Cyclosporine A, which has been effective for KD,[8,26] is not yet considered for MIS-C.[14] Collectively, the guidelines for MIS-C and those for KD should be synthesized considering the present global situation that distinguishing these two diseases is increasingly difficult.

4 | CONCLUSION

A Ukrainian infant with fever developed giant coronary aneurysms. Differentiation between KD and MIS-C has been ambiguous. Under the current guidelines, the treatment for KD and that for MIS-C are mutually contradictory. Definitively differentiating KD versus MIS-C is increasingly difficult, while both illnesses may develop coronary aneurysms unless treated promptly. Therefore, guidelines for these hyperinflammatory illnesses should be synthesized, so that treatment can be initiated without rigorous differentiation of these clinical entities.

AUTHOR CONTRIBUTIONS

Yuliia Klymyshyn: Data curation; investigation; validation. **Oleksii Datsko:** Data curation; investigation. **Yuriy Stepanovskyy:** Data curation; supervision. **Yoshiro Nagao:** Writing – original draft. **Yugo Nagayama:** Writing – original draft. **Satoshi Ueno:** Formal analysis; visualization. **Marta Sheremet:** Data curation; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

All the data related to this manuscript is available from the corresponding author on request.

ETHICS APPROVAL

This study was approved by the Ethics Committee of Western Ukrainian Specialized Children's Medical Center and that of Ukrainian Children's Cardiac Center.

PATIENT CONSENT

Written informed consent was obtained from the guardians of the patient.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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