Multisystem inflammatory syndrome in children and Kawasaki disease in infants: 2 sides of the same coin?

To the editor,

The world has been plagued by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the global pandemic of coronavirus disease 2019 (COVID-19). A new disease entity, called multisystem inflammatory syndrome in children (MIS-C), emerged in late April to early May 2020, affected clusters of children in Europe and North America, and showed a temporal association with SARS-CoV-2 infection. This article presents an infant with MIS-C and features of Kawasaki disease shock syndrome (KDSS) who was treated in a tertiary hospital in Sabah, Malaysia. This study aimed to assess the laboratory and clinical characteristics of MIS-C in infants, along with its similarities and differences with Kawasaki disease (KD).

A healthy 4-month-old girl was diagnosed with SARS-CoV-2 infection. One month after being diagnosed, she presented with fever, vomiting, rash, bilateral nonpurulent conjunctivitis, dry fissured red lips, and poor feeding. She went into shock 12 hours after admission and was transferred to the pediatric intensive care unit for invasive mechanical ventilation.

Her white blood cell count was $5.8 \times 10^3/\mu L$ (absolute lymphocyte count, $1.5 \times 10^3/\mu L$), her platelet count was $65 \times 10^3/\mu L$, and she had hypoalbuminemia (24 g/L). Her inflammatory markers were elevated: C-reactive protein, 102.6 mg/L; and ferritin, 504 ng/mL. She had a deranged coagulation profile (prothrombin time, 17 seconds; activated partial thromboplastin time, 75.1 seconds; international normalized ratio, 1.45) and an elevated D-dimer level (2.3 μg/mL). Her chest radiography findings were normal.

She had an unremitting fever of up to 39.7°C daily. She was hypotensive and required intravenous (IV) adrenaline and noradrenaline. Given this constellation of findings, she received IV immunoglobulin (IVIG) 1 g/kg dose for 2 days, IV methylprednisolone 2 mg/kg daily for 5 days, and oral prednisolone. She was weaned off of the vasopressors and extubated on day 7 of hospitalization.

Oral aspirin and subcutaneous enoxaparin were administered to treat thrombocytosis. The patient was discharged 19 days after hospitalization. Follow-up echocardiography 1 month later revealed normal coronary arteries and resolved pericardial effusion.

We compared 5 infants from published case reports in PubMed, who fulfilled case definitions for MIS-C of the Centers for Disease Control or World Health Organization with our case described above. These cases were further analyzed to determine if they fulfilled the diagnostic criteria for KD, incomplete KD, or KDSS (Table 1).

None of the infants had any underlying comorbidity except for infant 2, who was born prematurely (gestational age, 26 weeks); had chronic lung disease, swallowing difficulty, and periventricular hemorrhage; and had recently undergone a surgical gastrostomy procedure. All infants presented with persistent fever for at least 3-day duration. Among the infants that fulfilled the diagnostic criteria of KD or incomplete KD, the most consistent features were rash and conjunctival injection. All but infant 2 received IVIG; this was the only infant who died.

MIS-C is a new disease entity with a heterogeneous clinical presentation. It seems to predominantly affect older children, whereby the median age reported was 7–9 years. The majority of the above infants (5 of 6, 83%) presented with features consistent with KD, incomplete KD, or KDSS with prominent mucocutaneous features (rashes, cracked lips, and conjunctival injection) and cardiovascular involvement. These 5 infants were aged between 2 and 6 months in contrast to the mean age at presentation of typical KD of 3.4 years. It is important to note that typical KD is rarely reported in infants younger than 6 months of age. Furthermore, most MIS-C series reported male-to-female ratios of approximately 1.5:1, but there was a female preponderance of 2:1 in this cohort.

Multisystemic involvement, especially of the gastrointestinal and cardiovascular systems with shock, was more prominent in MIS-C than in typical KD. Inflammatory markers were markedly elevated in contrast to typical KD. Moreover, MIS-C shows many similarities to KDSS, a rare form of KD.

An important prerequisite for the diagnosis of MIS-C is exposure to SARS-CoV-2, confirmed by a positive reverse transcription-polymerase chain reaction (RT-PCR), antigen, or serology test. Past or previous infections were identified in most MIS-C.

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The younger age, female preponderance, and KD-like presentation in this cohort may suggest that these infants were genetically predisposed. SARS-CoV-2 may trigger activation of the inflammatory cascade in these infants. Another possible mechanism is the presence of autoantibodies due to T-cell recognition of self-antigens or viral antigens expressed on infected cells, resulting cases evidenced by positive antibody tests, and only a third had positive RT-PCR findings for SARS-CoV-2. A notable difference in the infants in this study was that a large proportion of infants (4 of 6, 66%) had acute current SARS-CoV-2 infection as evidenced by positive RT-PCR tests rather than previous infections evidenced by positive antibody tests (2 of 6, 33%) (Table 1).

| Variable | Infant 1 | Infant 2 | Infant 3 | Infant 4 | Infant 5 | Infant 6 |
|----------|---------|---------|---------|---------|---------|---------|
| Demographic | Kok et al. | Farias et al. | Orlanski-Meyer et al. | Acharyya et al. | Raut et al. | Jones et al. |
| Country | Malaysia | Brazil | Israel | India | India | USA |
| Age | 4 Months | 7 Months | 2 Months | 4 Months | 5 Months | 6 Months |
| Sex | Female | Female | Female | Male | Male | Female |
| Presenting features | | | | | | |
| Fever (duration) | √ (3 Days) | √ (3 Days) | √ (10 Days) | √ (4 Days) | √ (5 Days) | √ (4 Days) |
| Rash | √ | - | - | √ | √ | √ |
| Conjunctival injection | √ | - | - | √ | √ | √ |
| Cracked/red lips | √ | - | √ | √ | - | √ |
| Limb swelling | - | - | - | - | - | √ |
| Lymphadenopathy | - | - | - | - | - | √ |
| Respiratory | - | √ | - | - | - | √ |
| Neurological | - | √ | - | - | - | - |
| Gastrointestinal | - | √ | √ | - | - | - |
| Cardiovascular | √ | √ | √ | - | - | √ |
| Shock | √ | √ | √ | - | - | - |
| Investigations | | | | | | |
| RT-PCR SARS-CoV-2 | Positive (1st admission) | Positive | Negative | Positive | Positive | Positive |
| SARS-CoV-2 Serology | Positive IgG | NA | Positive IgG | NA | NA | NA |
| Total white cell count | Normal | ↑ | ↑ | Normal | Normal | NA |
| Lymphocyte count | ↓ | ↓ | NA | NA | Normal | NA |
| Platelet | ↓ | Normal | ↑ | ↓ | ↓ | Normal |
| C-reactive protein | ↑↑ | ↑ | ↑↑ | ↑↑ | ↑↑ | ↑↑ |
| Ferritin | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ |
| Troponin I/B-NP | Normal | ↑ | ↑ | NA | ↑ | NA |
| Albumin | ↓ | ↓ | ↓ | Normal | ↓ | ↓ |
| Echocardiography | Mild pericardial effusion | Mild pericardial effusion with diffuse hypo-contractility | Mild to moderate MR | Diffuse ectasia of coronary arteries | Left main and LAD coronary ectasia | Normal |
| Therapeutic Intervention | | | | | | |
| Ventilation | √ | √ | - | - | - | - |
| Inotropic support | √ | √ | - | - | - | - |
| Aspirin | √ | - | - | √ | √ | √ |
| Steroids | √ | √ | √ | √ | - | - |
| IV immunoglobulin | √ | - | √ | √ | √ | √ |
| Interleukin antagonist | - | - | √ | - | - | - |
| Outcome | Alive | Died | Alive | Alive | Alive | Alive |
| MIS-C criteria | Fulfilled | Fulfilled | Fulfilled | Fulfilled | Fulfilled | Fulfilled |
| Kawasaki criteria | KDSS | KDSS | KD | Incomplete KD | KD | KD |

RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; B-NP, B-type natriuretic peptide; IgG, immunoglobulin G; KD, Kawasaki disease; KDSS, Kawasaki disease shock syndrome; LAD, left anterior descending; MR, mitral regurgitation; IV, intravenous; NA, not applicable.

*Respiratory symptoms – cough/tachypnoea/reduced oxygen saturation. Neurological symptoms – seizure/apnea. Gastrointestinal – vomiting/diarrhea/upper gastrointestinal bleeding/lower gastrointestinal bleeding. Cardiovascular – features of pericarditis/myopericarditis/myocarditis. C-reactive protein > 100 mg/mL.
in a hyperimmune response state and cytokine storm caused by dysregulated immune responses.9)

KD usually responds well to IVIG therapy, and only 10%–20% of cases are resistant to IVIG requiring either corticosteroid or biologics. On the other hand, the marked hyperinflammatory response in children with MIS-C often warrants combination therapy with both IVIG and corticosteroids.

This study had several limitations. First, we reviewed only a small number of infants and were not able to draw any definite conclusions regarding ethnicity or sex predilection. Moreover, comparing laboratory findings was difficult because some laboratory results were not available.

In conclusion, MIS-C shows similarities to KD, especially KDSS, which most likely is a consequence of dysregulated immune responses secondary to SARS-CoV-2 infection. Hence, the early recognition and diagnosis of MIS-C, followed by prompt treatment with IVIG and corticosteroids, will lead to favorable outcomes. The current diagnostic criteria for MIS-C do not adequately differentiate MIS-C from severe COVID-19; further refinement would better facilitate its diagnosis.

Key message

Question: Are multisystem inflammatory syndrome in children (MIS-C) and Kawasaki disease (KD) in infants, 2 sides of the same coin?
Finding: Here we report on a 4-month-old girl with MIS-C and signs of KD with shock. Most (83%) infants with MIS-C had features of KD, especially KD shock syndrome.

Meaning: MIS-C is similar to KD, and likely is a consequence of dysregulated immune responses secondary to sudden acute respiratory syndrome coronavirus 2 infection.

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Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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