Multisystem inflammatory syndrome in children (MIS-C) occurring in temporal proximity between siblings

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SUMMARY
We report a pair of siblings who developed multisystem inflammatory syndrome in children (MIS-C) in close temporal proximity after recent exposure to SARS-CoV-2. Both siblings presented with Kawasaki disease-like features and haemodynamic instability, with the onset of symptoms within 6 days of each other. Remarkably, one of the siblings was the elder of a pair of monozygotic twins. The younger monozygotic twin, however, did not develop MIS-C.

BACKGROUND
Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 is an inflammatory complication in children with recent SARS-CoV-2 exposure. Although increasing cases of MIS-C are reported worldwide, none describe the occurrence of MIS-C in siblings. To the best of our knowledge, this is the first case of MIS-C occurring in siblings in close temporal proximity reported worldwide. We discuss the knowledge gaps leading to this unique presentation.

CASE PRESENTATION
Patient 1
An 8-year-old boy with surgically corrected complex congenital cyanotic heart disease who has been well under follow-up presented with 3 days of fever, myalgia, vomiting and diarrhoea. Physical examination revealed maculopapular rashes, conjunctival hyperaemia, cracked lips and bilateral cervical lymphadenopathy. An ejection systolic murmur was heard over the pulmonary area, but examination of the rest of the systems was unre- markable. On admission, his axillary temperature was 40°C, heart rate 120 beats per minute (bpm), blood pressure 98/62 mm Hg, respiratory rate 20 breaths per minute, and oxygen saturation 98% under room air.

Laboratory tests demonstrated lymphopaenia, thrombocytopaenia and increased markers of inflammation (figure 1A). His C reactive protein (CRP) measured 211 mg/L, D-dimer 4.62 µg/mL, fibrinogen 5.11 g/L and ferritin 1094.6 ng/mL. Nasopharyngeal swab for SARS-CoV-2 reverse transcription polymerase reaction (RT-PCR) was negative, but SARS-CoV-2 specific IgG antibodies were detected by chemiluminescent microparticle immunoassay (Architect, Abbott Laboratories). On day 2 of hospitalisation, he became drowsy and hypotensive, prompting transfer to the paediatric intensive care unit (PICU). The child required mechanical ventilation, fluid resuscitation and inotropic support. He was treated with intravenous immunoglobulin (IVIG) 2 g/kg, methylprednisolone 2 mg/kg/day, oral aspirin 30 mg/kg/day and subcutaneous low-molecular weight heparin. Empiric antibiotics (Ceftriaxone and Clindamycin) were started for possible toxic shock syndrome. The initial echocardiogram revealed reduced cardiac contractility (left ventricular ejection fraction 51.7%) and a coronary artery aneurysm over the left anterior descending (LAD) artery, which initially measured 2.6 mm (Z-score: +1.88) and progressed to 3.1 mm (Z-score: +3.20) on day 5 of hospitalisation.

His temperature persisted (figure 1B) with further clinical deterioration, necessitating a second dose of IVIG 2 g/kg 72 hours later. He developed anuric renal failure on day 5 of hospitalisation and pulmonary haemorrhage on day 7. He required renal replacement therapy in the form of peritoneal dialysis as continuous renal replacement therapy was unavailable at our centre. Clinical stability was attained on day 10 of hospitalisation, allowing inotropic support to be gradually withdrawn. He completed a total of 100 cycles of peritoneal dialysis over 7 days. He was successfully extubated to non-invasive ventilation on day 12 of admission and was weaned off oxygen support. His major organs experienced full functional recovery, but he unfortunately developed gangrene over the tip of his fingers and toes. After a 21-day stay in the intensive care unit, he was transferred out to continue rehabilitation in the paediatric ward. Neurological assessment on discharge was normal. He was able to ambulate independently but required some assistance with activities of daily living such as bathing and toilet activities.

Patient 2
While the patient described above was still in hospital (day 9 of hospitalisation), his 6-year-old sister, the elder of a pair of monozygotic twins presented with a 5 days history of abdominal pain associated with fever. Physical examination on admission revealed an irritable-looking child with cool, poorly perfused peripheries. An erythematous rash was noted over her periumbilical region and neck with bilateral conjunctival hyperaemia and red lips. On presentation, the axillary temperature was 40.1°C, heart rate 140 bpm, blood pressure 102/60 mm Hg. Her blood investigations were strikingly similar to her
elder sibling with lymphopaenia, raised CRP, D-dimer, fibrinogen and ferritin levels (figure 2A). Echocardiography revealed mildly dilated coronary arteries (LAD diameter 2.8 mm, Z-score: 3.08) with otherwise good cardiac contractility. She was transferred to the PICU and treated for MIS-C based on her clinical features and a sibling with a similar presentation. She required fluid resuscitation, inotropic support and supplemental oxygen via nasal cannula. She received IVIG 2 g/kg and methylprednisolone 1 mg/kg/day together with oral aspirin 30 mg/kg/day. Her fever resolved within 48 hours after IVIG and inotropes were discontinued on the same day (figure 2B). She recovered without complications and was transferred out from the PICU on day 5 of hospitalisation.

Like her elder sibling, she was tested negative by RT-PCR twice (taken 2 days apart), but SARS-CoV-2-specific IgG was detected by antibody testing. On further questioning, their mother revealed that all family members had a brief febrile upper respiratory tract infection 4 weeks before the elder brother’s hospital admission. However, the siblings were not investigated for COVID-19 at that time as they had no direct epidemiological link to confirmed cases. The family members were subsequently investigated, with details summarised in figure 3. RT-PCR for SARS-CoV-2 was negative for the rest of the household apart from the younger twin of patient 2, who had a positive RT-PCR with a single gene target detected (RNA-dependent RNA polymerase) at a cycle threshold (Ct) value of

Figure 1  (A) Serial changes in laboratory investigations for patient 1.  (B) Temperature trend over the hospital course for patient 1. Timing of various interventions such as mechanical ventilation, non-invasive ventilation, peritoneal dialysis, IVIG and methylprednisolone. IVIG, intravenous immunoglobulin.
SARS-CoV-2-specific IgG was detected in all household members. The younger twin did not develop MIS-C as of the time of writing (12 weeks later).

DIFFERENTIAL DIAGNOSIS
The diagnosis of MIS-C was made based on the clinical features mimicking Kawasaki disease and toxic shock syndrome with serological evidence of SARS-CoV-2 infection. Other infectious agents were ruled out. Both siblings were tested negative for cytomegalovirus, parvovirus, enterovirus, chikungunya, measles, herpes simplex virus, Epstein-Barr virus and blood cultures were sterile. Nasopharyngeal aspirate for detection of other respiratory viruses (influenza A, influenza B, parainfluenza 1/2/3, adenovirus, respiratory syncytial virus and human metapneumovirus) were negative as well.

DISCUSSION
SARS-CoV-2 infection among children generally results in less severe disease with favourable outcomes compared with adults. However, severe manifestations of COVID-19 in children have emerged with the progression of the pandemic worldwide. MIS-C is a severe multisystem inflammation associated with recent SARS-CoV-2 infection or COVID-19 exposure. This syndrome was first reported in Europe as clusters of children presenting to intensive care units due to an unexplained MIS with features similar to KD or toxic shock syndrome. Since then, the condition has been described in many countries worldwide. MIS-C is hypothesised to be a delayed, postinfectious complication of COVID-19. Epidemiological studies demonstrated a latency of 2–5 weeks between SARS-CoV-2 infection and the occurrence of MIS-C. Many affected children only had serologic evidence of infection but negative RT-PCR results.
Figure 3 Summary of investigations for SARS-CoV-2 performed for the household. RdRp, RNA-dependent RNA polymerase; RT-PCR, reverse transcription polymerase chain reaction.

We report two siblings with clinical features of KD and Kawasaki Disease Shock Syndrome (KDSS), who were diagnosed with MIS-C based on the criteria set by the US Centers for Disease Control. Coronary artery aneurysm, the most well-recognised complication of KD, was seen in both patients. KDSS is a severe form of KD that presents with haemodynamic instability during the course of illness. Although the clinical features of MIS-C overlap with KD and KDSS, they are unlikely to be of the same disease entity. Patients with MIS-C tend to present at an older age, have more gastrointestinal manifestation and are at greater risk for myocardial dysfunction and shock than classical KD.

To the best of our knowledge, this report is the first case of MIS-C occurring in siblings in close temporal proximity reported worldwide. Both siblings presented with a KD-like phenotype. Understanding the aetiology of KD could provide insights into the pathogenesis and risk factors for MIS-C. A review of simultaneous familial KD cases suggests that the development of KD is the result of a complex interaction between genetically predisposed hosts and an infectious trigger. The significance of genetic factors in the aetiology is evident from the presence of familial aggregation. Recent studies on children with MIS-C identified genetic variants impairing regulation of inflammatory signalling, revealing additional genetic mechanisms for susceptibility. However, genetic factors alone cannot explain the temporal clustering of KD cases or simultaneous occurrences between siblings. Such circumstances support an infectious aetiology. KD occurring within short time intervals among siblings has previously been reported due to parvovirus, adenovirus and streptococcal infections. In our case, SARS-CoV-2 was the likely aetiology since both siblings had serological evidence of infection and other possible infectious agents have been ruled out.

Patient 2 was interestingly, the elder of a pair of twins. Her younger twin was likely infected around the same period as her other family members, considering her positive serology results and RT-PCR with only a single gene detected at high Ct values. The younger monozygotic twin notably did not develop MIS-C at the time of writing, suggesting MIS-C is likely a multifactorial disease with a genetic predisposition. This phenomenon is a knowledge gap that needs to be explored. However, whole-exome sequencing studies investigating the genetic susceptibility of our patients were not carried out and would be the limitation of this report.

Our report highlights MIS-C occurring in close temporal relation between siblings, yet its absence in the patient’s twin. The complex pathophysiology and mechanisms by which SARS-CoV-2 triggers an abnormal immune response leading to MIS-C remain unknown. This underscores the need for further studies to provide more light on the pathogenesis. As the pandemic is ongoing and many children are yet to be vaccinated, they remain vulnerable to COVID-19. The occurrences of this hyperinflammatory syndrome could increase in the months ahead. Therefore, all healthcare providers should remain vigilant of its clinical presentation to establish a diagnosis and provide timely intervention.

Learning points

- Multisystem inflammatory syndrome in children (MIS-C) is a rare complication of COVID-19, which can be severe. The symptoms can overlap with Kawasaki disease and toxic shock syndrome.
- MIS-C can occur simultaneously in siblings with similar clinical presentation. However, only one of monozygotic twins were affected in this family.
- Genetic studies in families with MIS-C are necessary to determine predisposition to this inflammatory condition.

Acknowledgements We would like to thank the Director General of Health Malaysia for his permission to publish this article.

Contributors LL participated in the clinical care of the patient, conceptualised the manuscript, drafted the initial manuscript and revised the manuscript. SJL participated in the clinical care of the patient, drafted the initial manuscript, coordinated data collection and revised the manuscript. DCN conceptualised the manuscript, reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.
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