

CASE REPORT

Multisystem inflammatory syndrome in children or invasive bacterial infection?

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In the subacute period of coronavirus disease 2019 (COVID-19), a complication called multisystem inflammatory syndrome in children (MIS-C) may develop with signs of multi-organ involvement.^{1,2} The frequency of this complication is 2–11.4/100 000 in patients under 20 years of age, and its mortality is 1–2%.³ MIS-C can be confused with infectious diseases such as bacterial sepsis and toxic shock syndrome.⁴

We report a child who was initially thought to have MIS-C but was later diagnosed with invasive *Staphylococcus aureus* infection. We aim to draw attention to the importance of considering the differential diagnosis carefully when diagnosing MIS-C.

Case Report

A previously healthy 7-year-old female patient presented with headache, vomiting and altered consciousness. She had nausea, fatigue and fever for 1 day before admission. Physical examination revealed no pathological findings except blurred consciousness and agitation. The patient's mother had a history of COVID-19 4 months ago. The patient was asymptomatic during that period.

Key Points

- 1 When considering that a child may have multisystem inflammatory syndrome in children (MIS-C) disease, it is important to consider all other differential diagnoses.
- 2 The use of intravenous immunoglobulin, glucocorticoids and biologic agents for the treatment of MIS-C is currently not standardised and they are recommended based on clinical presentation.
- 3 In a child with suspected MIS-C, the diagnosis of bacterial sepsis should be strongly considered, and consideration given to starting empiric antibiotics while awaiting blood culture results.

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Her leukocyte count was $7.8 \times 10^9/L$ (93% neutrophils, 5% lymphocytes), serum C-reactive protein 109 mg/L, haemoglobin 12.1 g/dL, platelet count 131/L, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) 331/171 U/L (0–35), creatine kinase (CK) 106 U/L (0–145), lactate dehydrogenase (LDH) 630 U/L (110–295), international normalized ratio (INR) 2.7 (0.8–1.2), ferritin 182 ng/mL (10–58). Lumbar puncture was performed, due to signs of meningeal irritation up. The cerebrospinal fluid (CSF) contained $170/mm^3$ leukocytes (predominantly neutrophils), CSF glucose 3.7 mmol/L (serum glucose: 7.7 mmol/L), CSF protein 0.84 g/L, with no bacteria seen on CSF Gram stain. Nasopharyngeal SARS-CoV 2 polymerase chain reaction (PCR) test was negative. Vancomycin (60 mg/kg/day), cefotaxime (225 mg/kg/day), and acyclovir (45 mg/kg/day) were started. An electroencephalogram showed diffuse encephalopathy. Magnetic resonance imaging (MRI) of the brain showed diffuse areas of vasogenic oedema (Fig. 1). CSF multiplex PCR and respiratory tract viral multiplex PCR were

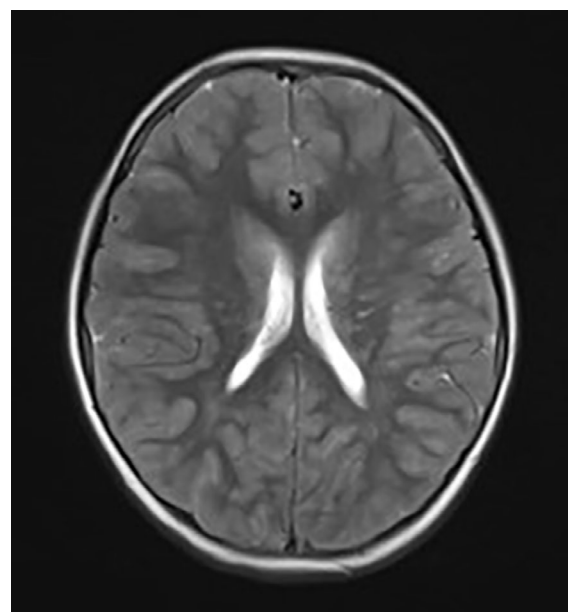


Fig. 1 Second day cranial magnetic resonance imaging: areas of diffuse vasogenic oedema.

negative, SARS-CoV-2 immunoglobulin G was positive. Because the imaging results and electroencephalogram were not compatible with herpes simplex virus (HSV) encephalitis, and CSF HSV PCR was negative, acyclovir treatment was discontinued.

On the second day of hospitalisation, the patient developed a maculopapular rash, more prominent on the trunk, which faded with pressure and a large ecchymosis on her left forearm (Fig. 2). Her leukocyte count was $5.8 \times 10^9/\text{L mm}^3$ (absolute lymphocyte count $0.24 \times 10^9/\text{L}$) and platelets had fallen to $47 \times 10^9/\text{L}$. Her CK was 445 U/L, troponin T was 21 ng/L (normal 0–14), CK-MB 24 U/L (0–24), and pro-PNP 977 pg/mL (0–125). She developed sudden hypotension necessitating inotropic medication. Echocardiography revealed myocarditis and an ejection fraction of 35%. Intravenous immunoglobulin (2 g/kg) was initiated with a preliminary diagnosis of MIS-C. The patient deteriorated and was intubated for acute respiratory distress with tachycardia and hypoxia.

The patient's blood and CSF cultures grew methicillin-sensitive *S. aureus* at 9 h after admission. Based on antimicrobial

susceptibility, ceftriaxone and vancomycin were stopped. Intravenous ampicillin-sulbactam (200 mg ampicillin/kg/day) was started, as oxacillin is not available in our country. Since the patient met criteria for staphylococcal toxic shock syndrome and the probable case definition, clindamycin was added to reduce toxin production. Because *S. aureus* was grown from blood on two consecutive days, and because CSF growth of *S. aureus* is suspicious of embolic spread, we suspected bacterial endocarditis. This was confirmed by echocardiography, performed on the fifth day of hospitalisation, which revealed mitral valve vegetations. We could not identify any predisposing factor or underlying heart disease for infective endocarditis in our patient. There was no growth in cultures after the fourth day of antimicrobial treatment. The patient responded clinically, becoming afebrile and enabling a reduction in inotropes. Cranial MRI imaging was planned for the patient because consciousness was delayed. Repeat brain MRI on day 14 showed nodular areas consistent with cerebritis (Fig. 3). The patient's ampicillin-sulbactam treatment was continued for 6 weeks to treat her infective endocarditis and cerebritis due to invasive *S. aureus*.

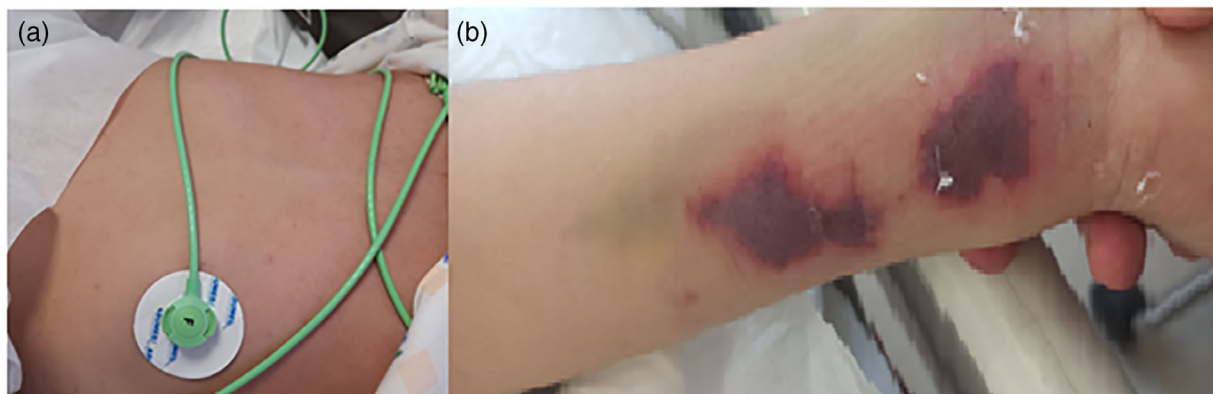


Fig. 2 (a) Maculopapular rash on trunk that faded with pressure. (b) Ecchymotic lesion on left forearm.

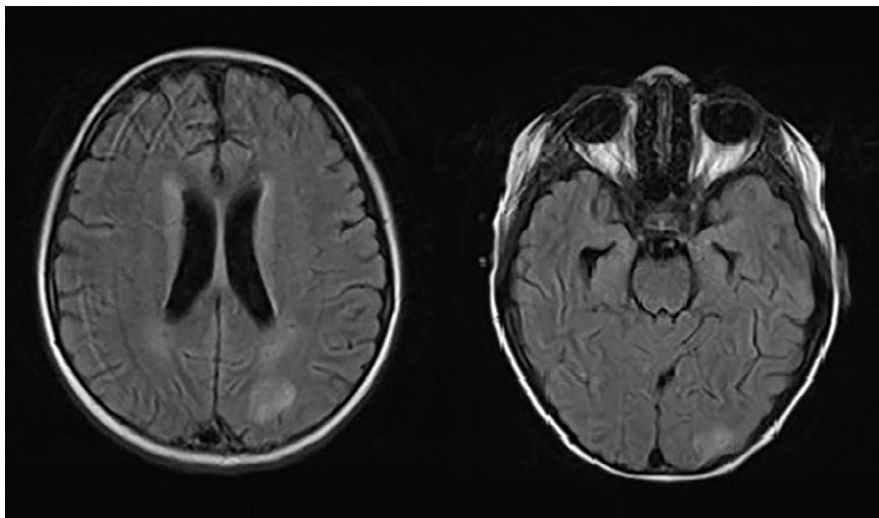


Fig. 3 Second cranial magnetic resonance imaging (2 weeks later). Imaging findings consistent with cerebritis. Nodular areas located in the left occipital cortical-subcortical region, medial to the right thalamus, in the cerebri of the mesencephalon crus, showing diffusion restriction on diffusion-weighted imaging.

Discussion

We present a case of invasive *S. aureus* infection mimicking MIS-C. Since the treatment differs between these two entities, differentiation of invasive bacterial infection and MIS-C is crucial.

Both diseases may cause persistent fever, elevated inflammatory markers, cardiological, respiratory, gastrointestinal, neurological, haematological, and skin findings.^{2,5} Our patient had multisystem involvement due to invasive bacterial infection. Our case had features consistent with MIS-C, but the growth of *S. aureus* from blood and CSF cultures caused us to revise our diagnosis. Aseptic meningitis and elevated leukocyte count in the CSF could be seen in patients with MIS-C. However, CSF culture positivity for *S. aureus* in our patient was thought to be associated with central nervous system infection.

It is important when considering that a child might have MIS-C to consider and exclude all other differential diagnoses.^{2,5} Kawasaki disease, severe acute COVID-19 disease, bacterial sepsis, toxic shock syndrome, systemic viral infections due to Epstein–Barr virus, cytomegalovirus, adenoviruses or enteroviruses, haemophagocytic lymphohistiocytosis, systemic lupus erythematosus, and vasculitis should be kept in mind. In a study of 39 patients evaluated for MIS-C, 11 were found to have non-SARS-CoV-2 infections, although 3 of these were also diagnosed with MIS-C.⁶

SARS CoV-2 serology positivity is included in the World Health Organization and Centers for Disease Control and Prevention criteria used in the diagnosis of MIS-C.^{3,5} Because antibody positivity has become increasingly common in the community with the pandemic, diagnosis should be based on clinical decisions rather than the laboratory. A patient can be incidentally sero-positive for COVID-19 but have another invasive disease.

We found a recent case report of a previously healthy 10-year-old with fatal *S. aureus* infective endocarditis, which was clinically compatible with MIS-C.⁷ The use of intravenous immunoglobulin, glucocorticoids and biologic agents for the treatment of MIS-C is currently not standardised and they are recommended

based on clinical presentation.² It is not known whether such therapies are harmful if the child with suspected MIS-C actually has bacterial sepsis. More importantly, in a child with suspected MIS-C, the possibility of bacterial sepsis should be strongly considered, and consideration given to starting empiric antibiotics while awaiting blood culture results.

Informed consent has been obtained from parents for incorporating the patient details and clinical photographs into the manuscript.

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