Case Report

Are we overdiagnosing multisystem inflammatory syndrome in children (MIS-C)? A case series of children with bacterial infection mimicking MIS-C

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Abstract

Introduction: Multisystem inflammatory syndrome in children (MIS-C) is a serious hyperinflammatory condition associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Usually, the diagnosis of MIS-C is made by criteria defined by international organizations, which include specific clinical features, laboratory findings, and evidence of SARS-CoV-2 infection. We hereby present a case series of three children. The objective of this case series, involving chart review of medical records of children admitted with MIS-C, is to emphasize that the features of MIS-C may overlap with other conditions.

Case presentation: Three children were presented with MIS-C based on WHO criteria and given treatment for the same. However, due to persistent symptoms, they were further worked up and diagnosed to have underlying bacterial infections which included liver abscess, enteric fever, or urinary tract infection.

Conclusions: The criteria for MIS-C may overlap with other conditions, particularly bacterial infection that may lead to overdiagnosis of MIS-C. Therefore, one should be very careful in making an MIS-C diagnosis and other differential diagnoses should be considered when the symptoms persist or worsen.

Key words: multisystem inflammatory syndrome; MIS-C; bacterial; tropical infections; SARS-CoV-2.


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Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a serious hyperinflammatory condition associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection [1]. It was first reported in the UK as a severe shock-like illness in children with features suggestive of incomplete Kawasaki disease (KD) [2]. Subsequently, the Centers for Disease Control and Prevention (CDC) named it MIS-C [3]. It is a rare but potentially serious condition that can occur in children and adolescents following coronavirus disease 2019 (COVID-19) infection, and is characterized by fever, elevated inflammatory markers, and multisystem organ involvement. The etiology is attributed to immunological deregulation once the acute illness subsides [4]. The diagnosis of MIS-C is based on criteria laid down by the World Health Organization (WHO), Royal College of Pediatrics and Child Health (RCPCH), and CDC [3,5,6]. These criteria are more or less similar and include clinical characteristics, laboratory investigation, and evidence of SARS-CoV-2 infection or exposure in the previous four weeks. Although these criteria are suitable for screening MIS-C, sometimes the criteria may overlap with severe illnesses. This overlap makes it challenging for clinicians to differentiate between them and provide timely management. We present a case series of three children who were initially diagnosed with MIS-C based on WHO criteria and treated following our national guidelines [7].

However, due to persistent symptoms, these children were further worked up and found to have an underlying bacterial infection.

Case description

All the three cases presented to us with high-grade fever with multi-organ involvement. Upon investigation, they fulfilled the WHO criteria for MIS-C, including the negative test for tropical infection at presentation. Hence, they were treated as MIS-C, and later on, they turned out to be bacterial infections.

Case one

A three-year-old male child presented with high-grade fever for three weeks and gastrointestinal symptoms (pain in the abdomen, vomiting, and loose motion) for three days. The investigation fulfilled the criteria of MIS-C (Table 1). He was treated for MIS-C
with intravenous (IV) methylprednisolone and aspirin per the standard protocol [7]. Since he had a persistent fever, additional workup was done, including a chest X-ray, urine microscopy, and culture; and they were all normal. Ultrasound sonography (USG) of abdomen showed a hypoechoic lesion in the left lobe of the liver, suggesting a liver abscess. The computed tomography (CT) scan of the abdomen further confirmed this. He was started on IV antibiotics (metronidazole and ceftriaxone) and underwent ultrasound-guided pigtail drainage. He became afebrile within three days of starting antibiotics; the drain was removed after eight days with the resolution of the collection, and he was discharged on oral antibiotics. There was no growth of any bacteria from blood and liver aspirates. He was given six weeks of antibiotics and had complete resolution of the lesion on a USG scan.

Case two
A 15-year-old girl presented with fever, vomiting, loose stools, and decreased urine output for three days. On examination, she had generalized erythematous rash and chelitis. The vitals and systemic examination were within normal limits. However, she developed shock on day one of admission, requiring inotropic support. Initial blood investigations showed elevated inflammatory markers, and coagulopathy with raised cardiac markers, and she was positive for COVID-19 serology. Investigation for tropical infections was negative (Table 1). She fulfilled the criteria of MIS-C and was treated with intravenous immunoglobulin (IVIG) at 2 gm/kg. However, she did not respond and had a persistent fever, so further work was done. The child had persistent fever spikes and further workup revealed *Salmonella typhi* in the blood culture, for which IV antibiotics were started. She became afebrile after two days and was discharged on oral antibiotics to complete the therapy.

Case three
A nine-month-old male infant presented with fever with peeling of skin from the palms and soles for five days, along with loose stool, vomiting, and intermittent abdominal pain for three days. He was febrile,
hemodynamically stable, and had a normal systemic examination. Blood investigations showed elevated inflammatory and cardiac markers and evidence of coagulopathy. Common tropical infections were ruled out, and urine microscopy was normal (Table 1). As the criteria for MIS-C were met, the child was given IVIG at 2 gm/kg and aspirin per the protocol [7]. However, the fever spikes persisted, and repeat sepsis workups were done. Meanwhile, a repeat urine culture indicated presence of Escherichia coli. Appropriate antibiotics were initiated based on the sensitivity pattern, and the child became afebrile within 48 hours of antibiotics; and was discharged on oral antibiotics to complete the therapy.

Discussion

These three cases highlight the importance of considering other potential causes of fever, and especially bacterial infection, in addition to MIS-C. All these cases fulfilled the WHO criteria for MIS-C, and treatment was started. However, they did not respond to the therapy and were diagnosed with a bacterial infection on further investigation. This report emphasizes that one should not diagnose MIS-C in a hurry, and instead maintain a high index of suspicion for other infections.

This case series highlights the diagnostic dilemma of the clinician when treating children with febrile illness and elevated inflammatory markers, which typically fit the criteria needed for MIS-C. Fever and gastrointestinal symptoms with elevated inflammatory markers and multisystem involvement are the characteristic features of MIS-C. However, these are nonspecific features and can be exactly similar in various infectious or inflammatory conditions making precise diagnosis quite challenging. A case series from the USA by Dworsky et al. described 5 children who were ultimately diagnosed with bacterial enteritis [8]. Similarly, Sudeep et al. reported nine children with fever, gastrointestinal symptoms, and raised inflammatory markers mimicking MIS-C. Five of them were positive for SARS-CoV-2 antibodies. However, blood cultures indicated Salmonella typhi in seven, and Escherichia coli and Enterococcus raffinosus in one each; leading to a final diagnosis of bacterial enteritis [9]. These authors also concluded that a high suspicion of other infections should be maintained while diagnosing MIS-C.

In this series, all the three children had SARS-CoV-2 antibody positivity, questioning the validity of positive serology in diagnosing MIS-C. As the SARS-CoV-2 pandemic was cyclical, most individuals may have been exposed (symptomatically or asymptotically) and would have developed antibodies. Thus, positive antibody titers did not guarantee the diagnosis of MIS-C. WHO defines evidence of SARS-CoV-2 infection in the form of at least one of the following: positive serology, reverse transcriptase polymerase chain reaction (RT-PCR), antigen test, and/or contact with an individual with COVID-19 [6]. None of these children had any other evidence of SARS-COV-2 except positive serology.

Furthermore, treatment of MIS-C (IVIG and/or steroids) can ameliorate the symptoms or signs of any underlying disease. The overall morbidity and mortality can increase due to flaring up of the underlying infection if present. Therefore, it is prudent to evaluate for any possible underlying infection before making a diagnosis of MIS-C and initiating the treatment.

Conclusions

The clinical and laboratory criteria of MIS-C are not very specific and can overlap with many other infections. Therefore, a high degree of suspicion of other infections should be maintained while diagnosing MIS-C. Furthermore, the presence of COVID-19 antibodies as evidence of SARS-COV-2 infection should be reconsidered.

Authors’ contribution

PK, LS, JPG: conceptualization of idea, literature search, initial manuscript preparation; AK, NR, KB: data collection, literature search, initial draft preparation. The manuscript was critically reviewed and approved for publication by all authors. PK will act as a guarantor for this manuscript.

References


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