JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Case Report

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

Anil Kumar[1], Nikhil Rajvanshi[1], Kalyana Prabhakaran[1], Lokesh Saini[1], Jagdish Prasad Goyal[1], Prawin Kumar[1]

[1] *Department of Pediatrics, All India Institute of Medical Sciences, Jodhpur, India*

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 World Health Organization (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.

J Infect Dev Ctries 2024; 18(5):822-825. doi:10.3855/jidc.18269

(Received 17 April 2023 – Accepted 08 November 2023)

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 cheilitis. 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,

Table1. Patient characteristics and laboratory investigations.

Criteria for MIS-C (as per the WHO)	**Case 1**	**Case 2**	**Case 3**
Age (0-19 years)	3 years	15 years	9 months
Gender	Male	Female	Male
Fever for ≥ 3 days	Yes	Yes	Yes
Clinical signs of multisystem involvement (at least 2 of the following):			
Rash, bilateral non-purulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)	No	Yes	Yes
Hypotension or shock	Yes	Yes	No
Cardiac dysfunction, pericarditis, valvulitis or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP)	Yes	Yes	Yes
BNP (Ref: 125 pg/mL)	206	889	559
Troponin (Ref: < 0.001ng/mL)	< 0.001	< 0.001	< 0.001
Echocardiogram	Normal	Normal	Normal
Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)	Yes	Yes	Yes
D-dimer (µg/mL) (Ref < 2 µg/mL)	> 20	3.5	> 20
Fibrinogen (Ref:< 150 mg/dL)	450	505	415
Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)	Yes	Yes	Yes
Elevated markers of inflammation (ESR, CRP, or procalcitonin)	Yes	Yes	Yes
CRP (mg/dL) (Ref < 10mg/L)	89	96	25
Procalcitonin Ref (< 1 ng/mL)	7.8	8.2	19.7
Ferritin (Ref < 7-140 ng/mL)	226	543	340
No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes	No	No	No
Tropical Infections			
Dengue	Negative	Negative	Negative
Malaria	Negative	Negative	Negative
Typhoid Serology	Negative	Negative	Negative
Evidence of SARS-CoV-2 infection (Any of the following):	Yes	Yes	Yes
Positive SARS-CoV-2 RT-PCR	-	-	-
SARS-CoV-2 antibody (Ref: < 50AU/mL)	126.7	116.2	154.2
Positive antigen test	-	-	-
Contact with an individual with COVID-19	-	-	-
Further work up			
Urine culture	Sterile	Sterile	*E. coli*
Blood culture	Sterile	*S. typhi*	Sterile
Final Diagnosis	**Liver abscess**	**Enteric fever**	**Complicated UTI**

MIS-C: multisystem inflammatory syndrome in children; BNP: brain natriuretic peptide; COVID-19: coronavirus disease-2019; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; SARS-CoV-2: severe-acute-respiratory-syndrome-related coronavirus -2; RT-PCR: real time polymerase chain reaction; UTI: urinary tract infection.

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 presented with fever, gastrointestinal symptoms, and hyperinflammation, and initially fulfilled the criteria of MIS-C. They 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 asymptomatically) 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

1. Kaushik A, Gupta S, Sood M, Sharma S, Verma S (2020) A systematic review of multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. Pediatr Infect Dis J: E340-E346. doi: 10.1097/INF.0000000000002888.
2. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P (2020) Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 395: 1607. doi: 10.1016/S0140-6736(20)31094-1.
3. Centers for Disease Control and Prevention (2022) Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). Available: https://www.cdc.gov/mis/mis-c/hcp/index.html. Accessed: 20 March 2023.
4. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, Behrens EM, Ferris A, Kernan KF, Schulert GS, Seo P, Son MBF, Tremoulet AH, Yeung RSM, Mudano AS, Turner AS, Karp DR, Mehta JJ (2022) American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and

hyperinflammation in pediatric COVID-19: version 3. Arthritis Rheumatol 74: e1-e20. doi: 10.1002/art.42062.
5. RCPCH (2020) Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. R Coll Paediatr Child Heal 57: 868. doi: 10.1007/s13312-020-1975-7.
6. WHO (2020) Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. Scientific brief. Available: https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19 . Accessed: 15 March 2023.
7. Singh S, Suri D, Chakrabartty S (2022) Standard treatment guidelines. Multisystem Inflammatory Syndrome in Children. Indian Academy of Pediatrics 2022: May.
8. Dworsky ZD, Roberts JE, Son MBF, Tremoulet AH, Newburger JW, Burns JC (2021) Mistaken MIS-C: a case series of bacterial enteritis mimicking MIS-C. Pediatr Infect Dis J 40: E159-E161. doi: 10.1097/INF.0000000000003050.
9. Sudeep KC, Awasthi P, Kumar S, Angurana SK, Nallasamy K, Angrup A, Bansal A, Muralidharan J (2022) MIS-C mimickers: a case series of bacterial enteritis and sepsis mistaken as MIS-C. Indian J Pediatr 89: 206. doi: 10.1007/s12098-021-04019-6..

Corresponding author

Prawin Kumar, MD.
Department of Pediatrics, All India Institute of Medical Sciences, Basani Phase -2, Jodhpur, Rajasthan, 342005, India.
Tel: 9540084230
Email: drprawin484@gmail.com

Conflict of interests: No conflict of interests is declared.