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Indian Journal of Medical Microbiology 39 (2021) 320–322

Contents lists available at ScienceDirect

Indian Journal of Medical Microbiology

journal homepage: www.journals.elsevier.com/indian-journal-of-medical-microbiology

Original Research Article

An unusual cause of fever and jaundice

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ARTICLE INFO

Keywords:
MIS-A
Adults

ABSTRACT

A 52 year old previously healthy woman from Mumbai presented with fever and jaundice of 10 days duration. At admission, she was jaundiced with tachycardia, tachypnea, hypoxia, hypotension, conjunctival congestion and mild erythematous flush over the skin. She had very high WBC counts and CRP's with direct hyperbilirubinemia and azotemia. Investigations for infectious causes of fever were negative. RT-PCR for SARS-CoV-2 in the nasopharynx was negative. However her SARS-CoV-2 antibodies were reactive. She also had echocardiographic and biochemical evidence of cardiac dysfunction. The diagnosis of Multisystem inflammatory syndrome–Adult (MIS-A) was thus established. She rapidly improved with intravenous immunoglobulin (2 gm/kg) and high dose steroids.

1. Case history

A 57-year-old previously healthy woman presented to our hospital emergency department with 10 day history of fever, abdominal pain, headache, nausea and yellowish discoloration of eyes and urine in September 2020. She was admitted to two hospitals before presenting to us. COVID-19 PCR in the nasopharynx was tested twice earlier and was negative. Previous investigations showed high white cell counts (39,000/μl) with high CRP (23 mg/dl) and high serum bilirubin 4.8 mg/dl, mainly direct). Tests for malaria and dengue were negative. She had been treated with multiple broad spectrum antibiotics with no improvement. Examination at admission revealed an acutely unwell looking lady with tachycardia (heart rate 122/min), tachypnea (respiratory rate 22/min), hypotension (blood pressure 90/60 mm Hg), hypoxemia (oxygen saturation 90% on room air), icterus, conjunctival injection and right hypochondrium tenderness. She also had a generalized flush of her skin that was particularly marked over the dorsum of the hands.

2. Differential diagnosis

Differentials of tropical illnesses including dengue, malaria, rickettsial infections, chikungunya, enteric fever, leptospirosis, streptococcal/staphylococcal toxic shock syndrome and gram negative sepsis were considered.

3. Clinical course and investigations

She was admitted to the intensive care unit and relevant investigations sent. Supportive care with oxygen by face mask, intravenous fluids, inotropes was initiated. Intravenous meropenem in doses adjusted to creatinine was also started pending reports. The nasopharyngeal swab for SARS-CoV-2 was negative yet again. Other investigation reports are detailed in Table 1. Notably, there was polymorphonuclear leukocytosis with high C-reactive protein (CRP) and procalcitonin (PCT), elevated creatinine, direct hyperbilirubinemia with normal alanine aminotransferase (ALT)/aspartate aminotransferase (AST). The thick smear for malaria and dengue serology (NS1, IgM and IgG by ELISA) was negative. A set of blood cultures and urine cultures was sent. The multiplex PCR in blood for tropical pathogens (dengue, chikungunya, leptospira, malaria, rickettsia, salmonella, West Nile virus) as tested by FTD tropical core kit (Fast Track Diagnostics, Luxembourg) was negative. A plain CT chest and abdomen was unremarkable.

There with persistent fever, increasing hypoxia and inotrope requirement over next 48 h. Laboratory parameters worsened (Table 1). At this time doxycycline, clindamycin and teicoplanin were added (to cover for rickettsia, streptococcal toxic shock and methicillin resistant *S. aureus*) and intravenous hydrocortisone was added @ 50 mg 6 hourly (in view of the refractory shock). The blood and urine cultures were negative at 48 h. Viral studies for hepatotropic viruses, EBV, CMV were

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https://doi.org/10.1016/j.ijmmb.2021.02.001
Received 8 November 2020; Received in revised form 14 February 2021; Accepted 15 February 2021
Available online 20 February 2021

Table 1
Serial investigations in the index case.

Investigations	Day 0	Day 1	Day 2	Day 3	Day 4	Day 6	Day 8
Haemoglobin(g/dl)	9.3	9.2	9.2	9.5	8.6	8.0	8.4
WBC (/microL)	39000	45000	49760	41590	18880	19840	22060
Platelets (10^5/microL)	1.29	1.06	1.13	1.37	1.55	1.76	4.30
T. Bilirubin (Direct bilirubin) (mg/dl)	6.0 (5.6)	6.9 (5.9)	7.7(6.9)	6.5 (5.9)	2.3(2.3)	1.6(1.3)	0.7(0.4)
CRP (mg/dl)	41.3			21.7	8.5	3.6	0.354
Procalcitonin (ng/ml)	9.06		3.42		1.5	0.7	
Ferritin (ng/ml)			2038.0		621.60		489.2
D-Dimer (ng/ml)			2261.0		2061.82		1059.56
IL-6 (pg/ml)			321.0				
Creatinine(mg/dl)	2.7	1.7	1.53	1.66	1.54	0.98	0.56
Troponin I (pg/ml)			3132.5		374.70	79.90	
NT pro BNP (pg/ml)			16939.0			2896	

negative. MRCP was normal. Autoimmune markers including ANA by IF, ANCA MPO and ANCA PR3 by ELISA were negative.

4. Additional investigations and final diagnosis

The patient was deteriorating and none of the investigations yielded a diagnosis. At this point an infectious disease consult was requested. The possibility of MIS-A was considered and further tests ordered. The SARS-CoV-2 total antibodies (IgM + IgG) were positive (electro-chemiluminescence immunoassay on Elecsys®, Roche, Switzerland). The 2D ECHO showed left ventricular ejection fraction of 45% with grade 2 diastolic dysfunction. The Troponin I (Trop I) and pro brain natriuretic peptide (pro BNP) were significantly elevated and so were the serum ferritin, IL-6 and D- Dimer (Table 1).

The case profile fulfilled the diagnostic criteria for Multi system inflammatory syndrome (MIS-A). These criteria include 1) a severe illness requiring hospitalization in a person aged ≥21 years 2) a positive test result for current or previous SARS-CoV-2 infection (nucleic acid, antigen, or antibody) during admission or in the previous 12 weeks 3) severe dysfunction of one or more extra pulmonary organ systems (heart/liver/kidney etc) 4) laboratory evidence of severe inflammation (e.g., elevated CRP, ferritin, D-dimer, or interleukin-6) 5) absence of severe respiratory illness and finally 6) absence of other infectious causes [1]. Treatment with high dose methylprednisolone 1 gm daily for 3 days and IVIG 120 gm over 48 h was started. Anticoagulation with dalteparin 2500 IU twice daily was also initiated. There was a dramatic improvement in her clinical and biochemical parameters over the next few days with cessation of requirement of inotropes and oxygen after third and fifth day respectively and resolution of jaundice, tachycardia and tachypnea. The laboratory parameters also normalized (Table 1, Fig. 1). Follow up ECHO showed normalization of the diastolic dysfunction. After the 3 pulses of 1 gm each, the steroids were reduced to 2 mg/kg of methylprednisolone. Anticoagulants continued and antibiotics were stopped. The steroid dose was further tapered. The patient was discharged after 2 weeks of hospital stay on tapering doses of oral prednisolone. She was well at a 2 week follow up.

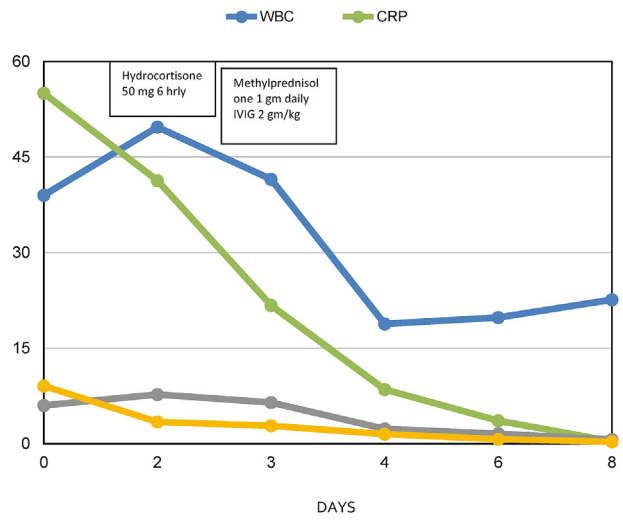

Fig. 1. Trend of investigations following the therapeutic intervention.

5. Clinical perspectives

Our patient fulfilled the criteria for MIS-A as discussed earlier. The clinical and laboratory features of our case are similar to those described previously from Europe and the USA [1].

The diagnosis did come as a surprise to the treating team as it was not a part of the initial differential diagnosis. This is because while multi system inflammatory syndrome (MIS) related to COVID-19 has been frequently described in children (MIS-C) [2,3] cases of MIS in adults (MIS-A) have only recently been reported [1,4]. Lack of awareness amongst physicians about this entity in adults is probably responsible for missed diagnosis at other centers and delay in diagnosis in this patient at our centre.

There are no guidelines pertaining to treatment of MIS-A in adults. So treatment protocols are extrapolated from pediatric studies and also from what is reported in literature [2,3]. Intravenous immunoglobulin with high dose steroids are considered to be the corner stone of therapy. Anticoagulation is crucial since MIS-A is a pro inflammatory and pro-thrombotic state. While in this patient IVIG could be given, the cost of IVIG is a limiting factor in resource limited settings such as ours. Hence there is a need to explore the possibility of using steroids alone in management of MIS-A especially in the milder variants.

6. Microbiologic perspectives

Exclusion of other causes of a sepsis like syndrome by appropriate microbiologic tests is crucial before diagnosing MIS-A. In India, tropical illnesses including malaria, leptospirosis, dengue, rickettsia and gram negative sepsis are likely to be commoner differentials of MIS-A as compared to streptococcal and staphylococcal toxic shock syndromes mentioned in Western literature. Also, in places with high prevalence of COVID-19, SARS-CoV-2 antibodies may be incidentally present in many individuals without a causal association with the sepsis syndrome [5].

7. Take home messages

We recommend that MIS-A be considered as a differential in adults presenting with fever and multi organ dysfunction in the setting of the

current COVID-19 pandemic once all other common infectious causes of sepsis are ruled out.

CRediT authorship contribution statement

Umesh Varyani: Conceptualization, Writing – original draft, Formal analysis. **Tanu Singhal:** Writing – original draft, Formal analysis. **Sharad Sheth:** Clinical management, Writing – original draft, Formal analysis. **Kiran Shetty:** Clinical management, Formal analysis, Investigation. **Pradnya Harshe:** Data curation, Formal analysis. **Sweta Shah:** Investigation, Formal analysis.

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