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Case Report

A rare case of multisystem inflammatory syndrome in adults – a diagnostic dilemma

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ABSTRACT

Multisystem inflammatory syndrome (MIS) is a rare and severe post-infectious inflammatory disorder involving multiple systems (cardiovascular, gastrointestinal, dermatologic, nervous system, and haematological) without significant respiratory involvement. It is predominantly seen in children but sometimes in adults, usually after 3-6 weeks of COVID-19 infection or vaccination. It is postulated to be due to immune dysregulation. This case report adds to the limited literature available on post COVID MIS in adults, emphasizing how to reach the diagnosis after ruling out other differentials. Timely initiation of treatment gives gratifying results in most patients.

Keywords: Multisystem inflammatory syndrome, MIS, Post-COVID infection

INTRODUCTION

MIS in adults (MIS-A) has been recognised as a severe multisystemic disorder requiring hospitalisation in a person aged more than or equal to 21 years, with laboratory evidence of current or previous COVID-19 infection within the preceding 12 weeks. It presents with severe extrapulmonary multiorgan dysfunction, laboratory evidence of severe inflammation and absence of severe respiratory disease.[1]

This syndrome (MIS) was first reported in children after COVID-19 infection (referred to as MIS-C).[2] But slowly, cases of MIS also cropped up in adults (referred to as MIS-A).

In general, MIS-A patients have significant overlapping clinical features with MIS-C, although the severity of myocardial involvement, thrombosis and mortality may be higher compared to children.[1] Now, MIS cases after COVID vaccination are also on the rise with the increasing vaccine cover in the world.[3]

CASE REPORT

A 50 years old female, non-diabetic and non-hypertensive, presented to emergency with complaints of high-grade fever with chills and rigours for five days, generalised maculopapular rash for three days. There was also a history of gastrointestinal symptoms like pain abdomen, diarrhoea (6-7 episodes a day) and vomiting from the last two days. The patient developed headaches, confusion, and altered sensorium one day prior to admission. In addition, there was a significant history of mild cough and sore throat 20 days back. At that time, she was diagnosed with mild reverse transcriptase-polymerase chain reaction (RT-PCR) positive COVID-19 illness, from which she recovered completely. At the time of presentation, she did not have respiratory complaints. On general physical examination, the patient was in shock with blood pressure of 90/60 mmHg, Glasgow coma scale (GCS) of 11/15 (E3 V4 M4) with bilateral pedal oedema. She had high-grade

fever with mucocutaneous lesions (generalised maculopapular rash along with petechiae symmetrically distributed over the trunk and extremities with bilateral conjunctivitis). Neurologically, her pupils were 3 mm (bilaterally equal and reactive to light) with no neck rigidity and focal neurological deficits. There was no disc oedema on fundus examination. The abdomen was diffusely tender with a palpable spleen, and chest examination was unremarkable.

The rest of the investigations like renal function test (RFT), cultures (blood, sputum and urine), antinuclear antibodies (ANA) profile, viral markers, cytoplasmic-antineutrophil cytoplasmic antibodies (C-ANCA) and perinuclear-ANCA (P-ANCA) were negative. Cerebrospinal fluid (CSF) was normocellular with normal proteins and glucose. All stains, cultures and Biofire panel for all organisms, including bacteria, viruses, and fungus, were negative in CSF, including COVID-19 PCR. Echo repeated twice was normal. Computed tomography (CT) of the chest showed mild bilateral pleural effusion with no evidence of pneumonitis. The flu panel from the nasopharyngeal swab was negative.

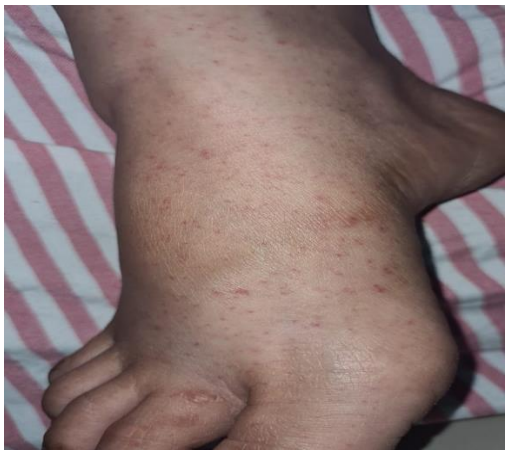

Figure 1: Maculopapular rash in patient.

Table 1: Investigations.

Investigations	19 May 2021	21 May 2021	24 May 2021	27 May 2021
RT-PCR COVID at time of admission	Negative			
COVID IgG antibodies	Positive			
TLC/DLC	11,200 93/4/3/0/0	21,600 81/16/2/1/0	15,800 83/13/2/2/0	11,800 76/20/4/0/0
Platelet (mm^3)	70,000	1,20,000	1,75,000	2,30,000
CRP (mg/dl)	336	294	29	9
Procalcitonin (ng/dl)	3.36	---	0.45	0.186
LFT				
S. bilirubin	0.6			
SGOT/SGPT	60/85			
Total serum protein	4.3			
S. albumin	2.3			
Globulin	2.0			
ALP	163			
IL-6 (pg/ml)	1189	---	9.6	--
Pro- BNP (pg/ml) N<125	7485	---	6588	3500
S. ferritin (ng/ml)	1946			

DISCUSSION

Our patient posed a tough diagnostic dilemma as this is a new entity. MIS-A is a real bedside challenge in which, on the one hand, one has to think about ruling out sepsis because of fever, leucocytosis and raised procalcitonin levels, while on the other hand, we think of immune-mediated multisystemic inflammatory disorder.

To summarise, 50 year female without any co-morbidities with a history of mild COVID illness 20 days back, now presented with acute onset fever with multiorgan involvement (GIT, skin, nervous system, asymptomatic cardiac involvement, haematological) over five days. She had no respiratory symptoms (both clinically and radiologically). She had raised inflammatory and coagulopathy markers like C-reactive protein (CRP), serum ferritin and D dimer. She also had a high level of procalcitonin and pro B-type natriuretic peptide (BNP). The serum COVID IgG antibodies were positive with negative nasopharyngeal COVID-19 PCR. Our patient underwent extensive workup to rule out sepsis, autoimmune disorder and other etiologies as the management can vary significantly.

Differential diagnosis

The following differentials were entertained and deciphered one by one.

Acute pulmonary COVID

This is one of the least possible diagnoses because the patient had RT-PCR positive mild COVID-19 illness 20 days back from which she has recovered completely. During this admission, she had normal oxygen saturation at room air with no respiratory complaints, negative RT-PCR, normal chest examination, and CT chest showing mild pleural effusion with no evidence of pneumonia to suggest pulmonary COVID-19.[4]

Acute non-pulmonary severe COVID

Extrapulmonary manifestations, elevated markers of coagulopathy and inflammation can also be seen in acute severe COVID-19. However, MIS-A appears to be a distinct post-acute, postinfectious illness, often after a recovery period, and is indicated by the onset of new symptoms. However, efforts are needed to distinguish it from the theoretical possibility of acute biphasic COVID-19. Some considered MIS-A might be a late sequela of acute COVID-19 infection. Further research is required to understand the immunopathogenesis of MIS-A and to prove or refute this assumption.[5]

Bacterial sepsis including leptospiral and rickettsia[4,6]

A solid possibility to be kept in mind, especially when the patient had fever with higher procalcitonin levels but ruled out as all cultures were negative, no focus of infection on any radiology. Furthermore, bacterial infection usually starts with one focus before involving multiple systems rather than simultaneously multiple organs. Increased Procalcitonin levels further add to the dilemma, but it is pertinent to mention that it can be raised even in non-infectious Inflammatory disorders, contrary to the usual notion.[7] Clinical features like myocardial involvement and coronary secondly, artery abnormalities favors the possibility of MIS-A. However, it is always safe to start empiric broad-spectrum antibiotics until all cultures are negative.

Staphylococcal and Streptococcal toxic shock syndrome

It can involve multiple systems at a rapid pace, but these can be differentiated based on skin lesions, with Nikolsky's sign often being present. Profuse prodromal diarrhoea followed by hypotension is a common symptom of Staphylococcal infection. Although, abdominal symptoms can be seen in both MIS-A and TSS but cardiac dysfunction is a hallmark of MIS-A.[4,8,9] Moreover, microbiologic tests (SARS COVID-19 testing, bacterial cultures) are necessary to rule out the possibility.

Viral sepsis and exanthematous fevers

Some viruses like human-immunodeficiency virus (HIV), adenoviruses, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) can present with multisystem involvement but usually in immunocompromised individuals.[4] Moreover, investigations failed to find any evidence of viral infection. The respiratory flu panel and CSF bio fire panel for all bacteria, viruses and fungus were negative. Furthermore, the excellent response to steroids favours post-inflammatory phenomenon rather than viral illness.

Autoimmune disorders like SLE

They may present multisystemic involvement, but renal, musculoskeletal and with CNS involvement is more prominent in autoimmune disorders. In addition, progression is usually slow. Sometimes SLE can present with fulminant illness, but such patients usually have fatigue and other constitutional symptoms before the onset of severe disease. However, patients with MIS-A are entirely well before the disease. Furthermore, the immunological workup was negative in our case.

Macrophage activation syndrome (MAS)

It is primarily a pediatric disorder triggered by infections, malignancy and autoimmune disease. There is a thin line between MIS and MAS as most symptoms overlap. Clinical features involving the gastrointestinal system, shock, swelling of hands and feet, and skin desquamation are seen predominantly in MIS, while cytopenia, transaminitis, and hepatosplenomegaly are more common with MAS. Hemophagocytosis on bone marrow, spleen or lymph nodes biopsy confirms the diagnosis.[10]

Our patient had acute onset fever, shock, multisystem involvement in the form of encephalopathy, mucocutaneous lesions, abdominal symptoms, thrombocytopenia, markedly elevated inflammatory markers, elevated pro-BNP levels in the absence of significant pulmonary symptoms and other etiologies and the background of the recent history of COVID-19 illness, positive COVID-19 antibodies, thus fulfilling all the criteria for rare diagnosis of MIS-A laid down by CDC.

MIS-A in adults is defined by CDC as given in Table 2.[11]

MIS-A can occur after an asymptomatic or symptomatic COVID-19 infection. Therefore, it can present heterogeneous clinical manifestations. The systematic review of 221 patients by Patel et al found that 96% of patients with MIS-A presented with fever, 60% had hypotension, cardiac dysfunction was seen in 54%, shortness of breath and diarrhoea each in 52%. The average number of organ systems involved in MIS were 5. Around 90% of patients had elevated coagulopathy and inflammatory markers, and 72% had positive SARS-CoV-2 serologic findings.[5]

Patients with COVID-19 can have a broad spectrum of cardiac complications. They can be asymptomatic with or without elevated TropT and Pro BNP levels or symptomatic with cardiac arrhythmia, myocarditis, left or right ventricular dysfunction, myocardial infarction, heart failure etc.[12] Similar multisystem abnormalities in MIS-A are also reported by different authors.[1,13]

The pathophysiology of MIS-A is poorly understood. However, the mechanism is proposed to be due to a dysregulated immune complex activation, causing direct endothelial damage, associated thrombo-inflammation and subsequent cytokine storm.[1]

Regarding treatment, there are no existing accepted guidelines yet for the diagnosis and treatment for MIS-A and management have been extrapolated from guidelines of MIS-C patients recommended by The American College of Rheumatology.[14] Treatment options include steroids, IVIG, tocilizumab and Anakinra.

On the management part, our patient was started on broad-spectrum antibiotics (till all cultures were negative), inotropes and iv steroids, i.e. methylprednisolone 1 gram per day for three days. There was a rapid improvement of symptoms with the resolution of fever, rash abdominal symptoms and sensorium. The patient was clinically stabilised with a gradual reduction in inotropes. Over the next few days, her inflammatory markers came to normal. She was discharged home with a tapering dose of oral prednisolone over two weeks. The patient's symptoms resolved when seen in the outpatient clinic two weeks following discharge from the hospital, although fatigue and mild general weakness persisted.

Table 2: CDC guidelines.

S. no.	CDC case definition for MIS-A
	A patient aged ≥21 years hospitalized for ≥24 hours, or with an illness resulting in death, who meets the following clinical and laboratory criteria. The patient should not have a more likely alternative diagnosis for the illness (e.g. bacterial sepsis, exacerbation of a chronic medical condition)
1.	Primary clinical criteria
	Severe cardiac illness Includes myocarditis, pericarditis, coronary artery dilatation/aneurysm, or new-onset right or left ventricular dysfunction (LVEF<50%), 2nd/3rd degree A-V block, or ventricular tachycardia. (Note: cardiac arrest alone does not meet this criterion)
	Rash AND non-purulent conjunctivitis
2.	Secondary clinical criteria
	New-onset neurologic signs and symptoms Includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome)
	Shock or hypotension not attributable to medical therapy (e.g. sedation, renal replacement therapy)
	Abdominal pain, vomiting, or diarrhea
	Thrombocytopenia (platelet count <150,000/microliter)
3.	Laboratory evidence
	The presence of laboratory evidence of inflammation and SARS-CoV-2 infection
	Elevated levels of at least two of the following: C-reactive protein, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin
	A positive SARS-CoV-2 test for current or recent infection by RT-PCR, serology, or antigen detection

Table 3: Learning points.

S. no.	Learning points
1.	MIS-A usually occurs after three to six weeks of post-acute COVID-19 infection and vaccination with heterogeneous clinical presentations and is likely due to dysregulated immune response
2.	MIS-A is a severe hyperinflammatory condition with extrapulmonary multiorgan dysfunction with absent or mild pulmonary involvement
3.	MIS -A is diagnosed based on the criterion devised by CDC and after ruling out all other differential diagnosis.
4.	The prompt treatment and diagnosis of MIS-A gives gratifying results as the response to steroids and IVIG is dramatic and life-saving
5.	Low-to-moderate doses of oral glucocorticoids may be considered for the treatment of hemodynamically stable MIS-A. High-dose IV pulse glucocorticoids or IVIG or both may be considered to treat patients with life-threatening complications, such as shock, CNS and myocardial involvement

CONCLUSION

MIS-A is a rare but severe complication seen post COVID-19 infection and COVID-19 vaccination. Physicians should always keep this in mind while encountering patients presenting with acute onset multiorgan dysfunction with no or mild pulmonary involvement with raised inflammatory markers after ruling out alternative etiology. The timely diagnosis is of utmost importance as delays in management will affect the outcome. Early treatment with steroids or IVIG can give excellent results. With COVID-19 infections and vaccinations making records with each passing day, we believe that cases of MIS-A will also rise. Therefore, suspicion of this rare but

treatable entity is the need of the hour.

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