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Short Paper

Post-COVID multisystem inflammatory syndrome in adults: a study from a tertiary care hospital in south India

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***Background & objectives*: There are limited data from India on the post-COVID multisystem inflammatory syndrome in adults (MIS-A). The objective of the present study was to evaluate the clinical profile of patients with MIS-A admitted to a tertiary care centre in southern India.**

***Methods*: This single-centre retrospective study was conducted from November 2020 to July 2021, and included patients aged >18 yr admitted to the hospital as per the inclusion and exclusion criteria.**

***Results*: Nine patients (5 male, mean age 40±13 yr) met the criteria for MIS-A. Five patients had proven COVID-19 infection or contact history 36.8±11.8 days back. All patients were positive for SARS-CoV-2 IgG antibody, negative for COVID-19 PCR, and had negative blood, urine and sputum cultures. All patients had fever and gastrointestinal (GI) symptoms, and five patients had left ventricular dysfunction. All patients had neutrophilic leucocytosis at presentation and elevated biomarkers such as C-reactive protein serum procalcitonin, D-dimer and ferritin. The majority of the patients (7/9 *i.e.* 77.78%) were treated with intravenous hydrocortisone (50-100 mg q6h-q8h). Six patients recovered completely whereas three patients expired.**

***Interpretation & conclusions*: Fever and GI symptoms were the most common presentation of MIS-A. Elevated serum procalcitonin may not be useful in differentiating bacterial sepsis from MIS-A. Most patients responded to corticosteroids.**

Key words Multiorgan involvement in adult - multisystem inflammatory syndrome in adults - post COVID - procalcitonin

COVID-19-associated multisystem inflammatory syndrome in adults or MIS-A results from a hyperinflammatory syndrome that begins with the failure of the regulatory immune response to SARS-CoV-2, including abnormal interferon (INF) production that drives macrophage hyperactivation[1]. This causes significant morbidity in post-COVID patients as there is multiorgan involvement and diagnostic dilemma[2]. The diagnostic criteria and treatment were described by Centres for Disease Control and Prevention (CDC), and subsequently, case series and systematic reviews were published[1,3-5]. There are limited data on MIS-A from India. This single-centre study was aimed to evaluate the clinical profile of patients with post-COVID MIS-A in an Indian setting.

Material & Methods

This single-centre retrospective study was conducted in a 650-bedded tertiary care hospital in south India (department of Infectious Diseases, Apollo Hospital, Chennai) from November 2020 to July 2021. All patients aged >18 yr of age admitted to the hospital within the study period were screened electronically as per the final diagnosis (discharge/death) of MIS-A, followed by the review of individual case sheets and electronic records of reports of the screened population. Those who met the CDC criteria except age criteria were included[3]. The age group of 18-21 yr was also included in this study as per the study by Patel *et al*[1]. SARS–CoV-2 IgG antibody was checked in VITROS 3600 immunodiagnostic system manufactured by Ortho Clinical Diagnostics, United States, by chemiluminescence method with a manufacturer-defined cut-off and a level of >75 IU/ml was considered positive. The ethical clearance was provided by the Institutional Ethical Committee (Ref: IEC App no-AMH-C-S-053/12/21).

Inclusion & exclusion criteria: For inclusion at least four of following five criteria including the age criterion were needed: (*i*) an individual ≥18 yr with documented fever (≥38°C); (*ii*) laboratory evidence of inflammation [Elevated C-reactive protein (CRP), ferritin]; (*iii*) evidence of; clinically severe illness requiring hospitalization with multisystem (≥2) organ involvement (cardiac, renal, respiratory, haematological, gastrointestinal (GI), hepatic, dermatologic or neurological system); (*iv*) no plausible alternate diagnosis; and (*v*) positive results for current or recent SARS-CoV-2 infection by reverse transcription-PCR, serologic analysis or exposure to a confirmed COVID-19 case within the 12 wk before the onset of symptoms. Patients <18 yr of age, pregnant women, those with proven sepsis/positive blood culture or any alternative diagnosis were excluded from the study.

The continuous variables were expressed as mean ± standard deviation; the categorical variables were expressed as actual numbers and percentages. As this study was a descriptive reporting of cases, no meaningful comparison and test of significance could be done because of the small number of patients.

Results & Discussion

A total of 20716 patients who were admitted during the study period were screened electronically as per the final diagnosis (discharged/death) of MIS-A. Twelve patients were screened out and their case sheets and electronic records of reports were reviewed individually. Only nine patients (5 male 55.6%, mean age 40±13 yr) met the criteria for MIS-A. Five patients did not have any pre-existing comorbidity. None of the patients were known to have an autoimmune disease. The comorbidities of four patients are depicted in the Table. Seven patients were not vaccinated for COVID-19 at the time of diagnosis; three of them could not recall any recent contact history or past COVID-19 infection. Among the two patients who were vaccinated, one had prior COVID-19 infection 30 days back and the second patient was a healthcare worker who could not recall any prior symptoms of COVID-19 infection. Five patients had a history of proven COVID-19 infection or a significant positive contact history with a COVID-19 patient with a mean duration of 36.8±11.8 days from the current hospitalization. Among these five patients, four had mild COVID-19 infection, not requiring hospitalization. All patients were positive for SARS-CoV-2 IgG antibodies, negative for RT-PCR, and had negative blood, sputum and urine cultures. The demographic details and the baseline clinical and laboratory findings of the patients are depicted in the Table.

All patients had documented fever as per the inclusion criteria and GI symptoms such as diarrhoea (88.9%), vomiting (33.3%), abdominal pain (22.2%) and abdominal discomfort (11.1%). One patient had an erythematous maculopapular rash over the upper limb and trunk and one patient presented with odynophagia and cervical lymphadenopathy. Cardiovascular (6/9, 66.6%), respiratory (6/9, 66.6%), renal (5/9, 55.6%) and hepatic (1/9, 11.1%) involvements were observed whereas none had haematological and central nervous system involvement. Five patients had left ventricular dysfunction with a mean left ventricular (LV) ejection fraction of 41±6. Seven patients had sinus tachycardia in ECG. One patient with rheumatic heart disease required ionotropic support although she had preserved ejection fraction initially, LV dysfunction was observed later in the course, and the patient finally succumbed to death. Five patients required inotropic support. Among these with deranged kidney functions, four patients required haemodialysis. The majority of the patients had neutrophilic leucocytosis at presentation (mean 16293.33±5255.33 cells/mm^3). The mean value of CRP was 286.55±82.55 mg/l. Serum procalcitonin levels were available for

Table. Demography, baseline clinical features and laboratory reports

Case	Age/ sex	Comorbidity	The interval (days) from prior COVID infection/ contact	Symptoms	WBC (cells/ mm^3)/N (%)/l (%)	AST (U/l)/ ALT (U/l)/ creatinine (mg/dl)	CRP (mg/l)/ procalcitonin (ng/ ml)/D dimer (µg/ ml)/ferritin (mg/ml)	Number of the organ involved	Duration of hospital stay (days)	Outcome
1	43/ female	Nil	27 (contact)	Fever, diarrhoea, vomiting, cough	19,830/89/5	42/41/0.6	271/7.32/2.59/1416	3 I	6	Discharged
2	34/ male	Nil	NA	Fever, diarrhoea, abdominal pain	14,860/90/8	107/41/1.3	282/6.02/1.95/-	2	6	Discharged
3	21/ female	Nil	NA	Fever, headache, diarrhoea, vomiting, abdominal pain, cough, rash	11,490/93/3	30/40/1	245/49.6/1.6/734.4	5 I, HD	8	Death
4	42/ female	Nil	NA	Fever, diarrhoea, breathlessness	20,110/74/6	39/35/0.6	165/10/2.5/-	2	4	Discharged
5	64/ male	DM/HTN/ CAD	30	Fever, diarrhoea, breathlessness	20,550/80/6	49/40/2.3	396/1.69/2.05/-	4 I, HD	7	Death
6	35/ male	Obese (BMI 42)	32	Fever, vomiting, odynophagia, neck swelling	16,050/88/9	25/42/1	408/-/1.91/1039.6	2	12	Discharged
7	22/ male	nil	35	Fever, diarrhoea, abdominal pain	9690/89/5	120/103/1.2	164/9.52/1.87/449.8	2	5	Discharged
8	48/ male	HTN/ hypothyroid	NA	Fever, diarrhoea, breathlessness	25,200/87/5	91/452/1.2	321/88.8/23.27/1390	5 I, HD	14	Discharged
9	52/ Female	RHD	60	Fever, diarrhoea, cough, breathlessness	8860/88/7	34/68/0.9	327/100/6.452056	3 I, HD	9	Death

BMI, basal metabolic index; CAD, coronary artery disease; DM, diabetes mellitus; HD, required haemodialysis; HTN, hypertension; I, required inotrope support; NA, not applicable; N, neutrophil; L, lymphocyte; RHD, rheumatic heart disease; WBC, white blood cells; CRP, C-reactive protein; AST, serum glutamic oxaloacetic transaminase; ALT, serum glutamic pyruvic transaminase

eight patients of whom two patients had very high values of procalcitonin (88.8 and 100 ng/ml) as compared to other patients. Procalcitonin values of six patients were taken into consideration to avoid skewing. The mean procalcitonin value was 6.91±2.98 ng/ml. Similarly, the D-dimer values of eight of the nine patients were considered for the calculation of the mean value as one patient had D-dimer of 23.27 µg/ml. The mean values of D-dimer and ferritin were 2.61±1.48 µg/ml and 1180.9±568.9 ng/ml, respectively. N-terminal pro-b-type natriuretic peptide (NT-pro BNP) was elevated in five patients with a mean value of 17241.4±14560.4 pg/ml. Trop I was done on three patients with an average value of 32.97 ng/ml. Lactate was done in five patients and the mean level was 1.14±0.12 mmol/l. Abdominal CT was done in four patients, two of them showed evidence of mesenteric lymphadenopathy or ileocecal wall thickening. Seven patients were treated with intravenous hydrocortisone (50-100 mg q6h-q8h) for 3-5 days followed by oral prednisolone with the dose of 1 mg/kg tapered over two weeks. One unvaccinated female patient presented with fever, diarrhoea and shortness of breath without any localization on imaging was treated with cefoperazone-sulbactam and doxycycline and did not require steroids. She was given tablet colchicine 0.5 mg twice daily for three days. She responded well in four days with supportive management and was discharged without oxygen. All the patients received antibiotics (parenteral) for average 5.55±1.94 days with ceftriaxone (2 patients), amoxicillin with clavulanic acid along with doxycycline (1 patient), cefoperazone with sulbactam and doxycycline (1 patient), piperacillin with tazobactam and doxycycline (1 patient) and meropenem with doxycycline (4 patients). Antibiotics were escalated empirically by the addition of polymyxin B and teicoplanin in three patients who did not survive. Three patients required the addition of intravenous immunoglobulin (2 g/kg) and pulse methylprednisolone (1 g/day for three days). One patient received injection tocilizumab 400 mg single dose. All the patients received parenteral anticoagulation (conventional or low–molecular-weight heparin). Six patients recovered completely and were discharged after a mean duration of 7.8±3.1 days whereas three patients expired.

Multisystem inflammatory syndrome in children (MIS-C) was initially reported from Europe as a Kawasaki-like disease[6] following which the multiple cases of inflammatory multiorgan involvement were reported from the different parts of the world in adults following recent COVID-19 infection. The immunopathogenesis of MIS-A is not well defined but is considered as hyperinflammation due to failure of the regulatory immune response to SARS-CoV-2, INF production that drives macrophage hyperactivation[1]. It is also postulated that MIS-A may be the result of extra-follicular B-cell activation where there is an expansion of plasmablast which causes a maladjusted inflammatory response[7,8]. Cheng *et al*[9] suggested that the hyperinflammatory syndrome in children, as well as adults, may be due to the superantigen-like motif unique to the SARS-CoV-2 that causes the cytokine storm. Davogustto *et al*[2] described a series of 15 cases (>21 yr) of MIS-A where the median age was 45.1 yr and the median interval from prior COVID-19 infection was 23 days, whereas in our study, we included individuals with age >18 yr with the mean age being 40 yr and the median interval from recent COVID-19 infection was 36.8 days. In a study by Davogustto *et al*[2], GI, haematologic and renal involvement were the most common presentations of organ involvement. A series of six cases from India described fever, GI system, and cardiovascular system involvement as the most common presentation of MIS-A[10]. In our study of nine patients, all the patients had GI symptoms. Six patients had cardiovascular and respiratory system involvement and five patients had renal involvement in our study (5 patients required ionotropic support and 4 patients required renal replacement therapy). Follow up echocardiography was done in two patients before discharge which showed normalization of ejection fraction with the improvement of haemodynamic after treatment which was similar to MIS-C cases reported by Patnaik *et al*[11] in which only 15 per cent of patients had mild LV dysfunction with normalization of hemodynamic. Patel *et al*[1] described MIS-A in >18 yr age group similar to the age criteria used in our study. This systemic review included 221 patients with MIS-A in which the median duration of hospitalization was eight (interquartile range, 5-12) days which was similar to our study where the average duration of hospital stay was 7.8 days. None of the patients in our study had arterial or venous thrombosis in contrast to the study by Patel *et al*[1] where five per cent of patients had arterial or venous thrombosis. Sepsis is a close differential to MIS-A. The absence of definite localization of any infective foci clinically and no radiological evidence of pneumonia, pyelonephritis or visceral abscess along with negative blood, sputum and urine cultures and no response to broad-spectrum

antibiotics with a compatible clinical background of MIS-A with dramatic response to steroid in the majority of these patients favoured the diagnosis of this post-COVID inflammatory syndrome. However, all the patients received antibiotics during the early period of admission. In contrast to sepsis, which is the most common differential diagnosis of such clinical scenario, early recognition of the disease and use of corticosteroids may lead to favourable outcome in MIS-A.

Our study reports a small number of patients with MIS-A which is not a common disease. It remains a diagnosis of exclusion and should be kept in mind in patients with recent COVID-19 infection. Sepsis remains the most common differential diagnosis. Elevated serum procalcitonin in MIS-A may not be useful in differentiating it from bacterial infection. Fever and GI symptoms were most common at the presentation. Most patients responded to corticosteroids.

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***Conflicts of Interest*:** None.

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