

Case Report

Post COVID-19 multisystem inflammatory syndrome in adults: a new clinical challenge

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Received: 01 June 2021

Revised: 22 June 2021

Accepted: 23 June 2021

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ABSTRACT

The spectrum of novel coronavirus disease (COVID-19) continues to evolve since its outbreak in November 2019. Although COVID-19 most commonly causes substantial respiratory pathology, it can also result in several extra pulmonary manifestations. Association between COVID-19 disease and a multisystem inflammatory syndrome in children (MIS-C) and adolescents has now been well defined. However, case reports describing a similar phenomenon in adults are sparse. We presented a case of 42 year old male who presented 3 weeks after initial COVID-19 infection with acute ST elevation myocardial infarction, splenic artery thrombosis, generalized anasarca, with hepatic and renal dysfunction, but minimal respiratory symptoms. He had a turbulent hospital course. However timely suspicion of presence of multisystem inflammatory syndrome in adult (MIS-A) and use of hemoadsorption filters helped to save his life.

Keywords: COVID-19, Multisystem inflammatory syndrome-adults, HA 330 filters

INTRODUCTION

The ongoing pandemic of coronavirus disease 2019 (COVID-19) has resulted in an unprecedented health crisis all over the world. It commonly presents with a simple flu-like illness, but there is a significant morbidity and mortality across the globe. In April 2020, a cluster of eight children exposed to COVID-19 was reported presenting with hyper-inflammation, shock and variable features of Kawasaki disease or toxic shock syndrome in London.¹ It was termed MIS-C. Since then, MIS-C has been reported from various parts of the world.² A similar clinical spectrum of post COVID-19 MIS-A. While very few case reports have been published on the topic, MIS-A is gaining recognition among adults.

CASE REPORT

A 42 year old male, non-hypertensive, not a known diabetic, with no previous history of any systemic ailment was diagnosed SARS COVID-19 positive with moderate severity on 21 August 2020. He was treated with remdesivir, steroids and low molecular weight heparin. He had an uneventful course and was discharged after 5 days of treatment. He presented again on 11 September 2020 (3 weeks after index admission for SARS COVID-19) with sudden onset of chest pain and diaphoresis. Electrocardiography (ECG) revealed acute ST elevation inferior wall myocardial infarction with elevated troponin I (3.8 ng/ml, cut-off <0.02 ng/ml). Bedside ECHO revealed inferior wall hypokinesia with mild left ventricular systolic dysfunction, ejection fraction of 45%.

Patient was hemodynamically stable. Total leukocyte count of 16,500 cells/cmm (normal 4,000-11,000 cells/cmm) with neutrophilic predominance. Blood sugar levels were high, with HbA1c of 11.6%. Urine examination was negative for ketone bodies. Inflammatory markers were grossly deranged (Table 1). Tests for SARS-COV2 active infection were negative at

admission. Patient had sufficient COVID-19 IgG antibody titers which ruled out active infection.

Patient was treated with anticoagulants, anti-platelets and low dose steroids. Coronary angiogram was performed on 15 September 2020 which revealed recanalized right coronary artery.

Table 1: Selected biochemical parameters.

Parameters	Normal values	11 September 2020 (3 week since initial infection)	15 September 2020	13 October 2020 (8 week since initial infection)	16 October 2020	20 October 2020	26 October 2020	8 January 2021
Total leucocyte count (/ul)	4000-10000	18,400	14,400	10,000	13000	10,700	10,700	14,100
Polymorphs (%)	40-70	87	88	68	80	91	78	54
Lymphocyte (%)	20-40	6	7	21	12	6.3	15	30
IL-6 (pg/ml)	<7	294			117	116		
D-dimer (ng/ml)	<500	1040	1540	4363		4940	5000	194
LDH (U/l)	313-618	255				203		
Ferritin (ng/ml)	17.9-464	1150				1210		110
CRP (mg/l)	0-6	98	76	88		68		4
Total bilirubin (mg/dl)	0.2-1.3	1.44		1.35				1.1
SGPT (IU/l)	<35	79		1262	1700	750	64	32
SGOT (IU/l)	14-36	55		1829	1495	1192	191	35
Total serum protein (g/dl)	6.3-8.2	6.4		6.1			6.4	8.4
Serum albumin (g/dl)	3.5-5.0	3.3		2.8			3.8	4.0
Blood urea (mg/dl)	15-30				56	115	223	30
Serum creatinine (mg/dl)	0.5-1.4	0.8		0.88	2.47	3.42	2.28	1.27

On 16 September 2020, the patient developed left upper abdominal pain, radiating to left shoulder. Contrast enhanced computerized tomography (CECT) of abdomen revealed splenic artery thrombosis, splenic infarct with abscesses and mild reactive left pleural and pericardial effusion. Blood culture was sterile. Transthoracic and transoesophageal echocardiogram didn't show any vegetation over valves. Patient was managed conservatively initially but his condition deteriorated. After discussion with family members and surgical gastroenterologist, he underwent splenectomy on 22 September 2020. Intraoperative findings showed splenic artery and intra splenic arterioles thrombosis. At the time of discharge inflammatory markers including D-dimer levels were still elevated. Patient was discharged on oral antibiotics and novel oral anticoagulant.

Two weeks after discharge, on 13 October 2020 (approximately 8 weeks after index admission) the patient presented with generalized anasarca, bilateral

pitting edema and breathlessness at rest. Chest roentogram was suggestive of left sided large pleural effusion and mild pericardial effusion with no significant lung parenchymal changes. Echocardiogram showed inferior wall hypokinesia with mild left ventricular systolic dysfunction, ejection fraction 47% and mild pericardial effusion with pericardial thickening with significant respiratory variations across the mitral and tricuspid flow velocities, suggestive of effusive constrictive pericarditis. He was admitted and underwent intercostal drainage. After therapeutic thoracentesis patient improved symptomatically with no need of oxygen support. However, 3 days later the patient again developed generalized anasarca with bilateral pleural effusions, ascites and scrotal edema. Pleural fluid cytology was suggestive of exudative physiology. Pleural fluid ADA was 29 U/l (normal <30 U/l). Pleural fluid culture was negative for any pathogens. Patient had vomiting, loose stools and loss of appetite. Complete blood counts showed leukocytosis with lymphopenia and neutrophilia.

There was sudden deterioration in liver and renal function tests but the patient remained normotensive without any inotropic support. Repeat blood culture was sterile. He was treated with albumin infusions, steroids, antibiotics and anticoagulants. He developed anuria despite normal arterial pressure for which he underwent 2 sessions of renal replacement therapy using HA 330 filters (Jafro, Zuhai City, China). This led to rapid clinical improvement with resolution of generalized anasarca and normalization of hepatic and renal parameters. Inflammatory markers like CRP and IL-6 started declining, but D-dimer levels remained elevated. Patient was discharged in stable condition on oral steroids and novel oral anticoagulants on 26 October 2020.

At 1 month follow up patient was asymptomatic with normal liver and renal parameters and inflammatory markers. D-dimer levels were still elevated (2450 ng/ml). Low dose oral steroid and novel oral anticoagulants continued. D-dimer levels normalized after 3 months.

DISCUSSION

Severe SARS-CoV-2 infection causes hyperinflammation and multiorgan system involvement with respiratory failure as the predominant manifestation. Contrary to that, MIS-A is associated with minimal respiratory symptoms, hypoxemia or radiological abnormalities. One has to exclude all other etiologies like sepsis before considering the diagnosis of MIS-A. There are well laid criteria for diagnosis of MIS-C. Based on MIS-C criteria, criteria for diagnosis of MIS-A has been proposed (Table 2).³⁻⁵

This patient presented with generalized anasarca and mild pericardial effusion. Our initial diagnosis was effusive constrictive pericarditis leading to entire constellation of symptom and signs. However, persistently elevated inflammatory markers with a history of recent SARS COVID-19 infection led to a suspicion of MIS-A. The patient was managed empirically with steroids, anticoagulants, and diuretics. However, real improvement started when patient underwent renal replacement therapy using HA 330 filters. HA 330 filter has been used successfully along with renal replacement therapy to treat cytokine storm in some clinical cases. It has been used to adsorb and remove cytokines like IL-1, IL-6, IL-8 and TNF alpha.

Optimal treatment is unclear at this time and will likely require evidence outside of randomized controlled trials given the rarity of this syndrome. Intravenous immunoglobulin, steroids and other immunomodulatory agents have been used to treat suspected cases of MIS-A, with clinical improvement noted in some instances. Along with steroids, renal replacement therapy with HA 330 filters worked well in the present case. Hemoadsorption therapy (CytoSorb) with tocilizumab has been reported in management of acute severe SARS COVID-19 infection but its use has not been reported in

MIS-A.^{6,7} The role of hemoadsorption therapy in patients with MIS-A with acute kidney injury with elevated IL-6 needs to be further evaluated. Though unproven, we used novel oral anticoagulants until normalization of D-dimer levels.

The criteria for diagnosis of MIS-C and MIS-A are as follows.

MIS-C CDC criteria³

All 4 criterias must be met: (1) age ≤ 21 years; (2) clinical presentation consistent with MIS-C, including (a) fever (b) laboratory evidence of inflammation (elevated CRP, IL-6, ESR, D-dimer, ferritin, LDH, procalcitonin, fibrinogen, lymphopenia, neutrophilia, hypoalbuminemia), (c) multisystem involvement (2 or more of organ systems involved, cardiac, respiratory, renal, neurologic, hematologic, gastrointestinal, dermatologic), (d) severe illness requiring hospitalization; (3) no alternative plausible diagnosis; (4) recent or current SARS-COV-2 infection or exposure like positive SARS COV-2 RT-PCR, positive serology, positive antigen test, COVID -19 exposure ≤ 4 weeks prior to onset of symptoms.

MIS-C WHO criteria⁴

All 6 criterias must be met: (1) age 0-19 years; (2) fever for ≥ 3 days; (3) clinical signs of multisystem involvement, atleast 2 of following: (a) rash, bilateral mucopurulent conjunctivitis or mucocutaneous inflammation signs(oral, hands, feet), (b) hypotension or shock, (c) cardiac dysfunction: pericarditis, valvulitis or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP), (d) evidence of coagulopathy (prolonged PT/APTT, elevated D-dimer), (e) acute gastrointestinal symptoms (diarrhea, vomiting, abdominal pain); (4) elevated markers of inflammation like ESR, CRP or procalcitonin; (5) no other obvious microbial cause of inflammation; (6) evidence of SARS COV2 infection, any of the following: (a) positive SARS COV-2 RT-PCR, (b) positive serology, (c) positive antigen test, (d) contact with an individual with COVID-19.

Proposed criteria for MIS-A⁵

All 5 must be met: (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 (e.g. hypotension or shock, cardiac dysfunction, arterial or venous thrombosis or thromboembolism or acute liver injury); (4) laboratory evidence of severe inflammation (e.g. elevated CRP, ferritin, D-dimer, or interleukin-6); (5) absence of severe respiratory illness (to exclude patients in which

inflammation and organ dysfunction might be attributable simply to tissue hypoxia).

CONCLUSION

MIS-A is a rare presentation but it should be kept in mind when a COVID-19 recovered patient presents with multisystem constellation of symptoms and signs, which cannot be explained by any other diagnosis. Steroids remain the cornerstone of therapy. Renal replacement therapy with HA 330 filters was effective in management of this case. However, role of such treatment need to be further investigated.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Babu TS, Sinha SC, Darimireddy SK, Chakravarthy KK, Sagar KV. Post COVID-19 multisystem inflammatory syndrome in adults: a new clinical challenge. *Int J Res Med Sci* 2021;9:2128-31.