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Case report

Adult Presentation of Multisystem Inflammatory Syndrome (MIS-A) Post COVID-19 Infection Associated with Myocarditis and Heart Failure: A Case Report

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Abstract

During the Coronavirus disease 2019 (COVID-19) pandemic, several complications can be noted with different pathophysiology, one of which is multisystem inflammatory syndrome in adults (MIS-A). MIS-A can affect various organ systems, including cardiovascular, gastrointestinal, and neurologic systems without important respiratory involvement. A previously healthy 39-year-old man presented with fever of three days duration accompanied by diaphoresis, conjunctivitis, acute kidney injury, abdominal pain, lethargy, and vomiting. After a comprehensive infectious workup that was unremarkable, his clinical symptoms along with elevated inflammatory markers in the setting of a recent SARS-CoV-2 infection, associated with a trans-thoracic echocardiography revealing biventricular systolic dysfunction, elevated troponin level and normal coronary arteries as evidenced by his angiography, are in favor of myocarditis. Given the constellation of myocarditis, acute kidney injury, conjunctival injection and negative infectious workup, on top of an underlying hyper inflammatory process, the diagnosis of MIS-A was concluded. The patient received supportive treatment with intravenous methylprednisolone. He was started on angiotensin converting enzymes inhibitor (ACE inhibitor) and Beta blocker. He later demonstrated recovery of cardiac function and normalization of inflammatory markers. As the COVID-19 pandemic continues to be a worldwide life-threatening infection, it is important to recognize and diagnose MIS-A, as a potentially fatal clinical syndrome that can lead to severe cardiovascular complications. Further studies and reviews must be focused on more specifications and risk stratifications of this complication, to ensure more feasible and rapid diagnosis, and to avoid its related multi-organ morbidity and mortality.

Keywords: ***SARS-CoV-2; COVID-19; systolic dysfunction; Acute heart failure; Case report; MIS-A; Multisystem inflammatory syndrome; Myocarditis.***

Introduction

COVID-19 is an infectious disease caused by a recently discovered SARS-COV2 [1]. Usually elderly patients and those with underlying medical problems such as diabetes mellitus, hypertension, malignancy, cardiovascular diseases, and chronic obstructive pulmonary disease (COPD) are more likely to develop critical illness [2,3]. During the course of COVID-19, a hyper inflammation syndrome with multiple extra pulmonary organ damage has been noted to affect patients in four to six weeks post infection with corona virus [4].

First, this rare syndrome had been reported in eight children in the UK in April 2020 as an atypical Kawasaki disease or toxic shock-like syndrome [5] and since then more cases have been documented and entitled "Multi System Inflammatory Syndrome in Children" (MIS-C). There are few case reports of the same condition in adults termed as multi system inflammatory syndrome in adults (MIS-A) [6,7]. Until now, there is a variation in the definition of multi system inflammatory syndrome between Center for disease control and prevention (CDC) and World Health Organization (WHO), but the main features of this syndrome are common to both definitions: fever, multi organ involvement, elevated inflammatory markers, and past infection of covid-19 in the last weeks [8,9]. This syndrome is presented with broad range of symptoms affecting multiple systems including cardiac, gastrointestinal tract, dermatological, or neurological without severe respiratory illness [10]. A hypothesis suggested that this syndrome results from a direct tissue damage due to dysregulated immune system activation [11] or an antibody-mediated process [12].

We report the case of a 39 years old male who presented with myocarditis associated with acute kidney injury after 3 days of fever and vomiting. He was diagnosed early with MIS-A and successfully treated. The aim of presenting this case is to provide a new case report about MIS-A which is rarely reported in Lebanon and to

demonstrate that early treatment of this syndrome can prevent further complications.

Case presentation

Mr. H. is a 39-year-old male Lebanese patient, previously healthy, who presented to the Emergency Department (ED) for a Fever that started three days prior to presentation; it was accompanied by diaphoresis, odynophagia, sore throat, generalized weakness, abdominal pain, and vomiting. He denied having any other respiratory symptoms.

During his initial ED visit, his systolic blood pressure was stable at 114 mmHg, he had a temperature of 39.2 celsius, a heart rate of 120 bpm, and an oxygen saturation of 96% on arrival. While he received 30cc/kg IV bolus of normal saline solution (NSS) 0.9%, blood and urine cultures were obtained and he was started on Ceftriaxone 2g IVD.

Six days prior to his admission, the patient sought over the counter medication at a pharmacy where he was started on oral azithromycin for tonsillitis, but his symptoms progressively worsened.

The patient had tested positive for SARS - CoV2 by PCR, four weeks ago when he was complaining of mild symptoms.

On physical exam, he appeared comfortable with no signs of respiratory distress; his posterior oropharynx was erythematous with exudates, and bilateral enlarged cervical lymphadenopathy were noted upon palpation. The patient was also noted to have mild conjunctivitis bilaterally, and mild diffuse abdominal tenderness.

His pulmonary and cardiac examinations were unremarkable other than tachycardia.

Before being admitted to regular floor, the patient had a negative polymerase chain reaction (PCR) for SARS-CoV2 in the ED.

His laboratory tests showed a peak CRP of 360 (normal range 0 to 10 mg/dL) with leukocytosis (WBCs 25400) and lymphopenia (4.63%). D-Dimers at 1154 ng/ml (normal range < 198 ng/ml)

LDH 349 U/L (normal range 140 to 280), Procalcitonin of 0.458, Troponin 2.380 ng/ml (normal range for male < 0.034),

Ferritin was 481.47 ng/ml (normal range for male 12-300 ng/ml) and he exhibited an elevation of creatinine value: 1.38 mg/dl pointing to acute kidney injury (AKI), with a mild elevation of AST to 75, ALT to 95 and GGT to 233 (**Table 1**).

Infectious workup was negative including blood and urine cultures, Influenza (A+B) testing, and Weil-Felix testing (**Table 2**).

Table 1: Serial blood test results

	Day 1	Day2	Day3	Day 4	Normal range
WBC(×1000cumm)	25.4	20.7	17.1	-	4-11
Hemoglobin (g/dl)	14.1	13	12.1	-	Male:13-18
Platelets(×1000cumm)	311	372	356	-	150-400
CRP (mg/dl)	360.9	307.1	259.7	153	0-10
LDH(IU/l)	304	349	-	-	140-280
Ferritin(ng/ml)	-	-	481.47	385.82	Male:21.8-274
D-dimers(ng/ml)	-	1154	-	-	<198
Creatinine(mg/dl)	1.38	1.13	0.93	0.75	Male:0.7-1.2
Troponin(ng/ml)	-	2.380	1.439	-	Male:<0.034
SGOT(IU/l)	75	43	-	-	8-45
SGPT(IU/l)	-	95	-	-	7-56
GGT(IU/l)	-	233	174	-	5-40
PCT (ng/ml)	-	0.458	-	-	0-0.5

WBC: white blood cells, CRP: C-reactive protein, LDH: lactate dehydrogenase, SOGT: serum glutamic-oxaloacetic transaminase, SGPT: serum glutamic pyruvic transaminase, GGT: gamma-glutamyl transferase, PCT: procalcitonin

Table 2: Infectious work up

Influenza A	**Negative**
Influenza B	Negative
Brucella direct	Negative
Brucella indirect	Negative
Salmonella	Negative
Weil-felix	Negative
Blood cultures	No growth
Urine culture	No growth

Initial chest x ray showed no signs of infiltrates, consolidations or pleural effusions, and his ECG showed sinus tachycardia.

Computed tomography of the abdomen and pelvis showed non-significant findings, without focal intra-abdominal source of infection (**Fig.1**).

Official trans-thoracic Echocardiography (TTE) revealed reduced left ventricular ejection fraction (LVEF) (35%-38%), dilated Inferior vena cava, dilated right ventricle, normal aortic root and small pericardial effusion without evidence of tamponade. All visualized valves appeared normal in structure, but color and Doppler analysis showed moderate tricuspid regurgitation and mild mitral regurgitation; this raised the concern for possible myocarditis.

CT Angiography of the chest was performed and only mild bilateral pleural thickening was found without signs of pulmonary embolism (**Fig.2**).

Coronary angiography revealed normal coronaries with no evidence of obstruction or aneurysms.

Given the constellation of myocarditis, acute kidney injury, conjunctival injection and negative infectious workup, the diagnosis of MIS-A was concluded. The patient received supportive treatment with IV methylprednisolone, knowing that IV immunoglobulins were not available.

Regarding his heart failure with reduced LVEF, he was started on ACE inhibitor and Beta blocker.

Over the next 48 hours, the patient's heart rate normalized, he defervesced and he reported general improvement; this confirmed the diagnosis of MIS-A after response to the treatment. After three days, his IV Methylprednisone was switched to oral prednisone and was tapered over three weeks. Mr. H. was discharged home on Bisoprolol and Ramipril for his heart failure.

To be noted that lab tests upon discharge showed a decrease in CRP to 153, ferritin to 385 ng/ml, WBCs to 17 000 his acute kidney injury (AKI) resolved and his creatinine upon discharge was 0.75 mg/dl.

The patient was followed up one month after his discharge and had a complete resolution of his symptoms, and a new TTE reported an LVEF of 55%.

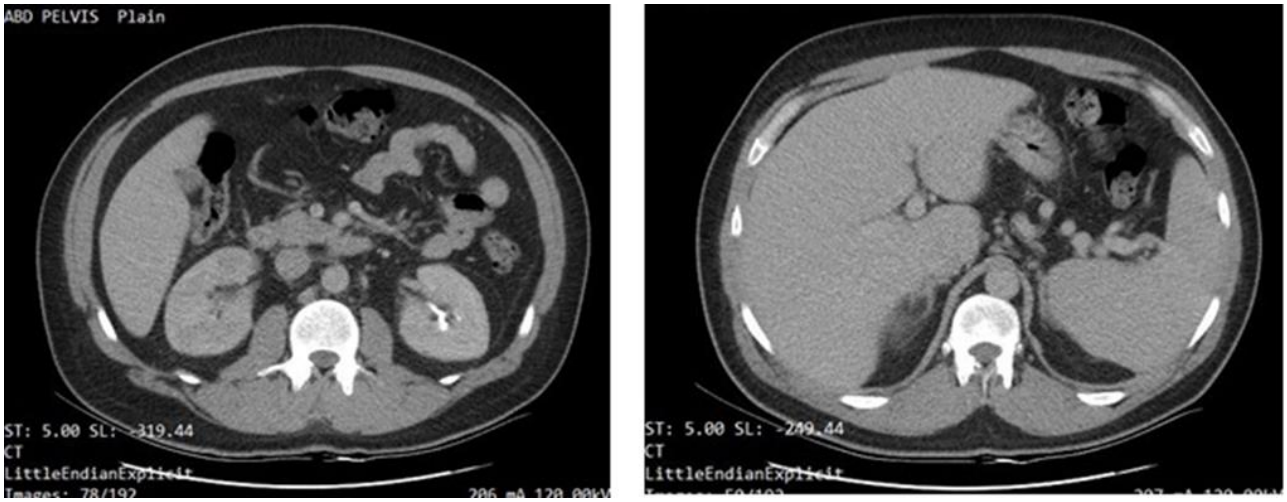

Figure 1: CT abdomen and pelvis

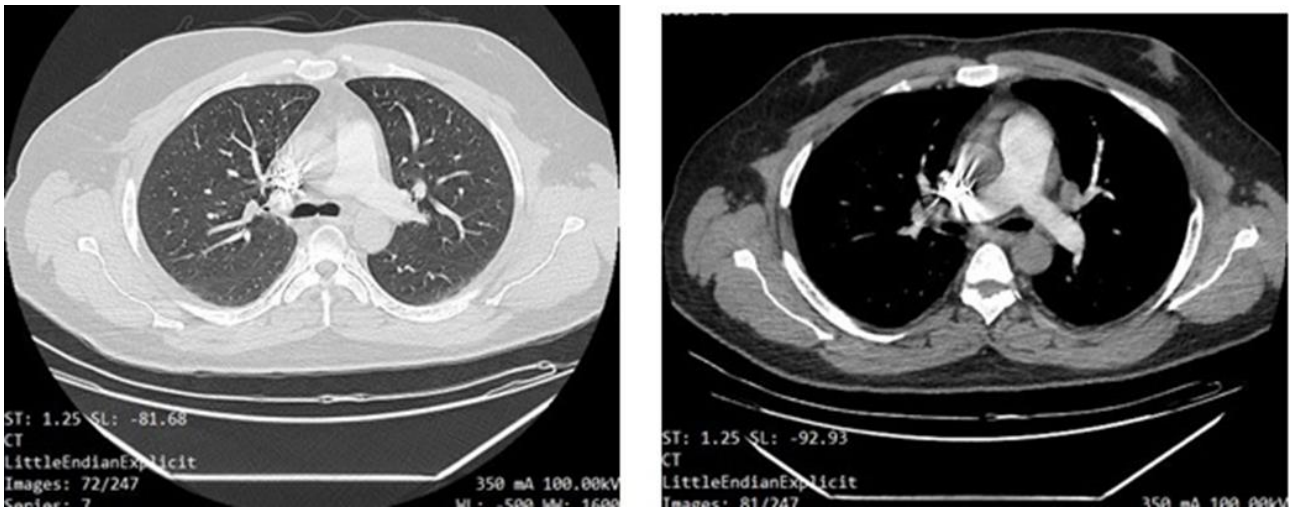

Figure 2: Chest CT angiography

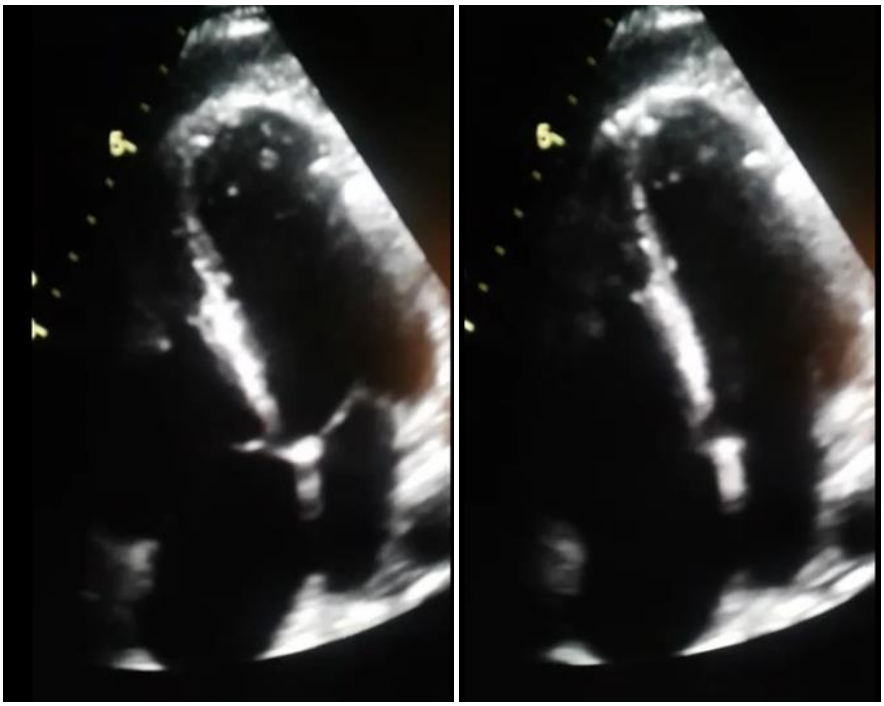

Figure 3: Trans-thoracis echocardiography with a left ventricular ejection fraction of about 35%

Discussion

Multisystem inflammatory syndrome in adults (MIS-A) was first mentioned in 2020 as multi-inflammatory syndrome in children or MISC, with the most recent theories proposing a delayed, dysregulated immune response as the cause [13]. Most patients with MIS-A presented with fever (96%), hypotension (60%), cardiac dysfunction (54%), shortness of breath (52%), and diarrhea (52%), and the median number of organ systems involved was five. The median hospital stay was 8 days; 57% were admitted to the intensive care unit, 47% required respiratory support, and 7% died [13]. Many definitions have been presented for MIS-A, one criterion being postulated by the CDC which included:

1. Age 21 years or older.
2. Presence of a severe illness requiring hospitalization ≥ 24 hours or illness resulting in death, which meets the following clinical and laboratory criteria:

- **Clinical criteria:**
  - Subjective fever or documented fever (≥38.0 °C) for ≥24 hours prior to hospitalization or within the first THREE days of hospitalization PLUS
  - At least THREE of the following clinical criteria occurring prior to hospitalization or within the first THREE days of hospitalization. At least ONE must be a primary clinical criterion:
- Primary clinical criteria:
  a. Severe cardiac illness
  b. Rash AND non-purulent conjunctivitis
- Secondary clinical criteria:
  a. New-onset neurologic signs and symptoms
  b. Shock or hypotension not attributable to medical therapy
  c. Abdominal pain, vomiting or diarrhea
  d. Thrombocytopenia
- **Laboratory criteria:**
  - Recent positive test result for SARS-CoV-2 infection (PCR, antigen or antibody)
  - Elevated levels of at least TWO of the following: C-reactive protein, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin

3. The patient should not have a more likely alternative diagnosis for the illness (e.g., bacterial sepsis, exacerbation of a chronic medical condition) [9].

The other proposed criterion includes the Brighton Collaboration Case Definition for MIS-A, which classifies MIS-A cases into "definite", "probable", "possible", and "insufficient evidence" [14].

In our case, the patient fulfilled the Brighton collaboration definition as a definite case; being ≥ 21 years old, with 3 days history of fever, having mucocutaneous (bilateral non exudative conjunctivitis) and gastrointestinal clinical features (abdominal pain and vomiting), with elevated CRP, ferritin and procalcitonin and three measures of disease activity (neutrophilia and lymphopenia, elevated troponin, reduced LVEF), all with laboratory confirmed SARS-CoV2 infection 4 weeks prior to his presentation. However, his CDC definition lacked the presence of a rash associated with his conjunctivitis as part of his three clinical criteria (along with the cardiac illness and gastrointestinal primary and secondary criteria respectively).

A systematic review published by Shekhar Kunal et al. on March 2022 regarding the treatment used in multiple MIS-A cases that were studied revealed that a variety of anti-inflammatory therapies were used including steroids (60.2%), intravenous immunoglobulin (IVIG) [37.2%] and biologics (10.2%) such as Tocilizumab and Anakinra. Concomitant antibiotic therapy was administered in 60.2% patients while 32% of the subjects' received anticoagulants. Data regarding the outcomes was available for all the 79 subjects involved in that systematic review of whom 4 (5.1%) died during the course of hospital stay while 75 (94.9%) were discharged from the hospital. These deaths were due to myocardial dysfunction leading to refractory shock in three and multiorgan failure in one. Only one of these four cases underwent autopsy which revealed cardiac endothelitis and vasculitis [15].

Most of the regimens used in the treatment for MIS-A were based on The American College of Rheumatology (ACR) guidelines on treatment of MIS-C which recommends immunomodulatory therapies such as glucocorticoids and/or IVIG to be the first line treatment modality and anticoagulation in patients with documented thrombosis, moderate-severe LV dysfunction and coronary arteries aneurysms (CAAs) [16].

Mr. H. was treated with broad spectrum antibiotics, aspirin, beta-blocker and ACE-inhibitor for his heart failure, steroids and prophylactic anticoagulation for a total of five days of hospitalization before being discharged on this same regimen with taper to his steroids over the next 3 weeks. Following up 1 month later with reversibility of his LV dysfunction.

Recovery of LVEF within a few weeks following MIS-A suggests that the LV dysfunction is usually a part of the systemic inflammatory response or acute stress rather than ischemic or a part of viral myocarditis [15].

Conclusion

MIS-A is currently considered as a part of many inflammatory syndromes post-COVID-19 infection. With little known about its mechanism of action, its vast clinical manifestations, having different definition criteria and treatment options, lots of challenges lie ahead with the objective of procuring unified guidelines for preventing, diagnosing and treating the severe outcomes of this complication.

Ethics approval and consent to participate

Consent was obtained or waived by the participant in this case report.

List of abbreviations

MIS-A: multisystem inflammatory syndrome in adults, COVID-19: Coronavirus disease 2019, ACE: angiotensin converting enzymes inhibitor, COPD: chronic obstructive pulmonary disease, MIS-C: Multi System Inflammatory Syndrome in Children, CDC: Center for disease control and prevention, WHO: World Health Organization, ED: Emergency Department, NSS: normal saline solution, PCR: polymerase chain reaction, AKI: acute kidney injury, TTE: trans-thoracic Echocardiography, LVEF: left ventricular ejection fraction, CRP: C-reactive protein, IVIG: intravenous immunoglobulin, ACR: American College of Rheumatology, CAAs: coronary arteries aneurysms.

Data Availability

Data that support the findings in this article are available from the corresponding author, [F. A. T], upon reasonable request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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None

Authors' contributions

All the authors have read and approved the final manuscript.

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N/A

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