## Review Article

# Multisystem Inflammatory Syndrome in Adults : The New Mask on an Old Evil

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The novel coronavirus disease (COVID-19) caused by SARS-CoV-2 has turned the world topsy-turvy since its emergence. Although COVID-19 is mostly associated with respiratory pathology, it can also result in several extra-pulmonary manifestations. Multisystem Inflammatory Syndrome in Adults (MIS-A) seems to be a new addition to the ever expanding COVID-19 puzzle and warrants extensive research to familiarize the phenotype, formulate a definitive treatment and prognosticate accordingly. This article highlights the case definition, pathogenesis, clinical features and treatment modalities of this new entity with a concise review of available literature at present.

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***Key words*** **: COVID-19, Multisystem Inflammatory Syndrome, Kawasaki disease.**

In April 2020, Multisystem Inflammatory Syndrome in Children (MIS-C) was first described in the context of COVID-19 in United Kingdom and Italy. These reports described a shock-like illness in children resembling Kawasaki disease or Toxic Shock Syndrome[1]. Similar reports soon came in from most parts of the World and the Centers for Disease Control and Prevention (CDC) published an alert (HAN00432) regarding the same on May 14, 2020. While several reports and studies have been published regarding MIS-C since then, there is comparatively paucity of literature on Multisystem Inflammatory Syndrome in Adults (MIS-A)[2]. The authors attempt to review the existing literature and discuss this new clinical entity so as to facilitate early recognition of the condition by healthcare providers to ensure prompt treatment and improve the prognosis.

***Editor's Comment :***

- Multisystem Inflammatory Syndrome in Adults (MIS-A) seems to be a new addition to the ever expanding COVID-19 puzzle.
- MIS-A patients more likely present with myocarditis, cardiac dysfunction, arterial thrombosis, pulmonary embolism, and/or deep vein thrombosis; than MIS-C.
- The manifestations of MIS-A may overlap with COVID-19 and make the diagnosis challenging.

## Case Definition :

The CDC defines a case of MIS-A as a patient aged at least 21 years who meets the following clinical and laboratory criteria, in the absence of any other likely alternative diagnosis[3] (Table 1).

## Clinical Features :

The clinical features of MIS-C encompass shock, cardiovascular decompensation, abdominal pain with markedly elevated inflammatory markers. Since June 2020, a similar syndrome with gastrointestinal, cardiovascular, dermatologic and neurologic symptoms in absence of severe respiratory ailment in adults has surfaced up in literature. Significant overlap between symptoms of acute COVID-19 per se and MIS-A makes the diagnosis of the latter a tad challenging[4]. Most common organ system involved seems to be the cardiovascular system[4]. There have also been reports of young adults presenting with the full spectrum of Kawasaki disease manifestation[5]. It is also important to exclude respiratory involvement resulting in severe pulmonary disease as tissue hypoxia could lead to organ dysfunction with similar features as that of MIS-A. Clinical features of MIS-A are described in Table 2[6].

## Pathogenesis :

The pathophysiology of MIS-A is poorly elucidated. As per reports received by CDC, 30% adults and 45% children with Multisystem Inflammatory Syndrome had

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Table 1 — *Case definition for multisystem inflammatory syndrome in adults*

Patient aged ≥21 years admitted for ≥24 hours, or with an illness resulting in death, meeting the following clinical and laboratory criteria in absence of a more likely alternative diagnosis for such illness

| Clinical criteria | | Laboratory criteria |
|---|---|---|
| Subjective or documented fever (at least 38.0 C) for at least 24 hours prior to hospitalisation or within the first 3 days of hospitalisation* and at least 3 of the following clinical criteria in the same time frame* (at least one being a primary clinical criterion) | | |
| Primary Criteria | Secondary Criteria | |
| (1) Severe cardiac illness - 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.<br>(2) Rash and non purulent conjunctivitis | (1) New onset neurological signs and symptoms- encephalopathy, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome)<br>(2) Shock or hypotension not attributable to medical therapy (sedation, dialysis)<br>(3) Abdominal pain, vomiting, diarrhoea<br>(4) Thrombocytopenia (<150,000/mcl) | (1) Elevated levels of at least 2 of the following - CRP, ferritin, IL-6, ESR, procalcitonin<br>(2) Positive SARS-CoV-2 test for current or recent infection by PCR, serology, or antigen detection |

** These criteria should be met by the end of hospital day-3, where the date of hospital admission is considered as day-0.*

negative PCR for SARS-CoV-2 and positive antibodies, suggesting a postinfectious pathophysiology. However, in contrary to moderate and severe COVID-19, usually accompanied by respiratory failure there has been an unexplained paucity of respiratory symptoms and signs in MIS-A[7]. In adults, COVID-19 is typically characterized by hyperactivation of the inflammatory cascade. Increasing evidence suggests that tissue damage in COVID-19 is mostly mediated by the host innate immunity[8].This disease is characterized by a cytokine storm resembling that of macrophage activation seen in viral-induced haemophagocytic lymphohistiocytosis. Immune dysregulation, malfunction of the renin-angiotensin-aldosterone axis, endothelial injury and thromboinflammation are the proposed mechanisms for MIS-A. However, blockade of type I and type III interferon responses resulting in unchecked viral proliferation may be also attributable[9]. In children, studies have shown reduced and/or ineffective titres of neutralizing SARS-CoV-2 antibodies in patients with MIS-C compared to patients with mild to severe COVID-19[10]. However, similar studies are yet to explore MIS-A. Cheng MH et al. also highlights the mechanism by which SARS-CoV-2 spike protein binds to T cell receptors like a superantigen similar to staphylococcal exotoxin B[11].

## Published Literature on MIS-A :

A recent systematic review documented the clinical characteristics of 221 patients with MIS-A. Around 70% of these patients had experienced a symptomatic COVID-19 like illness with complete recovery prior to onset of symptoms of MIS-A[12]. The median lag period (from COVID-19 like symptom onset to MIS-A symptom manifestation) was a month (28 days). Fever was the most presenting feature followed by hypotension, cardiac dysfunction, respiratory distress and diarrhoea in most cases. Kawasaki-like presentation was found in 11% MIS-A cases. The common organ systems involved were haematological, cardiovascular, gastrointestinal, and respiratory. Among laboratory parameters, elevated levels of atleast one coagulopathy and/or inflammation marker – interleukin-6 (98%), ferritin (91%), fibrinogen (91%), C-reactive protein (90%), N-terminal pro BNP (90%), and B-type natriuretic factor (74%)were documented. Treatment modalities in MIS-A ranged from anticoagulants (heparin, enoxaparin), corticosteroids, intravenous immunoglobulin, and immune modulators (tocilizumab). The illness was severe in around half the patients; vasoactive medications required for shock (51%), intensive care admission (57%), respiratory support including mechanical ventilation (47%). The median hospital stay was 8 days while fatal outcomes were encountered in 7% cases.

On comparing with patients with MIS-C[10,13,14], MIS-A patients were more likely to have documented previous COVID-19 infection, present with Myocarditis, cardiac dysfunction, Arterial thrombosis, Pulmonary embolism and/or deep vein thrombosis. On the other hand, MIS-C patients were found to report more mucocutaneous manifestations and received intravenous immunoglobulin as treatment compared to MIS-A patients. With respect to outcomes, patients with MIS-A had longer hospital stay, higher proportion needed mechanical ventilation, and more reported deaths.

## Treatment :

Based on prior benefits on the use of steroids in

| Table 2 — Clinical manifestations of multisystem inflammatory syndrome in adults | | |
|---|---|---|
| System involved | Symptom(s) | Clinical findings# |
| Cardiovascular | Chest pain, pressure and/or tightness<br>Palpitations with diaphoresis | Pericardial effusion<br>Mitral and tricuspid regurgitation<br>Shock(hypovolemic,vasoplegic,cardiogenic)<br>Heart block (complete, 1st and 2nd degree atrioventricular)<br>Atrial fibrillation / flutter with rapid ventricular response<br>ST segment changes<br>Arrhythmias<br>Myocarditis<br>Elevated troponin levels<br>Global wall hypokinesis<br>Coronary artery dilatation<br>Left or right ventricular dysfunction with reduced ejection fraction<br>Enlargement of the main pulmonary artery without pulmonary embolus<br>Elevated pulmonary artery pressure |
| Gastrointestinal* | Throat pain<br>Odynophagia<br>Abdominal pain<br>Profuse diarrhoea<br>Vomiting | Abdominal free fluid<br>Hepatic steatosis<br>Gallbladder wall edema<br>Peripancreatic fat stranding<br>Perinephric fat stranding<br>Retropharyngeal and parapharyngeal edema<br>Hypoalbuminaemia<br>Transaminitis |
| Neurological | Headache (occipital) | Stroke (large vessel)<br>Bilateral tinnitus |
| Dermatological (mucocutaneous) | Pruritus<br>Rash | Mucositis / glossitis<br>Diffuse exanthema / maculopapular rash<br>Edema / firm induration of hands and feet<br>Palmar erythema<br>Periorbital edema |
| Ocular | Pain, redness, irritation<br>Dimness of vision | Non-exudative conjunctivitis<br>Uveitis/ Conjunctivitis |
| Respiratory | Shortness of breath<br>Cough | Pneumonia<br>Pleural effusion<br>Atelectasis<br>Bronchial wall thickening<br>Acute respiratory distress syndrome |
| Reticulo-endothelial | Joint pain (polyarthralgia) | Lymphadenopathy (supraclavicular/ cervical/ anterior mediastinal)<br>Bilateral enlarged parotid glands<br>Throbbing neck pain<br>Kawasaki-like disease |
| Renal | Dark urine | Acute renal failure |
| Hematological | Weakness, easy fatigability<br>Petechial rash, mucocutaneous bleeding | Anaemia<br>Thrombocytosis<br>Leucocytosis |
| Constitutional | Fever, rigor, chills, malaise | |
| #Includes laboratory and radiological work-up findings<br>*Includes neckspace findings in Otorhinolaryngology | | |

management of COVID-19 pandemic, initiation of treatment with moderate-dose steroids have shown dramatic improvement in shock and end-organ failure in MIS-A[15,16]. Patients who were critically ill required inotrope or vasopressor support, intubation or mechanical ventilation, anticoagulants, or even convalescent plasma therapy. Other studies have highlighted the role of IVIG and the IL-1 receptor antagonist anakinrain the management of MIS-A. Due to its influence on regulatory T cells, which help to suppress the hyperinflammatory response, IVIG is considered first line therapy (with steroids as adjunct) in cases of distributive shock[17,18]. Anakinra has ignited interest due to its rapid onset of action, short half life, and large therapeutic window (especially in comparison to IL-6R inhibitor tocilizumab)[19]. These therapies are based on guidelines published by the American College of Rheumatology for treatment of MIS-C[20]. Randomized controlled trials in adults with MIS-A are awaited.

## Conclusion

MIS-A is a relatively nascent entity manifesting in the post-infectious period in association with COVID-19. The manifestations of MIS-A may overlap with COVID-19 and make the diagnosis challenging. As per treatment options are concerned, immuno-modulation is the cornerstone of therapy. The spectrum of MIS-A warrants further research on a large scale and clinicians must be vigilant of such an entity for prompt recognition and management.

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