Multisystem Inflammatory Syndrome in Adults (MIS-A) and SARS-CoV2: An Evolving Relationship

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Abstract: The SARS-CoV2 pandemic is the most significant global health emergency of the last century. While the pathophysiology of SARS-CoV2 is understood, the early and long-term outcomes of natural infection are increasingly being recognised. Multisystem inflammatory syndrome (MIS) represents a manifestation of the extreme immune dysfunction that SARS-CoV2 infection heralds and has been described in both children (MIS-C) and adults (MIS-A). Here, we discuss current knowledge of MIS-A and the vast questions that remain unanswered.

Keywords: MIS-A; SARS-CoV2; COVID-19; Kawasaki disease

1. Introduction

As of the 21st of February, there have been >750 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection globally, and >6.8 million associated deaths [1]. Only through the concerted efforts of the international community and measures including lockdowns, social distancing, immunomodulatory therapy and, most importantly, vaccination have disease incidence, hospitalisation and death begun to abate.

The pathophysiology of SAR-CoV2 infection involves direct viral cytotoxicity and perturbations to the renin–angiotensin–aldosterone system (RAAS) mediated by the angiotensin-converting enzyme 2 (ACE2) receptor, which is the target of the SARS-CoV2 spike(S) protein and is highly expressed throughout the body, but particularly in the lungs, heart, small intestine and blood-vessel endothelium [2].

As such, SARS-CoV2 infection presents itself in a multisystem manner with cardiac, dermatological, haematological, gastrointestinal, renal, neurological, ophthalmological, orthopaedic and endocrinological manifestations, all well described in the literature [3].

It is clear, however, that much of the associated morbidity and mortality associated with SARS-CoV2 is due to the associated immune-system dysregulation characterised by a cytokine storm principally involving TNFα and IL-6, as well as T-cell lymphopenia, relative interferon resistance and florid innate immune responses, resulting in multiorgan dysfunction and an increased risk of secondary infection. It is this cytokine storm which typifies the second phase of the SARS-CoV2 illness, where clinical deterioration and decompensation occurs following initial recovery, typically ~10 days post-symptom onset. This may manifest as acute respiratory distress syndrome (ARDS), circulatory collapse and the need for intensive care with treatment aiming to dampen the immune response [4,5].

2. MIS-A: What Is It?

In the majority of patients, after SARS-CoV2 infection, there is recovery and convalescence. In up to 25% of adults, post-acute sequelae of SARS-CoV2 (PASC) infection, also known as 'long COVID', are seen, particularly in hospitalised patients, and it commonly presents with persisting fatigue, headache, dyspnoea, sleep abnormalities and joint pain and may take months to resolve [6]. A more acute and serious sequela of SARS-CoV2

infection was first described in children presenting similarly to Kawasaki disease (KD) and toxic shock syndrome. This was termed multisystem inflammatory syndrome in children (MIS-C), and following this, the sequela was quickly described in adults (defined as ≥21 years old) (MIS-A) [7].

MIS-A appears to be a post-acute, post-infectious illness occurring after a period of recovery and typically 4–6 weeks post natural infection, and up to 12 weeks post-SARS-CoV2 vaccination [8–10]. At present, little is known regarding the true prevalence of MIS-A, with studies often retrospective in nature and hampered by the use of different case definitions. The prevalence of MIS-A seems to range from 0.2% to 11.7% of studied SARS-CoV2 infection cases, and many cases might be misdiagnosed as biphasic SARS-CoV2 infection [11,12]. Epidemiologically, MIS-A overwhelmingly presents in young males in up to >70% of cases, typically in the third decade of life, although cases up to the seventh decade have been described [11,12]. As per SARS-CoV2 infection, the ethnicity of MIS-A cases is unequal with black (non-Hispanic) individuals, making up to 80–90% of MIS-A diagnoses in case series [13,14] and 30–58% [8,12] in two large systematic reviews, with Caucasians making up a minority of cases. On review of global cases, it appears that the vast majority have been identified in Europe and America, with relative paucity in Asia [11]. This is interesting, given that KD, which MIS-A shares many characteristics with, occurs predominantly in Asia, with >1% of children >12 years of age having experienced the disease in Japan [15]. While this could reflect an underlying genetic predisposition for MIS-A development, differences in socioeconomic status and healthcare-seeking behaviours may explain these findings.

In SARS-CoV2 infection, hospitalisation and severe/fatal disease may be predicted by the presence of comorbidities including hypertension, diabetes and obesity [16]. In MIS-A, however 58–67% of patients have no comorbidities reported [8,12]. This makes risk stratification and prediction of MIS-A more challenging. The Brighton collaboration body and multiple case studies have reported a temporal but not causal association between various vaccination types, including live-attenuated (e.g., mumps, measles and rubella (MMR), whole-killed (e.g., Japanese encephalitis) and conjugate vaccines (e.g., haemophilus influenzae), and Kawasaki or Kawasaki-like disease [9,15]. The association, however, between MIS-A and SARS-CoV2 vaccination appears to be exceedingly rare, with 10 cases reported at the time of writing, of which eight were male. Post-vaccination MIS-A was seen post-primary or -secondary vaccination dose, with patients presenting between 1 and 23 days after vaccination, and often in the absence of previous SARS-CoV2 infection (n = 7). Importantly, all SARS-CoV2 vaccine types (subunit/inactive/viral vector/mRNA), were implicated in MIS-A development. However, four of the ten cases developed after the Pfizer, vaccine a novel mRNA vaccine [10,11,17,18]. Clinically, this vaccine-associated MIS-A appears to present identically as typical MIS-A with a good prognosis [17–19]. As such, while rare, it is important to clarify vaccination history in MIS-A cases and raise the question of whether these patients may be at higher risk of MIS-A recurrence following repeat vaccination after recovery. Given the expanding list of indications for 'booster' SARS-CoV2 vaccinations and the mixing of vaccine types, this phenomenon may become more prevalent in the future, in the setting of emerging SARS-CoV2 variants.

3. MIS-A Pathophysiology and How It Presents

The pathophysiology of MIS-A is unclear at present, with multiple theories including viral superantigens (e.g., 's-protein'), autoimmunity secondary to molecular mimicry with anti-Ro/La detectable in MIS-C patients months after recovery, persistently activated immune cells post infection and reservoirs of ongoing SARS-CoV2 infection [7,11,20]. The favoured pathophysiology, however, is macrophage activation and expansion through antibody-dependent enhancement (ADE). ADE is seen in multiple viral infections, including respiratory syncytial virus (RSV), measles and, importantly, in dengue virus, where it is thought to underpin dengue haemorrhagic fever pathogenesis. The mechanism of ADE is such that upon interaction with pre-existing non-neutralising antibodies and the binding

of the virus, there is Fc Gamma (FcγRIIa) receptor interaction during viral uptake into the phagocytes, facilitating viral proliferation and proinflammatory cytokine release, as well as the development of immune complexes enhancing inflammation [21,22]. While ADE has not been clinically seen in patients with SARS-CoV2 reinfection by different strains, it is something that may occur given the progressive changes noted within the S-protein of different strains of SARS-CoV2. It may also explain the link between vaccination and the development of MIS-A [23].

Therefore, MIS-A adds to a growing list of hyperinflammatory syndromes [24], each of which may complicate and be secondary to SARS-CoV2 infection, including secondary haemophagocytic lymphohistiocytosis (sHLH) [25] and capillary-leak syndrome (CLS) [26]) (Figure 1).
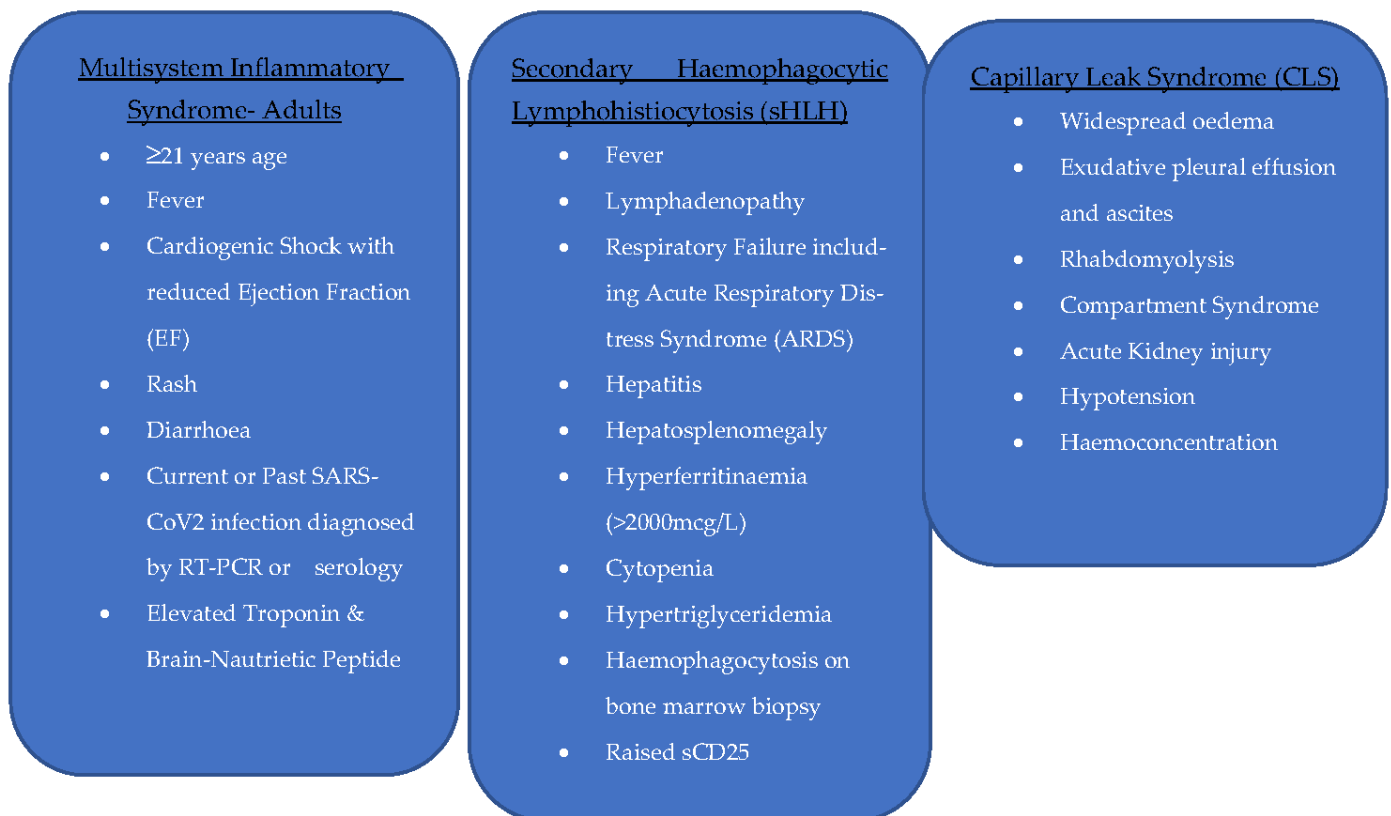
Multisystem Inflammatory Syndrome- Adults

- ≥21 years age
- Fever
- Cardiogenic Shock with reduced Ejection Fraction (EF)
- Rash
- Diarrhoea
- Current or Past SARS-CoV2 infection diagnosed by RT-PCR or serology
- Elevated Troponin & Brain-Nautrietic Peptide

Secondary Haemophagocytic Lymphohistiocytosis (sHLH)

- Fever
- Lymphadenopathy
- Respiratory Failure including Acute Respiratory Distress Syndrome (ARDS)
- Hepatitis
- Hepatosplenomegaly
- Hyperferritinaemia (>2000mcg/L)
- Cytopenia
- Hypertriglyceridemia
- Haemophagocytosis on bone marrow biopsy
- Raised sCD25

Capillary Leak Syndrome (CLS)

- Widespread oedema
- Exudative pleural effusion and ascites
- Rhabdomyolysis
- Compartment Syndrome
- Acute Kidney injury
- Hypotension
- Haemoconcentration

Figure 1. Key features and discriminators of MIS-A and other cytokine-storm syndromes [12,24,25].

The symptomatology of MIS-A is diverse. The case definition as per the Centers for Disease Control (CDC) highlights that the patient should be ≥21 years and present with acute illness (2–24 h) prior to hospitalisation. Primary classical signs include cardiac dysfunction (myocarditis, myopericarditis or arrhythmia), rash and nonpurulent conjunctivitis with secondary findings of thrombocytopenia, shock and new neurological signs in the setting of laboratory evidence of severe inflammation including elevated C-reactive protein (CRP) or proinflammatory cytokines (e.g., IL-6) and evidence of SARS-CoV2 infection by serology or RT-PCR [27].

MIS-A patients presented with fever (100%), which can be >39 °C with skin rash (57.8%), diarrhoea (51.6%), abdominal pain (40.6%), myalgia (39.1%) and headache (25%) [12]. Rarer presentations included sore throat (3.1%) and chest pain (12.5%). In addition, there are case reports of coronary-artery dissection, brain oedema, ischaemic/haemorrhagic stroke, status epilepticus, mononeuritis multiplex and thyroiditis [8,11].

Patients with MIS-A often show quick deterioration over hours to days, with 58.1–100% of patients requiring ICU admission for their management. The most com-

mon reason for ICU admission is cardiogenic shock, with between 46.1 and 58.5% of MIS-A patients requiring inotropic support and a minority requiring intra-aortic balloon-pump insertion and extracorporeal membrane oxygenation (ECMO). In <10% of case series, patients required noninvasive ventilation and dialysis [8,11,12]. Biochemically, >90% patients had an elevated D-dimer, CRP, brain nautrietic peptide (BNP) and IL-6 with coagulaopathy. Neutrophilia and lymphopenia were described in 81.8% and 67.5%, respectively, often with thrombocytopenia (51.4%) [8,9].

While serum ferritin is elevated, it rarely meets the criteria of sHLH (>2000 mcg/L) [24]. Procalcitonin (PCT) is a peptide precursor and serum biomarker that is more sensitive and specific than CRP, IL-6 and lactate, and is often relied upon in SARS-CoV2 infection as it positively correlates with SARS-CoV2 severity and can help predict poor outcome and identify coexistent bacterial infection [28]. However, there are many reasons for a falsely elevated serum PCT, including organ dysfunction, severe cardiogenic shock and autoimmune disease. As such, it can be falsely elevated in the setting of MIS-A, and it is unclear whether it offers similar prognostic information as in SARS-CoV2 infection [29,30]. In one case series including nine patients with MIS-A, the average serum PCT was 6.91 ng/mL, with two cases of a value >80 ng/mL noted [31]. Further studies are required to see if serum PCT and other inflammatory markers have diagnostic and prognostic properties in the context of MIS-A.

In those presenting with MIS-A, typically at least four bodily systems, of which the haematological, cardiovascular, neurological, gastrointestinal and dermatological systems are mainly affected. Unlike typical SARS-CoV2 infection, severe respiratory symptoms are not commonly seen and may, in fact, preclude the diagnosis of MIS-A [7,9,12]. Cutaneous involvement in SARS-CoV2 infection is well described and present in up to 20.4% of cases and ranges from urticarial to necrotic lesions, and in non-white populations, telogen effluvium and skin scaling may be observed [32,33]. In MIS-A, rash is seen in ~60% of patients, and diffuse maculopapular or erythrodermic rash is also often seen, representing early signs which may progress to a dusky plaque-like morphology [12,27]. While such mucocutaneous manifestations (e.g., strawberry tongue, malar rash, periorbital erythema, conjunctivitis) are less common than in MIS-C, in a haemodynamically unstable patient with coexistent rash and nonpurulent conjunctivitis, the possibility of MIS-A should be considered [34].

While overt symptoms of chest pain are often absent, biventricular cardiac involvement on a transthoracic echocardiogram (TTE) is a common finding (81% of cases) [12]. Unlike in SARS-CoV2-associated myocarditis, endomyocardial biopsy does not reveal S-protein positivity in MIS-A [13]. Importantly, there is often a prompt and full recovery of heart function without sequelae with appropriate treatment [8,35]. The acute cardiac dysfunction, however, can be severe. In one case series, the median left ventricular ejection fraction (LVEF) reduced to 35%, with >70% of MIS-A patients having a LVEF <50% [12,13]. This cardiac dysfunction is thought to be IL-6-dependent and, thus, inflammation may lead to myocardial stunning. In KD, however, coronary artery aneurysm formation is IL-1-mediated, highlighting the impact of cytokinaemia on organ dysfunction [36].

4. Management and Outcome

Treatment in MIS-A involves supportive care, including ventilation, inotropes, fluid resuscitation, anticoagulation and immunosuppression. In all cases of MIS-A, treatment with corticosteroids has been the mainstay, although it is varied markedly in terms of formulation (e.g., hydrocortisone, prednisolone and methylprednisolone), duration (3–10 days) and dosing (1 g/d, 1 mg/kg/day, 6 mg/day) [8,10,12]. In addition to corticosteroids, intravenous immunoglobulin (IVIG) has often been used as an adjuvant therapy with unclear benefits. Indeed, in children with MIS-C, treatments with IVIG ± glucocorticoids or glucocorticoids alone showed equivalent effects in terms of need for respiratory/inotropic support and mortality (OR 0.90 versus 0.93) [37].

Tocilizumab and Anakinra are biological therapies that target the IL-6 receptor and IL-1 receptor, respectively, and attenuate the immunopathology of severe SARS-CoV2 infection. They are also used in the setting of cytokine storm and autoimmune disease. Tocilizumab is currently used in severe SARS-CoV2 infection necessitating noninvasive/invasive respiratory support [38]. While the evidence for the effectiveness of biologic agents in MIS-A is lacking, being used in <5% of cases [12], there is anecdotal benefit of using Anakinra in poor responders to IVIG and systemic glucocorticoids in MIS-C [39]. The costs and availability of IVIG and biologic agents may however, preclude their use, particularly in lower-income countries. Unfortunately, given the lack of randomised control trial data and the relative rarity of this condition, the evidence for MIS-A treatment is based on expert opinions and experience with KD. Therefore, the evidence is insufficient and should be the target of future studies.

Colchicine may be a worthy non-immunosuppressive choice for future consideration in MIS-A, given its multiple anti-inflammatory mechanisms of action, including reductions in immune cell migration, proinflammatory cytokine release and inflammasome activation. Moreover, it exhibits efficacy in periodic fevers where IL-1 overproduction is evident [40]. Interestingly, colchicine has clear cardiovascular benefits in the setting of pericarditis and myocardial infarction and may hasten the resolution of cardiogenic shock in MIS-A. In children with MIS-C, colchicine has been used as part of combination treatment with a positive outcome in the presence of confounders and should be tried in MIS-A [40,41].

The overall mortality of MIS-A is between 5 and 7%, which is at least threefold higher than in MIS-C and may be skewed by both the lower number of patients and delays in diagnosis. In those who died, refractory shock and myocardial involvement seem to be the predominant causes, with limited available autopsy data revealing vasculitis and cardiac endothelilits [12,24]. The use of a serum lactate dehydrogenase/lymphocyte ratio (LLR) has been shown to predict mortality, with LLR >0.32 achieving 78% sensitivity and 70% specificity [24]. What remains unclear are the long-term sequelae after the resolution of MIS-A, particularly regarding any chronic cardiovascular sequelae, autoimmunity and unresolved symptomatology akin to post-acute sequelae of SARS-CoV2 (PASC).

5. Conclusions

In conclusion, MIS-A is a dangerous complication of natural infection or vaccination of SARS-CoV2. While its pathophysiology is likely linked to a primed immune system and antibody-dependent enhancement, it is unclear whether there is a genetic predisposition or other factors that confer risk in otherwise healthy young adults. While treatment strategies focus on immunosuppression, there lies great heterogeneity in employed therapies, with no randomised clinical trial data available. Physicians' awareness of MIS-A and a high index of suspicion are needed to manage this condition effectively, and long-term follow-up of survivors of MIS-A are required to ensure no increased risk of subsequent disease and MIS-A recurrence.

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