Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Case Reports and Series

Multisystem inflammatory syndrome in adults following COVID-19 infection: A case report presenting with colitis

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ABSTRACT

Background: Multisystem Inflammatory Syndrome in Adults (MIS-A) is a recently emerging condition that occurs as a delayed complication of COVID-19 infection. It involves inflammation of multiple extra-pulmonary organ systems. Diagnostic criteria and treatment recommendations have yet to be clearly defined. We present a case of a young adult with suspected MIS-A who initially displayed symptoms and radiological findings of colitis.

Case: A 22-year-old male with no past medical history suffered a minor respiratory illness for a few days and tested positive on SARS-CoV-2 RT-PCR. Approximately 6 weeks later, he presents after 3 days of right-sided abdominal pain, diarrhoea and fever. He is initially admitted with a working diagnosis of gastroenteritis. Sustained fever and escalating blood markers of illness led to abdominal CT; showing inflammation of ascending colon as well as some loops of small bowel. Hypotension becomes increasingly pronounced and on the fourth day of admission he developed type 1 respiratory failure with evidence of fluid overload. He was transferred to critical care for vasopressor and respiratory support. All microbiological and autoimmune screens performed return negative results but inflammatory markers were significantly elevated, he was diagnosed as MIS-A. IVIg was added to the antibiotics on day 4. His clinical condition dramatically improved and he was discharged home after 10 days in hospital. His blood tests have returned to normal and he has no lasting complications from his illness.

Discussion: This case displays the potential for MIS-A to present in various ways, with this example a primarily gastroenterological illness. It therefore highlights the importance of physicians in different fields having an awareness of the condition, in order to identify when MDT input is required to guide treatment. We review the current literature on various presentations and treatments of MIS-A, and discuss the need for clear case definition.

Case report

Introduction/background

MIS-A is an inflammatory condition affecting multiple extrapulmonary organ systems (cardiac, gastrointestinal tract, dermatological or neurological) (Centers for Disease Control and Prevention (CDC), 2020), attributed to a post-infectious and atypical complication occurring weeks to months after infection with COVID-19 (Morris et al. (2020); Tenforde and Morris, 2021).

COVID-19 associated hyper inflammation (COV-HI) in adults with acute COVID-19 infection is well described and is associated with poor patient outcome (Manson et al., 2020). MIS-A differs from COV-HI in that the inflammatory state presents weeks to months after the original infection (which may have been minimally symptomatic or asymptomatic), often when acute symptoms have subsided and nasal/throat SARS-CoV-2 RT-PCR testing is negative.

MIS-A is related to the more established and reported multisystem

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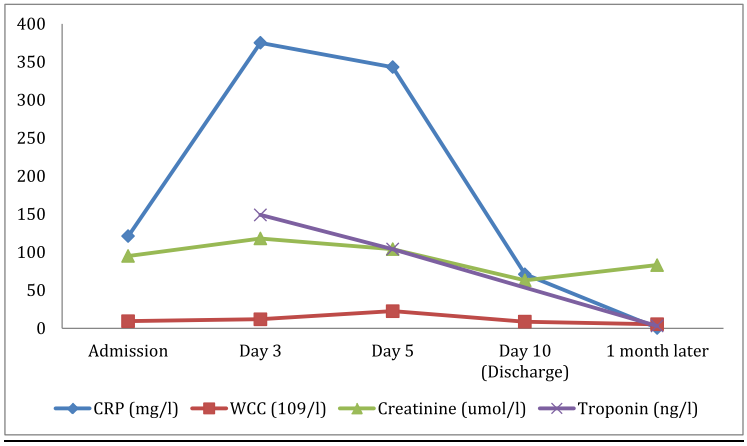
Table 1
Blood results during admission.



inflammatory syndrome in children (MIS-C) (World Health Organisation, 2020; Centers for Disease Control and Prevention (CDC), 2019), also known as paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS) (Royal College of Paediatrics and Child Health (RCPCH), 2020). There remains variation in the case definition and nomenclature between Royal College of Paediatrics and Child Health (RCPCH) (Harwood et al., 2021); Centers for Disease Control and Prevention (CDC) and World Health Organisation (WHO) (World Health Organisation, 2020) however the key features are common to all three definitions: elevated inflammatory markers, persistent fever, multi-organ involvement and a temporal relationship with COVID-19 infection.

The literature on MIS-A, although growing, remains sparse and is limited to small case series and reports, and as a result there are currently no clear guidelines for diagnosis or treatment of MIS-A. We describe a young man with colitis as the presenting feature of MIS-A and discuss the diagnostic difficulty and implications for practice.

Case presentation

A 22-year-old man attended the Emergency Department with a 3-day history of non-radiating, right-sided abdominal pain of insidious onset and fever. On the day of presentation, he had 5 episodes of diarrhoea, without blood and 3 episodes of vomiting. He had no dysuria, urinary frequency, respiratory symptoms or rash.

Prior to admission he had been well, taking no regular medications with no history of recent weight loss, night sweats and no relevant family history (including no family members with inflammatory bowel disease).

He was a full-time student with unlimited exercise tolerance and a non-smoker consuming only occasional alcohol and not using recreational drugs. He lived with friends, none of whom reported similar illness. He had no pets or recent foreign travel. He was heterosexual with a regular sexual partner. Six weeks previously he had experienced a mild illness with headache, cough, fatigue and mild photophobia lasting 1–2 weeks, which he managed at home and from which he had completely recovered. These symptoms had developed 2 days after he'd been informed of a COVID-19 positive contact and advised to isolate, via the NHS Test & Trace App. As a result he had presented for COVID-19 testing and been found to have a positive SARS-CoV-2 RT-PCR test.

On examination he appeared uncomfortable, his abdomen was soft and there was right-sided tenderness. There was no evidence of

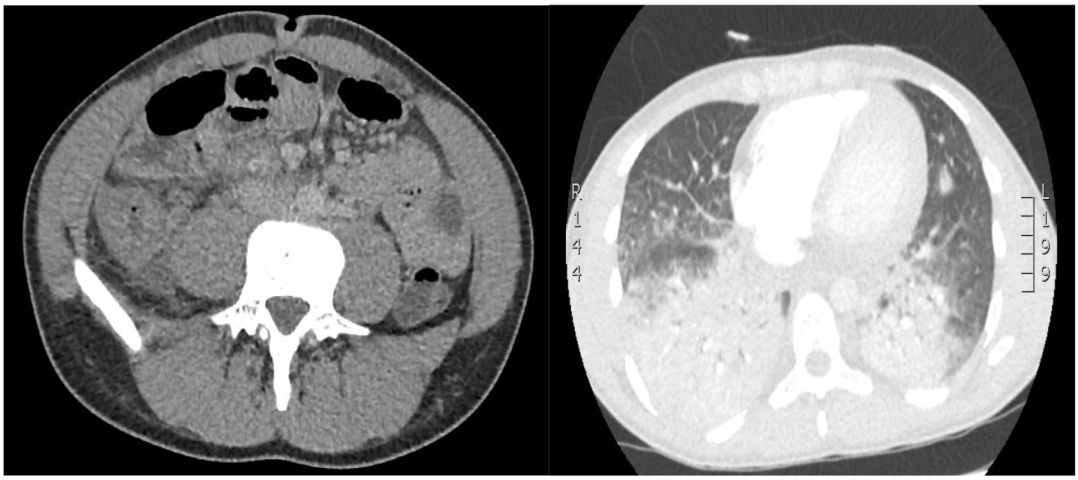


Fig. 1. CT abdomen Day 3 and CT thorax Day 4 (lower lobes displayed).
There are dilated fluid filled loops of small bowel, the caecum and ascending colon are also thick walled and oedematous in keeping with a colitis. There is fluid in the remainder of the colon. No transition point. No collection. No free gas. There is some free fluid which is more on the right side and there is also some inflammatory stranding more on the right side of the abdomen. There are two enlarged nodes adjacent to the caecum.
Good opacification of the pulmonary arteries. No pulmonary embolism. There is new enhancing consolidation in both lower lobes, worse on the right. Further smaller nodules of consolidation and ground glass in the apical segments of both lower lobes and the upper lobes. Bilateral small pleural effusions and bibasal interlobular septal thickening. This may be due to a combination of fluid overload and infection/aspiration.

Table 2
Relevant negative results.

Virology	
COVID-19 Nose/ Throat PCR	3 × Negative during admission
HIV Serology	Antigen and P24 negative
Hepatitis B Surface Antigen	Negative
Hepatitis C Antibody	Negative
Stool Enterovirus PCR	Negative
Stool Adenovirus PCR	Negative
Serum CMV PCR	Negative
Serum EBV PCR	Negative
Microbiology	
Blood Cultures	3 Negative Sets. Extended 10 day Incubation
Urinary *Legionella* Antigen	Negative
Stool *Clostridium Difficile* Antigen	Negative
Stool Culture	Negative *Salmonella spp, Shigella spp, Escherchia coli 0157, Campylobacter, Yersinia Enteroliticia*
Stool Ova, Cysts, Parasites	None seen
Sputum *Mycoplasma Pneumoniae* PCR	Negative
Sputum *Chlamydia Psittaci* PCR	Negative
Sputum Culture	Negative
Rheumatological	
ANA	Negative
C-ANCA	Negative
P-ANCA	Weak Positive (MPO negative, PR3 negative)
Rheumatoid Factor	Negative
Complement	Low C3 0.66 g/L (0.75–1.65) Low C4 0.06 g/L (0.14–0.54)
Immunoglobulins	IgG 16.12 g/L (6.0–16.0) IgA 0.97 g/L (0.8–2.8) IgM 1.39 g/L (0.5–1.9)

increased respiratory effort and chest was clear to auscultation. No rash, conjunctival injection or peripheral stigmata of endocarditis were seen. His observations showed temperature of 39.1 degrees Celsius, heart rate 87 beats per minute, blood pressure 110/74 mmHg, peripheral oxygen saturations 98% on room air.

Initial investigations included a raised C-reactive Protein (CRP), White Cell Count (WCC) with predominant neutrophils and low lymphocyte count (Table 1). A nasopharyngeal swab for SARS-CoV-2 was PCR negative. COVID-19 antibody status was not ascertained. Stool samples were sent to the laboratory to test for viral and bacterial causes of gastroenteritis. Mid-stream urine (MSU) and venous blood samples were also taken for bacterial culture. Ultrasound abdomen revealed normal appearance of abdominal solid organs without ascites.

He was admitted and started Intravenous (IV) fluid replacement, also receiving standard prophylactic dosing of Low molecular weight Heparin (LMWH). Antibiotics were not started on admission.

By Day 3 of his admission he remained persistently febrile with worsening abdominal pain. Despite generous IV fluid replacement of approximately 3–4 L over 24 hours, blood pressure remained low but maintaining above 95/60 mmHg with adequate urine output. There was an associated sinus tachycardia. His CRP had risen to 348 mg/l, Creatinine to 116umol/l and Lactate to 3.0 mmol/l; (Table 1) He was commenced on IV Cefuroxime and Metronidazole for presumed intra-abdominal source of sepsis.

Computed Tomography (CT) of the abdomen displayed dilated fluid-filled loops of small bowel with thick-walled oedematous caecum and ascending colon in keeping with colitis. The general surgical team was informed and the patient was counselled that if the clinical picture continued to deteriorate he might require surgery to remove the worst affected portion of bowel (Fig. 1).

On the morning of Day 4 he became acutely short of breath and developed a rapidly escalating oxygen requirement to a 15 L/minute Non-rebreathe mask). Arterial blood gas (ABG) demonstrated type 1 respiratory failure with significantly elevated alveolar to arterial gradient.

He was persistently hypotensive and tachycardic despite IV fluids and was transferred to High Dependency Unit (HDU) to commence vasoactive support. In the interim he had a CT of the thorax with pulmonary angiography (CTPA) which excluded pulmonary embolism, but showed consolidation of both lower lobes and repeat CT of the Abdomen which was similar to previous (Fig. 1).

The case was discussed with the on call microbiology and infectious diseases team as the patient appeared septic and may have infective colitis. Microbiological investigations of blood, stool and urine cultures were negative (Table 2). Upon MDT discussion a differential diagnosis was formulated as depicted in Box 1. Due to the recent COVID-19 illness there was a suspicion of Multisystem Inflammatory Syndrome in Adults (MIS-A). Treatment was commenced with 2 g/kg IV Immunoglobulins (Ig) split into 8 doses over 2 days. His antibiotics were escalated empirically to meropenem to cover possible gram negative sepsis, though there was no history of resistant organisms, and linezolid due to possible toxin producing bacterial sepsis.

At this stage serum ferritin was raised at 1233 μg/l (micrograms/l) [normal range = 30–400 μg/l]. Serial serum troponin were measured over 24 h: 149 ng/l (ng/l) -> 134 ng/l -> 104 ng/l [normal range is 0 – 14 ng/l].

Electrocardiogram (ECG) demonstrated sinus rhythm with T wave inversion in lateral leads. Bedside Echocardiogram performed by Intensive Care consultant suggested good biventricular systolic function, with a tiny rim of pericardial fluid. The Cardiology team felt the ECG changes and elevated Troponin represented myopericarditis.

Further progress

He remained in HDU for 5 days where the level of oxygen therapy and vasopressor support were gradually weaned down. On day 5 the patient was discharged from HDU straight to home. His rapid recovery upon commencing appropriate treatment was typical for inflammatory illness. His biochemical markers improved over the course of admission (Table 1).

The abdominal discomfort had improved, but he had developed a pressure headache, and felt slightly “cloudy”. Nasopharyngeal swabs had been taken on Days 1, 5 and 7 of the admission – all of these tested negative for SARS-CoV-2 on RT-PCR. Reports of other relevant investigations are shown in Table 2.

At telephone consultation one week later his headache was slowly resolving, and energy levels were gradually improving to the extent that he’d managed a steady 5 mile walk. Formal echocardiography 4 weeks after discharge revealed normal systolic and diastolic function of left and right ventricles.

Discussion

We report a possible case of Multisystem Inflammatory Syndrome in Adults (MIS-A) presenting as an acute colitis. It is important that all adult infection physicians are aware of this condition which is not limited to paediatrics. Doctors specialising in infectious diseases and microbiology may be consulted on these cases due to recent COVID-19 illness and sepsis-like presentation.

The absence of clinical guidance on MIS-A meant our management for this patient had to be extrapolated from the guidelines for MIS-C. This led to difficulty knowing which investigations to perform and treatment to instigate in our case. An emphasis on raising awareness of this condition as well as creating national guidelines should be a priority. Cross speciality working with paediatrics is likely to improve patient care.

In October 2020, CDC published a review of MIS-A cases reported to CDC as well as selected case reports and series in the published literature. They used five criteria to create a working case definition for MIS-A. (Box 2).

Box 1
: Differential Diagnosis.

- Multisystem Inflammatory Syndrome in Adults.
- Intraabdominal sepsis
- Group A streptococcal/ Staphylococcus aureus bacteraemia
- COVID-19 acute reinfection
- Vasculitis
- Flare of inflammatory bowel disease

We suspect our patient has been affected by MIS-A. This diagnosis was agreed by multi-disciplinary Team (MDT) discussion. The case we describe meets criteria 1–4. Criteria 5 requires the "absence of severe respiratory illness". Our patient developed type one respiratory failure whilst in hospital on day 4 of his admission. On presentation he had no respiratory symptoms or oxygen requirement; therefore we suspect his respiratory deterioration resulted from fluid overload and cardiac dysfunction, which is supported by CT findings (Fig. 1).

This diagnosis was considered within a differential diagnosis of other more common presentations, which need to be treated until they can be safely excluded, particularly bacterial sepsis. Once recognised or suspected MIS-A should be managed with MDT input involving Infectious Diseases, Rheumatology and teams who specialise in management of the affected organ systems, as well as Critical Care if required.

Gastrointestinal symptoms are common in MIS-A; however our report is the first of MIS-A presenting as a severe acute colitis. The CT findings show end organ inflammation and due to the severity of the case a surgical opinion was sought. Presentations of an 'appendicitis mimic' have been reported in children with MIS-C (Mahajna et al., 2020).

Many of the presentations that have been classed under the term MIS-A involved cardiogenic shock with reduced ejection fraction (Chau et al., 2020) or fulminant myocarditis (Hékimian et al., 2021); features which could equally be categorised as Acute CoVID-19 Cardiovascular Syndrome (ACovCS) (Hendren et al., 2020). ACovCS involves cardiac complications, typically occurring 1–4 weeks after initial COVID-19 infection, and also encompasses myocardial infarction/injury and arrhythmias. Overlapping clinical features have been discussed between ACovCS and the cardiac features of MIS-C (Most et al., 2021); with LV dysfunction in 20–55% and coronary artery aneurysm estimated in 20% of children affected by MIS-C (Henderson et al., 2020). Our patient displayed evidence of cardiac involvement with raised Troponin, T-wave inversion on ECG, clinical and radiological evidence of pulmonary oedema.

In MIS-C there is age variation in the organ systems that are most commonly affected (Dufort et al., 2020); myocarditis (80.8%) and gastrointestinal manifestations (73.1%) are most common in older patients (age 16–20), with less dermatological features than the younger age groups (61.5%). It fits with this trend that these were the features predominantly displayed by this 22-year old patient. This trend suggests that awareness of MIS-A ought to be raised particularly amongst adult physicians in Gastrointestinal and Cardiology who may be the admitting specialty for such patients.

Acute cerebrovascular disease was considered as an extrapulmonary organ dysfunction, meeting criteria for MIS-A when presenting with raised inflammatory markers, positive SARS-CoV-2 RT-PCR and only mild respiratory disease (Oxley et al., 2020). This further illustrates the wide array of presenting features for MIS-A.

In our case the patient had a recent illness with positive community nasal/throat respiratory PCR test confirming COVID-19 infection. However MIS-A can occur in patients after a relatively mild COVID-19 illness and patients may not have undergone testing. In these circumstances antibody testing, as recommended in children with MIS-C, can be useful in helping establish diagnosis (Rostad et al., 2020).

There is lack of clarity as to the appropriate treatment options for MIS-A. Treatment options utilised in previous case reports and series have included intravenous immunoglobulin, steroids and tocilizumab (Centers for Disease Control and Prevention (CDC), 2020). In our case we chose to use intravenous immunoglobulin as it is also utilised for treatment of severe toxin producing *Staphylococcus aureus* bacteraemia which we felt to be a less likely differential in this case. Further research is needed to clarify optimal management strategies or this condition. Many of the case reports for MIS-A report clinical improvement, as was observed in our case with IVIg, shortly after commencing directed immunomodulatory treatment.

Conclusion

MIS-A is a rare delayed onset complication of COVID-19 infection that appears to be hyperinflammatory in nature, and in its currently reported form can present with a wide variety of clinical features. Our case is the first to describe MIS-A presenting with acute colitis.

There is a need to raise awareness of this condition among physicians, and to develop national guidelines, in order to increase case recognition and optimise management.

Box 2
: Working diagnostic criteria for MIS-A in CDC published Case Series

1. A severe illness requiring hospitalization in a person aged $\geq$ 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 extrapulmonary 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); and
5. Absence of severe respiratory illness (to exclude patients in which inflammation and organ dysfunction might be attributable simply to tissue hypoxia).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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