

Adult presentation of multisystem inflammatory syndrome (MIS) associated with recent COVID-19 infection: lessons learnt in timely diagnosis and management

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SUMMARY

Multisystem inflammatory syndrome in adults (MIS-A) is an uncommon and under-recognised postinfectious manifestation that presents 4–6 weeks after COVID-19 infection. Patients affected tend to be young or middle-aged, from ethnic minority backgrounds and previously healthy. In addition to high fever and myalgia, there are a myriad of extrapulmonary symptoms and signs, including cardiac, gastrointestinal, neurological and dermatological involvement. Cardiovascular shock and markedly raised inflammatory markers are prominent features, while significant hypoxia is uncommon. Patients respond well to corticosteroid therapy, but failure of clinicians to recognise this recently identified phenomenon, which can mimic common conditions including sepsis, could delay diagnosis and treatment. Here we present a case of MIS-A in an adult woman, compare her presentation and management with other similar case reports, and reflect on how clinicians can learn from our experiences.

BACKGROUND

Throughout the course of the COVID-19 pandemic, a hyperinflammation syndrome has been noted to affect patients in the 4–6 weeks postinfectious period. With features similar to Kawasaki disease and toxic shock syndrome, patients display fever, shock, cardiac dysfunction, abdominal pain and grossly elevated inflammatory markers, without severe respiratory illness. Neurological symptoms including headache and meningeal signs have also been reported. Initially only reported in children, there are now isolated case reports in adults too. Terminologies are varied but two main names are used: 'multisystem inflammatory syndrome in adults' (MIS-A) and adult-onset 'paediatric multisystem inflammatory syndrome' (PIMS). Diagnosis can be delayed due to lack of awareness of this phenomenon by the clinician, as well as the unusual constellation of symptoms and signs acting as red herrings. Here, we report a case in an adult patient and reflect on the lessons learnt for timely diagnosis and commencing treatment.

CASE PRESENTATION

A 54-year-old Nigerian female healthcare worker with a background of asthma and hypertension presented with fever, dyspnoea, left-sided chest pain and extreme fatigue. Four weeks prior, she

tested positive for COVID-19 by PCR test in the community, although experienced only mild symptoms at the time. There was no recent travel history. She followed UK government guidance and self-isolated for the required time, and reported an initial clinical improvement in her symptoms before a gradual deterioration within the past week. Two days before this hospital admission, she presented to the emergency department (ED) with breathlessness and fever, for which a CT pulmonary angiogram was carried out. This showed patchy bibasal ground-glass changes in her lungs in keeping with known COVID-19 exposure (figure 1). Blood tests at this time were not particularly concerning, with total white blood cell count (WBC) of $12.1 \times 10^9/L$, C reactive protein (CRP) of 107 mg/L, negative D-dimer of 0.92 mg/L and negative troponin I of 7 pg/mL (table 1, day 0). COVID-19 PCR was also negative. She was discharged home with oral antibiotics as her vitals were stable and she did not require supplementary oxygen.

When she returned to the ED 2 days later with worsening symptoms, her vital signs revealed tachycardia and a high fever of 39.4°C, but normotensive and normal saturations on room air. Examination revealed normal heart sounds, mildly reduced air entry at both lung bases and a soft and non-tender abdomen. ECG showed sinus tachycardia without ischaemic changes. Chest X-ray showed subtle bilateral mid-lower zone airspace shadowing suggestive of infection (figure 2). Blood tests revealed worsened WBC of $13.4 \times 10^9/L$ (neutrophils $11.5 \times 10^9/L$, lymphocyte $4.1 \times 10^9/L$) and CRP of 221 mg/L. Liver function was also now deranged with alkaline phosphatase of 142 IU/L, alanine aminotransferase of 295 IU/L and bilirubin of $10 \mu\text{mol/L}$ (table 1, day 2). Her troponin and D-dimer were not checked again as they had been negative 2 days prior in the ED. She was admitted with an initial diagnosis of COVID-19 pneumonitis and started on intravenous antibiotics as per local policy. Corticosteroid therapy was not commenced as she had no oxygen requirement. COVID-19 serology was not done as this investigation was not available to the hospital at the time.

Over the next 48 hours the patient's condition rapidly worsened. She developed severe epigastric and right upper quadrant abdominal pain, an isolated episode of vomiting and diarrhoea, frontal headache, sore throat, and severe neck stiffness. There



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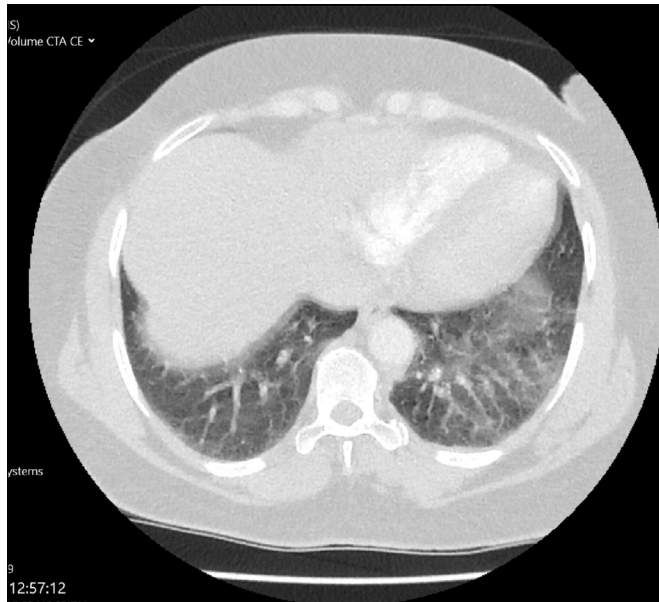


Figure 1 CT pulmonary angiogram showing bibasal ground-glass changes prior to admission.

were no focal neurological signs. A non-pruritic and blanching salmon-pink maculopapular rash developed, first on her chest wall and abdomen, and gradually spreading to cover her back and all four limbs. Mucosal and palmar surfaces were spared. Some lesions were discrete around 1–2 cm in size, other areas being more diffuse. There was no lymphadenopathy to find on examination. Her high fever and tachycardia continued despite regular paracetamol. She developed a mild oxygen requirement, and blood pressure started to sag to around 90 mmHg systolic, with only a moderate response to fluid resuscitation.

INVESTIGATIONS

Repeat blood tests showed worsening inflammatory markers, with total WBC peaking at $20.3 \times 10^9/L$ and CRP at 657 mg/L (table 1, days 3–4). Blood film reported neutrophilia with left shift, neutrophils with occasional nucleated red blood cells,



Figure 2 Admission chest X-ray showing subtle bilateral mid-lower zone airspace shadowing.

polychromasia positive and target cells positive. Renal function and amylase remained normal. Ferritin was mildly elevated at $876 \mu\text{g/L}$. Her lactate began to worsen, increasing from 1.8 mmol/L to 3.5 mmol/L. Blood and urine cultures taken on admission showed no growth to date.

Given the rapid development of her new symptoms and alarming rise in CRP, lumbar puncture was performed 48 hours into her admission to rule out meningoencephalitis, while ceftriaxone and oseltamivir were added to her treatment regimen. She was now on three intravenous antibiotics in total as per advice from the on-call microbiologist (amoxicillin, clarithromycin, ceftriaxone). Imaging of the brain was not carried out as it was felt that given her lack of focal neurology, its diagnostic value would be limited. CT of the abdomen and pelvis with contrast was done urgently given her gastrointestinal symptoms and deranged liver function, but this showed only non-specific intra-abdominal free fluid, no focal intra-abdominal source of sepsis, and persistent bibasal

Table 1 Serial blood test results

Investigations	Day										
	0	2	3	4	5	6	7	9	10	11	12
Haemoglobin (g/L)	107	110	95	95	85	80	80	93	93	98	101
WBC ($\times 10^9/L$)	12.1	13.4	20.3	18.6	19.3	15.7	10.5	19.6	16.3	10.5	9.4
Platelets ($\times 10^9/L$)	359	267	255	159	265	300	320	415	409	414	427
Total bilirubin ($\mu\text{mol/L}$)	4	5	10		7		4	5	5	5	5
CRP (mg/L)	107	221	525	657	624	349	231	84	52	48	38
LDH (IU/L)								387			
Ferritin ($\mu\text{g/L}$)	285			876							
D-dimer (mg/L)	0.92										
Creatinine ($\mu\text{mol/L}$)	82	76	72	86	67	73	70	60	65	65	69
CK (IU/L)	94										
Troponin I (pg/mL)	7										
ALP (IU/L)	85	142	142	131	134	137	169	146	129	127	129
ALT (IU/L)	34	295	147		84		395	265	182	142	119
GGT (IU/L)				240							

Day 0: Emergency Department presentation 2 days prior to admission; Day 2: admission to hospital; Day 4: commencement of dexamethasone.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; CK, Creatine kinase; CRP, C reactive protein; GGT, Gamma-glutamyl transferase; LDH, lactate dehydrogenase; WBC, white blood cell count.

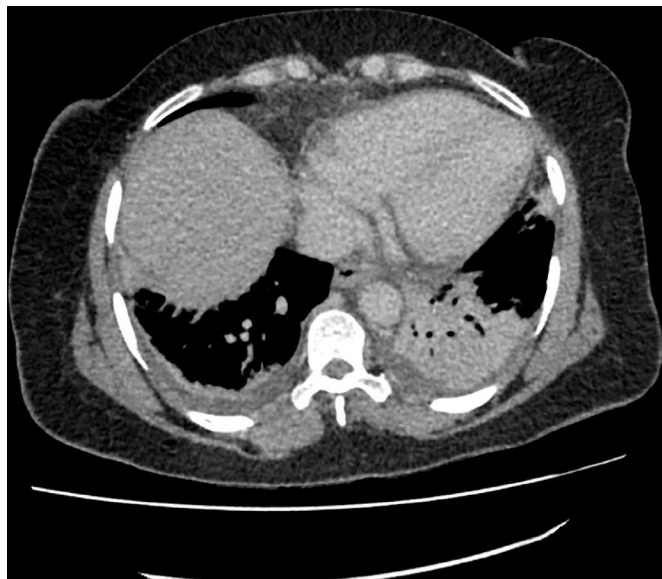


Figure 3 CT of the abdomen and pelvis during admission capturing lung bases, showing bibasal consolidation with small pleural effusions.

lung consolidation and small pleural effusions consistent with COVID-19 pneumonitis (figures 3 and 4). Cerebrospinal fluid (CSF) results came back as unremarkable (table 2). Autoimmune screen, atypical pneumonia and viral screen were sent for completion, including hepatitis, HIV, antinuclear antibodies (ANA) and complement. COVID-19 PCR was resent twice more during her admission, both of which remained negative.

DIFFERENTIAL DIAGNOSIS

Due to the unusual constellation of symptoms involving cardiac, gastrointestinal, neurological and dermatological systems, and rapid clinical deterioration despite broad-spectrum antibiotics, a



Figure 4 CT of the abdomen and pelvis (same scan as Figure 3 but shown using lung preset) during admission capturing lung bases, showing bibasal consolidation with small pleural effusions.

Table 2 Breakdown of CSF results

Glucose (mmol/L)	4.6
Protein (g/L)	0.27
White blood cells (cells/ μ L)	1
Red blood cells (cells/ μ L)	<1
No organisms seen with negative cultures	

CSF, Cerebrospinal fluid.

differential diagnosis of MIS-A related to COVID-19 was considered. Differentials including meningitis and intra-abdominal sepsis had already been excluded. Severe COVID-19 infection and atypical pneumonia were considered unlikely as PCR test was negative and there was no significant respiratory involvement. The lack of mucocutaneous involvement and lymphadenopathy excluded Kawasaki disease. Drug reaction with eosinophilia and systemic symptoms post antibiotic use was excluded as eosinophils were not raised. Haemophagocytic lymphohistiocytosis was also considered unlikely as platelets and haemoglobin were normal while ferritin was only mildly raised.

TREATMENT

As all imaging and cultures so far were negative for a focal source of sepsis, corticosteroid therapy was commenced in the form of oral dexamethasone 6 mg daily. Within 24–48 hours, the patient's vital signs stabilised and her symptoms started to improve. Over the following week, her rash disappeared and her biochemical markers normalised. Autoimmune screen, atypical pneumonia and viral screen came back as negative (table 3). Blood and urine cultures were confirmed sterile. Antibiotic therapy was stopped after 7 days. The patient recovered fully back to her baseline level of function, completed a 10-day course of dexamethasone and was discharged home on day 11 of admission.

OUTCOME AND FOLLOW-UP

Telephone follow-up 2 weeks after discharge revealed that the patient was still experiencing fatigue and headaches, but

Table 3 Autoimmune screen, atypical pneumonia screen and viral screen

ANA	Negative
Gastric parietal cell antibodies	Negative
Smooth muscle antibodies	Negative
Mitochondrial antibodies	Negative
Anti-LKM antibodies	Negative
Connective tissue disease antibodies (includes dsDNA, SM, ribosomal P, PCNA, U1-snRNP, Ro, La, Scl-70, centromere-P, fibrillarin, RNA pol III, Jo-1, Mi-2 and PM-Scl)	0.2 (reference range 0–1), negative
C3 (g/L)	2.14 (0.9–1.8)
C4 (g/L)	0.38 (0.1–0.4)
<i>Legionella</i> antigen	Negative
Pneumococcal antigen	Negative
HIV screen	Negative
HCV Ab	Negative
Anti-HB core	Negative
HbsAg	Negative
COVID-19 PCR testing day 0, day 6 and day 8	Negative

ANA, antinuclear antibody; Anti-HB core, Hepatitis B core antibody; Anti-LKM, Anti-liver kidney microsomal; dsDNA, double stranded DNA; HbsAg, Hepatitis B surface antigen; HCV Ab, Hepatitis C virus antibody; PCNA, proliferating cell nuclear antigen; SM, smooth muscle; U1-snRNP, U1 small nuclear ribonucleoprotein.

continued to improve. On further follow-up 3 months later, at the time of writing this report, the patient has returned to work full time, with complete resolution of her symptoms, apart from the occasional headache which she manages with simple analgesia.

DISCUSSION

Multisystem inflammatory syndrome (MIS) temporally associated with COVID-19 has been reported in both adults and children, and is becoming increasingly recognised as a separate phenomenon to severe COVID-19 infection due to the frequent lack of respiratory involvement. The syndrome is well described in children and has been defined by a number of organisations including the US and European Centres for Disease Control and Prevention (CDC), the World Health Organisation, and the UK's Royal College of Paediatrics and Child Health (RCPCH). Given its novelty, definitions still seem to be preliminary and non-specific, with a degree of overlap with other hyperinflammation syndromes including Kawasaki disease. Although there are now case reports of a similar syndrome seen in adult patients, health authorities have been slow to recognise and highlight it as a potential complication of COVID-19 infection. Thus, only the CDC has so far extended their diagnostic criteria to adults over 21 years old, naming the condition multisystem inflammatory syndrome in adults (online supplemental appendix 1).¹ The other name currently in use by the RCPCH is adult-onset paediatric multisystem inflammatory syndrome.

We reviewed a number of existing case reports of MIS-A and adult cases of PIMS,²⁻⁸ including a case series published by the US CDC in October 2020 of 16 cases, which we believe to be the largest cohort of reported MIS-A cases to date.¹ Our search yielded only two other case reports from the UK.^{7,8}

Although the symptoms and signs are diverse, there are striking similarities between the majority of cases reported and those seen in our patient. For example, patients tend to be middle-aged, of black, Asian or minority ethnic origin (mirroring the demographics of children more commonly affected by MIS),⁹ and without extensive previous comorbidities. Symptoms appeared between 4 and 6 weeks after confirmed COVID-19 infection or a non-specific viral illness, after a period of initial improvement. Common symptoms include high fever, dyspnoea, lethargy, myalgia, abdominal pain, vomiting and diarrhoea, neck pain or sore throat, and a widespread rash. The rash is described mostly as a diffuse maculopapular or erythematous rash, affecting particularly the torso, upper limbs and palmar surfaces. Hypoxia was not a prominent feature, but many had significant cardiac dysfunction including shock requiring inotropic and/or vasopressor support, and arrhythmias including atrial fibrillation and atrioventricular block were also seen. Headache and neck stiffness seem to be commonly described neurological features, but most patients were not investigated any further than CT imaging of the head and/or neck and lumbar puncture. Ahsan and Rani³ described a case of MIS-A with clinical bilateral facial nerve palsy for which an MRI brain and orbit was carried out (lumbar puncture was refused by the patient), which yielded no significant findings. It seems that while COVID-19 infection is known to be associated with a wide spectrum of neurological features including anosmia, ageusia, encephalopathy, encephalitis, Guillain-Barre syndrome and cerebrovascular events,¹⁰ these are not well described as part of MIS.

Similar to our patient, many had negative COVID-19 PCR tests acutely, but subsequently tested positive for the virus by serology, suggesting recent infection. This is important to

bear in mind, given that we know a significant proportion of COVID-19 infections are asymptomatic. The clinician should always ask about recent viral illnesses, possible COVID-19 contact, and if available test for COVID-19 serology routinely. A number of patients underwent extensive infectious and immunological work-up. Most patients also underwent CT imaging with findings of typical bilateral ground-glass shadowing in the lungs and non-specific findings in the abdomen and pelvis such as free fluid. Around half of the patients in the CDC case series had abnormal transthoracic echocardiogram findings including depressed left ventricular function. Some went on to have CT coronary angiograms which were unremarkable. Our patient did not receive any cardiac imaging, but on reflection an echocardiogram should have been arranged for completeness, given the anecdotal frequency of cardiac dysfunction as part of MIS-A.

Finally, similar to many of the other patients detailed in case reports, corticosteroid therapy led to brisk improvement of symptoms, clinical stabilisation and normalisation of biochemical parameters. The choice of steroid used included methylprednisolone, prednisolone and dexamethasone. All patients in the individual case reports we reviewed survived to discharge, as did 14 out of 16 patients in the CDC case series. The average length of stay in hospital was 10 days.

The pathogenesis of MIS is not fully understood, but the delay to presentation after COVID-19 infection is presumed to be due to initiation by the adaptive immune response.¹¹ Proposed mechanisms for extrapulmonary dysfunction include endothelial damage, dysregulated innate immune system and subsequent cytokine storm.¹² There are no existing guidelines for management of this condition, but what is clear from our review is that corticosteroids are an effective treatment, leading to often very rapid resolution of clinical and biochemical parameters. Other immune-modulating therapy administered, including intravenous immunoglobulin, anakinra (interleukin-1 receptor antagonist) and infliximab (tumour necrosis factor-alpha inhibitor), appear to be extrapolated from local management guidelines for other hyperinflammatory conditions such as Kawasaki disease and MIS in children.

COVID-19 remains a novel disease, and associated complications and overlap syndromes are likely to be under-recognised and under-reported. Definitions and classifications appear to be preliminary, non-specific and geographically different worldwide. As more clinical information is gathered, international

Learning points

- ▶ Consider a multisystemic inflammatory syndrome in adult patients presenting with high fever and a broad constellation of extrapulmonary symptoms without severe respiratory illness.
- ▶ This is especially relevant for patients with recent COVID-19 infection or viral illness.
- ▶ Carry out serology testing for COVID-19, even in those who test negative by PCR and in those who deny recent COVID-19 infection, contact or viral illness.
- ▶ Corticosteroid treatment is effective and should be commenced as soon as possible after focal sources of sepsis are ruled out.
- ▶ Escalate promptly to intensive care for further support if appropriate, as current available reports of multisystem inflammatory syndrome in both children and adults suggest mostly favourable outcomes.

efforts will be required to formulate more specific and globally recognised terminologies and diagnostic classifications. Furthermore, work is required to develop internationally accepted clinical guidelines for treatment strategies with the recognition of more cases and follow-up of medium-term and long-term outcomes.

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