Multisystem inflammatory syndrome in an adult with severe hypoxaemia and thyroiditis responsive to corticosteroid and interleukin 6 inhibitor treatment

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SUMMARY
Multisystem inflammatory syndrome in adults (MIS-A) has been reported as a rare but severe consequence of COVID-19 infection. Adult patients were more likely to present with hypotension and cardiac illness when compared with multisystem inflammatory syndrome in children. Although the exact prevalence of MIS-A is unknown, more cases have been observed in men and younger adults. The pathophysiology of MIS-A is also unclear, but is thought to be caused by a delayed, dysregulated immune response. Given no established guideline for treatment of MIS-A, treatment has been based on case reports. We present a case of MIS-A in a woman in her 60s who had severe hypotension, progressive dyspnoea, massive pleural effusion, hypoxaemia, thyroiditis and multiple organ failure, which dramatically improved after treatment with corticosteroid and interleukin 6 inhibitor.

BACKGROUND
Multisystem inflammatory syndrome (MIS) has been reported as a rare but severe consequence of COVID-19 infection. MIS has been linked to a hyperinflammatory process that develops 2–12 weeks after the initial COVID-19 infection.1 Clinical features of MIS in children are reported to be similar to Kawasaki disease or toxic shock syndrome, including fever, shock and rash, and therefore paediatric patients are often treated with intravenous immunoglobulin (IVIG) and/or corticosteroids. Since June 2020, several cases of a similar condition in adults have been reported (multisystem inflammatory syndrome in adults (MIS-A)).

The current MIS-A case definition, according to the US Centers for Disease Control and Prevention (CDC), is as follows: (1) a patient aged ≥21 years who has severe illness requiring hospitalisation; (2) has persistent fever; (3) meets at least three of the following clinical criteria: severe cardiac illness, rash, non-purulent conjunctivitis, new-onset neurological problems, shock or hypotension, gastrointestinal symptoms, and thrombocytopenia; (4) with elevated inflammatory markers; and (5) with current or recent COVID-19 infection. MIS-A is distinguished from severe COVID-19 by the absence of severe respiratory illness or hypoxaemia.1 However, according to a recent systematic review, half of patients with MIS-A developed shortness of breath, almost half required respiratory support, one-fifth developed acute respiratory distress syndrome and one-fifth had pleural effusion.2 Diagnosis of MIS-A may be delayed due to clinical unawareness. Inflammatory markers and information on a recent COVID-19 infection could aid in the diagnosis of MIS-A. Treatment of MIS-A is currently based on case reports, often with corticosteroids, IVIG as well as immunomodulators.2

In this case report, we present the case of a woman in her 60s with a history of COVID-19 infection who initially presented with neck pain, cervical lymphadenopathy and fever, and then developed loss of appetite, diarrhoea, vomiting, weight loss, fatigue and hypotension, and finally progressive dyspnoea, massive pleural effusion, hypoxaemia, thyroiditis and multiple organ failure. The level of interleukin 6 (IL-6) was found to be extremely high. She was successfully treated with dexamethasone and tocilizumab.

CASE PRESENTATION
A Thai woman in her 60s with underlying dyslipidaemia and multinodular goitre presented with neck pain and cervical lymphadenopathy for 1 week and reported being feverish for 2 days at an ear, nose and throat (ENT) outpatient clinic. Amoxicillin/clavulanic acid and naproxen were prescribed for a suspected cervical lymphadenitis. The patient had received her first dose of ChAdOx1/AZD1222 vaccine (Vaxzevria; AstraZeneca, Cambridge, UK). She had a recent asymptomatic COVID-19 infection, with SARS-CoV-2 detected on real-time reverse-transcription PCR (RT-PCR) 12 days after vaccination, and isolated at home for 14 days.

Three days after her ENT visit, she presented to the Digestive Disease Center with fatigue and multiple gastrointestinal symptoms (loss of appetite, diarrhoea and vomiting), but with no fever. Besides a relatively low blood pressure of 60/40 mm Hg and a significant weight loss from 44 kg to 39 kg in about 1 week, her vital signs were within normal limits (body temperature 36.8°C, heart rate 110 beats per minute, respiratory rate 24 breaths per minute and oxygen saturation 99% while breathing on ambient air). Physical examination revealed no significant abdominal abnormalities, whereas the cervical nodes remained tender and enlarged. Due to hypotension, she was given a loading dose of intravenous fluid replacement and blood was drawn for laboratory investigation. Complete blood count revealed leucocytosis with predominant neutrophils, anaemia and mild thrombocytopenia. Her
serum showed elevated alanine aminotransferase, creatinine, creatine kinase-MB and random cortisol (table 1). SARS-CoV-2 was not detected by real-time RT-PCR, whereas SARS-CoV-2 antispke IgG antibody was 2578.5 AU/mL. She was admitted to the intensive care unit (ICU). Septic work-up including blood culture, stool culture, stool Clostridioides difficile toxin A and B, urine analysis, urine culture and pleural fluid study all returned negative for infection. Procalcitonin was not assessed as the laboratory was not readily available on the day of admission. The Sequential Organ Failure Assessment (SOFA) score was not calculated because no arterial blood gas investigation was performed. Meropenem was prescribed as an empirical treatment for a potentially serious bacterial infection.

On the next day, she developed afebrile dyspnoea and her oxygen saturation dropped to 80%–90%. Her chest X-ray showed right lower lung infiltration and minimal bilateral pleural effusions (figure 1A). High-flow oxygen therapy was given. As she had new-onset atrial fibrillation (AF) with rapid ventricular response rate of 170–180 beats per minute, antiarhythmic drug was administered, but she was only minimally responsive. Echocardiogram reported left ventricular ejection fraction (LVEF) of 64%, no pericardial effusion, no pulmonary hypertension, and no intracardiac thrombus or vegetation seen.

Electrocardiography showed sinus tachycardia, which then developed to AF. Thyroid stimulating hormone (TSH) was lower than 0.004 uU/mL, with normal free triiodothyronine (free T3; 1.84 ng/dL) and slightly elevated thyroxine (free T4; 1.84 ng/dL), suggesting thyrotoxicosis and/or probable subacute thyroiditis. Thyroid ultrasound showed evidence of an enlarged thyroid

Table 1  Laboratory findings

| Laboratory                           | Normal range | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 12 | Day 22* | Day 29 | Day 36 | Day 57 |
|--------------------------------------|--------------|-------|-------|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|
| White cell count (×10^3 cells/L)     | 4.5–10.0     | 17.8  | 26.3  | 35.6  | 26.1  | 30.4  | 26.1  | 28.9  | 10.7  | 5.9    | 5.3    | –      | –      |
| Neutrophil (%)                       | 55.0–75.0    | 96.0  | 25.5  | 92.0  | 95.7  | 95.7  | 95.7  | 98.0  | 93.5  | 80.8   | 68.7   | –      | –      |
| Lymphocyte (%)                       | 20.0–35.0    | 1.0   | 1.4   | 1.0   | 4.0   | 2.0   | 2.5   | 1.0   | 3.7   | 10.2   | 19.8   | –      | –      |
| Haemoglobin (g/L)                    | 12.0–16.0    | 10.4  | 10.3  | 10.2  | 10.0  | 10.0  | 10.5  | 11.1  | 11.6  | 10.4   | 12.2   | –      | –      |
| Haematocrit (vol%)                   | 37.0–47.0    | 30.3  | 29.5  | 28.5  | 27.2  | 27.5  | 29.9  | 31.5  | 33.6  | 31.1   | 36.8   | –      | –      |
| Platelet count (×10^3 cells/L)       | 150–450      | 130   | 146   | 207   | 175   | 180   | 152   | 141   | 202   | 311    | 224    | –      | –      |
| Cortisol (random) (μg/dL)            |              |       |       |       |       |       |       |       |       |        |        |        |        |
| Morning:                             |              | 56.5  | –     | –     | –     | –     | –     | –     | –     | –      | –      | –      | –      |
| Evening:                             | 3.7–19.4     |       | 2.9–17.3 |       |       |       |       |       |       | –      | –      | –      | –      |
| Lactate dehydrogenase (U/L)          |              |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| C reactive protein (mg/dl)           |              |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| 0.00–0.50                           |              |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| D-dimer (ng/mL) Fibrinogen Equivalent Units | 0–500        |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Ferritin (ng/mL)                     | 10.0–250.0   |       |       |       |       |       |       |       |       |       |       | –      | –      |
| Erythrocyte sedimentation rate (mm/hour) | 0–29        |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Procalcitonin (ng/mL)                | 0.00–0.50    |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Interleukin 6 (pg/mL)                | 0.0–7.0      |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Complement C3 (mg/dl)                | 83.0–193.0   |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Complement C4 (mg/dl)                | 15.0–57.0    |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Direct bilirubin (mg/dl)             | 0.0–0.5      |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Total bilirubin (mg/dl)              | 0.2–1.5      |       |       |       |       |       |       |       |       | –      | –      | –      | 0.6    |
| Alkaline phosphatase (U/L)           | 38–126       |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Aspartate aminotransferase (U/L)     | 10–45        |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Alanine aminotransferase (U/L)       | 0–45         |       |       |       |       |       |       |       |       | –      | –      | –      | 19     |
| Gamma-glutamyltransferase (U/L)      | 7–50         |       |       |       |       |       |       |       |       | –      | –      | –      | 19     |
| Creatinine (mg/dl)                   | 0.55–1.02    |       |       |       |       |       |       |       |       | –      | –      | 0.63   | –      |
| Blood Urea Nitrogen (mg/dl)          | 7.0–21.0     |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Creatine kinase-MB mass (ng/mL)      | 0.00–4.88    |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Free triiodothyronine (pg/mL)        | 1.71–3.71    |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Free thyroxine (ng/mL)               | 0.70–1.48    |       |       |       |       |       |       |       |       | <1.50  | 2.33   | 2.61   | –      |
| TSH (uU/mL)                          | 0.350–4.940  |       |       |       |       |       |       |       |       | <0.004 | 0.213  | 0.517  | –      |
| TSH receptor antibody (IU/L)         | 0.00–1.75    |       |       |       |       |       |       |       |       | <0.80  | –      | –      | –      |
| Thyroperoxidase antibody (IU/mL)     | 0.00–5.61    |       |       |       |       |       |       |       |       | –      | –      | –      | –      |
| Thyroglobulin antibody (IU/mL)       | 0.00–4.11    |       |       |       |       |       |       |       |       | –      | –      | –      | –      |

*Discharge date.

TSH, thyroid stimulating hormone.

Figure 1  Chest X-ray before treatment: (A) day 2 and (B) day 3.
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On the third day of admission, her dyspnoea clinically and radiologically progressed, with increased right pleural effusion (figure 1B). CT of the chest and abdomen found a large amount of right pleural effusion in the right pleural cavity, cardiomegaly, moderate ascites, periportal fluid or oedema, collapsed ascending colon with mild thickening of the entire ascending colonic wall, and generalised subcutaneous oedema on the chest, abdomen, back, buttocks and both thighs. She also developed fever, non-purulent conjunctivitis and palmar erythema (figure 2). A right thoracocentesis was performed, yielding 800 mL of clear yellow fluid (figure 3). MIS-A was suspected according to the US CDC, so additional laboratory investigations were performed. Given the significantly elevated inflammatory markers, including C reactive protein (CRP), D-dimer (23 195 ng/mL Fibrinogen Equivalent Units), ferritin, erythrocyte sedimentation rate and procalcitonin (table 1), 5 mg of dexamethasone were administered intravenously every 6 hours. After the second dose of dexamethasone, her haemodynamic parameters became more stable, requiring only a low dose of vasopressor. Dexamethasone was continued at a total daily dose of 20 mg.

On the fourth day of admission, she had markedly elevated liver enzymes, increased serum creatinine and decreased CRP. As the IL-6 level of the blood drawn on 27 August returned extremely high (table 1), tocilizumab (IL-6 receptor antagonist) was given 400 mg intravenously.

On the fifth day of admission, she had no fever and had normal blood pressure and reported less dyspnoea. Her oxygen saturation became 99% while on high-flow oxygen therapy. Vasopressor was tapered and then stopped. She had more urine output consistent with decreased serum creatinine. On 30 August, her clinical conditions and laboratory parameters improved. Her oxygen saturation was at the 95%–100% range with nasal cannula, and she regained her appetite. On 31 August, she was transferred out of the ICU. Her IL-6 level and liver enzymes improved (table 1). The empirical antibiotic (meropenem) was stopped. Intravenous dexamethasone was tapered to 15 mg/day (5 mg every 8 hours) for another 1 day, then oral dexamethasone 12 mg/day (6 mg every 12 hours) for another 4 days.

On the twelfth day after admission, laboratory tests showed decreased leucocytosis, CRP, D-dimer (5384 ng/mL FEU), alanine aminotransferase and creatinine. TSH and free triiodothyronine were very low, but free thyroxine returned to normal (table 1). Chest X-ray showed improved bilateral pleural effusion and atelectasis at bilateral lower lungs (figure 4A). Dexamethasone was switched to prednisolone 20 mg/day (10 mg every 12 hours) for another 4 days.

Twenty days after admission, her chest X-ray showed disappearance of bilateral pleural effusions (figure 4B). She was discharged after 22 days of admission with normal blood cell count, CRP, creatinine and blood urea nitrogen. D-dimer decreased to 963 ng/mL Fibrinogen Equivalent Units (table 1).

INVESTIGATIONS

As described in the Case presentation section and in table 1.

DIFFERENTIAL DIAGNOSIS

The first impression was sepsis/septic shock due to severe hypotension and leucocytosis, but the patient did not respond to a
**Patient’s perspective**

My story started when I contracted with COVID-19. Nonetheless, I was asymptomatic thus I had to quarantine for 14 days. During the middle of August, I experienced pain in my ears and thought it was a simple inflammation. As the pain increased, my husband took me to the hospital where the doctors prescribed some anti-inflammatory medicines. As a result, the pain in my ears had decreases, however I experienced great discomfort elsewhere. I had lost my appetite, felt great fatigue, was nauseous, had loose stool and had lost 5 kilograms within a week or two. As my case exasperated, my husband took the decision to take me to the hospital again where I got admitted the same day. The reason behind my admission in hospital initially was due to discomfort stomach, loose stool and weight loss. From my first day in hospital, my case seemed to have gotten worse by the day where my blood pressure level, sugar level, breathing and heartbeat had fluctuated so much that I was at great risk. Still at that time, the doctors were trying to figure out what was the cause of such deterioration which effected nearly all organs in my body. I am confident to say that, without the expertise, knowledge and professionalism from the doctors and multidisciplinary team at the hospital during my stay, I would most likely not be here today to share my story. Owing to the great team of several doctors and multidisciplinary team who saved my life, I would like to say a special thank you to the attending doctor who always came up very early in the morning to follow up my symptoms, followed with several consultant doctors who always supported me and my husband and finally my doctor who treated and encouraging me all the time and coming up with various menus and restaurants to increase my appetite. I also owed a great gratitude to the nursing and assistant nursing team who stayed by my side through the night and day and also updating and reassuring my husband and my daughter. Again, I sincerely thank you to the hospital and its medical specialists for their treatment, care, and kindness.

**Learning points**

- Multisystem inflammatory syndrome in adults (MIS-A) presents in a variety of clinical manifestations weeks to months after a mild or asymptomatic COVID-19 infection.
- Clinicians should be suspicious of MIS-A in all patients with severe illness and unexplained multiple organ failure.
- Severe respiratory symptoms and thyroiditis can be clinical presentations of MIS-A.
- Interleukin 6 (IL-6) assessment is not only important in the diagnosis of MIS-A but is also influential in the choice of treatment.
- Tocilizumab, an IL-6 receptor antagonist, has shown to be effective in the treatment of MIS-A.

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broad-spectrum antibiotic and her septic work-up also showed negative results. Acute kidney injury and transaminosis were suspected from hypoperfusion due to shock. Cardiac investigations showed no evidence of ischaemia or other causes of arrhythmia. Thyrotoxicosis and probable subacute thyroiditis were suspected as the cause of the new-onset AF. Since she had progressive dyspnoea and gastrointestinal symptoms, CT of the chest and abdomen was performed to seek out any hidden infections. CT of the chest revealed a large amount of right pleural effusion. Diagnostic thoracocentesis was performed but showed no evidence of infection. Because the patient’s clinical picture showed systemic inflammation, which may be linked to a previous COVID-19 infection, inflammatory markers were tested and the results confirmed the diagnosis of MIS-A.

**TREATMENT**

Treatment of MIS-A was started with intravenous dexamethasone 20 mg/day. Given the extremely high IL-6 level, tocilizumab, which is an IL-6 receptor antagonist, was given for one dose. Within 24 hours of starting the treatment, the patient’s general condition dramatically improved. On 26 August, venous thromboembolism prophylaxis with subcutaneous enoxaparin was administered for the duration of hospitalisation. Within 24 hours of starting the treatment, the patient’s general condition dramatically improved. On 26 August, venous thromboembolism prophylaxis with subcutaneous enoxaparin was administered for the duration of hospitalisation.

**OUTCOME AND FOLLOW-UP**

Within 12 hours after starting corticosteroid treatment, the patient’s haemodynamic parameters became more stable, but a low dose of vasopressor was still required. Vasopressor was tapered and then stopped within 1 day after a dose of tocilizumab. Oxygen saturation gradually increased to 95%–100% after tocilizumab treatment and she was transferred out of the ICU 4 days after starting treatment. Her chest X-rays showed gradual improvement, with the latest chest X-ray before discharge confirming complete resolution of the pleural effusion. The total length of hospital stay was 21 days.

At 1-week follow-up, the patient had left ankle oedema. When compared with the results before discharge, her D-dimer level was significantly higher (table 1). Doppler ultrasound of both legs confirmed acute deep vein thrombosis in the left calf, involving the peroneal and muscular veins. An oral anticoagulant was prescribed. Her left ankle oedema regressed at follow-up on 29 September and her D-dimer level also decreased. She was advised to continue the anticoagulant for a total of 3 months.

At 3-week follow-up, her D-dimer, liver function test and thyroid function test were all normal (table 1). Echocardiogram revealed a slight improvement of LVEF to 66%. The patient is back to her normal state.

**DISCUSSION**

In addition to the typical clinical and laboratory characteristics of MIS-A, along with a history of asymptomatic COVID-19 infection, our case exhibited severe respiratory symptoms (progressive dyspnoea, massive pleural effusion and severe hypoxaemia) as well as thyroid involvement. Our case had a dramatic response to corticosteroids and IL-6 treatment.

A recent systematic review on 221 patients in published literature suggested that approximately one-fifth of patients with MIS-A developed severe respiratory involvement, none of which had thyroiditis. Given the limited knowledge regarding COVID-19 and MIS-A at that time, an acute febrile illness with multiple organ dysfunction in a patient would be suspicious for sepsis. Evidence of previous COVID-19 infection (patient history and/or laboratory investigation) is crucial to the diagnosis and management of MIS-A.

Several inflammatory markers have been assessed in patients with MIS-A. CRP (79.64%, 176 of 221), ferritin (67.87%, 150 of 221) and D-dimer (62.44%, 138 of 221) were commonly examined in patients with MIS-A and were elevated in our case. Due to limited availability, IL-6 assessment was not as common (28%, 61 of 221) in the published literature; however, it has a
significantly higher sensitivity (98%) than the others (CRP 90%, ferritin 91% and D-dimer 91%).

Steroids, IVIG and immunomodulators (IL-1 and IL-6 receptor antagonists) had been used in 74%, 55% and 21% of reported cases of MIS-A, respectively, with successful results. Because sepsis could not be ruled out initially, we decided to use intravenous dexamethasone (20 mg/day) instead of a high-dose methylprednisolone (250–1000 mg/day) used in other case reports. We decided to try the IL-6 receptor antagonist (tocilizumab) because it is more convenient and less costly than IVIG. IL-6 assessment is not only important in the diagnosis of MIS-A but is also influential in the choice of treatment.

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