Rare presentation of multisystem inflammatory syndrome in an adult associated with SARS-CoV-2 infection: unilateral neck swelling

Mozhu Li, Waqas Haque , Suchith Vuppala, Ethan Tobias

Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, Texas, USA

Correspondence to
Dr Mozhu Li;
mozhu.li@utsouthwestern.edu

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SUMMARY

Multisystem inflammatory syndrome in adults (MIS-A) is a rare but often severe complication of SARS-CoV-2 infection. While several case reports about MIS-A in the setting of COVID-19 have been published since the term was first coined in June 2020, a clear description of the underlying pathophysiology and guideline-based recommendations on the diagnostic and therapeutic approach are lacking. What has been reported is that in the absence of severe respiratory illness, MIS-A can present with hypotension or shock, high-grade fever, abdominal pain, diarrhoea and severe weakness days to weeks after SARS-CoV-2 infection. Here, we present a case of a 28-year-old man who presented with a rarely described initial symptom: unilateral neck swelling. His presentation, disease progression and treatment course provide further information about MIS-A as a complication and in formulating diagnostic guidelines.

BACKGROUND

In the setting of the COVID-19 pandemic, a new multisystem inflammatory syndrome in children (MIS-C) has been reported as an uncommon and severe complication of COVID-19 infection.[1–3] The presentation of MIS-C in children has been described to be similar to Kawasaki disease or toxic shock syndrome.[4] Common clinical features include persistent fevers, gastrointestinal symptoms, shock, cardiac dysfunction and elevated inflammatory markers.[1 3 4]

More recently, cases of adult patients with current or previous COVID-19 infection developing hyperinflammatory syndrome resembling MIS-C have been reported since June 2020.[5–7] This newly described phenomenon was termed multisystem inflammatory syndrome in adults (MIS-A). Godfred-Cato *et al* in October 2020 summarised 27 reported cases from March to August.[3] In late 2020, two more case reports of a 25-year-old and an 18-year-old were published.[6 7] While MIS-A is emerging as a recognised and suspected diagnosis, there is currently a lack of diagnostic and therapeutic guidance given the novelty of the syndrome and THE lack of large-scale data on the phenomenon. Here, we present the case of a 28-year-old patient who presented initially with unilateral neck swelling a month after a positive COVID-19 test, with the purpose of adding to the literature on the variable presentation and clinical courses of MIS-A.

CASE PRESENTATION

A 28-year-old man presented to the hospital with a chief complaint of neck swelling. He reported pain and swelling on the right side of his neck, which began 5 days prior to presentation. He also endorsed a few days of fever, diaphoresis and malaise. Two days into his illness, he presented to an urgent care clinic and was prescribed doxycycline and prednisone, after which he reported temporary symptomatic improvement. However, the symptoms returned, prompting his visit to the emergency department. SARS-CoV-2 PCR testing was negative; however, the patient informed us that he tested positive 1 month previously. His only symptoms at that time were low-degree fever and mild headache, which both resolved within 2 days. He did not experience any respiratory symptoms or require hospital admission.

Review of systems was negative other than a transient itchy rash on both arms that the patient attributed to taking antibiotics. Medical history was notable for obesity but no other chronic medical problems. Family history and surgical history were unremarkable. Patient denied using tobacco, alcohol or any drugs.

On physical examination, he was febrile to 39.1°C, tachycardic with a rate of 125 beats/min, with an oxygen saturation of 98% on ambient air. He had palpable tender right submandibular lymph nodes and a slightly enlarged tonsil without erythema or exudate. The skin exam was otherwise unremarkable (he stated his raised red itchy rash on his arms had already resolved). Other than tachycardia, his cardiac, pulmonary and abdominal exam were unremarkable.

CT of the neck revealed multilevel, right-greater-than-left cervical lymphadenopathy. The patient was first started on broad-spectrum antibiotics for suspected bacterial infection in his pharynx or neck. Initial laboratory investigation was notable for leucocytosis of 13 800/mm^3, anaemia of 10.7 g/dL, mild transaminitis with Aspartate aminotransferase level of 59 units/L, Alanine transaminase of 102 units/L and total bilirubin of 1.4 mg/dL with direct bilirubin of 0.8 mg/dL. The patient's platelet count ranged from 159 to 312 during hospital admission. Metabolic panel was within normal limits. He continued to complain of neck pain and remained persistently febrile and tachycardic despite several days of broad-spectrum antibiotics.

INVESTIGATIONS

Given concern for an inflammatory condition, C reactive protein (CRP), brain natriuretic peptide

Table 1 Infectious disease panel with test results during the patient's hospitalisation

Name of the test	Result
Bacterial	
Anaplasma phagocytophilum IgG	<1:64
Bartonella henselae IgG	<1:128
B. henselae IgM	<1:20
B. quintana IgG	<1:128
B. quintana IgM	<1:20
Ehrlichia chaffeensis IgG	<1:64
Lyme Ab	Negative
Strep A Rapid	Negative
Brucella Ab, IgM and IgG ELISA	Negative
Rickettsia rickettsii Ab, IgM and IgG	<1:64
R. typhi Ab, IgM and IgG	<1:64
Viral	
Hepatitis A IgM	Non-reactive
Hepatitis B, HBc IgM and IgG	Non-reactive
Hepatitis C Ab	Non-reactive
HIV-1 RNA Detect and Quant	Undetected
HIV-1&2 Ag/Ab screen	Non-reactive
CMV IgG Serum	Positive
CMV IgM serum	Negative
EBV PL LOG	1.73
EBV PL RES	54
HSV 1 IgG Serum	Negative
HSV 2 IgG Serum	Negative
MONOSPOT	Negative
Parvovirus B19 IgM and IgG	Negative
West Nile Virus IgM and IgG	Negative
SARS-CoV-2 ID NOW	Negative
SARS-CoV-2 IgG	Positive
Coxsackie B virus antibody types I and IV	1:20
Coxsackie B virus antibody types II, III, V and VI	<1:10
Mycobacterial	
Quantiferon TB result	Negative

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; TB, tuberculosis.

(BNP), ferritin and troponin I levels were sent, and all results were elevated: troponin I high sensitivity at 11 908 ng/L, BNP at 1661 pg/mL, ferritin at 1588 mg/L and CRP at 304.2 mg/L. Transthoracic echocardiography showed mildly decreased left ventricular systolic function with an ejection fraction of 45%–55% by visual estimate. Magnetic resonance cardiac imaging with and without contrast showed mildly depressed right ventricular systolic function and trace pericardial effusion.

DIFFERENTIAL DIAGNOSIS

For infectious workup of cervical lymphadenopathy, we included HIV, *Streptococcus* species, herpes viruses (Epstein-Barr virus, cytomegalovirus (CMV) and herpes simplex virus), HIV, West Nile virus, parvovirus B-19, Coxsackie virus, tuberculosis (interferon gamma release assay), tick-borne diseases (*Rickettsia typhi*, *R. ricketsii*, Rocky Mountain spotted fever and *Ehrlichia*), *Brucella* and *Bartonella*. A detailed infectious panel with results is included in table 1. Other than the positive SARS-CoV-2 IgG that corresponded with patient history, the only positive result was CMV IgG. Given the negative CMV IgM, the patient was considered not actively infected with CMV at presentation. Also, since the patient's presenting symptoms, time course and medical history did not raise significant concern for an autoimmune process, the rheumatology consultant did not recommend ordering an antinuclear antibody test or immunofluorescence assay.

Several rheumatological conditions were also considered, including rheumatoid arthritis (RA), systemic lupus erythematous (SLE), vasculitis and adult-onset Still's disease (AOSD). Lack of synovitis on exam suggested against RA. Absence of oral ulcer, malar rash, hair loss and synovitis suggested against SLE. Absence of arthritis and arthralgia, typical rash and hepatosplenomegaly suggested against AOSD.

TREATMENT

The patient received supportive treatment while he was hospitalised with intravenous fluid resuscitation and antibiotics. Antibiotics were de-escalated from vancomycin and cefepime to ceftriaxone and he was discharged on doxycycline to complete a 10-day course for possible tick-related illness. Intravenous immunoglobulin for multisystem inflammatory syndrome secondary to COVID-19 was considered as a treatment option but never administered, given spontaneous improvement in the patient's lymphadenopathy and fever. He was also started on a beta blocker (metoprolol succinate 12.5 mg/day), and a low-dose ACE inhibitor (lisinopril 2.5 mg) given reduced ejection fraction on cardiac MRI and acute myocardial injury secondary to post-COVID multisystem inflammatory syndrome.

OUTCOME AND FOLLOW-UP

The patient was discharged home after 5 days of hospitalisation. At discharge, his right neck lymphadenopathy and fevers had resolved, and his tachycardia significantly improved. At his 1-month follow-up visit, he reported returning to his usual state of health. He had stopped taking lisinopril and metoprolol a few weeks after discharge. The medications were not restarted since the patient was asymptomatic and his troponin and BNP had returned to normal values. An erythrocyte sedimentation rate level was not obtained, but the C-reactive protein level was 1.1 mg/L, much lower than the patient's CRP near the time of hospital discharge of 182.5 mg/L. The patient's anaemia had resolved with a haemoglobin of 132 g/L, and the white blood cell count was within reference range at 6.05 K/μL.

DISCUSSION

The patient's fever, lymphadenopathy, leucocytosis and mild transaminitis were consistent with reports of MIS-C after COVID-19 infection, although this has typically been seen in children. In our case of COVID-19-related MIS-A in a young adult, the final diagnosis was not confirmed early in the presentation and was not suspected until he failed to improve on antibiotics. In retrospect, the constellation of findings—cardiac dysfunction and lymphadenopathy, and elevated inflammatory markers—is consistent with MIS-A after a known COVID-19 infection.

With the absence of diagnostic guidelines and testing algorithms for MIS-A, the case definition of MIS-C in children established by the Centers for Disease Control and Prevention (CDC) is often used to guide the diagnosis and treatment of MIS-A.[8] The CDC definition of MIS-C includes five criteria: (1) fever in an individual less than 21 years old; (2) elevated inflammatory markers; (3) severe illness requiring hospitalisation, with greater than two organ systems involved; (4) no other plausible alternative diagnosis; and (5) current or recent (4 weeks prior to onset of symptoms) positive SARS-CoV-2 infection. Our patient met all these criteria except for age.

Like MIS-C, the published literature on the newly described disease process of MIS-A is still at an early stage. Twenty-seven cases were included in a review by Godfred-Cato *et al*.[3] Another two cases described young adults who presented with multisystem inflammatory syndrome similar to MIS-C or Kawasaki's disease.[6 7] Among

these cases, all patients had illness severe enough to require hospitalisation. The most common initial presentations that led patients to seek medical attention were fever of 38°C or higher for at least 24 hours, extreme malaise and gastrointestinal symptoms, including abdominal pain, vomiting and diarrhoea. As opposed to adults with acute COVID-19 illness, few of these patients experienced predominant respiratory distresses or severe hypoxaemia.

Our case is similar to others described in the literature in several ways, including initial concern for sepsis, subsequent lack of improvement on broad-spectrum antibiotics and fluid resuscitation, evidence of multisystem end organ damage (troponinemia, transaminitis and skin findings) and absence of respiratory symptoms. A unique aspect of this case is the chief complaint and initial presentation of neck pain resulting from unilateral lymphadenopathy. In a young adult with swollen cervical lymph nodes, this presentation of MIS-A may resemble features of acute bacterial or viral pharyngitis. While there are many infectious aetiologies associated with lymphadenopathy that were ruled out with laboratory testing but not definitively ruled out with a lymph node biopsy, MIS-A should especially be suspected if the patient does not initially improve on antibiotics. During the COVID-19 pandemic, all patients should be asked if they have had a recent COVID-19 infection or symptoms consistent with it within the past year. It is important to rule out other conditions that can mimic this syndrome, which include parvovirus B19, murine typhus, *Bartonella*, Coxsackie virus and *Brucella*. While biopsies to further investigate MIS-A are scarce and have only found modest inflammation, such as macrocytic or lymphocytic infiltrate in endomyocardial biopsies, previous studies have not found strong reactive antinuclear antibodies after acute COVID-19 infection.[9 10]

In conclusion, our case report reveals a presentation of MIS-A that has not been reported before: unilateral cervical lymphadenopathy. In practice, clinicians and health systems should be aware that MIS-A can have a variable initial presentation. Obtaining a history on recent COVID-19 infection, ordering SARS-CoV-2 serological testing and inflammatory markers, and a through diagnostic evaluation are key to establishing the diagnosis.

Learning points

- Like multisystem inflammatory syndrome in children, adults who have been infected with COVID-19 can develop severe cardiovascular, gastrointestinal, neurological and dermatological symptoms without experiencing respiratory distress.
- Multisystem inflammatory syndrome in adults (MIS-A) can present as unilateral neck lymphadenopathy days to months after COVID-19 infection.
- Further research is needed to understand the pathogenesis of MIS-A, particularly given the lack of evidence-based guidelines on diagnostic criteria and testing algorithms.

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ORCID iD

Waqas Haque http://orcid.org/0000-0001-6754-7658

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