Para-aortic lymphadenopathy associated with adult COVID-19 multisystem inflammatory syndrome

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SUMMARY

A 21-year-old woman arrived at the emergency department with dyspnoea, arterial hypotension and abdominal pain after 5 days with a influenza-like syndrome. SARS-CoV-2 was detected by reverse transcription PCR in a nasopharyngeal swab specimen. CT of the chest and abdomen with contrast demonstrated a minimal amount of free intraperitoneal fluid, gallbladder with wall oedema, multiple para-aortic lymph node and interlobular septal thickening with ground glass opacities on the lungs. No pleural effusion or thromboembolism. Early broad-spectrum antibiotics, high-flow nasal cannula and norepinephrine were started. She was successfully treated with intravenous immunoglobulin and pulse corticosteroid therapy with methylprednisolone. The patient was discharged home with complete resolution of her symptoms and returned to her previous health status.

BACKGROUND

The multisystem inflammatory syndrome (MIS) associated with COVID-19 began to be reported in children and it was found to have many similarities with Kawasaki disease and macrophage activation syndrome.[1] The WHO and the CDC have defined diagnostic criteria to classify this paediatric condition.[2 3] However, reports of this syndrome started to appear in patients who met the proposed diagnostic criteria but did not fit the defined age range.[4] With that, it became clear that this syndrome could also affect adults and may lead to a fatal outcome. We report a case of an adult patient with COVID-19 MIS, where there was a real possibility of an unfavourable evolution due to the fact that its clinical presentation was very non-specific with several differential diagnoses. To the best of our knowledge, this is the first case in which para-aortic lymphadenopathy with abdominal pain was present in a COVID-19 MIS. The case highlights this entity as one of the differential diagnoses in severe COVID-19 and brings out the need to recognise it when present and treat it correctly as soon as possible.

CASE PRESENTATION

A 21-year-old Caucasian woman arrived at the hospital with dyspnoea and abdominal pain after a 5-day history of influenza-like symptoms: cough, headache, fever and sore throat. The patient had not received any medication other than analgesics. In the emergency department, a nasopharyngeal real-time reverse transcription PCR (RT-PCR) test was performed, which was positive for SARS-CoV-2. She was diaphoretic, with a blood pressure of 70/50 mm Hg, a heart rate of 100 beats/min, a respiratory rate of 40 breaths/min and oxygen saturation of 88% on room air. On physical examination, there were bilateral crackles in the lungs with a visible jugular venous pulse. On cardiac auscultation, there was only tachycardia, and her abdomen was tender on palpation, without signs of peritonitis. Hepatosplenomegaly was not present. Norepinephrine, ventilatory support with high flow nasal cannula and broad-spectrum antibiotic therapy were started pending the results of cultures.

INVESTIGATIONS

Laboratory tests showed platelet count of $66\,000\times10^9$/L (reference value: $150\,000–400\,000\times10^9$/L), serum N-Terminal-prohormone of Brain Natriuretic Peptide (NT-proBNP) level of 21 300 pg/mL (reference value: <123 pg/mL), troponin I of 1946 ng/L (reference value: <11 ng/L), ferritin of 2341 ng/mL (reference value: 10–291 ng/mL), C reactive protein (CRP) of 36.20 mg/dL (reference value: <1 mg/dL) and D-dimer of 8649.5 ng/mL (reference value: <500 ng/mL). An echocardiogram revealed left ventricular systolic enlargement and severe diffuse hypokinesis. CT scan of the chest and abdomen showed diffuse interlobular septal thickening with ground-glass opacifications in the lingula, middle and lower lobes of the lungs. No pleural effusion or thromboembolism was detected. The liver and spleen did not show enlargement, and there was a minimal amount of intraperitoneal free fluid. It also identified multiple para-aortic lymph nodes, the largest with 7 mm; no other enlarged lymph nodes were found (figure 1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of dyspnoea in patients with COVID-19 include a severe form of the disease per se, and if it is accompanied by arterial hypotension, sepsis shock should be considered and early antibiotics must be started after cultures. The presence of these features and the abdominal pain prompts imaging studies, including echocardiogram and CT scan of the chest and abdomen. The diagnosis of MIS-A in our patient was made by the constellation of multisystemic findings, severe inflammatory features and prominent abdominal discomfort with para-aortic lymphadenopathy. Other differential diagnoses of lymphadenopathy were investigated and for this, tests for HIV 1 and 2, viral hepatitis, cytomegalovirus, Epstein-Barr and syphilis were requested in addition to antinuclear

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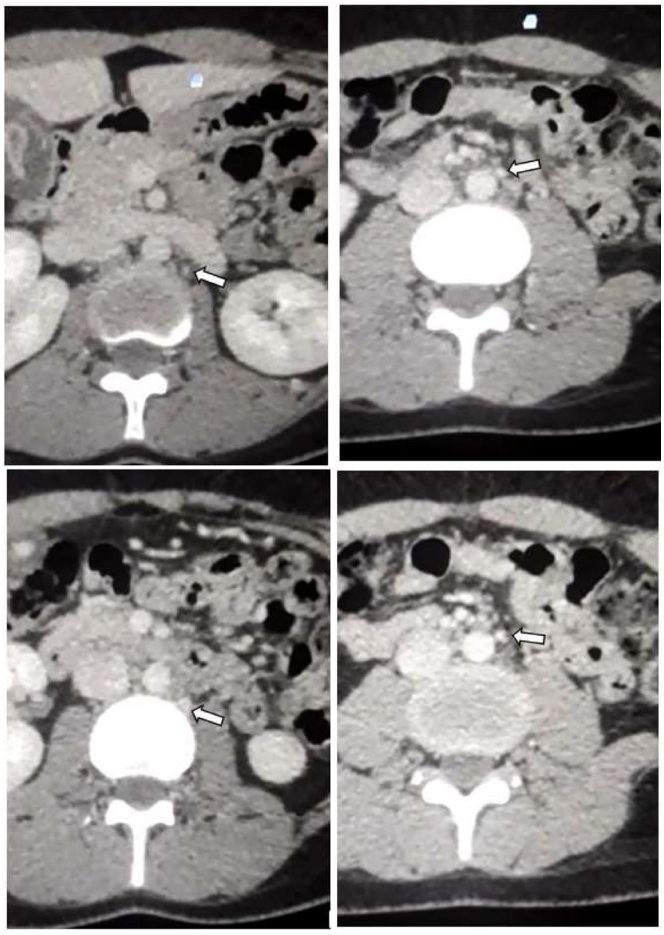

Figure 1 CT images demonstrating multiples para-aortic lymph nodes, the largest measuring 7 mm (Solid arrows).

antibodies (ANA) test, beta human chorionic gonadotropin (HCG) and rheumatoid factor, all with negative results. Cultures were negative for bacterial and fungal infection. Thus, other pathologies were ruled out.

TREATMENT

The patient was successfully treated with intravenous immunoglobulin (Ig) (2 g/kg in a single infusion over 12 hours) and methylprednisolone 1 g for 3 days.

OUTCOME AND FOLLOW-UP

After 1 week, vasoactive drugs and other therapies were discontinued. The patient was discharged home with complete resolution of her symptoms and returned to her previous health status.

DISCUSSION

MIS in children (MIS-C) is a rare and severe condition associated with COVID-19 and it is characterised by fever, markedly elevated inflammatory biomarkers, and multiple organ system involvement, frequently with prominent gastrointestinal symptoms in children or young adults (<21 years of age). It was first reported in April 2020 and since then there have been multiple paediatrics reports about it. Nevertheless, MIS in adults (MIS-A) is not so well established.[5] The primary clinical criteria according to CDC is a severe cardiac illness (eg, myocarditis, pericarditis and coronary artery dilatation/aneurysm) or skin rash and non-purulent conjunctivitis. The secondary clinical criteria include new-onset neurologic signs and symptoms (eg, encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs or peripheral neuropathy), shock or arterial hypotension not attributable to medical therapy (eg, sedation and renal replacement therapy), abdominal pain, vomiting or diarrhoea and thrombocytopenia (platelet count: <150 000/mL). The laboratory evidence is an elevated level of at least two of the following: CRP, ferritin, IL-6, erythrocyte sedimentation rate and procalcitonin; and positive SARS-CoV-2 test during the current illness by RT-PCR, serology or antigen detection.[2] The diagnosis can be a challenge because it involves distinguishing MIS-A from severe COVID-19, particularly in older patients with multiple comorbidities.[5] Therefore, severe COVID-19 is more related to respiratory symptoms, while MIS-A involves a post-infectious hyperinflammatory response affecting multiple organs, leading to fever, cardiac involvement and abdominal symptoms.[6]

Bastug *et al* performed a case-based review with 40 patients with COVID-19-associated MIS-A. In this report, 25 of the 40 patients were male, and the average age was 32.5 years. Five patients required mechanical ventilation, two required an intra-aortic balloon pump and another two required extracorporeal membrane oxygenation (ECMO). The length of hospital stay ranged from 3 days to 50 days, with an average of 13.4 days. None of them died. The most common symptoms were fever in 80% of the patients (32/40), followed by gastrointestinal complaints (eg, abdominal pain) in 77,5% (31/40) and respiratory symptoms in 47.5%. At admission, tachycardia occurred in 72,4% of the patients, followed by hypotension in 60%. The cardiac involvement with echocardiographic changes (eg, global hypokinesis) and high levels of troponin and NT-proBNP was frequently reported. Increases in inflammatory biomarkers (eg, CRP, ferritin and D-dimer) were present in almost all patients. Cervical lymphadenopathy was detected in two patients. The treatment of choice was steroids in 66% of the patients (24/36) and intravenous Ig was used in 16 patients (44%). Tocilizumab was given to only four patients in 36 patients reported. Supportive care with acetylsalicylic acid, anticoagulant treatment and vasopressor was also recommended.[7]

In the first described cases of COVID-19, the presence of lymphadenopathy was seen as a rare event, affecting mainly the mediastinal region. However, throughout the pandemic, it has been reported that this condition is otherwise frequent in critically ill patients with the classic form of SARS-CoV-2 infection seen as a reactive condition to the inflammatory process and viral infection.[8 9] Nevertheless, there are few cases of lymphadenopathy outside the thoracic region described in the literature. The most described lymphadenopathy location is cervical[4 7 10] followed by mesenteric adenopathy.[4 11] The patient reported in this case presented abdominal pain and para-aortic lymphadenopathy on CT. To the best of our knowledge, it is the first case described in the literature. This finding may have occurred due to the excess inflammation reaction in response to the viral infection, as previously described for the involvement of mediastinal region, and probably related to the severity of the case. Furthermore, lymphadenopathy should be considered a predictor of poor outcome. Nevertheless, the pathophysiological meaning of this finding related to host response to the virus infection and the possibility to use this information in the clinical management of patients with COVID-19 remain to be investigated.[12]

The presence of lymphadenopathy can also be seen in Kawasaki disease, affecting mainly the cervical region, but in acute phases, as described by Kashef *et al* it can affect para-aortic lymph nodes associated with other typical manifestations such

as bilateral conjunctival injection, polymorphous rash, mucosal changes and changes in the extremities.[13]

The patient described in our case meets all the criteria, following the guidelines defined by CDC for MIS-A.[2] The American College of Rheumatology has developed a clinical external guidance icon only for patients with MIS-C associated with COVID-19.[14] It provides a step-by-step approach to the immunomodulatory treatment of MIS-C with intravenous Ig and/or glucocorticoids, considered as first-line agents. Both intravenous Ig and glucocorticoids, alone or in combination, are the most commonly used immunomodulatory medications reported to date in patients with MIS-C. We adapted the MIS-C guidelines to her treatment regimen, as she received intravenous Ig and methylprednisolone.

Learning points

- Multisystem inflammatory syndrome in adults (MIS-A) associated with COVID-19 is a rare and severe condition that may affect multiple organs and systems with prominent gastrointestinal symptoms in adults aged ≥21 years with COVID-19.
- On rare occasions, COVID-19 may present with lymphadenopathy outside the thoracic region, including the abdomen.
- Our case has a unique feature of para-aortic lymphadenopathy associated with abdominal pain. Nevertheless, MIS-A should be considered in patients presenting with abdominal pain and severe COVID-19.
- Prompt diagnosis and treatment reduce the overall mortality of MIS-A associated with COVID-19 since it can be difficult in distinguishing this syndrome from severe COVID-19.

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