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ORIGINAL ARTICLE

Multisystem inflammatory syndrome in children associated with COVID-19 presenting as cervical inflammation

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Abstract

Aim: The major clinical manifestations multisystem inflammatory syndrome in children (MIS-C) are fever, gastrointestinal and cardiac. The aim of this study was to describe MIS-C in a series of patients who presented primarily with cervical manifestations.

Methods: We retrospectively reviewed medical records of all patients who met the Centers for Disease Control and Prevention and World Health Organization MIS-C diagnostic criteria treated at Hadassah-Hebrew University Medical Center between April 2020 and September 2021.

Results: Of 37 children diagnosed with MIS-C (median age: 10.2 years, range 1.5–18 years, 20 male) five, 13.5% (median age: 14.4 years, range 9.2–17.5 years) presented with cervical symptoms mimicking neck infections. One was hospitalised with a working diagnosis of retropharyngeal abscess, and four with acute cervical lymphadenitis that did not respond to early antibiotic treatment. All developed full MIS-C phenotype.

Conclusion: MIS-C may present as cervical inflammation. An ill-appearing child with symptoms and/or signs of cervical inflammation should be evaluated for clinical and laboratory features of MIS-C, thereby facilitating prompt treatment of this potentially fatal disorder.

KEYWORDS
cervical adenopathy, multi system inflammatory syndrome in children, neck infection, retropharyngeal abscess

1 | INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a recently described potentially lethal unique inflammatory syndrome. MIS-C occurs following infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) commonly referred to as COVID-19.[1,2] Similar to acute rheumatic fever, MIS-C is a reactive disease occurring weeks after the initial SARS-CoV-2 infection which may be mild or even asymptomatic in children.[3] Initially, MIS-C was thought to overlap with Kawasaki Disease,[4,5] but it is now recognised as a distinct syndrome. Both the US Centers for Disease Control and the World Health Organization have published case definitions for MIS-C. These include age, fever, organ dysfunction, laboratory markers of inflammation, exclusion of alternative diagnoses, and a history

Abbreviations: IVIG, intravenous immunoglobulins; MIS-C, Multi system inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Rebecca Brooks and Ron Fisher contributed equally to this work.

of SARS-CoV-2 infection or exposure.[6,7] The most prominent signs and symptoms of children with MIS-C typically involve the cardiovascular and gastrointestinal systems. Other commonly reported findings include mucosal changes, peripheral oedema, rash and conjunctivitis.[1,8–10] There were anecdotal reports of MIS-C presenting with prominent cervical manifestations.[11–14]

MIS-C is a potentially lethal disease, and early diagnosis and prompt treatment are essential.[10] We describe a series of five patients with MIS-C who presented with signs of cervical inflammation. The first case we describe was a patient who was retrospectively diagnosed with MIS-C and did not receive recommended treatment because of delay in diagnosis. Based on this experience, there was heightened awareness of the association between cervical manifestations and MIS-C. Subsequently, four additional children were diagnosed early in the course of their disease and promptly treated.

Key notes

- Multi system inflammatory syndrome in children (MIS-C), is a potentially lethal disease. Early diagnosis and treatment are essential.
- In our cohort, a significant proportion of children diagnosed with MIS-C presented with cervical manifestations.
- An ill-appearing child with suspected cervical inflammation should be evaluated for MIS-C, as prompt treatment of this potentially fatal disorder is essential.

2 | METHODS

We retrospectively reviewed medical records of all patients with MIS-C treated at the two campuses of Hadassah-Hebrew University Medical Center between 1 April 2020 and 30 September 2021. Diagnosis of MIS-C was established based on the case definitions of the Centers for Disease Control and Prevention and World Health Organization of MIS-C.[6,7] Demographic, clinical, laboratory and radiographic findings were recorded and analysed. The study was approved by the Hadassah university medical centre institutional review board for studies involving human subjects (0022-21-HMO).

3 | RESULTS

A total of 37 patients were admitted to the Hadassah-Hebrew University Medical Center with a diagnosis of MIS-C (median age: 10.2 years, range 1.5–18 years, 20 male). Five, 13.5% (median age: 14.4 years, range 9.2–17.5 years) presented with signs of cervical inflammation (Table 1). One was hospitalised with the diagnosis of a retropharyngeal abscess, and four with acute cervical lymphadenitis. All children were previously healthy. Four had known prior exposure to SARS-CoV-2. Three had mild SARS-CoV-2 symptoms and two were asymptomatic. On admission polymerase chain reaction for SARS-CoV-2 was negative and SARS-CoV-2 serology was positive in all five.

All patients were febrile and appeared to be ill, three became hypotensive needing inotropic support. Four developed cardiac involvement. All had lymphopenia, elevated C-reactive protein and D-Dimer levels.

Three patients were sufficiently ill to necessitate a transfer to the paediatric intensive care unit. Four patients were treated with corticosteroids and intravenous immunoglobulins (IVIG). All the patients survived and were discharged home after complete resolution of MIS-C. The median time to discharge was 8.4 days (range 7–10 days).

3.1 | Case one

A 15-year-old healthy female patient was seen in the emergency department with a 5-day history of severe neck pain, dysphagia and fever. On admission, she had hyperaemic, swollen tonsils with retropharyngeal bulging. A contrast-enhanced CT demonstrated cervical lymphadenopathy, with the largest node measuring 14 × 11 mm. There was central liquefaction (Figure 1A) and a retropharyngeal inflammatory collection (23 × 22 mm) leading to tracheal displacement (Figure 1B). She was treated with broad-spectrum antibiotics for a presumed retropharyngeal abscess. On day two of hospitalisation the patient developed trismus, severe abdominal pain and profound systolic and diastolic hypotension (65/34). She was transferred to the paediatric intensive care unit and an infusion of inotropes was initiated. Repeat laboratory tests were consistent with a diagnosis of MIS-C (Table 1). As the patient was showing signs of clinical improvement, she was not administered either corticosteroids or intravenous immunoglobulins. Cervical manifestations gradually resolved, allowing for a tapering of the inotrope infusion. She was discharged from the paediatric intensive care unit after 5 days.

3.2 | Case two

A 15-year-old healthy male presented to our emergency department with a 4-day history of severe unilateral neck pain, dysphagia and onset of fever 1 month after a confirmed SARS-CoV-2 infection. On admission, he was ill-appearing, febrile, tachycardic and complained of severe neck pain. Cervical ultrasound showed bilateral lymphadenopathy with the largest node measuring 11 mm in diameter. The involved lymph nodes were hypoechoic with disappearance of the normal fatty hilum, generally preserved in reactive nodes, consistent with infection or necrosis. Antibiotic treatment for presumed bacterial lymphadenitis was initiated. Fever, tachycardia and cervical pain persisted, and the patient began complaining of abdominal pain and developed signs of non-purulent conjunctivitis. Two days after admission he became hypotensive

TABLE 1 Demographic, clinical features, laboratory and outcome of patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)/ gender	15/ Female	15/ Male	17/ Female	15/ Male	9/ Male
Previous SARS-CoV-2 infection	3 weeks prior to admission. Asymptomatic	4 weeks prior to admission. Mild symptoms	4 weeks prior to admission. Mild symptoms	4 weeks prior to admission. Mild symptoms	No known contact or infection
SARS-CoV-2 testing	PCR (−), Ab (+)	PCR (−), Ab (+)	PCR (−), Ab (+)	PCR (−), Ab (+)	PCR (−), Ab (+)
Clinical involvement					
Cardiac involvement	None	Elevated cardiac enzymes	Elevated cardiac enzymes Echocardiogram: reduced systolic function, mild pericardial effusion	Elevated cardiac enzymes	Elevated cardiac enzymes ECG: ST changes
Other manifestations	Febrile, ill-appearing, hypotensive, Abdominal tenderness	Febrile, ill appearing, tachycardic, hypotensive, abdominal pain, non-purulent conjunctivitis	Febrile, ill-appearing, pale, hypotensive, abdominal tenderness, non-purulent conjunctivitis	Febrile, ill-appearing, vomiting, rash, non-purulent conjunctivitis	Febrile, ill-appearing, rash, non-purulent conjunctivitis
Laboratory studies (peak)	CRP 24 mg/dl, Lymphocytes 400 10^9/L, D-Dimer 4 mg/L	CRP 23 mg/dl, Lymphocytes 400 10^9/L, D-Dimer 5 mg/L	CRP 25 mg/dl, Lymphocytes 400 10^9/L, D-Dimer 6 mg/L	CRP 30 mg/dl, Lymphocytes 800 10^9/L, D-Dimer n/a	CRP 29 mg/dl, Lymphocytes 200 10^9/L, D-Dimer 10 mg/L
Outcome					
Resolution of cervical symptoms (days)	5	3	1	3	1
Length of hospitalisation (days)	10	8	7	7	10

Abbreviations: Ab, Antibodies; CRP, C-reactive protein; ECG; Electrocardiogram; PCR, Polymerase chain reaction.

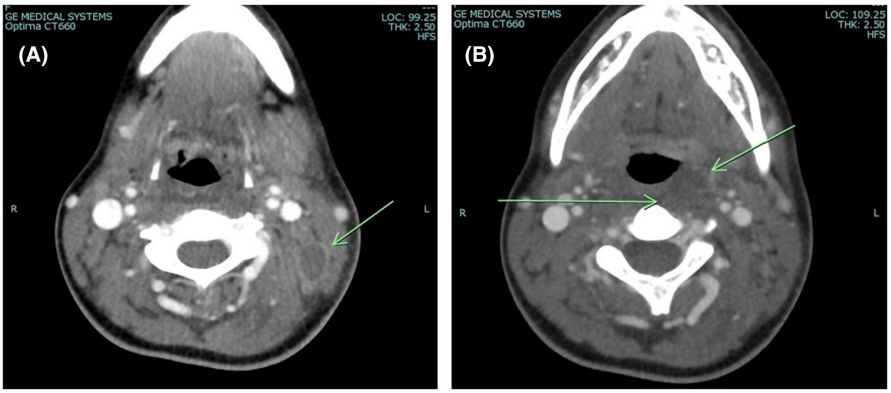

FIGURE 1 (A) CT scan – Cervical lymphadenopathy, the largest node measuring 14 × 11 mm with central liquefaction (arrow). (B) CT scan – Retropharyngeal inflammatory collection (23 × 22 mm) causing tracheal displacement (arrows).

and was transferred to the paediatric intensive care unit for inotropic support. Clinical and laboratory tests were consistent with MIS-C (Table 1). His condition rapidly improved following treatment with IVIG and corticosteroids.

3.3 | Case three

A 17-year-old healthy female patient presented with 5 days of fever, severe throat pain, dysphagia, dysphonia and mild abdominal pain 4 weeks after a mild symptomatic SARS-CoV-2 infection. On examination she was febrile, pale and hypotensive. She had painful bilateral cervical lymphadenopathy, trismus and a hyperaemic pharynx. Cardiac evaluation revealed reduced left ventricular function on echocardiogram and ST changes on ECG (Table 1). MIS-C was diagnosed and treatment with IVIG, corticosteroids and enoxaparin were initiated. Trismus and dysphonia resolved within hours after starting treatment. The hemodynamic status stabilised and gastrointestinal symptoms resolved within 24 h. Other manifestations including dysphagia and lymphadenopathy resolved during the next 3 days, and a repeat echocardiogram showed normal cardiac function.

3.4 | Case four

A 15-year-old healthy male presented with 4 days of fever, vomiting and worsening unilateral neck pain despite treatment with oral amoxicillin. In the emergency department, he was febrile with painful unilateral neck swelling involving the retromandibular area. Cervical ultrasound displayed bilateral enlarged, hypoechogenic lymph nodes lacking both normal structure and identifiable blood flow, consistent with necrosis. No improvement was noted following 36 h of intravenous antibiotic treatment for presumed bacterial lymphadenitis. He remained febrile and became tachycardic, with increasing weakness, developed a rash and non-purulent conjunctivitis. Laboratory tests at this stage were typical of MIS-C including elevated cardiac enzymes (Table 1). He was treated with IVIG and corticosteroids and his condition rapidly improved.

3.5 | Case five

A 9-year-old healthy male presented with a 2-day history of fever, severe dysphagia, sore throat, headache and mild abdominal pain. On examination he was febrile with unilateral, painful neck swelling and bilateral cervical lymphadenopathy. He had a hyperaemic throat, non-purulent conjunctivitis and a non-specific rash. Laboratory tests were typical of MIS-C (Table 1). Cervical ultrasound showed bilateral lymphadenopathy with the largest node measuring 25 mm in diameter. He was treated with IVIG, corticosteroids and enoxaparin which was followed by clinical improvement.

4 | DISCUSSION

We describe five patients who presented with signs and symptoms of cervical inflammation and were subsequently diagnosed with MIS-C based on the Centers for Disease Control and Prevention and World Health Organization criteria.[6,7] One patient who presented in the beginning of the pandemic spontaneously improved and the other four responded well to treatment with corticosteroids and IVIG.

Cervical lymphadenopathy in childhood is a common response to infection and may be associated with severe deep neck infections such as abscesses in the parapharyngeal and retropharyngeal space. Cervical lymphadenopathy also may occur as a manifestation of systemic infection or inflammatory process similar to acute Kawasaki disease.[15–17] In Kawasaki disease, deep neck inflammation is rare as shown in a cohort study in which only 0.6% of Kawasaki disease patients developed this complication. It is interesting to note that Kawasaki disease patients with deep neck involvement were older than the average patient with Kawasaki disease (age 5 vs. 2 years). This manifestation was associated with surgical procedures for presumed abscess and longer hospital stay.[18]

Similar to Kawasaki disease, deep neck manifestations are rare in acute SARS-CoV-2 infection among adults.[19–21] To date there have only been anecdotal case reports reporting deep neck infection in children associated with SARS-CoV-2.[11–14,22] In our cohort, 13.5% of patients had cervical manifestation as a primary presentation.

Radiological findings in our cohort were: retropharyngeal phlegmon on CT, enlarged necrotic cervical lymph nodes and large reactive lymph nodes. Blood and throat cultures were negative suggesting a non-bacterial inflammatory process. All children were treated with antibiotics for presumed deep neck infection; but only after initiation of treatment with systemic corticosteroids and IVIG rapid clinical and laboratory improvement was seen in four patients. One patient's condition resolved without corticosteroids and intravenous immunoglobulin treatment, her clinical course was prolonged and she required significant cardiovascular support.

MIS-C has been a widely described paediatric entity since the beginning of the SARS-CoV-2 pandemic, but the pathophysiology of this new hyperinflammatory syndrome is still unknown. The affinity of SARS-CoV-2 for the gastrointestinal and cardiovascular systems in MIS-C remains unexplained. Our observation of cervical involvement may be explained by the rich lymphatic presence in the neck which is activated by severe inflammatory processes that occur in systemic diseases such as Kawasaki disease. It is still an open question as to why cervical inflammation is a relatively rare complication in other multisystem inflammatory disorders.

5 | CONCLUSION

Cervical manifestations may be the presenting sign of MIS-C. Although many aspects of severe bacterial infections mimic MIS-C, children who appear to be ill with symptoms and/or signs of cervical inflammation should be evaluated for clinical and laboratory features of MIS-C, especially during or after waves of increased infection rates, so that targeted treatment can be initiated promptly for this potentially fatal disorder.

AUTHOR CONTRIBUTIONS

Rebecca Brooks, and Ron Fisher conceptualised, designed the data collection, collected data, carried out the initial analyses, drafted, reviewed and revised the manuscript. Charlotte Glicksman and Uri Pollak collected data, reviewed and revised the manuscript. Natalia Simanovsky collected, analysed imaging data, reviewed and revised the manuscript. Yackov Berkun conceptualised, designed the data collection, carried out the initial analyses, drafted, reviewed, revised the manuscript and supervised.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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