

Retropharyngeal involvement in multisystem inflammatory syndrome in children: Case report and review of literature

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Abstract

A diagnosis of multisystem inflammatory syndrome in children should be made in the appropriate context and after ruling out other infectious causes. At the same time, clinicians should be diligent as the initial presentation can be unusual and the clinical picture can evolve over time. We report a case that was initially diagnosed as a retropharyngeal infection that did not improve on appropriate antimicrobial coverage. However, as the clinical picture evolved, the patient was found to have multisystem inflammatory syndrome in children and appropriately responded to immunomodulatory treatment. Pediatric infectious diseases practice has been significantly affected by the COVID-19 virus and multisystem inflammatory syndrome in children; data are still emerging as the pandemic evolves. We report this case and conduct literature review to expand the body of evidence about the association between multisystem inflammatory syndrome in children and retropharyngeal involvement.

Keywords

COVID-19, SARS-CoV-2, multisystem inflammatory syndrome in children, retropharyngeal infection

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Introduction

Multisystem inflammatory syndrome in children (MIS-C) describes a life-threatening condition that may follow SARS-CoV-2 infection in some children. Manifestations of the inflammatory syndrome typically begin 4 weeks post infection, with a range of 2 weeks to 2 months post infection.¹ In order to increase the awareness in the beginning of the pandemic, the US Centers for Disease Control and Prevention (CDC)² and the World Health Organization (WHO)³ created criteria to diagnose MIS-C in children. MIS-C may include cardiac, mucocutaneous, and systemic symptoms. While there are criteria to diagnose MIS-C, it remains primarily a diagnosis of exclusion.²

To date, the literature about MIS-C is largely limited to case series and retrospective cohort studies. While the CDC and WHO criteria list the most common signs and symptoms of MIS-C in the beginning of the pandemic, it is likely that there are other manifestations that should alert a physician

that a child might be suffering MIS-C, just as anosmia and ageusia were not initially understood to be symptoms of COVID-19 infection in adults. As the COVID-19 pandemic continues to evolve, it is more likely that the virus will become endemic with continued infections, much like influenza. Thus, it is critical to fully characterize the sequelae of COVID-19 infection, such as MIS-C, to lead to prompt recognition and lifesaving treatment.

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Table 1. Lab values at initial ED evaluation, presentation to consult service, 48h post initiation of IVIG, and discharge.

WBC ($10^9/L$)	8.4	19.3	9.6	8.2
ANC ($10^9/L$)	6.9	17.9	7.1	4.6
Absolute lymphocytes ($10^9/L$)	0.6	0.4	1.2	2.7
Hemoglobin (g/dL)	12.5	9.5	9.1	11.8
Platelets ($10^9/L$)	208	255	277	360
CRP (mg/L)	129.3	315.6	213.8	100.5
ESR (mm/h)	55	45	–	–
D-dimer (ng/mL)	–	3743	5551	7391
INR	–	1.2	1.2	1.4
PTT (s)	–	31	31	30
Fibrinogen (mg/dL)	–	687	464	341
Ferritin (ng/mL)	–	290	352	248
Troponin (ng/L)	–	102	–	–
BNP (pg/mL)	–	2730.9	–	–
Albumin (g/dL)	–	2.6	–	–
ALT (IU/L)	–	6	–	–
AST (IU/L)	–	14	–	–

ED: emergency department; IVIG: intravenous immune globulin; WBC: white blood cell; ANC: absolute neutrophil count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; INR: international normalized ratio; PTT: partial thromboplastin time; BNP: brain natriuretic peptide; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Previous literature has raised attention on the association of MIS-C and retropharyngeal edema. We report the case of a child who presented with classic features of retropharyngeal phlegmon, yet quickly deteriorated and developed hemodynamic instability with cardiac and gastrointestinal (GI) symptoms. The child was subsequently recognized to have MIS-C. This report serves to strengthen the body of evidence showing an association between retropharyngeal phlegmon and MIS-C.

Case presentation

A 5-year-old male presented to the pediatric emergency department at Hasbro Children's Hospital in Providence, RI, USA, with 2 days of fever, neck pain,odynophagia, headache, nasal congestion, and lethargy. He had no cough, abdominal pain, vomiting, diarrhea, or rash. He had no sick contacts or recent travel. Of note, the patient and his family had a mild COVID-19 infection 6 weeks prior to presentation, and the patient was unvaccinated against COVID-19. Initial physical examination revealed tachycardia (142 bpm) and fever (103.4F), with remaining vital signs, including blood pressure, respiratory rate, and oxygen saturation, within normal limits. He had full range of motion of the neck with no respiratory distress or stridor. Other than shotty posterior cervical lymphadenopathy, his physical examination was unremarkable.

Initial laboratory findings included elevated inflammatory biomarkers: C-reactive protein (CRP) (129.3 mg/L) and erythrocyte sedimentation rate (ESR) (55 mm/h). Complete blood count revealed lymphopenia ($0.6 \times 10^9/L$) with normal white blood cell (WBC) ($8.4 \times 10^9/L$) and a basic

metabolic panel showed mild hyponatremia (133 meq/L) (Table 1). Rapid antigen testing for group A *Streptococcus*, nasopharyngeal polymerase chain reaction (PCR) for SARS-CoV-2, influenza A and B, and respiratory syncytial virus were all negative. In addition, blood cultures were sent. X-ray of the neck showed paravertebral soft tissue swelling, which raised the possibility of retropharyngeal cellulitis or abscess, and computed tomography (CT) of the neck suggested retropharyngeal phlegmonous changes or possible early abscess with bilateral reactive lymphadenopathy (Image 1). The patient was admitted, given one dose of dexamethasone for symptomatic relief, and started on intravenous (IV) ampicillin–sulbactam to cover most common pathogens causing retropharyngeal infections (e.g. *Staphylococcus*, *Streptococcus*, and respiratory anaerobes). Because of decreased oral intake, he was kept on maintenance IV fluids. Pediatric ear, nose, and throat (ENT) was consulted, and recommended antibiotics without drainage.

During the first 3 days of admission, the patient continued to have persistent high-grade fevers up to 102 F, tachycardia (120–140 s), and tachypnea (20–30 s). On the third night of admission, his clinical condition deteriorated with worsening tachycardia, tachypnea, borderline hypotension that responded to fluid resuscitation, ongoing fevers, softer voice, facial edema, and increased pain with neck motion in all directions, particularly with extension. The following morning, he continued to have fevers, tachycardia, tachypnea, hypotension, and was noted to have a new prominent cardiac gallop, 1+ soft pulses, and mild hepatomegaly on examination. His CRP had significantly increased to 315.6 mg/L. IV Vancomycin was added to broaden coverage and a repeat CT neck with IV contrast redemonstrated

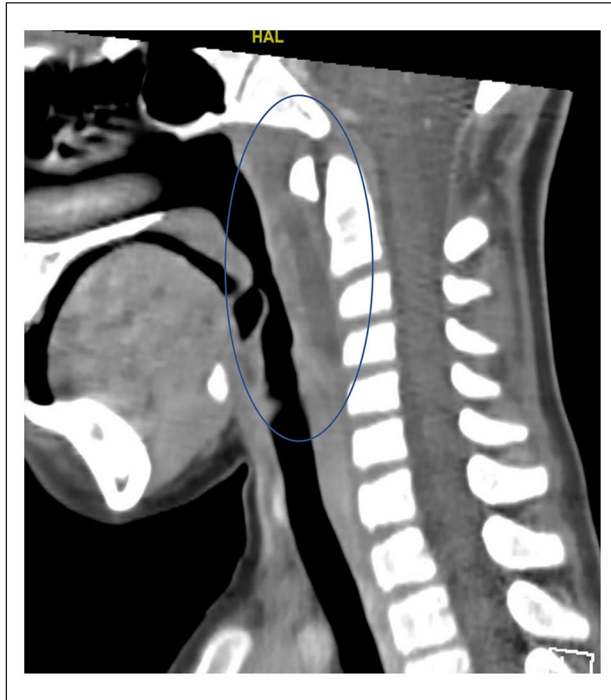


Image 1. Initial CT. CT neck with IV contrast on 2/21 showing 0.7 cm × 1.3 cm × 3.9 cm region of hypoattenuation within the suprahyoid retropharyngeal soft tissues without significant peripheral contrast enhancement. This area extends from the inferior aspect of the C1 vertebral body to approximately the base of C4.

retropharyngeal phlegmon that appeared unchanged in anterior–posterior (AP) diameter compared to prior CT imaging and persistent reactive cervical lymphadenopathy. A CT chest revealed bilateral pleural effusions with subsegmental atelectasis, periportal edema, and mediastinal lymphadenopathy (Image 2).

Over the next 6 h, the patient’s clinical status continued to deteriorate and he was transferred to the pediatric intensive care unit (PICU) for further management. An epinephrine infusion was initiated at a rate of 0.05 Mcg/min, and the patient was started on 10 L high-flow nasal cannula. His worsening clinical picture along with recent history of COVID-19 infection increased the suspicion for MIS-C. Notable findings at that time included a cardiac echocardiogram showing mild biventricular systolic dysfunction with mild four-chamber dilated chambers, positive SARS-CoV-2 serologies (anti-N-protein and anti-RBD IgG antibodies), elevated CRP (315.6 mg/L), troponin (102 ng/L), brain natriuretic peptide (BNP) (2730.9 pg/mL), D-dimer (3743 ng/mL), ferritin (290 ng/mL), fibrinogen (687 mg/dL), and international normalized ratio (INR) (1.2). Because the initial clinicians were unaware of this unusual association between retropharyngeal phlegmon and MIS-C and few



Image 2. Follow-up CT. CT neck with IV contrast on 2/24: redemonstrated retropharyngeal phlegmon. A rim-enhancing fluid collection is not demonstrated. As before, this extends from approximately the C1 to the C4 level. It appears mildly diminished in AP diameter compared to prior.

additional symptoms had developed, they attributed the initial CT findings to a bacterial process (Table 1). As the clinical picture evolved, differential diagnosis was broad and included MIS-C, sepsis, Kawasaki disease (KD), toxic shock syndrome, and infectious mononucleosis. Sepsis was unlikely due to negative cultures and lack of improvement on broad spectrum antibiotics. Toxic shock syndrome and KD did not explain the whole clinical picture. The absence of pharyngitis, having lymphopenia rather than reactive lymphocytosis made infectious mononucleosis less likely. In addition, infectious mononucleosis can rarely be associated with peritonsillar abscesses but not retropharyngeal collections. Once it was clear that he had >2 system involvement (cardiac, hematologic, and respiratory) and there were no other alternative plausible diagnoses, the diagnosis of MIS-C was made. The patient was started on intravenous immune globulin (IVIG) 2 g/kg, methylprednisolone 1 mg/kg/dose every 12 h, and enoxaparin 0.5 mg twice daily. The patient’s clinical status, laboratory, and imaging findings significantly improved within 48 h, and he was discharged on hospital day 8 on a prednisolone taper, amoxicillin–clavulanate, and aspirin 81 mg. A repeat cardiac echo 2 weeks after hospital discharge showed normal cardiac function and normal coronary arteries. His lack of improvement on antibiotics and appropriate response to MIS-C treatment further supports the MIS-C diagnosis.

Discussion

This 5-year-old male was admitted for presumed retropharyngeal phlegmon and inflammation. His clinical picture rapidly declined during his hospital stay leading to a diagnosis of MIS-C. His initial symptoms included fever, neck pain, headache, and odynophagia. Despite being on appropriate therapy for presumed retropharyngeal infection, he had persistent fever, worsening vital signs, hypotension, facial edema, new cardiac gallop, and hepatomegaly on physical examination. Initially, we suspected inappropriate antimicrobial coverage and progression of a presumed retropharyngeal infection, but repeat imaging unexpectedly showed mildly improved retropharyngeal inflammation.

Given his history of COVID-19 exposure 6 weeks prior to presentation, rapidly evolving symptoms, new physical exam findings, high inflammatory markers, and echocardiogram results, the patient was started on IVIG and steroids. He did fulfill the CDC diagnostic criteria for MIS-C (age below 21 years, fever, laboratory evidence of inflammation, multisystem involvement, and recent infection demonstrated by serology). In addition, his clinical picture could not be fully explained by any other plausible diagnoses.² He also fulfilled the WHO case definition for MIS-C.³ It is worth mentioning that in retrospect, his normal WBC and lymphopenia on presentation may have been early clues as bacterial infection would not typically cause lymphopenia, which can be frequently seen in MIS-C.⁴ In addition, hyponatremia is frequently seen in intense inflammatory conditions like KD⁴ and Juvenile Idiopathic Arthritis (JIA).⁵

Since the first case with MIS-C was diagnosed in the United Kingdom in April 2020, the literature has been rapidly documenting the clinical presentation and possible pathophysiology of the syndrome. It has been suggested that an abnormal immune response to the COVID-19 virus is the cause.⁶ However, the exact trigger and the exact pathophysiology is unknown. Our case helps to expand our understanding of the full spectrum of clinical findings which may be seen with MIS-C. Available case series show that the most common symptoms besides fever include GI symptoms, cardiovascular manifestations, rash, conjunctivitis, mucous membrane involvement, and respiratory symptoms.^{7,8} Neck-related symptoms are also reported in the literature.^{9,10}

The presence of retropharyngeal inflammation in MIS-C has previously been reported. We searched Ovid MEDLINE, PubMed, and Google Scholar using the Medical Subject Heading terms “retropharyngeal” and “multisystem inflammatory syndrome in children”; no limitations were applied. A summary of the reported cases is in Table 2. In addition to our case, we found 16 reported

cases. A large case series of 137 MIS-C patients showed that 4 patients had evidence of retropharyngeal inflammation proved by imaging.¹⁰ Another small case series reported retropharyngeal involvement in three MIS-C patients.¹¹ Additional case reports and series demonstrated similar findings.^{12–22} Our case and review of other reported cases strengthens the evidence of association between retropharyngeal inflammation and MIS-C. Absence of an association of retropharyngeal inflammation and MIS-C in the literature might have led to a relatively late diagnosis in some patients such as occurred with our patient. Our case among the other cases proves that retropharyngeal inflammation, mimicking phlegmon, may not only be associated with MIS-C but may be its presenting symptom.

Retropharyngeal edema is a known clinical sequela in another pediatric autoimmune inflammatory syndrome, KD.^{23,24} A population-based study estimated the incidence of deep neck space involvement in KD in the United States to be around 0.6%.²⁵ KD is a medium vessel vasculitis that usually affects children below 5 years of age. The clinical picture of MIS-C can overlap with KD, but they are different entities. The initial literature in 2020 suggested that MIS-C was a variant of KD;²⁶ however, as the pandemic progressed, it became clear that this is not accurate.^{7,27} MIS-C patients can have prominent GI symptoms, shock, and hemodynamic instability due to cardiac dysfunction, lymphopenia, hematological abnormalities, and higher inflammatory markers than KD patients.⁶ Furthermore, some features of KD such as lymphadenitis are uncommon in MIS-C.²⁸ Additional studies showed that KD features are not a good predictor of the MIS-C diagnosis or to the risk of developing coronary artery aneurysms.^{28,29} The exact pathophysiology of retropharyngeal involvement in KD and MIS-C is unknown but could be due to a diffuse inflammatory response.³⁰

Conclusion

In summary, we present a case demonstrating that MIS-C may initially present with neck symptoms and retropharyngeal involvement. Our review of the literature indicates that retropharyngeal involvement may occur in some patients found to have MIS-C. Physicians should be diligent in managing patients with presumed retropharyngeal infection and history of recent COVID-19 exposure or infection, especially if the patient does not respond to appropriate antimicrobial therapy. A diagnosis of MIS-C in this setting should be considered and work up initiated. Understanding retropharyngeal involvement in MIS-C may help us further characterize and understand this novel inflammatory syndrome in pediatric patients.

Table 2. Summary of MIS-C cases with retropharyngeal involvement.

N	Age (reference)	Country	Initial symptoms	Imaging	Surgical intervention	Treatment (all received antibiotics)
1	17 (10)	The United States	Fever, neck swelling, dysphagia, and headache	Right palatine tonsillitis, mild narrowing of the oropharyngeal airway, no drainable abscess. Large prevertebral/retropharyngeal fluid collection. Large right neck phlegmon	N	IVIG, steroids
2	16 (10)	The United States	Fever, neck pain and dysphagia, and conjunctival injection	Inflammatory cervical adenopathy on the right, with retropharyngeal edema	N	steroid
3	15 (10)	The United States	Fever, sore throat, neck pain, and conjunctival injection	Retropharyngeal lymphadenitis and prevertebral edema, no drainable abscess. Enlarged adenoids with obstruction of the nasopharyngeal passage	N	steroids
4	13 (10)	The United States	Fever, headache, neck pain and dysphagia, cardiogenic, shock, and neck swelling	Retropharyngeal/prevertebral edema vs fluid collection. Mild mass effect on the nasopharynx and oropharynx	N	IVIG, steroids
5	12 (11) (15)	The United States	Fever, neck swelling, trismus, voice change, cracked lips, rash, conjunctivitis, and cervical lymphadenopathy	Retropharyngeal fluid collection from the level of C2–C5 without peripheral enhancement, enlarged lymph nodes, soft tissue edema	Y	IVIG, remdesivir, anakinra
6	4 (11) (15)	The United States	Fever, sore throat, abdominal pain, conjunctivitis, rash, and vomiting	Pharyngeal mucosa inflammation, retropharyngeal fluid without enhancement suggestive of retropharyngeal edema	N	IVIG, steroids
7	13 (11) (15)	The United States	Fever, sore throat, neck pain, vomiting, diarrhea, cervical lymphadenopathy, and cracked lips	Retropharyngeal fluid collection 0.7 cm × 2.9 cm × 7.8 cm from the nasopharynx to the level of C4, pharyngeal soft tissues inflammation, cervical lymphadenopathy	N	IVIG, steroids
8	15 (13)	The United States	Fever, headache, sore throat, neck pain, and stiffness	Palatine tonsillar enlargement and a retropharyngeal fluid density extending down to C7/T1	N	IVIG, steroids, anakinra
9	4 (12)	India	Fever, neck swelling, pain and stiffness, generalized edema, irritability, and cardiogenic shock	Retropharyngeal fluid collection with soft tissue edema	N	IVIG, steroids
10	12 (14)	The United States	Fever, neck pain, swelling, trismus, odynophagia, rash, conjunctivitis, and cracked lips	Retropharyngeal fluid collection	Y	IVIG, anakinra, remdesivir
11	6 months (15)	The United States	Fever, an urticarial rash, lip redness, and cervical lymphadenopathy	CT scan showing a right-sided retropharyngeal abscess (1.2 cm × 2.8 cm × 3.7 cm) and right carotid arteritis	Not reported	None reported
12	18 (16) (preprint)	The United States	Fever, fatigue, headache, odynophagia, sore throat, vomiting, diarrhea, and abdominal pain	Retropharyngeal fluid collection, extending from C1 to C4 vertebral body level	N	IVIG, steroids, anakinra
13	15 (17)	Japan	Fever, lethargy, right neck pain, lip swelling, nausea, diarrhea, and headache	Retropharyngeal hypodensity	N	IVIG
14	17 (18)	India	Fever, right-sided neck pain, and odynophagia	Ill-defined subtle hypodensity in retropharyngeal space. Multiple enlarged cervical lymph nodes	Y	IVIG, steroids
15	10 (19) (20)	Turkey	Fever, neck pain vomiting, neck swelling and erythema, and conjunctivitis	Retropharyngeal edema, increased density in subcutaneous adipose tissue, lymphadenopathy, thickening of the right sternocleidomastoid muscle	N	IVIG
16	6 (21)	France	Five criteria of Kawasaki, neck pain, and cardiogenic shock	Retropharyngeal abscess	N	IVIG, steroids
17	10 (22)	The United States	Fever, diffuse rash, myalgias, sore throat, and right cervical tenderness	Retropharyngeal fluid with a dimension of 60 mm × 23 mm × 8 mm	N	IVIG, steroids
18	5 (our case)	The United States	Fever, neck pain, odynophagia, headache, nasal congestion, and lethargy	Retropharyngeal phlegmonous changes or possible early abscess with bilateral reactive lymphadenopathy	N	IVIG, steroids

MIS-C: multisystem inflammatory syndrome in children; IVIG: intravenous immune globulin; CT: computed tomography; N: no; Y: yes.

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Declaration of conflicting interests

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Disclaimer

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Ethical approval

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