



Extracardiac imaging findings in COVID-19-associated multisystem inflammatory syndrome in children

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Abstract

Background Coronavirus disease 2019 (COVID-19)-associated multisystem inflammatory syndrome in children (MIS-C) is an emerging syndrome that presents with a Kawasaki-like disease and multiorgan damage in children previously exposed to COVID-19.

Objective To review the extracardiac radiologic findings of MIS-C in a group of children and young adults with a confirmed diagnosis of MIS-C.

Materials and methods In a retrospective study from April 1, 2020, to July 31, 2020, we reviewed the imaging studies of 47 children and adolescents diagnosed with MIS-C, 25 females (53%) and 22 males (47%), with an average age of 8.4 years (range 1.3–20 years). Forty-five had chest radiographs, 8 had abdominal radiographs, 13 had abdominal US or MRI, 2 had neck US, and 4 had brain MRI.

Results Thirty-seven of 45 (82%) patients with chest radiographs had findings, with pulmonary opacities being the most common finding ($n=27$, 60%), most often bilateral and diffuse, followed by peribronchial thickening ($n=26$, 58%). Eight patients had normal chest radiographs. On abdominal imaging, small-volume ascites was the most common finding ($n=7$, 54%). Other findings included right lower quadrant bowel wall thickening ($n=3$, 23%), gallbladder wall thickening ($n=3$, 23%), and cervical ($n=2$) or abdominal ($n=2$) lymphadenopathy. Of the four patients with brain MRI, one had bilateral parieto-occipital abnormalities and another papilledema.

Conclusion The diagnosis of MIS-C and its distinction from other pathologies should be primarily based on clinical presentation and laboratory evidence of inflammation because imaging findings are nonspecific. However, it should be considered in the setting of bilateral diffuse pulmonary opacities, peribronchial thickening, right lower quadrant bowel inflammation or unexplained ascites in a child presenting with Kawasaki-like symptoms and a history of COVID-19 infection or recent COVID-19 exposure.

Keywords Abdomen · Children · Coronavirus disease 2019 · Lungs · Magnetic resonance imaging · Multisystem inflammatory syndrome in children · Radiography · Ultrasound

Introduction

In late April 2020, doctors in the United Kingdom reported an increased incidence of previously healthy children presenting with a severe hyperinflammatory syndrome similar to Kawasaki disease and testing positive for a current or recent

coronavirus disease 2019 (COVID-19) infection [1]. This syndrome has since been termed multisystem inflammatory syndrome in children (MIS-C) by the United States Centers for Disease Control and Prevention (CDC) and as pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PMIS-TS or PMIS) by the Royal College of Paediatrics and Child Health [2, 3]. Symptoms typically consist of a combination of fever, abdominal pain, rash and conjunctivitis, with laboratory evaluation consistently showing elevated inflammatory markers, and cardiac evaluation often demonstrating hypotensive shock, myocardial dysfunction and occasionally coronary artery dilation or aneurysms [4–7].

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This syndrome has quickly emerged as a serious delayed manifestation of COVID-19 infection in children, and radiologists should be aware of the associated imaging findings to better aid clinicians in making a timely diagnosis of a syndrome whose presentation can mimic other pathologies. Several studies and reviews have evaluated imaging findings in acute pediatric COVID-19 infections and in MIS-C [8–13]. We review the extracardiac imaging findings in a large group of children and adolescents diagnosed with MIS-C and discuss the utility of radiologic imaging in diagnosing the syndrome.

Materials and methods

This was a retrospective study performed at a quaternary-care children's hospital in New York City with institutional review board (IRB) approval that waived requirements for informed consent.

Subjects

We included pediatric patients younger than 21 years of age who were admitted through the emergency department or as a transfer from an outside hospital and were subsequently diagnosed with MIS-C during the period between April 1, 2020, and July 31, 2020. MIS-C diagnosis was made by the inpatient clinical services based on clinical presentation and CDC guidelines, which include: an individual age <21 years presenting with fever, laboratory evidence of inflammation, and clinically severe illness requiring hospitalization with multi-system organ involvement, with no alternative plausible diagnosis in the setting of a current or recent COVID-19 infection based on a reverse transcription polymerase chain reaction (RT-PCR), serology or antigen test, or with COVID-19 exposure within 4 weeks of symptom onset. Laboratory evidence of inflammation per the CDC guidelines includes one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, interleukin 6, or neutrophil count; or a reduced lymphocyte count or low albumin [2].

All patients had either COVID-19 RT-PCR testing via nasopharyngeal swab (Roche [Indianapolis, IN] or Cepheid [Sunnyvale, CA] commercial platforms); serology testing (in-house developed ELISA targeting the S trimer of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] as well as the Roche assay targeting the N protein); or both. We excluded patients with positive COVID-19 testing but not meeting diagnostic criteria for MIS-C. A total of 53 patients were diagnosed with MIS-C during the time period. Forty-seven of these 53 patients underwent some form of imaging in the radiology department during their admission and were included in our study population. We queried patient

electronic medical record charts to identify relevant patient information (age, gender, COVID-19 testing results, recent pneumonia or flu-like illness, presenting symptoms on admission, medical history, intensive care unit admission, discharge status, and imaging studies performed during admission excluding echocardiography).

Image analysis

We queried our picture archiving and communication system (PACS) to review all imaging studies performed in the patient population during admission. It should be noted that echocardiographic imaging was performed in all patients but was not reviewed for this study.

All imaging studies were initially interpreted in a clinical setting during patient admission by a fellowship-trained pediatric radiologist. Each exam was then independently re-reviewed by a fellowship-trained pediatric radiologist blinded to patient clinical data and the initial interpretation.

Pulmonary opacities were characterized according to distribution (unilateral or bilateral) and focality (focal, multifocal or diffuse). The presence of peribronchial thickening, septal thickening, cardiomegaly and pleural effusion was also noted. If patients had multiple chest radiographs during their admission, we reviewed all exams and based findings on a summary of findings at the most severe point of the patient's illness.

Statistical analysis

In the 45 children who had chest radiographs, we compared the imaging findings in the children younger than 10 years with findings in patients older than 10 years. We compared differences between the two groups using the Z-test. A *P*-value of 0.05 was considered to be significant.

Results

Patient population

A total of 47 patients diagnosed with MIS-C had an imaging study during admission (Table 1). Our patient population consisted of 25 females (53%) and 22 males (47%), with an average age of 8.4 years (range 1.3–20.0 years). Thirty-eight patients (81%) had no significant medical history. Five patients had mild or intermittent asthma, one had a history of developmental delay, one had a history of meningitis and urinary tract infections as an infant, one had a history of type 2 Von Willebrand disease, and one had a history of febrile seizures as an infant. All except 4 patients tested positive for COVID-19 on either or both RT-PCR and serology testing, with 39 of 47 patients (83%) testing positive on serology. Patients with negative COVID-19 testing had exposure to

Table 1 Descriptive patient data including demographics, coronavirus disease 2019 (COVID-19) lab testing results and imaging studies and findings

Demographics	Lab/testing results	n (%)
Number of patients with imaging (n)		47
Average age (years)		8.4
Age range (years)		1.3–20.0
Gender	F (%)	25 (53%)
	M (%)	22 (47%)
COVID-19 testing	RT-PCR – / serology +	26 (55%)
	RT-PCR + / serology +	13 (28%)
	RT-PCR + only	4 (9%)
	RT-PCR –	3 (6%)
	RT-PCR – / serology indeterminate	1 (2%)
Imaging studies		
Chest radiography		45 (96%)
Chest radiography only		22 (47%)
Opacity distribution	Bilateral	21 (47%)
	Unilateral	6 (13%)
Opacity focality	Diffuse	17 (38%)
	Focal	6 (13%)
	Multifocal	4 (9%)
Characteristics	Peribronchial thickening	26 (58%)
	Cardiomegaly	6 (13%)
	Small pleural effusion	5 (11%)
	Septal thickening	1 (2%)
	Normal	8 (18%)
Abdominal radiography		8 (17%)
	Adynamic ileus	2 (25%)
	Normal	6 (75%)
Abdomen/pelvic sonogram		13 (28%)
	Ascites	7 (54%)
	Gallbladder thickening	3 (23%)
	Gallbladder sludge	2 (15%)
	Right lower quadrant bowel thickening/inflammation	3 (23%)
	Right lower quadrant lymphadenopathy	2 (15%)
Abdominal MRI		2 (4%)
	Terminal ileal/rectosigmoid inflammation	1
	Only ascites	1
Neck US		2 (4%)
	Lymphadenopathy	2
Brain MRI		4 (9%)
	Parieto-occipital cortical abnormality, possible PRES	1
	MR evidence of papilledema	1
	Normal	2

COVID-19 coronavirus disease 2019, F female, M male, MRI magnetic resonance imaging, PRES posterior reversible encephalopathy syndrome, RT-PCR reverse transcription polymerase chain reaction, US ultrasound

family members who either tested positive for COVID-19 or had symptoms of COVID-19. One of these patients had an indeterminate serology result that was not retested.

All patients presented with fever and some combination of symptoms known to occur in MIS-C, including but not limited

to abdominal pain, rash and conjunctivitis. Many of the patients also presented in hypotensive shock, with 34 of 47 patients being admitted to the intensive care unit. Three patients also presented with cervical lymphadenopathy on physical exam, with two undergoing imaging evaluation. Notably, only

two patients — one patient with chest pain and dyspnea and another with cough — complained of any pulmonary symptoms, and these were revealed on review of systems and were not part of the initial presenting complaint. All patients were successfully discharged home following treatment.

Imaging findings

Chest

Of the 45 patients who underwent chest radiography, 8 had normal exams (18%). Twenty-seven patients had pulmonary opacities (60%), with bilateral opacities in 21 (47%) and unilateral opacity/opacities in 6 (13%). Opacities were diffuse in 17 patients (38%), focal in 6 (13%) and multifocal in 4 (9%). Peribronchial thickening was the next most common finding ($n=26$, 58%) (Fig. 1). Six patients had cardiomegaly, five had small pleural effusion and one had septal thickening. Bilateral diffuse pulmonary opacities and peribronchial thickening were the most common findings on chest radiography in all ages. There was no statistical difference in pulmonary findings

in patients younger than 10 years compared to patients older than 10 years.

Abdomen

In the eight patients who underwent abdominal radiographs, two patients had nonspecific bowel distention interpreted as adynamic ileus and the remaining six had normal exams. In the 13 patients who had abdominal cross-sectional imaging in the form of either abdominal sonogram or abdominal MRI (or both), 7 patients had small-volume ascites, 3 had gallbladder wall thickening (>4 mm), 2 had gallbladder sludge, 3 had right lower quadrant bowel wall thickening and inflammation — with one also showing rectosigmoid colon inflammation (Figs. 2 and 3), and 2 had right lower quadrant lymphadenopathy. Notably, the liver, spleen and kidneys appeared normal in all of these patients.

Head and neck

Two patients with suspected lymphadenopathy on physical exam had US evaluation confirming the presence of cervical

Fig. 1 Imaging in a 4-year-old boy with a medical history of prematurity and mild asthma who presented with fever, abdominal pain, diarrhea, hypotensive shock and evidence of myocardial dysfunction with positive coronavirus disease 2019 (COVID-19) reverse transcription polymerase chain reaction (RT-PCR) and serology results. **a** Anteroposterior chest radiograph demonstrates bilateral perihilar opacities and peribronchial thickening. **b** Supine radiograph of the abdomen demonstrates abdominal distention with gaseous distention of the colon down to the rectum, suggesting colonic ileus. **c** Transverse US image of the right lower abdominal quadrant at the level of the iliac vasculature demonstrates small-volume ascites (*arrow*). **d** Sagittal sonographic image of the gallbladder demonstrates gallbladder wall thickening (*arrowhead*) but no gallstones

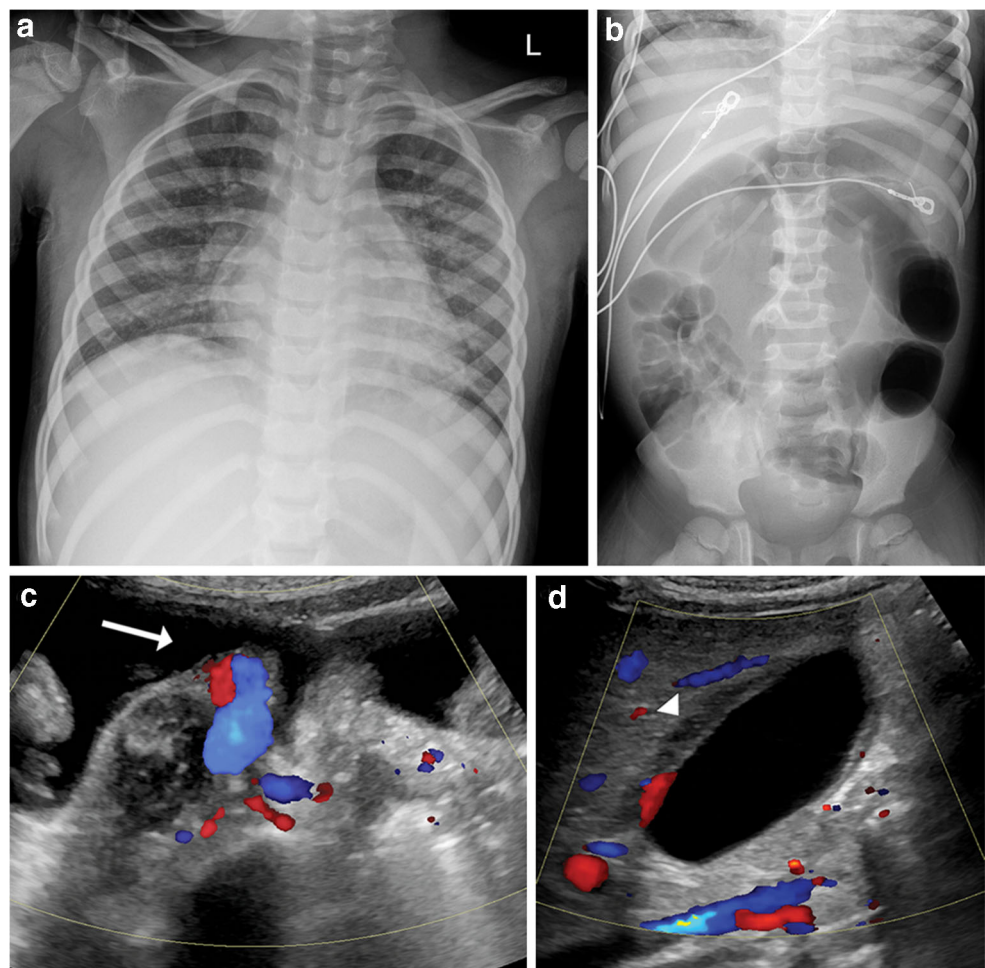
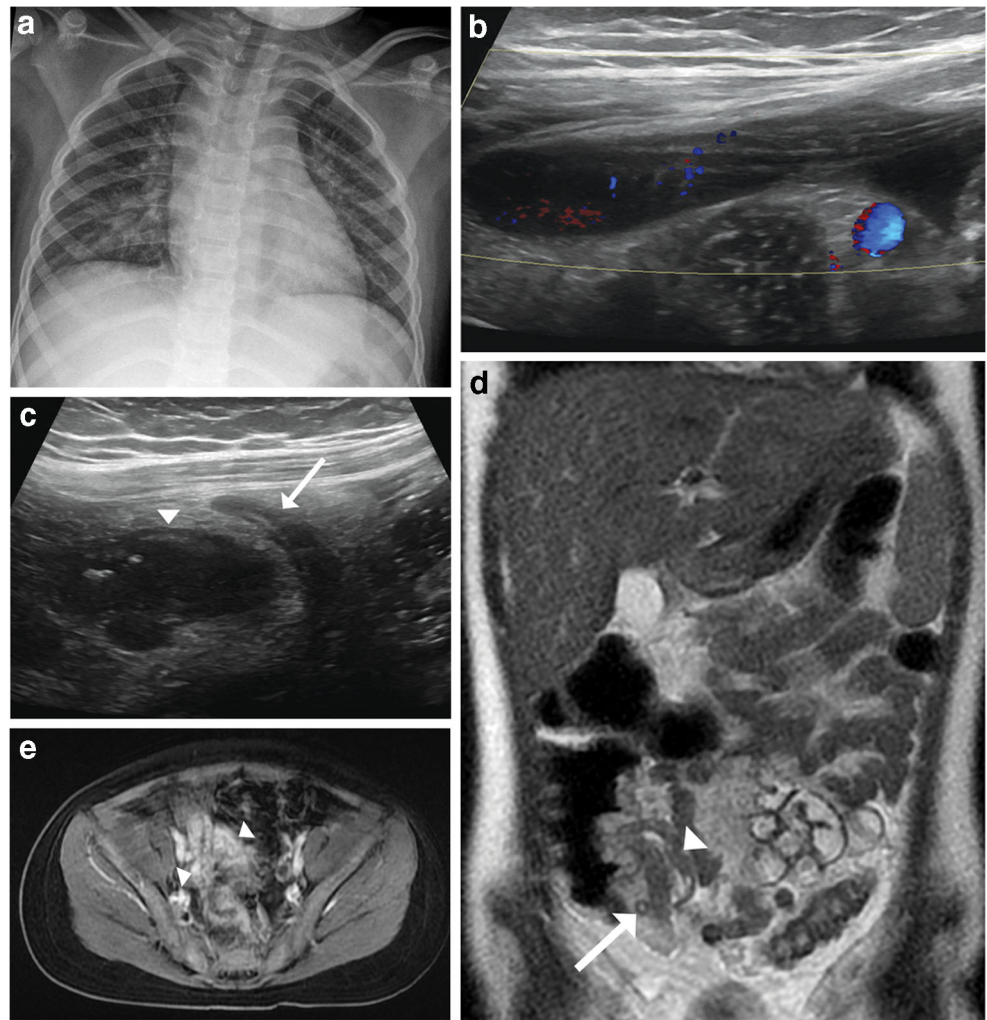


Fig. 2 Imaging in a 7-year-old girl who presented with fever, abdominal pain, diarrhea, rash and evidence of myocardial dysfunction with a positive coronavirus disease 2019 (COVID-19) reverse transcription polymerase chain reaction (RT-PCR) result. This child was initially worked up for appendicitis. **a** Anteroposterior chest radiograph demonstrates bilateral perihilar opacities and peribronchial thickening. **b, c** Transverse US color Doppler (**b**) and gray-scale (**c**) images of the right lower abdominal quadrant demonstrate small-volume ascites and mesenteric edema adjacent to a borderline enlarged appendix (*arrow*), and a thickened loop of distal ileum (*arrowhead*). **d, e** Abdominal MRI coronal T2-W (**d**) and axial T1-W (**e**) fat-saturated post-gadolinium liver acquisition with volume acceleration (LAVA) images demonstrate a normal appendix (*arrow*) and terminal ileal and rectosigmoid wall thickening and hyperenhancement consistent with inflammation (*arrowheads*)



lymphadenopathy (Fig. 4). Four patients underwent brain MRI. One of these patients, with fluctuating mental status that eventually improved and laboratory evidence of thrombotic

microangiopathy with hemolytic anemia, had fluid-attenuated inversion recovery (FLAIR) MRI hyperintensity/restricted diffusion involving the bilateral parieto-occipital

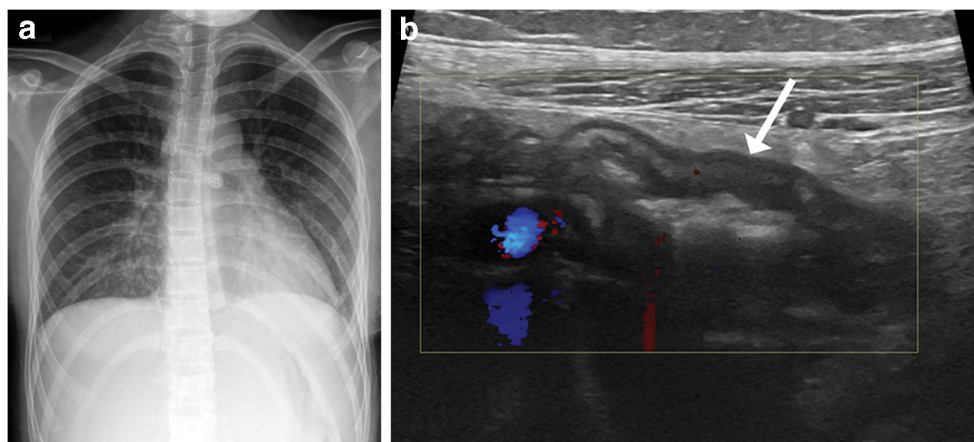
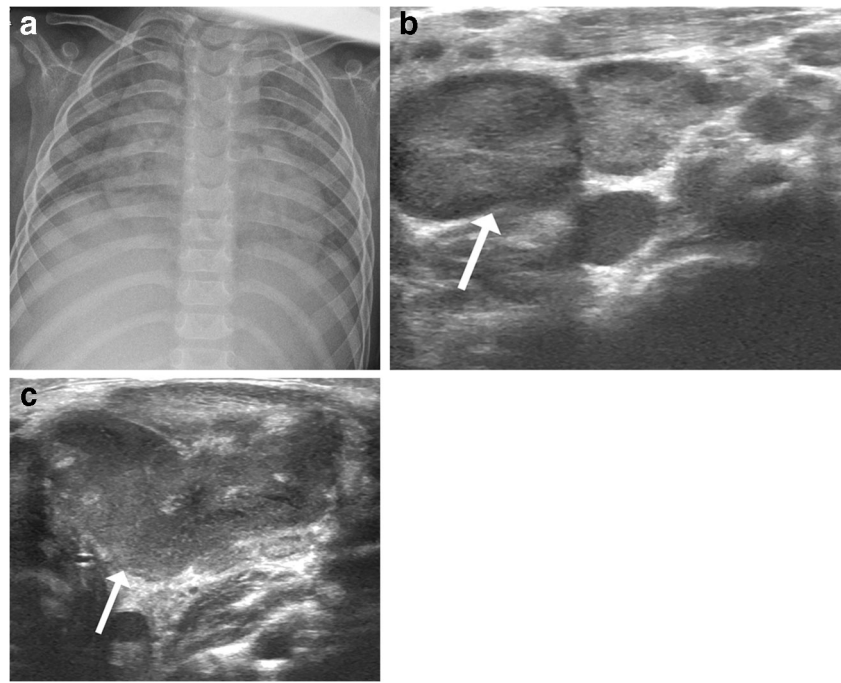


Fig. 3 Imaging in a 15-year-old girl presenting with fever, abdominal pain, conjunctivitis, headaches and hypotensive shock with positive coronavirus disease 2019 (COVID-19) reverse transcription polymerase chain reaction (RT-PCR) and serology results. **a** Anteroposterior chest

radiograph demonstrates bilateral perihilar opacities and peribronchial thickening. **b** Sagittal Doppler US image of the right lower abdominal quadrant demonstrates bowel wall thickening of the distal ileum (*arrow*) with surrounding mesenteric edema

Fig. 4 Imaging in a 15-month-old girl who presented with fever, cervical lymphadenopathy, rash, hand and foot swelling with skin peeling, and evidence of myocardial dysfunction. She had a negative coronavirus disease 2019 (COVID-19) reverse transcription polymerase chain reaction (RT-PCR) result but had sick family contacts who had tested positive for COVID-19. **a** Anteroposterior chest radiograph demonstrates low lung volumes and diffuse airspace opacities. **b, c** Targeted transverse US images of the left lateral neck demonstrate cervical lymphadenopathy (arrows)



cortices with mild cortical thickening, and punctate T2/FLAIR hyperintensity in the left frontoparietal centrum semiovale (Fig. 5). A second brain MRI requested for evaluation of vision complaints and cranial nerve VI palsy demonstrated MR findings compatible with papilledema. Two additional brain MRIs requested for altered mental status and headache were normal.

Discussion

In the months following the onset of the COVID-19 pandemic in Europe, reports of an unusual hyperinflammatory illness in children similar to Kawasaki disease began to emerge in the United Kingdom and Italy [1, 14, 15]. In early May 2020, the New York City Department of Health and Mental Hygiene

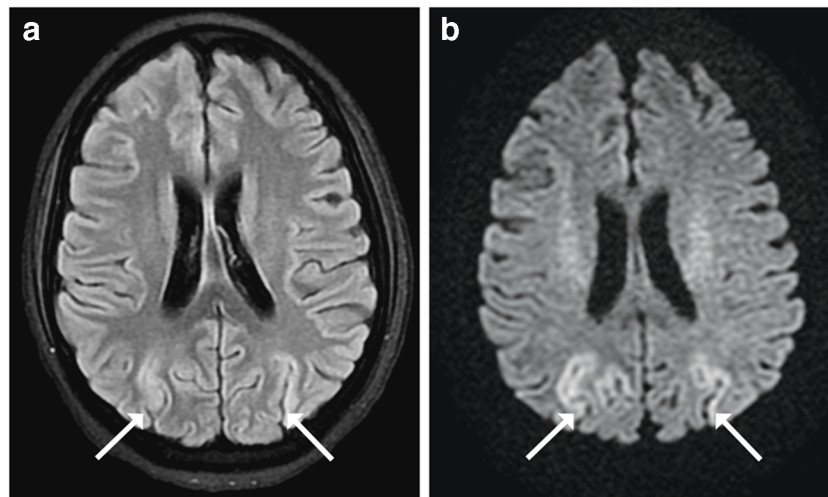


Fig. 5 Brain imaging in a 14-year-old girl who initially presented with typical symptoms of multisystem inflammatory syndrome in children (MIS-C) including fever, abdominal pain and evidence of myocardial dysfunction with a positive coronavirus disease 2019 (COVID-19) serology result. She then developed thrombotic microangiopathy with hemolytic anemia and fluctuating mental status during admission. **a, b**

Axial fluid-attenuated inversion recovery (FLAIR) MRI (**a**) and corresponding axial diffusion-weighted image (**b**) through the level of the bodies of the lateral ventricles and corona radiata demonstrate FLAIR hyperintensity/restricted diffusion involving the bilateral parieto-occipital cortices with mild cortical thickening (arrows)

began receiving reports of cases of a Kawasaki-like disease similar to reported cases in Europe, and by May 12, 2020, 102 children with the syndrome had been identified in New York City [2]. Despite its seemingly unrelated constellation of presenting symptoms and variable effects on a multitude of inflammatory markers and organ function, MIS-C is largely a clinical diagnosis because of its temporal occurrence soon after a COVID-19 infection and its consistent presentation among patients of different ages. Our experience with this syndrome provides several insights.

Although the majority of the patients in our study had positive serology studies indicating a prior exposure and immune response to COVID-19 ($n=39$, 83%), a portion also tested positive for an active infection on nasopharyngeal RT-PCR ($n=17$, 37%), including four patients who only tested positive on RT-PCR. Despite this, none of the patients was diagnosed with an acute COVID-19 infection because of the lack of pulmonary symptoms or flu-like illness. This emphasizes the important fact that MIS-C can present in a patient without laboratory confirmation of prior COVID-19 exposure/infection and that a positive RT-PCR result does not rule out the possibility of MIS-C, as iterated in the CDC diagnostic criteria for the syndrome [2].

Early on in our hospital's experience with MIS-C, just as it was becoming a recognized syndrome in several European countries, imaging was important in excluding other acute pathologies that could also present with fever and abdominal pain, particularly appendicitis. The absence of acute pathology on imaging prompted the admitting clinicians to think outside the box, and a careful review of COVID-19 exposure, review of systems and physical exam revealed other signs and symptoms that more aligned with a Kawasaki-like disease.

Two patients who presented early in the study had abdominal US ordered to exclude appendicitis in the setting of fever and abdominal pain. Both of these abdominal US exams demonstrated findings that were equivocal for appendicitis, which prompted a surgical consult and abdominal MRI. One US exam demonstrated a borderline enlarged appendix (7 mm in diameter), inflammatory changes in the right lower quadrant, and distal ileal thickening, which were initially interpreted by an overnight resident as equivocal for appendicitis, prompting an abdominal MRI. The subsequent MRI was interpreted as showing a normal appendix but also terminal ileal and rectosigmoid mural thickening, enhancement and edema that were more typical of inflammatory bowel disease (Fig. 2). The second abdominal US exam showed ascites and right lower quadrant lymphadenopathy, prompting a surgical consult and abdominal MRI, which showed a normal appendix but persistent unexpected ascites.

Pulmonary opacities were the most common finding on chest radiography ($n=27$, 60%) and were more often bilateral ($n=21$, 47%) and diffuse ($n=17$, 38%). This was followed by

peribronchial thickening ($n=26$, 58%). Pulmonary opacities are favored to have reflected cardiogenic and non-cardiogenic pulmonary edema/acute respiratory distress syndrome (ARDS) as a result of cardiac dysfunction and multi-system organ failure caused by a hyperinflammatory state. In the patients with a medical history of asthma, radiographic findings including peribronchial thickening were not favored to reflect an asthma exacerbation because the lack of pulmonary symptoms and the clinical presentation were more consistent with MIS-C. Importantly, findings on chest radiography in our patient population differed from those typically reported for acute pediatric COVID-19 infection [8, 9, 12]; most patients in our study had bilateral diffuse disease with peribronchial thickening rather than peripheral and subpleural opacities. Ultimately, however, there was significant overlap of findings on chest radiography between an acute COVID-19 infection and MIS-C as well as other infectious and non-infectious causes of pulmonary opacities and peribronchial thickening.

Our results on chest radiography closely match those of other retrospective case series studies. Peribronchial thickening was the second most common finding on chest radiographs in our study despite only two of our patients experiencing any lower respiratory symptoms. Hameed et al. [11] noted bronchial wall thickening in 34% of their patients despite none of their patients exhibiting lower respiratory tract symptoms. They postulated that this finding could reflect airway inflammation or pulmonary arteritis similar to that described in Kawasaki disease. They also reported small pleural effusions in 11% of patients and perihilar opacities in 46% of patients, although the distribution of opacities was not described. Right lower quadrant mesenteric inflammation and lymphadenopathy on US in 47% of their patient population also closely matched ours [11]. Blumfield et al. [13] noted findings consistent with cardiogenic pulmonary edema in a majority of their patients (56%) but did not comment on the distribution of opacities. Cardiomegaly and pleural effusions were more common in their patient population (62.5% and 44.0% of their patients, respectively), which might be explained by their smaller patient population or interobserver differences in thresholds for calling cardiomegaly or small pleural effusions [13].

Ascites was the most common finding on abdominal imaging ($n=7$, 54%). Other nonspecific findings — including bowel distention suggesting adynamic ileus, bowel wall thickening and inflammation in the right lower quadrant, and gallbladder wall thickening or sludge — were the only other findings on abdominal imaging, all likely reflecting a combination of changes related to bowel wall vasculitis and cardiac dysfunction. Similar findings of right lower quadrant intestinal inflammation were reported in an early series of patients with COVID-19 who presented with symptoms of atypical appendicitis before rapidly deteriorating as part of a

hyperinflammatory syndrome [10]. Interestingly, none of our abdominal imaging demonstrated abnormalities of the liver, spleen or kidneys, although many patients suffered from multi-organ failure that was evident clinically. This differs slightly from the findings reported in Hameed et al. [11], who found hepatosplenomegaly, splenic infarcts and echogenic kidneys in a minority of patients [11]. Head and neck imaging was performed in a minority of our patients. Targeted neck sonography confirmed two cases of cervical lymphadenopathy suspected on physical exam. One patient with fluctuating mental status and laboratory evidence of thrombotic microangiopathy with hemolytic anemia underwent brain MRI, which demonstrated findings favored to reflect an atypical presentation of posterior reversible encephalopathy syndrome. Another brain MRI demonstrated evidence of papilledema of unknown etiology. Hameed et al. [11] reported six patients with neurologic imaging that was mostly negative save for one example of a large cerebral infarct likely related to extracorporeal membrane oxygenation. It is difficult to draw any conclusions or comparisons about these isolated findings and their association with MIS-C.

Just as MIS-C shares commonalities with the clinical presentation of Kawasaki disease, there are many similarities between their extracardiac imaging findings. Typical imaging findings that may be seen in Kawasaki include pulmonary airspace opacities, peribronchial thickening and pleural effusions on chest radiography, and cervical lymphadenopathy on neck imaging. Less commonly reported imaging findings in the abdomen include gallbladder hydrops, ascites, ileus, bowel wall edema, abdominal lymphadenopathy and intussusception. None of our patients had significant gallbladder hydrops on abdominal imaging, but three did have gallbladder wall thickening, which is not typically described in Kawasaki disease [16, 17].

Our study is limited by the fact that imaging was acquired in each patient as clinically indicated because there was no routine extracardiac imaging protocol for MIS-C. Lack of more extensive cross-sectional imaging of the chest and abdomen is also a major limiting factor. Although the absence of cross-sectional imaging of the chest in our patients significantly limited further elucidation of nonspecific findings on chest radiographs, it further demonstrates the small role non-cardiac imaging plays in diagnosing and monitoring these patients. Besides chest radiography, additional imaging was rarely obtained in our patient population. In all imaging studies obtained, findings were nonspecific and variably present. In fact, 6 of the original 53 patients diagnosed with the syndrome during the time period had no radiologic imaging (excluding echocardiograms), 22 of 47 with imaging had only chest radiographs, and 8 of 45 chest radiographs were normal. Ultimately, all of the imaging findings in our patient population including the most common findings of bilateral diffuse

pulmonary opacities, peribronchial thickening, ascites, and bowel and gallbladder wall thickening are nonspecific because they can be seen in numerous other pathologies.

Conclusion

The diagnosis of COVID-19-associated MIS-C and its distinction from other acute pathologies should be primarily based on clinical presentation rather than imaging findings alone because radiologic imaging is nonspecific and more useful in excluding other pathologies. However, MIS-C should be considered by the clinical team when there are bilateral diffuse pulmonary opacities, peribronchial thickening, unexplained ascites, right lower quadrant bowel inflammation or gallbladder wall thickening in a child with a history of COVID-19 infection or recent COVID-19 exposure.

Compliance with ethical standards

Conflicts of interest None

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