Thoracic Imaging Findings of Multisystem Inflammatory Syndrome in Children Associated with COVID-19: What Radiologists Need to Know Now

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Conflicts of interest are listed at the end of this article.

The coronavirus disease 2019 (COVID-19) global pandemic is an ongoing public health emergency, with over 4 million confirmed cases worldwide. Due to the novel nature of this coronavirus and our evolving understanding of its pathophysiology, there is continued uncertainty surrounding diagnosis and management of COVID-19, especially in pediatric patients. In addition, a new febrile hyperinflammatory Kawasaki-like syndrome (also known as multisystem inflammatory syndrome in children, or MIS-C) has emerged in pediatric patients with temporal association to COVID-19 infection. This review article aims to provide an up-to-date review of the clinical and imaging findings of pediatric MIS-C associated with COVID-19, compared with typical acute pediatric COVID-19 infection, with an emphasis on thoracic imaging findings.

Supplemental material is available for this article.

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Orignating in Wuhan, China in December 2019, the coronavirus disease 2019 (COVID-19) global pandemic is an ongoing public health emergency, with more than 4 million confirmed cases and over 285,000 reported deaths, as of May 15, 2020 (1). As of April 20, 2020, in the United States, there were an estimated 2572 pediatric COVID-19 cases (1.7% of total U.S. COVID-19 cases) (2). Although no published estimates currently exist on the worldwide prevalence of pediatric COVID-19 infection, based on prior U.S. Centers for Disease Control and Prevention (CDC) and Chinese Center for Disease Control and Prevention data, an extrapolated estimate may be approximately 2% of overall worldwide cases (2,3). Still, knowledge of the thoracic manifestations of pediatric COVID-19 infection is limited.

In adults, COVID-19 is typically characterized by severe pneumonia and hyperactivation of the inflammatory cascade (4–7). Several early studies suggested that COVID-19 infection in children was relatively mild compared with adults, with very few pediatric fatalities reported and the majority of critically ill children possessing underlying medical comorbidities (2,8–11). However, Chao et al recently found a higher than previously recognized rate of severe illness in pediatric patients with COVID-19 (12). Furthermore, emerging new evidence suggests that COVID-19 infection in children and adolescents is associated with a multisystem inflammatory syndrome in children (MIS-C), with features similar to Kawasaki disease and toxic shock syndrome, frequently requiring intensive care unit (ICU) admissions (1).

In light of these new findings, it is clear that our understanding of the manifestations of pediatric COVID-19 infection is dynamic and evolving. For example, increasing evidence suggests that the respiratory tract is not the only organ system susceptible to infection (13). Furthermore, innate host immunity, possibly due to inflammatory hyperactivation and cytokine storm, may mediate much of the tissue damage in acute COVID-19 infection and drive the multisystem hyperinflammation in MIS-C (4,5,14,15). Therefore, it is becoming clear that COVID-19 is much more than simply a viral pneumonia, but rather a multiorgan systemic disease (4,5,13,16).

Given the current lack of available information related to the thoracic imaging findings of pediatric MIS-C associated with COVID-19 infection, the purpose of this article is to provide an up-to-date review of the clinical and imaging features of pediatric MIS-C associated with COVID-19 infection, compared with acute pediatric COVID-19 infection, with an emphasis on thoracic imaging findings.

What Is MIS-C Associated with COVID-19?

New Emergence of MIS-C Associated with COVID-19

In April 2020, after the peak of COVID-19 in many European countries, reports from western Europe warned of a new pediatric febrile hyperinflammatory syndrome, affecting children with temporal association to COVID-19 infection (15,17,18). For example, clinicians in the United Kingdom reported increased incidence of a severe inflammatory syndrome with Kawasaki disease–like features in mostly previously healthy children (17). Similarly, Verdoni et al reported a 30-fold increase in
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Patient Demographics

Although the clinical features of MIS-C resemble Kawasaki disease, there are important demographic differences between patients with MIS-C and patients with Kawasaki disease, including older age of onset and differences in ethnicity predisposition. First, although MIS-C associated with COVID-19 affects pediatric patients of all ages (reported cases range from 6 months to 16 years), the majority of patients with MIS-C are school-age children, with a mean age of 7.5–10 years (17–20,22). In contrast, the vast majority of patients with Kawasaki disease present before 5 years of age, most under 2 years of age (24). In addition, while the incidence of Kawasaki disease is highest in Asia, strikingly, there have been no reported cases of MIS-C in Asia, despite being an early hotspot of COVID-19 infection, with some of the earliest published series on acute pediatric COVID-19 infection emerging from China (15,24,25). Two series have found a predilection of MIS-C to affect children of Afro-Caribbean descent (17,26). Although the cause for difference in distribution of MIS-C worldwide is not definitively known, genetic predisposition has been suggestive as a factor in this predisposition for development of MIS-C (23). Different strains of the virus, due to mutation, could also possibly account for the increased incidence of MIS-C in Western Europe and North America compared with Asia. Similar to Kawasaki disease, two series of pediatric cases of MIS-C associated with COVID-19 have reported a male predilection (62.5%–70%), although a larger series found male and female patients to be equally affected (17,18,22). The most commonly reported comorbidities in children with MIS-C associated with COVID-19 were overweight status (body mass index ≥ 25 kg/m²; 17%–38%) and asthma (8.5%) (17,22).

Clinical Presentation

Children affected by MIS-C associated with COVID-19 typically present with persistent high fever (> 3 days) and systemic hyperinflammation, reflected in a constellation of symptoms involving multiple organ systems, frequently manifesting abdominal pain and gastrointestinal symptoms, Kawasaki disease–like features, and cardiogenic shock. In published series, the most common presenting signs and symptoms include prolonged high fever (94%–100%); weakness/malaise (100%); prominent gastrointestinal symptoms (60%–100%), typically abdominal pain, vomiting, and diarrhea; and less commonly, variable maculopapular rash (37%–57%) and respiratory distress (0%–65%) (17,18,22,26–29). A small number of reported patients with MIS-C have presented with such severe abdominal pain that laparoscopy was performed for suspected appendicitis (n = 3), two of which were found to have mesenteric adenitis and one was found to have aseptic peritonitis (22,26). Clinical features of Kawasaki disease, including nonvesicular skin rash, extremity changes, adenopathy, conjunctivitis, chilblains, and meningeal signs, are frequently reported; however, only six reported patients have met criteria for the classic form of Kawasaki disease (18,19,22,30).

The vast majority of patients with MIS-C present with cardiogenic shock requiring ICU admission. All patients had laboratory

Abbreviations

ARDS = acute respiratory distress syndrome, CDC = Centers for Disease Control and Prevention, COVID-19 = coronavirus disease 2019, ICU = intensive care unit, IL-6 = interleukin-6, MIS-C = multisystem inflammatory syndrome in children, RT-PCR = reverse-transcription polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Summary

MIS-C associated with COVID-19 is likely a postviral hyperinflammatory response capable of causing multiorgan damage, including heart failure; liver and kidney injury; and gastrointestinal, neurologic, and dermatologic manifestations.

Essentials

- Three main thoracic imaging findings that have been currently observed in pediatric patients with multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19) include heart failure, acute respiratory distress syndrome pattern, and pulmonary embolus.
- The postviral hyperinflammatory process presumed to cause MIS-C results in unique thoracic imaging abnormalities that differ from the thoracic imaging findings of acute pediatric COVID-19 infection.
- The clinical and imaging features of pediatric MIS-C associated with COVID-19 resemble late-stage adult COVID-19, possibly due to a similar hyperinflammatory cytokine storm.

incidence of a Kawasaki-like disease in children in Bergamo, Italy in the months following the peak of the COVID-19 pandemic (18). Children manifesting similar illness have also been recognized in the United States, especially in New York City area (19–21). As of May 12, 2020, the New York State Department of Health has identified 102 pediatric patients with similar hyperinflammatory illness (21). Referred to as pediatric COVID-19-associated multisystem inflammatory syndrome, or PMIS, or MIS-C associated with COVID-19, this hyperinflammatory syndrome occurs in children testing positive for current or recent infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (reverse-transcription polymerase chain reaction [RT-PCR] or serologic assay) or had an epidemiologic link to a patient known or suspected of having COVID-19 (1,21).

Temporally, MIS-C cases have been clinically manifesting approximately 1 month or more after the peak of COVID-19 cases in a geographic region (15). Although the etiology is unknown, MIS-C is presumed to reflect a postinfectious cytokine-mediated hyperinflammatory process, triggered by COVID-19 infection (15,22). Although a causal link between COVID-19 infection and the presumed postviral hyperinflammation of MIS-C has not yet been definitively established, it is strongly suggested by the temporal association and history of COVID-19 exposure in patients with MIS-C (23). Proposed mechanisms include direct triggering of autoimmune inflammatory response, possibly by molecular mimicry or unknown mechanism, and/or dysregulation of immune responses after COVID-19 infection, which could result in other environmental insults triggering a hyperinflammatory pathology in predisposed patients (23).
evidence of profound inflammation, including elevated levels of C-reactive protein, erythrocyte sedimentation rate, d-dimer, procalcitonin, and ferritin (15,17–20,22). Belhadjer et al found mild-moderate troponin elevation and marked brain natriuretic peptide elevation in all pediatric patients with MIS-C with acute heart failure (22). The vast majority of patients with MIS-C have positive SARS-CoV-2 antibodies (80%–100%), although a small percentage had positive RT-PCR testing for COVID-19 infection (20%–40%) (17–20,22).

**CDC MIS-C Case Definition**

The United States CDC has presented the following case definition for a diagnosis of MIS-C associated with COVID-19, with pediatric patients required to meet all three of the following criteria: (a) Individual under 21 years of age presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic); (b) No alternative plausible diagnosis; (c) Positive current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within 4 weeks prior to symptom onset. Fever is defined as temperature greater than 38.0°C for greater than 24 hours or a subjective fever greater than 24 hours. Laboratory evidence of inflammation is defined as including, but not limited to, elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactate dehydrogenase, and interleukin-6 (IL-6) (21).

**Clinical Course, Treatment, and Outcomes**

The vast majority of children affected with MIS-C associated with COVID-19 present in cardiogenic shock requiring inotropes (80%–100%) and mechanical ventilation (66%–88%) for cardiovascular stabilization (17,19,20,22). Over a quarter of children with MIS-C with acute heart failure at presentation require mechanical circulatory assistance with venoarterial extracorporeal membrane oxygenation (22). Given the limited information currently available on these findings at the time of this article preparation, future studies with larger pediatric population will be helpful for confirming these findings.

Although the CDC and World Health Organization have not provided treatment guidelines, common treatment approaches are similar to those for Kawasaki disease, including intravenous immunoglobulin, steroids, anticoagulation, and supportive care (17,18,22,31). Verdone et al found that children affected with pediatric MIS-C associated with COVID-19 often had a more severe clinical course compared with typical patients with Kawasaki, frequently with resistance to intravenous immunoglobulin, need for adjunctive steroids, and biochemical evidence of macrophage activation syndrome (18). Some authors have described the overall clinical picture of children affected by MIS-C associated with COVID-19 as similar to the late phase of adult COVID-19 infection, characterized by cytokine storm, hyperinflammation, and multiorgan damage (15,18).

Despite prolonged ICU admissions (mean ICU stay, 4–7 days), the reported clinical outcomes for pediatric patients with MIS-C associated with COVID-19 so far appear favorable (17,19,20,22,30). In a series of pediatric patients with MIS-C presenting with acute heart failure, Belhadjer et al found complete recovery of left ventricular function in more than two-thirds of patients with MIS-C (71%) after treatment, with mild-moderate residual systolic dysfunction (ejection fraction > 45%) in the remaining 29% (22). This recovery of systolic function after treatment may suggest that the mechanism of heart failure is not myocardial damage as seen in adults with COVID-19 infection; however, additional studies will be needed to assess whether long-term cardiac complications arise (22).

**Imaging Findings of MIS-C in Pediatric Patients**

Mainly due to its recent emergence, knowledge of the thoracic manifestations of MIS-C associated with COVID-19 is limited. However, the following imaging findings were observed in our 20 pediatric patients with confirmed MIS-C.

**Thoracic Manifestations**

Three main thoracic imaging findings have been observed in pediatric patients with MIS-C associated with COVID-19: heart failure, acute respiratory distress syndrome (ARDS) pattern, and pulmonary embolus.

**Heart failure.**—We observed that the majority of pediatric patients with MIS-C associated with COVID-19 present with cardiogenic shock, many with imaging findings of acute heart failure. This is in keeping with several reported series that found the majority of patients with MIS-C (43%–67%) present with myocarditis and heart failure (18,26,28,29).

Characterized by impaired left ventricular systolic dysfunction, elevated brain natriuretic peptide, and significantly elevated proinflammatory cytokines ("cytokine storm," including IL-6, C-reactive protein, and procalcitonin), the acute heart failure that is common in MIS-C is hypothesized to be the result of a postviral immune-mediated myocarditis (22,26,27). Most patients with MIS-C have positive SARS-CoV-2 antibodies (80%–100%), rather than positive RT-PCR result, supporting a postviral etiology (17–20,22). Infectious diseases have long been considered a trigger for autoimmune diseases, possibly via molecular mimicry or dysregulated immune response (23). IL-6, specifically, has been implicated in the pathogenesis of myocarditis (23).

Chest radiographs typically show cardiomegaly, pulmonary edema, and pleural effusions, in keeping with acute left-sided heart failure (Fig 1). Echocardiography typically reveals left ventricular systolic dysfunction with depressed ejection fraction (Movie [supplement]) (22). For example, in the largest reported series of patients with MIS-C presenting with acute heart failure, Belhadjer et al found left ventricular systolic dysfunction with an ejection fraction less than 30% in 10 of 35 (28%) patients and between 30%–50% in 25 of 35 (71%) patients, which is similar to the depressed left ventricular ejection fractions reported in other MIS-C series, which have ranged from 25% to 48% (18,22,29). Pericardial effusion is less commonly seen (9%–40%) in MIS-C (18,29). Coronary artery aneurysms have
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and imaging findings of ARDS (19). Chest radiographs demonstrate bilateral multifocal ground-glass and consolidative airspace opacities (Fig 2). In some pediatric patients with MIS-C associated with COVID-19 presenting with an ARDS pattern, airspace opacities were noted to be asymmetric.

Pulmonary embolism.— A prothrombotic coagulopathy is a hallmark of severe COVID-19 in adults (34). While severe COVID-19 infection in adults has been associated with high incidence of thrombotic complications, including deep venous thrombosis, pulmonary embolism, ischemic stroke, and myocardial infarction, this association has not yet been demonstrated in typical pediatric COVID-19 infection (35). Although the mechanism for adult thromboembolic complications of COVID-19 is not known, it has been suggested that overproduction of proinflammatory cytokines contribute to a prothrombotic coagulopathy (5). Interestingly, some authors have suggested that pediatric MIS-C and late-stage severe adult COVID-19 are characterized by a similar proinflammatory milieu, both characterized by elevated inflammatory markers, including fibrinogen, D-dimer, ferritin, and IL-6 (15,18,20). Poyiadji et al found that adult patients with COVID-19 with elevated D-dimer and C-reactive protein levels are significantly more likely to develop pulmonary emboli than patients without elevated inflammatory markers (36). Given that elevations in these inflammatory markers are a hallmark of pediatric MIS-C associated with COVID-19, it is conceivable that the hyperinflammatory state of MIS-C may predispose to a
similar prothrombotic coagulopathy and thromboembolic complications, including pulmonary emboli.

We observed small segmental pulmonary emboli in some pediatric patients affected by MIS-C associated with COVID-19. At CT pulmonary arterial angiography, pulmonary embolus appears as an expansile filling defect in a pulmonary artery in pediatric patients with MIS-C associated with COVID-19 (Fig 3). Currently, the clinical significance of these small segmental pulmonary emboli in pediatric patients with MIS-C is unclear (37,38). For example, Poyiadji et al found no significant difference in ICU admission, requirement for intubation, or duration of intubation between adult patients with COVID-19 who developed pulmonary embolism and those who did not (36). Further studies on the significance of pulmonary embolism in children with MIS-C associated with COVID-19 will be important.

**Extrathoracic Manifestations**

In addition to the characteristic thoracic imaging findings of MIS-C associated with COVID-19, characteristic extrathoracic imaging findings are also emerging in pediatric patients with MIS-C associated with COVID-19 infection. Abdominopelvic mesenteric lymphadenopathy, often most prominent in the right lower quadrant, sometimes with surrounding inflammatory fat stranding, with an overall appearance similar to mesenteric adenitis, is a common finding in MIS-C associated with COVID-19 (Fig 4). In fact, Belhadjer et al found two children with MIS-C associated with COVID-19 underwent appendectomy for suspected appendicitis, with an ultimate diagnosis of mesenteric adenitis (22). Indeed, mesenteric lymphadenopathy is in keeping with the impressive frequency of gastrointestinal symptoms in children with MIS-C as well as the likely propensity of the virus to infect the gastrointestinal tract (13). Additional abdominal findings observed in pediatric patients affected by MIS-C associated with COVID-19 include echogenic kidneys (Fig 5), ascites (Fig 5), hepatomegaly, and gallbladder wall thickening, in keeping with multiorgan involvement (17).

**Thoracic Imaging Findings of Typical COVID-19 versus MIS-C Associated with COVID-19 in Children: What Are the Differences?**

**Typical Chest Radiographic and CT Findings of Typical COVID-19 in Pediatric Patients**

The typical chest radiographic findings in typical acute pediatric COVID-19 infection include bilateral peripheral and subpleural ground-glass opacities and/or consolidations (39,40) (Fig 6a). On CT images, the most common appearance of typical acute pediatric COVID-19 infection is bilateral multifocal peripheral ground-glass opacities, with or without consolidations, often with a posterior and lower lobe predominant distribution (25,39,40) (Fig 6b). It has been suggested that there are three imaging phases of typical acute pediatric COVID-19 infection: early, progressive, and developed phases (40). As there is significant clinical and imaging variation between patients, there is, at present, no known timeline for demarcating these phases. Typically, the halo sign (Fig 6b), which denotes a rim of ground-glass opacity surrounding a nodule or consolidation, is often observed in the early phase (reported in up to half of cases), often progressing to ground glass (progressive phase), and ultimately...
developing into a confluent consolidation (developed phase) (25,40). Additional CT findings reported in typical acute pediatric COVID-19 infection include adjacent bronchial wall thickening and inflammation along the bronchovascular bundle which are more frequently reported in pediatric patients compared with adults (25). Fine mesh reticulations and “crazy paving” have also been reported, but with less frequency (25). Pleural effusions and thoracic adenopathy are rare and considered atypical (39,40).

Differences between Thoracic Imaging Findings of Typical Pediatric COVID-19 and MIS-C Associated with COVID-19

There are some differences between the thoracic imaging findings of typical pediatric COVID-19 infection and MIS-C associated with COVID-19 (Table). Such differences may be partially explained by the hypothesis that typical COVID-19 reflects an acute infection, whereas MIS-C associated with COVID-19, which typically occurs approximately 1 month after COVID-19 peak in a geographic region and is most often associated with positive antibodies (suggesting prior infection), most likely reflects postviral hyperinflammatory process (15,18,22).

The main radiologic difference between typical pediatric COVID-19 and MIS-C associated with COVID-19 is the location of imaging abnormalities. Typical pediatric COVID-19 infection predominantly affects the pulmonary parenchyma, manifesting primarily with bilateral peripheral and subpleural airspace opacities (25,39,40). Extrapulmonary abnormalities are rare and unexpected in typical acute pediatric COVID-19 infection (25,39,40). In contrast, pediatric MIS-C associated with COVID-19 is a systemic hyperinflammatory state characterized by multiorgan system involvement, often with prominent cardiovascular abnormalities, such as heart failure, manifesting with cardiomegaly, pulmonary edema, and pleural effusions (22). As previously described, the hyperinflammatory state of MIS-C associated with COVID-19 may contribute to a prothrombotic coagulopathy predisposing to thromboembolic complications, including pulmonary emboli (14,34–36). Furthermore, the hyperinflammatory state of MIS-C associated with COVID-19 is often associated with adenopathy, which is rare and unusual in typical pediatric COVID-19 infection (22,26,28,40). Last, ARDS, a common thoracic imaging pattern in late-stage adult COVID-19 infection, is also observed in some pediatric MIS-C cases, although is much less common in typical pediatric COVID-19 infection (39–42).

As previously described, it has been suggested that MIS-C associated with COVID-19 and late-stage adult COVID-19 may be characterized by a similar hyperinflammatory milieu, which may account for some overlap in imaging findings and pathophysiology, although more scientific evidence is needed for validation (15,18,20).
Radiology: Cardiothoracic Imaging

The growing number of pediatric cases of MIS-C associated with COVID-19 suggests that COVID-19 is likely far more than just a respiratory illness in the pediatric population. In addition to the previously described pulmonary parenchymal abnormalities seen in typical, presumed acute COVID-19 infection, MIS-C associated with COVID-19, which is likely a postviral hyperinflammatory process, is now known to cause multiorgan damage, including heart disease, liver injury, kidney failure, gastrointestinal and dermatologic manifestations, among others. This signals an important paradigm shift in our understanding of pediatric COVID-19 infection: from a primarily respiratory illness to multiorgan system disease.

Interestingly, many of the clinical and imaging features of MIS-C associated with COVID-19 resemble late-stage severe adult COVID-19 infection, possibly due to a similar hyperinflammatory cytokine storm, predisposing to some similar thoracic imaging manifestations, including heart failure, ARDS, and thromboembolic complications. Currently, more scientific evidence is needed to guide clinical and imaging study decisions for MIS-C associated with COVID-19. However, based on our preliminary observation of MIS-C associated with COVID-19 in our practice, a judicious approach to imaging pediatric patients, who meet the CDC criteria for a diagnosis of MIS-C associated with COVID-19 infection or exposure, may need to be broadened to include echocardiography, abdominal imaging, and CT pulmonary angiography in pediatric patients with high clinical suspicion for pulmonary embolism, in addition to typical chest radiography and/or CT.

As knowledge and scientific evidence about the imaging findings of MIS-C associated with COVID-19 grow, better understanding of the characteristic imaging findings and the need for specific imaging evaluations is expected in the future. In addition, because there is currently a lack of pathologic data explaining the underlying causes and imaging findings of MIS-C, future studies focusing on the radiology-pathology correlation will shed light on this new and challenging disorder, unique to the pediatric population.

Disclosures of Conflicts of Interest: A.J.W. disclosed no relevant relationships. E.B. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: author and spouse own a U.S. patent for segmentation of vertebral bodies from CT scans of the chest and abdomen (Automated Vertebral Body Image Segmentation for Medical Screening US20130077840. Publication date 3/28/2013. Einat Blumfield, Anthony Blumfield, Radiostics LLC); author and spouse are cofounders of Radiostics LLC; product is software for automated segmentation of vertebral bodies in chest and abdomen CT scans and automated calculation of bone mineral density. The company is currently inactive. They did not receive any financial compensation. Other relationships: disclosed no relevant relationships. E.Y.L. Activities related to the present article: disclosed no relevant relationships. E.Y.L. Activities related to the present article: disclosed no relevant relationships. E.Y.L. Activities related to the present article: disclosed no relevant relationships. M.C.L. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: author and spouse own a U.S. patent for segmentation of vertebral bodies from CT scans of the chest and abdomen (Automated Vertebral Body Image Segmentation for Medical Screening US20130077840. Publication date 3/28/2013. Einat Blumfield, Anthony Blumfield, Radiostics LLC); author and spouse are cofounders of Radiostics LLC; product is software for automated segmentation of vertebral bodies in chest and abdomen CT scans and automated calculation of bone mineral density. The company is currently inactive. They did not receive any financial compensation. Other relationships: disclosed no relevant relationships. J.K. disclosed no relevant relationships. A.M.E disclosed no relevant relationships. J.K. disclosed no relevant relationships. A.M.E disclosed no relevant relationships. A.M.E disclosed no relevant relationships.

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| Finding | MIS-C Associated with COVID-19 | Typical COVID-19 |
|---------|-------------------------------|-----------------|
| Pulmonary | Pulmonary edema | Bilateral, lower lobe predominant peripheral/subpleural GGOs and/or consolidations. |
|          | ARDS, possibly asymmetric | Halo sign (early phase) |
| Pleural  | Pleural effusions | None known at the time of publication |
| Cardiovascular | Heart failure/left ventricular systolic dysfunction | None known at the time of publication |
|          | Pericardial effusion | None known at the time of publication |
|          | Pulmonary embolism* | None known at the time of publication |
|          | Coronary artery dilatation | None known at the time of publication |
| Extrathoracic | Mesenteric lymphadenopathy | Echogenic renal parenchyma |
|          | Hepatomegaly | Ascites |
|          | Gallbladder wall thickening | Echogenic renal parenchyma |
|          | Echogenic renal parenchyma | Ascites |

Note.—ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, GGO = ground-glass opacity, MIS-C = multisystem inflammatory syndrome in children.

* Segmental pulmonary embolism has been observed so far.
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