Pediatric Rheumatologic Effects of COVID-19

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KEYWORDS

- COVID-19 • Multisystem inflammatory syndrome in children (MIS-C)
- Kawasaki disease • Intravenous immunoglobulin • Systemic steroids
- Rheumatology

KEY POINTS

- Multisystem inflammatory syndrome is a severe hyperinflammatory post–COVID-19 syndrome sharing characteristics with Kawasaki syndrome, toxic shock syndrome, and hemophagocytic lymphohistiocytosis occurring primarily in children.
- Multisystem inflammatory syndrome in children typically develops 2 to 6 weeks after infection; the usual presenting symptoms are persistent fever, conjunctivitis, peripheral edema, rash, extremity pain, gastrointestinal distress, and advancement to shock.
- Multisystem inflammatory syndrome in children is treated with combinations of systemic steroids, intravenous immunoglobulin, and anti-inflammatory monoclonal antibodies.
- Cardiac sequelae of multisystem inflammatory syndrome in children differ from those of Kawasaki syndrome; specifically coronary artery aneurysms may occur, but are more prominent in Kawasaki.
- Cardiac ventricular dysfunction is more common with multisystem inflammatory syndrome in children, leading to higher troponin levels.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was recognized as a novel coronavirus in Wuhan, Hubei Province, China, after several hospitalized patients presented with pneumonia of undetermined origin in December 2019 and January 2020.[1] In March 2020, coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization.[2] There is now a better understanding of the pathophysiology, disease course, outcomes, and treatment of this virus. It is

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recognized that COVID-19 affects adults and children differently, with the virus generally causing milder symptoms of infection in children as compared with adults.[3–5]

In adults, acute respiratory failure accounts for the most common complication from COVID-19.[6] In contrast, healthy children and adolescents may experience a hyperinflammatory syndrome owing to COVID-19 exposure causing a potentially life-threatening response.[6] The hyperinflammatory response seen in the pediatric population is similar in some respects to Kawasaki disease, systemic-onset juvenile idiopathic arthritis, or hemophagocytic lymphohistiocytosis.

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Multisystem inflammatory syndrome in children (MIS-C) as a result of SARS-CoV-2 exposure was first reported in April 2020 among 8 healthy children with hyperinflammatory shock over 10 days in the UK.[7] The hyperinflammatory shock was noticed to have comparable characteristics to incomplete Kawasaki disease, Kawasaki disease shock syndrome and toxic shock syndrome.[7] Similarly, between April 27 and May 11, 2020, there were 21 pediatric patients in Paris, France, admitted with Kawasaki-like symptoms associated with SARS-CoV-2.[8] In the United States, cases of MIS-C were noted as early as March 2020.[6] On May 14, 2020, the Centers for Disease Control and Prevention outlined a health advisory that remarked on clinical features of MIS-C and provided a case definition.[9]

Case Definition

The criteria for the proposed case definition of MIS-C are shown in **Table 1**. Per the Centers for Disease Control and Prevention, even if individuals fulfill the criteria for typical or atypical Kawasaki disease, yet meet the criteria for MIS-C, they should be reported.[9] Also, evidence of SARS-CoV-2 infection in any pediatric death should prompt consideration for MIS-C.[9]

PATHOPHYSIOLOGY

In a study of 2135 children (median age, 7 years) diagnosed with COVID-19 in China, the authors noted that SARS-CoV-2 seemed to cause less severe symptoms in children than adults, with more than 90% of children having asymptomatic, mild, or moderate infection.[10] The reasons are unclear, but may in part be owing to age-related nasal epithelium angiotensin-converting enzyme II receptor expression, limiting SARS-CoV-2 host entry via its spike (S) protein.[11,12] Although COVID-19 infection is milder in the pediatric population, a small percentage of the infected or exposed develop MIS-C, a potentially life-threatening condition in children.[6]

MIS-C seems to be temporally associated with COVID-19 infection with clinical symptoms and features (see **Table 1**) developing between 2 and 6 weeks after exposure to the virus.[13–16] Case reports have demonstrated that children admitted for MIS-C most often have positive serum immunoglobulin G (IgG) antibodies against SARS-CoV-2 and are less frequently positive for reverse transcription-polymerase chain reaction (RT-PCR), suggesting that MIS-C is likely a postviral hyperinflammation syndrome rather than an acute COVID-19 infection.[7,8,13–15,17–21]

Gruber and colleagues[13] examined how MIS-C influences the immune system and showed that, compared with pediatric patients with COVID-19, the inflammatory response of MIS-C triggered high levels of cytokines (IL-17A, CD40) and chemokines (CXCL5, CXCL11, CXCL1, CXCL6) that recruit natural killer and T cells. Further, it was noted that patients with MIS-C had increased expression of CD64 on their neutrophils

Table 1
Centers for Disease Control and Prevention case definition of MIS-C—all criteria must be met[9]

Criteria		
1	Age <21 y	
	Fever	≥38°C for ≥24 h or subjective fever ≥24 h
	≥1 elevated marker of inflammation	Including, but not limited to: C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, IL-6, neutrophilia, lymphocytopenia, hypoalbuminemia
	Clinically severe illness necessitating hospitalization	
	Involvement of ≥2 organ systems	Cardiovascular, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic[a]
2	No other reasonable diagnoses	
3	Evidence of SARS-CoV-2 infection or exposure	Positive SARS-CoV-2 infection by RT-PCR, serology or antigen test or COVID-19 exposure within 4 wk before symptom onset

Abbreviations: LDH, lactate dehydrogenase; RT-PCR, reverse transcription-polymerase chain reaction.

[a] Features of multisystem involvement of ≥2 organ systems may include: cardiovascular (eg, elevated troponin, elevated B-type natriuretic peptide, abnormal echocardiogram, shock, arrhythmia), renal (eg, renal failure, acute kidney injury), respiratory (eg, acute respiratory distress syndrome, pneumonia, pulmonary embolism), hematologic (eg, coagulopathy), gastrointestinal (eg, vomiting/diarrhea, abdominal pain, gastrointestinal bleeding, ileus), dermatologic (eg, rash, mucositis, erythroderma), neurologic (eg, seizure, aseptic meningitis, stroke).

(Table and contents adapted from the Centers for Disease Control and Prevention)[9].

and CD16$^+$ nonclassical monocytes, which are typically seen in autoimmune and autoinflammatory illnesses.[13,22]

Gruber and colleagues[13] hypothesized that MIS-C as a result of SARS-CoV-2 results from the adaptive immune response. They tested MIS-C plasma IgG and immunoglobulin A against a microarray of more than 21,000 human peptides and found 189 peptides that cross-reacted as autoantigens.[13] Interestingly, the tissue expression of these autoantigens was from endothelial, cardiac, and gastrointestinal tract tissue,[13] important sites of clinical involvement. Also noted, plasma IgG from patients with MIS-C reacted with anti-La (seen in systemic lupus erythematosus [SLE] and Sjogren syndrome) and anti–Jo-1 (seen in inflammatory myopathies) antigens.[13] MIS-C pathophysiology may share some mechanisms with these autoimmune diseases[13]; however, further studies need to be conducted to assess whether MIS-C autoantibodies cause an autoimmune pathology.

CLINICAL MANIFESTATIONS

In mid April 2020, the UK began reporting the first cases of 8 previously healthy children (mean age of 8 years) presenting with characteristics similar to incomplete Kawasaki disease or Kawasaki disease shock syndrome.[7] Now recognized as MIS-C,

symptoms included persistent fever, conjunctivitis, peripheral edema, rash, extremity pain, and gastrointestinal distress with all the children advancing to distributive shock requiring ionotropic agents.[7] Since these initial reports from the UK, similar cases from other European countries and the United States have emerged.[6,8,13–15,18–20,23]

In the United States, New York City was the first to report 15 cases of MIS-C. Similar to the UK's findings, all of the children (mean age of 12 years) had fever; 87% had gastrointestinal symptoms such as vomiting, abdominal pain, and diarrhea; and less than 50% presented with rash, conjunctivitis, and swollen hands and feet.[18] As in the UK, Riollano-Cruz[18] and colleagues described 87% of children being hypotensive with 60% requiring inotropic agents or vasopressors. In the UK, Riphagen and colleague[7]s noted that all but 1 child had cardiac involvement, mostly ventricular dysfunction, and in New York City almost 90% of MIS-C cases had severe cardiac pathology with 80% demonstrating abnormal transthoracic echocardiogram results, with 27% showing left ventricular dysfunction.[18]

In another study by Feldstein and colleagues[6] examining 186 pediatric patients with MIS-C (median age of 8.3 years) in 26 US states, the authors noted 92% of children with gastrointestinal involvement, 80% with cardiac involvement with 48% requiring vasopressors owing to cardiogenic shock and 74% with mucocutaneous symptoms,[6] consistent with findings of other case reports.[7,18] After the initial appearance of MIS-C cases in Europe and the United States, numerous other cases have been reported. Fever, abdominal symptoms (pain, emesis, diarrhea), skin rash, oropharyngeal mucosal changes, hypotensive shock, conjunctivitis, cardiac dysfunction, and mucocutaneous findings have been reported as symptoms and signs of MIS-C in the literature.[8,13–15,21,23–26]

LABORATORY TESTS AND IMAGING FINDINGS

Markers of inflammation are prominent in MIS-C and common laboratory studies have been obtained in various case reports with similar reported findings. These include elevations in the erythrocyte sedimentation rate, C-reactive protein, D-dimer, ferritin, fibrinogen, B-type natriuretic peptide, troponin, international normalized ratio, prothrombin time, lactate dehydrogenase, partial thromboplastin time, IL-6, IL-8, and procalcitonin, in addition to anemia, thrombocytopenia, hypoalbuminemia, hyponatremia, leukocytosis with neutrophilia, and lymphopenia.[6,8,13,14,16,18,20,21,23,26–31] These laboratory studies should be considered to help aid in the diagnosis of MIS-C.

In addition to the laboratory testing cited, an electrocardiogram, and echocardiogram should be obtained at baseline for suspected or confirmed patients with MIS-C given arrythmias, cardiac ventricular dysfunction, coronary artery aneurysms, and coronary artery dilation have been observed.[6–8,14,15,20,21,23,25,29] **Table 2** specifies the laboratory and imaging studies that should be considered for a suspected case of MIS-C.

KAWASAKI DISEASE VERSUS MULTISYSTEM INFLAMMATORY DISEASE IN CHILDREN

Kawasaki disease is an acute self-limited systemic small- and medium-sized vessel vasculitis in those typically 6 months to 5 years of age[32–34] with the clinical features presented in **Table 3**. Although the cause remains unknown, it is hypothesized that an infection may trigger the hyperinflammatory response seen in Kawasaki disease,[17] as does SARS-CoV-2 in MIS-C.[13–16] Kawasaki disease can be further distinguished into complete Kawasaki disease, incomplete Kawasaki disease, and Kawasaki disease shock syndrome, with some of their features presenting in MIS-C.[6,8,18,20] For

Table 2
Laboratory testing/imaging for suspected MIS-C[4,6–8,14,15,18,20,21,23,25,29,42,71]

Laboratory testing/Imaging	Values/Features
CMP	Na <135 mmol/L Albumin $\leq$ 3 g/dL
CBC with differential	Absolute lymphocyte count <1.0K cell/μL Platelets <150,000 cells/μL Neutrophilia
Erythrocyte sedimentation rate	$\geq$40 mm/h
C-reactive protein	$\geq$3 mg/dL
BNP or NT-proBNP	>200 pg/mL
Troponin T	Elevated
Procalcitonin	Elevated
Fibrinogen	>400 mg/dL
Ferritin	>600 ng/mL
AST/ALT	At least 2 times the upper limit of normal
Albumin	<3 g/dL
LDH	Elevated
Urinalysis: IL-6/IL-8	Elevated

Coagulation studies
   International normalized ratio
   Prothrombin time
   Partial thromboplastin time
	International normalized ratio > 1.1

D-Dimer	>3 mg/L
SARS-CoV-2	RT-PCR positive Antigen test positive Serology (IgG, immunoglobulin A, IgM) positive
Electrocardiogram	Arrythmias

Echocardiogram	Cardiac ventricular dysfunction,
	   coronary artery aneurysm,
	   coronary artery dilation

Abbreviations: CMP, comprehensive metabolic panel; CBC, complete blood count; NT-proBNP, N-terminal-pro hormone BNP; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IgM, immunoglobulin M; LDH, lactate dehydrogenase.

example, in their study of 186 patients with MIS-C, Feldstein and colleagues[6] report that 40% of patients having Kawasaki disease-like symptoms, and Toubiana and colleagues[8] describe that 52% of patients with MIS-C meeting complete Kawasaki disease criteria, 48% meeting incomplete Kawasaki disease criteria, and 57% developing Kawasaki disease shock syndrome. **Table 3** demonstrates the criteria for complete Kawasaki disease and incomplete Kawasaki disease.

In addition to the features described in **Table 3**, the liver, joints, lungs, central nervous system, and gastrointestinal tract can also be affected in Kawasaki disease.[17] Kawasaki disease shock syndrome includes the features of Kawasaki disease in addition to a 20% systolic blood pressure decrease compared with the patient's age group or signs of hypoperfusion.[35,36] Overlapping features and differences exist between Kawasaki disease and MIS-C. **Table 4** compares and contrasts Kawasaki disease and MIS-C.

Table 3	
Complete Kawasaki disease versus incomplete Kawasaki disease[3,6,24,32]	
Disease	**Features/Criteria**
Complete Kawasaki disease	Elevated fever ≥ 5 d AND At least 4 of 5 of the following: Bilateral nonexudative conjunctivitis Oropharyngeal mucosal changes Cervical lymphadenopathy >1.5 cm Redness and swelling of the hands and feet Erythematous rash
Incomplete Kawasaki disease	Elevated fever ≥5 d AND At least 2 of the 5 characteristics in complete Kawasaki disease (see above) AND C-reactive protein of ≥3 mg/dL or erythrocyte sedimentation rate of ≥40 mm/h AND ≥3 of the following laboratory abnormalities Low hemoglobin for age Platelets of ≥450,000 after fever for 7 d Albumin of ≤3 g/dL White blood count of ≥15,000/mm³ ALT of >40 U/L OR Cardiac involvement on echocardiogram (eg, coronary artery aneurysms, ventricular dysfunction)

Children with MIS-C and Kawasaki disease shock syndrome tend to have higher C-reactive protein, platelet count, creatinine, N-terminal-pro hormone B-type natriuretic peptide, and troponin levels than those with Kawasaki disease, as well as cardiac ventricular dysfunction.[17] Untreated, 20% to 25% of Kawasaki disease cases will develop coronary artery aneurysms,[32,33] whereas in MIS-C and Kawasaki disease shock syndrome, cardiac ventricular dysfunction is more commonly seen.[7,14,20] In Kawasaki disease, high levels of IL-1 are typically seen, whereas in MIS-C IL-6 and IL-8 are increased, as demonstrated by all 15 MIS-C cases in the study by Riollano-Cruz and associates[18] having high levels of IL-6 and IL-8, and normal IL-1 levels. These findings, in combination with **Table 4**, demonstrate that Kawasaki disease and MIS-C, although sharing similar features, are separate entities.

MULTISYSTEM INFLAMMATORY DISEASE IN CHILDREN TREATMENT

Various treatment options exist for MIS-C (**Table 5**) and many intersect with strategies used for Kawasaki disease. A combination of intravenous immunoglobulin (IVIG) and aspirin are the first-line treatments in the healing process of Kawasaki disease.[32,33] IVIG comprises pooled human IgG antibodies that may work through neutralizing antigens,[37] inhibit proliferation of antigen-specific T cells,[38] prevent the interaction between endothelial and natural killer cells,[39] and induce the secretion of IL-8 and IL-1 receptor antagonist .[40] IVIG has been shown to decrease fever more quickly and decrease the development of coronary artery aneurysms, whereas aspirin aids in decreasing inflammation and inhibiting platelet aggregation in Kawasaki disease.[33]

Table 4
Comparing/contrasting Kawasaki disease and MIS-C[6–8,14–18,20,21,23,25,27,29,31–33,41]

Common similarities	Hyperinflammation Fever, conjunctivitis, oropharyngeal mucosal changes (eg, red cracked lips, strawberry tongue) cervical lymphadenopathy, rash, red and/or swollen hands and feet	
Common differences	Kawasaki Disease	MIS-C
Demographics	Tend to be of East Asian descent, younger (<5 y)	Tend to be Hispanic/Latino, Black/African/Afro-Caribbean descent, Older (around 6–14 y)
Symptoms/signs	Fewer gastrointestinal symptoms	Tend to have more gastrointestinal upset (pain, emesis, diarrhea), hypotension/shock
Laboratory findings	IL-1 > IL-6, leukocytosis with neutrophilia, thrombocytosis	IL-6 > IL-1, lymphopenia, thrombocytopenia, higher: ferritin, C-reactive protein, NT-proBNP, troponin
Cardiac involvement	Tend to have more coronary artery aneurysms	Tend to have more cardiac ventricular dysfunction

Abbreviations: NT-proBNP, N-terminal (NT)-pro hormone BNP.

Owing to the similarities between MIS-C and Kawasaki disease, IVIG and aspirin have been used in the treatment of MIS-C.[7,8,18,20,25] The American College of Rheumatology MIS-C task force recommends using high-dose IVIG (2 g/kg) in patients with MIS-C requiring hospitalization and/or fulfilling the Kawasaki disease criteria, in addition to aspirin if there are no contraindications.[41]

Riollano and colleagues[18] used IVIG and aspirin when Kawasaki disease criteria was met or in those with evidence of cardiac injury. Dufort and colleagues[15] analyzed MIS-C cases in New York state between March and May 2020 and noted that 70% of patients were given IVIG as part of the treatment regimen. Further, Toubiana and colleagues[8] described 21 pediatric patients with MIS-C with gastrointestinal symptoms likely related to bowel vessel vasculitis who all received IVIG with resolution of their symptoms thereafter. Verdoni and colleagues[20] also reported 10 patients between February and April 2020 who all received IVIG in addition to either aspirin or methylprednisolone or both with good response. Corticosteroids tend to be added to the treatment regimen when patients with MIS-C are in shock, if there is an increased risk of developing coronary artery aneurysms, or if the patient is considered high risk, presenting with features similar to incomplete Kawasaki disease.[14,25] Steroids should also be considered when fevers persist for more than 24 hours after IVIG treatment.[42]

Several second -line treatments such as biologics and antiviral analogs are used for MIS-C.[18,23] Remdesivir, an antiviral nucleoside analog, is given to those who meet compassionate use criteria, especially in those who have a positive PCR or presentation typical of COVID-19 infection.[18,23,27] Markedly, biologic agents tocilizumab, an anti–IL-6 receptor monoclonal antibody (anti–IL-6R), and anakinra, a recombinant human IL-1 receptor antagonist, have been used for refractory MIS-C not responding to IVIG,[18,42] just as anakinra has been used in IVIG-resistant Kawasaki disease[43,44] and

tocilizumab for juvenile idiopathic arthritis.[45] Guidelines from the Inova health system recommend that anakinra be given for refractory MIS-C when fevers persist for more than 24 hours after IVIG or steroids and ferritin levels are greater than 1000 ng/mL or for worsening echocardiogram findings, whereas tocilizumab should be given for MIS-C refractory to anakinra.[42]

In their study, Riollano and colleagues[18] report tocilizumab and anakinra use for patients with MIS-C with hemodynamic instability and rapid clinical deterioration. Some patients with MIS-C received anakinra for unresolving severe inflammation, respiratory distress, persistent fevers, thrombocytopenia, or unresolving cardiac dysfunction.[14,29,31] Further, some received tocilizumab for high IL-6 levels, which play a part in the cytokine storm and the subsequent myocardial injury seen in MIS-C.[23] In a series of 9 patients with MIS-C in New York City between April and June 2020, all were treated with either IVIG or tocilizumab within 1 day of admission with resolution of their symptoms leading to favorable outcomes and a median 6-day admission.[13]

Waltuch and colleagues[46] describe case reports in children with MIS-C treated with IVIG and biologic agents. In 1 case, a 13-year-old patient presented with features of atypical Kawasaki disease, toxic shock syndrome, and COVID-19 cytokine storm with elevated IL-6 levels for which he was treated with IVIG, anakinra, and tocilizumab.[46] In another case, a 10-year-old boy with elevated IL-6 levels was treated with IVIG and tocilizumab for atypical Kawasaki disease and cytokine storm, respectively.[46] Balasubramanian and colleagues[47] report a case of an 8-year-old boy with MIS-C presenting with features of toxic shock syndrome and Kawasaki disease who was initially treated with IVIG and then tocilizumab 72 hours later owing to continued high-grade fevers and elevated C-reactive protein. At 12 hours after receiving 8 mg/kg IV tocilizumab infused over 2 hours, his fevers improved and his markers of inflammation normalized. Alongside other case reports and studies, the authors demonstrate that tocilizumab seems successful in decreasing the hyperinflammatory response in IVIG refractory MIS-C.[47]

In addition to using anakinra and tocilizumab as treatments for MIS-C, in a case series Whittaker and colleagues report that 8 of 58 patients with MIS-C received infliximab, a tumor necrosis factor (TNF)-alpha antagonist.[21] Similarly, Dolinger and colleagues[48] describe a 14-year-old boy presenting with active Crohn's disease and MIS-C with high levels of IL-6, IL-8, and TNF-alpha levels with a deteriorating clinical course including hypotension, tachycardia and persistent fevers. To treat both the Crohn's disease and the MIS-C in the setting of elevated TNF-alpha levels, 10 mg/kg infliximab was given with resolution of the fevers, hypotension, and tachycardia within hours, normalization of TNF-alpha levels, and a decrease in other cytokine levels.[48] In another study by Abdel-Haq and coworkers,[49] infliximab was used as a second-line therapy in 12 of 22 critically ill patients with MIS-C (median age of 7 years) with myocardial dysfunction refractory to IVIG, or persistent inflammation/fever with consequent improvement after treatment. These studies suggest that infliximab may be another beneficial treatment for MIS-C in those presenting with worsening systemic signs and high cytokine levels.

In a cohort of 185 patients with MIS-C, Feldstein and colleagues[6] reported that 77% of patients received IVIG, 49% received steroids, 8% received tocilizumab or siltuximab (anti–IL-6R), and 13% received anakinra. Similar studies examining patients with MIS-C used treatments that also included a combination of IVIG, aspirin, steroids, and/or IL-6 and IL-1 inhibitors.[14,18,20,23,25] Similarly, an 11-year-old girl with MIS-C and elevated IL-6 levels significantly improved within 24 hours after combination treatment with tocilizumab, convalescent plasma, remdesivir, steroids, and IVIG with resolution of fevers, tachycardia, and discontinuation of pressor support.[50]

Table 5
Treatment strategies to be considered in MIS-C[4,7,8,13,14,18,20,23,25,27,29,41,42]

Therapy	Dosage/Duration	Indication
IVIG (neutralizes autoantibodies)	Single 2 g/kg/d infusion ×1 over 10–12 h Refrain from giving a second dose for refractory MIS-C owing to potential volume overload and hemolytic anemia risk	KD-like illness Cardiac involvement Severe hyperinflammation (ferritin of >700 ng/mL, C-reactive protein of >30 g/dL) Multisystem organ failure
Aspirin[a]	3–5 mg/kg/d for at least 4–6 wk until inflammatory markers, platelet count and echocardiogram findings have normalized	
Steroids	1–2 mg/kg/d prednisolone or methylprednisolone for 5 d followed by a 2-wk taper Consider high dose methylprednisolone 10–30 mg/kg/d (max 1 g) IV for 3 d with taper in those with shock	Adjunct to IVIG in those with severe disease/high risk Infants, C-reactive protein of >130 g/dL, echocardiogram Z score of >2.5 or aneurysms, shock Refractory disease
Biologics		
Tocilizumab (anti–IL-6R)[c]	Weight < 30 kg = 12 mg/kg/dose ×1 Weight ≥ 30 kg = 8 mg/kg/dose (max 800 mg) ×1 Repeat 12 h later if needed	Refractory to IVIG and steroids or contraindication to IVIG/steroids Hemodynamic instability or acute clinical decompensation Persistent hyperinflammation
Anakinra (anti–IL-1R)	2–4 mg/kg/d IV or SQ (max 100 mg/dose)	
Infliximab (TNF-alpha antagonist)	10 mg/kg IV	
Remdesivir (antiviral nucleoside analog)	5 mg/kg load IV once (max dose 200 mg) on day 1, then 2.5 mg/kg (100 mg max dose) IV daily for 9 d	Presentation consistent with SARS-CoV-2 infection AND/OR Positive RT-PCR for COVID-19
Anticoagulation	Consult hematology for appropriate dosing Continue for at least 2 wk after discharge	Consider for moderate to severe LV dysfunction (LVEF of <35%) Coronary artery aneurysm z-score of ≥10[b] Thrombosis Critically ill patients

Abbreviations: anti–IL-1R, interleukin-1 receptor antagonist; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; LV, left ventricular; LVEF, left ventricular ejection fraction; SQ, subcutaneous; TNF, tumor necrosis factor.

[a] Platelet count should be ≥80,0000 cells/μL to give aspirin and it should be avoided in active bleeding or in those with high bleeding risk. For the acute phase of illness, some institutions recommend aspirin 30 to 80 mg/kg/d divided 4 times a day and 3 to 5 mg/kg/d for at least 4 wk once afebrile for 24 to 72 h.

[b] Continue lifelong therapy for coronary artery aneurysm z-score of ≥10.

[c] American College of Rheumatology MIS-C task force does not recommend tocilizumab for most COVID-19 pediatric patients based on randomized control adult studies in those with COVID-19 pneumonia that show this medication does not decrease mortality at 28 d and instead prefer Anakinra.

Interestingly, in the United States 5% of patients who present with Kawasaki disease require vasoactive support for cardiogenic shock, whereas Feldstein and colleagues[6] report almost 50% of their patients with MIS-C needing such agents, highlighting that MIS-C tends to cause more shock than Kawasaki disease. Vasopressors and ionotropic agents were widely used in those having shock with MIS-C in other case reports.[14,15,18,19,24] Further, anticoagulation, most notably enoxaparin, has been used in the treatment of patients with MIS-C as either prophylaxis or in those with high D-dimer, fibrinogen, electrocardiogram changes, left ventricular dysfunction, or coronary artery abnormalities.[18,23,25]

RHEUMATOLOGIC MANIFESTATIONS OF SARS-CoV-2

COVID-19 has been shown to cause a hyperinflammatory response in children (MIS-C),[7] similar to how rheumatologic disorders such as juvenile idiopathic arthritis and SLE may induce a hyperinflammatory state like in macrophage activation syndrome (MAS).[51] SARS-CoV-2 enters cells via the host angiotensin-converting enzyme II receptor that, in addition to the respiratory tract, can be found in skeletal muscle, smooth muscle, synovial fluids, small vessel endothelium, and bowel tissue causing symptoms such as fatigue, myalgia, and arthralgias, which are also seen in rheumatologic pathology.[52] Viral infections can trigger rheumatologic diseases,[52] and case reports have demonstrated that SARS-CoV-2 infection may trigger rheumatologic entities in children and adolescents such as SLE, arthritis, MAS, chilblains, and antiphospholipid syndrome.[20,53–55] Understanding that COVID-19 may present with or potentially precipitate rheumatologic manifestations aides in improving patient care by expanding the differential diagnosis to enhance treatment plans and to consider COVID-19 infection as part of the work-up in an individual presenting with new-onset rheumatologic disease in correlation with the clinical picture.

COVID-19 AND MACROPHAGE ACTIVATION SYNDROME

MAS is characterized by high serum ferritin levels and cytokines causing hyperinflammation leading to multiorgan failure, similar to what is seen in MIS-C.[20,56] In their case series, Verdoni and colleagues[20] describe a group of children diagnosed with Kawasaki-like disease in which 50% also met MAS criteria in the setting of SARS-CoV-2 exposure (80% with positive IgG serology). SARS-CoV-2 infection induces a hyperinflammatory syndrome as seen in MIS-C, which has similar features to MAS, a hyperferritinemic syndrome where macrophage activation allows for high levels of ferritin release (ferritin of >300 ng/mL).[51,56] MAS, commonly treated by rheumatologists, already has established treatment methods (such as steroids, anakinra and tocilizumab)[27] and understanding the overlapping clinical features and pathogenesis between MAS and MIS-C will likely aid in the treatment strategies for this new inflammatory entity.

COVID-19 AND NEW-ONSET SYSTEMIC LUPUS ERYTHEMATOUS

Systemic lupus erythematous is a relapsing and remitting chronic multisystemic autoimmune disorder resulting from autoantibodies against host cytoplasmic and nuclear antigens that can be triggered by viral infections.[53,57] Mantovani and colleagues[53] described the first case of an 18-year-old Hispanic girl with a positive COVID-19 PCR result with a past medical history of autism and panic disorder presenting with new-onset SLE and probable antiphospholipid syndrome. The patient presented with shortness of breath, productive cough, fevers, upper respiratory symptoms,

pericardial effusion, and fatigue with consequent hemodynamic instability leading to cardiac arrest with ROSC.[53] RT-PCR for SARS-CoV-2 was negative twice and, owing to continued high clinical suspicion for COVID-19 infection, she was retested a third time with RT-PCR resulting positive.[53] During her hospital course, she developed kidney failure and had lymphopenia, anemia, proteinuria, and hematuria.[53] Also, she was found to have positive serology for antinuclear antibodies (1:2560), anti–double stranded DNA, low complement (C3 and C4) levels, leading to a diagnosis of SLE based on the American College of Rheumatology/European League Against Rheumatism 2019 criteria.[53] Further, she was treated for possible antiphospholipid syndrome in the setting of multiple deep venous thromboses and thrombocytopenia in the setting of anticardiolipin antibodies and positive lupus anticoagulant.[53]

Adaptive immunity in SLE does not function as well as in healthy individuals and thus may be further weakened by COVID-19.[53] SLE decrease the T helper cell type 1 response by impairing the production of cytokines such as IL-1, IL-2, and TNF-alpha.[53] This process causes a less effective T helper cell type 2 response to evade viruses owing to SLE causing increased autoantibodies and heightened autoreactivity of helper, cytotoxic T cells, and B-cell differentiation.[53] This concept of changing from a T helper cell type 1 response to a T helper cell type 2 response owing to autoreactivity and autoantibodies altering cytokine profiles has been seen in HIV and may explain the autoimmune phenomena seen in COVID-19.[53]

COVID-19 AND NEW-ONSET CUTANEOUS LESIONS

Chilblain-like lesions have been described as vaso-occlusive erythematous to purpuric, violaceous-edematous lesions with cyanotic areas on the toes, hands, and fingers measuring between 5 and 20 mm in diameter.[54,58–63] Outbreaks of chilblain-like lesions, also known as pseudo-chilblain, pernio-like, acute acro-ischemia, or COVID toes have been increasingly documented in the setting of the SARS-CoV-2 pandemic,[54,58–60,64] associating a potential relationship between the lesions and the virus. To further demonstrate this correlation, in a study by Colmenero and colleagues,[65] skin biopsies from 7 children showed lymphocytic vasculitis and immunohistochemistry demonstrated SARS-CoV-2 in the endothelial and epithelial cells of eccrine glands. Moreover, in a case series of 19 adolescents (mean age 14 years) with chilblain-like lesions, El Hachem and colleagues[66] report positive immunoglobulin A serology for the S1 domain of the COVID-19 spike protein.

Chilblains tend to be more common in adults than children resulting from an inflammatory vascular response.[54] Cold, nonfreezing temperatures typically induce primary chilblains, whereas secondary chilblains can be due to autoimmune disorders and viral infections.[54,58] The term chilblain-like has been used given these lesions do not seem to be precipitated by cold and there is typically no prior personal history of these cutaneous manifestations, even though they look similar to chilblains.[54,58,67] In Italy, Piccolo and colleagues[58] reported 63 healthy patients (median age of 14 years) with erythematous–edematous chilblain-like lesions mostly affecting the toes and soles (85.7%), but also observed on the hands. Although 25.4% of the lesions were asymptomatic, there was pain and pruritis in more than 50% of cases.[58] In the study, it was difficult to attain COVID-19 status for all cases; however, some patients had either positive serology or PCR or both, although others in the study had individuals they lived with that were positive for SARS-CoV-2.[58] In another case report, Locatelli and colleagues[67] describe a 16-year-old boy who tested positive by RT-PCR for SARS-CoV-2 with erythematous–edematous macules and plaques on the fingers and toes with histology consistent with chilblains.

COVID-19 can cause a type I interferon response that in turn causes microvascular injury as seen in chilblains and retinal vasculitis. Interestingly, Quintana-Castanedo and coworkers[63] report the first case of an otherwise healthy asymptomatic 11-year-old boy presenting with a 2-week history of chilblains on his dorsal toes bilaterally and retinal vasculitis in the setting of positive IgG serology to SARS-CoV-2. An eye examination was performed as routine owing to possible thromboembolic events owing to COVID-19.[63] Further, in a case series during the highest COVID peak in northern Spain where 85.2% of cases were less than 21 years of age (median age of 14 years) with no history of rheumatic disease, Gómez-Fernández and associates[68] reported chilblain-like lesions with positive cryofibrinogen proteins in 68.2% of patients between the ages of 0 and 20 years. This finding could potentially suggest that cryofibrinogenemia may play a role in the pathogenesis of chilblains owing to COVID-19.[68]

Gallizzi and colleagues[69] report 9 cases of chilblain-like lesions during the COVID-19 outbreak in Italy in children aged 5 to 15 years old with more than 50% experiencing systemic symptoms around 2 weeks before developing the lesions. Antinuclear antibodies and antiphospholipid antibodies were positive in 4 children.[69] One child with a history of Raynaud phenomenon a few years prior was noted to be positive for extractable nuclear antigens autoantibodies SS-A and rheumatoid factor, in addition to antinuclear antibodies (1:5120), leading the authors to diagnose him with a connective tissue disorder and, although it is hard to say, COVID-19 could have potentially been the trigger given the timing of the onset of events.[69]

Piccolo and colleagues[58] reported only 6 of 63 patients with an autoimmune disorder, and other case reports reported similar findings,[54,60,67] suggesting that chilblain-like lesions are likely not due to an underlying rheumatic disease, but rather exposure to SAR-CoV-2 infection. Chilblain-like lesions seemed to manifest after systemic symptoms, such as gastrointestinal and respiratory distress, headache, and fever,[54,58,59,62,67] and can present with itchiness and pain.[54,59,62] Typically, these patients were negative for COVID-19 PCR or serology; however, there were patients in case reports who had coinhabitants with confirmed COVID-19 infection, upper respiratory tract symptoms, or potential COVID-19 exposure from family that worked closely with these patients.[54,58,59,61,62] Further, in a case series of 20 pediatric patients with Chilblain-like lesions, RT-PCR and serology were negative for COVID-19.[70] PCR and serology seem to be negative in those presenting with Chilblain-like lesions, and this observation seems to indicate that the lesions are a late manifestation of COVID-19.[54,62,68] Observing chilblain-like lesions in a pediatric patient may prompt an investigation of previous COVID-19 infection and help to mitigate efforts for surveillance and screening of this virus.

COVID-19 AND NEW-ONSET ARTHRITIS

Reactive arthritis tends to occur in men between the ages of 20 to 50 years.[55] It is also a postinfectious arthritis with sterile synovial fluid mostly occurring secondary to sexually transmitted or gastrointestinal infections and less commonly from viral infections.[55] Houshmand and colleagues[55] describe a case of a 10-year-old boy with positive SARS-CoV-2 RT-PCR presenting with a 1-week of history of fever and urticaria and 5 days of swelling and pain in his bilateral knees and right elbow. Other than morning stiffness and pain with movement, he had no other systemic symptoms.[55] On physical examination, he had warmth, tenderness, swelling, and decreased range of motion of affected joints.[55] His rheumatoid factor and antinuclear antibodies were normal and knee joint aspiration did not reveal any fluid.[55] He improved with supportive treatment and antihistamines.[55] Although difficult to

discern whether SARS-CoV-2 infection induces reactive arthritis, this case describes potential postviral arthritis, likely owing to COVID-19 in the setting of positive serology.[55]

SUMMARY

SARS-CoV-2 continues to spread widely around the world. The more we learn about COVID-19, including its presentation and pathophysiology, the better its features become recognized to diagnose and treat its manifestations. In children, the Kawasaki-like disease, multisystem inflammatory syndrome, causes severe life-threatening symptoms. Although not common, several case reports have documented new-onset rheumatologic disease in children concerning SARS-CoV-2 infection, such as SLE, arthritis, and MAS. Rheumatologists commonly treat hyperinflammation syndromes and these same therapies have been used to direct treatment for the severe hyperinflammation seen in COVID-19. As reviewed in this article, the literature documents rheumatologic manifestations owing to prior SAR-CoV-2 infection in children. Although it is difficult to pinpoint definitively whether the virus triggered these rheumatologic presentations, these cases raise awareness that there could be a link between COVID-19 and new-onset rheumatologic diseases, which will help to guide future research efforts to further understand this correlation, establish diagnoses, and initiate treatment plans.

CLINICS CARE POINTS

- Children with COVID-19 infection generally have asymptomatic or mild disease.
- MIS-C is a severe post–COVID-19 syndrome similar to Kawasaki disease, but differing in several ways.
- COVID-19 can cause an inflammatory vascular response leading to chilblains in children.
- Flares of existing or new onset of rheumatologic diseases have been reported in children with COVID-19.

DISCLOSURE

The authors declare no conflict of interest.

UNCITED REFERENCE

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REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727–33.
2. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed 2020;91(1):157–60.
3. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. N Engl J Med 2020; 382(17):1663–5.
4. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr 2020;109(6):1088–95.

5. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome corona-virus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. JAMA Pediatr 2020;174(9):882–9.

6. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383(4):334–46.

7. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet 2020;395(10237):1607–8.

8. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369:m2094.

9. Centers for Disease Control and Prevention Health Alert Network (HAN). Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19) 2020. Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed March 20, 2021.

10. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics 2020;145(6):e20200702.

11. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579(7798):270–3.

12. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. J Am Med Assoc 2020;323(23):2427–9.

13. Gruber CN, Patel RS, Trachtman R, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell 2020;183(4):982–95.e14.

14. Belhadjer Z, Méot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation 2020;142(5):429–36.

15. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383(4):347–58.

16. Levin M. Childhood multisystem inflammatory syndrome - a new challenge in the pandemic. N Engl J Med 2020;383(4):393–5.

17. Nakra NA, Blumberg DA, Herrera-Guerra A, et al. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. Children (Basel) 2020;7(7):69.

18. Riollano-Cruz M, Akkoyun E, Briceno-Brito E, et al. Multisystem inflammatory syndrome in children related to COVID-19: a New York City experience [published online ahead of print, 2020 Jun 25]. J Med Virol 2020;93:424–33. https://doi.org/10.1002/jmv.26224.

19. Belot A, Antona D, Renolleau S, et al. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. Euro Surveill 2020;25(22):2001010.

20. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395(10239):1771–8.

21. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. J Am Med Assoc 2020;324(3):259–69.

22. Li Y, Lee PY, Sobel ES, et al. Increased expression of FcgammaRI/CD64 on circulating monocytes parallels ongoing inflammation and nephritis in lupus. Arthritis Res Ther 2009;11(1):R6.

23. Kaushik S, Aydin SI, Derespina KR, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): a multi-institutional study from New York City. J Pediatr 2020; 224:24–9.

24. Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-associated multisystem inflammatory syndrome in children - United States, March-July 2020. MMWR Morb Mortal Wkly Rep 2020;69(32):1074–80.

25. Capone CA, Subramony A, Sweberg T, et al. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory syndrome of childhood associated with severe acute respiratory syndrome coronavirus 2 infection. J Pediatr 2020;224:141–5.

26. Miller J, Cantor A, Zachariah P, et al. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children that is related to coronavirus disease 2019: a single center experience of 44 cases. Gastroenterology 2020;159(4):1571–4.e2.

27. Hennon TR, Penque MD, Abdul-Aziz R, et al. COVID-19 associated multisystem inflammatory syndrome in children (MIS-C) guidelines; a Western New York approach [published online ahead of print, 2020 May 23]. Prog Pediatr Cardiol 2020;101232.

28. Davies P, Evans C, Kanthimathinathan HK, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study [published correction appears in Lancet Child Adolesc Health. 2020 Jul 17]. Lancet Child Adolesc Health 2020;4(9):669–77.

29. Pouletty M, Borocco C, Ouldali N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis 2020;79(8):999–1006.

30. Licciardi F, Pruccoli G, Denina M, et al. SARS-CoV-2-induced Kawasaki-like hyperinflammatory syndrome: a novel COVID phenotype in children. Pediatrics 2020;146(2):e20201711.

31. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. J Pediatr Infect Dis Soc 2020;9(3):393–8.

32. Kawasaki T. Kawasaki disease. Proc Jpn Acad Ser B Phys Biol Sci 2006;82(2): 59–71.

33. Burns JC, Glodé MP. Kawasaki syndrome. The Lancet 2004;364(9433):533–44.

34. Elakabawi K, Lin J, Jiao F, et al. Kawasaki disease: global burden and genetic background. Cardiol Res 2020;11(1):9–14.

35. Zhang MM, Shi L, Li XH, et al. Clinical analysis of Kawasaki disease shock syndrome. Chin Med J (Engl) 2017;130(23):2891–2.

36. Gatterre P, Oualha M, Dupic L, et al. Kawasaki disease: an unexpected etiology of shock and multiple organ dysfunction syndrome. Intensive Care Med 2012; 38(5):872–8.

37. Jolles S, Sewell WA, Misbah SA. Clinical uses of intravenous immunoglobulin. Clin Exp Immunol 2005;142(1):1–11.

38. Aktas O, Waiczies S, Grieger U, et al. Polyspecific immunoglobulins (IVIg) suppress proliferation of human (auto)antigen-specific T cells without inducing apoptosis. J Neuroimmunol 2001;114(1–2):160–7.

39. Finberg RW, Newburger JW, Mikati MA, et al. Effect of high doses of intravenously administered immune globulin on natural killer cell activity in peripheral blood. J Pediatr 1992;120(3):376–80.

40. Ruiz de Souza V, Carreno MP, Kaveri SV, et al. Selective induction of interleukin-1 receptor antagonist and interleukin-8 in human monocytes by normal polyspecific IgG (intravenous immunoglobulin). Eur J Immunol 1995;25(5):1267–73.

41. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for pediatric patients with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in COVID-19. version 2. Arthritis Rheum 2021;72(11):1791–805.

42. Developed by pediatric infectious diseases, critical care, cardiology, rheumatology, and pharmacy providers. Guideline: evaluation and management of COVID-19 multisystem inflammatory syndrome in children (MIS-C). Falls Church (VA): Inova Health System; 2020.

43. Kone-Paut I, Cimaz R, Herberg J, et al. The use of interleukin 1 receptor antagonist (anakinra) in Kawasaki disease: a retrospective cases series. Autoimmun Rev 2018;17(8):768–74.

44. Blonz G, Lacroix S, Benbrik N, et al. Severe late-onset Kawasaki Disease successfully treated with anakinra. J Clin Rheumatol 2020;26(2):e42–3.

45. Brunner HI, Ruperto N, Zuber Z, et al. Efficacy and safety of tocilizumab for polyarticular-course juvenile idiopathic arthritis in the open-label 2-year extension of a phase 3 trial [published online ahead of print, 2020 Sep 20]. Arthritis Rheum 2015;74:1110–7.

46. Waltuch T, Gill P, Zinns LE, et al. Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department. Am J Emerg Med 2020;38(10):2246.e3–6.

47. Balasubramanian S, Nagendran TM, Ramachandran B, et al. Hyper-inflammatory syndrome in a child with COVID-19 treated successfully with intravenous immunoglobulin and tocilizumab. Indian Pediatr 2020;57(7):681–3.

48. Dolinger MT, Person H, Smith R, et al. Pediatric Crohn disease and multisystem inflammatory syndrome in children (MIS-C) and COVID-19 treated with infliximab. J Pediatr Gastroenterol Nutr 2020;71(2):153–5.

49. Abdel-Haq N, Asmar BI, Deza Leon MP, et al. SARS-CoV-2-associated multisystem inflammatory syndrome in children: clinical manifestations and the role of infliximab treatment [published online ahead of print, 2021 Jan 16]. Eur J Pediatr 2021;180(5):1–11.

50. Greene AG, Saleh M, Roseman E, et al. Toxic shock-like syndrome and COVID-19: multisystem inflammatory syndrome in children (MIS-C). Am J Emerg Med 2020;38(11):2492.e5–6.

51. Cron RQ, Chatham WW. The rheumatologist's role in COVID-19. J Rheumatol 2020;47(5):639–42.

52. Ciaffi J, Meliconi R, Ruscitti P, et al. Rheumatic manifestations of COVID-19: a systematic review and meta-analysis. BMC Rheumatol 2020;4:65.

53. Mantovani Cardoso E, Hundal J, Feterman D, et al. Concomitant new diagnosis of systemic lupus erythematosus and COVID-19 with possible antiphospholipid syndrome. Just a coincidence? A case report and review of intertwining pathophysiology. Clin Rheumatol 2020;39(9):2811–5.

54. Andina D, Noguera-Morel L, Bascuas-Arribas M, et al. Chilblains in children in the setting of COVID-19 pandemic. Pediatr Dermatol 2020;37(3):406–11.

55. Houshmand H, Abounoori M, Ghaemi R, et al. Ten-year-old boy with atypical COVID-19 symptom presentation: a case report [published online ahead of print, 2020 Nov 16]. Clin Case Rep 2021;9(1):304–8.

56. Colafrancesco S, Alessandri C, Conti F, et al. COVID-19 gone bad: a new character in the spectrum of the hyperferritinemic syndrome? Autoimmun Rev 2020; 19(7):102573.
57. Fortuna G, Brennan MT. Systemic lupus erythematosus: epidemiology, pathophysiology, manifestations, and management. Dent Clin North Am 2013;57(4): 631–55.
58. Piccolo V, Neri I, Filippeschi C, et al. Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients. J Eur Acad Dermatol Venereol 2020;34(7):e291–3.
59. Colonna C, Monzani NA, Rocchi A, et al. Chilblain-like lesions in children following suspected COVID-19 infection. Pediatr Dermatol 2020;37(3):437–40.
60. Mazzotta F, Troccoli T, Bonifazi E. A new vasculitis at the time of COVID-19. Eur J Pediat Dermatol 2020;30(2):75–8.
61. Landa N, Mendieta-Eckert M, Fonda-Pascual P, et al. Chilblain-like lesions on feet and hands during the COVID-19 Pandemic. Int J Dermatol 2020;59(6):739–43.
62. Cordoro KM, Reynolds SD, Wattier R, et al. Clustered cases of acral perniosis: clinical features, histopathology, and relationship to COVID-19. Pediatr Dermatol 2020;37(3):419–23.
63. Quintana-Castanedo L, Feito-Rodríguez M, Fernández-Alcalde C, et al. Concurrent chilblains and retinal vasculitis in a child with COVID-19. J Eur Acad Dermatol Venereol 2020;34(12):e764–6.
64. Hernandez C, Bruckner AL. Focus on "COVID Toes". JAMA Dermatol 2020; 156(9):1003.
65. Colmenero I, Santonja C, Alonso-Riaño M, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. Br J Dermatol 2020;183(4):729–37.
66. El Hachem M, Diociaiuti A, Concato C, et al. A clinical, histopathological and laboratory study of 19 consecutive Italian paediatric patients with chilblain-like lesions: lights and shadows on the relationship with COVID-19 infection. J Eur Acad Dermatol Venereol 2020;34(11):2620–9.
67. Locatelli AG, Robustelli Test E, Vezzoli P, et al. Histologic features of long-lasting chilblain-like lesions in a paediatric COVID-19 patient. J Eur Acad Dermatol Venereol 2020;34(8):e365–8.
68. Gómez-Fernández C, López-Sundh AE, González-Vela C, et al. High prevalence of cryofibrinogenemia in patients with chilblains during the COVID-19 outbreak. Int J Dermatol 2020;59(12):1475–84.
69. Gallizzi R, Sutera D, Spagnolo A, et al. Management of pernio-like cutaneous manifestations in children during the outbreak of COVID-19 [published online ahead of print, 2020 Sep 19]. Dermatol Ther 2020;33(6):e14312. https://doi.org/ 10.1111/dth.14312.
70. Roca-Ginés J, Torres-Navarro I, Sánchez-Arráez J, et al. Assessment of acute acral lesions in a case series of children and adolescents during the COVID-19 pandemic. JAMA Dermatol 2020;156(9):992–7.
71. Centers for Disease Control and Prevention. Information for healthcare provides about multisystem inflammatory syndrome in children (MIS-C). Available at: https://www.cdc.gov/mis-c/hcp/. Accessed August 28, 2020; National Center for Immunization and Respiratory Diseases (NCIRD).
72. Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. Nat Rev Immunol 2020;20(8):453–4.