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Dermatologic manifestations of COVID-19-associated multisystem inflammatory syndrome in children

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Abstract Multisystem inflammatory syndrome in children (MIS-C) affects a small percentage of pediatric patients infected with COVID-19 and is characterized by fever, laboratory evidence of inflammation, multisystem involvement, and severe illness necessitating hospitalization. Skin findings are often present in these patients, and when initially compared with Kawasaki disease, they likely represent distinct phenomena and overall remain poorly characterized. In this retrospective review of 34 case reports and series, we identified cutaneous manifestations documented in 417 of 736 patients (57%) with MIS-C associated with COVID-19. "Rash" was the sole descriptor of skin findings in nearly half of patients. Case reports and smaller case series provided more detail, outlining a broad range of lesion morphologies (polymorphic, maculopapular, morbilliform, erythrodermic, urticarial, reticular, petechial, purpuric) in variable anatomic distribution. More thorough descriptions of dermatologic manifestations in patients with MIS-C are warranted to better characterize this syndrome, as they may lend important insight into pathogenic mechanisms of disease.

Introduction

At the outset of the novel coronavirus disease 2019 (COVID-19) pandemic, it was thought that children were generally unaffected by the deadly viral infection rapidly sweeping across the globe. This was likely due to the disproportionately lower rates at which children are affected by COVID-19 compared with adults, in terms of both infection rates and severity of clinical manifestations.[1,2] Despite a relatively benign clinical course for most, pediatric patients may rarely exhibit exaggerated immune responses that fall on a spectrum ranging from a mild febrile inflammatory state without multisystem involvement, to a moderate Kawasaki disease (KD)–like illness, to a severe multisystem inflammatory syndrome with shock.[3]

Beginning in late April 2020, multisystem inflammatory syndrome in children (MIS-C) became an increasingly recognized hyperinflammatory phenotype in pediatric patients with evidence of COVID-19 infection. On May 14, 2020, the Centers for Disease Control and Prevention (CDC) issued a national advisory to report all cases meeting criteria for MIS-C. Cases were defined as individuals aged <21 years with

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Table 1 Diagnostic criteria for multisystem inflammatory syndrome in children and Kawasaki disease

Diagnostic criteria for multisystem inflammatory syndrome in children[4]
1. Age <21 years
2. Fever (documented ≥38.0°C ≥24 hours *or* subjective fever ≥24 hours)
3. Laboratory evidence of inflammation (elevated erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase [LDH], interleukin 6 [IL-6], neutrophilia, lymphocytopenia, hypoalbuminemia)
4. Multisystem involvement (≥2 organ systems)
5. Severe illness requiring hospitalization
6. No alternative plausible diagnoses
7. Recent or current SARS-CoV-2 infection (as confirmed by RT-PCR, serology, or antigen test) or exposure within 4 weeks before onset of clinical manifestations
Diagnostic criteria for Kawasaki disease[56]
Fever for ≥5 days plus ≥4 of the following features:
1. Bilateral bulbar conjunctival injection
2. Oral mucositis (erythematous or fissured lips, injected pharynx, or strawberry tongue)
3. Extremity changes (erythema of palms or soles, edema of hands or feet, periungual desquamation)
4. Polymorphous rash
5. Cervical lymphadenopathy

severe illness requiring hospitalization, minimum 24-hour history of fever (>38°C), laboratory evidence of inflammation, multisystem (≥2) organ involvement, and laboratory-confirmed positive SARS-CoV-2 infection (via real-time reverse transcriptase polymerase chain reaction [RT-PCR] or antibody test) or epidemiologic connection to a person with COVID-19 infection (Table 1).[4] Following this call for reporting, 570 cases of MIS-C have been reported to the CDC as of July 29, 2020.[5]

With overlapping features of KD and toxic shock syndrome, patients with MIS-C exhibit a constellation of variable mucocutaneous as well as gastrointestinal, cardiac, hematologic, and respiratory findings.[5-8] Cutaneous features are present in the majority of patients with MIS-C and are currently not well characterized. Detailed descriptions of eruption morphology in these patients are limited to small case series and case reports, whereas larger studies typically document the presence of a "rash," but they do not elaborate further and lack precise dermatologic description. Dermatologists are instrumental in classifying this hyperinflammatory syndrome, particularly in delineating differences between the novel MIS-C associated with COVID-19 and other well-known entities such as KD, should they exist.

Epidemiology of MIS-C

Individuals below the age of 18 years account for less than 8% of all COVID-19 infections in the United States[9]; however, case numbers have been rising in recent months.[10] MIS-C appears to be a rare complication of COVD-19 in children, with one study reporting 2 per 100,000 COVID-19 cases.[7] According to CDC data from the 570 reported MIS-C cases, median age at presentation was 8 years (range, 2 weeks to 20 years).[5] Approximately half (55.4%) were boys. Race or ethnicity was documented in 81% of cases. Of these, 40.5% were Hispanic, 33.1% were black, 13.2% were white, and 2.8% were Asian. Underlying medical conditions existed in one-third of patients and included obesity (25.6%) and chronic lung disease (8.4%). Two large studies of 186 cases 6 and 99 cases 7 describe similar epidemiologic characteristics. Notably, however, there is likely significant patient overlap between these studies and the CDC-reported data.

In the United Kingdom, 78 cases of pediatric inflammatory multisystem syndrome were reported being temporally associated with SARS-CoV-2 (PIMS-TS), which is very similar to MIS-C but with a slightly less restrictive case definition; particularly, patients may exhibit single organ system dysfunction and may or may not require hospitalization.[11] Their cohort had a somewhat higher male predominance (67%) and age of presentation (median, 11 years, interquartile range 8-14).[8] Regarding ethnicity, 47% of their patients were Afrocaribbean, 28% were Asian, 22% were white, and 3% were documented as other. Underlying comorbidities were present in 22% of patients. Of note, cases of MIS-C are less prevalent, even absent, in Asia with some nations with high COVID-19 rates reporting zero cases since the start of the pandemic.[12-14]

Dermatologic presentation

Skin lesions are present in anywhere from 0.2% to 20% of adults with COVID-19 infection[15,16] and are typically transient with highly variable morphology.[17] Morbilliform, urticarial, pseudochilblain, vesicular, papulosquamous, perniolike, livedoid, and necrotic lesions have all been described in large case series and systematic reviews.[16-19] Pediatric

patients with COVID-19 who do not have MIS-C have been described as having similar eruptions as adults, such as acral chilblain-like,[20,21] generalized papulovesicular, maculopapular, and morbilliform eruptions.[17] Cutaneous findings specific to MIS-C, however, are not as well outlined in the current literature.

We identified a total of 34 case series[3,6-8,22-40] and case reports[41-51] published between May and July 2020 that mention dermatologic findings in 736 unique children with MIS-C. Cutaneous manifestations were present in 417 of 736 patients (57%). Fifteen (44%) of these articles state "rash" as the sole descriptor of skin findings. Some smaller case series and case reports provide more detailed characterizations: Polymorphic, maculopapular, morbilliform, and diffuse erythroderma were the most common morphologies noted.[3,25,34,38-40,45,46,48,51] Skin lesions in single case reports were described as urticarial,[34] reticular,[47] petechial,[32] and purpuric.[46]

With regard to distribution, some rashes were generalized, whereas others were localized to the face, trunk, extremities, or acral regions. Palm and sole involvement including edema or erythema were present in some patients,[30,32,41,46,47] whereas others had desquamation of the extremities and/or digits.[24,30,42,51] Conjunctivitis and cheilitis were described in many patients. Erythema, edema, and/or induration of the extremities and/or hands and feet were also frequently reported.

The time to rash appearance in relation to fever and other clinical manifestation onset was not commonly included but ranged from day 2 to day 6 of illness,[40-42,48] and in one case the rash appeared 12 days after positive COVID-19 test result.[40] Symptomatology was infrequently documented, but varied with skin lesions described as nonpruritic in several cases[40,43,48] pruritic in one,[47] and painful in another.[50]

Specific dermatologic diagnoses other than KD were made in three cases of MIS-C associated with COVID-19. Target lesions consistent with erythema multiforme were described in two cases.[30,44] Schnapp et al reported a case of biopsy-proven leukocytoclastic vasculitis on the scalp of a 16-year-old male.[50] Deposition of C3 and IgA was observed in a vascular pattern on direct immunofluorescence. This was the only paper to include cutaneous histopathologic findings among the 34 articles.

Pathogenesis

The pathogenic mechanisms and etiology of MIS-C as it relates to COVID-19 infection are unknown. Some propose that it is due to a delayed, postviral immune dysregulation as opposed to a true viral response.[52] This is supported by the fact that many children do not display typical preceding clinical manifestations of COVID-19 infection before developing MIS-C.[53] Further, many patients test positive for anti-SARS-CoV-2 antibodies at the time of MIS-C diagnosis, but lack polymerase chain reaction (PCR) positivity for the virus.[32,53] Others speculate that MIS-C is a result of the known ability of SARS-CoV-2 to block type I and type III interferon responses, resulting in unrestrained viral proliferation and high viral load.[54]

Additionally, appropriate questions have been raised surrounding the lack of cases in Asia: Is this a result of mutational differences of SARS-CoV-2 in different geographic regions or are there genetic susceptibilities that predispose individuals to develop MIS-C? Further research is necessary to address these questions.

Comparison to Kawasaki disease

Commonalities exist between the clinical spectrum of MIS-C and the better-known KD. KD is a medium-vessel vasculitis that occurs in young children ≤5 years of age. Clinical features of KD include prolonged fever, rash, cervical lymphadenopathy, and mucosal changes (Table 1); however, other organ systems (cardiovascular, hepatic, respiratory, gastrointestinal, neurologic) may be involved.[52]

Like in KD, patients with MIS-C variably show a range of clinical features, including polymorphous exanthema, conjunctivitis, mucositis, and extremity changes.[6-8] Many patients with MIS-C meet criteria for complete or incomplete KD; however, gastrointestinal clinical manifestations (abdominal pain, vomiting, diarrhea) are more predominant and cardiovascular abnormalities (myocarditis, ventricular dysfunction, coronary artery aneurysms, hypotension) are reportedly more severe in MIS-C, even in patients who lack overlapping features of KD.[6,31,52] Mucosal involvement is also less consistently present in MIS-C than KD.[8]

Regarding laboratory evaluation, MIS-C patients show higher elevations in inflammatory markers (procalcitonin, ESR, CRP, ferritin) and relative cytopenias (leukocytopenia, thrombocytopenia), as well as elevated ventricular natriuretic peptide compared with those with KD.[31,54] Patients with MIS-C are significantly older with a broader age range than the patients who traditionally develop KD.[31] An apparent predilection for Hispanic and black populations exists in MIS-C,[6,7,31] whereas Asians typically have the highest rates of KD.[54] This may be a reflection of the generally higher COVID-19 infection rates in these populations in the United States[55]; however, reports of MIS-C are nearly absent in Asia.[12,14]

Although significant overlap exists among these syndromes, many of their shared features are nonspecific findings observed in numerous infectious disease processes in children.[54] Their differing epidemiologic trends and laboratory features, as well as the inconsistent overlap of their clinical signs altogether suggest that these are perhaps related but distinct phenomena. A small subset (≤5%) of patients with KD may progress to develop "KD shock syndrome," which more closely resembles MIS-C in terms of laboratory findings and disease severity.[52]

Conclusions

Although rare, MIS-C is a novel syndrome in pediatric patients that is increasingly recognized. Skin manifestations are present in the majority of those affected but are not well documented in the literature. More detailed descriptions of cutaneous findings by dermatologists are warranted to further characterize this syndrome, as they may yield important morphologic clues. Skin biopsies are generally not performed in children with MIS-C but could serve to better guide future understanding of pathophysiologic mechanisms of disease.

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