Open Forum Infectious Diseases

BRIEF REPORT

Cutaneous Findings in SARS-CoV-2-Associated Multisystem Inflammatory Disease in Children

Allison M. Blatz,[1] Michelle Oboite,[2,4] Kathleen Chiotos,[1,3,4] Leslie Castelo-Soccio,[2,4] and Audrey R. Odom John[1,4]; for the Children's Hospital of Philadelphia MIS-C Research Collaborative

[1]Division of Infectious Diseases, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, [2]Dermatology Section, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, [3]Division of Critical Care Medicine, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, and [4]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Rash is a common feature of multisystem inflammatory syndrome in children (MIS-C), a postinfectious hyperinflammatory disease associated with prior severe acute respiratory syndrome coronavirus 2 infection. Because the differential diagnosis of fever and rash in children is broad, understanding clinical characteristics of MIS-C may assist with diagnosis. Here we describe the cutaneous findings observed in a series of children with MIS-C-associated rash.

Keywords. MIS-C; pediatric infectious diseases; rash; SARS-CoV-2.

In April 2020, a hyperinflammatory condition apparently associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was recognized in children. This syndrome, now termed multisystem inflammatory syndrome in children (MIS-C) [1], is characterized by fever, profound systemic inflammation, multi-organ involvement, and often rash [2, 3]. Here, we describe the dermatologic manifestations of MIS-C at a single institution.

METHODS

All children admitted to our tertiary care, academic, pediatric medical center with concern for MIS-C per Centers for Disease Control and Prevention criteria are routinely evaluated by an expert multidisciplinary committee to reach diagnostic consensus [4]. Skin findings were photographed and included in the secure electronic health record. Clinical characteristics were abstracted through chart review. As of July 28, 2020, a total of 24 children were diagnosed with MIS-C, of whom 18 (75%) exhibited mucocutaneous changes, and photographs had been obtained during the course of clinical care for 10 (41.7%). Consent was obtained for 7 patients. Clinical and laboratory findings of patients 1, 2, and 4 have been previously reported [5].

Patient Consent

The design of this work was reviewed by the Institutional Review Board of the Children's Hospital of Philadelphia, which deemed this exempt research. Verbal informed consent for photograph use was obtained from the parents or legal guardians of all children whose images are included in this study.

RESULTS

Patients with MIS-C exhibited a variety of cutaneous clinical findings (Figure 1, Table 1). Palmar and plantar erythema were observed in 3/7 (43%) patients; no patient exhibited plantar erythema in the absence of palmar erythema. While discrete lesions were noted in all body locations, lesions on the chest and upper extremities were common (4/7, 57%) (Figure 1A-D), and the lower extremities were uniformly involved (7/7 of patients) (Figure IE-H). In particular, 5/7 patients (71%) had lesions of the proximal medial thigh. Two patients exhibited rash on or around the ears (2/7, 29%) and neck (Figure 1I, J). Although mucosal changes were common (6/7, 86%), including lip changes, the remaining face was less frequently involved: 1 patient each had lesions on the forehead/hairline (Figure 1I) and cheek (not shown).

A variety of erythematous lesions were observed, classified as urticarial, morbilliform, and livedoid. These skin changes were observed in patients with diverse skin tones and pigmentation. The most common lesions observed were small-to-medium annular plaques (taking on an urticarial appearance) in 57% (4/7) of patients, although morbilliform eruptions with coalescing papules to plaques (Figure 1K) and coalescing macules were also noted, each in 1 patient. Reticulated plaques and patches (taking on a livedoid appearance) were noted in 2 patients (29%) (Figure 1L, M, N). Twenty-nine percent (2 of 7) of children described the rash as mildly pruritic. In 1 patient, rash did not occur until the fourth hospital day, following recrudescent fever after intravenous immune globulin (IVIG) and steroids; the rash resolved with an additional dose of IVIG. Purpura were seen in 4 (57%) of 7 patients. Most commonly (3 of 4), purpura were noted in the center of annular (urticarial) plaques, mimicking the appearance of erythema multiforme–like lesions. All skin findings completely resolved by the time of hospital discharge. In contrast to rashes associated with Kawasaki disease, none of the rashes desquamated.

Received 28 October 2020; editorial decision 8 February 2021; accepted 9 February 2021.

Correspondence: Audrey R. Odom John, MD, PhD, 907C ARC, Children's Hospital of Philadelphia, 3615 Civic Center Blvd., Philadelphia, PA 19104-4318 (johna3@email.chop.edu).

Open Forum Infectious Diseases®2021

DOI: 10.1093/ofid/ofab074

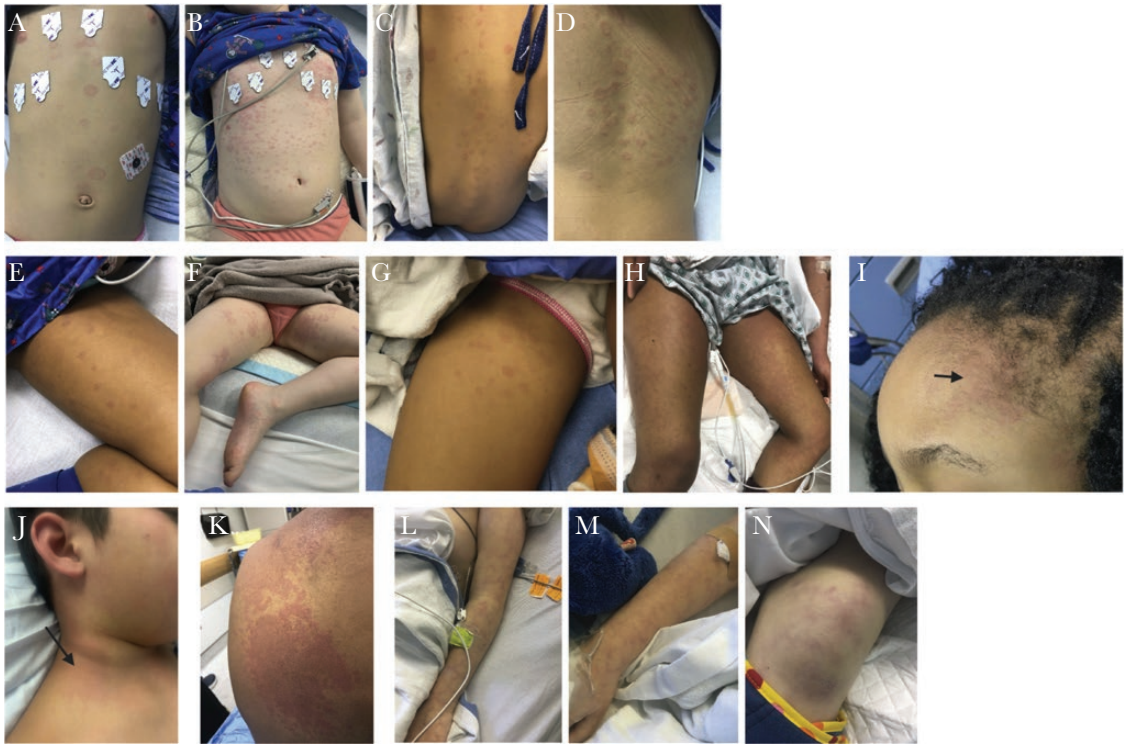

Figure 1. Characteristic cutaneous findings in pediatric multisystem inflammatory syndrome in children. Arrows indicate regions of erythema.

Table 1. Clinical and Dermatological Characteristics of Patients With MIS-C

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Figure 1 panel	A, C, D, G, I	B, F	E	H	J	K	L, M, N
Age, y, sex	8 F	5 F	8 F	14 F	11 M	10 M	7 F
BMI, kg/m^2/ comorbidities	15.26/asthma	16.0/none	23.8/none	18.8/none	ND/autism	35.9/none	26.2/none
Presenting symptoms							
Fever	+	+	+	+	+	+	+
Diarrhea	-	+	+	+	+	+	+
Abdominal pain/emesis	+	+	+	-	+	+	+
Rash	+	+	+	+	+	+	-
Conjunctivitis	+	-	+	-	+	+	+
Fissured lips/ strawberry tongue	-	+	+	-	+	+	+
Lymphade- nopathy	-	-	-	-	-	-	-
Extremity edema	-	+	-	-	-	+	+
Headache	-	-	+	+	-	-	+
Altered mental status/ irritability	-	-	-	-	-	-	-
Respiratory failure	-	+	+	+	-	-	+
Shock	+	+	+	+	-	+	+
Key initial findings							

Table 1. Continued

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
C-reactive protein, mg/dL	18.9	16.8	8.7	34.3	5.7	23.5	35.3
Procalcitonin, ng/mL	ND	69.97	22.82	15.29	ND	14.18	27.15
Ferritin, ng/mL	806.8	512.6	644	1096	857.3	377.4	3559.5
Platelets, 10^3/mL	251	98	232	150	96	155	94
Brain type natriuretic peptide, pg/mL	77	606	72.6	ND	16.2	722.6	291
Absolute lymphocyte count, cells/μL	1080	910	1310	170	240	1030	400
Troponin, ng/mL	0.03	0.3	0.19	ND	0.01	0.65	0.04
SARS-CoV-2 testing							
Nasopharyngeal SARS-CoV-2 PCR (cycle threshold if +)	Negative	Positive (40.21)	Negative	Negative	Positive (40.08)	Negative	Positive (35.17)
Anti-SARS-CoV-2 IgG	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Outcome	Home	Home	Home	Home	Home	Home	Home
Key dermatological findings							
Rash details							
Fitzpatrick phototypes (I–VI)	IV	II	V	V	III	V	II
Morphology	Annular plaques	Annular plaques	Annular plaques	Macules and patches	Macules and patches	Papules and plaques (some annular, some reticulated)	Reticulated patches
Affected body parts	Neck, trunk (back, chest), lower extremities (inner thighs) including skin folds (axilla, inguinal crease)	Trunk (chest and abdomen), lower extremities (inner thighs) including skin folds (popliteal fossa), feet	Lower extremities (inner thighs) including skin folds (inguinal crease), palms	Upper and lower extremities (inner/anterior thighs, knees) including skin folds (popliteal fossa), palms and soles	Trunk (back), upper and lower extremities (inner thighs)	Neck and trunk (back), upper and lower extremities	Upper extremities (shoulder and hand), lower extremities (knees)
Purpura	-	+	+	+	-	+	-
Classification	Urticarial	Urticarial	Urticarial	Morbilliform	Morbilliform	Urticarial	Livedoid
Mucosal involvement (erythema of the lips, tongue, and/or ocular conjunctivitis)	+	+	+	-	+	+	+
Acral erythema	-	+	+	+	-	-	-

Abbreviations: BMI, body mass index; IgG, immunoglobulin G; MIS-C, multisystem inflammatory syndrome in children; ND, not done; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

DISCUSSION

MIS-C, thought to be a postinfectious complication of SARS-CoV-2 infection, remains largely a diagnosis of exclusion, as its clinical manifestations, including fever, gastrointestinal distress, and rash, are common to many other pediatric infections. Acute coronavirus disease 2019 has presented with a myriad of cutaneous findings in children, including erythema multiforme, urticaria, vesicular exanthem, polymorphic rash, purpura, and pityriasis rosea–like eruption [6]. The pathophysiology of SARS-CoV-2-associated

rashes is poorly understood and may overlap with that of MIS-C-associated mucocutaneous changes.

We find that no unique, stereotypic rash was observed in patients who were treated for MIS-C, although annular plaques in the proximal medial lower extremities were common, a finding that warrants further study in larger cohorts. We note overlap between cutaneous findings of MIS-C and those observed in rickettsial illness (palmar/plantar involvement), toxic shock syndrome (diffuse rash and some erythroderma), Kawasaki disease (diffuse rash, mucocutaneous changes, extremity changes), and viral exanthems, which continue to pose a significant diagnostic dilemma.

Limitations include a small sample size, due in part to the rarity of MIS-C and challenges imposed by isolation precautions, as well as the imprecision of MIS-C diagnostic criteria.

CONCLUSIONS

Cutaneous manifestations are common in MIS-C, although the underlying pathophysiology is not well understood. We anticipate that these images and descriptions will aid clinicians in the diagnosis of future cases.

Acknowledgments

We thank the Children's Hospital of Philadelphia MIS-C Research Collaborative for its contribution to the work described, especially Hamid Bassiri, Edward M. Behrens, Caroline Diorio, Julie C. Fitzgerald, Therese Giglia, Michele Lambert, Whitney Petrosa, David T. Teachey, Laura A. Vella, and Char Witmer. A.B. is supported by National Institutes of Health (NIH) T32-GM075766. K.C. is supported by AHRQ K12-HS026393. L.S.C. is supported by the Dermatology Foundation. A.O.J. is supported by NIH/National Institute of Allergy and Infectious Diseases R01-AI103280, R21-AI123808, and R21-AI130584, and A.O.J. is an Investigator in the Pathogenesis of Infectious Diseases (PATH) of the Burroughs Wellcome Fund.

Potential conflicts of interest. None of the authors (A.M.B., M.O., K.C., L.C.S., or A.O.J.) report an association that may pose a conflict of interest with the current study. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. **In press**.
2. 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.
3. 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**; 395:1771–8.
4. Centers for Disease Control and Prevention. 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 30 July 2020.
5. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. J Pediatric Infect Dis Soc. **In press**.
6. Andina D, Belloni-Fortina A, Bodemer C, et al. Skin manifestations of COVID-19 in children: part 2. Clin Exp Dermatol. **In press**.