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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Mucocutaneous disease and related clinical characteristics in hospitalized children and adolescents with COVID-19 and multisystem inflammatory syndrome in children

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Background: Little is known about mucocutaneous disease in acutely ill children and adolescents with COVID-19 and multisystem inflammatory syndrome in children (MIS-C).

Objective: To characterize mucocutaneous disease and its relation to clinical course among hospitalized patients with COVID-19 and MIS-C.

Methods: Descriptive cohort study of prospectively and consecutively hospitalized eligible patients between May 11, 2020 and June 5, 2020.

Results: In COVID-19 patients, 4 of 12 (33%) had rash and/or mucositis, including erythema, morbilliform pattern, and lip mucositis. In MIS-C patients, 9 of 19 (47%) had rash and/or mucositis, including erythema, morbilliform, retiform purpura, targetoid and urticarial patterns, along with acral edema, lip mucositis, tongue papillitis, and conjunctivitis. COVID-19 patients with rash had less frequent respiratory symptoms, pediatric intensive care unit admission, invasive ventilation, and shorter stay versus COVID-19 patients without rash. MIS-C patients with rash had less frequent pediatric intensive care unit admission, shock, ventilation, as well as lower levels of C-reactive protein, ferritin, D-dimer, and troponin (vs MIS-C without rash). Neutrophil-to-lymphocyte ratio was similar for patients with and without rash in both groups. None of the MIS-C patients met criteria for Kawasaki disease.

Limitations: Small sample sizes.

Conclusions: Mucocutaneous disease is common among children and adolescents with COVID-19 and MIS-C. Laboratory trends observed in patients with rash may prognosticate a less severe course. (J Am Acad Dermatol 2021;84:408-14.)

Key words: COVID-19; Kawasaki; MIS-C; multisystem inflammatory syndrome in children; pediatrics; prevalence; rash; SARS-CoV-2.

INTRODUCTION

COVID-19 has variability within its constellation of findings among children and adolescents.[1-5] In addition to fever and respiratory symptoms, pediatric patients infected with SARS-CoV-2, the pathogen in COVID-19, also get eruptions and mucositis. Yet,

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little is understood about the morphologic spectrum of mucocutaneous disease and its relation to outcomes among acutely ill children and adolescents with COVID-19, or its presumed sequela, multisystem inflammatory syndrome in children (MIS-C). The New York metropolitan area was an epicenter for the pandemic in the United States,[6] which provided an opportunity to characterize mucocutaneous disease in pediatric hospitalized patients with COVID-19 and MIS-C. The purpose of this study was to estimate prevalence of integumentary findings in hospitalized patients with COVID-19 and MIS-C, characterize their morphologic patterns, evaluate whether rash prognosticates clinical course, and determine how closely features in MIS-C align with Kawasaki disease (KD).

CAPSULE SUMMARY

- Little is known about the morphologic spectrum of mucocutaneous disease and its relation to clinical course in acutely ill children with COVID-19 or multisystem inflammatory syndrome in children (MIS-C).
- This study highlights novel mucocutaneous observations associated with SARS-CoV-2 infection, which may support recognition of infection and its potential relevance to prognosis and the development of diagnostic criteria for MIS-C.

METHODS

This study was performed at Cohen Children's Hospital (Northwell Health), a tertiary hospital located in Queens, New York. The study sample consisted of all hospitalized patients between May 11, 2020 and June 5, 2020 who were 18 years and younger and who were suspected of having COVID-19 or MIS-C. Criteria for confirming the diagnosis of MIS-C included age less than 21 years, fever for 24 hours or more, clinically severe illness requiring hospitalization, multisystem organ involvement, no alternative plausible diagnosis, and exposure to a suspected or confirmed COVID-19 case or positive SARS-CoV-2 infection by polymerase chain reaction (PCR)/serology testing.[7] The sample was limited to patients who had (1) diagnosis of MIS-C based on all 6 criteria above, and this group comprised the MIS-C cohort or (2) positive COVID-19 PCR test among those not meeting the definition of MIS-C, and this group comprised the COVID-19 cohort.

Consecutive prospective skin examinations were performed for eligible patients, and photographs of mucocutaneous findings were taken as part of their care. Morphologic patterns and locations of rash were assessed based on photographs collected during clinical evaluation and were independently classified by two raters. Differing classifications were adjudicated via discussion. For each patient, raters also determined whether each mucocutaneous finding was pre-existing or likely to be unrelated to SARS-CoV-2 infection. Examples included observations of atopic eczema, furunculosis, and scar. All patients who had mucocutaneous manifestations without an otherwise known etiology were considered to have a COVID-19-related rash.

For their description, patients with COVID-19 and MIS-C were further stratified according to presence of at least one COVID-19—related rash. We categorized COVID-19 and MIS-C patients separately because these diseases have different clinical characteristics and disease courses and because MIS-C is considered to be a later, noninfectious complication of COVID-19.

DATA ANALYSIS

Given the anticipated sample size, and consequently low statistical power, the intent of our analysis was descriptive and hypothesis generating. Medians (interquartile range [IQR]) were used to describe continuous variables, and frequencies (percentages) were used to describe categorical variables. This study was approved by the institutional review board at the Feinstein Institutes of Medical Research at Northwell Health.

RESULTS

Of 39 hospitalized pediatric patients identified as possible COVID-19 or MIS-C cases during the study period, 31 were eligible for inclusion. Six patients did not test positive for SARS-CoV-2 by PCR and were also ruled out for MIS-C prior to discharge. Others excluded were 1 child whose family deferred skin examination and 1 newborn having limb necrosis with negative SARS-CoV-2 PCR and IgM antibody who was felt to have fetal compartment syndrome. Demographic characteristics for 12 patients classified as COVID-19 and 19 patients classified as MIS-C are listed in Table I.

COVID-19 cohort

In patients with COVID-19, 4 of 12 (33%) had rash and/or mucositis (Supplemental Fig 1; available at: https://data.mendeley.com/datasets/wrzffv27cx/1). Those with rash were younger (Table I). Only 3 of 12 (25%) were febrile (≥100.4°F) during hospitalization.

Abbreviations used:

IQR: interquartile range
KD: Kawasaki disease
MIS-C: multisystem inflammatory syndrome in children
PCR: polymerase chain reaction

Type and frequencies of morphologic patterns observed in patients with COVID-19 are described in Table I. None of the hospitalized COVID-19 patients with rash had pernio-like lesions of the toes or fingers, and none had conjunctivitis. Locations and frequencies of mucocutaneous eruptions in patients with COVID-19 are described in Fig 1.

Compared with COVID-19 patients without rash, those with rash were observed to have less frequent respiratory symptoms, admission to the pediatric intensive care unit, ventilation, and shorter length of hospital stay. Maximum neutrophil-to-lymphocyte ratio (NLR) observed during hospitalization was similar for patients with and without rash (Table I).

MIS-C COHORT

In patients with MIS-C, 9 of 19 (47%) had rash and/or mucositis. (Fig 2; Supplemental Fig 2; available at: https://data.mendeley.com/datasets/wrzffv27cx/1). All 19 patients (100%) were febrile during hospitalization.

Morphologic patterns were heterogeneous (Table I). Lip fissuring or cracking was present in 44% (4 of 9), whereas papillitis of the tongue was present in 22% (2 of 9). Conjunctivitis was present in 22% (2 of 9) of patients with rash. Locations and frequencies of mucocutaneous eruptions in patients with MIS-C are described in Fig 1.

Compared with MIS-C patients without rash, those with rash were observed to have less frequent pediatric intensive care unit admission, shock, and requirement for invasive mechanical ventilation. Patients with rash also had lower levels of inflammatory markers. Maximum NLR observed during hospitalization was similar for patients with and without rash (Table II).

Among the 19 patients with MIS-C, none met 2017 American Heart Association criteria for KD.[8] With requirement for fever of at least 5 consecutive days in the stem, only 1 (5.3%) patient met at least 3 of 5 criteria and only the same patient (1/19; 5.3%) met at least 2 of 5 criteria. With inclusion of coronary aneurysm as an additional sub-criterion, still none met at least 4 of 6 criteria for KD diagnosis. In this expanded construct, 1 (5.3%) patient met at least 3 of 6 criteria and only 2 (10.5%) patients met at least 2 of 6 criteria. Among the 19 MIS-C patients, 5 (26.3%) had fever for 5 or more days, 2 (10.5%) had cervical lymphadenopathy, 2 (10.5%) had edema or erythema of hands or feet, and 2 (10.5%) had a morbilliform or erythema-multiforme–like eruption.

DISCUSSION

Although presence of rash in MIS-C patients has been reported,[9-11] morphologic characterization of mucocutaneous eruptions in hospitalized pediatric patients with COVID-19 and MIS-C is otherwise absent to date. In this analysis, we estimated prevalence of rash and/or mucositis among hospitalized pediatric patients with COVID-19 and MIS-C. We have characterized morphologic features and distributions of these eruptions, and we distinguished subtypes that occurred only in MIS-C patients. We observed that presence of rash appears to predict a less-severe clinical course. Finally, we observed that MIS-C and KD might be more dissimilar than presently postulated.

Although disease-defining integumentary patterns did not emerge in either group, some patterns of mucocutaneous disease appeared to have distinguished MIS-C from COVID-19. Retiform purpura, targetoid, urticarial, acral edema or erythema, papillitis of the tongue, and conjunctivitis were observed only among MIS-C patients. The observation of unilateral retiform purpura of the arm in a patient suggests potential for endothelial cell involvement or injury of cutaneous vessels by the virus or the presence of coagulopathy induced by the infection. Vessel involvement through endothelial cell infection of the kidney and lung in adults has been seen,[12,13] and this phenomenon warrants further study in children.

Presence of nonspecific erythema, morbilliform eruption, or lip mucositis did not distinguish COVID-19 and MIS-C. Pernio-like patches and plaques on the fingers or toes were not observed in either group, which reinforces the suggestion that patients with this presentation tend to have mild disease course.[14]

Almost all hospitalized COVID-19 patients with rash had involvement of at least the face. Rash among MIS-C patients was most often peripherally distributed. Although lips were frequently involved in MIS-C patients, tongue and eye involvement were less frequent. Continued localization of mucocutaneous disease in COVID-19 and MIS-C may identify distinct patterns that differentiate the 2 conditions.

Several clinical and laboratory indicators suggested that pediatric patients with COVID-19 and

Table I. Demographics and characteristics of mucocutaneous disease

Characteristic	COVID-19 with mucocutaneous disease n = 4	COVID-19 without mucocutaneous disease n = 8	MIS-C with mucocutaneous disease n = 9	MIS-C without mucocutaneous disease n = 10
Age	5 (1.75, 10)	10 (7.25, 16)	8 (7, 10)	10.5 (10, 13)
Male sex (%)	1 (25)	5 (63)	7 (78)	6 (60)
Race*		n = 7	n = 8	n = 8
African American	0 (0)	1 (14)	4 (50)	1 (13)
Asian	0 (0)	1 (14)	1 (13)	1 (13)
White	0 (0)	0 (0)	1 (13)	1 (13)
Other/multiracial	4 (100)	5 (71)	2 (25)	5 (63)
Cutaneous morphologic patterns				
Nonspecific erythema	3 (75)	—	3 (33)	—
Morbilliform	1 (25)	—	1 (11)	—
Retiform purpura	0 (0)	—	1 (11)	—
Targetoid	0 (0)	—	1 (11)	—
Urticarial	0 (0)	—	1 (11)	—
Edema (acral)	0 (0)	—	1 (11)	—
Pernio-like lesions	0 (0)	—	0 (0)	—
Mucositis				
Lip cracking or fissuring	1 (25)	—	4 (44)	—
Papillitis of tongue	0 (0)	—	2 (22)	—
Conjunctivitis	0 (0)	—	2 (22)	—

Note. Percentages may not sum to 100 due to rounding. Continuous variables are presented as median (IQR). Categorical variables are presented as frequency (percent).
*Self-reported race.

MIS-C with rash may have less severe disease course. MIS-C patients with rash may have a modified and/or muted cytokine response, which preferentially involves the integument and which may result in a less severe course. Whether presence of rash in COVID-19 and MIS-C can predict prognosis in children and adolescents and the basis for preferential involvement of skin warrants further study.

The NLRs were similar between COVID-19 patients with and without rash and between MIS-C patients with and without rash. We did observe, however, higher NLR in MIS-C patients compared with COVID-19 patients, and this may prove to be a useful differentiating marker. In adults, NLR has been observed to distinguish mild from severe cases of COVID-19.[15-17]

There are shared features between MIS-C and KD, including presence of mucocutaneous disease, although the distinction between MIS-C and KD remains uncertain.[18] None of the MIS-C in our sample met criteria for KD, and few met partial criteria, even when criteria were expanded to include coronary aneurysm. Only 5 patients met criterion for fever of greater than 5 consecutive days, and few had lymphadenopathy or edema/erythema of hands or feet. Although there may exist some overlapping features between MIS-C and KD, our observations suggest that MIS-C may warrant development of distinct criteria, which should include broadening the morphologic patterns of mucocutaneous disease observed.

Here we provided detailed morphologic characterization of mucocutaneous findings in prospectively and consecutively examined patients with confirmed diagnoses of COVID-19 and MIS-C. Limitations to this study include the fact that most pediatric patients with COVID-19 have a course that does not require hospitalization, and there were fewer hospitalized cases of MIS-C in mid May and June of 2020 in the New York metropolitan area. As such, we had inadequate power to perform hypothesis tests, and we cannot rule out that differences observed between groups were due to chance. However, the finding of less-severe course was observed across several indicators among both COVID-19 and MIS-C patients with rash. Pathology was not obtained, as there was no clear indication this could specify diagnoses or change the courses of care.

Mucocutaneous disease is common among children and adolescents with COVID-19 and MIS-C. Trends observed in pediatric patients with rash may

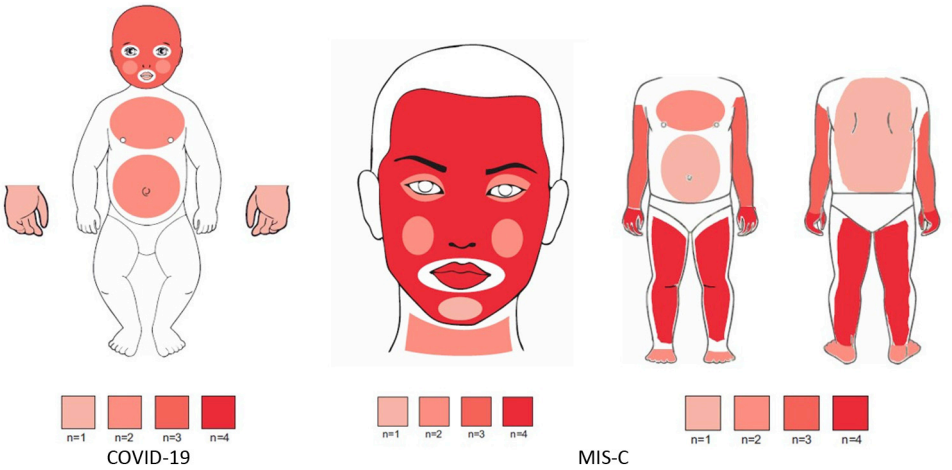

Fig 1. Frequencies of children with mucocutaneous disease in COVID-19 and MIS-C by area of involvement.

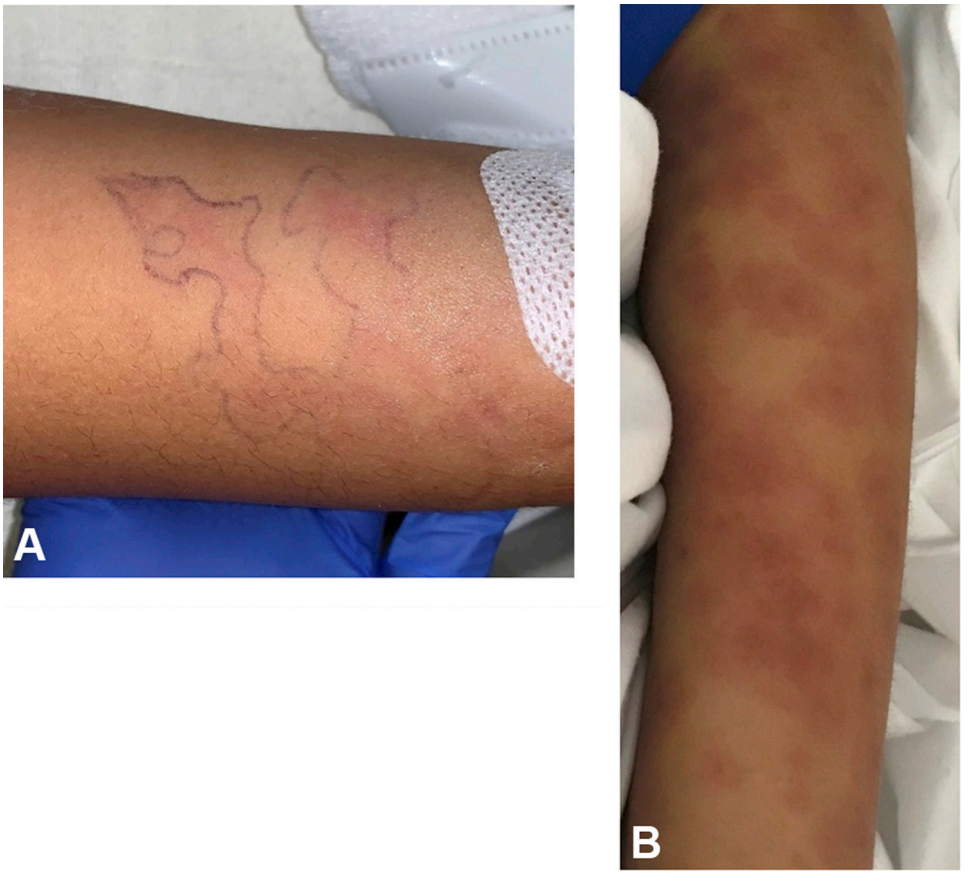

Fig 2. **A** and **B**, Mucocutaneous disease in children and adolescents with MISC-C. **A**, Retiform purpura, arm. **B**, Targetoid erythema, arm.

suggest a less-severe clinical course, although confirmatory studies are required to assess the generalizability of these observations. This study highlights several novel observations in hospitalized children and adolescents with COVID-19 and MIS-C, many of which will support the research agenda to further characterize mucocutaneous disease associated with SARS-CoV-2, to recognize its potential relevance in prognosticating disease courses, and to develop diagnosis criteria for MIS-C.

Table II. Clinical characteristics of patients with and without mucocutaneous disease

	COVID-19 with mucocutaneous disease n = 4	COVID-19 without mucocutaneous disease n = 8	MIS-C with mucocutaneous disease n = 9	MIS-C without mucocutaneous disease n = 10
Fever, peak	99.8 (99.4, 100.6)	99.8 (99.6, 100.3)	103.1 (102.9, 103.6)	103.4 (103.1, 104.8)
Fever ≥5 consecutive days	0 (0)	0 (0)	3 (33)	2 (20)
Laterocervical lymphadenopathy	0 (0)	0 (0)	1 (11)	1 (10)
Respiratory symptoms	0 (0)	3 (38)	5 (56)	6 (60)
Gastrointestinal symptoms	3 (75)	4 (50)	9 (100)	10 (100)
Shock	0 (0)	1 (13)	3 (33)	8 (80)
Coronary aneurysm or pericardial effusion	0 (0)	1 (13)	4 (44)	6 (60)
Myocardial infarction	0 (0)	0 (0)	0 (0)	0 (0)
Venous thrombosis or thromboembolism	0 (0)	0 (0)	0 (0)	0 (0)
Arterial thrombosis	0 (0)	1 (13)	0 (0)	0 (0)
Treatment with intravenous immunoglobulin	0 (0)	0 (0)	9 (100)	10 (100)
Treatment with aspirin	0 (0)	1 (13)	9 (100)	9 (90)
Admission to pediatric intensive care unit	0 (0)	3 (38)	3 (33)	9 (90)
Ventilation	0 (0)	1 (13)	1 (13)	4 (40)
Hospital length of stay,* days	2.5 (2, 6)	5 (1.5, 17)	7 (5, 9)	7 (5, 10)
Lymphocyte count, minimum†	1.23 (0.34, 4.70)‡	1.50 (0.97, 2.17)	0.61 (0.48, 0.93)	0.58 (0.44, 0.87)
Neutrophil count, maximum	4.20 (0.31, 8.02)‡	7.62 (3.39, 11.57)	17.00 (10.26, 19.37)	18.85 (14.31, 24.22)
Neutrophil/lymphocyte ratio, maximum¶	0.84 (0.58, 6.52)‡	3.51 (1.76, 8.69)	15.01 (8.62, 17.18)	13.21 (8.66, 23.04)
C-reactive protein, maximum, mg/dL	1.4 (1.2, 3.9)‡	1.6 (0.8, 2.2)§	15.2 (15, 17)	26.3 (19.1, 28.2)
Ferritin, maximum, ng/mL (normal, 30-400)	731 (93, 3024)	200 (144, 369)§	578 (370, 1091)	1457 (808, 2214)
Lactate dehydrogenase, maximum, U/L (normal, 50-242)	263 (197, 465)	257 (202, 650)‡	346 (233, 533)	322 (260, 415)
Albumin, minimum, g/dL (normal, 3.5-5.0)	3.7 (3.5, 3.8)	3.5 (3.3, 4.1)	2.6 (2.1, 2.8)	2.1 (1.8, 2.7)
Procalcitonin, maximum, ng/mL (normal, 0.02-0.10)	0.22 (0.17, 0.53)‡	0.13 (0.08, 0.24)‡	6.24 (2.00, 14.44)	9.4 (3.4, 29.0)
D-Dimer, maximum, ng/mL (normal, ≤229)	570 (439, 952)	300 (263, 904)	1492 (1287, 2681)	4147 (2538, 5011)
Fibrinogen, maximum, mg/dL (normal, 300-520)	525 (486, 577)	510 (506, 535)	718 (698, 884)	802 (713, 908)
Troponin, maximum, ng/L (normal, <6-14)	5 (5, 15)‡	8 (5, 11)§	18 (8, 38)	70 (17, 114)
proBNP, maximum, pg/mL (normal, <300)	172 (21, 326)	545 (10, 909)‡	3946 (3351, 6455)	5065 (2754, 10980)
SarsCOV2 + PCR, %	4 (100)	8 (100)	3 (33)	2 (20)
SarsCOV2 + IgM/IgG, %	2 (50)	2 (25)	7 (78)	10 (100)

proBNP, N-terminal pro b-type natriuretic peptide.

*Median length of stay (25th percentile, 75th percentile) calculated using the Kaplan-Meier survival estimate to account for patients who were not discharged as of the date of chart abstraction.

†Maximum and minimum refer to each patient's maximum or minimum value during hospitalization. The summary measure represents the median across all of the individual patient maximums/minimums. Continuous variables are presented as median (IQR). Categorical variables are presented as frequency (percent).

‡Based on 3 non-missing values. Raw data values are reported, rather than median and IQR.

§Based on 4 non-missing values.

¶Ratio was calculated by dividing the neutrophil count by the lymphocyte count from the same test result. The maximum ratio during hospitalization for each patient was then selected and summarized by group using the median and IQR.

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