

Mucocutaneous Findings of Multisystem Inflammatory Syndrome in Children: A Single-Center Experience

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ABSTRACT

This descriptive study aimed to evaluate the frequency and the types of mucocutaneous manifestations associated with multisystem inflammatory syndrome in children (MIS-C). A cohort of 49 patients was reviewed. There were 6 patients (12.2%) whose mucocutaneous findings were observed by the clinicians on admission, whereas 26 (53%) patients had at least one of the histories of rash or desquamation associated with fever before the admission. Exanthems in our experience demonstrated a variety of morphologies, including morbilliform, urticarial, petechial, and maculopapular forms. Mucosal involvement (conjunctivitis and strawberry tongue) was observed only in 2/6 (34%) patients. In the coronavirus disease 2019 pandemic era, while evaluating the criteria for MIS-C, the history of previous cutaneous findings given by parents/caregivers is also important. There was no pathognomonic rash for MIS-C and a variety of cutaneous findings with a short lifespan can be associated with MIS-C.

KEYWORDS: children, COVID-19, multisystem inflammatory syndrome in children, SARS-CoV-2, skin rashes

INTRODUCTION

The pediatric severe and life-threatening forms of coronavirus disease 2019 (COVID-19) infections are reported to be rare in children comparing the adults. However, after the onset of the COVID-19 pandemic a severe and fatal novel clinical entity was defined in children. In May 2020, several European countries following the UK reported pediatric cases

with a hyperinflammatory course that was similar to atypical Kawasaki's disease, Kawasaki's disease shock syndrome, and toxic shock syndrome, considered to be related to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection [1–5]. Later than, the Centers for Disease Control and Prevention (CDC) [6] and World Health Organization (WHO) [7] described this post-

infectious inflammatory response of the immune system as Multisystem Inflammatory Syndrome in Children (MIS-C) and released their diagnostic criteria. A holistic approach to the diagnosis of MIS-C included fever, elevated inflammatory markers, the involvement of two or more organs, mucocutaneous findings, and either a positive test or exposure within 4 weeks of clinical manifestations. Although the etiology and immunological background have not been elucidated yet, it is considered to be similar to acute rheumatic fever, which is a post-infectious systemic inflammatory syndrome that occurs as an immunological response to a superantigen, and toxic shock syndrome which is a systemic inflammatory syndrome with shock [8].

Cutaneous manifestations have been reported in a significant proportion of patients besides the gastrointestinal, cardiac, hematologic and respiratory findings [9]. However, there is not a specific well-defined characteristic of the skin lesions or rashes due to the variability of the patterns. This descriptive study was aimed to evaluate the frequency and the types of cutaneous manifestations associated with MIS-C.

MATERIALS AND METHODS

This descriptive study was conducted during the period between 1 June 2020, and 1 February 2021, at Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital. The hospital is a referral center for pediatric patients in the Aegean Region of Turkey with an annual ~600 000 outpatients and 24 000 hospitalizations. A cohort of 49 patients under 18 years old and diagnosed as MIS-C according to CDC and/or WHO criteria was included in the study. In addition to the presence of persistent fever, increased inflammatory biomarkers, findings of multi-organ involvement, and exclusion of any other diagnosis, epidemiological linkage to COVID-19 infection were the criteria of definite diagnosis. All patients required proof of SARS-CoV-2 exposure via nasopharyngeal real-time reverse-transcription polymerase chain reaction (RT-PCR) analysis and/or SARS-CoV-2 antibody test. The exclusion of other diagnoses was performed using several microbiological and molecular diagnostic tests including multiplex PCR tests for common respiratory pathogens, rapid antigen tests for influenza,

serological tests for Epstein–Barr virus (EBV), conventional culture tests including blood culture and throat culture in addition to peripheral smears, ultrasonography etc.

Demographic data, symptoms and medical history of the patients, characteristic features of rashes were collected via the electronic medical record system and patient files.

Statistical analysis was performed using SPSS Statistical Software (version 22; SPSS, Chicago, IL, USA). Continuous variables were presented as means \pm SD and categorical variables as frequencies and percentages.

Ethics approval for this study was obtained from the Institutional Review Board of Dr. Behçet Uz Children's Training and Research Hospital.

RESULTS

Of the 49 patients, there were 6 patients (12.2%) whose mucocutaneous findings were observed by the clinicians on admission, while 26 (53%) patients had at least one of the histories of rash or desquamation associated with fever before the admission. Of six patients, five (84%) were male. The mean age of the patients was 9.5 ± 3.2 years (range 5–13 years). The SARS-CoV-2 RT-PCR was negative and the serology was positive in all patients. Additional tests (multiplex PCR, EBV serology, throat culture and blood culture) for differential diagnosis were needed in all patients. The mean duration of fever was 5.2 ± 2.3 days (range 3–9 days) The mean duration of rash was 3.5 ± 2.1 days (range 1–6 days). None of the patients had a chronic disease. Characteristics of the patients were summarized in Table 1.

Patient 1

A 12-year-old female presented following 4 days of fever, sore throat and nausea. Physical examination was remarkable for an urticarial rash on the trunk and upper limbs (Figs 1 and 2), and painful lymphadenopathy in the left cervical region. The fever persisted for 24 h, and at the 36th hour of admission, she developed respiratory distress. Chest X-ray revealed bilateral pleural effusion and right lower zone consolidation. She was admitted to the pediatric intensive care unit (PICU) for non-invasive respiratory support. Rashes resolved within 24 h.

Table 1. Characteristics of the patients

| Patient | Gender | Age (years) | Rash type, localization | Other symptoms and signs | Duration of fever | Duration of rash | Laboratory abnormalities | Clinical progress and treatment | RT-PCR ^a or antibody test results |
|-----------|--------|-------------|--|--|-------------------|------------------|---|---|--|
| Patient 1 | Female | 12 | Urticarial eruption on the trunk and upper limbs | Fever, sore throat, vomiting and cervical lymphadenopathy | 5 days | <24 h | Lymphopenia ($880 \times 10^3/\mu\text{l}$), thrombocytopenia ($100\,000\,10^3/\mu\text{l}$), hyponatremia [127 mmol/l], hypoalbuminemia [2.7 g/dl] ($3.8\text{--}5.4\text{ g/dl}$), elevated C-reactive protein [13.6 mg/dl] ($<0.5\text{ mg/dl}$), procalcitonin [1.24 ng/ml] ($<0.1\text{ ng/ml}$), troponin [0.12 ng/ml] ($0.02\text{--}0.06\text{ ng/ml}$) and D-dimer [2159 ng/ml] ($0\text{--}243\text{ ng/ml}$) | PICU ^b referral IVI ^c 2 g/kg MPS ^d 2 mg/kg (1 month with gradual dose reduction) Ceftriaxone (10 days) Vancomycin (7 days) Enoxaparin (10 days) | SARS-CoV-2 PCR: – SARS-CoV-2 IgG: + |
| Patient 2 | Male | 7 | Macular erythema on dorsolateral surface of the feet Bilateral palmoplantar erythema on the hands and feet | Fever, abdominal pain, conjunctivitis, hypotension and strawberry tongue | 6 days | 4 days | Elevated C-reactive protein [9.97 mg/dl] ($<0.5\text{ mg/dl}$), procalcitonin [8.94 ng/ml] ($<0.1\text{ ng/ml}$), troponin [0.084 ng/ml] ($0.02\text{--}0.06\text{ ng/ml}$), D-dimer [1686 ng/ml] ($0\text{--}243\text{ ng/ml}$) | PICU referral IVI ^c 2 g/kg Vancomycin (5 days) Meropenem (7 days) Enoxaparin (15 days) | SARS CoV-2 PCR: – SARS CoV-2 IgG: + |
| Patient 3 | Male | 13 | Morbiliform eruption on the bilateral dorsal surface of hands, trunk, antecubital region and lower limbs Periorbital erythema | Fever | 4 days | 6 days | Lymphopenia ($450 \times 10^3/\mu\text{l}$), thrombocytopenia ($122\,000\,10^3/\mu\text{l}$), Elevated C-reactive protein [17.26 mg/dl] ($<0.5\text{ mg/dl}$), procalcitonin [1.39 ng/ml] ($<0.1\text{ ng/ml}$), D-dimer [1723 ng/ml] ($0\text{--}243\text{ ng/ml}$) | No complication IVI ^c 2 g/kg MPS 2 mg/kg (21 days with gradual dose reduction) Ceftriaxone (7 days) Enoxaparin (10 days) | SARS CoV-2 PCR: – SARS CoV-2 IgG: + |
| Patient 4 | Male | 5 | Maculopapular eruption on the trunk | Fever, diarrhea, myalgia, conjunctivitis | 9 days | <24 h | Lymphopenia ($1350 \times 10^3/\mu\text{l}$), elevated C-reactive protein [12.2 mg/dl] ($<0.5\text{ mg/dl}$) | No complication IVI ^c 2 g/kg Ertapenem (7 days) Enoxaparin (14 days) | SARS CoV-2 PCR: – SARS CoV-2 IgG: + |

(continued)

Table 1. (continued)

| Patient | Gender | Age (years) | Rash type, localization | Other symptoms and signs | Duration of fever | Duration of rash | Laboratory abnormalities | Clinical progress and treatment | RT-PCR ^a or antibody test results |
|---------|--------|-------------|---------------------------------------|---|-------------------|------------------|---|---|--|
| 5 | Male | 12 | Petechia on lower limbs | Fever, diarrhea, vomiting, hypotension, confusion | 4 days | 4 days | procalcitonin [0.47 ng/ml (<0.1 ng/ml)], D-dimer [607 ng/ml (0–243 ng/ml)], creatine kinase [1228 IU/ml (20–300 IU/ml)] Elevated C-reactive protein [21.18 mg/dl (<0.5 mg/dl)], procalcitonin [36.46 ng/ml (<0.1 ng/ml)], troponin [0.318 ng/ml (0.02–0.06 ng/ml)], D-dimer [1045 ng/ml (0–243 ng/ml)], hyponatremia [129 mmol/l (136–145 mmol/l)] | PICU referral IVIg 2 g/kg MPS 2 mg/kg (21 days with gradual dose reduction) Vancomycin (7 days) Meropenem (10 days) Enoxaparin (14 days) | SARS CoV-2 PCR: – SARS CoV-2 IgG: + |
| 6 | Male | 8 | Maculopapular eruption on lower limbs | Fever, abdominal pain, arthralgia | 3 days | 5 days | Lymphopenia (1360 × 10 ³ /μl) elevated D-dimer [891 ng/ml (0–243 ng/ml)] and C-reactive protein [16.51 mg/dl (<0.5 mg/dl)] | No complication IVIg 2 gr/kg Ceftriaxone (7 days) Enoxaparin (16 days) | SARS CoV-2 PCR: – SARS-CoV-2 IgG: + |

^aRT-PCR, real time-polymerase chain reaction.

^bPICU, pediatric intensive care unit.

^cIVIg, intravenous immunoglobulin.

^dMPS, methylprednisolone.



Fig. 1. Patient 1. Urticarial eruption on the trunk.



Fig. 2. Patient 1. Urticarial eruption on the left upper limb.

Patient 2

A 7-year-old male presented with a fever up to 39°C for 5 days with associated abdominal pain, and a rash that appeared the day before admission. On examination, he had a strawberry tongue, macular erythema on the dorsolateral surface of the feet and bilateral palmoplantar erythema with edema on the hands and feet. (Figs 3 and 4) Multiplex PCR for other viral agents was negative. Two days after admission, he became resistantly hypotensive and was admitted to the PICU for inotropic support. On the fourth day of hospitalization, fever and rash resolved concomitantly.

Patient 3

A 13-year-old male presented with 3 days of fever up to 39.6°C and a rash. Physical examination revealed morbilliform eruption on the bilateral dorsal surface of hands, trunk, antecubital region and lower limbs and periorbital erythema with edema. (Figs 5 and 6) The fever persisted for 24 h after admission. It was observed that the rashes disappeared 2 days after the

fever subsided. EBV viral capsid antigen (VCA) IgM and EBV VCA IgG were negative.

Patient 4

A 5-year-old male presented with 7 days of fever accompanying diarrhea, conjunctivitis and myalgia. On the first day of admission, he had a maculopapular eruption on the trunk resolving within 24 h. (Fig. 7) It was observed that the fever subsided 24 h after the rashes disappeared. EBV VCA IgM and EBV VCA IgG were negative.

Patient 5

A 12-year-old male presented with 4 days of fever with associated diarrhea, vomiting and 3 days of rash. Physical examination revealed altered mental status, tachycardia, hypotension and petechial rash on the lower limbs (Figs 8 and 9), and he was admitted to PICU. Multiplex PCR for other respiratory viruses and blood culture resulted negative. Rashes resolved on the second day of hospitalization.



Fig. 3. Patient 2. Macular erythema on the dorsolateral surface of the right foot.



Fig. 4. Patient 2. Palmoplantar erythema on the left hand.



Fig. 5. Patient 3. Periorbital erythema and edema.



Fig. 6. Patient 3. Morbilliform eruption on the trunk.



Fig. 7. Patient 4. Maculopapular eruption on the trunk.



Fig. 8. Patient 5. Purpura on the feet.



Fig. 9. Patient 5. Purpura on the left lower limb.



Fig. 10. Patient 6. Maculopapular eruption on the lower limbs.

Patient 6

An 8-year-old male presented with abdominal pain, arthralgia and, 3 days of fever that starts concurrently with a maculopapular eruption on the lower limb (Fig. 10). Rashes resolved 2 days after admission.

DISCUSSION

In our cohort, we reviewed our experience with MIS-C and cutaneous findings. In our experience, although more than half of the patients had a history of mucocutaneous findings, we were able to observe the findings at a very low rate at admission. The patients presented with a wide spectrum and polymorphic cutaneous findings. Exanthems in our experience demonstrated a variety of morphologies, including morbilliform, urticarial, petechial, and maculopapular forms. Mucosal involvement (conjunctivitis and strawberry tongue) was observed only in two of the patients (34%). Some patients experienced fever before recognition of the rashes, whereas others developed fever and rashes concomitantly. Extremities were involved in all patients except Patient 4.

Mucocutaneous manifestations in the course of MIS-C have been reported at high rates in the literature [3, 10, 11]. A meta-analysis reviewing 16 articles with a total of 600 patients revealed that skin rashes were the third common presentation after the fever and gastrointestinal symptoms [9]. Feldstein, *et al.* [12] reported that mucocutaneous findings were recognized in up to 74% of hospitalized patients with MIS-C. In our study, the rate was found to be much lower. The possible reason for this may be that the rashes were short-term and were not noticed by the parents before admission to the hospital.

Although studies on skin manifestations associated with MIS-C included a limited number of cases, nonspecific erythema, urticarial, morbilliform, scarlatiniform, and purpuric exanthema have been reported so far [13, 14]. Rekthman, *et al.* [13] reported that extremities are involved more frequently [13]. Hand and feet anomalies (erythema and/or induration) were found in 50% of Italian patients [3] and 48% of French patients [15]. However, a characteristic body region for MIS-C involvement has not been identified. Hence, common childhood viral or bacterial diseases (such as EBV, measles, parvovirus, meningococemia, scarlet fever etc.) and drug

eruptions are frequently included in the differential diagnosis requiring the proper diagnostic tests and the initiation of empirical antimicrobial treatment.

This study has several limitations. First, histories of mucocutaneous changes before hospital admission are based on parents' statements. Second, none of the patients underwent a skin biopsy which might reveal the pathogenesis of rash in MIS-C. Third, some of the rashes may not be able to distinguish due to fact that some of the lesions disappear quickly and some of them are indistinct.

In conclusion, in the COVID-19 pandemic era, while evaluating the criteria for MIS-C, not only the presence of the cutaneous findings, but also the history of previous cutaneous findings given by parents/caregivers are important. As shown in this article, there was no pathognomonic rash for MIS-C and a variety of cutaneous findings with a short lifespan can be associated with MIS-C.

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