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CONFLICT OF INTEREST

All authors declare no conflict of interest regarding the content of this manuscript.

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Evaluation of cutaneous symptoms in children infected with COVID-19

To the Editor,

Severe acute respiratory syndrome causing coronavirus (SARS-CoV-2) is a new coronavirus responsible for the pandemic named coronavirus disease 2019 (COVID-19). Although the pathogenesis of the disease has not been completely understood yet, it may cause clinical pictures with various degrees of multisystem involvement.1,2 Studies have indicated that coronavirus can also cause cutaneous lesions; however, specific cutaneous symptoms of COVID-19 infection have not been disclosed yet. The prevalence of cutaneous
manifestations in COVID-19 patients was between 0.2% and 20.4% in the recently published studies and 3.4% in a review including 28 studies where the patients aged between 0 and 18 years age had COVID-19. In this respect, we aimed to analyze the incidence and the types of cutaneous manifestations associated with COVID-19 infections in pediatric patients.

Children who were diagnosed COVID-19 in Ankara City Hospital, Children’s Hospital in Turkey between March 11 and September 30, 2020, were evaluated in this prospective study. The study protocol was approved by the Institutional Ethics Committee of Ankara City Hospital (E1-20-546).

Of the 5143 children infected with SARS-CoV-2, only 13 (0.25%) developed cutaneous lesions during the period of study. The median age of those children was 80 months (IQR: 19-118.5 months), and 10 of them were boys (76.90%) (Table 1). Only 2 of the patients had a chronic disease; epilepsy; and undefined immunodeficiency (Tables 1 and 2).

Common cutaneous manifestations of infected children in our hospital were maculopapular exanthema and urticaria: 61.5%(n:8) and 23%(n:3), respectively. One of the patients developed erythema nodosum. Two of them were presented as severe cutaneous adverse reactions (SCARs); drug rash with eosinophilia and systemic symptoms (DRESS); and Stevens-Johnson syndrome (SJS), respectively, and two patients developed multisystem inflammatory syndrome in children (MIS-C) (Tables 1 and 2).

Cutaneous symptoms began before the COVID-19 symptoms (2 days before) only in one patient, and 10 of the patients presented cutaneous manifestations after the COVID-19 symptoms (median 3 days after). Cutaneous symptoms coincided with the onset of other COVID-19 symptoms in two of the patients. The mean of the duration time of rashes was 5.6 days. Additionally, all patients had a fever. Cough, dyspnea, vomiting, diarrhea, abdominal pain, and vertigo; 30.8%(n:4), 23.1%(n:3), 23.1%(n:3), 30.8%(n:4), 15.4%(n:2), and 7.7%(n:1), respectively, were also observed at the admission of the patients (Table 2).

In our study, there were six patients with a history of drug usage. We terminated the usage of any suspicious drug due to the rash in combination with the medication history of the patient. The aforementioned patients did not have any reported history of drug allergy. On the second day of the treatment and after 2 hours of the dose, maculopapular exanthema was observed in the trunk, face, and legs of the patient who was treated with hydroxychloroquine. The hydroxychloroquine treatment was terminated in 1 day (patient nine). One of the patients received favipiravir and ampicillin-sulbactam treatments. Maculopapular exanthema was seen at the trunk of the patient after 1 hour of the first dose of ampicillin-sulbactam. After termination of the ampicillin-sulbactam treatment, rashes were revealed in 1 day while favipiravir treatment was continued (patient three) (Table 2). It was observed that one of the patient has developed DRESS. An eight-year-old boy having epilepsy disease presented with fever, cough, and rashes in trunk, face, and lower extremities. The patient was on the ninth day of amoxicillin-clavulanic acid treatment and on the 19th day of carbamazepine treatment when the rash started. In his laboratory findings, serum transaminases and eosinophil level were elevated and viral markers were negative. Hence, the carbamazepine treatment and amoxicillin-clavulanic acid treatment were terminated. He received levetiracetam treatment for epilepsy (patient ten) (Table 2).

One patient was presented with SJS. The patient was prescribed amoxicillin-clavulanate for complaints of fever, throat pain, and cough. After 2 days of amoxicillin-clavulanate usage, he applied to the hospital with fever, maculopapular lesions, mucosal lesions in oral and anal mucosa, blisters, and severe respiratory distress was examined (patient eleven) (Table 2).

In one patient, COVID-19 infection was presented with cough and fever. Erythema nodosum developed at the bilateral extensor surface of the hands and pretibial surface of the bilateral lower extremity on the 8th day of his hospitalization (Table 2). He was treated with ceftriaxone, macrolide, teicoplanin, azithromycin, favipiravir, clexane, dexamethasone, and interferon-alpha treatment. Erythema nodosum was observed one day after the termination of the interferon treatment. The patient showed improvement in one day without termination of any other treatment (patient four).

Two patients with a diagnosis of MIS-C had rashes. The first MIS-C patient had high and persistent fever, bilateral non-purulent conjunctivitis, polymorphic rash in the trunk and gluteal area, strawberry tongue, and palmpoplantar erythema. Rashes began after the second day of cefixime and after 3 days of abdominal pain, diarrhea, and fever. We terminated the usage of the drug (patient twelve).

### Table 1: Characteristics of patients and cutaneous symptoms (n = 13)

| Characteristics of patients | % (n) |
|-----------------------------|-------|
| Age (median, IQR, ‘month’)   | 80 (19-118.5) month |
| Gender (female/male)         | 3/10 patient |
| Having chronic disease       | 15.3% (n:2) |

| Cutaneous symptoms           | % (n) |
|-------------------------------|-------|
| Maculopapular exanthema       | 61.5% (n:8) |
| Urticaria                     | 23% (n:3) |
| Palmoplantar erythema         | 7.6% (n:1) |
| Bullous lesion                | 7.6% (n:1) |
| Erythema nodosum              | 7.6% (n:1) |

| Associated clinical entities  | % (n) |
|-------------------------------|-------|
| DRESSa                        | 7.6% (n:1) |
| SJSa                          | 7.6% (n:1) |
| MIS-C disease                 | 15.3% (n:2) |

| Rash location                  | % (n) |
|-------------------------------|-------|
| Trunk                         | 76.9% (n:10) |
| Face                          | 69.2% (n:9) |
| Extremity                     | 38.4% (n:5) |
| Gluteal legion                | 15.3% (n:2) |
| Hand and Foot                 | 15.3% (n:2) |

aThere was drug exposure that also could be cause of the symptoms.
| Patient number | Gender | Age (Month) | Symptoms at admission | Rash type | Rash localization | Rash onset time | Clinical progress | Concomitant drug use |
|----------------|--------|-------------|-----------------------|-----------|-------------------|----------------|------------------|---------------------|
| 1. Patient     | Male   | 20          | Fever, rash           | Maculopapular | Face and trunk    | Rash developed at the 2nd day of the disease | Rash subsided in 4 days | Symptoms resolved completely | No                  |
| 2. Patient     | Male   | 43          | Rash, fever, and swelling at knee joint | Urticaria, Face, trunk, extremities | Rash developed at the first day of the disease | At the second day fever and swelling at knee joint developed | Rash subsided in 4 days | Symptoms resolved completely | No                  |
| 3. Patient     | Male   | 160         | Fever, cough, and vertigo | Maculopapular | Face and trunk | Rash developed at the 4th day of the disease | Rash subsided in 1 day. | Symptoms resolved completely | Ampicillin-subbactam: 1th day, 1th dose |
| 4. Patient     | Male   | 150         | Fever, cough, dyspnea, and weakness | Erythema nodosum | Dorsum of the hands and pretibial surface | Rash developed at the 14th day of the disease | Developed bilateral rales, hypotension Cold type autoimmune hemolytic anemia was added to the clinical picture Rash subsided in 1 day. Symptoms resolved completely | Ceftriaksone, macrolide, teicoplanin, azithromycin, favipiravir, clexane, and interferon treatments were given. After three dose/week interferon treatment, it was terminated and rash coincided one day after interferon treatment termination but other treatments continued. (He was diagnosed with an undefined immunodeficiency) |
| 5. Patient     | Male   | 80          | Fever, rash           | Urticaria | Face and trunk | Rash coincided at the same time of fever | Rash subsided in 1 day. | Symptoms resolved completely | No                  |
| 6. Patient     | Female | 5           | Fever, cough, vomiting, diarrhea, and rash | Maculopapular | Face | Rash developed at the 2th day of the disease | Rash subsided in 1 day. | Symptoms resolved completely | No                  |
| 7. Patient     | Male   | 13          | Fever, vomiting, diarrhea, and rash | Maculopapular | Face, trunk, extremities | Rash developed at the 10th day of the disease | Rash subsided in 4 days. | Symptoms resolved completely | No                  |
| 8. Patient     | Male   | 18          | Fever, diarrhea, and rash | Urticaria | Rash developed at the 3rd day of the disease | Rash subsided in 3 days. | Symptoms resolved completely | No                  |
| 9. Patient     | Male   | 133         | Fever, dyspnea        | Maculopapular | Face and trunk | Rash developed at the 4th day of the disease | Rash subsided in 15 days. | Symptoms resolved completely | Hydroxychloroquine 2th day, 2th dose |

(Continues)
| Patient number | Gender | Age (Month) | Symptoms at admission | Rash type | Rash localization | Rash onset time | Clinical progress | Concomitant drug use |
|----------------|--------|-------------|-----------------------|-----------|-------------------|----------------|-------------------|---------------------|
| 10. Patient    | Male   | 92          | Fever, cough, and rash| Maculopapular | Face, trunk, extremities | Rash developed at the first day of the disease and coincided with the other symptoms | Developed DRESS with liver involvement | Amoxicillin-clavulanic acid 9th day and Carbamazepinene 19th day (He was diagnosed with epilepsy) |
| 11. Patient    | Male   | 84          | Fever, throat pain, cough, rash, and mucosal lesions | Maculopapular and bullous epidermal detachment and mucosal lesions | Face, scalp, neck, trunk | Mucosa involvement: Oral and anal Rash developed at the 2nd day of the disease | Developed SJS with pulmonary involvement | Amoxicillin-clavulonic acid 2nd day |
| 12. Patient    | Female | 104         | Fever, abdominal pain, diarrhea, weakness, bilateral conjunctivitis, strawberry tongue, and rash | Maculopapular, Bilateral palmoplantar erythema, | Face, trunk, and gluteal location | Rash developed at the 5th day of the disease | Developed MIS-C (Myocardial dysfunction) | Cefixim 2nd day |
| 13. Patient    | Female | 70          | Fever, abdominal pain, vomiting, bilateral conjunctivitis, and rash | Maculopapular trunk, axilla, and gluteal location | Rash developed at the 3rd day of the disease | Developed MIS-C (pleural and pericardial effusion, myocardial dysfunction) | Rash subsided in 3 days. Symptoms resolved completely | No |
The second patient with MIS-C had fever, vomiting, and abdominal pain on the fourth day. Bilateral conjunctivitis, maculopapular exanthemas on trunk, gluteal region, and bilateral axilla developed after 3 days of the onset of COVID-19 symptoms. The patient did not have a history of drug usage (Table 2).

The patients were discharged when they were healed, and one of them was deceased (SJS).

Limited studies have investigated the cutaneous manifestations in COVID-19 only in children.

Erythematous rash and localized or diffuse urticarial and chickenpox-like lesions are the most common manifestations in COVID-19. In the literature, there is one case indicating the relationship between coronavirus and DRESS syndrome. Maculopapular rashes such as erythema multiforme-like or diffuse erythroderma are the commonly observed cutaneous manifestations of MIS-C. Whitaker and et al reported that 30 of the 58 children patients who were diagnosed as MIS-C had erythematous rashes. In genetically predisposed individuals, SARS-CoV-2 can trigger the development of a rapid autoimmune and/or autoinflammatory dysregulation and lead to severe interstitial pneumonia. A case report reported that a 58-year-old female patient developed SJS and TEN overlap syndrome with COVID-19 positivity. The pathogenesis of cutaneous symptoms is not understood yet. In COVID-infected patients, cutaneous manifestations may be directly related to coronavirus or caused by another underlying viral infection or due to adverse drug reactions that are newly started. Adverse drug effects, drug-drug interactions, and hypersensitivity reactions may develop with drugs used during COVID-19 therapy. Therefore, COVID-19 patients should be followed up carefully.

The cutaneous symptoms during COVID-19 may be mild (maculopapular exanthem and urticarial) or severe (SJS, DRESS, and MIS-C). In the present study, it was not clear if six of 13 patients presented the symptoms of the drug given or virus. More studies should be conducted to confirm and understand the skin involvement in COVID-19.

**AUTHOR CONTRIBUTIONS**

Azize Pınar Metbulut: Data curation (equal); Formal analysis (equal); Investigation (equal); Writing-original draft (equal); Writing-review & editing (equal). Aslınur & Ozkaya Parlakay: Project administration (equal); Resources (equal); Supervision (equal); Visualization (equal).

Gülsüm İclal Bayhan: Methodology (equal); Resources (equal); Supervision (equal); Visualization (equal). Saliha Kanik: Data curation (equal); Investigation (equal); Methodology (equal). Belgin Gölhan: Formal analysis (equal); Methodology (equal); Resources (equal); Supervision (equal). Zeynep Şengül Emeksiz: Data curation (equal); Methodology (equal); Resources (equal). Emrah Şenel: Visualization (equal); Writing-review & editing (equal). Emine Dibek Mısırlıoğlu: Project administration (equal); Writing-original draft (equal); Writing-review & editing (equal).

**CONFLICT OF INTEREST**

The authors have no conflicts of interest to declare.

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SARS-CoV-2-specific IgG1/IgG3 but not IgM in children with Pediatric Inflammatory Multi-System Syndrome

To the Editor,

There is a low rate of symptomatology associated with SARS-CoV-2 infection in children and a substantially lower risk of death than in adults. Nevertheless, in rare cases, some children present with features of a multisystem inflammatory syndrome with overlapping features of Kawasaki disease and toxic shock syndrome. In the United Kingdom, this is termed pediatric inflammatory multisystem syndrome—temporally associated with SARS-CoV-2 (PIMS-TS), and in the United States, multisystem inflammatory system in children (MIS-C). Since children with PIMS-TS can be PCR-negative for SARS-CoV-2, understanding the antibody response to SARS-CoV-2 in these children may help develop diagnostic strategies and help understand the nature of the immune response.

Two antigens have been included in most serology tests—the surface-exposed spike (S) glycoprotein and the non-exposed nucleocapsid (N) protein. Serological tests for antiviral antibodies have not been useful to date in the immediate diagnosis of active COVID-19 infection, largely due to the 7- to 14-day lag between infection and antibody responses developing. In primary infections, IgM responses develop first, before eventually declining and IgG responses dominate thereafter. High levels of IgG without IgM are typically suggestive of infection weeks previously. This may be relevant in diseases such as PIMS-TS, since if it follows the pattern of Kawasaki disease, then the causative agent is often not determinable at the time of clinical presentation.

We examined antibody responses in sera from eight patients of mixed ethnicity (five male and median age 9 [range 7-14] years) admitted to hospital between April 28 and May 8, 2020, with a case definition consistent with the criteria described by the Royal College of Paediatrics and Child Health. In all cases, PCR tests for SARS-CoV-2 infection were negative. Seven patients had overlapping features of hyperinflammation with either typical or atypical Kawasaki disease, and one patient had overlapping features of hyperinflammation and toxic shock syndrome. All patients had fever and at least one gastrointestinal symptom (abdominal pain, vomiting, and diarrhea), whereas six patients had a rash and non-exudative conjunctivitis. Four children showed mucosal and peripheral changes and only two children presented with lymphadenopathy.

Hyperinflammation was supported by presence of fever and the median (IQR) CRP was 188 (136-255) mg/L and ferritin was 1325 (819-2121) µg/L in this cohort of children. 63% of patients had impaired myocardial function on echocardiography. 75% required admission to pediatric intensive care predominantly for cardiovascular support due to hypotension. All patients improved with supportive therapy that included immunomodulation with immunoglobulins and/or steroids and were discharged from PICU, remaining hospital inpatients.

Antibodies to the trimeric viral spike glycoprotein (S) were detected by a commercially available ELISA to detect combined IgG, IgA, and IgM (The Binding Site). This test was also modified to detect individual antibody isotypes. Nucleocapsid (N) antibodies were detected using an in-house ELISA. To both antigens, the adapted ELISA used HRP-labeled mouse monoclonal anti-human IgG, IgA, IgM, IgG1,4 secondary antibodies, generated at the University of Birmingham (available from Abingdon Health Ltd).

Sera from these eight children were tested against viral S glycoprotein. For negative controls, we used sera obtained from adults before 2019, and as positive controls, we used plasma from adults hospitalized with PCR-confirmed severe COVID-19. Screening of sera, diluted 1:40, to detect IgG, IgA, and IgM demonstrated that all children had antibodies against the SARS-CoV-2 S glycoprotein (Figure 1A). Since antibody isotypes can reflect recent infection (IgM), or more historic infections (IgG and IgA), we examined individual antibody isotypes and presented these results as area under the curve (AUC). In children, IgM levels were higher pre-2019 sera; in contrast, both S glycoprotein and N-specific IgM levels were higher in adult ITU COVID-19 patients (Figure 1B). Although anti-S IgA and IgG were more similar in children and adult

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