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SHORT PAPER

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Familial clustering of COVID-19 skin manifestations

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Abstract

The medical community in the past months has seen a flourishing of information related to the SARS-CoV-2 virus responsible for the COVID-19 pandemic. From the early days of the pandemic, the SARS-CoV-2 virus has been linked to multiple different types of skin involvement. To the best of our knowledge, we are the first to report on a case of familial clustering of a maculopapular COVID-19 rash. Eight persons presented COVID-19 symptoms, six were confirmed via SAR-CoV-2 chemoluminescent immunoassays, and the four related by blood presented skin manifestations. Although, it has not been fully established if the SARS-CoV-2 can in fact cause viral exanthems, our observations regarding the familial clustering and the temporal evolution seen in this family seem to present strong evidence of a viral exanthema related to SARS-CoV-2 infection.

KEYWORDS

COVID-19, familial clustering, genetics, immunology, virology

The medical community in the past months has seen a flourishing of information related to the SARS-CoV-2 virus responsible for the COVID-19 pandemic. From the early days of the pandemic, the SARS-CoV-2 virus has been linked to multiple different types of skin involvement including erythematous maculopapular rashes, urticaria, COVID-19-related vesicular eruptions, livedo, and chilblain-like lesions,[1-4] There have so far been two other cases published of familial clustering of COVID-19 cutaneous manifestation. One case series observed the appearance of transient urticarial weals in two related patients who had confirmed serology for SARS-CoV-2 viral infection.[5] The second noted two groups of three related adolescent patients that presented acral perniosis, but in which SARS-CoV-2 polymerase chain reaction was negative.[6] To the best of our knowledge, we are the first to report on a case of familial clustering of maculopapular COVID-19 skin manifestations, and we do so in hope that it help shed light on the nature of the cutaneous pathophysiology of the virus.

A 34-year-old female patient presented to our dermatology department's outpatient service with an erythematous maculopapular rash organizing into erythematous placards on the trunk, extremities, and face. The patient had also presented to our hospital's infectious disease department 16 days prior with cough, myalgia, anosmia, general malaise, and fever that had been ongoing over the past 5 days. A chemoluminescent-immunoassay done the day of her presentation demonstrated positive anti-SARS-CoV-2 IgM, and she was treated in hospital with plaquenil, azithromycin, clexane, dexamethasone, codeine, and other symptomatic medication with a favorable evolution. She was hospitalized for 9 days until the IgM antibodies were no longer detectable. At the time of her presentation in our service, she did not have any other symptoms, and vital signs were all within normal limits. Of note is that the patient reported oral mucocutaneous lesions, but none were found at the time of examination, and none were identified during her previous in-hospital stay. From anamnesis, we establish that the rash began 4 days prior (17 days after initial COVID-19 symptoms) on the antecubital fossa and evolved the next day to encompass the trunk, followed by the extremities, and the face. The patient is known with thrombophilia and is known to be a homozygous carrier for the MTHFRa1298c gene (Figure 1 and 2).

The diagnosis of viral exanthema related to the SARS-CoV-2 was evoked, and the decision was taken to treat her as an outpatient with montelukast and rupatadine in order to disrupt inflammatory cytokine cascades through the blocking of H1-receptors, platelet-activating factor-receptor, and anti-leukotrine receptors that may have led to the cutaneous manifestations, but also to limit corticosteroid use which had been administered previously but proved ineffective at preventing the rash. She was called in for a revaluation at 14 days. 2 days later she presented at the emergency department with

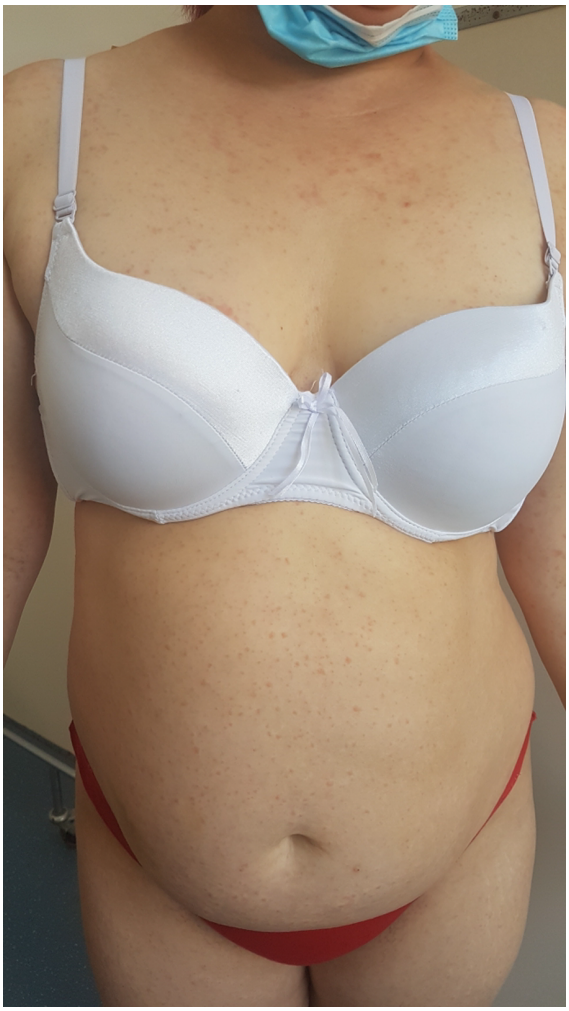

FIGURE 1 Maculopapular eruption on female patient on day 21 after initial respiratory symptoms

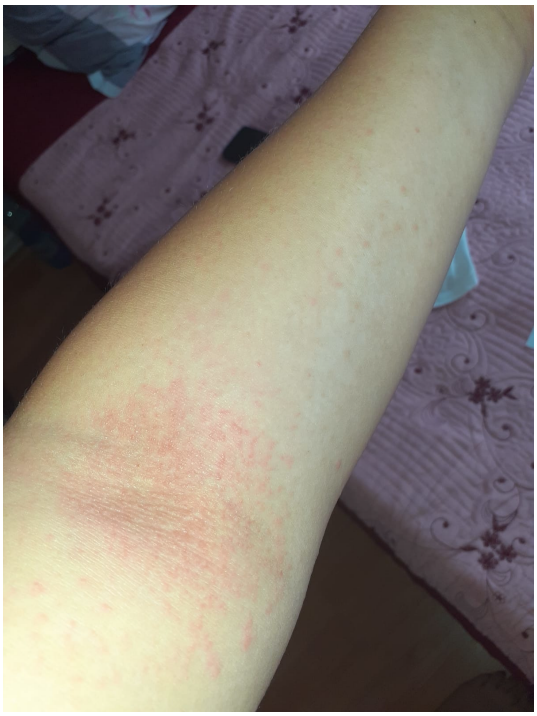

FIGURE 2 Maculopapular euruption on the antecubital fossa of female patient, 18 days after initial respiratory symptoms

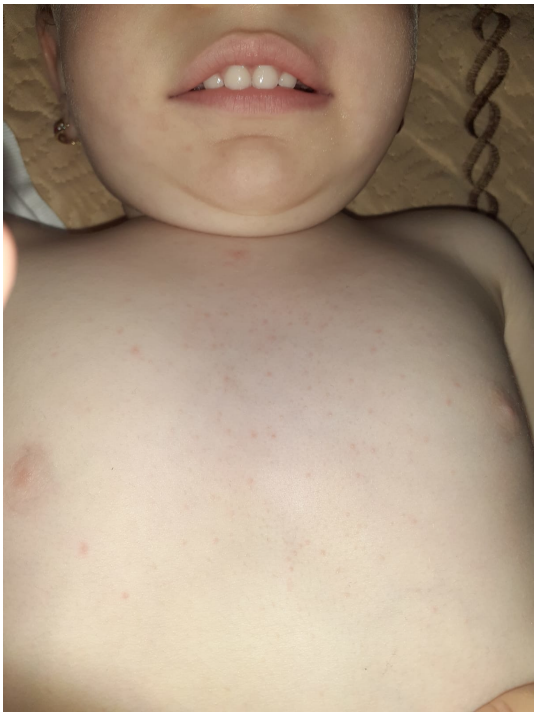

FIGURE 3 Maculopapular eruption on 6 year old daughter, 18 days after initial respiratory symptoms

generalized erythroderma, facial paresthesia, and severe asthenia. She was admitted as having a non-specific allergic reaction, and was administered a single dose of 100 mg hydrocortisone hemisuccinate before being transferred back to our hospital. Paraclinical examination showed leukocytosis ($29.8 \times 10^3/\mu L$), neutrophilia ($24.92 \times 10^3/\mu L$) with a regenerative left shift, negative inflammatory markers, and no other significant modifications. A repeat of the anti-SARS-CoV-2 immunoassay continues to show negative IgM antibodies and positive IgG antibodies. This patient's known thrombophilia may raise her risk of thrombotic complications related to COVID-19 disease. Elevated D-Dimers and prothrombin times have been associated with a more severe disease progression, and elevations are also noted in a greater percentage of patients requiring treatment in intensive care units.[7] Our patient's coagulation profile was found to be within normal limits with D-Dimers measured at 195.95 ng/mL, and a prothrombin time of 11.6 s, but it is noted that she did receive anticoagulant therapy during her initial hospitalization. She was treated in our service with four doses of 50 mg hydrocortisone hemisuccinate followed by one 8 mg dose of dexamethasone, bromazepam, desloratadine, calcium gluconate, furosemide, metoprolol, NSAIDs, and topical corticosteroids with a favorable evolution. Her viral exanthema completely disappeared after 4 days, but the facial paresthesia and asthenia persisted for another 3 days before beginning to remit.

FIGURE 4 Fixed erythema with papular and urticarial elements associated with dermographism on patient's son on day 17 after initial respiratory symptoms

Through anamnesis we discovered that seven other family members presented similar symptoms including her sister, sister-in-law, mother-in-law, grandmother, husband, and their two children; a boy and a girl. Only the sister, mother-in-law, sister-in-law, grandmother, and daughter underwent SARS-CoV-2-immunoassays, for which they all showed evidence of previous SARS-CoV-2 infection. All of those related to the patient by blood, with the notable exception of the grandmother who remained asymptomatic and was only incidentally discovered with positive IgG anti-SARS-CoV-2 antibodies, presented with dermatologic manifestations.

The girl, age 1, is reported to have had COVID-19 symptoms with fever and chills 2 days prior to those of the mother. Her eruption began 16 days later appearing as a maculopapular erythematous rash typical of a non-specific viral exanthema. An immunoassay was done showing positive anti-SARS-CoV-2 IgG antibodies and negative IgM antibodies. The rash remitted 7 days later with no associated symptoms (Figure 3).

The boy, age 6, is reported to have had only mild symptoms with some coughing beginning in parallel with the mother. He remained afebrile and no immunoassay test was performed. However, 17 days later, at the same time as the mother, he developed fixed erythema with papular and urticarial elements associated with dermographism on the trunk. It also convalesced without associated complaints 7 days later (Figure 4).

TABLE 1 Summary of findings; patients 1 to 5 are blood relatives, as are patients 6 to 8

Patient	Age	Sex	Cutaneous findings	Systemic findings	Workup (modified)	Treatment
1	34	F	Erythematous maculopapular rash appearing 17 days after initial respiratory symptoms	Cough, myalgia, anosmia, malaise, facial paresthesia, fever	Positive IgM and IgG SARS-CoV-2-immunoassays; leukocytosis (29.8x103/uL); neutrophilia (24.92x103/uL) Repeated SARS-CoV-2-immunoassays showing only positive IgG	plaquenil, azithromycine, clexane, dexamethasone codeine, hydrocortisone hemisuccinate, montelukast, rupatadine, dexamethasone, bromazepam, desloratadine, calcium gluconate, furosemide, metoprolol, NSAIDs, topical corticosteroids
2	1	F	Erythematous maculopapular rash appearing 17 days after initial respiratory symptoms	Fever, cough, chills	Positive IgG SARS-CoV-2-immunoassays	Unknown
3	6	M	Fixed erythema with papular and urticarial elements associated with dermographism appearing 17 days after initial symptoms	Cough, general malaise	None	Montelukast received 1-month prior
4	46	F	10 cm erythematous patch on the antecubital fossa appearing 17 days after initial respiratory symptoms	Fever, cough, malaise	Positive IgG SARS-CoV-2-immunoassays	Unknown
5	90	F	None	None	Positive IgG SARS-CoV-2-immunoassays	None
6	36	M	None	Fever, cough, malaise	None	Unknown
7	62	F	None	Fever, cough, malaise	Positive IgG SARS-CoV-2-immunoassays	Unknown
8	30	F	None	Fever, cough, malaise	Positive IgG SARS-CoV-2-immunoassays	Unknown

The sister, aged 46, had infectious symptoms that debuted 2 days after those of our patient. Her antibody serology was positive for SARS-CoV-2 infection. The infection is reported to have run a mild course. 17 days later she presented with a 10 cm erythematous patch on the antecubital fossa. This lesion disappeared within a few days, and did not generalize (Table 1 and Figure 5).

Although, it has not been fully established if the SARS-CoV-2 can in fact cause viral exanthems, our observations regarding the familial clustering and the temporal evolution seen in this family seem to present strong evidence of a viral exanthema related to SARS-CoV-2 infection. The dermatological findings in these patients are congruent with similar skin manifestations reported by other authors. Galvan-Casas et al published a case series of 375 patients in Spain attempting to classify different skin manifestations possibly related to the SARS-CoV-2 virus infection of which a plurality of 176 patients (47%) presented with similar maculopapular rashes as those seen in our patients.[1] Similar findings have been found in other reports during this pandemic.[2-4] The majority of the patients we presented had upper respiratory tract symptoms, and viral transmission within the family was likely accomplished via inoculation of the upper airways, but seeing as these patients have been living in close-quarters, we cannot ignore the possibility of other potential routes of transmission such as through the digestive tract, sexual contact, or through contact with viral particles present on sebum-rich skin.[8,9] The question raised by our findings regards the extent to which genetics plays a role in the manifestation of viral exanthems, as out of the eight people in this family who contracted the SARS-CoV-2 virus, only the four which were all blood-related presented dermatological manifestations. The exact process through which viral exanthems appear is poorly understood at present. A recent report has demonstrated SARS-CoV-2 viral spike proteins present in the vascular endothelial cells and eccrine cells of the dermis in a patient with chilblain-like lesions, which would lend to the idea that the virus is capable of directly infecting cutaneous cells.[10] However, it is generally believed that classic maculopapular viral exanthems are the result of an immune reaction to the viral insult rather than from direct virally mediated destruction of the cell populations found within the skin. It is not surprising that viral exanthems can be mistaken for drug reactions, as not only do they appear similar, but their pathological bases may share common elements. A 21 patient case series observed that the appearance of either a macular, petechial, or a combined enanthema on the palate of patients with COVID-19-related cutaneous manifestations was more likely related to a viral infection than to a drug eruption, and thus may serve as a possible distinguishing feature between the two. However, we were unable to confirm any oral lesions in our patients, and the same study reports that viral enanthemas were not associated in patients with maculopapular eruptions.[11] Histopathological examination of viral exanthems is not usually done, as it often shows nonspecific changes such as lymphocitic exocytosis, dermal leukocytic infiltrate, focal spongiosis, papillary edema, keratinocyte necrosis, and/or basal cell destruction.[12] Patients with viral exanthems have been shown to present differences in peripheral lymphocytic expression of skin homing receptor CLA, CD69, and increased TH0 mRNA cytokine patterns.[13] To what extent such cellular mechanisms are influenced by individual genetic differences is up to further research, but cases such as the one we report might help provide some small insight towards the greater gestalt of our current understanding.

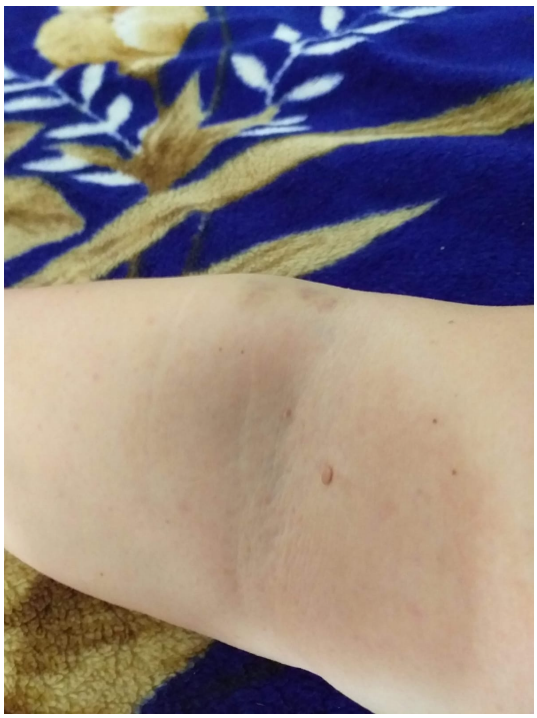

FIGURE 5 Ten centimeter patch on the antecubital fossa of patient's sister on day 18 after initial respiratory symptoms

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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