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REVIEW ARTICLE

Cutaneous manifestations of COVID-19 in children: literature review

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Abstract

Objectives: The COVID-19 pandemic currently represents a major challenge. The lungs are the main site of infection, with symptoms ranging from mild to lethal respiratory distress, in addition to involvement of various organs or systems. The pediatric population seems to be affected lesser and less severely, with the majority of cases described as asymptomatic, mild or moderate. Several cases have cutaneous manifestations. The purpose of this article is to review the findings described in the literature, particularly in the pediatric group, helping us to understand the disease and clinical suspicion. **Methods:** Articles published since the beginning of the pandemic were searched through the PubMed database. **Results:** Among the reports of skin manifestations, the most common finding was the maculopapular rash, followed by papulovesicular lesions varicella-like and urticariform lesions. There was also the description of purpuric acral lesions, livedo reticularis and petechiae. The described lesions mainly affected the trunk, hands and feet. **Conclusion:** The cutaneous findings of COVID-19 are similar to those found in other viral diseases. There is also the possibility that the lesions are due to the various medications that, particularly, patients with more severe clinical conditions use. We must also pay attention to the possibility of the initial manifestation of the disease being cutaneous. The authors warn of the possibility that patients in the pediatric group have skin lesions as a single manifestation or accompanied by mild symptoms, and that these may be similar to other diseases common in childhood.

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INTRODUCTION

Since COVID-19, a clinical syndrome caused by the novel coronavirus (SARS-CoV-2 – severe acute respiratory syndrome coronavirus *2*), was first reported in Wuhan, China, more than 3.3 million people have been infected around the world[1] and 230,104 individuals have died with the disease. High infection rates, low virulence, and asymptomatic transmission promoted the quick dissemination of the condition throughout different regions of the world, leading the WHO to elevate it to the status of a pandemic on March 11, 2020.

The COVID-19 pandemic was declared an international public health emergency by the World Health Organization (WHO) for the devastating effects it has had around the globe[1].

SARS-CoV-2 is an enveloped virus containing a single strand of RNA that belongs to the coronavirus family[1]. The virus penetrates cells through the angiotensin-converting enzyme 2 (ACE2) receptor found on the cell surface[1]. The lungs are the primary site of infection by COVID-19, with patients presenting symptoms ranging from a common cold to fulminant pneumonia with lethal respiratory distress, in addition to multiple organ or system involvement leading to sepsis and septic shock with organ dysfunction[2]. The pediatric population seems to be affected in smaller proportions and less severily than adults, with only 2% of the described cases affecting individuals aged less than 20 years[1]. In a series comprising 731 children, 90% of the patients were asymptomatic and had mild to moderate disease.

In addition to the clinical spectrum described above, a number of individuals with COVID-19 have also presented cutaneous manifestations[3] described primarily in adult cohorts subsequently reported in pediatric patients. The first description of cutaneous findings in individuals with COVID-19 was reported by Recalcati[4]. In a series with 88 patients, 18 (20.4%) had cutaneous alterations; eight reported cutaneous manifestations before the start of respiratory symptoms, and the remaining reported the onset of cutaneous alterations after hospitalization. The following findings were described: maculopapular rash (14 patients), diffuse urticaria (three patients), and varicella-like papulovesicular lesions (one patient). The author indicated that the cutaneous alterations found in individuals with COVID-19 were similar to findings seen in other viral diseases. Other authors have since reported more cases with cutaneous manifestations, although a clear association has not been established between these findings and the disease, a link that would otherwise help to identify potentially infected individuals and shed light on the damages arising from COVID-19. This literature review reports the findings described to this point in pediatric patients in an attempt to improve our understanding of the disease and factors considered in early clinical suspicion.

METHODS

A search on PUBMED was made for original articles and review papers published from the start of the pandemic to April 2020. The following keywords were used in the search: "COVID-19", "2019-nCoV", "SARS-Cov-2", "coronavirus" combined with "skin", "dermatology", "cutaneous", "urticaria", "rash"; the search included only papers written in English. The main cutaneous alterations described in the selected papers for the general population were compiled, along with the findings tied specifically to pediatric patients.

RESULTS

Sachdeva et al.[5] reviewed papers published between February and April 2020. The mean age of the patients included in the reviewed studies was 53 years; 38.9% were males and 27.8% were females; the sex of the remaining patients was not reported. The most common cutaneous manifestations seen in these individuals was measles-like maculopapular rash (36.1%) (example on Figure 1), while 34.7% had papulovesicular lesions (example on Figure 2), and 9.7% had urticaria (example on Figure 3). Painful acral purpuric lesions – also reported by Zhang et al.[6] – were described in 15.3 % of the patients (example on Figure 4); 2.8% of the patients presented with livedo reticularis, as also described by Manalo et al.[7], and 1.4% had petechiae. The described lesions were found primarily on the torso (69.4%), hands, and feet. Time of lesion onset varied widely, from three days before to 13 days after the subjects were diagnosed with COVID-19. Almost three quarters (74%) of the patients presenting cutaneous alterations after the start of respiratory symptoms had skin lesions up to seven days after diagnosis. All lesions resolved within ten days, leaving no sequelae.

Some authors have described petechiae as a possible early manifestation of the disease[8-10]. They



Figure 1. Erythematous maculopapular rash.



Figure 2. Papulovesicular lesions.

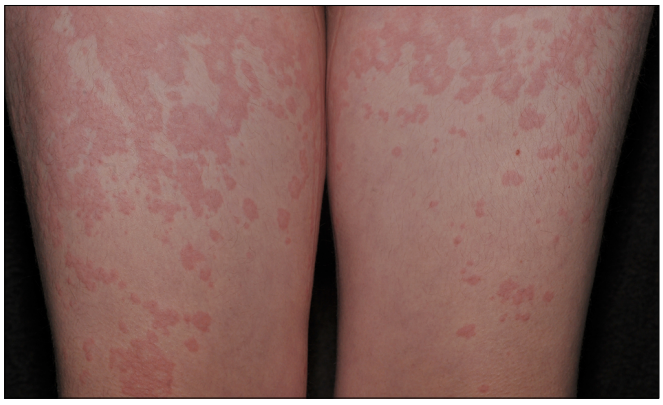


Figure 3. Urticaria-like lesions.



Figure 4. Erythematous-violaceous acral lesions.

described the lesions as similar to the ones observed in cases of dengue fever[9-11].

Some authors have also described findings in children. Piccolo[12] et al. collected data from 63 patients aged 14 years on average, showing lesions primarily in their feet and some in their hands, 31 with erythema and swelling, and 23 with vesicular/bullous lesions, some described as painful and others itchy.

Recalcati[13] et al. described 11 children aged 14 years on average with skin lesions consistent with erythematous-violaceous maculopapular rash in acral regions at times presenting with bullae (example on Figure 4), two with target-like erythematous, papulous lesions in their elbows.

Genovesi[14] et al. described the case of an eight-year-old with mild coughing for six days who developed some 40 papulovesicular lesions in the torso three days into it. Three days after the appearance of the lesions, the child's parents and grandmother developed fever and coughing. Child and family tested positive for COVID-19. Skin and systemic symptoms resolved fully in seven days. Marzano[15] et al. described the cases of 22 patients affected primarily by diffuse papulovesicular lesions, some predominantly with papules and others with vesicular lesions. Biopsy performed in some patients was consistent with most viral infections. (example on Figure 2).

Jones[16] et al. described the case of an infant aged six months who developed signs consistent with Kawasaki disease, starting with cutaneous manifestations and later testing positive for COVID-19. The infant had non-specific fever at first, and on the second day presented with non-itchy, confluent erythematous rash (example on Figure 1). The infant later developed conjunctivitis, palmoplantar edema, and raspberry tongue.

Chesser[17] et al. described the case of a female eight-month-old infant with acute hemorrhagic edema of infancy, low fever, and coughing diagnosed with infection by coronavirus. The infant had purpura and edema in her extremities, violaceous plaques on her face, ears, torso, and feet, and bilateral conjunctivitis. The lesions in her feet disappeared in three days. The strain isolated was NL63, but it may present the signs manifested in other pathological coronavirus strains.

Lu[18] et al. described three cases in a family tested positive for coronavirus infection, one with generalized urticarial erythema (example on Figure 3) associated with mild coughing, and two other family members without skin lesions.

In Spain, two cases of skin manifestations were described in children diagnosed with COVID-19. A six-year-old hospitalized for cholestatic liver disease presented with liver disorder, low fever, and confluent maculopapular rash (Figure 1) without pruritus, starting in the torso and extending onto the arms, legs, and palms. The symptoms lasted for five days and resolved without sequelae. The second case involved a two-month-old infant with acute urticaria lasting for four days at the time of hospitalization developing from the cranial to the caudal direction, who lived with individuals diagnosed with COVID-19. The infant's RT-PCR test came back positive, but symptoms were not observed in other organs or systems[19].

DISCUSSION

Skin manifestations from COVID-19 occur rarely. Characteristic findings include fever, dry coughing, respiratory distress, myalgia, fatigue, and sore throat, as amply described in literature from all over the world. Children are less frequently and less intensely affected, and suffer predominantly with mild clinical symptoms[20-22]. Skin manifestations have been described in case reports and case series. This review included data from papers describing cutaneous manifestations, with particular emphasis on reports comprising pediatric patients.

The first paper to describe cutaneous involvement in patients with COVID-19 was published by Recalcati[4] et al. in Lombardy, Italy. More than a fifth (20.4%) of the 88 individuals with confirmed diagnoses of COVID-19 included in the study developed skin alterations. The most common alterations were maculopapular rash (77.8%) (Figure 1), urticaria (16.7%) (Figure 3), and vesicular lesions (5.5%) (Figure 2). The proportions reported in this study mirror the distribution seen in other viral diseases.

Skin manifestations are relevant in the diagnosis of numerous infectious diseases, such as toxic shock syndrome, meningococcemia, rickettsial diseases, measles, and scarlet fever, all of which more commonly seen in pediatric individuals than COVID-19[23-25]. Since COVID-19 may also present without respiratory symptoms for as long as 14 days after infection, skin alterations may serve as an indication of disease. Therefore, health care workers seeing potential cases of COVID-19 should seek skin manifestations that may precede the respiratory signs characteristically seen in individuals with this and other more prevalent infectious diseases. The incidence of diagnostic error may thereby decrease, as illustrated in the case reported by Joob[8] et al., in which the diagnosis of COVID-19 of a patient with skin signs mimicking dengue fever was delayed.

The mechanisms tied to the skin manifestations seen in individuals with COVID-19 have not been elucidated, although some theories have become more prevalent. It has been postulated that viral particles present in skin blood vessels of patients with the disease may develop lymphocytic vasculitis similarly to the cases seen in immune complexes secondary to massive cytokine activation, an event that may explain the late appearance of lesions in disease progression known as hyperinflammation[3,5]. It may also be associated with aggression to keratinocytes secondary to the activation of the Langerhans cells in the physiopathogenesis of the disease as an immune response to infection, resulting in the onset of vasodilation[3,5]. Other theories have been described to explain the appearance of livedo reticularis and even necrosis, via the accumulation of microthrombi originated in other organs, thereby decreasing blood flow into the skin's microvasculature, or even by thrombogenic vasculopathy with complement deposition[26]. It is unknown whether skin symptoms are the consequence of respiratory infection or primary skin infection, since cases have been described in which skin manifestations preceded respiratory symptoms. It is likely that these factors act in combination.

The dermatological findings reported by Piccolo[12] et al. included chilblain-like lesions characteristically seen in individuals exposed to low temperatures or presenting skin disorders derived from autoimmune conditions. The patients included in this study claimed they had not been exposed to cold weather and had no history of autoimmune disease, although they had painful erythematous-violaceous lesions in their hands and feet (Figure 4) and were free of systemic symptoms, except for three individuals with mild coughing and fever before the appearance of cutaneous lesions. The lesion resolved fully within four weeks. Workup results were normal, negative serology was seen for a number of diseases, including COVID-19 in some cases. However, since the patients had no other discernible triggering disease and were in a COVID-19 hot spot, SARS-Cov-2 was suggested as a probable etiology.

Recalcati[13] et al. reported that the erythematous-violaceous acral lesions (Figure 4) or target-like lesions in the hands or elbows of 11 children resolved without sequelae. Although some tested negative for COVID-19, the lack of another diagnosis, the widespread dissemination of SARS-Cov-2 in the region, and the significant increase seen in a type of skin lesion otherwise uncommon in the general population supported the potential ties between this finding and the pandemic. The fact that many of the patients had negative swab tests may be explained by the stage of the disease they were in, since detectable viral loads are no longer present after the initial stages of the condition. Therefore, the hypothesis is that the skin lesions seen in this case series might account for late manifestations produced by COVID-19 in healthy young individuals, possibly due to the immune response involving skin blood vessels. The absence of acute findings similar to these in older patients further supports the idea. Children may facilitate viral transmission in the early stages of the disease, even before the onset of skin alterations. Serology tests for COVID-19 might validate this thesis, since they can pick patients with later-stage disease.

Genovese[14] et al. described the case of an eight-year-old with papulovesicular lesions (Figure 2) appearing three days after the onset of dry coughing, disseminated symmetrically throughout the torso, with fever starting two days after the appearance of cutaneous lesions and a low platelet count as the only remarkable workup finding. On the same day the child and her family tested positive for COVID-19. The child recovered fully in seven days from the skin lesions and her platelet count increased. Alternative conditions such as varicella were considered, but the child had fallen ill with the disease a year before. Acute prurigo was thought of, but the child did not have pruritus. Although these findings are not sufficient to prove that the rash described by the authors was definitely tied to SARS-Cov-2, they may be helpful in diagnosis children with paucisymptomatic COVID-19. Since children develop milder symptoms and no severe respiratory

symptoms, finding skin lesions combined with mild or no symptoms on other organs and systems may indicate they have COVID-19.

Jones[16] et al. recently described the case of a six-month-old patient diagnosed with and treated for Kawasaki disease, tested positive for COVID-19, who presented with exuberant skin lesions two days after the onset of respiratory tract symptoms and was followed in an outpatient basis for viral infection without complication. The infant had polymorphic confluent maculopapular rash (Figure 1) and palmar/plantar edema. These findings match the criteria for Kawasaki disease. The causes for the condition remain unclear, but the idea that infection may trigger it has been considered, with 9% to 42% of the patients testing positive for respiratory viral infection for as long as 30 days before the onset of Kawasaki disease. Other coronavirus strains (229E, HKU1, OC43)[27] associated with the disease have been isolated.

Acute hemorrhagic edema of infancy (AHEI) has been linked to strain NL63 of the coronavirus. Symptoms include leukocytoclastic vasculitis in children aged 4-24 months, with purpuric lesions quickly developing in the patient's face, extremities, and ears, concomitantly with edema of the extremities and maintenance of the patient's general condition. Three in four patients have a history of respiratory infection prior to the appearance of lesions, immunization, and/or antibiotic therapy. Although the trigger for AHEI is rarely identified, in this case coronavirus infection may indicate an association between the two[13].

Kamali[28] et al. reported the case of a 15-day-old neonate with an untested symptomatic mother suffering from lethargy, fever, skin lesions, and signs of sepsis. RT-PCR testing came back positive for COVID-19. However, the skin findings may be due to sepsis. Mazzotta[29] et al. described cases of asymptomatic children and adolescents with acral ischemic lesions (Figure 4), two of which tested positive for COVID-19. The lesions in the hands and feet were painful. They first started as erythematous-violaceous spots and progressed to bullae and crusts before resolving completely within two weeks.

To sum up with, the described skin lesions were erythematous rash, urticaria, varicella-like papulovesicular lesions, yellowish erythematous papules, maculopapular rash, livedoid plaque, livedo reticularis-like lesions, target-like purpuric rash, petechiae, erythematous-purpuric lesions, Kawasaki disease, and one case of acute hemorrhagic edema of infancy.

CONCLUSIONS

One cannot state with certainty that the cutaneous findings seen in patients with clinical signs consistent with COVID-19 originate from infection by SARS-Cov2. A number of limitations must be considered when interpreting the findings from this literature review. First, the small number of cases described in each of the included papers precludes the extrapolation of their findings to the general population, particularly to pediatric patients, since they account for a small subset of cases. Besides, a lot is still being learned about the disease, and the information in the reviewed papers portrays the experience gathered to this point. We should also be mindful that in many case series, particularly the ones including patients with severe clinical signs, individuals are being prescribed various therapies, from which skin alterations may stem. However, since the clinical manifestations tied to COVID-19 are still being uncovered, the description of other systemic findings such as skin lesions may help to build a clearer picture of the novel disease. We must consider the possibility of the disease manifesting firstly via skin lesions and test certain patients for COVID-19. Another factor to consider is that viral rashes are similar in terms of clinical and histology traits to drug adverse reactions, particularly as numerous medications are prescribed empirically to combat the disease[11].

Pediatric patients with COVID-19 may present with skin lesions alone or in conjunction with mild symptoms. These skin lesions may be similar to lesions seen in other common childhood diseases.

The pictures used in this literature review were taken from the archives of the Dermatology Service of the São Paulo State University at Botucatu. Since only a handful of cases have been reported and even fewer contain photographic evidence attached, we opted to use archive pictures to exemplify the types of lesions described in the literature.

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