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Review Article

Cutaneous manifestations of COVID-19 in pediatric patients: literature review

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ABSTRACT

Cutaneous manifestations of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are neglected during the early period of the spread of the pandemic. Moreover, the rational that children are immune against COVID-19 infections, allowed unnoticeable spread of the disease among children and adolescents. This review article aimed to shed light on the different cutaneous manifestations of COVID-19 among pediatric age group, its related pathogenesis and histopathological features. Review of literature published since the release of the details about the disease was conducted to examine various cutaneous manifestations related to the SARS-CoV-2 infection. Review of 35 articles concerned with COVID19-related skin manifestations in pediatrics showed that it was varied and included chilblain-like, maculopapular, urticarial, vesicular, targetoid, erythema multiforme-like and COVID-19 Kawasaki disease-like multisystem inflammatory syndrome in children (MIS-C), which is serious health condition. Despite of the previously documented higher production of interferon-α in children and adolescents, children are not immune against SARS-CoV-19 infection. Cutaneous manifestations in children are usually asymptomatic and are curable unless they are drug-related side effects during the course of treatment of COVID-19. This literature review and photo atlas provide a mini-analysis of COVID-19-related skin manifestations among pediatrics with reference to their tissue histopathological changes.

Keywords: Coronavirus disease 2019, Children, Cutaneous manifestations, Histological findings, Pediatrics, COVID-19, Rash, Exanthem

INTRODUCTION

The pandemic of COVID-19, caused by SARS-CoV-2, has become a global health threat.[1] COVID-19 can affect all age groups, but the severity of its clinical course varies with age, where in neonates COVID-19 is rare and with non-specific symptoms, and in infants and children it has milder course than in adults.[2]

The SARS-CoV-2 uses its surface glycoprotein (spike) to bind to angiotensin-converting enzyme 2 (ACE2) and enter the host cell.[3] The ACE2 is most abundant on type II alveolar cells, so lungs are the organs most affected by SARS-CoV-2. Respiratory manifestations such as cough, sputum production and shortness of breath remain the most common symptoms, following fever.[4] SARS-CoV-2 infections may also involve other organs/systems and present with extra-respiratory manifestations that may occasionally be the initial presentation of SARS-CoV-2 infection, prior to fever or respiratory manifestations.[1]

Various cases of diverse dermatological manifestations of COVID-19 had reported.[5] The incidence of the cutaneous manifestation in COVID-19 patients ranges between 0.2% and 20.5%, as reported in different case series and is possibly due to the under-recognition of those asymptomatic or pauci-symptomatic cases and also,

depends on the region of origin of the studied series; 0.2–1.2% in China and 20.5% in Italy.[6,7] The severity and outcome of COVID-19 differ in pediatric patients than in adults and elderly patients and so similarly skin manifestations behave.[8] The prevalence of COVID-19 related skin manifestations in children and adolescents ranges from 0.25 to 3%, affected patients were in age range of 11-17 with male gender predilection.[9]

The most widespread cutaneous manifestation of COVID-19 in children include chilblain-like lesions, erythema multiforme, urticaria and Kawasaki disease-like inflammatory multisystemic syndrome (MSI).[10] Pediatric COVID19-associated skin lesions may be asymptomatic or associated with few mild general symptoms.[8] Moreover, the time lag between appearance of general symptoms and cutaneous lesions ranges between one and 88 days and usually disappear either spontaneously or with corticosteroid therapy within 3 to 88 days.[9]

CLINICAL TYPES

Chilblain-like Lesions

Generally, chilblain-like lesions usually occur in children and adolescents older than 10 years and are usually multiple, round, affect the entire toe with a clear demarcation at the metatarsophalangeal level and appear as erythematous, violaceous or purpuric patches and swellings. The spectrum of acral ischemic cutaneous manifestations is shown in (Figure 1).[8]

Figure 1: The spectrum of acral ischemic lesions in children with COVID-19.[8]

Recalcati et al presented a series of 11 children within age range of 11–18 years and had COVID-19 cutaneous lesions that were localized to the feet in 8 children, on hands in 3 cases and on both sites in 2 children with mild itch in three cases. Skin lesions included acral eruption with erythemato-violaceous papules and macules, with possible bullous evolution, or digital swelling (Figure 2) in majority of patients.[6] In two children erythemato-papular targetoid lesions on the hands and elbows were detected, all lesions had resolved after 2–4 weeks without treatment.

Klimach et al presented a case of 13-y old child presented by an axillary erythematous papular eruption with multiple tender erythematous papules of about 1-cm in diameter on the plantar surface and erythematous macules with associated petechiae that were scattered near to the macules on lower extremities and lead to an annular lesion after patient's discharge (Figure 3).[11]

Figure 1: (A) Papules & digital swelling on the feet of a 14-y old girl with a small overlying blister on the big toe, (B) purple macules on the right foot of an 18-y girl. (C) erythematous macules & targetoid lesions on Lt-hand of a 14-year-old girl (D) yargetoid lesions on the elbows of a 11-year-old boy.[6]

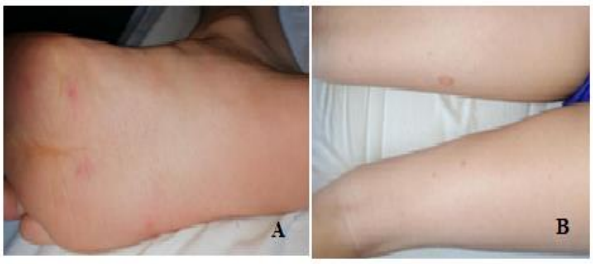

Figure 3: Skin manifestations in a case of COVID-19 patients.[12]

Cordoro et al presented a series of 6 patients aged 12-17 years healthy appearing with normal vital signs and similar cutaneous morphology. Lesions appear as red to violet macules and/or purpuric plaques scattered on middle and distal phalanges.

Figure 4: Skin manifestations in a series of 6 COVID-19 patients.

In case of severe affections, edema, superficial bullae and focal hemorrhagic crust may be present. Several patients had scattered petechial and purpuric macules on heels, soles and distal aspect of the dorsal feet, especially along the lateral foot. Half of patients had livedo reticularis involving the flexor surfaces of the forearms, the dorsal

hands and/or the dorsal feet and some patients had erythematous macules around the distal nail folds (Figure 4).[12]

Erythema multiforme-like lesions

Torrelo et al presented four children; 3 male and a female, aged 11-17 years.[13] Clinically, chilblains on the feet were present in the four cases and on the hands of two cases. Additionally, target (three rings) and targetoid (two rings), confluent macules, papules and plaques, with different sizes, some with hemorrhage or a small central crust were on examination of the hands with perniotic erythema on fingertips, elbows, forearms, and thighs and knee. Generally, 3 patients complained of itching and one of them had mild pain in the lesions. No preceding or concurrent lip sores.

Figure 5: Targetoid lesions in a series of 4 COVID-19 children.[13]

Labé et al presented a case of 6-year-old male who was presented by severe erosive cheilitis with massive gingival erosions and thick hemorrhagic crusts, bilateral conjunctivitis, along with multiple target lesions in the sole of the foot and palm of the hand. First PCR was negative, while the second PCR was positive.[14]

Figure 6: Severe erosive cheilitis with targetoid lesions in a COVID-19 child.[14]

COVID-19 KAWASAKI DISEASE-LIKE MULTISYSTEM INFLAMMATORY SYNDROME (MSI)

Yozgat et al presented a case of 3-year-old girl had fever since 6-days and recently a polymorphous rash varying from macular to maculopapular or morbilliform appeared on the trunk and spread over the extremities. Patient's face was mildly engorged with edema, red, swollen, and cracked lips. Persistent fever, mucosal findings, echogenicity of coroner vessels, and hypotension led to a clinical diagnosis of Kawasaki-like illness as a subtype of MSI in children (MSI-C) related to COVID-19 infection.[15]

Figure 7: COVID-19 Kawasaki disease-like MSI.[15]

Labé et al presented a 3-year-old male had >39.0°C for 8 days with a family history of previous COVID-19 disease, three weeks earlier. There was generalized exanthema, bilateral palmar edema, glossitis, and desquamation of the extremities was noted during a subsequent examination. Despite negative COVID-19 PC R test, CT scan revealed ground-glass opacities and consolidation in the right posterobasal area, suggestive of COVID-19 pneumonia. A final diagnosis was COVID-19-associated Kawasaki disease.[14]

Figure 8: COVID-19 3-y child showing skin manifestations with desquamation of extremities.[14]

PATHOGENESIS

Pathogenesis of cutaneous lesions associated with COVID-19 infection is indefinite, and multiple possible pathogenic mechanisms were proposed for each type of lesions.

Chilblain-like lesions

Virus-induced type-I interferonopathy hypothesis

Patients with severe COVID-19 have an impaired interferon-α (IFN-α) response with increased tumor necrosis factor and interleukin production.[16]. This interferonopathy can stimulate the development of microangiopathic changes and these changes lead to development of chilblain lesions which are the most consistent feature of interferonopathy of type-I.[17] On contrary, children and adolescents had higher production rate of INF-α.[18]

Thrombosis/coagulopathy hypothesis

Patients with SARS-CoV-2-infection have an increased risk of thromboembolism leading to the development of acral ischemia and had observed in chilblains.[19]

Vasculitis hypothesis

Pericytes have the highest expression levels of Angiotensin-converting enzyme (ACE)-2 that was proposed as the membrane receptor of SARS-CoV-2, thus making the pericyte a good candidate to explain microvascular inflammation and hypercoagulopathy in SARS-CoV-2 infection, and endothelialitis or lymphocytic vasculitis seen in COVID-19 chilblains.[20-22]

Urticaria

Kaushik et al had proposed the following possible mechanisms for viral infection-induced urticaria or angioedema 1) increased levels of interleukin-6 stimulate mast cells leading to activation and subsequent degranulation of mast cells and release of histamine, which is responsible for induction of urticarial reaction up to angioedema 2) deposition of antigen-antibody complexes with complement activation leading to mast cell degranulation 3) drug-induced immediate hypersensitivity reaction.[23]

Vesicular lesions

Vesicular lesions were considered as specific cutaneous manifestations of COVID-19 and so their identification could be useful for diagnosis. Etiologically vesicular lesions are unrelated to antiviral drugs or other COVID-19 treatments, but could be a result of an immune system overactivity causing a potential ‘‘cytokine storm’’ involving the skin or to a direct cytopathic effect of SARS-CoV-2 on endothelium dermal vessels, which produce the vesicular lesions.[24,25]

COVID-19 Kawasaki disease-like MSI-C

Certain possible pathogenic mechanisms were proposed for MIS-C in relation to COVID-19 infection:

Delayed post-viral immune dysregulation, a supposition that was supported by two observations; firstly, many children do not display typical preceding clinical manifestations of COVID-19 infection before developing MIS-C.[26,27] Moreover, many patients had positive anti-SARSCoV-2 antibodies test at the time of MIS-C diagnosis, but PCR for COVID-19 was negative.[28] MIS-C could be attributed to the ability of SARS-CoV-2 to block type I and type III interferon responses, resulting in unrestrained viral proliferation and high viral load.[29]

Livedoid or Necrotic Lesions

Livedoid lesions could be a sequalae of vascular micro-occlusion and acral ischemia secondary to deterioration of patient’s general condition or to COVID-19 induced coagulation disorders attributed to COVID-19.[30]

HISTOLOGICAL FINDINGS

Chilblains-like Lesions

El Hachem et al studied the results of histopathological examination of skin biopsies obtained from 18 patients with COVID-19 chilblain-like lesions and found all specimens showed red cell extravasation, perivascular lymphocytic infiltration localized around the eccrine glands in both the superficial and deep dermis with perivascular infiltrate also in the hypodermis. Also, epidermis showed mild changes characterized by spongiosis in 13 cases, slight vacuolation of basal layer in 14 cases and edema of the papillary dermis was observed in 12 cases. Alcian stain defined the presence of minimal mucin deposits mostly in the deep dermis in 10 cases with a diffuse involvement of subcutis (Figure 9). Also, Zengarini et al presented the histological changes in a cutaneous biopsy obtained from a COVID-19 induced viral rash showing slight superficial perivascular lymphocytic infiltrate with extremely dilated vessel in the papillary and mid dermis (Figure 10).[32]

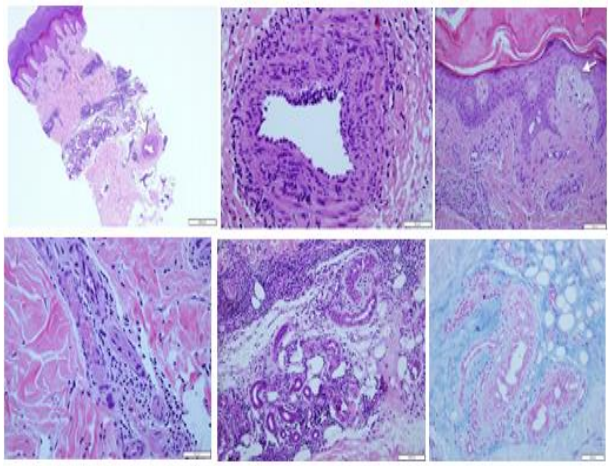

Figure 9: Histological examination of skin biopsies obtained from 18 patients with COVID-19 induced chilblain-like lesions.[31]

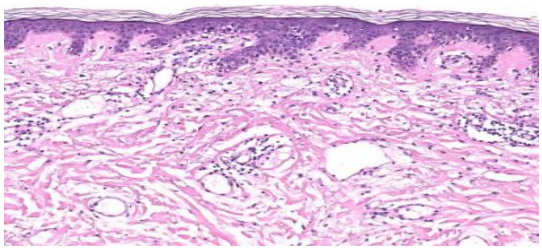

Figure 10: Histological examination of skin biopsies obtained from a patient with COVID-19 induced chilblain-like lesions.[32]

Vesicular and chickenpox-like lesions

Fernandez-Nieto et al showed the results of histological examination of skin biopsies obtained from patients with COVID-19 vesicular rash showed an intra epidermal vesicle containing scattered multinucleated and ballooned keratinocytes, with mild acantolisis. Deeper section of the vesicle reveals more extensive damage, with epidermal detachment, confluent keratinocytic necrosis and intravesicular fibrinoid material with acute inflammation (Figure 11).[24]

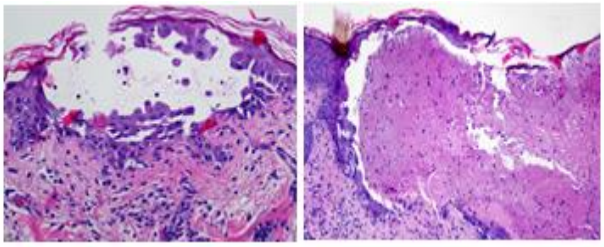

Figure 11: Histopathological picture of biopsy of COVID-19 vesicular rash skin lesion; H&Ex20 in A & x10 in B.[24]

Marzano et al showed the results of histological examination of biopsy obtained from affected skin by COVID-19 induced vesicular lesions that included Basket-wave hyperkeratosis; slightly atrophic epidermis; and vacuolar degeneration of the basal layer with multinucleate, hyperchromatic keratinocytes and dyskeratotic cells with absence of inflammatory infiltrate.

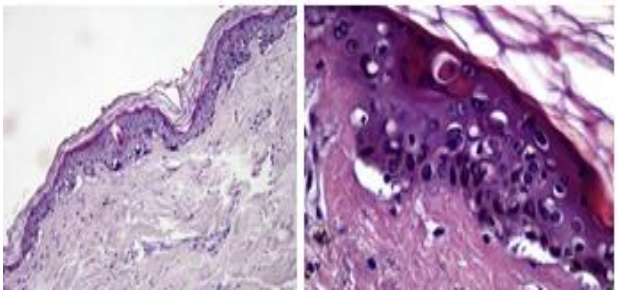

Figure 12: Histopathological picture of biopsy of COVID-19 vesicular skin lesion; H&Ex4 in A & x20 in B.[33]

Maculopapular rash

COVID-19 induced maculopapular lesions showed a variable range of features such as a superficial perivascular dermatitis with mild spongiosis, thrombosis of small vessels in mid dermis, extravasated RBC due to endothelial damage and superficial perivascular dermatitis with lymphocytic vasculitis in mid dermis; dyskeratotic, ballooning and necrotic keratinocytes with lymphocytic exocytosis (Figure 13).[34]

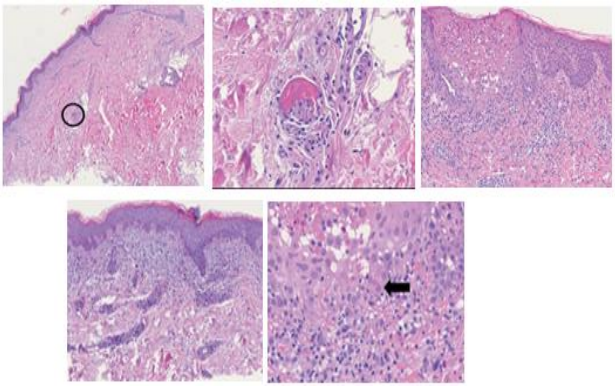

Figure 13: Histological examination of skin biopsies obtained from patients with COVID-19 induced maculopapular rash.[34]

Erythema multiforme-like lesions

Torrelo et al presented results of histological examination of skin biopsy of two cases of COVID-19 induced erythema multiforme-like lesions; biopsies showed interface dermatitis with superficial and deep perivascular lymphocytic inflammation, inflammation and vascular ectasia, exocytosis; mild and moderate with vacuolar changes and spongiosis, deep extension of the inflammatory infiltrate involving eccrine glands and a mid-dermal vessel showing transmural lymphocytic infiltration and plump endothelial lining (Figure 14).[13]

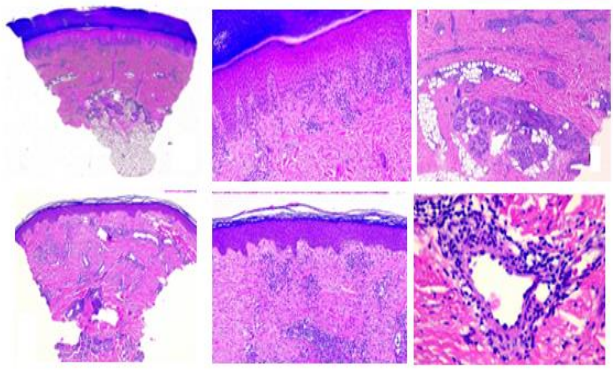

Figure 14: Histological examination of skin biopsies obtained from 2 patients with COVID-19 induced erythema multiforme-like lesions.[13]

Livedoid lesions

Serial sections of livedoid lesions showed nests of Langerhans cells (red arrow) in the epidermis and in the deep dermis and occasionally in the superficial dermis with large and microthrombi (black arrows) admixed with nuclear and eosinophilic debris (Figure 15).[34]

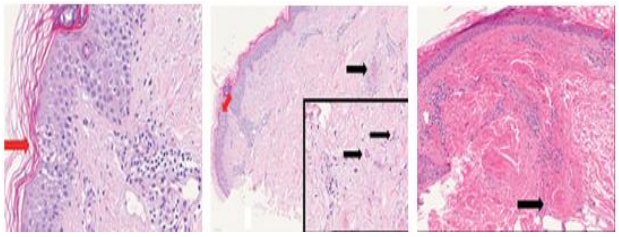

Figure 15: Histological examination of skin biopsies obtained from patients with COVID-19 induced livedoid lesions.[34]

CONCLUSION

Although high production rate of interferon-α is a finding in children and adolescent, they are not immune against SARS-CoV-19 infection. However, clinical manifestations are milder in pediatrics than in adults and associated cutaneous manifestations are usually asymptomatic and are curable, making the cutaneous manifestations in children under-evaluated. This review article and photo atlas provide a mini-analysis of COVID-19-related skin lesions with reference to their tissue histopathological effects.

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