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Review

Cutaneous Manifestation in COVID-19: A Lesson Over 2 Years Into the Pandemic

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Cutaneous manifestations related to Coronavirus Disease-19 (COVID-19) have been reported over 2 years since the pandemic began. This research aimed to review articles published in English that describe cutaneous manifestations related to COVID-19/SARS-CoV-2. A data search for case reports, original studies, and review articles from the onset of the current COVID-19 pandemic to December 31, 2022, was performed using PUBMED, Cochrane Library, ResearchGate, and Google search engines. Keywords were "*coronavirus*", "*novel coronavirus 2019*", "*COVID-19*", "*SARS-CoV-2*", and *"2019-nCoV"* in combination with "*cutaneous*", "*skin*" and "*dermatology*". The extracted data included authors, region, sex, age, number of participants with skin signs, cutaneous signs, its location, symptoms, extracutaneous/associated symptoms, suspected or confirmed status for COVID-19, timeline, and healing duration. Six authors independently reviewed the abstracts and full-texts to identify publications providing these details concerning cutaneous manifestations related to COVID-19. A total of 139 publications with full text (122 case reports, 10 case series, and 7 review articles) that reported cutaneous manifestations were identified, and reviewed from 5 continents. The most common cutaneous manifestations of COVID-19 were maculopapular, followed by chilblain-like lesion, urticarial, livedoid/necrotic, vesicular, and other/non-descript rashes/skin lesions. After 2 years into the COVID-19 pandemic, we can conclude that there is no pathognomonic cutaneous manifestation of COVID-19, since it can be also found in other viral infections.

Keywords: Coronavirus Disease-19; COVID-19; Cutaneous manifestation

Coronavirus Disease 2019 (COVID-19) began in December 2019 in Wuhan, the capital of Hubei province, China. The disease is caused by a novel coronavirus that is structurally related to the virus that causes Severe Acute Respiratory Syndrome (SARS).[1] The outbreak of COVID-19 was declared on January 30, 2020 by the World Health Organization (WHO) as a Public Health Emergency of International Concern (PHEIC).[2] Within 2 weeks, on March 11, 2020, the WHO declared that the COVID-19 outbreak was an official pandemic, based on the high level of global spread and the severity of the disease.[3] As of February 17, 2023, the total number of confirmed COVID-19 cases was 756,581,850 worldwide, and the total number of deaths was 6,844,267.[4]

Typically, the symptoms of COVID-19 disease are similar to other viral respiratory infections. Fever (88%) is the most frequently reported clinical symptom of COVID-19 in laboratory-confirmed cases, followed by dry cough (68%), fatigue (38%), sputum production (33%), dyspnoea (19%), myalgia

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or arthralgia (15%), sore throat (14%), and headache (14%).[5,6] The 'Cytokine Storm' syndrome has an immunopathogenic role in disease progression due to excessive proinflammatory cytokines, contributing to the development of severe disease,[7] and late onset of skin lesions.[8]

In a study involving 1,099 cases in China, Guan et al[9] reported the first signs of skin manifestations in two patients with SARS disease. Unfortunately, the report did not describe the characteristics and progression of the lesions. Later in Lecco Hospital in Italy, Recalcati[10] provided a fuller description of the cutaneous manifestations of 148 patients confirmed positive for COVID-19 infection. The description of skin symptoms in 20.4% of patients identified three main types: erythematous rash, urticaria, and chickenpox-like lesions. Interestingly, these cutaneous lesions did not correlate with disease severity. Recently, more reports have been published describing skin manifestations in patients with COVID-19 from five continents: Asia, Africa, Europe, North America, and South America.

Using a prospective nationwide consensus study in Spain, Galvan Casas et al[11] made a classification of the cutaneous manifestations in confirmed and suspected cases. They classified the lesions as pseudo-chilblain, other vesicular eruptions, urticarial lesions, other maculopapular eruptions, and livedo or necrotic lesions. After 2 years into the pandemic, we aim to provide a review of what has been learned related to cutaneous manifestation in COVID-19 cases.

Methods

A comprehensive data search of case reports, case series, original studies, and review articles from the onset of the current COVID-19 pandemic to December 31, 2022, was performed using PUBMED, Cochrane Library, ResearchGate, and Google search engines. Keywords were "*coronavirus*", "*novel coronavirus 2019*", "*COVID-19*", "*SARS-CoV-2*", and "*2019-nCoV*" in combination with "*cutaneous*", "*skin*" and "*dermatology*". Additionally, hand-searching of reference lists for related publications was done. The extracted data were author, region, sex, age, number of participants with skin signs (when not detailed), cutaneous signs, its location, symptoms, extracutaneous/associated symptoms, suspected or confirmed status for COVID-19, and timeline and healing duration. Six authors independently reviewed the abstracts and full texts to identify studies describing cutaneous manifestations related to COVID-19.

Results

A total of 139 publications with full text (122 case reports, 10 case series, and 7 review articles) that reported cutaneous manifestations were identified and reviewed by the initial search from 5 continents (Africa, Asia, Europe, North America, and South America). All articles were included in the study to give comprehensive learning during 2 years into the pandemic from across the globe. The most common cutaneous manifestations of COVID-19 were maculopapular rash (31.16%) followed by chilblain-like lesions (CLL) (26.81%), urticarial (23.19), livedoid/necrotic (8.7%), vesicular (7.97%), and other/non-descript rashes/skin lesions. Most lesions were localized on the trunk and some patients experienced cutaneous manifestations on their hands and feet.

Skin findings may present at any stage of the infection both in children and in adults. Some of the cutaneous manifestations preceded the onset of fever and other systemic symptoms which are more commonly associated with COVID-19;[10] others appeared the same day with systemic symptoms,[12-14] after systemic symptoms/confirmation of COVID-19,[8,10,12,15-67,142] or they occurred without other symptoms.[12,52,68-70] Within 10 days, these lesions in all patients spontaneously healed and disappeared.

Globally, cutaneous manifestations of COVID-19 were reported in cases from Asia including China,[9,36,47,1-75] Thailand,[76,77] Iran,[12,61,78-81] Indonesia,[19,46,60,67,82,142] Malaysia,[60] Qatar,[77] India,[83] Turkey,[14,84-86] and Kuwait;[87] from Africa including Morocco[20,88] Tunisia,[88] and Egypt;[89] from Europe including Austria,[90] Italy,[10,12,15,18,21,24,25,32-35,43,52,53,57,65,69,75,91-104] France,[12,26,31,105-114] Spain,[8,11,16,17,22,27,28,41-45,48,51,55,68,70, 15-126] Belgium,[40,127] Ireland,[62] Germany,[128] The Netherlands[12] Poland,[13,62,66,77,90] United Kingdom,[12,58] Switzerland,[58] and Russia;[54] from North America including USA,[12,29,30,37-39,50,63,129-133] Canada,[12] Mexico;[12,23,49,56] and from South America including Brazil.[134] The majority of the studies reported no correlation between COVID-19 severity and skin lesions.

Vascular Lesions

There have been several reported cases of vascular lesions in patients with COVID-19, including acro-ischemia or CLL,[11,12,15,17,18,24-28,30,34,35,37,40,50-52,55,64,69,73,81,87,91,99-102,106,112,113,121-123,125,126,130] dry gangrene,[74] livedo-like rash,[11,26,29,30,53,59,64,65,81,82,112,124] petechiae/purpuric eruptions,[41,44,62,69,76 81,82,93,112] lesions resembling urticarial vasculitis,[120,55,64,83,114] and vasculitic purpura/vasculitis.[48,58,97,114,133]

Maculopapular Lesions

Maculopapular lesions have been reported in the different types of viral exanthem-morbilliform-maculopapular lesions-erythematous rash,[8,10,11,21,26,32,33,38,39,42,44-47,49,54,56,59,64,72,75,81-83,85,92,95,98,102,104,107,108,110,112,114,117,126,129,130,132,134-137] pityriasis rosea-like eruptions,[57,78,82,106)] and digitate papulosquamous rash.[109] These lesions are a common morphology seen in the course of viral infection accompanied by prodromal signs such as fever, headache, and muscle pain. A few cases which included pseudovesicular lesions or were similar to erythema elevatum diutinum and erythema multiforme, presented with infiltrated papules on the extremities, mostly on the dorsum of the hands.[11]

Urticaria

Urticaria has been reported by several authors.[10,11,19,22,23,25,26,39,45,47,56,64,71,75,81,83,84,97,102,105-107,112,114-116,118,127,130,134-136]

These lesions are appearing as a possible COVID-19 skin manifestation.

Vesicular Eruption

Cases with vesicular eruption include vesicles,[16,56,63,66,81-83,107,112,114,135] blisters,[89] and varicella-like exanthem.[10,11,21,26,43,75,94,96,106] These lesions were described as specific to COVID-19, highlighting that no patient with these skin manifestations was given any new medications in the 2 weeks before eruption onset.

Erythema Multiforme-like Rash

Erythema multiforme-like (EM-like) rash was reported as a cutaneous sign related to COVID-19.[17,20,28,68,70,75,83,119,123] Jimenez-Cauhe et al[119] proposed EM-like or target-like exanthem is another form of exanthem related with COVID-19 infection. Amatore et al[108] and van Damme et al[127] reported targetoid lesions in exanthems of patients with COVID-19 infection.

Mucosal Lesions

Mucosal lesions have been reported as a sign of COVID-19 infection.[46,54,107,111,117] Martin Carreras-Presas et al[117] presented three cases (two suspected and one confirmed) of patients presenting with ulcers in the oral cavity. This manifestation is commonly observed in other viral processes, including aphthous fever, hand, foot, and mouth disease, and herpetic gingivostomatitis. Olisova et al[54] describe a girl confirmed positive for COVID-19 infection with erythematous macules and purpuric eruptions on her face and swollen tongue with pronounced lingual papillae. These lesions completely disappeared within three days without treatment.

Miscellaneous

There have been several reports of patients with COVID-19 having unusual skin eruptions such as acrodynia,[112] dyshidrosis-like lesions,[112] periorbital erythema,[131] eyelid dermatitis,[36,80]skin rash resembling symmetrical drug-related intertriginous and flexural exanthema,[31] mottling,[79] erythema nodosum-like lesions,[56,57,60,61,64,67,77,81,82,88,90,102,103,138] cutaneous hyperesthesia,[13] fixed erythema,[65] facial edema,[64] dermatomyositis,[90] ecchymoses,[64] erythema pernio-like,[135] erythema nodosum-like Sweet's syndrome,[14] and follicular eruption.[142]

Discussion

Since the pandemic began more than 2 years ago, we have seen many cutaneous manifestations. The previously described cutaneous manifestation such as pseudo-chilblain, other vesicular eruptions, urticarial lesions, other maculopapular eruptions, and livedo or necrotic lesions[81] had all been seen over the past 2 years. This suggests that there is no single pathognomonic cutaneous manifestation of COVID-19 since the same clinical appearance can also be found in other viral infections.[139,140]

We do not yet fully understood the reason and pathophysiology behind the cutaneous manifestation and the reason why a certain patient can develop certain skin manifestations while others do not. Angiotensin-converting enzyme receptor found on the skin was thought to play a role in cutaneous manifestation.[81] Cytokines and mediator inflammatory such as interleukins (ILs), interferons (IFNs), and Tumor Necrosis Factor-Alpha (TNF-alpha) was also thought to be responsible for the skin manifestation.[139,141] Other than this mechanism, thrombosis over the vessel in the underlying skin was also thought to play a role.[67] Nevertheless, we still do not know why the inflammatory mechanism differs from person to person.

Another lesson to be noted was that at the beginning of the COVID-19 pandemic, the clinician did not focus too much on cutaneous manifestation. Attention was given more to respiratory manifestation, yet we know that in the course of the pandemic, there are cases in which the only manifestation of COVID-19 were the cutaneous manifestations.[12,52,68-70] For unrecognized COVID-19 patient with only skin manifestation, the danger of spreading the disease is also imminent. This means that we have to be prepared for a similar scenario in case of another possible pandemic.

Over 2 years of the COVID-19 pandemic, several messages can be reflected. Skin manifestation can happen in viral infection due to an inflammatory process. It can happen before, during, and after the respiratory symptoms. Sometimes it is the only manifestation and critical judgment is needed during the pandemic.

Conclusion

There are various cutaneous manifestations of COVID-19 reported in the last 2 years, and the pathophysiology has not been fully understood. The reported cutaneous manifestations of COVID-19 fell into the category of pseudo-chilblain, other vesicular eruptions, urticarial lesions, other maculopapular eruptions, and livedo or necrotic lesions. It can appear before, during, after, or manifest as the only manifestation.

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Reference #142 was added by the authors during galley proofing, and thus, appears out of order in the text.

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