

Cutaneous involvement in COVID-19 patients

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ABSTRACT

The ongoing coronavirus disease 2019 (COVID-19) outbreak was declared a pandemic by the World Health organization in early March 2020.

The disease typically presents with viral respiratory symptoms that could progress to acute respiratory distress syndrome. Emerging evidence suggests different possible dermatologic manifestations of COVID-19, including: acral lesions (pernio-like, pseudo-chillblain), vesicular eruptions, macular and papular exanthema, urticaria, livedoid, purpuric and petechial rashes. However, specific skin manifestations of the COVID-19 disease have not yet been clearly established and the relationship between the appearance of skin lesions and SARS-CoV-2 infection is still unclear. These highly variable skin changes could represent a direct consequence of the viral infection, an immunological response to viral nucleotides, adverse reactions to drugs frequently used for the treatment of COVID-19, or other disorders.

In a global effort to comprehend the exact cutaneous features of COVID-19, several international dermatological societies have initiated nationwide studies to analyze COVID-19 cutaneous manifestations during this pandemic.

This paper represents a literature review of the scientific data available on the clinical characteristics and symptoms of the cutaneous manifestations associated with COVID-19.

Such findings are extremely useful in establishing if dermatological manifestations in COVID-19 patients could harbor a diagnostic significance and subsequently be used as prognostic factors for outcomes of COVID-19.

Keywords: COVID-19, SARS-CoV-2, cutaneous manifestation, skin

INTRODUCTION

"COVID-19" is the acronym of "coronavirus disease 2019", an acute respiratory illness caused by a novel coronavirus, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) (1). This new extremely contagious virus was first identified in late 2019 as the cause of a cluster of unexplained pneumo-

nia cases in the city of Wuhan, China, and has quickly spread globally. On March 11, WHO (World Health Organization) declared the COVID-19 a global pandemic (2).

The current pandemic is a public health crisis, further heightened by the limited amount of data available on the associated clinical findings. The suspicion

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of COVID-19 disease is usually based on clinical data, vital parameters, and suggestive imaging (radiography, computed tomography) (3). Recent publications reported the presence of various skin changes, suggestive of SARS-CoV-2 infection, but, however, specific skin manifestations of the COVID-19 disease have not yet been clearly established (4). It is still unclear whether skin lesions in patients with COVID-19 are related directly with the viral infection or are a consequence of the host's immune response. Nonetheless, cutaneous manifestations may represent a reaction to systemic medications administered for the treatment of COVID-19.

Further research in this direction is pursued. Several studies are currently focusing on cutaneous manifestations that are emerging in COVID-19 patients and whether there is a significant relation between the appearance of skin lesions and SARS-CoV-2 infection.

OBJECTIVE

This paper represents a literature review of the current state of knowledge related to the clinical characteristics and symptoms of the cutaneous manifestations associated with COVID-19. Such findings are extremely useful in supporting the early diagnosis of infection, as well as the prevention of widespread community transmission.

MAIN PATTERNS OF SKIN MANIFESTATIONS DETECTED IN COVID-19 PATIENTS

Recalcati was the first to analyze the cutaneous involvement in COVID-19 patients, in the Lecco Hospital in Lombardy, Italy. In this study, 18 out of 88 COVID-19 patients developed cutaneous manifestations, such as erythematous rash ($n = 14$), urticaria ($n = 3$) and chickenpox-like vesicles ($n = 1$). However, no clinical images are available in the article due to safety concerns about the increased risk of transmission of the virus (4).

After this first perspective offered by Recalcati, a wide variety of skin manifestations, with different morphology, arrangement, and distribution of the skin lesions were described in COVID-19 patients. The American Academy of Dermatology task force has compiled an online registry to collect cases of skin

manifestations that seem to be associated with COVID-19. This is an international registry that's open to any healthcare provider and physician who is caring for patients who develop any dermatological manifestations of COVID-19 (5). Multiple countries, such as France or Spain have rapidly initiated nationwide studies to analyze COVID-19 cutaneous manifestations during this pandemic (6,7).

This global clinical effort against COVID-19 aims to rapidly provide novel information and illustrative images that will help clinicians and researchers worldwide to better understand the whole range of dermatologic manifestations of this new disease, the relationship between the SARS-CoV-2 infection and skin manifestations, and establish whether any of these cutaneous findings can help with early disease detection.

The following broad categories have been identified so far: acral lesions similar to perniosis (pseudo-chilblain), vesicular eruptions, maculopapular exanthema, urticaria, livedo, purpuric and petechial rashes.

Acral lesions

Dermatologists around the world are reporting acral lesions thought to be associated with COVID-19.

On a press release on April the 6th, the French National Union of Dermatologists-Venereologists (SNDV), the largest association of dermatologists in France, announced that new-onset skin lesions similar to frostbite and chilblain on the fingers and toes are potential emerging skin manifestations of COVID-19. These lesions are now frequently referred to as "COVID toes" and, in some cases, have been pointed as only indicators of the disease, in otherwise asymptomatic patients (6).

A multicentric study in Spain, that included a sample of 375 patients, investigated the cutaneous manifestations of COVID-19. Acral "pernio-like lesions" were identified in 19% of cases and were described as areas of erythema and edema, associated with vesicles or pustules. The most affected were young patients suffering from a less severe forms of COVID-19. Furthermore, these lesions appeared later in the course of the disease and were rarely associated with positive results in SARS-CoV-2 RT-PCR tests (reverse transcription polymerase chain reaction) (7).

Despite the growing evidence showing an association between perniosis and COVID-19, the strength of

this relationship as well as the underlying pathophysiology remain unclear.

Classical perniosis is a disorder defined by the development of erythematous to violaceous skin lesions, due to an abnormal vascular response to cold exposure (8). It has been reported independently (idiopathic pernio) or in association with various diseases, including autoimmune diseases (e.g. cutaneous lupus erythematosus, antiphospholipid antibody syndrome, an undifferentiated connective tissue disease, rheumatoid arthritis), hematologic disorders (eg, paraproteinemia), viral hepatitis or malignancy (9).

Vesicular exanthema

Marzano et al. reported in April 2020 a multicentre case series of 22 cases of varicella-like exanthema as a specific cutaneous manifestation associated with COVID-19. Papulo-vesicular lesions were located mainly on the trunk and, less frequently, on the limbs. Skin biopsy was performed in 7 patients and the histologic changes were characteristic of viral skin infections (10).

The prospective nationwide consensus study in Spain proposes a new classification of skin manifestations of COVID-19, describing monomorphic disseminated vesicular lesions (not polymorphic, as in chickenpox-like). Viral infections can manifest with extremely variable rashes in general, but this pattern has been designated as “probably quite specific” for COVID-19. It was more frequently observed among middle-aged patients, especially before the onset of other symptoms, and it was associated with a moderate form of the disease (7).

Maculopapular exanthema and urticaria

Multiple reports document maculopapular rash and urticarial eruption in COVID-19 patients (11-14), but data are insufficient to confirm a causative relationship between SARS-CoV-2 infection and such occurrences.

Maculopapular exanthema and urticaria are common disorders, and it is often hard to distinguish (both clinically and histologically) whether they are caused by the viral infection itself, the medication prescribed to treat COVID-19 or other factors.

In a letter to the editor, van Dame et al. warned clinicians that new-onset urticaria accompanied by fever can represent the first manifestation of

COVID-19, in patients not necessarily showing any respiratory symptoms (15).

Livedo

In another recent paper, Manolo et al., from Emory University, Atlanta, presented two cases of transient unilateral livedo reticularis as a dermatological manifestation of COVID-19. The authors postulated the condition was most likely caused by a transient low-grade disseminated intravascular coagulation (DIC), induced by the SARS-CoV-2 infection (16).

According to the consensus study in Spain, livedoid presentations and necrotic lesions are suggestive of occlusive vascular disease in elderly patients, with more severe manifestations of COVID-19. However, they are relatively uncommon (6% in a sample of 375 patients) (7).

Purpuric lesions

In a retrospective observational study of cutaneous manifestations during COVID-19 pandemic in France, Bouaziz et al. described the following vascular skin lesions in 7 patients that tested positive for SARS-Cov-2 by rRT-PCR (real time RT-PCR): bluish-purple macules characterized as “porcelain-like” (n = 1), livedoid lesions (n = 1), non-necrotic purpuric rash (n=1), purpuric lesions with skin necrosis (n=1), acral chilblain-like lesions with Raynaud’s phenomenon (n = 1), chilblain (n = 1), sudden onset of multiple cherry angiomas (n = 1).

The pathophysiology of these skin findings is unclear and the authors highlight it may be related to abnormal immune response, vasculitis, microthrombosis or neovascularization processes (17).

A recent publication also reported new-onset purpuric lesions on the lower extremity of a 65-year-old woman diagnosed with SARS-CoV-2 infection, highlighting the occurrence of COVID-19-induced immune thrombocytopenia in this patient (18).

Petechial rashes

A paper by Joob et al. described the case of a COVID-19 patient from Thailand (the second country in which the SARS-CoV-2 infection was reported) that developed a petechial (small non-blanching lesions) rash (19). The rash was initially misdiagnosed for Dengue disease, a mosquito-borne viral infection that may present with a wide spectrum of clinical

presentations including fever, a macular rash, and petechia (20). The authors highlighted the possibility that, in regions where Dengue is very common, a COVID-19 patient can present with a dengue-like petechial rash and be easily misdiagnosed.

Kawasaki-like skin changes in children

Reports of Kawasaki disease (KD) or Kawasaki like illnesses are rapidly emerging in children who've been affected by the novel coronavirus.

On April 26, NHS England issued an emergency alert warning that COVID-19 disease in children could be accompanied by an atypical form of KD (21).

On April 7, Jones *et al.* had reported the first case of KD with concomitant COVID-19 infection. Two days after the onset of fever, the 6-month-old infant developed classical features of KD: an erythematous macular exanthema followed by non-exudative conjunctivitis, oral mucositis, extensive morbilliform rash

and edema in the upper and lower extremities. The patient also tested positive for SARS-Cov-2 by rRT-PCR (22).

Further study of the potential association between pediatric COVID-19 with KD is warranted.

CONCLUSIONS

There are limited data regarding the clinical characteristics and symptoms of the cutaneous manifestations associated with COVID-19. Our understanding of the spectrum of dermatological manifestations in COVID-19 patients as well as the underlying pathological mechanism continues to evolve.

Dermatologists have a unique opportunity to study, report, and describe skin manifestations in this pandemic. Sharing our collective experiences will lead to a better understanding of this disease, this being a priority for the entire medical and scientific community around the world.

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