

## REVIEW ARTICLE

# Six months into the pandemic. A review of skin manifestations in SARS-CoV-2 infection

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Email: emanuele.cozzani@unige.it**Abstract**

During the COVID-19 pandemic, various cutaneous manifestations have been described as associated with SARS-CoV2 infection. It is debated if skin lesions could represent a diagnostic or prognostic indicator. Specifically, it is unclear whether skin lesions may be used to perform an early diagnosis and/or to predict worse outcomes. In this review, we described the cutaneous signs so far reported as COVID-19-related and discussed their incidence, clinico-pathological features, and diagnostic and prognostic value.

**KEYWORDS**

coronavirus, COVID-19, cutaneous manifestations, SARS-CoV2, skin

## 1 | INTRODUCTION

In December 2019, the coronavirus disease of 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2), was identified in Wuhan, China. In the ensuing months, the COVID-19 pandemic has spread across the world. Emergency departments have adopted screening and triage procedures to identify potential cases and isolate them during evaluation.<sup>1</sup>

Suspect of COVID-19 is mainly made on clinical signs (fever, fatigue, dry cough, anorexia, dyspnea, rhinorrhea, ageusia, anosmia), vital parameters (temperature, pulse oximetry saturation), and radiological settings (X-ray, Chest CT scan). Laboratory findings often demonstrate lymphopenia and elevated LDH. Nasopharyngeal and oropharyngeal swabs, allowing the virus isolation, confirms the diagnosis.<sup>2</sup>

Recently, the suspect that skin manifestations could be a sign of infection is increasing day by day, due to growing publication of case reports and case series. The exact incidence of skin reactions due to COVID-19 is still unknown. Also, it is unclear whether COVID-19 affects skin and whether a possible link between skin reactions and infection severity exists.

For these reasons, the aim of this paper is to review the available evidence on the cutaneous reactions related to COVID-19.

## 2 | METHODS

Up to 10 September 2020, a literature search was conducted in the PubMed/MEDLINE database, using the terms "COVID-19" and "SARS-CoV-2" in combination with the terms "skin", "cutaneous", "rash". Language was restricted to English.

To limit interference from isolated reports or chance associations, as we aimed to provide an overview on the most frequently observed skin manifestations in the setting of Sars-CoV-2 infection, only the original articles and case series reporting at least 10 patients were comprised.

Two blinded reviewers independently screened articles for fulfillment of inclusion criteria. Articles from the references cited in the retrieved papers were considered as well.

## 3 | RESULTS

Initial and updated searches found 1736 titles, with 1107 titles once duplicates were removed. A total of 629 full-text papers were reviewed and checked for inclusion criteria. The final analysis included 36 papers, with a total of 1340 patients with SARS-Cov-2 skin manifestations.

The characteristics of the cutaneous symptoms were clustered together into categories, following a method elsewhere described,<sup>3</sup> and included: vesicular eruption (88 cases), urticarial eruptions

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(86 cases), erythematous and maculopapular exanthemas (451 cases), and vascular skin lesions (715). The latter category was subdivided as follows: livedo, purpuric lesions (23), and chilblain-like and erythema multiforme-like lesions (692).

It was not possible to separate the cases confirmed by swab test or biopsy from patients whose diagnosis was not confirmed, as this datum was not always reported.

### 3.1 | Vesicular eruptions

In a multicenter Italian analysis, chickenpox-like vesicular eruptions were reported in 22 inpatients with PCR-confirmed SARS-CoV-2 infection.<sup>4</sup> Lesions were asymptomatic or mildly itching and spared face and mucosae. Almost all patients had fever. Seven patients underwent skin biopsies; histological findings were consistent with viral infection. These eruptions did not result in predicting better or worse outcomes. The authors did not specify the number of patients evaluated, thus no conclusion can be made about the incidence of this kind of rash.<sup>4</sup> Recalcati et al.<sup>2</sup> reported only one case of chickenpox-like eruption among 88 inpatients evaluated.

However, the definition of "chickenpox-like" vesicular rash is under debate, because histological features (ie, prominent acantholysis and dyskeratosis with constitution of a unilocular intra-epidermal vesicle in a suprabasal location) are not consistent with those found in chickenpox.<sup>5</sup> A Spanish multicentric study on 375 patients with rash and COVID-19-compatible symptoms reported 34 (9%) cases of monomorphic vesicular eruptions, 17 of them with PCR-confirmed SARS-CoV-2 infection.<sup>6</sup> A more recent prospective study on 24 COVID-19 patients with vesicular skin lesions described a disseminated pattern in 75% of them; 79% of patients developed the rash after the onset of COVID-19 symptoms. The authors performed PCR for SARS-CoV-2 from the vesicles of 4 patients, with negative results.<sup>7</sup> Two patients with diffuse vesicular eruption were reported in a French study involving both outpatients and inpatients.<sup>8</sup> Vesicular eruptions have been described also in Thailand, in 2 out of 153 patients diagnosed of COVID-19.<sup>9</sup> A similar rash was described in one patient in Barcelona, whereas 2 out of 130 inpatients evaluated in a hospital in Rome showed herpetiform grouped vesicles. The latter could have been caused, according to the authors, by human herpes virus 1 or 2.<sup>3</sup> Human herpes virus reactivation would not be surprising among critical inpatients; Hedou et al. reported one in an intubated patient with SARS-CoV-2 infection, as well as Rerknimitr et al.<sup>9,10</sup> A higher incidence of herpes zoster has also been reported.<sup>6</sup>

Also, a Grover-like picture has been described by Matar et al.<sup>11</sup> Except for one patient presenting with clinical and histological features of an acantholytic, Grover-like disease,<sup>12</sup> there is no certain report about vesicular rash in outpatients.

### 3.2 | Urticarial eruptions

Urticarial eruptions among COVID-19 patients have been reported.<sup>8,13</sup> A prospective Italian study on 103 PCR-confirmed

COVID-19 patients identified 2 patients with urticarial rash.<sup>12</sup> In an Italian study, 3 out of 88 COVID-19 inpatients showed urticarial eruptions.<sup>2</sup> A Spanish multicentric study on 375 patients with COVID-19-compatible symptoms and cutaneous lesions reported 73 patients with urticarial rash, of which 49 were PCR-confirmed cases.<sup>6</sup>

Among 153 patients diagnosed with SARS-CoV-2 infection in Bangkok, Thailand, who were retrospectively interviewed to collect data on skin manifestations, urticarial rash was the most commonly reported dermatological sign.<sup>9</sup>

Wheals were also the most frequent skin manifestations (3 out of 10 patients with cutaneous lesions, among 138 COVID-19 inpatients) in a hospital in India.<sup>14</sup>

### 3.3 | Erythematous and maculopapular exanthemas

Erythematous, macular, and papular exanthemas have been widely reported.<sup>8,12,15</sup> Erythematous rash was the most common cutaneous manifestation (14 out of 88 COVID-19 inpatients) described by Recalcati et al.<sup>2</sup>

According to Galván-Casas et al.,<sup>5</sup> half of the cutaneous manifestations in COVID-19 patients were maculopapular rashes. Maculopapular exanthema was the most common skin manifestation among 759 COVID-19 patients in a hospital in Paris, France; still, it was very rarely recognized.<sup>11</sup> Erythematous scaly rash and maculopapular rash accounted respectively for 32.7% and 23% of skin manifestations among 210 COVID-19 patients in a hospital in Turkey, 52 of whom developed skin lesions during infection.<sup>16</sup> According to a Spanish study, mucosal enanthes were found in 6 out of 21 PCR-positive patients showing a skin rash.<sup>17</sup> Four out of 153 COVID-19 patients showed a maculopapular eruption in a study conducted in Thailand.<sup>9</sup> Pangti et al. reported only one case of macular erythematous rash among 138 SARS-CoV-2-positive inpatients.<sup>14</sup> Another Indian study reported 13 patients with cutaneous manifestations out of 102 COVID-19 patients; however, itching with no skin lesions was the most common sign, followed by maculopapular rash, which was described in 3 patients only.<sup>18</sup>

A case of eruptive pseudoangiomatosis, a skin condition related to viral infections, was reported.<sup>8</sup>

### 3.4 | Vascular skin lesions

Vascular cutaneous lesions are of interest because their possible pathogenic mechanisms could be the same affecting other organs, leading to a systemic clinical picture.

Livedo, necrotic purpura, and dry gangrene were rarely found in studies with large samples<sup>6,8,9,14</sup>; and numerous series reported no case of vascular lesions.<sup>2,12</sup>

More commonly, chilblain-like lesions were found on the extremities. They are described in both inpatients and outpatients. Histology of these skin lesions were described by Kanitakis et al., although in PCR-negative patients.<sup>19</sup> Most reports involve young outpatients.<sup>20,21</sup>

Analyzing the results of a large study,<sup>6</sup> the mean age of patients with severe vascular skin lesions is significantly higher, whereas patients showing chilblain-like lesions are significantly younger (63.1 vs 32.5 years). In Spain, a real outbreak of acral chilblain-like lesions was described during the pandemic; several studies investigated its relation with COVID-19 but, in general, failed to prove SARS-CoV-2 infection in their patients.<sup>22-26</sup> A large American case series<sup>27</sup> described 318 patients with chilblain-like lesions: only 7% of them where laboratory-confirmed COVID-19 patients. Mahieu et al.<sup>28</sup> performed PCR and serology on 10 patients with chilblain-like lesions, with negative results. Similar results were obtained by an Italian study; however, IgA against SARS-CoV-2 were positive in 6 patients.<sup>29</sup> The series by Recalcati et al. relates to 14 patients whose age ranged from 13 to 18 years: none of them had a PCR-confirmed diagnosis, but the study was conducted in the worst-hit area of Italy; of note, there were 3 couple of siblings in the sample. Histology of 2 cases revealed lymphocytic infiltrate, mostly perivascular.<sup>20</sup> On the other hand, Gaspari et al. described similar acral lesions in 6 COVID-19 inpatients.<sup>30</sup> Galvàn-Casas et al. reported chilblain-like skin lesions in 71 patients with suspected SARS-CoV2 infection, 29 of them PCR-confirmed; only 13% of them needed hospitalization.<sup>6</sup>

Fernandez-Nieto et al. reported both chilblain-like and erythema multiforme-like acral lesions: they were found in 95 and 37 patients respectively. They were all outpatients evaluated during the COVID-19 epidemic; mean age was 19.9 years; 54 patients had close contact with a confirmed COVID-19 patient, 28 patients had close contact with a health worker, and 19 patients were clinically diagnosed with COVID-19.<sup>31</sup> Recalcati et al. reported 2 patients with chilblain-like lesions who also developed erythema-multiforme-like targetoid lesions on dorsum of hands and elbows; histology showed superficial perivascular dermatitis.<sup>20</sup>

Interestingly, among 153 patients who were positive for SARS-CoV-2 in a hospital in Thailand, none reported acral lesions.<sup>9</sup> Only one out of 138 SARS-CoV-2-positive inpatients in a hospital in India had chilblain-like lesions.<sup>14</sup> Gianotti et al. performed a histopathological evaluation of patients with chilblain-like lesions, sometimes overlapped with erythema multiforme-like or urticarial-like lesions, confirming the presence of microthrombi. It is noteworthy that these patients all tested negative for SARS-CoV-2 infection, but they were all living with COVID-19 patients.<sup>12</sup>

In all 38 children with chilblain-like lesions analyzed by Caselli et al., both PCR and serological tests were negative.<sup>32</sup> Similarly, a French study conducted on 311 patients with chilblain-like lesions reported a very low rate of PCR-positivity (6%); only 7% of the tested patients were positive to serological tests.<sup>33</sup> Also Rizzoli et al. performed serological tests on 12 patients with chilblain-like lesions: only one patient showed presence of IgG.<sup>34</sup> Similar results were reported in a Belgian hospital.<sup>35</sup>

## 4 | DISCUSSION

Since COVID-19 outbreak, new skin reactions probably due to the infection are reported in literature daily. The exact incidence of skin

reactions due to COVID-19 is still unknown, and it seems higher in reports from Italy compared to reports from China.<sup>2,37</sup> Both climatic and genetic factors have been proposed to explain the difference in the incidence of skin manifestations between Europe and Asia.<sup>14</sup> Besides, as Italy was one of the most involved countries and a strong effort was asked to all health workers, dermatologists were involved in first line as well. This can explain why Italian physicians reported new cutaneous reactions every day, unlike Chinese colleagues.

We collected the cases reported so far, to better understand the link between skin lesions and SARS-CoV-2 infection. Unfortunately, the reports often share the following limitations: the majority of patients were tested for COVID-19, but not all of them; skin biopsy was performed only in few cases; information about concomitant medications was frequently missing and the pathogenic role of drugs, or a synergic action of drugs and virus cannot be excluded as the real cause of cutaneous lesions. Above all, paucisymptomatic outpatients were often not tested by nasal swabs in the worst-hit areas; also, patients with no symptoms but with skin eruptions, especially mild, are likely to be unreported. Therefore, further studies on these populations are necessary to understand the real incidence of skin reactions in COVID-19 patients.

Anyway, from the collected data we can classify the skin manifestations in four patterns: vesicular, urticarial, erythematous and maculopapular exanthemas, and vascular skin lesions. Though additional data are needed to clarify the connection between skin eruption and infection severity, vesicular rashes seem to complicate severe forms that require hospitalization. Still, the available data suggest rarity of this kind of rash, though some of the reports do not provide the number of patients evaluated.

In several studies, erythematous and maculopapular exanthemas were the most common cutaneous findings associated with COVID-19. Their incidence was variable among studies. However, exanthemas, as well as urticarial eruptions, do not represent a specific finding. Their association with viral infection in general is well known.

COVID-19-associated vascular cutaneous lesions could be divided into two groups: severe, necrotic manifestations and mild, acral signs. The former tend to be recognized in hospitalized, critical patients, often in the setting of IT; the latter are generally found in patients with moderate disease, mostly outpatients, often young. Although many of the outpatients were negative or not tested for SARS-CoV-2 (maybe because many of them lacked testing access due to testing criteria),<sup>27</sup> all over the world an increased incidence of acral chilblain-like lesions was noticed in spring 2020. Moreover, patients developing this kind of lesions were often in familial clusters, for example, were relatives of COVID-19 patients. Thus, we could reasonably suppose that mild acral manifestations could reveal previous infection with a sufficient control of it (probably IgA-mediated, according to serologic findings),<sup>29</sup> while serious manifestations could be part of a systemic process causing severe disease. The real link between mild, acral chilblain-like lesions, and SARS-CoV-2 infection is widely disputed, since patients were often negative when tested by RT-PCR on nasal swabs or by serological tests. Anyway, this could be explained as an Interferon type I induced (IFN-I) protein upregulation, since active viral replication is not necessary to mount an efficient IFN

response in SARS-CoV infection; inhibition of coronavirus replication by Interferon-induced trans-membrane protein and depletion of B cells caused by high expression of IFN-I may explain negative PCR and serological tests, respectively.<sup>36</sup>

Finally, it is still to be investigated whether cutaneous lesions may herald the systemic signs of the disease.

## 5 | CONCLUSIONS

Although many reports are available about cutaneous findings associated with SARS-CoV-2 infection, no specific skin manifestation, which could be useful for COVID-19 diagnosis, has been found yet. Although repeatedly described, vesicular and urticarial rashes, as well as exanthemas, should be considered uncommon and not specific. Severe vascular skin manifestations, such as, livedo and necrosis should be regarded as exceptional cutaneous signs of a severe systemic disease. Mild vascular cutaneous signs, for example, chilblain-like lesions, seem to arise only when the infection is resolved, in patients who had good control of it; plus, their relation with SARS-CoV-2 infection is only assumed, not proven. To conclude, more studies on confirmed cases of infection are needed to demonstrate a certain relation between cutaneous manifestations and SARS-CoV-2 infection.

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### CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available on Pubmed (see reference list)

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