

# Dermatological manifestations during COVID-19 infection: a case series and discussion on the problem of differential diagnosis

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**Abstract.** On March 11, 2019 the World Health Organization (WHO) declared Coronavirus disease-2019 (COVID-19), caused by SARS-CoV-2, as a pandemic. As of 15/01/2021, more than ninety million cases of infections have been confirmed, with almost two million related deaths. SARS-CoV-2 causes bilateral interstitial pneumonia, which can be responsible of respiratory failure in the most severe cases, but the virus has also a wide range of other manifestations, including gastrointestinal, cardiovascular, neurological, and cutaneous signs and symptoms. Cutaneous manifestations are an important matter of study for allergy specialists, as they can be specific signs of the infection, but also manifestations of adverse reactions to the medical therapy in use. In this case series, we report four different cases of dermatological manifestations in COVID patients, two in hospitalised patients and two in patients with mild disease, treated at home. The first reported case is a woman, who develops urticaria while being treated at home with mild COVID-infection; the second and the third case reported are drug- hypersensitivity reactions to remdesevir and low molecular weight heparin. The last case reported is a man with mild covid, with vasculitic sacral lesions.

**Key words:** COVID pandemic, SARS-CoV-2, dermatological manifestation in covid infections, remdesevir hypersensitivity, covid and urticaria, covid and vasculitic lesions.

## Introduction

On March 11, 2019 the World Health Organization (WHO) declared Coronavirus disease-2019 (COVID-19), caused by SARS-CoV-2, as a pandemic. Until 15/01/2021, more than ninety million cases of infections have been confirmed, with almost two millions related deaths (1).

SARS-CoV-2, a novel coronavirus first reported in December 2019 in the city of Wuhan in the Hubei province of China (2), infects human cells through the bond of its surface protein, the so-called spike

(S) protein, to the angiotensin-converting enzyme 2 (ACE2), a transmembrane protein expressed mainly by the lung type II alveolar cells, but also by other cellular lines like endothelial cells, small intestinal epithelial cells and nasal epithelia(3).

Clinical features of SARS-CoV-2 infections are extremely variable: some patients can remain completely asymptomatic or have a fever for a few days, in some cases associated with the characteristic feature of anosmia and ageusia (loss of smell and taste), while others could develop interstitial pneumonia, ranging from mild to severe grade, requiring oxygen-therapy or mechanical ventilation.

While the initial reports of the infections did not mention COVID-related dermatologic manifestations or defined them as very rare, more recent studies defined the incidence of these manifestation between 5 and 20%(4, 5).

The most characteristic are the vasculitic lesions, such as chill-blade like lesions on hands and feet, livedo reticularis and truncal or acral petechiae or purpura; less common are the reports of urticaria, maculopapular erythema and vesicular eruption (6, 7).

Urticaria accounts for almost 20% of the dermatologic manifestations of COVID-19, and affects patients with respiratory involvement as patients with no pulmonary symptoms; it usually appears at the same time as the other symptoms, but it can also be later, while less frequently is the onset symptom of the infection. It usually affects the trunk eventually in association with arms and legs, while the head, hands and feet are commonly spared (8).

Maculopapular rash represent over 40% of cutaneous manifestations in COVID-19 patients; the erythematous lesions, which sometimes flows into larger erythematous patches, are usually located in the trunk and limbs, usually sparing palmoplantar skin and mucosa. This condition is commonly associated with a more severe course of the disease (8).

Vesicular rash, accounting for less than 10% of COVID-19 manifestations, tend to appear in the early stages of the infection, sometimes before all the other symptoms. The typical lesions, affecting mainly the trunk and the limbs, are monomorphic and can have haemorrhagic content. It seems to be associated with intermedium severity of the disease (8).

While vasculitic manifestations are caused by the pro-thrombotic effects of the viral infection, remains to be clarified how the virus can cause the other cutaneous manifestations. It is known that any viral infections can be a trigger for urticarial (9), but in the case of COVID-19 the immune upregulation, typical of this infection, could lead to an aberrant activation and degranulation of the dormant mast cells caused by the activated complement system and the altered cytokine-chemokine activity.

As of today, none of the dermatological manifestations of COVID has a specific treatment; they seem to respond well to steroid therapy, which has become one of the main treatment in COVID

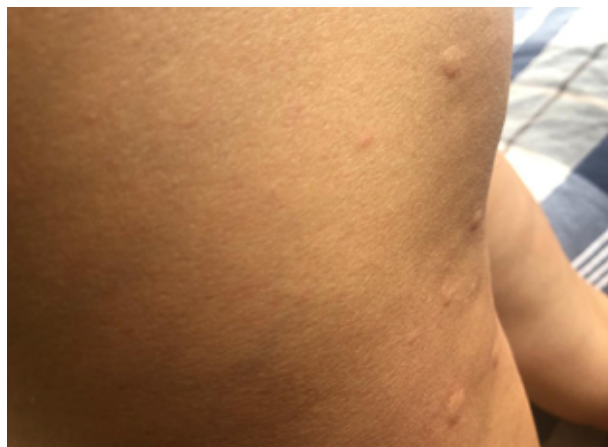
patients, and for urticaria the response the antihistamine therapy is similar to other causes of urticarial (10, 11).

Since all of the mentioned manifestations can develop before, in conjunction or after the beginning of the respiratory symptoms and possibly after the administration of medical therapy, a differential diagnosis between dermatological manifestation of COVID-19 and adverse reaction to drugs must be evaluated.

In this case series we report four different cases of dermatological manifestations in COVID patients, two in hospitalised patients, and the other in patients with mild disease, treated at home.

### First case

A woman with fever, asthenia and cough for three days, subsequently developing anosmia and ageusia. The general practitioner (GP) prescribed COVID swab, which resulted positive. Because the symptoms were mild and the peripheral saturation was steadily over 95-96%, the GP started at home therapy with paracetamol and low molecular weight heparin. A couple of days later, as the woman reported feeling of shortness of breath, steroid therapy with methylprednisolone was prescribed. After four days of steroid therapy the fever was gone, and the dyspnea had improved, but the woman called the GP, reporting acute onset of urticaria, with itching hives on the belly and the back. The GP replaced methylprednisolone with prednisone, deeming urticaria as an allergic reaction to the steroid therapy. After a couple of days of antihistamine therapy, the woman reported complete resolution of urticaria, which eventually relapsed after a couple of days, urticaria, this time affecting all over the trunk, arms and legs. The GP did not change the medications, carrying on the steroid therapy and prescribing a longer antihistamine therapy, which was enough to treat the acute presentation of urticaria without another relapse. After a total of twelve days since the beginning of the therapy, the woman was afebrile and regained the sense of taste; after three weeks the COVID swab became negative. The antihistamine therapy was suspended after a total of two consecutive weeks, with no subsequent episodes of urticaria.



**Figure 1.** Hives during the first day of urticaria



**Figure 2 and 3.** Hives during the relapse of urticaria

### Second case

Allergological consultation was requested for a man hospitalized for bilateral interstitial pneumonia COVID-related, with moderate acute respiratory distress syndrome ( $\text{PaO}_2/\text{FiO}_2 < 200$  mmHg), treated HFNOT (high-flow nasal oxygen therapy).

The patient was obese, smoker and suffering from arterial hypertension. After two days of therapy with dexamethasone 6 mg/die and low molecular weight heparin with no improvement in the  $\text{PaO}_2/\text{FiO}_2$  ratio, antiviral therapy with remdesevir was started. One hour after the administration of the first dose of the drug, he developed an itching maculo-papular rash under the neck, which later expanded on the upper trunk. Subsequent blood test revealed no eosinophilia nor elevated tryptase; the consultant decided to withdraw remdesevir therapy and prescribed antihistamine therapy with intramuscular chlorphenamine, continuing steroid and LMWH therapy. The rash did not expand further, and disappeared in the subsequent days.



**Figure 4.** Maculopapular rash after one hour of remdesevir administration.



**Figure 5.** Maculopapular rash the day after.

### Third case

A woman, overweight, smoker and suffering from diabetes was hospitalized with a diagnosis of bilateral interstitial pneumonia with severe respiratory failure, initially treated with HFNOT and then with c-PAP. Initial medical therapy included azithromycin, lopinavir/ritonavir and LMWH, followed by tocilizumab. During the 35th day of hospitalization, the patient developed a fixed erythema on the trunk and the limbs; since antiviral and the anti-IL6 mAb have been suspended from more than ten days, the reaction was attributed to enoxaparin. The doctors decided to stop the treatment with enoxaparin, replacing it with fondaparinux, as the patient had important thrombotic risk factor. A brief course of methylprednisolone 40 mg/die was done, with subsequent resolution of the rash in the course of a few days.



**Figure 6 and 7.** Fixed erythema on the trunk and belly.

#### Fourth case

Man, 45 years of age, overweight (99 kg), non-smoker, with a positive COVID-19 swab, with episodes of dyspnea and desaturation (91-92%). The man was treated at home after refusal of hospitalization, with steroid therapy (desamethasone 6 mg/die), azithromycin 500 mg/die and LMWH (enoxaparin 6000 UI/die).

After twelve days since the diagnosis of SARS-CoV-2 infection, the man developed sacral vasculitic lesions, without pain or itching; as the respiratory symptoms was improving and no other vasculitic lesion were found, the general practitioner decided not to modify the treatment. After an initial increase in the extension of the lesion, in two weeks the doctor observed a complete spontaneous resolution.



**Figure 8.** Sacral vasculitic manifestations.

#### Discussion and conclusions

Dermatological and allergic manifestation during COVID-19 infection are not very common, but not as rare as the first studies have reported. As of today, the presence of dermatological manifestations of COVID-19 has not been related to more severe disease or has been defined as a clinical subtype of the disease.

Vascular and thrombotic lesion are more characteristic of the SARS-CoV-2 infection and they are more easily recognisable, but the early use of heparin in hospitalized patient and in patients treated at home with known risk factors for thrombotic events may have lowered their global frequency since the initial reports. In the case of our patient, it is possible that the daily dose of heparin was too low to prevent the development of thrombotic lesions.

Less typical cutaneous rash, such as urticarial, vesicular or maculo-papular rash, can also appear in these patients, in some cases associated with more common symptoms, such as cough, dyspnea and fever, but also as one of the main features of the infection, in patients without respiratory symptoms. In these time of pandemic is therefore important for clinicians to be familiar with these cutaneous manifestations and, in regards to urticaria, to evaluate unusual cases of acute onset in subjects without previous history of urticaria, as it can be the first symptom of the infection. An early diagnosis is important not only for a timely treatment of the patients, but also to limit the viral spread. In these patients urticaria is as important to be properly treated as the other symptoms, as it can be bothersome or cause of concern. As the response to antihistamine therapy is good, a normal route of antihistamine therapy is always recommended as these drugs are usually well tolerated, while in patients with concomitant respiratory symptoms, a brief cycle of steroid therapy can have a positive impact on the cutaneous manifestation as on the respiratory ones. These patients have to be re-evaluated in the long term after the infection's resolution, to define any cases of chronic urticaria if the symptoms last longer than six weeks.

It is also important to keep in mind that in COVID patients multiple drugs are often used in the same time. They include antibiotics, usually azithromycin or a beta-lactam, associated with low molecular

weight heparin, sometimes with concomitant steroid therapy and/or an antiviral drug and eventually with monoclonal antibodies. In case of an adverse dermatological reaction, is therefore important the presence of an allergy consultant, not only to treat the acute cutaneous manifestation, but also to define a follow up path to complete the eventual diagnosis of drug hypersensitivity; in the case we reported of fixed erythema associated to enoxaparin, the woman was referred to allergist consultation to better defined the diagnosis of drug hypersensitivity.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Received: 1 January 2021

Accepted: 16 January 2021

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