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COVID-19–related skin manifestations: Update on therapy



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Abstract An increasing body of evidence has been produced in a very limited period to improve the understanding of skin involvement in the current coronavirus 2019 disease pandemic, and how this novel disease affects the management of dermatologic patients. A little explored area is represented by the therapeutic approach adopted for the different skin manifestations associated with the infection. An overview of the current scenario is provided, through review of the English-language literature published until October 30, 2020, and comparison with the personal experience of the authors. As dermatologists, our primary aim is to support patients with the highest standard of care and relieve suffering, even with lesions not life-threatening. With asymptomatic COVID-19 patients, patient discomfort related to skin lesions should not be undervalued and intervention to accelerate healing should be provided. Consensus protocols are warranted to assess the best skin-targeted treatments in COVID-19 patients.

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Introduction

From the March 11, 2020, declaration of coronavirus 2019 disease (COVID-19) as a pandemic,¹ skin involvement has progressively gained the attention of the medical community, from early limited case series to now a significant body of evidence.^{2–18} Although actual worldwide prevalence is still far from being clearly defined, it has been estimated to approach 1% to 2% of the world's population.¹⁹ The presentation is very polymorphic, and according to the Spanish prospective nationwide consensus,⁴ three patterns are most characteristics: chilblain-*pernio*-like lesions, ischemic-livedoid/necrotic lesions, and the varicelliform-like/vesicular eruption. Less specific manifestations include erythematous,

urticarial, purpuric, maculopapular, or papulo-squamous eruptions. There is even a peculiar Kawasaki-like presentation in children until October 30, 2020, named “multisystem inflammatory syndrome” (MIS).^{20–22}

Interpretation of the underlying pathogenetic mechanisms is a current challenge that commits numerous research groups around the world to distinguish among specific viral skin injuries and the consequences of the multisystemic involvement.^{23–34} Substantial breakthroughs will occur, with the development of specific SARS-CoV-2 assays for histopathologic, immunohistochemical, and ultrastructural study of the skin; however, a little explored area is represented by the treatment options adopted to manage these cutaneous manifestations. It may depend on the tendency to the spontaneous recovery of most conditions; alternatively, the therapy of skin lesions may have received less attention in view of the greater severity of lung and multiorgan involvement.

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We have reviewed the English-language literature published through and augmented our findings with the personal experience of the authors, because symptomatic and supportive treatment are important to relieve the patient discomfort and accelerate skin lesions' healing.

Materials and methods

A retrieval of published English-language literature was performed until October 30, 2020, collecting original cases or case series of cutaneous manifestations related to COVID-19, with specific information on the treatment adopted. The following databases were consulted: PubMed, Google Scholar, and Research Gate. Key terms included "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) or "COVID-19" combined with each of the following:

- skin
- cutaneous
- dermatologic or dermatology
- management
- treatment
- therapy

We then analyzed the descriptions of skin manifestations and the related treatments. Treatments of adverse skin reactions to COVID-19 therapies were excluded. Management of common chronic inflammatory skin diseases, and skin cancers or consequences of personal protective devices use were also discarded. Very few reports explicitly included as keywords or title the therapeutic approach for the occurrence of skin lesions associated with COVID-19 infection,^{35,36} and several expert reviews were also considered for collecting information on recommended treatment.¹³⁻¹⁶

In parallel, an observational retrospective study was performed on all patients presenting to the Dermatology Unit of the Alessandro Manzoni Hospital in Lecco (Italy). Data collected included demographics, type of skin manifestations, systemic and topical treatment employed, and outcome.

Observations

Our findings are summarized in [Table 1](#).

The majority of reports concerned chilblain/pernio-like cutaneous manifestations and specify that no treatment was needed.^{28,36-40} For isolated cases,^{41,42} two expert opinion leaders suggested that high-potency topical corticosteroids may be helpful, if the lesions were causing discomfort.^{16,43}

For acro-ischemic lesions, medication with topical corticosteroids, alone or in combination with topical antibiotics, is more widely reported.^{4,5,18,44} As these manifestations occur in severely ill patients, due to the prothrombotic setting, treatment with low-molecular-weight heparin can be beneficial.³¹ This has been included in standard COVID-19 protocols.⁴⁵

For exanthematous eruption associated with COVID-19, the most specific finding represented by the varicelliform-like/vesicular lesions is usually not specifically treated or discussed in general COVID-19 protocols.^{3,4} A prospective observational study from China and Italy documented an overall rate of 7.8% inflammatory cutaneous findings in confirmed COVID-19 patients. These have a self-limiting course and resolution without specific therapy.⁶ Several authors have suggested the use of corticosteroids, either topical or oral, plus the administration of oral antihistamines.^{4,46-49} One report recommended the use of vitamin C.⁴⁹ A systematic review and case series of acute urticaria in COVID-19 patients recommend treatment with antihistamines,⁵⁰⁻⁵³ with additional low-dose prednisone to be considered on an individualized basis.⁵⁴ The skin lesions resolved within 24 hours or up to 2 weeks.

Low-dose systemic steroid was also suggested to treat COVID-19-related anagen effluvium in a 35-year-old Iranian woman with a concomitant mixed urticarial and maculopapular dermatitis.⁵⁵ Purpuric, petechial, and/or livedoid eruptions are associated with severe COVID-19 and, thus again, beneficiaries of the same supportive measures and anticoagulant treatment of the systemic disease.^{30,56,57} More severe erythema multiforme-like eruptions can be treated with systemic steroids,^{58,59} as well as leukocytoclastic vasculitis associated with COVID-19. A dose of 0.5 mg/kg daily has been reported as efficacious,^{60,61} although a patient already under steroids developed a purpuric leukocytoclastic vasculitis.⁶² Further isolated anecdotal case reports were not included in this review.

Lecco Hospital observations

[Table 2](#) presents the findings from Lecco Hospital for patients with skin manifestations. Additional information includes both inpatients (36 patients) and outpatients (48 patients), as well as the recovery times, ranging from 1 to 8 weeks. An example of chilblain/pernio-like lesions ([Figure 1](#)) and erythema polymorphous lesions ([Figures 2 and 3](#)) are provided.

Discussion

The exponential rise of pandemic COVID-19 affects all of medicine, notwithstanding dermatology. The disease is so new and different from any previous viral outbreak that protocols and guidelines are lacking.⁶³ Granted, there is a wide body of evidence being rapidly produced from case reports, observational studies, and systematic reviews. Skin manifestations are often mild and self-limited, except for the severely ill COVID-19 patients who may have experienced disseminated thromboembolic events, accompanied by purpuric eruptions and acro-ischemic lesions.

Table 1 Treatment of skin manifestations associated with COVID-19		
Skin manifestations	Proposed treatment	References
Chilblain/pernio-like lesions	No treatment	28,36-38
	Topical corticosteroids for discomfort	16,39,41,42
Acro-ischemic lesions	Topical corticosteroids alone and/or in combination with topical antibiotics	4,5,18,40,43-45
	Low-molecular-weight heparin	31
Varicelliform-like/vesicular lesions	Wait and see	3,4
	COVID-19 protocols	
Maculopapular eruption	Topical corticosteroids	4,47,49
	Oral antihistamines	
	Oral corticosteroids	
	Vitamin C	50
Urticarial eruption	Topical corticosteroids	
	Oral antihistamines	3,51-54
	Oral steroids	55
Purpuric/petechial/livedoid lesions	Support measures	30,57,58
	Anticoagulation	
Erythema multiforme-like eruption	Systemic steroids (if leukocytoclastic vasculitis see below)	
	Systemic steroids	59,60
Leukocytoclastic vasculitis	Systemic steroids	61,62



Fig. 1 A 14-year-old girl with pernio-like lesions on the feet (A), partial response to 14 days of topical treatment with corticosteroid-antibiotic cream (B), further treated with oral steroids.

Table 2 Treatment of skin manifestations associated with COVID-19 from the retrospective study at the Dermatology Unit of the Alessandro Manzoni Hospital in Lecco, Italy

Skin manifestations	No. of cases	Systemic therapy for COVID-19	Targeted skin treatment		Outcome (healing interval)
			Systemic	Topical	
Chilblain-pernio-like lesions	36 outpatients	None	20: None 7: Antihistamines 3: Systemic steroids	9: Topical steroids 25: None	2-8 weeks
Maculopapular eruption	23 22 inpatients	COVID-19 protocols	Oxatomide or chlorpheniramine	None	1-2 weeks
	1 outpatient	Azithromycin Enoxaparin	None	None	2 days
Urticarial dermatitis	7 3 inpatients 4 outpatients	COVID-19 protocols None	Antihistamines Antihistamines 2: Systemic steroids	None None	1-2 weeks 1-2 weeks
	Vesicular dermatitis	7 2 inpatients 5 outpatients	COVID-19 protocols 1: Clarithromycin, hydroxychloroquine 1: Clarithromycin, systemic steroid	None None None	1-2 weeks 1-2 weeks
Erythema multiforme	4 3 inpatients	COVID-19 protocols	Systemic steroids	None	2-4 weeks
	1 outpatient	None	Systemic steroids	None	3 weeks
Skin vasculitis	3 inpatients	COVID-19 protocols	Systemic steroids	Topical antibiotics	5-8 weeks
Acro-ischemic	2 inpatients	COVID-19 protocols	None	Topical antibiotics	2-6 weeks
Thrombotic vasculopathy	1 inpatient	COVID-19 protocols	Enoxaparin	Topical antibiotics	6 weeks
Livedo reticularis	1 outpatient	COVID-19 protocols	None	None	2 days

**Fig. 2** A 35-year-old man with erythema multiforme-like lesions of the hands (dorsal aspects). Response to oral prednisone treatment after 3 weeks.



Fig. 3 Same 35-year-old man with erythema multiforme-like lesions of the palmar aspects of the hands, before and after treatment with oral prednisone.

Unfortunately, both from the literature review and the authors' personal experience found at the Lecco Hospital, skin disease has been relegated to a general wait-and-see approach. As might be expected, when dealing with a very new disease, priority has been given not to aggravate the infection; for example, the use of systemic corticosteroids was initially avoided for fear of prolonging the COVID-19 disease duration and increasing the mortality rate.⁴⁵ Actual guidelines derived from randomized clinical trials now include strong recommendations for the use of corticosteroids in critically ill patients with COVID-19.^{64,65}

Another controversial point concerned antihistamines and their effect on the QT interval, especially mizolastine and ebastine, which might trigger cardiac arrhythmias if hydroxychloroquine or azithromycin were concomitantly administered.⁶⁶ To avoid such risks, antihistamines devoid of these hazardous drug interactions should be prescribed for maculopapular and urticarial eruption. Hospitalized patients usually benefit from the general supportive cares and constant specialized assistance. Outpatients should be offered targeted skin therapy to shorten the duration of clinical manifestations, when skin manifestations tend to persist longer than expected. Exanthematous eruptions could benefit from topical steroids, alone or in combination with topical antibiotics to relieve tissue inflammation, and accelerate healing. A similar regiment is indicated both for mild chilblain/pernio-like lesions and for more severe acro-ischemic manifestations. Lesions with consistent vascular damage, in the setting of hypercoagulation disease (acro-ischemic, purpuric and livedoid lesions, leukocytoclastic vasculitis), may benefit from the current COVID-19 standard of care, including subcutaneous low-molecular-weight heparins and systemic steroids.

Conclusions

As dermatologists, our primary aim is to support patients with the highest standard of care and to relieve the associated discomfort, even though the lesions may not be

life-threatening. Patients with mild or asymptomatic disease may benefit from a targeted therapeutic approach that would shorten the course of the disease and reduce discomfort.

Conflicts of interest

None of the authors have conflicts of interest to disclose.

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