

Review

Covid-19 pandemic and the skin

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Conflict of interest: Dr. Drenovska reports personal fees from Roche, Abbvie, Johnson & Johnson, Novartis, and Eli Lilly, outside the submitted work. Dr. Schmidt reports grants and personal fees from UCB, grants and personal fees from Biotest, grants from Incyte, grants from Euroimmun, personal fees from Novartis, grants and personal fees from ArgenX, personal fees from Astra Zeneca, grants and personal fees from Fresenius Medical Care, grants from Dompe, grants from Synthon, grants from Admix, and personal fees from Thermo Fischer, outside the submitted work. Dr. Vassileva reports personal fees from Abbvie, Novartis, Johnson & Johnson, Eli Lilly, Sanofi, Roche, UCB, and Berlin Chemie, outside of the submitted work.

Funding source: None.

doi: 10.1111/ijd.15189

Introduction

The current coronavirus disease (COVID-19) manifests itself predominantly as a disorder of the lower respiratory tract leading to pneumonia. It spreads through droplets, aerosols, and contact surfaces and causes fever, fatigue, dry cough, and subsequent shortness of breath.¹ Headache, myalgia, arthralgia,

Abstract

In the beginning of the COVID-19 outbreak, skin manifestations, if present, were not paid enough attention. Then, the focus moved toward the impact of the prolonged use of personal protective measures in both healthcare workers and patients. In the meantime, attention is increasingly paid to dermatology as a result of the concern for certain groups of dermatologic patients, including those whose condition may worsen by the thorough disinfection measures and those treated with immunosuppressants or immunomodulators. Following patients with psoriasis on biological therapy, as well as other inflammatory and autoimmune cutaneous disorders such as atopic dermatitis, pemphigus, pemphigoid diseases, and skin cancer provoked the interest of dermatologists. Finally, an intriguing question to the dermatologic society was whether skin changes during COVID-19 infection exist and what could be their diagnostic or prognostic value. Here, we summarize skin conditions during the COVID-19 pandemic, patient information, and expert recommendations and give an overview about the registries launched to document skin changes during COVID-19, as well as details about certain patient groups infected with SARS-CoV-2, for example, psoriasis, atopic dermatitis, and autoimmune bullous diseases.

and gastrointestinal symptoms may occur in 5–15% of patients.²

In the very beginning of the COVID-19 outbreak, data on skin manifestations were scarce. The first look toward dermatology focused on the prevention of the skin and mucous membranes from contact with the infection. Chinese dermatologists were the first to publish a consensus on the adequate measures for

topical disinfection in the new pandemic situation.³ Wearing protective masks, goggles, and gloves, thorough hand washing, as well as frequent use of topical antiseptics became obligatory for a broad spectrum of the population and medical staff. Very soon this resulted in occupational skin damage among medical specialists including facial skin injury on the back of the nose, forehead, and suprazygomatic area.^{4,5} Additionally, damage of the skin barrier through aggressive disinfection or wearing gloves could be considered a prerequisite for provoking or exacerbating of contact or atopic dermatitis, chronic hand eczema, skin candidiasis, etc.

Expert recommendations and patient information during COVID-19

The second wave of COVID-19-related dermatological publications was provoked by the concern to all patients with severe dermatological diseases who undergo treatment with biological agents or other types of immunosuppressive or immunomodulatory therapies.^{6–8} Psoriasis vulgaris treated with biologics has already been reported to exacerbate from various infectious diseases like zika and dengue virus.⁹ Psoriasis was the first dermatosis during the COVID-19 pandemic that drew the attention of dermatologists owing to the wide scope of cytotoxic or biological agents used for its treatment.^{10,11} Patients with hidradenitis suppurativa or other rare diseases who probably face similar problems were provided information on the necessary preventive measures and optional treatment regimens by the *European Reference Networks (ERN)*.¹² Atopic dermatitis patients who demonstrate elevated risk of respiratory comorbidities were advised by the *European Academy of Dermatology and Venereology (EADV)* task force on atopic dermatitis not to modify by themselves previously stable immune-modulating or immunosuppressive therapies because of increased risk of relapses.¹³ Patients with autoimmune bullous dermatoses, especially those suffering from pemphigus and mucous membrane pemphigoid, were informed by the respective AIBD task force on the effects of systemic corticosteroids, steroid-sparing agents, rituximab, and other treatment options during the COVID-19 pandemic.^{14–16} Patients with connective tissue diseases on disease-modifying antirheumatic drugs, biologics, or other immunosuppressive medications were advised to consult their rheumatologist and stop these drugs during an infection, while noninfected patients are required to continue their medication during the epidemic.^{17,18} Expert consensus-based guidance was elaborated on the use of systemic immunosuppressive therapies for inflammatory skin diseases in children during COVID-19 infection along with recommendations concerning the management of infantile hemangiomas.^{19,20} In the meanwhile, dermatologic surgeons and dermoscopists alarmed on the possible delay and risk of complications in diagnosing and treatment of non-melanoma skin cancer, melanoma, and lymphoma.^{21–26} Reorganization of the work in dermatology units was proposed for

maximum safety of both patients and staff.^{27–29} Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) took place among the streptococcal infections, varicella, measles, hepatitis B and C, and AIDS with which dermatologists are often in contact.³⁰ Patient recommendations and guidelines on specific dermatological conditions during the COVID-19 pandemic are detailed in Table 1.

Skin manifestations during COVID-19 disease

The most intriguing question to all dermatologists was whether specific skin manifestations of COVID-19 exist. A look back to previous coronavirus infections found only sporadic reports on coronavirus NL63-related acute hemorrhagic edema of infancy (AHEI), a rare form of leukocytoclastic vasculitis of early childhood.³¹ Another etiologic study with a panel of respiratory viruses in 58 children with petechial rash has detected 2 human coronavirus (HCoV) positive samples of 39 virus-positive children.³²

Cutaneous involvement during the COVID-19 disease was estimated to be 0.2% in China where only two patients of 1,099 with confirmed SARS-CoV-2 infection presented with “skin rash” without further characteristics.² In Italy, the range of reported skin manifestations reached 20.4%, given that 18 of 88 COVID-19 patients had it. They presented with erythematous rash (14 patients), widespread urticarial lesions (three patients), and chickenpox-like vesicles (one patient). The lesions were asymptomatic or slightly pruritic and affected mainly the trunk. They appeared at the onset of the infection or in the course of hospitalization and were healing within a few days. As no correlation with the disease severity was found, a nonspecific character was presumed.³³ In a French prospective study on the incidence and types of COVID-19-associated cutaneous manifestations, skin involvement was reported in only 4.9% (five patients of 103) and presented as erythematous rash (two patients) and urticaria (two patients). Lesions appeared during the illness or the prodromal phase, affected mainly the face and upper part of the body, were pruritic, and resolved between 24 hours and 6 days. The authors concluded that cutaneous manifestations of COVID-19 were unusual and mostly nonspecific.³⁴ These initial data were followed by a growing number of individual reports and case series.

Erythematous rashes

Morbilliform rash as a presenting symptom of COVID-19 was reported in a 20-year-old previously healthy man from the USA. Extensive maculopapular and nonpruritic lesions on the trunk and extremities were consistent with viral exanthema. The patient demonstrated both positive SARS-CoV-2 polymerase chain reaction (PCR) test and bilateral multifocal pneumonia on chest radiograph.³⁵ *Asymptomatic malar erythema and slight edema* were described in another 26-year-old man from the USA who was treated with adalimumab 40 mg biweekly for

Table 1 Patient information and expert recommendations on dermatological conditions during the COVID-19 pandemic

Dermatological condition	Patient information	Expert recommendation
Severe skin diseases on biological or immunomodulation therapy	https://www.nice.org.uk/guidance/ng169 http://www.bad.org.uk/healthcare-professionals/covid-19	NICE guideline ⁶ BAD – advice for dermatology HCPs ⁷
Psoriasis vulgaris	https://www.eadv.org/covid-19/task-force https://www.psoriasis-council.org/blog/Statement-on-COVID-19-and-Psoriasis.htm	Conforti <i>et al.</i> ¹⁰ Lebwohl <i>et al.</i> ¹¹ Bodemer <i>et al.</i> ¹²
Hidradenitis suppurativa and other rare skin diseases	https://ern-skin.eu/covid-19/ https://www.eadv.org/covid-19/task-force	Wollenberg <i>et al.</i> ¹³ Kasperkiewicz <i>et al.</i> ¹⁵ Shakshouk <i>et al.</i> ¹⁶
Atopic dermatitis	https://www.eadv.org/covid-19/task-force	
Autoimmune blistering diseases	https://www.eadv.org/covid-19/task-force http://www.pemphigus.org/information-for-pemphigus-and-pemphigoid-patients-related-to-coronavirus-disease-covid-19/	
Rheumatologic skin diseases	https://www.rheumatology.org.uk/news-policy/details/Covid19-Coronavirus-update-members https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-Patients-with-Rheumatic-Diseases.pdf	Arora <i>et al.</i> ¹⁷ Mikuls <i>et al.</i> ¹⁸
Inflammatory skin diseases in children	https://pedsderm.net/resources/general-information-for-patients-and-caregivers-about-covid-19/	Reynolds <i>et al.</i> ¹⁹
Infantile hemangiomas	https://doi.org/10.1111/pde.14196	Frieden <i>et al.</i> ²⁰
Nonmelanoma skin cancer, melanoma, and lymphoma	https://www.nccn.org/covid-19/default.aspx https://www.skincancer.org/treatment-resources/support-resources/robins-nest/covid-19-and-you https://www.rcr.ac.uk/sites/default/files/non-melanoma-skin-cancer-covid19.pdf https://www.rcr.ac.uk/sites/default/files/melanoma-treatment-covid19.pdf https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/melanoma-in-the-covid-19-era	Der Sarkissian <i>et al.</i> ²¹ Jakhar <i>et al.</i> ²² Royal College of Radiologists ^{23,24} Conforti <i>et al.</i> ²⁵ Zic JA <i>et al.</i> ²⁶
Management of dermatological practice	https://www.aad.org/member/practice/managing/coronavirus https://doi.org/10.1016/j.jaad.2020.04.091	AAD instructions ²⁸ Lim <i>et al.</i> ²⁹

Crohn's disease in remission. This patient was not tested, but his condition followed a contact with SARS-CoV-2-infected persons. The skin eruption was preceded by general symptoms of infection and resolved within 20 days. It was considered a typical viral exanthema with a possible clinical modification by the adalimumab treatment, the latter being on hold until the patient's full recovery.³⁶ *Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)-like* erythematous rash was observed in a 64-year-old diabetic woman from France. She took oral paracetamol for fever and asthenia and 4 days later developed an erythematous rash on both antecubital fossae that further extended to the trunk and axillary folds. The patient was positive for SARS-CoV-2 RNA by PCR and chest computed tomography. The rash resolved within 5 days without paracetamol discontinuation. Relation to the infection was discussed as SDRIFE has previously been associated with both drug intake and viral infection, primarily parvovirus B19.³⁷

Urticaria-like rashes

Urticarial eruption on the face and extremities of a 27-year-old woman from France preceded any other symptom of disease that developed within the following 48 hours and were supported by positive SARS-CoV-2 test.³⁸ *Urticaria-like rash* was documented in another 32-year-old woman with COVID-19 from Spain. Skin lesions appeared 6 days after the onset of

symptoms and faded under oral antihistamines in another 5 days. In contrast to previous reports, histologic examination has been performed and revealed a perivascular infiltrate of lymphocytes, some eosinophils, and edema in the upper dermis. The authors considered the rash nonspecific and prospectively observed other cases of maculopapular rash, some of them with a purpuric component, and urticaria.³⁹ *Urticaria, urticarial vasculitis, idiopathic plantar hidradenitis, or neutrophilic dermatosis* was considered in the differential diagnosis of another COVID-19 case from Spain. A 28-year-old woman without previous medical history complained of pruritic erythematous-yellowish papules on both heels that further enlarged to erythematous patches and hardened. The lesions appeared during her convalescence period and 10 days after the last paracetamol intake. A biopsy was not performed, but the skin changes could be related to the viral infection or patient's immune response.⁴⁰

Vesiculobullous rashes

Varicella-like papulovesicular exanthema was reported in a series of 22 patients from Italy as a rare but specific cutaneous manifestation of COVID-19. The rash developed on average within 3 days after systemic symptoms and affected mostly men with median age of 60 years. Lesions predominantly affected the trunk, and mild itching was reported in 40% of the

patients. Histology was consistent with viral infection. The lesions regressed within 8 days without scarring.⁴¹ Another prospective observational study from Spain including 24 patients with COVID-19-related vesicular rashes suggested two presentation patterns, diffuse and localized, respectively. The diffuse pattern was polymorphic, widespread, and resembling hand-foot-mouth disease, while the localized was monomorphic, involving mostly the trunk, and resembling chickenpox. In this series, COVID-19 vesicular rashes also developed mostly after the onset of typical COVID-19 symptoms. Their histological presentation was consistent with viral infection. PCR tests failed to detect SARS-CoV-2 inside the vesicles so the direct relation to the virus itself remains unclear.⁴² Varicella-like exanthema was considered a COVID-19-associated skin manifestation and a possible diagnostic clue in children.⁴³

Acral ischemia and chilblain-like rashes

Acral ischemia was initially observed in isolated cases of young and otherwise healthy individuals who presented with occasionally itchy or burning erythematous bluish macules or papules on solitary digits. Some of the patients remained healthy although SARS-CoV-2 positive, while others developed general symptoms of infection.^{44,45} A new type of COVID-19-related vasculitis was suggested based on the large number of similar cases from Italy and France. Secondary microthrombosis caused by endothelial damage and vascular disorders was suspected, and vasculitis-like changes were histologically confirmed.^{34,46} *Lupus erythematosus (LE)-like chilblains* of the feet associated with normal coagulation status were explained with microangiopathic changes as a result of early interferon (IFN)-I response.⁴⁷ "Covid toes" was the term introduced recently for these pernio-like lesions in the absence of previous exposure to cold temperatures.⁴⁸ *Chilblain-like lesions (CLL)* "outbreak" was detected in Italy in a series of 63 otherwise healthy adolescents with occasional history of initial general symptoms. Cutaneous lesions were painful or itchy, stable, and mostly affected toes and soles in two different patterns: erythematous-edematous and blistering type. Despite the low rate of laboratory-proven SARS-CoV-2 infection, the authors supported the hypothesis of a delayed immune-mediated reaction to the virus in genetically predisposed patients.⁴⁹ A retrospective nationwide study in France including 277 outpatients with median age 27 years (range 2–98 years) also detected high predominance of acral changes ($n = 142$, 80%) presenting mainly as CLL ($n = 106/142$, 75%). Among the 277 patients, 34 had a SARS-Cov2 PCR test, of which 25 were positive (74%). Seven of these 25 (28%) had acral lesions. Additionally, 59 patients had isolated CLL, without associated extracutaneous symptoms. Histological examination of three CLL showed a lichenoid dermatitis with a perivascular and eccrine mononuclear infiltrate, and vascular microthrombi in 2 cases.⁵⁰ Another retrospective study from Spain reported 132 nonhospitalized patients with median age 19.9 (range 1–54 years) and predominantly acral involvement. Mild COVID-19

symptoms preceded skin lesions in 16 patients, with a mean latency time of 9.2 days (range 3–30 days), and in three patients, their onset coincided. The average duration of the skin lesions was 8.7 days (range 2–24 days). Two main patterns of acro-ischemic lesions were differentiated: chilblain-like pattern in 95 (72%) patients and erythema multiforme-like pattern in 37 (28%).⁵¹ *Acute acral cyanosis* in the absence of chilblains has also been seen in an unpublished observation. In contrast to the above-mentioned young and asymptomatic cases, reports from Wuhan described acral ischemia of the lower limbs bilaterally and of solitary fingers of the hands in critically ill COVID-19 patients.⁵² Chinese patients, aged above 60, had multiple comorbidities and were hospitalized in the intensive-care unit with severe COVID-19 pneumonia. Hypercoagulopathy, elevated D-dimers, and antiphospholipid antibodies (anticardiolipin IgA, anti- β 2-glycoprotein I IgA, and IgG antibodies) in the course of severe infection could explain the presence of ischemic skin lesions.⁵³ The induced thrombotic events were difficult to differentiate from other causes of multifocal thromboses in critically ill patients, such as disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia, and thrombotic microangiopathy.⁵⁴

Dengue-like and petechial rashes

Dengue-like rash was reported in a single case from Taiwan, the second country, affected by COVID-19 with 48 patients detected at that time. Neither photographs were made nor skin biopsy was performed since it was not a routine practice according to the dengue clinical practice guideline. The patient further developed respiratory problems and was confirmed COVID-19 positive by real-time PCR.⁵⁵ *Petechial rash* was also observed in Spain, where an 84-year-old woman with arterial hypertension and dyslipidemia was treated with hydroxychloroquine and lopinavir/ritonavir for bilateral COVID-19 pneumonia. Three days after her hospitalization (11 days since the onset of COVID-19 symptoms), she developed slightly pruritic, mostly periaxillary, erythemo-purpuric, coalescing macules. Either the triggering role of the infection itself or the drug intake was discussed.⁵⁶

Livedo-like rashes

Livedo reticularis was reported in two mild COVID-19-positive cases from the USA. Both patients, a 67-year-old man and 47-year-old woman, experienced unilateral, nonpruritic net-like rash which resolved within 19 hours and 20 minutes, respectively. The skin lesions appeared about a week after infection onset and did not reappear on challenge. It was suggested that microthromboses such as in DIC may cause transient livedo in mild-to-moderate COVID-19 cases or acrocyanosis in critically ill patients.⁵⁷ Initially, major histological changes were not detected in the skin biopsies of three patients from China, although the presence or absence of skin lesions in these cases was not clearly declared.⁵⁸ Later, in three of five critically ill

SARS-CoV-2-infected patients from the USA presenting with retiform and purpuric lesions, a generalized thrombotic microvascular injury was detected in both pulmonary and cutaneous biopsies. Histological tests from cutaneous lesions and normal-appearing skin revealed a pauci-inflammatory complement-mediated microthrombotic disease with C5b-9 and C4d deposition.⁵⁹

Androgenetic alopecia

Androgenetic alopecia (AGA) could possibly be related to SARS-CoV-2 infection as both conditions are considered to be androgen mediated.⁶⁰ Clinically significant AGA was found in 29 (71%) of the 41 Caucasian men with bilateral SARS-CoV-2 pneumonia hospitalized in two tertiary Spanish hospitals. In comparison, the prevalence of AGA among healthy Spanish Caucasian men was estimated at approximately 31–53%.⁶¹ Future case-controlled studies may potentially confirm AGA as a predictive factor for increased COVID-19 severity and contribute to the development of antiandrogen therapy for SARS-CoV-2 infection.⁶²

Neonatal rashes

Skin rashes in newborns of COVID-19-infected mothers were reported in two boys out of four infants from China. *Maculopapular rash* scattered throughout the body was observed in one of the boys who was not tested for SARS-CoV-2. The rash resolved rapidly without treatment and was followed by desquamation. *Ulcerated facial skin* on the forehead was detected in the other boy who was proven to be SARS-CoV-2 negative. Lesions were quickly followed by diffuse red papules that spontaneously healed within 10 days. None of the four newborns of COVID-19-infected mothers developed disease, and no vertical transmission was detected.⁶³ *Kawasaki disease*, an acute vasculitis of unknown origin, is another possible but unproven manifestation during COVID-19. It was reported in a 6-month-old, full-term, previously healthy and SARS-CoV-2 positive girl who

presented with fever, nonpruritic erythematous maculopapular rash, and other symptoms consistent with classical Kawasaki disease.⁶⁴

Pigment disorders

Diffuse melanoderma of acute onset was reported from Wuhan in two severely ill Chinese doctors. The exact reason for the observed diffuse skin darkening remained unknown, but hormonal imbalance related to liver dysfunction or drug side effects were suspected, and the changes were considered reversible.⁶⁵

Classification of the cutaneous manifestations of COVID-19

A prospective nationwide consensus study conducted among dermatologists in Spain summarized clinical data and images of 375 confirmed or suspected COVID-19 cases with cutaneous manifestations. Based on this case collection survey, the authors suggested five cutaneous clinical patterns and several subpatterns associated with COVID-19, as well as few familial clusters. Lesions were classified as acral erythema with vesicles or pustules (pseudo-chilblain) (19%), other vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%), and livedo or necrosis (6%). It was also pointed out that the separate types of skin involvement appeared at various points of the disease course and were associated with different duration, severity, and prognosis. This classification might be helpful in recognition of paucisymptomatic patients, epidemiological control, and prognostic evaluation.⁶⁶

COVID-19 registries

In an online registry launched by the American Academy of Dermatology (AAD) in collaboration with the International League of Dermatological Societies (ILDS), all patients with skin lesions during or following COVID-19 can be reported (Table 2).⁶⁷ The primary purpose is to rapidly collect dermatologic manifestations

Table 2 International patient registries for dermatological conditions during the COVID-19 pandemic

Dermatological condition	Patient information	Organization
Skin diseases in general	https://www.aad.org/member/practice/coronavirus/registry	American Academy of Dermatology
Psoriasis vulgaris	https://psoprotect.org/	PsoProtect
Atopic dermatitis	https://www.eczemacouncil.org/news/coronavirus-secure-ad-registry/	SECURE-Dermatology
Autoimmune blistering diseases (AIBD)	https://recovab.umcg.nl	EADV Task Force for AIBD
Lupus erythematosus, systemic sclerosis, dermatomyositis (from Europe)	https://www.eular.org/eular_covid19_database.cfm	European League Against Rheumatism
Lupus erythematosus, systemic sclerosis, dermatomyositis (outside Europe)	https://rheum-covid.org/	American College of Rheumatology
Hidradenitis suppurativa	https://hscovid.ucsf.edu/	University of California San Francisco
Alopecia areata	https://www.secure-derm.com/secure-alopecia/	SECURE-Dermatology

EADV, European Academy of Dermatology and Venereology.

of COVID-19 in order to enable prompt dissemination of the information to the dermatology community and frontline health-care workers. Similar registries based on the submission of downloadable forms have been initiated by the French and Spanish dermatological societies. These registries will certainly help to describe the whole spectrum of COVID-19-related skin changes. Systematic studies on dermatoses during acute COVID-19 may not be expected within the near future and are certainly hampered by the most likely benign course of these skin changes and the lack of involvement of dermatologists in the acute treatment of COVID-19.

Furthermore, disease-specific registries have been initiated, for example, for patients with psoriasis (by PsoProtect), atopic dermatitis (by Secure-AD-registry), connective tissues diseases (by EULAR), and autoimmune blistering diseases (by the corresponding EADV task force) (Table 2).

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