

SPECIAL ISSUE ARTICLE

COVID-19 with dermatologic manifestations and implications: An unfolding conundrum

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Abstract

The novel coronavirus SARS-CoV-2 has caused Coronavirus Disease 2019, widely known as COVID-19, now a pandemic with extraordinary infectivity, mortality, and fomite adhesiveness. We delineate cutaneous manifestations of COVID-19, some of which may represent adverse cutaneous drug reactions, and skin changes associated with COVID-19 lifestyle alterations in patients and health care workers. We review COVID-19 from both a dermatologic and public health perspective.

KEYWORDS

urticaria, skin signs of systemic disease, infection—bacterial/fungal/viral, drug reaction, therapy—topical, inflammatory disorders

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) that was first reported from Wuhan in central China in December 2019.¹⁻⁵ In a short span of 5 months, it has spread to almost all the countries around the world, resulting in the ongoing 2019-20 coronavirus pandemic.⁶ The World Health Organization (WHO) declared it a Public Health Emergency of International Concern on January 30, 2020⁷ and a pandemic on March 11, 2020.⁶

COVID-19 is a flu-like syndrome commonly characterized by fever, cough and dyspnea. Other symptoms associated with it include malaise, myalgia, diarrhea, sore throat, abdominal pain, and loss of smell and a variety of other acute neurologic manifestations.^{1,8} In fact, smell dysfunction has been characterized as a biomarker for COVID-19, as one study showed 59 of 60 patients exhibited some smell dysfunction with 35 of them either anosmic or severely microsmic.⁸ While more than 90% of COVID-19 patients reported mild symptoms, some do require hospitalization and develop severe pneumonia and eventually multi-organ failure, meriting management in an intensive care unit.

2 | THE VIRUS AND ITS TRANSMISSION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the seventh coronavirus known to infect humans with SARS-CoV-1,

MERS-CoV and SARS-CoV-2 capable of causing severe disease. The four others produce only mild symptoms. SARS-CoV-2 is a novel coronavirus, an RNA virus closely related to the original SARS-CoV.⁹ It has been proclaimed as unlikely to have been derived through laboratory manipulation of a related SARS-CoV-like coronavirus.¹⁰

SARS-CoV-2 is spread through close contact with infected individuals and by droplets released into the air during coughing, sneezing and talking. In addition, fomite spread is an important feature, which is not surprising, because it had played a central role in the SARS 2003 epidemic. However, fomites have also proven important during other outbreaks.^{5,10} Bed curtains, restroom fixtures, and countertops touched are good examples.

3 | CLINICAL APPROACH

COVID-19 typically takes approximately 5 days for the first symptoms to manifest, but this period can vary from 2 to 14 days.¹⁻⁵ The virus is most contagious when people are symptomatic. The diagnosis is rendered usually by real-time reverse transcription polymerase chain reaction (rRT-PCR) from a nasal swab, which is generally used as a standard diagnostic method. The spread of infection can be markedly diminished by taking certain preventive measures including frequent hand washing, social distancing by maintaining physical distance from others, covering coughs and sneezes with a tissue or inner elbow and keeping unwashed hands away from the face. The use of masks when appropriate is also

believed to limit its spread and has been recommended by many countries. Current management involves symptomatic treatment, supportive care, isolation, and certain experimental therapeutic measures.

4 | PATHOPHYSIOLOGY

Lungs are the most severely affected organ by COVID-19 because the virus enters the host cells via the integral membrane protein angiotensin-converting enzyme 2 (ACE2), which is attached to cellular membranes in the lungs, arteries, heart, kidney, and intestines. It is most abundantly found in the type II alveolar cells of the lungs. The virus uses a special surface glycoprotein called a “spike” (peplomer) to connect to ACE2 and gain entry into the host cell.¹⁰

The virus also affects gastrointestinal organs as ACE2 is abundantly expressed in the glandular cells of gastric, duodenal and rectal epithelium as well as endothelial cells and enterocytes of the small intestines.¹¹ It also effects the cardiovascular system,^{12,13} where it causes acute injury to myocardium, more commonly documented in critically ill patients. They also have a high incidence of thromboses and venous thromboembolisms, the presence of which is associated with a poor prognosis.^{14,15}

4.1 | Pathology

Increasing data is becoming available about the microscopic changes occurring in various organs with COVID-19.¹⁶ Autopsy specimens

have highlighted pulmonary involvement with a severe pneumonia showing diffuse alveolar damage with diffuse alveolar exudates, findings linked with acute respiratory distress syndrome and severe hypoxemia. Other findings include disseminated intravascular coagulation and a leukoerythroblastic reaction.

5 | DERMATOLOGICAL IMPLICATIONS

Dermatological implications fall into four main groupings: cutaneous manifestations of COVID-19, skin changes from COVID-19 lifestyle alterations, cutaneous adverse reactions to COVID-19 medications, and effects of COVID-19 and its therapy on primary skin diseases and their management. COVID-19 has been associated with suggestive skin manifestations which we classify into 6 categories with three distinct patterns: vesicular (varicella-like), vasculopathic, and chilblains-like (“COVID toes”) plus three less indicative ones: dermatitic, maculopapular, and urticarial morphologies.

Cutaneous manifestations are varied,¹⁷⁻³² as noted in some of our COVID-19 patients, which include urticaria, varicella-like vesicles, transient livedoid eruptions, livedoid vasculopathy, purpuric eruptions, lichenoid photodermatitis, erythroderma, photo-contact dermatitis, and generalized pustular figurate erythema (Figure 1-11). Similar findings were observed by others and in about one-fifth of patients with COVID-19 at a hospital near the shores of Lake Como in northern Italy.¹⁸ Of the 88 hospitalized patients visited either directly or indirectly by dermatologists often involved because of a lack of general physicians, 20.4% developed skin manifestations. Eight of the 18 (44%)



FIGURE 1 Urticaria in COVID-19 patient

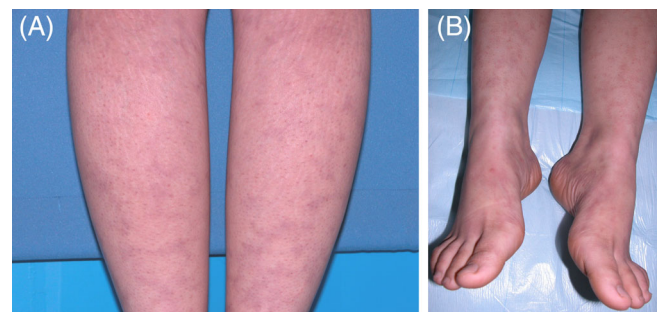


FIGURE 3 A and B, Transient livedoid eruptions in COVID-19 patients



FIGURE 2 A and B, Varicella-like vesicles in COVID-19 patient

FIGURE 4 A and B, Livedoid vasculopathy in COVID-19 patient

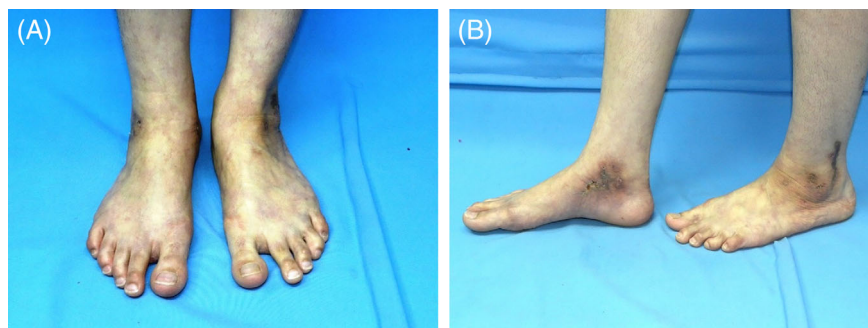


FIGURE 5 A and B, Purpuric eruption in COVID-19 patient

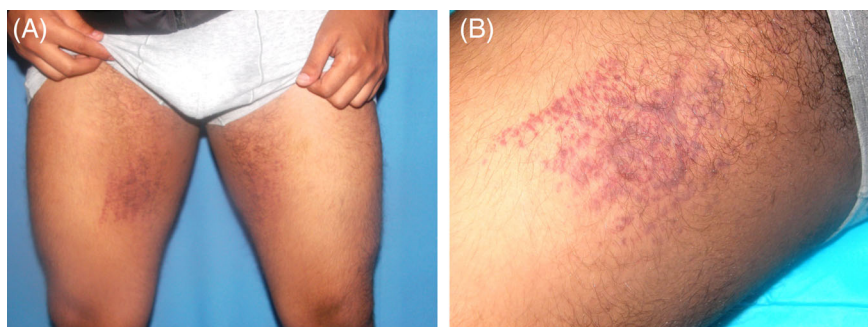


FIGURE 6 Purpuric eruption in COVID-19 patient



FIGURE 7 Purpuric eruption in COVID-19 patient

had a skin eruption at onset of symptoms, and the remainder after hospitalization. Fourteen (78%) had an erythematous rash, three had widespread urticaria, and one had chickenpox-like vesicles. The most commonly affected area was the trunk. Itching was mild or absent; lesions usually healed in a few days. The skin manifestations did not usually correlate with disease severity. It was speculated that the above cutaneous findings are similar to those occurring during common viral infections. However, others from Italy have suggested the varicella-like exanthem as a rare but specific COVID-19-associated skin manifestation with scattered truncal distribution, little or no pruritus, and an onset 3 days after systemic symptoms but disappearance without

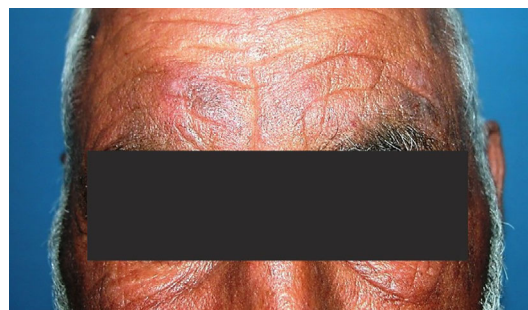


FIGURE 8 Lichenoid photodermatitis in COVID-19 patient

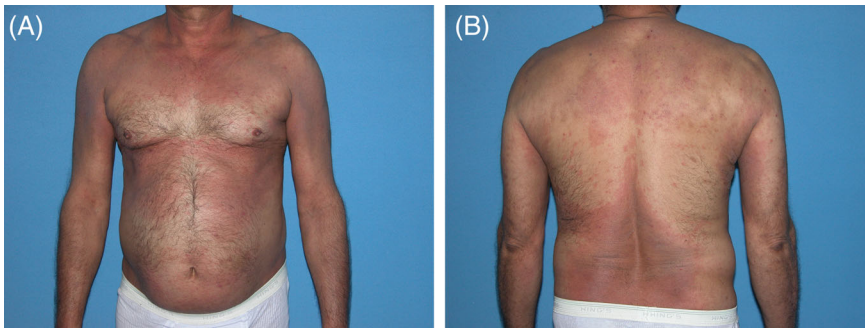


FIGURE 9 A and B, Erythroderma in COVID-19 patient

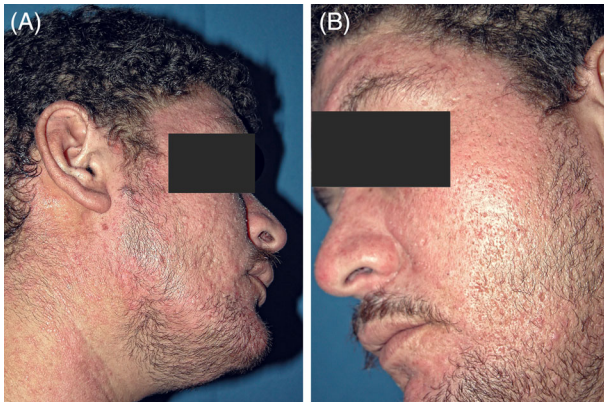


FIGURE 10 A and B, Photo-contact dermatitis in COVID-19 patient

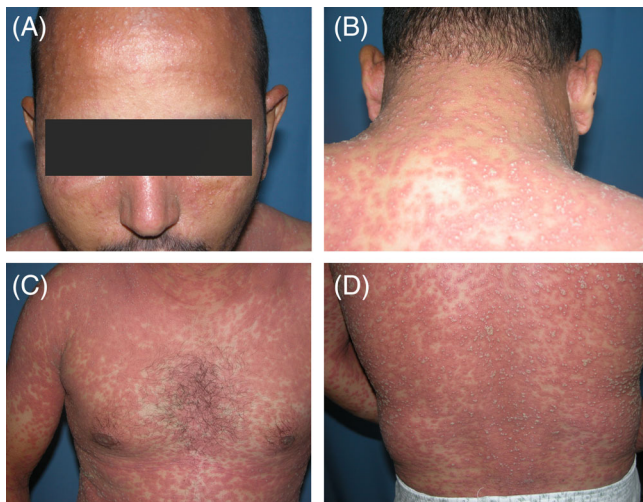


FIGURE 11 A-D, Generalized pustular figurate erythema in COVID-19 patient

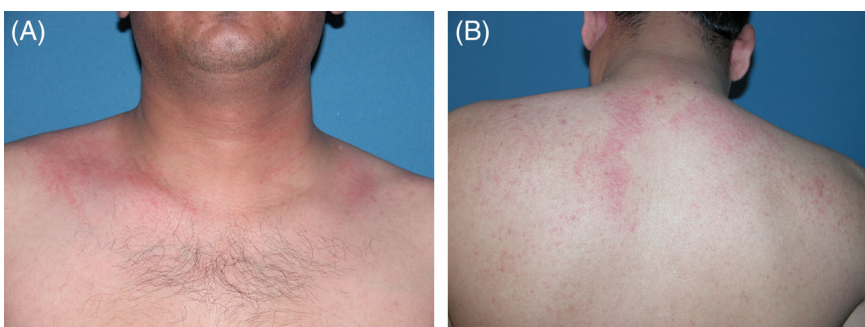


FIGURE 12 Contact urticaria

scarring in 8 days.²⁴ COVID-19 patients may also have cutaneous eruptions reflecting vascular considerations.¹⁹⁻²⁴ Petechial and transient livedo reticularis-like eruptions are being described.¹⁹⁻²¹ A patient in a Bangkok hospital had a petechial eruption and other findings that resembled dengue fever.^{19,20} Seven critically ill Chinese patients from Wuhan had acro-ischemia presentations including finger/toe cyanosis, skin bulla and dry gangrene.³⁰ Four of them were diagnosed with disseminated intravascular coagulation. Others with COVID-19 develop lesions resembling chilblains disease, referred to by some as “COVID toes”.²²

Changes in lifestyle, including prolonged contact to personal protective equipment, and excessive personal hygiene, may produce cutaneous findings, including pressure injury, contact dermatitis, and contact urticaria, as we have noted too (Figure 12-15).³³⁻³⁸ The exacerbation of preexisting skin diseases like seborrheic dermatitis, atopic dermatitis, and acne, can be anticipated.³³ Most frontline health care workers will develop cutaneous lesions affecting the nasal bridge, hands, cheek, and forehead. As expected, frequent hand hygiene was associated with a higher incidence of hand dermatitis. There is also an enhanced risk of developing the Goldman-Fox syndrome of pseudomonas-infected green nails, with the possibility of transmitting pseudomonas to otherwise compromised patients.³⁸ The use of preventive measures, including emollients, barrier creams, and moisturizers, may be desirable in ameliorating skin complications aggravated by protective measures during this pandemic.^{35,37}

Although there are as yet no proven effective therapies for COVID-19, many medications have been suggested as efficacious. Drug interactions or adverse cutaneous drug reactions have been observed in COVID-19 positive patients being treated with experimental agents or the high-risk groups like health care workers being given possibly prophylactic anti-COVID drugs. The antimalarials, specifically chloroquine and hydroxychloroquine, are a popular option,

which can aggravate preexisting psoriasis or produce a variety of cutaneous reactions.³⁹ Recent interest has focused on generalized pustular figurate erythema (Figure 11), a newly delineated potentially life-threatening severe cutaneous drug reaction previously classified as atypical acute generalized eruptive pustulosis (AGEP) or AGEP/Steven-Johnson syndrome overlap.⁴⁰

Another important concern is management of patients with autoimmune and chronic inflammatory disorders being treated with biologic drugs or immunosuppressants, specifically those with psoriasis, atopic dermatitis, connective tissue diseases, and hidradenitis suppurativa.⁴¹ European Task force Dermatology Specific Guidelines were published,⁴² suggesting continuing all immune-modulating treatments, including immunosuppressive therapy, since exacerbations of underlying diseases can have a large negative impact on patient immunity. It lamented that many conventional systemic immune-modulating agents, such as cyclosporine, may interact with the human body's defense mechanisms against viral disease, but warned that it is not currently known how



FIGURE 13 Contact dermatitis due to prolonged use of PPE, face

FIGURE 14 Irritant contact dermatitis, hands

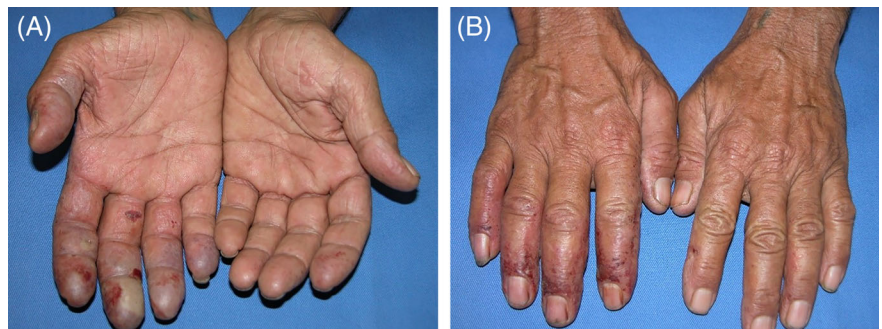
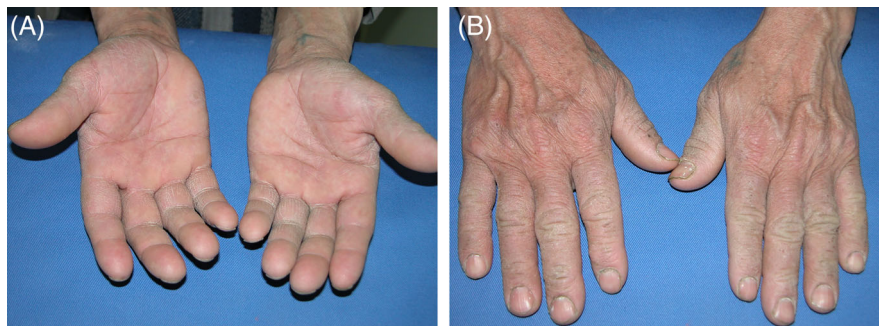


FIGURE 15 A and B, Contact dermatitis, hands



SARS-CoV-2 affects atopic dermatitis patients and specifically those on immune-modulating therapies.

6 | RISK FACTORS AND PREVENTION

Public health policy is pivotal and varied.^{5,43-51} Enclosed space air cleansing devices should be widely employed.⁴⁵ At-home testing and monitoring for possible COVID-19 represent a solid approach to keeping these COVID-19 patients out of understaffed limited-equipment hospitals.⁵² As another measure to prevent people from being hospitalized, it might be wise to actively discourage health care workers at high-risk, no matter how well-meaning, from being present at health care facilities, given both direct and fomite COVID-19 spread. Since risk is stratified by age, with deaths concentrated at older ages, and underlying co-morbidities, recommendations by us have been made (Table 1). Calling for older health care workers to volunteer is questionable. A study of 663 COVID-19 patients from Wuhan, China stressed that patients more than 60 years old and those with chronic diseases were at enhanced risk of severe COVID-19, and more likely to die.⁴⁶ A larger Chinese study using multivariate Cox regression analysis showed that age ≥ 65 years, coronary heart disease, cerebrovascular disease, and dyspnea were independent risk factors associated with fatal outcome.⁴⁷

We urge that health care workers over 65 years of age be strongly encouraged to shelter at home and to telecommute unless they are immune from COVID-19, presumably after surviving an infection, assuming post-infection immunity can be proven. Appropriate precautions should be taken to minimize the risk of virus transmission to others, especially in health care settings when performing

TABLE 1 Recommendations for at-risk health care workers (HCW) during COVID-19 pandemic until effective therapy, vaccination, or proven immunity

- Encourage HCW over 65 years old to avoid seeing patients in-person
- Encourage HCW over 70 years old to avoid physical presence at public health care facilities and medical centers
- If at-risk by age or morbidity, encourage performing only truly essential in-person professional tasks
- Follow recommendations of governmental authorities
- Encourage older physicians to reduce or eliminate direct patient contact and encourage working from home using on-line tools to connect with patients, colleagues, and medical students and other trainees

procedures that can generate aerosols.⁴³ The United States Centers for Disease Control and Prevention recommends placing the COVID-19 patients in an Airborne Infection Isolation Room, in addition to standard, contact, and airborne precautions.⁴⁴

One must also recall that co-infections may occur, with emerging epidemics of pathogens such as *Candida auris* lurking with particular ferociousness in intensive care units.⁵³ Like SARS-CoV-2, *Candida auris* may rest on fomites such as plastic and stainless steel, copper and cardboard, with viable virus and/or fungus on these surfaces.^{53,54} Preliminary results showed that fomite transmission of SARS-CoV-2 is plausible with this virus remaining viable on surfaces up to days.⁵⁴

Neuropsychiatric sequelae of COVID-19 should be a concern.⁵⁵⁻⁶¹ We recommend considering the post-pandemic neuropsychiatric complications of the two major pandemics of the last century, the Spanish flu of 1917 and the Asian flu of 1957, appreciating the meticulous work of von Economo⁵⁵ and of Kapila⁵⁶ in what has later become known as von Economo's disease and the Kapila syndrome. In influenza and recent CoV outbreaks, neuropsychiatric symptoms are often overlooked in favor of respiratory and other symptoms. During the more recent influenza epidemics and other coronavirus infections (SARS-CoV-1 epidemic and the Middle East respiratory syndrome coronavirus), neuropsychiatric sequelae have been described including narcolepsy, seizures, encephalitis, encephalopathy, and the Guillain-Barre syndrome.

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How to cite this article: Almutairi N, Schwartz RA. COVID-19 with dermatologic manifestations and implications: An unfolding conundrum. *Dermatologic Therapy*. 2020;33:e13544. <https://doi.org/10.1111/dth.13544>