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COVID-19–specific skin changes related to SARS-CoV-2: Visualizing a monumental public health challenge

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Abstract The novel coronavirus SARS-CoV-2 has caused coronavirus disease-2019, known as COVID-19, now a pandemic stressing millions of individuals worldwide. COVID-19 is a systemic respiratory infection that may have dermatologic signs and systemic sequelae, a devastating public health challenge with parallels to the two great influenza pandemics of the last century. Skin lesions linked with COVID-19 have been grouped into six categories, with three distinct indicative patterns: vesicular (varicella-like), vasculopathic, and chilblains-like (including "COVID toes" and "COVID fingers") plus the following three less suggestive patterns: dermatitic, maculopapular, and urticarial morphologies. Vasculopathic changes are the most concerning, in some patients, reflecting a devastating blood clotting dysfunction. We discuss the ways to detect, prevent, and treat COVID-19, keeping in mind the context of possible cutaneous markers of COVID-19 to enhance detection.

Introduction

Coronavirus disease 2019 (COVID-19), a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported from Wuhan in central China in December 2019.[1-5] Within a few months, the virus disseminated globally, capturing international attention with an early huge outbreak in northern Italy,[4] creating the current pandemic.[6] The World Health Organization defined COVID-19 a Public Health Emergency of International Concern on January 30, 2020,[7] and as a pandemic on March 11, 2020.[6] According to the COVID-19 Dashboard of the Center for Systems Science and Engineering at Johns Hopkins University, as of August 26,2020, this pandemic has resulted in 821,933 global deaths among 24,007,049 cases.[8] By the same date, the United States alone had reported 5,810,192 cases, including 179,310 deaths, with New York state leading the nation's death toll with 32,921 people having died.[8]

SARS-CoV-2 is the seventh coronavirus known to infect humans, with SARS-CoV, MERS-CoV, and SARS-CoV-2 capable of causing severe disease.[9,10] The four other known coronaviruses have produced only mild symptoms. SARS-CoV-2 is a novel coronavirus, a ribonucleic acid virus closely related to the original SARS-CoV, but far more deadly.

The virus and its transmission

This flu-like syndrome is also noteworthy for neurologic findings, especially loss or reduced sense of smell.[1,9,10] Smell dysfunction has been delineated as a biomarker for early COVID-19.[9] Although most COVID-19 patients have reported mild symptoms, many others have not been as

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fortunate. This flu-like syndrome spreads through close contact with infected individuals and by droplets released into the air during coughing, sneezing, and talking with fomite spread being a salient factor, as it was in the SARS 2003 epidemic.[11] In addition, other respiratory infections may coexist—whether viral, bacterial, or fungal—providing additional challenges, with particular concern centered on the ongoing global epidemic of iatrogenic *Candida* auris pulmonary infection in intensive care units.[12] The number of COVID-19 individuals diagnosed, often utilizing real-time reverse transcription polymerase chain reaction from a nasal swab, understandably rises as more people become tested, causing public consternation, as, concurrently, systemic extrapulmonary involvement and possible sequelae are being highlighted,[11,13,14] including cutaneous findings that reflect clinically salient vascular thromboses.[11,13]

Cutaneous

Skin lesions linked with COVID-19 are noteworthy.[11-34] Cutaneous findings with the infection itself may produce skin changes which have been classified into six categories with the following three distinct indicative patterns: vesicular (varicella-like), vasculopathic, and chilblains-like (including "COVID fingers" or "COVID toes" [Figures 1–3]) plus the following three less suggestive patterns: dermatitic, maculopapular, and urticarial morphologies (Figure 4,[1] Table 1). In addition, separating these six categories from a variety of similar but non-COVID-19–associated cutaneous changes may be challenging.[11,13,15] A Spanish study classified the cutaneous manifestations associated with COVID-19 into

Fig. 1 Vasculopathic COVID-19 skin, a distinct indicative pattern.[11]

Fig. 2 Chilblains-like COVID-19 fingers, a distinct indicative pattern. (Courtesy of Giuseppe Micali, MD, University of Catania, Italy.)

Fig. 3 Vesicular (varicella-like) COVID-19 skin, a distinct indicative pattern.[11]

Table 1 Six categories of skin changes directly linked to COVID-19 infection

Distinct suggestive patterns
Vesicular (varicella-like)
Vasculopathic
Chilblains-like ("COVID toes")
Less indicative morphologies
Dermatitic
Maculopapular
Urticarial

Fig. 4 Urticarial pattern COVID-19 skin, a less suggestive morphology.[11]

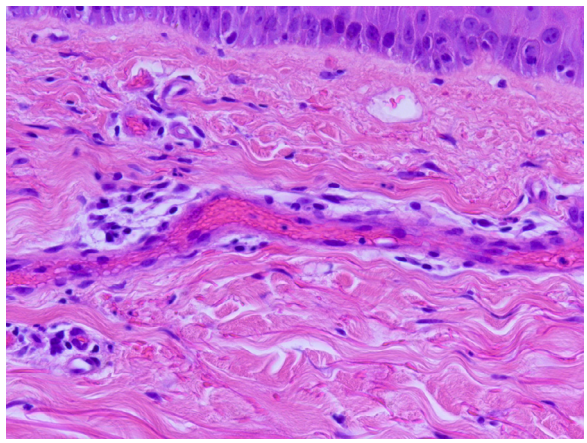

Fig. 5 Histologic view of vasculopathic COVID-19 skin, presenting extensive intravascular coagulation with exaggerated demarcation of erythrocytes from surrounding vascular contents and dissipation of erythrocytes into the surrounding dermis. (Hematoxylin-eosin, original magnification × 680. Photomicrograph by W.C.L.).

five clinical patterns: acral erythema with vesicles or pustules (pseudo-chilblain), other vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%), and livedo or necrosis (6%).[19] From these maculopapular eruptions the following 7 maculopapular patterns were delineated: (1) morbilliform, (2) other maculopapular, (3) purpuric, (4) erythema multiforme-like, (5) pityriasis rosea-like, (6) erythema elevatum diutinum-like, and (7) perifollicular.[20]

Early in the pandemic, Lecco Hospital in Lombardy, northern Italy, reported that, of 148 COVID-19 patients, 88 claimed to have not used any recent new medications. Of these 88, approximately 1 in 5 had skin findings.[4] Of the 88 hospitalized patients, 18 had cutaneous manifestations, of whom eight (44%) had skin eruptions at the onset of symptoms, and the remainder after hospitalization. A total of 14 (78%) had an erythematous rash, three widespread urticaria, and one varicella-like vesicles. In most patients, the trunk was mainly involved. The skin manifestations were short lived, either mildly or not pruritic, and did not usually correlate with disease severity. It was speculated that these cutaneous findings are similar to those occurring during common viral infections. Others have suggested that the varicella-like exanthem is a rare but specific cutaneous sign of COVID-19.[26]

A binational, multicenter study evaluated cutaneous involvement in COVID-19 between January 1, 2020, and March 15, 2020, collected prospectively by experienced dermatologists in Wuhan, Hubei province, China, and in Lecco, Lombardy region, Italy.[24] Of 678 patients with confirmed COVID-19, 53 patients (7.8%) had new dermatologic conditions detected at admission or during hospitalization, 44% evident initially and the remaining detected at a mean of 11.7 days (range, 2-23 days after hospitalization). Of these 53 patients, the most common finding was a mildly pruritic short-lived spontaneously resolving erythematous rash (70%) of macular, papular, maculopapular, or erythema multiforme-like morphology, followed by diffuse urticaria (26%). Scattered vesicles were observed in two patients (4%), characterized as varicelliform eruptions but proven by performing polymerase chain reaction not to be herpetic in origin. Thirteen patients had manifestations associated with clotting disorders: diffuse petechiae, purpura, or acro-ischemia evident as primarily finger or toe cyanosis.

The vasculopathic patterns are particularly concerning with regard to the possible development of disseminated intravascular coagulation in patients with COVID-19.[11,13,16,17] Clinical patterns with disseminated intravascular coagulation in COVID-19 disease range from petechial and transient livedo reticularis-like eruptions to retiform purpura and acro-ischemic findings including finger or toe cyanosis, skin bullae, and dry gangrene, which in some cases resembles chilblains.[11,18,28,30,31] One should differentiate the thrombotic or coagulopathic vasculopathic acral ischemia of disseminated intravascular coagulation from COVID-19 chilblain-like lesions ("blue COVID fingers or toes" [Figure 3]).[17,18] Histopathologic examination of the vasculopathic lesions demonstrates extensive intravascular coagulation often with exaggerated demarcation of erythrocytes from surrounding vascular contents and dissipation of erythrocytes into the surrounding dermis (Figure 5). This acral ischemia results from thrombosis and reflects a hypercoagulable state and highly elevated D-dimer levels. Chilblain or perniosis-like lesions do not appear to be directly caused by COVID-19 infection,[19] although they have been identified as one of three indicative skin patterns for COVID-19 diagnosis.[11] The COVID-19-associated chilblain and thrombotic retiform purpura have a different pathogenesis.[31] These chilblain-like lesions clinically and histologically strongly resemble idiopathic and autoimmune-related chilblains.[20] Acral ischemia associated with disseminated intravascular coagulation in COVID-19 patients and in patient with

chilblain-like symptoms does not reflect different degrees of involvement within the same spectrum.[11,16,21,22,31]

Another dermatologic finding has been considered. A high frequency of male pattern hair loss among those admitted for COVID-19 has been suggested, which was attributed to possible androgen expression as a clue to COVID-19 severity.[35] A 35-year-old woman with COVID-19 and anagen effluvium was described.[36]

COVID-19 disease may be associated with adverse reactions to anti–COVID-19 disease medications,[11,34,37-39] particularly as there is an understandable and appropriate effort to find and explore inexpensive, safe, easy-to-use, and readily available options such as azithromycin,[37] some with years of clinical experience with both oral and topical administration.[38,39] Many clinical trials are in progress. Varying degrees of enthusiasm have centered on hydroxychloroquine,[40] which has a specific risk of a potentially lethal cardiac arrythmia,[41] and of a potentially serious adverse cutaneous eruption delineated as generalized pustular figurate erythema.[11,42,43] COVID-19 has also resulted in many lifestyle changes with cutaneous consequences, including acne and contact and irritant dermatitis due to masks.[11]

Reducing risk

The death rate in patients with COVID-19 disease varies markedly among individuals, depending on age and comorbidities. The age distribution is remarkable, with the young at low risk and the elderly at extremely high risk of serious COVID morbidity and mortality, resulting in proposals to protect those most vulnerable.[11] However, patients with a "Do Not Resuscitate (DNR)" notation on their medical chart are often not offered treatment with a respirator even when their physicians believe that it is indicated for treatment of their COVID-19 disease. This status may be a major contributor to their high mortality rate.[44]

The spread of the COVID-19 virus may be reduced by frequent prolonged handwashing, use of sanitizer, air cleansing, and appropriate social distancing with mask usage.[11,45-47] Frequent handwashing may produce a dermatitis and possibly favor bacterial infections of skin and nails as exemplified by chloronychia, the Goldman-Fox syndrome associated with *Pseudomonas aeruginosa*, an opportunistic pathogen shown to penetrate gloves from affected nails of properly washed and gloved medical care providers to patients.[47]

Rendering spaces safer can be extremely important.[48] Special air-space cleaning devises may be worthy of consideration for public facilities, buses, and airplanes. Modifying the air and minimizing the danger within enclosed spaces can be pivotal. Room ventilation limits viral aerosol transmission. There are at least two methods of cleansing the air containing this virus . These solutions are applicable whether in a waiting room, on a commercial airliner, on a cruise ship, or in a sports arena. Air scrubbing utilizes a device that decontaminates and then recirculates the air within a room, often with high-efficiency air filtration along with internal high output ultraviolet light-C (254-nanometer wavelength) irradiation. Another approach is the use of a chemical mist-employing devices that spray hydrogen peroxide or hypochloric acid. These approaches are important. However, a forceful sneeze or cough most likely requires more, a mask to reduce the distance a cough or sneeze travels with viral aerosol deposition on floors and other surfaces requiring effective sanitization as well.

Prevention enhances the need to minimize risk beyond the recommendations detailed in this report. It is a good idea to discourage health care workers older than 65 years or who have significant morbidities from in-person encounters with patients and to assist older physicians reduce or eliminate direct patient contact through telemedicine so they may communicate with patients and others.[11]

Future prospects

Vaccines development has been accelerated, as efforts to find effective therapy continue with some of us feeling that the world may be drowning in this pandemic, which is exemplified by a famous sculpture made decades earlier (Figure 6). Rather than being overwhelmed by water, we are enveloped by the air around us, from which we must eliminate the respiratory virus causing COVID-19 disease.[48] Air defense is essential. As one looks to the future, one should also evaluate experience with 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, including the classic work of Constantin von Economo[49] (1876-1931) and of C. C. Kapila,[50] so that neuropsychiatric symptoms and sequelae will not be overlooked in favor of cutaneous and respiratory ones.[11,14, 51]

Fig. 6 La Manos de Punta del Este, Uruguay. (Photograph by R.A.S. Taken during the 31st Reunión Anual de Dermatólogos Latinoamericanos, 2013.)

Conflict of Interest

The authors declare no conflict of interest.

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