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Dermatological Manifestations in Patients With covid-19

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Introduction:

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a respiratory tract infection that has rapidly spread worldwide since its first identification in Wuhan, China, during December of 2019. The asymptomatic transmission, high infection rate, and high mortality rate among the elderly and immunocompromised associated with this disease led the World Health Organization to declare it as a pandemic in March 2020. As of early August 2020, in excess of 20 million cases of COVID-19 have been confirmed globally with more than 750,000 deaths reported in over 200 countries and territories.

SARS-CoV-2 is a novel enveloped, positive-sense, single-stranded RNA virus that is part of the genus Betacoronavirus.[(1)]

Angiotensin-converting enzyme 2 (ACE2) is a protein that functions as the sole receptor for SARS-CoV-2 to invade cells and cause infection in humans. Although this virus primarily attacks the respiratory tract, ACE2 gene expression has been discovered in several human tissues, including gastrointestinal and skin tissue. Have found that among human organs, small intestine, testis, kidneys, heart, thyroid, and adipose tissue have the highest ACE2 expression levels, while blood, spleen, bone marrow, brain, blood vessels, and muscle have the lowest ACE2 expression levels.

Other organs like lungs, colon, liver, bladder, and adrenal glands have medium expression of ACE2 in the human body. The expression of ACE2 was significantly higher in keratinocytes than other cellular compartments in skin tissues, such as fibroblasts and melanocytes. Have found that out of all ACE2-positive cells in skin, keratinocytes account for 97.37% followed by sweat gland cells that account for 2.63%. The widespread expression of ACE2 suggests that this virus might be responsible for infecting other human tissues alongside the lungs, and could potentially result in additional clinical manifestations.[(2)]

COVID-19 has a high infectivity rate, primarily due to its spread through respiratory droplets. After an incubation period of 1–14 days, common clinical symptoms such as “fever, cough, fatigue, sputum production, shortness of breath, sore throat, and headache” begin to appear.[1]

In addition to these common symptoms, novel symptoms such as a variety of cutaneous manifestations have been reported worldwide. Early data from China reported skin symptoms were present in only 0.2% of 1,099 confirmed COVID-19 cases. However, data from Italy later revealed a higher percentage with skin manifestations present in 20.4% of 88 positive COVID-19 patients. Despite differences in prevalence, reports of cutaneous lesions have become increasingly common in many age groups, including children who were once thought to be asymptomatic to the infection. Although not much is known concerning the pathophysiologic mechanisms of these cutaneous manifestations, their identification may be vital to early diagnosis and lead to possible better prognosis in COVID-19 patients.

Cutaneous Manifestations in Patients With COVID-19:

COVID-19 indirectly involves the skin just like any other viral infection and is independent of the disease stage or severity. Cutaneous manifestations of COVID-19 present a few days after the first general symptoms of the disease. However, there has been a report of disseminated pruritic erythematous plaques on the face and acral regions described 48 hours before the onset of first symptoms. The appearance of cutaneous manifestations before the onset of early respiratory symptoms can promote early recognition of COVID-19 in such cases.[3]

Generalized erythematous rash:

Erythematous rash, extensive urticaria , and vesicles resembling chickenpox predominantly in the trunk area, with minimal or no pruritus, have been described in 20.4% of the patients that were tested positive with COVID-19.COVID-19 may also present as morbilliform, maculopapular, nonpruritic rash, which should not be disregarded. Another report documented bilateral, confluent, erythematous, yellow pruritic papules on heels, resistant to topical corticosteroids, 13 days after onset of COVID-19 symptoms. The rash progressed to hard erythematous plaques with no other lesions noted on the rest of the skin. The rash could be a direct manifestation of COVID-19 or a probable immune response to the virus.[(4)]

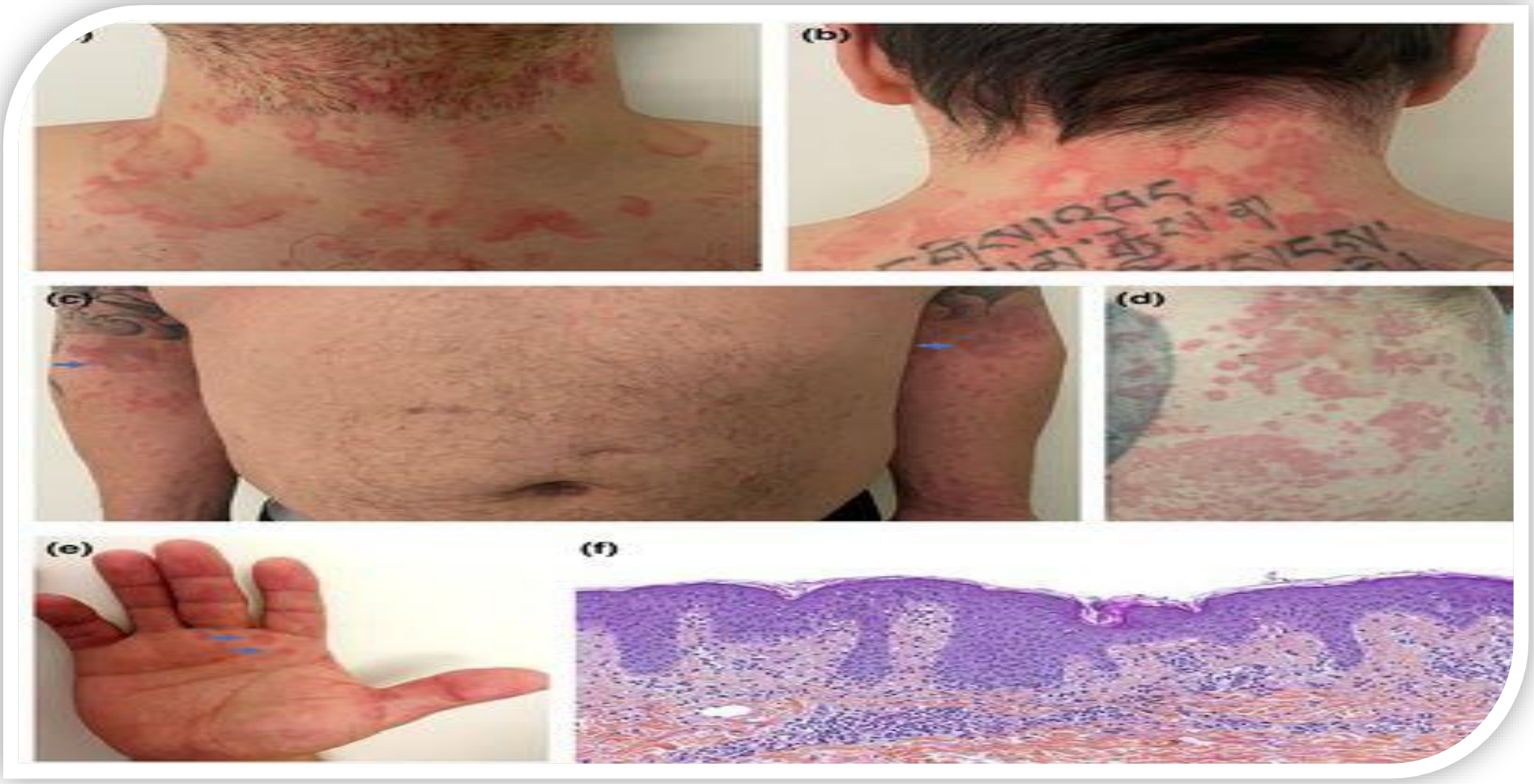
Confluent erythematous-yellowish papules in right (a) and left heel (b).

Dengue-like rash:

A recent study reported skin rash-like petechiae, resembling dengue fever, coexisting with thrombocytopenia, as an early presentation of COVID-19.[(5)]

Erythema multiform-like lesions:

Erythematous, annular, polycyclic, circinate, non-pruritic, edematous plaques presenting on arms, palms, chest, neck, and abdomen have also been described. The histological examination of the rash showed superficial perivascular lymphocytic infiltrate, spongiosis, papillary dermal edema, interface dermatitis, dyskeratotic basilar keratinocytes, occasional neutrophils but no eosinophils.[(6)] Atypical erythema multiform-like lesions characterized by rounded, erythematous, coalescing macules and vesicles, smaller in diameter when compared to classical erythema multiform lesions, have also been reported.



Clinical and histological features of Covid-19-associated febrile rash. (a, b) Erythematous, edematous, annular and circinate plaques involving the anterior and posterior neck. © Symmetrical distribution of lesions on the upper limbs. (d) Well-defined polycyclic erythematous plaques of various diameters on the right flank. € Annular papules of the palms. (f) HPS ×200. Histological findings were unspecific but consistent with viral exanthemata: superficial perivascular lymphocytic infiltrate, papillary dermal edema, mild spongiosis, lichenoid and vacuolar interface dermatitis, dyskeratotic basilar eratinocytes, occasional neutrophils but no eosinophils within the dermal.

Chilblain or acro-ischemia:

A rare presentation of acral ischemic rash, resembling chilblains in two asymptomatic cases of COVID-19 was reported, suggesting ischemia to be the probable cause of the lesions. Acro-ischemia (digital cyanosis, bulla, and dry gangrene) and disseminated intravascular coagulation (DIC) have also been described with a progressive increase in D-dimer and fibrin and fibrinogen degradation product (FDP) levels corresponding to the severity of the disease. More clinical studies are required to explore the importance of anticoagulation therapy to treat hypercoagulable states of COVID-19 patients.[(7)] Additionally, French dermatologists reported several chilblain-like lesions, with or without Raynaud phenomena, in close contact with COVID-19 patients and consequently described it as a new feature of paucisymptomatic COVID-19 infection.

Vasculitis-like lesions:

Vascular skin lesions presenting as violaceous, porcelain-like macules, livedo, necrotic/non-necrotic purpura, eruptive cherry angiomas were also reported.Microscopic and immunohistochemical analysis of the purpuric skin of severely infected COVID-19 patients demonstrated extensive pauci-inflammatory vascular thrombosis, endothelial cell injury, and c5b-9 and C4d deposits in the microvasculature. Correspondingly, thrombotic occlusive vasculopathy have also been reported in the biopsies of purpuric lesions in a severely infected COVID-19 patient. The biopsy revealed hyaline thrombi in dilated blood vessels with mild neutrophilic infiltrate and focal fibrinoid necrosis. Degeneration of sweat gland with necrosis has been described as well.[(8)]

Clinical features of COVID-19 + patients with skin vascular symptoms a: violaceous macules with porcelain appearance in a patient in intensive care unit for respiratory distress. b: livedo of the trunk with chest pain and cough. c: violaceous macule and Raynaud's phenomenom 10 days after fever and cough. d: necrotic purpura in a patient treated with leflunomide and systemic steroids for rheumatoid arthritis. e: chilblain appearance and Raynaud's phenomenom in a patient with anosmia, fever and cough. f: chilblains in a patient with cough. g: eruptive cherry angioma 21 days after COVID-19 healing of clinical symptoms.

Pathophysiology:

The pathophysiology of cutaneous lesions in COVID-19 is unclear, however, is attributed to immune dysregulation, vasculitis, vessel thrombosis, neogenesis, hypercoagulable states, or simple hypersensitivity in COVID-19.Endothelial swelling with presence of SARS-CoV-2 viral particles in the endothelial cells have also been seen on electron microscopy, which could be a possible mechanism in the pathogenesis of chilblains in COVID-19.Some studies have postulated that papulosquamous and perifollicular lesions are more likely to be because of primary cell mediated response, whereas, chickenpox-like and zosteriform blisters could be secondary to viremia and cytopathic effect. Microthrombi formation or immune complex deposition has been associated with the pathogenesis of covid feet, livedoid, and vasculopathy.[(9)]

Cutaneous manifestations of COVID-19 in pediatric patients

In the initial days of COVID-19 pandemic, pediatric infections were uncommon, but now with time they have steadily emerged because of community and familial transmission of the virus. Cutaneous manifestations such as erythematous rash, widespread urticaria, and chickenpox-like vesicles have also been reported in COVID-19 positive pediatric patients.[(10)]

Multiple erythemato-edematous macules and plaques on dorsal aspects of the fingers resembling chilblain-like lesions have also been described. Kawasaki-like hyperinflammatory syndrome and bluish-red circumscribed edematous lesions on the dorsal surfaces of the toes resembling pernio has also been reported in children with a possible COVID-19 infection.

Cutaneous manifestations of COVID-19 in neonates

Several authors have posited that there is still no confirmation on vertical transmission or intrauterine infection of COVID-19 in infected pregnant women. On the contrary, one study recently reported neonates, born to two positive mothers, that were tested positive for COVID-19 just after birth. One of the neonates presented with an extensive maculopapular rash of unfamiliar etiology with 0.3 x 0.5 cm2 ulcer on the forehead. The rash subsided with desquamation without any medication. In the same study, the other neonate presented with a rash on the forehead which formed into erythematous milias on day 2 and subsided without treatment on day 10.[(11)]

Cutaneous adverse effects to personal protective equipment

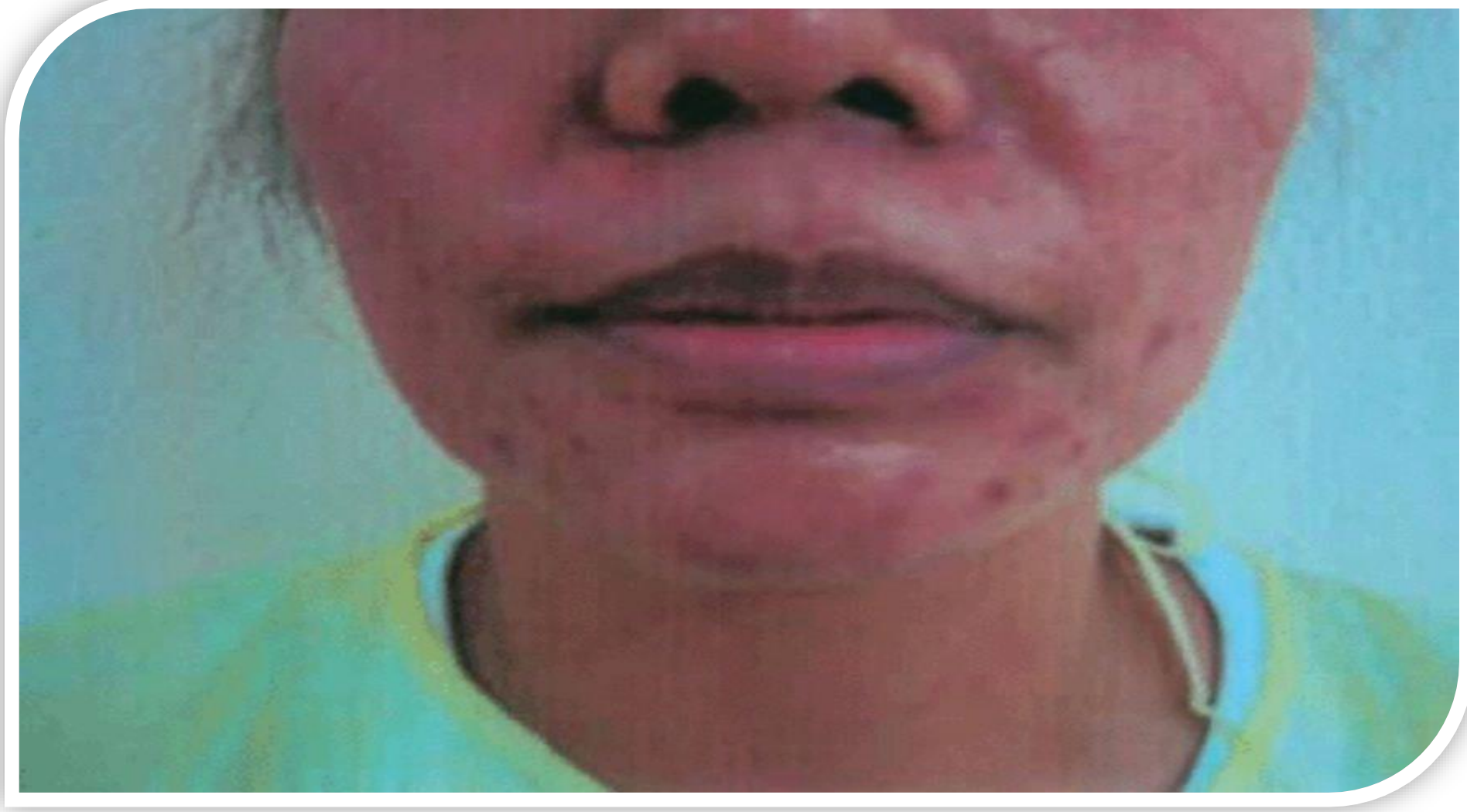
Personal protective equipment (PPE) includes surgical masks, N-95 particulate respirators, eye gear, caps, gloves, clothing, and knee-high footwear, all of which are responsible for a gamut of dermatoses. During this COVID-19 pandemic, a variety of PPE is being used extensively by physicians, hospital staff, patient relatives, and patients as well as the general population.

Allergic dermatitis, irritant dermatitis, friction blisters, contact urticaria, acne, PIH, and infections are commonly reported with the use of PPE.In a recent survey among frontline workers, the prevalence rate of skin damage related to enhanced prevention measures during the COVID-19 pandemic was documented as 97%.Dryness, tightness, and desquamation were reported as common symptoms (70.3%), and the nasal bridge was the most affected site (83.1%). Healthcare workers who wore PPE for more than 6 hours had a greater risk of developing skin damage, as compared to those who did for lesser hours.[(12)]

Masks and particulate respirators:

N95 respirators can cause dermatitis, which has been attributed to the utilization of free formaldehyde in the manufacturing of these non-woven propylene masks. Patients with known allergy, or who have been patch tested for quaternium 15 and ethylene urea melamine-formaldehyde, have presented with contact urticaria and allergic contact dermatitis on use of the N-95 respirators.The flexible aluminium or steel nose clip and the overlaying polyurethane foam can be possible allergens in masks that cause contact dermatitis. A case of eyelid dermatitis characterized by erythematous, pruritic rash, with lichenification and pustules, was reported with the use of a surgical mask. Adhesives that are used in surgical masks to affix the blue/white strip of textile enfolding the nasal clip contain a preservative, dibromodicyanobutane, which was the identified allergen that caused the contact dermatitis in this same patient. Nodular acne has been reported with the use of masks and N-95 respirators because of possible occlusion of the pilosebaceous units. Pigmentation probably because of post-inflammatory hyperpigmentation (PIH) has been reported in areas where the mask presses on the face like the nasal bridge, cheeks and chin. Few patients furthermore developed permanent scarring on the nose bridge.[(13)]

Facial pressure injuries induced by personal protective equipment. (A) Mask indentations on the nose and cheek. (B) Blisters caused by the N95 mask on the nose.



Twenty-seven-year-old woman with acne papules and nodules on the face over the area occluded by the N95 mask

Gloves:

The use of gloves is recommended for protection against mechanical hazards, and gloves are frequently used by healthcare workers, cleaners, visitors in the outpatient and inpatient facilities treating COVID positive patients. There is insufficient evidence to recommend that individuals in public places and occupational settings should use gloves to reduce the risk of contamination with SARS-CoV-2. Prolonged use of gloves has the potential to cause increased incidences of allergic and irritant hand dermatitis, most commonly because of latex allergy. A retrospective review diagnosed 61% of healthcare workers with irritant contact dermatitis, 31% with allergic contact dermatitis, and 27% with contact urticaria to latex.[(14)] Latex or rubber accelerators like triphenyl guanidine (TPG) and diphenyl guanidine (DPG), which give the gloves their tensile strength and resilience, are common culprits of hand dermatitis.A recent survey reported that 12.4% of healthcare workers wore three layers of gloves at once during work hours. Overhydration of the stratum corneum leading to maceration and erosion characterized by whitening,

softening, and wrinkling of the skin of the hands have been described.[15] Allergic and irritant contact dermatitis have been documented in approximately 31% of healthcare workers because of glove elements like thiuram mix, carba mix, and mercaptobenzothiazole, of which thiurams have been reported as the most common agent causing allergic contact dermatitis.Repetitive use of gloves have a cumulative effect on the impairment of barrier function because of increased transepidermal water loss.Powder-free, low powder, latex-free, or accelerator free gloves provide alternatives to reduce the incidence of occupational hand dermatitis among frontline workers during the COVID-19 pandemic.

Hand sanitizer:

SARS-CoV-2 is effectively destroyed with UV disinfection, 75% ethanol, temperature of more than 56°C, and chlorine containing disinfectants.Campaigns promoting hand hygiene with frequent handwashing and the use of alcohol-based hand rubs have been advocated to limit the spread of COVID-19. However, little is known about hand rubs available in the market that have exceeding, undeclared levels of methanol, which can cause desquamation of the skin and dermatitis.A cross-sectional study conducted among nurses demonstrated that previous history of allergy and hand washing more than 15 times per work shift increases the risk for the development of irritant hand dermatitis.Exogenous factors such as winter season, low relative and absolute humidity, as well as low temperatures can influence the development of irritant hand dermatitis.

Previous studies have illustrated that the use of hand sanitizer before wearing gloves increases the amount of rubber accelerator-diphenyl guanidine (DPG) levels on the hands, which can increase the likelihood of hand dermatitis.Repeated handwashing with strong disinfecting handwashes, containing common irritants such as sodium lauryl sulphate, sodium hydroxide, and benzalkonium chloride, can also cause

irritant contact dermatitis.While using alcohol rubs and repeated handwashing undeniably helps in the prevention or reduction of COVID-19 infections, it is also imperative to maintain the epidermal barrier and innate defenses of the skin. The stratum corneum barrier has antimicrobial peptides such as S100 protein, cathelicidin, LL-37, and human β-defensin2 (hBD2), disruption of which can lead to an increased possibility of infections. Sanitizers and detergents can tear down the stratum corneum leading to increased transepidermal water loss and release of pro-inflammatory cytokines. Prolonged barrier impairment and decrease in stratum corneum hydration can clinically present as xerosis, scaling, hyperkeratosis, and inflammation. A recent Chinese survey reported that 66.1% of health care workers washed their hand more than 10 times a day, and only 22.1% took protective skin care measures. Topical calcineurin inhibitors and frequent use of barrier-protection and barrier-repair creams containing ceramides, hyaluronic acid, vitamin E, and urea are recommended to help restore the structural and functional integrity of the stratum corneum.[15] Irritant patch testing with low concentrations of sodium lauryl sulfate can help distinguish individuals with a high risk of hand dermatitis, especially among frontline workers, in this current scenario.

Eyewear:

COVID-19 can pass through the conjunctiva. Therefore, healthcare workers are advised to wear protective eye gear that protects the eye and does not allow touching of periorbital skin with contaminated hands. Prolonged wearing of tight-fitting goggles can cause pressure injuries such as swelling, bruises, contact dermatitis, urticaria, poor blood circulation, skin indentation, friction blisters, erosive lesions, secondary infection, tissue hypoxia, and ischemia. The prevailing method for the prevention of these adverse effects is to use a well-fitted goggle and adjusting its positions repeatedly, along with cold compresses and the application of hydrating gels before its use. Hydrogel eye patches, hydrocolloid, and foam dressings have good

compliance and biocompatibility and therefore should be encouraged among healthcare workers in COVID-19 pandemic to prevent pressure-related injuries.[16]

Caps/Headgear:

Surgical caps or headgear are being widely used by healthcare workers, caring for COVID-19 patients, to prevent contamination of the scalp and hair. Because of poor permeability of helmets and headgear, its prolonged use can cause scalp pruritus, seborrheic dermatitis, and folliculitis among healthcare workers. [16]

Conclusions:

Discussions regarding the novel coronavirus and its spread are dominating the academic community in the recent months. The SARS coronavirus-2 has spawned a global crisis because of its uninterrupted person-to-person transmission across the globe in unison. Though dermatologists are not directly involved in treating cases of COVID-19, the disease can present with many cutaneous manifestations just like any viral infection and may be of diagnostic value in due course of time. The use of PPE and ongoing hand hygiene protocols, in view of COVID-19, can instigate various dermatoses that should be easily recognized and managed by all dermatologists. COVID-19 continues to pose a threat to the immunocompromised, which also applies to dermatology patients suffering from severe inflammatory skin diseases treated with systemic immunomodulators, biologics, and corticosteroids. Dermatologists have an essential role in imparting information to healthcare workers and the general public in appropriate skin disinfecting techniques, general skincare during the pandemic, and prevention of contact dermatitis or pressure injuries because of PPE.

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