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LET'S HEAR FROM A COLLEAGUE

Cutaneous manifestations in SARS-CoV-2 (COVID-19) infection: A review of clinical, histopathologic features, and management

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ABSTRACT

BACKGROUND Numerous studies have demonstrated various information about COVID-19 infection. With this, the authors intend to abridge, present, and synthesize current available information, focusing on the cutaneous manifestations of COVID-19 infection, to help guide dermatologists in understanding the dermatologic aspect of this disease.

OBJECTIVE This study aims to review the different cutaneous manifestations of COVID-19 by morphology and to evaluate the lesions seen in the different age groups. Furthermore, this study aims to discuss cutaneous findings together with histologic evidence and hypothesized pathophysiology, and to review the management used in treating COVID-19-related cutaneous manifestations.

METHODS OVID® and PubMed databases were used to search in detail for COVID-19-induced skin lesions across all ages and their management.

DISCUSSION COVID-19 affects the skin, hair and nails of patients. These may be attributed to the different virologic phases as well as the immune response of the body. Histopathologic findings of these lesions vary depending on the clinical presentation. Use of corticosteroid therapy and antihistamines as treatment for some cutaneous manifestations of COVID-19 showed good response.

CONCLUSION COVID-19 infection-associated cutaneous manifestations present with different morphologies. It is important for dermatologists to gain better understanding of this disease in order to promptly identify and suspect the possibility of this illness, as well as provide appropriate actions.

KEYWORDS COVID-19, coronavirus, skin, cutaneous manifestations, COVID-19 management

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INTRODUCTION

An outbreak of respiratory diseases was first reported in Wuhan, China, in December 2019. The causative agent was then discovered to be a novel betacoronavirus of the same subgenus as SARS-CoV; hence, it was called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), commonly identified as coronavirus disease 2019 (COVID-19). The disease was subsequently announced as a public health emergency of international concern in January 2020, which rapidly disseminated worldwide by February 2020. With clinical manifestations ranging from mild respiratory symptoms to severe pneumonia, fatality rate of COVID-19 is estimated at around 2%. COVID-19 was then declared a pandemic by World Health Organization (WHO) in March 2020, with person-to-person transmission occurring in the community and healthcare settings.[1,2] Common clinical features of this virus infection include fever, cough, headache, diarrhea, fatigue, headache, and myalgia. Meanwhile, cutaneous manifestations are reported sporadically, ranging from erythematous rash, urticaria to livedo reticularis and acrocyanosis in patients of all age groups. The roles of these skin lesions in early recognition and disease progression have yet to be extensively studied.[2,3]

With more than a year since the discovery of COVID-19 and declaration of a pandemic, there had been overwhelming publications regarding COVID-19 made available. Using the numerous data collected, the authors intend to present information in a more abridged and orderly man-

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ner, focusing on COVID-19 cutaneous manifestations. This study aims to review the different cutaneous manifestations of COVID-19 by morphology and to review COVID-19 manifestations in the different age groups, including the pediatric and the pregnant populations. Furthermore, it aims to discuss cutaneous findings together with histologic evidence, pathophysiology of cutaneous manifestations and to review the management used in treating COVID-related cutaneous manifestations to help dermatologists better understand the disease.

METHODS

A systematic search was done using two databases (1) OVID® with resources from EMBASE Classic and OVID Medline®, and (2) PubMed. The following keywords were used: SARS-CoV-2, COVID-19, pandemic, coronavirus, skin, cutaneous, dermatologic manifestations, urticaria, pregnancy, neonatal, pediatric, and COVID-19 management. The search was refined using Boolean operators and limits such as the English language and publication date from January 2020 up to March 25, 2021. All relevant articles were considered regardless of the type.

RESULTS AND DISCUSSION

Different cutaneous manifestations have been documented in suspected and confirmed COVID-19 patients. Presentations may vary due to the different virologic phases as well as the distinct immune response of the body.[4] The frequency of cutaneous manifestations of COVID-19 vary from 0.2%, (N=2/1099),[5] 5.95%,[6] 7.8% (N=53/678),[7] and 20.4% (N=18/88).[8] The median age of patients having cutaneous lesions was 57-years with a median duration of 12 days.[9]

CUTANEOUS MANIFESTATIONS, CLINICAL, AND HISTOPATHOLOGIC FEATURES

MACULOPAPULAR ERUPTION

The maculopapular or exanthemic eruption was the most frequently reported cutaneous manifestation in patients with COVID-19 infection with median age of 52-years (36-66 years) at presentation (Table1).[10] Lesions were erythematous macules, papules, maculopapular, some coalescing to form plaques.[9-11] It starts on the trunk with progression to the extremities[12] with associated pruritus being the most common cutaneous symptom.[6,9,10,12] The onset of the rash varied from the same time[12] or after the onset[6,10] of systemic symptoms with median duration of 10 days (7-14.5 days)[9] (Table 1). Association with COVID-19 severity was unclear but in one study, it failed to show increased risk for moderate or severe COVID-19 infection.[9]

In the Spanish study, maculopapular eruption accounted for 47% (N=176/375) of cutaneous lesions among suspected and confirmed cases.[12] A follow-up study was done to subclassify this eruption (Figure1). The patients were further classified into (1)morbilliform, (2)other maculopapular, (3)purpuric erythematous, (4)erythema multiforme-like (EM-like), (5)pityriasis rosea-like (PR-like), (6)erythema elevatum diutinum-like (EED-like), and (7)perifollicular eruption.[13] The authors concluded an increased risk of being admitted at the intensive care unit (ICU) among patients with morbilliform and EM-like lesions and an increased administration of systemic medications was noted among patients with purpuric erythematous, morbilliform, other maculopapular, and EM-like eruptions (Figure1).[13] Exanthematous petechial eruptions were also documented that mimicked dengue hemorrhagic fever (DHF) in Thailand[14] and a case of an 84-year-old female with flexural accentuation.[15]

The histopathology from these types of cutaneous eruptions showed mild spongiosis, vacuolar interface change, dermal edema with superficial perivascular lymphocytic infiltrate, and few extravasated red blood cells (RBCs).[16,17] In addition, the presence of dilated superficial dermal vessels[17,18] and rare eosinophils[17] were seen in other biopsies. Electron microscopic (EM) studies showed viral inclusions within the endothelial cells in biopsies of erythematous exanthemic and purpuric eruptions from patients with positive and negative reverse transcriptase-polymerase chain reaction (RT-PCR) for COVID-19, respectively.[19] EM-like eruption from both confirmed and suspected COVID-19 patients failed to show classic EM features.[17,20] These lesions showed superficial and deep perivascular and perieccrine lymphocytic infiltrate with dilated vessels and lymphocytic vasculitis, which was more suggestive of perniosis. Subsequent immunohistochemical (IHC) study for SARS-CoV-2 spike protein showed cytoplasmic granular positivity within the endothelial cells and eccrine glands.[20]

CHILBLAIN-LIKE LESIONS (CLL)

Also known as pseudo-chilblain or pernio-like lesions, CLL is the second most common cutaneous manifestation in patients with suspected and confirmed COVID-19 infection, with frequencies of 18%10 to 24.6%[9] (Table1). Most patients were asymptomatic and had no history of cold exposure. This cutaneous manifestation was described as edematous, erythematous to violaceous macules, papules, with or without vesicles or bullae.[21,22] A subclassification into (1) erythemato-edematous type and (2) blistering type was also proposed.[23] CLL were seen in the younger age group with the median age of 35-years (22-59 years) (Table 1).[10] The areas involved were the hands and feet, usually asymmetrical, with varying localization from toes, heels,[24] fingers, or both toes and fingers.[12,21,23] The most common associated cutaneous symptoms were pain and burning (Table1).[6,10,12] These lesions usually occurred after the onset of systemic symptoms[6,9] and have the most prolonged duration lasting for two to four weeks.[4,22] CLL was also consistently associated with absent to mild COVID-19 systemic symptoms.[6,9,10,12]

The most common histopathologic findings were dense superficial and deep perivascular and perieccrine lymphocytic infiltrate.[22,25] Other reports showed vacuolar interface change

Table 1. Summary of COVID-19 Cutaneous Manifestations

	Maculopapular / Exanthematous	Chilblain-like lesions	Urticarial Eruption	Vesicular Eruption	Livedoid /Necrotic lesions / Vascular
Frequency %	78† 25.7§ 47‡ 22^ 37.3#	 24.6§ 19‡ 18^ 18.4#	17† 10.2§ 19‡ 16^ 15#	6† 15.5§ 9‡ 11^ 15#	 2.1§ 6%‡ 6.4^ 9.2#
Number of patients (Number of patients rash/N)	14/18† 176/375‡ 38/171^ 223/1847#	 46/171§ 71/375‡ 31/171^ 110/1847#	3/18† 19/171§ 73/375‡ 27/171^ 89/18847#	1/18† 29/171§ 34/375‡ 18/171^ 89/1847#	 4/171§ 21/375‡ 11/171^ 55/1847#
Gender %					
Male	44‡ 50^ 49%#	32‡ 48^ 44#	36‡ 22^ 33#	44‡ 44^ 51#	90‡ 82^ 61#
Female	56‡ 50^ 51#	68‡ 52^ 56#	64‡ 78^ 67#	56‡ 56^ 49#	10‡ 18^ 39#
Age					
Median age in years (IQR)	52 (36-66)^	35 (22-59)^	42 (29-54)^	55 (36-58)^	66 (51-73)^
Mean age in years	55.3‡ 56.4#	32.5‡ 40.7#	48.7‡ 46.3#	45.6‡ 56.1#	63.1‡ 72.3#
Onset of lesions					
Before the onset of COVID-19 systemic symptoms %	5‡ 7.9^ 6#	7‡ 16^ 11#	4‡ 7.4^ 6#	15‡ 5.6^ 6#	5‡ 1^ 2#
At the onset of COVID-19 systemic symptoms %	61‡ 13^ 41#	34‡ 22^ 23#	61‡ 67^ 47#	56‡ 22^ 20#	86‡ 6^ 39#
After the onset of COVID-19 systemic symptoms %	34‡ 76^ 51#	59‡ 22^ 49#	35‡ 22^ 43.5#	10‡ 72^ 74#	10‡ 91%F 58.5#
No other COVID-19 symptoms %	2.6%^	19^	3.7^		
Duration of lesions					
Median duration in days (IQR)	10 (7-14.5) § 7(3-10) ^	22 (15-32) § 14 (8-24) ^	8 (5-13) §	10 (7-14) §	14(5-27) § 7(3-10)^
Mean duration in days	8.6‡	12.7‡	6.8‡	10.4‡	9.4‡
Associated cutaneous symptoms %					
Pruritus	56‡ 61^ 75#	73‡ 36^ 38#	92‡ 74^ 27.5#	68‡ 72^ 89#	14‡ 22#
Pain	2‡ 7.5#	11‡ 63.5#	1‡ 7.5#	3‡ 63.5#	29‡ 17#
Burning	5‡ 14#	30‡ 54#	1‡ 9#	2‡ 14.5#	10‡ 11#
Pain/Burning	16^	71^	22^	50^	9.1^
Asymptomatic	21^	9.7^	3.7^	11^	73^
Disease Severity %					
3.1#	3.6#	2.2#	3.4#	18.2#	5#
Moderate	63‡ 43#	13‡ 14#	44‡ 35#	32‡ 29#	86‡ 27#

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Severe	61‡ 18#	3‡ 4#	11‡ 14#	6‡ 21#	33‡ 68#
Death	3.1#	3.6#	2.2#	3.4#	18.2#
COVID-19 status %					
Suspected	31‡	59‡	33‡	50‡	19‡
Confirmed	69‡	41‡	67‡	50‡	81‡

IQR – Interquartile range
† Recalcati[8] – N=18/88 confirmed COVID-19 cases developed cutaneous manifestation.
§ Marzano et al.[9] – An Italian multicenter study of 187 of confirmed and probable COVID-19 infection presenting with one cutaneous phenotype.
‡ Gálvan Casas et al.[12] – A Spanish prospective nationwide study in Spain consisting of 375 suspected and confirmed COVID-19 infection who developed cutaneous lesions.
^ Freeman et al.[10] – An international registry for COVID-19 manifestation from 31 countries. 700 patients were registered but only 171 patients had confirmed COVID-19 infection.
# Jamshidi et al.[6] – A systematic review which consisted of 1,847 confirmed COVID-19 infection.

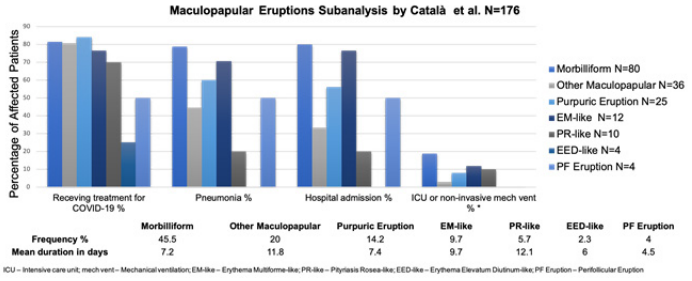

Figure 1. Subanalysis of maculopapular eruptions in COVID-19 infected patient. The most common subclassification was morbilliform. The subclassifications associated with systemic treatment were morbilliform, other maculopapular, purpuric, and EM-like eruptions. While most patients who were admitted at the ICU or needed non-invasive mechanical ventilation were patients who had morbilliform and EM-like eruptions.

and fibrin deposition beneath the ulcer base.[19,26] Some studies showed evidence of thrombus formation associated with lymphocytic vasculitis with endothelial swelling and intense inflammation in the deeper dermis.[17,19,27] An EM study on CLL in a 17-year-old male with (-)RT-PCR for COVID-19 showed viral inclusion within the endothelial cells.[19]

URTICARIAL ERUPTION

Urticaria was a common cutaneous manifestation with frequencies of 10.2%[9] to 19%[12] (Table 1). The lesions were scattered wheals on the trunk,[12] some coalescing to form larger plaques.[28,29] The median age of affected patients was 42-years (29-54 years) (Table 1).[10] The onset of the eruption occurred same time as systemic symptoms[6,12] with a shorter duration of 6.8 (mean) days[12] (Table 1). The most frequent cutaneous symptom was pruritus.[6,10,12] Like the maculopapular eruption, the association with COVID-19 infection severity was not clearly established.[9]

VESICULAR ERUPTION

Also referred to as chicken pox-like lesions,[8] its frequency varied from as low as 1.1%[8] to 9%.[12] The eruption occurred with median age of 55.1-years (36-58 years)[10] (Table 1), which was described as scattered small monomorphic vesicles on the trunk with a tendency to coalesce, rupture, and form hemorrhagic crusts.[12] Other reports showed localized grouped vesicles on the trunk with surrounding erythema.[30] Testing for varicella-zoster (VZV) and herpes simplex viruses (HSV) were not constantly mentioned in the reports. A study done in China and Italy performed PCR for both VZV and HSV in patients with vesicular eruption, which were negative.[7] The eruption mostly occurred after the onset of systemic symptoms[6,10] lasting for 10.4 (mean) days.[12] The most common cutaneous symptom was pruritus (Table 1).[6,10,12] Similar to maculopapular and urticarial eruptions, there was no clear association between having a vesicular eruption and developing moderate to severe COVID-19 infection.[9]

Skin biopsies from these patients showed two different patterns, (1) focal acantholytic dyskeratosis with a collection of Langerhans cells in the epidermis, superficial dilated capillaries, and patchy bandlike lymphocytic infiltrate in the dermis[17] and (2) vacuolar interface change with disorganized and multinucleated keratinocytes in the epidermis and minimal inflammatory cells in the dermis.[31]

LIVEDOID, RETIFORM PURPURA, AND NECROTIC LESIONS

These are the least common dermatologic manifestations with frequencies of 2.1%[9] to 9.2%[6] (Table 1). These were purpuric retiform lesions[10] with a predilection to truncal, acral sites,[12] legs, and buttocks.[10] Elderly patients with the median age of 66-years (51-73 years) were mostly affected.[10] These occurred after the onset of COVID-19 systemic symptoms.[6,10] However, other studies reported at the onset of the infection.[12] Most lesions were asymptomatic,[10] and some reported pruritus[6,12] with the mean duration of 9.4 days[12] (Table 1). This manifestation was consistently associated with severe COVID-19 infection[9,10,12] and with a 10% mortality rate.[12]

Histopathologic findings showed consistent features of pauci-inflammatory thrombotic vasculopathy.[10,17,32] Complement studies were done using IHC, which showed deposition of C4d and C5b-9 within the vessel walls. C5b-9 was also present in the normal skin of these patients. Interestingly, similar findings

were also seen in the lungs and skin.[32]

CUTANEOUS MANIFESTATIONS OF COVID-19 IN PREGNANT PATIENTS

The clinical characteristics of pregnant patients with COVID-19 infection were similar to those of non-pregnant adults.[33] At present, there is still no evidence for intrauterine infection caused by vertical transmission in COVID-19 infected pregnant women.[33–35]

A recent study, however, reported two cases of fetal transient skin edema during the second trimester of pregnancy in women with COVID-19, which authors attribute to possible fetal infection or the consequence of the maternal infection in the fetal physiology.[36]

CUTANEOUS MANIFESTATIONS OF COVID-19 IN NEONATAL AND PEDIATRIC PATIENTS

At the beginning of the pandemic, no cutaneous manifestations of COVID-19 in the pediatric population were reported; however, as the pandemic spread, more neonatal and pediatric cases emerged.

A recent study presented two cases of neonates born to two COVID-19 positive mothers, who were tested positive for COVID-19 soon after birth.[34] These two infants presented with cutaneous manifestations differently—one had a generalized maculopapular rash with a solitary 0.3 × 0.5 cm^2 ulcer on the forehead, while the other presented with diffuse small miliary red papules on the second day of life.[34] The rashes of neonates resolved without any treatment, with the appearance of skin desquamation on day two and day ten, respectively.[34]

In the pediatric population, cutaneous manifestations of COVID-19 infection are similar to what is witnessed in adults and other viral exanthems, including macular, papular, vesicular, and urticarial eruptions, some with acral involvement.[37,38] One of the most commonly reported cutaneous manifestations of COVID-19 in pediatric population is an erythematous maculopapular rash—one reported similar to roseola and another accompanied by mild pruritus—spreading from the face to the extremities then the trunk.[38] A recent case report revealed a 12-year-old boy who, 4 weeks after a full recovery from COVID-19, presented with a generalized maculopapular exanthem resembling pityriasis rosea, on the trunk, arms and legs that lasted for 2 weeks. This unusual prolonged dermatological manifestation from a post-COVID-19 infection has rarely been reported.[39] EM-like eruption on the arms, legs, and ears, alongside multiple erythemato-edematous macules and plaques on dorsal aspects of the fingers and toes, resembling CLL, have also been described.[25,37] Suggested by some studies, CLL should be considered a newly recognized manifestation of COVID-19 in the pediatric population.[40] These cutaneous manifestations were reported to fade after 7-10 days and had an excellent prognosis, without complications or severe disease manifestations.[40] CLL is most commonly associated with asymptomatic to mild COVID-19 infection.[6,10,12,37] Other accompanying symptoms reported include headache, myalgia, pharyngeal erythema, and gastrointestinal clinical manifestations.[37,38] Interestingly, a papulovesicular eruption consistent with Gianotti-crosti syndrome was documented in a 10-month-old patient with (+)RT-PCR for COVID-19 four weeks before the appearance of the rash.[41]

A recent case report showed a COVID-19 infected boy who presented with conjunctivitis and eyelid dermatitis without any other symptoms.[42]

HAIR-ASSOCIATED CONDITION AND HAIR CHANGES

Increasing interest in androgenetic alopecia (AGA) as a potential marker of severe COVID-19 infection has been studied.[43–45] This was referred as the "Gabrin Sign" to recognize the first American physician with AGA who died from severe COVID-19 infection.[46] In one study, it was observed that patients with Hamilton-Norwood Scale (HNS) of >3 had worse hospitalization outcome.[46] Authors hypothesized the role of androgen receptors in regulating transmembrane protease, serine 2 (TMPRSS2).[22,45,25] Studies have shown that androgen regulates TMPSS2, which primes the binding of SARS-CoV-2 to the Angiotensin Converting Enzyme-2 receptor (ACE-2).[27,44,47] In addition, men have more ACE-2 receptors than women, thereby allowing more viruses to bind to these receptors.[48] This could explain the higher incidence of mortality among men[46] with a difference in the mortality rate of 58% for men and 42% for women.[45] However, this was challenged in a study done in Brazil wherein they found no evidence linking AGA and worse COVID-19 outcome.[43] Despite these growing data on AGA as a potential marker for severe COVID-19 infection, clinicians should not solely rely on this parameter to associate severity of COVID-19 infection because multiple factors can contribute to the disease, such as age, obesity, and comorbidities. These studies had a small sample size; thus, further studies are needed to prove the association between AGA and the severity of COVID-19.[46,49]

Post-infectious telogen effluvium (TE) cases were not surprisingly reported as well.[43] The occurrence of TE was similar to any other systemic insults that prematurely convert anagen hairs to telogen hairs. However, the presence of TE may be also due to drugs and stress aside from probable infectious etiology.[50]

NAIL CHANGES

There were a few case reports, which documented nail changes post-COVID-19 infection. A case of Beau's lines described as transverse grooves on both fingernails and toenails that appeared 3.5 months after COVID-19 infection.[51] Nail changes may be seen post-viral infection, especially with the Coxsackie virus, which causes onychomadesis in children who had hand-foot-and-mouth disease.[52] Similar to Beau's lines documented in post-COVID-19 infection, these nail changes are due to the temporary arrest of growth in the nail matrix.

The "red half-moon sign" was another nail finding that presented as a transient convex erythronichial band distal to the lunula, which appeared two weeks after being discharged

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from the hospital.[53] An 89-year-old female who presented with transverse orange discoloration at the distal nail bed, which appeared 16 weeks post-COVID-19 infection, was also reported.[54] The changes were probably due to microvascular injury and a reflection of anemia and sarcopenia, respectively.[53,54]

PATHOPHYSIOLOGY OF CUTANEOUS MANIFESTATIONS

SARS-Cov-2 invades human cells by binding the virus's S-protein to the ACE-2 of the human cells. The ACE-2 receptors are not only present in the lung epithelium, but also in endothelium, oral cavity, renal tubule, adipocytes, keratinocytes, and cells of the epidermis. The presence of ACE-2 in different cell types may explain the various signs and symptoms associated with COVID-19 infection. Severe diseases might also be attributed to the increased expression of ACE-2 in the elderly and obese patients.[48] In addition, the binding of SARS-CoV-2 to ACE-2 causes overstimulation of the Renin-Angiotensin-Aldosterone-System (RAAS), leading to catastrophic endothelial dysfunction, inflammation, hypercoagulation, and respiratory collapse.[27,48,55] These cascade might explain the occurrence of thrombotic vasculopathy manifested as livedoid, retiform purpura, or necrotic lesions in patients with severe COVID-19 infection. A complement-associated microvascular injury and thrombosis presented with retiform purpuric lesions were demonstrated in a series by Magro et al.[56] This mechanism involves the activation of both alternative and lectin complement pathways leading to a complement cascade with the generation of terminal membrane attack complex (C5b-9), which causes direct cytolysis.[56]

In contrast, in young and immunocompetent individuals, the clearance of the virus is achieved by immune response involving the type I interferon (IFN-1), leading to short-lived to absent systemic symptoms.[26] IFN-1 is elevated during viral infection, autoimmune diseases such as systemic lupus erythematosus (SLE), and monogenic autoinflammatory interferonopathies (MAI).[26] Interestingly, patients with SLE and MAI present with perniosis similar to CLL in COVID-19 infection. Hence, SARS-Cov-2 might trigger an exaggerated IFN-1 response causing CLL.[57] The other proposed mechanism of CLL is the effect on the RAAS in the acral vasculature, which promotes vasoconstriction.[27] Despite this evidence, direct causality remains unclear due to inconsistent COVID-19 test positivity.[5,21,22] However, the sudden increase of these lesions during the pandemic might support an infectious etiology.[23] Physicians should be vigilant in recognizing these lesions as they may be the potential spreaders of the virus since most of them have mild infection. It is also important to emphasize that CLL should not be referred to as acro-ischemic lesions. Both cutaneous manifestations can present on the acral sites but with very different features, the former being more erythematous and edematous while the latter tends to be violaceous, purpuric to necrotic with a retiform pattern. Histopathologic features of both may have microthrombi in the deep dermis. Retiform purpuric lesions, however, show more extensive thrombus with very minimal inflammation.[56] Patients who presented with CLL have decreased risk for developing moderate to severe COVID-19 infection while livedoid, retiform purpura, or necrotic lesions have the increased risk of developing severe infection.[9]

We should always rule out the possibility of drug reactions when we encounter these skin manifestations, especially those presenting with maculopapular, urticarial, and vesicular eruptions. These are common manifestations of both viral and drug reactions. Furthermore, in a tropical country with prevalent mosquito-borne diseases, COVID-19 may manifest as an erythematous maculopapular rash like DHF.[15]

Evidence pointing out the presence of viral particles within the vascular system has been established.[19] However, the potential infectivity of these particles is not yet clear, Standard precautions must be in place during surgical management. As health care providers, we should be equipped whenever we attend to suspected COVID-19 patients.

MANAGEMENT OF CUTANEOUS MANIFESTATIONS IN COVID-19 PATIENTS

CORTICOSTEROID THERAPY

Low-dose systemic corticosteroids have been suggested as a therapeutic option for COVID-19 associated with urticarial rash, severe and widespread cases of confluent erythematous, maculopapular, morbilliform rash, and severe cases of purpuric "vasculitic" pattern (with necrotic-ulcerative lesions and widespread presentation). On the other hand, topical corticosteroids have been successfully used for treating mild confluent erythematous rashes.[10,24,29,58–62]

ANTIHISTAMINES

Oral antihistamines contributed to clinical and symptomatic improvement in patients with urticarial rash.[10,24,29,58,60,63] It is well known that urticaria and angioedema can be triggered by viral and bacterial agents, such as cytomegalovirus, herpesvirus, Epstein-Barr virus and mycoplasma.[3] As with the case of COVID-19 infection, urticarial eruptions associated with this disease have been reported by Reaccati[8] in his cohort of hospitalized patients. Urticaria is caused by immunoglobulin E- and non–immunoglobulin E-mediated histamine release and other inflammatory mediators from mast cells and basophils;63 hence, treatment with an antihistamine to control histamine release can be of benefit.

There is currently no specific treatment or core guidelines recommended in the management of cutaneous manifestations of COVID-19. Policies and guidelines for the treatment of COVID-19 were different among countries, and some researchers refused to give any treatments for asymptomatic patients or those with mild symptoms because the symptoms may remit spontaneously after several days. With the limited availability of significant therapeutic options and given the tendency to spontaneously

heal for these lesions associated with COVID-19, a "wait-and-see" strategy has frequently been suggested. Several studies have also demonstrated the usage of corticosteroid therapy and antihistamine in managing some of the skin manifestations of COVID-19, which yielded a good response.[2,58]

In a study by Shanshal,[62] the author hypothesized that low-dose systemic corticosteroids, combined with nonsedating antihistamines, can help manage the hyperactivity of the immune system in COVID-19 with their anti-inflammatory properties. Usage of systemic corticosteroids, however, can potentially increase the risk of infection as well. This may, therefore, restrict the use of these medicines for cutaneous lesions of COVID-19 patients.[29]

CONCLUSION

COVID-19 infection-associated cutaneous manifestations present with different phenotypes. Dermatologists should familiarize themselves as they may be the first to identify and suspect the possibility of COVID-19 infection, especially for those who are mildly symptomatic. CLL and livedoid lesions are the cutaneous manifestations associated with mild and severe COVID-19 infection, respectively. Other cutaneous manifestations fall in this spectrum and have yet to be studied to provide the causal relationship with disease severity. Hair and nail manifestations are potential research areas to explore and to further contribute to the pathogenesis of COVID-19. Histopathologic findings of these lesions vary depending on the clinical presentation. These changes can be attributed to the body's immune response directed against the virus or a consequence of a systemic disturbance due to COVID-19 infection. At present, there are limited therapeutic options for COVID-19-induced cutaneous manifestations, using mainly corticosteroid therapy and antihistamines, as numerous studies have revealed spontaneous resolution of the lesions and excellent prognosis.

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