








## REVIEW

# Dermatological manifestations associated with COVID-19: A comprehensive review of the current knowledge

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## Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has become a significant health problem globally. The virus has spread widely and become a global pandemic. The pathophysiology for SARS-CoV-2 has not been explained clearly. It has been associated with several multiorgan symptoms, among which its dermatological manifestations are of great interest. Primarily, there has been no report of skin features among COVID-19 patients. Nevertheless, recently there have been several reports regarding COVID-19 patients who presented with cutaneous manifestations. In the current review, we focus on the various cutaneous manifestations of COVID-19 infection.

## KEYWORDS

COVID-19, cutaneous manifestations, SARS-CoV-2, skin manifestations

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) was initially known to cause respiratory and gastrointestinal symptoms. However, as the pandemic progressed, many atypical features of this infection have become noticed.<sup>1</sup> A dermatologic event has been identified as a significant atypical extrapulmonary involvement of COVID-19.<sup>2</sup> Figure 1 illustrates a summary of the multiorgan manifestations of COVID-19. The incidence of cutaneous involvement in COVID-19 varies from 1% to 20% in different reports.<sup>3</sup> Skin eruptions vary in morphology, time of onset, location, and duration. Several studies have reported some COVID-19-related skin involvements that were unexpected before their onset.<sup>4</sup>

In general, dermatological complications associated with COVID-19 may be caused directly by severe acute respiratory

syndrome coronavirus-2 (SARS-CoV-2) infection or occur due to preventative measures applied in this pandemic. Virus-induced skin eruptions are either direct or indirect effects of the infection<sup>5</sup> or the result of drug hypersensitivity,<sup>6</sup> while non-virus-related skin damage can be caused either by personal protective equipment (PPE) or disinfectants.<sup>7</sup> PPEs, such as N95 masks, goggles, and face shields, can cause mechanical damage primarily to the facial skin. Besides this, allergic dermatitis induced by hypersensitivity to mask materials, pompholyx such as blisters due to latex gloves, folliculitis resulting from heat stress, dehydration induced by long hours of gowns wear, and fungal infections of the lower limbs due to humidity insulted by protective boots can all be induced by PPEs. Furthermore, frequent hand washing and the use of disinfectants, such as alcohol solutions, can lead to allergic contact dermatitis (ACD).<sup>8</sup>

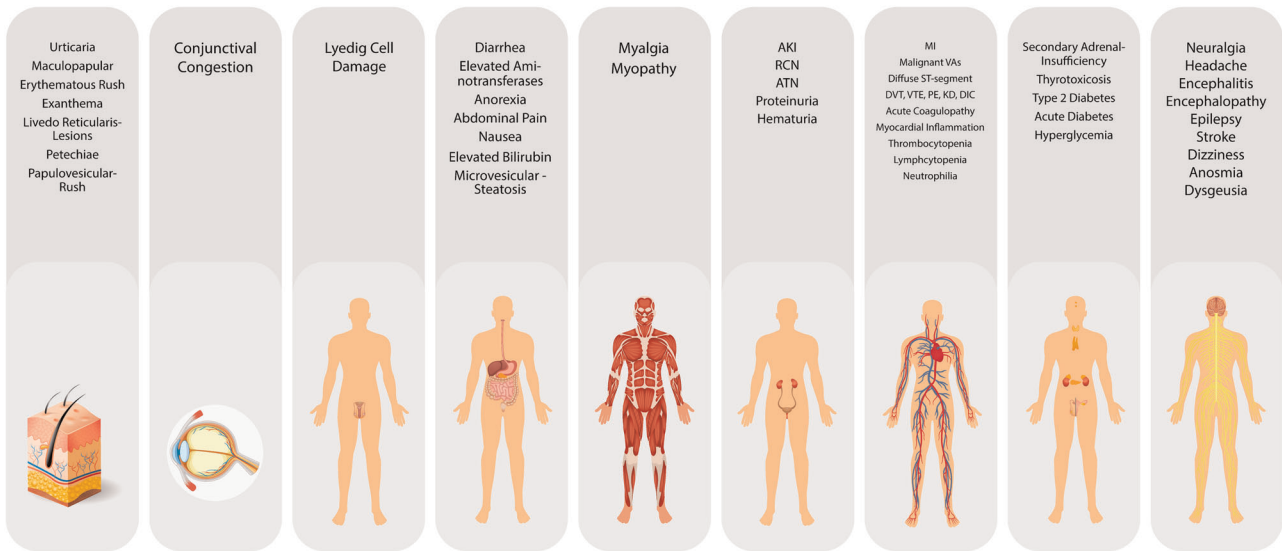


FIGURE 1 A summary of multiorgan complications of COVID-19

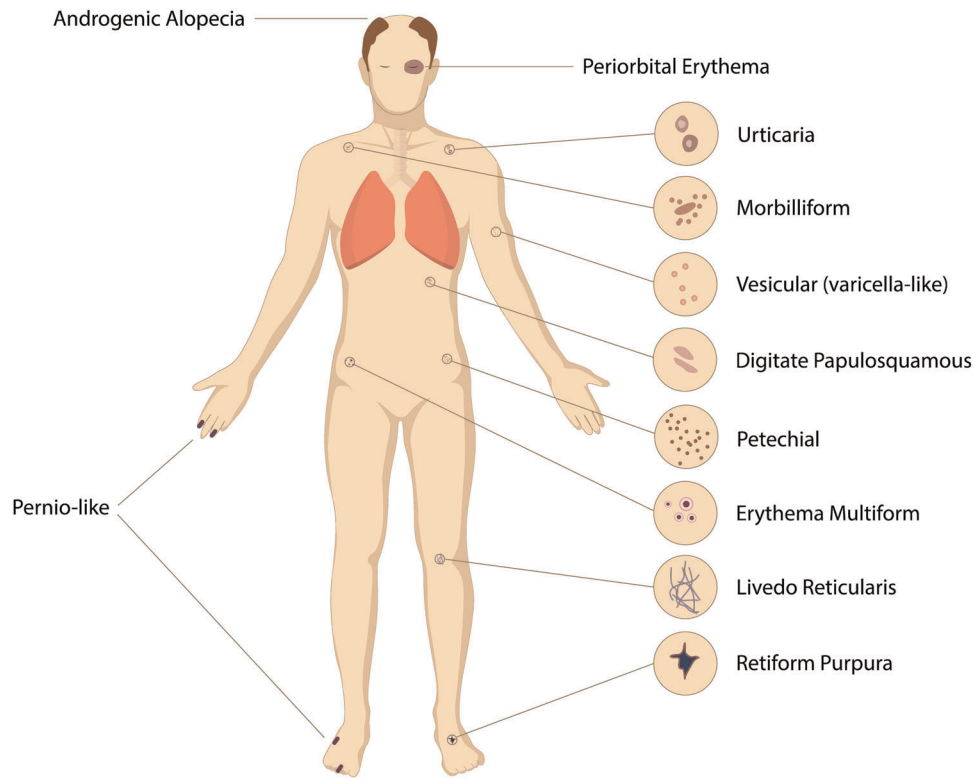


FIGURE 2 A summary of cutaneous manifestations of COVID-19

## 2 | PATHOPHYSIOLOGY

The presence of the angiotensin-converting enzyme 2 (ACE2), which is the primary receptor for SARS-CoV-2 entering skin cells, might explain some of the vascular skin lesions of COVID-19 infection due to significant immune antiviral response.<sup>9</sup> The virus

can directly induce cutaneous lesions or indirectly due to vascular dysfunctions, such as imposed vasculitis and thrombotic vasculopathy. The former may occur through direct viral inoculation, viral reactivation from a distant site, or immunotherapy.<sup>10</sup> Figure 2 illustrates a summary of the cutaneous manifestations of COVID-19.

### 3 | MORPHOLOGY

Dermatological manifestations of COVID-19 are significantly more polymorphic than any viral infection so far.<sup>11</sup> Maculopapular, vesicular, and urticarial lesions are the most common cutaneous eruptions, respectively.<sup>3</sup> Several studies have been conducted to build consensus on categorizing COVID-19 skin presentations as follows.

#### 3.1 | Urticarial rash

Before the SARS-CoV-2 pandemic, many viral and bacterial pathogens such as cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), and mycoplasma were prevalent infectious triggers of urticarial eruptions and angioedema.<sup>12</sup> Itching is almost always present under these circumstances. This dermatological complication usually takes one week to resolve during moderate to severe COVID-19 in approximately 20% of the patients.<sup>13</sup> These lesions are frequently localized on the trunk and extremities, usually with sacral sparing.<sup>14</sup> As with other hypersensitivities and allergic dermatitis, low-dose oral corticosteroids, in addition to antihistamines, can provide appropriate relief.<sup>15</sup>

#### 3.2 | Erythematous/maculopapular/morbilliform rash

Occurring in about 21.3% of the patients, these eruptions are sometimes pruritic and usually appear on the trunk and extremities. They may appear at the same time or evolve from mild involvement to a more diffuse pattern. These lesions can result from SARS-CoV-2 itself, or drugs used to treat COVID-19 infection, are variably pruritic and can last up to one week.<sup>16</sup> Topical glucocorticoids, and in more severe cases, systemic corticosteroids can provide a suitable remedy.<sup>17</sup>

#### 3.3 | Papulovesicular exanthem

These lesions can differ from diffuse polymorphic eruptions to a localized monomorphic pattern, usually on the chest, upper abdomen, or back.<sup>18</sup> Affecting about 29.4% of the patients, their duration can range from a few days up to 2 weeks, and they mainly occur in the context of moderate to severe COVID-19.<sup>19</sup> These eruptions are also known as “varicella-like” eruptions because of their morphology and common characteristics common to the varicella-zoster virus (VZV). However, as the VZV can also be superimposed on pre-existing COVID-19,<sup>20</sup> performing a Tzanck smear or polymerase chain reaction (PCR) of the vesicle fluid may be beneficial in excluding herpesviruses as the inciting factor.<sup>21</sup> The lesions are usually non-pruritic, do not leave scars and are self-limiting.<sup>22</sup> Some studies have included Grover's disease in the category of papulovesicular eruptions associated with COVID-19.<sup>23</sup> It is believed that some papulovesicular eruptions of COVID-19 may be the “pseudo-herpetic” variant of Grover's disease.<sup>24</sup>

#### 3.4 | Chilblain-like acral pattern

These lesions are defined as erythematous-violaceous patches or plaques usually located on the feet, sometimes on the hands, and rarely on the auricular area. They may be accompanied by itching, pain, or a burning sensation. “COVID toes,” also known as pseudo-chilblain or pernio-like lesions, are vasculopathy rashes located in acral areas affecting up to 63% of the patients.<sup>25</sup> The eruptions usually occur in mild or even asymptomatic cases of COVID-19 and more commonly in children and young adults.<sup>26</sup> Increased interferon release due to the cytokine response, direct viral damage of the endothelium, obliterative microangiopathy, and coagulopathy resulting from ischemia can be the causative mechanisms. These lesions tend to subside spontaneously as well.<sup>27</sup>

#### 3.5 | Livedo reticularis/racemosa-like pattern

This skin involvement appears as a cross-linked pattern accompanied by bluish discoloration of the skin and can occur either as a typical livedo reticularis or livedo racemosa.<sup>28</sup> May involves about 6% of the patients,<sup>25</sup> these lesions are first symmetrical and lace-like, resulting from cutaneous vasoconstriction or vascular flow disturbances and disappearing by themselves.<sup>29</sup> On the other hand, the latter usually consisted of more oversized, more irregular, and asymmetrical lesions related to focal blood flow disturbances and may be associated with severe coagulopathies. These eruptions are more common in the elderly and patients with severe COVID-19 infection. Both types are usually self-limited.<sup>29</sup>

#### 3.6 | Purpuric “vasculitic” pattern

This cutaneous manifestation is usually due to vasculitic changes resulting from direct endothelial lesions or exaggerated inflammatory reactions. They are sometimes accompanied by necrotic lesions and can be diffusely distributed in the intertriginous areas or localized peripherally.<sup>30</sup> The same lesions are in the form of polyarteritis nodosa associated with hepatitis B infection.<sup>31</sup> Kawasaki-like eruptions caused by COVID-19 in children are thought to have a vascular origin,<sup>32</sup> which can be misdiagnosed as dengue virus-induced eruptions in endemic regions.<sup>33</sup> Consequently, viral hemorrhagic fevers should always be included in the differential diagnoses. Mild cases can be treated with topical glucocorticoids, while more severe cases need systemic corticosteroids.<sup>34</sup> Although not classified, ischemic and ecchymotic acral lesions have been reported in almost 10% of the patients, especially in those with severe COVID-19 infection due to hypercoagulation and disseminated intravascular coagulation. COVID-19-related acral lesions have been distributed on the extremities' digital, dorsal, and ventral surfaces and the heels and wrists.<sup>35</sup>

### 3.7 | The erythema multiforme-like lesions

These lesions are characterized by annular erythematous macules and vesicles with a darker center and paler halo. In the context of COVID-19, these lesions may be smaller than the classic form and may not demonstrate target-shaped or iris-like features.<sup>36</sup> Several other lesions have been reported for COVID-19, some of which cannot be categorized into one of the mentioned groups. Examples include pityriasis rosea-like rash,<sup>37</sup> Grover's disease-like eruptions,<sup>23,38</sup> acro-ischemia,<sup>39</sup> malar erythema, and facial edema,<sup>40</sup> palmar erythema,<sup>41</sup> symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)-like eruptions,<sup>42</sup> hand-foot-mouth-like diseases,<sup>24</sup> "COVID toes" or pernio-like eruptions,<sup>43</sup> Dengue-like rashes,<sup>33</sup> diffuse melanoderma,<sup>44</sup> gangrene,<sup>45</sup> paronychia,<sup>46</sup> sacral and buttocks ulcerations,<sup>47</sup> mottling,<sup>48</sup> lichenoid eruptions,<sup>49</sup> drug reaction with eosinophilia and systemic symptom (DRESS),<sup>50</sup> acute generalized exanthematous pustulosis (AGEP),<sup>51</sup> Raynaud's phenomenon,<sup>52</sup> eruptive cherry angioma,<sup>1</sup> violaceous macules with "porcelain-like" appearance,<sup>53</sup> IgA vasculitis,<sup>54</sup> leukocytoclastic vasculitis,<sup>55</sup> retiform purpura, eosinophilic panniculitis,<sup>56</sup> and periorbital dyschromia.<sup>57</sup>

## 4 | COVID-19 AND HAIR

The impact of COVID-19 on hair can be described under four categories.

### 4.1 | Telogen effluvium

Telogen effluvium (TE) is a widespread form of hair loss characterized by a diffuse hair loss resulting from a stressor that disturbs the hair cycle's adjustment and causing it to enter the telogen phase earlier. Infection with COVID-19 may be a significant trigger for TE, possibly due to psychosocial or physiological stress.

### 4.2 | Anagen effluvium

Sudden and excessive hair loss and temporary alopecia may occur during SARS-CoV2 infection, like any other infection, due to COVID-19 related to anagen effluvium (AE) resulting from the severe inflammatory response.<sup>58</sup>

### 4.3 | Alopecia areata

Alopecia areata (AA) is a chronic autoimmune disease characterized by sudden hair loss coursing with spontaneous remission and exacerbation. In several COVID-19 patients, acute or chronic psycho-emotional stress may cause AA's onset or progression, presented as alopecia totalis or alopecia universalis.

### 4.4 | Androgenetic alopecia

The relationship between SARS-CoV-2 infection and the androgenic pathway has been previously explained, and several cases of androgenetic alopecia have been reported in COVID-19 patients.<sup>59</sup>

## 5 | COVID-19 AND NAILS

Polydactylous erythronychia or "COVID red half-moon" nail sign is manifested by distal half-moon-shaped red bands surrounding the distal part of the lunula on fingernails,<sup>60</sup> which is the result of capillary changes to the nail fold bed indicative of microvascular involvement.<sup>61</sup>

## 6 | LOCATION OF COVID-19-RELATED CUTANEOUS LESIONS

Locations of the cutaneous lesions vary widely. Some are located on the trunk, while others are focused on the extremities.<sup>62</sup>

## 7 | TIME OF CUTANEOUS ERUPTIONS RELATED TO THE MAIN SYMPTOMS OF COVID-19

Some of the lesions may occur during the onset of typical COVID-19 symptoms, while others may occur before or after the onset of other symptoms. In cases where skin eruptions occur before COVID-19 general manifestations, asymptomatic carriers are suspected, while in cases that develop cutaneous lesions during the course of the infection or after recovery, the immunological response is more likely suspected.<sup>3</sup>

## 8 | RELATION OF SKIN INVOLVEMENT TO DISEASE SEVERITY

The presence of skin lesions may not be affected by the severity of COVID-19.<sup>63</sup> However, cyanosis, purpura, haemaphysalis, and gangrene, which result from multiple organ injuries and ischemia, are primarily observed in severe forms of COVID-19 infection.<sup>64</sup>

## 9 | RELATION OF COVID-19-INDUCED SKIN ERUPTIONS MORPHOLOGY TO PATIENT'S AGE

Age is also an essential factor in the type of dermatological involvement in COVID-19. For example, compared to adults, children usually presented with chilblain-like, papulovesicular, or Kawasaki disease-like eruptions, mostly on acral areas.<sup>26</sup> On the other hand,

older adults are more vulnerable to stasis dermatitis than others. Becoming sedentary due to isolation and social distancing measures is the primary risk factor for this condition, which, with the alteration of venous drainage of the lower limbs, results in this complication in geriatrics.<sup>65</sup>

## 10 | COVID-19 SKIN INVOLVEMENT IN CHILDREN

The skin manifestations of COVID-19 among children are somewhat different from those of adults.<sup>66</sup> Urticarial, vesicular, purpuric, and livedoid eruptions are the most frequent skin eruptions in pediatrics.<sup>67</sup> Moreover, pityriasis rosea- and chilblains-like lesions<sup>68</sup> are more common in children than adults.<sup>26</sup>

Neonatal rashes, including erythematous maculopapular eruptions, have been demonstrated in newborns infected with COVID-19.<sup>69</sup> A Kawasaki-like manifestation has recently been attributed to SARS-CoV-2 infection, called multisystem inflammatory syndrome (MIS).<sup>70</sup> This condition, which is of vasculitic origin, is presented with mucocutaneous involvement, including polymorphic eruptions, palmar and plantar erythema, and other Kawasaki disease features.<sup>71</sup>

## 11 | COURSE AND PROGNOSIS OF DERMATOLOGICAL LESIONS IN COVID-19

Most skin lesions associated with COVID-19 can disappear spontaneously, while others may persist longer. This duration has been reported as hours to weeks.<sup>72</sup>

## 12 | MEDICATION-RELATED SKIN ERUPTIONS

As various medications are being tried and used to treat COVID-19 infection, skin reactions to drugs are common in these patients. Adverse skin reactions associated with the medication may be immediate or delayed hypersensitivity reactions.<sup>6</sup>

## 13 | THE CLASSIFICATION OF COVID-19-RELATED DRUG ERUPTIONS ACCORDING TO THEIR MORPHOLOGIC TYPE

The drug-induced urticaria eruption mediated by IgE, activation of mast cells, immune complexes, or supplements can manifest as the first episode or may present with exacerbation of the pre-existing urticaria.<sup>15</sup>

A drug-induced maculopapular eruption that may be associated with eosinophilia results from a perivascular cutaneous lymphohistiocytic infiltrate.<sup>73</sup>

Severe cutaneous adverse drug reactions like DRESS (drug reaction with eosinophilia and systemic symptoms) are generally associated with

liver abnormalities, eosinophilia, facial swelling, and lymph node involvement.<sup>50</sup>

Vasculitis induced by drugs such as livedo racemosa or purpura, which results from complex immune deposits, is a typical presentation following drug consumption.<sup>74</sup> The type of drug eruptions is, to some extent, dependent on the medication used. Antivirals, antibiotics, anticoagulants, biologic drugs, and immunosuppressive and immunomodulatory agents are applied separately or simultaneously, leading to drug-induced skin eruptions.<sup>75</sup> Hydroxychloroquine is the most known drug responsible for drug eruptions caused by COVID-19.<sup>76</sup> This agent may cause multiple skin lesions like hyperpigmentation,<sup>77</sup> hair whitening,<sup>78</sup> and psoriasis exacerbation.<sup>79</sup> Stevens-Johnson syndrome (SJS)<sup>80</sup> and acute generalized exanthematous pustulosis (AGEP)<sup>81</sup> were also reported in a patient with COVID-19 treating with hydroxychloroquine. However, these effects are primarily associated with high doses of the drug.<sup>82</sup>

Hair loss and photoallergic eczematous reactions with ribavirin,<sup>83</sup> maculopapular eruptions and AGEP with lopinavir/ritonavir,<sup>84</sup> urticaria, generalized eczema and papules with interferons,<sup>85</sup> AGEP,<sup>86</sup> DRESS,<sup>87</sup> and SJS<sup>88</sup> with tocilizumab, and rare cases of maculopapular rashes associated with remdesivir have also been reported.<sup>89</sup>

Furthermore, mechanical pressure due to noninvasive ventilation (NIV) oronasal mask can cause discomfort and perioral pressure ulcers, particularly in patients with delicate, sensitive skin.<sup>86</sup> Moreover, xerostomia induced by NIV can lead to mouth ulcers.<sup>90</sup>

## 14 | VIRAL AND DRUG-INDUCED ERUPTIONS DIFFERENTIATIONS

Dermatological events related to COVID-19 occur due to viral infection or adverse reactions to medications used to treat it.<sup>91</sup> One way to distinguish these two entities is the presence of enanthema (oral cavity lesions), which favors viral-induced eruptions.<sup>92</sup> Therefore, examining the oral cavity is warranted in any COVID-19 patient with enanthema. Furthermore, the morphology of the skin lesions can help differentiate those two skin eruptions. For example, some morphologic patterns of enanthema, such as pustular and dusky lesions, suggest drug eruptions, while petechial or vesicular lesions with distributions on the buttocks or acral sites favor virus-induced eruptions.<sup>91</sup> Another finding that can help us differentiate these two conditions might be histopathological features. Demonstrating multinucleated ballooning cells in the dermal biopsy specimen is mostly confirming COVID-19-related lesions.<sup>93</sup> Histologic features indicative of drug-induced eruptions include lymphocytic exocytosis, perivascular lymphohistiocytic infiltrate with or without eosinophils, interface changes (vacuolar degeneration of basal layer, apoptotic keratinocytes, exocytosis of lymphocytes), lichenoid, spongiotic, or psoriasiform changes, and papillary dermal edema.<sup>3,94</sup>

## 15 | HISTOPATHOLOGY

The histopathological features of COVID-19-associated skin lesions are various and primarily associated with the lesions' morphologic type. As COVID-19-related skin lesions are nonspecific, histopathology can have an essential role in their characterization during the current pandemic.<sup>95</sup> The following features have been demonstrated in the histopathological examination of COVID-19-related cutaneous lesions:

### 15.1 | Maculopapular eruptions

The predominant histopathological findings of erythematous lesions are the superficial perivascular lymphocytic infiltration, focal acantholytic suprabasal clefts, dyskeratotic, and ballooning herpes-like keratinocytes, and swollen vessels with dense lymphocyte infiltration.<sup>96</sup>

### 15.2 | Varicella-like papulovesicular exanthems

Varicella-like papulovesicular exanthems, recommended to be named "COVID-19-associated acantholytic rash," are vacuolar degenerations of the basal layer with multinucleate, hyperchromatic keratinocytes and dyskeratotic cells and inflammatory infiltrate, acantholysis, intraepidermal vesicles with suprabasal clefts.

### 15.3 | Urticarial lesions

Histopathological findings can vary from an erythema multiforme-like pattern, such as vacuolar interface dermatitis and necrotic keratinocytes, to lichenoid dermatitis, accompanied by spongiosis dyskeratotic basal keratinocytes, and superficial perivascular lymphocytic infiltrate.<sup>19</sup>

### 15.4 | Papulovesicular exanthema

Histopathological findings of these lesions include acantholysis and dyskeratosis associated with the presence of a unilocular intraepidermal vesicle in a suprabasal location and ballooned keratinocytes.<sup>97</sup>

### 15.5 | Acral chilblain-like lesions

They are necrotic epidermal keratinocytes accompanied by dermal edema and diffuse dense lymphoid infiltrate of the superficial and deep dermis and hypodermis. They have a general perivascular pattern and signs of endothelial activation, such as endotheliitis, occasionally red cell extravasation, focal thrombosis in papillary dermal capillaries, and vessels of the reticular dermis,<sup>98</sup> and periecrine sweat gland lymphocytic inflammation.<sup>39</sup>

### 15.6 | Livedoid lesions (livedo reticularis/racemosa-like pattern)

It is a pauci-inflammatory thrombogenic vasculopathy accompanied by extensive deposition of C5b-9 and C4b within the microvasculature.<sup>99</sup>

### 15.7 | Purpuric "vasculitic" pattern

They can be defined as leukocytoclastic vasculitis, with neutrophilic infiltrate within the small vessel walls, lymphocytic perivascular infiltrates, and the presence of fibrin and endothelial swelling.<sup>100</sup>

### 15.8 | Pityriasis rosea-like lesions

It is a diffuse spongiosis in the epidermis and rounded spongiotic vesicles containing aggregates of lymphocytes and Langerhans cells with mild papillary edema and lymphohistiocytic infiltrate in the dermis.

### 15.9 | Kawasaki-like lesions

Findings for these lesions are consistent with leukocytoclastic vasculitis, including necrosis of the epidermis and dermis with extravasation of erythrocytes and fibrin accumulation in the capillaries and infiltration of neutrophils with nuclear debris in vessel walls.

### 15.10 | Subcutaneous lesions

Lobular panniculitis with the presence of lymphocytes, histiocytes, and eosinophils is consistent with eosinophilic panniculitis.

### 15.11 | Pustular lesions

Subcorneal pustules with mild focal acanthosis and spongiosis, neutrophilic exocytosis, keratinocyte necrosis, and a perivascular lymphocytic infiltrate accompanied by a small number of neutrophils and eosinophils are consistent with acute generalized exanthematous pustulosis.

## 16 | PSYCHOLOGICAL IMPACTS OF COVID-19 ON SKIN

Social isolation and quarantine can adversely affect many aspects of a healthy lifestyle. Stress and anxiety induced by this condition can lead to exacerbation of underlying chronic dermatoses.<sup>101</sup> Examples

are seborrheic dermatitis (SD)<sup>102</sup> and psoriasis,<sup>103</sup> for which psychological factors play a significant role. On the other hand, some neurodermatitis disorders, such as atopic eczema, rosacea, and facial acne, are aggravated due to emotional pressures during the outbreak, which should be managed with psychological counseling.<sup>104</sup>

## 17 | CHALLENGES OF DERMATOLOGISTS IN THE COVID-19 ERA

Many chronic disorders have been affected directly or indirectly by the COVID-19 pandemic. Chronic dermatoses are one of those conditions that may be aggravated during the current pandemic due to multiple reasons.<sup>105</sup> Biological drugs or immunosuppressive/immunomodulatory agents are commonly used to treat various skin disorders.<sup>106</sup> Individuals who develop COVID-19 while being on those medications may experience more severe symptoms like any immunosuppressed patient. However, some studies argue against this concept and report no more severe manifestations among those treated with immunosuppressive agents.<sup>107</sup>

Furthermore, many dermatoses are accompanied by comorbidities like metabolic syndrome or respiratory and cardiovascular dysfunction, such as psoriatic or atopic dermatitis, hidradenitis suppurative immunobullous connective tissue diseases, which may cause a severe form of COVID-19 infection and a poorer prognosis for those patients.<sup>108</sup> On the other hand, psychological or physical stress imposed by COVID-19 may exacerbate the underlying dermatoses.<sup>109</sup> Therefore, some individuals might discontinue or delay their immunosuppressive medications to prevent infection, leading to the underlying skin disorder exacerbation. Hence, there should be protocols for individuals with chronic skin disorders. Those who are neither infected nor at risk of infection can continue their immunomodulation treatment. However, those at higher risk of infection, display an upper respiratory infection, or are suspected of being infected have better changed their medication regimen either with dose reduction or temporary discontinuation for at least two weeks. In this condition, steroids' dosage can be decreased while medications like apremilast and dupilumab can be continued without dose adjustments.<sup>67</sup> Moreover, as soon as active COVID-19 infection has been confirmed, systemic biologic or other immunosuppressive agents, including steroids, should be discontinued for at least one month or until complete clinical improvement. However, if the stopping systemic agents are expected to be problematic with the underlying disease, they can be temporarily replaced with equivalent topical agents like IL-17 inhibitors with minor immunosuppressive effects.<sup>110</sup>

In general, due to the possibility of relapse in skin diseases like psoriasis, hidradenitis suppurativa, rosacea, pemphigus, and bullous pemphigoid, continuing biologic drugs is the ideal goal during the COVID-19 pandemic unless the pulmonary and systemic condition of the patient does not allow.<sup>111</sup> Psoriasis and autoimmune bullous diseases are examples of dermatoses for which immunosuppressive medications are vital for preventing morbidity and mortality

increase.<sup>112</sup> Therefore, if infected with SARS-CoV-2 infection, discontinue azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, and cyclosporine with continuing topical corticosteroids, colchicine, and intravenous immunoglobulin and tapering of systemic corticosteroids might be the best clinical option.<sup>113</sup>

Another interesting issue is the secondary COVID-19-associated dermatoses that follow the course of this infection.<sup>114</sup> These conditions can occur as a result of COVID-19-induced stress, such as alopecia areata,<sup>115</sup> herpes simplex or herpes zoster,<sup>116</sup> or emerging of new chronic dermatologic disorders like telogen-effluvium,<sup>117</sup> or psycho-cutaneous disorders. Moreover, implementing strict personal precautions like frequent handwashing and disinfectant, mask, or gloves usage can trigger acute urticarial or contact dermatitis and skin xerosis, further complicating the mentioned conditions.<sup>8</sup> Many dermatologic and cosmetic procedures and surgeries have been postponed or deferred because of social distancing rules or personal fear of the infection.<sup>118</sup> Another challenge COVID-19 has posed in the dermatology field is the potential delay of skin cancers (BCCs, SCCs, melanoma, non-melanoma cancers, and hemangioma) diagnosis and treatment.<sup>119</sup> This delay may lead to unfavorable outcomes, including wider excision, metastasis, and death.<sup>120</sup>

## 18 | PERSONAL PROTECTIVE EQUIPMENT-INDUCED OCCUPATIONAL SKIN DISORDERS

The skin is the first and foremost defense barrier against many infections, insults, contaminations, and traumas. Therefore, disruption of its integrity can lead to many complications.<sup>121</sup> Thus, it can be damaged by protective measures through two mechanisms:

1. Skin injury due to PPE.
2. Skin damage as a result of excessive hand sanitizer use.<sup>122</sup>

The great need for hand washing and implementing precautionary prevention measures, such as putting on gloves and goggles, has given rise to a new set of problems in the COVID-19 era.<sup>107</sup> Cutaneous complications due to preventive measures are more prevalent among healthcare workers (HCWs). HCWs wash their hands 20 times a day on average, while hand washing more than 10 times a day is reported to harm the skin adversely.<sup>123</sup> The new term, "COVID hand dermatitis," is proposed for irritant dermatitis during the COVID-19 period.<sup>124</sup> Sanitizers such as alcohol-based hand-rubs disrupt the epidermal barrier due to their lipid solubility, leading to a burning or stinging sensation followed by itching and scratching.<sup>125</sup> Constant goggle-, face shield-, and mask-wearing can lead to ulceration, abrasion, and pressure sores on the face which not only is a bothersome cosmetic problem but also can reduce the efficacy of protective mask due to becoming unfit as a result of involuntary manipulations done to decrease the pressure.<sup>126</sup>

The most common sites of facial skin damage are the nasal bridge, cheek, and forehead.<sup>127</sup> Moreover, frequent hand washing can lead to tinea or candida infection. Gloves, especially latex ones, are also significant causes of contact dermatitis. Latex-free gloves can be a reasonable solution to this pandemic-related problem.<sup>128</sup>

In general, occupational skin complications during the COVID-19 pandemic can be classified into four subgroups.

### 18.1 | Mechanical skin damage

This entity results from direct trauma and pressure on the skin epidermis and dermis beneath the PPEs. The most common lesions are nasal bridge ulcerations. Erythema, papules, maceration, and scaling on the nose, cheeks, forehead, and hands are other findings. Burning, itching, and stinging sensations are the apparent features. This condition is more prominent in men than women and can be controlled with hydrocolloid dressings and emollients at pressure sites.<sup>129</sup>

### 18.2 | Moist-associated skin damage

This condition is due to maceration and occlusion of skin pores, elevated skin temperature, humidity, excessive water immersion, or hyperhydration. The most commonly involved areas are the folds and interdigital webs and manifest as erosions, intertrigo, tinea, immersion foot, dyshidrosis, or miliaria.<sup>130</sup> Interestingly, a case of aquagenic syringal acrokeratoderma or transient aquagenic palmar hyperwrinkling has been reported due to prolonged water immersion.<sup>131</sup> This complication can be managed with topical aluminum, calcium or zinc preparations, antifungals or steroids, or topical antibiotics if superinfected.<sup>129</sup>

### 18.3 | Contact reactions

This event can be either irritant dermatitis or allergic dermatitis; they are mainly located on the face and hands, places which are covered with gloves and masks; however, occupational airborne ACD due to formaldehyde<sup>132</sup> and retro-auricular dermatitis due to face mask ear loops have also been reported.<sup>133</sup> This condition is most commonly associated with detergent use or latex gloves and can present with dry, pruritic, or chapped skin with apparent erythema, papules, scaling, and fissures.<sup>7</sup> This complication can be easily managed with topical steroids or calcineurin inhibitors, H<sub>1</sub>-antihistamines, and emollients.<sup>129</sup>

### 18.4 | Exacerbation of pre-existing dermatoses

Chronic skin disorders that can be aggravated in this setting include acne, rosacea, perioral dermatitis, seborrheic dermatitis, and atopic dermatitis. Nevertheless, these conditions can be managed individually depending on that specific dermatosis. Prolonged hours of protective gloves use can induce pruritus and folliculitis. Moreover, increased humidity due to prolonged mask-wearing can result in pilosebaceous duct occlusion and acne exacerbation.<sup>134</sup>

All the mentioned dermatologic complications can be prevented by several measures, including reducing or avoiding contact with the responsible PPE (e.g., gowns, goggles, gloves, helmet, boots, or masks), taking 15-min breaks every 2 h at duty,<sup>135</sup> using foam dressing, barrier creams or skin powder beneath the PPE, using ear savers,<sup>136</sup> checking the appropriate size of the PPE, using emollients whenever the PPE is put off, using pH-neutral, soap-free cleansing agents for personal hygiene,<sup>129</sup> avoiding excessive washing of the skin and frequent disinfectants use,<sup>137</sup> avoiding tight gowns and ingestion of sufficient amounts of liquids<sup>138</sup> and use of low pH disinfectants and moisturizers.<sup>65</sup>

## 19 | TREATMENT OF SKIN MANIFESTATIONS

Exanthematous COVID-19 related eruptions can be relieved by medication such as topical corticosteroids.<sup>139</sup> As skin injuries are more common in HCWs, they should apply measures to relieve new-onset skin involvement in primary stages. They can use moisturizers and low potency topical steroids for xerosis and mild dermatitis. However, antihistamines and more potent topical steroids are indicated for severe, more pruritic lesions.<sup>140</sup> Vascular skin lesions in the settings of hypercoagulable conditions, such as acro-ischemic, purpuric, and livedoid lesions, or leukocytoclastic vasculitis, usually subside when COVID-19 resolves; however, anticoagulant therapy is the primary key for their improvement. If secondary bacterial or fungal infection is superimposed on COVID-19 related cutaneous complications, an antimicrobial or antifungal agent can be administered.<sup>137</sup>

In cases of pre-existing dermatoses exacerbation, prompt dermatologist referral is recommended.<sup>122</sup> For drug-induced cutaneous rashes, temporary or persistent discontinuation of the responsible medication may be needed.<sup>4</sup>

## 20 | CONCLUSION

All clinicians, primarily dermatologists, should be aware of cutaneous lesions in the context of the COVID-19 pandemic, either as the first presentation of the infection, leading to early diagnosis of COVID-19, or as an indicator of the deterioration of the patient's wellbeing. Moreover, they should be of interest and play a critical role in adjusting and modulating the dermatologic patients' treatment plan to avoid infection susceptibility while maintaining their remission.

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### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.



## AUTHOR CONTRIBUTIONS

Zeinab Mohseni Afshar and Soheil Ebrahimpour were involved in review concepts, design, and critical revision for important intellectual content. Arefeh Babazadeh, Mohammad Barary, Babak Sayad, Alireza Janbakhsh, Zeinab Aryanian, and Soheil Ebrahimpour performed the literature search and drafted the manuscript. Amirhossein Hasanpour was involved in the visualization and software of the study, Mohammad Barary was involved in the critical revision of the manuscript. All authors read and confirmed the final version of the manuscript.

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