

## CASE REPORT

# COVID-19 and COVID-19 vaccine-related dermatological reactions: An interesting case series with a narrative review of the potential critical and non-critical mucocutaneous adverse effects related to virus, therapy, and the vaccination

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## Abstract

This narrative review article was conducted to lay out a summarized but exhaustive review of current literature over mucocutaneous manifestations in 4 dimensions of SARS-CoV-2 pandemic: virus itself, treatment-related, vaccine-induced, and alteration of chronic dermatologic diseases following infection. Virus and vaccine-related were mainly self-limited and non-severe. Treatment-related reactions could be life-threatening.

## KEYWORDS

adverse events, Atlas, clinical Atlas, coronavirus, COVID-19, cutaneous, dermatology, histopathology, image series, manifestation, mucocutaneous, mucosal, pathology, presentation, review, SARS-CoV-2, side effect, skin, therapy, treatment, vaccination, vaccine

## 1 | INTRODUCTION

COVID-19 infection has effects on several organ systems such as respiratory, cardiovascular, gastrointestinal, central nervous system, and skin.<sup>1</sup> Considering its

dermatologic aspect, numerous publications declared different cutaneous manifestations in COVID-19 patients which drew attention to the COVID-19-associated skin lesions.<sup>2</sup> The prevalence of skin manifestations was estimated between 7.8% and 20.4% and the broad spectrum

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of cutaneous manifestation was recognized. Among COVID-19 skin-affected patients, the most common skin eruptions were non-specific maculopapular rashes (47%).<sup>3</sup>

Given dermatologic side effects of COVID-19 treatments, they had a prevalence of 0.004% to 4.15% and antivirals, antimalarials, azithromycin, and tocilizumab were the most culprit drugs. Moreover, morbilliform/exanthematous maculopapular rashes or urticarial eruptions were typical types of skin reactions in this category.<sup>4</sup>

Furthermore, in view of mucocutaneous adverse reactions of COVID-19 vaccination, injection site reactions, and delayed large local site reactions were the most frequently observed side effects in different studies.<sup>5–7</sup>

In this image series and literature review, we aimed to provide a summarized yet comprehensive review of this broad spectrum of dermatologic features of the COVID-19 disease, treatment, and vaccine-related eruptions with elucidating clinical image cases, all of which from patients we visited at our dermatology clinic in a tertiary referral hospital; as well as outlining a categorization of critical and self-limited manifestations of the disease and eventually pointing out the alterations in underlying dermatologic conditions. We carried out a comprehensive search in PubMed database with keywords including but not limited to "COVID-19," "SARS-CoV-2," "Mucocutaneous," "Dermatologic," "Manifestations," "Treatment," "Severe," "Life-threatening," "Adverse events," "Pathology," "Dermatologic Conditions," and "Vaccine," we scrutinized relative studies and extracted the most common findings, and conjoining the epidemiologic data with our genuine image cases.

## 2 | CLASSIFICATION

### 2.1 | Virus related

In this category, two possible mechanisms have been proposed for skin involvement: (1) local direct cytopathic interactions of immune cells with the virus within the skin and mucosa and (2) Eruptions secondary to excessive immune response and cytokine release due to viremia.<sup>8,9</sup>

The mean time to occurrence of skin lesions following the onset of constitutional symptoms was 9.92 days in one study and skin manifestations were less common as an initial symptom. Fever is the most prevalent among COVID-19 presentations. In this group, the most common type of skin eruption was patchy exanthematous rash, and the trunk was the most common site of involvement.<sup>10</sup> Furthermore, most patients complained of significant pruritus.<sup>11</sup> In addition, ischemic and necrotic mucocutaneous involvement in COVID-19 patients increases

the likelihood of disease severity as a reflection of organ damages.<sup>12</sup>

Types of virus-related skin lesions:

#### 1. Non-severe skin eruptions

Maculopapular rash: small papules covering erythematous scaly macules which the mean total duration of their presence has been reported to be 9 days in patients (Figure 1A).<sup>13</sup> Urticaria: acute erythematous swollen plaques which usually last for about 6.8 days and most commonly affect the trunk. In 92% of these patients, pruritus is predominantly observed (Figure 1B).<sup>13</sup> Vesicular lesions: small blisters filled with clear liquid with an erythematous base and monomorphic shape, mean duration of their appearance is about 10.4 days. Lesions develop mostly on the skin of the extremities and trunk, and they are usually antecedent to the other symptoms in most cases.<sup>13</sup> Petechiae/purpura: subdermal hemorrhages of various sizes, this may reflect either thrombocytopenia which has multiple underlying etiologies in the context of COVID-19 infection, comprising hemophagocytic lymphohistiocytosis (HLH), thrombotic thrombocytopenic purpura (TTP), sepsis, heparin-induced thrombocytopenia (HIT), drug-induced thrombocytopenia, and finally immune thrombocytopenic purpura (ITP) or vasculitic causes.<sup>13,14</sup> It spares palmoplantar, face, and mucosa (Figure 1G). Complement deposition (C5b-9 and C4d) and pauci-inflammatory thrombogenic vasculopathy were reported in histopathologic investigations.<sup>15</sup> Chilblains "COVID toes:" erythematous and edematous skin eruption on the extremities predominantly present in children and young adults with asymmetrical distribution. Typical symptoms of COVID-19 are rare among patients with chilblain lesions. Lymphocytic vasculitis and vascular damage were frequently noted in histological features. These lesions disappeared spontaneously without treatment within 8 weeks of follow-up.<sup>16</sup> In our experience, lichenoid eruptions (Figure 1C), pityriasis rosea (Figure 1D), herpes simplex reactivation (Figure 1E), and herpes zoster (Figure 1F) were observed following COVID-19 infection.

#### 2. Severe skin eruptions

Vascular lesions: tissue ischemia and necrosis were the most frequent pathology among severe skin eruptions in patients with COVID-19 (Figure 1H–J). It most commonly affected the extremities and put patients aged 60 years and older at higher mortality risk than the rest.<sup>12</sup> Ischemic complications lead to the tissue necrosis which highlights the importance of the emergent vascular surgery consultation to consider intravenous thrombolytic therapy.<sup>13</sup> Hypercoagulation

**FIGURE 1** Infection-related mucocutaneous manifestations of COVID-19. Panel A: nonspecific maculopapular eruptions. Panel B: generalized Urticaria, Panel C: lichenoid eruptions, Panel D: post-infection pityriasis rosea, Panel E: Herpes simplex reactivation, Panel F: Herpes Zoster, Panel G: Purpuric eruptions, Panel H, I and J: vasculopathic and necrotic lesions



state in severe COVID-19 resulting in hemostatic disturbances and disseminated intravascular coagulation (DIC) is another cause for mortality.<sup>15</sup> Angioedema: angiotensin-converting enzyme 2 plays a key role in acute respiratory distress syndrome in COVID-19 patients and excessive amounts of bradykinin give rise to the development of angioedema. Its most common location is face and trunk and the average therapeutic course duration after systemic corticosteroids and antihistamines is between 1 and 22 days.<sup>17</sup> Toxic Shock Syndrome (TSS): it is a consequence of Multisystem Inflammatory Syndrome (MIS-C), found primarily in children due to systemic inflammatory status. It overlaps with Kawasaki disease shock syndrome (KDSS) including lymphadenopathy, skin rash, an elevation of inflammatory biomarkers, strawberry tongue, and left ventricular systolic dysfunction.<sup>12</sup> Acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson-like syndrome (SJS)/toxic epidermal necrolysis (TEN), erythema multiform major (EM) were also reported rarely in this category.<sup>12</sup>

## 2.2 | Treatment-related

Due to the lack of a definite therapeutic approach for COVID-19 infection, physicians from different specialties implement various drugs to improve the outcomes. Each drug could carry a potential risk of mucocutaneous adverse events that might be life-threatening particularly in the elderly who are more susceptible to multiple drug reactions.<sup>18,19</sup>

### 2.2.1 | Antimalaria

During the generation time of COVID-19, chloroquine (CQ) and hydroxychloroquine (HCQ) were extensively used as an urgent treatment regime. CQ and HCQ have been pulled from COVID-19 treatment guidelines in many countries.<sup>20</sup>

Cutaneous eruptions of antimalarials include AGEP, SJS-like syndrome, exfoliations, pruritus, dry skin, urticarial, exanthematous rash (Figure 2A), mucocutaneous

dyspigmentation, hair whitening, and alopecia. Most of these side effects can be managed by discontinuing the culprit drug or administering antihistamines accompanied by topical or systemic steroids treatment. Moreover, HCQ showed a higher average interval between drug initiation and skin lesions.<sup>4,21</sup>

### 2.2.2 | Azithromycin

It was used widely due to its anti-inflammatory and immunomodulatory properties. Cutaneous adverse events of azithromycin consist of cutaneous leukocytoclastic vasculitis, anaphylaxis, angioedema, DRESS syndrome, skin peeling, toxic pustuloderma, generalized red or purple lesions, blistering, burning in eyes, skin pain, and fixed drug eruptions.<sup>4,21</sup>

### 2.2.3 | Antivirals

(Oseltamivir/Favipiravir/Umifenovir, Ribavirin, Lopinavir/Ritonavir, Remdesivir, Sofosbuvir, Nita-zoxanide)—these agents are chiefly utilized to treat parainfluenza 1 virus, influenza A, B viruses, and HIV diseases besides SARS-CoV-2 infection.<sup>4,21</sup> Dermatologic side effects reported for this antiviral group are angioedema,

SJS/TEN (Figure 2D), maculopapular or eczematous rash, urticaria (Figure 2B), lichenoid drug eruption, localized scleroderma, paronychia, and acneiform eruptions, allergic or idiosyncratic cutaneous drug reactions, exfoliative erythroderma, photosensitivity, and annular erythema, bite hypersensitivity, skin dryness, redness and pruritus, lipodystrophy, injection site reactions, hyperpigmentation, and alopecia.<sup>4,21</sup> Among the drugs in this antiviral group, dermatologic drug reactions are most commonly seen in association with lopinavir/ritonavir. Umifenovir and favipiravir had few or no reports of skin reactions. A higher frequency of drug usage increases the risk of dermatologic adverse effects.<sup>4,21</sup>

### 2.2.4 | Biologic or chemical targeted therapies (Checkpoints inhibitors, Janus kinase inhibitors, Anakinra, TNF- $\alpha$ inhibitors, Tocilizumab, Camostat mesylate)

Skin adverse reactions related to this group included urticaria, angioedema, morbilliform, or eczematous rash, hyperhidrosis, vitiligo, hair color changes, palmoplantar pustulosis-like eruption, psoriasis, and psoriasisiform-like lesions, exfoliations, photosensitivity, skin hypersensitivity reactions, lupus-like syndromes, alopecia, stomatitis, lichenoid eruptions, pruritus, cutaneous vasculitis,



**FIGURE 2** Treatment-related eruptions of COVID-19. Panel A: Exanthematous drug eruption, Panel B: Drug-induced urticaria, Panel C: Steroid induced acne, Panel D: Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), Panel E: Mucormycosis in a COVID-19 patient under treatment with immunosuppressive drugs

xerosis, granulomatous reactions, skin infections, cutaneous lymphoma, melanoma or nonmelanoma skin cancers, periungual pyogenic granuloma-like lesions, and non-healing wound.<sup>4,21</sup>

### 2.2.5 | Classic immunomodulators (Interferons, Colchicine, Corticosteroids, and IVIG)

Drug-related mucocutaneous reaction of this group comprised eczematous drug reactions, psoriasis, lichenoid drug reactions, anaphylactic reaction, morbilliform rash, urticaria, maculopapular rash, erythema, edema, fissures, TEN-like reaction, eczematous and lichenoid drug reactions, psoriasis, lupus, acneiform eruptions (Figure 2C), skin atrophy, papular and pustular lesions, petechiae, cutaneous vasculitis lesions, folliculitis, sarcoidosis, dryness, burning, stinging, alopecia and hirsutism, pruritus, striae, telangiectasia, erythema-nodosum, and erythema-bullous-like lesions, erythema multiforme, and injection site reactions.<sup>4,21</sup> Excessive use of corticosteroids and poor glycemic control could lead to opportunistic infections such as mucormycosis (Figure 2E).

## 2.3 | Vaccines

During the pandemic, the development of COVID-19 vaccination has been growing to protect global health and limit disease transmission. The reports of vaccine-related dermatologic effects have been increasing in people who got vaccinated. Currently, three principal types of COVID-19 vaccines are widely used<sup>22</sup>:

1. Messenger RNA (mRNA)-based
2. Inactivated whole-virus
3. Adenoviral vector

Injection site reactions are the most widespread cutaneous side effects, including pain (88%), swelling (15%), erythema (20%), pruritus (35%), and induration (25%). It is more common among the younger population compared with older people. Some other skin findings have been reported among Moderna's vaccinated such as eczema, contact and atopic dermatitis, hypersensitivity reactions, exfoliative rash, injection site urticaria, and vesicular rash. Sputnik V's vaccinated subjects reported acneiform rash, alopecia, allergic dermatitis, eczema, and petechial rash.<sup>7,9</sup>

Other types of skin eruption ascribed to vaccination include delayed large local reactions: (delayed T-cell-mediated hypersensitivity reaction): they present as an erythematous targetoid and edematous patch to large

plaques appearing at least 4 days following vaccination at the site of injection. It is more common in patients who received mRNA COVID-19 vaccines. Histopathological findings demonstrate perivascular eosinophils and lymphocytic infiltration.<sup>7,9</sup>

Delayed inflammatory reactions to dermal hyaluronic acid fillers (DIRs): inflammation and swelling presented in participants who were previously treated with fillers in 1–2 years before immunization. When oral lisinopril was prescribed in these patients, it subsided the symptoms which pertained to the high expression of angiotensin-converting enzyme (ACE) 2 receptors at the injected site.<sup>7,9</sup>

Morbilliform rashes: skin biopsy indicated dermal perivascular lymphocytic infiltration and spongiosis which imply an immune-mediated reaction rather than direct virus effects.<sup>7</sup> Pernio and Chilblains: erythematous and painless macules and papules on extremities occurred after inoculation, which were previously noticed with COVID-19 patients suggesting that they share a similar immune mechanism.<sup>7,9</sup>

Urticaria (Figure 3A,B), angioedema (Figure 3C), erythromelalgia, erythema multiforme-like lesions (Figure 3K), pityriasis rosea-like reactions (Figure 3F), lichen planus, varicella-zoster and herpes simplex reactivation (Figure 3D,E), and petechial and purpuric rash were also reported. In our experience, we detected ecchymotic lesions (Figure 3H), guttate psoriasis (Figure 3G), fixed drug eruptions (Figure 3I), and alopecia areata (Figure 3J) post COVID-19 vaccination. All of our cases were vaccinated with BBIBP-CorV (Sinopharm) and the mucocutaneous adverse events occurred at both or any of the two doses. Most of the skin manifestations resolved spontaneously.

## 2.4 | Chronic skin diseases affected by COVID-19

There is a paucity of consensus over the pattern of alteration in underlying mucocutaneous conditions amid the COVID-19 pandemic. Majority of records are confined to case reports, essentially regarding psoriasis. Some evidence report no change of pattern in psoriasis in patients who stick to their treatment regimen, particularly under treatment with biologic agents, while they experienced mild or asymptomatic COVID-19 infection, contributed to the immunomodulatory effect of these drugs in the inflammatory phase of the infection.<sup>23</sup> Other studies indicated exacerbation or relapse of psoriasis in those abandoning their drug course or in cases in which HCQ, a known cause of drug-induced psoriasis was administered. There was no consensus over methotrexate.<sup>23</sup> It could be postulated that psoriatic patients are not at further risk of mortality from COVID-19



**FIGURE 3** COVID-19 vaccine-associated eruptions. Panel A and B: Urticaria, Panel C: Angioedema, Panel D: Herpes zoster, Panel E: Herpes simplex reactivation (Maxillary nerve region), Panel F: Pityriasis rosea, Panel G: Guttate psoriasis, Panel H: ecchymotic and necrotic lesions, Panel I: Fixed drug eruptions, Panel J: Alopecia Areata, Panel K: Erythema Multiforme-like lesions

compared with the general population.<sup>24</sup> According to other studies, patients with atopic dermatitis experienced 26% to 43% of exacerbation during active COVID-19 infection. Alopecia areata patients reported 42.5% relapse almost 2 months after COVID-19 infection, which was found significant compared with the control group.<sup>23</sup> In addition, the incidence of new autoimmune diseases such as psoriasis and morphea has been reported after infection.<sup>25</sup> According to one study, patients with autoimmune bullous dermatoses such as pemphigus vulgaris and bullous pemphigoid are not at increased risk for severe or fatal COVID-19; therefore, discontinuation of important immunomodulatory treatments is not recommended, however, it is advised to

reduce prednisone/prednisolone to <10–20 mg/day in active infection.<sup>26</sup>

## 2.5 | Histopathological evaluation of the mucocutaneous biopsy samples

Histopathological findings of common non-severe skin eruptions of SARS-CoV-2 infection incorporate maculopapular purpuric exanths, erythrocyte extravasations, perivascular lymphocytic and eosinophilic infiltrates, epidermal spongiosis, and papillary dermal edema. Superficial and deep lichenoid, perivascular infiltrates,

and perieccrine lymphocytic infiltration without vasculopathy were observed in chilblain lesions. Moreover, samples of petechia had frequent RBC extravasation, focal parakeratosis, and scattered dyskeratotic cells.<sup>27</sup>

Biopsy samples of severe COVID-19 skin eruptions such as livedoid and necrotic lesions were consistent with pauci-inflammatory thrombotic vasculopathy, with full-thickness fibrinoid necrosis of epidermis and adnexal structures including eccrine gland coil, with perivascular and interstitial neutrophilic infiltration accompanied by thrombosis. Furthermore, immunohistochemical (IHC) staining denoted C5b-9 deposition in microvasculature.<sup>27</sup> According to the treatment-related adverse effects, particularly AGEP in patients who developed it following HCQ and lopinavir/ritonavir administration, pathology findings demonstrated sub- and intra-corneal pustulosis, focal acanthosis, keratinocyte necrosis, neutrophil exocytosis, and lymphocyte infiltration.<sup>4</sup> A case of DRESS who was treated by Azithromycin and HCQ showed dermis edema with perivascular infiltrations of lymphohistiocytic cells and eosinophils.<sup>4</sup> Biopsy samples of two patients with generalized pustular figurative erythema following HCQ indicated intra- and sub-corneal pustulosis with spongiosis, intraepidermal pustulosis with acanthosis, and parakeratosis along with erythrocyte extravasation in the upper dermis and dilated capillaries.<sup>4</sup>

### 3 | DISCUSSION

Based on the reviewed literature, majority of common COVID-19 infection-related mucocutaneous manifestations comprising non-specific maculopapular eruptions, urticaria, vesicular, petechial and chilblain lesions, have self-limited courses and may require non to minimal supportive treatment, which was consistent with our personal experience.<sup>11</sup>

As the largest organ in the body, skin could be a visible reflection of histopathological incidents in vital organs such as the brain, kidney, and lungs.<sup>28</sup> On the contrary to the above, the vasculopathic ischemic and necrotic lesions, as consequences of hypercoagulopathic inflammatory storm, could be a salient indication of end-organ damage and critical underlying conditions such as DIC and purpura fulminant, which lead to poor prognostic outcomes and a possible increase in mortality.<sup>12</sup>

Despite the diverse drug regimen administered for COVID-19 patients, the treatment-related mucocutaneous eruptions were predominantly trivial, yet more life-threatening hypersensitivity reactions such as AGEP, SJS/TEN, and DRESS were reported in this group.<sup>4</sup>

COVID-19 vaccine-associated mucocutaneous adverse events comprising local acute and delayed

injection site reactions, non-specific/maculopapular/morbilliform eruptions, urticaria, virus reactivations, and angioedema were scarcely reported, and despite some rare anaphylactic reactions, had excellent prognosis.<sup>7,9</sup>

The authors of this study have worked on several aspects of COVID-19 including reviews regarding various dermatologic and prognostic concerns in this global calamity.<sup>9,29-36</sup> This article aimed to yield a comprehensive review and some brief points on common mucocutaneous manifestations of the COVID-19 disease, treatment, and vaccine-related dermatologic adverse events, and finally, the disease pattern in patients with underlying dermatologic conditions in the context of SARS-CoV-2 infection.

Dermatologists and physicians of all the other specialties should be familiarized with severe mucocutaneous manifestations in COVID-19 patients since they might predict critical forms of the illness.<sup>37</sup> Particularly, vascular events and severe hypersensitivity drug eruptions must be identified promptly, and proper treatment is warranted which is further challenging in ICU admitted patients with multiple underlying conditions.<sup>1</sup>

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHOR CONTRIBUTIONS

All authors contributed to the preparation and finalization of this article.

### CONSENT

Written informed consent was obtained from the patients for publishing the images for scientific and educational purposes.

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