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# Dermatopathology of COVID-19 infection and vaccination

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## Abstract

**Background:** Many peculiar skin changes have been described in relation to both coronavirus disease 2019 (COVID-19) infection and vaccination.

**Objective:** This paper provides an overview of these dermatologic manifestations, focusing on their dermatopathological appearances.

**Results:** Most COVID-19 patients develop variegated maculopapular eruptions with a combination of histological patterns commonly including keratinocyte apoptosis and eosinophilia. Urticaria-like lesions often show a combination of spongiotic and lichenoid patterns and are more frequent in individuals with severe disease. Vesicular lesions can be disseminated; in some cases, they become pustular and in others show dyskeratosis and a peculiar form of ballooning. Some patients develop vesicular Grover disease on the trunk. Young patients with a strong immunological response can eliminate the virus easily but may develop chilblains as a consequence of the high interferon response. Conversely, older individuals with immunosenescence and a tendency toward hypercoagulability can present livedoid and ischemic areas. Regarding COVID-19 vaccination, hypersensitivity reactions are most frequent, including “COVID-arm.” Nonetheless, a combination of local and systemic cutaneous manifestations (reactogenicity) is commonly seen. Histopathologically, lichenoid and spongiotic changes and a variable number of eosinophils are typical of rashes characterized by papules and plaques. Other dermatological side effects of COVID-19 vaccination include lesions mimicking well-defined dermatoses such as lichen planus or bullous pemphigoid and triggering of collagenous diseases.

**Conclusion:** Well-characterized skin manifestations of coronavirus disease 2019 (COVID-19) include chilblains, livedo necrotic lesions, vesicular eruptions, urticarial lesions, and maculopapular eruptions. Hypersensitivity reactions are common after SARS-CoV-2 mRNA vaccination. Vaccine reactions may also mimic other dermatosis such as bullous pemphigoid or lichen planus, stimulate herpes reactivation, or trigger the development of autoimmune diseases.

### Keywords

Skin · SARS-CoV-2 · Vaccine · Histopathology · Cutaneous manifestations

The coronavirus disease 2019 (COVID-19) pandemic has been associated with a marked rise in reports of associated inflammatory dermatoses and the activation or reactivation of immunological diseases. During the first wave, these were especially common in Europe and the USA and less frequent in Asian countries [1]. Their prevalence has decreased since the second wave [2], probably because immunoactivation played a major

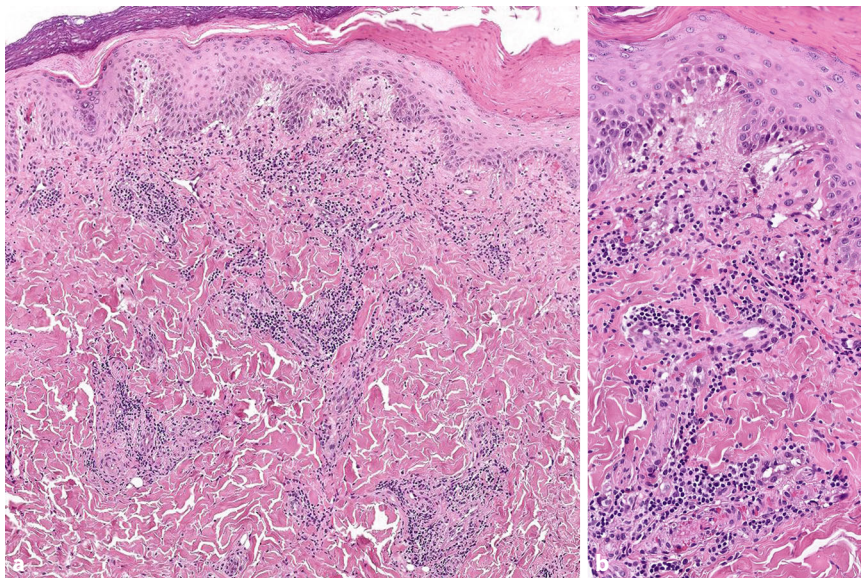
role in their development [3]. In parallel, the cutaneous side effects of COVID-19 vaccinations have been observed and reported with increasing frequency, becoming a new field of study [4].

### Distinctive COVID-19-associated inflammatory dermatitis

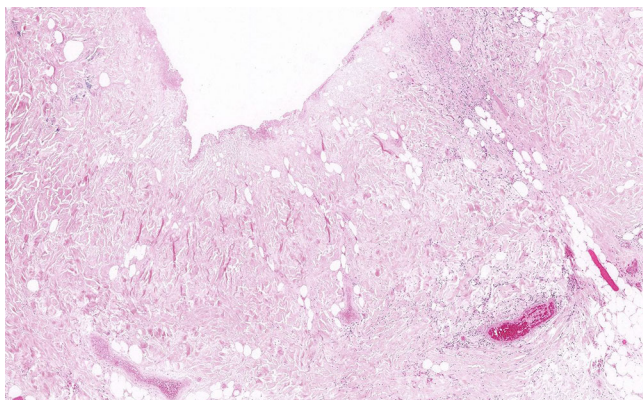
The most characteristic manifestations of COVID-19 in the skin can be clinically clas-



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**Fig. 1** ▲ COVID-associated chilblains showing (a) lichenoid changes in the epidermis and a prominent perivascular lymphocytic infiltrate that, a higher magnification, (b) shows endothelial tumefaction, red blood extravasation and occlusive fibrin deposition



**Fig. 2** ◀ Sacral ischemic necrosis showing occlusive thrombosis and a minimal inflammatory reaction

sified into five main groups corresponding to (I) chilblains, (II) livedoid and necrotic lesions, (III) vesicular eruptions, (IV) urticarial lesions, and (V) maculopapular eruptions [5].

COVID-19-associated chilblains tend to involve young individuals with mild COVID-19. Histologically, these lesions are indistinguishable from other types of perniosis, either idiopathic or associated with collagen diseases. Nonetheless, biopsy specimens from COVID-19 patients tend to show greater basal vacuolar change and vascular damage with fibrin deposition, purpura, and thrombosis than other variants (■ Fig. 1; [6]). This conspicuous vascular damage explains why some authors initially included chilblains in the group of acral livedoid lesions, even though they develop in patients with

a different background and prognosis [7]. Interestingly, despite the marked increase in reporting and severity of chilblain cases during the pandemic, an epidemiological correlation between serologically demonstrated COVID-19 infection and chilblains has never been statistically demonstrated [8]. The most feasible explanation is that after contact with the virus, the robust innate responses of younger individuals lead to abortive seronegative infections. However, this salutary reaction is associated with high levels of type I interferon that favor the microvascular damage responsible for chilblains [8]. The presence of aggregates of interferon-induced (and producing) plasmacytoid dendritic cells in all types of chilblains, regardless of their etiology, supports this hypothesis [6, 9].

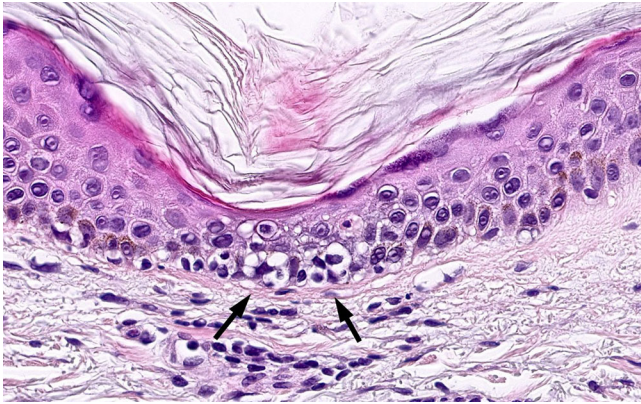
Livedoid and necrotic lesions are typically acral or located in the sacral area and buttocks of older patients with a poor outcome [5]. Age-related immunosenescence and a tendency toward hypercoagulability would facilitate development of the “cytokine storm” and systemic thrombotic events. Histologically these lesions are characterized by extensive areas of ischemic necrosis secondary to occlusive microthrombi involving small and medium-sized vessels. Sometimes there is fibrin deposition within the vessel walls, but without other features of vasculitis (■ Fig. 2). In biopsy specimens of these lesions, the inflammatory infiltrate is minimal and often limited to the edges of the infarcted areas, where sweat gland necrosis, a manifestation of low blood supply, is also evident.

Vesicular eruptions correspond to the third group. Some patients develop widespread polymorphic lesions that can be pustulous or acquire a varicella-like appearance. Histologically, they may contain keratinocytes with vacuolar degeneration, apoptosis, and a peculiar ballooning [10], with large vacuoles that provide a slightly lipoblast-like appearance (■ Fig. 3). In other cases, lesions are monomorphic, localized predominantly to the trunk, and show areas of acantholytic dyskeratosis [11] typical of vesicular Grover disease [12].

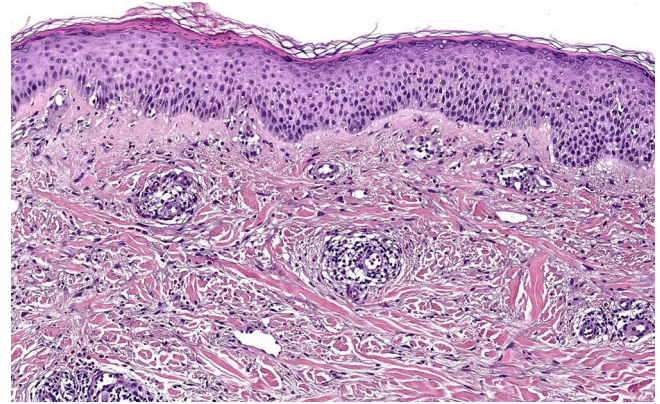
Lesions clinically defined as urticarial are more common in individuals with severe disease [5]. Microscopically, in addition to dermal edema, there is a combination of histological patterns such as lichenoid, spongiotic, and urticarial vasculitis [10]. Eosinophilia is a common finding, always raising the differential diagnosis of a drug eruption. Nonetheless, in the first wave, these patients received only limited support treatment, making a pharmacological reaction unfeasible.

Finally, the larger group of patients presented the heterogeneous group of maculopapular eruptions, including morbilliform and pityriasis rosea-like exanths, pseudovesicular lesions resembling erythema elevatum diutinum, purpuric erythema multiforme-like eruptions, and others [5, 10]. In some cases, the histological findings correlate with the appearance expected according to the clinical picture, but more often these biopsies





**Fig. 3** ▲ Keratinocyte ballooning is common in disseminated vesicular lesions of COVID-19 patients, but sometimes can occur in association with other inflammatory patterns. The large cytoplasmic vacuoles sometimes causing indentation in the nuclear shape (arrows) provide the squamous cells with a peculiar lipoblast-like appearance



**Fig. 4** ▲ This biopsy from a clinically eczematous eruption shows only mild spongiosis. Conversely, there is focal interface dermatitis and perivascular and interstitial lymphoid infiltrate with scant exocytosis, many eosinophils, and dermal edema

showed unexpected combinations of patterns. For instance, lesions that for a well-trained clinical dermatologist are clearly eczematous show microscopically marked lichenoid changes, and vice versa (■ Fig. 4). In any case, some degree of keratinocyte apoptosis and eosinophilia are common findings. Oral lesions, ranging from ulcerations to macules or enanthema [13], tend to be mild, and the few biopsied cases show non-specific histopathological changes.

In children, cutaneous lesions are infrequent and similar to those of young adults. Chilblains are the most common manifestation, but a small number of patients develop the severe multisystem inflammatory Kawasaki disease (KD)-like syndrome. KD-like syndrome is clinically and histologically similar to KD, but carries a higher risk of severe gastrointestinal symptoms, myocarditis, and shock. Patients with KD-like syndrome may develop non-exudative conjunctivitis, a polymorphic rash, perineal and facial desquamation, and hand and foot erythema with edema and induration. Histologically, these lesions are rather non-specific, but may present edema, purpura, or thrombosis [14].

### Other cutaneous alterations related to COVID-19 infection

Hyperstimulation of the immune system can lead to reactivation of autoimmune diseases, graft-versus-host disease, and other skin disorders with an immunolog-

ical background. Some individuals, especially those with increased susceptibility, can develop autoimmune disorders de novo, possibly as a consequence of the production of antibodies with cross-reactive potential [15, 16].

In addition, some patients develop flares of non-autoimmune dermatitis such as inflammatory porokeratosis [17] and other conditions. Conversely, cutaneous drug reactions are not especially frequent in COVID-19 patients [18] and the use of personal protective equipment leads to only mild problems. Incidentally, there are occasional reports of partial or complete remission of mycosis fungoides and Sezary syndrome after SARS-CoV-2 infection [19, 20].

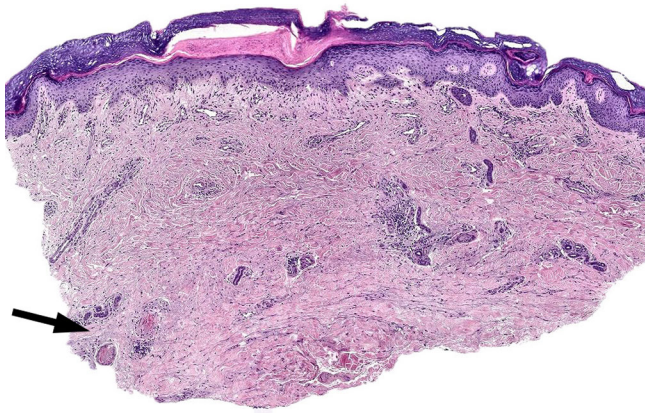
### Cutaneous side effects of COVID-19 vaccination

The rapid development of COVID-19 vaccines has greatly contributed to mitigating the human and economic impact of the pandemic, but also carries many adverse effects. Cutaneous reactions to COVID-19 vaccines are more frequent in women; although they tend to be mild, they may represent a vital risk [21].

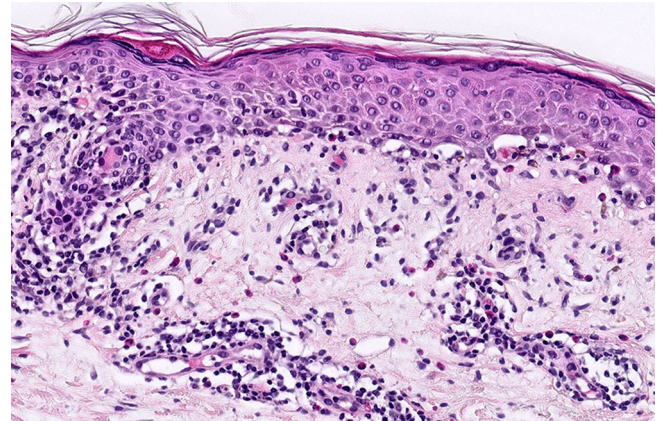
According to the pathogenesis of these cutaneous reactions, they can be classified into seven groups [4]: (I) immediate and (II) delayed hypersensitivity reactions; (III) type I and (IV) type IV hypersensitivity reactions; (V) autoimmune reactions; (VI) disorders with autoimmune mecha-

nisms; and (VII) an heterogeneous group of processes considered to be related to functional angiopathies. Nonetheless, since many individuals simultaneously experience multiple local and distant reaction types, the “American Academy of Dermatology/International League of Dermatological Societies registry on reaction location and COVID vaccine type” has coined the term “reactogenicity” for the ensemble of local and systemic reactions occurring shortly after vaccination [22].

In clinical practice, “COVID-arm” is one of the most common side effects of SARS-CoV-2 mRNA vaccination. The histological appearance of this hypersensitivity reaction is characterized by a CD4+ T-lymphocytic infiltrate with spongiosis and variable eosinophilia [23]. Other hypersensitivity reactions include morbilliform and erythema multiforme-like rashes and inflammatory reactions to dermal fillers and tattoos. The mimicry between viral proteins from viral vector-based vaccines and human components seems to be responsible for autoimmune-mediated side effects including leucocytoclastic vasculitis, collagen diseases ([24]; ■ Fig. 5), and the vaccine-induced prothrombotic immune thrombocytopenia that can be fatal in some cases [25]. Many individuals develop non-specific rashes with spongiosis, sometimes lichenoid changes, and a variable number of eosinophils. The term “vaccine-related eruption of papules and plaques” (V-REPP) has been proposed for this eruption ([26]; ■ Fig. 6).



**Fig. 5** ▲ Lichenoid changes and occlusive small and medium-sized vessel vasculopathy (arrow) are typical of the painful digital ulcerated papules of anti-MDA-5 dermatomyositis. This patient, with a family history of collagenopathies, developed the disease shortly after viral vector COVID-19 vaccination



**Fig. 6** ▲ Vaccine-related eruption of papules and plaques showing spongiosis, lichenoid changes, and eosinophilia

Less frequently, vaccination triggers the development of lesions clinically and histologically similar to well-known dermatoses, such as bullous pemphigoid-like lesions or lichen planus-like eruptions [26]. There is also description of a striking bullous drug eruption with massive apoptosis resembling Stevens–Johnson syndrome but with resolution within a week [27], and two patients with a facial pustular eruption that raised the differential diagnoses of rosacea fulminans, facial neutrophilic dermatosis, or infection, but which disappeared spontaneously in 7 to 10 days [28]. In addition, there are many reports of dermal hypersensitivity reactions, perniosis, and reactivation of viral diseases, especially herpes infections. Finally, after vaccination, some patients reproduce the same cutaneous reactions that they presented in the course of prior COVID-19 infection, probably due to activation of the same immunological pathways. Incidentally, cases of exacerbation or improvement of cutaneous lymphomas have also been reported [22, 26, 29, 30].

#### Practical conclusion

- Well-characterized skin manifestations of coronavirus disease 2019 (COVID-19) include chilblains, livedo necrotic lesions, vesicular eruptions, urticarial lesions, and maculopapular eruptions.
- COVID-associated chilblains tend to have marked basal and vascular damage.
- Livedo necrotic lesions show small vessel thrombosis with minimal inflammation.

- Vesicular eruptions include cases of Grover disease, pustulous eruptions, and varicella-like rashes with ballooning and dyskeratosis.
- Urticarial and maculopapular eruptions tend to present a combination of patterns with eosinophils.
- Hypersensitivity reactions are common after SARS-CoV-2 mRNA vaccination. “COVID-arm” shows CD4+ T-lymphocytic infiltrate, spongiosis, and variable eosinophilia. Non-specific eruptions or inflammation of foreign materials such as dermal fillers or tattoos can also occur.
- Vaccine reactions may also mimic other dermatosis such as bullous pemphigoid or lichen planus, stimulate herpes reactivation, or trigger the development of autoimmune diseases.

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#### Declarations

**Conflict of interest.** M.-T. Fernández-Figueras declares that she has no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

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## Dermatopathologie der COVID-19-Infektion und -Impfung

**Hintergrund:** Viele eigenartige Hautveränderungen wurden sowohl im Zusammenhang mit einer COVID-19-Infektion („coronavirus disease 2019“) als auch mit einer Impfung beschrieben.

**Ziel der Arbeit:** In der vorliegenden Arbeit wird ein Überblick über diese dermatologischen Manifestationen gegeben, der Fokus liegt dabei auf den dermatopathologischen Erscheinungen.

**Ergebnisse:** Die meisten COVID-19-Patienten entwickeln vielfältige makulopapulöse Eruptionen mit einer Kombination histologischer Muster, die üblicherweise Keratinozytenapoptose und Eosinophilie umfassen. Urtikariaähnliche Läsionen zeigen oft eine Kombination aus spongiosen und lichenoiden Mustern und treten häufiger bei Personen mit schwerer Erkrankung auf. Vesikuläre Läsionen können verbreitet sein; in manchen Fällen werden sie pustulös, und in anderen zeigen sie Dyskeratose und eine eigentümliche Form von Ballonbildung. Einige Patienten entwickeln eine vesikuläre Grover-Krankheit am Stamm. Junge Patienten mit einer starken immunologischen Reaktion können das Virus zwar leicht eliminieren, aber als Folge der starken Interferonreaktion Frostbeulen entwickeln. Umgekehrt können ältere Personen mit Immunseneszenz und Tendenz zur Hyperkoagulabilität livide und ischämische Bereiche aufweisen. Bei der COVID-19-Impfung sind die häufigsten Reaktionen Überempfindlichkeitsreaktionen, einschließlich des „COVID-Arms“. Dennoch wird häufig eine Kombination aus lokalen und systemischen kutanen Manifestationen (Reaktogenität) beobachtet. Histopathologisch sind lichenoid und spongiosische Veränderungen und eine variable Anzahl von Eosinophilen typisch für Hautausschläge, die durch Papeln und Plaques gekennzeichnet sind. Andere dermatologische Nebenwirkungen der COVID-19-Impfung umfassen Läsionen, die gut definierte Dermatosen wie Lichen planus oder bullöses Pemphigoid imitieren, und das Auslösen von Kollagenerkrankungen.

**Schlussfolgerung:** Zu den gut charakterisierten Hautmanifestationen bei einer COVID-19-Infektion gehören Frostbeulen, Livedo bzw. nekrotische Läsionen, vesikuläre Eruptionen, urtikarielle Läsionen und makulopapulöse Eruptionen. Überempfindlichkeitsreaktionen treten häufig nach Impfung mit einem SARS-CoV-2-mRNA-Impfstoff auf. Impfreaktionen können auch andere Dermatosen wie z. B. bullöses Pemphigoid oder Lichen planus imitieren, eine Herpesreaktivierung induzieren oder die Entstehung von Autoimmunerkrankungen triggern.

### Schlüsselwörter

Haut · SARS-CoV-2 · Impfstoff · Histopathologie · Hauptmanifestationen

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