

# Cutaneous manifestations of COVID-19 and vaccines for its prevention: a review of the existing literature

## *Manifestações cutâneas da doença COVID-19 e vacinas para a sua prevenção: uma revisão da literatura*

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### Abstract

The coronavirus SARS-CoV-2 first appeared in December 2019 in Wuhan, China, spreading rapidly as a novel pathogen primarily affecting the respiratory system. It soon evolved into a global pandemic that challenged healthcare systems worldwide. Intense research interest emerged early, revealing numerous cutaneous manifestations associated with both the virus itself – through its tropism for the angiotensin-converting enzyme 2 receptor – and the systemic complications it induced, such as cytokine storm and severe inflammatory reactions. Cutaneous findings were attributed to multiple mechanisms, including direct viral effects, immune dysregulation, drug reactions from early therapeutic regimens, and reactivation of autoimmune processes. Moreover, the vaccines developed to curb viral transmission and morbidity also presented certain dermatologic adverse effects, some resembling infection-induced manifestations, while others were linked to vaccine components and immune responses. This review summarizes the wide spectrum of skin manifestations associated with COVID-19 infection, vaccination, and the use of personal protective equipment, as well as the exacerbation of pre-existing dermatoses during the pandemic. Psychological stress and social isolation are also discussed as contributing factors to dermatologic morbidity. By synthesizing present scientific literature, this study provides a concise yet comprehensive overview of COVID-19- and vaccine-related skin manifestations, highlighting their clinical relevance and the need for further research on underlying mechanisms and management strategies.

**Keywords:** COVID-19. Skin. Vaccination. Adverse events.

### Resumo

O coronavírus SARS-CoV-2 surgiu pela primeira vez em dezembro de 2019 em Wuhan, na China, espalhando-se rapidamente como um novo agente patogênico que afeta principalmente o sistema respiratório. Logo evoluiu para uma pandemia global que desafiou os sistemas de saúde em todo o mundo. Um intenso interesse em pesquisa surgiu precocemente, revelando inúmeras manifestações cutâneas associadas tanto ao próprio vírus – através do seu tropismo pelo receptor da enzima conversora de angiotensina II (ACE2) – quanto às complicações sistêmicas que induziu, como a tempestade de citocinas e reações inflamatórias graves. Os achados cutâneos foram atribuídos a múltiplos mecanismos, incluindo efeitos virais diretos, desregulação imune, reações medicamentosas de regimes terapêuticos precoces e reativação de processos autoimunes.

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Além disso, as vacinas desenvolvidas para conter a transmissão viral e a morbidade também apresentaram certos efeitos adversos dermatológicos, alguns semelhantes às manifestações induzidas pela infecção, enquanto outros foram associados a componentes da vacina e respostas imunes. Esta revisão resume o amplo espectro de manifestações cutâneas associadas à infecção por COVID-19, à vacinação e ao uso de equipamentos de proteção individual, bem como à exacerbação de dermatoses pré-existentes durante a pandemia. O stress psicológico e o isolamento social também são discutidos como fatores contribuintes para a morbidade dermatológica. Ao sintetizar a literatura científica atual, este estudo fornece uma visão geral concisa, mas abrangente, das manifestações cutâneas relacionadas à COVID-19 e às vacinas, destacando sua relevância clínica e a necessidade de mais pesquisas sobre os mecanismos subjacentes e as estratégias de gestão.

**Palavras-chave:** COVID-19 e a pele. Vacinação contra a COVID-19. Manifestações cutâneas da COVID-19.

## Introduction

In December 2019, a new pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began to spread, causing acute respiratory distress syndrome, initially in the Wuhan region of China. The coronavirus has had a significant impact on global health, with over 700 million cases worldwide according to the World Health Organization study. It is thought to originate from bats and is transmitted by droplets. Once the virus enters the body, its envelope protein S binds to the angiotensin 2 receptor on host cells and enters the cell by endocytosis. After entering the body, the virus multiplies, resulting in the secretion of cytokines, such as interleukin (IL)-8, IL-10, IL-12, tumor necrosis factor- $\alpha$ , Interferon- $\beta$ , leading to a pro inflammatory state.<sup>1</sup>

The angiotensin-converting enzyme 2 (ACE2) receptor is found in many cells in the human body, mainly in alveolar cells in the lungs, in the myocardium, in esophageal epithelial cells, in neurons, but also in the oral cavity, including epidermal cells and adnexal keratinocytes, and in vascular epithelial cells. This can explain the great variety and number of skin manifestations associated with coronavirus.<sup>2</sup> Another possible mechanism for the occurrence of skin manifestations is the hypersensitivity of the immune system induced by the coronavirus, which leads to the so-called cytokine storm, but also to the fact that the coronavirus creates a prothrombotic state in the body, which results in the formation of microthrombi and, by extension, the appearance of vasculitis.<sup>3</sup>

The frequency of these manifestations was different in various populations worldwide, with a smaller number of skin manifestations observed in Asia and Japan compared to Europe. Skin manifestations, initially described in Italy,<sup>4</sup> appeared in individuals of all ages and genders, with a slight predominance in women. Furthermore, some of them were associated with disease severity. However, it has been reported that skin manifestations may precede the onset of coronavirus

symptoms and be the first indication for the clinician or dermatologist that the patient has been infected with coronavirus. Accordingly, they may appear during the course of the disease or even after the symptoms have subsided, most commonly within a month of infection, and in some cases, cutaneous manifestations may be the only manifestation.<sup>5</sup>

To prevent further transmission of the coronavirus and stop the epidemic, RNA vaccines have been used. These vaccines have proven effective in limiting the epidemic and reducing hospitalizations, but they also have some dermatological adverse effects.<sup>6</sup> At the same time, the use of such extensive and skin-unfriendly protective equipment, as well as the reactivation of skin diseases that were reawakened by the immune response caused by the coronavirus, were issues that were unprecedented for the global community. Consequently, extensive interest was developed by researchers, as well as clinicians involved in the diagnosis and treatment of the coronavirus and its skin manifestations.<sup>7</sup> The methodology chosen in this paper is presented below.

## Methodology

For this study, a search of the relevant literature was conducted in PubMed/Medline and the search terms used were, "COVID-19 and the skin, dermatological manifestations of SARS-COVID, rashes and COVID-19 severity, influence of covid infection to the skin, COVID-19 and the nails and hair, skin diseases related with covid." At the same time, terms, such as skin complications of covid vaccines, adverse effects of the medicines for covid to the skin, skin disease related to covid protection in health workers and case reports, vasculitis and covid, erythema multiforme and covid, bullous diseases and covid and alopecia associated with coronavirus infection, as well as adverse effects of coronavirus vaccines were used without emphasizing any specific vaccine but an examination of all side effects was made.

During the literature search, a wide range of recent articles from 2021 onward that dealt with the topics under consideration emerged, and 91 of them were ultimately selected. The selection criterion was the completeness with which they addressed the topics under discussion, to facilitate the purpose of this work. In particular, the aim is to provide a concise but thorough presentation of the skin manifestations of coronavirus as a disease in itself, but also as an infection that can cause dermatological diseases even indirectly. Dermatological diseases may arise due to the use of the drugs that were and are used in the initial treatment of coronavirus, but also through immunological mechanisms and the action of cytokines observed in coronavirus, which can trigger autoimmunity and lead to an exacerbation of autoimmune skin diseases. According to the literature, such diseases include psoriasis and alopecia or bullous pemphigoid.<sup>8</sup>

In addition, healthcare professionals were involved in the chain of skin manifestations, as they used protective equipment to a large extent, the use of which was unprecedented for some countries that had not previously faced large epidemic waves. Finally, coronavirus vaccines were studied in terms of skin complications because they caused some complications that were particular and simulated the manifestations of the original disease, but in a smaller scope and severity. A total of 63 articles were thoroughly examined, which dealt with the issue of skin manifestations of coronavirus, even in various age groups, such as children and the elderly, who were more susceptible to skin manifestations. At the same time, reductions were made to the rest of the population, and various manifestations and mechanisms of these manifestations were analyzed to the extent that they have been understood to date by researchers. At the same time, 28 articles were examined that discussed the skin manifestations of coronavirus vaccines and how to deal with them. It is characteristic that during the study of the bibliography, the universality of the coronavirus phenomenon is extracted, giving impetus to researchers from all over the world to publish studies on the dermatological manifestations they observed in their clinics. Accordingly, at the national level, each country engaged in an effort to detect and track this pandemic, which was now an issue that concerned doctors of all specialties, including dermatologists.

## Discussion

Since the emergence of COVID-19 in late 2019, the infection has been associated with a broad range of cutaneous manifestations involving diverse morphological patterns and pathogenetic mechanisms. The dermatologic spectrum linked to SARS-CoV-2 encompasses rashes commonly seen in viral infections, immune-mediated conditions, vascular phenomena, and adverse effects arising from medications, vaccines, and pandemic-related interventions, such as personal protective equipment (PPE).<sup>1,9</sup>

A fundamental aspect of COVID-19 skin involvement relates to the viral tropism for ACE2 receptors, widely expressed in endothelial cells and keratinocytes. Viral entry and replication, coupled with dysregulated immune responses, including cytokine storm, microvascular injury, and complement activation, contribute to the cutaneous phenotypes observed during and after infection.<sup>10,11</sup> Furthermore, psychosocial stress, pharmacologic interventions, and widespread use of PPE during the pandemic have exacerbated pre-existing dermatoses and triggered new-onset conditions, highlighting the multifactorial nature of dermatologic sequelae.<sup>2</sup>

Among the earliest and most frequently reported skin manifestations is the morbilliform maculopapular rash, characterized by widespread erythematous macules and papules predominantly affecting the trunk and extremities, typically emerging within 2 weeks of symptom onset.<sup>1,9</sup> Although initially attributed to drug hypersensitivity from therapeutic agents, such as hydroxychloroquine or antivirals, subsequent observations in untreated patients confirmed a direct association with COVID-19 infection itself.<sup>6</sup> Histopathologic findings commonly reveal perivascular lymphocytic infiltrates and occasional microthrombi, supporting an immune-mediated rather than a purely cytopathic mechanism.<sup>12</sup>

Similarly, urticaria and, less frequently, angioedema constitute notable cutaneous reactions, often coinciding with systemic symptoms, such as fever or respiratory distress.<sup>13</sup> These lesions reflect mast cell activation and histamine release driven by immune dysregulation, cytokine release, or drug exposure.<sup>14</sup> Urticarial vasculitis, though rare, has also been documented, presenting with persistent wheals and histologic evidence of deposition of an immune complex, often containing viral particles and small-vessel inflammation.<sup>15</sup>

Pseudovaricella eruptions manifesting as monomorphic or diffuse vesicles have been described

predominantly in middle-aged adults with mild to moderate disease severity.<sup>1</sup> These lesions, frequently pruritic or hemorrhagic, appear either before or after respiratory symptoms and resolve spontaneously without scarring.<sup>9</sup> Histologic examination typically reveals keratinocyte necrosis, ballooning degeneration, and superficial perivascular infiltrates.<sup>16</sup>

Perhaps the most distinctive dermatologic signature of COVID-19 lies in its vascular manifestations, ranging from benign chilblain-like lesions (“COVID toes”) to severe ischemic complications.<sup>17</sup> Chilblain-like acral lesions, frequently affecting children and young adults with mild or asymptomatic disease, present as erythematous or violaceous plaques on the toes and fingers, occasionally accompanied by pain or pruritus.<sup>9</sup> While histologically indistinguishable from idiopathic pernio, their occurrence in warm climates and absence of cold exposure implicate interferon-mediated endothelial injury and microangiopathy.<sup>18</sup>

Conversely, acro-ischemia, livedo reticularis, retiform purpura, and even gangrene signify severe systemic involvement, correlating with coagulopathy, endothelial dysfunction, and complement activation seen in critical COVID-19 illness.<sup>19,20</sup> These lesions often portend a poor prognosis, especially in elderly patients with multisystem disease.<sup>1</sup>

Beyond exanthematous and vascular lesions, COVID-19 has triggered or exacerbated several immune-mediated dermatoses. Erythema multiforme, leukocytoclastic vasculitis, and pityriasis rosea-like eruptions have been repeatedly documented, reflecting post-viral immune dysregulation and molecular mimicry phenomena.<sup>12,21,22</sup> The reactivation of latent herpesviruses, particularly human herpesviruses-6/7 and varicella-zoster virus, further complicates the dermatologic landscape, resulting in increased incidence of herpes zoster and pityriasis rosea during the pandemic period.<sup>23</sup>

Similarly, multisystem inflammatory syndrome in children (MIS-C), a hyperinflammatory condition temporally associated with SARS-CoV-2 infection, frequently presents with mucocutaneous involvement, including polymorphous rashes, conjunctivitis, and periorbital edema.<sup>24</sup> Dermatologic signs in MIS-C not only aid early recognition but also parallel systemic hypercytokinemia, coronary vasculitis, and gastrointestinal inflammation.<sup>25</sup>

COVID-19 has also affected skin appendages, with telogen effluvium emerging as a common sequela several weeks after the acute infection.<sup>7</sup> Proposed mechanisms include cytokine-driven apoptosis of hair matrix

keratinocytes, microthrombotic injury to follicular vasculature, and systemic stress responses.<sup>26</sup> More acute anagen effluvium and alopecia areata flares have similarly been attributed to immune dysregulation and psychological stressors imposed by the pandemic.<sup>27</sup> Trichodynia, characterized by scalp dysesthesia with pain, pruritus, or burning sensation, frequently accompanies post-COVID-19 hair loss.<sup>9</sup>

Nail changes, such as Beau’s lines, transverse leukonychia, the “red half-moon” nail sign, and longitudinal melanonychia, have been increasingly recognized post-infection.<sup>28</sup> These findings, although non-specific, reflect transient growth arrest, vascular compromise, or drug exposure during illness.<sup>29</sup>

Mass vaccination campaigns worldwide have revealed diverse cutaneous reactions ranging from mild local responses to rare immune-mediated phenomena.<sup>3</sup> Immediate injection-site reactions, including erythema, swelling, and pain, represent the majority of events, typically resolving within days without sequelae.<sup>30</sup> Delayed large local reactions, colloquially termed “COVID arm,” present as pruritic erythematous plaques appearing a week post-vaccination, particularly with mRNA types.<sup>31</sup>

Urticaria, angioedema, and morbilliform eruptions have also been observed after both mRNA and viral vector vaccines, generally within days of administration.<sup>5</sup> Although most cases remain self-limited, rare instances of anaphylaxis needed vigilance, especially in individuals with prior allergy histories.<sup>3</sup> Reactivation of herpes zoster following vaccination, reported predominantly in elderly or immunocompromised recipients, is hypothesized to result from transient immune perturbations rather than direct viral effects.<sup>32</sup>

Autoimmune blistering diseases, including bullous pemphigoid and pemphigus vulgaris, have been described post-vaccination, primarily in older adults after mRNA vaccines.<sup>33</sup> Similarly, new-onset or flares of psoriasis, lupus erythematosus, and lichen planus underscore the capacity of vaccine-induced immune stimulation to unmask or exacerbate latent autoimmunity.<sup>34</sup> Nonetheless, the overwhelming consensus affirms that cutaneous adverse events remain infrequent, predominantly mild, and vastly outweighed by the benefits of vaccination in preventing severe COVID-19 outcomes.<sup>12</sup>

The prolonged use of PPE among healthcare workers and the general population has precipitated a surge in irritant and allergic contact dermatitis, acne mechanica (“maskne”), rosacea flares, and occupational hand eczema.<sup>2</sup> Occlusion, friction, sweating, and exposure

to disinfectants collectively disrupt the epidermal barrier, alter skin microbiota, and induce inflammatory dermatoses, emphasizing the occupational dermatology dimension of pandemic response.<sup>35</sup>

The cutaneous manifestations of COVID-19 and its vaccines reflect complex interactions between direct viral cytopathologic effect, immune dysregulation, vascular injury, pharmacologic triggers, and environmental factors. While most lesions remain self-limited with a favorable prognosis, certain phenotypes – including retiform purpura, acral ischemia, and multi-system inflammatory presentations – carry diagnostic and prognostic significance, warranting prompt recognition.<sup>1</sup>

For dermatologists, familiarity with this evolving spectrum aids differential diagnosis, guides biopsy and laboratory evaluation when indicated, and informs patient counseling regarding vaccine safety and expected reactions.<sup>9</sup> Moreover, understanding the temporal patterns, morphologic variants, and systemic associations of COVID-19-related skin findings enrich interdisciplinary collaboration across infectious disease, dermatology, pneumonology, rheumatology, pediatrics, and critical care settings.<sup>17</sup>

Finally, ongoing research into pathogenetic mechanisms underlying these manifestations promises to elucidate links between viral infections, immune activation, autoimmunity, and skin biology, offering broader insights into dermatologic science beyond the present pandemic context.<sup>12</sup>

## Conclusion

The COVID-19 pandemic has been one of the greatest challenges for healthcare systems worldwide, with the interest of the scientific community extending beyond the respiratory system to the dermatological findings of the disease.

As knowledge about the dermatological manifestations of COVID-19 is constantly enriched, it is becoming apparent that they may also function as diagnostic indicators, warning of the severity of the disease or even preceding respiratory symptomatology.

COVID-19 vaccines, although effective, are not without dermatological side effects. Particular attention is required in patients with pre-existing skin or autoimmune diseases.

The need for further research is obvious and multifaceted. Initially, it is necessary to establish national and international registries to classify and document skin manifestations associated with COVID-19 and

vaccines. Across the collection of big data, a clearer epidemiological profile can be formed, which will help both in prevention and treatment.

In addition, long-term patient follow-up studies are needed to determine whether certain skin diseases develop into a chronic form or reappear after new exposure to the virus or booster vaccinations. The association of the cutaneous immune response with the type of vaccine (mRNA, vector-based, etc.) is also an area of significant research interest.

Particular emphasis should be placed on the education of health professionals – and especially general practitioners and dermatologists – for the early recognition of cutaneous signs, which often precede the full manifestation of the infection or are the only manifestations in asymptomatic patients.

Furthermore, the development of new, more targeted and safer vaccines with minimal dermatological impact, as well as the investigation of prophylactic and therapeutic dermatological interventions to address complications, should be priorities for the coming period.

Finally, strengthening interdisciplinary collaboration between dermatologists, infectious disease specialists, immunologists, and epidemiologists can offer substantial solutions and strengthen the comprehensive approach to addressing COVID-19 and its multifaceted impacts.

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## Conflicts of interest

None.

## Ethical considerations

**Protection of human subjects and animals.** The authors declare that no experiments on humans or animals were performed for this research.

**Confidentiality, informed consent, and ethical approval.** The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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