



WORLD JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

www.wjcmpr.com

ISSN: 2582-0222

The cutaneous manifestations of COVID-19, personal protective equipment and treatment.

Afaf Haddad^{*12}, Isabelle Haddad³

¹ Associate Professor, School of Medicine, University of Notre Dame, Sydney, Australia

² Surgical Pathologist, Anapath Services, Melbourne, Australia

³ School of Pharmacy, Monash University Parkville, Australia

Abstract

Since the beginning of COVID-19 pandemic in late 2019, the symptoms and signs detailed in the medical literature and the media concentrated on the effect of causative virus SARS-COV-2 on the respiratory tract, the coagulopathy associated with severe forms of the disease and the febrile flu like illness in the mild cases. The widespread publicising of the symptoms has been one of the important public health measures in combatting the rapid spread of COVID-19. Less known is the direct or indirect effect of COVID-19 on the skin and underlying soft tissue. Recognising the various cutaneous manifestations may prove a useful tool in early detection and management of COVID-19.

Article History:



Received: 19.08.2022

Revised: 09.09.2022

Accepted: 06.10.2022

Keywords:

COVID-19, vaccine, rash, inflammation, vasculitis, pernio.

*Corresponding Author

A/Professor Afaf Haddad

DOI: <https://doi.org/10.37022/wjcmpr.v4i5.229>

This article is licensed under a Creative Commons Attribution-Non-commercial 4.0 International License.

Copyright © 2022 Author(s) retain the copyright of this article.



Introduction

COVID-19 may affect the skin at various stages of the disease and although in few cases the rash preceded the fever and respiratory symptoms [1, 2], the more common scenario is an eruption that followed the flu like illness. Distinction between a rash attributed to COVID-19 alone or complicated by therapy may be difficult and specific histological findings have not been found.

The pathophysiology of skin involvement is thought to mirror other organs involvement via direct injury of the cells through immune response to viral nucleotides or vessels damage leading to vasculitic injury and thrombotic vasculopathy with a key role of angiotensin converting enzyme 2 (ACE2) [1-3].

A large number of cases detailing skin involvement in COVID19 patients has been reported since the start of the pandemic. One of the largest case series published to date was by Freeman et al. from the record of the international registry established by the American Academy of Dermatology and International League of Dermatological Societies that incorporated 716 cases of confirmed or suspected COVID-19 (4). Upon review of the literature, the heterogeneity of the cutaneous manifestations of COVID-19 was evident and various clinical and pathological classifications have been suggested or used by different groups [1, 4-12]. All ages were affected with females and males equally represented in most series [7]. In addition to the rash, symptoms included pruritus in a large proportion of cases followed by burning sensation and pain whilst some patients were asymptomatic [6, 7]. As the virus may affect the epithelial cells and vessels, the cutaneous manifestations mirrored the cellular involvement and may be classified into two broad categories of inflammatory and vasculitic patterns [10]. A more detailed classification used the different clinical manifestations

and included urticaria, erythematous/maculopapular/morbilliform forms, papulovesicular rash, acral chilblain like, livedo reticularis-livedo racemosa like and pruritic/vasculitic pattern [1, 4-12] with the first three subtypes representing the inflammatory category and the last three the vasculitic category. Selective distribution of the different types of lesions has been reported and to some extent reflected the skin manifestations associated with the various inflammatory and vasculitic rashes seen with viral and non-viral infections, systemic autoimmune diseases, vasculitides and drug attributed rashes. Whilst the inflammatory maculopapular/morbilliform and papulovesicular rashes affected predominantly but not exclusively the trunk, it was evident that the vasculitic pattern of chilblain like, livedo and pruritis were more often limited to the lower limbs with chilblain like lesions exclusively affecting the feet. Urticarial rash had a more heterogenous and widespread distribution with involvement of trunk and limbs [11]. As the different terminology used to describe the rashes is self-explanatory, it is useful to mention that the skin lesions vary from hives to macules/papules, red papules/vesicles in the three inflammatory patterns to reddish purple macules, papules, ill-defined patches and ulcers in the vasculitic patterns [11]. Although these manifestations may be seen at all ages, there has been cases of multisystem inflammatory syndrome and erythema multiforme like eruptions almost exclusively seen in children [12].



Figure 1: Diffuse maculopapular rash.



Figure 2: Chilblain like lesions.

A study of PCR confirmed 144 hospitalised COVID-19 patients in the second wave reported a much lower incidence (3.5%) of livedoid lesions and less common maculopapular rash. This variation has been attributed to different antigenicity of the virus and different treatment regimens limited to remdesivir, tocilizumab and dexamethasone [13].

At the cellular level, the changes seen in the cases which underwent skin biopsy showed equivalent findings to similar rash caused by various aetiologies or alternatively non-specific inflammation. In the inflammatory category, the urticarial rash displayed perivascular lymphocytic or eosinophilic infiltrate and papillary oedema. Both erythematous and maculopapular lesions featured spongiosis, intraepidermal/subcorneal pustules, dermal oedema, variable numbers of dermal neutrophils and or eosinophils and fibrin thrombi, necrotic keratinocytes were observed in the maculopapular lesions and basal vacuolar degeneration was limited to the erythematous rash. The vasculitic patterns were characterised by a superficial and deep lymphocytic infiltrate with perivascular or periadnexal accentuation in livedo and chilblain like lesions. Lichenoid vacuolar basal layer changes, purpura with or without vascular complement deposition and with no vasculitis were seen in livedo racemosa whilst endothelial activation, red blood cells extravasation with or without vasculitis, partial epidermal necrosis, microthrombi and vascular complement have been reported in acral lesions. Lichenoid changes were limited to chilblain like acral pattern. Pruritic vasculitis manifested with leukocytoclastic vasculitis, epidermal and adnexal necrosis and thrombogenic vasculopathy [14-17]. Rare cases of erythema multiforme like eruption showed mild spongiosis, perivascular and interstitial lymphocytic infiltrate, dilated vessels filled with neutrophils and extravasated red

blood cells with or without vacuolar changes of basal layer [18].

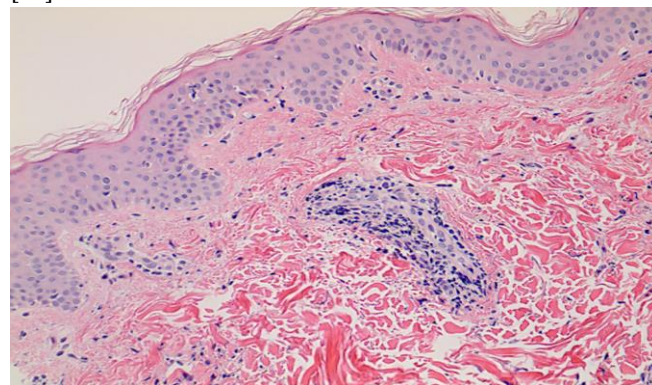


Figure 3: Photomicrograph of maculopapular rash with superficial perivascular lymphocytic infiltrate and mild lymphocyte exocytosis (H&E, 100x)

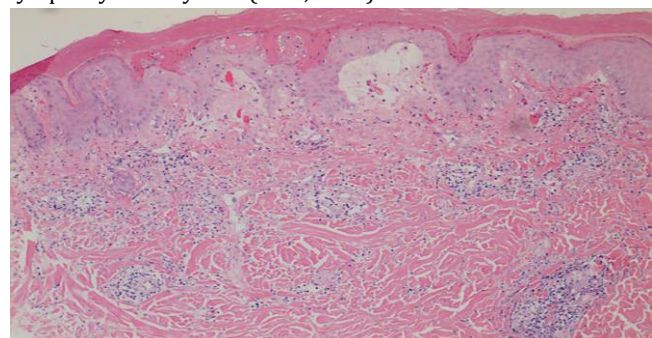


Figure 2: Photomicrograph of chilblain like lesion with marked papillary oedema, superficial and deep perivascular lymphocytic infiltrate (H&E, 40x)

Nails may also be affected and the so called "Covid nails" were usually seen following the generalised symptoms and range from the red "half-moon nail sign" regarded by some as a reliable sign of COVID-19 infection and featuring a red crescent immediately above the lunula to the less specific white horizontal Mee's lines or Beau's lines which are in fact horizontal dents or ridges. Nail changes were temporary and disappeared within months of the infection.

In the fight against Covid-19, using personal protective equipment (PPE) including face masks, goggles, face shields, gloves and gowns and the constant use of hand hygiene solutions and gels led to cutaneous side effects amongst health care workers and the general population alike. Various surveys of healthcare workers showed prevalence ranging from 58.5% to 74.5% [19-22], with most reporting dermatoses of the face commonly at the pressure sites of fitted masks or shields on the nose, cheeks, forehead and above or behind the ears. The most prevalent symptoms were redness, itching and dryness and the commonest manifestations were eczema, acne and exacerbations of seborrheic dermatitis with fewer cases reporting erosion/ulcer, scale crust formation, desquamation, itchy papules, vesicles and even pustules. Exacerbation of pre-existing dermatoses such as atopic or seborrheic dermatitis, urticaria and acne have also been reported [23]. A direct relationship has been established with the duration of PPE usage and in some settings a higher prevalence was observed amongst healthcare workers in hospitals with larger numbers of Covid patients in more severe epidemic settings [19].

Dermatoses of the hands were also quite common more so with excessive hand hygiene exceeding ten times daily (21) with rare adverse reactions attributed to gowns. Only a small percentage of affected workers (5%) sought medical attention and treatment.

Covid treatment may adversely affect the skin but fortunately can be easily managed with topical corticosteroids and occasionally with oral antihistamines and oral corticosteroids. From the controversially used hydroxychloroquine to antibiotics such as Azithromycin to broad spectrum antivirals such as Remdesivir, Oseltamivir & interferons or HIV antivirals such as Lopinavir, various dermatologic reaction or rashes have been reported from urticaria, maculopapular and eczematous lesions, photosensitivity and hyperpigmentation in the mild forms to blistering or pustular rashes, leukocytoclastic vasculitis and toxic epidermal necrolysis in the severe forms. 2% of patients with mild to moderate risk of progression to severe COVID-19 using Sotrovimab have reported a rash. Recently approved oral drugs such as Molnupiravir may lead to hives, itching and rash and the combination of Nirmatrelvir and Ritonavir may be associated with itching, rash, flushing, yellow discoloration or redness of skin [24]. Exacerbation of pre-existing skin conditions such as psoriasis, acne and herpes simplex and herpes zoster reactivation have been reported and both alopecia and hirsutism are known side effects. Corticosteroids and various immunomodulatory agents have also been used and may cause mild/transient rash or more severe cutaneous pustulosis, vasculitis and erythema multiforme like reaction. Local reaction at the injection site including pain, erythema, pruritis, swelling, induration and ulceration have been attributed to Remdesivir and Sotrovimab, interferon, Anakinra and Lopinavir [25-29]. Pre-exposure preventative drugs including Tixagevimab and Cilgavimab have been implicated in similar rash and injection site reaction [30, 31].

Lastly, the various COVID-19 vaccines have been linked to dermatological symptoms and signs mostly local reaction such as redness, swelling and pain at the injection site seen with all types of vaccines in both clinical trials and mass vaccination settings. Less prevalent are allergic dermatitis, eczema, injection site or papular urticaria and vesicular rash reported during clinical trials of Moderna vaccine and allergic dermatitis, eczema, petechial rash and alopecia reported with Sputnik V. In non-trial setting, morbilliform and maculopapular rashes, urticaria and pernio like lesions have been observed following Pfizer and Moderna vaccine [32]. Isolated cases of de novo or exacerbated lichen planus, erythema multiforme, pityriasis rosea, varicella zoster and herpes simplex reactivation, papulovesicular rash, petechial and purpuric rash have been attributed to mRNA vaccines which have also been implicated in a bizarre delayed inflammatory reaction to hyaluronic acid fillers [32-34].

We have reviewed the cutaneous inflammatory and vasculitic manifestations of Covid19 and the side effect of treatment, vaccines and PPE on the skin. We summarised the histological findings of the different types of rashes attributed to Covid 19. As the pandemic continues, it is essential to monitor the clinical signs of the disease, correlate the severity with involvement of specific organs and track the iatrogenic side effects secondary to treatment and preventative measures.

No conflict of interest exists.

References

1. Gottlieb M and Long B. Dermatologic manifestations and complications of COVID-19. *Am J Emerg Med* [Internet]. 2020 Sep; 38(9):1715-21. Available from: <https://pubmed.ncbi.nlm.nih.gov/32731141/>
2. Zara A, Fleming R, Lee K and Lynde C. The COVID-19 pandemic and its skin effects. *Can Fam Physician* [Internet]. 2021 Aug; 67(8):582-7. Available from: <https://pubmed.ncbi.nlm.nih.gov/34385203/#:~:text=Evidence%20ranged%20from%20levels%20.%2C%20and%20Kawasaki%2Dlike%20rashes.>
3. Suchonwanit P, Leerunyakul K, Kositkuljorn C. Cutaneous manifestations in COVID-19: Lessons learned from current evidence. *J Am Acad Dermatol* [Internet]. 2020 Jul; 83(1):e57-e60. Available from: <https://pubmed.ncbi.nlm.nih.gov/32339706/>
4. Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Kovarik C, Desai SR, Harp J, Takeshita J, French LE, Lim HW, Thiers BH, Hruza GJ, Fox LP. The spectrum of COVID-19 associated dermatologic manifestations: An international registry of 716 patients from 31 countries. *J Am Acad Dermatol* [Internet]. 2020 Oct; 83(4):1118-129. Available from: <https://pubmed.ncbi.nlm.nih.gov/32622888/>
5. Wollina U, Karadag AY, Rowland-Payne C, Chiriac A, Lotti T. Cutaneous signs in COVID-19 patients: A review. *Dermatol Ther* [Internet]. 2020 Sep; 33(5):e13549. Available from: <https://pubmed.ncbi.nlm.nih.gov/32390279/>
6. Gisondi P, Plasero S, Bordin C, Alaibac M, Girolomoni G and Naldi L. Cutaneous manifestations of SARS-CoV-2 infection: a clinical update. *J Eur Acad Dermatol Venereol* [Internet]. 2020 Nov; 34(11):2499-504. Available from: <https://pubmed.ncbi.nlm.nih.gov/32585074/#:~:text=The%20patterns%20of%20dermatological%20manifestations,urticarial%20and%20acro%2Dpapular%20eruption.>
7. Matar S, Oules B, Sohler P, Chosidow O, Beylot-Barry M, Dupin N and Aractingi S. Cutaneous Manifestations in SARS-CoV-2 infection (COVID-19): a French experience and systematic review of the literature. *J Eur Acad Dermatol Venereol* [Internet]. 2020 Jul; 34(11):e686-9. Available from: <https://pubmed.ncbi.nlm.nih.gov/32589293/>
8. Rahimi A and Tehranchinia Z. A comprehensive review of cutaneous manifestations associated with COVID-19. *BioMed Research International* [Internet]. 2020 July. Available from: <https://www.hindawi.com/journals/bmri/2020/1236520/>
9. Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Kovarik C, Takeshita J, French LE, Thiers BH, Hruza GJ, Fox LP. Pernio-like skin lesions associated with COVID-19: A case series of 318 patients from 8

10. countries. J Am Acad Dermatol [Internet]. 2020 Aug; 83(2):486-92. Available from: <https://pubmed.ncbi.nlm.nih.gov/32479979/#:~:text=Results%3A%20We%20documented%20505%20patients,with%20relatively%20mild%20COVID%2D19>.
11. Marzano AV, Cassano N, Genovese G, Moltrasio C and Vena GA. Cutaneous manifestations in patients with COVID-19 preliminary review of an emerging issues. Br J Dermatol [Internet]. 2020 Sep;183(3):431-42. Available from: <https://pubmed.ncbi.nlm.nih.gov/32479680/>
12. Genovese G, Moltrasio C, Berti E, Marzano AV. Skin Manifestations associated with COVID-19: Current knowledge and future perspectives. Dermatology [Internet]. 2021 Nov; 237(1):1-12. Available from: <https://pubmed.ncbi.nlm.nih.gov/33232965/>
13. Lavery MJ, Bouvier CA, Thompson B. Cutaneous manifestations of COVID-19 in children (and adults): A virus hat does not discriminate. Clin Dermatol [Internet]. 2021 Apr; 39(2):323-8. Available from: <https://pubmed.ncbi.nlm.nih.gov/34272030/>
14. Fernandez-Nieto D, Ortega-Quijano D, Suarez-Valle A, Jimenez-Cauhe J, Jaen-Olasolo P and Fernandez-Guarino M. Lack of skin manifestations in COVID-19 hospitalised patients during the second epidemic wave in Spain: a possible association with a novel SARS-CoV-2 variant – a cross-sectional study. J Eur Acad Dermatol Venereol [Internet]. 2021 Mar;35(3):e183-5. Available at: <https://pubmed.ncbi.nlm.nih.gov/33259091/>
15. Sohler P, Matar S, Meritet JF, Laurent-Roussel S. Histopathological features of Chillblain-like lesions developing in the setting of the COVID-19. Arch Pathol Lab Med [Internet]. 2021 Feb;145(2):137-44. Available from: <https://pubmed.ncbi.nlm.nih.gov/33501498/> pandemic.
16. Nobari NN, Seirafinapour F, Dodangeh M, Sadeghzadeh-Bazargan A, Behrangi E, Mozafarpour S. A systematic review of histopathologic survey on skin biopsies in patients with Corona Virus Disease 2019 (COVID-19) who developed virus or drug-related mucocutaneous manifestations. Exp Dermatol [Internet]. 2021 Sep;30(9):1233-53. Available from: <https://pubmed.ncbi.nlm.nih.gov/33977531/>
17. Gomez MC, Gonzalez-Cruz C, Ferrer B, Barbera MJ. Leucocytoclastic vasculitis in a patient with COVID-19 with positive SARS-CoV-2 PCR in skin biopsy. BMJ Case Rep [Internet]. 2020 Oct. 13(10):e238039. Available from: <https://pubmed.ncbi.nlm.nih.gov/33122236/>
18. Shehi E, Chilimuri S, Shin D, Patel M, Ali N and Niazi M. Microthrombi in skin biopsy of a patient with COVID-19. JAAD Case Rep [Internet]. 2020 Dec; 6(12):1327-9. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7550272/>
19. Jimenez-Cauhe J, Ortega-Quijano D, Carretero-Barrio I, Suarez-Valle A, Saceda-Corralo D, Moreno-Garcia Del
20. Real C et al. Erythema multiforme-like eruption in patients with COVID-19 infection: clinical and histological findings. Clin Exp Dermatol [Internet]. 2020 Oct; 45(7):892-5. Available from: <https://pubmed.ncbi.nlm.nih.gov/32385858/>
21. Lin P, Zhu S, Huang Y, Li L, Tao J, Lei T et al. Adverse skin reactions amongst healthcare workers during the coronavirus disease 2019 outbreak: a survey in Wuhan and its surrounding regions. Br J Dermatol [Internet]. 2020 May; 183(1):190-2. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7262186/#:~:text=Adverse%20skin%20reactions%20were%20reported.%25%20during%20the%20SARS%20outbreak>
22. Deoghare S, Pol D, Kothari R, Kumar A, Deora MS. Dermatological manifestations among doctors using personal protective equipment in coronavirus disease 19 pandemic: a study based on self-reported questionnaire and telephonic consultations. Indian J Dermatol Venereol Leprol [Internet]. 2022 Feb; 6(1):42-6. Available at: <https://cdriadvlkn.org/article.asp?issn=2542-551X;year=2022;volume=6;issue=1;page=42;epage=46;aulast=Deoghare;type=3>
23. Lan J, Song Z, Miao X, Li H, Li Y, Dong L et al. Skin damage among healthcare workers managing coronavirus disease-2019. J Am Acad Dermatol [Internet]. 2020 May; 82(5):1215-6. Available at: <https://pubmed.ncbi.nlm.nih.gov/32171808/>
24. Zuo Y, Hua W, Luo Y and Li L. Skin reactions of N95 masks and medial masks among health-care personnel: A self-report questionnaire survey in China. Contact Dermatitis [Internet]. 2020 Aug; 83(2): 145-7. Available at: <https://pubmed.ncbi.nlm.nih.gov/32297349/>
25. Sushma, I, Simon N, Pravin AJS, Padmaprasad MK, Vijayabharathi M, Varghese MG. Clinical evaluation of mark induced dermatitis on healthcare workers during COVID-19 pandemic: a cross sectional study. Int J Res Dermatol [Internet]. 2021 May; 7(3):413-7. Available at: <https://www.ijord.com/index.php/ijord/article/view/1306>
26. Painter WE, Holman W, Bush JA, Almazedi F, Malik H, Eraut N et al. Human Safety, tolerability and pharmacokinetics of Molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. Antimicrob Agents Chemother [Internet] 2021 Mar;65(5):e02428-20. Available at: <https://pubmed.ncbi.nlm.nih.gov/33649113/>
27. Tursen U, Tursen B, Lotti T. Cutaneous side-effects of the potential COVID-19 drugs. Dermatol Ther [Internet]. 2020 Jul; 33(4):e13476. Available at: <https://pubmed.ncbi.nlm.nih.gov/32358890/>
28. MIMS online. Remdesivir. (2022). Cited 2022 June 20. Available from <https://www.mimsonline.com.au>
29. MIMS online. Sotrovimab. (2022). Cited 2022 June 20. Available from <https://www.mimsonline.com.au>

30. MIMS online. Anakinra. (2022). Cited 2022 June 20.
Available from <https://www.mimsonline.com.au>
31. MIMS online. Lopinavir. (2022). Cited 2022 June 20.
Available from <https://www.mimsonline.com.au>
32. MIMS online. Tixagevimab. (2022). Cited 2022 June 20. Available from <https://www.mimsonline.com.au>
33. MIMS online. Cilgavimab. (2022). Cited 2022 June 20. Available from <https://www.mimsonline.com.au>
34. Sun Q, Fathy R, McMahon DE, Freeman E. COVID-19 Vaccines and the Skin. *Dermatol Clin* [Internet]. 2021 Oct;39(4):653-73. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8165093/>
35. Burlando M, Russo R, Cozzani E, Parodi A. COVID-19 “second wave” and vaccines: the dermatologists’ perspective. *Int J Dermatol* [Internet]. 2021 Jul; 60(7):889-90. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8251220/>
36. Freeman EE, Sun Q, McMahon DE, Singh R, Fathy R, Tyagi A *et al*. Skin reactions to COVID-19 vaccines: An American Academy of Dermatology/International League of Dermatological Societies registry update on reaction location and COVID vaccine type. *J Am Acad Dermatol* [Internet]. 2022 Apr; 86(4):e165-7. Available at: <https://pubmed.ncbi.nlm.nih.gov/34800601/>