

Mucocutaneous manifestations of COVID-19: a prospective study of 100 patients in Iran

Fahimeh Abdollahimajd, MD ^{1,2,3*}
Reem Diab, MD ¹
Hamideh Moravvej, MD ⁴
Ayda Bahmanjahromi, MD ^{4*}
Sahar Dadkhahfar, MD ^{2, 4}
Azadeh Goodarzi, MD ⁵
Afsaneh Sadeghzadeh Bazargan, MD ⁵
Sayyed Mojtaba Nekooghadam, MD ⁶
Mohammad Nikvar, MD ⁷
Mohammad Shahidi Dadras, MD ⁴

1. Department of Dermatology, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. USERN Office, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Clinical Research Development Unit, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5. Department of Dermatology, Rasool Akram Medical Complex Clinical Research Development Center (RCRDC), School of Medicine, Iran University of Medical Sciences, Tehran, Iran
6. Department of Internal Medicine, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
7. Pharmacology Department, Islamic Azad University Science and Research Branch, Tehran, Iran

*Corresponding authors:

Fahimeh Abdollahimajd, MD
Department of Dermatology, Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email: fabdollahimajd@sbm.ac.ir

Ayda Bahmanjahromi, MD
Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email: a.bahmanjahromi@sbm.ac.ir

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Background: Cutaneous manifestations of coronavirus disease 2019 (COVID-19) are not uncommon and can be the presenting sign of the disease. We aimed to investigate the cutaneous manifestations in COVID-19 patients.

Methods: This cross-sectional study was performed on COVID-19 patients referred to Shohada-e Tajrish and Modarres hospitals, Tehran, Iran, from January 1, 2021 to March 31, 2021. Patients with cutaneous lesions were included in the study; if needed, patients were visited in person, and a biopsy was taken.

Results: Of the 100 COVID-19 patients in this study, with a mean age of 45.53 ± 17.75 years, 37 (37%) were males. The most common cutaneous manifestation was urticaria (21%), followed by maculopapular eruptions (17%), petechiae/purpura (15%), pityriasis rosea-like lesions (15%), erythema multiforme (7%), pernio (6%), Vesicles/pseudovesicles/bullae (5%), and others (24%). Most lesions were erythematous (87.63%). Legs (40%) were most frequently involved. The most common accompanying symptom was pruritus (52%), followed by burning sensations (18%) and pain (7%). Six patients had mucosal lesions; these lesions were the only mucocutaneous manifestations in three of them. Skin biopsies were taken from 11 patients, revealing epidermal changes in 10 (90.9%), dermal changes in 7 (63.6%), mucin deposition in 1 (9.1%), perivascular lymphocyte infiltration in 10 (90.9%), and neutrophil infiltration in 1 (9.1%).

Conclusion: The frequency of skin manifestations was relatively high in this study, with urticaria as the most common cutaneous presentation of COVID-19. Special attention must be paid to the cutaneous lesions of COVID-19.

Keywords: COVID-19, cutaneous, skin, enanthem, mucocutaneous, Iran

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 ¹. While many COVID-19



patients have mild or no symptoms, some progress into severe disease with serious complications². The most common COVID-19 symptoms are fever, cough, and fatigue. Muscle pain, rhinorrhea, sore throat, anosmia, ageusia, and gastrointestinal symptoms have also been described³⁻⁵.

Not much attention was paid to the potential skin manifestations of COVID-19 at the early stages of the pandemic; however, cutaneous presentations have grown as a matter of concern, and studies have described different types of skin involvements in patients with COVID-19⁶⁻⁸. The cutaneous manifestations of COVID-19 may include vesicular, urticaria-like, chilblain-like lesions and maculopapular rashes^{6,9-12}. Nevertheless, it is unclear whether these manifestations result from direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) activity or that they occur as complications of the infection^{13,14}. Furthermore, cutaneous presentations in some patients might be drug side effects^{15,16}. Of note, skin manifestations of COVID-19 can occur before its commonly associated signs and symptoms, indicating that cutaneous involvement can be the presenting sign of the disease¹⁷. In the current study, we aimed to evaluate different skin manifestations in COVID-19 patients.

METHODS

Participants and study design

This cross-sectional study was performed on COVID-19 patients referred to Shohada-e Tajrish and Modarres hospitals, Tehran, Iran, from January 1, 2021 to March 31, 2021. COVID-19 was diagnosed in the patients based on positive results of the reverse transcriptase-polymerase chain reaction (RT-PCR) test or COVID-19 serology tests, COVID-19 symptoms, or typical COVID-19 findings in chest computed tomography (CT) scans. All patients with cutaneous lesions were selected through census sampling and referred to a dermatologist for teleconsultation. Skin lesions were detected using the images sent by the patients. If needed, patients were visited in person, and a biopsy was taken when necessary.

Patients' age, gender, occupation, comorbidities, and duration of comorbidities were recorded in a checklist. The dermatologist determined the cutaneous and mucosal lesions' type, color, and site. Patients were asked if they had any accompanying

symptoms, such as burning sensations, pruritus, and pain. Moreover, we noted whether patients were hospitalized (general wards or intensive care unit [ICU] with or without intubation) or visited as outpatients. In addition, patients' drug history within the past month was reviewed.

The study received ethics approval from the Ethics Committee of our institute and complied with the statements of the Declaration of Helsinki. Informed consent was obtained from all participants.

Data analysis

We used the Statistical Package for the Social Sciences (SPSS) software (version 25.0, Armonk, NY: IBM Corp., USA) for data analysis. Quantitative variables are reported using means and standard deviations. Qualitative variables are reported using frequencies and percentages.

RESULTS

Of the 100 COVID-19 patients included in this study with a mean age of 45.53 ± 17.75 years, 37 (37%) were males and 63 (63%) were females. General characteristics of the patients are presented in Table 1. COVID-19 RT-PCR or serology were positive in 76 (76%). Symptoms of COVID-19 were present in 19 (19%), and 3 (3%) had positive CT scans in favor of COVID-19. Also, two patients (2%) had both COVID-19 symptoms and positive CT scans. Twenty-two (22%) of the patients were healthcare workers. Twenty-eight patients (28%) had comorbidities, including diabetes (13%), hypertension (12%), malignancies (2%), cardiovascular diseases (CVD) (9%), and other diseases (11%). Of these, the duration of comorbidities was less than one year in 3 (10.7%) and more than one year in 25 (89.3%).

The most common cutaneous manifestation was urticarial eruption (21%), followed by maculopapular eruption (17%), petechiae/purpuric eruption/vasculitis (15%), pityriasis rosea (PR-like lesions) (15%), erythema multiforme (7%), pernio/pseudo chilblain (6%), vesicular eruption/pseudovesicular/vesiculobullous lesions (5%), enanthem (2%), and palmar erythema (4%). Other manifestations such as acneiform lesions, necrosis/gangrene, livedo reticularis, lichenoid eruption, panniculitis, prurigo nodularis-like lesions, generalized pustular lesions (like pustular psoriasis and acute generalized

Table 1. General characteristics of the study participants

Variable	Value
Age (years), mean \pm SD	45.53 \pm 17.75
Gender, n (%)	
Male	37 (37.0)
Female	63 (63.0)
Occupation, n (%)	
Healthcare worker	22 (22.0)
Non-healthcare worker	78 (78.0)
Comorbidities, n (%)	28 (28.0)
Diabetes	13 (13.0)
Hypertension	12 (12.0)
Malignancy	2 (2.0)
Cardiovascular disease	9 (9.0)
Other*	11 (11.0)
Duration of the comorbidity, n (%)	
\leq 1 year	3 (3.0)
$>$ 1 year	25 (25.0)
COVID-19 diagnosis, n (%)	
Positive RT-PCR/serology	76 (76.0)
Positive CT	3 (3.0)
COVID-19 symptoms	19 (19.0)
Positive CT + symptoms	2 (2.0)
Pathology findings in 11 patients, n (%)	
Skin biopsy performed	11 (11.0)
Epidermal change	10 (90.9)
Dermal change	7 (63.6)
Mucin deposition	1 (9.1)
Perivascular infiltration	
Lymphocytes	10 (90.9)
Neutrophils	1 (9.1)

Abbreviations: n, number; SD, standard deviation; RT-PCR, reverse transcriptase-polymerase chain reaction; CT, computed tomography. *Acneiform lesions, panniculitis, ischemia, disseminated intravascular coagulation, prurigo-like lesions, generalized pustules (like psoriasis), and lichenoid eruption

exanthematous pustulosis), and herpes zoster reactivation were observed in 24% of patients (Figure 1, Appendix 1 (supplementary file in website)). Also, among the six patients with mucosal lesions, three had accompanying cutaneous lesions, and the rest were exclusively mucosal lesions. None of the patients had pressure sores. Most lesions (87.63%) were erythematous, while 5.15% were ecchymotic, 4.12% were purple, and 3.09% had other colors. Lesions were most frequently present on the legs (40%), anterior (39%) and posterior trunk (36%), forearms (36%), thighs (36%), and arms (34%). The most common accompanying symptom was pruritus (52%), followed by burning sensations (18%) and pain (7%). In 10% of the patients, mucocutaneous lesions presented within 24 hours, in 70% 1–7 days, in 10% 8–14 days, and in 10% $>$ 14 days before evaluation.

Among the 59 patients with a positive drug history within the past month, 20 had received azithromycin, 17 hydroxychloroquine, 10 other antibiotics, 7 lopinavir/ritonavir, and 38 other medications. Of these, 21 (35.6%) had developed cutaneous/mucosal lesions before medical therapy and 38 (64.4%) after medical therapy, among whom lesions developed $<$ 1 week after therapy in 14 (36.8%), 2–3 weeks after therapy in 17 (44.7%), and $>$ 3 weeks after therapy in 7 (18.4%).

Overall, 39 patients (39%) were hospitalized, while the rest were treated as outpatients. Among the hospitalized patients, 24 (61.5%) were admitted

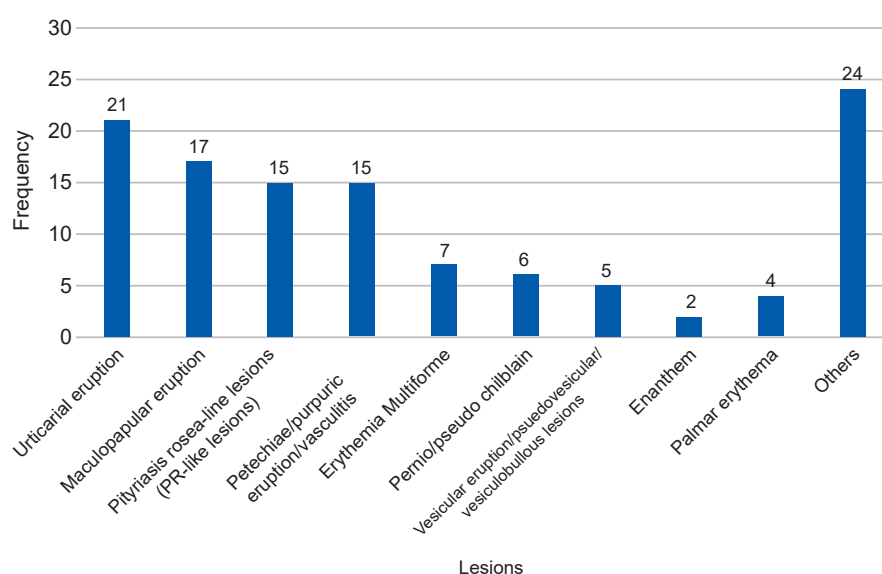
**Figure 1.** Cutaneous manifestations of COVID-19 in 100 patients.

Table 2. Distribution of the cutaneous manifestations of COVID-19

Sites	n (%)
Scalp	1 (1.0)
Face	7 (7.0)
Neck	12 (12.0)
Anterior trunk	39 (39.0)
Posterior trunk	36 (36.0)
Axilla	3 (3.0)
Arm	34 (34.0)
Forearm	36 (36.0)
Hand	23 (23.0)
Palm	12 (12.0)
Thigh	36 (36.0)
Leg	40 (40.0)
Foot	28 (28.0)
Sole	6 (6.0)
Groin	3 (3.0)
Genitalia	2 (2.0)
Buttock	5 (5.0)

Abbreviations: n, number

to general wards, 10 (25.6%) were admitted to the ICU but were not intubated, and 5 (12.8%) were admitted to the ICU and intubated. In addition, cutaneous/mucosal lesions had occurred before hospital admission in 14 (35.9%) and after admission in 25 (64.1%).

Skin biopsies were taken from 11 patients. The results revealed epidermal changes in 10 (90.9%), dermal changes in 7 (63.6%), mucin deposition in 1 (9.1%), and perivascular infiltration in all, including lymphocyte infiltration in 10 (90.9%) and neutrophil infiltration in 1 (9.1%) (Table 2).

DISCUSSION

In the current study, we found urticaria as the most common cutaneous manifestation of COVID-19, occurring in approximately one-fifth of our patients, followed by maculopapular eruption, petechiae/purpura, and PR-like lesions. In line with our findings, Tan *et al.* listed urticarial lesions, macules, and papules among the five most common skin lesions of COVID-19¹⁸. Our results also agree with reports from a recent systematic review¹⁹ and two other studies by Almeida *et al.*²⁰ and Galvan *et al.*⁸. Mast cell degranulation following the cross-reaction of mast cell IgE and SARS-CoV-2 antibodies has been hypothesized as the pathophysiology of urticaria in COVID-19 settings^{21,22}. Contrary to our findings, the highest frequency of COVID-19 skin presentations

belonged to confluent erythematous/maculopapular/morbilliform rash in 25.7% as well as chilblain-like acral pattern in 24.6% of patients reported by Marzano *et al.*²³. Moreover, an erythematous rash was the most common cutaneous feature in the study by Zhao *et al.*²⁴; nevertheless, it was accompanied by urticaria in most of these patients. The variety of COVID-19 cutaneous manifestations and their frequency can be explained by the demographic differences in study populations, various degrees of COVID-19 severity, comorbidities, and patients' drug history. An atypical cutaneous manifestation mimicking an arthropod bite reaction with necrotic crust has also been reported with COVID-19²⁵. Also, purpura and petechiae, erythematous papules and macules, and urticarial eruptions have been observed in three previous cases from Iran²⁶.

The female-to-male ratio was 1.7 in our study, comparable with the findings of Zhao *et al.*²⁴. This ratio was 1.1 in a systematic review of 56 studies including 1,020 patients²⁷. The higher proportion of female patients with mucocutaneous manifestations in our study may be justified because female patients are generally more sensitive toward skin presentations than men and may have recognized lesions more frequently.

In the current study, the legs were the most common site of skin lesions, followed by the anterior trunk. The posterior trunk, forearm, and thigh were equally involved in the third place. Similarly, the trunk was the preferred localization of skin manifestations in the study of Matar *et al.*²⁷. Also, in a preliminary report from Italy and Spain, the skin lesions of the affected patients were present on their trunk²⁸.

Over half of our patients had a positive drug history within the past month. These drugs included azithromycin and other antibiotics, hydroxychloroquine, lopinavir/ritonavir, and other medications. Interestingly, 38 patients developed mucocutaneous lesions after medical therapy; nevertheless, in only 14, the lesions occurred within a week of therapy, while the time interval was much longer in others. Although the temporal course of cutaneous manifestations can give us a clue as to whether the lesions result from drug use, this cannot be definitively determined.

Six patients in our study had mucosal lesions; three exclusively had these lesions, while the rest had accompanying cutaneous lesions. This finding is

inconsistent with the results of previous studies^{23,29}; they reported mucous membrane lesions in none of their patients. However, mucous involvement was also infrequent in our study. The reason behind the rarity of mucosal lesions in COVID-19 is not clear since angiotensin-converting enzyme 2 (ACE2) receptors, responsible for SARS-CoV-2 entry into host cells, are expressed in both keratinocytes and the oral cavity^{30,31}.

One limitation of the current study was its small sample size, which restricts the generalizability of our findings. Another limitation was that COVID-19 was not confirmed in all patients based on SARS-CoV-2 RT-PCR results. Furthermore, the severity of COVID-19 was not clear in our patients, as previous studies have shown an association between certain types of COVID-19 cutaneous lesions and disease severity²⁷.

CONCLUSION

This study found urticaria as the most common cutaneous presentation of COVID-19 and legs and trunk as the most frequent involvement sites. COVID-19 patients can benefit from a thorough skin examination. Also, special attention must be paid to the cutaneous lesions of COVID-19 since these may be the presenting signs or the only presentation of the disease.

Abbreviations

- ACE2: angiotensin-converting enzyme 2
- COVID-19: coronavirus disease 2019
- RT-PCR: reverse transcriptase-polymerase chain reaction
- CT: computed tomography
- ICU: intensive care unit
- CVD: cardiovascular disease
- PR: pityriasis rosea

Authors contributions

F. A and M. S. D contributed to the conception or design of the work. F. A, M. S. D, R. D, A. B, S. D, A. G, A. S, H. M, S. M. N and M. N contributed to the acquisition, analysis, or interpretation of data for the work. A. B drafted the manuscript. F. A critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

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REFERENCES

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. Switzerland: Geneva; 2020.
2. Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak—an update on the status. *Mil Med Res.* 2020;7(1):1-10.
3. Lei S, Jiang F, Su W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. *EClinicalMedicine.* 2020;21:100331.
4. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. *Travel Med Infect Dis.* 2020;34:101623.
5. Lechien JR, Chiesa-Estomba CM, De Sisti DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Oto-Rhino-L.* 2020;277(8):2251-61.
6. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol.* 2020;34(5).
7. Kaur I, Sharma A, Jakhar D, et al. Coronavirus disease (COVID-19): an updated review based on current knowledge and existing literature for dermatologists. *Dermatol Ther.* 2020;33(4):e13677.
8. Casas CG, Catala A, Hernández GC, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol.* 2020;183(1):71-7.
9. Giavedoni P, Podlipnik S, Pericàs JM, et al. Skin manifestations in COVID-19: prevalence and relationship with disease severity. *J Clin Med.* 2020;9(10):3261.
10. Estébanez A, Pérez-Santiago L, Silva E, et al. Cutaneous manifestations in COVID-19: a new contribution. *J Eur Acad Dermatol Venereol.* 2020; 34(6):e250.
11. Diaz-Guimaraens B, Dominguez-Santas M, Suarez-Valle A, et al. Petechial skin rash associated with severe acute respiratory syndrome coronavirus 2 infection. *JAMA Dermatol.* 2020;156(7):820-2.
12. Piccolo V, Neri I, Filippeschi C, et al. Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients. *J Eur Acad Dermatol Venereol.* 2020; 34(7):e291.
13. Landa N, Mendieta-Eckert M, Fonda-Pascual P, et al. Chilblain-like lesions on feet and hands during the

- COVID-19 Pandemic. *Int J Dermatol.* 2020;59(6):739.
14. Colonna C, Monzani NA, Rocchi A, et al. Chilblain-like lesions in children following suspected COVID-19 infection. *Pediatr Dermatol.* 2020;37(3):437-40.
 15. Sachdeva M, Gianotti R, Shah M, et al. Cutaneous manifestations of COVID-19: report of three cases and a review of literature. *J Dermatol Sci.* 2020;98(2):75-81.
 16. Suchonwanit P, Leerunyakul K, Kositkuljorn C. Cutaneous manifestations in COVID-19: lessons learned from current evidence. *J Am Acad Dermatol.* 2020;83(1):e57-60.
 17. Young S, Fernandez AP. Skin manifestations of COVID-19. *Cleve Clin J Med.* 2020.
 18. Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: a worldwide review. *J Am Acad Dermatol.* 2021;2:119-33.
 19. Singh H, Kaur H, Singh K, et al. Cutaneous manifestations of COVID-19: a systematic review. *Adv Wound Care.* 2021;10(2):51-80.
 20. Almeida G, Arruda S, Marques E, et al. Presentation and management of cutaneous manifestations of COVID-19. *J Drugs Dermatol.* 2021; 20(1):76-83.
 21. Imbalzano E, Casciaro M, Quartuccio S, et al. Association between urticaria and virus infections: a systematic review. *Allergy Asthma Proc.* 2016;37(1):18-22.
 22. Cao X. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol.* 2020;20(5):269-70.
 23. Marzano AV, Genovese G, Moltrasio C, et al. The clinical spectrum of COVID-19-associated cutaneous manifestations: an Italian multicenter study of 200 adult patients. *J Am Acad Dermatol.* 2021;84(5):1356-63.
 24. Zhao Q, Fang X, Pang Z, et al. COVID-19 and cutaneous manifestations: a systematic review. *J Eur Acad Dermatol Venereol.* 2020;34(11):2505-10.
 25. Shahidi Dadras M, Zargari O, Abolghasemi R, et al. A probable atypical skin manifestation of COVID-19 infection. *J Dermatol Treat.* 2020; 33(2):1188-90.
 26. Shahidi Dadras M, Dadkhahfar S, Bahmanjahromi A, et al. Skin manifestations in three cases of COVID-19 infection from Iran and a narrative literature review. *Iran J Dermatol.* 2020;23(Suppl. 1):60-6.
 27. Matar S, Oulès B, Sohier P, et al. Cutaneous manifestations in SARS-CoV-2 infection (COVID-19): a French experience and a systematic review of the literature. *J Eur Acad Dermatol Venereol.* 2020;34(11):e686-e689.
 28. Tamaro A, Adebajo GAR, Parisella FR, et al. Cutaneous manifestations in COVID-19: the experiences of Barcelona and Rome. *J Eur Acad Dermatol Venereol.* 2020;34(7):e306-e307.
 29. Zhou G, Chen S, Chen Z. Advances in COVID-19: the virus, the pathogenesis, and evidence-based control and therapeutic strategies. *Front Med.* 2020;14(2):117-25.
 30. Novak N, Peng W, Naegeli MC, et al. SARS-CoV-2, COVID-19, skin and immunology—What do we know so far? *Allergy.* 2021;76(3):698-713.
 31. Xue X, Mi Z, Wang Z, et al. High expression of ACE2 on keratinocytes reveals skin as a potential target for SARS-CoV-2. *J Invest Dermatol.* 2021;141(1):206-9.