

A Study of Cutaneous Manifestations of COVID-19: An Indian Perspective

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Abstract

Background: Coronavirus disease-2019 (COVID-19) has been shown to involve multiple-organ systems during disease process. Dermatologists have also reported various findings in patients of COVID-19 and have pointed out few cutaneous manifestations that are novel and are probably related to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, currently very limited data are available regarding various aspects of cutaneous involvement. **Aims:** This study aimed to investigate various aspects of cutaneous involvement in COVID-19. **Methods:** Institutional ethics committee approval was secured before conducting a study. Patients with at least one positive nasopharyngeal swab result for SARS-CoV-2 carried out by reverse transcription polymerase chain reaction (RT-PCR) were enrolled. After informed consent subjects were interviewed and monitored for appearance of any cutaneous signs and symptoms. Those with relevant findings were evaluated for characteristics of cutaneous findings. Data of all patients were collected and analyzed. **Results:** A total of 303 patients were enrolled for the study. Approximately 1.98% of patients developed cutaneous manifestations. Four types of skin lesions were observed in study subjects: urticarial lesions, maculopapular rash, acro-ischemia, and glossitis. **Limitations:** Relatively less number of patients, collection of data from single center, and absence of histopathological confirmation were limitations of the study. **Conclusion:** COVID-19 disease process has a cutaneous component; however, incidence of cutaneous findings remains low. Urticaria was the most common type of cutaneous finding, whereas acro-ischemia was the most characteristic one.

Keywords: Acro-ischemia, COVID-19, cutaneous manifestations, SARS-CoV-2, urticarial lesions

INTRODUCTION

Toward the end of 2019, an outbreak of previously unseen pneumonia cases was reported from Wuhan, China.^[1]

A novel coronavirus “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) was identified as a causative agent for this outbreak.^[2]

The virus rapidly spread around the world and on March 11, 2020 World Health Organization (WHO) declared coronavirus disease-2019 (COVID-19) as a pandemic.^[3]

As the pandemic progressed, dermatologists started to investigate possible cutaneous involvement in patients with COVID-19. As a result, various case reports and review

articles started pouring in, describing the possible scope of cutaneous involvement in patients with COVID-19.^[4-7]

However, to the best of author’s knowledge only few studies have been conducted in this regard.^[5] As for India, currently there is only one published study about cutaneous manifestations in Indian patients.^[8]

Currently, there are limited data available regarding incidence and characteristic clinical features of skin lesions (if any) in patients with COVID-19. Also, the association of various clinical parameters of patients with skin lesions remains unclear.

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We planned to conduct a study to investigate above aspects as it may prove to be useful in patients which are otherwise asymptomatic except presence of skin lesions and refer them for diagnostic tests to rule out SARS-CoV-2 infection.

COVID-19 has been shown to involve multiple-organ systems during the disease course by various mechanisms.^[9] During the conduct of this study, we sought to find out if it has any cutaneous component? If cutaneous findings are present, then what are its characteristics?

Are there any defining cutaneous manifestations for COVID-19 which can be used for identifying potential undiagnosed cases or prognosticating already diagnosed cases so as to help managing physicians to take clinical decisions?

METHODOLOGY

This study was conducted in a tertiary care center (designated COVID-19 care center) in western India. The study was conducted after getting approval from the institutional ethics committee (ethics committee approval number: BVDUMC/IEC/13). Ours was an observational study.

We enrolled the patients who were diagnosed with COVID-19 and admitted at our institute for management. Written informed consent was obtained from all participants or next of kin (in case of minors or critical patients).

We only included the patients with at least one positive real-time reverse transcription-polymerase chain reaction (RT-PCR) result for SARS-CoV-2 in nasopharyngeal swab sample and subsequently admitted for further management at our center.

Patients with clinical suspicion of COVID-19 but negative RT-PCR test were excluded. Participants who were not willing for consent were also excluded.

Methods

Eligible participants in study duration were enrolled.

Written informed consent was obtained from the patients.

Demographic and Baseline characteristics of the participants were recorded in the predesigned proforma.

General condition of the patient, cutaneous findings if any, clinical, epidemiological and laboratory parameters of the patient were noted at the time of admission in the ward/ intensive care unit.

On admission all participants were enquired for cutaneous lesions of recent onset (previous 2 weeks), if any.

Participants who had relevant positive history were subjected to cutaneous examination to note for characteristics of rash. The skin lesions were noted and photographed for purpose of documentation and follow-up. The evolution of rash was followed up till the final outcome of patient for COVID-19.

Rest all participants who did not have history of any rash were kept under monitoring for appearance of relevant skin lesions in the duration of their admission.

We collected clinical records of all study subjects.

In addition, we also interacted with patients who were clinically stable, to gather information about appearance of any relevant skin lesions of new-onset in the last 2 weeks. If found relevant, the data were collected and entered.

For patients admitted in intensive care unit (ICU) clinical records were the main source of data for us. Whenever possible next of kin were interacted with for any additional information. However, reliability of data obtained from relatives was limited.

Unfortunately, we could not conduct biopsy for any of the patients owing to difficulty in accessing the patients and possibility of contracting infection by health care workers.

Statistical analysis

All statistical analysis was carried out by Statistical Package for the Social Sciences (SPSS) software program, version 25.0. Continuous variables results shown by descriptive statistics and categorical variable results were shown by frequency and percentages. Student's *t* test was used for continuous variables with normal distribution and Mann-Whitney *U* test was used for continuous variables with abnormal distribution. Throughout results, 5% level of significance was used. All results were shown with 95% of confidence. A value of *P* < 0.05% was considered statistically significant.

RESULTS

During the course of our study, we enrolled a total of 360 patients. Of those 303 patients could be included in the final data. The mean age of the study group was 40.25 ± 16.17 years. Clinical characteristics of the entire group of patients are as mentioned in Table 1.

During our study we found 2.64% (*n* = 8) had cutaneous complaints.

However, on evaluation 1.98% (*n* = 6) patients had cutaneous findings which were attributable to COVID-19.

Table 1: Clinical characteristics of patients in entire study group

No. of patients	Sex		Mean age	Systemic symptoms										
	M	F		Fever	Chills	Cough	Sore throat	Dyspnea	Muscle Pain	Abdominal pain	Diarrhea	Nausea/vomiting	Anosmia	Cutaneous problem
303	65%	35%	40.25±16.17	45.87%	9.57%	41.91%	12.21	24.75%	13.2%	3.30%	4.95%	3.30%	0.33%	1.98%

The male-to-female ratio of patients with cutaneous complaints was 5:1. Clinical characteristics of patients who developed skin lesions are as per [Table 2].

We observed the following four types of lesions in our subjects.

Urticarial lesions

These were the most common type of lesions in our patients. Of 6 patients 50% (*n* = 3) patients had urticarial lesions. The lesions predominantly involved trunk. In one patient, lesions were also present on face. All patients responded to oral antihistamines promptly [Figure 1].

Maculopapular rash

Approximately 16.7% (*n* = 1) was found to develop maculopapular rash. On day 1 of fever patient developed mildly erythematous rash which blanched on pressure. The rash was asymptomatic and subsided with oral antihistamines within 24h.

Acro-ischemia

We encountered one patient with findings suggestive of acral ischemia. The patient was 51-year-old man with history of hypertension. He was diagnosed with

COVID-19 and was admitted for management. He recovered uneventfully and was discharged. One day after his discharge he again visited the facility with complaints of bluish discoloration and throbbing pain in right foot and toes. No past history of similar complaints was present. On further evaluation pulsations of ipsilateral dorsalis pedis artery were not palpable. On laboratory evaluation D-dimer levels were found to be raised (1038 ng/mL, > 4 times the normal levels). Patient also had findings of hypokalemia and raised C-reactive protein (CRP) levels. The diagnosis of right sided dorsalis pedis thrombosis was ascertained. Patient was again admitted and managed in consultation with vascular surgeon. He was administered low molecular weight heparin, cilostazol. Patient rapidly recovered and was discharged.

Glossitis

One patient (16.7%) reported complaints suggestive of oral mucositis during the course of admission. On examination features suggestive of glossitis were observed [Figure 2]. No past history of similar complaints in the past could be elicited. Patient was managed symptomatically.

Clinical characteristics of the patients with COVID-19 with cutaneous findings are provided in Table 2.

Table 2: Clinical information of COVID-19 patients developing cutaneous lesions

	Urticarial lesions	Maculopapular rash	Acro-ischemia	Glossitis
No. of patients	50% (<i>n</i> = 3)	16.7% (<i>n</i> = 1)	16.7% (<i>n</i> = 1)	16.7% (<i>n</i> = 1)
Sex				
M	3	0	1	1
F	0	1	0	0
Age	46 year; 56 years; 62 years	26 years	51 years	23 years
Systemic symptoms				
Fever	66.66%	100%	100%	100%
Chills	0	100%	0%	0
Cough	33.33%	100%	100%	100%
Sore throat	0	100%	100%	0
Dyspnea	0	0	100%	0
Muscle pain	0	100%	0%	100%
Abdominal pain	0	0	0%	0
Diarrhea	0	0	0	0
Nausea/vomiting	0	0	0	0
Anosmia	0	0	0	0
Cutaneous symptoms	Itching (100%)	Asymptomatic	Pain at local site	Burning
Comorbidities	DM (33.33%)	None	HTN	0
Duration of rash	1 day; 1 day; 3 days	1 day	1 day	1 day
Drugs given				
Paracetamol	100%	100%	100%	100%
NSAID's	0	0	0	0
Hydroxychloroquine	0	0	0	0
Corticosteroids	0	0	0	0
Azithromycin	66.66%	100%	100%	0
Oseltamivir	66.66%	100%	100%	0
Amoxicillin-clavulanic acid	0	0	0	0
Any other drugs	Multivitamins, antihistamines	Multivitamins, antihistamines	Aspirin, cilostazole, LMWH, amlodipine	Multivitamins

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Figure 1: Urticarial lesions on back in patient with COVID-19



Figure 2: Lesions of glossitis in patient with COVID-19

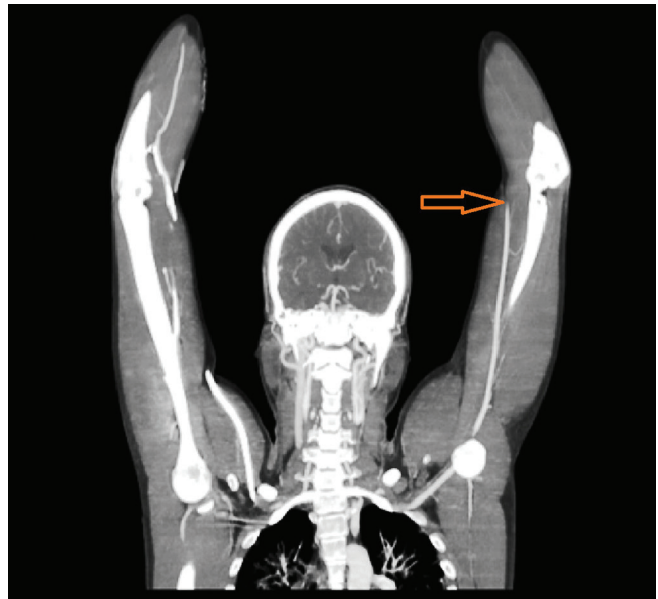


Figure 3: CT angiogram of patient with signs of acro-ischemia showing abrupt cutoff of distal left brachial artery, beginning approximately 3.5 proximal to the elbow joint

No patient from the above set had changes suggestive of COVID-19 on the chest radiograph.

One patient (16.7%) who had changes of acro-ischemia was admitted in ICU, whereas the rest of the patients (83.3%) were admitted in ward.

All above patients were discharged after treatment of COVID-19 and adverse outcomes were not reported in any of them.

On statistical analysis, it was observed that except CRP all variables followed normal distribution pattern. The difference between groups of patients with skin manifestations and those without was not statistically significant for parameters like temperature, SpO₂, hemoglobin, total leucocyte counts, neutrophil count, platelets, CRP levels ($P > 0.05$) [Tables 3 and 4].

The difference in lymphocyte counts between two groups was found statistically significant ($P < 0.05$). The patients without skin manifestations had comparatively lower lymphocyte counts than those with skin manifestations.

Besides these six patients we also came across two patients which were associated indirectly with COVID-19.

One patient, 34-year-old man developed urticaria secondary to administration of favipiravir for COVID-19.

Another patient a 30-year-old man developed papulopustular lesions on back shortly after discharge. The lesions were suggestive of acneiform eruption and records had documentation of receiving parenteral corticosteroids during the hospital stay. Hence the

Table 3: Statistical analysis of parameters following normal distribution by independent *t* test

Parameter	Skin problem	N	Mean	SD	<i>t</i> Value	P Value
Temperature (°F)	Yes	6	97.58	1.88	0.1600	0.87
	No	296	97.46	1.23		
SpO ₂	Yes	6	97.67	1.37	0.1360	0.89
	No	296	97.59	2.15		
Hemoglobin (g/dL)	Yes	6	13.95	0.93	2.1800	0.71
	No	268	13.08	2.00		
Total leucocyte count	Yes	6	7433.33	2377.95	1.2300	0.27
	No	266	6222.74	2165.61		
Neutrophil count	Yes	6	70.50	13.34	1.9700	0.103
	No	267	59.64	12.41		
Lymphocyte count	Yes	6	19.17	11.65	2.5500	0.011
	No	267	31.30	11.52		
Platelet count	Yes	6	269500.00	111878.06	0.59	0.58
	No	262	242526.72	83087.48		

Difference between group of patients with skin manifestations and those without skin manifestations was not statistically significant for temperature, SpO₂, hemoglobin, total leucocyte count, neutrophil count, and platelets count. The difference was statistically significant for lymphocyte count among two groups

Table 4: CRP levels did not follow normal distribution pattern and was analyzed by Mann–Whitney *U* test

Parameter	Skin problem	N	Median	P Value
CRP	Yes	6	22.71	0.92
	No	269	19.73	
	Total	275		

Difference between the group with cutaneous manifestations and those without was not statistically significant

diagnosis of steroid-induced acneiform eruption was confirmed.

DISCUSSION

In the initial days of the current pandemic main focus of health care providers was on respiratory system involvement as patient symptoms were predominantly that of respiratory in nature. It was evident from a study in China, which reported 67.8% of subjects had complaints of cough, whereas 18.7% complained shortness of breath.^[10]

However as pandemic progressed newer facets emerged regarding multisystem involvement in COVID-19.^[9] Naturally, dermatologists also started to try and look for any aspect of disease process which involved skin so as to do our bit in dealing and helping our colleagues on the frontlines of this battle.

This was manifest in the publications of many case reports and few studies which tried to establish useful leads of COVID-19 and skin.^[4-7] Many of these links are awaiting evaluation to determine causality.

The picture is still not complete owing to the difficulties regarding quarantines, difficulty in accessing dermatology

opinion, lack of awareness among general public (especially in country like India), difficulty in collecting data due to patient isolations and possibility of not reporting minor skin manifestations even by healthcare workers owing to overwhelming burdens on public health care systems.

We also encountered these problems because of limited access to patients as there was fear of contracting infection during interaction with patients.

During the conduct of this study we found that like other viral infections COVID-19 also has cutaneous manifestations.

Incidence of cutaneous rash during COVID-19 in this study was 1.98%.

Some of the initial reports about COVID-19 which were published by authors in China reported the incidence of cutaneous rash as a mere 0.2%.^[10] In a study from Spain by Herrero-Moyano *et al.*,^[11] the authors reported the incidence of cutaneous manifestations among hospitalized patients with COVID-19 as 0.7%. A study from Italy by Recalcati^[4] reported that 20.4% of patients developed cutaneous manifestations. There is only one published study from India regarding cutaneous findings in COVID-19 by Dalal *et al.*^[8] In this study 1.9% of patients had urticarial lesions, 2.9% of patients had maculopapular rash, and 7.8% of patients had complaints of pruritus without any signs. In total, 12.7% of patients had cutaneous symptoms during COVID-19.

In this study, we only included the patients who developed demonstrable cutaneous sign and excluded patients who did not have relevant signs and symptoms.

In general, all studies have indicated that COVID-19 has a cutaneous component; however, the incidence of cutaneous manifestations remains a contested point. In general majority of studies have shown low incidence.

In course of this study, we encountered four types of skin lesions- urticaria, maculopapular rash, acral ischemia, and glossitis.

Total four patients developed urticaria during the course of disease. One patient of them was suspected to have developed urticaria secondary to administration of favipiravir. Rest three patients however had no other attributable cause aside from SARS-CoV-2 infection.

Urticaria was the most common cutaneous manifestation among patients with COVID-19 in our study. All patients promptly responded to course of oral antihistamines.

One patient developed maculopapular rash on day 1 of fever. The rash was mildly erythematous and resolved within 24 h with oral antihistamines.

Drug rash should be considered an important differential diagnosis when patients with COVID-19 develop urticarial lesions, maculopapular rash. A proper history taking about drug intake and timing of onset of rash can help to rule out drug rash.

We encountered one patient with findings of acro-ischemia. Multiple authors have reported this finding across the world; however, we are yet to come across report of such finding from India. To the best of our knowledge, this might be the first reported case of such type from India.

Besides the above-reported case we also came across another similar case at our institute where a 35-year-old male patient with COVID-19 developed complaints of cyanosis and pain in the left upper limb. On computed tomography (CT) angiogram examination patient was diagnosed with left brachial and subclavian artery thrombosis [Figures 3 and 4]. D-dimer and CRP levels were also found to be raised. The patient had to be operated to restore blood flow. When this patient presented to us, we had already finished compilation of data and statistical analysis. So unfortunately, his data could not be included in the study. However, we decided to discuss this case in the manuscript to point out the importance of acro-ischemia in patients with COVID-19.

From our experience signs of acro-ischemia can be considered as characteristic cutaneous feature of COVID-19 and can be used to suspect/monitor COVID-19.

This presentation of acro-ischemia is proposed to be due to SARS-CoV-2 induced coagulopathy which culminates in thrombotic events.^[12] This coagulopathy is a prominent feature of COVID-19 and presence of coagulopathy has been associated with poor prognosis.^[12,13]

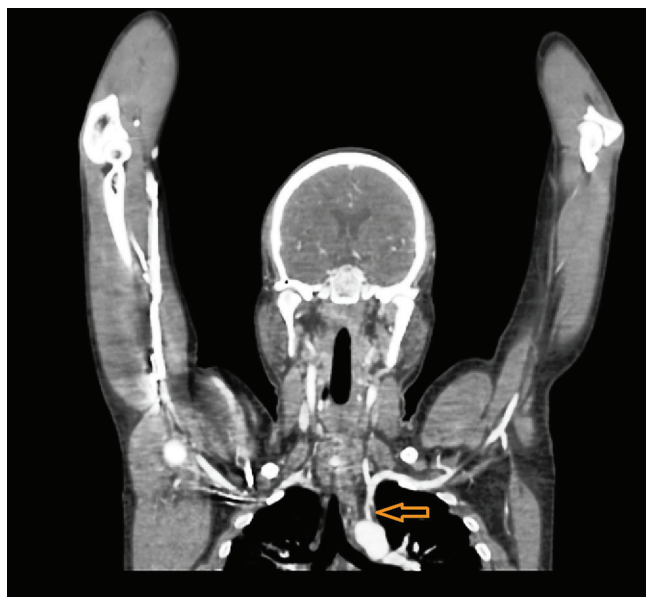


Figure 4: CT angiogram of patient with signs of acro-ischemia showing eccentric partial thrombus in the origin of left subclavian artery

In our study, we came across a patient of glossitis. However, we are of opinion that association of this finding cannot be linked to COVID-19 firmly and could be an incidental finding.

Casas *et al.*^[5] published a major study outlining cutaneous manifestations from Spain. In the study, authors developed consensus on five clinical types of rash associated with SARS-CoV-2 infection (Pseudo chilblain, vesicular, urticarial, maculopapular, and necrotic).

We did not encounter any patient with pseudo chilblain and vesicular types of rash.

Vesicular rash has however been reported by multiple other studies in context of COVID-19.^[4-6] A study by Fernandez-Nieto^[14] carried out polymerase chain reaction on the fluid obtained from vesicles in patients with COVID-19. However, PCR assays failed to detect the presence of SARS-CoV-2 inside the vesicles.

As for pseudo-chilblain the evidence is not yet conclusive. According to two recent studies published concluded that there was no microbiological and serological evidence to implicate SARS-CoV-2 in causation of chilblain-like or pernicious lesions.^[15,16] However, another study has suggested that chilblain-like lesions are associated with mild or asymptomatic SARS-CoV-2 infection.^[17]

We are of opinion that this needs to be further investigated to draw final conclusions.

These differences in clinical presentation may be due to genetic and ethnic differences among patients.

A statistically significant difference between lymphocyte counts in groups of patients with and without cutaneous manifestations was observed. Further clinical studies may shed light on clinical relevance and impact of this finding.

Collection of data from single center, relatively lower number of patients, and absence of histopathological examination can be considered as limitations of the study. This can be remedied by conducting large study involving multiple centers.

CONCLUSION

COVID-19 disease process has a cutaneous component; however, the incidence of cutaneous signs in COVID-19 remains low.

Urticaria is the most common cutaneous manifestation of infection with SARS-CoV-2. Other cutaneous manifestations are maculopapular exanthem and acro-ischemia.

Presence of urticarial lesions, maculopapular rash, or signs of acro-ischemia in appropriate clinical settings should alert the dermatologist regarding the possibility of infection with SARS-CoV-2.

Signs of acro-ischemia can be considered as a characteristic cutaneous manifestation of COVID-19.

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Conflicts of interest

There are no conflicts of interest.

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