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Original Research Article

Cutaneous manifestations in COVID-19 patients in a district COVID care centre

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ABSTRACT

Background: COVID-19, initially started as respiratory illness and evolved to involve various systems. Skin has been the least targeted organ with manifestations limited to case reports and series in a foreign scenario. Here, we tried to understand a same in an Indian scenario.
Methods: This was cross-sectional study done in district COVID centre among patients with a confirmed diagnosis of COVID-19 with cutaneous manifestations for 3 months. A detailed history, complete cutaneous examination was carried out. Timing in relation to other symptoms and severity was assessed.
Results: Among the 1603 patients, 39 (2.4%) had skin manifestations. Urticaria (20.5%), petechiae/purpura (17.9%), pruritis (15.4%) were the most common followed by maculo-papular rash (7.7%), manifestations secondary to drugs (7.7%), diffuse hair fall (7.7%), pseudo-chilblains (5.1%), vesicular eruptions (5.1%), infections (5.1%), cellulitis, gangrene and livedoid vasculitis. Timing of skin lesions ranged from 2 days before (10.3%) onset of COVID-19 symptoms or diagnosis to 10 days after (69.2%). Urticaria, petechiae, maculopapular rash were seen more commonly in patients with fever and respiratory symptoms. Asymptomatic cases showed urticaria, petechiae and pseudo-chilblains. Majority were in mild and moderate disease and livedoid vasculitis patient had severe disease.
Conclusions: Skin manifestations in COVID-19 are relatively uncommon in Indian scenario. However, few of the manifestations give a hint of infection while some correlate with the severity of disease.

Keywords: COVID-19, Cutaneous manifestions, Asymptomatic cases

INTRODUCTION

The first case of SARS-CoV-2 was reported in Wuhan, China.[1] High rate of infectivity, low virulence and asymptomatic transmission has resulted in rapid spread across the geographic boundaries and was declared a pandemic by WHO on 11 March 2020.[2,3] Globally, as of 6:28 pm CEST, 14 September 2021 there have been 225,024,781 confirmed cases of COVID-19 including 4,636,153 deaths, reported to WHO. In India, from 3 January 2020 to 6:28 pm CEST, 14 September 2021, there have been 33,289,579 confirmed cases of COVID-19 with 443,213 deaths, reported to WHO. SARS-CoV-2 is an enveloped virus composed of positive-sense single-stranded RNA and belongs to the coronavirus family. The primary site of infection for COVID-19 is the lung and patients present with symptoms ranging from mild flu-like to fulminant pneumonia and potentially lethal respiratory distress.[4] As we tried to understand it, we were posed with numerous challenges day in and day out, with conceptions turning into misconceptions with the approach of a new dawn.

An infection that started as a respiratory illness manifested with varied presentations involving various other systems. Skin manifestations in COVID were never

heard of initially, but in recent times various skin manifestations were attributed to the disease worldwide. The frequency varied from 0.2% from China to 20% from Italy.[5] The present data was limited to few case reports and case series. We tried to study the Indian scenario and also tried to establish an association between the manifestations and the disease severity.

Aim of the study was to evaluate skin manifestations and its association with other clinical findings in patients diagnosed with COVID-19.

METHODS

The study was conducted in our hospital, which was designated district COVID care centre in Vijayawada, Andhra Pradesh, India, over a period of 3 months. All patients diagnosed with COVID-19 either with a positive RT-PCR or CT chest findings were included in the study.

After taking an informed consent, a detailed history was taken and a cutaneous examination was carried out. Timing of these cutaneous manifestations in relation to onset of disease and severity of COVID-19 disease was assessed.

The severity of pulmonary involvement was assessed based on interim clinical guidance for management of COVID-19 (version 1.5) by AIIMS, New Delhi. The patient was classified as having mild disease if a patient had upper respiratory tract symptoms without shortness of breath or hypoxia and moderate disease, if respiratory rate greater than or equal to 24 /min, SpO_2 less than 94% on room air and severe disease, if respiratory rate greater than or equal to 30 /min, SpO_2 less than 90% on room air.

RESULTS

Among 1,603 confirmed COVID-19 patients, 39 (2.4%) had cutaneous manifestations. The mean age was 41.76±16.07 years with a male:female ratio of 1:1.4. Extremities were more commonly involved, followed by trunk and face. The most common cutaneous manifestations observed were urticaria (20.5%), petechiae/purpura (17.9%), pruritus (15.4%) followed by maculopapular rash, manifestations secondary to drugs and diffuse hair fall in 7.7% cases each and pseudo-chilblains, vesicular eruptions and infections in 5.1% cases each (Table 1) (Figure 1, 2, 3-5 a and b).

Table 1: Skin manifestations and their timing with diagnosis in COVID-19 patients.

Skin manifestations	Percentage (%)	Timing with COVID-19 symptoms	
		At	After
		N (%)	N (%)
Urticaria	20.5	3 (37.5)	4 (50)
Purpura/petechiae	17.9	2 (28.6)	5 (71.4)
Pruritus	15.4	4 (66.6)	3 (50)
Maculo-papular rash	7.7	1 (33.3)	2 (66.6)
Manifestations secondary to drugs	7.7	-	3 (100)
Diffuse hair fall	7.7	-	3 (100)
Pseudo-chilblains	5.1	1 (50)	1 (50)
Vesicular eruptions	5.1	-	2 (100)
Infections (*Herpes labialis, Herpes zoster*)	5.1	-	2 (100)
Cellulitis	2.6	1 (100)	-
Gangrene	2.6	-	1 (100)
Livedoid vasculitis like	2.6	-	1 (100)
Total	100	12 (30.7)	27 (69.3)

Table 2: Relation of cutaneous features in COVID-19 with other clinical manifestations.

Symptoms	Urticaria (n=8) (%)	Petechaie / Purpura (n=7) (%)	Vesicular (n=2) (%)	Pseudochill blains (n=2) (%)	Maculo-papular Rash (n=3) (%)	Livedoid vasculitis like (n=1) (%)
Fever	3 (37.5)	2 (28.5)	1 (50)	1 (50)	3 (100)	1 (100)
Cough	4 (50)	1 (14.28)	-	1 (50)	2 (66.6)	1 (100)
Dyspnea	3 (37.5)	1 (14.28)	-	1 (50)	2 (66.6)	1 (100)
Headache	1 (12.5)	2 (28.5)	1 (50)	-	1 (33.3)	-
Nausea/vomiting/diarrhoea	1 (12.5)	2 (28.5)	-	-	2 (66.6)	-
Anosmia	1 (12.5)	-	1 (50)	-	-	-
Pneumonia	1 (12.5)	1 (14.28)	-	1 (50)	1 (33.3)	1 (100)
Asymptomatic	2 (25)	1 (14.28)	-	1 (50)	-	-

Table 3: Relation of cutaneous manifestations with severity of the disease.

Skin manifestations	Percentage (%)	Severity		
		Mild	Moderate	Severe
		N (%)	N (%)	N (%)
Urticaria	20.5	4 (50)	3 (37.5)	1 (12.5)
Purpura/petechiae	17.9	4 (57.1)	2 (28.6)	1 (14.3)
Pruritus	15.4	4 (66.6)	2 (33.3)	
Maculo-papular rash	7.7	1 (33.3)	1 (33.3)	1 (33.3)
Manifestations secondary to drugs	7.7	1 (33.3)	2 (66.7)	-
Diffuse hair fall	7.7	2 (66.6)	1 (33.3)	-
Pseudo-chilblains	5.1	1 (50)	-	1 (100)
Vesicular eruptions	5.1	1 (50)	1 (50)	
Infections (*Herpes labialis, Herpes zoster*)	5.1	2 (100)	-	-
Cellulitis	2.6	1 (100)	-	-
Gangrene	2.6	-	1 (100)	-
Livedoid vasculitis like	2.6	-	-	1 (100)
Total	100	21 (53.8)	13 (33.3)	5 (12.9)

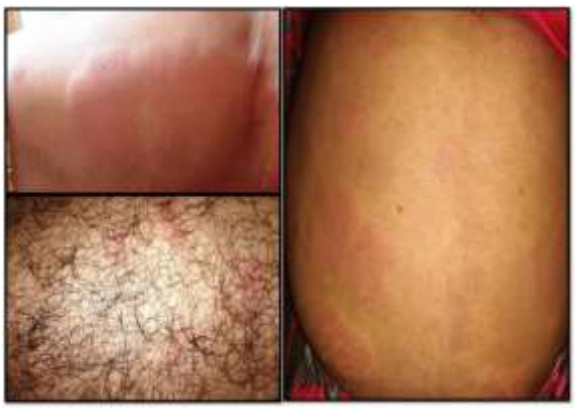

Figure 1: Urticaria.

Figure 2: Purpuric lesions.

Less commonly, we observed gangrene, cellulitis and livedoid vasculitis-like lesions in one patient (2.6%) each (Figure 5 c-e). Urticarial lesions were present over the trunk and extremities and there was no H/O angioedema. Pruritus in 2 patients was generalized and in 4 patients, it was localized to extremities. The maculopapular rash was seen over the trunk. Out of three patients with manifestations secondary to drugs, heparin-induced ecchymoses were seen in 66.7% of patients and in 33.3%, steroid-induced acne was seen. In patients with pseudo-chilblains, violaceous to erythematous patches were present over hands and feet. There was no history of cold exposure and their D-dimers and coagulation profile were normal.

Figure 3: (a) Echymosis due to heparin; (b) steroid acne.

Urticaria, petechiae, maculo-papular rash were seen in patients with fever and respiratory symptoms (Table 2). Asymptomatic cases showed urticaria (n=2), petechiae (n=1) and pesudo chilblains (n=1). The majority of cutaneous manifestations were seen in mild and moderate disease (Table 3). Livedoid vasculitis was seen in severe disease and the patient succumbed to respiratory illness.

Figure 4: (a) Pseudo chilblains; (b) vesicular eruptions.

Figure 5: :(a) *Herpes zoster*; (b) *Herpes labialis*; (c) gangrene; (d) cellulitis; (e) livedoid vascilitis like lesions.

DISCUSSION

The repercussions of the SARS-CoV-2 pandemic were substantial, impacting millions of patients medically, financially and socially.[7] Dermatologic manifestations of COVID-19 were rare, with common clinical features including fever, dry cough, shortness of breath, myalgia and fatigue seen in relatively large-scale case studies of COVID-19 pneumonia patients.[6] Tay described that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected cells expressing the surface receptors angiotensin-converting enzyme 2 (ACE2) and TMPRSS2.[8] This triggered the generation of pro-inflammatory cytokines and chemokines. These proteins attracted monocytes, macrophages and T cells to the site of infection, promoting further inflammation and establishing a pro-inflammatory feedback loop. ACE 2 was most abundantly expressed in type II alveolar cells followed by epithelial cells of the intestine, kidney, blood vessels. Importantly, Hamming et al demonstrated that ACE2 was also presented in the basal cell layer of the epidermis extending to the basal cell layer of hair follicles, which might explain the cutaneous manifestation of COVID-19.[9]

The mechanisms of COVID-19 cutaneous disturbances were not yet well known but some common theories were prevalent.[10] It can be postulated that the viral particles presented in the cutaneous blood vessels in patients with COVID-19 infection could lead to a lymphocytic vasculitis similar to those observed in thrombophilic arteritis induced by blood immune complexes that activate cytokines. Further theories suggested livedo reticularis-resembling manifestations can result due to the accumulation of micro-thromboses originating in other organs, thus reducing blood flow to the cutaneous microvasculature system.[11] It was still unclear whether cutaneous symptoms were a secondary consequence of respiratory-related infection or primary infection of the skin itself.

Joob et al described in Thailand, the first case of COVID-19 with skin rash with petechiae misdiagnosed as dengue fever. In our study, 2.4% of patients had cutaneous manifestations.[12] In a Chinese COHORT, Guan et al reported 2/1099 (0.2%) cases with a cutaneous rash.[13] In the present study, urticaria was seen in majority (20.5%) followed by purpura (17.9%), pruritus (15.4%), maculopapular rash (7.7%), manifestations secondary to drugs in 7.7% of patients and diffuse hair fall in 7.7% of patients. Vesicular eruptions were probably because of viraemia, pseudo-chilblains because of cytokine storm leading to microangiopathic changes, infections may be due to viraemia or immune-suppression were seen in 5.1% of patients each. Casas et al did a nationwide survey of 375 cases in Spain and classified the dermatological manifestations into five types of clinical patterns: acral erythema with vesicles or pustules; so-called pseudo-chilblains (19%), vesicular eruptions (9%), maculo-papular eruptions (47%), urticaria (19%), livedo or necrosis (6%).[14] Recalcati et al from Italy reported skin manifestations in 20.4% confirmed positive patients which included erythematous rashes (78%) and then urticarial (3 cases) and chickenpox-like vesicles (1 case).[15] Generalized macular or maculopapular exanthem (morbilliform) appeared to be the most common cutaneous manifestation in COVID-19 in a review article by Sachedev et al with 36.1% of patients presenting such lesions on their skin.[9] A papulovesicular rash (vesicles) was seen in 34.7% (25/72) of patients. Urticaria occurred in 9.7% of reported patients and the presence of painful acral red, purple papules with or without vesicles was seen in 15.3% of patients overall. Lastly, 2.8% presented with livedo reticularis lesions and one patient presented with petechiae. Zhang et al Wuhan China reported acro-ischemia presentations including finger/toe cyanosis, skin

bulla and dry gangrene in 7 patients.[16] In Jindal study, which included 458 confirmed COVID-19 cases, the most common cutaneous manifestation was macular/maculopapular rash (42.5%), followed by acute urticaria (17.9%), vesicular rash (15.3%), pseudo-chilblain or acral purpuric lesions (15.1%) and livedo-reticularis (4.4%).[17] Freman et al in their registry, collected 716 cases of new-onset dermatologic symptoms in patients with confirmed/suspected COVID-19.[18] Of the 171 patients in the registry with laboratory-confirmed COVID-19, the most common morphologies were morbilliform (22%), pernio-like (18%), urticarial (16%), macular erythema (13%), vesicular (11%), papulosquamous (9.9%) and retiform purpura (6.4%). In a study done in Italy 22 patients had a papulovesicular rash and they concluded that though rare, it was specific for COVID-19.[19] Sernicola et al reported incidents of toxic erythema and eosinophilia in patients being treated with tocilizumab.[20] Robustelli et al reported cases with acute generalized exanthematous pustulosis and erythema multiforme in patients on treatment for COVID-19.[21]

In our study, 12 patients had cutaneous manifestations when they presented to us, while 27 developed skin lesions later, during the hospital stay. In Casas study nine patients had before, 147 had simultaneously and 77 patients after other symptoms.[14] DeGiorgi in his study, out of 53 patients with cutaneous manifestations, 23 had before and 30 had after other symptoms.[22] In Recalcati et al study, eight patients had skin symptoms at the onset and 10 of them developed it after hospitalization.[15]

In the present study majority of cutaneous manifestations were seen in the mild and moderate disease. Livedoid vasculitis was seen in severe disease and the patient succumbed to respiratory illness as in the Casas et al study. Casas et al and Giorgi et al reported an association between cutaneous manifestations and the severity of COVID-19 infection; both reported that diffuse petechiae, dependent purpura and acral ischemia/necrosis were associated with the severe disease with coagulation defects.[14,22]

The rash should drive the physician to enquire regarding other symptoms of COVID-19 with a proper history and other clinical clues, to decide whether the patient should be tested for the disease. This will ascertain an early diagnosis and treatment in patients who did not have other features of COVID-19. If there were cutaneous manifestations that were pathognomic for infection, they may be sufficient for diagnosis in lieu of testing in geographic areas where test availability was problematic. Due to the lack of enough data and evidence, the typical or diagnostic presentation of the rash in COVID-19 had been a grey area till now.[23] Misdiagnosis of COVID-19 patients can hinder community transmission control efforts because of potential asymptomatic transmission.[24]

Limitations

Data on the duration and severity of the disease was limited to the time when the patient was observed and no follow up was done.

CONCLUSION

The virus continues to spread silently, mainly through asymptomatic carriers. Cutaneous findings like urticaria, acral lesions and petechiae may be vital in identifying these cases and thereby play an important role in limiting the spread. Lesions like livedoid vasculitis may help in assessing the severity. Awareness of COVID-19 cutaneous symptoms helps in preventing misdiagnosis of the disease. We conclude that physicians can consider skin manifestations as an important clinical clue in the diagnosis of patients with COVID-19. However, further studies are required to relate cutaneous findings to disease outcomes in COVID patients.

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