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Title: **Cutaneous manifestations of Coronavirus Disease 2019.**

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Abstract

Background: COVID-19 has been linked to a variety of dermatological conditions.

Objective: To determine the presence of various cutaneous manifestations in patients with COVID-19, also to define their features in relation to the systemic symptoms.

Methods: This research enrolled a total of 1206 lab-confirmed COVID-19 individuals at a tertiary care hospital in Karachi, Pakistan. Expert dermatologists assessed patients for COVID-related skin conditions. COVID-19 severity was categorized as asymptomatic/mild, moderate, or severe.

Results: Of the 102 (85.7%) patients with only one cutaneous sign, 26.5% developed maculo-papular/morbiliform/erythematous rash; 14.7% urticaria; 9.85% vesicular/pustular exanthem; 14.7% vascular pattern; 12.7% infections, 7.8% miscellaneous and 9.8% late cutaneous findings A longer-lasting vascular pattern was related with an older age and a fatal COVID-19 outcomes (P: 0.000) compared to mild/moderate disease. Most of the retiform purpura presented exclusively with thromboembolic episodes. The moderate severity was correlated with maculopapular/morbiliform/exanthematous phenotype (P: 0.009), whereas urticaria was attributed to asymptomatic/mild disease (0.001) compared to moderate/severe infection.

Limitations: Single-Centre and observational study.

Conclusion: Vascular lesions were correlated with disastrous COVID-19 outcomes, whereas retiform purpura was linked to adverse outcomes. The maculopapular/morbiliform/erythematous rash was associated with moderate severity, whilst the urticarial rash was linked to milder course compared to moderate/severe severity infection.

Introduction:

The COVID-19 pandemic caught us all off guard, and the entire globe comes to a halt. People continue to debate whether they should remove the mask or keep it on, and whether or not to put the city on lockdown.[1] On November 06, 2021, the Worldometer reported 250,008,210 cases, 5,057,149 fatalities, and 226,333,168 recoveries. So far during a pandemic, COVID-19 is most recognized for eliciting respiratory symptoms, [2] it has been linked to extrapulmonary symptoms also such as cutaneous manifestations; which have been recorded more frequently in recent months. [3] As COVID-19 is a multi-organ disease that needs multidisciplinary management, dermatologists have been in the frontline of the attempts to comprehend the pandemic's wide spectrum of clinical cutaneous signs. [4] The cutaneous signs of COVID-19, unlike many other symptoms, have been reported in patients of different ages. [5] Even though early case studies rarely identified skin abnormalities, probably due to the inability to conduct a comprehensive cutaneous examination, subsequent research has revealed considerably greater rates of skin involvement. Several reports were published with descriptions of morbilliform, urticaria, erythema multiforme, Kawasaki, Grover's, vasculitis-like, livedo, retiform, and vasculopathy as well as others. [4] [5] A number of these morphologies are associated with various viral infections, on the other hand, in rare circumstances, may point to a person's immunological response or complications. [6] Recently, a review by Freeman et al effectively raises awareness of the numerous dermatologic findings potentially associated with severity of COVID-19 infection. In severely ill patients of COVID-19, the author made the significant finding that retiform purpura, livedo racemosa, and acral ischemia may be signs of a thrombotic event. [7]

Despite the fact that it has only been a year almost since the outbreak began, it appears that we have gone a long way. Because most early descriptions relied on the dermatologist's judgment, a variety of nomenclatures were employed,[8] which leads to the need to create a categorization that is more practical for dermatologists using clinical-pathological correlation. There is a lack of certainty of whether these dermatologic manifestations represented direct infection or were a reactive process with systemic illness or due to medication. Their true frequency and if they can be a diagnostic clue to COVID-19 is yet to be defined. Any links between these phenotypes and the disease course of COVID-19 and if retiform purpura in COVID-19 patients acts as a warning indicator of hypercoagulability. [9][10] These are just a few of the many questions that arise as testing the advancing knowledge of these cutaneous signs and are specific interests to this research, which could aid in the early detection, the identification of the most effective management options and lead to possible better clinical outcomes in COVID-19.

Methods

Study design: This cross sectional cohort study of COVID-19 patients was carried out from 31 July 2020 to 1 August 2021 in a tertiary-care hospital, Karachi, Pakistan. The endorsement was granted from the Institution's Ethics Committee and Board and enrolment with the Clinical Trials was done. Standard informed consent was obtained to record pictures and data from patients themselves or caregivers of ventilated patients. For follow-up, phone calls were made.

Data collection: This study enrolled a total of 1026 outpatients and inpatients with RT-PCR confirmed COVID-2019. Non-probability convenience sampling was used. Epidemiologic and clinical data were obtained from patients or their caregivers. Qualified dermatologists examined patients for COVID-related skin conditions. Epidemiologic data comprised of age, gender, and co-morbidities. Clinical data involved presence or absence of skin lesions, cutaneous symptoms, patterns and duration of skin manifestations if applicable, the appearance of skin symptoms at a specific point in time, presence or absence of systemic symptoms, type and duration of systemic symptoms, the lag between the cutaneous features and systemic symptoms, and severity of COVID-2019. Order of COVID-2019 severity was done as asymptomatic/mild (fever, gastrointestinal symptoms, and/or cough), moderate (findings of pneumonia radiologically or dyspnea) along with progressive rise in inflammatory markers, or severe (the ventilator use, thrombotic event, or death), with inflammatory markers being monitored in each of them.

Inclusion criteria: Patients old enough 20 years or more, polymerase chain reaction (PCR) positive for Severe Acute Respiratory Syndrome - Corona Virus – 2 (SARS-CoV-2), independently of clinical signs and symptoms.

Exclusion criteria: Cutaneous eruptions within 15 days after commencing new medication,[7] prior history of skin, hair, or nail disease, recently (past about fourteen days) immunized for COVID-19, diagnosed case of autoimmune disease, pregnancy or lactating women, known case of malignancy or undergoing chemotherapy, recurrent transfusion history, diagnosed case of malabsorption syndrome and already taking immunosuppressant.

Statistical analysis: Data were analyzed using IBM SPSS version 23. The mean and standard deviation (SD) were calculated for expression for age and duration of disease of the skin. The median and interquartile range (IQR) were calculated for the duration of systemic symptoms, age at the time of disease outcomes and the latent period between the skin manifestations and systemic symptoms. Frequencies and percentages were calculated for the gender, co-morbidities, presence or absence of dermatological and systemic signs, cutaneous patterns, dermatologic symptoms, the appearance of skin signs at a specific point in time, and systemic disease outcomes. Stratification was used to control effect modifiers such as age, gender, weight, co-morbidities, and the duration of symptoms. The chi-square test was used to compute the post-stratification results. A p-value of less than 0.05 percent was defined as significant.

Results:

A total of 1206 COVID-19 subjects with PCR confirmation were recruited for the study, with 119 of them having cutaneous signs (9.9%). The patients were mostly male (n = 62; 52%) and had a median age of 41.34 years when they were diagnosed with COVID-19 (SD: 12.080). At least one comorbidity was experienced by 39 (32.7%) of the 119 cases.

In the 119 individuals, 17 (14.2%) had more than 1 skin morphologies, therefore they were eliminated from the subgroup analysis of patients with laboratory verified COVID-19-related skin manifestations. The lesions of only one cutaneous manifestation (n=102, 85.7%) were categorized as early (less than 6 weeks) and late (more than 6 weeks). The early lesions (n=93, 91%) included: Twenty-seven (26.5 percent) maculo-papular/morbiliform/erythematous rash (Figure: 1a); 15 (14.7 percent) urticaria; 10 (9.8 percent) vesicular/pustular exanthem; 15 (14.7 percent) a vascular pattern: 8 (7.8 percent) retiform purpura, 2 (1.9%) vasculitis (Figure: 1b) , 2 (1.9%) pernio-like lesion, 2 (1.9%) blue toe syndrome (Figure: 1c), and 1 (1.9%) livedo reticularis-like pattern; 13 (12.7%) infections including 5 (4.9%) scabies, 4 (3.9%) tinea, 2 (1.9%) pityriasis versicolor, and 2 (1.9%) herpes zoster and 5 (4.9%) papulosquamous rash. Other cutaneous findings (7.8%) included 2 (1.9%) bullous pemphigoid; 2 (1.9%) erythema multiforme; 2 (2.9%) aphthous ulcer; 1 (0.9%) acral peeling; and 1 (0.9%) pemphigus vulgaris. A few cutaneous signs were reported late (n=9, 8.7%) in the disease in 9 (8.7%) cases: 5 (4.9%) telogen effluvium; 3 (2.9%) beau's lines; and one (0.9%) trichodynia. Patients with multiple morphologies included 13 cases of telogen effluvium plus morbilliform/ urticarial/ vesicular rash and 4 cases of morbilliform rash with urticaria (n: 17; 14.2 percent). The pruritus was the most common cutaneous symptom (n: 49; 58 percent), followed by pain/burning (n: 27; 32 percent) while 9 of the participants experienced no cutaneous symptoms. Table I summarizes the demographic and clinical characteristics of the patients.

The mean (SD) age of 119 participants was 41.3±12.0 years. In the 119 cases, the median lag between cutaneous signs and systemic symptoms was 7 days (IQR: 1-29). The mean (SD) age, duration of various cutaneous signs, as well as the median (IQR) lag between these and systemic symptoms, are shown in Table I.

Among 102 patients, severe COVID-19 had a substantially higher median (median: 56, IQR: 33-75) age than those with mild (median: 26, IQR: 22-45) moderate (median: 40, IQR: 22-66) COVID-19. Seven (47%) individuals with an urticarial rash had gastrointestinal symptoms, but no additional cutaneous category was associated to this subgroup. The majority of the patients (40%) developed skin signs current with the systemic symptoms. Most of the urticarial rashes (60%) appeared before systemic symptoms.

It's worth mentioning that vascular lesions were linked to an elevated incidence of severe COVID-19 (Chi-square =0.000; P =0.000) compared to mild/moderate severity SARS-CoV-2 infection. On the other hand, the urticarial rash was linked to mild COVID-19 (Chi-square =0.001; P =.001), and maculopapular/morbilliform/erythematous rash was associated with moderate severity of COVID-19 (Chi-square =0.010; P =.009). Patients with retiform purpura were critically ill; 100% (n=8) were admitted to the hospital, and 87.5 percent (n=7) had a thromboembolic episode. Two young patients with livedo-reticularis/racemosa who had no comorbidities were admitted to the hospital for a prolonged period and needed invasive mechanical ventilation. The correlation between skin manifestations with severity of COVID-19 is shown in figure 2.

Discussion:

Since the advent of findings on COVID-19-related cutaneous symptoms,[11][12][13] COVID-19 has transformed the workforce and the way dermatologists work and learn, encouraging

patients to get tested by PCR and/or antibody testing.[14] It's been questioned whether all individuals with COVID-19 skin symptoms require skilled dermatologic treatment. [8]

The extensive range of cutaneous symptoms of COVID-19 is highlighted in our study. The most common dermatological phenotypes were maculopapular/morbilliform/erythematous rash (26.5 percent), followed by urticarial and vascular lesions, 15 percent each of the 102 individuals whereas the papulosquamous pattern was the least common (4.9 percent), followed by the infectious group (12.7 percent). The median lag between the emergence of cutaneous signs and the beginning of systemic symptoms was 7 days (ranging from 3 days for maculopapular/morbilliform/erythematous rash to 15 days for vascular lesions). The cutaneous signs lasted an average of 15 days (ranging from 6 days in the case of urticarial rash to 16 days in the case of a vascular pattern).

Infections were incidental non-specific manifestations of COVID-19.

Telogen Effluvium was frequently reported in (n=9) late and more than one cutaneous sign, a finding frequently observed in a recent study. [15]

New-onset bullous pemphigoid and pemphigus vulgaris, the skin manifestations of the miscellaneous group, were reported in 2 and 1 patients respectively; the findings that add into here through prior studies. [16] [17]

Very few of our patients had pernio-like lesions, which was contrary to previous reports. [3][7][18] J Jimenez-Cauhe et al reports erythema multiforme in 4 elderly women, however, they couldn't exclude the involvement of various drugs, [19] although it was documented in 2 young males in our research, it was unclear if they were related to COVID-19 or any other infectious agent.

Exploring the relationship between skin manifestations and the severity of COVID-19 was the key strength of our study. Recent cohort studies of COVID-19-associated dermatological manifestations revealed a progression of more severe systemic symptoms, ranging from chilblain rash to livedo/necrotic lesions. [3][7] However, unlike these studies, our study vascular lesions were linked to an elevated incidence of severe COVID-19 when compared to mild/moderate COVID-19 severity. On the other hand, urticarial rash and maculopapular/morbilliform/ erythematous rash were linked to mild and moderate COVID-19 respectively. These two publications also mention pernio as a common finding, [3] [7] however our study revealed very few cases of pernio-like lesions, probably owing to demographic, racial and environmental variations.

The maculopapular/morbilliform/erythematous rash was linked to moderate severity of COVID-19 in comparison to mild/severe COVID-19. This analysis is opposite to Marzano et al multi-center study who reports severe COVID-19 in association with maculopapular/morbilliform/erythematous rash. [18] Although individuals with severe illness were frequent in the maculopapular/morbilliform/erythematous and vesicular/pustular groups, none of them were substantially linked to a higher probability of COVID-19 severity.

Furthermore, the vascular phenotype was related to an older age at the time of COVID-19 diagnosis, and the majority of the patients with retiform purpura experienced a thromboembolic event (84%), which are consistent with findings in Freeman et al's article (64%).[7] These

occlusive skin lesions may be due to thrombotic illness (87.5%) occurring in our critically unwell patients.

The close connection established in our study between urticarial rash and gastrointestinal symptoms is fascinating because it shows that this pattern is indicative of COVID-19-associated gastrointestinal involvement, an observation that coincides with Marzano et al's article. [18] The relationship between urticarial and intestinal symptoms might be due to "cytokine storm" triggered by SARS-CoV-2.[21] However, no association was found between it and any other cutaneous patterns. According to Algaadi's literature review, urticaria may be a diagnostic sign in COVID-19, [20] which is consistent with our findings.

The single-center and observational data are the study's principal limitations. To corroborate these findings, multi-center researches are needed.

Conclusion:

The study is critical in recognizing various clinical cutaneous manifestations of COVID-19, how cutaneous signs may aid in the diagnosis and understanding of COVID-19, and the evaluation of the associations between dermatological manifestations and COVID-19 severity and offers vital insight to the literature. Our article features that vascular lesions are related to fatal COVID-19 outcomes, while retiform purpura is related to extreme outcomes in critically sick patients. The maculopapular/morbilliform/erythematous rash was related to moderate severity of COVID-19 in comparison to mild/severe disease while the benign course was related to urticarial rash. Very few pernio-like lesions were reported. To validate these findings, multi-centre studies are required.

Abbrevations:

PCR, Polymerase chain reaction

SD, Standard Deviation

IQR, interquartile Range

SARS-CoV-2, Severe Acute Respiratory Syndrome - Corona Virus – 2

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Figure 1: All patient shown had lab-confirmed COVID-19. (a) Macular erythema on trunk of a male patient. (b) Vasculitic ulcers on index and middle finger. (c) Blue toe syndrome due to acral ischemia.

Figure 2: The chart shows relationship between various types of COVID-19 associated skin manifestations with severity of COVID-19.

* Patients with more than one skin manifestation were excluded from the analysis.

Table I: Characteristics of 85* patients with COVID-19 related skin conditions.

*Patients of late, miscellaneous and more than 1 skin manifestations were excluded from the analysis.

** Percentages of 102 patients with only one skin morphology.

IQR, Interquartile Range

P-value, Probability value

SD, Standard Deviation

Table I: Characteristics of 85* patients with COVID-19 related skin conditions.

Characteristics	Maculo-papular rash	Urticaria	Vesicular/Pustular	Vascular	Infections	Papulos-qumaous
Cutaneous patterns, n %	27 (26.5)	15 (14.7)	10 (9.8)	15 (14.7)	13 (12.7)	5 (4.9)
Age, years, mean ± SD	38.9±11.5	40.4±11.5	46.7±7.8	56.2±11.4	34.6±14.2	31.4±8.3
Duration of Skin manifestations, days, mean ± SD	15.85 ± 4.0	6.3 ± 2.3	13.5 ± 2.7	16.5 ± 4.7	13.3 ± 2.3	10.4 ± 2.7
Onset of rash, n (%) Before systemic symptoms After systemic symptoms With systemic symptoms Without systemic symptoms	5 (18.5) 6 (22.2) 14 (51.8) 2 (7.4)	9 (60) 1 (6.6) 3 (20) 2 (13.4)	1 (10) 5 (50) 4 (40) ----	1 (6.6) 5 (33.3) 8 (53.3) 1 (6.6)	---- 8 (61.5) 5 (38.5) ----	2 (40) 1 (10) ---- 2 (40)
Duration of systemic symptoms (days, median (IQR))	24(14-45)	14(7-24)	12(7-19)	33(12-57)	12(6-21)	10(8-15)
The lag between skin signs & systemic symptoms days, median, IQR	3(2-29)	6(1-22)	6.50(5-12)	15(2-18)	8(3-14)	6(7-16)
Skin Symptoms n (%) Asymptomatic Pain/burning Pruritus	3 (11) 5 (18.5) 19 (70.4)	---- 6 (40) 9 (60)	2 (20) 1 (10) 7 (70)	2 (13.3) 13 (86.6) ----	---- 2 (15.4) 11 (84.6)	2 (40) ---- 3 (60)

*Patients of late, miscellaneous and more than 1 skin manifestations were excluded from the analysis.

** Percentages of 102 patients with only one skin morphology.

IQR, Interquartile Range

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SD, Standard Deviation

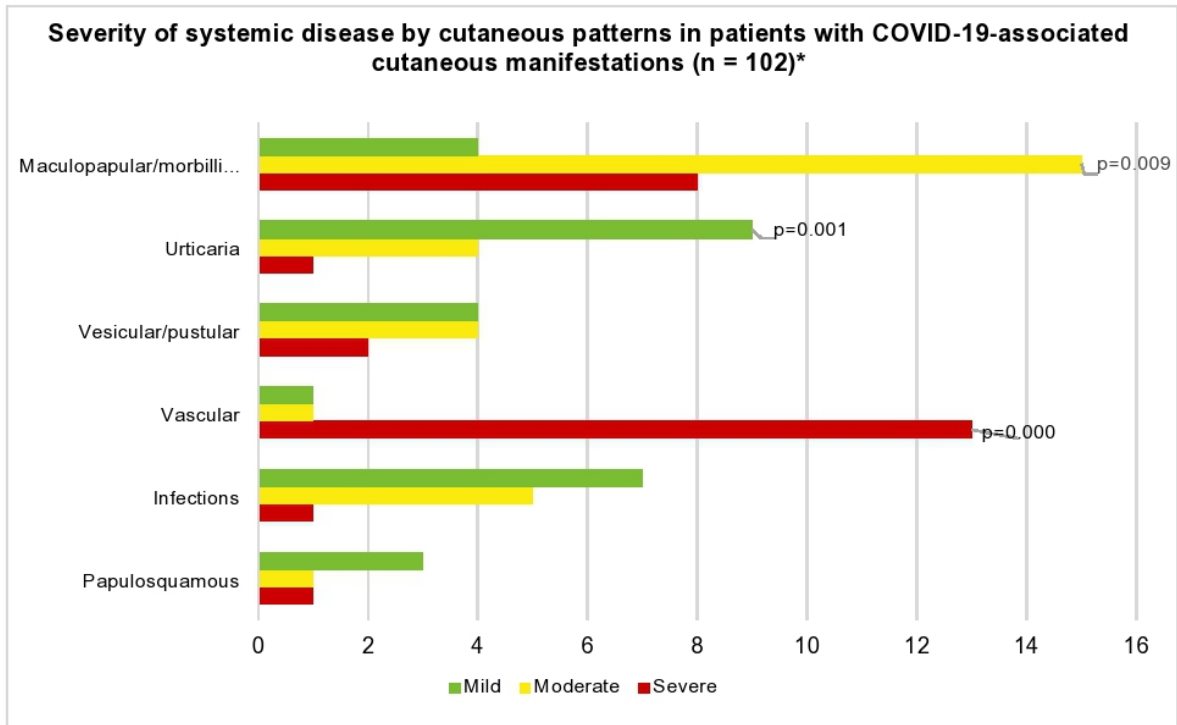JOCD_15258_covidpic (2).jpg

Figure 2: The chart shows relationship between various types of COVID-19 associated skin manifestations with severity of COVID-19.

* Patients with more than one skin manifestation were excluded from the analysis.