FREQUENCY OF CUTANEOUS MANIFESTATIONS IN COVID-19

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ABSTRACT

Objective: To provide an insight into the frequency of cutaneous manifestations in patients with Corona Virus Disease of 2019 (COVID-19), along with an association of these findings with the severity of the disease.

Study Design: Cross-sectional study.

Place and Duration of Study: Tertiary care hospital, Rawalpindi Pakistan, from May to Jul 2020.

Methodology: We collected data from 412 confirmed cases of COVID-19 patients directly who were >12 years of age. The data included names of patients, their genders, ages, dates of admission, severity category, presence or absence of symptoms and cutaneous findings along with description of cutaneous findings if present. The data was evaluated using Statistical Package for the Social Sciences (SPSS) version 23.

Results: Eleven out of the total 412 patients with COVID-19 included in our study were found to have cutaneous findings. The frequency of cutaneous manifestations associated with COVID-19 was calculated to be 11 (2.7%). Increasing age proved to be positively correlated with increasing severity of the disease whereas no association was found between gender and severity of the disease.

Conclusion: Infection with COVID-19 may result in dermatological manifestations with various clinical presentations, which may aid in better understanding and management of the disease.

Keywords: COVID-19, Cutaneous manifestations, Frequency, Skin findings.

INTRODUCTION

The Corona Virus Disease-2019 (COVID-19), is caused by the novel Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). Initially, pneumonia of unknown etiology was reported in a large group of patients in Wuhan, China, in December 2019. The high rate of infection and asymptomatic transmission has resulted in a pandemic arising from its rapid spread. SARS-CoV-2 is an enveloped virus composed of a single-stranded ribonucleic acid (RNA) and belongs to the Coronaviridae family[1]. Disease confirmation is achieved by detecting viral RNA in nasopharyngeal swabs or bronchoalveolar fluid by reverse transcriptase polymerase chain reaction (RT-PCR)[2].

Infection with SARS-CoV-2 can be asymptomatic or cause a wide range of symptoms, from mild symptoms of upper respiratory infection to life-threatening sepsis. Interestingly, in patients with COVID-19, different cutaneous manifestations have been observed. The understanding of the pathogenesis of the skin lesions is still under evolution, though it appears to be an inflammatory process primarily[3-6]. The demonstration of SARS-CoV-2, by immunohisto-chemistry and electron microscopy, in endothelial cells of lesional skin biopsies in a small series of pediatric patients, suggests a virus-induced vascular injury as a possible mechanism of pathogenesis[7]. Further theories suggest that the manifestations resembling livedo reticularis can result due to micro thromboses as occurs in other organs, therefore, blood flow to the skin microvasculature system is decreased[8]. In larger studies, however, these results need to be confirmed.

The prevalence of dermatologic manifestations is still being evaluated. The reported prevalence of these dermatologic findings in some specific regions ranges from 9 (0.2%) to 10 (20.4%). In Pakistan, little work has been done on the assessment of prevalence of cutaneous manifestations of COVID-19 till date. Although, COVID-19 skin manifestations are uncommon, they are of major benefit to all clinicians, as their knowledge can lead to earlier diagnosis and better disease management, both in asymptomatic and mildly symptomatic patients and to assess the burden of disease from dermatological point of view. We conducted this study with the objective to report the number of patients who were diagnosed with COVID-19 and had associated dermatologic manifestations and thus estimate the frequency of cutaneous manifestations in COVID-19.

METHODOLOGY

We conducted this cross-sectional study at Pak Arab Emirates Military Hospital Rawalpindi, which

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has been exclusively dedicated to screen and manage the patients with COVID-19 infection, to estimate the frequency of cutaneous manifestations in COVID-19. The duration of the study was 3 months (May to July 2020). The study was authorized by the ethics committee of the same hospital (A/28/EC/163/2020). The evaluation of clinical patterns has been done only on the basis of morphology by experts in dermatology.

By using open epi sample size calculator, at 20% prevalence of cutaneous manifestations in patients with COVID-19[9,10], by keeping 95% confidence interval and 5% margin of error, the calculated sample size is 246. To have more enriched results we increased the sample size and collected data from 412 patients directly who were confirmed cases of COVID-19. All of them had positive polymerase chain reaction (PCR) for SARS-CoV-2 RNA and were >12 years of age. Consecutive sampling technique was used. We collected names, genders, ages, dates of admission, severity category, presence or absence of symptoms and cutaneous findings along with description of cutaneous findings if present. We excluded 1 patient based on the presence of previous skin disease; the patient had tinea cruris for the past 2 months. All symptomatic patients with negative PCR for SARS-CoV-2-RNA and high resolution computed tomography (HRCT) Scan of chest non-suggestive of COVID-19 were also excluded. The patients were divided into two major groups; asymptomatic and symptomatic, then further divided according to the severity category of the disease. The disease was categorized according to the criteria adapted from the management published by Liang *et al*[9]. All asymptomatic cases were categorized under "mild" disease. The symptomatic cases included all the three categories; Mild, Moderate and Severe. Photographic evidence was also recorded for most of the cutaneous findings in patients with COVID-19. Informed consent was given by the patients themselves, or the next of kin of mechanically ventilated patients, for their participation and use of their pictures in publications.

The data was entered and analyzed in Statistical Package for the Social Sciences (SPSS) version 23. Continuous variables were presented in the form of Mean ± Standard Deviation (SD) and categorical variables were presented in the form of frequency and percentages. Data was stratified according to gender and severity of disease. Independent sample t-test was applied for the comparison of continuous dependent and independent variables with two categories. One way Analysis of Variance (ANOVA) was applied for the comparison of continuous dependent and independent variables with more than two categories. For comparison between categorical variable, Chi square and Fisher's Exact tests were applied. Probability value (*p*-value) ≤0.05 was considered to be significant.

RESULTS

We included 412 patients in our study, with the mean age of 44 ± 16.32. Out of these, 42 (10.2%) were females and 370 (89.8%) were males with the mean age of 48.45 ± 17.397 and 43.49 ± 16.142 respectively (*p*=0.06). Out of 412 patients, 294 (71.4%) had mild, 85 (20.6%) had moderate and 33 (8.0%) of the patients had severe disease and there was no association between the gender and severity of disease (*p*=0.107). In mild disease category, 101 (34.4%) patients were symptomatic and 193 (66%) were asymptomatic. Frequency of cutaneous manifestations in our study population was 2.7% (11/412), out of which 10 (91%) and 1 (9%) were males and females respectively. However, no gender based significant association was observed (*p*=1.000) (table-I).

Table-I: Comparison of frequency of disease severity and presence of cutaneous manifestations based on gender.

Variables		Gender		*p*-value
		Male: 370 (89.8%)	Female: 42(10.2%)	
Age		43.49 ± 16.142	48.45 ± 17.397	0.06
Disease Severity	Mild	268 (65%)	26 (6.3%)	0.107
	Moderate	71 (17.2%)	14 (3.4%)	
	Severe	31 (7.5%)	2 (0.5%)	
Cutaneous Symptoms	Yes	10 (2.4%)	1 (0.2%)	1.000
	No	360 (89.8%)	41 (100%)	

Table-II: Association of age and presence of cutaneous symptoms with the severity of disease.

Variables	Disease			*p*-value
	Mild	Moderate	Severe	
Age	39.05 ± 13.52	54.96 ± 16.65	59.76 ± 14.82	<0.001
Cutaneous, Yes	1 (0.2%)	2 (0.5%)	8 (1.9%)	<0.001
Symptoms, No	293 (71.1%)	83 (20.1%)	25 (6.1%)	

In our study population, patients with the mild disease had mean age of 39.05 ± 13.52 which was lowest mean age amongst the all three categories of disease severity. Hence increasing age was found to be significantly associated with increasing severity of disease (*p*-value<0.001). When the cutaneous symptoms were stratified according to the disease severity, a positive association was seen. The patients with severe disease were found to have cutaneous symptoms more than the other two categories (*p*-value<0.001) (table-II).

The skin lesions included herpes labialis in the patient with mild COVID-19. Viral exanthem (macular rash) and vasculitic rash was seen in patients with moderate disease. Livedo reticularis was found to be associated with severe disease (table-III).

Table-III: Frequencies and morphologic types of rash among COVID-19 patients (n=11).

Morphology of Cutaneous Findings	n(%)
Herpes labialis	1 (9.09)
Erythematous atypical targetoid eruptions on hands	1 (9.09)
Acral areas of erythema-edema (pseudo-chilblain)	2 (18.18)
Macular/Maculopapular rash (purpuric/perifollicular)	5 (45.46)
Livedo reticularis	2 (18.18)

DISCUSSION

We have described the occurence of the cutaneous manifestations in COVID-19 along with an account of the skin findings that contributed to the estimation of frequency, in a tertiary care hospital in the city Rawalpindi of Pakistan. According to this study, the estimated frequency is 2.7% and was found to be positively associated with the increasing severity of the disease.

Cutaneous manifestations are considered one of the many presentations of COVID-19[11]. There has been a steady increase in the literature regarding the various dermatologic manifestations of COVID-19. There is still little data available on the prevalence of the skin manifestations. Most of the work done includes case reports and case series. With the involvement of dermatologists in the management of the disease, the interest in the cutaneous signs of SARS-CoV-2 infection also increased.

Recalcarti *et al*[10], in the report on 88 COVID-19 patients, documented cutaneous findings in 18 patients (20.4%) of whom 8 patients developed dermatologic signs at the onset and 10 patients after the hospitalization but neither histology was available nor photo-graphs were taken. Whereas the study from Central China by Guan *et al*[9], al reported low prevalence of cutaneous signs in COVID-19 patients. Only 0.2% of the 1099 confirmed cases in Wuhan had skin findings. A thorough review of the skin lesions is not given in this report. In our study, 2.7% of the patients with COVID-19 had cutaneous findings. These skin manifestations included herpes labialis, acral areas of erythemaedema (pseudochilblain), erythematous atypical targetoid eruptions on hands, macular rash on legs, maculopapules (some purpuric and some perifollicular) and livedo reticularis (fig-2). Most of these skin lesions corresponded with the clinical patterns described by Casas *et al*[12].

Another study from Thailand reported that dermatologic signs were present in nearly all COVID-19 patients[13]. In a study carried out in a hospital in Spain, 58 out of the 2761 patients (2.1%) either consulting to the emergency room or admitted to the hospital for COVID-19 suspicion during the study period presented COVID-19 related skin lesions[14]. In another study performed in France in 103 patients, 5 of these (4.9%) had skin signs of erythematous or urticarial rashes, mainly in the face and upper trunk[15]. The reason for these different results is not clear. A possible explanation to this is the setting in which the patients were managed. Patients admitted with severe disease in intensive care unit (ICU) will be given more consideration to all their possible clinical findings against those with mild disease being managed in an outpatient facility.

Figure-1: All of the patients were confirmed cases of corona virus disease-2019. (A) herpes labialis. (B) erythematous atypical targetoid eruptions on hands. (C) acral areas of erythemaedema (pseudochilblain).

The sample size of this study is potentially representative of the general distribution of cutaneous signs in COVID-19, given the large number of patients. In addition, we have correlated the frequency with the

Figure-2: All of the patients shown had confirmed Corona Virus Disease-2019. (Figure-2A, 2B) macular rash. (Figure-2C, 2D, 2E) Maculopapular rash. (Figure-2F, 2G, 2H, 2I, 2J, 2K) Livedo reticularis in patients with severe COVID-19.

severity of symptoms. We attempted to identify the lesions in less severe cases to draw attention towards the paucity of cutaneous signs in patients with mild disease in our region. This also highlights that these findings contribute less in making a diagnosis of COVID-19. Livedoid or necrotic lesions arise late in the course of the disease and are potentially informative for assessing the severity of the disease. They are consistent with vascular damage caused by COVID-19. A state of hypercoagulability has been proposed behind this manifestation[16,17]. We have also given a brief description of the cutaneous findings along with a pictorial evidence, to provide knowledge about the cutaneous manifestations of COVID-19. In addition, it has been observed that most of the patients with mild disease were in the lower age range as compared to those with severe disease. This is in accordance with the previous researches which have indicated that the risk of significant COVID-19-associated illness is higher in older patients[18].

LIMITATION OF STUDY

Limitation of this study is that the data on severity of the disease is restrained to the time when the patient was observed. However, our study included any inexplicable skin lesions in patients with COVID-19, so there is a possibility that some of them had alternative causes, against this, we took a detailed history of any skin eruption or disease in the past. We propose that further research could be pursued by having more investigations to exclude other infections and by describing the histopathological findings of the skin lesions.

This article implicates that although the cutaneous manifestations of COVID-19 are not frequent, they are of great importance for the dermatologists, as the enhanced awareness of skin manifestations will improve their ability to deliver better clinical care. This could also help to assess the burden of disease from dermatological point of view. As per this study in our

region, the dermatologic involvement is minimal in asymptomatic or paucisymptomatic patients as compared to the prevalence estimated by Recalcati *et al*[5]. In most of the cases, skin lesions constitute a late manifestation of COVID-19.

CONCLUSION

Knowledge about the frequency of cutaneous manifestations of COVID-19 will enable clinicians, including the dermatologists to have high index of suspicion of the diagnosis in patients with dermatologic involvement. This will lead to better management of the disease. Dermatologic manifestations are more prevalent in severe disease explained by extensive involvement of the cutaneous microvasculature. This study indicates that the spectrum of clinical features associated with this infection should take into account these dermatologic signs.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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