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Dermatological Manifestations of COVID-19 Patients

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Abstract

Background: COVID-19 is a highly contagious respiratory tract infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in China, in December 2019. Almost 10% of the patients develop dermatological manifestations before the onset of respiratory illness, with cutaneous signs that can appear from before to several days after the diagnosis of COVID-19. We believe that the dermatologist can play an important role through early recognition of skin lesions suggestive of COVID-19, particularly in asymptomatic infections where this recognition could direct toward an early diagnosis of infection that certainly leads to a better prognosis.

Objective: To explore the pattern of dermatological manifestations among COVID-19 Bangladeshi patients.

Materials and Methods: A cross sectional study was carried out May 2020 to October 2021 with COVID 19 positive hospital admitted patients. Data were collected through a group of Dermatologists who were serving at

COVID dedicated Hospitals. Dermatologists, who were working in different medical college hospital and health complexes, were attached with the study as research associate.

Results: Among the muco-cutaneous findings, maculopapular eruption 52(53.6%) was the most common, followed by chilblain like eruption 40(41.2%), petechiae or purpura 16 (16.5%), urticarial lesions 13(13.4%), vesicular lesion 10(10.3%), Bilateral conjunctivitis with clear/mucoid discharge 10 (10.3%), aphthous stomatitis 13 (13.4%), Alopecia 16(16.5%), Darkening of the face 13 (13.4%), Eczematoid reaction 13 (13.4%), livedo reticularis like eruption 5(5.2%) etc.

Conclusion: The major dermatological patterns of COVID-19 can be classified as inflammatory reactions (maculopapular, urticarial and vesicular rashes), or lesions of vascular origin (chilblain like rashes, petechiae/purpura, and livedo reticularis like pattern).

Keywords: COVID-19, Maculopapular Rash, Urticarial Rash, Chilblain like Rash, Purpura

Introduction

On 29 December 2019, a novel coronavirus, designated SARS-CoV-2, was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China among people with history of direct contact with wildlife [1]. It spreads rapidly, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world [2]. On January 30, 2020, the WHO declared the COVID-19 outbreak a public health emergency of international concern. In February 2020, the World Health Organization designated the disease COVID-19, which stands for coronavirus disease 2019 [3]. Pneumonia appears to be the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging [4,5]. However, other features, including upper respiratory tract symptoms, dyspnea, dry cough, fatigue, anorexia, myalgias, diarrhea, smell or taste disorders, sputum production are also common. Other reported symptoms have included headache, sore throat and rhinorrhea. Conjunctivitis has also been described [6]. COVID-19 pandemic hit the entire world with severe health and economic consequences. Although the infection primarily affected the respiratory system, it was soon recognized that COVID-19 has a multi-systemic component with various manifestations including dermatological involvement. Dermatological manifestations may appear to both asymptomatic patients and severe patients [7].

The estimated incidence of cutaneous manifestations secondary to COVID-19 is between 4% and 20.4% [8]. The skin manifestations associated with COVID-19 infection are numerous and can vary widely and are not well characterized. There have been reports of maculopapular, urticarial, and vesicular eruptions and transient livedo reticularis [9, 10]. Reddish-purple nodules on the distal digits similar in appearance to pernio (chilblains) have also been described, mainly in children and young adults with documented or suspected COVID-19 [9]. The skin manifestations are similar to cutaneous involvement occurring during common viral infections. Skin eruptions appear with onset of symptom of COVID-19 or after hospitalization. Red rashes, widespread urticaria, and chickenpox-like vesicles may develop. The most commonly affected area may be the trunk and itching may be mild or absent and lesions usually healed up in a few days [10]. COVID-19 can feature signs of small blood vessel occlusion- these can be petechiae or tiny bruises and non-pruritic blanching, transient, unilateral, livedoid eruptions. It suggests vaso-occlusion. Whether it's neurogenic, microthrombotic or immune complex mediated, but it's a skin finding that can help clinicians as they work up their patients with COVID-19 symptoms [11].

The diagnosis of COVID-19 is made by detection of SARS-CoV-2 RNA by reverse transcription polymerase chain reaction (RT-PCR) [2]. This standard test uses respiratory secretions collected using a nasopharyngeal swab. This test uses real-time rRT-PCR which detects presence of viral RNA fragments [4, 8]. Bangladesh is a developing country and majority of the people are in low socioeconomic condition. Our study explored pattern of skin manifestations among the COVID-19. Therefore, it becomes prudent for the dermatologists as well as primary health care physicians to be aware of the cutaneous manifestations of COVID-19 to prevent misdiagnosis and missing the cases if skin involvement precedes other symptoms.

Materials and Methods

A cross sectional study was carried out May 2020 to October 2021 with COVID 19 positive patients with the aims to explore the pattern of dermatological findings among COVID 19 positive Bangladeshi patients. Data were collected from COVID 19 positive hospital admitted patients either males or females of all age through our research associate. Data were collected through a group of Dermatologists who were serving at COVID dedicated Hospitals like Kurmitola General Hospital, Combined Military Hospital (CMH), Kuwait-Bangladesh Friendship govt hospital, Mugda Medical College Hospital, Dhaka Medical College Hospital, Rajarbag police hospital and Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Dermatologists who were working in different medical college hospital and health complexes, were attached with the study as research associate. A semi structured data collection sheet was the Research instrument.

Among the total number of 2000 patients with COVID-19 positive, only 97 patients had skin manifestations and they were agreed freely to give their informed consent and finally were selected for the study. Prior to the commencement of this study, approval from Institutional Review Board (IRB) was taken. Consecutive type of non-probability sampling was the Sampling technique. Before enrollment of the

patients into the study, the aims and objectives of the study along with its risks and benefits of this study were explained to the patients in easily understandable local language, so that they can make independent decision about their participation. All the participants were elaborately informed about the natural history and the prognosis of their disease. The patients were assured that all information and records will be kept confidential, and the study results will be helpful for both the patients and the physicians in making rational approach of the case management and control of this health issue. The patients were explained that they have the right to refuse or accept to participate in the study in its any stage and it do not hamper their treatment procedure and they will not receive financial benefit from this study. Finally, the informed written consent was taken from each of the patient. Participant data without names and identifiers were made available after approval from Institutional Review Board (IRB). Patient unwilling to participate in this study, suspected COVID-19 case and COVID positive patients but expired were excluded from the study. Researchers directly communicated with patients and their families to ascertain epidemiological factors, dermatological factors, laboratory, radiological and CT characteristics of laboratory-confirmed COVID-19 positive cases. Statistical analysis of the results was obtained by using window-based computer software devised with Statistical Packages for Social Sciences (SPSS-22) (SPSS Inc, Chicago, IL, USA).

Results

This cross-sectional study was conducted during the period of May 2020 to October 2021. A total of ninety-seven COVID-19 patients were included in this study. The observations and results were as follows:

Table 1: Distribution of the study patients by age and sex

Age	Percentage
<20 years	1(1.0%)
21-30 years	12(12.4%)
31-40 years	21 (21.6%)
41-50 years	27(27.8%)
51-60 years	36(37.1%)
Gender	
Male	72(73.2%)
Female	25(26.8%)

Table I: Showed that majority of the patients 36(37.1%) belonged to the age group 51-60 years followed by 27(27.8%) in the age group 41-50 years, 21(21.6%) in the age group 31-40 years, 12(12.4%) in the age group 21-30 years and 1(1%) was in the age group of <20 years. Regarding gender, most of the patients 72 (73.2 %) were male and female was 25(26.8 %).

Table 2: Mucocutaneous manifestations in COVID-19 patients (n=97)

Mucocutaneous manifestation in COVID-19 patients	Percentage (%)
Maculopapular eruption	52(53.6%)
Chilblain like lesion	40(41.2%)
Urticarial eruption	13(13.4%)
Vesicular eruptions	10(10.3%)
Petechiae/purpuric eruption	16(16.5%)
livedo reticularis like eruption	5(5.2%)
Bilateral conjunctivitis with mucoid discharge	10(10.3%)
Multiple erythematous and violaceous plaques	3(3.1%)

Swelling of the hands, feet, and eyelid	3(3.1%)
Aphthous stomatitis	13(13.4%)
Pityriasis rosea like eruption	5(5.2%)
Alopecia	16 (16.5%)
Lichenoid eruption	5(5.2%)
Darkening of the face	13(13.4%)
Cheilitis	5(5.2%)
Oral pigmentation	2(2.1%),
Eczematoid reaction	13(13.4%)
Pityriasis Versicolor like eruption	5(5.2%)

Multiple response*

Table 2: Showed that among the muco-cutaneous findings, maculo-papular eruption 52(53.6%) were more common, followed by chilblain like eruption 40(41.2%), petechiae/purpura 16 (16.5%), urticarial lesions 13(13.4%), vesicular lesion 10(10.3%), livedo reticularis like eruption 5(5.2%), Bilateral conjunctivitis with clear/mucoid discharge 10 (10.3%), Multiple erythematous and violaceous nonblanching plaques 3(3.1%), Swelling of the hands, feet, and eyelid 3(3.1%), aphthous stomatitis 13 (13.4%), Pityriasis rosea like eruption 5(5.2%), Alopecia 16(16.5%), Lichenoid eruption 5(5.2%), Darkening of the face 13 (13.4%), Cheilitis 5(5.2%), Oral pigmentation 2(2.1%), Eczematoid reaction 13 (13.4%) and Pityriasis Versicolor like eruption 5(5.2%).

Discussion

The main objective of this study was to evaluate the patterns of dermatological manifestations among COVID-19 patients who required hospitalization. Among the muco-cutaneous findings, maculo-papular eruption 52(53.6%) was more common in our study. Maculopapular lesions are the most prevalent cutaneous manifestations seen throughout the COVID-19 pandemic, being observed up to 70% of patients by Annunziata *et al* [12]. A case series of 375 patients with skin lesions associated with COVID-19 by Galvan Casas *et al* identified a 47% prevalence of maculopapular lesions [13]. Studies of Herrero- Moyano, Reymundo *et al* and Rubio Muniz *et al* were reported the maculopapular rashes in middle-aged patients [14, 15, 16]. Anatomically, the majority of these lesions were located on the trunk of the body [14, 15]. The case series from Spain reported simultaneous onset of maculopapular lesions with COVID-19's symptoms [13], while other studies had noticed a later onset in their populations (average latency times of 27 days) [14]. The exanthems lasted for a short period (from 8.6 to 11.6 days) [13, 14, 15]. Galvan Casas *et al*. reported that pruritus was present in 56% of patients with maculopapular lesions and suggested that maculopapular rashes are associated with greater severity of COVID-19 infections [13]. A hypothesis on the etiopathology of these manifestations involves adverse drug reaction, considering that many drugs (e.g., chloroquine, hydrochloroquine, lopinavir/ritonavir), used in the treatment of COVID-19 infection are responsible for maculopapular rash [17] and this agrees with the fact that lesions occur more frequently in patients with more severe infections and who have therefore taken more medication [13]. Herrero-Moyano *et al*. hypothesized that these rashes could be caused by a cytokine storm produced by a hyperactive immune system against the virus [14]. Urticarial lesions were found 13(13.4%) among our study patients. It is one of COVID-19's most frequent cutaneous manifestations. These lesions are typically distributed on the

trunk or limbs reported by Galvan Casas *et al* and dalal *et al* [13, 18]. Askin *et al* reported that, the rash can be generalized across the entire body or localized to the face [19]. Onset is thought to occur at the same time as other systemic symptoms of COVID-19 with an average duration of 6.8 days and more severe COVID-19 cases. Pruritus is reported in 92% of patients with urticaria, revealed by Galvan Casas *et al* [13]. Anti-COVID-19 drugs such as chloroquine, hydroxychloroquine, lopinavir/ ritonavir, corticosteroids, baricitinib, IVIG treatments, have urticaria as a side effect [17]. Moreover, another possible pathophysiological mechanism leading to urticaria could be the 'cytokine storm' [20].

Chilblain like eruption was found 40(41.2%) in our study. Freeman *et al*. documented 505 patients with dermatologic manifestations associated with COVID-19, including 318 (63%) with pernio-like lesions [21]. Other studies have reported prevalence between 14.3% and 72% [13, 19, 21-23]. Chilblain-like lesions or pernio-like lesions represent late manifestations of COVID-19 and, in contrast to other COVID-19-related skin manifestations, they are more often reported in children and young adults [21-25]. These manifestations typically occur later in the course of the infection and last longer (for about a week or two on average) than erythematous rashes and usually appear in asymptomatic patients or with mild COVID-19 disease [13, 21]. As for clinical manifestations, pain, pruritus, and burning are the symptoms frequently recorded in patients with pernio-like lesions [21, 22]. Pathogenesis behind chilblain could involve host viral response, vasculitis, vessel thrombosis, or neoangiogenesis [26].

Vesicular lesion was 10(10.3%) in our study. Vesicular lesions among COVID-19 patients reported in different studies range from 3.77% to 15%. These manifestations are typically seen in middle-aged patients [13, 19, 27, 28]. The trunk of the body is commonly affected in the localized forms of this type of rash; however, a diffuse pattern is described with polymorphic lesions also involving the extremities [13, 19, 29, 27, 28]. The time of onset of cutaneous manifestations relative to other COVID-19 symptoms to vesicle eruption was 14 days (range 4–30 days) [13, 30]. Duration of rash reported by various studies ranged between 8 and 10 days [13, 28, 30]. Vesicular lesions result to be associated with intermediate severity of COVID-19 [13, 27]. The pathophysiologic mechanisms involved with vesicular lesions could be based on an overactivation of the immune system causing a 'cytokine storm' affecting the skin [27]. Another possible event behind the formation of vesicles is the direct cytopathic effect of SARS-CoV-2 on endothelium dermal vessels [20]. As opposed to maculopapular and urticarial rashes, vesicular lesions associated with COVID-19 are considered unrelated to antiviral medications [27]. Moreover, vesicular lesions have been described as 'specific cutaneous manifestations' of COVID-19 [28].

Petechiae/purpura was found 16 (16.5%) in our study, not similar to the study of Askin *et al*. They performed a retrospective study which reported that petechial patterns were present in only 3% of patients and localization of the lesions included trunk and extremities [19]. Petechiae/purpuric lesions onset is reported to be after COVID-19 symptoms [16, 31]. Various studies reported that palpable purpuric lesions are more frequent in middle-aged patients recovering from severe COVID-19 infections [29, 31].

Proposed pathogenesis for petechiae/purpura skin lesions involves a pauci-inflammatory thrombogenic vasculopathy. Magro *et al* examined skin tissues from three patients with severe COVID-19 characterized by respiratory failure and purpuric skin rash that displayed a pauci-inflammatory thrombogenic vasculopathy, with deposition of C5b-9 and C4d in both involved and normally appearing skin. In addition, there was co-localization of COVID-19 spike glycoproteins with complement components. Adverse dermatological effects associated with COVID-19 drugs can be an aetiologic hypothesis, considering petechiae usually occur in patients with severe forms of COVID-19. Finally, a direct cutaneous manifestation from SARS-CoV-2 could be a possibility considering petechiae are the result of other viral infections such as parvovirus B19 and dengue virus^[31]. About 5(5.2%) was found livedo reticularis like eruption, similar to the study of Galvan Casas *et al*. In their study of 375 COVID-19 patients with cutaneous manifestations, only 6% of them presented with livedo reticularis-like pattern^[13]. These lesions are generally localized on the trunk, flexor surface of forearms, dorsal hand, and dorsal foot^[13, 26, 32]. These lesions occurred at the same time as other COVID-19 symptoms and appeared in elderly patients with severe infections. Mean duration of this lesions was 9.4 days^[13, 26, 32]. As for the pathogenesis, the relationship of hypercoagulability to COVID-19 infections is a possible mechanism, confirmed by the presence of higher D-dimer and fibrin degradation product levels in patients with severe COVID-19 and livedoid lesions^[33]. The mortality rate among patients with livedoid lesions resulted to be the highest of all cutaneous manifestations at 10%^[13]. About 16(16.5%), was found Alopecia in COVID-19 patients in our study, similar to the study of Olds *et al* and Christensen *et al*^[34, 35]. Olds *et al*. Retrospectively reviewed medical records of 552 patients with a diagnosis of COVID-19 infection^[34]. Ten patients were identified with telogen effluvium (TE) attributed to COVID-19 infection, 90% female. On average, the hair shedding began 50 days after the first symptoms^[34]. Moreover, COVID-19 may play a role in various immune-related dermatologic conditions. Alopecia areata is thought to be a dermatologic manifestation of COVID-19, with cases most often appearing 1–2 months following infection^[35].

Conclusions

Dermatological manifestations of COVID-19 are variable. Maculopapular eruption, chilblain like lesions, petechiae or purpura, urticarial eruption, vesicular lesion, bilateral conjunctivitis with clear/mucoid discharge, alopecia, aphthous stomatitis, darkening of face, eczematoid reaction and livedo reticularis like eruption were found the most common dermatological manifestations and skin findings can be clues to diagnosis in case of COVID-19 infection.

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