

Skin Manifestations in Confirmed COVID 19 Patients; A Short Prospective Multicenter Case Series Cohort Study

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Introduction

Coronaviruses are enveloped non-segmented RNA viruses belonging to the family Corona viridae. In December, 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China, with clinical presentations greatly resembling viral pneumonia [1].

The disease has rapidly spread from Wuhan to other areas in China. Internationally cases have been reported in 24 countries and 5 continents. So in January 2020, the 2019 novel coronavirus (2019-nCoV - SARS-CoV-2) has been reported. It was identified in samples of bronchoalveolar lavage fluid from a patient in Wuhan [2]. Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus, which was named 2019 novel coronavirus (2019-nCoV).

COVID-19 outbreak, globally, had a significant impact on the medical approaches among different specialties. Current global pandemic has been implicated in a plethora of dermatological manifestations, such as pseudo-chilblain, vesicular, urticarial, maculopapular, and livedo/necrosis-type lesions [3]. These cutaneous manifestations which are suggesting clues of COVID-19 infection are of great importance, as several articles have been introduced patients with primary skin, mucosal, and nail complaints as an initial or evolving presenting signs of COVID-19 [4,5]. Maculopapular eruptions, urticaria, or the acral vasculopathic rashes (pseudo chilblains, pernio-like lesions) recognized as the "COVID toe", are the most common mucocutaneous manifestations of new corona virus; while the patients usually develop the common symptoms of COVID-19, few days after the initiation of these skin eruptions [5]. A recent Spanish study including 375 cases, five clinical patterns were described: maculopapular eruptions (47%), acral areas of erythema with vesicles or pustules (pseudo-chilblain) (19%), urticarial lesions (19%), other vesicular eruptions (9%) and livedo or necrosis (6%) [6]. The lesions are mainly localized in the trunk and extremities (hands and feet), sparing the face; however, lesions located on the face, neck, mouth and axillary folds have also been reported. The majority of patients were male, aged between 4.5 and 89 years. Another study has showed that affected patients were mainly adults, a minority of patients were children (between 4.5 and

14 years) and were presenting with acral, chilblain-like lesions, papulo-vesicular eruptions on the trunk or pediatric inflammatory multisystem syndrome [7].

There are many pre-existing chronic dermatoses which become poorly-controlled or aggravated post COVID19 infection, whatever systemic or non-systemic immune-mediated cutaneous disorders e.g (immunobullous disorders, rheumatologic skin diseases, psoriasis, hidradenitis suppurativa, alopecia areata, lichen planus and etc.) [8,9]. Telogen effluvium hair loss is very common complain post COVID19 infection, which was seen frequently in our OPD figure (1), COVID-19 infection is now a frequent and a common cause of acute telogen effluvium. Hence, clinicians should be aware about the relation between this infection and this pattern of hair loss [10]. Identifying COVID-19 infection as a potential cause of acute TE will help the clinicians counsel the patients that after recovery from COVID-19, the factor triggering acute TE has been resolved. Educating the patients about the transient nature of the condition is essential to alleviate their stress. Patients should be advised to ensure a healthy diet and informed that it may take up to 18 months for the hair thickness to return to the baseline [11].

A recent study has introduced an extra – comorbid relation between COVID 19 and skin manifestations away from specific reported dermatological signs of Coronavirus or post COVID-19 infection, this study has shown dermatological diseases presented before COVID-19 [5,6]. This is the first report and perspective of concomitant dermatologic diseases before diagnosed COVID-19 infection, it has been found that mostly patients with psoriasis and superficial fungal infections more vulnerable to the COVID-19 [12]. In our study COVID 19 infection confirmed patient has shown extensive axillary erythrasma which was confirmed by Wood lamp, Erythrasma is a superficial infection of the skin typically caused by *Corynebacterium minutissimum* [13].

The possible similarity between cutaneous and mucosal immunity and immunosuppression suggests that patients with some dermatologic diseases especially superficial fungal infections and psoriasis may be more vulnerable to the COVID-19.

Chilblain-like lesions are a commonly reported manifestation involving the digits. They are also known as ‘COVID toes,’ even though they can also affect fingers, and they present as erythematous, purpuric, papules and macules on the dorsal phalanges, nail folds and digital pulps. Chilblain-like lesions are predominantly found in children and adolescents. Nail findings have been reported in association with chilblain-like lesions [14,15].

The pathological mechanisms of skin lesions in COVID-19 patients remain poorly understood, cutaneous manifestations in COVID-19 may be classified into two major groups according underlying pathophysiology [16,17]:

1. clinical features similar to viral exanthems (an immune response to viral nucleotides).
2. cutaneous eruptions secondary to systemic consequences caused by COVID-19 (especially vasculitis and thrombotic vasculopathy).

The possible actions of SARS-CoV-2 on human skin and the resulting potential dermatological manifestations can be summarized as follows: SARS-CoV-2 is a single-stranded RNA virus composed of 16 nonstructural proteins (NSP 1–16) with specific roles in the replication of coronaviruses (CoVs). NSP3 has the ability to block the host’s innate immune response and promote cytokine expression, while NSP5 can inhibit interferon (IFN) signalling, and NSP16 avoids MAD5 (melanoma differentiation-associated gene 5) recognition, depressing innate immunity. Some studies have shown direct T cell viral infection by the detection SARS-like viral particles and SARS-CoV-2 RNA in T lymphocytes. In a subset of patients, overactive immune responses may induce immunopathological conditions, or “**cytokine storm**” (i.e., an increase in pro-inflammatory cytokines, in particular, IL-6); these cytokines could reach the skin and stimulate dermal dendritic

cells, macrophages, mast cells, lymphocytes and neutrophils, and promote eruptions such as erythema, urticarial lesions, vesicles and other skin manifestations [18].

COVID-19 related enanemas or exanemas might raise suspicion of SARS-CoV -2 infection, but these can also occur in various other different types of viral infections, like rubella or measles. This preference of the SARS-CoV-2 virus for skin tissues with a high ACE2 receptor concentration when taken with the fact that ACE2 is upregulated during proinflammatory states may be a possible mechanism for a localized susceptibility. IL-6 and IL-2 also play a role in COVID-19 outcomes, with increasing levels being able to predict prognosis and disease severity in patients. Tocilizumab, a monoclonal antibody that directly blocks both the membrane-bound and soluble IL-6 receptors, has shown promise in treating severe SARS-CoV-2 disease, including skin manifestations [19].

Strategy of study

Our study was approved by institutional ethical committee and approval from each hospital director was taken. The study has been conducted for 3 months from 15/8/2021 to 15/11/2021 at multi-hospital in Kuwait. All patients who were admitted as SARS-CoV-2 positive after RT-PCR test report in wards and ICU during that period were enrolled for the study.

A specially designed form was used for data collection and pictures were taken for all the skin manifestations were detected in those patients. All patients or their **next of kin** gave their informed consent to participate and explicit consent to use their pictures in publications. During the first month of the study, weekly visits for each hospital were done.



Figure 1: Telogen effluvium in a middle age female post COVID19 infection



Figure 2: Extensive axillary erythrasma in COVID19 confirmed patient.

Results

Total patients admitted to isolations centres were 270 COVID19 confirmed patients, 20 patients of them showed skin manifestations of variable presentations. In the first month ,there were213 COVID19 patients ,14 patients showed skin manifestations, in the second month 35 COVID19 patients were admitted 4patients showed skin manifestations. In third month 22 COVID19 patients only were admitted to isolation centres, 2 patients only showed skin manifestations. The skin manifestations were of different variants as 6 patients had exanthemata’s maculopapular/papulovesicular rash, 4 patients had purpuric “vasculitic” pattern, 2 cases chilblain-like acral pattern and 2 cases dry gangrene one of them was young adult 27 years pregnant female who was on ECMO for 40 days.

Table 1: Dermographic features of COVID-19-associated cutaneous manifestations

Morphology	age	sex	Mainsit	Surface area	duration	Mucous Memb	symptoms	Co.morb.	Admission Place
Exanthematous maculopapular /papulovesicular rash (6,30%)									
C1	26	M	T	10%	4d	Non	Non	CD	ward
C2	34	F	Ex	20%	2d	Non	Non	DM	ward
C3	52	F	Ex	03%	7d	Non	Non	Non	ward
C4	42	M	Ex	25%	5d	eye	Non	Non	ICU
C5	56	M	Ex	25%	14d	Non	Non	DMHT	ICU
C6	47	F	Ex	30%	6d	Non	burning	non	ICU
Purpuric “vasculitic” pattern (4 , 20%)									
C1	61	F	Ex	10%	6d	Non	Non	DM.ESR	ward
C2	36	F	T	10%	14d	Non	Non	Non	ward
C3	77	F	Ex	10%	7d	Non	Non	DM HT	ward
C4	67	M	Ex	10%	7d	Non	Non	DM HT	ward
Chilblain-like acral pattern (2,10%)									
C*1	80	F	Ex	15%	5d	Non	Non	HTost,dys	ward
C2									
Dry Gangrene (2, 10%)									
C1	38	F	Ex	<10%	21 d	Non	Non	Non	ward
C2	27	F	Ex	<10%	30 d	Non	Non	Non	ICU
Livedo reticularis /racemosa- (1,5%)like pattern/blue toe									
c1									
Confluent erythematous / Morbilliform rash(1,5%)									
C1	52	M	T	35%	4d	Non	Non	HT	ward
Miscelanous Skin rashes(4,20%)									
EM	19	M	Ex	10%	10d	Non	Burning	Ep.B	ward
V.R	26	M	Ex	25%	4d	Non	Non	Non	ICU
E.H	4	F	T	30%	7d	Non	Itch	Card.	ward
E.D	78	F	Ex, T	70%	10d	eyes	burning	Ht Dm	ward

T.trunk , Ex. Extremities, M.male ,F.female, CD. cardiac disease, DM. diabetes mellitus, HT. hypertension.,O.obesity. more than one skin rash,

C*: accompanied more morphological rash type, 2*(chilblain,pupura)

E.M.: Erythema multiform, E.H: Eczma herpeticum,, , E.D: Exfoliative dermatitis

Clinical features of COVID-19-associated cutaneous manifestations.

A. Morbilliform rash	B. Purpuric vasculitis	C. Drygangrene	D. Maculopapularexanthesma	E. Livedo reticularis/ racemose
				
<p data-bbox="204 891 264 920">F.E.M</p> 	<p data-bbox="467 891 815 920">G. Milleara crystallina Like pattern</p> 	<p data-bbox="1018 891 1094 920">H. E.D</p> 	<p data-bbox="1326 891 1402 920">I.E.H</p> 	

Discussion

Secondary dermatoses to Coronavirus-2 (SARS-CoV-2) are other concerns in this new pandemic, these dermatoses could be of an acute to stress-related causes such as herpes simplex, herpes zoster, patchy alopecia areata and some due to physical-environmental causes like acute allergic or irritant contact dermatitis or acute urticarial [20].

There are also dermatoses most likely drug reactions related to COVID-19 treatment, especially the generalized pustular rash due to hydroxychloroquine [21].

In addition to dermatological diseases presented before COVID-19, such as psoriasis and superficial fungal infections This is the first report and perspective of concomitant dermatologic diseases before diagnosed COVID-19. According to a recent study, it was the first report and perspective of concomitant dermatologic diseases before diagnosed COVID-19 which showed that, superficial fungal infections, psoriasis, seborrheic dermatitis, actinic keratosis, and herpes simplex are the most common dermatologic diseases before COVID-19 infection ,in our study a case of erythrasma has been

reported during following COVID-19 inpatients ,the occurrence of erythrasma concurrent with COVID-19 infection hasnot been reported before according to our knowledge. Erythrasma caused by *Corynebacterium minutissimum* [12]. In our study a case of erythrasma has been reported during following COVID-19 inpatient, the occurrence of erythrasma concurrent or before COVID-19 infection has not been reported before according to our knowledge, its occurrence in this patient might be due to high fever and subsequent over sweating, as it is commonly affects the groin, axillae, intergluteal folds, sub-mammary region, and interdigital spaces of the toes. Heat, humidity, obesity, diabetes mellitus, hyperhidrosis, and poor hygiene are predisposing factors [22]. In other hand there are a plethora of semi-specific determined known cutaneous manifestations have been reported in a floods of publications as **six main clinical patterns of COVID-19-associated cutaneous manifestations urticarialrash**, confluent erythematous/maculopapular/morbilliform rash, papulovesicular exanthem, chilblain like acral pattern, and livedo reticularis/racemosa-like pattern (24,25,26). A six cases of exanthematous maculopapular /papulovesicular rash COVID-19-associated, papulovesicular exanthema was first extensively reported in a multicenter Italian [27].

COVID-19-associated papulovesicular exanthem lesions have been started on extremities then spread to involve trunk namely trunk involvement, scattered distribution and mild/absent pruritus, differentiated it from “true” varicella [27]. In our study 4 patients were reported with purpuric “vasculitic” pattern changes probably due to the direct damage of endothelial cells by the virus or dysregulated host inflammatory responses induced by COVID-19. Purpuric lesions may be with or without necrosis as reported in the series by Freeman et al, our reported cases were without necrosis. Two cases for each chilblain-like acral pattern and dry gangrene were reported in our study [28]. Galván Casas et al. have divided acral lesions into 2 groups as chilblains-like lesions (perniosis-like lesions and pseudo-chilblain) and Acral ischemia (livedo or necrosis) [24]. No association with cold exposure, comorbidities, or drug intake was recorded [29]. Confluent erythematous/Morbilliform rash, one case only reported in our study, this pattern is predominantly localized on the trunk as in our case being associated with pruritus in most cases but not in our case these lesions occurred more frequently after COVID-19 systemic symptoms’ onset, as mentioned in series study [30].

There miscellaneous cases were reported in our study one case E.M in a young adult male, erythema multiform as a cutaneous manifestation in patients with COVID-19 infection are increasingly being reported [31].

Eczema herpeticum (EH) is a severe skin-related complication of herpes simplex virus (HSV) type 1 or 2 infection that is also known as Kaposi’s varicelliform eruption (KVE) in children patients with atopic background [32]. One case of EH in atopic 4 years’ female child was reported in our study, also she has congenital heart disease and confirmed as COVID-19 infection. data on effects of SARS-CoV-2 infection on eczema patients have not been published. Since T cells are centrally involved in the complex immuno-pathophysiology of eczema and associated diseases, SARS-CoV-2 infections may be of special concern in eczema patients with comorbid diseases such as asthma/chronic obstructive lung disease, eosinophilic esophagitis, or severe allergies, although respiratory and cutaneous viral infections may worsen or complicate atopic dermatitis and other types of eczema **Vesicular rash VR another skin findings which recently attempts to unify the concepts of isotopic response and Koebner phenomena have had the result of suggesting that the Wolf isotopic response may be a form of Koebner and may eventually become regarded as the fifth category of Koebner phenomenon, one case in our study showed this type of lesion. Lastly an elderly female patient in our study was admitted with exfoliative dermatitis erythroderma ED and of course COVID-19 PCR was requested, in addition to big list of lab blood tests and investigative imaging for screening underlying malignancy. All investigations for that patient has not shown any abnormalities, except positivity of COVID -19 infection. Away from progression of previously psoriatic patients who developed psoriatic erythroderma, no reported erythroderma cases due to COVID 19 infection up to date [33-37].**

Conclusion

Coronavirus-2 (SARS-CoV-2) could be considered as a new member of different viruses giving skin manifestations, these dermatoses were well known secondary to previous viruses, but newly reported to CORONA VIRUS COVID-19-associated cutaneous manifestations have been increasingly reported in the last few months, garnering attention both from the international scientific community and from the media. To date, several skin manifestations related to COVID-19 have been reported,

but additional efforts are needed to collect further data. Still more time and much more needed studies needed to build up our understanding of the pathophysiology of COVID-19 and ultimately contributing to the development of effective treatments and protocols that will mitigate the complications of this infection.

Limitations in our study

As there was decreasing in the SARS-cov-2 positive patients and decrease the hospitals admission, so COVID19 isolations wards were fortunately closing, the number of SARS-CoV-2 positive decreased after 70% of Kuwaiti population were vaccinated (this according to statics mentioned from Central Statistical Bureau (and this was a limitation in total numbers of these study.

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