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Abstract
Since the beginning of COVID-19 pandemic in late 2019, the symptoms and signs detailed in the medical literature and the media concentrated on the effect of causative virus SARS-COV-2 on the respiratory tract, the coagulopathy associated with severe forms of the disease and the febrile flu like illness in the mild cases. The widespread publicising of the symptoms has been one of the important public health measures in combating the rapid spread of COVID-19. Less known is the direct or indirect effect of COVID-19 on the skin and underlying soft tissue. Recognising the various cutaneous manifestations may prove a useful tool in early detection and management of COVID-19.

Introduction
COVID-19 may affect the skin at various stages of the disease and although in few cases the rash preceded the fever and respiratory symptoms [1, 2], the more common scenario is an eruption that followed the flu like illness. Distinction between a rash attributed to COVID-19 alone or complicated by therapy may be difficult and specific histological findings have not been found.

The pathophysiology of skin involvement is thought to mirror other organs involvement via direct injury of the cells through immune response to viral nucleotides or vessels damage leading to vasculitic injury and thrombotic vasculopathy with a key role of angiotensin converting enzyme 2 (ACE2) [1-3].

A large number of cases detailing skin involvement in COVID19 patients has been reported since the start of the pandemic. One of the largest case series published to date was by Freeman et al. from the record of the international registry established by the American Academy of Dermatology and International League of Dermatological Societies that incorporated 716 cases of confirmed or suspected COVID-19 [4]. Upon review of the literature, the heterogeneity of the cutaneous manifestations of COVID-19 was evident and various clinical and pathological classifications have been suggested or used by different groups [1, 4-12]. All ages were affected with females and males equally represented in most series [7]. In addition to the rash, symptoms included pruritus in a large proportion of cases followed by burning sensation and pain whilst some patients were asymptomatic [6, 7]. As the virus may affect the epithelial cells and vessels, the cutaneous manifestations mirrored the cellular involvement and may be classified into two broad categories of inflammatory and vasculitic patterns [10]. A more detailed classification used the different clinical manifestations and included urticaria, erythematous/maculopapular/morbilliform forms, papulovesicular rash, acral chilblain like, livedo reticularis-livedo racemosa like and pruritic/vasculitic pattern [1, 4-12] with the first three subtypes representing the inflammatory category and the last three the vasculitic category. Selective distribution of the different types of lesions has been reported and to some extent reflected the skin manifestations associated with the various inflammatory and vasculitic rashes seen with viral and non-viral infections, systemic autoimmune diseases, vasculitides and drug attributed rashes. Whilst the inflammatory maculopapular/morbilliform and papulovesicular rashes affected predominantly but not exclusively the trunk, it was evident that the vasculitic pattern of chilblain like, livedo and pruritus were more often limited to the lower limbs with chilblain like lesions exclusively affecting the feet. Urticarial rash had a more heterogeneous and widespread distribution with involvement of trunk and limbs [11]. As the different terminology used to describe the rashes is self-explanatory, it is useful to mention that the skin lesions vary from hives to macules/papules, red papules-vesicles in the three inflammatory patterns to reddish purple macules, papules, ill-defined patches and ulcers in the vasculitic patterns [11]. Although these manifestations may be seen at all ages, there has been cases of multisystem inflammatory syndrome and erythema multiforme like eruptions almost exclusively seen in children [12].
A study of PCR confirmed 144 hospitalised COVID-19 patients in the second wave reported a much lower incidence (3.5%) of livedoid lesions and less common maculopapular rash. This variation has been attributed to different antigenicity of the virus and different treatment regimens limited to remdesivir, tociluzumab and dexamethasone [13].

At the cellular level, the changes seen in the cases which underwent skin biopsy showed equivalent findings to similar rash caused by various aetiologies or alternatively non-specific inflammation. In the inflammatory category, the urticarial rash displayed perivascular lymphocytic or eosinophilic infiltrate and papillary oedema. Both erythematous and maculopapular lesions featured spongiosis, intraepidermal/subcorneal pustules, dermal oedema, variable numbers of dermal neutrophils and eosinophils and fibrin thrombi, necrotic keratinocytes were observed in the maculopapular lesions and basal vacuolar degeneration was limited to the erythematous rash. The vasculitic patterns were characterised by a superficial and deep lymphocytic infiltrate with perivascular or periadnexal accentuation in livedo and chilblain like lesions. Lichenoid vacuolar basal layer changes, purpura with or without vascular complement deposition and with no vasculitis have been reported in acral lesions. Lichenoid changes were limited to chilblain like acral pattern. Pruritic vasculitis manifested with leukocytoclastic vasculitis, epidermal and adnexal necrosis and thrombogenic vasculopathy [14-17]. Rare cases of erythema multiforme like eruption showed mild spongiosis, perivascular and interstitial lymphocytic infiltrate, dilated vessels filled with neutrophils and extravasated red blood cells with or without vacuolar changes of basal layer [18].

Nails may also be affected and the so called “Covid nails” were usually seen following the generalised symptoms and range from the red “half-moon nail sign” regarded by some as a reliable sign of COVID-19 infection and featuring a red crescent immediately above the lunula to the less specific white horizontal Mee’s lines or Beau’s lines which are in fact horizontal dents or ridges. Nail changes were temporary and disappeared within months of the infection.

In the fight against Covid-19, using personal protective equipment (PPE) including face masks, goggles, face shields, gloves and gowns and the constant use of hand hygiene solutions and gels led to cutaneous side effects amongst health care workers and the general population alike. Various surveys of healthcare workers showed prevalence ranging from 58.5% to 74.5% [19-22], with most reporting dermatoses of the face commonly at the pressure sites of fitted masks or shields on the nose, cheeks, forehead and above or behind the ears. The most prevalent symptoms were redness, itching and dryness and the commonest manifestations were eczema, acne and exacerbations of seborrheic dermatitis with fewer cases reporting erosion/ulcer, scale crust formation, desquamation, itchy papules, vesicles and even pustules. Exacerbation of pre-existing dermatoses such as atopic or seborrheic dermatitis, urticaria and acne have also been reported [23]. A direct relationship has been established with the duration of PPE usage and in some settings a higher prevalence was observed amongst healthcare workers in hospitals with larger numbers of Covid patients in more severe epidemic settings [19].
Dermatoses of the hands were also quite common more so with excessive hand hygiene exceeding ten days (21) with rare adverse reactions attributed to gowns. Only a small percentage of affected workers (5%) sought medical attention and treatment.

Covid treatment may adversely affect the skin but fortunately can be easily managed with topical corticosteroids and occasionally with oral antihistamines and oral corticosteroids. From the controversially used hydroxychloroquine to antibiotics such as Azithromycin to broad spectrum antivirals such as Remdesivir, Oseltamivir & interferons or HIV antivirals such as Lopinavir, various dermatologic reaction or rashes have been reported from urticaria, maculopapular and eczematous lesions, photosensitivity and hyperpigmentation in the mild forms to blistering or purpuric rashes, leukocytoclastic vasculitis and toxic epidermal necrolysis in the severe forms. 2% of patients with mild to moderate risk of progression to severe COVID-19 using Sotrovimab have reported a rash. Recently approved oral drugs such as Molnupiravir may lead to hives, itching and rash and the combination of Nirmatrelvir and Ritonavir may be associated with itching, rash, flushing, yellow discoloration or redness of skin [24]. Exacerbation of pre-existing skin conditions such as psoriasis, acne and herpes simplex and herpes zoster reactivation have been reported and both alopecia and hirsutism are known side effects. Corticosteroids and various immunomodulatory agents have also been used and may cause mild/transient rash or more severe cutaneous pustulosis, vasculitis and erythema multiforme like reaction. Local reaction at the injection site including pain, erythema, pruritis, swelling, induration and ulceration have been attributed to Remdesivir and Sotrovimab, interferon, Anakinra and Lopinavir [25-29]. Pre-exposure preventative drugs including Tixagevimab and Cilgavimab have been implicated in similar rash and injection site reaction [30, 31].

Lastly, the various COVID-19 vaccines have been linked to dermatological symptoms and signs mostly local reaction such as redness, swelling and pain at the injection site seen with all types of vaccines in both clinical trials and mass vaccination settings. Less prevalent are allergic dermatitis, eczema, injection site or papular urticaria and vesicular rash reported during clinical trials of Moderna vaccine and allergic dermatitis, eczema, petechial rash and alopecia reported with Sputnik V. In non-trial setting, morbilliform and maculopapular rashes, urticaria and pernio like lesions have been observed following Pfizer and Moderna vaccine [32]. Isolated cases of de novo or exacerbated lichen planus, erythema multiforme, pityriasis rosea, varicella zoster and herpes simplex reactivation, papulovesicular rash, petechial and purpuric rash have been attributed to mRNA vaccines which have also been implicated in a bizarre delayed inflammatory reaction to hyaluronic acid fillers [32-34].

We have reviewed the cutaneous inflammatory and vasculitic manifestations of Covid19 and the side effect of treatment, vaccines and PPE on the skin. We summarised the histological findings of the different types of rashes attributed to Covid 19. As the pandemic continues, it is essential to monitor the clinical signs of the disease, correlate the severity with involvement of specific organs and track the iatrogenic side effects secondary to treatment and preventative measures.

No conflict of interest exists.

References


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