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The Dermatological Spectrum of Coronavirus Disease-19 Disease: Cutaneous Signs for Diagnostics and Prognosis and an Expanded Classification

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Abstract

During severe acute respiratory syndrome coronavirus (CoV)-2- induced CoV disease (COVID)-19 pandemic cutaneous signs of the disease gained increasing interest for early diagnosis, to establish a prognosis and for differential diagnoses. The present review aims to summarize current knowledge on cutaneous findings in COVID-19. The findings are classified and described clinically. The spectrum of cutaneous signs include acro-ischemic lesions, rash, chilblain-like eruptions, and androgenetic alopecia. Their significance is given, and treatment options are presented. This may allow the clinicians to support triage and optimal treatment for COVID-19 patients.

Key Bullets

- The COVID-19 pandemic has affected patients world-wide. Despite the leading symptoms are in the respiratory, cardiovascular, hematologic, and neurologic systems, cutaneous manifestations are increasingly be observed.
- Cutaneous findings in COVID-19 patients may have prognostic and therapeutic consequences. This review attempts to classify cutaneous symptoms, document the observed frequency of their occurrence, the significance for triage of COVID-19-patients, and the treatment of cutaneous manifestations.

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Introduction

The coronavirus (CoV) disease (COVID)-19 pandemic originated in Wuhan, China, and is caused by a new beta-CoV, named severe acute respiratory syndrome-CoV (SARS-CoV)-2 [1]. The virus enters host cells with the support of its surface spike proteins. Angiotensin-converting enzyme 2 (ACE2) has been identified as the entry receptor and employs the cellular serine protease TMPRSS2 for S protein priming [2]. Since ACE2 is regulated by androgens, this may contribute to the higher rate of males affected [3].

Infection can be from animals to humans and human-to-human. Among humans, the most common transmission is by respiratory droplets. The primary entry point is the respiratory system, although the virus can also infect the digestive, urinary, neurologic, and hematologic system. Other possible ways of

transmission are fecal-oral and mother-to-child. Incubation time varies between 5 and 14 days, seldom longer [4].

Typical symptoms of infection by SARS-CoV-2 are fever, fatigue, dry cough, dyspnea, with or without nasal congestion, runny nose or other upper respiratory symptoms, lymphopenia, thrombocytopenia, and leukopenia. Patients may present with atypical symptoms such as headache, vomiting, diarrhea, and hemoptysis or stay asymptomatic [5], [6].

Complications include the acute respiratory distress syndrome, acute heart injury, stroke, encephalopathy, and secondary infections [5], [7], [8]. Patients older than 60 years and/or comorbidities are at higher risk for complications, hospitalization, and mortality. The rate of patients to be treated at the intensive care unit (ICU) varies from nearly 30% in the initial Wuhan epidemic to around 12% on northern Italy and 7% in Germany [9], [10], [11].

Distribution of SARS-CoV-2 in Human Tissues

Three autopsy cases from Chongqing, China, demonstrated by immunohistochemistry that alveolar epithelia and macrophages were partially positive for the 2019-nCoV antigen. Real-time -polymerase chain reaction (RT-PCR) analyses identified positive signals for 2019-nCoV nucleic acid [12]. In two autopsies from Cleveland/OH, USA, viral RNA was detected in lungs, bronchi, lymph nodes, and spleen using quantitative RT-PCR method on formalin-fixed paraffin-embedded tissue specimen [13]. Among 26 autopsy cases from Wuhan, China, immunostaining with SARS-CoV nucleoprotein antibody was positive in renal tubules [14]. In 12 patients who died from COVID-19 in Hamburg/ Germany, SARS-CoV-2 RNA was detected in the lung at high concentrations. Viremia in 6 of 10 and 5 of 12 patients demonstrated high viral RNA titers in the liver, kidney, or heart during autopsy [15]. In three autopsy cases from Zürich, Switzerland, presence of viral elements within endothelial cells and the induction of endotheliitis in several organs as a direct consequence of viral involvement have been documented [16].

The expression of ACE2 was demonstrated in human skin samples using single-cell RNA sequencing. It was significantly higher in keratinocytes than other cell types in skin, such as fibroblasts and melanocytes. Immunostainings for ACE2 were positive in epidermal basal layer, stratum spinosum and stratum granulosum [17]. SARS-CoV-2, on the contrary, has not been detected in skin [12].

By the support of neuronal network possible conceptual associations from unstructured text and triangulation with insights from single cell RNA-sequencing (seq), bulk RNAseq and proteomics from diverse tissue types have been analyzed. It could be demonstrated that tongue keratinocytes, olfactory epithelial cells, airway club cells, and respiratory ciliated cells are potential reservoirs of the SARS-CoV-2 receptor. The gut was identified as the putative hotspot of COVID-19, where a maturation correlated transcriptional signature is shared in small intestine enterocytes among CoV receptors (ACE2 and others) [18].

Epidemiology of Cutaneous Manifestation of COVID-19

The initial trials from Wuhan suggested a low prevalence of 0.2% of any cutaneous findings among symptomatic patients [19]. The prevalence of cutaneous manifestations in uncontrolled trials and reports varies

extremely from zero (Tibetan highland) to almost 100% (Thailand) [20].

There is a need for better epidemiological data on the subject. One initiative to improve data collection and analysis comes from the American Academy of Dermatology [21].

Classification of COVID-19-related Cutaneous Manifestations

A nationwide Spanish study among dermatologists included 375 COVID-19 cases with cutaneous manifestations. Based on this large data set, the authors tried to classify the cutaneous findings into five categories [22]:

- Asymmetrical distributed chilblain-like acral areas of erythema and/or edema with some vesicles or pustules (pseudo-chilblain) on digits hand and feet and heels
- Vesicular monomorphic eruptions (varicella-like)
- Urticarial lesions
- Maculopapular rash
- Acro-ischemic lesions (Livedo or necrosis).

We had like to add some more possible cutaneous findings:

1. Symmetrical flexural and intertriginous exanthema
2. Purpuric rash
3. Erythema multiforme-like rash and Kawasaki-like disease/multisystemic inflammatory syndrome in children (MIS-C)
4. Others (Mottling, Sweet syndrome-like, pustular eruptions, and androgenetic alopecia [AGA]) (Table 1).

Table 1: Cutaneous signs of COVID-19, their frequency and significance

Cutaneous signs	Frequency	Remarks	Significance
CE	up to 19%	Mostly children	Mild or silent disease
Vesicular eruptions	9–15%	Symptomatic adults	Could be a sign of a viral coinfection
Urticarial lesions	1.4–19%	Often with pyrexia	In case of eosinophilia, the prognosis might be better
Maculopapular rash	up to 47%	Mostly adults	Nonspecific, drug hypersensitivity should be excluded
Acro-ischemic lesions	2.8–6%	Thromboembolic, DIC	Red flag for severe course, mortality is high
SDRIFE-like	Rare		Exclude a drug reaction
Purpuric rash	Unknown	Underestimated in developing countries	Exclude other viral diseases, coinfections with dengue possible
EM	Rare		Unknown
KD	Unknown	Children	Severe course, but often good prognosis
MIS-C	Unknown	Children	Severe disease, ICU support
Mottling	Rare	Newborn	Unknown
SS-like	Rare	Adults	Adults
Pustular eruptions	Rare	Adults	Probably hydroxychloroquine-induced
AGA	≤75% (males)	Adults, More severe course	Mediterranean Sea

AGA: Androgenetic alopecia, CE: Chilblain-like eruptions, EM: Erythema multiforme, DIC: Diffuse intravascular coagulation, KD: Kawasaki disease, MIS-C: Multisystemic Inflammatory Syndrome in Children, SS-like: Sweet syndrome-like eruptions, SDRIFE-like: Symmetrical flexural and intertriginous exanthema.

Chilblain-like Acral Lesions

Clinics

Mostly asymmetrical distributed chilblain-like violaceous, infiltrated acral areas of erythema, and/or edema with some vesicles or pustules ("pseudo-chilblain") can be observed on hand and feet (Figure 1) [22]. Proximal nail fold capillaroscopy/dermoscopy remains normal [23].

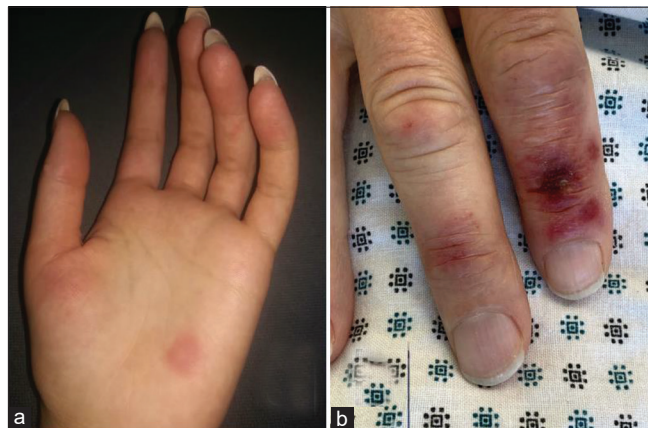


Figure 1: Asymmetric chilblain-like lesions. (a) Erythematous plaque on the antithenar. (b) Ill-defined infiltrations on two fingers. Nail fold capillaries are without abnormalities

There is a number of case reports on chilblain-like lesions mainly in children and adolescents. Pruritus and (mild) burning pain are two equally distributed major symptoms [24], [25], [26]. In a series of 63 patients, there was no significant gender difference. The median age was 14 years and feet alone were mostly affected (85.7%), followed by feet/hands together (7%) and hands alone (6%). Asymptomatic lesions were present in 25.4% of cases [27].

Frequency

The nationwide Spanish study reported chilblain-like lesions in 19% of cases [22]. In a retrospective observational nationwide study among French private practices, 277 patients were enrolled with a median age of 27 years. Chilblain-like lesions were the most frequent acral lesions (n=106/142, 75%) [28].

In the rare cases with a lesional skin biopsy, vasculitis signs were noted in small to medium sized vessels with endothelial cell swelling and red blood cell extravasation. Fibrin thrombi was evident in superficial capillary vessels [29]. In an adult case, absence of significant papillary dermal edema was associated with a superficial and deep lymphoplasmacytic infiltrate, vacuolar interface dermatitis with some apoptotic keratinocytes and smudging of the basement membrane zone. The venules surrounded by the lymphoplasmacytic infiltrate had plump endothelial cells. Neither

intraluminal fibrin thrombi nor venule wall fibrin deposits were detected. Direct immunofluorescence result was negative. Altogether these findings suggest a type I interferon response [30].

Significance

The percentage of patients with this type of cutaneous lesions tested positive for SARS-CoV-2 is between 15% (prospective study) and 25% (retrospective study). This raises questions, if the chilblain-like lesions are markers of COVID-19 [31]. Some authors recommend SARS-CoV-2 testing in children and adolescents with chilblain-like lesions to support early detection of silent carriers [32].

Treatment

In uncomplicated cases topical mometasone furoate and heparin gel for a few days is recommended [33].

Vesicular Monomorphic Eruptions

Clinics

Vesicular monomorphic eruptions on the trunk or the extremities, with possible hemorrhagic content have been observed mostly in symptomatic COVID-19 cases [22].

These lesions present initially as erythematous papules with a tendency to superficial vesiculation that eventually leads to crust formation. The presentation is varicella-like although most patients may be in good general health condition [34]. In a series of 22 patients from Northern Italy tested positive for SARS-Cov2, the median age was 60 years, and 72.7% of patients were male. The trunk as involved in all cases and the median time to remission was 8 days. Facial skin and mucosa were spared. Itch was noted in about 40% of patients [35].

Frequency

Vesicular monomorphic eruptions on the trunk or the extremities, with possible hemorrhagic content accounted for 9% of cases in the Spanish nationwide study [22]. In France, vesicular eruptions were observed in 41 outpatient cases (15%) [28].

Significance

The vesicular eruptions are considered probably COVID-19 specific, but vesicular drug-reactions and

other viral (co-)infections might contribute [36], [37]. Further studies are needed.

Treatment

These eruptions do not need any treatment, they can pass by itself. Wet dressing can be done to relieve the patient from itch. Topical antibacterial cream can be added if secondary impetiginization occurs.

Urticarial Rash

Clinics

Urticaria with wheals and flares is a non-specific cutaneous symptom in COVID-19 patients (Figure 2). Here, urticarial lesions occur mostly on the trunk, rarely palmar. Pyrexia with urticaria may be more characteristic than urticaria alone [22].



Figure 2: Urticaria

Frequency

Urticaria was observed in 19% of Spanish COVID-19 patients and in 1/14 in a French study [22], [26]. Among 140 hospitalized Chinese patients in Wuhan 1.4% self-reported urticarial [38]. A recent literature review reported urticaria in 9.7% of cases (7/72) [39].

Significance

In case of urticaria with eosinophils, theoretically a better outcome is possible [40]. Differential diagnoses include idiopathic urticaria, drug eruptions, and other viral infections with urticarial rash. If the patient is not taking medication and does not have idiopathic urticaria diagnosis, it is more likely to think of COVID-19 specific urticaria.

Treatment

Symptomatic treatment with oral antihistamines and topical corticosteroids is an option.

Maculopapular Rash

Clinics

Maculopapular rash is a non-specific cutaneous finding in COVID-19 patients (Figure 3). Lesions may show a possible perifollicular distribution. Variants were described as pityriasis rosea-like with a variable degree of purpuric areas or erythema elevatum diutinum-like. The rash lasts on average 9 days. It is uncommon among children affected by COVID-19 [20].



Figure 3: Maculopapular rash. (a) Follicular type, (b) confluent lesions, (c) lichenoid follicular type

Erythema multiforme-like eruptions have rarely been reported. They can spread to facial and palmoplantar skin and the average duration is double as long as the usual maculopapular rash with nearly 20 days. In a series of four adult patients, histologic examination revealed a normal basket-weave stratum corneum, and mild-to-moderate epidermal spongiosis. Dermal vessels were dilated and filled with neutrophils with some extravasation of red blood cells, and lymphocytic perivascular and interstitial infiltrate. These patients needed systemic corticosteroids [41].

Pityriasis rosea-like eruptions are a rare pruritic cutaneous manifestation of COVID-19 [42].

Frequency

In the Spanish trial maculopapular rash was a common cutaneous finding observed in 47% of cases [22]. Face and palmoplantar skin is usually spared. Histologic and clinical presentation is not uniform. If needed, symptomatic topical treatment with corticosteroids and oral antihistamines can be used [20].

Significance

Maculopapular rash is a non-specific cutaneous finding in COVID-19. The most important differential diagnosis is drug-induced exanthema.

Treatment

Symptomatic treatment with oral antihistamines and topical corticosteroids is an option.

Acro-ischemic Lesion (Livedo or Necrosis)

Clinics

Transient livedo reticularis-like lesions have occasionally been observed in symptomatic COVID-19 patients. The livedoid changes may be unilateral in nature. They can eventually result in skin necrosis. The lesions are thought to be secondary to SARS-CoV-2-induced thrombotic vasculopathy [22], [26]. Acro-ischemia presenting with finger and toe cyanosis, skin bullae, and dry gangrene are a red-flag sign for severe illness (Figure 4).



Figure 4: Acro-ischemic ulcerations. (a) Transitory livedoid erythema. (b) Ulcerated papule. Disseminated ulcerated papules may be a sign of DIC. (c) Two neighboring ulcerations on the foot. (d) Ulcerated lesion on the heel

Frequency

The frequency of livedo and necrosis was 6% in Spain and 2.8% in a recent literature review [22], [39].

Significance

If livedoid and necrotic eruptions occur in COVID-19 patients, this could be a clue for systemic thrombotic vasculopathy. It will be particularly important to recognize the eruptions clinically, since they may

have (strong negative) prognostic value in these patients.

It is important to separate acral lesions in the elderly from chilblain-like eruptions in youngsters since these could have a necrotic outcome [43]. Acro-ischemia presentations are associated with severe COVID-19 disease and high mortality [44].

Treatment

Treatment is dependent on underlying pathology (acral ischemia, and disseminated intravascular coagulopathy [DIC]). In the initial phase of the SARS-CoV-2 infection, D-dimer and fibrinogen levels are increased, while prothrombin time, activated partial prothrombin time, and platelet counts are often normal. Diagnosis of DIC needs laboratory evaluation of soluble fibrin, protein C, and plasminogen activator inhibitor 1.

For hospitalized COVID-19 patients, thromboprophylaxis using low-molecular-weight heparin is recommended [45]. Recombinant human soluble thrombomodulin has proven clinically useful for treating DIC leading to a higher resolution rate after 7 days of application [46]. Adjuvant plasmapheresis has been used occasionally in DIC [47].

Symmetrical Flexural and Intertriginous Exanthema

Clinics

Symmetrical flexural and intertriginous exanthema are a rare manifestation of COVID-19. It resembles clinically Symmetrical Drug-Related Intertriginous and Flexural Exanthema (SDRIFE).

Frequency

This symptom has been seen in single cases several days after the COVID-19 fever developed [48].

Significance

Drug-induced SDRIFE needs to be excluded before the diagnosis of COVID-19 SDRIFE can be made.

Treatment

Symmetrical flexural and intertriginous exanthema is temporary. In one case, it disappeared after 18 days without any specific treatment [48].

Purpuric Rash

Clinics

Acute undifferentiated febrile illness is one of the initial presentations of COVID-19. Purpuric rash in COVID-19 may resemble other viral rashes like dengue fever [49], [50]. Very rare is Schamberg's-like purpura in mild COVID-19 [51].

Frequency

The frequency is obviously dramatically underestimated in tropical countries [52].

Significance

In hotspots of arboviral diseases, these disorders need to be excluded [53]. On the other hand, SARS-CoV-2 and dengue fever have been reported as coinfections from various developing countries [54], [55], [41].

Treatment

Antipyretics and topical corticosteroids can be combined.

Erythema Multiforme-like Rash and Kawasaki-like Disease/MIS-C

Clinics

Four female hospitalized COVID-19 patients in Madrid, Spain, presented an erythema multiforme-like rash. The mean age was 66.8 years. The mean time between onset of COVID-19 to the appearance of erythematous lesions was 19.5 days. Three patients developed the rash 4–7 days after clinical improvement with negative COVID-19 PCR test. These lesions developed from erythematous papules on the upper trunk that progressively turned into targetoid erythematous or violaceous patches with a dusky center, and a pseudo-vesicle in the middle. They spread to the face and limbs within 1 week, but spared palms and soles. Oral mucosa was also involved with palatal macules and petechiae. Histological examination showed dilated dermal vessels filled with neutrophils, extravasation of red blood cells, and lymphocytic perivascular and interstitial infiltrate [41]. One case report from France described a 6-year-old boy with erythema multiforme-like mucocutaneous lesions [56].

A prospective observational study from Paris, France, reported on 14 children with COVID-19

and Kawasaki-like disease. Almost 60% originated from sub-Saharan Africa or Caribbean islands. All children had marked gastrointestinal symptoms and high levels of inflammatory markers. Eleven patients presented with Kawasaki disease (KD) shock syndrome requiring ICU support, and 12 suffered from myocarditis [57]. Kawasaki-like eruptions including generalized exanthema, cheilitis, stomatitis, and bilateral conjunctivitis, bilateral palmar edema, glossitis, and cervical lymphadenopathy had been reported in a 3-year-old boy. Cutaneous desquamation of the extremities was noted later on [56]. A 6-year-old girl with rT-PCR confirmed COVID-19 met criteria for incomplete KD, including fever for more than 7 days with conjunctivitis, rash, edema of the hands and feet, elevated CRP and erythrocyte sedimentation rate, hypoalbuminemia, anemia, and 2-D echocardiogram findings suggestive of myocarditis [58].

An important differential diagnosis of Kawasaki-like disease is MIS-C. MIS-C is characterized by (1) prominent cardiac dysfunction with troponin leak and extremely elevated brain natriuretic peptide, (2) frequent and often severe enteropathy, and (3) relative thrombocytopenia. In some patients, fever and gastrointestinal symptoms precede the classical KD features such as cutaneous rash, conjunctivitis, mucous membrane changes, and extremity edema [59].

Frequency

One series of 17 children and several case reports have been published so far [41], [56], [57], [60], [61].

Significance

Other viral (co-) infections such as parvovirus B19 and herpes simplex have to be excluded. Kawasaki-like disease often needs ICU support for affected children.

Treatment

If necessary, oral corticosteroids may be given temporary for erythema multiforme-like eruptions. In case of Kawasaki-like disease, intravenous immunoglobulins at 2 g/kg, systemic corticosteroids, and aspirin have been recommended [57], [61].

Other Cutaneous Findings

Mottling

A 15-day-old neonate of a SARS-CoV-2 positive mother developed COVID-19 without cough.

The cutaneous findings were described as mottling. The newborn was isolated and subjected to supportive care. Antibiotic and antiviral treatment was initiated. The outcome was complete remission after 6 days [58].

Sweet syndrome-like eruptions

A 61-year-old woman without respiratory symptoms but fever, fatigue, arthralgia, and myalgia, was admitted to a hospital in Istanbul, Turkey. On examination, she presented numerous erythematous nodules on the cheeks, scalp, extremities, and the trunk. Minor aphthous ulcers were observed on the hard palate and buccal mucosa. Thoracic computerized tomography presented multifocal ground-glass opacities. The laboratory was remarkable for leukocytosis, neutrophilia, and mild lymphopenia, C-reactive protein was elevated with 78.2 (<5.0 mg/L). Although an initial SARS-CoV-2 rT-PCR was negative, a repeated test became positive. A skin biopsy from the elbow revealed a diffuse neutrophilic infiltration in the upper dermis and vascular proliferations with swollen endothelial cells and extravasated erythrocytes. In the lower dermis and at the periphery of the lobules of subcutaneous fat tissue, there were granulomas, composed of epithelioid histiocytes and multinuclear giant cells and other inflammatory cells. Clinical and histopathological features were considered as erythema nodosum-like Sweet syndrome [62]. Another case is shown in Figure 5.



Figure 5: Sweet-like plaques and pustules on the arms

Pustular rash

A 69-year-old woman from Madrid, Spain, with confirmed COVID-19 disease developed a pustular rash resembling acute exanthematous pustulosis 33 days after onset of COVID-19 symptoms. Histology revealed subcorneal pustulosis, spongiosis, papillary edema, and discrete neutrophilic inflammatory infiltrate [63]. Several other cases have been reported in adult COVID-19 patients [64], [65]. Since these patients were treated with hydroxychloroquine, a delayed drug-reaction is

possible [66]. A direct effect of SARS-CoV-2 remains unproven (Figure 6).



Figure 6: Acute exanthematous pustulosis due to hydroxychloroquine treatment of COVID-19

AGA; Gabrin sign

AGA severity reflects the androgen activity over age. Among 175 confirmed and hospitalized COVID-19 patients in Spain, 122 were males and 53 were females. AGA was present in 67% of the patients, 70 patients presented with clinically relevant AGA. The frequency of AGA was 79% in males and 42% in females. The prevalence of age matched males in a similar Caucasian population was estimated to be 31–53%, in females >70 years and the prevalence reported was 38% [67]. This argues for a significant higher rate of AGA at least in COVID-19 positive males. Furthermore, it seems to be a marker for a more severe course of COVID-19 [68].

Dr. Gabrin was the first physician to die from COVID-19 in the US and suffering from AGA. Therefore, the eponym "Gabrin sign" has been proposed for AGA in COVID-19 patients [67].

Conclusions

During the COVID-19 pandemic dermatologists play an active role in patients' triage, in early diagnosis of cutaneous signs, in the recognition of cutaneous red-flags for an unfortunate course of the disease. Their active participation is necessary to record cutaneous findings, to confirm diagnoses and make the necessary differential diagnostic procedures [69]. The most important diseases to be considered are tropical and other viral disorders and drug hypersensitivities. However, we are still at the beginning and should be aware of unexpected findings.

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