SARS-CoV-2, COVID-19, skin and vascular system - what do we know so far?

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Abstract

The pandemic condition Coronavirus-disease (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can take asymptomatic, mild, moderate, and severe courses. COVID-19 affects primarily the respiratory airways leading to dry cough, fever, myalgia, headache, fatigue, and diarrhea and can end up in interstitial pneumonia and severe respiratory failure. Different clinical symptoms caused by involvement of organs outside the respiratory system have been also described. Interestingly, reports about the manifestation of various skin lesions and lesions of the vascular system in some subgroups of SARS-CoV-2 positive patients as such features outside the respiratory sphere, are rapidly emerging. However, knowledge about prevalence and pattern of skin involvement, time of onset, predilection, and its direct or indirect relation to SARS-CoV-2 is still limited. In order to update information gained, we provide a systematic overview of the skin lesions described in COVID-19 patients, discuss potential causative factors and describe differential diagnostic evaluations.

Introduction

The story behind the virus with the crown

Coronaviruses belong to a large group of related viruses, named coronavirus family, which can infect humans and animals and lead to diseases of the airways, the gut, liver, and the nervous system. Some members of coronavirus family may infect the upper airways with rather mild courses and others - as severe acute respiratory syndrome coronavirus SARS-CoV-2 – may affect the lower respiratory airways with pneumonia and fatal courses (Table 1) (**1, 2**).

Belonging to the β-Coronavirus genus, SARS-CoV-2 is the pathogen that causes the new infectious respiratory disease, termed as coronavirus disease 19 (COVID-19), which emerged in December 2019, in Wuhan (Hubei province, China) first and later turned to be a global pandemic (**2**). SARS-CoV-2 displays 79% nucleotide identity with SARS-CoV and 51.8% nucleotide identity with MERS-CoV, but most importantly shares 96% identity across the entire genome with a bat coronavirus, which is supposed to be the natural origin of SARS-CoV-2 (**1, 3, 4**).

As other coronaviruses, SARS-CoV-2 is an enveloped, positive-sense single-stranded RNA virus with spikes that protrude from the virus surface resembling a crown or "corona" (Fig. 1). Most importantly, the spike (S) protein of coronaviruses is essential for viral infection of host cells. During the virus entry procedure,

the S protein engages its cellular receptor, angiotensin-converting enzyme 2 (ACE2), which facilitates viral attachment to the cell surface of target cells. As a next step, the engaged S protein is further primed by the cellular serine protease (Transmembrane Protease Serine 2) TMPRSS2, which mediates membrane fusion and viral entry into the cells (Fig. 1) (**5, 6**). Importantly, as the efficiency of ACE2-S interaction largely determines SARS-CoV transmissibility (**7-9**), the expression of ACE2 receptors represents a major risk factor for the vulnerability to SARS-CoV-2 infection. In humans, the ACE2 receptors are expressed by $CD8^+$ T cells (**10**), resting and activated natural killer (NK) cells (**10**), alveolar epithelial cells of type II (**11**), vascular endothelial cells, macrophages and adipocytes (**12**). The nose and the nasal epithelium plays an important role for infection and viral spreading (**13, 14**). High ACE2 expression has also been demonstrated on epithelial cells of the oral mucosa, in particular the tongue, so that this receptor might provide an entry route for the virus and designates the oral cavity as a potential organ at high risk for viral spreading from one individual to the other (**15**). Tissue distribution of the *ACE2* gene includes the small intestine, testis, kidneys, heart, thyroid, and adipose tissue with relatively high expression (**12**). It has been recently demonstrated that the inflammatory cytokines interferon (IFN)-α2 and IFN-γ increase the expression of ACE2 and is supposed that tissue inflammation may modulate the receptor expression and thereby change the risk of immune cells to be infected by SARS-CoV-2 (**14**). So far, a positive correlation of *ACE2* gene expression to $CD8^+$ cells in the skin has been shown**12**).

Binding of SARS-CoV-2 to ACE2 downregulates its expression and impacts thereby on its main function, the regulation of the renin-angiotensin system. This downregulation leads to a dysregulation of the balance of soluble factors, electrolytes, blood pressure combined with an increase of vascular permeability and lung inflammation (**1**). Usually, virus-specific T cells recruited to the site of inflammation eliminate the virus with neutralizing antibodies generated from B cells and macrophages and prevent thereby virus spreading in an immunocompetent individual (**1, 16**). However, inflammation-induced cell death of infected cells and damage-released molecular patterns might induce proinflammatory cytokines and chemokines and recruitment of inflammatory cells to the lung (Fig. 2). Thus, the lung tissue damage caused by SARS-CoV-2 infection and replication, may thereby destroy step-wise the lung structure with the development of pulmonary fibrosis by transformation of adipocytes into myofibroblasts (**17**). The knowledge accumulated from SARS and MERS, together with current clinical observations from COVID-19 patients, suggest that type-I IFN-mediated antiviral responses and activation of both $CD4^+$ Th1 and $CD8^+$ cytotoxic T lymphocytes (CTLs) result in viral clearance in SARS-CoV-2 infected subjects with mild symptoms. However, insufficient initiation of antiviral immune responses, increased production of inflammatory cytokines, as well as lung infiltration of monocytes and neutrophils, contribute to a cytokine storm in SARS-CoV-2 positive patients (**18, 19**). Moreover, the cytokine storm elicited from the overproduction of pro-inflammatory mediators such as interleukin (IL)-1, IL-6, IL-12, and tumor necrosis factor (TNF)-α, not only leads to increased vascular permeability and inflammation in the lung (**18, 19**) but may reach other organs through the vascular system. In the worst case, this might induce injury of multiple other organs including the cardiac, renal or hepatic system (Fig. 2) (**1**). This cascade of events might lead despite intensive care and a lot of other measures initiated, to fatal courses and death, in particular in elderly patients and individuals with pre-existing diseases.

SARS-CoV-2 infection and COVID19

Transmission and symptoms

Transmission of SARS-CoV-2 is mediated mainly via respiratory droplets from an infected person (**20, 21**). Of note, SARS-CoV-2 positive patients emit respiratory droplets in high numbers during speaking, which remain in the air up to 8-14 minutes (**22**). The average incubation time until the onset of COVID-19 is 4-11 days (**23**). The immune responses resulting from SARS-CoV-2 infection vary broadly and range from asymptomatic courses, over mild, moderate to severe courses with a need for hospitalization and intensive care. Typical symptoms of COVID-19 include dry cough, fever, myalgia, headache, anosmia and ageusia (**24**). Depending on the severity of the disease, even other organ systems such as the gastrointestinal tract, the liver, the renal system as well as the cardiac system might be involved and become symptomatic as well

(Fig. 3).

Factors associated with poor prognosis

Comorbidities

Skin lesions might at least in part or completely result from the reactivation or aggravation of pre-existing skin diseases such as urticaria, autoimmune disease or other diseases with SARS-CoV-2 and soluble mediators and immune mechanisms induced both in the organs involved and systemically in the blood (**25**). Comorbidity rate increases the rate of mortality of COVID-19 with cardiovascular diseases, hypertension, diabetes mellitus and obesity being major risk factors (**26**). Sine adipocytes express ACE2 and might serve as a reservoir for SARS-CoV-2, this fact might explain in part the higher risk of obese patients (**17**).

Gender and sex hormones

Circulating plasma levels of ACE2 have been demonstrated to be higher in men with heart failure than in women and might indicate higher tissue expression of the SARS-CoV-2 entry receptor in man as a risk factor for more fatal courses of COVID-19 (**27**). The expression of ACE2 in the myocard is regulated by androgen in mouse models (**28, 29**). Male mice with hypertension had higher ACE2 expression, which was reduced after orchiectomy. These data indicate that testosterone might negatively impact on the risk for COVID-19.

In a study on patients with asthma, male gender, African Americans race and history of diabetes mellitus, was associated with higher expression of ACE2 and TMPRSS2 in sputum cells of patients with asthma (**30**).

Whether gender differences in terms of nature and frequency of the skin lesions exist, needs to be elucidated in further studies.

However, several gender differences in relation to virus responses and responses to viral vaccines have been described in the past. These include higher susceptibility of men to infectious diseases or stronger antibody titers inducible by a number of different types of vaccines in women as opposed to men. Moreover, plasmacytoid dendritic cell-mediated type I IFN responses have been demonstrated to be stronger in women than in men, another factor of putative importance for viral clearance even in the context of SARS-CoV-2 infections (**31, 32**). Higher susceptibility, need for hospitalization, longer duration of the disease and higher rate of mortality in men versus women has been also described for other virus infections such as with influenza virus (**33**). Together, these observations point to SARS-CoV-2 specific as well as general differences in viral immunity in man versus women.

Age, ethnic and genetic risk factors and senescence of the immune system

In the context of SARS-CoV-2 age seems to be one of the highest predictors of the probability to get infected as well as of the extent of symptoms and severity of COVID-19. One reason besides a higher number of comorbidities and drugs take in the group of elder patients might be that ACE2 expression increases with age (**34**). Younger age groups seem to be not only at lower risk but maybe even protected from infection or severe viral spreading within the body. This could be managed for example by the presence of cross-reactive antibodies derived from other rather mild coronavirus infections in the past and an immunocompetent viral defense system at different immunologic levels. Another reason might be the presence of allelic variants interfering with the binding of the S-protein of SARS-CoV-2 to ACE2 and putative protection of the carriers from SARS-CoV-2 infection (**35**). In contrast, higher allele frequencies of variants in the *ACE2*coding gene region, which go along with higher ACE2 expression in the tissue, have been observed in populations from east Asia (**36**) and might indicated a specific risk, related to ethnic groups.

Finally, senescence of the immune system with lower antigen response of T and B cells from elder individuals as well as weaker effector functions and limited number of $CD8^+$ memory cells capable to react do different pathogens might among other factors play a role for attenuated virus clearance and lower number of anti-inflammatory cytokines and mediators, innate immune regulatory proteins or regulatory cell mechanisms in higher age groups (**37, 38).**

Skin lesions observed in relation to SARS-CoV-2

Besides the typical symptoms described above, more and more reports about skin lesion and lesions of the vascular system observed in patients tested positive for SARS-CoV-2 and patients suspected to be infected by SARS-CoV-2 are coming up in countries all over the world (**39, 40**). The percentage of patients with skin lesions varies from lower than 1% to up to 20% of all SARS-CoV-2 patients and has to be estimated exactly in systematic studies on this issue.

The spectrum of skin lesions in SARS-CoV-2 patients described and published so far contain skin lesions occurring in other infectious and viral diseases such as maculopapular-exanthema, vesicular exanthema or urticarial eruptions (**39, 41-46**). Furthermore, the skin lesions might also be related to virus induced or indirectly induced vascular dysfunctions, such as livedo reticularis, petechiae or cutaneous acro-ischemia (**39-42, 47**). Chilblain lesions have been described as well (**48-50**). Considering frequency, most reports exist on maculopapular exanthema/vesicular exanthema, urticarial, and chilblain lesions (**41**). Less reports exist on acro-ischemia or livedo reticularis and other skin lesions.

Based on the largest collection of skin lesions from patients from Spain, lesions have been recently categorized into 5 main groups (**41**) summarized in Fig. 4A-E.

1. Vesicular eruptions, predate in about 15% COVID-19 symptoms or occur with symptoms, last 10-12 days and go along with COVID-19 with intermediate severity, patients affected are middle aged and lesions are accompanied by moderate itch (Fig. 4A).
2. Maculopapular exanthema manifests together with COVID-19 symptoms, often in more severe cases with a mortality rate up to 2%, lasts 7-9 days and is in over 50% of the cases accompanied by itch (Fig. 4B).
3. Urticarial eruptions occur at the same time as other symptoms in more severe COVID-19 cases are accompanied by itching and last 6-8 days (Fig. 4C).
4. Livedo or necrosis and other vasculitis forms tend to occur in older and more severe cases, with relatively high mortality (up to 10%) and the onset was together with COVID-19 symptoms (Fig. 4D).
5. Chilblain was observed in younger patients with mild or even asymptomatic courses, the onset is late, duration 12-14 days and in one third are the lesions accompanied by pain and itch (**22-23**) (Fig. 4E).

Methods

Since it is quite difficult to verify, in which context the skin lesions occur in terms of SARS-CoV-2 infections, we would like to summarize in the next few sections current knowledge about the pathophysiologic background of virus-induced and drug-induced lesions of the skin and the vascular system.

Data for this Review were identified by searches of MEDLINE, Current Contents, PubMed, and references from relevant articles using the search terms “SARS-CoV-2”, “COVID-19”, “skin”, ”vascular system“, ”virus (infection)“ and ”drug hypersensitivity reaction“. Only articles published in English between 1995 and 2020 were included.

Possible pathogenic mechanisms involved for skin manifestations

Viral rashes

Viral exanthema is defined as a skin rash, which is sometimes associated with an enanthem and goes along with fever and other systemic symptoms (**51, 52**). In this context, it is important to notice that also the ACE2 receptor has been described to be expressed in the oral cavity (**11**), lesions of the mucous membranes have not been reported so far to occur very frequently together with skin lesions in SARS-CoV-2 positive cases,

In principle, skin manifestation of viral infections can derive by

1. direct inoculation of the virus,
2. dissemination or reactivation of the virus from another site or

3. interaction of the virus with the immune system in general and related cellular and humoral immune responses including virus-specific lymphocytes and antibodies (**51**).

The onset of the skin lesions in relation to viremia and general symptoms can help to understand the pathophysiologic mechanisms behind the lesions in COVID-19 patients. In the case of skin lesions precede general symptoms or might even be the only sign for a putative infection, they might serve as important early indicators of the disease or indicator for asymptomatic virus carriers. On the other hand-side, skin symptoms, which occur quite late during infection or even after resolution of main symptoms might indicate a lack of viral clearance and cascades of immune responses induced by the virus .

Viremia often predates the typical COVID-19 symptoms and virus-specific virology might be both, false negative or false positive due to cross-reactivity to other members of the coronavirus family, but could provide important information about acute or previous infection by the analysis of virus-specific IgM and IgG. Nucleotide testing of tissue specimens is highly sensitive and specific, but stability of samples and RNA, contamination, and other issues may occur and limit information gained, so that even part of smear taken from the mouth remain false negative (**52**).

1.1 Virus induced maculopapular exanthema

Although skin biopsies are rarely taken from viral skin lesions, because the features observed are mostly not very specific, biopsies might be an option to differentiate viral exanthema from drug-induced exanthema in COVID-19 patients, in these cases it is essential to do the differential diagnosis and rule out the pharmacological cause.

To distinguish infectious exanthema from exanthema induced by drug-hypersensitivity reactions, histologic features and immunologic changes in the skin might help to diagnostically differentiate both entities.

Immunologic features of maculopapular virus exanthema known so far are summarized in Fig. 5A. Typical histologic features of infectious exanthema induced by viremia or dissemination of infectious agents through the blood are shown in Table 2 and Fig. 6A.

1.2 Virus induced vesicular eruptions

Virus induced vesicular eruptions are quite common for herpes simplex virus or varicella zoster virus induced skin lesions in which the vesicles are caused by intraepidermal blister and epithelial necrosis. Either reticular degeneration of the epidermis or ballooning of keratinocytes might cause intraepidermal vesicle formation (**53, 54**) (Table 2). Another example for virus induced vesicular eruptions are caused by Coxsackie A16 virus, an enterovirus, which is responsible for Hand-foot-and mouth diseases. Intraepidermal vesicles with reticular degeneration and ballooned cells are characteristic features. Papillary edema and mild perivascular infiltrates might be detectable as well. In all of those virus induced skin eruptions, viral antigens are detectable in various cutaneous structures using different methods such as antibody staining, electron-microscopy or others (**53, 54**).

Whether vesicular eruptions observed in part of the COVID-19 patients are caused by SARS-CoV-2, needs to be evaluated in further studies.

Some reports of erythemato-violaceous papules and patches with a pseudo-vesicle in the center, resembling erythema-multiforme and an enanthem of the oral cavity in some of those patients during or after improvement of COVID-19 symptoms exist (**55-58**). If those lesions are related to SARS-CoV-2 infection or drugs applied in this context or both remains to be elucidated in further studies.

1.3 Virus induced urticarial rashes

Urticaria and acute urticarial rashes go along with up to 50% of all cases with infections of the upper respiratory tract (**59**) and are most often mediated by complement activation and serum sickness induced by viral antigens or secondary mechanisms, due to the interaction of the immune system with viral antigens. This could be also the case in part of the SARS-CoV-2 positive patients with urticarial eruptions (Fig. 7).

1.4 Virus induced vasculitis

Infectious diseases are the cause of over 20% of cutaneous vasculitis (**60**). Most of them have a self-limiting course, but the involvement of other organs is possible.

Vasculitis can affect small, medium and large vessels (Fig. 8). Mechanisms might be type III or immune complex-mediated reactions to viral antigens or part of viral antigens. In this context, large immune complexes might precipitate and accumulate within vessels, a process leading to vascular injury (Fig. 8A) (**61**). Histologic features of vasculitis are an inflammatory infiltrate in wall of dermal or subcutaneous vessels (which can be neutrophilic, lymphocytic or granulomatous), red blood cell extravasation, variable fibrinoid necrosis of vessel walls, and nuclear debris. Further on, deposits of immunoglobulin, complement or fibrin in the vessel wall are detectable by direct immunofluorescence staining (**62**). Polyarthritis nodosa related to Hepatitis B infection is one example for a vasculitis directly induced by a viral antigen (**63**). Interestingly, specific virus genotypes of Hepatitis B and C Virus have been identified, which are associated with particular forms of vasculitis, which explains in part why only a subgroup of virus-infected patients develops such cutaneous vascular reactions in some viral diseases (**60**).

Cell-mediated hypersensitivity, in which exposure to viral antigens induce recruitment of lymphocytes, which release proinflammatory cytokines and further attract macrophages and more lymphocytes leading to tissue damage of the vessels, has also been described as a pathway in some infectious vasculitis types (Fig. 8B).

Furthermore, abnormal immune regulation including different expression of adhesion molecules and cytokines in vascular endothelium by different virus-related processes as well as direct endothelial cell invasion of the virus (Fig. 8C) or direct stimulation of the immune system by infectious agents might take place (**62**).

Whether and which kind of virus induced mechanisms of infectious vasculitis play a major role in SARS-CoV-2 vascular lesions is unclear, but immune complex mediated mechanisms are likely to be of relevance.

Furthermore, since ACE2 expression has been described for endothelial cells (**63, 64**), it is quite speculative but still conceivable at this time point - but even possible - that the virus directly interacts with endothelial cells leading to tissue damage and the resulting skin lesions.

In children an association of COVID-19 with Kawasaki-like disease with mucocutaneous involvement, polymorphic rash, erythema of the palms and soles, firm induration of the hands or feet, or both besides other symptoms of Kawasakis disease has been postulated (**65).**Kawasaki disease is classified a systemic vasculitis of medium size vessels (Fig. 8) and pathogens including different virus types have been suspected as one causative factor in a rather multifactorial pathogenesis. Further studies are needed to demonstrate a correlation of Kawasaki disease with SARS-CoV-2 in larger patient groups and time courses.

2. Previous skin diseases

Skin manifestations, such as urticaria, psoriasis, autoimmune diseases, or others, might result from the SARS-CoV-2 related reactivation or aggravation of pre-existing skin diseases.

Chilblain

Idiopathic chilblain or also called acro-ischemic lesions, presenting as violaceous, infiltrated painful and sometimes even pruritic plaques on erythematous skin with predilection on the back of the toes or feet has been described to occur in a special group of SARS-CoV-2 positive, suspected patients as well as asymptomatic or non-infected patients (Fig. 4F) (**66, 67**). Histologic features of these lesions were typical for a lymphocytic vasculitis, with a superficial and deeper lymphocytic infiltration around vessels and close to eccrine glands, a papillary edema, vacuolar degeneration of the basal layer as well as lymphocytic exocytosis to the epidermis. Red cell extravasation as well as focal thrombosis in papillary dermal capillaries as well as vessels of the reticular dermis were described in some reports as well (**49, 68**). The pathologic pathways behind these lesions are still unknown and remain to be elucidated. If it is related to SARS-Cov-2 infection remains to be demonstrated.

3. Cutaneous drug reactions

Cutaneous drug reactions are classified into immediate and nonimmediate drug hypersensitivity reactions. The latter have been subclassified into 5 groups based on the type of immune mechanisms in the foreground (Table 3). Part of the skin and vascular lesions are most likely related to drug hypersensitivity reactions.

3.1 Drug induced urticarial rashes

Urticaria and urticarial rashes belong at least in part to cutaneous type I (IgE-mediated) drug- hypersensitivity reactions (Table 3)(Fig. 7). Other mechanisms involved are direct mast cell activation, immune complex formation/precipitation (Fig. 7) and activation of complement during serum sickness or interaction with metabolic pathways of drugs such as arachidonic acid metabolism (**69**). Urticaria or urticarial rashes in SARS-CoV-2 patients could be drug induced, induced by drugs, viral RNA or a mixture of both. Infection-associated re-activation or exacerbation of pre-existing urticaria might be possible as well.

3.2 Drug induced maculopapular exanthema

In general, about 7% of hospitalized patients develop drug hypersensitivity reactions of variable severity, and exanthema occurs in 2-3% of these cases (**70, 71**).

Both, drugs and metabolites of drugs might elicit exanthematous drug-hypersensitivity reactions (Table 4).

Some skin lesions observed in COVID-19 patients might result from cutaneous type IV (T-cell mediated) drug hypersensitivity reactions. Typical immunologic characteristics of maculopapular eruptions are summarized in Figure 5B (type IVb) and 5C (type IVc) and histologic features are summarized in Table 5 and shown in Figure 6B. The most common histologic feature of drug-induced maculopapular exanthema is a perivascular dermal lymphohistiocytic infiltrate with or without infiltration of eosinophilic granulocytes. The epidermis can be normal or exhibit interface changes with vacuolar degeneration of the basal layer, apoptotic keratinocytes and exocytosis of lymphocytes can be present. Additional features can be edema in the upper dermis, extravasation of red blood cells and dilatation of blood vessels. It is often impossible to histologically distinguish viral and drug induced exanthema. Lichenoid – and less frequently- spongiotic or psoriasiform pattern of reactions may be related to maculopapular drug reactions. Sometimes even systemic eosinophilia and elevated CRP levels might occur (**72**). Typical immunologic characteristics of maculopapular eruptions are summarized in Figure 5B (type IVb) and 5C (type IVc) and histologic features are summarized in Table 5 and shown on Figure 6B.

3.3 Severe cutaneous adverse drug reaction

There are COVID-19 positive cases with DRESS (drug reaction with eosinophilia and systemic symptoms) described (unpublished reports), which is a severe cutaneous drug reaction with non-specific histologic findings (Figure 9A and B). The diagnosis is based on a combination of clinical symptoms and laboratory parameters including frequently occurring hepatic abnormalities, eosinophilia and exanthema with facial swelling and lymphadenopathy (**73**). The culprit drug should be stopped immediately upon identification. In some cases, eosinophilia could hardly be controlled with corticosteroids, which led to the successful use of agents interfering with the IL-5 axis (unpublished reports).

4. Drug induced vasculitis

Drug hypersensitivity reactions with changes of the vasculature or vascular pathways such as vasculitis, livedo racemosa or purpura represent a proportion of 10-20% of cutaneous reactions to drugs and can occur relatively late (7-14 days) during or even after drug exposure, but the time of onset to the related drug varies and depending on the causative drug (**74**).

Numerous drugs can induce vasculitis, which manifests primarily as cutaneous vasculitis, mediated as III hypersensitivity reactions (Table 3), i.e. immune complex deposits with antigen excess in arteries, arterioles, venules or capillaries (Fig. 8). It is of notice that some drugs might also induce antibody production (**62**).

Drug-induced vasculitis includes leukocytoclastic or hypersensitivity vasculitis, necrotizing vasculitis, Panarteritis-nodosa like vasculitis and others (**62**).

Histologic features of vasculitis are an inflammatory infiltrate in the wall of dermal or subcutaneous vessels (which can be neutrophilic, lymphocytic or granulomatous), red blood cell extravasation, variable fribrinoid necrosis of vessel walls and nuclear debris (**74**).

The number of drugs, which have been reported to be applied to COVID-19 patients all over the world is high and ranges from specific antiviral drugs, antiphlogistics, antibiotics, anti-coagulants, immunosuppressive as well as immunoregulatory drugs. All of these drugs are approved and tested for other infectious diseases or entities so that not much experience about putative side effects in COVID-19 patients exists and knowledge gained about skin lesions induced by drugs applied during other diseases can only be used and transferred to speculate on this issue.

Summing up, COVID-19 skin manifestations, could be caused for each one or a mixture of the components mentioned above i.e. reaction to the infection, drug hypersensitivity reaction, pre-existing immune state of the skin/immune system, combined with an impaired general health condition and other co-factors such as age of the individual. Therefore, it is important to discuss also putative additional trigger factors related primarily to the susceptibility to infection with SARS-CoV-2 and the risk to undergo severe courses of COVID-19 as an indirect factor predisposing subsets of patients to skin and vascular lesions.

Conclusion

Recent observation of involvement of the skin and the vasculature in subgroups of SARS-CoV-2 infected patients illustrates the need for a precise stratification and differential diagnostic evaluation of those patients in order to gain more insight into mechanisms of this novel virus. So far, pathophysiologic mechanisms behind the skin lesions occurring in the context of COVID-19 are speculative, could be related to the virus, drugs and other co-factors. Knowledge from other viral infections and drug induced lesions of the skin and vascular system might be transferred and observations on SARS-CoV-2 patients systematically evaluated to rapidly increase our knowledge on this issue. For mild cases of COVID-19, skin lesions can be a diagnostic hint; for severe cases, due to multiorganic involvement and interdisciplinary approach is of outmost importance.

Upper respiratory airways	**Lower respiratory airways**
229E	SARS-CoV
NL63	SARS-CoV-2
OC43	MERS-CoV
HKU1	

Table 1: Human coronaviruses

SARS: severe respiratory syndrome coronavirus; MERS: Middle East respiratory syndrome coronavirus

Table 2: Histologic characteristics of infectious exanthemas (adapted from 51)

Location	**Histology**
Capillary endothelium dermis	Damage of vessels, endothelial swelling, perivascular edema, hemorrhage
Dermis	Edema, cellular infiltrate, hemorrhage, visualization of organism by electron microscopy
Epidermis	Cytopathic effects of the virus, i.e., inclusion, ballooning, vacuolar degeneration, necrosis

Table 3 : Immunological classification of (cutaneous) drug reactions (modified from 75).

I	Specific IgE		Anaphylaxis
II	IgG or IgM		Hemolytic anemia
III	IgG or IgM		Serum sickness
Type IVa	Th1 (IFN-γ)	Monocyte activation	Eczema
Type IVb	Th2 (IL-4/IL-5)	Eosinophilic inflammation	Maculopapular exanthema, Drug Rush with Eosinophilia and systemic symptoms (DRESS)
Type IVc	CTL Perforin/ Granzyme B	CD4/CD8 mediated killing of cells	Maculopapular exanthema Toxic epidermal necrolysis
Type IVd	T cells (IL-8)	Neutrophil activation	Acute generalized exanthematic pustulosis (AGEP)
Type IVe	Th2 cells	CD4/CD8 cell activation	

Common	**Less common**	**Severe cutaneous drug reactions**
Maculo-papular exanthems	Lichenoid eruptions	DRESS
Urticaria	Pityiriasis rosea-like eruptions	AGEP
	Purpura	
	Vasculitis	

Table 4: Common and less common cutaneous (drug) eruptions (modified from 76), which have also been described in COVID-19 patients.

Dress=Drug Rash and Eosinophilia and Systemic Sympotms; AGEP= Acute generalized exanthematic pustulosis

Table 5: Features of drug-induced exanthema (modified from 72)

Lymphocytic exocytosis

Perivascular lymphohistiocytic infiltrate with or without eosinophils

Interface changes (vacuolar degeneration of basal layer, apoptotic keratinocytes, exocytosis of lymphocytes), lichenoid-, spongiotic- or psoriasiform changes

Papillary dermal edema

Extravasation of red blood cells

Elevated serum CRP and eosinophilia

Figure legends:

Figure 1: Structure of SARS-CoV-2 Virus with its typical capsid and the spikes, “corona”.

ssRNA=single stranded RNA; ACE2=Angiotensin receptor 2; TMPRSS2=transmembrane protease serine subtype 2.

Figure 2: Symptoms of COVID-19.

Figure 3: Cascade of events in lung epithelium during SARS-CoV-2 infection. SARS-CoV-2 infects lung epithelial cells via ACE2 and TMPRSS2 receptor, the host cells undergo apoptosis in consequence of virus replication and release and the undergoing cell releases damage-associated molecular patterns, which induce the production of pro-inflammatory mediators by epithel and endothel cells in the neighbourhood. Inflammatory cells such as monocytes, macrophages, and T cells are recruited from the blood to the lung epithel, increase the production of inflammatory mediates and further infiltration of the lung by inflammatory cells, leading to damage of the lung structure and a "cytokine storm", which reaches the vasculature and other organs.

ssRNA=single stranded RNA; ACE2=Angiotensin receptor 2; TMPRSS2=transmembrane protease serine subtype 2; Mo=monocyte, T=T lymphocyte, M=macrophage.

Figure 4 A: Typical skin lesions (vesicular eruptions occurring early during COVID-19 (A), with symptoms of COVID-19, i.e. maculopapular exanthema (B), urticarial rash (C), vasculitis (D) and later during COVID-19 disease Chilblain eruptions (E).

Figure 5: Immunologic features in the skin of virus-induced maculopapular exanthema (A) with virus antibody activation and interaction with immune cells in the blood, recruitment of activated cells to the skin, extravasation of erythrocytes through the blood vessels,, cytokine production and keratinocyte apoptosis and related changes to the dermis and epidermis and drug-induced maculopapular rush type IVb (B) and IVc (C) derived by activated T cells, extravasation of erythrocytes, perivascular infiltrates and perforin and granzyme B and Th1 cytokines as well as different chemokines and recruitment of T cells and eosinophils to the dermis and respective changes to the dermis and epidermis; DC=dendritic cell; B=B cell; Mo=monocyte, Eo=Eosinophil.

Figure 6: Histologic features of skin biopsies taken from two SARS-CoV-2 positive patients with maculopapular eruptions.

A: Skin sections showing epidermis with mild hyperkeratosis, keratinocytes with frosted glass nuclei, with intranulcular and occasionally multinucleate inclusions,

reminiscent of cytopathic damage. Dermis without edema, perivascular inflammatory infiltrate extending focally to the basal layer, causing slight vacuolate damage and

pigmentary incontinence. No eosnophils are observed

B: Histology (H&E stain) showing an inconspicous epdermis and a very subtle perivascular lymphohistiocytic infiltrate in the upper dermis with admixture of few eosinophilic granulocytes.

Figure 7: IgE-, direct- and antigen-immuncomplex-mediated mast cell activation in urticaria.

Figure 8: Vasculitis of small, medium and large vessels, with formation of antigen-immune-complexes, which accumulate within the vessels and damage of the endothel, which leads to extravasation of cells and neutrophil recruitment.

Figure 9 A: 58-year old male patient diagnosed with COVID-19 and DRESS syndrome.

B: Histology (H&E stain) showing interface changes (vacuolar degeneration of the basal layer, apoptotic keratinocytes, exocytosis of lymphocytes) as well as spongiotic changes with hyperparakeratosis. Perivascular lymphohistiocytic infiltrate with admixture of few eosinophilic granulocytes. Mild extravasation of erythrocytes.

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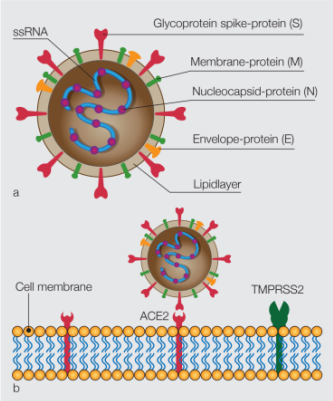


Figure 1

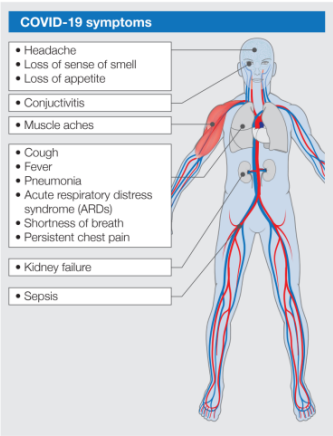


Figure 2

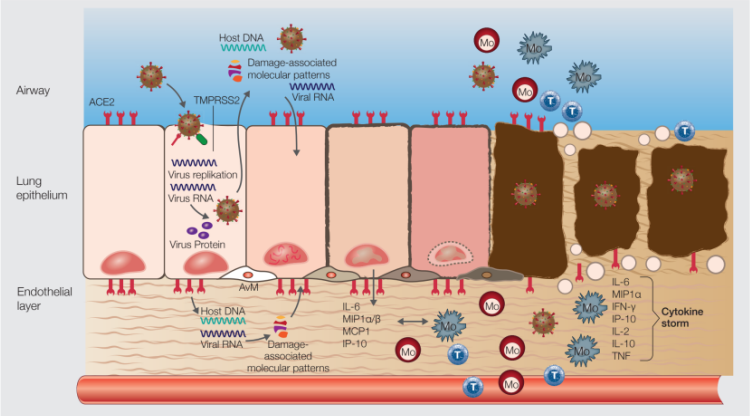


Figure 3

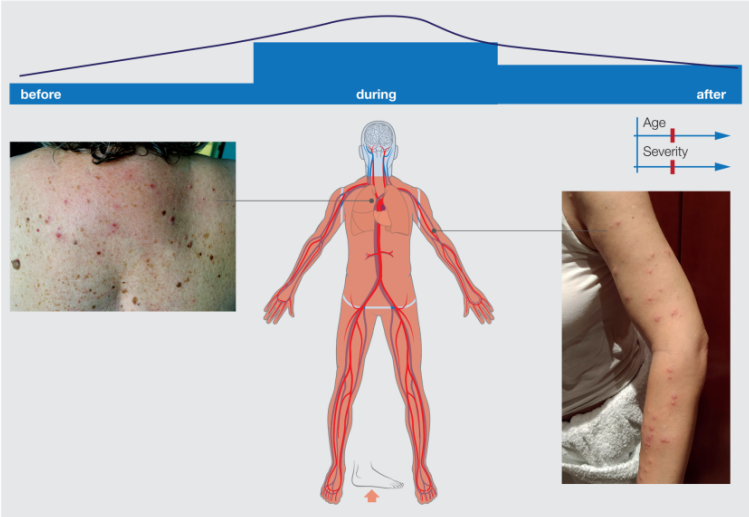
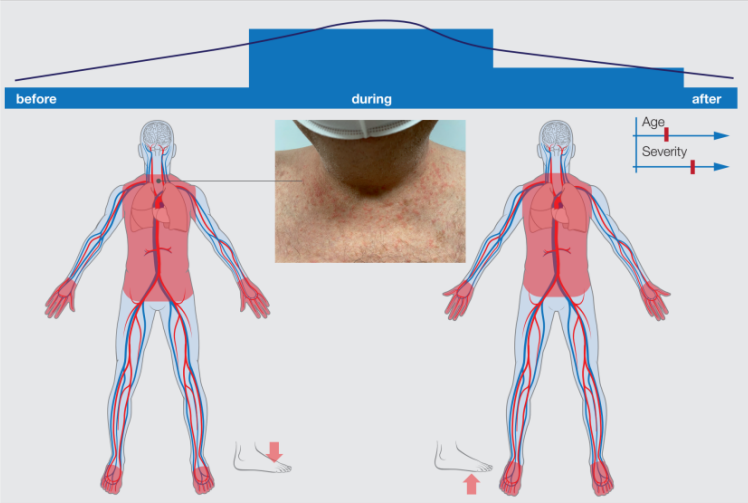


Figure 4A



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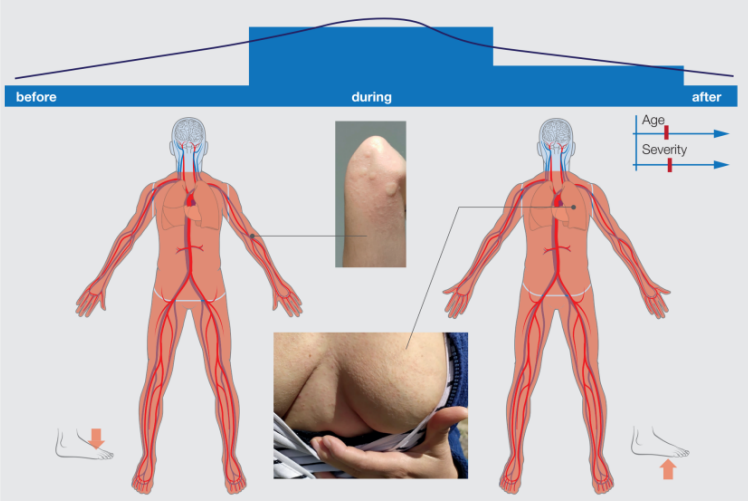

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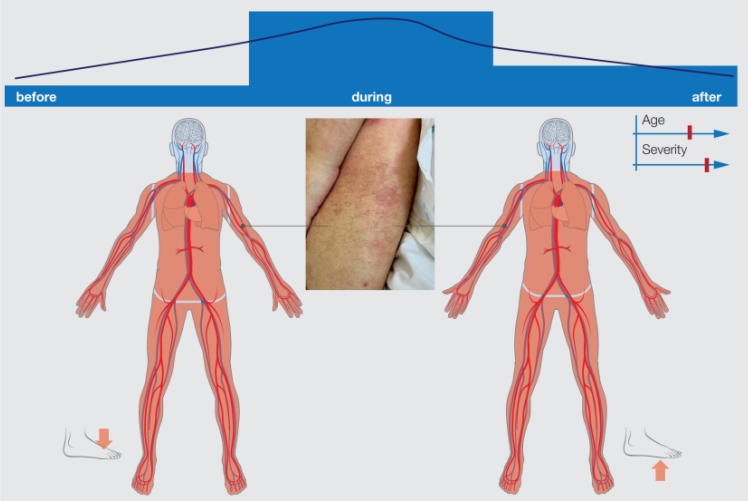
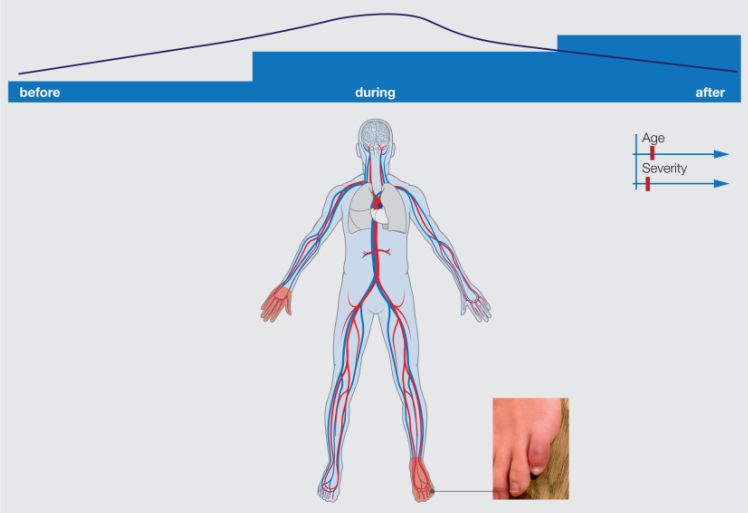


Figure 4D



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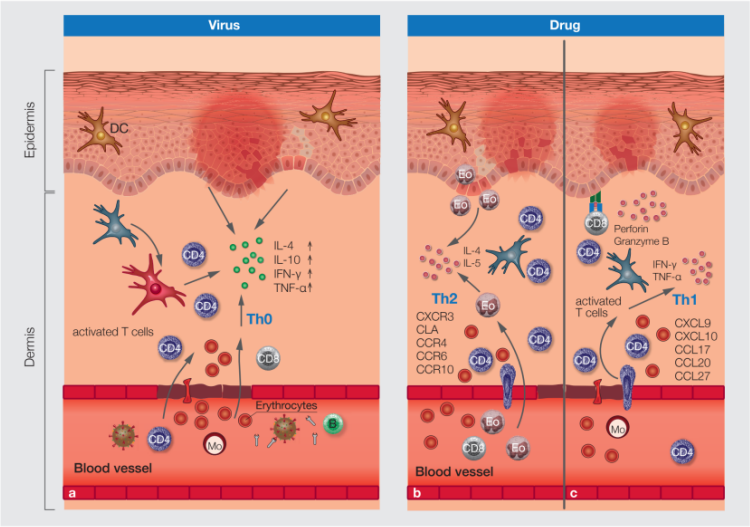

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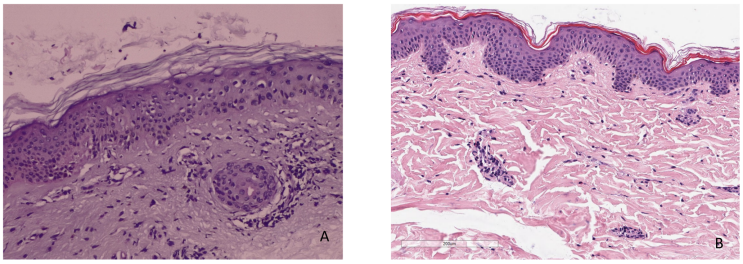

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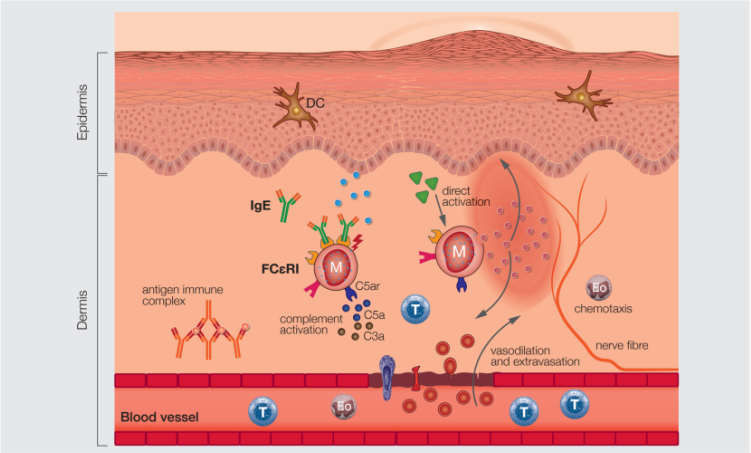

Figure 7

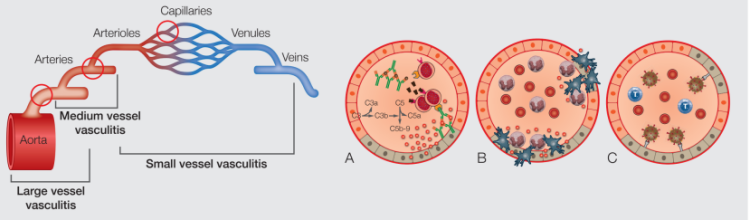

Figure 8

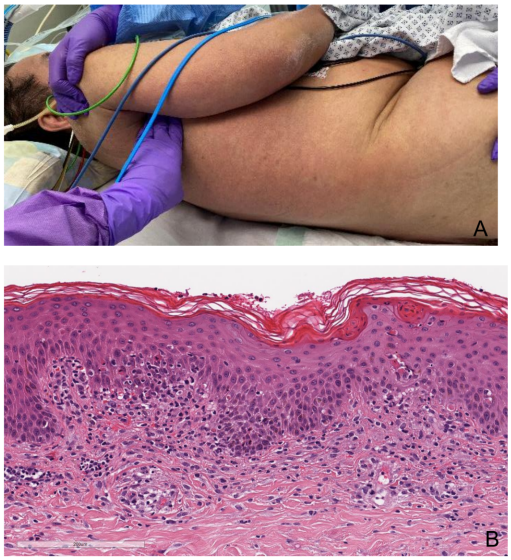

Figure 9