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1. Aktuelle Fachinformation TREMFYA®. 2. Reich K et al. Lancet. 2019;394(10201):831–839. 3. Reich K et al. Br J Dermatol. 2021 Jun 9. doi:10.1111/bjd.20568.
4. Mease P et al. The Lancet 2020; [https://doi.org/10.1016/S0140-6736\(20\)30263-4](https://doi.org/10.1016/S0140-6736(20)30263-4) (Supplementary)

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Submitted: 5.6.2020

Accepted: 20.7.2020

Conflict of interest

None.

DOI: 10.1111/ddg.14353

Skin manifestations reported in association with COVID-19 infection

Dirk Tomsitz, Tilo Biedermann, Knut Brockow

Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munich, Germany

Summary

The prevalence of all cutaneous manifestations directly associated with COVID-19 infection is unknown, but the number of reports is rapidly increasing and provisional knowledge is rapidly evolving. Skin manifestations reported can be classified into (1) manifestations unspecifically indicating possible infectious diseases, i.e. maculopapular exanthem, urticaria and erythema multiforme, and (2) manifestations more specifically indicating COVID-19 infection, i.e. varicella-like, livedo reticularis or chilblain-like eruptions. The latter appear to be associated with thrombovascular events and vascular pathologies.

Introduction

In December 2019, the first cases of coronavirus disease 2019 (COVID-19), an infectious lung disease caused by a novel, enveloped RNA betacoronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in Wuhan, China. Within the following months, the virus rapidly spread around the world and was responsible for many cases of severe lung diseases leading to many deaths. Recently, more and more data on skin changes of patients with COVID-19 have been published. In this narrative review, we want to give an overview of skin eruptions that have been described in association with COVID-19 (Figure 1, Table 1).

Skin manifestations can be divided into (1) skin changes commonly occurring in many infectious diseases without being specific for COVID-19 and (2) those skin changes that, according to current data, may be typical and indicative of possible COVID-19 disease. In the latter, the COVID-19 pathology points towards endothelial involvement and microangiopathy.

Skin changes indicating infectious disease

Maculopapular rash

During the onset of the pandemic COVID-19 outbreak, skin changes were not often documented. In a group of 1,099 patients “skin rash” has only been reported in two patients (0.2 %) [2]. An Italian study performed by dermatologists

documented a rash in 18 out of 88 patients with COVID-19 (20.4 %) [3]. Out of these 18 patients, 14 individuals developed an erythematous maculopapular rash. These rashes involved mainly the trunk without or with only mild pruritus. The rash intensity did not correlate with COVID-19 severity and it healed within a few days. Two cases of morbilliform rashes were diagnosed in COVID-19 patients in the USA without involvement of the face and mucous membranes, in one of them with mild pruritus [4, 5]. A prospective study in a COVID-19 population observed two erythematous rashes among a total of 103 patients [6]. Skin biopsy results are available from one COVID-19 patient with macular exanthem of the torso, arms and legs. Histologic analysis was consistent with a viral exanthem, but interestingly also revealed microthrombi in the vessels of the dermis [7]. In the currently largest prospective study in Spain, out of 375 patients who developed a skin disease and were diagnosed with or suspected of COVID-19, almost every second patient developed a maculopapular rash (n = 176, 47 %) [8], making this the most common skin manifestation in patients with COVID-19.

Urticaria

Widespread urticaria was described in three out of 18 patients with COVID-19 who developed skin eruptions [3]. Another case of urticaria was documented in a patient who presented with wheals, odynophagia and arthralgia, but without cough or fever. Not until 48 hours later did the patient develop fever, chills and chest pain and was tested positive



Figure 1 Skin manifestations. Maculopapular exanthema [3] (a, b), urticaria [8] (c–e), erythema multiforme [12] (f), varicella-like exanthema [13] (g), livedo reticularis [15] (h), chilblain-like lesions [20] (i), pruritic plaque on the heel [24] (j), acro-ischemia [28] (k).

for SARS-CoV-2 [9]. A patient with a very similar course was described in Spain, who presented first with urticaria, but no fever, coughing or typical corona symptoms. However, he was also tested positive for SARS-CoV-2, but remained afebrile during the following course [10]. In France, one out of 14 COVID-19 patients with skin eruptions was diagnosed with cold urticaria [11]. A prospective French study reported two cases of urticaria among 103 COVID-19 patients, of which a total of five had some type of skin symptoms [6]. In the prospective study from Spain, 19 % of 375 (n = 73) patients diagnosed with or suspected of COVID-19 infection with skin eruptions had urticaria [8].

Erythema multiforme

Two patients diagnosed with COVID-19 in Morocco (a 17-year-old adolescent and a 29-year-old male) developed targetoid plaques exclusively on the palms 15 days and twelve days after first symptoms of COVID-19 infection. In both patients, there was no history of herpes virus infections and the lesions healed within a few days [12]. In four Spanish women diagnosed with COVID-19, a multiform rash developed

16–24 days after onset of COVID-19 symptoms. The rash began at the upper trunk, spread over the body and resolved after 2–3 weeks of treatment with systemic corticosteroids. None of the patients showed any recurrence of COVID-19 symptoms [13].

Skin changes possibly indicating COVID-19

Varicella-like exanthem

In the Italian study, out of 88 patients with COVID-19, chickenpox-like vesicles were described in only one patient [3]. Another eight-year-old Italian girl developed a rash described as being varicella-like. Contrary to genuine varicella infection, the rash predominantly affected the trunk with no oral lesions and no pruritus [14]. A history of varicella infection one year earlier ruled out this diagnosis. Five days after the onset of the rash, she started to develop fever and cough and was afterwards tested positive for SARS-CoV-2. After nine days, the skin lesions healed without any intervention. In an

Table 1 Skin manifestations reported to be associated with COVID-19 infections (adapted from [1]).

Manifestation	Clinical description	Relative frequency*	Similarity to skin rashes of other infections	References
Maculopapular exanthem	Acute erupting, widespread distribution of multiple small, round to oval erythematous macules and/or papules with different degrees of confluence. Mostly trunk, low pruritus.	47 %	Unspecific for COVID-19; infections are common elicitors for maculopapular exanthem	[3, 4, 5, 6, 7, 8]
Urticaria	Sudden appearance of wheals with a fleeting nature. Continual appearance and disappearance of new lesions is characteristic.	19 %	Unspecific for COVID-19; infections are common elicitors for acute urticaria	[3, 6, 8, 9, 10, 11]
Erythema multiforme	Acute erupting, targetoid macules/plaques, sometimes with central blistering. Often affecting the palms, but also widespread distribution possible. Occurring > 12 days after onset of COVID-19 symptoms	Individual case reports	Unspecific for COVID-19; infections, especially herpes simplex virus and mycoplasma common elicitors for erythema multiforme	[12, 13]
Varicella-like exanthem	Monomorphic papulovesicular skin eruption. Erythematous papules and vesicles bilaterally and symmetrically mostly on the trunk.	9 %	May be more specific, vesicles are quite uncommon for virus exanthems and more specific for varicella	[3, 8, 15, 16]
Livedo reticularis	Transient macular erythema in a broad reticular pattern on thigh unilaterally.	6 % together with cutaneous acro-ischemia	Unclear, may be more specific, if causality can be confirmed	[8, 11, 16, 17]
Chilblain-like lesions	Acute-onset, violaceous, infiltrated and painful plaques on the toes and lateral feet. Vesicles and erosions may be present.	19 %	Probably more specific, often occurs in asymptomatic and younger patients.	[8, 18, 19, 20, 21]
Symmetrical drug-related intertriginous exanthema (SDRIFE)	Flexural erythematous maculopapular exanthem on axillary lesions and trunk +/-antecubital fossae.	Individual case reports	Untypical for infectious exanthems	[22]
Purpuric rash	Skin rash with petechiae	Individual case report	Untypical for infectious exanthems, except e.g. Parvovirus 19 and Coxsackie virus.	[24]
Pruritic plaques on both heels	Confluent, erythematous-yellowish papules in both heels	Individual case report	Untypical for infectious exanthems	[25]
Cherry angiomas	Not specified in the literature	Individual case report	Untypical for infectious exanthems	[11]
Acro-ischemia	Livid macules and plaques with finger/toe cyanosis, skin bulla and dry gangrene.	6 % together with livedo reticularis	Typical for severely ill patients with sepsis	[8, 26]

Relative frequency in percent of skin manifestations associated with COVID-19 infections according to [8]. *In cases where no numbers are given, only individual case reports exist.

Italian multicenter-study, 22 patients with varicella-like exanthem and COVID-19 were analyzed [15]. The mean time interval between COVID-19 symptoms and the beginning of the rash was three days (–2 to 12 days) and it persisted for eight days (4–15 days). The trunk was constantly involved, and in some cases also the limbs. No involvement of mucous membranes was seen, and pruritus was either mild or absent. Of the 375 patients with diagnosed or suspected COVID-19 with skin symptoms, 34 (9 %) were described as having a vesicular rash [8].

Livedo reticularis

Two patients in the USA diagnosed with COVID-19 were described with a transient livedo reticularis, both unilateral, without symptoms, and lasting only for 19 hours or 20 minutes, respectively [16]. In both cases, the rash started ten days after the first COVID-19 symptoms. A similar skin manifestation has been described in one patient of the prospective study by Bouaziz [11]. Another patient having a rash consistent with livedo reticularis on the chest, legs and arms had elevated D-dimer (1,187 ng/ml). A skin biopsy was performed showing modest perivascular lymphocytic infiltrate in the superficial dermis along with small thrombi within rare venules of the deep dermis, in the absence of a clear vasculitis [17].

Chilblain-like lesions

Shortly after the beginning of the COVID-19 pandemic, physicians observed an increasing number of asymptomatic children and adolescents with acute and self-healing livid lesions on the hands and toes. Although the majority of these children finally tested negative for COVID-19 and the causality thus remains speculative, the massive outbreak of chilblain-like lesions specifically at localizations severely affected with COVID-19 (Italy, Spain) argues for a causal relationship. Patients had no vascular predispositions like Raynaud's phenomenon or acrocyanosis. In an analysis of 41 patients with chilblain-like lesions, the median age was 16 years and all skin changes resolved within few days [18]. Although a test for COVID-19 was only performed for 19 patients and turned out negative, six patients cohabited with at least one person having confirmed COVID-19 infection. Another group collected 58 patients with chilblain-like lesions in a prospective study. Among these patients, 19 were not tested, 38 were negative for SARS-CoV-2, and one patient with vascular ulcers tested positive [19]. In 63 patients with chilblain-like lesions identified via teledermatological consultation, only eleven patients received diagnostic work-up and only two tested positive for COVID-19 [20]. Other case reports described two patients with chilblain-like lesi-

ons in Kuwait and one patient in Belgium, all were positive for COVID-19 [21]. In the latter, histological work-up of a skin biopsy showed a superficial and deep lichenoid, perivascular and peri-ecrine infiltrate of lymphocytes with occasional plasma cells. There was vacuolar alteration along the basal layer of the epidermis with scattered necrotic keratinocytes, which were occasionally present in superficial layers of the epidermis consistent with chilblains. In the large prospective Spanish study, out of 375 patients with suspected or diagnosed COVID-19, 71 [19 %] patients with a mean age of 32.5 skin eruptions were having chilblain-like lesions.

Rarely described skin changes or those associated with complications of COVID-19 infection

Some patients with skin eruptions could not be categorized into one of the above-mentioned groups, because of single descriptions only or suspected indirect consequences to COVID-19 infections. One patient developed an erythematopurpuric maculous flexural rash with mild pruritus mainly located in the axillary region eleven days after the onset of COVID-19 symptoms [13]. One rash of a COVID-19 patient in France was described as being symmetrical drug related intertriginous and flexural exanthema-like (SDRIFE) [22]. Drug-induced rashes can be a valid differential diagnosis particularly in those, but also in other cases with urticaria or exanthems [23]. Another rash of a COVID-19 patient was diagnosed as dengue-like with petechia and concomitant thrombopenia [24]. A patient with COVID-19 was reported with pruritic plaques on both heels [25], another with cherry angiomas [11].

Some skin eruptions were not directly seen as a consequence of COVID-19 infection, but as the result of complications. In China, acro-ischemia was described in seven patients treated in intensive care units, most likely due to disseminated intravascular coagulopathy [26]. Also, the incidence of children who developed Kawasaki syndrome during COVID-19 pandemic notably increased. As documented in a prospective study in France, of 21 patients who developed a complete or incomplete Kawasaki syndrome, SARS-CoV-2 was detectable in 8 patients (38 %) and IgG antibodies in 19 patients (90 %). 76 % of the patients developed a polymorphic skin rash as well as changes to lips and oral cavity [27].

In order to gather more information about skin changes in patients with COVID-19, special registries were established, for instance the International Dermatology COVID-19 Registry, a collaboration between the International League of Dermatological Societies and the American Academy of Dermatology.

Acknowledgements

Open access funding enabled and organized by Projekt DEAL.

Correspondence to

Knut Brockow, MD
Department of Dermatology and Allergy Biederstein
Technical University of Munich

Biedersteiner Strasse 29
80802 Munich, Germany

E-mail: knut.brockow@tum.de

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