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COVID-19 dermatological manifestations

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Abstract

COVID-19 is an ongoing multisystemic viral infection, which affects both adults and children. The virus has a complicated and not fully understood pathophysiological mechanism of damaging different organs and systems, including the skin. Cutaneous manifestations classification is complicated by the great variety of lesions and histological appearances, neither specific. Herein, a thorough overview of the clinical and pathological peculiarities of skin changes observed in the acute and re-convalescent stages of COVID-19 infection, is highlighted. The pathophysiological mechanisms, suggested to trigger and sustain the dermatological dysfunction, are also considered in the vicinity of authors' personal experience.

Keywords: COVID-19; Skin lesions; Dermatological features

1. Introduction

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is an infection, caused by single-stranded, positive-sense RNA virus, belonging to the Coronaviridae family, Coronavirinae subfamily, genus beta, B lineage [1]. The first case report came from Wuhan, China in December 2019 to shortly acclaim the term COVID-19 by the World Health Organization as the name of this noval and totally mysterious viral disease [2]. Soon after, the infection critically disseminated worldwide, affecting both adults and children, and caused a pandemic on 11th March 2020 [3].

Despite its outstanding pulmonary tropism [4], the virus shows high affinity to the capillary endothelium, thus disseminating to a broad spectrum of internal organs, triggering multisystemic dysfunction. Herein, a didactive review of the dermatological changes in a pathological correlation to the dermatological damage, is presented [5, 6].

2. COVID-19 dermatological features

The accumulated number of case reports and group series describe different COVID-19 related dermatological changes, which vary according to the time setting, associated systemic involvement, and chronicity. In the first category, the onset of cutaneous manifestations may be either concomitant with the respiratory symptoms, e.g., acute, or retardant – appearing long after the obtained PCR negativity of the affected subject [7, 8]. Meanwhile, these dermatological lesions can occur either solitary or in the context of multiorgan dysfunction [9]. The duration of the skin symptoms also differs, showing either transitory, intermittent appearance, usually in the acute phase of the disease; or refractory, chronic course that may experience several flares [10].

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Our personal observations reveal more common chronic involvement with an onset around 1-2 months after an asymptomatic or a mild respiratory COVID-19 infection. Of course, this phenomenon can be restricted to the logistic peculiarities, since in the acute infection stage most patients refer to infectious and intensive care units, which underestimates the accuracy of their dermatological evaluation.

The morphological diagnosis of skin changes is of utmost importance. Therefore, the clinical classification of dermatological COVID-19 related changes requires close attention. The updated consensus, accepted worldwide, differentiates seven main categories of skin lesions: 1. purpuric lesions (mostly acral, including pseudo-chilblain and necrotic); 2. morbilliform or maculopapular rash; 3. erythema multiforme-like; 4. urticarial lesions; 5. vesicular; 6. Kawasaki-like;7. miscellaneous/heterogenous/combination of the abovementioned [11,12]. Most of the skin lesions show no specific body predilection, although face and mucosal membranes are usually spared. Majority of patients experience mild to moderate itch. Some reports observed male predisposition, which has not been largely accepted. Our experience shows no sex predilection. Most of the skin lesions appear spontaneously and follow a course of self-resolution.

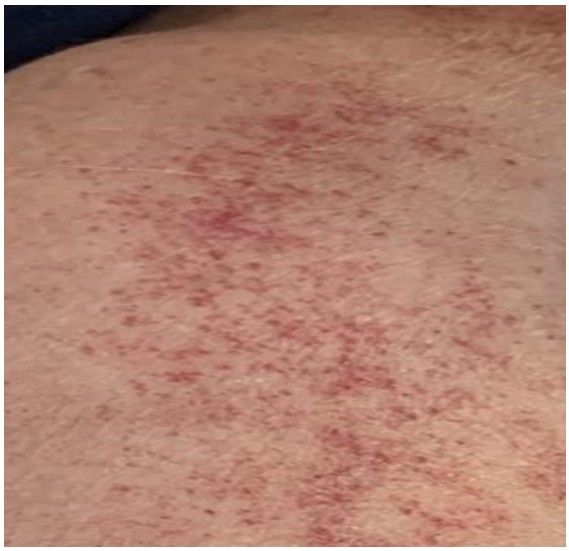

Figure 1 Disseminated petechial haemorrhagic skin changes in a patient with COVID-19 sepsis

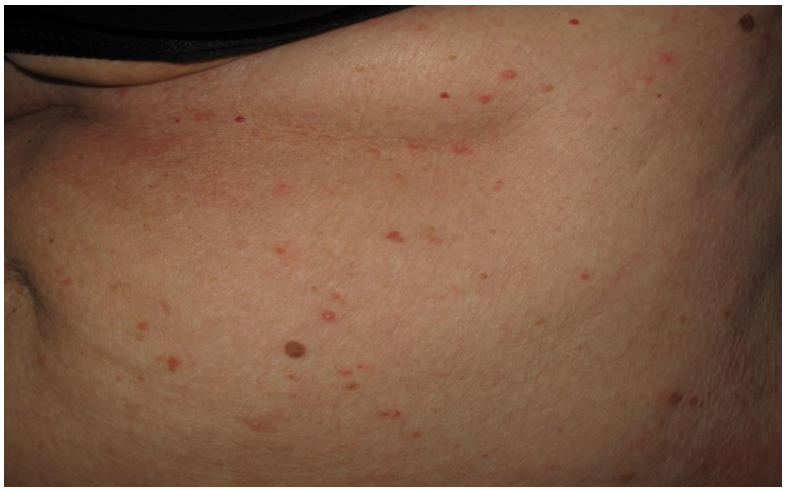

Figure 2 Papulo-vesicular rash disseminated on the patient's trunk

In our opinion, the most accurate classification of skin changes should be based on clinical course and progression of the disease. In this respect, we consider that dermatological manifestations must be divided in two main groups: skin lesions due to thrombosis and obstructive coagulopathy and non-specific maculo-papulo-vesicular exanthema seen commonly in the context of various viral infections. The first category usually encompasses purpuric and papulo-necrotic changes that occur in older patients, at the onset of the acute COVID-19 infection simultaneously with

thrombotic complications (Fig. 1). The second group of skin lesions seems to have a benign chronic course, and survival rate over 90%. These skin lesions may appear up to two months after the viral inoculation and commonly feature a heterogeneous morphological phenotype, combining papulo-vesicular (Fig. 2) and a targetoid, erythema multiforme-like phenotype. They can sometimes clinically mimic Grover's disease or bullous pemphigoid. Usually, the trunk and extremities are involved, including hands and feet. Lesions tend to be lenticular, disseminated, erythematous, smooth-surfaced, and well-defined.

Some of our patients developed erythemo-papulo-desquamative efflorescence as an extensive psoriasiform rash, which does not cover the predilection sites for its clinical prototype – elbows, knees and capillitium. This observation differs from the widely accepted morphological categories, typical for COVID-19 infection and probably is due to a specific incountry-predilected immunogenicity (Fig.3). These skin changes should also be classified to the second group of indolent, non-specific dermatological manifestations that suggest better clinical outcome.

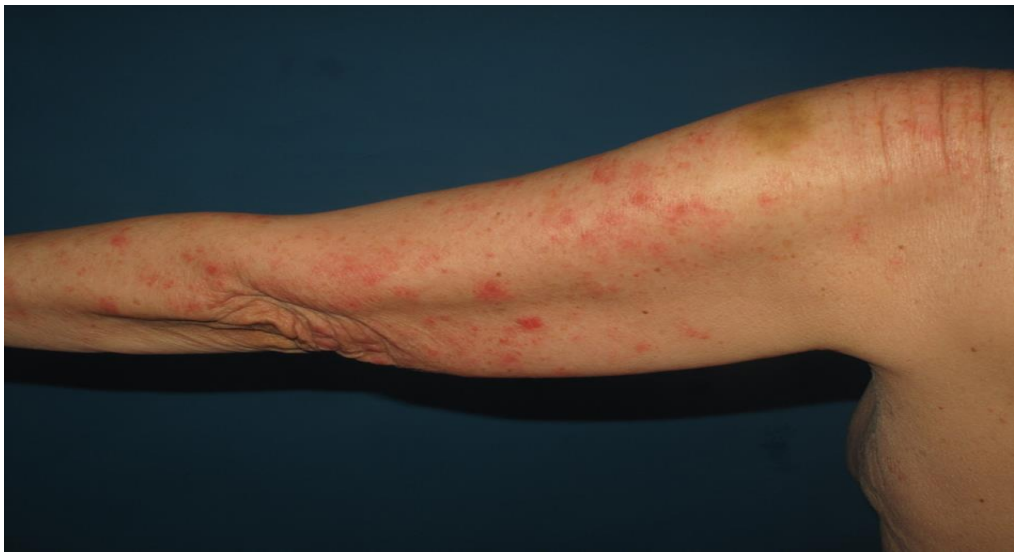

Figure 3 Psoriasiform exanthema in a patient with a 2-week negativity of SARS-CoV-2 PCR test

3. Histology findings

So far, the reported cases presenting the clinical appearance of the COVID-19 related skin lesions outnumber the histological analysis. Analogical to the wide variety of the lesions' morphology, there are many corresponding histological features, none of which specific. The most commonly reported characteristics include: acanthosis, spongiosis, acantholysis, dyskeratotic cells, papillary dermal edema, extravasation of erythrocytes and variable lympho-histiocytic infiltrates [9].

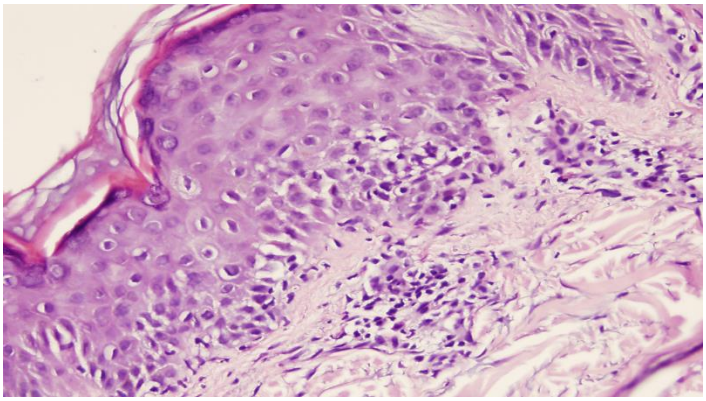

Figure 4 Focal suprabasalacantholysis and ballooning of spinous keratinocytes mimicking transitory acantolyticdisease (Morbus Grover) in a patient with re-convalescent COVID-19 infection (H&E, x 100)

The epidermal changes include thickening of the keratinocytic layers and mild to moderate intercellular edema, which usually is formed as a by-stander phenomenon due to florid chemotaxis of inflammatory cells in the papillary dermis [10]. Intercellular edema with ballooning of the keratinocytes and respective degeneration represents the direct viral cytopatic effect, which morphologically corresponds to the formation of an intact vesicle on top of an erythematous papule [13].

Dyskeratotic cells, acantholysis and the mixed inflammatory infiltrate sometimes in combination with dermal edema are the most commonly viewed features in our histopathological analysis. The focal suprabasal acantholysis (Fig. 4), mimicking Grover's disease characterizes the direct keratinocytic viral damage. In these cases, a direct immunofluorescence study is needed to rule out an autoimmune blistering dermatosis.

The other most common histological feature is the intensive, predominantly perivascular round cell inflammatory infiltrate (Fig.5), which corresponds to a profound immune reaction in the context of macrophage activation syndrome. Interestingly, we have not observed obstructive coagulopathy or vasculitis features, probably due to the acute nature of these complications and the unavailability of skin biopsies from such severely-affected patients.

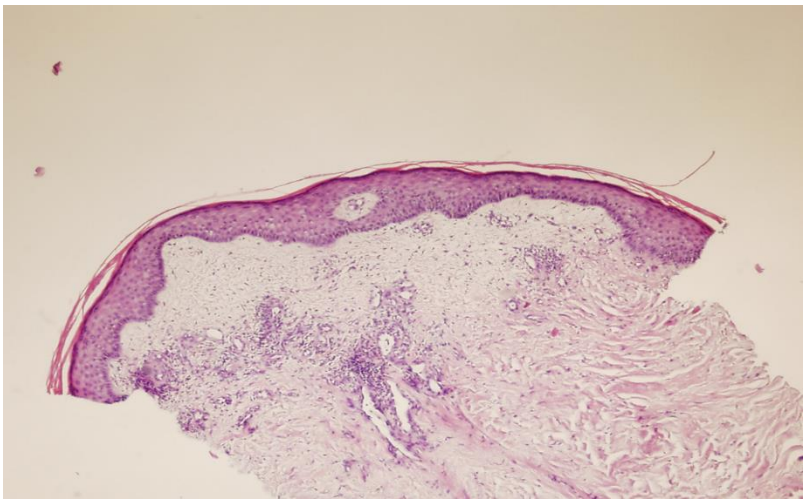

Figure 5 Severe papillary edema with moderate perivascular lympho-plasmocytic inflammatory infiltrate in the upper dermis (H&E, x 40)

4. Pathophysiological hypotheses

The intimate pathophysiological mechanism for the formation of skin lesions is not yet fully understood. Several hypotheses have been suggested, mostly focus on direct viral cytopathic effect, vasculitis-induced reactivity, and the consequences of the systemic inflammatory reaction [14].

The most credential theory speculates on the impact of angiotensin-converting enzyme 2 (ACE2) receptors in the skin [15]. These are membrane-bound receptors, distributed on the surface of the basal keratinocytes and eccrine sweat glands, most-widely distributed on palms and soles. Normally, ACE2 receptors are protected by the water-lipid barrier of the corneal layer, however, an epidermal injury thoroughly reveals them to the external invaders thus facilitating the intracellular penetration and replication of the virus through the activation of pleiades of various trans-membrane intracytoplasmic toll-like receptors. The recruitment of inflammatory cells is triggered by complement activation and massive release of cytokine mediators such as interleukin-6 and tumor-necrosis factor that drive macrophage and ferritin synthesis and provoke thrombotic events with the release of the tissue plasminogen activator [16]. The humoral immunity enhances the formation of antiphospholipid antibodies, which can explain the formation of acral necrosis and livedo racemose – like skin changes seen in patients with acute, thrombotic complications.

Other pathophysiological hypotheses include direct cell damage, caused by the virus itself and type III hypersensitivity reaction in the vascular endothelium [17]. Viral sepsis can also explain the multiorgan damage. It seems that TNF-alpha induces apoptosis of the infected keratinocytes and promotes endothelial damage, especially in patients with pre-existing microvascular dysfunction in the context of diabetes mellitus and cardio-vascular disease.

Moreover, Kolivras et al. hypothesized that the individual immune reactivity to the virus depends upon the induction of type I interferon (IFN) response [18]. They suggested that an early IFN response suppresses the uncontrolled release of diverse pro-inflammatory mediators, thus minimizing the risk of a cytokine storm. The corresponding skin lesions in this clinical context are livedoid microangiopathic acral lesions, mimicking chilblains. The disease follows mild, benign, although prolonged course. On the opposite, a delayed type IFN induction leads to macrophage activation syndrome, acute ischemic lesions, and severe disease course with lethal outcome. It usually occurs in elder patients with associated co-morbidities and immunosuppression.

Any of these theories could be the reason for the common findings of vasculitis and coagulopathy (formation of microthrombi in situ or in the contest of disseminated intravascular coagulation) in patients with cutaneous lesion associated with COVID-19 [19]. With the help of electron microscopy viral inclusion structures were viewed in endothelial cells in different organs as long with diffuse endotheliitis. In addition, many of the clinical cutaneous manifestation are actually different forms of vasculitis (urticaria-vasculitis, Kawasaki-like lesions, etc.) [17].

5. Disease course and progression

The above-mentioned pathophysiological mechanisms acclaim two main groups of skin manifestations: cytopathogenic presented by morbilliform, urticarial or varicella-like lesions and dermatological by-standers of inflammatory immune response. The second group should be sub-classified to: 1. a self-resolving, benign category, which presents with chilblain-like lesions and is due to an early type I IFN response; and 2. acute, thrombotic changes that provoke acral ischemia, gangrene, retiform purple and livedo racemosa, evolve in the setting of macrophage activation syndrome, and exert a very bad prognosis, usually with lethal outcome. The accurate clinical differentiation of these specific cutaneous lesions gains utmost prognostic value and is critical in the rational patient management.

6. Conclusion

The classification of COVID-related cutaneous manifestations is extremely difficult due to the broad variety of clinical presentations. Skin lesions can precede, accompany or follow systemic involvement, and can even evolve as a solitary symptom in the viral inoculation. Emerging awareness of the specificity of dermatological damage occurring in the context of COVID-19 infection proves more accurate clinico-pathological correlation that can facilitates the proper patient management and treatment modalities.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There is no conflict of interest to declare.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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