COMMENTARY

The crucial role of clinicopathological correlation in COVID-19-related cutaneous manifestations

Skin is one of target organs affected by the novel coronavirus SARS-CoV-2, and a fast body of literature has emerged on cutaneous manifestations related to coronavirus disease 2019 (COVID-19). However, in contrast with the abundance of epidemiological and clinical reports, histopathologic characterization of skin manifestations is more limited, based on small case series and individual observations. A plausible explanation is that in view of the greater severity of lung and multiorgan involvement, invasive skin assessment has been postponed avoiding additional sufferance to the patient. Moreover, at least initially, there were many difficulties in obtaining skin biopsies in COVID-19 patients, and the transient course of many types of eruption has complicated the issue. Nevertheless, skin histopathology might be crucial to differentiate clinically similar lesions and deepen the comprehension of pathogenetic mechanisms that are effectively associated with COVID-19. In this issue, Barrera-Godínez et al describe a series of 28 inpatients with a confirmed diagnosis of COVID-19 who during their admission developed skin lesions, which have been studied with biopsies and the accompanying histopathological findings.[1] The most common clinical patterns of presentations included morbilliform- and urticaria-like exanthems in 17 patients (77%). Spongiosis, basal vacuolar degeneration, a superficial perivascular mixed infiltrate composed of lymphocytes, histiocytes with neutrophils and eosinophils were the histopathological hallmarks of these lesions. Although these findings were consistent with previous reports,[2,3] they do not show any specific signs that could help to differentiate COVID-19 skin lesions from non-COVID-19 causes such as drugs or other viral infections. However, some aspects of interface vacuolar dermatitis that have been observed in all of the urticaria-like exanthems are of interest because they would not be normally expected in acute common urticaria. Therefore, it has been suggested that a skin biopsy is useful in differentiating urticaria-like viral exanthems from acute urticaria in the setting of COVID-19. Additional histopathologic findings described in the literature in COVID-19-related exanthematous eruptions, such as dyskeratotic keratinocytes, herpes-like changes, Grover-like changes, nest of Langerhans cells, subepidermal oedema, periadnexal lymphocytic infiltrate and thrombosed vessels have not been found in the current patients.[4] Whether this is due to an evaluation of lesions of different pathogenesis or to an early administration of corticosteroids and heparin is yet to be verified. A peculiar pattern of a purely papular eruption made by disseminated, discrete, red non-confluent papules distinct from previous reports of COVID-19-associated exanthems that featured a maculopapular morphology was observed in four patients; in this setting, histopathology showed a non-specific variable, inflammatory perivascular pattern with again the presence of interface vacuolar alteration. Histological features of neutrophilic eccrine hidradenitis were also observed in one of these patients. Further studies are needed to confirm whether this purely papular presentation could be actually linked to COVID-19. It is likely that these morbilliform eruptions are not related to a direct viral cytopathic effect but they rather correspond to a paraviral phenomenon, also considering that the presence of SARS-CoV2 was not found when searched in cutaneous samples by *in situ* hybridization and immunohistochemistry[5] In any case, when evaluating a maculopapular rash of unknown origin, and in the appropriate epidemiological context, COVID-19 should be considered in the differential diagnosis, especially if the histopathological findings show a vacuolar pattern of interface dermatitis.

No cases of pernio-like lesions were reported. It should be noted that histopathology of pernio-like lesions in the setting of COVID-19 are considered one of the most reproducible patterns including a mild to moderate perivascular and perieccrine inflammatory dermal infiltrate with no or minimum involvement of the epidermis, endothelial alterations of the dermal plexus without leukocytoclastic vasculitis and sometimes sparse necrotic keratinocytes or small intravascular thrombi.[5] Demonstration of SARS-CoV-2 in endothelial cells and epithelial cells of eccrine glands explains the pathogenesis of the pernio-like lesions in COVID-19 patients, although serological and RT-PCR tests have been found often negative.[6] The hypothesis that anticoagulative therapy in this Mexican case series could prevent the development of clinically evident pernio-like lesions by inhibiting vasculopathy and thrombus formation has been suggested.

A vesiculobullous morphology was described in four patients in whom the histopathological findings showed epidermal necrosis with signs of interface dermatitis and dermal inflammatory infiltrate consistent with erythema multiforme-like eruption. These cases are different from those patients presenting with the varicella-like eruption, another specific pattern linked

to SARS-CoV2, in which cytopathic changes consistent with viral injury were described.[7]

The differential diagnosis of exanthematous eruptions associated with SARS-CoV2 remains a big challenge because many other viral infections develop similar rashes. Epstein–Barr virus, human herpes virus 6 and 7, cytomegalovirus, herpes simplex may develop or reactivate as an effect of the treatments to contrast COVID-19.[8] However, the main differential diagnosis is with adverse drug reactions whose histopathology includes a wide range of microscopic patterns,[9] from spongiotic or perivascular mixed infiltrate to interface dermatitis. Temporal correlation with drug administration, as well as the spectrum of reactions associated with a specific drug,[10] together with main histologic features may help distinguish COVID-19 lesions from drug-related ones. For instance, pustular eruptions such as acute generalized exanthematous pustulosis are more frequently associated with hydroxychloroquine and macrolides than to viral infections.[11]

In conclusion, a great heterogeneity of skin manifestations is increasingly associated with SARS-COV-2 infection, and categorization is necessary to distinguish among pathognomonic signs, and non-specific consequences of the COVID-19 systemic involvement or management, including adverse drug reactions. Clinicopathological correlation has a crucial role in distinguishing coincidence from causal correlation to COVID-19, but more skin biopsies are warrant. Substantial breakthroughs may derive also from improvement of immunohistochemistry, RNA detection of SARS-CoV-2 strain by real-time PCR-based assay and electron microscopic studies. In any case, the paper of Barrera-Godínez et al highlights that routine histopathology with special stains is paramount and often can be enough to rule out cutaneous manifestations independent of COVID-19. In fact, an association with COVID-19 was discarded in almost one-third of the dermatoses observed just because of the supporting histopathological findings.

Conflicts of interest

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