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HYPOTHESIS

A Working Hypothesis on Vesicular Lesions Related to COVID-19 Infection, Koebner Phenomena Type V, and a Short Review of Related Data

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Abstract: SARS-CoV-2 has recently been associated with the reactivation of varicella zoster virus in patients. This is potentially an observation of a local susceptibility of the skin in areas of vesicle formation. This article explores the dermatologic manifestations that have been linked to the SARS-CoV-2 virus, their infectious risk, as well as potential confounding factors. An isotopic response may be occurring due to the occurrence of an immunocompromised district incited by sustained inflammation mediated by inflammatory cytokines.

Keywords: COVID-19, SARS-CoV-2, Koebner phenomenon, wolf isotopic response, locus minoris resistentiae, vesicular rash

Objectives

We attempt to investigate recently published data to characterize SARS-CoV-2 skin manifestations with a focus on the newly described COVID vesicles, their temporal course when related to recent reports of other concomitant dermatologic manifestations, and to describe the pathogenesis that is associated with a localized susceptibility in the skin areas where they appear. We attempt to generate a hypothesis that may help explain some of the recent reports related to these newly observed skin phenomena caused by the SARS-CoV-2 virus.

Introduction

The SARS-CoV-2 virus responsible for the current global pandemic has been implicated in a plethora of dermatological manifestations, such as pseudo-chilblain, vesicular, urticarial, maculopapular, and livedo/necrosis-type lesions.[1] COVID-19 related enantemas or exantemas might raise suspicion of SARS-CoV -2 infection, but these can also occur in various other different types of viral infections, like rubella or measles. While the predominant route of SARS-CoV-2 transmission is through the respiratory tract, other routes such as sexual or fecal-oral routes have been proposed.[2] There is evidence of viral RNA found in both seminal fluid and in the gastrointestinal tract, so close sexual contact with SARS-CoV-2 infected patients may potentially lead to transmission.[3] Certain risk factors like contact with areas of high sebum production or concomitant infection with *Demodex folliculorum* may increase this risk.[4,5] Familial clustering of COVID-19 rashes have been described in patients sharing close-quarters.[6] At present, there is

no current consensus on whether vesicular rashes could be a source of transmission, and the majority of these eruptions are not specific to any one viral agent, thus often making the etiology unclear and difficult to determine. Interestingly, some authors have reported cases of varicella zoster virus (VZV) in two patients, who subsequently developed suggestive symptoms and were diagnosed with SARS-CoV-2.[7] Both were immunocompetent and both responded to oral antivirals. The authors postulated that their patients' VZV infection may have been brought on by an initial subclinical SARS-CoV-2 infection.[7] A case report of 4 patients who developed necrotic VZV on the second branch of the trigeminal nerve and responded to oral antivirals in the context of SARS-CoV-2 infection was reported.[8] The authors postulated that the diminished absolute lymphocyte count may have been a basis for the VZV infections. In another case series of 4 patients (2 children and 2 adults) presenting with VZV ophthalmicus, the SARS-CoV-2 infection preceded the VZV ophthalmicus by several days.[9] The authors postulated here that the underlying physical and emotional stress of the SARS-CoV-2 infection may have been the basis for the VZV ophthalmicus infection. Both case series featured lymphopenia, which was a postulated trigger factor for the VZV.[8,9] This latter postulate does not, however, account for the level of severity of the SARS-CoV-2 infection, which was not extreme in both case series. For this reason, we believe that it is possible that this may be an observation of the Koebner phenomenon type V occurring in patients infected with SARS-CoV-2, and that the virus may be causing a local susceptibility to concomitant viral reactivation. Recent attempts to unify the concepts of isotopic response and Koebner phenomena have had the result of suggesting that the Wolf isotopic response may be a form of Koebner and may eventually become regarded as the fifth category of Koebner phenomenon.[10] Happle R and Kluger N concluded that the "isotopic response" is merely a variant of the Koebner reaction. In fact, all forms of Koebner reaction can be taken as variants of each other.[11–13] The first description of the isotopic response was regarding the site of a healed herpes zoster lesion. The authors later extended this definition to include not just zoster lesions, but the appearance of any new skin lesion at the site of an unrelated and already healed skin lesion. The use of a more inclusive and overarching term, such as "immunocompromised district" that encompasses both the isotopic response and locus minoris resistance, is probably more appropriate in instances where the previous disease is not yet fully healed. The Koebner phenomenon exists as four separate categories: I – true isomorphic; II – pseudoisomorphic; III – occasional lesions; and IV – poor or questionable. Much of what is described in the literature as Wolf's isotopic response likely overlaps with the definitions of Koebner III and IV. It is likely that Wolf's isotopic response is simply a variant of the Koebner phenomenon, and recent attempts at unifying these concepts have also tried to relabel Wolf's isotopic response as a type V Koebner phenomenon.[10,14]

Characterization of Newly Described COVID Vesicles

The SARS-CoV-2 virus has been linked to vesicular eruptions in certain subsets of patients. It is important to determine whether these are unique manifestations related to COVID-19 and to differentiate these from similarly appearing vesicular lesions, such as those appearing in herpes virus or varicella zoster virus reactivations. Marzano et al concluded from an observational study on data collected from 8 Italian centers that included 22 patients with positive nasopharyngeal swab testing for SARS-CoV-2 virus that a vesicular exanthem can be associated with, and is specific for, SARS-CoV-2 infection. The histopathological examinations of the lesions were suggestive of a viral infection presenting with hyperkeratosis, epidermal atrophy, vacuolar degeneration, and dyskeratotic cells.[15] The issue of whether these rashes contain SARS-CoV-2 viral particles has not been clarified. Recently, Mahe and colleagues have suggested that the microscopic evaluations of COVID-19 linked vesicular eruptions show features that are unlike varicella, but that real-time polymerase chain reaction (RT-PCR) assays for SARS-COV-2 are negative when taken from inside the vesicles. They describe unique histologic features of these vesicles that include a "pomegranate-like" eosinophilic dyskeratosis, suprabasal non-ballooning acantholysis forming a unilocular vesicle, and the absence of vasculitis.[16] Another recent study on the subject was equally unable to find viral RNA in suspected COVID-19 linked vesicles using PCR, but it included a small sample size of only four patients, and it notes that low viral loads may lead to false-negative results due to the lack of standardization of RT-PCR skin assays. This study also speculates that even if a viral presence was detectable, it would be too low to pose a serious risk of infectivity.[17] In a study done by Liu et al, autopsies on patients known

to be infected with the SARS-CoV-2 virus all showed mild degrees of dermatitis and vasculitis with lymphocytic infiltration, despite not having clinically apparent dermatologic manifestations. Furthermore, they also demonstrate a higher likelihood for viral spike protein to exist within cells that preferentially express ACE2 over TMPRSS2, such as Krt7+ eccrine secretory cells of the dermis and CD31+ vascular endothelial cells. Immunohistochemistry and immunofluorescence were used to demonstrate the existence of the viral spike protein, and the presence of viral particles in the skin was confirmed by electron microscopy.[18] While the debate remains open as to the infectivity of such lesions, it seems quite likely that these vesicles can be attributed to SARS-CoV-2 and that they can cause specific changes at the level of the epidermis.

Skin Changes That May Cause an Immunocompromised District

What remains unanswered is why these lesions appear only in a certain subset of patients. It may be possible that such vesicle formation is happening in areas of already susceptible skin, such as skin that has previously been affected by a cutaneous lesion that created a *locus minoris resistentiae*, which underlies the Wolf isotopic response, or Koebner type V phenomenon. This may parallel other observations in which the Koebner phenomenon type V has been seen occurring in areas of previously healed zoster lesions.[19] One possible mechanism could be related to the generalized immunosuppression due to SARS-CoV-2 infection, or resulting from immunosuppressive therapy (such as steroids) administered during the course of this disorder, or both, which may predispose to latent viral reactivation, especially of *herpesviridae*; thus, VZV manifestations in areas affected by SARS-CoV-2. The overlapping mechanisms involved in the Koebner phenomenon V, systemic immunosuppression, and locus minoris resistentiae at the level of the skin work in conjunction to cause a local immunosuppression which may also help explain these observations. The inverse situation in which previously healed lesions of another underlying pathology could contribute to the appearance of SARS-CoV-2 skin manifestations should also be explored. Prior inflammation of the skin may cause a local susceptibility by causing upregulation of ACE2 expression within epidermal basal cells. Patients with psoriasis were found to have increased expression of ACE2 within psoriatic plaques, but not within unaffected skin, which expressed similar levels as those found within healthy subjects. This expression was also significantly decreased by inhibiting IL-17a with secukinumab, showing that IL-17a mediated inflammation may play a pivotal role in the upregulation of ACE2 at this level.[20] This preference of the SARS-CoV-2 virus for skin tissues with a high ACE2 receptor concentration when taken with the fact that ACE2 is upregulated during proinflammatory states may be a possible mechanism for a localized susceptibility. IL-6 and IL-2 also play a role in COVID-19 outcomes, with increasing levels being able to predict prognosis and disease severity in patients. Tocilizumab, a monoclonal antibody that directly blocks both the membrane-bound and soluble IL-6 receptors, has shown promise in treating severe SARS-CoV-2 disease, including skin manifestations.[21] Additionally, skin parasites, mites, both exogenous and endogenous (such as *Demodex folliculorum*, or *Sarcoptes*), may contribute to the local susceptibility by both carrying viral particles through the molecular attraction forces between their chitin exoskeleton and the lipid viral membrane, and by causing the localized inflammation that triggers vesicle appearance (either directly, or by causing an upregulation of ACE receptors).[5] Finally, there is also a potential that trauma and disruption of these vesicles through scratching or other forms of mechanical stress would cause a worsening of the condition, either through autoinoculation if these vesicles are infectious, or through a classic type I Koebner reaction. Until such possibilities can be ruled out, it is prudent to recommend patients avoid traumatizing such vesicles. From this perspective and from our clinical experience, local treatments that are desiccating, such as mixtures, antiseptic alcohol-based solutions, and non-steroidal anti-inflammatory medications, could be recommended for the management of COVID vesicles alongside COVID19 systemic treatment.

Conclusion

The localized susceptibility caused by SARS-CoV-2 manifestations may be the potentiating factor that allows reactivation of latent viral infections. These events could be explained by a local susceptibility of previously damaged skin which underpins concepts like the Wolf isotopic response or/equal to Koebner phenomena type V. These categorizations of the observed phenomena receive attention due to their increasing recognition in clinical practice, but continue to incite debate due to their overlapping definitions; a result of what is probably a unifying

mechanism that underlies their very nature, which we consider to be a localized susceptibility for further insults – probably mediated by immunologic mechanisms and/or cytokines – as a result of an overarching explanation such as that of the immunocompromised district or *locus minoris resistentiae*.[10,14] The skin's memory may last a lifetime and this is particularly true concerning immunologic memory.[22] This matter may be complicated by whether we consider that the predisposition to COVID-19 vesicular lesions is due to previously healed varicella or herpes zoster lesions, or vice-versa, by small or subclinically healed COVID vesicular lesions which can predispose to the appearance of herpes zoster in that specific area. Localized susceptibility may occur through inflammation causing increased ACE2 receptor expression, generalized immunodeficiency, local immunologic dysregulation, concomitant parasitic or mite infections, or even mechanical trauma from pruritic lesions. It may be difficult to determine a non-specific eruption's etiology, as even certain drug reactions may mimic viral eruptions both clinically and histologically. Some drugs, such as beta-blockers may even have the potential to create a local susceptibility to viral eruptions themselves.[23] It therefore follows that establishing a clear history is paramount when confronted with patients presenting these types of COVID19-related rashes and will help to reduce potential confounders. The presence of vesicular lesions on a patient should call for prudence in order to avoid traumatizing these lesions and maintain a traditional approach to local therapy by using treatments that are desiccating, such as mixtures, antiseptic alcohol-based solutions, and non-steroidal anti-inflammatory medications; a recommendation which physicians should offer to their patients in order to avoid autoinoculation or creating a Koebner reaction (a final integrative unifying concept for the terminology such type I or type V, or Wolf isotopic response).

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All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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