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COVID-19: Important Updates and Developments
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Pityriasis rosea, pityriasis rosea–like eruptions, and herpes zoster in the setting of COVID-19 and COVID-19 vaccination

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Abstract Pityriasis rosea (PR), PR–like eruptions (PR-LE), and herpes zoster have been frequently reported during the COVID-19 pandemic and following COVID-19 vaccination. PR is a self-limiting exanthematous disease and herpes zoster is a treatable condition; therefore, their occurrence does not require discontinuation of the vaccination schedule. PR-LE is a hypersensitivity reaction and is, therefore, less predictable in its course. In the case of a booster dose, the clinical manifestation may not recur, may be different from PR-LE, or may present with systemic symptoms; however, in the case of PR-LE, the possibility of mild and predominantly cutaneous adverse events should not discourage all eligible candidates from receiving and completing the COVID-19 vaccination program, as such adverse reactions represent a small risk considering the possible severe and fatal outcome of COVID-19. We emphasize the relevance of looking for any viral reactivation in patients infected with SARS-CoV-2 who have skin eruptions. The search for viral reactivations could be useful not only for distinguishing between PR and PR-LE but also because viral reactivations may contribute to a patient's systemic inflammation and influence the course of the disease.

Introduction

Numerous skin manifestations have been reported during the coronavirus disease 2019 (COVID-19) pandemic, which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] Pityriasis rosea (PR) and PR–like eruptions (PR-LE) have been repeatedly described,[1] and authors have recorded a fivefold increase in the number of PR cases during the pandemic.[2] PR and PR-LE have also been frequently described following different COVID-19 vaccines.[3-6] In addition, an increase in herpes zoster (HZ) cases and other viral reactivations in patients with COVID-19 and an increase in HZ cases following COVID-19 vaccinations have been reported.[1] These observations raise many critical issues, namely the following: Is it possible to distinguish between PR and PR-LE? Can SARS-CoV-2 infection trigger viral reactivations? Why do PR, PR-LE, and HZ occur following COVID-19 vaccination?

PR, PR-LE, and HZ during COVID-19: the issue of viral reactivations

PR is a common, self-limiting exanthematous disease associated with the endogenous systemic reactivation of human herpesvirus 6 (HHV-6) and/or HHV-7. The disease typically begins with a single, erythematous plaque followed

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by a secondary eruption with lesions on the cleavage lines of the trunk (configuration as a "theatre curtain"). In the classic form of PR, duration may vary from 2 weeks to a few months.[7] Although some authors have not been able to demonstrate this association, the relationship of PR with systemic active HHV-6 and HHV-7 infection is based on many and consistent observations. Several studies have identified HHV-6 and HHV-7 DNA by polymerase chain reaction (PCR) and real-time calibrated quantitative-PCR in plasma, peripheral blood mononuclear cells and skin samples of patients with PR[8]; mRNA expression and specific antigens have been documented in PR skin lesions by in situ hybridization and immunohistochemistry respectively.[8,9] In addition, a plasma load of HHV-6 and HHV-7, a direct marker of viral replication, is associated with the development of systemic symptoms as well as with a significant reduction of the humoral neutralizing antibodies, further supporting that PR is associated with the endogenous reactivation of HHV-7 or HHV-6 infection.[8] Herpesvirus virions in various stages of morphogenesis were detected by electron microscopy in PR skin lesions[10] and in the supernatant of co-cultured peripheral blood mononuclear cells of patients with PR.[8] Lastly, the increased levels of interferon (IFN) α, interleukin 17 (IL17), IFN-γ, vascular endothelial growth factor (VEGF), and C-X-C motif chemokine ligand 10 (CXCL10) in the sera of patients with PR could again support a viral role in PR pathogenesis.[11] The fact that other authors have reported contradictory results in their studies on PR is likely to be attributed to the sensitivity and specificity of the methods used. Sampling the patient in the acute phase or in convalescence, for example, is not immaterial, and the type of biologic material studied (peripheral blood mononuclear cells, plasma, tissue) and its combination with the method of study are of paramount importance.

Conversely, PR-LE is not a true form of PR. Although it is often difficult to distinguish clinically the two eruptions, PR-LE has a completely different pathogenesis. Unlike PR, PR-LE is not associated with HHV-6 and/or HHV-7 systemic reactivation, but it has a pathogenesis more similar to that of other drug eruptions.[12,13] PR-LE can be compared to PR just as morbilliform drug eruptions to measles. Clinical, histopathologic, and, primarily, virologic criteria have been proposed for distinguishing between the two forms (Table 1).[12,13] Remarkably, in patients with skin eruptions during SARS-CoV-2 infection or after vaccination, virologic investigations are crucial not only to distinguish between PR and PR-LE but also to know whether SARS-CoV-2 or COVID-19 vaccination may have reactivated HHV-6 and/or HHV-7. Regrettably, the authors describing cases of PR and PR-LE during COVID-19 and following COVID-19 vaccinations did not perform specific investigations to search for HHV-6/HHV-7 reactivation.[3-6,14] HHV-6, HHV-7, and Epstein-Barr virus concurrent systemic reactivations have been detected in a patient with PR and COVID-19[15]; likewise, Ebstein-Barr virus systemic reactivation has been documented in a patient with diffuse papulosquamous eruption and COVID-19.[16]

The varicella zoster virus (VZV) reactivation explains the high number of cases of HZ observed during SARS-CoV-2 infection.[1] The psychologic stress linked to the pandemic and the immunosuppression associated with SARS-CoV-2 infection may act enabling the reactivation of latent viral infections.[17] Actually, SARS-CoV-2 infection decreases number and efficiency of T lymphocytes, particularly $CD4^+$ T cells, $CD8^+$ T cells and natural killer cells. Conversely, Th17 cells, interleukin 17A (IL17A) and the Th17/T regulatory (Treg) cell ratio increases in peripheral blood of patients with COVID-19.[18-20] Similarly, higher levels of circulating Th17 cells and of IL17A have been detected in the serum of patients with HZ compared to normal participants.[21] paragraph A recent study, using bioinformatic analyses of COVID-19 and HZ-associated genes, shed new light on the pathogenetic mechanisms by which SARS-CoV-2 can promote VZV reactivation.[22] By analyzing the list of genes involved in the pathogenesis of COVID-19 and HZ, a series of disease-related genes were found that overlapped.A possible genetic crosstalk during VZV and SARS-CoV-2 infections has been discovered with additive and synergistic interactions leading to an excessive Th17 differentiation and consequent increase of the circulating IL17A.[22] This abnormal interleukin-17 genetic signaling is stronger in case of simultaneous occurrence of COVID-19 and HZ compared to one of the two diseases taken individually.[22] As a result, the augmented Th17 cells differentiation, IL17A signaling and Th17/Treg cell ratio could explain the increased risk of HZ in patients with COVID-19. It has been demonstrated that an imbalance between Th17/Treg cells and increased level of IL17 could directly support latency, reactivation and lytic infection of VZV and other herpesviruses.[23]

IL17 is the main cytokine produced by Th17 cells, a T-cell subset involved in controlling opportunistic extracellular bacterial infections and fungi and pathogenic invasion at different mucosal sites.[24] Th17 role in immune response against viruses is multifaceted, not yet fully understood and, in some ways, contradictory. Stimulated by cytokines from dendritic cells, Th17 cells and IL17 increase during acute or chronic viral infections but their role is generally considered harmful to the host.[25] IL17 can promote viral persistence increasing both pro-inflammatory and anti-apoptotic cytokines and impairing target cell destruction by cytotoxic $CD8^+$T cells.[25] Decreasing the production of IL2 and interferon-γ, IL17 can inhibit Th1 differentiation, prevent viral clearance and cause inflammatory tissue damage. Th17 cells and IL17 can increase not only during HZ or herpes simplex virus (HSV) infections but also during other infections, favoring viral replication and persistence.[26-28] Conversely, in viral infections such as rotavirus or influenza, Th17 cells may play a defensive role contributing to viral clearance.[29-31] Generally, the role of Th17 cells in viral infections changes depending on the host's genetic background, on the virus type and on the

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Table 1 Clinical, histopathologic, and virologic criteria for distinguishing between PR and PR-LE

	Classic PR	PR-LE
Pathogenesis	HHV-6/HHV-7 systemic reactivation	Adverse reaction to a drug/vaccine
Lesions morphology	Erythemathous papulosquamous lesions	Dusky-red macules/papules with occasional desquamation
Marginal collarettes of scales	Present in most lesions	Less common
Herald patch	Present in most cases	Present in 25% of cases
Distribution of the lesion	"Theater curtain" or "Christmas tree" pattern on the trunk	Lesions diffuse and more confluent on trunk, limbs, and face
Appearance of new lesions	Development in crops over a period of 1-2 wk after the onset of the herald patch	Eruption reaches the peak in a few days
Oropharyngeal lesions	Possible (16% of cases)	Frequent (>50% of cases)
Itch	Mild or absent	Present and sometimes intense
Prodromal symptoms	Frequently present	Absent
Routine laboratory findings	Within normal ranges	Occasional peripheral eosinophilia (42% of cases)
Virologic investigations	HHV-6/HHV-7 DNA present in plasma; immunoglobulin M antibodies against HHV-6/HHV-7 occasionally positive in serum	No signs of HHV-6/HHV-7 systemic reactivation in the plasma or serum
Histopathologic features	Epidermal focal parakeratosis and spongiosis; few scattered dyskeratotic keratinocytes; extravasated red blood cells and perivascular infiltrate of lymphocytes, histiocytes, and occasionally eosinophils in the papillary dermis	Occasional features of interface dermatitis with scattered single necrotic keratinocytes; more dyskeratotic keratinocytes (occasionally in clusters); acrosyringeal presence of necrotic keratinocytes; more abundant and diffuse perivascular infiltrate of lymphocytes, histiocytes, and eosinophils in the papillary and reticular dermis; enlargement of endothelial cells
Duration	45 d on average	14 d on average after discontinuation of the drug
Therapy	Rest	Drug withdrawal

HHV, human herpesvirus; PR, pityriasis rosea; PR-LE, pityriasis rosea–like eruptions.

Th17/Treg cell ratio. The Th17/Treg cell ratio was statistically significantly higher in patients during HZ than controls and this imbalance may play a role in the pathogenesis of HZ.[21]

Conflicting findings on the Th17/Treg cell ratio have been reported, possibly depending on the disease activity, because the amount of Treg cells varies according to the acute or chronic stage of the viral infection.[32-34] The burst of HZ with VZV active replication may act inducing and activating Tregs which, in turn, can control the Th17 initial immune response. Tregs induction is a common event during viral infections, accounting for the transient immunosuppression that can occur during the illness and after recovery.[35] A similar mechanism orchestrated by dysregulated Th17 immune response could also mediate HHV-6 and/or HHV-7 reactivation and the occurrence of PR during COVID-19. As well as in HZ, Th17 cells and IL17 are increased in the acute stage of PR and their amount is related to severity and duration of the disease.[36,37] In addition to creating a dysregulated Th17 immune response, SARS-CoV-2 infection may have a direct trans-activating role, triggering HHV-6 and/or HHV-7 reactivation and causing, indirectly, the onset of PR.[38] Really, it has been described in critically ill patients with COVID-19 that the concurrent reactivation of other HHV, such as HSV-1 and VZV, can influence disease outcomes resulting in sudden worsening of the symptoms.[39-41]

PR, PR-LE, and HZ following COVID-19 vaccination

PR, PR-LE, and HZ have also been described following COVID-19 vaccination.[3-6,14] PR and PR-LE have been reported following influenza, diphtheria, tuberculosis, poliomyelitis, tetanus, yellow fever, hepatitis A, rabies, Japanese encephalitis, and human papilloma virus vaccines. Usually, PR develops a few weeks after vaccination whereas PR-LE after a few days. This different latency is due to the time required for HHV-6 or HHV-7 reactivation resulting in PR longer than the immunological hypersensitivity reaction originating PR-LE.[42,43] Unfortunately, also in PR and PR-LE cases occurring following COVID-19 vaccination the mark-

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ers of HHV-6 and HHV-7 systemic reactivation, such as detection of HHV 6/7 DNA in plasma and detection of positive IgM antibodies against HHV-6/7 in serum, have never been investigated.[44] VZV and HSV reactivations accounted for 3% to 14% of cutaneous reactions after mRNA COVID-19 and Oxford/AstraZeneca AZD1222 vaccines in a large case series of participants.[45,46] VZV reactivation was more frequent after BNT162b2 (Pfizer) vaccination and in men. The time elapsed before a viral reactivation was on average 7 days and reactivation was more frequent after the first dose than after the second (63% versus 37% of cases).[45,46] paragraph-The pathogenesis of HZ, PR, and PR-LE after vaccination is unknown. Generally, adverse events following immunization may be fortuitous or closely related to the vaccine. In genetically susceptible individuals, humoral and cellular adaptive immune response and the amount of plasma cytokines induced by vaccines may cause immune dysregulation which may play a role in the reactivation of latent VZV, HHV-6, and HHV-7 infection. This phenomenon may be compared to the so-called "immune reconstitution inflammatory syndrome" (IRIS), following the introduction of antiretroviral therapy in patients infected with HIV, and associated with paradoxical worsening or reactivation of pre-existing infections.[47-49] paragraphThe pathogenesis of IRIS is still unknown but amplifying inflammatory reaction with increased plasma levels of several cytokines (primarily interleukin-6 and soluble CD30) and reduction of T-reg cells signaling play a role. HSV-2 reactivation and increased frequency of HSV-2 shedding as well as VZV, HHV-8, and cytomegalovirus reactivation have been related to IRIS.[47-49] Strongly stimulating immune response and polarizing it to a committed-induced T cell response against a definite infectious agent, a vaccine may temporarily distract the T-cell-mediated control on the latent infections, such as VZV, HHV-6, and HHV-7, which may reactivate causing PR.[42,43] paragraphA dysregulated Treg cells function, depending on the host's immunologic background, may contribute to an exaggerated cytokine response to COVID-19 vaccination encouraging viral reactivation. Indeed, Treg cells coordinate not only immune response against viral infections but also dampen and coordinate foreign antigen specific immunity following vaccination.[34] On the contrary, PR-LE may occur as a delayed hypersensitivity response to a vaccine as well as a drug. paragraphA possible mechanism is molecular mimicry between a viral epitope such as SARS-CoV-2 spike glycoprotein, viral vector or a vaccine ingredient and host proteins that could result in a T-cell-mediated hypersensitivity skin reaction.[50] One group a [51] detected by Immunohistochemistry SARS-CoV-2 spike protein in endothelial cells and perivascular lymphocytes in the skin of a patient with PR-LE and COVID-19 . They defined PR-LE the skin manifestation and did not perform specific investigations for HHV-6 and HHV-7. These findings suggest that SARS-CoV-2 viral infection or immune response against spike protein-based vaccines may cause PR-LE.[51]

Conclusions

PR, PR-LE, and HZ have been frequently reported during the COVID-19 pandemic and following COVID-19 vaccination. Because PR is a self-limiting exanthem and HZ is a treatable condition, their occurrence does not require discontinuation of the vaccination schedule. Regarding PR, in our experience, it is unlikely that HHV-6 and HHV-7 reactivation occurs following the booster dose.[43,44] Conversely, PR-LE is a hypersensitivity reaction and, as such, is less predictable. In the case of booster dose, the clinical manifestation may not recur, be different from PR-LE, or present with systemic symptoms. Overall, the possibility of mild and self-limiting cutaneous adverse events should not discourage all eligible candidates from receiving COVID-19 vaccination; such adverse reactions represent a small risk in relation to the possible severe and fatal outcome of COVID-19.

Lastly, we emphasize the relevance of looking for any viral reactivations in patients infected with SARS-CoV-2 who have cutaneous manifestations such as viral exanthems; the search for viral reactivations could be useful not only for distinguishing between PR and PR-LE but also because they may contribute to a patient's systemic inflammation and influence the course of the disease itself.[39-41]

Conflict of interest

The authors have no conflicts of interest to disclose.

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