

CORRESPONDENCE

The significance of investigating clinical, histopathologic and virological features in pityriasis rosea and pityriasis rosea-like eruptions following COVID-19 vaccinations

Dear Editor,

The article by Martora F. et al. on a series of patients with pityriasis rosea (PR) after Moderna COVID-19 vaccine¹ recently published in your journal prompted us to make some observations.

We agree with the authors that SARS-CoV-2 infection may play a role in the reactivation of latent viral infections such as human herpesvirus (HHV)-6 and HHV-7 and consequently, as we previously demonstrated,^{2,3} it may induce, indirectly, the skin manifestations of PR. Actually, a large body of evidence supports the role of the HHV-6 and/or HHV-7 reactivation in PR pathogenesis. Such reactivation is not limited to a single tissue but it is systemic, since the active infection by these viruses has been demonstrated in multiple tissues. Several studies have identified HHV-6 and HHV-7 DNA by PCR and real-time cq-PCR in plasma, peripheral blood mononuclear cells (PBMCs) and lesional skin of patients with PR. Furthermore, HHV-6 messenger RNA expression by *in situ* hybridization and HHV-6 and HHV-7 specific antigens (as HHV-7 pp85 and HHV-6 p41) by immunohistochemistry were repeatedly detected in PR skin lesions; herpes virus particles in various stages of morphogenesis were shown in both PR lesions and supernatant of co-cultured PBMCs from PR patients by electron microscopy (EM).^{4,5} Though EM cannot definitively distinguish HHV-6 and -7 from other herpesviruses and the specific type of herpesvirus should be confirmed by immunohistochemical methods, in our previous EM studies we found several features of viral morphogenesis in tissues and cultures^{4,5} that were uncommon among other herpesviruses and closely resembled those of HHV-6 and HHV-7.^{6,7}

Such features are: the finding of empty and full capsids in the nucleus of the infected cells, the tegument visible only when the viruses are located in the nuclear membranes of the infected cells or when they have budded through the nuclear membrane into the cytoplasm, the capsid almost invariably full and surrounded by a prominent electrodense tegument (Figure 1A and B).⁴⁻⁷ Notably, enveloped viral particles with a full nucleocapsid and a dense tegument are found not only in the extracellular space of the infected cells but also into clear cytoplasmic vacuoles. This last finding is in common only with cytomegalovirus, but in the latter the tegument is less demarcated. Generally, unlike HHV-6 and -7, in other herpesviruses the tegument layer is an ill-defined area.^{6,7}

Most of the findings described above are clear markers of active viral infection. Lastly, several inflammatory mediators with key roles in host defense against pathogens (interleukin 17), in direct antiviral activity (interferon- γ) and in controlling viral replication (IP-10) resulted to be upregulated in sera of PR patients compared to controls.⁸

Martora et al. diagnosed their three patients as affected by PR based on their clinical history (onset of the exanthem 6–11 days after the first vaccine dose) and physical examination (erythematous desquamative lesions over the trunk with a Christmas tree distribution).¹ However, some of the main clinical features of PR, as the presence of the herald patch, the oropharyngeal involvement⁹ and the exanthem duration, have not been described and, regrettably, no specific virologic investigations were performed in their patients to detect the possible HHV-6/7 systemic reactivation.

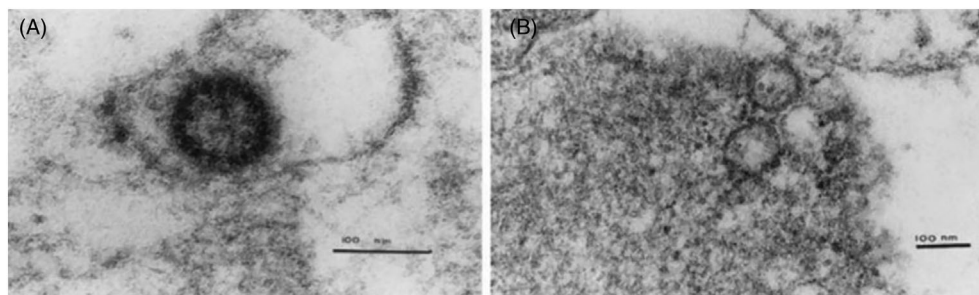


FIGURE 1 Electron microscopy study of PR skin samples shows in the epidermis and dermis herpes virus-like particles in various stages of morphogenesis: (A) these virions contain an electrodense cylindrical core, a capsid, a tegument and an envelope with spikes and (B) virions are interspersed among keratinocytes near to the dermal-epidermal junction

Importantly, the assessment of these features and, in doubtful cases, histopathology may allow to distinguish between typical PR and PR-like eruptions (PR-LE).¹⁰

PR-LE has a pathogenesis completely different from PR: it is not associated with HHV-6 and/or HHV-7 systemic reactivation but it is rather a drug-induced or a vaccine-induced exanthem with clinical features that can resemble a classic PR. In a few words, PR-LE can be compared to PR just as morbilliform eruptions to measles. In PR-LE the herald patch is usually absent, the skin lesions are more itchy, diffuse and confluent and the mucous membranes can be involved more frequently than in typical PR. Prodromal symptoms are present in about 69% of typical PR cases whereas they are uncommon in PR-LE following the administration of a drug. However, few prodromal symptoms (usually low fever) for a couple of days may be present in PR-LE following the administration of a vaccine. In addition, patients with PR-LE may have blood eosinophilia and, importantly, have no signs of HHV-6 and HHV-7 systemic reactivation in plasma and tissues, usually present in typical PR.¹⁰ Therefore, based on the clinical description provided by the authors,¹ it cannot be excluded that their patient's eruptions were PR-LE instead of genuine PR. In our experience, following the criteria recently described,¹¹ the majority of post COVID-19 vaccination eruptions can be considered PR-LE and not genuine PR (only in 2 cases we found HHV-6 systemic reactivation, unpublished data). Generally, our experience agrees with the literature regarding onset time after vaccination (on average 7 days for PR-LE, longer for PR) and the duration of the eruption (1–2 weeks for PR-LE, longer for PR).^{12–15}

Concerning therapy, since PR is a self-limiting disease, the best treatment is reassuring the patient and suggesting only bed rest. A recent Cochrane review found that oral acyclovir improves PR when compared with placebo or no treatment.¹¹ We suggest to prescribe oral acyclovir only when the skin lesions are particularly widespread and itchy and constitutional symptoms are severe, as in cases of persistent or relapsing PR and, possibly, in PR during pregnancy when the onset is within the 15th gestational week and the risk of miscarriage is higher.¹² Only high doses of acyclovir proved to have an anti-HHV-6 effect and to improve PR.^{16,17} Other antivirals such as cidofovir, ganciclovir and foscarnet are more active than acyclovir on HHV-6, both in vitro and in vivo, but the use of these agents is burdened by serious side effects (myelosuppression, cytopenias, nephrotoxicity).¹⁶ Overall, the possibility of mild and self-limiting cutaneous adverse events should not discourage the eligible candidates to receive COVID-19 vaccination. It should, however, be noted that PR is a self-limiting exanthem and that in our experience, it is unusual for HHV-6 and -7 reactivation to occur again after subsequent booster doses. Conversely, PR-LE is a less predictable hypersensitivity reaction and in case of booster doses, the clinical manifestation may not recur or be different from PR-LE, also presenting with systemic symptoms. Finally, we emphasize the importance of performing specific laboratory investigations to detect HHV-6 and or -7 systemic reactivation and therefore to distinguish typical PR from PR-LE.

Histopathology may clarify the distinction and molecular approaches may help to detect any viruses in the skin samples.

AUTHOR CONTRIBUTIONS

Giulia Ciccarese conceived the analysis; Giulia Ciccarese and Francesco Drago wrote the paper in consultation with Aurora Parodi.

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None.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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