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LETTER TO THE EDITOR

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Pityriasis rosea during COVID-19: Pathogenesis, diagnosis, and treatment

Dear Editor,

The article by Martora et al. on a COVID-19 related atypical form of pityriasis rosea (PR)[1] that was recently published in your journal prompted us to make some observations. We agree with the authors that SARS-CoV-2 infection may be a trigger of PR but, remarkably not directly. Indeed, it has been demonstrated that SARS-CoV-2 infection may reactivate several latent viral infections such as human herpesvirus 6 (HHV-6) and HHV-7, and, therefore indirectly, induce the skin manifestations of PR.[2–4]

Although Martora et al. stated that PR pathogenesis is still unknown,[1] actually, a large body of evidence using the most modern biological techniques has highlighted a close relationship between PR and HHV-6 and/or HHV-7 systemic active infection. Indeed, HHV-6 and HHV-7 DNA have been repeatedly detected by polymerase chain reaction (PCR) in plasma, peripheral blood mononuclear cells (PBMCs), and lesional skin of patients with PR.[5,6] Furthermore, HHV-6 messenger RNA expression by in situ hybridization and HHV-6/-7 specific antigens by immunohistochemistry were repeatedly detected in PR skin lesions[6,7] and herpesvirus particles in various stages of morphogenesis by electron microscopy in both PR lesions and supernatant of cocultured PBMCs from PR patients.[5,7,8] Neutralizing antibodies and high avidity IgG antibodies, the latter indicating a viral endogenous reactivation, against HHV-6 and HHV-7 have been demonstrated in patients with PR.[7] These findings are all clear markers of viral systemic active infection.[5–7] Finally, several inflammatory mediators such as interleukin-17, interferon (IFN)-γ, vascular endothelial growth factor, and the IFN-γ-induced protein 10 resulted to be increased in sera of PR patients compared with controls, supporting the active immunological response against a virus.[8] Martora et al. diagnosed PR in their patient based on clinical history (onset of the exanthem 6 weeks before the first visit), physical examination (erythematous-squamous papules and plaques on the trunk), and histopathological examination of a skin biopsy (spongiosis, focal exocytosis of lymphocytes and parakeratosis).[1] However, though there were no histological features pathognomonic for PR, they mentioned neither absence nor decrease of the granular cell layers nor the presence of extravasated red blood cells in the dermis, findings quite typical of PR.[9] Finally, the authors declared that patient's serology and PCR for HHV-6/-7 were negative without specifying in which tissue PCR was performed.[1] The fact that serology and PCR (we suppose that PCR was performed on the serum) were negative for HHV-6/-7 in the patient described by Martora et al.[1] is not surprising. Indeed, serologic assays, especially without the detection of specific IgG subclasses using an antibody avidity test, cannot be sufficient to diagnose viral reactivation and direct methods like quantitative real-time PCR are crucial. Indeed, only bona fide quantitative methods, which measure the HHV-6 and HHV-7 viral load in tissues, blood cells, and, particularly, plasma and serum, are diagnostic of reactivation, can support a causal link between virus and pathology and allow the follow-up of the infection. It should also be pointed out that in PR, which may be associated with the active replication of either or both HHV-6/-7, quantitative PCR assays may detect only one virus depending on the phase of the disease in which the patient's blood is collected. In fact, HHV-7 behavior is unique in PR since it replicates before HHV-6, but its replication tends to cease in the advanced phases of the disease.[10] Finally, the authors described their case of PR as "refractory to conventional therapy."[1] However, conventional therapy for PR does not exist and, however, is not a steroid one. On the basis of evidence-based medicine, no treatment is recommended, since PR is a self-limiting exanthemous disease that needs just reassurance and rest. Low-dosage antiviral treatment with acyclovir should be considered only in distinct cases of extensive, relapsing/persistent PR with associated systemic symptoms to shorten the course of the disease,[11] as it could be in the patient described by Martora et al. Also in PR during pregnancy, when several risk factors such as onset before Week 15, associated systemic symptoms, the presence of oropharyngeal lesions and a diffuse cutaneous involvement are simultaneously present, antiviral treatment with oral acyclovir should be considered for reducing the risk for HHV-6 intrauterine transmission of infection from the mother to the fetus and the possibility of fetal complications.[12]

CONFLICTS OF INTEREST

The authors declare no conflictS of interest.

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REFERENCES

1. Martora F, Picone V, Fornaro L, Fabbrocini G, Marasca C. Can COVID-19 cause atypical forms of pityriasis rosea refractory to conventional therapies? *J Med Virol*. 2021;94:1292-1293. doi:10.1002/jmv.27535
2. Drago F, Broccolo F, Ciccarese G. Pityriasis rosea, pityriasis rosea-like eruptions and herpes zoster in the setting of COVID-19 and COVID-19 vaccination. *Clin Dermatol*. 2022.
3. Drago F, Ciccarese G, Rebora A, Parodi A. Human herpesvirus-6, -7, and Epstein-Barr virus reactivation in pityriasis rosea during COVID-19. *J Med Virol*. 2021;93:1850-1851.
4. Ciccarese G, Parodi A, Drago F. SARS-CoV-2 as a possible inducer of viral reactivations. *Dermatol Ther*. 2020;33:e13878.
5. Drago F, Ranieri E, Malaguti F, Battifoglio ML, Losi E, Rebora A. Human herpesvirus 7 in patients with pityriasis rosea. Electron microscopy investigations and polymerase chain reaction in mononuclear cells, plasma and skin. *Dermatology*. 1997;195:374-378.
6. Watanabe T, Kawamura T, Aquilino EA, et al. Pityriasis rosea is associated with systemic active infection with both human herpesvirus-7 and human herpesvirus-6. *J Invest Dermatol*. 2002;119:793-797.
7. Broccolo F, Drago F, Careddu AM, et al. Additional evidence that pityriasis rosea is associated with reactivation of human herpesvirus-6 and -7. *J Invest Dermatol*. 2005;124:1234-1240.
8. Drago F, Ciccarese G, Broccolo F, et al. The role of cytokines, chemokines, and growth factors in the pathogenesis of pityriasis rosea. *Mediators Inflamm*. 2015;2015:438963.
9. Panizzon R, Bloch PH. Histopathology of pityriasis rosea Gibert. Qualitative and quantitative light-microscopic study of 62 biopsies of 40 patients. *Dermatologica*. 1982;165:551-558.
10. Drago F, Ciccarese G, Rebora A. Distinguishing the status of human herpesvirus 6 and 7 infection. *Int J Dermatol*. 2015;54:e361-e375.
11. Drago F, Ciccarese G, Rebora A, Parodi A. The efficacy of macrolides and acyclovir in pityriasis rosea. *Indian J Dermatol Venereol Leprol*. 2015;81:56.
12. Drago F, Ciccarese G, Herzum A, Rebora A, Parodi A. Pityriasis rosea during pregnancy: major and minor alarming signs. *Dermatology*. 2018;234:31-36.