Negative SARS-CoV-2 antibodies in patients with positive immunohistochemistry for spike protein in pityriasis rosea-like eruptions

Dear Editor

Pityriasis rosea-like eruptions (PR-LE) have been recently associated with COVID-19 infection and vaccines. Negative SARS-CoV-2 PCR and serology have been reported in patients with skin manifestations, suggestive of COVID-19 with positive immunohistochemistry (IHC) for SARS-CoV-2 spike protein in skin biopsies. SARS-CoV-2 IHC studies in biopsies of PR-LE are limited to a case report. Herein, we report on 3 patients with PR-LE with positive IHC for SARS-CoV-2 spike protein and negative serology.

Three patients were evaluated between January and May 2021, and none of them had received COVID-19 vaccines at the time of evaluation or biopsy. IHC with SARS-CoV/SARS-CoV-2 was performed on all cases [SARS-CoV/SARS-CoV-2 (COVID-19) spike antibody (1A9), dilution 1:100, lot no.43943, GTX632604; GeneTex Inc., Irvine, CA, USA]. The clone employed has shown specific immunoreactivity. We performed positive controls on placental tissue of postpartum women with SARS-CoV-2 infection, and negative controls on normal skin and in 7 skin biopsies with a pityriasis rosea diagnosis from 2019.

The first case is a 22-year-old man with a 7-day history of a papulosquamous rash on his trunk, arms and legs (Fig. 1a), and petechiae in the feet dorsum. He referred fatigue, sore throat and close contact with a person diagnosed with COVID-19. IHC for SARS-CoV/SARS-CoV-2 spike protein was positive on the endothelium. IgG antibody testing for SARS-CoV-2 spike and nucleocapsid protein were both negative 5 months after the initial diagnosis.

Figure 1 (a) Pityriasis rosea-like eruption in the trunk. (b) Positive control on placenta showing cytotrophoblast cells with nuclear and cytoplasmic SARS-CoV/SARS-CoV-2 spike protein positivity (10×). (c) Skin biopsy with acanthosis, focal parakeratosis, mild spongiosis, extravasated erythrocytes and a perivascular superficial lymphocytic infiltrate (haematoxylin and eosin, 10×). (d) Positive immunohistochemistry for SARS-CoV/SARS-CoV-2 spike protein in the endothelium and perivascular lymphocytes (40×).
The second case is a 26-year-old woman with a 2-week history of a disseminated rash on her trunk and arms. She referred headache and sore throat 2 weeks prior. IHC for SARS-CoV/SARS-CoV-2 spike protein was positive on the endothelium. IgG antibody testing for SARS-CoV-2 spike and nucleocapsid protein were both negative 5 months after the initial diagnosis.

The third case is a 31-year-old woman with a 1-month history of a disseminated rash on her trunk and arms. She referred headache during the last month. IHC for SARS-CoV/SARS-CoV-2 spike protein was positive on the endothelium and perivascular lymphocytes (Fig. 1d). IgG antibody testing for SARS-CoV-2 spike protein was negative 3 weeks after the initial evaluation.

All the biopsy specimens presented acanthosis, focal parakeratosis, mild spongiosis, extravasated erythrocytes and a superficial perivascular lymphocytic infiltrate in the dermis (Fig. 1c). Minimal neutrophils were present in the stratum spinosum similar to another case reported. Due to the clinical features, evolution, histological findings and lack of human herpesvirus 6 (HHV-6) and 7 testing, we diagnosed the patients as having PR-LE.

All three patients were treated with topical corticosteroids, and the rash resolved after 1 week without recurrence; the first patient received his first dose and the third patient received two doses of the COVID-19 vaccine without adverse events.

The relationship between pernio and other cutaneous findings in COVID-19 has been challenging and complex. In SARS-CoV-2-associated pernio, recent hypotheses have postulated that a robust innate and intrinsic immune activity driven by interferon-1 may explain the negative serological and PCR testing as it may drive viral clearance without inducing detectable antibody production. If a similar immunological cascade happens in other COVID-19-associated manifestations, it warrants further investigation, but may explain the negative testing in the patients reported herein. More studies with IHC analysis of skin biopsies and lymphocyte assays for SARS-CoV-2-reactive T cells are necessary to clarify the relationship between SARS-CoV-2 and skin manifestations. Limitations of our report include the lack of HHV-6/7 testing and the possibility of cross-reaction with other antigens or viruses.

In conclusion, IHC for SARS-CoV-2 may represent an important tool in the diagnosis of COVID-19 PR-LE especially in patients with negative serology or PCR. The prognosis of the dermatosis seems similar to other causes of PR-LE.

Acknowledgement
The patients in this manuscript have given written informed consent to the publication of their case details.

Conflicts of interest
None to declare.

Funding sources
None.

Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

E. Welsh, J.A. Cardenas-de la Garza, E. Brussolo-Marroquin, A. Cuellar-Barboza, R. Franco-Marquez, G. Ramos-Montanez

Welsh Dermatology and Associates, Monterrey, Nuevo Leon, Mexico,
Academia Mexicana de Dermatologia, Monterrey, Mexico, Rheumatology Department, Universidad Autonoma de Nuevo Leon, Hospital Universitario "Dr. Jose Eleuterio Gonzalez", Monterrey, Nuevo Leon, Mexico, Departamento de Ciencias Clinicas, Division Clinicas de la Salud, Universidad de Monterrey, San Pedro Garza Garcia, Mexico, Dermatology Department, Universidad Autonoma de Nuevo Leon, Hospital Universitario "Dr. Jose Eleuterio Gonzalez", Monterrey, Nuevo Leon, Mexico, Pathology Department, Universidad Autonoma de Nuevo Leon, Hospital Universitario "Dr. Jose Eleuterio Gonzalez", Monterrey, Nuevo Leon, Mexico, Facultad de Medicina Unidad Saltillo, Universidad Autonoma de Coahuila, Saltillo, Coahuila, Mexico

*Correspondence: J.A. Cardenas-de la Garza. E-mail: cardenasde-lagarza@gmail.com.

References
1 Ko CJ, Harigopal M, Gehilhausen JR, Bosenberg M, McNiff JM, Damsky W. Discordant anti-SARS-CoV-2 spike protein and RNA staining in cutaneous perniosis. J Cutan Pathol 2021; 48: 47–52.
2 Torrelo A, Andina D, Santonja C et al. Erythema multiforme-like lesions in children and COVID-19. Pediatr Dermatol 2020; 37: 442–446.
3 Colmenero I, Santonja C, Alonso-Riano M et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. Br J Dermatol 2020; 183: 729–737.
4 Welsh E, Cardenas-de la Garza JA, Cuellar-Barboza A, Franco-Marquez R, Arazo Rivera RI. SARS-CoV-2 spike protein positivity in pityriasis rosea-like and urticaria-like rashes of COVID-19. Br J Dermatol 2021; 184: 1194–1195.
5 Szabolcs M, Sauter JL, Frosina D et al. Identification of Immunohistochemical reagents for in situ protein expression analysis of coronavirus-associated changes in human tissues. Appl Immunohistochem Mol Morphol 2021; 29: 5–12.
6 Martora F, Picone V, Fornaro L, Fabbrocini G, Marasca C. Can COVID-19 cause atypical forms of pityriasis rosea refractory to conventional therapy? J Med Virol 2021; 94: 1292–1293.
7 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.
8 Arkin LM, Moon JJ, Tran JM et al. From your nose to your toes: a review of severe acute respiratory syndrome coronavirus 2 Pandemic. Assoc Perinat. J Invest Dermatol 2021; 141: 2791–2796.
9 Cappel MA, Cappel JA, Wetter DA. Pernio (chilblains), SARS-CoV-2, and COVID toes unified through cutaneous and systemic mechanisms. Mayo Clin Proc 2021; 96: 989–1005.

DOI: 10.1111/jdv.18186