nas 38911 a 38915. Disponible en: https://www.boe.es/boe/dias/2007/09/25/pdfs/A38911-38915.pdf.
4. González-Cruz C, Descalzo MÁ, Arias-Santiago S, Molina-Leyva A, Gilaberte Y, Fernández-Crehuet P, et al. Proportion of potentially avoidable referrals from primary care to dermatologists for cystic lesions or benign neoplasms in spain: analysis of data from the DIADERM study. Actas Dermosifiliogr. 2019;110:659–65.
5. Jayakumar KL, Lipoff JB. Trends in the dermatology residency match from 2007 to 2018: Implications for the dermatology workforce. J Am Acad Dermatol. 2019;80:788–90.
6. Alam M, Waldman A, Maher IA. Practice and educational gaps in surgery for skin cancer. Dermatol Clin. 2016;34:335–9.
7. Wang JV, O'Connor M, McGuinn K, Albornoz CA, Keller M. Feedback practices in dermatology residency programs: building a culture for millennials. Clin Dermatol. 2019;37:282–3.
8. Gallup. https://www.gallup.com/workplace/238073/millennials-work-live.aspx, 2016. Acceso el 18 de enero de 2020.
9. St Claire KM, Rietcheck HR, Patel RR, Dellavalle RP. An assessment of social media usage by dermatology residency programs. Dermatol Online J. 2019;25.
10. Huang WW, Feldman SR. The cost of applying to dermatology residency. J Am Acad Dermatol. 2016;74:775–6.

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Immunoglobulin A Antiphospholipid Antibodies in Patients With Chilblain-like Lesions During the COVID-19 Pandemic☆

Presencia de anticuerpos antifosfolípidos IgA en pacientes con lesiones pernióticas asociadas a COVID-19

To the Editor,

Owing to the information provided in the media about a possible association between skin lesions and SARS-CoV-2, we received many patients with self-limiting purpuric acral lesions during the month of April 2020.[1]

This situation paves the way for several lines of study, in which laboratory analysis can play an essential role and in which differences in the behavior of the virus in the body can be explained in many settings by cutaneous manifestations, both at diagnosis and during follow-up. We consider that, during the initial stage of the infection, the mucous membrane may play a key role with respect to immunoglobulin (Ig) A antibodies.

We retrospectively reviewed the cases of 11 patients with chilblain-like lesions[2,3] seen at Hospital de Almansa, Albacete, Spain (Fig. 1). Some of the patients had had clinical manifestations associated with SARS-CoV-2 infection up to 2 weeks before the onset of the skin lesions. Patients were aged 2 to 40 years. The lesions comprised acral erythematous purpuric macules and papules[4,5] accompanied by edema and occasionally progressing to blisters, vesicles, pseudopustules, and crusts (Fig. 2).

We requested the following analyses: complete blood count, liver enzymes, ferritin, antinuclear antibody, lupus anticoagulant, immunoglobulins, and anticardiolipin IgA, IgG, and IgM.[6,7] We also analyzed anti-$ß_2$-glycoprotein anti-

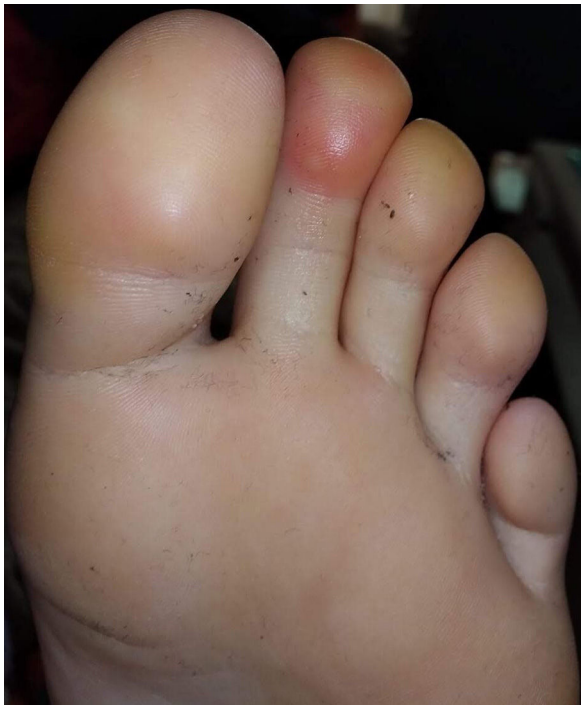

Fig. 1 Typical image of chilblains that was common to all patients.

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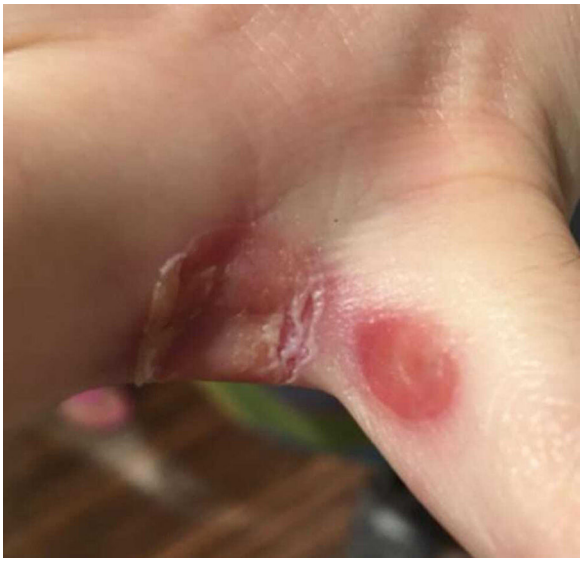

Fig. 2 Progression to blisters and crusts.

bodies and complement C3 and C4 and ran a lateral-flow immunochromatographic assay (COVID-19 IgG/IgM Rapid Test Cassette, Zhenjiang Orient Gene Biotech Co., Ltd).

The Cov2019 polymerase chain reaction (PCR) assay, which is based on nasopharyngeal swab specimens, was performed in 2 cases where the patients had active symptoms and yielded a positive result in 1. The IgM/IgG rapid test, which was performed in all cases, yielded positive results in only 3 patients, 1 of whom had active disease (PCR+), and 2 asymptomatic patients, who had had self-limiting infection for 2 weeks, after which time they presented with chilblains. Laboratory tests revealed reduced complement C3 in 5 patients. All 5 had increased IgA anticardiolipin antibody; while this increase was slightly high, it was not considered positive according to the reference parameters of the external laboratory.

Analysis of the similarities between SARS CoV-2 infection and dermatologic syndromes involving antibodies enables conclusions to be drawn with respect to the following:

1. The viral etiology of autoimmune diseases,[6] as well as genetic and environmental diseases. Infection by SARS-CoV-2 is followed by a first stage of viral infection and a second stage that is similar to acute and transient autoimmune syndrome (in a genetically predisposed patient).
2. Generation of autoantibodies: SARS-CoV-2 takes advantage of the body's machinery to replicate. Microparticles (i.e., phospholipids such as phosphatidylserine), which are found on the cell membrane, stimulate production of autoantibodies. Exposure in blood vessels can lead to transient antiphospholipid syndrome, as reported in the literature,[6] and could account for the skin lesions, as in antiphospholipid syndrome and chilblain lupus.
3. Generation of IgA against the mucous membrane, where the first contact with the virus is made,[6,8] thus explaining why the immune response has no memory (self-limiting conditions) and why only a few patients present memory IgG. It would also account for the severe symptoms that affect the mucous membranes, such as odynophagia, dysphagia, anosmia, and loss of taste, all of which are common in autoimmune diseases.

It is important to take into account the role of IgA autoantibodies in resolution of infection, especially in patients with mild symptoms, since SARS-CoV-2 affects the respiratory mucous membranes in the early stages of infection. This analysis could pave the way for early diagnostic and therapeutic strategies.[8]

The Ministry of Health document[9] of April 24 on interpretation of diagnostic tests for SARS-CoV-2, distinguishes between 4 stages:

1. Presymptomatic stage (PCR+).
2. Initial stage (1-7 days). PCR+, with potentially positive IgA/IgM levels. Both symptomatic and asymptomatic individuals can transmit the infection.
3. Second stage (8-14 days). IgA returns to negative values, and PCR may yield a negative result. IgM is positive and IgG may be positive. During this stage, the infection has usually resolved in asymptomatic individuals and in those with mild symptoms, and the risk of infection is minimal.
4. Third stage (> 15 days). The PCR result may be positive and there may be an increase in IgG and IgM antibody levels. The infection has resolved in asymptomatic individuals and in those with mild symptoms. The infection is not considered to have resolved in severely ill patients until after 50 days.

In the patients reviewed here, anticardiolipin antibody tests were performed 4 to 8 weeks after onset of skin conditions owing to the difficulty associated with the pandemic.

In conclusion, the presence of antiphospholipid antibodies, whether in the context of systemic lupus erythematosus or primary antiphospholipid syndrome, has been associated with the development of chilblains. In this case, it would involve antiphospholipid syndrome secondary to acute and transient infection by coronavirus or another virus. This surprising clinical picture is atypical because it has a clear association with infection during the previous days,[5] and not with extreme cold temperatures. In addition, although it has a temporal association with the pandemic, clear evidence of SARS-Cov-2 infection was only detected in 3 cases. The transient increases in immunoglobulins highlight the need for laboratory tests in the initial stage (i.e., the most infective stage). Furthermore, microparticles (phospholipids, glycoproteins) generate antibodies/autoantibodies, which disappear rapidly if they are IgA.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

1. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad. Dermatol Venereol. 2020 Mar 26. DOI: https://doi.org/10.1111/jdv.16387 (epub antes de impression).
2. Zhang Y, Cao W, Xiao M, Li YJ, Yang Y, Zhao J, et al. Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia. Zhonghua Xue Ye Xue Za Zhi. 2020;28:41.
3. Fernandez-Nieto D, Jimenez-Cauhe J, Suarez-Valle A, Moreno-Arrones OM, Saceda-Corralo D, Arana-Raja A, et al. Characterization of acute acro-ischemic lesions in non-hospitalized patients: a case series of 132 patients during the COVID-19 outbreak. J Am Aca Dermatol. 2020 Apr 24;83:e61–3. DOI: https://doi.org/10.1016/j.jaad.2020.04.093. [Epub antes de impresión].
4. Mazzotta F, Troccoli T. A new vasculitis at the time of COVID-19. Eur J Pediatr Dermatol (Monday's case). 2020;30:75–8 http://ejpd.com,. Accessed 13/4/2020.
5. Romaní J, Baselga E, Mitjà O, Riera-Martí N, Garbayo P, Vicente A, et al. Chilblain and Acral Purpuric Lesions in Spain During Covid Confinement: Retrospective Analysis of 12 Cases. Actas Dermosifiliogr. 2020 Apr 22;111:426–9, doi: https://doi.org/10.1016/j.ad202004.002. Online ahead of print.
6. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jianng W, et al. Coagulopathy and Antiphospholipid Antibodies in Pathients with Covid-19. N Engl J Med. 2020;382:e38.
7. Uthman IW, Gharavi AE. Viral infections and antiphospholipid antibodies. Semin Arthritis Rheum. 2002;31:256–63.
8. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. Mayo. 2020, medRxiv preprint https://doi.org/10.1101/2020.03.30.20047365 [Epub antes de impresión].
9. Documento de Interpretación de las pruebas diagnósticas frentea SARS-CoV-2 del 24 de abril de 2020. Versión 2. Ministerio deSanidad. Aprobado por la Ponencia de Alertas, Preparación yRespuesta con la colaboración de la SEIMC.

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