

- 2 Shiohara T, Mizukawa Y. Fixed drug eruption: a disease mediated by self-inflicted responses of intraepidermal T cells. *Eur J Dermatol* 2007; **17**: 201–208.
- 3 Byrd RC, Mournighan KJ, Baca-Atlas M, Helton MR, Sun NZ, Siegel MB. Generalized bullous fixed-drug eruption secondary to the influenza vaccine. *JAAD Case Rep* 2018; **4**: 953–955.
- 4 Pyl J, Aerts O, Siozopoulou V *et al*. Bullous fixed drug eruption following Human Papilloma Virus vaccination. *J Eur Acad Dermatol Venereol* 2020; **34**: e697–e698.
- 5 Sako EY, Rubin A, Young LC. Localized bullous fixed drug eruption following yellow fever vaccine. *J Am Acad Dermatol* 2014; **70**: e113–e114.
- 6 Gee J, Marquez P, Su J *et al*. First month of COVID-19 vaccine safety monitoring - United States, December 14, 2020-January 13, 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70**: 283–288.
- 7 FDA. FDA Briefing Document, Pfizer-BioNTech COVID-19 Vaccine. U.S. Food and Drug Administration; 2020. URL <https://www.fda.gov/media/144245/download> (last accessed: 16 March 2021).
- 8 Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines. *Eur Rev Med Pharmacol Sci* 2021; **25**: 1663–1669.
- 9 Hiltun I, Sarriugarte J, Martínez-de-Espronedá I *et al*. Lichen planus arising after COVID-19 vaccination. *J Eur Acad Dermatol Venereol* 2021; **35**: e414–e415.
- 10 Jedlowski PM, Jedlowski MF. Morbilliform rash after administration of Pfizer-BioNTech COVID-19 mRNA vaccine. *Dermatol Online J* 2021; **27**: 1–3.
- 11 Soyfer V, Gutfeld O, Shamai S, Schlocker A, Merimsky O. COVID-19 vaccine induced radiation recall phenomenon. *Int J Radiat Oncol Biol Phys* 2021; **110**: 957–961.
- 12 Corbeddu M, Diociaiuti A, Vinci M *et al*. Transient cutaneous manifestations after administration of Pfizer-BioNTech COVID-19 Vaccine: an

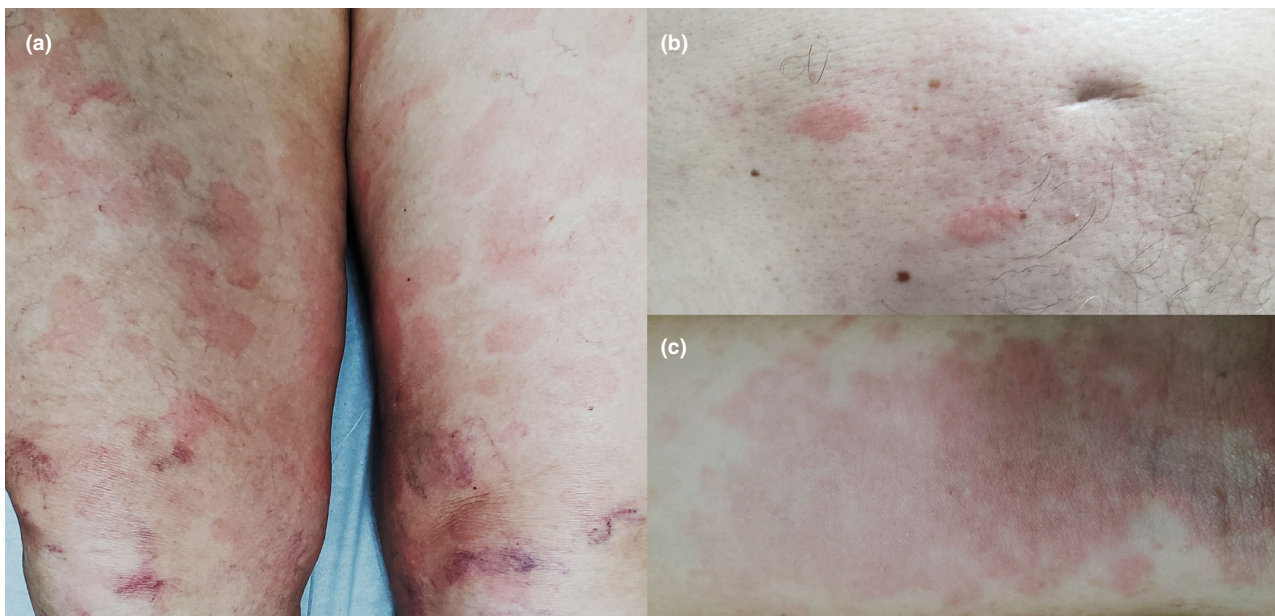
Italian single-centre case series. *J Eur Acad Dermatol Venereol* 2021; **35**: e483–e485.

DOI: 10.1111/jdv.17390

## Urticarial vasculitis revealing immunolabelled nucleocapsid protein of SARS-CoV-2 in two Brazilian asymptomatic patients: the tip of the COVID-19 hidden iceberg?

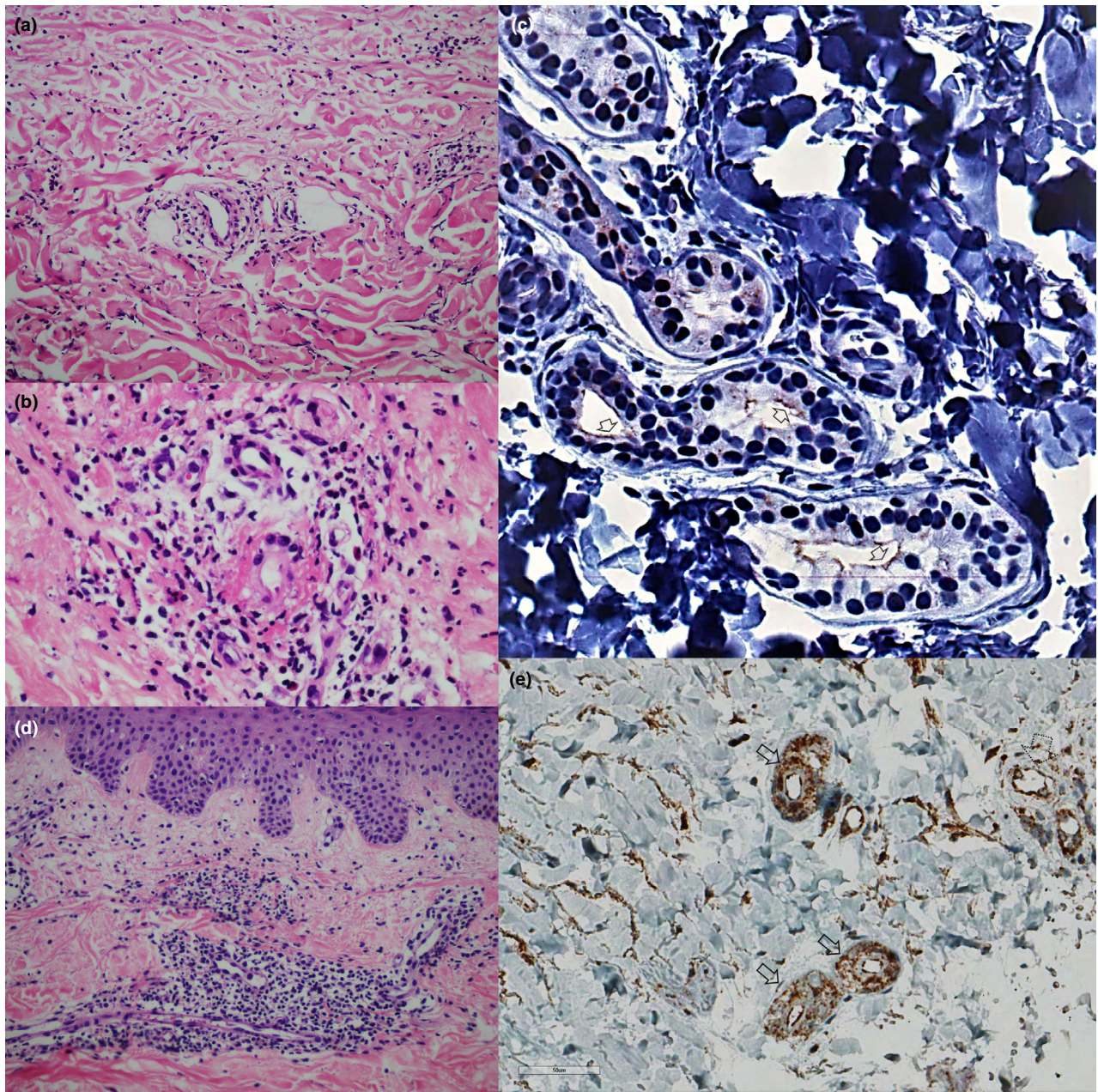
Dear Editor,

Urticarial vasculitis (UV) presents with persistent urticarial lesions that resolve with residual hyperpigmentation and histopathologic features of leukocytoclastic vasculitis. Both acute urticarial lesions and exacerbation of chronic spontaneous urticaria (CSU) were described associated with COVID-19.<sup>1–3</sup> Reports of UV associated with SARS-CoV-2 infection/COVID-19 are few and, to our knowledge, immunolabelled SARS-CoV-2 antigens in skin biopsies from UV under immunohistochemistry have never been demonstrated.<sup>4,5</sup>



**Figure 1** (a) Patient 1 – wheals involving the bilateral thighs; (b) patient 2 – two erythematous-oedematous lesions on the right upper abdomen; (c) patient 2 – urticated plaques on the right posterior forearm.





**Figure 2** (a) Patient 1 – histopathological examination from right leg showing oedema and perivascular infiltrate around dermal blood vessels, as well as scattered neutrophils in mid-dermis (H.E., 200×); (b) patient 1 – fibrinoid necrosis in wall of dermal blood vessel (black arrow) and leukocytoclasia in skin biopsy from right thigh (H.E., 400×); (c) patient 1 – immunohistochemical study demonstrating immunolabelled nucleocapsid (brown-black colour) in reticular dermal eccrine glands (white arrows). (d) patient 2 – histopathological exam showing perivascular lymphocytic infiltrate around dermal blood vessels, extravasated red blood cells and nuclear dusk (leukocytoclasia; H.E., 200×) and (e) patient 2 – immunohistochemical study demonstrating immunolabelled nucleocapsid (brown-black colour) in eccrine glands (thick line arrow) and in small dermal blood vessels (thick dotted arrow).

A 69-year-old Caucasian woman presented with itching and hives for 20 days. She denied any new medications or acute disease. On skin exam, >50 wheals on trunk and extremities were

noted (Fig. 1a–d). Lesions often resolved in 24–36 h in the same site and no signs of UV were observed. She was started on bilastine 80 mg/day with partial control of lesions. CBC, CRP, IgE,



C3, C4, CH50, ANA and rheumatoid factor (RF) were normal or negative. SARS-CoV-2 IgM serology was positive (immunochromatography assay; LUMIRATEK COVID-19<sup>®</sup>, LumiraDx from Bristol, UK; positive predictive value 94%<sup>6</sup>). After 2 weeks, she was started on omalizumab 300 mg every 4 weeks, with progression of urticaria after two doses. Patient underwent two skin biopsies, from right leg and right thigh. Immunohistochemical staining was performed on Ventana Automatic Stainer – Ventana Benchmark Ultra (Ventana Medical Systems, Tucson, AZ, USA). SARS-CoV-2 (2019-nCoV) nucleocapsid antibody and rabbit MAb (Rabbit Monoclonal antibody; Cat No 40143-R019; Sino Biological, Beijing, China) were used at 1:1500 dilution, for 32 minutes. Skin biopsy from right leg and right thigh revealed neutrophilic urticaria (Fig. 2a) and leukocytoclastic vasculitis (Fig. 1e–f), respectively. Immunohistochemistry study in paraffinized skin sample was performed using antibodies against SARS-CoV-2 nucleocapsid. Immunolabelled eccrine gland cells were found in the inner portion of eccrine glands (Fig. 1g). Patient was started on colchicine 1.5 mg plus bilastine 80 mg/day with partial control. After 30 days, hydroxychloroquine was added, and patient cleared completely in one month. A 61-year-old Caucasian man presented with a 2-week history of itchy lesions on trunk and limbs. He denied systemic symptoms, arthralgia or previous use of medications. Lesions were urticarial and annular on upper left abdomen (Fig. 2a,b) and wheals were noted in other areas (Fig. 2c–f). Skin biopsy from left upper abdomen demonstrated perivascular dermal inflammation (Fig. 2g,h) and oedema, as well as leukocytoclasia (Fig. 2i). Serology for SARS-CoV-2 demonstrated positive IgM. CBC, CRP, ANA, C3, C4, CH50, SPEP, RF, Hepatitis B, C and HIV serologies were negative or normal. Immunohistochemical staining performed under same method applied to patient 1 demonstrated immunolabelled nucleocapsid for SARS-CoV-2 in eccrine glands, interstitial dermal cells and small blood vessels (Fig. 2j). Patient received bilastine 80 mg/day plus hydroxychloroquine 400 mg/day with partial control of lesions.

Urinalysis in both patients was within normal limits. Nasopharyngeal RT-PCR testing for SARS-CoV-2 was not performed since it is not recommended after 7 days of symptom onset and should be limited to symptomatic patients with suspected COVID-19. Both of our patients demonstrated uncontrolled urticaria only and did not have classical COVID-19 general symptoms, perhaps being classified as oligosymptomatic for SARS-CoV-2 infection<sup>7</sup>.

Our cases occurred in asymptomatic COVID-19 patients and were refractory to conventional CSU treatment. Up until November 19, 2020, there was only one case reported of UV after symptomatic COVID-19, but nasopharyngeal RT-PCR was negative, and IgM/IgG serology was positive.<sup>3</sup>

False-positive immunological reactions in serum and histopathological examination were unlikely in our patients

because the positive predictive value of immunochromatography assay used for SARS-CoV-2 IgM serology is high (94%).<sup>6</sup> Furthermore, Roden *et al.*<sup>8</sup> demonstrated 100% specificity for SARS-CoV-2 antigens on immunohistochemistry in human tissues.

SARS-CoV-2 antigens in the skin may induce leukocytoclastic vasculitis with clinical urticarial lesions, with a similar immune mechanism as in erythema nodosum leprosum.<sup>9</sup>

Visconti *et al.*<sup>10</sup> analysed data from an online survey involving 11 546 respondents to investigate skin-specific symptoms of SARS-CoV-2 infection. Seventeen percentage of positive RT-PCR for SARS-CoV-2 nasopharyngeal swab cases reported skin rashes as the first sign, and 21% as the only clinical sign of COVID-19.<sup>1</sup> Our two cases are examples of asymptomatic SARS-CoV-2 patients or with non-classical COVID-19 symptoms who presented associated skin eruptions.

Cutaneous disease may be potentially triggered by SARS-CoV-2 asymptomatic infection and antigen exposure could lead to leukocytoclastic vasculitis. In these cases, physicians should be alert and perform SARS-CoV-2 serology, as well as cutaneous biopsies and immunohistochemistry study for SARS-CoV-2 antigens in the skin, when available. A single cutaneous eruption may be the tip of the iceberg, a hidden SARS-CoV-2 infection.

## Acknowledgements





The patients in this manuscript have given written informed consent to publication of their case details. Our sincere gratitude to Professor Raffaele Gianotti who passed during the months of the submission of this correspondence.

## Conflict of interest

None of the authors have any conflicts of interest to disclose.

## Funding source

None.

P.R. Criado,<sup>1,2</sup>  R.F.J. Criado,<sup>1,2</sup> R. Gianotti,<sup>3</sup>   
B.A.Z. Abdalla,<sup>1</sup>  T.P.H. Pincelli,<sup>4,\*</sup>  A.O. Michalany,<sup>5</sup>  
N.S. Michalany<sup>5</sup>

<sup>1</sup>UCARE (Urticaria Center of Reference and Excellence), Centro Universitário Saúde ABC (Faculdade de Medicina do ABC), Santo André, Brazil, <sup>2</sup>Alergoskin Alergia e Dermatologia, Santo André, Brazil, <sup>3</sup>Clinica Dermatologica, Università degli Studi di Milano, Milano, Italy, <sup>4</sup>Department of Dermatology, Mayo Clinic, Jacksonville, FL, USA, <sup>5</sup>Laboratório Paulista de Dermatologia, São Paulo, Brazil

\*Correspondence: T.P. Pincelli. E-mail: pincelli.thais@mayo.edu

## References

- Allegra A, Asero R, Giovannetti A, Isola S, Gangemi S. Urticaria and coronavirus infection: a lesson from SARS-CoV-2 pandemic. *Eur Ann Allergy Clin Immunol* 2021; **53**: 51–54.
- Criado PR, Criado RFJ, Pincelli TP, Yoshimoto TA, Naufal GGA, Abdalla BMZ. Chronic spontaneous urticaria exacerbation in a patient with

- COVID-19: rapid and excellent response to omalizumab. *Int J Dermatol* 2020; **59**: 1294–1295.
- 3 Kocatürk E, Salman A, Cherrez-Ojeda I *et al*. The global impact of the COVID-19 pandemic on the management and course of chronic urticaria. *Allergy* 2021; **76**: 816–830.
  - 4 Nasiri S, Dadkhahfar S, Abasifar H, Mortazavi N, Gheisari M. Urticarial vasculitis in a COVID-19 recovered patient. *Int J Dermatol* 2020; **59**: 1285–1286.
  - 5 de Perosanz-Lobo D, Fernandez-Nieto D, Burgos-Blasco P *et al*. Urticarial vasculitis in COVID-19 infection: a vasculopathy-related symptom? *J Eur Acad Dermatol Venereol* 2020; **34**: e566–e568.
  - 6 Castro R, Luz PM, Wakimoto MD, Veloso VG, Grinsztejn B, Perazzo H. COVID-19: a meta-analysis of diagnostic test accuracy of commercial assays registered in Brazil. *Braz J Infect Dis* 2020; **24**: 180–187.
  - 7 Möckel M, Corman VM, Stegemann MS *et al*. SARS-CoV-2 antigen rapid immunoassay for diagnosis of COVID-19 in the emergency department. *Biomarkers* 2021; **26**: 213–220.
  - 8 Roden AC, Vrana JA, Koepllin JW *et al*. Comparison of in situ hybridization, immunohistochemistry and reverse transcription-droplet digital polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 (SARSCoV-2)-testing in tissue. *Arch Pathol Lab Med* 2021; **145**: 785–796.
  - 9 Kahawita IP, Lockwood DN. Towards understanding the pathology of erythema nodosum leprosum. *Trans R Soc Trop Med Hyg* 2008; **102**: 329–337.
  - 10 Visconti A, Bataille V, Rossi N *et al*. Diagnostic value of cutaneous manifestation of SARS-CoV-2 infection. *Br J Dermatol* 2021; **184**: 880–887.

DOI: 10.1111/jdv.17391

## Frequency of relapse and persistent cutaneous symptoms after a first episode of chilblain-like lesion during the COVID-19 pandemic

Dear Editor,

Chilblain-like lesions (CLL) have been extensively reported during coronavirus disease-19 (COVID-19) pandemic in March–April 2020.<sup>1</sup> While the link between these lesions and severe acute respiratory coronavirus 2 (SARS-CoV-2) is still unclear,<sup>2</sup> emerging evidence of ‘long COVID’, with extra-cutaneous COVID-19 symptoms persisting over 60 days, is reported.<sup>3</sup> The aim of this study was to assess the evolution of the CLL overtime. We performed a retrospective study to evaluate the frequency and the characteristics of CLL relapses and the persistence of other cutaneous symptoms. In January 2021, a survey was sent to 132 patients who were addressed to the dermatology department of Saint-Louis hospital, Paris between 1 March and 30 April 2020 for CLL lesions. Ninety-five answers were obtained.

Features of the initial CLL episode are presented in Table 1. It involved the feet in 85 cases (89%), with a median severity of 6

and a median duration of 20 days. Fifty-two patients (55%) had at least one relapse, of which 46 (89%) relapsed after 1 October 2020 (Fig. 1a). Among them, 37 (71%) had one new relapse, 12 (23%) had two and 3 (6%) had more than three. Global duration and severity of the relapses were stable (Fig. 1b).

The first CLL relapse appeared after a median remission duration of 7.2 months (IQR 6–8), 11 patients (21%) had a contact with COVID-19-positive patients or suggestive general symptoms and one patient had a positive nasopharyngeal RT-PCR out of 13 (8%). Only eleven patients (21%) changed their lifestyle before the CLL relapse (eight lockdowns, two increased physical activity and one hallux valgus surgery). During the 2nd, 3rd and 4th relapses, respectively, 2/15 (13%), 1/3 and 1/3 patients had suggestive general symptoms, and all the RT-PCRs were negative ( $n = 4$ ).

In January 2021, 27 patients (28%) had persistent extra-cutaneous symptoms (mainly asthenia, joint pain, myalgia, anxiety, concentration disorder, shortening of the breath) and 64 (67%) had persistent cutaneous symptoms other than CLL (acral paraesthesia, acrocyanosis, erythralgia, Raynaud phenomenon, livedo). There was a significant association between persistent COVID-19 extra-cutaneous symptoms and persistent cutaneous symptoms ( $P < 0.05$ ).

**Table 1** Demographic and clinical characteristics of patients and COVID-19 documentation during the initial CLL episode in March 2020.

	Total (N = 95)
<b>Demography</b>	
Age (median, IQR)	33 (27–48.8)
Female (n, %)	60 (63%)
<b>Symptoms (n, %)<sup>†</sup></b>	
CLL feet	85/95 (89%)
CLL hands	20/95 (21%)
Urticarial lesions	8/95 (8%)
Vesicular eruptions	7/95 (7%)
Livedo	18/95 (19%)
Morbiform eruption	9/95 (9%)
<b>Duration</b> (days) (median, IQR)	20 (10–30)
<b>Severity</b> (numeric scale) (median, IQR)	6 (4–7)
<b>Treatment (n, %)<sup>†</sup></b>	
Topical steroids	13/95 (14%)
Systemic steroids	2/95 (2%)
Colchicine	2/95 (2%)
Others (antihistamines, antibiotics, anticoagulants, topical tacrolimus, ketoprofen)	14/95 (14%)
<b>SARS-CoV-2 documentation (n, %)</b>	
Suggestive general symptoms	23/95 (24%)
Contact with COVID-positive patients	21/95 (22%)
Positive RT-PCR	1/59 (2%)
Positive serological test	4/75 (5%)

<sup>†</sup>Patients can have more than one manifestation or treatment.