particularly in patients with connective tissue diseases. Anti-TNF-α agent therapy, as used in case 1, may be more appropriate for refractory LV through suppressing the coagulation–inflammation cascade.[11,12]

Identification of a rare enity such as LV, differentiation from its mimickers, and exclusion of associated comorbidities remain a challenging dilemma; it may be misinterpreted or underdiagnosed in histopathologic practice. We report such entities aiming to reinforce the awareness of the diagnostic approach and characteristics of this rare entity.

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Cutaneous Lymphocytic Vasculitis After Administration of the Second Dose of AZD1222 (Oxford–AstraZeneca) Severe Acute Respiratory Syndrome Coronavirus 2 Vaccination: Casuality or Causality?

To the Editor:

Adverse reactions to COVID-19 vaccinations have been expected.[1] We report a cutaneous rash post anti-Covid-19 (AZD1222 Oxford-AstraZeneca) vaccination in a 64-year-old man in good health, with no comorbidities or previous history of Covid 19 infection. As known, the vaccine is composed of a chimpanzee adenovirus unable to replicate itself (ChAdOx1—Chimpanzee Adenovirus Oxford 1) and modified to convey the genetic information intended to produce the spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) virus. On May 3, 2021 the patient received the first dose of the vaccine, without any skin manifestation and other side effects. The patient was in good health and on July 20, 2021, he was given the second dose of anti-Covid-19 (AZD1222 Oxford-AstraZeneca) vaccine. In both occasions, he reported taking paracetamol immediately after the vaccine administration. About 3 days after the second vaccine administration, the patient developed a slightly itchy maculopapular rash, initially on the limbs (where there was a purpuric aspect) and later also on the trunk (Fig. 1A). The skin manifestation did not resolve and after 10 days, the patient presented for a dermatologic examination. He reported that he was healthy and had not taken any other medications. Meanwhile he worked in his garden. The dermatologic evaluation therefore proposed a differential diagnosis between vasculitides and bites of harvest mites. No therapy was given, but blood tests were prescribed. Two skin punch biopsies were performed, respectively from the right leg and the left flank, for histologic examination. No direct immunofluorescence was investigated. Skin morphology was identical in the 2 biopsies. Histologic examination showed both superficial and deep perivascular infiltrates of small lymphocytes, with wall aggression, and some extravasation of erythrocytes and endothelial swelling, in the absence of fibrinoid necrosis and thrombus (Figs. 1B, C). There was no evidence of lichenoid dermatitis. The dermis included moderately abundant interfibrillar mucins (colloidal iron staining). The typing of the lymphoid population showed a T phenotype, without antigenic losses and with a prevalence of $CD4^+$ (Dako; clone C8/144B) lymphocytes (Fig. 1D) compared with $CD8^+$ (Leika; clone 4B12) lymphocytes (Fig. 1E). Scattered plasmacytoid dendritic cells (CD123+), especially in the context of the perivascular small lymphocyte population. Immunostaining with anti-SARS-CoV-2, monoclonal antibody anti-S (clone 007, cat. Num. 40150-R007), and polyclonal antibody anti-N (cat. Num. 40588-T62) from Sino Biological did not show any specific reactivity (test performed at the A.S.S.T. Brescia Spedali Civili Laboratory). The proposed diagnosis was lymphocytic vasculitis. To dermatologic control after about 2 weeks, the skin lesions had spontaneously resolved almost completely (Fig. 1F). The blood tests showed normal liver and kidney function, normal VES and blood counts. The autoimmune profile (ANA, ENA screening) was negative. A slight increase in fibrinogen (353 mg/dL) was noted instead.

A number of skin manifestations caused by SARS-CoV-2 have been described in individual case reports and nationwide case series: urticarial rash, confluent erythematous/maculopapular/

The authors declare no conflicts of interest.

This is a single case report and no identifiable patient information/characteristics are included in the case report. Therefore, there is no need to obtain the patient's consent.

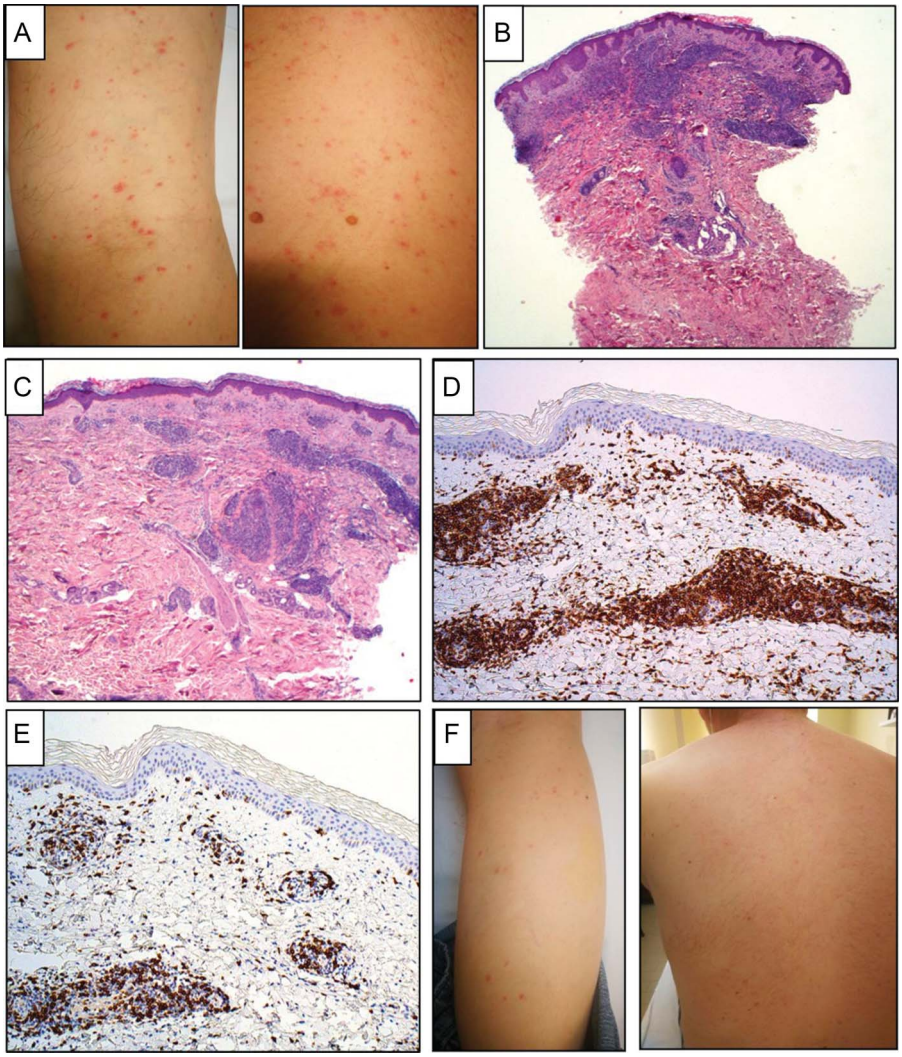

FIGURE 1. A, Diffuse maculopapular and purpuric rash-right leg and left flank (×2.5). B, Histology of right leg (×2.5) and (C) left flank (×10)—dermal perivascular lymphocytic infiltrate with endothelial swelling of small vessels (hematoxylin and eosin); (D) CD4+ lymphocytes predominate over CD8+ cells (E) in the perivascular infiltrate (×20). F, Almost complete resolution of the maculopapular, purpuric rash (right leg and back).

morbilliform rash, papulovesicular exanthem, a chilblain-like acral pattern, a livedo reticularis/racemosa-like pattern, and a purpuric vasculitic pattern.[2] Galvan Casas et al[3] found that maculopapular eruptions accounted for almost half of the cutaneous manifestations in their study. In fact, the maculopapular manifestation is one of the most frequently seen and associated with a direct effect of the virus on the skin.[3] Vojdani et al[4] described broad immune cross-reactivity between SARS-CoV-2 antibodies and different groups of antigens may play a role in the multisystem disease process of COVID-19. Involvement of the vascular wall could explain the late vascular side effect such as the rash of chilblains described among the most frequent skin manifestations of COVID 19, sometimes also with lymphocytic vasculitis.[5,6] Lyons-Weiler[7] compared the immunogenic epitopes of SARS-CoV-2 with human proteins and found a high degree of homology with various tissues, including the skin. Therefore, the immune response against viral antigens after infection or vaccination may cross-react with human tissue antigens, resulting in autoimmune reactivity, how can be cutaneous lymphocytic vasculitis. In fact, vasculitides have been also reported as adverse events following immunization after various vaccines administration, more often associated with influenza and pertussis vaccines.[8,9] Vasculitides have been reported following vaccination with Oxford–AstraZeneca. Gillion et al[10] reported the case of a 77-year-old man who developed acute granulomatous nephritis associated with vasculitis 4 weeks after the first dose of the AstraZeneca vaccine. Recently, Vassallo et al[11] described the case of a 51-year-old patient in general good health with symptomatic Covid-19 infection in April 2020, with no concomitant skin manifestation. The day after the first dose of Covid-19 vaccination (BNT162B2/Pfizer), the woman experienced an itchy maculopapular rash, which started from the limbs and spread to the trunk after another 24 hours. The histologic diagnosis was lymphocytic vasculitis, with a prevalence of CD4 + T cells compared with CD8 + T cells. Immunofluorescence directed to fibrinogen IgG, IgM, IgA, and C3 was also negative. As in our case, immunostaining with anti-SARS-CoV-2 nucleocapsid was negative. The patient was treated with systemic antihistamine and local steroid therapy with resolution of the manifestations in a week. As for the patient described by Vassallo et al,[11] also in our patient, the clinical picture suggests a postvaccination rash resembling a paraviral rash rather than a vaccine allergic rash characterized by anaphylactic or urticarial features.[2] Compared with the case described by Vassallo et al, our patient does not seem to have ever been infected with COVID 19 and the skin manifestations appeared at the second dose of a different type of vaccine.

The causes of lymphocytic vasculitis are very numerous, among others connective tissue disease, drug eruptions, and infection (especially viral and rickettsial). Cutaneous lupus erythematosus can also present with lymphocytic vasculitis; however, autoimmune serology was negative in our patient.

In summary, although causality between the rash and the AstraZeneca vaccine cannot be definitively proven, the timing and the absence of other causes makes the link between the 2

plausible. To the best of our knowledge, we describe the first case of the onset of a lymphocytic vasculitis after the second dose of Covid-19 vaccine (AstraZeneca-Oxford) histologically characterized by lymphocytic vasculitis, which resolved spontaneously within about 2 weeks.

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