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Small-vessel vasculitis following Oxford-AstraZeneca vaccination against SARS-CoV-2

Dear Editor,

The COVID-19 pandemic has caused significant economic and socio-sanitary effects on a global level. Its high transmission capacity coupled with the lack of effective treatment led to the rapid development of vaccines that, today, have been administered in a wide list of countries. As a result, new postvaccination adverse events continue to be described.

A 57-year-old woman with a personal history of hypertension and hypothyroidism presented to the emergency room for skin lesions of 4 days of evolution. Five days prior to the onset of symptoms, she had received the first dose of the Oxford-AstraZeneca COVID-19 vaccine and within the next 24 h of the administration, she presented with a fever of up to 38.5°C, generalized myalgias and general malaise with local pain at the injection site that self-limited without treatment. She denied previous similar episodes or recent use of new drugs. She denied any associated systemic symptoms or having previously had SARS-CoV-2 infection. On examination, she presented confluent palpable purpura lesions in the buttocks and in a splashed way in the legs and arms, being in the latter location practically resolved (Fig. 1). Histological examination revealed an intact epidermis and, in the dermis, a neutrophil-predominant perivascular infiltrate with leukocytoclasia and some eosinophils, features consistent with small-vessel leukocytoclastic vasculitis (Fig. 2). Direct inmunofluorescence was negative. Further work-up with blood and urine tests showed a slight increase in C-reactive protein and no other abnormalities. Complementary examinations were negative for antinuclear antibodies, antineutrophil cytoplasmic antibodies and cryoglobulins, and serology for hepatotropic viruses and HIV was negative. A rapid diagnostic test for COVID was also performed, which was negative. On follow-up without treatment 5 days later, she presented postinflammatory pigmentation and no new lesions were seen.

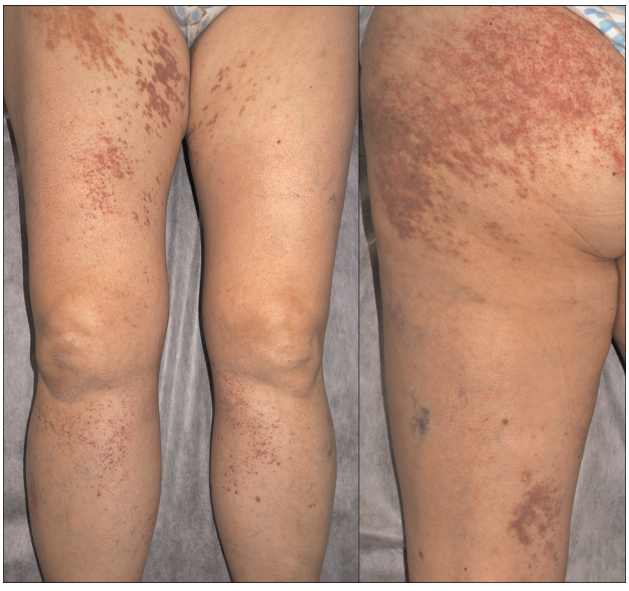

Figure 1 Physical examination showed palpable purpura lesions in the buttocks and in a splashed way in the legs.

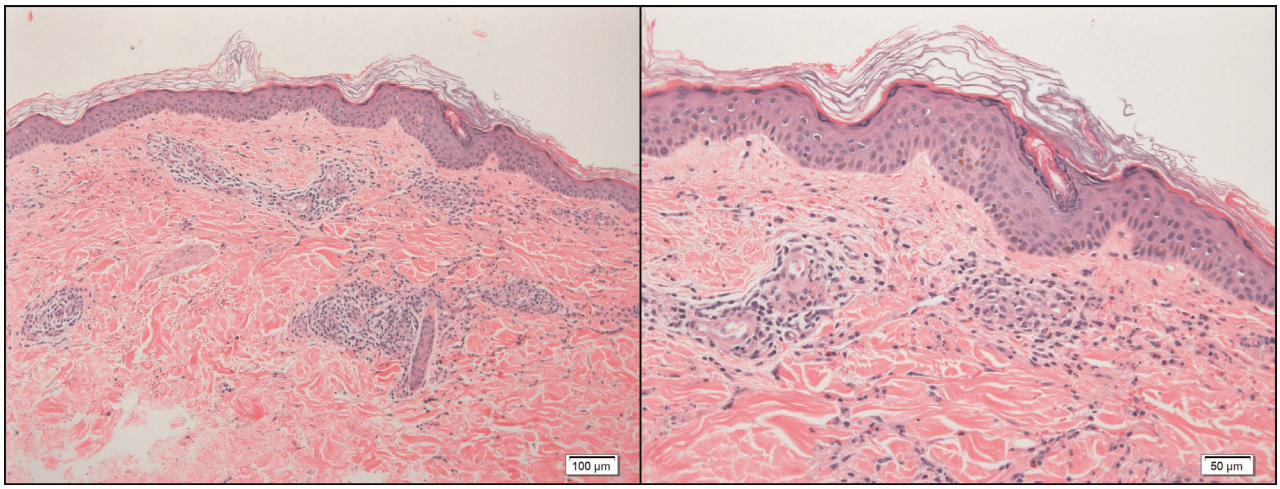

Figure 2 Histopathology a perivascular inflammatory infiltrate with leukocytoclasia consisting predominantly of neutrophils and some eosinophils, consistent with small-vessel leukocytoclastic vasculitis (original magnification ×10 & ×20).

Cutaneous small-vessel vasculitis is an inflammatory process that primarily affects the dermal postcapillary venules. It is often idiopathic but may be secondary to an underlying cause such as infection or medication.[1] Although it is controversial whether vaccination can be considered a promotor of any kind of vasculitis or not, several types of vasculitis have been reported in temporal association with their administration. A systematic review revealed that influenza vaccine is the most often reported in postvaccination cases of vasculitis.[2] Postvaccination vasculitis pathogenesis remains unclear although an innate immunity-mediated response to viral agents or vaccine excipients via molecular mimicry has been proposed.[3]

Vasculitis after COVID-19 vaccination has already been reported. A recent study that evaluated 417 cases of cutaneous reactions after mRNA COVID-19 vaccines found a frequency of 2.9% and 0.7% of vasculitis after the first dose of Pfizer (New York, NY, USA)-BioNTech (Mainz, Germany) (BNT162b2) and Moderna (mRNA-1273) vaccine, respectively.[4]

Moreover, cases of vasculitis secondary to SARS-CoV-2 infection have also been reported,[5,6] although there is still no solid evidence about the role of SARS-CoV-2 in the etiopathogenic mechanism of the skin lesions.[6]

The Oxford–AstraZeneca COVID-19 vaccine (AZD1222) is based on a chimpanzee modified adenovirus (ChAdOx1) expressing the spike protein of SARS-CoV-2, which allows development of a humoral and cellular immune response against the virus.[7] During the phase 2/3 clinical trial of the Oxford-Astrazeneca vaccine, injection site pain and tenderness were the most common local adverse reactions reported, whereas fatigue, headache, feverishness and myalgia were the most common systemic adverse reactions.[8] In that study, no vasculitis was reported as an adverse reaction and we have not found published cases in the literature of vasculitis after Oxford–AstraZeneca COVID-19 vaccination.

Given the recent commercialization of this vaccine, the report of new and potentially severe cutaneous adverse events is highly recommended to better characterize the vaccine security profile and study the potential association between vasculitis and COVID-19 vaccines.

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Author contributions

Dr Guzmán-Pérez had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Guzmán-Pérez *contributed to study concept and design*. Puerta-Peña, Rodríguez-Peralto and Sanz-Bueno *contributed to acquisition, analysis and interpretation of data*. Guzmán Pérez, Puerta-Peña, Falkenhain-López, Montero-Menárguez and Gutierréz-Collar *contributed to drafting of the manuscript*. Rodriguez-Peralto and Sanz-Bueno *contributed to critical revision of the manuscript for important intellectual content*. Guzmán Pérez, Puerta-Peña, Falkenhain-López, Montero-Menárguez and Gutierréz-Collar contributed to a*dministrative, technical or material support*. Rodriguez-Peralto and Sanz-Bueno contributed to *study supervision*.

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Omalizumab prevents anaphylactoid reactions to mRNA COVID-19 vaccine

Dear Editor,

Within the first days of initiating mass vaccination with the novel COVID-19 vaccines several anaphylactic reactions have been reported.[1] We present two cases experiencing angioedema with or without urticarial rash after the first dose of the mRNA-1273 vaccine. Both patients tolerated the second vaccination after a pretreatment with the anti-IgE antibody omalizumab.

The first patient, a 27 years old woman with no known allergies, developed dyspnoea, throat tightness, lip and tongue swelling, and flushing within the first hour after administration of the first vaccination. After treatment with intravenous antihistamines and glucocorticoids, the symptoms resolved. The second case, a 31 years old woman, developed an urticarial rash and subsequently a swelling of tongue and upper eye lids 10 days after receiving the first dose of the vaccine (Fig. 1). The symptoms reoccurred during the period of 9 days but resolved after 7 days of treatment with oral glucocorticoids as well as oral antihistamines. The patient reported on no other allergies apart from a type IV-sensitization to nickel.

In both patients, serological quantifications of total IgE, specific IgE to aeroallergens and tryptase levels revealed no hints of pre-existing type I-sensitizations or mast cell activation disorders (Table 1).

After a washout period of >14 days upon cessation of systemic anti-allergic treatments, skin prick tests using residuals of the mRNA-1273 vaccine displayed no positive response (Fig. 1). In addition, flow-assisted basophil activation assays determining CD63 expression showed no sensitizations neither to polyethylene glycol (PEG) nor to the mRNA-1273 vaccine (Table 1).

Thus, we found no evidence of pre-existing or newly acquired hypersensitivities to the mRNA-1273 vaccine or its components explaining the reactions in these cases. Hence, the immunological mechanisms behind the anaphylactoid reactions remain unclear. Acute allergic reactions to the novel mRNA COVID-19 vaccines have been described based on self-reports.[2] However, so far no type I-sensitization has been proven. Several publications reported on the efficacy of omalizumab, a recombinant humanized monoclonal anti-IgE antibody, in preventing hypersensitivity reactions even in cases without known triggers.[3]

Against this background, both patients were pretreated with a single dose of 300 mg omalizumab 2 and 7 days, respectively, prior to the second vaccination. Neither patient experienced angiooedema or urticarial rashes as immediate reactions after the second dose of the vaccine. The second patient showed a delayed reaction with fever and subsequent development of urticaria 8 days following the vaccination. However, this time the rash was by far less severe and thus no treatment with systemic glucocorticoids was required. Based on the clinical course and allergologic examinations, one could argue that the urticaria in the second case was most likely triggered by the delayed reactogenicity symptoms the patient experienced after the vaccination. Further, McMahon *et al*.[4] reported on urticarial rashes showing low second-dose recurrences. Hence, we cannot rule out that our second patient would have experienced less symptoms even without pretreatment with omalizumab.

