developed such lesion. This could be explained by the fact that we did not include paediatric patients, where pernio commonly manifests.[1] Retiform purpura and skin necrosis are cutaneous manifestations that correlate strongly with severe COVID-19 infection; the Spanish Workgroup that studied 375 patients reported that individuals who developed these cutaneous manifestations have a mortality of 10%.[1,2]

Results obtained from our study are similar to what is reported in literature. In the database collected by the AAD, manifestations considered to be related with a favourable-intermediate prognosis were pernio, morbilliform exanthem, urticaria, macular erythema, vesicular eruption and papulosquamous eruption.

We conclude that dermatological manifestations in COVID-19 are relatively common. These could be useful as prognostic markers, especially in hospitals or primary healthcare centres with limited resources, since their relationship with the clinical severity of the disease depends on the type of dermatological manifestation.

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None.

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Persistent maculopapular rash after the first dose of Pfizer-BioNTech COVID-19 vaccine

To The Editor,

The ongoing global pandemic COVID-19 led regulatory agencies to recently issue an emergency authorization for two effective COVID-19 vaccines from Pfizer-BioNTech and Moderna. Both vaccines use a novel technology of administering vaccination, namely a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding the spike glycoprotein of SARS-CoV-2 for subsequent antigen presentation and immune system activation.[1]

Although this novel vaccine technology is purported to be generally safe, the adverse effects and especially skin effects of mRNA vaccines are not yet completely characterized. In phase III clinical trial of Pfizer-BioNTechCOVID-19 vaccine[2] and in the first post-market morbi–mortality report,[3] the main skin manifestations reported are anaphylaxis skin symptoms like urticaria and diffuse erythematous rash and non-anaphylaxis allergic symptoms as an injection-site reaction, pruritus and rash without any semiological description.[2–4]

Recently, it was reported a case of a pruritic erythematous macular morbilliform eruption in a patient after each of the two injections of the Pfizer-BioNTechCOVID-19 vaccine with spontaneous resolution in 24 h.[5] Herein, we report a case of a different persistent maculopapular eruption onset for a few hours after the first injection of the Pfizer-BioNTech COVID-19 vaccine associated with liver damage, not described before.

A 55-year-old male hospital nurse, with no past medical history and no drug allergy, received the first dose of the Pfizer-BioNTech COVID-19 vaccine. Three hours after vaccination, the patient experienced injection-site soreness in the deltoid region with localized pruritic erythematous eruption which later spread on the face, trunk, upper extremities and thighs. During week 3, facing this persistent and unchanged eruption the patient presented at the dermatological consultation wondering about the safety of the second dose of vaccine. Clinical examination confirmed a maculopapular exanthema with 30% of body surface area involved (Fig. 1). Oral and genital mucosa was preserved and there was no fever, arthralgia or other systemic symptoms. HIV, HBV, HCV, CMV, EBV and measles serologies were negative and blood test only showed slight hepatic cytolysis (ASAT and GGT 2N). A punch biopsy was performed and haematoxylin and eosin-stained sections showed slight lymphocytic perivascular infiltrate, compatible with non-severe maculopapular toxidermia late biopsied.

It was decided not to perform the second dose because of the persistence of the rash, the liver damage and the known risk of more severe reaction after a first sensibilization, and the case was reported at the pharmacovigilance authority.

The rash persisted over a month with a gradual improvement over the days with dermocorticoid treatment in parallel with the improvement of liver enzymes.

The particular interest of our case is the early development of the rash with localized onset and its persistence over time with liver involvement, which led not to perform the second dose of vaccine. This is an example of the important role that healthcare providers and the dermatologists, in particular, play in the safety of these new vaccines by being vigilant in recognizing and reporting adverse events to the competent pharmacovigilance

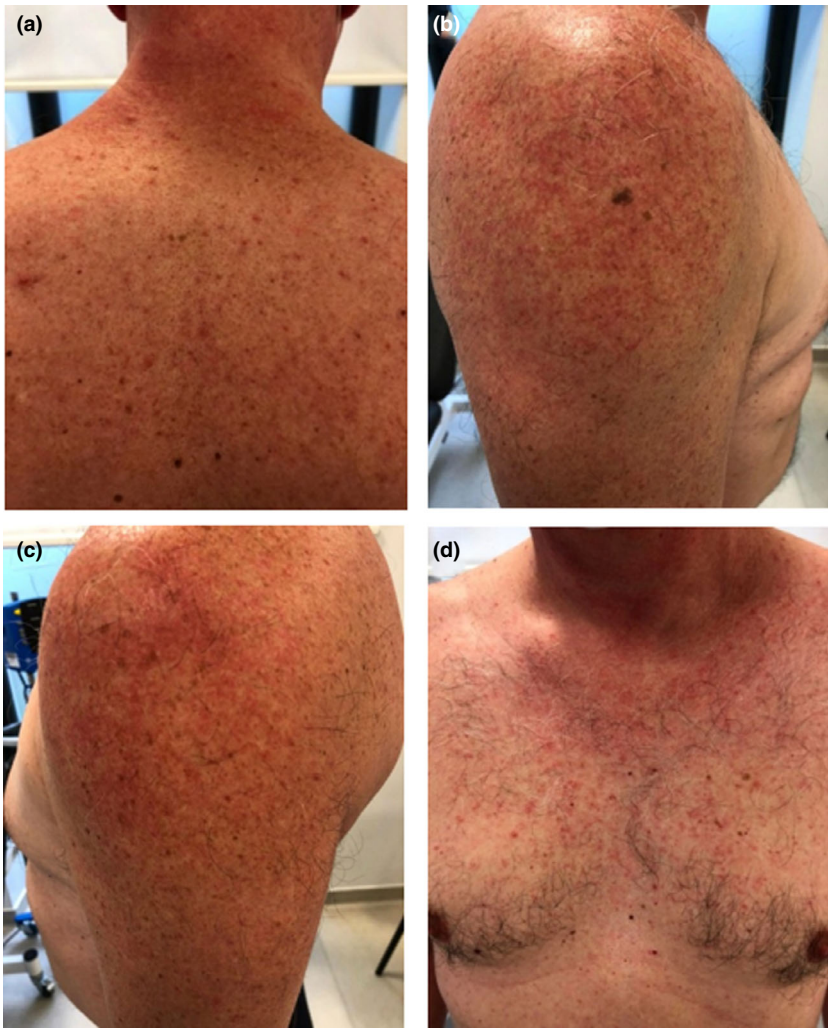

Figure 1 Maculopapular eruption: (a) Upper back (b) Right shoulder (c) Left shoulder (d) Chest.

authority, but also in describing the emerging reactions to help better understand them, which could have an implication for the vaccination strategy.

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Skin manifestations of the BNT162b2 mRNA COVID-19 vaccine in healthcare workers. 'COVID-arm': a clinical and histological characterization

Dear Editor,

The coronavirus disease 2019 (COVID-19) has been associated to a wide clinical spectrum of skin manifestations, including chilblain-like, urticarial, vesicular, maculopapular, livedoid and vasculitic lesions, among others.[1,2] However, the exact pathophysiology for the appearance of skin lesions is still unknown. Several hypotheses have been suggested, including viral hypersensitivity reactions, overexpression of type I interferons, COVID-19 induced coagulopathy, thrombotic microangiopathy and direct viral damage.[3–6] Potentially, some skin manifestations could also appear after vaccination with mRNA vaccines encoding the spike (S) protein of SARS-CoV-2. A delayed hypersensitivity reaction at the injection site of Moderna (mRNA-1273)[7] and Pfizer-BioNTech, Puurs, Belgium (BNT162b2)[8] vaccines has been recently described in the mass media as 'COVID-arm'. The mRNA-1273 vaccine clinical trial reported delayed injection-site reactions (onset after day 8) in 0.8% participants after the first dose and in 0.2% after the second dose.[7] The BNT162b2 clinical trial does not differentiate between immediate and delayed injection-site reactions, with an overall incidence of 5–7% after the first and second dose.[8] In addition, delayed inflammatory reactions to dermal fillers have also been described.[9]

We designed a retrospective study to characterize the skin manifestations of the BNT162b2 mRNA COVID-19 vaccine in a tertiary referral hospital of Spain. A registry of vaccine-related side effects was created by the Occupational Health Department, including delayed injection-site reactions (Table 1). This vaccination campaign was conducted from January 11 to February 12 2021. Physical examination and duration of the skin manifestations were either directly evaluated or indirectly evaluated through clinical pictures. A skin biopsy was also performed in two cases.

Table 1 Characteristics and demographic data of the subjects with delayed injection-site reaction obtained from the registry of the BNT162b2 mRNA COVID-19 vaccine

Characteristics	
Number of subjects	103
Age, mean, years (range)	40.4 (20-64)
Sex, male (%)	12 (11.7%)
Sex, female (%)	91 (88.3%)
After 1st dose	49 (47.6%)
After 2nd dose	54 (52.4%)
Itch (%)	70 (68.0%)
Duration <8h (%)	23 (22.3%)
Duration 8-24h (%)	28 (27.1%)
Duration 24-72h (%)	38 (36.9%)
Duration >72h (%)	14 (13.6%)

From 4775 subjects that underwent BNT162b2 mRNA vaccination, a total of 864 overall side effects were registered (18.1%). The mean age was 43.2 years (range 19–72), and 721 (83.4%) patients were female. A delayed injection-site reaction (Fig. 1a) was present in 103 subjects (2.1%), either after the first dose (49/103; 47.6%) or after the second dose (54/103, 52.4%). 16/49 subjects (32.7%) had recurrent lesions with the second dose. It lasted for less than 8 h in 23 patients (22.3%), between 8 and 24 h in 27 patients (26.2%), between 48 and 72 h in 38 patients (36.9%) and more than 72 h in 14 patients (13.6%). Itch was reported in 70 patients (68.0%). Five patients (4.9%) also presented disseminated lesions. None of these patients developed anaphylactic symptoms. In addition, two cases (2/4775; 0.04%) of vaccine-related urticaria were registered, lasting less than a week and responding to oral antihistamines. Histologic examination of a delayed injection-site reaction (Fig. 1b) showed a superficial and deep perivascular lymphocytic infiltrate, with dilated vessels and intraluminal neutrophils. Immunohistochemistry for the SARS-CoV-2 spike 1A9 protein (GeneTex, Irvine, CA, USA) was negative.

Currently, there are scarce reports of skin side effects related to COVID-19 vaccines. Recently, a case series of delayed large local reactions to the mRNA-1273 vaccine has been published, including 12 cases.[10] The median onset was on day 8 (range 4–11) after the first dose and resolved in a median of 6 days (range 2–11). Half of the patients had similar recurrent reactions after the second dose.

This delayed injection-site reaction shows similar features to COVID-19 exanthems.[3] Whether it corresponds to a hypersensitivity reaction to the spike protein or to different components of the vaccine is still unknown. We also found two cases of urticaria triggered by the vaccine, in a similar fashion to the actual SARS-CoV-2 infection.[6] The main limitation of the study is the self-reported and retrospective nature of the registry, so skin manifestations are probably under-ascertained. No severe cutaneous reactions were present in the study, suggesting that the

