Viral-like Reaction or Hypersensitivity? Erythema Multiforme Minor Reaction and Moderate Eosinophilia After the Pfizer-BioNTech BNT162b2 (mRNA-Based) SARS-CoV-2 Vaccine

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The outbreak of the worldwide COVID-19 pandemic has necessitated urgent research into and development of specific vaccines against SARS-Cov-2. Currently, 2 of the COVID-19 vaccines are based on mRNA: mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) [1]. The incidence of acute allergic reactions in clinical trials has been reported to be less than 1.3 per million inhabitants, and delayed hypersensitivity reactions have not yet been reported [1,2].

Erythema multiforme minor (EMm) is a skin reaction involving typical target lesions without muco-sal damage that is usually self-limiting. Its origin is mainly associated with viral infections and delayed hypersensitivity reactions to drugs. Interestingly, the few cases of EMm reported in patients with COVID-19 assume that SARS-Cov-2 virus can induce this type of reaction [3].

Excipients have been considered the culprit agents in hypersensitivity to mRNA-based COVID-19 vaccines [4], specifically, polyethylene glycol-2000 (PEG), which is present in mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech), and tromethamine/trometamol, which is present in mRNA-1273 (Moderna).

Polyethylene glycol is widely used in cosmetics and drugs owing to its physicochemical properties and is a well-known allergen that induces contact dermatitis. However, it has not been linked to the development of EMm–like reaction [5].

We report the case of a 47-year-old nurse with a history of herpes labialis (caused by *Human her-pesvirus 1*) who was vaccinated with the Cominarty vaccine (BNT162b2, Pfizer-BioNTech). The patient gave her written informed consent for her medical data to be reported. Twenty-four hours after the second dose, she developed pruritus at the injection site, mild maculopapular rash, and disperse papules in the right axillary region. The lesions then extended to the neck, thorax, flexor surface of the upper extremities, abdomen, back, groin, and thighs, with maximum extension on the fifth day after vaccination. The maculopapular exanthema was patchy, and the papules evolved to well-defined targeted lesions surrounded by a peripheral erythematous ring (Supplementary Figure, A) with a symmetrical distribution on the extensor surfaces of the acral extremities and the neck (Supplementary Figures, B and C). The patient presented intense pruritus without mucosal involvement or fever. She denied taking new drugs and insect bites.

During the episode, the patient did not develop herpes labialis lesions or lip discomfort at any time. Biopsy of the targeted lesions revealed superficial and interstitial perivascular dermatitis, with lymphohistiocytic infiltrate and eosinophils. Intraepidermal and subcorneal spongiotic vesicles were also visible (Figure).

On the sixth day after the skin lesions appeared, the patient started cetirizine 10 mg in 1 tablet every 12 hours to treat the discomfort caused by pruritus. Corticosteroids were not prescribed owing to the improvement in her lesions at day 5.

Serology testing revealed positive IgG and negative IgM (previous infection) for Epstein-Barr virus, *Toxoplasma gondii, Human herpesvirus 1,* cytomegalovirus, *Human herpesvirus 3* (varicella-zoster), *Mycoplasma pneumoniae*, and parvovirus B19.

The laboratory work-up performed 14 days after vaccination highlighted mild eosinophilia (21.2% eosinophils, 1300 × 10^3 cells/µL [baseline, 300 × 10^3 cells/µL]). A complete metabolic panel, eryth-rocyte sedimentation rate, and C-reactive protein panel were within normal ranges. HLA typing was also requested (LOCUS A *02, –, LOCUS B *27, *44, LOCUS C *01, *05, LOCUS DRB1 *10, *11, LOCUS DQA1 *01, *05, LOCUS DQB1 *03, *05, DQ5, DQ7.5).

The skin lesion disappeared 1 month after onset without desquamation, and the eosinophil count returned to normal values (100× 10^3 cells/µL eosinophils).

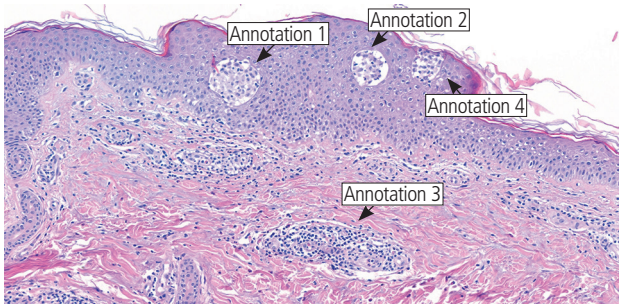

Figure. Histopathology image from the left popliteal fossa (hematoxylin-eosin) showing superficial perivascular and interstitial dermatitis with mixed cell infiltration (lymphohistiocytic and eosinophils) (annotation 3), intraepidermal vesicles (annotations 1 and 2), and subcorneal vesicles (annotation 4).

The allergy work-up with in vivo testing was performed 6 weeks after the reaction. We used polyethylene glycol 1500 (Roxall) [6] at concentrations of 0.1%, 1%, and 10% (wt/vol) for prick testing, with a negative result at an immediate and delayed reading. Patch testing with PEG 400 (allergEAZE) was also carried out and yielded a negative result at day 2 (48 hours) and day 4 (96 hours).

We present an EMm–like reaction that appeared the day after the second dose of BNT162b2 (Pfizer-BioNTech) mRNA-based vaccine associated with acute peripheral transient eosinophilia. EMm–like reactions are usually induced by drugs or viruses, including SARS-CoV-2 [5]. In the present case, the administration of the COVID-19 vaccine, which contains the mRNA encoding the spike protein of the virus (the part which enables it to enter cells to replicate and induce infection), produced a cutaneous reaction similar to that previously described during the disease. However, no other infectious symptoms (eg, fever) were reported.

EMm has also been related to drug hypersensitivity, and the biopsy analysis in the present case proved to be compatible with an allergic reaction, mainly because of the presence of the eosinophilic infiltrate. In support of the diagnosis of an allergic reaction to the vaccine, we also found peripheral eosinophilia, a phenomenon that is usually linked to allergy and is not consistent with observations made for COVID-19 [7]. The reliability of skin testing (which has not yet been well established) is limited, with the result that hypersensitivity cannot be excluded, despite the negative results recorded. In addition, BNT162b2 (Pfizer-BioNTech) contains PEG 2000, and the excipient tested in the present case was PEG 1500. Furthermore, although the allergy work-up for adverse reactions after administration of COVID-19 vaccine is based on skin tests with the vaccine, the shortage of doses necessary to immunize the general population means that, in practice, it is difficult to perform tests with the vaccine.

This case may be considered revolutionary in that it is the first report of an EMm–like reaction and concomitant peripheral eosinophilia after an mRNA-based COVID-19 vaccine. Further investigations are needed to elucidate whether the case involved a drug hypersensitivity reaction to the components of the vaccine (including polyethylene glycol 2000) or the patient's reaction was an adverse effect of a COVID-19 vaccine that mimics the infectious disease.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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