

Viral-like reaction or hypersensitivity? Erythema multiforme minor reaction and moderate eosinophilia after receiving Pfizer-BioNTech BNT162b2 (mRNA-based SARS-CoV-2 vaccine)

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0757

Key words: COVID-19, Vaccine, Hypersensitivity Erythema Multiforme, Eosinophilia.

Palabras clave: COVID-19, Vacuna, Eritema Multiforme, Hipersensibilidad, Eosinofilia.

The outbreak of the COVID19 pandemic around the world has required urgent research and development of specific vaccines against SARS Cov2. Currently, two of the COVID-19 vaccines are based on mRNA: mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) [1]. In the clinical trials, the reporting of acute allergic reactions has been less than 1.3 per million inhabitants and delayed hypersensitivity reactions have not been reported yet [1,2].

Erythema multiforme minor (EMm) is a skin reaction constituted by typical target lesions without mucosal damage, usually self-limited in nature. Its origin is mainly associated with viral infections and delayed hypersensitivity reactions to drugs. Interestingly, a few cases have been described in the literature during COVID19 disease, assuming that SARS Cov2 virus may induce this type of reaction [3].

Related to the COVID-19 mRNA-based vaccines and the development of hypersensitivity reactions, the excipients [4] have been pointed as the culprit agents. Specifically, the polyethylene glycol-2000 (PEG), presents in mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) vaccines; and the tromethamine/trometamol in mRNA-1273 (Moderna).

Polyethylene glycol is an excipient with widespread use in cosmetics and several drugs due to its physicochemical properties and it is a well-known allergen that induces contact dermatitis. However, it has not been linked to the development of erythema multiforme-like reaction [5].

We report a case of a 47-year-old woman, a nurse with a history of herpes labialis (caused by Herpes simplex virus type I), who was vaccinated with Cominarty® vaccine (BNT162b2, Pfizer-BioNTech). Twenty-four hours after the second dose, she developed pruritus in the injection-site, mild maculopapular rash and dispersed papules in the right axillary region. The lesions then extend to the neck, thorax, flexor face of upper extremities, abdomen, back, groin and thighs, with a maximum extension on the 5th day post-vaccination. The maculopapular exanthema presented a patchy distribution and the papules evolved to well-defined targeted lesions, surrounded by a peripheral erythematous ring (**Supplementary Figure A**) with symmetrically 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 new drug introduction or insect bites.

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

The 6th day after the skin lesions appeared, the patient started treatment with cetirizine 10 mg 1 tablet every 12 hours starting to treat the uncomfortable pruritus presented by the patient. Corticosteroids were not prescribed due to lesions improvement after the 5th day of evolution.

Serologies revealed positive IgG and negative IgM (past infection) for Epstein Barr, *Toxoplasma gondii*, Herpes simplex virus, Cytomegalovirus, Varicella Zoster virus, *Mycoplasma pneumoniae* and Parvovirus B19.

Laboratory workup was done 14 days after vaccination, standing out mild eosinophilia (21.2% eosinophils: 1300×10^3 cells/mcL; baseline of 300×10^3 cells/mcL). 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 one month after their initiation without desquamation and the eosinophils count become also normal (100×10^3 cells/mcL eosinophils).

The allergy workout with *in vivo* testing was performed six weeks after the reaction. We used polyethylene glycol 1500 (Roxall) [6] at 0.1%, 1% and 10% (p/v) concentrations for prick testing with a negative result at an immediate and delayed lecture. Also, an epicutaneous test with PEG 400 (allergEAZE[®]) was carried out with a negative result at day 2 (48 hours) and day 4 (96 hours).

We present an EMm-like reaction that appears the day after the second dose of BNT162b2 (Pfizer-BioNTech) mRNA-based vaccine associated with an acute peripheral transient eosinophilia. EMm-like reactions are usually induced by drugs or viruses, including SARS CoV2 [5]. In our case, the administration of the COVID-19 vaccine which contains the mRNA which encodes the spike protein of the virus (the part which enables it to enter our cells to replicate and induce the infection), produced a similar cutaneous reaction, previously described during the disease. However, no other infectious symptoms were referred such as fever.

On the other hand, the EMm has been also related to drug hypersensitivity and the biopsy analysis of our patient turned out to be compatible with an allergic reaction mainly because of the presence of eosinophilic infiltrate. Supporting the diagnosis of an allergic reaction to the vaccine, we also found peripheral eosinophilia, a phenomenon which is usually linked to allergy and which is an opposite observation with those described during COVID-19 [7]. Despite the negative results obtained from the cutaneous tests, hypersensitivity cannot be excluded due to their limited reliability, not well established yet. In addition, because BNT162b2 (Pfizer-BioNTech) vaccine contains PEG

2000 and one tested in our patient was PEG 1500. Although the allergy workout protocol to investigate adverse reactions after COVID-19 vaccines administration is the performance of skin tests with the vaccine, in actual practice it is difficult to carry out due to the need for doses to complete the vaccination programs to immunize the population.

This case is a rather revolutionary observation since it is the first case described of an EMm-like reaction and concomitant peripheral eosinophilia after receiving a mRNA-based COVID-19 vaccine. Further investigations are needed to elucidate whether the presented case is a drug hypersensitivity reaction to the components of the vaccine (including polyethylene glycol 2000) or the reaction of our patient was an adverse effect to a COVID-19 vaccine that mimics the infectious disease.

Disclosure statement

There are no known conflicts of interest associated with this publication and that there has been no significant financial support for this work.

Written informed consent was obtained from the patient.

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Figure legend. Anatomic pathology image from the left popliteal fossa stained with hematoxylin-eosin which shows a superficial perivascular and interstitial dermatitis with mixed - cell infiltration (lymphohistiocytic and eosinophils) (annotation 3) with intraepidermal (annotation 1 and 2) and subcorneal (annotation 4) vesicles.

