CASE REPORT
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Case of Polyethylene Glycol Allergy Confirmed with Basophil Activation Test and Oral Challenge Successfully Immunized with SARS-CoV-2 Vaccine

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ABSTRACT

Polyethylene glycols (PEG) or macrogols are polymers of ethylene oxide widely used in drugs either as active substances or, more commonly, as excipients. We report a Caucasian 32-year-old woman with referred anaphylaxis almost instantly after oral intake of a macrogol-containing laxative. Despite an anaphylactic reaction, the patient showed negative results for both the skin test and specific IgE to the monomer, while the basophil activation test and oral challenge were positive. The patient was later successfully vaccinated with a polysorbate 80-containing SARS-CoV-2 vaccine following an additional work-up. As a result, the inactive form of PEG cannot be fully diagnosed, and it is considered a "hidden" allergen. PEG derivatives like polysorbates need special consideration due to their possible cross-reactivity.

Keywords: Basophil activation test; COVID-19 vaccine; Drug allergy; Drug provocation test; Polyethylene glycol

INTRODUCTION

Polyethylene glycols (PEG) or macrogols are polymers of ethylene oxide widely used in drugs as active substances or excipients. Notably, PEGylation, which is common in immunotherapies and COVID-19 vaccines, intends to lower active substance immunogenicity. Moreover, PEG can be found in medicinal or hygiene products, cosmetics, and food. Sensitization is believed to occur from topical low molecular weight (MW) PEG as well as non-immediate hypersensitivity reactions. Immediate reactions though are reported with higher MWs (and doses) like in laxatives. Synonyms and derivatives with cross-reactivity (polysorbates, poloxamers), as well as insufficient labeling, render it a peculiar allergen, and the quality of life of sensitized patients is greatly affected.[1,2]

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CASE PRESENTATION

A 32-year-old Caucasian woman visited our Drug Allergy Outpatient Clinic, reporting immediate onset of urticaria, dysphonia, and palpitations within 1 minute after receiving macrogol ("Effecol", Epsilon Health, K. Palama 4, Salonica, Greece, 13.3g of 3350MW) orally for constipation 3 months earlier. Thirty minutes later, she was most probably treated with intravenous antihistamines and corticosteroids in an Emergency Department. The reaction subsided within 30 minutes, and she fully recovered 6 hours later. Personal medical history included glucose-6-phosphate dehydrogenase (G6PD) deficiency, rhinitis, childhood asthma, thyroid nodules, past gastroesophageal reflux, and a cesarian delivery. No previous exposure to the same or similar drug was reported. No remarkable findings from the physical examination were noted. The culprit commercial preparation stated above was used for both skin prick tests (SPT) and intradermal tests (IDT), prepared in sterile conditions in hospital's pharmacy, and were performed 12 weeks after the aforementioned reaction: SPT undiluted, IDT at 1/10,000, 1/1,000, 1/100 concentrations of the original ~100mg/mL solution (using normal saline as diluent), with normal saline for negative and histamine (10 mg/mL) for positive control markers. No reactions were observed at the challenge sites. However, 30 minutes after the last administration, the patient developed several urticarial wheals at distant sites and mild hoarseness. Laryngoscopy revealed mild edema of the arytenoid cartilage. Serum tryptase measured 2 hours post-reaction was 4.7 μg/L, though no baseline value is available. Follow-up laryngoscopy, 6 months later, was normal without any specific intervention, such as proton pump inhibitor therapy.

In vitro evaluation: (1) negative specific IgE quantification (ImmunoCAP Phadia) of ethylene oxide (0.1 kU/L; total IgE 243 IU/mL) and (2) positive basophil activation test (BAT, $CCR3^+/CD63^+$ surface markers) with stimulation index of 4.00, at 2 μM concentration. Higher concentrations were also tested were highly cytotoxic (Figure 1).

Despite proof of causality, single-blind placebo-controlled oral challenge (SBPCOC) with the same product aimed to determine the reaction threshold since the patient could possibly tolerate trace amounts. Conventional protocol was used starting from 0.1% with 10-fold graduation every 30 minutes. Thirty minutes after the second dose (133 mg), the patient developed systemic symptoms with few urticarial wheals and slightly discernible hoarseness without findings from endoscopy performed within 15 minutes, while spontaneous resolution occurred at that time.

Re-evaluation prior to SARS-CoV-2 immunization: Three years later, the patient expressed eagerness to be immunized to SARS-CoV-2 (available preparations contained PEG 2000 or polysorbate 80) and was willing to be further evaluated for potential polysorbate 80 tolerance.

Meanwhile, the patient had avoided macrogol and its derivatives in all pharmaceutical forms except for use on intact skin. However, an ultrasound gel was applicated to the vaginal mucosa due to incorrect label reading. The patient had been prescribed an autoinjectable epinephrine due to the ubiquitous nature of PEG. Due to the avoidance measures, the patient's quality of life had been greatly affected.

SPT with Ad26.COV2. S (Janssen, 1125 Trenton-Harbourton Road, Titusville, New Jersey, United States) and polysorbate 80 (Tween 80, 50 mg/mL, Sigma-Aldrich, PO Box 14508, St. Louis, United States) undiluted and IDT with polysorbate 80, 0.001%, 0.01%, 0.1% (diluted with normal saline) turned out negative. Next, we conducted an SBPCOC with a drug containing polysorbate 80 ("Nurofen for children", an oral suspension of ibuprofen, Reckitt Benckiser, 215 Bath Road, Slough, United Kingdom), which she passed. The rationale for this intermediate step was: (1) a SARS-CoV-2 vaccine challenge or desensitization protocol has not been established, ensuring its efficacy, (2) the oral administration route is safer than the intramuscular. In the end, the patient received the vaccine shot uneventfully.

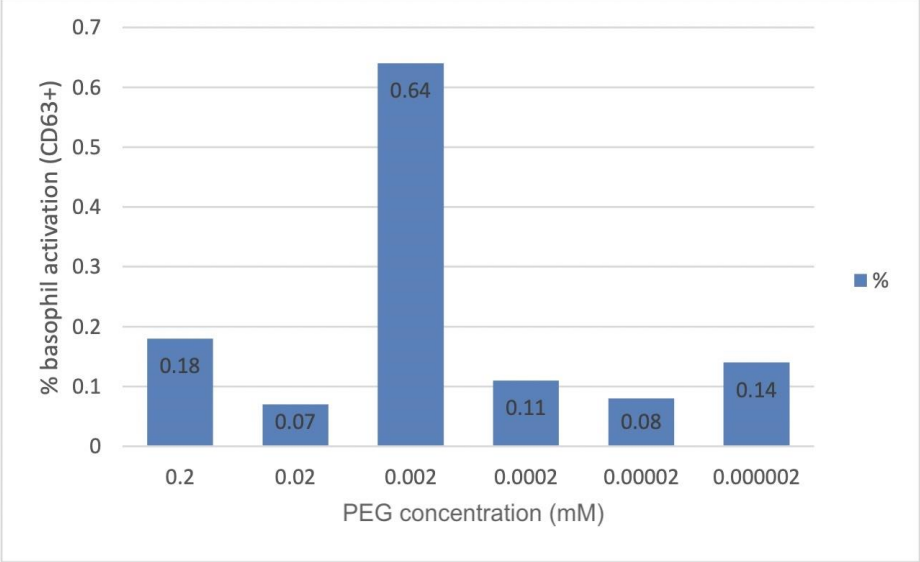

Figure 1. Basophil activation test results at different polyethylene glycol (PEG) 3350 concentrations

DISCUSSION

Our patient's initial reaction was confirmed as anaphylaxis based on the positive BAT result as well as the reactions during the skin tests and the oral challenge. However, the exact immunologic path could not be elucidated since the specific IgE was negative, and BAT cannot identify through which mechanism basophils react.

About 50 patients have been reported to experience systemic or mild anaphylaxis to near-fatal and fatal reactions to PEG and its derivatives.[1,3] In more than half of the cases, a laxative is the offending drug, and symptoms usually begin almost instantly. Even skin products can provoke systemic reactions, yet not anaphylactic ones, but this observation does not apply to the mucosa or a compromised epidermis.[1]

Skin tests require special safety considerations. IDT should begin as low as 0.0001%, and even dilute SPTs should be considered. Moreover, the reading time frame should be extended to up to 30 minutes. Almost whenever performed, skin tests have turned out positive, and, in some cases, they progress to systemic reactions[1]. Similar to our patient, there are cases where systemic reactions occur during skin tests despite the fact that the tests themselves turn out negative.[3]

Specific IgE to the monomer using common techniques (e.g., radioallergosorbent test, RAST) has never been detected, even though they have not been routinely performed, most likely because skin tests seem to be highly sensitive.[1] Stone and coworkers were the first to detect anti-PEG IgE using electrochemiluminescence (demonstrating stronger binding for higher MWs), yet another successful method is a dual cytometric bead assay developed by Zhou et al.[4] Moreover, pre-existing complement activating anti-IgM and genetic predisposition are also investigated.[5] Positive BATs have been reported in cases confirmed with skin tests.[6]

The role of PEG in multiple drug intolerance syndrome, idiopathic or perioperative anaphylaxis has probably been neglected until the emergence of COVID-19 vaccines.[1,7] Future research could focus on determining the role of PEG, PEGylation, anti-PEG antibodies, and low-MW PEG in preventing allergic reactions.[5,8,9] PEG allergic patients need to be evaluated for polysorbate cross-reactivity.[1,10]

STATEMENT OF ETHICS

Statement of Ethics approval code: 1320/20

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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