Novel Insights from Clinical Practice

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Anaphylaxis from the Influenza Virus Vaccine

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Established Facts

- Allergic reactions to influenza vaccine are usually associated with sensitivity to egg or gelatin.

Novel Insights

- This case report shows evidence of an IgE-mediated anaphylactic reaction to the infectious agent (hemagglutinin) in the influenza vaccine.

Key Words
Anaphylactic reaction · Gelatin · Immediate-type hypersensitivity · Influenza virus · Vaccine

Abstract
Background: Allergic reactions to the influenza vaccine are uncommon and usually associated with sensitivity to egg or gelatin. The aim of this study was to report the case of anaphylaxis to the influenza vaccine. ***Methods:*** Allergy percutaneous skin testing, serum specific IgE testing and IgE immunoblotting were performed to the influenza vaccine, egg, and gelatin. ***Results:*** Percutaneous skin testing to the influenza vaccine and gelatin were positive and egg (white, whole, and yolk) was negative. Immunocap® serum-specific IgE testing to egg (white, whole, and yolk) and gelatin were negative (<0.35 kU/l). IgE immunoblots were performed with 2 cord blood serums and the patient's serum at a 1:20 dilution against 10 μg of the Fluzone influenza vaccine. The patient's IgE immunoblot showed a protein band at 100 kDa which is similar to the molecular weight of gelatin protein, a 68-kDa protein which is similar to the molecular weight of hemagglutinin protein from the influenza vaccine, and a 45-kDa protein band that is similar to the molecular weight of ovalbumin protein from chicken embryo/egg. ***Conclusion:*** Based on clinical symptoms, skin testing, Immunocap testing and immunoblot evaluation, we feel that our patient is allergic to the infectious agent in the influenza vaccine as well as gelatin and ovalbumin in egg.

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Fig. 1. Erythematous cheeks of our patient after influenza vaccine injection.

Fig. 2. Localized cutaneous reaction at his right deltoid influenza vaccine injection site.

Introduction

Influenza epidemics in the United States are associated with approximately 36,000 deaths per year [1]. Outbreaks are primarily prevented through immunization with the influenza virus vaccine. Adverse effects from these vaccinations consist mostly of injection site reactions. Systemic anaphylactic reactions to the influenza vaccine include generalized urticaria, airway edema, dyspnea, wheezing and hypotension. These reactions are extremely uncommon, occurring in 0.002% of individuals receiving the influenza vaccine [2–5]. Allergic reactions to the vaccine are usually associated with sensitivity to egg or gelatin [6–9]. We present a rare case of systemic anaphylaxis from administration of the inactivated influenza virus vaccine.

Case Report

A 37-year-old male returned to the immunization clinic complaining of a warm sensation over his entire body 15 min after receiving a 0.5-ml intramuscular injection of the influenza virus vaccine (Fluzone; Aventis Pasteur, Swiftwater, Pa., USA). He also experienced face tingling and redness (fig. 1), pruritus, postnasal drip, and lip numbness. He had a localized cutaneous reaction at his right deltoid injection site (fig. 2). He denied chest tightness, shortness of breath, and wheezing. Based on his symptoms, he was given 10 mg of cetirizine and observed. Over the next 15 min he developed lip swelling, worsening facial flushing, and heartburn with audible belching. He was then treated with 0.3 ml of epinephrine intramuscularly and 150 mg of ranitidine orally. His symptoms resolved over the next 30 min.

His past medical history was significant for a 4 × 4 cm right arm localized reaction to an influenza vaccine (unknown manufacturer) given 4 years prior that occurred within 15 min. He had received other immunizations in the past without any adverse effects. He denied food allergies including eggs and gelatin.

The Fluzone influenza virus vaccine that our patient received contained hemagglutinin representative of the three relevant influenza strains. It was prepared from influenza viruses propagated in embryonated chicken eggs. It also contained 0.05% gelatin (0.025 mg) which acts as a stabilizer and the preservative thimerosal, a mercury derivative at 25 μg of mercury per dose.

As part of his evaluation, the patient returned to the Allergy Clinic on a separate day for skin prick testing. He was skin tested to the influenza vaccine, native egg (white, yolk, and whole) and gelatin (Jell-O sugared gelatin, Kraft Foods, Rye Brook, N.Y., USA). His skin testing response to the influenza vaccine was positive (3 × 4 mm wheal and 5 × 7 mm flare), gelatin was positive (3 × 4 mm wheal and 5 × 5 mm flare) and egg was negative (egg white: 0 × 0 mm wheal and 4 × 4 mm flare; egg whole: 2 × 2 mm wheal and 3 × 3 mm flare, and egg yolk: 2 × 2 mm wheal and 4 × 4 mm flare). His histamine-positive control was 4 × 5 mm wheal and 26 × 30 mm flare, and the diluent negative control was 0 × 0 mm wheal and 0 × 0 mm flare. Results of concomitant gelatin skin tests on 2 control subjects (clinic staff) were negative (0 × 0 mm wheal and 0 × 0 flare). Immunocap® specific IgE testing to egg (white, whole, and yolk) and gelatin were negative (<0.35 kU/l). IgE immunoblots were performed with 2 cord blood serums and the patient's serum at a 1:20 dilution against 10 μg of the Fluzone influenza vaccine (fig. 3). The patient's IgE immunoblot showed a protein band at 100 kDa which is similar to the molecular weight of gelatin protein, a 68 kDa protein which is similar to the molecular weight of hemagglutinin protein from the influenza vaccine, and a 45-kDa protein band that is similar to the molecular weight of ovalbumin protein from chicken embryo/egg. These IgE immunoblot bands were not found on the 2 cord blood non-atopic serum specimens.

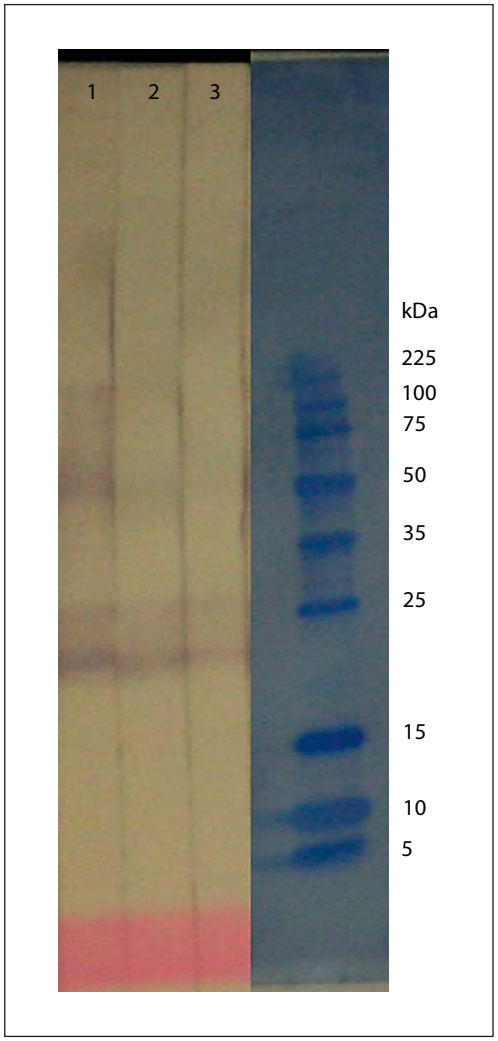

Fig. 3. IgE immunoblotting with serum from our patient in lane 1; cord blood serum from two samples is shown in lanes 2 and 3. Molecular weight markers (in kDa) are also shown. The patient's IgE immunoblot showed a 100-kDa protein band which is similar to the molecular weight of gelatin protein, a 68-kDa protein band which is similar to the molecular weight of hemagglutinin protein from the influenza vaccine, and a 45-kDa protein band that is similar to the molecular weight of ovalbumin protein from chicken embryo/egg. These IgE immunoblot bands were not found on the 2 cord blood serum specimens. There is non-specific binding toward the bottom of each lane.

Discussion

Allergic reactions occur after inoculation with the influenza virus vaccine for a variety of reasons. As with other avian-based vaccines, many of these reactions are attributed to the egg protein component of the vaccine. Cox [6] reviewed egg-based vaccines including influenza in 2006. She stated that currently there are three inactivated influenza vaccines used in the United States, and these vaccines are grown in either chorioallantoic fluid or ovalbumin of chick embryos. The author noted that the allergenicity is highly dependent on the preparation method with whole virus from red cell eluates containing more chick egg protein than centrifuged or chemically precipitated vaccines. In addition, there appears to be a high degree of variability in egg protein present in the lots of these influenza vaccines [7].

Although the amount of egg protein is limited, its presence can trigger an immediate hypersensitivity reaction in egg-allergic individuals. Obtaining prior allergy history before vaccine administration and determining the indication for vaccination is paramount. Prior reactions of generalized urticaria, hypotension, upper or lower airway obstruction, or documentation of IgE-mediated hypersensitivity to egg protein may place these individuals at higher risk for an adverse event. This potentially increased risk must be weighed against the benefits of receiving the vaccine. In circumstances where the benefits outweigh the risks for the patient, skin testing to the influenza vaccine can be performed and the vaccine can be given in graded doses in a supervised setting [8, 9]. However, persons with a history of severe anaphylactic reactions to egg protein should not receive this vaccine [10].

Another component of the influenza virus vaccine is thimerosal, a mercury-containing preservative used in multidose vials that acts as a preservative by inhibiting bacterial contamination. Thimerosal is a common allergen in contact dermatitis [11, 12]. In the literature, there has been a case report of a patient positive to thimerosal on patch testing who developed a generalized cutaneous erythematous, maculopapular eruption after receiving an influenza vaccine [13].

The influenza virus vaccine also contains gelatin, which can trigger an anaphylactic reaction in gelatin-allergic patients. Gelatin is primarily used in viral vaccines to stabilize the viability of the virus [14]. There have been reports of IgE- and non-IgE-mediated allergic reactions attributed to gelatin in foods (candy fruit chews and gummy bears) [15, 16] and in other medical products including intravenous fluids (modified fluid gelatins) [17], chloral hydrate suppositories [18], erythropoietin [19], and a gelatin-containing surgical sponge [20]. In addition, allergic reactions have been reported from vaccines that contain gelatin, specifically the measles-mumps-rubella and varicella vaccines [21–23].

Finally, the influenza vaccine contains the inactivated influenza virus (hemagglutinin representative of the three relevant influenza strains). Individuals may be allergic to the inactivated influenza virus in the vaccine. From the US Vaccine Adverse Event Reporting System, seven reports of possible anaphylaxis were attributed to the live intranasal influenza vaccine during the 2003–2004 and the 2004–2005 influenza seasons [2]. These events included 4 individuals who developed throat swelling and 1 serious event in a patient who reported periorbital swelling. Unfortunately, additional details and evaluations were not available on these individuals to establish the cause of their anaphylactic reactions.

In conclusion, we present a patient who developed an immediate systemic anaphylactic reaction to the inactivated influenza virus vaccine. Based on clinical symptoms, skin testing, Immunocap testing and immunoblot evaluation, we feel that our patient is allergic to the infectious agent (hemagglutinin) in the influenza vaccine. This allergic mechanism may be applicable to other patients who have anaphylactic reactions to viral vaccines. In addition, our patient may be allergic to injectable gelatin and ovalbumin contained in the influenza vaccine. Although the patient tolerates oral gelatin, he may have had an anaphylaxis to the injectable gelatin in the influenza vaccine as reported by Sakaguchi et al. [23] in a study of patients who had anaphylactic reactions to injected gelatin but could tolerate ingested gelatin. In addition, our patient may have reacted to the ovalbumin in the vaccine as some patients can tolerate cooked eggs but have allergic reactions to heat-labile egg proteins [24]. Our patient was instructed not to receive the influenza vaccine in the future; however, he may be a candidate to receive the influenza vaccine in graded doses if needed for a critical indication.

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