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SHORT COMMUNICATION



Acute hypersensitivity reaction to Crotalidae polyvalent immune Fab (CroFab) as initial presentation of galactose- α -1,3-galactose (α -gal) allergy

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ABSTRACT

Crotalidae polyvalent immune Fab antivenom (CroFab), commonly used for the treatment of clinically significant North American crotalinae envenomation, is generally well-tolerated. A novel form of anaphylaxis due to an IgE antibody response to the mammalian oligosaccharide galactose- α -1,3-galactose (α -gal) has been established following red-meat consumption as well as IV administration of cetuximab, which contain the α -gal epitope. We present a case of α -gal allergy discovered after acute hypersensitivity reaction to FabAV. A 61-year-old healthy female was bitten on her left ankle by *Agkistrodon contortrix*. Given the patient's rapid progression of pain and swelling, she was given FabAV. During infusion of FabAV, she developed diffuse hives over her entire body and itching, but denied respiratory or gastrointestinal symptoms and her vital signs remained stable. The FabAV was immediately discontinued and she received intravenous diphenhydramine and famotidine with gradual resolution of symptoms. On further discussion, she denied a history of α -gal or papaya allergy but rarely ate red meat and endorsed sustaining frequent tick bites. Subsequent antibody testing was significant for an α -1,3-galactose IgE concentration of 45,000 U/L (normal <3500 U/L), confirming α -gal allergy. To our knowledge, this is the first report of FabAV hypersensitivity associated with an underlying α -gal allergy.

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KEYWORDS

α -Gal; allergy; CroFab; hypersensitivity

Introduction

Snakebite envenomation in USA is almost exclusively due to Viperidae, with a substantial portion of these attributed to Copperhead snakes (*Agkistrodon contortrix*) [1]. Crotalidae polyvalent immune Fab antivenom (CroFab) is commonly used for the treatment of clinically significant North American crotalinae envenomation [2]. As with any biologic product, immediate hypersensitivity reactions can occur following antivenom administration; however, CroFab has had significantly fewer reported adverse effects than the previously available product, Wyeth antivenin (Crotalidae) Polyvalent [2]. While individual studies have documented varying rates of hypersensitivity reactions, the best available recent evidence shows that hypersensitivity reactions occur at a rate of ~8% [2–4].

A novel form of anaphylaxis due to IgE antibody (Ab) response to mammalian oligosaccharide, galactose- α -1,3-galactose (α -gal) has been established in response to mammalian meat consumption as well as to intravenous administration of cetuximab, both of which contain the α -gal epitope [5,6]. The α -gal oligosaccharide is a blood group substance of non-primate mammals; reactions can occur in response to ingestion of mammalian meat such as beef, lamb, pork, and venison. IgE antibodies to α -gal are found in up to 20% of patients (and controls) receiving cetuximab infusions in Tennessee, Virginia, North Carolina, Arkansas, and southern Missouri [7]. Allergic reactions to α -gal have been

noted outside USA as well [8,9]. The mechanism of sensitization has been found to be associated with bites from the lone star tick (*Amblyomma americanum*) [10]. We present a case of α -gal allergy discovered after acute hypersensitivity reaction to FabAV.

Case report

A 61-year-old healthy female was bitten on her left ankle by a Copperhead snake (*A. contortrix*). Within 20 min from the time of bite, she developed both ecchymosis and swelling of the left ankle. She presented to the emergency department, and was noted to have a single puncture wound 2 inches superior to the left medial malleolus with ecchymosis and edema extending both proximally up the calf 5 inches as well as distally down to the midfoot. The edema was most significant over the medial and lateral malleoli. She had no past medical or surgical history and endorsed no known allergies. Her initial vital signs were heart rate 82, blood pressure 133/61 mmHg, respiratory rate 18, and oxygen saturation 100% on room air. Laboratory work including platelets, coagulation studies, and creatine kinase were normal. She was given 1 mg hydromorphone intravenously (IV) for pain and started on a normal saline IV bolus. Given the patient's rapid progression of pain and swelling following the envenomation, FabAV was administered. The infusion was started ~20 min after receiving hydromorphone. She denied

any known allergy to papaya. The patient had received approximately half of the 4 g infusion when she began to complain of bilateral palmar and groin itching as well as hives on her inner right thigh and abdomen. Within 5–10 min, she developed diffuse hives over her entire body and endorsed itching in her hands, groin, legs, and soles of both feet. She reported a “pulsating” sensation over her entire body but denied respiratory or gastrointestinal symptoms. Her vital signs remained stable; other than urticaria, she developed no signs of anaphylaxis or angioedema. The FabAV was immediately discontinued and she received 25 mg of IV diphenhydramine and 40 mg of IV famotidine with gradual resolution of hives and itching over ~2 h. Further FabAV was not administered because it was felt that the risk of further reaction outweighed the potential benefit. Given the rarity of reaction in a patient who had never received this infusion, and the fact that FabAV is a purified ovine antibody, concern existed for potential α -gal allergy in a patient that lives in a region where α -gal is endemic. On further discussion with the patient, she denied a history of meat allergy; however, she admitted to rarely eating red meat, usually only once per year. She endorsed living in a wooded area and sustained frequent tick bites. With the patient’s agreement, subsequent antibody testing was significant for an α -1,3 galactose IgE level of 45,000 U/L (normal <3500 U/L), confirming α -gal allergy. She was instructed to avoid red meat and follow-up with an allergist. During admission, she did not require any further medications for allergic symptoms and her pain was controlled with oral acetaminophen. The following day, the swelling had significantly improved and the patient was able to bear weight. She did not develop any coagulopathy. She was subsequently discharged home.

Discussion

This is a case of hypersensitivity reaction to FabAV leading to the determination of the presence of α -gal allergy in a patient. To our knowledge this is the first report of FabAV hypersensitivity associated with an underlying α -gal allergy. Over 1000 patients with α -gal allergy have been identified in USA and globally [5,7–9]. Anaphylaxis has been noted after administration of IV cetuximab and medications that contain magnesium stearate (a meat byproduct), both of which contain the α -gal epitope [5,6,10]. It is not possible to determine whether or not the patient’s α -gal allergy was the true causation of this particular hypersensitivity reaction to FabAV, and the patient possibly has a concomitant allergy to FabAV

that is not related to α -gal. However, data from previous reports suggest that mammalian derived products can cause adverse drug reactions in α -gal sensitized individuals; as an ovine antibody, FabAV would be expected to be glycosylated with galactose- α -1,3-galactose [6]. Similarly, while it is not possible to exclude hypersensitivity to hydromorphone as the cause of our patient’s reaction, it seems less likely than hypersensitivity to FabAV; most opioid-induced hypersensitivity is related to non-allergic histamine release and tends to occur shortly after drug administration. Clinicians should be aware of the possible cross-reactivity and should incorporate the query of potential red-meat allergy into the decision making process prior to FabAV administration.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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