Delayed Onset and Biphasic Anaphylaxis following Hymenoptera Immunotherapy

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Abstract
Anaphylaxis is an acute IgE mediated, potentially life-threatening reaction which typically occurs within 30 minutes of allergen exposure. Approximately 1,500 fatal anaphylactic reactions occur in the United States annually. Delayed onset anaphylaxis classically develops one to two days following exposure to an antigen. Biphasic anaphylaxis is characterized by an initial phase of symptoms which resolve completely, and then recur most often 8–10 hours later. There may be an association between delayed administration of epinephrine in the initial phase of treatment and the occurrence of biphasic anaphylaxis. The recurrent symptoms seen in biphasic anaphylaxis tend to be refractory to standard therapy.

Keywords: Anaphylaxis; Delayed Onset; Biphasic; Hymenoptera Immunotherapy

Case Presentation
A thirty-eight year old healthy male presented to the Emergency Department (ED) complaining of generalized urticaria, pruritis, voice hoarseness and chest tightness. He denied any swelling of his tongue, throat, or extremities. He reported that he had received his 2nd dose of venom extract immunotherapy nine days prior for an anaphylactic sensitivity to hymenoptera. On review of his electronic medical record (EMR), it was documented that he had been “stung by an insect” in 1999. Approximately 32 hours later, he had developed urticaria, shortness of breath and airway edema, and required intubation at an outside hospital. In 2004, he had been stung by a yellow jacket, had similar symptoms, and was started on steroids and antihistamines. Per the EMR, while tapering the steroids six days after the sting, he had recurrent urticaria. He had normal phonation, no lip or tongue edema, and no stridor or wheezing, but reported a feeling of increasing throat and chest tightness similar to the previous episodes that had resulted in his eventual intubation. Repeated IM epinephrine injections were administered which improved his symptoms only transiently. He was then started on an epinephrine infusion at 0.1 mcg/kg/min and admitted to the intensive care unit (ICU) for delayed and refractory anaphylaxis.

After starting immunotherapy (doses and type unknown), the patient was noted to have diffuse urticaria, and complained of tightness in his neck within 24 hours. Outpatient immunotherapy was deemed unsafe at that time. The patient was admitted to our facility for rush immunotherapy in 2005, and was premedicated with H1 and H2 antihistamines, Prednisone, Montelukast and Celecoxib. He successfully tolerated immunotherapy with 40 and 60 mcg wasp venom, as well as 120 and 180 mcg mixed vespid venom. He was transitioned to a weekly maintenance dose of 100 mcg wasp and 300 mcg mixed vespid venoms while continuing all of the above oral medications.

The patient continued weekly maintenance immunotherapy for five years, during which time he was stung on three separate occasions by yellow jackets and experienced no symptoms. As a result, in 2010 it was recommended that he stop immunotherapy. Later in 2010, he was stung by on the leg by a yellow jacket, with documented tachycardia, hypertension, immediate leg swelling and urticaria unrelieved by Prednisone and Cetirizine that he had taken at home. In 2012, he was again stung, hospitalized at another facility, and ultimately intubated. Clinic notes made mention of serum tryptase and IgE testing, but no results were documented. After hospital discharge, he was restarted on outpatient immunotherapy of which he was in the process when he was seen in our ED.

The patient reported that two days prior to this visit (7 days after receiving 0.1 mcg of mixed vespid venom extract) he presented to an area ED with urticaria, hoarseness, neck tightness and flushing. He reported he had been taking Prednisone and Cetirizine daily as instructed by the Allergy and Immunology Clinic. He received intravenous Diphenhydramine and Famotidine with complete resolution of his symptoms, and was discharged to home. Six hours prior to this visit, the patient reported that he began experiencing urticaria, pruritis, voice hoarseness and chest tightness (consistent with his previous episodes of documented anaphylaxis), at which time he self-administered intramuscular (IM) epinephrine (0.3 mg).

Shortly after administering the epinephrine, the patient stated his symptoms resolved, but recurred three hours later, prompting his return to the ED. Upon arrival to the ED, he had initial documented vital signs of Temperature 36.3 C, Heart Rate 100, Respiratory Rate 18, Blood Pressure 154/100, and Oxygen Saturation 100%. Physical exam was significant for generalized urticarial rash. The patient had normal phonation, no lip or tongue edema, and no stridor or wheezing, but reported a feeling of increasing throat and chest tightness similar to the previous episodes that had resulted in his eventual intubation. Repeated IM epinephrine injections were administered which improved his symptoms only transiently. He was then started on an epinephrine infusion at 0.1 mcg/kg/min and admitted to the intensive care unit (ICU) for delayed and refractory anaphylaxis.

Of note, in follow up review of the patient’s EMR, after discharge, he again underwent inpatient rush immunotherapy in the ICU. It was documented during that time he experienced episodes of urticaria, flushing and hypertension. Mention again was made in notes regarding serum IgE and tryptase levels, but no results were noted in the EMR. He was again successfully transitioned to weekly maintenance immunotherapy until 2017 at which time there was a shortage of hymenoptera immunotherapy, and he was unable to...
Anaphylaxis is highly likely when any one of the following three criteria is fulfilled

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized urticaria, itching or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING:
   A) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   B) Reduced blood pressure or associated symptoms of end organ dysfunction (e.g., hypotonia (collapse), syncope, incontinence) OR

2. Two or more of the following that occur rapidly (minutes to several hours) after exposure to a likely allergen for that patient
   A) Involvement of the skin-mucosal tissue (e.g., generalized urticaria, itch-flush, swollen lips-tongue-uvula)
   B) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   C) Reduced blood pressure or associated symptoms (e.g., hypotonia (collapse), syncope, incontinence)
   D) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting) OR

Reduced blood pressure after exposure (minutes to several hours) to a likely allergen for that patient
   A) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
   B) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that patient’s baseline

Table 1: Clinical Criteria for the Diagnosis of Anaphylaxis [7].

receive treatment. The patient just one week prior to submission of this case report had undergone rush immunotherapy in the ICU, eventually tolerating 240 mcg of mixed vespid venom extract, but in order to do so, required premedication with Prednisone, Famotidine, Cetirizine, Montelukast and Fluticasone. He again had episodes of flushing and hypertension as well as urticaria local to the injection site during that hospitalization.

Discussion

Anaphylaxis was first described by Portier and Richet in 1902, the study for which Richet was awarded the 1913 Nobel Prize in Medicine or Physiology [1]. Anaphylaxis is an acute IgE-mediated reaction which normally involves dermatologic, respiratory, and cardiovascular systems and can progress to a life-threatening condition [2]. The onset of anaphylaxis typically occurs within 30 minutes after exposure to the relevant allergen [3]. The classic and most commonly observed symptoms of anaphylaxis include urticaria, angioedema, hypotension, and respiratory distress [4,5]. Other symptoms may include, but are not limited to, nausea, vomiting, lightheadedness, headache, abdominal cramps, the feeling of impending doom, and loss of consciousness [6]. The diagnosis of anaphylaxis is made based on specific criteria (Table 1) [7]. Current estimates of the prevalence of fatal allergic reactions in the U.S. are 1,500 annually (0.7-2.0% of all cases) [8].

The differential diagnosis of anaphylaxis is broad. Other conditions such as septic shock, asthma, foreign body aspiration, vasovagal reaction, post-prandial syndromes and anxiety can have similar clinical presentations, and need to be differentiated by the clinician [5]. The most common triggers of anaphylaxis are food, insect envenomations and medicatons, with dermatologic and respiratory symptoms being the most common manifestations of the syndrome [7]. With the potential for rapid deterioration, the clinical recognition of anaphylaxis is critical. The detailed pathophysiology of anaphylaxis will not be discussed as it is well described in the literature. In general, anaphylaxis can result from IgE-mediated activation of mast cells and basophils, or from direct activation of mast cells (radiocontrast media reactions) [9]. Mast cell and basophil degranulation results in the release of multiple chemical modulators that are responsible for the symptoms of anaphylaxis [9]. Laboratory tests (most commonly serum histamine and tryptase levels) may assist in the diagnosis of anaphylaxis in cases where certainty of diagnosis is clinically unclear, but there are limitations in their utility. Plasma histamine can be measured, typically rising within 5-10 minutes, and peaking 30-60 minutes after symptom onset. Serum tryptase can also be measured, peaking 60-90 minutes after onset and remaining elevated for up to five hours [5]. The low sensitivity of tryptase levels limits the utility of their use, but may assist in differentiation of anaphylaxis from other hemodynamically unstable conditions [10].

Per the 2011 World Allergy Organization (WAO) position paper, “These tests are not universally available, not performed on an emergency basis, and not specific for anaphylaxis” [7]. Furthermore the WAO position paper states; “(tryptase) levels are often within normal limits in patients with anaphylaxis triggered by food and...
those who are normotenive", and "Normal levels of either trypstatine or histamine do not rule out the clinical diagnosis of anaphylaxis" [7].

The patient in our case presented with symptoms consistent with known previous episodes of anaphylaxis, documented by multiple Allergist-Immunologists that had resulted in his intubation on two separate occasions. It was for this reason that other etiologies for his symptoms seemed unlikely and were not pursued clinically. He had also had episodes of hypertension documented on two occasions during reported anaphylactic reactions. Although hypotension is a criterion used in the diagnosis of anaphylaxis, anaphylaxis with hypertension has been reported in the literature, and is postulated to be due to the release of catecholamines, and endothelin-1 among other vasoactive substances [11].

The standard treatment of anaphylaxis involves discontinuing exposure to the potential allergen, basic life support procedures (airway, breathing, and circulation), and most importantly the early administration of epinephrine [2]. Early intervention should always be considered and a definitive airway should be established if there is any concern for airway edema. H1 and H2 histamine receptor antagonists, corticosteroids, are also mainstays of therapy [2]. Of note, anaphylaxis may be refractory to standard therapy in patients receiving beta blocker therapy [12].

Acute anaphylaxis is a potentially life threatening condition which requires immediate recognition and treatment by emergency providers. Biphasic anaphylaxis was first reported in 1984 by Popa and Lerner 6, and is defined as a recurrence of anaphylactic symptoms after an initial remission has occurred [13]. Recurrent reactions are more likely if symptoms developed at least 30 minutes after exposure to the stimulus, or if the culprit agent had been ingested [6]. An estimated 1–23% of anaphylactic reactions are biphasic, and recurrent symptoms have been reported up to 72 hours (typically 9 to 10 hours) after apparent resolution of the initial phase [6]. While patients may initially respond to standard treatment, a biphasic reaction may occur in a matter of hours to days, and the second phase reaction is commonly refractory to standard therapy. Delayed administration of epinephrine may be associated with the occurrence of biphasic anaphylaxis [14].

Cases of delayed anaphylaxis are well described in the literature. One reported case occurred 13 hours after provocation testing, with recurrence of symptoms 3 hours following treatment with epinephrine and corticosteroids [3]. Delayed anaphylaxis to red meat was first described in 2009 when anaphylaxis developed 3-6 hours after ingestion [15]. There is a documented case of an otherwise healthy patient who developed anaphylaxis 12 days following a hymenoptera sting [16]. Subcutaneous allergen immunotherapy is commonly used in the treatment of allergic rhinitis, asthma, and hymenoptera hypersensitivity [17]. The incidence of late onset (> 30 minutes) and severe systemic reactions were found to be 14% and less than 1% respectively. Reisman reported six patients who developed late onset reactions following venom extract immunotherapy and intradermal venom skin testing. The onset of symptoms was reported to be between 4-12 hours following therapy/testing, and persisted between 48-72 hours [4].

While anaphylaxis usually occurs within 30 minutes of allergen exposure, some reactions develop hours or even days later. Late onset reactions have been associated with foods, envenomations, and pharmacotherapeutic agents. Our case began 7 days following the second administration of 0.1 mcg mixed venom extract, with complete resolution of symptoms after standard therapy, but with relapse 2 days later. The recurrent symptoms were refractory to standard epinephrine dosing, and required an epinephrine infusion. From our review this is the only reported case of delayed and biphasic anaphylaxis associated with immunotherapy and refractory to standard treatment.

Conflicts of Interest
No conflicts to declare.

References


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