Idiopathic Anaphylaxis: A Diagnosis of Exclusion

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Abstract
We report the case of a 67-year-old female with hypertension and rheumatoid arthritis who had 5 unprovoked episodes of anaphylaxis in an 18-month period of time. We review idiopathic anaphylaxis, including its definition, diagnostic work-up, and differential diagnosis.

Keywords
idiopathic anaphylaxis, case report, diagnosis of exclusion, anaphylaxis

Anaphylaxis is a severe allergic reaction that can present with involvement of the gastrointestinal (GI), cardiovascular, dermatological, and/or respiratory systems. It typically occurs after exposure to an allergen though in rare cases it can happen without any trigger; this is known as idiopathic anaphylaxis (IA). IA is a diagnosis of exclusion made after a comprehensive clinical evaluation is performed and potential allergens are excluded. We report a case of multiple anaphylactic events with no identifiable trigger and negative work-up suspicious for IA.

The patient was a 67-year-old female with hypertension and rheumatoid arthritis who presented for evaluation of recurrent episodes of anaphylaxis. She experienced 5 episodes within an 18-month span. Her initial event occurred the morning after eating a chicken salad from a restaurant. She awoke with generalized pruritus, urticaria, oral swelling, and an isolated episode of nonbloody diarrhea. She was seen at an immediate care clinic and managed with oral corticosteroids and diphenhydramine. This episode escalated rapidly over a period of several minutes and resolved completely within 4 h. Her next episode occurred 10 to 15 m after she ate a vanilla-flavored wafer for breakfast and started to experience pruritus of her hands and feet, swelling of her lips and tongue, and acute onset of a single episode of nonbloody diarrhea. She was seen at an immediate care clinic and managed with oral corticosteroids and diphenhydramine. This episode escalated rapidly over a 5-min time period. She did not experience any flushing with this event. There was no visible rash. She was treated in an emergency department (ED) with intravenous solumedrol and intravenous fluids and diphenhydramine. This episode escalated over a period of several minutes and resolved completely within 4 h. Her next episode occurred 10 to 15 m after she ate a vanilla-flavored wafer for breakfast and started to experience pruritus of her hands and feet, swelling of her lips and tongue, and acute onset of a single episode of nonbloody diarrhea. The symptoms developed over a 5-min time period. She did not experience any flushing with this event. There was no visible rash. She was treated in an emergency department (ED) with intravenous solumedrol and intravenous fluids and diphenhydramine, with a resolution of symptoms within 4 h. The patient had an additional episode 1 month later while she was walking outside. She had sudden onset of lip and tongue swelling, generalized pruritus, and an isolated episode of nonbloody diarrhea that improved with diphenhydramine and rest. Again, there was no visible rash. She returned to baseline within 2 h of symptom onset. She had a similar event while working at a sewing machine in her basement when she suddenly developed swelling of the lips and tongue, generalized pruritus, and nonbloody diarrhea. She managed this herself with diphenhydramine and prednisone at home. Her most recent event occurred 2 months prior to her initial presentation. She was a passenger in her husband’s car when symptoms suddenly occurred. Although this event began with swelling of the lips and tongue and generalized pruritus, she also developed chest tightness and shortness of breath. She was not eating or drinking any substances. She also recalls that the car windows were closed. She was not sick or taking any new medications. Symptoms were not alleviated with 50 mg diphenhydramine, and she was taken to a nearby urgent care center. She was found to be hypotensive to 82/49. She was transferred by Emergency Medical Services to the ED and was treated with intramuscular (IM) epinephrine and supplemental oxygen en route. A review of the ED records indicates that her presenting blood pressure at the ED was 112/57. Due to persistent wheezing and lip and tongue swelling, she was administered a second dose of IM epinephrine and a bolus of intravenous fluids and subsequently treated with antihistamines and steroids. She did not have a rash. She returned to baseline within 4 h.

On our initial evaluation, we obtained a detailed history and performed a thorough physical exam which was
unremarkable. The patient denies any previous history of asthma, rhinitis symptoms, atopic dermatitis, food allergy, or urticaria. Additionally, she denies any allergies to stinging insects or medications. The patient’s home medications included omeprazole 20 mg daily, aspirin 81 mg daily, amlo-dipine 5 mg daily, atorvastatin 20 mg daily, metoprolol succinate 50 mg daily, nabumetone 750 mg daily, and a daily probiotic. She has been on these medications without any dose changes for several years and has remained on each of these over the ensuing 14 months of follow-up care in our clinic without any additional anaphylactic events. Percutaneous testing for environmental allergies was positive to cat dander and negative to tree pollens, grass pollens, weed pollens, ragweed pollens, molds, dust mites, dogs, cockroaches, and mice. The patient has not been around cats for several years, but previously experienced pruritic and watery eyes with cat exposure. Serum testing for environmental allergies corroborated the percutaneous testing by showing sensitization to cats and none of the other allergens tested. Serologic testing for galactose-α-1,3-galactose (alpha-gal) was also negative. Additionally, no hidden agents or cofactors including exercise, alcohol, latex, nonsteroidal antiinflammatory drugs (NSAIDs), or spices were identified in the episodes.

Anaphylaxis varies in duration and severity. Symptoms are usually rapid in onset and in severe cases may be life-threatening. Patients can present with a combination of symptoms that may involve the skin, respiratory, GI, and cardiovascular systems. When investigating an anaphylactic event, it is important to obtain an extensive history of each episode. Work-up should include details leading up to the event such as ingestion of any foods or drugs, activities prior to and during the episode, and history of exposure to stinging insects. Excluding other possible diagnoses such as mastocytosis is important as well. If no precipitating factor can be identified, IA becomes the diagnosis of exclusion.

IA can be categorized into either frequent or infrequent based on the number of episodes per year. Frequent IA involves 6 or more episodes per year or 2 episodes in the last 2 months. IA can be further categorized into generalized or angioedema-predominant, depending on the nature of the symptoms. Additionally, when episodes of IA are difficult to control without prednisone, it is further classified as corticosteroid-dependent IA.

The pathogenesis of IA remains unclear, though several theories have been proposed. One theory is that patients with IA have an increased number of mast cells, but studies have only found a modest to no increase at all in the number of mast cells in affected patients. Another theory that has been explored is increased lymphocyte activation in IA patients. In 1 study, Grammer et al used flow cytometry to evaluate the immunological differences between IA patients during acute episodes versus those in remission and healthy controls. It was noted that IA patients in an acute event had statistically significant increases in T-cell activation markers when compared to those in remission and controls. Additionally, B-cell activation markers were elevated in both groups of IA patients. Other theories include the potential effects of estrogen or progesterone on basophil activation, as IA is noted to have a higher incidence in women. A study performed by the US National Institutes of Health involving 8 symptomatic women and 10 control subjects showed no difference in basophil activation in response to progesterone or estrogen. Despite the multitude of proposed theories, the pathogenesis of IA remains elusive.

IA is a steroid-responsive disease that clinically presents no differently than other forms of anaphylaxis. In acute attacks, treatment consists of epinephrine, antihistamines, and corticosteroids if indicated. Long-term treatments are considered based on the frequency and the severity of episodes. Corticosteroids and antihistamines are used in patients with frequent or severe episodes though long-term adverse effects of steroids may limit therapy. Additionally, there are isolated case reports documenting success with therapies such as omalizumab and ketotifen.

In our patient’s case, she experienced 5 anaphylactic episodes where no foods, medications, hidden allergens, or cofactors (including exercise, alcohol, latex, NSAIDs, spices, or mammalian meats) triggering the events could be identified. As such, the working diagnosis was thought to be IA, which was further categorized as generalized and infrequent. The patient was prescribed an emergency kit that included autoinjectable epinephrine, prednisone, and cetirizine to always carry on her person. Dust mite anaphylaxis was considered, but since the patient is not allergic to dust mites, this possibility was ruled out. Additionally, although clinical suspicion for hereditary or acquired angioedema was extremely low, since many of the episodes involved lip and tongue swelling, labs obtained as part of our additional work-up included quantitative Cl esterase, Cl esterase function, C4 complement level, and C1q; all of which were found to be normal. A baseline tryptase level was also obtained at the time of initial consultation (when the patient was well) and was noted to be within normal limits at 5.3 μg/L (reference range <11). Due to this finding, no further testing for mast cell disease including additional blood tests or bone marrow biopsy was pursued. Additional tryptase levels have not been obtained, since the patient has not had any additional events. Given her history of rheumatoid arthritis, we considered evaluating markers of B-cell activation, including B cell activating factor (BAFF), but these studies have not been performed to date. The patient has been followed closely for the past 14 months and has not had any recurrence of episodes.

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Statement of Informed Consent
There are no human subjects in this article and informed consent is not applicable.

Trial Registration
Not applicable, because this article does not contain any clinical trials.

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