

Two contrasting cases of anaphylaxis seen simultaneously

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INTRODUCTION

Anaphylaxis is a disease in which the expertise of an allergist is required to determine the cause and guide in the management of either allergen-induced anaphylaxis, exercise-induced anaphylaxis, or idiopathic anaphylaxis.

We present two cases of anaphylaxis seen simultaneously in our allergy and immunology service. The marked difference in the nature of these cases illustrates the diagnostic ability required to differentiate the problems.

CASE ONE

Chief complaint

Acute onset urticaria, throat swelling, and lightheadedness.

History of present illness

The patient is a 39-year-old white male from Dallas with a past medical history of urticaria and angioedema secondary to injection with a local anesthetic in 1984. Since that time he has experienced similar symptoms as well as lightheadedness averaging once per month, for which he would take 50 mg of diphenhydramine and proceed to the emergency department for observa-

tion. In 1989, he was begun on terfenadine 60 mg twice daily regularly at an outside institution whereupon symptoms were reduced to about two episodes per year. There was no temporal relation to foods, drugs, physical causes, or insect stings, and a diagnosis of idiopathic urticaria/angioedema was made.

The patient had no other significant past medical history and took no medications other than terfenadine. He subsequently moved to Chicago and began to develop his typical symptoms of angioedema, urticaria, and lightheadedness on average 2 times per month after he had run out of his medication. He developed worsening urticaria and throat angioedema over a 4-month period, prior to our initial evaluation.

The patient presented to our allergy division in July 1997 with these complaints. A diagnosis of idiopathic anaphylaxis-generalized-frequent (IA-G-F) was made, and the patient was begun on prednisone 60 mg daily, albuterol 2 mg 3 times per day, hydroxyzine 25 mg nightly, and cetirizine 10 mg each morning. He was given an Epipen® for emergency use and sent home with a prednisone tapering schedule. The patient had no symptoms on this regimen and after 2 weeks his prednisone was reduced to 60 mg every other day, with further 5 mg reductions in prednisone to occur weekly. On August 24, 1997 he experienced a severe anaphylactic reaction while walking to work. He developed whole body erythema, urticaria, throat swelling, and lightheadedness while on

45 mg of prednisone on alternate days. He administered his Epipen and also took an extra 40 mg of prednisone and 25 mg of hydroxyzine. The patient was taken via taxi to our emergency department where he was found to be unconscious, in the rear of the taxi, with a blood pressure of 70/40, pulse rate 118, respirations of 32. The physical exam was significant for uvular enlargement, tachycardia without murmur, and generalized urticaria. The patient had no wheezing, stridor, or vomiting. Resuscitative measures were instituted with a rapid infusion of intravenous saline, 0.3 mg of 1:1000 subcutaneous epinephrine, 50 mg of IV diphenhydramine, and 125 mg of IV methylprednisolone. The patient quickly responded to this protocol and was observed in the emergency department for several hours. Laboratory studies, including complete blood count, electrolytes, urinalysis, and cardiac enzymes were normal. An electrocardiogram revealed sinus tachycardia. The patient refused overnight admission to the hospital and was sent home on prednisone 60 mg daily and his previous regimen.

Following this episode, he was begun on ketotifen, a mast cell stabilizer not available in the United States, 2 mg 3 times daily and a slow prednisone taper was begun. The patient continued to have several small urticarial outbreaks for which he is instructed to take an extra 25 to 50 mg of hydroxyzine, but has had no other life-threatening reactions over a 3-month period. His current therapy includes ketotifen 2 mg 3 times daily, hy-

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droxizine 25 mg nightly, albuterol 2 mg 3 times daily, ceterizine 10 mg daily, and prednisone 35 mg every other day.

CASE TWO

Chief complaint

Whole body "swelling."

History of present illness

A 25-year-old obese white female, with a past medical history of non-insulin-dependent diabetes mellitus and polycystic ovarian disease was referred to our service for evaluation of presumed idiopathic anaphylaxis (IA).

The patient, accompanied by her mother, reported a 2-year history of persistent "whole body swelling" with "daily" transient fluctuations. This pattern was preceded by 6 months of the transient swellings alone, without the persistent symptoms. These symptoms have had no relation to foods, medicines, activity, or time of day. The patient also noted difficult breathing which she described as an inability to inhale deeply throughout each day. She also complained of periodic episodes of diarrhea, but did not experience nausea, vomiting, or abdominal pain. She had never had urticaria, wheezing, or throat tightness. She also had a history of four spontaneous abortions, each at less than 16 weeks gestation, as well as a 3-year history of amenorrhea. The patient had experienced gradual weight gain over the past 5 years, and at the time of her visit weighed over 300 pounds.

Although the patient sought opinions from over 15 different physicians over a 2-year period, including internists, allergists, and endocrinologists, no definitive diagnosis had been reached. She had been evaluated on four separate occasions in various emergency departments for dyspnea, but never admitted.

The patient was a high school graduate, living with her mother and brother, and was a 2 pack per day cigarette smoker. Of note, her brother had similar complaints of swelling which the family believed was directly related to their father's exposure to

"Agent Orange" during the Vietnam War. This reported exposure occurred years prior to the birth of either the patient or her brother.

Upon our evaluation, the patient's medications were as follows: prednisone 100 mg daily, hydroxyzine 50 mg 3 times daily, albuterol 2 mg 3 times daily, and twice daily self-administration of 0.3 mL of 1:1000 epinephrine via an EpiPen for the 2 weeks prior to our consultation with the patient. Other medications included troglitazone daily, ranitidine 150 mg nightly, and furosemide in varying dosages.

Physical exam revealed a morbidly obese, cushingoid-appearing female in no distress. The remaining physical exam was unremarkable, with the exception of 2+ pitting lower extremity edema. Laboratory evaluations, including electrolyte panel, complete blood count, and C3 and C4 levels were normal. Emergency department records, and photographs taken during "attacks" were requested prior to our initial consultation, but the patient forgot to bring them to the appointment. These as yet have not been forwarded to our service, although a period of several months has elapsed. During the initial consultation, the diagnosis of undifferentiated somatoform idiopathic anaphylaxis (US-IA) was made and the patient was told to taper off prednisone and to discontinue using her EpiPen. It was advised that she seek psychiatric counseling. Both the patient and her mother became angered by this suggestion and disagreed with this advice. They subsequently left unsatisfied and have not returned for followup.

QUESTIONS

1. What are the definitions of IA and US-IA?
2. Do either of these cases fit the criteria of IA or US-IA?
3. How does one differentiate between the two diagnoses?
4. What is the appropriate management of each case?

Table 1. Differential Diagnosis of Idiopathic Anaphylaxis for Ambulatory Patients*

- I. Known causes of immediate generalized reactions.
 - A. IgE mediated
 1. Foods
 2. Medications
 - a. Penicillins
 - b. Cephalosporins
 3. Food Supplements
 - a. Psyllium
 - b. Bee pollen
 - B. Exercise induced anaphylaxis
 - C. Food plus exercise induced anaphylaxis
 - D. Medication induced reactions
 1. Aspirin
 2. Nonsteroidal antiinflammatory drugs
 3. Angiotensin-converting enzyme inhibitors
 4. Opiates
 - E. Radiographic contrast media reactions
- II. Hereditary Angioedema
 - A. Classical form
 1. Absent C1 inhibitor
 2. Dysfunctional C1 inhibitor
 - B. Acquired form
 1. B cell lymphoproliferative disorder
 2. Autoantibodies to C1 inhibitor
- III. Systemic Mastocytosis
- IV. Asthma masquerading as anaphylaxis
- V. Munchausen's stridor
- VI. Munchausen's anaphylaxis
- VII. Undifferentiated Somatoform idiopathic anaphylaxis
- VIII. Miscellaneous Diagnoses
 - A. Panic Attacks
 - B. Globus Hystericus
 - C. Histamine-rich food induced flushing
 - D. Carcinoid syndrome
 - E. Pheochromocytoma

* This list is not all inclusive.

Adapted from Patterson R, Idiopathic Anaphylaxis. Rhode Island. Oceanside publications, Inc. 1997:8.

DISCUSSION

Idiopathic anaphylaxis is a diagnosis of exclusion. Idiopathic anaphylaxis was first described in the late 1970s when several patients with anaphylactoid reactions of unknown cause were evaluated.¹ Since that time multiple cases have been reported.²⁻⁶ Idiopathic anaphylaxis is defined as an immediate, life-threatening event with no external allergen triggering the onset via

an IgE antibody-mediated reaction.⁷ Other diagnoses in the differential must be excluded on the basis of history and physical (Table 1). The syndrome consists of urticaria or angioedema with at least one of the following symptoms: hypotension, syncope, bronchospasm, or gastrointestinal complaints of pain and acute diarrhea. The angioedema may involve the upper airway so that pharyngeal or uvular edema may occur, resulting in dysphagia, dysphonia, and vocal cord edema. Undifferentiated somatoform idiopathic anaphylaxis is the term applied when patients who have no organic disease describe symptoms consistent with IA, and have a diagnosis of somatoform disorder using the criteria according to the DSM-IV. The diagnostic criteria for undifferentiated somatoform disorder is one or more physical complaints that persist for 6 months or longer. The symptoms cannot be explained by any known general medical condition or by any direct effect of a substance. The symptoms must also cause clinically significant distress or impairment in social, occupational, or other areas of functioning and not be explained by another mental disorder. The diagnosis has been increasingly recognized as more IA cases have been diagnosed.^{8,9} The classification of IA/US-IA is shown in Table 2.

In case 1, the patient experienced symptoms consistent with IA, with predominant lightheadedness, pruritus, urticaria, and throat angioedema. Furthermore, this episode necessitated emergent intervention, requiring full resuscitative measures. Of note, objective physical evidence was obtained in the emergency department. This included documentation of severe hypotension, urticaria, tachycardia, and tachypnea. From this evidence, along with a lack of any other obvious cause, a diagnosis of IA was made.

The second case describes a patient whose symptoms are typical of US-IA. Clues to the nonorganic nature of the disease begin with a thorough history. Undifferentiated somatoform idiopathic anaphylaxis patients often describe vague, fleeting, or nonspecific

symptoms, such as our patients “swellings,” and subjective breathing difficulties. These symptoms are often not apparent even to close family members. Documentation from emergency department visits is not produced when requested or is without firm objective findings. More important, US-IA patients typically fail to improve with a diagnostic-therapeutic regimen of prednisone, hydroxyzine, and albuterol. Idiopathic anaphylaxis is prednisone responsive^{7,10} with very few patients requiring more than 60 mg of prednisone every other day to control symptoms.^{5,11} Once true IA has been diagnosed, a protocol of therapy should be instituted, beginning with prednisone, hydroxyzine, and albuterol. This protocol has been well established.⁷ Idiopathic anaphylaxis is typically controlled with 1 to 4 weeks of daily prednisone. Control is then generally maintained with alternate day prednisone, and tapered by 10-mg weekly increments. Idiopathic anaphylaxis becomes corticosteroid-dependent IA (CSD-IA) when lowering the dose of prednisone results in recurrent IA at a threshold dose. This dose varies

with different patients. In these cases, ketotifen has been shown to be effective in lowering the threshold dose, and in some cases, eliminating the need for prednisone.¹¹⁻¹² Patients whose status is unclear, or for whom no documentation exists should be treated as IA until US-IA is apparent. If no response is seen, the diagnosis must be questioned and alternative diagnoses should be sought.

Although the differentiation between IA and US-IA appears straightforward, often the distinction can be quite difficult. In two series of cases,^{8,9} the following characteristics have been observed in regard to US-IA: (1) the referring physician generally does not recognize the nonorganic nature of the problem; (2) medical costs resulting from hospitalizations, emergency department visits and laboratory tests are high; and (3) unnecessary treatment with corticosteroids may occur. It is of utmost importance to taper US-IA patients off corticosteroids, as well as other medications that may have harmful side effects without benefit. Also, reassurance regarding the absence of risk of fatality, and referral for psychi-

Table 2. Classification of Idiopathic Anaphylaxis

Disease	Symptoms
IA-G-F	Urticaria or angioedema with bronchospasm, hypotension, syncope, or gastrointestinal symptoms with or without airway compromise with frequent episodes (≥6 episodes per year).
IA-A-I	Urticaria or angioedema with upper airway compromise, such as laryngeal edema, or massive tongue edema without other systemic manifestations with infrequent episodes (<6 episodes per year).
IA-A-F	Urticaria or angioedema with upper airway compromise such as laryngeal edema, severe pharyngeal edema, or massive tongue edema without other systemic manifestations with frequent episodes (≥6 episodes per year).
IA-Q	This diagnosis is applied for a patient whose history of episodes of IA are inconsistent with IA-G or IA-A; diagnosis is questionable until further documentation can be achieved.
IA-V	This diagnosis is applied for a patient whose history and physical findings do not completely fit IA-G or IA-A and may later be changed to IA-G, IA-A, or IA-Q.
US-IA	This diagnosis is applied for a patient whose history mimics IA but lacks correlating objective physical findings, shows no response to the therapeutic regimen for IA, and meets the DSM-IV criteria for undifferentiated somatoform disorders.

Reprinted with permission, Choy AC, Patterson R, Patterson DR, et al. Undifferentiated somatoform idiopathic anaphylaxis: nonorganic symptoms mimicking idiopathic anaphylaxis. *J Allergy Clin Immunol* 1995;96:894.

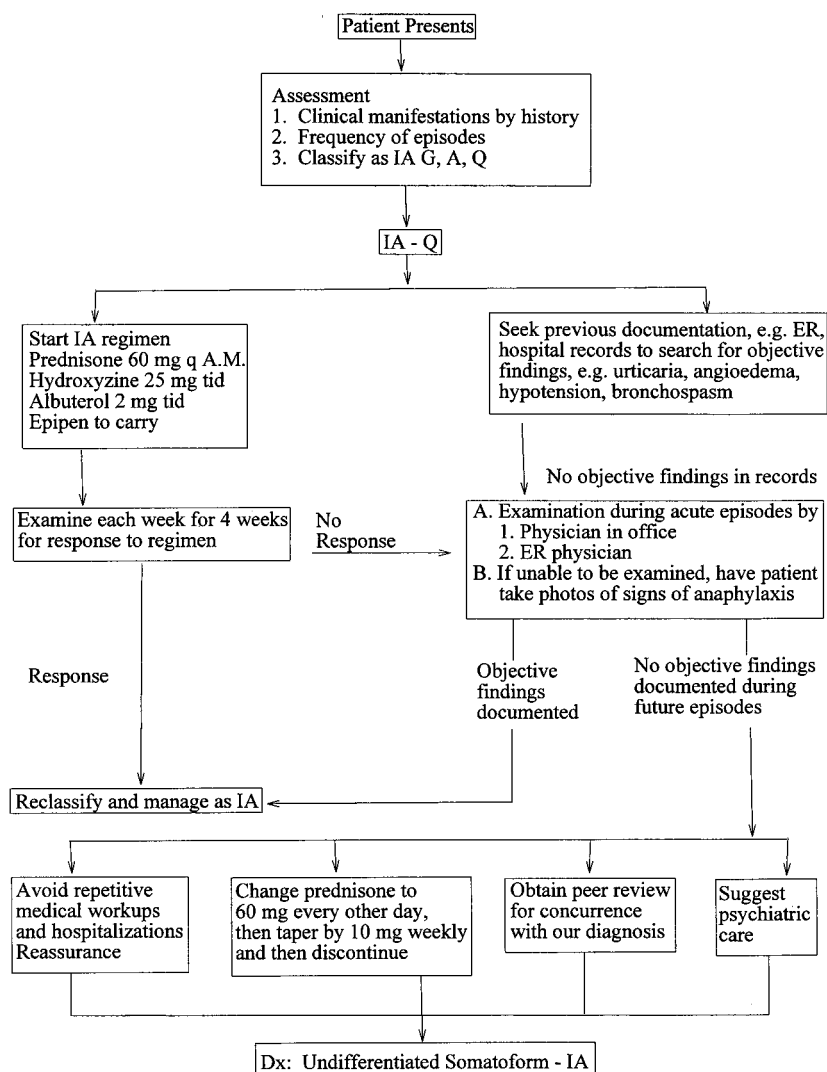


Figure 1. Two contrasting cases of anaphylaxis seen simultaneously.

atric evaluation are necessary for the proper treatment of this disorder (Fig 1). Unfortunately, as was the case with our US-IA patient, the suggestion that their disease is nonorganic and that psychiatric consultation is needed, is often met with hostility, anger, and disbelief. This is also seen among family members and at times by referring physicians.

Idiopathic anaphylaxis is a disease that if not properly diagnosed and treated is potentially fatal. Undifferentiated somatoform idiopathic anaphylaxis is a disorder that mimics IA without having any true life-threatening

symptoms. For the proper treatment of both these diseases it is necessary that physicians have an understanding of the natural course and response to therapy of each of these disorders. In this way, significant morbidity, mortality, and expense can be avoided.

REFERENCES

1. Bacal E, Patterson R, Zeiss CR. Evaluation of severe (anaphylactic) reactions. *Clin Allergy* 1978;8:295-299.
2. Boxer M, Greenberger PA, Patterson R. Clinical summary and course of idiopathic anaphylaxis in 73 patients. *Arch Intern Med* 1987;147:269-272.

3. Wiggins CA, Dykewicz MS, Patterson R. Idiopathic anaphylaxis: classification, evaluation, and treatment of 123 patients. *J Allergy Clin Immunol* 1988; 82:849-855.
4. Wong S, Dykewicz MS, Patterson R. Idiopathic anaphylaxis. A clinical summary of 175 patients. *Arch Intern Med* 1990;150:1323-1328.
5. Orfan NA, Stoloff RS, Harris KE, Patterson R. Idiopathic anaphylaxis: total experience with 225 patients. *Allergy Proc* 1992;13:35-43.
6. Ditto AM, Harris KE, Krasnick J, et al. Idiopathic anaphylaxis: a series of 335 cases. *Ann Allergy Asthma Immunol* 1996;77:285-291.
7. Patterson R, Harris KE. Idiopathic anaphylaxis. In: Patterson R, Grammer LC, Greenberger PA, 5th eds. *Allergic diseases: diagnosis and management*. Philadelphia: Lippincott-Raven, 1997: 459-465.
8. Patterson R, Greenberger PA, Orfan NA, Stoloff R. Idiopathic anaphylaxis: diagnostic variants and the problem of nonorganic diseases. *Allergy Proc* 1992;13:133-137.
9. Choy AC, Patterson R, Patterson DR, et al. Undifferentiated somatoform idiopathic anaphylaxis: Nonorganic symptoms mimicking idiopathic anaphylaxis. *J Allergy Clin Immunol* 1995;96:893-900.
10. Ditto AM, Grammer LC, Kern RC. The use of laryngoscopy with provocative challenge to distinguish life threatening laryngeal edema from non-organic disease: a case report. *Ann Allergy* 1995;75:25-28.
11. Wong S, Patterson R, Harris KE, Dykewicz MS. Efficacy of ketotifen in corticosteroid-dependent idiopathic anaphylaxis. *Ann Allergy* 1991;67: 359-364.
12. Patterson R, Fitzsimons EJ, Choy AC, Harris KE. Malignant and corticosteroid dependent idiopathic anaphylaxis: successful responses to ketotifen. *Ann Allergy Asthma Immunol* 1997;79: 138-144.

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