

Recurrent Anaphylactic Reactions: An Uncommon Debut of Lymphocytic Hypophysitis

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Established Facts

- Lymphocytic hypophysitis is a rare chronic autoimmune disease, in which the adenopituitary impairment typically affects corticotropic function. Consequently, subnormal cortisol production during acute severe disease may result in adrenal crisis (so-called functional or relative adrenal insufficiency).

Novel Insights

- A clinical picture of recurrent anaphylactic reactions, the result of complicated secondary adrenal crises following asthma attacks, was a manifestation of lymphocytic hypophysitis.
- This unusual case report stresses the importance of a comprehensive differential diagnosis of anaphylaxis, and the need to perform an extensive and thorough diagnostic workup in uncommon cases, especially when the causative agents are unknown.

Key Words

Adrenal crisis · Anaphylaxis · Chronic urticaria ·
Lymphocytic hypophysitis

Abstract

We report on a 24-year-old male, with exercise-induced asthma and intermittent abdominal pain since puberty, who suffered from recurrent anaphylactic reactions. He also complained of occasional headaches. After extensive studies he

was eventually diagnosed with idiopathic anaphylaxis, once the following diagnoses had been excluded: allergic origin [foods (including ω 5-gliadin), latex and drugs], hydatidosis, carcinoid syndrome, systemic mastocytosis, autonomic epilepsy, hereditary angioedema, pheocromocytoma, Meckel diverticle, medullar thyroid carcinoma, leukemia, hyper-IgE and hypereosinophilic syndromes. Given the frequency and severity of the attacks, we started off-label treatment with omalizumab, initially well tolerated. Some days after the second dose the patient started to develop recurrent urticaria.

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Because of these new symptoms, blood work was repeated, and elevated TSH, decreased T4, positive antithyroid antibodies and decreased cortisol levels with normal ACTH were found. The antiadrenal autoantibodies were negative. The MRI showed a slight thickening of the infundibulum, without pituitary adenoma. Suspecting an autoimmune hypophysitis, we looked for antipituitary antibodies; the result was positive. A clinical picture of recurrent anaphylactic reactions, the result of complicated adrenal crises in an asthmatic patient, was a manifestation of lymphocytic hypophysitis, a rare chronic inflammatory disease of autoimmune etiology. One year after replacement therapy had been started, the patient remained asymptomatic.

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Introduction

Lymphocytic hypophysitis (LyHy) is a rare chronic inflammatory disease of autoimmune etiology, with an incidence of 1/9,000,000/year [1]. The adenopituitary impairment typically affects corticotropic (ACTH) function, unlike the pituitary adenoma, in which the somatotrophic and gonadotrophic functions are usually the first to be impaired. The diagnosis is based on different patterns of endocrinological dysfunctions (dependent on anterior pituitary or infundibulum involvement), typical findings on MRI (such as thickening of the infundibulum) and the presence of immunological markers (positive antipituitary antibodies) [2].

Case Report

We report on a 24-year-old male, with a personal history of exercise-induced asthma, moderate persistent asthma with sensitization to grass pollen and *Alternaria alternata* and intermittent abdominal pain since puberty. He was referred to our Allergy Department in 2006 for recurrent episodes consisting of intense oppressive chest pain, dyspnea and wheezing, followed shortly by periumbilical pain, diarrhea, malaise and hypotension. On some occasions he also experienced dizziness, confusion and, once, even loss of consciousness. In the emergency room, his symptoms responded to repeated doses of corticosteroids and intravenous fluids in under 2 h, with complete cessation of the abdominal pain within 2–3 days. The episodes had occurred at night, every 3–4 months, within the last 3 years before consulting, usually associated with emotional stress or physical exercise (twice while dancing). He also complained of occasional headaches.

After extensive studies (blood and urine analyses, PET-CT, pan-endoscopy), he was eventually diagnosed with idiopathic anaphylactic/anaphylactoid episodes, once the following diagnoses had been excluded: allergic origin [foods (including ω5-glia-

Table 1. Dynamics of the hormonal and autoimmune profiles

	Initial study ^a	Study of the chronic urticaria ^b	Normal values
C4, mg/dl	11.6 ^c	12.6 ^c	14.00–60.00
TSH, μIU/ml	2.72	10.15 ^c	0.27–4.20
T4, ng/dl	1.40	1.10	0.93–1.70
ACTH, pg/ml	29	11	5.0–77.0
Cortisol, μg/dl	9.6	2.3 ^c	5.0–25.0
Antithyroid autoantibodies, IU/ml			
Antiperoxidase	20.75	90.26 ^c	0.00–34.0
Antithyroid globulin	59.8	863 ^c	0.0–115.0
Adrenal autoantibodies	NP	negative	negative
Antihypophysitis autoantibodies	NP	positive ^c	negative
		1:10 IFI	

^a Study of the recurrent anaphylactic episodes, when the patient was referred to our department in 2006.

^b Study after 2 months of daily hives in 2009.

^c Abnormal levels.

ACTH = Adenocorticotrophic hormone; IFI = indirect immunofluorescence; NP = not performed; T4 = free thyroxine; TSH = thyroid-stimulating hormone.

din), latex, drugs], hydatidosis, carcinoid syndrome, systemic mastocytosis, autonomic epilepsy, vocal cord dysfunction, hereditary angioedema, pheochromocytoma, Meckel diverticle, medullary thyroid carcinoma, leukemia, hyper-IgE, hypereosinophilic and capillary leak syndromes. The thyroid and corticoadrenal functions were found to be normal. The only abnormality was a hypocomplementemia (C4: 11.6 mg/dl, normal range 14–60 mg/dl). The endocrinological and autoimmune profiles at this point are summarized in table 1 (in the column ‘Initial study’). The continuous therapy with inhaled corticosteroids and long-acting beta-agonists, antihistamines and short cycles of oral steroids only slightly decreased the severity of the attacks. Thus, in December 2008, we decided to start off-label treatment with omalizumab [3], 150 mg/month (the patient’s body weight was 65 kg, total serum IgE 98 kU/l), after obtaining written informed consent from the patient and Spanish Health Authorities approval.

The treatment was initially well tolerated, but some days after the second dose the patient started to develop daily urticarial rashes that disappeared after treatment with antihistamines. Two more doses of omalizumab were administered, and the patient experienced no more anaphylactic events, but kept complaining of moderate pruritus. Because of these new symptoms, blood work was repeated and elevated TSH, decreased T4, positive antithyroid antibodies and the persistence of diminished C4 levels were found. The patient was referred to the Endocrinology Department, where cortisol levels were found to be decreased, with inferior-borderline normal ACTH (table 1, column ‘Study of the chronic urticaria’). The antiadrenal autoantibodies were negative. The MRI showed a slight thickening of the infundibulum, with no finding of pituitary adenoma (fig. 1). Suspecting an autoim-



Fig. 1. The MRI showed an intact sellar floor with stalk thickening (see arrow).

mune hypophysitis, we looked for antipituitary antibodies; the result was positive, which confirmed the diagnosis. The replacement treatment with hydrocortisone (20 mg/12 h) and levothyroxine (75 mg/day) was initiated, and the omalizumab treatment was stopped. After periodic attempts to withdraw the antihistamines, followed by relapse of the urticaria, the cutaneous manifestations eventually disappeared 4 months after the replacement treatment had been started. One year later in the follow-up visit, the patient had not experienced any more anaphylactoid reactions, abdominal pain or headaches. He referred 3–4 episodes of urticaria that were controlled with hydroxyzine.

Discussion

The patient who was the subject of our report presented with repeated anaphylactoid reactions, apparently idiopathic, that responded well to steroids and then to omalizumab. During this period, a subclinical autoimmune hypothyroidism and a secondary adrenal insufficiency were diagnosed. Although there is no pathognomonic feature of LyHy, the simultaneous presence in this patient of corticotrophic impairment, normal MRI and positive antipituitary antibodies is highly suggestive of this disorder, and, more precisely, of lymphocytic adenohypophysitis, a subtype that is associated with headaches

in 53% of cases [2] – as in our patient. A posteriori, the decrease of complement levels, suggesting an autoimmune pathology, and the recurrent abdominal pains he had presented since the beginning, can be interpreted as the insidious debut of LyHy, despite initially maintaining normal cortisol levels on baseline conditions.

Stress or acute illness, such as exercise-induced asthma, may unmask partial ACTH deficiency, resulting in acute clinically significant hypocortisolism (abdominal pain, diarrhea, hypotension and vascular collapse) reflecting the reduction of the ACTH reserve. Subnormal cortisol production during acute severe disease is called functional or relative adrenal insufficiency [4]: an increase in cortisol level does occur, but this is insufficient to control the inflammatory reaction and to maintain the blood pressure. The anaphylactoid reactions experienced by this patient may be interpreted as adrenal crises following asthma attacks, especially if we consider the positive response to intravenous steroids and fluids [4].

An association with other autoimmune diseases in 30% of patients, usually a thyroiditis [5], also pointed towards LyHy. In this particular case, the chronic urticaria accompanying the autoimmune thyroiditis [6] triggered the investigations that led to the final diagnosis. As omalizumab was no longer indicated, it was rapidly discontinued, so the 2 doses received after the onset of urticaria were not sufficient to control it [7].

However, the histological confirmation of LyHy is obtained only when surgery is indicated (chiasm compression that does not respond to medical treatment [2]). The pathological findings are characterized by lymphocytic infiltration of the pituitary, but eosinophils are also found in 12% of biopsies [2].

On the other hand, the self-antigens involved in the pathogenesis remain unknown. They might react to IgE antibodies, as has been described with other self-antigens in several autoimmune diseases [8], thus explaining the improvement of symptoms during the treatment with omalizumab, or this might be simply due to achieving better asthma control. When omalizumab was discontinued, the patient had already started the replacement hormone treatment, shortly afterwards reaching normal cortisol levels.

This case report stresses the importance of a comprehensive differential diagnosis of anaphylaxis, and the need to perform an extensive and thorough diagnostic workup in uncommon cases, especially when the causative agents are unknown.

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