

The Syndrome of Thyroid Autoimmunity and Idiopathic Chronic Urticaria and Angioedema Presenting as Anaphylaxis

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ABSTRACT

Previous observations have shown that the syndrome of thyroid autoimmunity and idiopathic urticaria and angioedema (ICUA) can be associated with a marked worsening of reactive airway disease. Possibly, mediators released in this syndrome may contribute to acute bronchospasm and associated respiratory symptoms in some patients. In this study, two patients presenting with overlapping clinical presentations of the syndrome of thyroid immunity and ICUA are described in whom a diagnosis of anaphylaxis to food and antibiotics, respectively, was initially suspected but ruled out by testing and challenges. These cases illustrate clinical overlap between presentations of ICUA and anaphylaxis. We suggest that patients with idiopathic anaphylaxis be evaluated for the presence of antithyroid microsomal (peroxidase) antibodies or antithyroglobulin antibodies, particularly because the diagnosis of thyroid antibody-positive ICUA may suggest additional therapeutic options. (Allergy and Asthma Proc 24:171–174, 2003)

A syndrome of thyroid autoimmunity and idiopathic chronic urticaria and angioedema (ICUA) has been described previously¹ in which antibodies against thyroid tissues, either antithyroid microsomal (peroxidase) antibodies or antithyroglobulin antibodies, are present simultaneously with idiopathic urticaria and/or angioedema. In the initial description of thyroid autoimmunity and ICUA, some

patients had only angioedema, rather than both angioedema and urticaria as the chief symptom,¹ suggesting some variation in the clinical presentation of the syndrome. In this syndrome the relationship between autoantibodies against thyroid tissues and release of vasoactive mediators from mast cells has not been established, although autoantibodies directed at the immunoglobulin E (IgE) receptor are noted in other forms of ICUA².

Because a significant number of patients with ICUA may have thyroid autoimmunity, screening for thyroid autoantibodies has been advocated in patients with ICUA, and in some cases treatment with levothyroxine can promote resolution of symptoms.^{3–5} This study concerns two patients who presented with suspected anaphylaxis to shellfish and antibiotics, respectively, and subsequently were diagnosed with the syndrome of thyroid autoimmunity and ICUA. In these patients, the initial diagnosis of anaphylaxis to various coincidental allergens in the diet or medications rather than ICUA occurred because the presenting symptom was primarily of respiratory symptoms such as stridor and chest tightness in addition to urticaria and angioedema.

We previously described a pediatric patient with reactive airway disease and thyroid autoantibody-positive ICUA whose reactive airway disease became both steroid resistant and intractable with the onset of thyroid antibody-positive ICUA.⁴ This patient's reactive airway disease returned to mild severity with resolution of the ICUA after treatment with thyroid hormone, suggesting that the release of mast cell mediators associated with ICUA could also trigger significant bronchospasm. Based on this previous patient and the patients described in this study, we hypothesize that a combination of bronchospasm and angioedema in some

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individuals with ICUA could lead to an anaphylactic clinical presentation because of a combination of symptoms from angioedema and reactive airway disease responsive to ICUA mediators. Therefore, screening for thyroid autoimmunity, specifically the presence of either antithyroid microsomal (peroxidase) antibodies or antithyroglobulin antibodies may be advisable in the evaluation of idiopathic anaphylaxis⁶ to clarify the diagnosis and also to suggest additional therapy directed at underlying thyroid disease if present.

CASE REPORTS

Patient 1 (Index Patient)

A 63-year-old woman was referred for evaluation of suspected allergy to shellfish. Stridor and facial swelling had developed in a restaurant soon after she had ingested lobster with crabmeat stuffing. Before this episode, she had exhibited no evidence of food allergy. Epinephrine, albuterol, antihistamines, and corticosteroids were administered in a hospital emergency room setting to control respiratory symptoms. She reported milder episodes of facial swelling over the previous several months but without stridor or respiratory symptoms. These symptoms were associated with some pruritus and urticaria.

She had a history of autoimmune thyroid disease and a complete thyroidectomy. She received a replacement dose of levothyroxine (125 μ g/day) and was euthyroid. She also had a previous history of an anticardiolipin antibody syndrome. Additional laboratory evaluation revealed no evidence of food allergy to shellfish. Skin-prick testing to a panel of common foods and aeroallergens was completely negative with a positive control. Radioallergosorbent testing (Pharmacia CapRAST, Quest Diagnostics, Wallingford, CT) to shellfish species associated with the suspected allergic reaction including lobster, crab, and shrimp were negative (class 0, antibody absent or at undetectable levels). A challenge in the office to a serving of lobster stuffed with crabmeat showed no evidence of any allergic reaction during or after ingestion of these foods. Additional evaluation revealed evidence of ongoing thyroid autoimmunity (antithyroglobulin antibody, 8.4 IU/mL, normal <2.0; antithyroid peroxidase antibody, 22.4 IU/mL, normal <2.0). Total complement (CH50) and complement C2, C4, and C1q inhibitor were within normal limits and serum IgE was not elevated.

Because of the lack of any IgE-mediated sensitivity to shellfish or other atopic disease we considered the possibility that her symptoms were related to underlying thyroid disease and the syndrome of ICUA, which presented with symptoms clinically consistent with anaphylaxis. Because she was already on a high dose of levothyroxine and had other medical illnesses, her dose of levothyroxine could not be increased, although this has been advocated as a therapeutic option in some patients with thyroid autoimmunity

and ICUA who present while taking thyroid hormone therapy.³

She was treated with oral corticosteroids (prednisone, 20 mg/day for 1 week), an H1-specific antihistamine (cetirizine), and colchicine (0.6 mg twice per day). Colchicine was provided as an anti-inflammatory agent, sometimes effective in idiopathic urticaria. Epinephrine was prescribed for emergency use. She did not have a history of asthma but pulmonary function testing was obtained because of respiratory symptoms noted. Pulmonary testing (on prednisone) showed a forced expiratory volume in 1 second (FEV₁) of 2.15 L, 87% of predicted, and a forced vital capacity (FVC) of 2.62 L, 85% of predicted. A forced expiratory flow 25%/75% (FEF_{25/75}) of 2.46 L/s, 95% of predicted, did not show obstruction, although the peak flow was low 3.19 L/s (55%). A 2% increase in FEV₁, 16% increase in FEF_{25/75}, and 77% increase in peak flow were noted after albuterol, suggesting some benefit of bronchodilator therapy, although not sufficient to establish a diagnosis of reactive airway disease. She began therapy with a leukotriene antagonist (montelukast) and with as needed bronchodilator (albuterol). The patient subsequently discontinued prednisone, colchicine, montelukast, and albuterol over the next month without return of respiratory symptoms, although she continued to take cetirizine for urticaria.

A correlation was noted clinically between her urticaria and angioedema and her acute respiratory symptoms, and with subsequent clinical remission of urticaria, no further respiratory events were noted over >2 years of follow-up. Titers of antithyroid antibodies remained elevated at follow-up 2 years after initial presentation. She resumed eating shellfish and did not report any further symptoms associated with ingestion of shellfish.

Patient 2

A 57-year-old woman was referred for evaluation of chronic sinusitis and urticaria. She had a history of allergen immunotherapy for dust-mite allergy. Allergy to ragweed, feather, and dust mites was confirmed by skin testing. Azithromycin was instituted for chronic sinusitis. She also took some amoxicillin-clavulanic acid from a previous prescription simultaneously with the azithromycin and over the next 24 hours developed hives, swelling of the hands and feet, and chest tightness/shortness of breath. Antibiotics were discontinued, and symptoms responded to antihistamines and a short course of prednisone (60 mg of prednisone on day 1, tapered to 10 mg/day).

Additional evaluation showed no evidence of penicillin allergy by skin testing to penicillin major and minor determinants, and oral challenges in the office to both amoxicillin-clavulanic acid and azithromycin were negative. Because of her history of chronic urticaria, additional laboratory studies for ICUA were obtained and showed euthyroid status with evidence of thyroid autoimmunity (thyroid-stimulating hormone, 1.8 mIU/L, normal, 0.4–4.2;

antithyroglobulin antibody, 2.8 IU/mL, normal <2.0; anti-thyroid peroxidase antibody, 200 IU/mL, normal <2.0). She continued to have episodes of urticaria and chest tightness in the absence of any specific triggers, which responded to antihistamines and short courses of oral corticosteroids; however, these episodes resolved completely after treatment with levothyroxine, 25 µg/day, 1/3 of a replacement dose of thyroid hormone.

Pulmonary function testing was obtained after her urticaria was in remission on thyroid hormone therapy because of her respiratory symptoms during flares of urticaria. She had not reported a history of asthma. FEV₁, 2.41 L (91%); FVC, 3.57 L (109%); FEF_{25/75}, 1.39 L/s (49%); and peak flow, 4.79 L/s (79%), indicated obstruction that did not improve with albuterol. After a 1-month trial of inhaled corticosteroids (budesonide Turbuhaler [Pulmicort, Astra-Zeneca, Wilmington, DE], 200 µg twice daily), FEV₁, 2.97 L (112%); FVC, 3.77 L (115%); FEF_{25/75}, 2.74 L (96%); and peak flow, 7.34 L/s (121%), were all significantly improved. Subsequently, decreases in FEV₁ were noted during upper respiratory infections or when inhaled corticosteroids were discontinued, consistent with underlying mild to moderate asthma. Interestingly, her airway function remained relatively unresponsive to albuterol, although improved on inhaled corticosteroids. She has remained well without evidence of urticaria or respiratory symptoms for a period of >2 years on levothyroxine. Respiratory symptoms and urticaria/angioedema have recurred simultaneously during attempts to discontinue levothyroxine.

DISCUSSION

These observations suggest that patients with respiratory symptoms and the syndrome of thyroid antibody-positive ICUA may be suspected to have or may be diagnosed with anaphylaxis to various coincidental antigens present in their diet or medications. Previously, we have suggested that inflammatory mediators may be released in the syndrome of thyroid autoimmunity and ICUA and trigger acute bronchoconstriction in patients with asthma, causing previously mild to moderate reactive airway disease to become steroid resistant and intractable.⁴ We noted that flares of thyroid antibody-positive ICUA were linked temporally to a marked worsening of reactive airway disease in a pediatric patient observed under careful observation as an inpatient in a respiratory hospital.⁴

Now, two additional patients with overlapping clinical presentations are described with respiratory symptoms possibly attributed to thyroid antibody-positive ICUA. Patient 1, initially suspected to have shellfish allergy, had objective and subjective relief of respiratory symptoms after albuterol, although pulmonary function did not establish a diagnosis of reactive airway disease (possibly because of concurrent use of oral corticosteroids). Patient 2, suspected to have antibiotic allergy, had more conclusive evidence of reactive airway disease and significant increases in pulmonary function after inhaled corticosteroids.

To determine whether patients with ICUA frequently had respiratory symptoms leading to a diagnosis of anaphylaxis, we reviewed additional records of six additional patients diagnosed with thyroid antibody-positive ICUA presenting to our practice over a 6-month interval coincident with the diagnosis of the two patients reported. Additional patients were not suspected of having anaphylaxis if they did not have respiratory symptoms with their ICUA (data not shown). Thus, it seems that only a minority of patients with thyroid antibody-positive ICUA have respiratory symptoms associated with ICUA, but these patients are at risk for misdiagnosis with anaphylaxis to various coincidental triggers.

These observations may be relevant to the diagnosis and treatment of idiopathic anaphylaxis. A large case series has shown that many patients with idiopathic anaphylaxis previously have been diagnosed with either idiopathic urticaria and/or asthma.⁶ Diagnostic overlap between idiopathic angioedema and anaphylaxis has also been noted.⁷ Evidence of abnormal T-cell activation is evident in idiopathic anaphylaxis⁸ and could contribute to autoantibody production evident in many patients with ICUA² and also to airway reactivity.

Although it is tempting to speculate that autoantibodies against the human IgE receptor present in many patients with ICUA are also present in patients with the syndrome of thyroid immunity and ICUA,⁹ there is no evidence to our knowledge that thyroid autoantibodies are related directly to antibodies against the IgE receptor. More recent studies on antibodies against the human IgE receptor in patients with ICUA have shown a complex relationship between these antibodies and ability of serum from patients with ICUA to trigger human mast cells *in vitro*, suggesting that these autoantibodies do not entirely define the syndrome,¹⁰ which may reflect an underlying chronic inflammatory or autoimmune disease.¹¹

Additional characterization of mediators released in the syndrome of thyroid autoimmunity and ICUA might also help to clarify the underlying pathogenesis of this syndrome. Although a small percentage of the general population has evidence of antithyroid antibodies without any evident disease,¹ the observation that these antibodies are significantly more common in patients with ICUA could reflect shared antigenic determinants between mast cells and thyroid tissue or rather be a marker of circulating immune complexes, which in turn trigger mast cell release. Alternatively, cytokines or other products released from thyroid tissues or bystander cells due to autoimmune damage by T lymphocytes or other immune effector cells could trigger mast cell release.

Based on our experience, we suggest that ICUA can present as a syndrome virtually indistinguishable from anaphylaxis in patients who present with significant respiratory symptoms such as stridor or chest tightness as well as urticaria/angioedema. Screening for thyroid autoimmunity including thyroid function testing, titers of thyroid antimicrosomal (peroxidase) antibodies, and antithyroglobulin an-

tibodies should be considered in evaluation of patients with ICUA or undefined anaphylaxis. This screening may be useful both in identification of unsuspected thyroid disease and in suggesting therapy with levothyroxine, an effective therapy in patient 2 described in this study and described elsewhere.³⁻⁵

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