

Case Report

Type 1 diabetes, autoimmune thyroid disease, and chronic urticaria

Hyman SJ, Shreffler WG, Rapaport R. Type 1 diabetes, autoimmune thyroid disease, and chronic urticaria. *Pediatric Diabetes* 2008.

Abstract: A 12-yr-old boy initially presented with chronic urticaria. Autoimmune thyroid disease was then diagnosed during routine evaluation. He developed type 1 diabetes shortly after thyroid hormone replacement was initiated. This case emphasizes the importance of routine screening for other autoimmune disorders in patients in whom one disorder is already present.

**Sharon J Hyman^a,
Wayne G Shreffler^b and
Robert Rapaport^a**

^aDivision of Pediatric Endocrinology and Diabetes, Department of Pediatrics, Mount Sinai School of Medicine, New York, NY, USA; and ^bDivision of Pediatric Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine, New York, NY, USA

Key words: anti-thyroid antibodies – autoimmune disorders – autoimmune thyroid disease – chronic urticaria – type 1 diabetes mellitus

Corresponding author:
Sharon J Hyman, MD
Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics
Mount Sinai School of Medicine
One Gustave L. Levy Place
P.O. Box 1616
New York, NY 10029
USA.
Tel: (212) 241-8487 (office)/(516) 466-3088 (home);
fax: (212) 876-2503;
e-mail: sjhyman01@yahoo.com

Submitted 12 October 2007. Accepted for publication 27 February 2008

Case report

A 12-yr-old boy with a 7-month history of chronic urticaria was evaluated for thyroid status. The hives began 3 wk following streptococcal pharyngitis were initially intermittent and involved his whole body; they were sometimes associated with angioedema without wheezing or other systemic symptoms. Antihistamines did not alleviate his symptoms, and he was treated with cortisone injections. He progressed to having almost daily urticaria and angioedema and was treated with intermittent oral steroids.

At presentation, he had been taking oral dexamethasone daily for 10 d and hydroxyzine with little improvement. Previous testing revealed a thyroid-stimulating hormone (TSH) level of 7.26 μ IU/mL

(normal 0.34–5.60 μ IU/mL), a thyroxine (T4) of 7.43 μ g/dL (normal 6.21–12.2 μ g/dL), thyroperoxidase antibodies of 4.4 IU/mL (normal <2.0 IU/mL), and negative thyroglobulin antibodies. He had no symptoms of hypothyroidism or hyperthyroidism.

The patient was adopted at 4 months of age, and there was no information about his birth or family history. His past medical history was significant for mild intermittent asthma, for which he was using albuterol as needed, and seasonal allergic rhinitis.

On physical examination, his weight was 41.8 kg and height was 147 cm, both at approximately the 50th percentile for age. His thyroid gland was not palpable, and he had no adenopathy. He had no urticaria at this time. He was prepubertal, Tanner stage 1.

Repeat thyroid function tests confirmed the elevated TSH level; triiodothyronine (T3) and free T4 were within normal limits (TSH 7.34 μ IU/mL, normal 0.35–5.5 μ IU/mL; T3 125 ng%, normal 45–137 ng%; and free T4 1.17 ng/dL, normal 0.89–1.76 ng/dL). Thyroperoxidase antibodies were again positive (1.7 U/mL, normal <0.3 U/mL), and thyroglobulin antibodies and thyroid-stimulating immunoglobulins (Igs) were negative. Because of the patient's repeated, albeit slight, elevation in TSH, positive thyroperoxidase antibody level, and poor response of his urticaria to treatment with steroids, T4 replacement (50 mcg daily) was started.

One month later, the patient presented to his pediatrician with abdominal pain, fatigue, and glycosuria. He had a 2-wk history of polyuria, polydipsia, nocturia, decreased appetite, weight loss, fatigue, and blurred vision. The patient had received a 7-d course of oral dexamethasone for an exacerbation of his urticaria.

Laboratory evaluations were significant for a finger-stick glucose of 443 mg/dL, a hemoglobin A1c of 8.7% (normal <6%), glycosuria, and trace ketonuria. His insulin level was 10.5 μ U/mL (normal 6–27 μ U/mL), and C-peptide level was 0.8 ng/mL (normal 1.1–5 ng/mL) with a concomitant preserved glucose of 366 mg/dL. His diabetes-related autoantibodies were positive: anti-insulin antibodies 28.6 U/mL (normal <0.9 U/mL), anti-glutamic acid decarboxylase (GAD) antibodies 43.8 U/mL (normal <1.5 U/mL), and anti-islet cell antibodies >1:8 (normal <1:2).

The patient was started on glargine and aspart insulin (0.3 units/kg/d) for treatment of type 1 diabetes mellitus.

Additional immunological evaluation 1 yr after the onset of his chronic urticaria revealed normal erythrocyte sedimentation rate; normal total IgG, IgM, and IgA; negative tissue transglutaminase IgA and IgG antibodies, and negative anti-adrenal antibodies. IgE was undetectable (<2 U/mL), which was unusual given his history of asthma and allergic rhinitis. C3, C4, and CH50 levels were normal. The absence of detectable serum IgE suggested the possibility of an anti-IgE autoantibody. To evaluate for this, we used a flow cytometry-based basophil activation test (Fig. 1). The patient's serum activated normal donor basophils as measured by upregulation of CD63 on the surface of basophils. This strongly suggested the presence of anti-IgE autoantibodies. Histocompatibility locus antigen (HLA) typing revealed the haplotype HLA-DR*0401.

The patient continued to have intermittent urticaria despite treatment with fexofenadine, montelukast, ranitidine, and hydroxyzine as needed. These episodes ultimately resolved, and he has been asymptomatic for 1 yr. He remains on T4 replacement of 50 mcg daily and is clinically and biochemically euthyroid. His thyroperoxidase antibody level continues to be posi-

tive. The patient's symptoms of hyperglycemia resolved, and his hemoglobin A1c decreased. He was transitioned to continuous subcutaneous insulin infusion by an insulin pump and now has an insulin requirement of 0.6 units/kg/d.

Discussion

Chronic urticaria is characterized by continuous or frequently recurrent hives for more than 6 wk. In many cases, the etiology is unknown (1–6). However, in a subset of patients, the urticaria has been classified as autoimmune because of the presence of anti-IgE and/or anti-IgE receptor (Fc ϵ RI) antibodies and an association with thyroid autoimmunity (1–8). The detection of autoantibody capable of inducing degranulation of mast cells by IgE/Fc ϵ RI cross-linking has classically been made using the autologous serum skin test. We have instead used a non-invasive *in vitro* test that measures the degranulation of basophils by detecting the upregulation of the molecule CD63 (lysosomal-associated membrane protein-3) from the secretory granule to the plasma membrane, an event that is inextricably linked to histamine and other granule content release. The measurement of CD63 upregulation has been shown to correspond with both the magnitude and the kinetics of anti-IgE-induced histamine release (9, 10).

The possible mechanisms whereby thyroid autoimmunity could contribute to chronic urticaria are unclear. Rottem et al. reported that chronic urticaria and autoimmune thyroid disease are likely associated autoimmune events (1). Rumbyrt et al., however, hypothesized that thyroid inflammation is the predominant feature of chronic urticaria (3). He proposed that thyroid inflammation caused by anti-thyroid antibodies results in the release of normally sequestered thyroid antigens into the circulation. This stimulates a further immune response ultimately resulting in degranulation of mast cells.

Studies, mostly in adults, have shown an increased frequency of autoimmune thyroid disease in patients with chronic urticaria (2–4, 7, 8). Turktas et al. detected thyroglobulin antibodies in 11.7% and thyroid microsomal antibodies in 9.6% of patients with chronic urticaria (4). Anti-thyroid antibodies were detected in only 3.7% of control patients. Verneuil et al. detected the frequency of thyroid autoantibodies to be significantly higher in patients with chronic urticaria (26.7%) than in healthy controls (3.3%) (8). In a study by Levy et al. of 187 children and adolescents with chronic urticaria, elevated anti-thyroid antibodies were detected in 8 patients, 3 of whom were clinically hypothyroid requiring treatment with T4 replacement (2). The prevalence of thyroid autoimmunity in this study was 4.3%, which although lower than that reported in adult patients with chronic urticaria was significantly

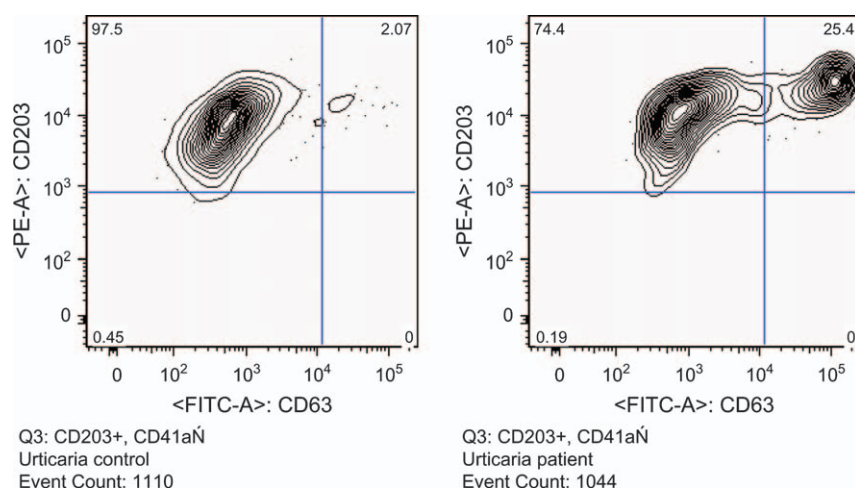


Fig. 1. Patient serum activates normal donor basophils. Whole blood cells from an anonymous donor were washed twice in phosphate buffered saline to remove autologous plasma and then incubated for 30 min with control serum (from atopic patient with no history of chronic urticaria) or patient serum. Basophil reactivity was stopped by addition of ethylenediaminetetraacetic acid, and cells were washed and stained with monoclonal antibodies specific for CD41a, CD63, CD123, CD203c, HLA-DR, and a lineage marker cocktail (CD3, CD14, and CD19). Basophils were identified as lineage negative, CD123+, CD203c+, and HLA-DR negative. Activated basophils were identified as CD63 bright basophils (9). Twenty-five percent of the normal donor basophils were activated by incubation with the serum of our patient with chronic urticaria vs. 2% by incubation with control serum.

higher than the prevalence reported for age-matched children (0.35–1.6%). Because of this known association between chronic urticaria and autoimmune thyroid disease, most authors recommend screening for thyroid autoimmunity in all patients with chronic urticaria as part of the routine evaluation (1–4, 6, 8).

Our patient had a mildly elevated TSH concentration that persisted in addition to one positive anti-thyroid antibody titer. This biochemical profile may not always indicate the presence of autoimmune hypothyroidism; however, given that our patient had two other autoimmune disorders, we assumed that he did have lymphocytic thyroiditis. In addition, the decision to start our patient on treatment with T4 was made partly as a means of improving his urticaria, which had been poorly responsive to treatment with steroids. Rumbyrt et al. studied 10 euthyroid patients with refractory urticaria who were treated with T4 (6). Of those, seven patients with elevated anti-thyroid antibodies had resolution of their symptoms within 4 wk; the three patients without elevated antibodies did not respond to treatment. They concluded that treatment with thyroid hormone can result in clinical remission. Turktaş et al., however, reported that in the majority of their patients with chronic urticaria and autoimmune hypothyroidism, T4 failed to completely clear the urticarial lesions (4).

Not only was our patient diagnosed with chronic urticaria and autoimmune thyroid disease but also the detection of a third autoimmune disorder, type 1 diabetes mellitus, occurred shortly thereafter. About 20–30% of children with type 1 diabetes have elevated anti-thyroid antibodies (11, 12). These two conditions are the most common autoimmune endocrine disease

associations, and their etiologies may involve common genetic factors (13). Previous cases of multiple autoimmune disorders including chronic urticaria have been described mostly in adult patients. Asero et al. reported a 33-yr-old woman with type 1 diabetes and Graves' disease followed 7–8 yr later by chronic urticaria (14). Autoantibodies for GAD, insulin, FcεRI, and TSH receptor were detected. Our patient is unusual with respect to his young age at diagnosis, male gender, and the rapid development of all three autoimmune conditions in less than 1 yr.

This case exemplifies the tendency for autoimmune disorders to cluster together in the same patient. It also emphasizes the importance of routine screening for other autoimmune disorders in patients in whom one disorder is already present.

References

1. ROTTEM M. Chronic urticaria and autoimmune thyroid disease: is there a link? *Autoimmun Rev* 2003; 2: 69–72.
2. LEVY Y, SEGAL N, WEINTROB N, DANON YL. Chronic urticaria: association with thyroid autoimmunity. *Arch Dis Child* 2003; 88: 517–519.
3. RUMBYRT JS, SCHOCKET AL. Chronic urticaria and thyroid disease. *Immunol Allergy Clin North Am* 2004; 24: 215–223.
4. TURKTAS I, GOKCORA N, DEMIRSOY S, CAKIR N, ONAL E. The association of chronic urticaria and angioedema with autoimmune thyroiditis. *Int J Dermatol* 1997; 36: 187–190.
5. KAPLAN AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol* 2004; 114: 465–474.
6. RUMBYRT JS, KATZ JL, SCHOCKET AL. Resolution of chronic urticaria in patients with thyroid autoimmunity. *J Allergy Clin Immunol* 1995; 96: 901–905.

7. O'DONNELL BF, FRANCIS DM, SWANA GT, SEED PT, KOBZA BA, GREAVES MW. Thyroid autoimmunity in chronic urticaria. *Br J Dermatol* 2005; 153: 331–335.
8. VERNEUIL L, LECONTE C, BALLETT JJ et al. Association between chronic urticaria and thyroid autoimmunity: a prospective study involving 99 patients. *Dermatology* 2004; 208: 98–103.
9. SHREFFLER WG. Evaluation of basophil activation in food allergy. *Curr Opin Allergy Clin Immunol* 2006; 6: 226–233.
10. KNOL EF, MUL FP, JANSEN H et al. Monitoring human basophil activation via CD63 monoclonal antibody 435. *J Allergy Clin Immunol* 1991; 88: 328–338.
11. KORDONOURI O, KLINGHAMMER A, LANG EB, GRUTERS-KIESLICH A, GRABERT M, HOLL RW. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. *Diabetes Care* 2002; 25: 1346–1350.
12. KIM EY, SHIN CH, YANG SW. Polymorphisms of HLA class II predispose children and adolescents with type 1 diabetes mellitus to autoimmune thyroid disease. *Autoimmunity* 2003; 36: 177–181.
13. LEVIN L, TOMER Y. The etiology of autoimmune diabetes and thyroiditis: evidence for common genetic susceptibility. *Autoimmun Rev* 2003; 2: 377–386.
14. ASERO R, ORSATTI A, TEDESCHI A, LORINI M. Autoimmune chronic urticaria associated with type 1 diabetes and Graves' disease. *J Allergy Clin Immunol* 2005; 115: 1088–1089.