

Treatment of Chronic Urticaria with Thyroxine in an Euthyroid Patient with Thyroglobulin and Microsomal Antibodies

C K Koh,*^{MBChB, Dip Derm, MRCP (UK)}, F L Hew,**^{MD, MRCP (UK), FRACP}, C L Chiu,***^{MBChB, FRCA}

Abstract

Introduction: The association of chronic urticaria and thyroid autoimmunity is not well recognised and the potential use of thyroxine in the treatment of chronic urticaria in patients with thyroid autoimmunity is even less well known. **Clinical Picture:** We report a case of chronic urticaria in an euthyroid patient with evidence of significantly elevated levels of thyroglobulin and microsomal antibodies. **Treatment and Outcome:** Treatment with thyroxine has brought about clinical remission of the chronic urticaria but no change in the thyroid antibody levels could be demonstrated. **Conclusion:** Patients with chronic urticaria should be screened for evidence of thyroid autoimmunity. A closely monitored trial of thyroxine therapy for those who have thyroid autoimmunity can be rewarding.

Ann Acad Med Singapore 2000; 29:528-30

Key words: Autoimmune disease, Chronic urticaria, Thyroxine

Introduction

Chronic urticaria is defined as daily outbreaks of urticaria of at least 6 weeks duration. Despite being a common disorder, the cause of chronic urticaria is often obscure and not easily treatable. Symptomatic treatment with antihistamines and corticosteroids often provides only partial and temporary relief to some patients.

Histopathological studies of chronic urticaria reveal a different cellular pattern when compared with the lesions of acute urticaria. Autoantibodies against IgE receptor in the serum, together with infiltration of mast cells, eosinophils, mononuclear cells and activated CD4-positive T cells within the lesions suggest that autoimmunity may play a significant role in the pathogenesis of chronic urticaria.^{1,2}

Leznoff et al³ first described the association of chronic urticaria with thyroid autoimmunity. This association was confirmed more recently by others.⁴⁻⁷ Subsequently other workers have reported successful use of thyroxine in euthyroid patients with chronic urticaria that were associated with thyroid autoimmunity.^{8,9}

This is the first reported case in Malaysia where thyroxine is used successfully to treat chronic urticaria in an euthyroid patient with thyroid autoimmunity.

Case Report

A 33-year-old Chinese male presented with more than 2 years' history of severe chronic urticaria. He has daily outbreaks affecting his trunk, limbs and face. He had seen several dermatologists and had tried various antihistamines, including combinations with histamine-2 blockers such as ranitidine and famotidine. He was on a minimum of 4 antihistamines (loratidine 10 mg daily, acrivastine 8 mg 3 times daily, hydroxazine 25 mg twice daily and polaramine 6 mg at night) combination but still suffered occasional severe flare-ups requiring intramuscular steroid injection (triamcinolone). Dietary restrictions and medications only provided temporary symptomatic relief. There is no family history of urticaria or eczema. His mother and maternal aunt had thyrotoxicosis.

Thorough investigations including full blood count, erythrocyte sedimentation rate, liver function, renal profile, lipid profile, rheumatoid factor, venereal disease research laboratory test (VDRL), hepatitis screen, tumour markers, urine analysis, glucose and thyroid function were all normal.

Apart from the urticaria, he was clinically well. There was no goitre and he was euthyroid (Table I). However, repeated thyroid function test together with thyroid

* Consultant Dermatologist
Private Practice

** Lecturer
Department of Medicine

*** Lecturer
Department of Anaesthesia
Faculty of Medicine, University of Malaya

Address for Reprints: Dr C K Koh, Koh Skin Specialist Clinic, 5M, Jalan SS 21/1A, Damansara Utama, Petaling Jaya, Selangor, Malaysia.

autoantibodies revealed antithyroglobulin level of 1:1600 and antimicrosomal level of 1:400 which strongly suggested the presence of thyroid autoimmunity (Table I).

He was started on thyroxine replacement at 25 µg daily. His urticaria attacks became less frequent after 4 weeks, thyroxine was gradually increased to 50 µg under regular monitoring and repeat thyroid function test for the next 12 weeks (Table I). He remained urticaria-free and no longer needed any antihistamines. However, when he attempted to discontinue the thyroxine replacement, he developed recurrence of his urticaria within a week. This recurrence resolved within days of recommencing on thyroxine. At the most recent follow-up, the thyroid function test remained normal and the antithyroglobulin level was 1:1600 and antimicrosomal level was 1:1600 (Table I).

TABLE I: THE THYROID FUNCTION TEST AND THE ANTIBODIES LEVELS OF THE PATIENT*

Date	28/4/99	3/6/99	21/9/99	22/2/00
Thyroxine dose	Nil	25 µg	50 µg	50 µg
Total thyroxine nmol/L (64 to 167)	122.7	106.0	136.5	97.7
TSH uIU/mL (0.3 to 5.1)	0.03	0.03	0.13	0.11
Antithyroglobulin antibody	1:1600	NA	1:1600	1:1600
Microsomal antibody	1:400	NA	1:1600	1:1600

* Followed up over a 12-week period starting from his presentation on 28/4/99; thyroxine was started on that day at 25 µg/day. The thyroxine dose in the table reflects the dose used commencing from the visit prior as indicated from the dates.

NA: not available

Discussion

Chronic urticaria is now considered an autoimmune disease. It is associated with a wide spectrum of other autoimmune diseases such as thyroid disease, in particular, Hashimoto's thyroiditis, Addison's disease, vitiligo, diabetes mellitus, and pernicious anaemia.¹⁰ Thyroid autoimmunity is the most common of the organ-specific autoimmune disease with 3% to 6% of the population demonstrating significantly raised titres of thyroid antibodies.¹¹

The mechanism by which urticaria and thyroid autoimmunity is linked is not well defined. The discovery of the involvement of activated CD4-positive T lymphocytes, inflammatory cells including neutrophils, eosinophils and monocytes in stimulating mast cells to release histamine on urticarial skin lesions confirm the autoimmune process.²

Rumbryt et al⁸ believed that antithyroid antibodies are not pathogenic, serving only as indicators of autoimmune process, and suggested that other factors were involved. These factors produced from the recruitment of inflammatory cells such as cytokines, autoantibodies and histamine releasing factors perpetuated a chronic inflammatory state and decreased the mast cells threshold to endogenous peptides or exogenous allergens or stimulants.

Leznoff et al³ were the first to successfully treat chronic urticaria and angio-oedema with thyroxine in patients with hypothyroidism and documented thyroid autoimmunity.³ They subsequently followed up another 46 patients.¹⁰ However, their patients were mainly either hypothyroid or had an elevated thyroid stimulating hormone. In 1995, Rambryt et al⁸ studied 10 euthyroid patients with refractory urticaria. These patients were treated with thyroxine (25 to 100 µg). Seven of the 10 patients responded within 4 weeks. These 7 patients were found to have autoimmunity. The remaining 3 patients who did not respond to thyroxine therapy did not have autoantibodies. However, there were no correlation between clinical response and the levels of antithyroid antibodies. Most patients appeared to respond within 4 weeks of treatment. Some patients developed recurrence once thyroxine was stopped but responded again after recommencing the thyroxine therapy.

The mechanism by which thyroid hormone acts in chronic urticaria patients with thyroid autoimmunity remains unknown. It is possible that by giving the patient exogenous thyroxine, the thyroid stimulating hormone (TSH) is suppressed, which otherwise would increase the antigen expression on thyroid cell surfaces stimulating autoantibodies production.¹² This may be the mechanism by which recurrence rate of hyperthyroidism can be reduced with thyroxine administration in Graves' disease.¹² How thyroid antigen-derived antibody can lead to the development of urticaria is yet unknown. It is possible that suppression of thyroid antibodies may reduce the stimulation to autoimmunity that leads to the development of urticaria. An effect on mast cells stability with reduction of antibodies titre has also been postulated.⁸

Thyroxine therapy in our patient has not resulted in any reduction in the TSH levels (Table I). It is interesting that the TSH was suppressed in this patient prior to commencement of thyroxine therapy. This may be due to the presence of subclinical thyrotoxicosis. The thyroxine therapy subsequently may serve to reduce the endogenous thyroxine production and hence the output of thyroid antigen(s) reducing the stimulation of autoimmunity. This hypothesis is supported by a case report of remission of urticaria and angio-oedema in a patient with Hashimoto's thyroiditis after thyroidectomy.¹³ In our patient, the

microsomal antibody has in fact increased with thyroxine therapy (Table I) but the clinical improvement seen in the urticaria is quite dramatic. This is in keeping with the findings of Rambyrt and co-workers who found no correlation between clinical response and the levels of antithyroid antibodies to thyroxine therapy.⁸

The association between chronic urticaria and thyroid autoimmunity has been known for the last 15 years.³ However, this fact is still not widely known amongst the medical community. This has led to, as in this case, certain groups of patients, whom for years have been given various combinations of antihistamines and corticosteroids without being properly investigated and adequately treated. It is only by chance when they developed symptoms of thyroid malfunction years later and commenced on thyroxine that the urticaria disappeared.

There is a possibility of a latency period with chronic urticaria appearing first before the development of thyroid autoimmunity, as in Graves' ophthalmopathy in Graves' disease.¹³ Therefore, we propose that patients with chronic urticaria should not only have thyroid function test but also thyroid autoantibodies tested even if they are clinically euthyroid. Should this be positive, a closely monitored trial of thyroxine therapy may produce a rewarding outcome.

REFERENCES

1. Nabotny S F, Philips M E, Elias J M, Godfrey H P, Kaplan A P. Histologic studies of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1983; 71:177-83.
2. Mekori Y A, Giorno R C, Anderson P, Kohler P F. Lymphocyte subpopulations in the skin of patients with chronic urticaria. *J Allergy Clin Immunol* 1983; 72:681-4.
3. Leznoff A, Josse R G, Denburg J, Dolovich J. Association of chronic urticaria and angioedema with thyroid autoimmunity. *Arch Dermatol* 1983; 119:636-40.
4. Amoroso A, Garzia P, Pasquarelli C, Sportelli G, Afeltra A. Hashimoto's thyroiditis associated with urticaria and angio-oedema: disappearance of cutaneous and mucosal manifestations after thyroidectomy. *J Clin Pathol* 1997; 50:254-6.
5. Turkas I, Gokcora N, Demirsoy S, Cakir N, Onal E. The association of chronic urticaria and angioedema with autoimmune thyroiditis. *Int J Dermatol* 1997; 36:187-90.
6. Peltz S, Barchuk W, Oppenheimer J, Druce H, Bielory L. Chronic angioedema of the tongue associated with pernicious anaemia and Hashimoto's thyroiditis. *Clin Exp Dermatol* 1995; 20:351-2.
7. Henderson C A, Highet A S. Urticaria associated with thyrotoxicosis. *Clin Exp Dermatol* 1995; 20:173-4.
8. Rumbyrt J S, Katz J L, Schocket A L. Resolution of chronic urticaria in patients with thyroid autoimmunity. *J Allergy Clin Immunol* 1995; 96:901-5.
9. Heymann W R. Chronic urticaria and angioedema associated with thyroid autoimmunity: review and therapeutic implications. *J Am Acad Dermatol* 1999; 40:229-32.
10. Leznoff A, Sussman G L. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol* 1989; 84:66-71.
11. Turnbridge W M, Evered D C, Hall K. The spectrum of thyroid disease in a community: the Wickham survey. *Clin Endocrinol* 1977; 7:481-93.
12. Hashizume K, Ichikawa K, Sakurai A, Suzuki S, Takeda T, Kobayashi M, et al. Administration of thyroxine in treated Graves' disease. Effects on the level of antibodies to thyroid stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. *N Engl J Med* 1991; 324:947-53.
13. Hoffenberg R. Thyroid disorders. In: Weatherall D J, Ledingham J G G, Warrell D A, editors. *Oxford Textbook of Medicine*. 2nd ed. New York: Oxford Univ Press, 1987.