

Chronic Urticaria Associated With Thyroid Carcinoma: Report of 4 Cases

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■ Abstract

Chronic urticaria is a common condition that can be very disabling when severe. A variety of causes has been reported to induce urticaria, including food, infections, drugs and other factors. In more than 50% of cases of chronic urticaria, however, the cause remains unknown and cannot be ascribed to allergic, physical, environmental or other factors. Although an association between chronic idiopathic urticaria and malignancy has been occasionally reported, such an association remains controversial because it is difficult to demonstrate it is not just coincidental. Here we report the cases of four female patients with occult papillary carcinoma of the thyroid who developed chronic urticaria. In all of these cases, removal of the tumor led to prompt resolution of the urticarial lesions, thus suggesting a pathogenetic relationship between the two. This is the first report of papillary thyroid carcinomas associated with chronic urticaria and highlights how chronic urticaria may be an important cutaneous marker for patients with thyroid carcinoma.

Key Words: Chronic urticaria. Hypochoic nodule. Occult papillary carcinoma. Thyroid.

■ Resumen

La urticaria crónica es un trastorno común que puede ser muy incapacitante cuando es grave. Las causas capaces de inducir urticaria son diversas, e incluyen alimentos, infecciones, fármacos y otros factores. No obstante, en más de un 50% de los casos de urticaria crónica, la etiología es desconocida y no parece responder a factores alérgicos, físicos, medioambientales, ni de otro tipo. Aunque ocasionalmente se ha referido la relación entre la urticaria idiopática crónica y las neoplasias malignas, dicha asociación sigue siendo motivo de controversia porque es difícil demostrar que no se trate de una mera coincidencia. Describimos el caso de cuatro mujeres con carcinoma papilar oculto de la glándula tiroides que presentaban urticaria crónica. En todos los casos, la extirpación del tumor resultó en la pronta desaparición de las lesiones urticariales, lo cual sugiere la existencia de una relación patogenética entre los dos. Este es el primer informe en que se revela la asociación de los carcinomas papilares de tiroides con la urticaria crónica y destaca cómo la urticaria crónica puede ser un marcador cutáneo importante para pacientes con carcinoma de tiroides.

Palabras clave: Urticaria crónica. Nódulo hipoecoico. Carcinoma papilar oculto. Tiroides.

Introduction

Chronic urticaria, by definition, lasts more than six weeks and can persist for months or years. The etiology is unknown in about 50% of cases [1]. A variety of causes has been reported to induce urticaria, including food, infections, drugs and other factors. Chronic urticaria affects above all adults and it is approximately two times more frequent in women than in men. More than 40% of patients with chronic urticaria for more than six months, remain affected by the pathology for

ten years [2]. For this reason, chronic urticaria is a common condition that can be very disabling when severe. Over the past few years several cases of malignancies have been associated with urticaria together with a possible role for the thyroid gland. Many investigators [3] have referred to the possible link between autoimmune thyroid disease and chronic urticaria because the association between thyroid disease and pruritus and urticaria dates back more than 50 years. We present four patients with occult papillary thyroid carcinoma who developed chronic urticaria.

Case Description

Case 1

A 39-year-old woman was admitted to our department as a result of a 3-month history of urticaria involving the face, extremities and trunk, which was associated with intense pruritus. She was otherwise healthy and taking no medications and had no history of atopy. Urticaria persisted despite oral antihistamine therapy (oxatomide 60 mg/d), even in association with oral corticosteroids (betamethasone 4 mg/d). The urticarial episodes usually lasted for less than 24 hours, but often persisted for up to 2 to 3 days. Laboratory testing (Table 1) revealed no abnormalities in blood count, liver and kidney function, sedimentation rate, inflammatory indexes, complement fraction, and C1 esterase inhibitor levels. Antinuclear antibodies and thyroid autoantibodies were negative, and thyroid function was normal (TSH 0.98 mU/L, fT4 11.2 pg/mL, fT3 3.5 pg/mL). An autologous serum skin test was not performed. Chest X-ray was also performed, and revealed no abnormalities. Before steroid therapy was begun, a biopsy of the wheal on the trunk was performed. This showed a small perivascular dermal infiltrate of mononuclear cells with no sign of vasculitis. Direct immunofluorescence (DIF) failed to detect any immunoglobulin (Ig) G, IgM, IgA, C3 or fibrinogen deposits. In order to find a cause for such a resistant urticaria that was affecting the patient's quality of life, we performed an ultrasound examination of the neck, even though no symptoms or signs attributable to the thyroid gland were present. This examination revealed a 10 mm hypoechoic area in the right lobe of the thyroid with foci of calcification. No

lymphadenopathy was noted. Fine-needle aspiration biopsy with ultrasound guide revealed the presence of a papillary carcinoma of the thyroid. The patient underwent total thyroidectomy and after just two days, the urticaria resolved and no other episodes recurred after 6 years.

Case 2

A 32-year-old woman presented with a 12-week history of persistent generalized urticaria. She had no other medical problems and was not taking any medications. Different therapeutic procedures such as antihistamine therapy (chlorpheniramine maleate 8 mg/d), oral and intravenous corticosteroids (betamethasone) yielded no improvement. Again laboratory testing revealed no abnormalities in blood count, liver, kidney and thyroid function (TSH 0.48 mU/L, fT4 14.2 pg/mL, fT3 2.8 pg/mL), sedimentation rate, inflammatory indexes, complement fraction, and C1 esterase inhibitor levels. Tests for antinuclear antibodies and also thyroid autoantibodies were negative. An autologous serum skin test was not performed. Skin biopsy of the wheal on the arm was performed before steroid therapy was begun, and this showed histological changes compatible with chronic urticaria. DIF was negative. Chest X-ray revealed no abnormalities. Despite the patient having no signs or symptoms attributable to the thyroid, an ultrasound examination of the neck revealed a 7 mm hypoechoic nodule in the right lobe of the thyroid. Fine-needle aspiration with ultrasound guide and subsequent intraoperative biopsy revealed a papillary thyroid carcinoma. The patient underwent total thyroidectomy and just four days after the removal of the tumor, the urticaria resolved. At present, seven years later, the patient has had no further relapses of urticaria.

Table 1. Characteristics of the 4 Cases of Chronic Urticaria*.

Test	Result
Routine blood tests, tests for inflammatory markers, markers of autoimmunity, C1-INH, TSH, fT4, fT3, anti-thyroglobulin, anti-thyroperoxidase, and fecal parasite test	Negative
Histologic examination of skin biopsy	Small perivascular dermal infiltrate of mononuclear cells with no signs of vasculitis; DIF: negative
Persistence of skin lesions	More than 24 hours
Antihistaminic therapy and steroid therapy administered orally or intravenously	No response
Chest X-ray	Negative
Ultrasound examination of the neck	Hypoechoic area in a lobe of the thyroid gland
Fine-needle aspiration biopsy	Presence of an occult papillary carcinoma

*DIF indicates direct immunofluorescence.

Case 3

A 61-year-old woman was admitted to our department because of 2-month history of urticaria involving the face, extremities and trunk, which was associated with intense pruritus. Laboratory tests were negative but an autologous serum skin test was not performed. A skin biopsy of the wheal on the trunk was taken before steroid therapy was begun and this showed a normal epidermis, dermal edema, sparse perivascular and interstitial eosinophils, lymphocytes, neutrophils and mast cells. DIF was negative. Urticaria persisted despite oral antihistamine therapy (oxatomide 60 mg/d), even in association with oral corticosteroids (betamethasone 2mg/d). Chest X-ray was negative for the thyroid gland. An ultrasound examination of the neck revealed a 9 mm hypoechoic nodule in the left lobe of the thyroid but thyroid function (TSH 1.34 mU/L, fT4 13.6 pg/mL, fT3 3.2 pg/mL) was normal. Fine-needle aspiration biopsy with ultrasound guide revealed a papillary thyroid carcinoma. The patient underwent total thyroidectomy. After one day urticaria resolved. Five years later the patient has had no urticarial lesions.

Case 4

A 42-year-old woman was admitted to our department complaining of very pruritic evanescent wheals during the previous 8 months, especially on the trunk. Different therapeutic procedures such as antihistamine therapy (oxatomide 60 mg/d), oral and intravenous corticosteroids (betamethasone) yielded no improvement. There were no symptoms or signs attributable to the thyroid gland. Tests for thyroid autoantibodies and thyroid function (TSH 3.02 mU/L, fT4 9.5 pg/mL, fT3 2.6 pg/mL) were within normal limits. Laboratory tests and chest X-ray were normal. An autologous serum skin test was not performed. Skin biopsy of the wheal on the trunk was performed before steroid therapy was begun and this showed histological changes consistent with urticaria. DIF failed to detect any IgG, IgM, IgA, C3 or fibrinogen deposits. An ultrasound examination of the neck showed a 5 mm hypoechoic nodule in the right lobe of the thyroid. Fine-needle aspiration with ultrasound guide and subsequent intraoperative biopsy showed an occult papillary carcinoma. The patient underwent total thyroidectomy and 3 days after removal of the tumor urticaria gradually resolved and no other episodes occurred.

In all 4 cases this chronic urticaria was characterized by negative results from routine tests, the persistence of skin lesions for more than 24 hours with a histologic examination showing no signs of vasculitis and negative DIF test results. X-rays of the chest were negative and none of the cases responded to common treatments such as oral and intravenous antihistamines and steroids (Table 1). Autologous serum skin tests were not performed because no patient was treated with antibiotics or antiserum and none had arthralgia or fever. Even in the absence of symptoms suggesting a thyroid disorder, we found a hypoechoic nodule in the thyroid on ultrasound examination of the neck and fine-needle aspiration with ultrasound guide showed the presence of a papillary thyroid carcinoma. In all cases, removal of the tumor led to

prompt resolution of the urticarial lesions, thus suggesting a pathogenetic relationship between the two.

Discussion

Chronic urticaria is a common condition that can be very disabling when severe. A variety of causes has been reported to induce urticaria, including food, infections, drugs and other factors. In more than 80% of cases of chronic urticaria, however, the cause remains unknown and cannot be ascribed to allergic, physical, environmental or other factors [4]. Although an association between chronic idiopathic urticaria and malignancy has been occasionally reported, such an association remains controversial because it is difficult to demonstrate it is not just coincidental [5].

We have described 4 cases of chronic urticaria coexisting with thyroid carcinoma. In the literature, cases of angioneurotic edema that can be related to thyroid tumors [6], and cases in which a superior vena cava obstruction secondary to thyroid carcinoma may be misdiagnosed as angio-oedema have been reported [7]. To the best of our knowledge, this is the first report of papillary thyroid carcinoma associated with chronic urticaria. Several cases of malignancies have been reported over the past few years as being associated with urticaria. These include principally leukemias and lymphomas [8,9], but also myeloma [10], testicular cancer [11], ovarian carcinoma [12], bladder carcinoma [13], and lung cancer [14]. At present it is not known if the coexistence of chronic urticaria and thyroid carcinoma is more than a coincidence and if they share etiological factors. Not enough is currently known about the pathogenesis of neoplasias and of chronic urticaria to answer to this question. Hematological, immunological and endocrine assays are needed to provide direct or indirect evidence of systemic allergic inflammatory or autoimmune processes that may cause chronic urticaria [15]. For several years the association between autoimmune thyroid disorders and chronic urticaria has been well established [16] and an extensive study of the thyroid is often seen in the dermatology departments to which cases of chronic urticaria have been referred. Generally, work-ups would include thyroid function (TSH, fT4, fT3), auto-antibodies to thyroid (anti-thyroglobulin, anti-thyroperoxidase) and, in the case of symptomatic nodules or nodules palpable on physical examination, an ultrasound examination of the neck. In all our clinical cases nothing led us to suspect a disease of the thyroid. Serum tests were all negative, there was no familiar history, no history of radiotherapy, and no long term residency in areas where goitre was endemic. However, in an attempt to find a cause for a resistant urticaria that was affecting our patients' quality of life, we found a hypoechoic nodule in the thyroid using ultrasound examination of the neck. This nodule was a papillary carcinoma of the thyroid. This has led us to prepare a protocol to explore all chronic urticarias with these characteristics using an ultrasound examination of the neck.

References

1. Kaplan AP. Chronic urticaria: Pathogenesis and treatment. *J Allergy Clin Immunol.* 2004;114:465-474.

2. Fitzpatrick TB, Johnson RA, Wolff K, Polano MK and Suurmond D. Urticaria In Color Atlas and Synopsis of Clinical Dermatology. Common and Serious Diseases. Third Edition. U.S.A.: McGraw-Hill 1997, p 316.
3. Rumblyr JS, Schocket AL. Chronic urticaria and thyroid disease. *Immunol Allergy Clin North Am.* 2004;24(2): 215-223.
4. Greaves MW. Chronic urticaria. *New Engl J Med.* 1995;332:1767-1772.
5. Lindelof B, Sigurgeirsson B, Wahlgren CF, Eklund G. Chronic urticaria and cancer: an epidemiological study of 1155 patients. *Br J Dermatol.* 1990;123:453-6.
6. Vallent K, Feher J, Somogyi A, Joos A. Angioneurotic edema and Hypocomplementemia in patients with thyroid cancer. *Acta Chir Acad Sci Hung.* 1982;23(3):163-171.
7. O'Donnell BF, Foulds IS. Thyroid carcinoma presenting as angio-oedema. *Br J Dermatol.* 1993;128(5):588-9.
8. Alonso R, Cistero-Bahima A, Enrique E, Besses C. Chronic urticaria associated with chronic myelomonocytic leukaemia. *J Investig Allergol Clin Immunol.* 2000;10(6):380-1.
9. Clore LS Jr, Stafford CT. Chronic urticaria as a presenting sign of hairy cell leukaemia. *Allergy Asthma Proc.* 1999;20(1):515.
10. Lipsker D, Cribier B, Maloysel F, Heid E, Grosshans E. Chronic urticaria and IgA myeloma. *Acta Derm Venereol.* 1998;78(5):395.
11. Mowad CM, Mowad JJ, Cirigliano MD. Testicular cancer presenting as urticaria. *Cutis.* 1998;61(3):147-8.
12. Reinhold U, Bruske T, Schupp G. Paraneoplastic urticaria in a patient with ovarian carcinoma. *J Am Acad Dermatol.* 1996;35(6):988-9.
13. Bourezane Y, Hachelaf M, Voltz M, Blanc D, Aubin F, Humbert P. Urticaire chronique révélatrice d'un phéochromocytome vesical. *Presse Med.* 1994;23(15):717.
14. Hills EA. Adenocarcinoma of the bronchus with Cushing's Syndrome, carcinoid syndrome, neuromyopathy and urticaria. *Br J Chest Dis.* 1968;62(2):88-92.
15. Ring J, Gauger A, Rudiger H. Clinical efficacy of desloratadine in chronic urticaria. *Clin Drug Invest.* 2002;22 suppl 2:33-41.
16. Niepomniszcze H, Amad RH. Skin disorders and thyroid diseases. *J Endocrinol Invest.* 2001;24(8):628-638.

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