Elephantiasic Pretibial Myxedema in Graves' Disease: Report of Two Cases

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Abstract

Pretibial myxedema (PTM) is usually a late manifestation of Graves' disease and is relatively rare. The elephantiasis nostras variant comprises less than one percent of patient with pretibial myxedema. We report two cases of elephantiasic PTM and review the literature regarding its treatment. Therapy of the elephantiasic variant of PTM remains suboptimal at present. (J Intern Med Taiwan 2004; 15: 268-273)

Key Words: Elephantiasic pretibial myxedema, Graves' disease

Introduction

Pretibial myxedema (PTM), or thyroid dermopathy, occurs in 0.5 to 4.3 percent of patients with Graves' disease (GD). It is almost always associated with Graves' ophthalmopathy (GO) and found in 10 to 12 percent of those patients. PTM is associated with accumulation of glycosaminoglycans. It is frequently present in a symmetrical pattern on the anterior tibiae and dorsae of the feet and occasionally of other sites such as forearms and shoulders. Dermopathy associated with GD is classified into the following four forms: nonpitting edema; plaque; nodular; and elephantiasic. The most common form is diffuse non-pitting edema. In 20 years' experience at the Mayo clinic, 7671 patients with GD yielded 150 with PTM, of whom only one had the elephantiasic form. Elephantiasic pretibial myxedema is a severe manifestation of Graves' disease and refractory to treatment. We report two cases of elephantiasic PTM and review current treatment in the English literature.

Case Reports

Case 1

A 37-year-old man presented to the department of internal medicine of the National Taiwan University Hospital, with chief complaint of long-standing pretibial swelling. In 1998 he had fatigue, hand tremor, and heat intolerance. Thyrotoxicosis was diagnosed, and he was treated with propylthiouracil (PTU) 100 mg b.i.d.. He developed progressive exophthalmos, diplopia, sore eyes with epiphora and pretibial myxedema in 1999. These symptoms gradually became more severe despite treatment with anti-thyroid agents. He discontinued PTU himself and started herbal medication.
in April, 2002. In recent one year, he was treated once with an unknown drugs by intralesional injection. However, his condition deteriorated.

Physical examinations revealed body weight of 78 kg, body height of 172 cm, and blood pressure 140/80 mmHg. Pulse rate was 85 beats per minute and irregular, with normal respiratory rate and body temperature. Conjunctivae were mildly injected and proptosis was present with lid retraction, erythema and edema. Lago sign was positive. Extraocular muscles were intact. The thyroid was grade II diffusely enlarged without tenderness, thrill or bruit. Chest and abdominal examinations were unremarkable.

There were painless erythematous nodular plaques with nonpitting edema over bilateral pretibial areas with extension to ankles, lateral and posterior aspects of lower legs. [Fig. 1]

Biochemistry studies and complete blood counts were within normal range. Thyroid profile revealed high sensitivity thyroid-stimulating hormone (hsTSH) 0.006 mIU/L (normal, 0.1 to 4.5) and free thyroxine (free T4) 50.70 pmol/L (normal, 7.72 to 22.52). An antibody to TSH receptor was positive and thyrotropin binding inhibitory immunoglobulin (TBII) was 64.6% (normal <15%). Assays for both microsomal antibodies and thyroglobulin antibodies were negative. Electrocardiogram showed atrial fibrillation with ventricular rate of 125 per minute. Orbital computerized tomography showed increased volume of bilateral extraocular muscles.

The patient was treated with carbimazole 10 mg t.i.d, propranolol 10 mg b.i.d, and diazepam 5 mg b.i.d. He refused skin biopsy or systemic corticosteroid. He was treated with local intralesional injection of corticosteroid once, but response was poor.

Case 2

A 84-year-old man was diagnosed as GD when he was 54 years old. He was treated with radioactive iodine (131I). Subsequent thyroxine replacement with L-thyroxine sodium 100 µg daily was given for treating radioiodine-induced hypothyroidism. However he took it irregularly. Three years after radioactive iodine therapy, progressive exophthalmos, sore eyes with epiphora, blurred vision and pretibial myxedema developed. These symptoms progressed in the last two years.

Physical exam revealed proptosis with eyelid retraction, conjunctiva edema, and eyelid edema. All extraocular movements were restricted. Both Lago and Grafe's signs were present. The thyroid was not palpable. Both legs and feet significantly enlarged along with malodorous verrucous hyperplasia with multiple firm, hyperpigmented nodules surrounded by deep fissures and folds, particularly around the ankles and dorsae of the feet. [Fig. 2]

Biochemistry studies and complete blood counts were within normal range. Thyroid profile revealed hsTSH 0.16 mIU/L and T4 101 nmol/L (normal, 59.2 to 167). An antibody to TSH receptor was positive and TBII was 52.5%. Both microsomal
antibodies and thyroglobulin antibodies were negative. The patient refused skin biopsy, corticosteroids, or octreotide therapy. He was treated with pentoxifylline 100 mg t.i.d. and thyroxine 50 µg qd without improvement.

Discussion

PTM, or thyroid dermopathy, is a well-known manifestation of GD. It usually occurs in association with diffuse thyroid gland enlargement, thyrotoxicosis, exophthalmos, and thyroid acropathy. PTM occurs in 0.5 to 4.3 percent of patients with GD 1. Lesions typically appear first on the anterior aspect of the lower limbs and may extend to the lateral and dorsal areas of the legs and feet. However, other affected areas have been reported, such as abdomen, upper back, face, pinna, hands, neck, shoulder, forearm, and scalp2. Lesions usually arise at sites of previous injury 1. PTM seems to occur most commonly after therapy for thyrotoxicosis (thyroidectomy or radioactive iodide treatment) as seen in our second patient. But it may precede or occur concomitantly with GD 4-7. Most affected patients have severe GO and high serum titers of thyrotropin receptor antibodies (TSH-R) 8. In a review of 150 consecutive patients diagnosed with PTM over a 20 year period, only one patient lacked ophthalmopathy, whereas 88 percent had significant proptosis and 30 percent required orbital decompression 2. However, minimal ophthalmopathy could not be fully excluded in that patient 2. Both our patients had severe and active ophthalmopathy and needed to be treated with high-dose intravenous corticosteroid. Classical pretibial myxedema presents with bilateral, painless, plaque-like, waxy swelling and induration. The lesions are mostly yellow-brown or reddish, and are non-pitting. PTM is classified into the following four forms: non-pitting edema; plaque; nodular; or elephantiasic 2. Much less common is the elephantiasis nostras variant as seen in our patients. In a review 2, 58 percent of patients had nonpitting edema, 21 percent had plaque form, 20 percent had nodular form and less than 1 percent had elephantiasic form. Characteristics of elephantiasic PTM include massive edema, skin fibrosis and verrucous nodular formation. Histopathologic features consist of normal collagen in the papillary dermis and separation of the collagen bundles by mucin. Mucin staining demonstrates abundant diffuse mucin within the dermal fenestrations as large amounts of glycosaminoglycans diffusely disperse in the reticular part of the dermis 9. This increased deposition apparently results from increased fibroblast stimulation10-11, but the cause of this stimulation is not yet clear.

Although controlling the functional status of thyroid is important for patient's overall health, it has no effect on associated dermopathy 12. Mild PTM has been seen to resolve spontaneously after an average of 3.5 years 13. Usually, the goal of treatment for dermopathy is symptomatic. Various treatment modalities for PTM have been
employed, including topical, intra-lesional, and systemic steroids; compression therapy with pneumatic pump devices; plasmapheresis alone or in combination with immunosuppressive agents (such as corticosteroid or azathioprine); high-dose intravenous immunoglobulin (IVIG); somatostatin analogue (octreotide); pentoxifylline; and surgical therapy 1-3,7,14-16.

Topical corticosteroids are more likely to be used than systemic therapy 2. Side effects include atrophy, telangiectasis and ecchymosis. Combination with compression is useful, especially when lymphatic involvement is strongly suspected. Intra-lesional corticosteroid is less favorable, because of their tendency to cause lumpy-appearing skin and the frequent recurrence of disease after treatment 1. Systemic immunomodulations, such as systemic corticosteroids and cytotoxic therapy 3, is rarely used unless concomitant therapy for the associated ophthalmopathy. Both plasmapheresis and IVIG are not popular options due to the availability and costs. The extraocular muscles, fat and fibroblasts are immunoreactive to insulin-like growth hormone-1 (IGF-1). Octreotide is a long-acting somatostatin analogue 17, which suppresses IGF-1 activity either indirectly, by reducing plasma concentrations of growth hormone, or directly by blocking the effect of IGF-1 on peripheral tissue 18. Theses effects inhibit glycosaminoglycans synthesis by fibroblasts in the orbit and skin. Hence, it is effective in the treatment of GO and PTM 19-20. Pentoxifylline, an analogue of the methylxanthine theobrome, inhibits the proliferation and certain biosynthetic activities of fibroblasts derived from normal human skin and from skin of patients with some fibrotic disorders. It causes a dose-dependent inhibition of serum-driven fibroblast proliferation in vitro 15. Although surgical therapy alone is often met with recurrence and may even aggravate the dermopathy, there is a case report of successful surgical outcome when combined with somatostatin analogue to suppress IGF-1 activity 7.

Although there are many treatment modalities for PTM, the severe elephantiasic variant is typically progressive and refractory to treatment 3. Susser et al 12. reported a patient with elephantiasic PTM being treated successfully with complete decongestive physiotherapy. It is a combination of manual lymphatic drainage, banding, exercise and scrupulous skin care, and is useful for elephantiasic PTM as well as refractory lymphedema. Although both our patients had severe ophthalmopathy and elephantiasic PTM, they were not treated with systemic corticosteroid or octreotide. Instead, they were treated with intra-lesional injection of corticosteroid and pentoxifylline, respectively. But lower efficacy was noted. In conclusion, we reported two rare cases of elephantiasic pretibial myxedema. Pathogenesis of the disorder is unclear and there is no effective treatment available at present. Management for elephantiasic PTM remains a therapeutic challenge.
References
11. Stadlmayr W, Spitzweg C, Bichlmair AM, Heufelder AE. TSH receptor transcripts and TSH receptor-like immunoreactivity in orbital and pretibial fibroblasts of patients with Graves' ophthalmopathy and pretibial myxedema. Thyroid 1997; 7: 3-12.
15. Chang CC, Chang TC, Kao SC, Kuo YF, Chien LF. Pentoxifylline inhibits the proliferation and glycosaminoglycan synthesis of cultured fibroblasts derived from patients with Graves' ophthalmopathy and pretibial myxoedema. Acta Endocrinol
(Copenh) 1993; 129: 322-7.

Fig.1 Case 1  — Pretibial myxedema, elephantiasic type

Fig.2 Case 2  — Pretibial myxedema, elephantiasic type

象皮樣脛前黏液水腫——葛瑞夫茲氏病的一種罕見表現：兩個病例報告
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摘要
脛前黏液水腫是葛瑞夫茲氏病的一種乾期且罕見的表現。通常於甲狀腺功能亢進及眼病變診斷後出現。有數種型態的脛前黏液水腫，而其中最少見的象皮樣脛前黏液水腫，發生率少於1%。我們報告兩個象皮樣脛前黏液水腫的病人及回顧文獻上的治療方式。

第一個病人—三十七歲的男性，在西元1998年時被診斷為甲狀腺功能亢進，之後接受抗甲狀腺藥物治療。一年後，開始出現漸進性的凸眼、複視及脛前黏液水腫，這些症狀愈來愈嚴重。兩側下肢有明顯又厚又紅，呈結節塊狀的皮膚病變。病人拒絕接受皮膚切片及全身性類固醇治療，最後接受局部類固醇注射。

第二個病人—八十四歲的男性，在五十四歲時被診斷為葛瑞夫茲氏病。接受放射性原子碘(131I)治療；之後，因甲狀腺功能低下而接受甲狀腺素治療。三年後逐漸出現凸眼、眼睛酸、流眼淚及脛前黏液水腫。兩側下肢明顯腫大，有很多惡臭、疣狀的增生及由深的裂縫及皺摺圍繞著的許多硬性、過度色素沉著的結節，尤其是腳踝及足背。病人拒絕接受皮膚切片、全身性類固醇及體制素治療。病人
接受口服 pentoxiphylline。
有許多方法被用來治療脛前黏液水腫，但是象皮樣脛前黏液水腫的治療非常困難。目前仍沒有一個有效的治療方法。