Nodular Pretibial Myxedema with Graves' Disease: A Case Report

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ABSTRACT:

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Pretibial myxedema is one of the classic clinical triad of Graves' disease, along with diffuse thyroid gland enlargement and exophthalmos. It is characterized by cutaneous induration due to mucin deposition and typically occurred on extensor surfaces of the legs. The pathogenesis of localized dermopathy is still not fully understood, but it is most likely due to dermal fibroblasts stimulation caused by anti-thyroid stimulating hormone (TSH) antibodies, resulting in excessive production of glycosaminoglcans and hyaluronic acid. Other trigger factors include trauma, smoking, and obesity. There are five distinct clinical variants for pretibial myxedema including the typical diffuse and non-pitting edema form, plaques form, nodular form, mixture form, and the most severe elephantiasis form. Although cutaneous lesions can persist even with effective treatment for thyroid, supportive and symptomatic treatment may be considered. In this case report, we report a case of bilateral pretibial myxedema with an uncommon nodular variant with improvement after intralesional corticosteroids was administered.

Key words: Pretibial myxedema, Graves' disease

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Pretibial myxedema is an infiltrative dermopathy due to mucin deposition that is presented as part of the classic clinical triad of Graves' disease along with a diffuse enlargement of the thyroid and infiltrative exophthalmos[1]. About 50% of the patients develop diffuse and non-pitting edema lesions on the shins, while the plaques, nodular, and elephantiasis cutaneous lesion mimicking lymphedema are less commonly observed[2].

Case presentation

A 57-year-old female presented with a six-month history of asymptomatic infiltrative and enlarging cutaneous nodules involving the pretibial region of both lower legs. The nodules have slowly and progressively enlarged over time. Her past medical history included thyrotoxicosis with loss to follow-up for thirty years. Physical examination revealed exophthalmos and diffuse thyroid enlargement with dermatologic examination revealing bilateral, well circumscribed, erythematous indurated nodules and plaques on both shins (Figure 1A). There was no hair or nail involvement.

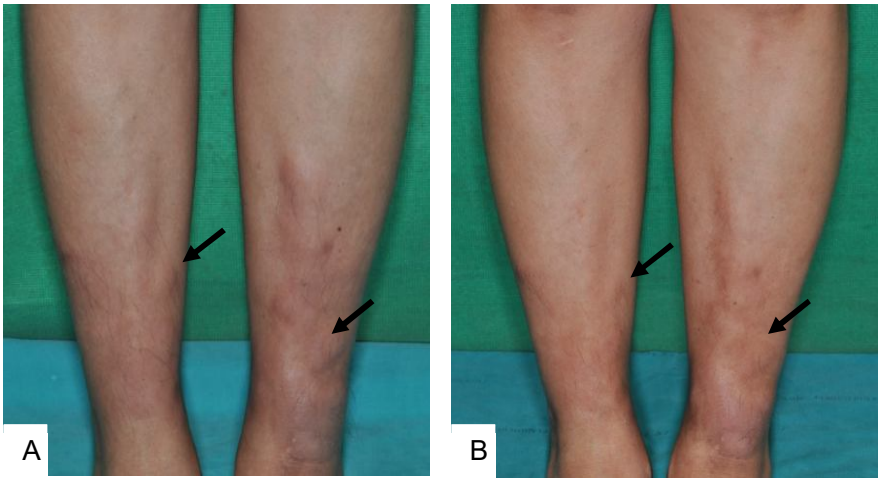

Figure 1 A) Bilateral, non-tender, erythematous indurated nodules on both shins. B) Clinical improvement seen after two doses of monthly intralesional corticosteroids injection.

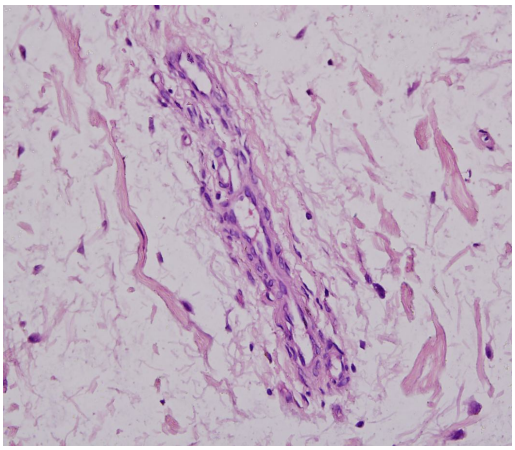

Figure 2 Skin biopsy specimen from left lower leg demonstrated widening of intercollagenous space with mucin deposition in the upper dermis with mild lymphocytic infiltration. No deep dermal inflammation was evident. (H&E; original magnification: A. X4, B. X40)

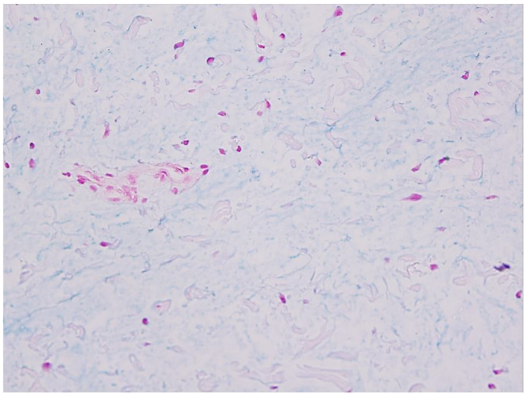

Figure 3 Alcian blue staining showed marked mucin material deposition in the upper dermis.

At the time of diagnosis, thyroid function test was performed and demonstrated a low level of thyroid stimulating hormone, high free thyroxine 3 and 4. Anti-thyroglobulin antibodies and anti-thyroid peroxidase antibodies were high. The patient's clinical history, physical examination and blood test results were compatible with Graves' disease. Histopathology demonstrated slightly epidermal acanthosis, hyperkeratosis, but neither spongiosis nor interface change was seen. There was intercollagenous space widening with mucin deposition in the upper dermis with mild lymphocytic infiltration. No deep dermal inflammation was evident (Figure 2). Alcian blue staining showed marked mucin material deposition in the upper dermis (Figure 3). In term of treatment, for Graves' disease, specific treatment of methimazole (20 mg/day) was prescribed. Cutaneous lesions were treated with intralesional corticosteroids (10 mg/ml) with clinical improvement seen after two doses of monthly intralesional corticosteroids injection (Figure 1B).

Discussion

Pretibial myxedema also known as localized myxedema is an uncommon infiltrative dermopathy associated with autoimmune thyroiditis, particularly in Graves' disease, but only up to 4.3% of patients with Graves' disease developed pretibial myxedema[1]. Such cutaneous manifestation can infrequently occur in the setting of hypothyroidism and euthyroidism. The

disease is characterized by localized skin thickening, most commonly located in the pretibial region, hence it is often referred to as pretibial myxedema[2]. Such lesion usually presents within 1 to 2 years after the diagnosis of Graves' disease and is almost always associated with severe Graves' ophthalmopathy[1]. Though, about 12% of patients, pretibial myxedema develops 4-12 years after the disease diagnosis, our patient is the first case report of pretibial myxedema presenting 30 years after the disease diagnosis[3]. The delay onset of the lesion may be due to the patient lost to follow-up and treatment discontinuation. Furthermore, Salvi et al. has suggested that dermopathy is much more prevalent at the subclinical level by using ultrasonography, thus increased glycosaminoglycans (GAGs) deposition may occur without clinical manifestations with the propensity to develop localized myxedema[4].

The exact pathophysiology of pretibial myxedema is still uncertain. Although, immunologically, it is probably due to dermal fibroblasts stimulation caused by anti-thyroid stimulating hormone triggering the release of cytokines from T-lymphocytes resulting in excessive production of GAGs in reticular dermis[5]. Khalilzadeh et al. study reveals that cytotoxic T-lymphocyte associated protein 4 (CTLA-4) has an inhibitory effect on T-cell functions and polymorphism in this gene has been associated with the incidence of pretibial myxedema in Graves' disease patients[6]. Mechanical contribution to the disease pathogenesis has been recognized as lesion usually develops in repetitive trauma sites[7]. Other known triggers are smoking and obesity yet the exact mechanism to this association remains unknown[2].

Thyroid dermopathy is an indicative of a severe autoimmune process[3,8]. The most prevalent presentation of thyroid dermopathy is diffuse, erythematous to flesh-colored skin, non-pitting edema resembling peau d'orange appearance and texture (44%) followed by nodular type (21%), plaque type (15%), mixture type (8%), and the most severe elephantiasic form (7%) which is observed in advanced cases. Although, the nodular type is less frequently presented, this variant can disappear spontaneously as compared to other variants which can worsen intermittently and may require more intensive therapy. Furthermore, Lan et al. study has demonstrated that the nodular variant has a lower level of thyroid-stimulating hormone receptor antibody comparing to other variants, and such antibody level correlates with the fluctuation of autoimmune activity and also clinical remission and relapse of lesions[3]. Typical location involves pretibial region or the feet with symmetrical distribution. Localized manifestations on other areas were reported including face, shoulders, upper extremities,

lower abdomen, burn or surgical scar, and previous vaccination site are extremely rare[7,9-12].

Clinically, thyroid dermopathy is often asymptomatic with minimal morbidity and only of cosmetic concern[2,5]. Itching or tenderness is rare. If present, hypertrichosis, hyperpigmentation and hyperhidrosis are limited to the pretibial myxedematous skin. Occasionally, functional impairment may occur such as difficulty wearing shoes, and peroneal nerve entrapment resulting in foot drop or faulty dorsiflexion[13].

Other associated manifestations of Graves' disease include thyroid dysfunction, Graves' ophthalmopathy, and thyroid acropachy[1,2,5]. All patients with pretibial myxedema have laboratory evidence of thyroid autoimmunity with 90% of cases having history of hyperthyroidism and the remaining are either in hypothyroid or euthyroid state[2]. The ophthalmic signs of unilateral or bilateral eyelid retraction and exophthalmos usually precede dermopathy and are almost always present with pretibial myxedema[14]. Though, thyroid acropachy, a triad which consists of digital clubbing, soft tissue swelling of the hands and feet, and periosteal new bone formation, is the least common finding of Graves' disease, along with dermopathy it is a marker of a severe autoimmune process.

In patients with Graves' disease, system signs and symptoms of hypertension are variably presented. Common presentations include heat intolerance, sweating, fatigue, weight loss, palpitation, hyper defecation, and tremors[15]. Other symptoms include insomnia, anxiety, nervousness, hyperkinesia, dyspnea, pruritus, polyuria, oligomenorrhea or amenorrhea in women, and loss of libido in men. Clinical findings and complications include tachycardia, atrial fibrillation, high-output cardiac failure, fine tremors, warm and moist skin, muscle weakness and altered mental status. Untreated hyperthyroidism can lead to thyroid storm, a rare but severe and potentially life-threatening complication, characterized by high fever, confusion, and dehydration.

The diagnosis of pretibial myxedema is based on the clinical history and physical examination, with the aid of histology to confirm the diagnosis. The characteristic findings include dermal thickening due to extensive mucin deposition in the upper dermis. A perivascular and periadnexal lymphocytic infiltration with mast cells and large stellate fibroblasts are observed. In addition, hyperkeratosis, papillomatosis and epidermal hyperplasia are often demonstrated[16]. Differential diagnosis includes lichen myxedematosus (localized variant), erythema nodosum, lipodermatosclerosis, and subcutaneous sarcoidosis.

Thyroid dermopathy can persist even with effective treatment for thyroid disease. Still, it has a potential of spontaneous resolution after an

average disease course of 3.5 years[17]. In terms of dermatology perspective, since the lesions are often asymptomatic, therapeutic management is appropriate for severe cases and patients with cosmetic concern. The first-line treatment for pretibial myxedema is corticosteroids, either under occlusive dressing or intralesional injection. Supportive treatment with compressive stockings and gradient pneumatic compression are beneficial for lymphedema by enhancing function, avoiding tissue breakdown, and limiting disfigurement extension. In severe elephantiasis form, treatment options such as intravenous immunoglobulin, rituximab, plasmapheresis, octreotide, and surgical intervention may be considered. Avoiding risk factors of smoking and obesity is strongly recommended.

In our patient, the clinical history, physical examination, and histopathology were compatible with nodular pretibial myxedema with Graves' disease. In term of treatment, oral methimazole (20 mg/day) were prescribed for Graves' disease, while cutaneous lesions were treated with intralesional corticosteroids (10 mg/ml). The overall clinical improvement was seen after two doses of monthly intralesional corticosteroids injection.

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