Case Report

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Elephantiasic Pretibial Myxedema: A Rare Manifestation in Graves' Disease

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Abtract:

Elephantiasic pretibial myxedema is an extremely rare condition, affecting patients with thyroid disease. The clinical manifestation is difficult to diagnosis, and the treatment is challenging. Herein, the authors report on a case of a patient with Graves' disease, who had a long-standing enlargement of bilateral legs, and histopathologic studies confirmed the diagnosis as; pretibial myxedema. The patient was treated with an antithyroid drug, iodine-131 (^{131}I) irradiation, a potent topical corticosteroid, with occlusion, and compression therapy, however, the patient's skin condition remained unchanged. This report aims to demonstrate a rare form of pretibial myxedema, to review the clinical presentations, differential diagnosis as well as therapeutic options.

Keywords: dermatopathology, elephantiasis, Graves' disease, pretibial myxedema, thyroid dermopathy

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Introduction

Pretibial myxedema is an infrequent manifestation of Graves' disease, occurring in up to 4.3% of patients suffering from this disease, and 15.0% of patients with Graves' ophthalmopathy.[1] It may exist in various clinical forms, with the most common form of pretibial myxedema being; the non-pitting edema type, composing of one-half of cases, and the nodular and plaque-like forms occuring in approximately 20.0% of cases. The polypoid and elephantiasic types are rare, presenting in less than 3.0% of cases.[1,2] We reported on the case of elephantiasic pretibial myxedema, with a fascinating clinical presentation, aiming to compare two histopathologic studies between; non-pitting edema and polypoid skin lesions, and then review the treatment modalities.

Case report

A 48-year-old man presented with progressive bilateral, leg swelling for three years. He reported the right leg had developed before the other site. Four years earlier, he had been diagnosed with thyrotoxicosis, which was treated with methimazole and propranolol, at an outside hospital. Upon his first visit, the physical examination showed exophthalmos of both eyes, diffused thyroid gland enlargement (greater than 80 g), and a thyroid bruit. Skin examination revealed well-demarcated indurated plaques, with peau d'orange and cobblestone-like appearances on both legs (Figure 1).

The patient's clinical characteristics presented as peau d'orange in appearance, which was a specific sign of infiltrative dermatoses. The differential diagnosis was elephantiasis or lymphatic filariasis, caused commonly by *Wuchereria bancrofti* and *Brugia malayi*, non-filarial elephantiasis, or podoconiosis, chronic lymphedema as well as other infiltrative diseases, including; elephantiasic pretibial myxedema.



Figure 1 Clinical pictures of elephantiasic pretibial myxedema

Thyroid function testing showed thyroid-stimulating hormone (TSH) 0.008 (0.25-4.00) mIU/L, free thyroxine (Free-T4) >6.99 (0.70-1.75) ng/dL, and free triiodothyronine (Free-T3) >22.8 (2.00-4.40) pg/mL. Thyroid auto antibody tests revealed anti-thyroid peroxidase antibodies (Anti-TPO) >600 (0-34) IU/ml, and thyroid stimulating hormone receptor antibodies (TRAb) 37.91 (0-1.75). Two incisional skin biopsies were performed on both legs. The first skin biopsy was from the left shin, with clinical non-pitting edema, and revealed a classic diagnosis of pretibial myxedema; showing epidermal hyperplasia, with separation collagen bundles in dermis, and also demonstrating a positive stain of mucin (Figure 2A-C). The other one, from polypoid lesions on the right lower leg, representing advanced skin lesions, showed pseudocarcinomatosis of the epidermis, increased dermal collagen, and a negative stain of mucin (Figure 2D-F).

The patient was treated with antithyroid drugs, and three separate sessions of iodine-131 (^{131}I) irradiation. In pretibial myxedema management, he has managed with topical class I corticosteroid, with occlusion and compression therapy. The patient was followed up for two years

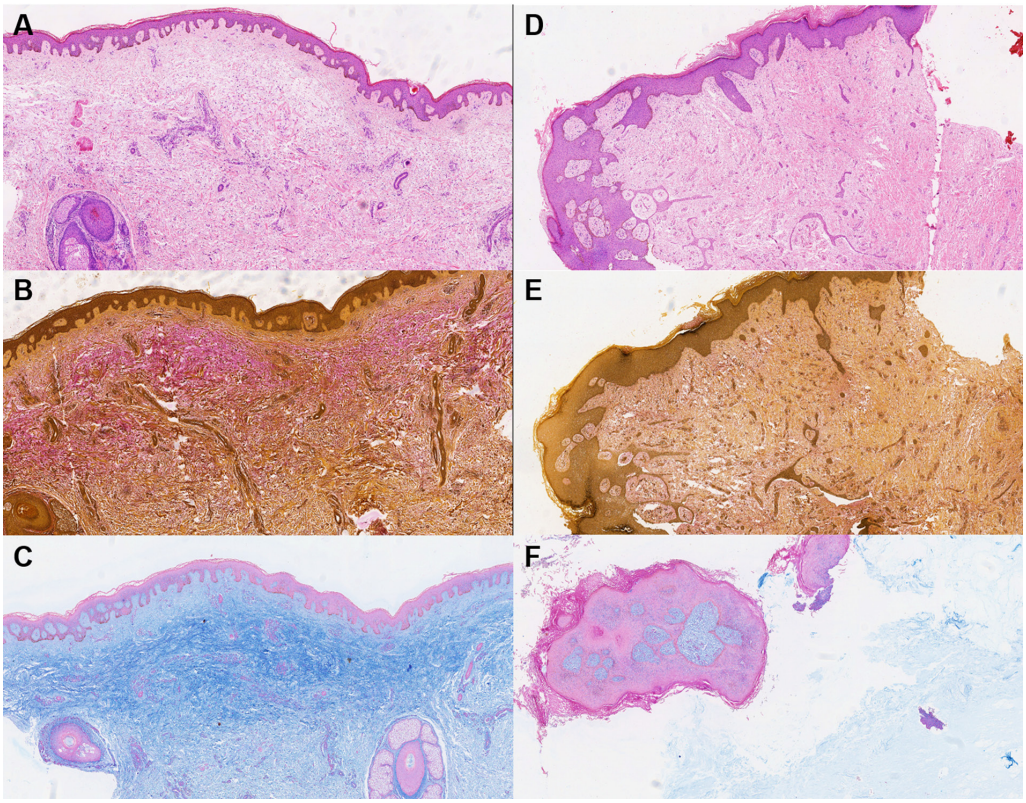


Figure 2 Dermatopathological studies of elephantiasic pretibial myxedema. A–C, A skin biopsy from a non–pitting edema type on the left shin, showing epidermal acanthosis; dermis with separation of the collagen fibers, and positive staining of mucin. D–F. A skin biopsy from a polypoid form, on the right shin, showing pseudoepitheliomatous of the epidermis, with increased dermal fibrosis, and negative staining of mucin. (magnification 40x; A and D, Hematoxylin and Eosin Stain; B and E, Hematoxylin–Lac–Curcuma Polychrome Stain; C and F, Alchian Blue pH 2.5 Stain.)

with good compliance of treatment, which resulted in a significant decrease in further thyroid function tests. The patient reported his left shin, which was the clinical non–pitting edema type, had more improvement than the right one, however, his overall skin conditions still remained.

Discussion

Pretibial myxedema, or thyroid dermopathy is commonly localization on the lateral aspect of the pretibial area. The lesions are non–pitting, firm, raised flesh color, or yellowish brown, and hyperkeratosis may change the color with time. The indurated lesions are similar to an orange peel (peau d'orange). The most advanced form is elephantiasis, which is associated with: lymphatic obstruction, lymphedema, nodularity and polyploid, or fungating lesions.[3]

The precise pathogenesis of pretibial myxedema remains unknown. However, there are many theories which explain the pathogenesis, with the most plausible theory being that a target cell in the skin, presumably the fibroblast, is being stimulated to produce abnormally high amounts of glycosaminoglycans, by autoantibodies directed against a thyroid antigen.[3,4]

Table 1 Comparision of dermatopathology between the early, and advanced stages of pretibial myxedema

Histology	Early pretibial myxedema	Advanced pretibial myxedema
Epidermis	Regular acanthosis	Papillomatosis, irregular acanthosis, pseudoepithiliomatosis
	Increase basal hyperpigmentation	Hyperkeratosis
Dermis	Abundant of glycosaminoglycans	Less amount of glycosaminoglycan
	Separation of collagen bundles	Increase fibrosis
	Increase fibroblasts	Increase fibroblasts
	Increase mast cells	
	Minimal lymphocytes infiltrate	

The classic histopathology of the skin biopsy specimens shows an abundance of glycosaminoglycans, the presence of few lymphocytes, and a moderate increase in mast cells. Alcian blue and the Periodic Acid–Schiff stains demonstrate mucinous material between collagen fibers. In advanced cases, as in this case report, hyperkeratosis, acanthosis, papillomatosis, and pseudo-epitheliomatosis can be observed. The possible explanation for this might result from long-standing stimulation of auto antibodies, which could promote the dermal fibroblasts, and these affects might result from stimulating epidermal proliferation. However, an in-depth study in both; cell-cell and cell-matrix interaction should be conducted for any patients with pretibial myxedema. We proposed a comparison between the early and advanced stages of pretibial myxedema, based on the histopathology that could be used by any dermatologist or pathologist (Table 1).[3-5]

Therapy is less efficient, especially in patients having suffered with this disease for a long duration, and when the extension of the said disease has increased. Treatment in advanced cases, including the elephantiasic form, is difficult because of no relationship with thyrotoxicosis coupled with temporary improvement, or relapse after receiving the intervention. Based on this case report, the histology of the lesions, with advancement, have more severity of fibrosis and epidermal growth. These results could support the difficulties of treatment. Previous case reports, and therapeutic options of elephantiasic pretibial myxedema are summarized in Table 2.[4-10]

Table 2 The literature, reported results of treatment for: Elephantiasic pretibial myxedema

Unsuccessful	Successful
Topical and intralesional corticosteroid	Decongestive physiotherapy
PUVA	^{131}I ingestion
Pentoxifylline	Low-dose prednisolone
Acitretin	Low-dose IVIg
Octreotide	Rituximab with plasmapheresis
Hyaluronidase	
Cyclophosphamide	
Thalidomide	
Infliximab	
High-dose IVIg	
Surgery	

PUVA=psorialen and ultraviolet A, IVIg=intravenous immunoglobulin

Conclusion

The elephantiasic form is a very rare manifestation of pretibial myxedema. Dermatopathological studies vary from the clinical patterns. In advanced clinical lesions, which experience more fibrosis and aggressive epidermal proliferation, are very challenging to treat.

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