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Case Report

A Case of Pretibial Myxedema Associated with Hypothyroidism and Thyroid-stimulating Hormone Receptor Antibodies

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Abstract

Pretibial myxedema (PTM) is an infiltrative dermopathy seen in Graves' disease. It is also infrequently associated with hypothyroidism. Here, we describe a rare case of PTM with hypothyroidism in which thyroid-stimulating hormone receptor antibodies were found. An 82-year-old female presented with a 1-year history of a large pruritic plaque which was present over both her legs and feet. Histopathology of a skin biopsy showed markedly increased dermal mucin. These changes were suggestive of PTM. This case provides evidence that an autoimmune mechanism could play a central pathogenetic role in such cutaneous manifestations.

Keywords: Hypothyroidism, pretibial myxedema, thyroid-stimulating hormone receptor antibodies

Introduction

Pretibial myxedema (PTM) or thyroid dermopathy is an infiltrative lesion of the dermis and subcutaneous tissue associated with autoimmune thyroid diseases. It is seen in Graves' disease. It is also infrequently associated with hypothyroidism.[1] The development of PTM is not related to thyroid function. Patients may be hyperthyroid, euthyroid, or hypothyroid at the time of presentation.[2] Lesions are typically localized within the skin of the pretibial region as nonpitting edema, followed by nodular and plaque forms.[3] They usually appear over a period of several months and then stabilize or, in some cases, regress spontaneously. In rare patients, lesions may progress to involve legs, feet, or hands completely, resulting in a severe form reminiscent of elephantiasis with multiple polypoid and fungating nodules.[4]

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Although the pathogenesis of PTM is not known, it is thought that both mechanical and immunological factors may contribute to the pathophysiology of this disorder.[5] The presence of antibodies to thyroid-stimulating hormone (TSH) receptor (TSHR) is the hallmark of Graves' disease. Antibodies to TSHR mimic the action of TSH, resulting in TSHR stimulation and hyperthyroidism. These antibodies have been associated with extrathyroidal manifestations of Graves' disease.[6] They are also considered for the causative agents of PTM.[7]

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Here, we present an elderly woman with long-standing hypothyroidism treated for over 30 years with levothyroxine, who developed PTM associated with increased titers of TSHR antibodies (TRAbs).

Case Report

The patient, an 82-year-old female, presented with a 1-year history of large, irregular nodular swollen lesions present over both her legs and feet. She suffered a hip fracture a year before presentation without receiving any treatment. As a result, her movement was severely impaired. Her limited walking movement resulted in gradual swelling of the legs. Raised, plaque-like lesions appeared over the anterior aspects of the tibia bilaterally, extending to involve both feet but sparing toes. The patient stated that she had been treated with levothyroxine (100 μg/day) for over 30 years. She had neither taken a thyroid function test nor changed the dose in the past year. She was a nonsmoker. She was taking amlodipine (5 mg) for high blood pressure.

On examination, the patient looked well. She was clinically euthyroid. There were no signs of ophthalmopathy. Her thyroid gland was not palpable. Although she had no swelling in her face [Figure 1a], prominent lesions of PTM were noted on shins and dorsum of her feet [Figure 1b]. Her bilateral pretibial polypoid nodular lesions were nonpitting, hyperpigmented, firm, confluent, and asymmetric. There were plaques between and over these nodules with an orange peel appearance. Her pulse was 81 beats/min with regular rhythm. Her blood pressure was 130/84 mmHg.

Thyroid function test revealed hypothyroidism, with levels of TSH of 20.08 μIU/mL (reference range: 0.35–5.50 μIU/mL), free triiodothyronine (T3) of 0.55 ng/mL (reference range: 0.60–1.81 ng/mL), and free thyroxine (T4) of 0.86 ng/dL (reference range: 0.89–1.76 ng/dL). She had a thyroglobulin antibody titer of >4000 IU/mL (reference range: 0–115 IU/mL), thyroid peroxidase antibody level of 183 IU/mL (reference range: 0–34 IU/ml), TSH-binding inhibitory immunoglobulin (TBII) level of >40 IU/L (reference range: 0–1.75 IU/L), and positive thyroid-stimulating antibody (TSAb) of 547.7%. Blood examination did not reveal the presence of the filarial parasite. Furthermore, filarial antigen and antibody tests were negative. Other hematological and biochemical investigations, including serum creatinine, lipid profile, and plasma glucose, were within normal limits. There was no heart failure, pulmonary hypertension, renal disease, or liver disease.

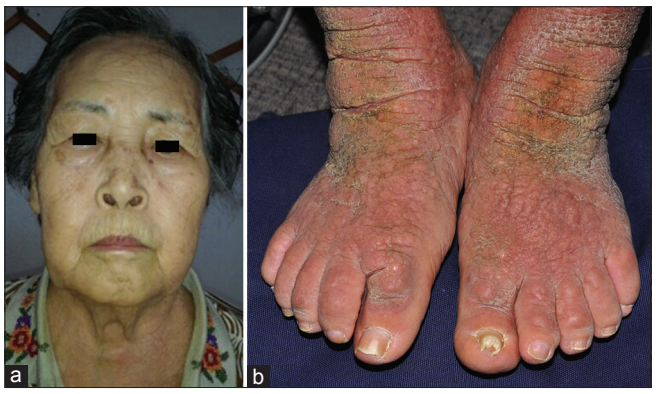

Figure 1: (a) There were no signs of ophthalmopathy and her thyroid gland was not palpable. (b) Prominent lesions of pretibial myxedema were noted on the dorsum of her feet

Lymphatic drainage of the lower extremity was assessed using radionuclide lymphoscintigraphy. Nearly invisible bilateral lymphatics were observed. There was one lymph node on the left inguinal area. There was no inguinal lymph node on the right side. Deep vein thrombosis was excluded through evaluation by compression ultrasonography with Doppler. Histopathology of skin biopsy samples from the right dorsum of the foot and left shin showed markedly increased connective tissue mucin deposition in the reticular dermis, consistent with findings of PTM [Figure 2]. Ultrasound examination showed small-to-normal size of thyroid and a diffusely heterogeneous texture of the thyroid parenchyma intermingled with areas of lower echogenicity. Amplitude color Doppler demonstrated increased vascularization of the thyroid gland. These findings of ultrasonography were consistent with the diagnosis of chronic autoimmune thyroiditis. A fine-needle aspiration biopsy of the thyroid was not performed.

Treatment was started with 125 μg/day of levothyroxine and steroid ointment with a tight occlusive bandage for pretibial swelling. After 3 months of therapy, euthyroidism was restored with a modest decrease in nodular PTM.

Discussion

We described a case where a patient with long-standing hypothyroidism developed elephantiasis PTM associated with increased titers of TRAbs. PTM (also called localized myxedema, thyroid dermopathy, or infiltrative dermopathy) is an infrequent manifestation of Graves' disease.[8] Very rarely, it can occur in patients with no past or present thyroid dysfunction and in patients with chronic autoimmune thyroiditis such as Hashimoto's thyroiditis.[9-11]

Hashimoto's thyroiditis usually has clinical manifestations similar to those of hypothyroidism. It has an autoimmune

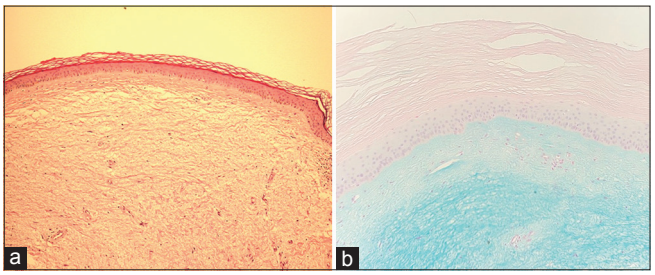

Figure 2: (a) Histopathological examination shows normal epidermis, with collagen fibers in reticular dermis mildly separated by deposits of mucin and mild perivascular lymphocyte infiltrate (H and E, ×100). (b) Alcian blue stain reveals mucin deposition in the dermis

etiology similar to that of Graves' disease, a common cause of hyperthyroidism. Due to this shared etiology, similar dermatologic and ophthalmologic findings such as conjunctivitis, diplopia, and blurred vision along with a cutaneous myxedema are seen. All these patients have laboratory evidence of autoimmune thyroid disease.[4] In the current case, she might have Hashimoto's thyroiditis initially. The transition from thyroid stimulation-blocking antibody to TSAb might have occurred after long-standing levothyroxine therapy, and then, PTM developed. Unfortunately, she was not exactly aware of her medical history relevant to the initial diagnosis of hypothyroidism. We have no data about antibody testing results at the initial diagnosis.

There are reports that TSHR-blocking antibodies play a pathogenic role in patients with primary myxedema.[12] All patients with active thyroid dermopathy have positive levels of thyroid-stimulating immunoglobulin and laboratory evidence of thyroid autoimmunity, including antibodies against the TSHR (TRAb).[13,14] TRAb has been measured by different assay methods with various names. TBII and TSAb have been measured as TRAb to diagnose Graves' disease.[15] TBII is measured as a receptor assay, while TSAb is measured as a stimulator assay using porcine thyroid cells.[16] TSAb indicates the stimulation activity of TRAb.

PTM results from the accumulation of glycosaminoglycans (GAG) in the dermis and the stimulation of cytokines.[5] Its pathogenesis is similar to that of thyroid-associated ophthalmopathy.[17] Cytokines arise from lymphocytic infiltration, which is best seen in early lesions. Resulting characteristic pathologic changes include mucinous edema and fragmentation of dermal collagen fibers with subsequent extension into deeper tissue.[8] TSHR present in fibroblasts is the antigen involved in the initiation of humoral and cellular autoimmunity. TRAbs and/or antigen-specific T cells initiate inflammatory response which stimulates the production of GAG.[18] Cytokines such as tumor necrosis factor alpha and gamma interferon induce GAG release from fibroblasts. These cytokines might be secreted by Th1-type T cells activated by TSHR antigen.

Clinically, The elephantiasic form of PTM resembles lymphedema. It is thought that mucin deposition in the dermis causes compression of the dermal lymphatics, which results in dermal edema and the clinical features of lymphedema.[19] The elephantiasic form of PTM is a rare and extreme form of thyroid dermopathy. It constitutes less than 1% of PTM.[3] The development of PTM is not related to thyroid function.[2] Characteristics of elephantiasic PTM include massive edema, skin fibrosis, and verrucous nodular formation. Its histopathologic features consist of normal collagen in the papillary dermis and separation of collagen bundles by mucin. Mucin staining demonstrates abundant diffuse mucin within dermal fenestrations as large amounts of GAG diffusely disperse in the reticular part of the dermis.[4]

PTM is not restricted to the pretibial area. It may spread to the ankle and dorsum of the foot. It may be present on the elbows, knees, upper back, and neck. The exact cause of localization in the pretibial area is not known. However, mechanical factors, trauma, and dependent position are likely to be contributing factors.[7] Among them, trauma to the pretibial region may be the most common precipitating factor initiating an inflammatory response.[20] In this case, the patient had positive TRAbs. She suffered a hip fracture and developed PTM after the trauma. An etiologic role for TRAbs and TSHR-specific T cells could also explain occasional worsening of dermopathy after trauma. Most cases of thyroid dermopathy do not require any therapy. Lesions usually resolve spontaneously.[5] In more severe cases, therapies such as potent topical steroids, intralesional steroids, gamma globulin, pentoxifylline, surgery, and radiotherapy are indicated. When significant edema and elephantiasis are present, local compressive therapy may have added benefit. In this case, the patient was treated with an increased dose of levothyroxine and steroid ointment with a tight occlusive bandage for pretibial swelling. Current modalities of therapy for thyroid dermopathy are at best palliative. Better and safer means of immunomodulation are needed.

Conclusion

This case presented as a rare entity of PTM and hypothyroidism with positive TRAbs. Although the etiology of PTM is not known, PTM with the presence of TRAbs suggests that an autoimmune mechanism could play a central pathogenetic role in such cutaneous manifestations.

Acknowledgment

We would like to thank the patient described herein for agreeing to participate in this Case Report and for her contribution to medical literature on this subject.

Informed consent

The patient has provided her consent for the contents of this report to be published.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initial will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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