Treatment of Elephantiasic Pretibial Myxedema With Rituximab Therapy

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PRACTICE **POINTS**

- Pretibial myxedema (PTM) is bilateral, nonpitting, scaly thickening and induration of the skin that most commonly occurs on the anterior aspects of the legs and feet.
- Although many therapeutic modalities have been described for the management of the elephantiasis variant of PTM, few treatments have shown notable efficacy.
- Rituximab may be an effective therapy to consider in the treatment of elephantiasic PTM.

To the Editor:

Pretibial myxedema (PTM) is bilateral, nonpitting, scaly thickening and induration of the skin that most commonly occurs on the anterior aspects of the legs and feet. Pretibial myxedema occurs in approximately 0.5% to 4.3% of patients with hyperthyroidism.[1] Thyroid dermopathy often is thought of as the classic nonpitting PTM with skin induration and color change. However, rarer forms of PTM, including plaque, nodular, and elephantiasic, also are important to note.[2]

Elephantiasic PTM is extremely rare, occurring in less than 1% of patients with PTM.[2] Elephantiasic PTM is characterized by the persistent swelling of 1 or both legs; thickening of the skin overlying the dorsum of the feet, ankles, and toes; and verrucous irregular plaques that often are fleshy and flattened. The clinical differential diagnosis of elephantiasic PTM includes elephantiasis nostra verrucosa, a late-stage complication of chronic lymphedema that can be related to a variety of infectious or noninfectious obstructive processes. Few effective therapeutic modalities exist in the treatment of elephantiasic PTM. We present a case of elephantiasic PTM.

A 59-year-old man presented to dermatology with leonine facies with pronounced glabellar creases and indentations of the earlobes. He had diffuse woody induration, hyperpigmentation, and nonpitting edema of the lower extremities as well as several flesh-colored exophytic nodules scattered throughout the anterior shins and dorsal feet (Figure 1). On the left posterior calf, there was a large, 3-cm, exophytic, firm, flesh-colored nodule. Examination of the hands revealed mild hyperpigmentation of the distal digits, clubbing of the distal phalanges, and cheiroarthropathy.

The patient was diagnosed with Graves disease after experiencing the classic symptoms of hyperthyroidism, including heat intolerance, tremor, palpitations, and anxiety. He received thyroid ablation and subsequently was supplemented with levothyroxine 75 mg daily. Twelve years later, he was diagnosed with Graves ophthalmopathy with ocular proptosis requiring multiple courses of retro-orbital irradiation and surgical procedures for decompression. Approximately 1 year later, he noted increased swelling, firmness, and darkening of the pretibial surfaces. Initially, he was referred to vascular surgery and underwent bilateral saphenous vein ablation. He also was referred to a lymphedema specialist, and workup revealed an unremarkable lymphatic system. Minimal improvement was noted following the saphenous vein

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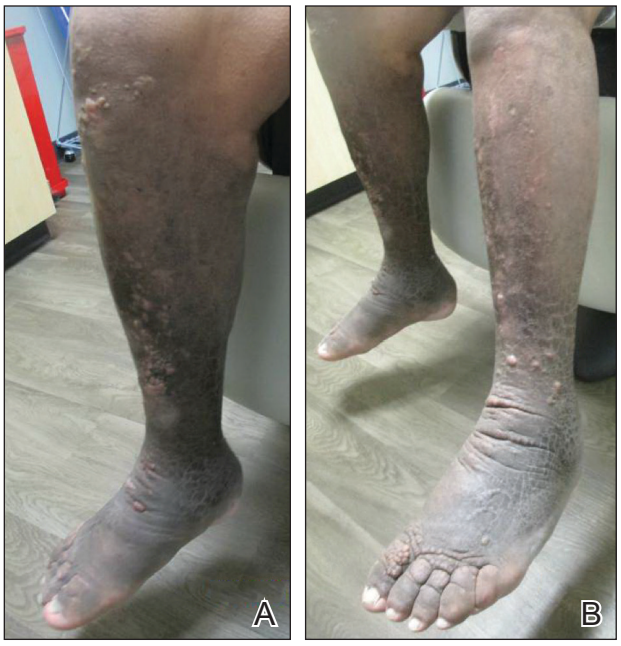

FIGURE 1. A, Diffuse woody induration, hyperpigmentation, and nonpitting edema on the right leg. B, Several flesh-colored papules were scattered throughout the anterior shins and dorsal aspects of the feet.

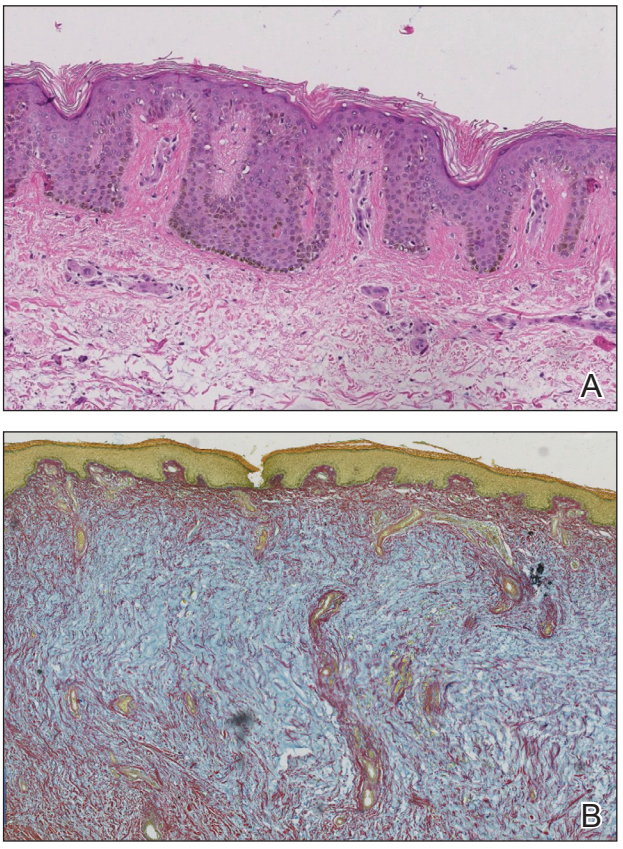

FIGURE 2. A, A biopsy of the left posterior calf showed marked mucin deposition in the superficial and deep dermis with deep fibroplasia (H&E). B, Colloidal iron staining highlighted the prominent mucin within the dermis. The notable deposition exceeds the typical amount of mucin seen in the setting of stasis, which pointed to a thyroid origin of disease.

ablation, and he subsequently was referred to dermatology for further workup.

At the current presentation, laboratory analysis revealed a low thyrotropin level (0.03 mIU/L [reference range, 0.4–4.2 mIU/L]), and free thyroxine was within reference range. Radiography of the chest was unremarkable; however, radiography of the hand demonstrated arthrosis of the left fifth proximal interphalangeal joint. Nuclear medicine lymphoscintigraphy and lower extremity ultrasonography were unremarkable. Punch biopsies were performed of the left lateral leg and posterior calf. Hematoxylin and eosin staining demonstrated marked mucin deposition extending to the deep dermis along with deep fibroplasia and was read as consistent with PTM. Colloidal iron highlighted prominent mucin within the dermis (Figure 2).

The patient's medical history, physical examination, laboratory analysis, imaging, and biopsies were considered, and a diagnosis of elephantiasic PTM was made. Minimal improvement was noted with initial therapeutic interventions including compression therapy and application of super high–potency topical corticosteroids. After further evaluation in our multidisciplinary rheumatology-dermatology clinic, the decision was made to initiate rituximab infusions.

Two months after 1 course of rituximab consisting of two 1000-mg infusions separated by 2 weeks, the patient showed substantial clinical improvement. There was striking improvement of the pretibial surfaces with resolution of the exophytic nodules and improvement of the induration (Figure 3). In addition, there was decreased induration of the glabella and earlobes and decreased fullness of the digital pulp on the hands. The patient also reported subjective improvements in mobility.

Our patient demonstrated all 3 aspects of the Diamond triad: PTM, exophthalmos, and acropachy. Patients present with all 3 features in less than 1% of reported cases of Graves disease.[3] Although all 3 features are seen together infrequently, thyroid dermopathy and acropachy often are markers of severe Graves ophthalmopathy. In a study of 114 patients with Graves ophthalmopathy, patients who also had dermopathy and acropachy were more likely to have optic neuropathy or require orbital decompression.[4]

After overcoming the diagnostic dilemma that the elephantiasic presentation of PTM can present, therapeutic management remains a challenge. Heyes et al[5] documented the successful treatment of highly recalcitrant elephantiasic PTM with rituximab and plasmapheresis therapy. In this case, a 44-year-old woman with an 11-year history of Graves disease and elephantiasic PTM received 29 rituximab infusions and 241 plasmapheresis treatments over the course of 3.5 years. Her elephantiasic PTM clinically resolved, and she was able to resume daily

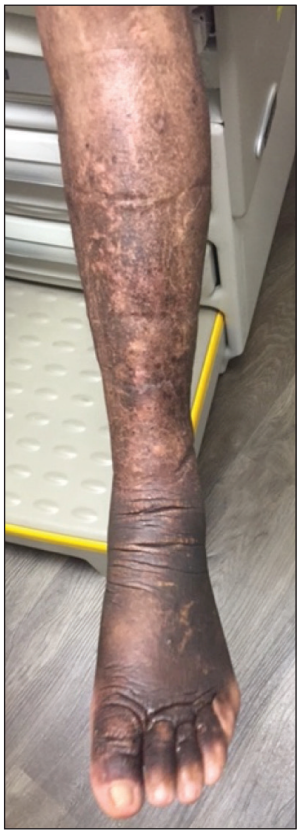

FIGURE 3. Following treatment with rituximab, there was striking improvement of the pretibial surfaces with nodules resolving; the induration substantially improved.

activities and wear normal shoes after being nonambulatory for years.[5]

Rituximab is a monoclonal antibody against CD20, a protein found primarily on the surface of B-cell lymphocytes. Although rituximab initially was approved by the US Food and Drug administration for the treatment of malignant lymphoma, it has had an increasing role in the treatment of autoimmune disorders such as rheumatoid arthritis. Rituximab is postulated to target B lymphocytes and halt their progression to plasma cells. By limiting the population of long-lasting, antibody-producing plasma cells and decreasing the autoantibodies that cause many of the symptoms in Graves disease, rituximab may be an effective therapy to consider in the treatment of elephantiasic PTM.[6]

Although the exact mechanism is poorly understood, PTM likely is a sequela of hyperthyroidism because of the expression of thyroid-stimulating hormone receptor proteins found on normal dermal fibroblasts. Thyroid-stimulating hormone receptor autoantibodies are thought to stimulate these fibroblasts to produce glycosaminoglycans. Histopathologically, accumulation of glycosaminoglycans deposited in the reticular dermis with high concentrations of hyaluronic acid is observed in PTM.[7]

Treatment of elephantiasic PTM remains a therapeutic challenge. Given the rarity of the disease process and limited information on effective therapeutic modalities, rituximab should be viewed as a viable treatment option in the management of recalcitrant elephantiasic PTM.

REFERENCES

1. Schwartz KM, Fatourechi V, Ahmed DDF, et al. Dermopathy of Graves' disease (pretibial myxedema): long-term outcome. *J Clin Endocrinol Metab*. 2002;87:438-446.
2. Kakati S, Doley B, Pal S, et al. Elephantiasis nostras verrucosa: a rare thyroid dermopathy in Graves' disease. *J Assoc Physicians India*. 2005;53:571-572.
3. Anderson CK, Miller OF 3rd. Triad of exophthalmos, pretibial myxedema, and acropachy in a patient with Graves' disease. *J Am Acad Dermatol*. 2003;48:970-972.
4. Fatourechi V, Bartley GB, Eghbali-Fatourechi GZ, et al. Graves' dermopathy and acropachy are markers of severe Graves' ophthalmopathy. *Thyroid*. 2003;13:1141-1144.
5. Heyes C, Nolan R, Leahy M, et al. Treatment-resistant elephantiasic thyroid dermopathy responding to rituximab and plasmapheresis. *Australas J Dermatol*. 2012;53:E1-E4.
6. Salvi M, Vannucchi G, Campi I, et al. Treatment of Graves' disease and associated ophthalmopathy with the anti-CD20 monoclonal antibody rituximab: an open study. *Eur J Endocrinol*. 2007;156:33-40.
7. Heufelder AE, Dutton CM, Sarkar G, et al. Detection of TSH receptor RNA in cultured fibroblasts from patients with Graves' ophthalmopathy and pretibial dermopathy. *Thyroid*. 1993;3:297-300.