

Severe Pretibial Myxedema Refractory to Systemic Immunosuppressants

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PRACTICE POINTS

- Pretibial myxedema (PM) is a known manifestation of Graves disease that almost always occurs in the presence of Graves ophthalmopathy.
- The proposed pathogenesis of PM is cross-reaction of autoantibodies directed against the thyroid receptors with the fibroblasts of the skin. It is not known why there is a predilection for the anterior shins, but mechanical factors and dependent position may be involved.
- The mainstay of treatment for PM is topical and intralesional corticosteroids, which may have a benefit in mild to moderate disease; however, in cases of severe disease that is refractory to intralesional and topical corticosteroids under occlusion, more aggressive treatment is required.

To the Editor:

A 55-year-old man with a history of Graves disease treated with radioactive iodine and Graves ophthalmopathy was referred to our dermatology clinic by his endocrinologist with a 2-year history of severe pretibial myxedema (PM) that had failed treatment with systemic immunosuppressants after diagnosis by an outside dermatologist in the United Kingdom approximately 2 years prior. In addition to burning pain and difficulty walking associated with progressive “enlarging” of the lower legs and feet (Figure, A and B), the patient reported that he consistently had to find larger shoes

(size 13 at the current presentation). His medications included gabapentin for foot pain and levothyroxine for hypothyroidism.

Physical examination revealed diffuse, waxy, indurated, flesh-colored and erythematous plaques and nodules with a peau d’orange appearance on the dorsal feet, ankles, and lower legs. Laboratory evaluation revealed a thyroid stimulating immunoglobulin level of 617% (reference range, <140%) and mild anemia. His thyroid stimulating hormone and free T4 levels, a comprehensive metabolic panel, and lipid panel were all within reference range.

Treatment with oral, intravenous, and intralesional steroids; cyclosporine; and azathioprine were tried prior to presentation to our clinic with no improvement. The patient was started on pentoxifylline (400 mg 3 times daily), intralesional triamcinolone acetonide (5 mg/mL every 3–4 weeks), clobetasol propionate ointment 0.05% under occlusion twice daily, short-stretch bandages, and compression stockings (20–30 mm Hg). The baseline circumference of the extremities also were measured (right ankle, 12 in; left ankle, 11.5 in; right and left mid-plantar feet, 12 in).

At 3-week follow-up, the lesions had flattened with softening of the skin. The patient reported his legs were smaller and he had bought a new pair of shoes at size 8.5 (Figure, C). He noted less pain and difficulty with walking. The circumference of the extremities was measured again (right ankle, 10.2 in; left ankle, 10 in; right and left mid-plantar feet, 10.5 in). The patient continued treatment and was followed for 3 months. At each visit, clinical improvement was noted as well as report of decreased pain while walking (Figure, D).

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The authors report no conflict of interest.

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A and B, Severe pretibial myxedema. At baseline, progressive swelling of the lower legs and feet was noted. C and D, At 3-week and 2-month follow-up, respectively, the extremities were notably smaller.

Pretibial myxedema is a known manifestation of Graves disease that almost always occurs in the presence of Graves ophthalmopathy. Pretibial myxedema occurs in 0.5% to 4.3% of patients with Graves disease and variably manifests as diffuse non-pitting edema or localized, waxy, indurated plaques or nodules.^{1,2}

The proposed pathogenesis of PM is that autoantibodies directed against the thyroid receptors cross-react with the fibroblasts of the skin,^{2,3} which stimulates the fibroblasts to produce high amounts of glycosaminoglycans, especially hyaluronic acid, in the dermis and subcutis of the pretibial area. It is not known why there is a predilection for the anterior shins, but

mechanical factors and dependent position (ie, leg position is lower than the level of the heart) may be involved.⁴

The mainstay of treatment for PM is topical and intralesional corticosteroids, which may have a benefit in mild to moderate disease; however, in cases of severe disease that is refractory to intralesional and topical corticosteroids under occlusion, more aggressive treatment is required. Systemic immunosuppressants such as cyclosporine, azathioprine, and corticosteroids have proven useful in some but not all cases.^{5,6}

Our patient did not respond to treatment with systemic and intralesional corticosteroids, cyclosporine, or azathioprine before he presented to our clinic; however,

the lesions were dramatically improved after 3 weeks of treatment with pentoxifylline, intralesional and topical corticosteroids under occlusion, short-stretch bandages, and compression stockings.

Pentoxifylline inhibits the proliferation and glycosaminoglycan synthesis of cultured fibroblasts derived from patients with Graves ophthalmology and PM.⁷ It has been shown to reduce thickness of skin lesions when used in combination with topical or intralesional steroids.^{3,8} Corticosteroids are thought to block fibroblast-mediated glycosaminoglycan production.^{3,9} The deposition of mucin, which is comprised of glycosaminoglycans, expands the dermal tissue and causes fluid to accumulate; it also causes compression of dermal lymphatics, worsening the dermal edema. Because fluid accumulates, the use of short-stretch bandages and compression stockings may provide additional benefit, as was seen in our patient, whose shoe size decreased from a 13 to an 8.5 within 3 weeks of treatment.

In conclusion, the combination of pentoxifylline, intralesional and topical corticosteroids under occlusion, short-stretch bandages, and compression garments can cause substantial improvement in severe PM refractory to systemic immunosuppressants.

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