Pretibial myxedema successfully treated with intralesional hyaluronidase

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Pretibial myxedema (PTM) is a rare form of diffuse dermal mucinosis caused by glycosaminoglycan deposition in pretibial skin. It generally occurs in association with autoimmune thyroid disorders and affects 0.5% to 4.3% of patients with Graves disease (GD).[1] PTM rarely improves with correction of the hyperthyroid state and may lead to pain, pruritus, or cosmetic concerns.[2] Therefore, treatment is usually desired. Topical and intralesional corticosteroids, octreotide, and systemic immunomodulating agents have been used with largely unsatisfactory results.[3]

Hyaluronidase is a naturally occurring enzyme that degrades hyaluronic acid (HA), a primary constituent of dermal mucin. Its current US Food and Drug Administration–approved indications include hypodermoclysis, enhancement of subcutaneous absorption of injected drugs, and improving resorption of radiopaque agents during subcutaneous urography.[4,5] Given its efficacy and safety in the degradation of HA, intralesional hyaluronidase (ILH) should be considered in the treatment of cutaneous mucinoses. Here we describe 2 patients with severe PTM successfully treated with ILH.

Abbreviations used:

GD: Graves disease
HA: hyaluronic acid
ILH: intralesional hyaluronidase
PTM: pretibial myxedema

REPORT OF CASES

Case 1

A woman in her 60s with a history of GD treated with thyroid ablation 7 years previously presented with a 5-year history of pruritic lesions on her shins and feet. She had a prior diagnosis of PTM, which was refractory to clobetasol cream twice daily under occlusion for the last several months. Intralesional corticosteroids and oral pentoxifylline had also failed. Physical examination found confluent, indurated, peau d'orange plaques involving the shins and feet (Fig 1, *A*). After negative intradermal allergy testing, plaques on the left foot were treated with ILH (150 U/mL). The regimen was week 0, 75 U in 5 equal aliquots; week 6, 105 U, 7 aliquots; week 12, 150 U, 10 aliquots; and week 18, 105 U, 7 aliquots.

Clobetasol cream twice daily under occlusion was continued for both feet. The left foot gradually improved throughout the treatment course, with substantial plaque regression observed after 24 weeks (Fig 1, *B*). The right foot did not improve. No adverse events occurred.

Case 2

A woman in her 60s with a history of GD presented with a 7-year history of progressive painful induration involving the lower extremities and feet. She denied prior topical treatments. Her GD was treated 2 years prior with total thyroidectomy and levothyroxine. Physical examination found multiple indurated skin-colored plaques involving the ankles and feet, consistent with PTM (Fig 2, *A*). After negative intradermal allergy testing, a 5- × 5-cm plaque on the left dorsal foot was treated with ILH (150 U/mL; 1.0 mL) injected in 10 equal aliquots. Treatment was repeated at weeks 6, 12, and 18, with progressive flattening of the targeted plaque and resolution of pain (Fig 2, *B*). The patient reported

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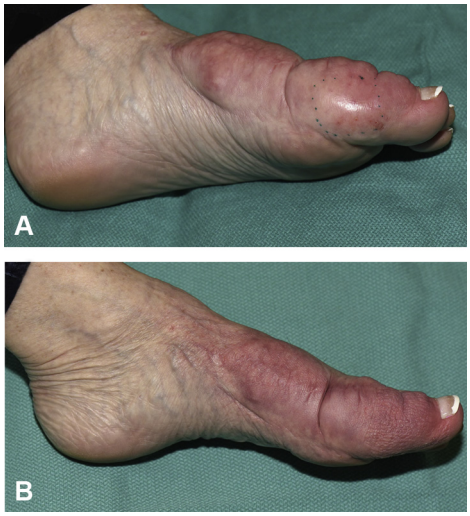

Fig 1. Case 1 (**A**) before and (**B**) after 4 treatments with ILH at 6-week intervals.

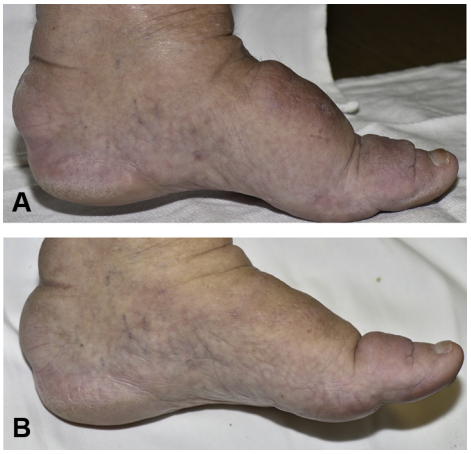

Fig 2. Case 2 (**A**) before and (**B**) after 4 treatments with ILH at 6-week intervals.

mild discomfort during injections and no other complications. There was no improvement in the untreated, right foot.

DISCUSSION

PTM is a chronic form of dermal mucinosis that occurs in association with GD or less commonly Hashimoto thyroiditis.[2] Although recognizing and correcting the underlying abnormal thyroid state is critical, it rarely improves the mucinosis. Pretibial plaques are most commonly treated with immunomodulating agents including topical, intralesional, and systemic corticosteroids, oral octreotide, intravenous immunoglobulin, and plasmapheresis.[1,3] Although these therapies may have some benefit in early or mild disease, results are generally disappointing.

The indurated plaques in PTM arise as a result of excessive mucin production by dermal fibroblasts.[1] Mucin comprises various glycosaminoglycans, with HA being most abundant. Therefore, HA represents a potential therapeutic target in patients affected by PTM. Hyaluronidase is a commercially available hexosaminidase that functions in HA degradation through hydrolysis. Its current approved uses are in the enhanced dispersion or absorption of subcutaneous drugs. Off-label uses include the dissolution of misplaced hyaluronic acid filler during facial rejuvenation.[4] Although hyaluronidase did effectively treat 2 cases of PTM in 1949 and 1950,[6,7] subsequent reports of its use in the treatment of PTM are rare.[8]

In the current cases, 2 patients with severe PTM showed notable improvement after 4 ILH treatments. Case 1 showed a response even after not responding to prolonged courses of conventional therapies. The anticipated treatment protocol in each case was 1.0 mL (150 U) injected at 6-week intervals. In case 1, doses were decreased because of mild discomfort during injections. Still, this patient showed considerable response to therapy, and it is unclear whether higher doses would have resulted in greater improvement. Continued treatments at regular intervals are anticipated for both patients, as hyaluronidase is not expected to alter fibroblast mucin production.

The most common adverse effects of hyaluronidase are transient erythema and pruritus at the injection site, occurring in up to 25% of patients.[9] Although severe hypersensitivity reactions such as angioedema and anaphylaxis have been reported, the incidence is estimated to be less than 0.1%.[10] Anaphylaxis risk appears to be especially low if human recombinant hyaluronidase, rather than product derived from bovine or ovine tissues, is used.[9,10] Pretreatment skin allergy testing to hyaluronidase is still often advocated even for the human recombinant formulation despite its low risk of adverse immunogenic responses.[11]

ILH may be an effective, well-tolerated, and underutilized treatment for PTM and should be considered in cases refractory to conventional therapies. Prospective studies are needed to determine dosing schedules that maximize efficacy and durability of response.

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