**Intralesional Hyaluronidase with Triamcinolone for Recalcitrant Pretibial Myxedema**

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**Abstract**

Pretibial myxedema resulting in progressively worsening cutaneous induration and expanding nodules can lead to pain, discomfort and functional impairment. Treatment of resistant lesions presents a special challenge when novel topical therapies are insufficient, and systemic therapies are met with poor tolerability, low rate of effectiveness and the added risk of side effects. We report a patient with resistant pretibial myxedema nodules who demonstrated marked overall improvement of great toe lesions, including nodule size and associated discomfort, with repeat injections of hyaluronidase (Vitrase) both with and without triamcinolone acetate.

**Introduction**

Pretibial or localized myxedema is deposition of dermal mucin resulting from thyroid disease, commonly Graves' disease, hence the synonymous term “dermopathy of Graves’ disease.” Pretibial myxedema lesions are comprised of hyaluronic acid and can result in fluid retention, edema and elephantiasis.1 Myxedematous indurated nodules can also cause pain and functional impairment. We present a case in which the patient was debilitated by pretibial myxedematous lesions and failed standard treatment options. We formulated a treatment option, hyaluronidase injections (Vitrase) with and without triamcinolone, that led to functional and cosmetic improvement of the patient's refractory myxedematous lesions. While hyaluronidase has been briefly described previously in literature, we propose an updated and regulated regimen for use of hyaluronidase injections in refractory pretibial myxedema.

**Case Report**

A 44-year-old Caucasian female with a past medical history of Graves' disease, treated with radioactive iodine thyroid ablation, presented to our office with a two-year history of bilateral lower extremity swelling. Her post-procedural hypothyroidism had since been well-controlled with levothyroxine, with no recurrence of initial hyperthyroid-related symptoms. Past medical history also included migraines, as well as multiple unrelated surgical procedures. Periodic laboratory testing revealed normal thyroid stimulating hormone (TSH) levels despite progressively worsening cutaneous lesions. Of note, the patient had persistently elevated thyroid-stimulating immunoglobulins (TSI), consistent with active thyroid dermopathy. The patient complained of a nine-month history of “raised circles on the right shin and toes.” The right lower extremity lesions were intermittently pruritic, but without associated pain, numbness or paresthesias. She had recent surgical excision of a degenerated sesamoid bone on her right foot, and of masses on bilateral great toes that revealed benign fibroconnective tissue with a myxoid-mucoid background.

Physical exam revealed erythematous, indurated nodules on the right anterior and posterior lower leg. The patient had 3+ nonpitting edema of bilateral lower legs and feet, and new onset of progressive swelling of bilateral hands. The great toes were markedly enlarged, with overlying scarring at surgical incision sites (Figure 1).

As the pain and discomfort of her great toes and lower extremities remained debilitating and refractory to all first- and second-line treatment options for pretibial myxedema, we formulated a novel treatment option involving injection of the enzyme hyaluronidase. Hyaluronidase degrades glycosaminoglycans (GAGs), which accumulate in the dermis of localized myxedema lesions.1 An intradermal allergy test was performed first, revealing no hypersensitivity to hyaluronidase. Initially, hyaluronidase (200 units/1.2 cc) mixed with triamcinolone acetate (Kenalog 10 mg/cc) was injected into the left great toe, while hyaluronidase (200 units/1.2 cc) with lidocaine 1% was injected into the right great toe for comparison. The regimen was administered as follows:

**Left great toe:** 0.15 cc (25 units) hyaluronidase + 0.15 cc triamcinolone acetate 10 mg/cc = 0.3 cc total mixed syringe in two evenly distributed aliquots with 30G needle (two on dorsal aspect) (Figure 3).

**Right great toe:** 0.15 cc (25 units) hyaluronidase + 0.15 cc lidocaine 1% = 0.3 cc total mixed syringe in two evenly distributed aliquots with 30G needle (one on dorsal aspect and one on plantar aspect) (Figure 3).

At one-month follow-up, a slight decrease in swelling and discomfort was observed, with the right and left toes affected equally. At that time, a repeat dose of hyaluronidase with lidocaine was administered to bilateral halluciae:

**Left great toe:** 0.15 cc (25 units) hyaluronidase + 0.15 cc lidocaine 2% = 0.3 cc total mixed syringe in four evenly distributed aliquots with 30G needle (two on dorsal aspect and one on plantar aspect).

**Right great toe:** 0.15 cc (25 units) hyaluronidase + 0.15 cc lidocaine 2% = 0.3 cc total mixed syringe in three evenly distributed aliquots with 30G needle (two on dorsal aspect and one on plantar aspect).

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**Figure 1.** Prior to treatment, bilateral great toe enlargement and scars from prior surgical incisions.

**Figure 2.** Punch biopsy of right lower leg showing abundant mucin within the reticular dermis, consistent with pretibial myxedema.

**Figure 3.**
Two weeks post-procedure, there was again only a slight decrease in swelling, subjective discomfort, and impact on quality of life. Therefore, we increased the volume of hyaluronidase, added triamcinolone acetate 40 mg/cc, and increased the frequency of injections to every two weeks. At this time, we administered:

**Left great toe:** 0.30 cc (50 units) hyaluronidase + 0.30 cc triamcinolone acetate 40 mg/cc = 0.60 cc

**Right great toe:** 0.30 cc (50 units) hyaluronidase + 0.30 cc triamcinolone acetate 40 mg/cc = 0.60 cc

At two-week follow-up, the patient demonstrated a marked decrease in great toe pain, discomfort and size (Figure 4). The patient further reported substantial improvement in quality of life, including comfort while wearing shoes and overall satisfaction. Throughout the course of treatment, our patient did not report any significant adverse effects, noting only discomfort during injections, as well as slight injection site soreness lasting two to three days post-procedure. The patient will be continued on this most recent regimen of injections every two weeks, for maintenance and tight control of her symptoms. The patient is also being considered for adjunctive rituximab with IVIG therapy due to persistently elevated TSI levels and diffuse edema of dorsal feet and hands.

**Discussion**

Localized or pretibial myxedema is characterized by cutaneous induration of skin due to mucin deposition in the dermis. Localized myxedema is also known as "dermatopathy of Graves' disease" or "thyroid dermopathy" because it is often a sign of Graves' disease. Localized myxedema commonly occurs on the lower extremities due to their dependent position and subjection to mechanical stress. Furthermore, the first sign of disease frequently involves the hallux secondary to trauma caused by shoes. Rarely, myxedema can involve the face, upper extremities, lower abdomen and sites with traumatic history.

Diffuse non-pitting edema is seen due to dermal mucin retaining fluid, which can eventually evolve into elephantiasis. The lesions may be asymptomatic and primarily of cosmetic concern. However, quality of life is affected when edema and myxedematous lesions enlarge to create difficulty and pain while walking and wearing shoes.

Mucin is a component of dermal extracellular matrix located in the dermis and subcutaneous tissue. Normally, mucin is produced in small amounts by fibroblasts and is composed largely of GAGs. GAGs include those attached to a protein core, such as dermatan sulfate and chondroitin sulfate, and those without attachments, as in hyaluronic acid (HA).

First-line treatment includes high-potency topical corticosteroids with occlusion, intralesional corticosteroids, and compression stockings. The role of steroids is to improve symptoms and relieve pruritus. For refractory disease, second-line treatment includes pentoxifylline. Pentoxifylline is an analog of methylxanthine theobromine, which inhibits proliferation of fibroblasts and GAG synthesis.

As our patient failed treatment with corticosteroids, and was unable to tolerate pentoxifylline, we proposed injecting hyaluronidase, a naturally occurring enzyme that degrades HA and to some extent chondroitin and chondroitin sulfates. Hyaluronidase works by cleaving beta-1,4 glycosidic bond between C1 (N-acetylgalactosamine) and C4 (glucuronic acid).

In English literature, there are three manuscripts discussing the use of hyaluronidase to treat localized myxedema. All of the reports were in the wake of discovering the contents of myxedema lesions. In 1948, Melvin L. Grais presented a patient with pretibial myxedema lesions refractory to thyroid extract and propylthiouracil that were cosmetically displeasing. Hyaluronidase in increasing concentrations, mixed with saline, was injected into myxedematous plaques. The lesions decreased markedly in size and resolved without scar. However, this patient developed local injection site reactions, including erythema and edema. At high concentration, the patient developed systemic signs including fever and chills, which resolved within 48 hours. There is a disclosure in the article that the labeled strength of hyaluronidase preparation is not an accurate index of actual hyaluronidase activity at the time of use and that the authors cannot conclude the exact dose injected per treatment.

In 1949, Bloom et al. reported two cases of myxedematous lesions injected with hyaluronidase and normal saline. Both cases resulted in flattening of lesions without any adverse reactions. One of the case's injections were discontinued after only a few weeks because the lesions became firm and resisted any injection of fluid. Donald Rosman in 1950 employed hyaluronidase injections in higher concentrations than previously reported plus normal saline, and subsequently applied pressure dressings to the lesions. Lesions resolved in both patients, with only erythema and occasional pain during injections reported as adverse events. Lesions injected only with normal saline did not improve. Upon discontinuation, lesions recurred; however, this is expected, since hyaluronidase is a palliative treatment directed toward a manifestation of the disease.

We used Vitrase, a commercially available hyaluronidase of ovine testicular origin. Vitrase is indicated to increase absorption of other drugs, increase tissue permeability to facilitate subcutaneous hydration and improve resorption of radiopaque agents. Off-label, it is used to treat vitreous hemorrhage and for reversal of hyaluronic acid filler. Reported adverse effects include, most commonly, local injection site reactions, and rarely (< 0.1%) allergic reactions. Our theory is that commercial hyaluronidase at regulated concentrations will break down the mucin and increase drainage of the excess GAGs, as well as facilitate absorption and effectiveness of concomitant triamcinolone acetate. Based on this mechanism of action, we expect that twice-monthly injections of hyaluronidase with triamcinolone acetate will ultimately continue decreasing the size of our patient's lesions and provide remarkable symptomatic relief. To date, repeat courses of hyaluronidase both with and without triamcinolone acetate injections have been performed, and have resulted in significant overall improvement of cosmesis, lesional size, and associated pain and discomfort.

**Conclusion**

Pretibial myxedema can affect a patient's quality of life when lesions are of cosmetic concern, cause pain and/or result in difficulty ambulating, as seen in our case presentation. We have provided another successful treatment option, intralesional hyaluronidase with or without triamcinolone, that should be considered when lesions are refractory to first-line treatment options, such as topical and intralesional corticosteroids. Hyaluronidase injections decrease size and improve appearance of lesions, resulting in improvement of debilitating symptoms.
References


