Pretibial myxedema (elephantiasic form): treatment with cytotoxic therapy

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One of the four major components of Graves' disease, pretibial myxedema (PTM), occurs in approximately 0.5% to 4.3% of patients with ophthalmic goiter and is often seen following treatment of the goiter. An advanced case of elephantiasic PTM is reported.

Index terms: Elephantiasis • Goiter • Graves' disease
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Pretibial myxedema (PTM) is one of the four major components of Graves' disease.[1] The other three components are ophthalmopathy, hyperthyroidism caused by diffuse goiter, and the presence of abnormal serum levels of long-acting thyroid stimulator (LATS). Lynch et al[1] believed that a diagnosis of Graves' disease could be made when at least two of the four components were present.

The incidence of PTM in Graves' disease is 0.5%–4.3%.[2–4] The clinical lesions of PTM usually appear as skin-colored or erythematous plaques or nodules on the lower legs. Mild cases may resolve spontaneously, and little if any treatment is indicated.[4,5] More severe elephantiasic forms of PTM have occasionally been reported.[4,6,7] These cases usually are associated with ophthalmic goiter and often occur following treatment of the goiter.[5]

The severe elephantiasic form of PTM is often progressive and is refractory to treatment. Patients are uncomfortable with their thickened, weighty legs and feet and have trouble walking. The wearing of shoes, stockings, and slacks may become nearly impossible. We describe our experience in treating a patient with a particularly advanced case of elephantiasic PTM.

Case report

A 44-year-old man with malignant exophthalmos, thyrotoxic goiter, and PTM was seen in November 1973. He was treated with radioactive iodine in November 1974 and February 1975. Multiple ocular decompression procedures were performed in 1974 and 1975. The patient was referred to the Cleveland Clinic in October 1975 for progressive elephantiasic enlargement of both lower extremities. Examination at that time revealed severe exophthalmos of both eyes (*Fig. 1*) and marked enlargement of both legs (*Fig. 2*), the dorsal aspect of the feet, and toes (*Fig. 3*). The skin on the legs had a verrucous appearance with multiple brownish red nodules surrounded by deep fissures. The skin around the ankles was thickly folded. Skin biopsy specimens were obtained from the verrucous pretibial areas as well as the normal-appearing skin on the extensor forearm and upper eyelid. The biopsy sites on the forearm left shiny pinkish brown nodules after healing (*Fig. 4*).

Laboratory studies. Most laboratory values were normal. Results of a liver biopsy were also normal. The effective thyroxine ratio was 1.02, which indicated a normal thyroid. However, an abnormal 7S gamma globulin was identified on serum protein electrophoresis. An assay for LATS by the mouse bioassay method revealed a 1750% increase (normal, 80%–120%).

Histopathology. Skin biopsy specimens from the pretibial areas showed hyperkeratosis, irregular acanthosis, and a white material replacing much of the reticular dermis in a band-like fashion (*Fig. 5*). A colloidal iron stain identified the substance as acid mucopolysaccharide (*Fig. 6*). The

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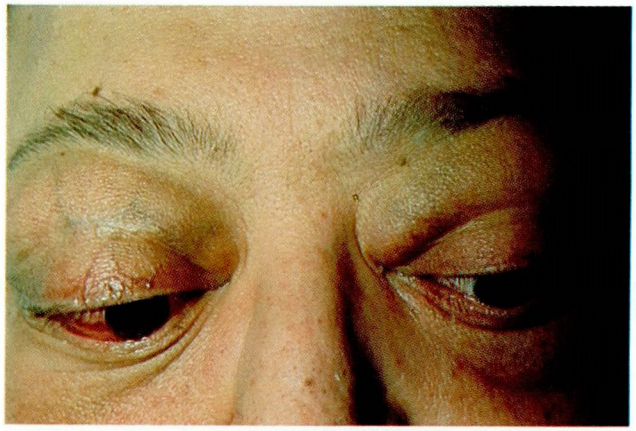


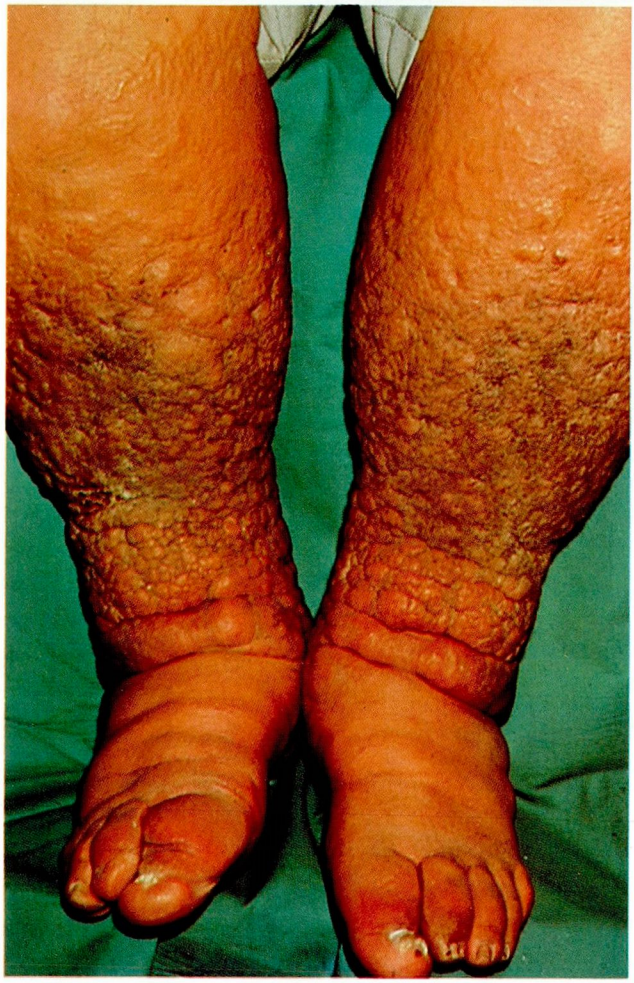
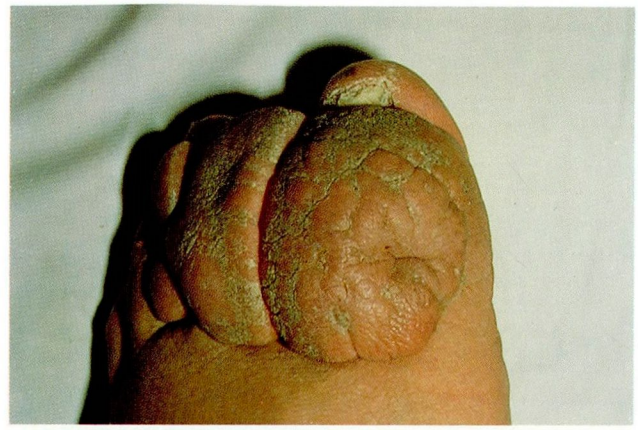


Figure 1. Malignant exophthalmos with marked edema of the upper eyelids.

Figure 2. Elephantiasic enlargement of legs in a patient with pretibial myxedema.

material was digestible with hyaluronidase. Colloidal iron stains on the biopsy specimens from normal-appearing skin on the forearm and upper eyelid also showed moderate mucin deposition between the collagen bundles. The mucin was also digestible with hyaluronidase. A colloidal iron stain on the liver biopsy specimen showed no mucin deposition.



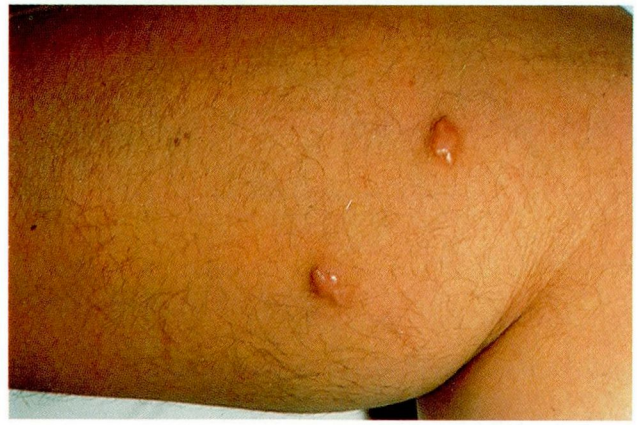


Figure 3. Nodular hyaluronic acid deposits on the dorsal aspect of the toes associated with pretibial myxedema.

Figure 4. Healed skin biopsy sites on the forearm of a patient with elephantiasic pretibial myxedema. The biopsy sites have healed with scars that are heavily laden with hyaluronic acid.

Tissue culture studies

Methods. Fibroblasts from the verrucous pretibial areas were studied in tissue culture. Skin biopsy specimens were dissected into small pieces with sterile scalpel blades and implanted as explants into 25-ml flasks. PTM fibroblasts were isolated and grown in conjunction with fibroblasts from the pretibial area of normal control patients. The fibroblasts were grown on modified LJL media enriched with 10% fetal calf serum, which was changed every three days. The fibroblasts were cultured for two weeks, trypsinized, and then deposited in 75-ml flasks. Fibroblasts from the sixth to the tenth passage were used for the study.

The studies were conducted in 100-ml Petri dishes with inoculum densities of 400,000 cells. The rates of growth of the fibroblasts were compared. On the tenth day, the fibroblasts were extracted with 0.3N potassium hydroxide to measure the deoxyribonucleic acid (DNA) and protein in both PTM and the normal control fibroblasts. The effect of antimitotic drugs on the growth rate of the fibroblasts was studied by comparing the DNA and protein content of an untreated group of PTM fibroblasts and a group treated with the following cytotoxic drugs: melphalan (0.08 mg/L of media), cyclophosphamide (20 mg/L of media), nitrogen mustard (10 mg/L of media), and methotrexate (1 mg/L of media). The concentrations were calculated according to

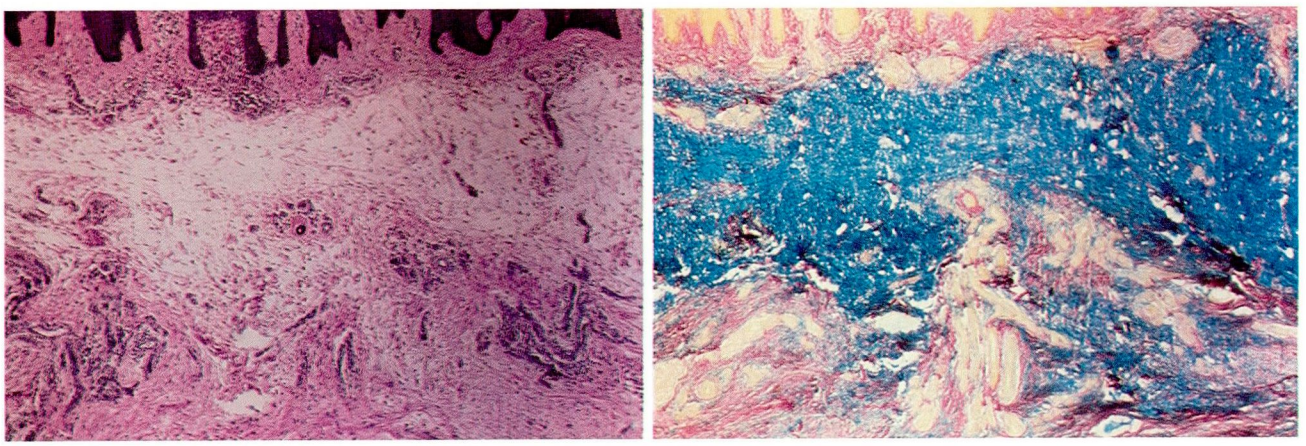


Figure 5. Skin biopsy from the leg of a patient with pretibial myxedema, showing a gray-white material replacing the reticular dermis. The material was digestible with hyaluronidase (hematoxylin and eosin stain, ×10).

Figure 6. Skin biopsy from the leg of a patient with pretibial myxedema. The blue material is hyaluronic acid (colloidal iron stain, ×10).

standard clinical doses. A total blood volume of 5 L was assumed.

Treatment of the PTM fibroblasts with cytotoxic drugs was started on the fourth day after implanting and was continued for five days. On the tenth day, the fibroblasts were extracted with 1.3 N potassium hydroxide to measure the DNA and protein. Hyaluronic acid synthesis by PTM fibroblasts and normal control fibroblasts was measured with a modified carbazole reaction.[8] The effect of the cytotoxic drugs on PTM fibroblasts was measured in a separate set of Petri dishes. Another set of Petri dishes was used for collagen extraction and estimation of hydroxyproline.[9] The fibroblast cultures were examined with phase-contrast microscopy. Some cultures were grown on cover slips and stained with hematoxylin and eosin, Giemsa, and PAS.

Results. Results are shown in *Table 1*. PTM fibroblasts treated with cytotoxic drugs showed a marked decrease in DNA content compared with untreated PTM and normal control fibroblasts. Melphalan caused the greatest reduction in the amount of hyaluronic acid released. The PTM fibroblasts produced more hyaluronic acid than normal even after treatment with each of the four cytotoxic drugs. There was no statistically significant difference between the four drugs with regard to their effect on PTM fibroblasts. The DNA-total protein ratio showed no statistically significant change from normal. Collagen was formed in a normal amount by PTM fibroblasts compared to normal control fibroblasts (*Table 2*).

PTM fibroblasts were larger than normal and had larger nuclei when examined with phase-contrast microscopy. A peculiar vacuolation of the fibroblasts not otherwise observed in vitro was present.

Clinical course. The patient underwent orbital decompression procedures for several months with reduction of the bilateral exophthalmos. Daily leg pumpings and intralesional steroids were administered to the dorsal aspect of the feet and legs and resulted in temporary softening of the indurated verrucous areas. Topical steroids were not beneficial. Excision and grafting of the extremely thickened skin was considered too great a risk because the patient weighed more than 300 pounds, and he showed little interest in reducing his weight. In addition, surgery was contraindicated since unsuccessfully grafted areas of skin might have left large areas of exposed tissue.

In view of the gradually worsening PTM with the continued appearance of new red verrucous nodules on the legs, systemic chemotherapy was considered. In vitro studies had shown that melphalan had the greatest cytotoxic effect on the PTM fibroblasts; consequently, the drug was administered orally (8 mg/day) for four consecutive days. This regimen was repeated monthly for six months. The diameters of the upper legs and ankles both decreased by 6 cm

Table 1. Hyaluronic acid synthesis by normal control fibroblasts, PTM fibroblasts, and PTM fibroblasts treated with antimitotic drugs

Sample	DNA (Hgm)	Total protein	Hyaluronic acid (mg)	DNA/total protein	Hyaluronic acid/DNA
Normal control fibroblasts	60.01	499.82	104.86	0.12	1.74
PTM fibroblasts (untreated)	59.89	497.08	332.96	0.12	5.56
PTM fibroblasts (treated)					
Melphalan	23.90	265.98	130.00	0.09	5.40
Cyclophosphamide	30.91	396.80	199.20	0.08	5.40
Methotrexate	32.90	388.08	171.20	0.08	5.20
Nitrogen mustard	25.89	353.19	180.60	0.08	6.90

Table 2. Collagen synthesis in normal control and PTM fibroblasts

Sample	Collagen (mg)	Collagen/ DNA
Normal control fibroblasts	51.10	0.85
PTM fibroblasts	51.77	0.84

during the first two months of treatment. The patient could see the improvement, and reported that his legs felt more comfortable. By the fourth month, however, his legs had enlarged again to the pretreatment state. Two more months of therapy resulted in no improvement. Separate courses of nitrogen mustard administered intravenously, and cyclophosphamide and methotrexate administered orally were given for periods of four to six months with no improvement. Another trial of melphalan showed no improvement. On two occasions, with discontinuation of systemic chemotherapy for several months, cellulitis developed in the right leg. Apparently, a large fissure between the toes gave rise to the infection in both instances. The cellulitis promptly responded to treatment with antibiotics administered intravenously and bed rest. The patient was instructed to soak his legs in a povidone-iodine solution at home on a daily basis to suppress the bacterial growth that had colonized in the deep leg fissures.

The patient was doing well when last seen in February 1979; however, leg measurements showed a slow progression of the disease.

Discussion

The growth rate of PTM fibroblasts in our patient was the same as the growth rate of normal control fibroblasts. The most characteristic feature of PTM fibroblasts is their ability to produce three times as much hyaluronic acid as normal control fibroblasts. This could have been anticipated as Sisson[10] reported that plaques of PTM contained six to 16 times more acid mucopolysaccharide than normal skin. In addition, Cheung et al[11] reported increased hyaluronic acid synthesis by fibroblasts in a tissue culture from the pretibial areas of patients with PTM. Hyaluronic acid makes up nearly 100% of the acid mucopolysaccharide in PTM, but only 57% in normal skin. Beierwaltes and Bollet[12] found a higher content of acid mucopolysaccharide in the normal-appearing skin of PTM patients than in normal controls. A circulating factor such as LATS may be able to transform normal-appearing fibroblasts into abnormal cells, which produce large amounts of hyaluronic acid. Kriss et al[13] hypothesized that PTM is caused by an antigen-antibody reaction in the area of the skin disease and that LATS might be the antibody involved. The antigen, however, was not found by Schermer et al[5] when using direct immunofluorescence to identify antigen-antibody reactions in tissue sections from PTM lesions. Possibly, no localized antigen-antibody reaction occurs in the PTM lesions; however, the presence of LATS or some other undefined systemic factor transforms the pretibial fibroblasts into abnormal mucin-producing cells. The mucin accumulation in the dermis then leads to the clinical lesions of PTM. Increased amounts of acid mucopolysaccharide on histochemical staining of normal-appearing forearm and eyelid skin suggest further that a systemic factor is involved in PTM.

Exophthalmic goiter with associated PTM may be an autoimmune disorder even though a localized antigen-antibody reaction may not be present in PTM lesions. This is suggested by the fact that exophthalmic goiter has been associated with numerous autoimmune conditions, including pernicious anemia, rheumatoid arthritis, myasthenia gravis, lymphocytic infiltration of the thyroid, struma lymphomatosa, and enlargement of the thymus. Autoantibodies against gastric parietal-cell microsomes, an intrinsic factor, and thyroid tissue fractions have been identified. The thyroid antigen release caused by iodine 131, thyroiditis, or hyperthyroidism could result in the production of an antibody such as LATS.[13] The antibody would then circulate and cause fibroblasts in the lower leg and other areas to produce excess mucin.

LATS is a 7S gamma globulin, which has been found in most patients with PTM.[5,14–17] The serum LATS titers do not correlate well with the severity of the skin lesions.[5] Our patient, however, had severe PTM and high LATS titer. The site of origin of LATS is unknown, but its antigen may be in the microsomal portion of thyroid tissue.[18] It is not known if LATS is a pathogenetic agent in PTM or just a manifestation of altered immunity. Cell-mediated immunity may also play a role.[19,20]

McKenzie et al[21] believe that the technique whereby cyclic AMP (adenosine 3′:5′-cyclic phosphate) is measured in incubated human thyroid slices is more sensitive for detecting LATS than the traditional mouse bioassay technique. Whether this new technique will allow LATS to be measured in all patients with PTM remains to be demonstrated.

The precise cause of exophthalmos in Graves' disease is unknown. LATS may be a causative factor; however, it is not the sole factor responsible. It can be present or absent in the serum of patients with minimal to severe exophthalmos.[22] Animal studies have shown that the increase in

volume of the fatty retro-orbital tissues in experimental exophthalmos is caused by increased amounts of acid mucopolysaccharide.[23] The increase in acid mucopolysaccharide is accompanied by a corresponding increase in water, which presumably produces the exophthalmos. However, Rundle et al[24] reports that some cases of exophthalmos are due to enlargement of the intrinsic eye musculature. Although either intrinsic eye muscle enlargement or retro-orbital mucin accumulation may produce exophthalmos, it is not clear why one process predominates in an individual.

Although the fissures of the elephantiasic form of PTM do not always lead to infection,[4] odor should immediately alert the clinician to infection. We believe that daily immersions of the legs and feet in a povidone-iodine solution are effective in minimizing such infection in our patient. On two occasions when our patient had been neglecting his daily soakings, cellulitis of the right leg developed. In both instances, one of us was able to identify an infected deep fissure on the foot that presumably had preceded the cellulitis on the leg. Fortunately, the cellulitis responded rapidly to antibiotics administered intravenously.

It is not known why PTM preferentially affects the legs. Schermer et al[5] believed that hydrostatic forces play a role. Venous stasis, varicosities, focal extravasation of blood, and local trauma might all lead to focal accumulations of mucin on the legs.

A number of therapies; such as thyroid preparations administered orally,[25] tri-iodothyronine[26] and hyaluronidase[4] administered intralesionally, and radiation;[4] have been tried for PTM, usually with negative or inconsistent results. Positive results have been reported with prednisone administered orally, triamcinolone administered intralesionally, and 0.2% fluocinolone cream with plastic occlusion administered topically.[17,27] Our patient could not tolerate long-term systemic prednisone therapy; steroids administered topically and intralesionally failed.

The severe elephantiasic form of PTM has been treated infrequently with surgery. Patterson[7] reported a patient with rapid recurrence of the PTM following excision and grafting of the verrucous dorsal foot tissues. Theoretically, major problems with infection can occur if the skin grafts do not heal and large areas of exposed tissue are created. Our patient, because he was overweight, was a poor operative risk. The appearance of keloidlike areas on his forearm following skin biopsies of normal-appearing skin was another contraindication.[4]

We decided to initiate trials with cytotoxic agents for three reasons: (1) our patient's PTM was becoming steadily worse; (2) traditional methods of treatment, such as steroids administered topically and intralesionally had failed; and (3) the results of in vitro susceptibility studies with fibroblast cultures had been encouraging since all four cytotoxic agents reduced the amount of hyaluronic acid produced by PTM fibroblasts. Melphalan and methotrexate had the greatest effect on PTM fibroblasts in tissue culture. In addition, melphalan was useful in the treatment of scleromyxedema, another disease involving dermal mucin deposition.[28] Clinically, melphalan had the greatest effect of the four drugs that were tried. The improvement, however, was temporary, and the PTM was worse four months later in spite of continued treatment.

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