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SHORT COMMUNICATION

Efficacy of Trimodality Therapy for Pretibial Myxoedema: A Case Series of 20 Patients

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Pretibial myxoedema (PTM) occurs in 0.5–4.3% of patients with Graves' disease (GD) and occasionally in Hashimoto's thyroiditis (1). It usually appears after the onset of severe Graves' ophthalmopathy (GO) (2) and can be classified into 4 forms: non-pitting oedema, plaque, nodular, and elephantiasic forms (2). The typical histopathological features of PTM are epidermal hyperkeratosis, accumulation of glycosaminoglycans (GAG), mainly hyaluronic acid in dermis and lymphocyte infiltration. The pathogenesis of PTM is unclear, but it appears to be the consequence of superimposition of immunological, cellular, genetic and mechanical factors (3). Thyroid-stimulating hormone receptor antibodies (TRAb) is the principal autoantibody for GD, GO and PTM.

A number of treatments have been reported for PTM, including localized and systemic glucocorticoid, oral octreotide, intravenous immunoglobulin, plasmapheresis, surgery and compressive therapy (3–5). We conducted an uncontrolled prospective study of combination therapy with topical glucocorticoid under occlusive dressing, intralesional injection with glucocorticoid and high-dose ultraviolet 1 (UVA1) phototherapy for patients with PTM. The clinical outcome was evaluated by recording the thickness of the dermis using ultrasonography (6) in addition to clinical evaluation.

METHODS

This study was conducted from March 2011 through November 2014 and was approved by the Institutional Review Board of Rui Jin Hospital. All subjects provided written informed consent. Diagnostic criteria included a history of Graves' hyperthyroidism, characteristic distribution of thickness over the pretibial skin and a biopsy finding consistent with PTM (GAG diffusely dispersed in the reticular dermis, stained with Alcian blue). In all patients, the titre of TRAb was > 40 U/l (normal range < 1.75 U/l). Two of the patients with nodular type PTM previously had intralesional steroid injection, which turned out to be inefficient. Severe dermopathy and small dosage of steroid may account for this; 5 other patients had been treated with intravenous steroid pulse therapy (methylprednisolone 500 mg for 3 days, 80 mg for 3 days followed by oral therapy with gradual tapering over 2–3 months) previously in other hospitals. The patients responded well to this therapy, but all relapsed in 2–5 months. The most common side-effect was development of Cushingoid facies ($n = 5$), hyperglycaemia ($n = 2$) and hypokalaemia ($n = 2$). The patients were initially admitted for 2 weeks for formal assessment and initiation of the trimodality therapy, after which treatment was continued in an outpatient setting. All patients were treated with topical glucocorticoid, intralesional glucocorticoid injection and high-dose UVA1 phototherapy for 12 consecutive weeks. A solution of 1 ml Diprospan (betamethasone dipropionate 5 mg, betamethasone disodium phosphate 2 mg, Schering-Plough) was prepared in a 1:4 dilution with 4 ml 2% lidocaine in a 5 ml syringe. Multipoint intralesional injections were conducted with a single-point dose of 0.5 ml solution, separated by approximately 2 cm between each point with a 26-gauge needle. The injection was repeated every 2–3 weeks, for a total of 12 weeks; the total dosage of Diprospan was 4–6 ml. Meanwhile, the patients applied topical Elocon (0.1% mometasone furoate cream, Schering-Plough) under occlusive dressing every other night for 12 weeks. The UVA1 cabin (Sigma, Shanghai, China) emits in the 340–400 nm range. UVA1 irradiance at the surface of the skin was approximately 65 mW/cm^2. The dose was 80 J/cm^2 per treatment. Frequency of phototherapy was 3 times a week for 2 weeks, twice a week for 2 weeks and once a week for 8 weeks. The total cumulative dose was 1,440 J/cm^2.

An ultrasound scanner Mylab90 (Esaote, Genova, Italy), equipped with LA523, 4–13 MHz probe, was used to record the dermal thickness (the depth of GAG deposition) either at the thickest plaque and nodule (plaque, nodular and elephantiasic form) or at the lower one-fourth of the distance between the fibular head and lateral malleolus (non-pitting oedema form) (6, 7).

Clinical outcome was assessed by the dermatologist along with the patient. Complete remission was defined as near absence of clinical dermopathy. Partial remission was defined as flattening of a plaque or nodule or reduction of oedema. No improvement was defined as no change or worsening (3).

Skin thickness at baseline was compared with after 12-weeks' treatment, by paired *t*-test using SPSS software. All data were expressed as mean value ± standard deviation (SD). The efficacy of the treatment was shown as the mean improvement of dermal thickness with 95% confidence interval (95% CI).

RESULTS

Twenty patients with PTM (9 females, 11 males) were included. The clinical features of the patients are summarized in Table SI[1]. Mean duration of GD was 4.75 years (range 1–15 years), GO was found in 18 out of 20 patients with a mean duration of 3.75 years (range 0.5–9.5 years) and the mean duration of PTM was 3.0 years (range 1 month–9 years). There were 8 patients with non-pitting oedema form, 6 with plaque form, 3 with nodular form, and 3 with elephantiasic form. Involvement of the hands was observed in 2 patients. One clinical example is shown in Fig. 1. All patients' histopathological features were consistent with PTM (results not shown). During skin biopsying, transparent jelly-like mucus was observed in 2 patients whose

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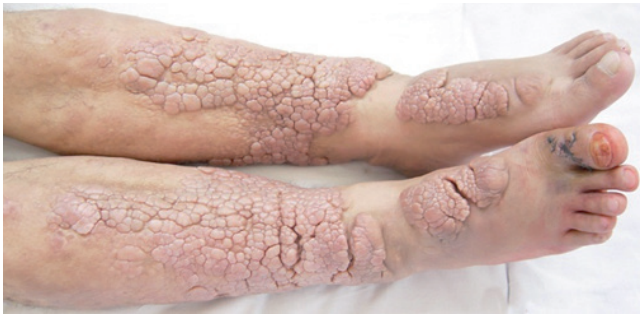

Fig. 1. Example of plaque form of pretibial myxoedema.

dermatopathy was characterized by soft, non-pitting oedema plaques with short duration. As to the prior treatments for GD, 11 patients received radioactive iodine therapy, 4 patients underwent thyroidectomy, and 5 patients were on anti-thyroid drugs. At baseline, patients were euthyroid without therapy ($n = 1$), on levothyroxine (L-T4) replacement ($n = 11$) and on anti-thyroid agents ($n = 8$). Seven patients underwent other treatments (intralesional injection of glucocorticoid in 2 patients and systemic glucocorticoid in 5 patients), with only partial remission and subsequent relapse of PTM.

At the end of the trimodality treatment, 8 and 12 patients achieved complete and partial remission, respectively. Dermal thickness was 5.55 ± 1.12 mm before and 2.63 ± 0.83 mm after treatment ($t = 18.86$, $p < 0.001$).

The main side-effect of the treatment consisted in a moderate to severe pain upon intralesional injection, and occurred in 14 patients.

The follow-up period ranged from 3 to 27 months (mean 12.3 months); one patient was lost to follow-up. The long-term effects were assessed in 14 patients who had been followed up > 12 months: near complete remission of PTM was observed in 5 patients, while 8 patients had a partial response. One patient had simultaneous relapse of skin lesions and aggravation of exophthalmos.

DISCUSSION

Our preliminary result indicates that the duration of PTM, as well as the severity of dermopathy, may play a critical role in the response to treatment, which is consistent with the results of an 11-year study on 30 patients with PTM in India (8).

Most of our patients had severe and extensive dermopathy, therefore we combined potent glucocorticoids under plastic wrap occlusion (to maximize efficiency), with long-acting glucocorticoid intralesional injections and UVA1 therapy.

High-dose UVA1 is defined as either an output of 70–130 J/cm^2 or a cumulative dose of 975–1,840 J/cm^2 (9). UVA1 has been shown to induce T-cell apoptosis, increase collagenase (matrix metalloproteinase-1, MMP-1) expression, decrease interferon (IFN)-γ levels, reduce the number of Langerhans cells and mast cells in the dermis (10) and to induce fibroblasts apoptosis (11).

No serious systemic side-effects were encountered in our trimodality therapy. The most frequent side-effect is pain during injection ($n = 14$). In order to minimize this sensation, we diluted 1 ml Diprospan with 4 ml 2% lidocaine before injection and used a 26-gauge syringe needle.

Limitations of this study are the small sample size, open design and short follow-up duration, which may lead to bias in the outcome of patients. Therefore, a randomized control trial will be necessary to enable comparison between the efficacy of this combined treatment and other treatment modalities.

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