Thyroid dermopathy responds to teprotumumab therapy

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Summary

Thyroid dermopathy is an uncommon manifestation of thyroid disease that impairs the quality of life in certain cases. Currently, the available treatments offer limited results and a chance of recurrence. Teprotumumab, a novel medication that results in the regression of thyroid ophthalmopathy, may have similar effects on dermopathy. We describe four patients treated with teprotumumab for their thyroid ophthalmopathy who concomitantly had dermopathy upon initiation of their infusions. Patients improved after two to three infusions and three out of the four patients have not suffered a recurrence. Teprotumumab is a monoclonal antibody (MAB) that attenuates an inflammatory response, resulting in decreased edema and tissue expansion. Given the similarities of their pathophysiology, we believe that the resolution of thyroid dermopathy and regression of thyroid eye disease occurs via the same mechanism. We encourage further investigation utilizing teprotumumab for patients whose dermopathy is associated with impaired quality of life.

Learning points:

- Thyroid dermopathy (TD), an uncommon manifestation of thyroid disease, may occasionally impair function and quality of life.
- There are only a few treatments for TD, with limited results and high rates of recurrence.
- Teprotumumab is a Food and Drug Administration-approved medication used for thyroid eye disease (TED).
- Our patients treated with teprotumumab for TED showed improvement of TD, which demonstrates its potential use for this condition.

Background

Thyroid dermopathy (TD), also known as pretibial myxedema, is an uncommon manifestation of thyroid disease, mostly associated with hyperthyroidism (90%) (1). The prevalence of TD in patients with Graves’ disease (GD) is 0.5–4.3%, and the presence of TD is almost always associated with thyroid ophthalmopathy, commonly known as thyroid eye disease (TED) (1, 2). Patients with TED and TD also typically have elevated thyroid-stimulating immunoglobulin (TSI). The dermopathy is often overlooked as the eye symptoms and signs are more alarming to the patient and family (2).

TD is usually clinically seen in the lower extremities, typically in the pretibial area, but can appear in the feet and toes, and uncommonly in upper extremities, shoulders, upper back, pinnae, and nose in isolated cases (2). Although lesions can be asymptomatic, they often have cosmetic sequelae, and occasionally can impair function and quality of life (2). There are four types of clinical variants:
nonpitting form (43%), plaque form (27%), nodular form (18%), and elephantiasic form (5%) (1).

Currently, the treatment options for thyroid dermatopathy are limited but include the management of risk factors (smoking and obesity) and thyroid dysfunction, local corticosteroid therapy (topical and injections), compressive therapy, and surgical resection. These approaches often have poor results, with recurrence of TD occurring commonly (2). In severe cases, oral corticosteroids have been tried with mixed results.

Complete remission can occur without intervention but takes several years (2). Recently, teprotumumab, a novel human monoclonal insulin-like growth factor 1 receptor (IGF-1R) inhibitor, has been approved in the US for the treatment of TED. Teprotumumab binds to the IGF-1R. In TED, TSI binds to IGF-1R creating a complex that promotes orbital inflammation (3). By reducing the downstream signaling due to the degradation of the antibody-receptor complex (3), recent work has demonstrated a marked reduction of extraocular muscle and orbital fat volume (4). It is therefore feasible that similar effects may be seen in the other sites of the body where soft tissue expansion has occurred (i.e. the skin and pretibial myxedema manifestation) because of autoimmune thyroid disease.

This case series reviews the impact that teprotumumab had on the concomitant TD in patients who were being treated for TED.

Case presentation

Patient 1

A 66-year-old man with a history of GD (TSI of 382% and thyroid-stimulating hormone (TSH) of 0.11 µIU/mL) treated with RAI (achieving a euthyroid state on a maintenance dose of levothyroxine 150 µg/day) and an 11-year history of progressive bilateral pretibial myxedema, presented to the clinic with new-onset proptosis, lid swelling, conjunctival injection, orbital pain, and diplopia. He was diagnosed with moderate-to-severe Graves' ophthalmopathy. His pretibial myxedema initially affected his distal shin portions of the right lower limb and posteriorly extending to both feet and toes. The pretibial myxedema impacted his quality of life, impairing his ability to walk (limitation of range of motion (ROM) of his ankle) and playing golf. He had increased shoe size and his pretibial myxedema was unsightly and accompanied by pigmentary changes (Fig. 1). The patient initially had a biopsy confirming the diagnosis of pretibial myxedema. Further treatment included multiple topical creams (including 1% hydrocortisone) and antibiotics. Compressive stocking provided short-term relief.

The patient entered a clinical trial and started on teprotumumab, receiving an initial dose of 10 mg/kg intravenously and 20 mg/kg intravenously every 3 weeks to complete a total of eight infusions over a 6-month period.

Patient 2

A 75-year-old Caucasian woman with a history of GD, diabetes, hypertension, anxiety, alcoholism, and opioid addiction presented with her second episode of severe TED, manifesting with bilateral proptosis, decreased vision, dysmotility. She also reported a several-year history of thyroid nonpitting pretibial dermopathy (TD). She had
been diagnosed with GD 19 years prior and had received RAI (at that time, her TSI index was 450% and TSH <0.7 µIU/mL). Her first episode of TED commenced 9 years after RAI, manifesting with progressive vision loss, proptosis, redness, and swelling of her eyelids. Treatment at that time included IV and oral corticosteroids, as well as bilateral orbital decompression and lateral tarsorrhaphy over her right eye. In this second bout of TED associated with TD, she was commenced on teprotumumab.

**Patient 3**

A 79-year-old African American man with GD, chronic kidney disease, and diabetes presented with pain, proptosis, vision loss, and thyroid nonpitting pretibial dermopathy. He was diagnosed with GD 4 years prior (TSI of 425% and TSH within limits). He had undergone right orbital decompression 2 years previously and subsequently developed worsening of his vision. Previous treatments also included IV steroids. CT scan of the orbits showed bilateral extraocular muscle enlargement with crowding of the optic nerve at the apex. The patient was initiated on teprotumumab.

**Patient 4**

A 52-year-old Caucasian female with GD (TSI of 111% and TSH of 0.1 mIU/L) disease presented with a 2-year history of TED. She had previously been treated for inflammatory orbital symptoms, proptosis, and diplopia with the EUGOGO recommended regimen of IV methylprednisolone. Her CT scan revealed bilateral enlargement of extraocular muscles and orbital fat. She also had bilateral pretibial myxedema that had occurred shortly after the diagnosis of TED. She received eight infusions of teprotumumab.

**Investigation**

Explained in case presentation.

**Treatment**

Treatment started is briefly described in the case presentation.

**Outcome and follow-up**

**Patient 1**

The patient showed a significant improvement of his pretibial myxedema after his third infusion. By the eighth infusion, the patient achieved an increased range of motion of both ankles, decreased shoe size, decreased edema, especially over his left hallux, and an improvement in his daily activities (Fig. 2). The patient’s TD remained stable for 12 months following his last infusion. A recurrence after 12 months has occurred; the patient states he would like retreatment with teprotumumab for his TD, as his TED was stable.

**Patient 2**

Her TD began to resolve after the second dose of teprotumumab and was completely resolved by the eighth

Figure 2

July 2018 after teprotumumab. Note that the nodular growth on the right leg has flattened significantly and overall swelling of both legs and ankles have decreased. Marked improvement in both halluxes, especially nodularity on left.
infusion. She has not had a further recurrence of the TD since her last infusion 1 year ago.

Patient 3
After three infusions of teprotumumab, improvement of TED occurred, evidenced by reduction of proptosis, periorbital edema, and eyelid erythema. His TD began to resolve after the second dose of teprotumumab and was completely resolved by the eighth infusion. The response has been durable with the patient’s last infusion 2 months ago.

Patient 4
The patient found that following treatment, there was a marked decrease in proptosis, with associated reduction of the orbital muscle and fat volume, along with a resolution of her TD. Her TD has not returned after 1 year since stopping her teprotumumab.

Discussion
Teprotumumab is a MAB that acts to block the IGF-1R and has been approved as a ‘breakthrough therapy’ for treatment for TED. Patients who received teprotumumab had reductions in (i) proptosis; (ii) the Clinical Activity Score (a scale measuring orbital inflammation); (iii) the Graves’ orbitopathy-quality of life survey; (iv) subjective diplopia (4, 5). IGF-1R, a tyrosine kinase receptor, is overexpressed by orbital fibroblasts and B and T cells in patients with thyroid ophthalmopathy (6). In TED, TSI forms a complex with the thyrotropin receptor and IGF-1R, which in turn causes hyaluronan production and cytokine expression (7). This results in edema and tissue expansion, creating the findings in TED. By blocking IGF-1R action, teprotumumab attenuates the thyrotropin receptor/IGF-1R complex signaling, thereby reducing inflammation and destruction (8).

Dermal fibroblasts also express IGF-IR and have been linked in the pathophysiology of TD (2, 9). Activation of these fibroblasts by increased TSI levels, promoting its binding to the IGF-IR resulting in increased production of proinflammatory cytokines and hyaluronan (2). Histopathologic features of pretibial myxedema demonstrate a large amount of hyaluronan accumulation in the reticular dermis and subcutaneous tissue and lymphocytic infiltration, similar to the changes seen in patients with TED (2).

Given the similarities in pathophysiology between soft tissue expansion in TED and TD, it is likely that the resolution of TD which occurred in our patients was due to inhibition of the IGF-1R cascade with Teprotumumab. Varma et al. described a case of resolution of TD after teprotumumab therapy, where their patient also responded after the second dose (case reported after completing seven of eight infusions) (10). Our case series extends the observations of Varma et al. to provide a longer period of observation and suggests a durable response to teprotumumab therapy on TD.

Clinical trials have demonstrated that patients tolerate teprotumumab well (11). Most adverse effects (AEs) were transient and resolved while patients continued in their study group (4, 5). The most common side effects reported are muscle spasms (25%), nausea (17%), alopecia (13%), diarrhea (12%), fatigue (12%), hyperglycemia, and hearing impairment (10%) (11). Serious AEs were uncommon in both trials (11). Due to the increased risk of diarrhea, special attention is to be placed on patients with inflammatory bowel disease due to the increased risk of exacerbation. Hyperglycemia was reported in 10% of patients, regardless of if they were diabetics or not. However, these values were controlled with medication and diet adjustment and levels returned to baseline after completion of teprotumumab in all patients (11). Hearing impairment was also reported in five patients, which all resolved (4). However, in a recent report by Kossler et al. (12) where 28 patients were followed receiving teprotumumab infusion and 46% complained of hearing symptoms. Three of these patients (23%) had sensorineural hearing loss, where one experience improvement of symptoms while the other two had not after 3 months (12). Further follow-up is not discussed.

Our case series has limitations due to the small number of patients and lack of long-term follow-up teprotumumab has only recently been approved). However, our results are compelling due to the clear-cut improvement of TD in all, with full remission in most (3/4) in the same short timeframe after teprotumumab initiation. It appears therefore, teprotumumab has a similar effect on the TD as it does on the TED. To our knowledge, there are no reported cases of TED recurrence after teprotumumab therapy in the literature. We believe that decisions about the further need for retreatments must be taken after more data are collected.

There are limited options for the treatment of TD and given its potential to have functional and quality of life impacts on those affected, further work is encouraged, and it is envisioned that this case series could serve as the impetus.
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Declaration of interest
R D – Consultant Horizon Therapeutics, Immunovant Corporation, Veridian Corporation; K C – Consultant Horizon Therapeutics, Veridian Pharmaceuticals and 3T Ophthalmics; J S, R D, and R T – involved in clinical trials funded by Horizon; J S and R T – advisory board for Horizon; R C and D L G – no conflict of interest.

Funding
This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Patient consent
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Author contribution statement
R T and J S conceptualized the manuscript. R C T was the lead administrator and devised the project. D L G, S U, K C, and R D wrote the case reports. All authors contributed with data analysis and discussion. R C T, J S, and S U revised bibliography and wrote the manuscript with input from all authors. All authors discussed the results and contributed to the final manuscript.

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Received in final form 1 February 2022
Accepted 21 February 2022