Rituximab therapy for a severe case of pretibial myxedema

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Key words: Graves disease; pretibial myxedema; rituximab; thyroid-stimulating hormone receptor antibody.

INTRODUCTION
Pretibial myxedema (PTM) (thyroid dermopathy) is a known manifestation of Graves disease (GD), commonly presenting as localized, circumscribed, or infiltrated plaques over the pretibial areas. PTM is present in up to 4.3% of GD patients and in 15% of patients with Graves ophthalmopathy.1 Rituximab (RTX) has shown potential to become a novel therapy for the treatment of severe cases of Graves ophthalmopathy in recent years; however, it is not well-documented for the treatment of PTM.2 We present a case of a patient with severe PTM refractory to systemic, intralesional, and topical corticosteroid therapy and compression, who showed a rapid and sustained response when treated with RTX in addition to topical corticosteroids under occlusion. The objective markers of improvement included a reduction in calf and ankle measurements, loss of swelling of the fingers and toes, and a reduction in thyroid-stimulating hormone receptor antibodies (TSHR-ab).

CASE DESCRIPTION
A 27-year old woman presented to the dermatology clinic with firm infiltrated plaques located on the toes, feet, and pretibial areas, and hypertrophy of the fingers consistent with PTM. She had an 8-year history of hypothyroidism and subsequent GD and ophthalmopathy status post-irradiation. A diagnosis of PTM had been confirmed with punch biopsies of the bilateral lower aspects of the legs revealing dermal mucinosis, 1 year earlier. For the past year and a half the treatments that were trialed included prednisone 10 mg daily for 6 weeks, 0.05% clobetasol ointment twice daily under occlusion, 0.05% betamethasone cream twice a day under occlusion, and intralesional triamcinolone 10 mg/mL. At the time of presentation, her medications included levothyroxine 175 mcg daily and 0.05% betamethasone dipropionate cream twice daily under occlusion, with daily use of compression stockings. RTX therapy 1, 000 mg given 2 weeks apart with continued use of 0.05% betamethasone dipropionate cream twice daily under occlusion was initiated as an alternative option, given lack of response to previous therapy and persistently elevated TSHR-ab levels.

Three months after her first RTX infusion, the patient presented for follow-up with softening of the indurated plaques present on her bilateral lower aspects of the legs, dorsal feet, hands, and digits with a reported improvement of itching and discomfort in the areas of swelling (Fig 1, A). Measurements of the left and right ankle circumferences marked by the site of her prior skin biopsies were 29.8 cm and 30.5 cm, respectively. Her levothyroxine dose had also recently been decreased to 150 mcg daily by her endocrinologist. Lab-based evaluation revealed a decreased TSHR-ab level of 28.7 IU/L from 33.9 IU/L (N < 1.75 IU/L) 6 months earlier.

The patient received 3 additional RTX infusions, every 6 months, during which time she also

Abbreviations used:
GD: Graves disease
PTM: pretibial myxedema
RTX: rituximab
TSHR-ab: thyroid-stimulating hormone receptor antibodies

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Funding sources: None.

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JAAD Case Reports 2021;10:28-30.
continued daily use of betamethasone cream under occlusion. Follow-up exams after each infusion revealed a gradual reduction in the induration and swelling of the lower aspects of her legs, with near-complete resolution of the swelling in her toes and fingers (Fig 1, A-D). After her fourth RTX infusion, her left and right ankle measurements had decreased to 28.1 cm and 29.3 cm, respectively. TSHR-ab levels had also decreased to 20.9 IU/L.

DISCUSSION

PTM is a rare extrathyroidal manifestation of GD and often correlates with the severity of the disease. The condition results from the abnormal accumulation of hydrophilic glycosaminoglycans in the dermis that are secreted by dermal fibroblasts under the stimulation of local cytokines by what has been hypothesized to be overactivation of autoantibodies directed at TSHR-ab, although the exact pathogenesis is not clearly understood. The chronic production of mucinous edema leads to variable clinical findings of non-pitting edema, or localized, waxy, indurated plaques or nodules. Lesions are often localized to the anterior and lateral surfaces of both tibias, but may also be found in other sites exposed to pressure or repetitive trauma.

The mainstay of pharmacologic treatment for PTM includes medium-to-high-potency systemic corticosteroids with or without occlusion or intralesional corticosteroids. RTX is an anti-CD20 monoclonal antibody, which has been used successfully for treatment of Graves ophthalmopathy. Despite a similar proposed immunopathogenesis, RTX has only been documented as a treatment for refractory PTM in few cases. By depleting B-lymphocytes, the medication may also cause a decreased production of pathogenic autoantibodies, such as TSHR-ab, the serum levels of which correlate positively with severity and progression of extrathyroidal manifestations of GD.

Our patient had a minimal response to corticosteroid treatments, which led to the addition of RTX to her current regimen of topical corticosteroids. Not only did her symptoms and the appearance of her skin improve, she also went from struggling to even wear shoes prior to RTX treatments to now being

Fig 1. Pretibial myxedema of the bilateral aspects of the lower legs and toes prior to (A,B) and after (C,D) receiving a total of 4 rituximab infusions (tattoos were covered in A and C). PM, pretibial myxedema; RTX, rituximab.
able to wear athletic shoes. This response was also evident in the reduction of her measured ankle swelling and in all 3 post-infusion serum TSHR-ab levels. Given her response, the patient will continue to receive RTX infusions pending a continued improvement, with the goal to minimize her symptoms while reaching undetectable antibody titers.

RTX is reported to be well-tolerated for the treatment of GD, with most adverse effects being infusion-related and few cases of adverse reactions involving gastrointestinal symptoms and arthralgias.\textsuperscript{2} The patient presented here had no adverse effects to rituximab; however, transient hypertension and injection-site thrombophlebitis has been reported in a patient receiving RTX specifically for PTM.\textsuperscript{6} Consideration should also be given to the risks of repeated RTX infusions such as hepatitis B infection/reactivation and cytopenias.\textsuperscript{7} Hypogammaglobinemia and susceptibility to infectious agents, such as the JC virus, is rarely reported for RTX used for other autoimmune conditions.\textsuperscript{8}

In conclusion, our case highlights RTX as an effective therapy when used in addition to topical corticosteroids for a patient struggling with a refractory case of PTM. While future documented evidence is necessary to determine the extent of its therapeutic benefits, we encourage practitioners, as well as patients struggling with this condition, to consider RTX as a potential option for treatment.

Conflicts of interest

None disclosed.

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