

# An atypical presentation of pretibial myxedema in a euthyroid patient with absent antithyroid autoantibodies



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**Key words:** autoantibodies; euthyroid; myxedema; pretibial myxedema; radiation; thyroid disease; topical corticosteroids.

## INTRODUCTION

Pretibial myxedema (PTM) is a rare form of thyroid dermopathy caused by increased production of glycosaminoglycans by fibroblasts in the reticular dermis of the anterior lower legs.<sup>1</sup> It most commonly affects women in their fifth or sixth decade of life and is observed almost exclusively in association with Graves' disease, typically developing 1 to 2 years after disease onset.<sup>1</sup> However, there are several reports of PTM occurring in association with Hashimoto's thyroiditis,<sup>2</sup> idiopathic hypothyroidism,<sup>3</sup> and even in patients without thyroid disease.<sup>4,5</sup>

Herein, we report a unique case of the diffuse swelling variant of PTM occurring 16 years after the development of radiation-induced hypothyroidism complicated by hemithyroidectomy years later. The absence of thyroid-directed autoantibodies, the symmetric and circumferential nature of the PTM, and the euthyroid status of the patient at the time of diagnosis are all distinctive features of this case.

## CASE REPORT

A 77-year-old man was seen for a 3-week history of asymptomatic redness and swelling on the dorsal surface of his feet with gradual extension symmetrically up his lower legs, stopping below the knees. He denied having any associated fevers or chills. He was hospitalized for suspected bilateral cellulitis after 7 days of outpatient treatment with trimethoprim-sulfamethoxazole failed.

His past medical history was notable for T0N2M0 p16+ squamous cell carcinoma of the cervical lymph nodes, which was treated with nodal excision plus

### Abbreviations used:

PTM: pretibial myxedema  
TSH: thyroid-stimulating hormone  
TSH-R: TSH receptor

adjuvant cisplatin and radiation therapy in 2004. He remained in remission until February 2015, when extensive local recurrence in the left oropharynx was treated with total laryngectomy, bilateral neck dissection, and right hemithyroidectomy with 2 months of adjuvant cetuximab and radiation. In 2005, postradiation hypothyroidism developed in the patient, requiring thyroid hormone replacement therapy with levothyroxine. Between 2005 and 2020, he was noted to have elevated thyroid-stimulating hormone (TSH) levels at least once per year caused by self-reported noncompliance with medication.

The initial physical examination revealed sharply demarcated, bright pink-red, partially blanching, thin plaques with fine scale on the dorsal surfaces of both feet extending symmetrically and circumferentially to just below the knees (Fig 1).

Peau d'orange-like surface changes were absent. One-plus pitting edema was present to the mid-shins. Periorbital edema, eyelid retraction, exophthalmos, and digital swelling and clubbing were absent. Laboratory findings revealed mild leukopenia (3.3 K/ $\mu$ L) and minimally elevated brain natriuretic peptide (230 pg/mL). Levels of TSH (2.85 mU/L), thyroglobulin antibody (<1 IU/mL), thyroid peroxidase antibody (<1 IU/mL), and thyroid-stimulating antibody (<89% of baseline,

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Funding sources: None.

IRB approval status: Not applicable.

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JAAD Case Reports 2021;12:88-90.

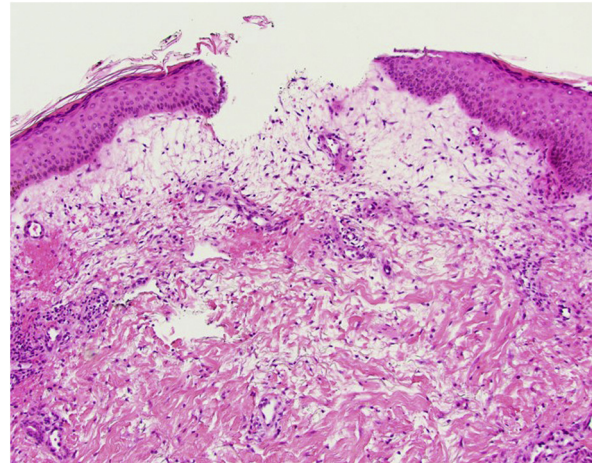
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<https://doi.org/10.1016/j.jidcr.2021.04.018>



**Fig 1.** Prebiopsy photograph of the right lower leg demonstrating sharply demarcated, circumferential, bright pink-red, thin plaque with fine scaling of the lower leg. These findings were observed symmetrically on both lower legs.



**Fig 2.** Histopathology of right shin biopsy showing papillary dermal edema, extravasated erythrocytes, and sparse perivascular lymphocytic inflammation in the papillary dermis, with strands of mucin and splaying of collagen fibers in the deep dermis. (Hematoxylin-eosin stain; original magnification:  $\times 20$ .)

reference range  $\leq 140\%$  of baseline) were unremarkable.

A 3-mm punch biopsy was performed on the right shin. Hematoxylin and eosin staining demonstrated papillary dermal edema, extravasated erythrocytes, and sparse perivascular lymphocytic inflammation with strands of mucin and splaying of collagen fibers in the reticular dermis (Fig 2) consistent with PTM.

Topical triamcinolone 0.1% ointment twice daily, compression stockings, and frequent leg elevation were initiated. At the 6-week follow up, the patient's examination findings had changed dramatically. The plaques had become reddish-brown with both peau d'orange and cobblestone surface changes (Fig 3, A and B), representing a mixed clinical variant of PTM.

## DISCUSSION

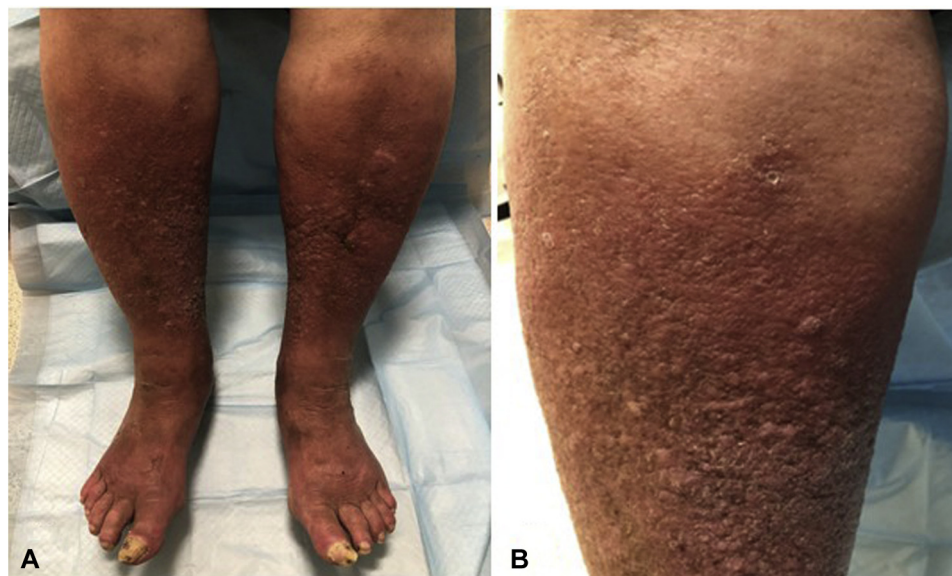
PTM is a clinical diagnosis, although skin biopsy may be indicated in atypical or equivocal cases. On hematoxylin and eosin staining, large amounts of mucin can be seen throughout the dermis, with resultant splaying of collagen fibers.<sup>1</sup>

The role of PTM in the classic triad of extrathyroidal manifestations of Graves' disease has been extensively documented. Ophthalmopathy develops in approximately 20% to 40% of patients with Graves' disease, with eyelid retraction, exophthalmos, and/or blurry vision. PTM will develop in 4% to 13% of these patients. Among those with PTM, acropachy, the most severe form of thyroid dermopathy, characterized by digital swelling and clubbing, will subsequently develop in 20% of patients. The development of dermopathy in the absence of ophthalmopathy is exceedingly rare.<sup>1</sup>

The pathogenesis of PTM is not fully understood. The leading hypothesis, that TSH receptor (TSH-R) antibodies directly stimulate fibroblasts to produce glycosaminoglycans, has been supported by multiple retrospective clinical studies and in vitro experiments on tissue fibroblasts.<sup>1</sup> A recent case-control study of 400 cases of PTM and 800 controls selected at random using a 1:1 male-to-female allocation scheme equally across 8 age groups (400 with Graves' disease and no PTM and 400 patients without known thyroid disease) found a strong correlation between TSH-R antibody titer and the presence of PTM (odds ratio 42.93).<sup>6</sup> In our patient and in other cases reported in the literature, TSH-R antibodies were negative.<sup>4,5</sup> Clearly, an alternative driving mechanism must exist in these cases, but it remains unknown.

A recent case series of 216 patients identified six major clinical variants of PTM: diffuse swelling (44.4%), nodule (20.8%), plaque (15.3%), mixture (7.9%), elephantiasis (6.9%), and tumor (4.6%). PTM was noted to progress through distinct clinical stages: active, stable, sclerotic, and recession. Although patients often oscillated between stages, all clinical variants could progress to more severe and debilitating disease if left untreated. This progression was correlated with TSH-R antibody titers and the degree of perivascular lymphocytic infiltration.<sup>7</sup>

Intralesional and topical corticosteroids are considered first-line therapy for PTM, although topical application appears to be significantly less effective.<sup>1,8,9</sup> Zhang et al<sup>8</sup> reported nearly 100%



**Fig 3.** **A**, Symmetric, well-demarcated, reddish-brown plaques over the dorsal surfaces of both feet and the lower legs with areas of peau d'orange and cobblestone surface changes. **B**, Close-up of the right medial lower leg highlighting the peau d'orange and cobblestone surface changes.

complete response rates to weekly injections of intralesional triamcinolone 10 mg/mL for all variants with the exception of elephantiasis, which had a partial response in 73% of patients. In a case series of 178 patients with PTM, only 20.8% of the 96 patients treated with topical corticosteroids achieved complete remission over an average of 8.8 years.<sup>9</sup> Alternative therapies for PTM with variable efficacy have been reported, including pentoxifylline, octreotide, plasmapheresis, radiotherapy, excision, and intralesional hyaluronidase.<sup>1,10</sup>

This case has several distinguishing features. Foremost, the brightly erythematous and circumferential presentation of the diffuse swelling PTM variant can lead to diagnostic confusion with bilateral cellulitis. Second, the absence of TSH-R antibodies, although previously reported,<sup>4,5</sup> is atypical in PTM. Although we were unable to identify any cases of PTM occurring in the setting of radiation-induced hypothyroidism, only one other case of PTM developing after partial thyroidectomy in a patient with negative thyroid antibodies has been published.<sup>5</sup> Although both patients were euthyroid at the time of presentation, our patient had large fluctuations in TSH levels due to inconsistent compliance with thyroid replacement therapy, whereas PTM developed in the above-cited patient despite consistent euthyroidism for 15 years. Finally, these cases provide further anecdotal evidence that an alternative mechanism or alternative mechanisms other than

TSH-R antibody stimulation of fibroblasts must exist in the pathogenesis of PTM.

#### Conflicts of interest

None disclosed.

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