



Painless nodules on legs

The location of the nodules and the patient's history were important diagnostic clues. The punch biopsy confirmed our suspicions.

A 34-YEAR-OLD MAN presented with a 6-month history of asymptomatic, progressively enlarging subcutaneous nodules over his bilateral lower legs. He denied any history of injury, and there was no bleeding or discharge. The patient had a history of Graves disease that had been treated with radioiodine therapy 2 years prior, followed by thyroxine replacement (150 mcg/d, 5 d/wk and 125 mcg/d, 2 d/wk). At the time of presentation, his thyroid function tests indicated subclinical hypothyroidism: free T4, 21.2 pmol/L (normal range, 11.8-24.6 pmol/L) and thyroid-

stimulating hormone (TSH), 14.07 mIU/L (normal range, 0.27-4.2 mIU/L).

Examination revealed nontender, soft brown nodules over the bilateral shins, with minimal overlying lichenification (FIGURE 1). There was no *peau d'orange* (orange peel) appearance to suggest significant edema. A punch biopsy was performed.

- WHAT IS YOUR DIAGNOSIS?
- HOW WOULD YOU TREAT THIS PATIENT?

FIGURE 1

Subcutaneous nodules without significant epidermal change



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**Diagnosis:
Pretibial myxedema**

The patient's history, paired with the results of the punch biopsy, were consistent with a diagnosis of pretibial myxedema, part of the triad of Graves disease along with thyroid ophthalmopathy and acropachy (soft-tissue swelling of the hands and clubbing of the fingers). Histopathologic findings revealed wide separation of collagen bundles throughout the entire reticular dermis without fibroplasia (FIGURE 2A). The spaces contained basophilic strands (FIGURE 2B), and the strands stained strongly positive on Alcian blue (FIGURE 2C), confirming the presence of dermal mucin. Widely separated collagen fibers and deposited mucin are indicative of pretibial myxedema. No granulomas or lymphoid proliferations were seen.

■ **The pathogenesis** of pretibial myxedema is widely postulated to be due to the stimulation of dermal fibroblasts by anti-TSH antibodies, causing overproduction of glycosaminoglycans and hyaluronic acid¹ and obstructing lymphatic microcirculation, resulting in nonpitting edema.²

■ **There are 5 distinct clinical variants** of pretibial myxedema^{1,3}:

- **The diffuse form** is the most common. It manifests on the lower leg with hard, nonpitting edema

and cutaneous thickening.

- **The plaque form** manifests on the lower leg as well-demarcated erythematous or pigmented flat-topped lesions.
- **The nodular form**, which our patient had, typically manifests on the lower leg as well-demarcated erythematous, pigmented, or skin-colored raised, solid lesions. There may be 1 lesion or several.
- **The mixed form** manifests as 2 or more of the other variants.
- **The elephantiasic form** is the rarest and the most severe. There are widespread swollen nodules and plaques on the lower legs and/or arms.

A rare, late manifestation

Although pathognomonic for Graves disease, pretibial myxedema is a late manifestation that occurs in less than 5% of these patients.⁴ The most common site of involvement is the pretibial region, although less common sites include the face, arms, shoulders, abdomen, pinna, and the location of previous scars.⁴

While pretibial myxedema usually is associated with hyperthyroidism, it can occur after treatment (as was the case here), while the patient is in a euthyroid or hypothyroid state. Radioiodine therapy has been reported to be a trigger for pretibial myxedema in 1 case report, although the pathophysiology is not fully understood.⁵

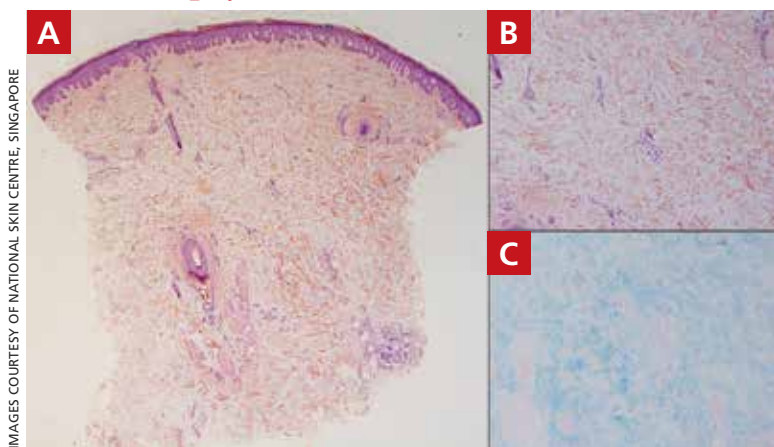
More serious conditions must be ruled out

The differential for painless nodules includes cutaneous lymphoma and atypical infections of fungal or mycobacterial etiology.

■ **Cutaneous lymphoma** that manifests with leg tumors includes primary cutaneous anaplastic CD30+ large cell lymphoma (PCALCL) and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBL-LT). The former may occur in young patients, whereas the latter tends to manifest in the elderly. Biopsy shows a neoplastic proliferation of atypical lymphocytes within the dermis,⁶ differing from our case.

■ **Atypical infections** may be detected

FIGURE 2
Punch biopsy confirmed the Dx



IMAGES COURTESY OF NATIONAL SKIN CENTRE, SINGAPORE

The epidermis was hyperplastic and the reticular dermis revealed widely spaced collagen bundles throughout the entire thickness (A) (hematoxylin and eosin, original magnification 12.5x). The spaces contained deposits of mucin, appearing as basophilic strands (B) (hematoxylin and eosin, original magnification 40x). Alcian blue stain was strongly positive, confirming the presence of mucin (C) (Alcian blue, original magnification 40x).

through bacterial, mycobacterial, or fungal cultures, and may be accompanied by elevated inflammatory markers or other systemic symptoms of the infection, setting it apart from pretibial myxedema.

Treatment is simple and noninvasive

Pretibial myxedema is usually asymptomatic, with minimal morbidity. The nodular variant may resolve spontaneously; thus, therapeutic management often is reserved for severe cases or for those with cosmetic concerns. Treatment options include mid- to high-potency topical corticosteroids with an occlusive dressing for 1 to 2 weeks (or until resolution) or an intralesional triamcinolone injection (5-10 mg/mL, single or monthly until resolution), compres-

sion stockings, and pneumatic compression.²

This patient was treated with a single intralesional injection of triamcinolone 10 mg/mL. The nodules resolved within a month. **JFP**

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CLINICAL INQUIRIES

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Editor's takeaway

The available evidence on vaginal estrogen replacement reassures us of its safety. After decades spent studying hormone replacement therapy with vacillating conclusions and opinions, these cohorts—the best evidence we may ever get—along with a consensus of expert opinions, consistently demonstrate no adverse CV outcomes. **JFP**

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