Pretibial myxedema in a patient with HIV and hypothyroid to hyperthyroid transformation

Maggie Chen, BS, Shealinna Ge, MD, and Marcia Driscoll, MD, PharmD

Key words: human immunodeficiency virus; hyperthyroidism; pretibial myxedema.

INTRODUCTION

Pretibial myxedema is a complication of Graves' disease presenting with nonpitting edema in the pretibial region due to the intradermal mucin deposition.[1] Pretibial myxedema develops in ≤5% with Graves' thyrotoxicosis and 15% of patients with Graves' ophthalmopathy.[1] However, rare cases have been reported in the setting of hypothyroidism or euthyroidism.[1,2] We present a rare case of pretibial myxedema in a patient with history of hypothyroidism and HIV infection with hyperthyroid transformation.

CASE REPORT

A 41-year-old African American woman presented with a 1-year history of dark plaques on bilateral shins that expanded to involve the dorsal feet. There is no associated drainage, discharge, pruritus, or pain. On examination, hyperpigmented indurated plaques with boggy nonpitting edema were observed on the lower shins extending to the dorsal feet bilaterally (Fig 1). Exophthalmos was also noted. Her medical history included a 12-year history of hypothyroidism treated with levothyroxine 100 mcg, thyroid stimulating hormone (TSH) (4.68 uIU/mL), and free T4 (0.49 ng/dL) levels 6 months before the presentation were consistent with a hypothyroid state. The patient also had a history of HIV treated with antiretroviral therapy (ART) since 2012 and was taking bictegravir 50 mg/emtricitabine 200 mg/tenofovir 25 mg. HIV viral load and CD4 count 1 month prior to the presentation were 98 copies/mL and 422 cells/mm^3, respectively. Biopsy from the left shin showed large amounts of mucin deposition in the reticular dermis, confirmed by a colloidal iron stain (Fig 2). Diagnosis of pretibial myxedema was relayed to the patient's endocrinologist, and she was subsequently found to be in a hyperthyroid state with positive thyroid stimulating immunoglobulins (421 IU/mL) and thyroid peroxidase antibodies (12 IU/mL) with TSH <0.02 uIU/mL.

Fig 1. Hyperpigmented indurated plaques with boggy nonpitting edema in bilateral lower shins and dorsal feet.

DISCUSSION

Pretibial myxedema is associated with autoimmune thyroid disease, most frequently Graves'

From the Department of Dermatology, University of Maryland School of Medicine, Baltimore, Maryland.

Funding Source: None.

IRB approval status: Not applicable.

Correspondence to: Shealinna Ge, MD, University of Maryland School of Medicine, Department of Dermatology, 419 W Redwood Street, Suite 235, Baltimore, MD 21201. E-mail: SGe@som.umaryland.edu.

JAAD Case Reports 2023;36:75-7.

2352-5126

https://doi.org/10.1016/j.jdcr.2023.04.005

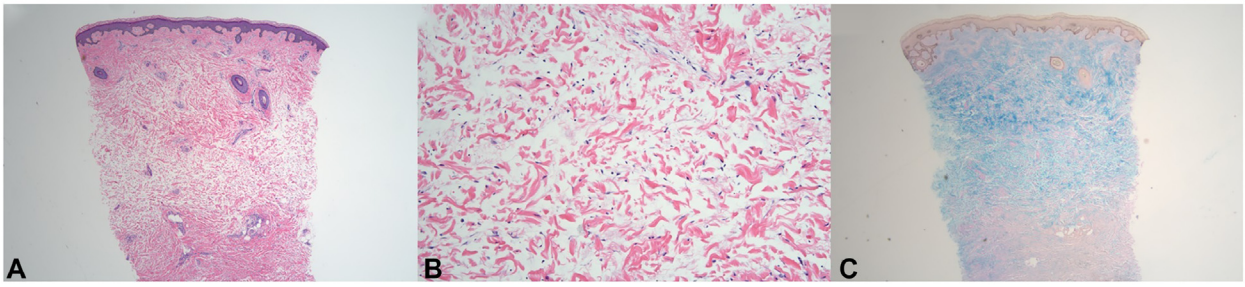

Fig 2. Unremarkable epidermis with significant mucin deposition in the reticular dermis, causing separation of the collagen fibers (original magnifications: **A,** ×10; **B,** ×40), confirmed by a positive colloidal iron stain (original magnification: **C,** ×10).

disease. The classic presentation of pretibial myxedema includes indurated nonpitting edematous plaques and nodules in the pretibial area and occasionally in the feet and toes. Lesions are usually asymptomatic, but can lead to cosmetic or functional sequelae.[1] Histological evaluation of pretibial myxedema reveals large amounts of mucin deposition in the reticular dermis causing the separation of collagen fibers without inflammation.[1,2]

In Graves' disease, binding of autoantibodies (TSHR-Abs) to thyrotropin receptors (TSHR) mimics TSH's effect and activates thyroid follicular cells, inducing elevated thyroid hormone synthesis and secretion.[3] TSHR-Abs binding to TSHR on orbital and cutaneous fibroblasts may directly promote their activation, proliferation, and subsequent overproduction of glycosaminoglycans (GAGs) in the dermis and subcutaneous tissue, causing findings of Graves' ophthalmopathy and pretibial myxedema.[1,4] Cutaneous T cells may play an indirect role in fibroblast activation via cross-sensitization to morphologically similar antigens expressed by thyroid follicular cells and fibroblasts, such as parts of the TSH receptor.[1] Subsequent dermal infiltration and cytokine release by sensitized T cells may encourage GAG production.[1] Localization to the pretibial area is likely due to local factors such as dependent position and mechanical stress.[1]

Patients with the highest TSHR-Abs titers typically have the most severe form of Graves' disease.[4] However, TSHR-Abs can prevent TSH binding to TSHR and ultimately lead to thyroid atrophy and hypothyroidism. This may explain the poor correlation between the thyroid function and the serum TSHR-Abs titers.[4]

Pretibial myxedema tends to persist unless treated, and can be managed symptomatically with topical or intralesional corticosteroids and compression therapies.[1] Smoking cessation and normalization of thyroid function are recommended, but may not improve pretibial myxedema.[1] However, a retrospective case series of 178 patients found that more than half of the patients who were not treated achieved partial or complete remission within 25 years.[1]

Conversion from hypothyroidism to hyperthyroidism/Graves' disease

The appearance of pretibial myxedema associated with conversion from hypothyroidism to hyperthyroidism is rare.[1] In one such instance, the authors speculated that hyperthyroidism development may be due to excessive levothyroxine.[2] However, TSH remained suppressed and TSHR-Ab was found even after reduction of levothyroxine dosage, supporting a diagnosis of Graves' disease.[2] In another case, hyperthyroidism, ophthalmopathy, and prominent pretibial myxedema developed in a patient with a longstanding history of Hashimoto's thyroiditis.[5] The authors surmised that de novo TSHR-Ab synthesis enabled the conversion from Hashimoto thyroiditis to Graves' disease.[5]

The mechanism of hyperthyroidism arising in the setting of chronic hypothyroidism is unclear, but several theories have been proposed. Some suggest that the balance of stimulatory and inhibitory TSHR-Abs can be influenced by environmental triggers leading to changes in thyroid status.[6] Others postulate that variable interactions between TSHR-Abs and TSHR may be responsible for this conversion.[6] Another theory suggests that thyroid damage may lead to initial hypothyroidism, but the subsequent development of TSHR-Abs can stimulate thyroid tissue recovery, leading to hyperthyroidism.[6] Further studies are required to elucidate the mechanisms underlying the conversion of hypothyroidism to hyperthyroidism.

Relationship to HIV

Viral infection and immune-modulating agents are risk factors for Graves' disease.[7] Graves' disease developed in some patients with HIV during immune reconstitution, but the mechanism remains unclear.[8] The rapid expansion of naïve CD4 and CD8 T cells

following ART[9] may cause immune restoration disease and the development of autoreactive T cells and autoantibodies,[10] especially in those who are lymphopenic. As a result, thyroid function tests prior to ART induction have been suggested for patients with HIV.[9] Although hyperthyroidism has been reported following ART initiation, the development of hypothyroidism is more common. Additional studies exploring the association between HIV, ART, and thyroid dysfunction should be pursued.

CONCLUSION

We present the case of a 41-year-old African American woman with a longstanding history of hypothyroidism and HIV infection with conversion to hyperthyroidism with exophthalmos and pretibial myxedema. Pretibial myxedema is often associated with Graves' disease and typically presents with indurated nonpitting edematous plaques and nodules in the pretibial region. Circulating TSHR-Abs not only induced thyroid hormone synthesis and secretion, but also localized overproduction of GAGs causing the eye and skin findings in Graves' disease. Our patient's conversion from hypothyroidism to hyperthyroidism in the setting of HIV is rare and not well understood. The combination of stimulatory and inhibitory TSHR-Abs-, HIV-, and ART-mediated immune reconstitution may play a role. Additional studies are needed to determine the role of HIV and ART agents in the conversion of hypothyroidism to hyperthyroidism.

Conflicts of interest

None declared.

REFERENCES

1. Fatourechi V. Pretibial myxedema: pathophysiology and treatment options. *Am J Clin Dermatol*. 2005;6(5):295-309. https://doi.org/10.2165/00128071-200506050-00003
2. Bruinstroop E, Cairo I, Drillenburg P, van Dam PS. Hypothyroidism to Graves' disease and late appearance of pretibial myxoedema. *Lancet*. 2019;394(10206):1364. https://doi.org/10.1016/S0140-6736(19)32281-0
3. Dong YH, Fu DG. Autoimmune thyroid disease: mechanism, genetics and current knowledge. *Eur Rev Med Pharmacol Sci*. 2014;18(23):3611-3618.
4. Ando T, Latif R, Davies TF. Thyrotropin receptor antibodies: new insights into their actions and clinical relevance. *Best Pract Res Clin Endocrinol Metab*. 2005;19(1):33-52. https://doi.org/10.1016/j.beem.2004.11.005
5. Kamath C, Young S, Kabelis K, et al. Thyrotrophin receptor antibody characteristics in a woman with long-standing Hashimoto's who developed Graves' disease and pretibial myxoedema. *Clin Endocrinol (Oxf)*. 2012;77(3):465-470. https://doi.org/10.1111/j.1365-2265.2012.04397.x
6. Ahmad E, Hafeez K, Arshad MF, Isuga J, Vrettos A. Hypothyroidism conversion to hyperthyroidism: it's never too late. *Endocrinol Diabetes Metab Case Rep*. 2018:18-0047. https://doi.org/10.1530/EDM-18-0047
7. Graves' disease. *Nat Rev Dis Primers*. 2020;6(1):53. https://doi.org/10.1038/s41572-020-0195-8
8. Visković K, Stemberger L, Brnić Z, Begovac J. Repeated presentation of Graves' disease as a manifestation of immune reconstitution syndrome in an HIV-infected patient taking HAART: case report. *Acta Clin Croat*. 2013;52(1):125-127.
9. Madeddu G, Spanu A, Chessa F, et al. Thyroid function in human immunodeficiency virus patients treated with highly active antiretroviral therapy (HAART): a longitudinal study. *Clin Endocrinol (Oxf)*. 2006;0(0):060222010233012. https://doi.org/10.1111/j.1365-2265.2006.02472.x
10. Sheikh V, Dersimonian R, Richterman AG, et al. Graves' disease as immune reconstitution disease in HIV-positive patients is associated with naive and primary thymic emigrant CD4+ T-cell recovery. *AIDS*. 2014;28(1):31-39. https://doi.org/10.1097/QAD.0000000000000006