



Pretibial Myxedema: Paradoxical Manifestation of Thyroid Dermopathy after I-131 Ablation Therapy

Bing-Sian Lin¹, Yi-Hsien Chen², Chih-Tsung Hung²

Departments of ¹Medicine and ²Dermatology, National Defense Medical Center, Tri-Service General Hospital, Taipei, Taiwan

Pretibial myxedema (PM) is an unusual extrathyroidal manifestation of Graves' disease (GD), which affects approximately 1%–5% of the patients. In addition, PM usually occurs in the hyperthyroid state of GD, and the high level of thyroid autoantibodies is considered to be the cause of PM. Here, we present a rare case of a patient who developed PM after undergoing I-131 ablation therapy, with normal levels of thyroid autoantibodies. Our report aims to document the features of PM in a male adult with hypothyroidism and to provide a potential mechanism of the onset of PM.

Key words: Pretibial myxedema, I-131 therapy, Graves' disease, autoantibodies

INTRODUCTION

Pretibial myxedema (PM) is an unusual extrathyroidal manifestation of Graves' disease (GD), which affects approximately 1%–5% of the patients. Besides, PM usually occurs in the hyperthyroid state of GD,^{1,2} and the high level of thyroid autoantibodies is considered to be the cause of PM. However, the level of thyroid autoantibodies will decrease after the treatment; thus, the occurrence of PM after I-131 ablation therapy is perplexed, and the mechanism may be more complex than we think. Here, we present a rare case of a patient who developed PM after undergoing I-131 ablation therapy, with the normal level of thyroid autoantibodies.

CASE REPORT

A 43-year-old male presented with multiple painless protruding masses over bilateral lower legs for 2 months before visiting our department of dermatology. He had no trauma or surgical history and was diagnosed with GD with hyperthyroidism and thyroid eye disease of both eyes with exophthalmos, lid retraction, and extraocular muscles limitation for years and I-131 ablation therapy, 3 months

prior due to GD with hyperthyroidism. We evaluated his thyroid function and found that he had hypothyroidism (free T4 < 0.79 ng/dL) and high thyroid-stimulating hormone (TSH) levels (6.79 μ IU/mL), which was consistent with his medical history.

Physical examination of his extremities revealed multiple asymptomatic, unmovable, firm, cobblestone-like subcutaneous nodules over bilateral pretibial regions, which extended to his calves [Figure 1]. Suspecting panniculitis, PM, or any other deposition or granulomatous diseases, a biopsy was performed using a skin sample from the right pretibial region.

Microscopically, the dermis was filled with basophilic mucinous material and haphazardly scattered collagen fibers [Figure 2]. Based on the clinical and pathological findings, he was diagnosed with PM.

DISCUSSION

GD is an autoimmune condition that causes hyperthyroidism and unique extrathyroidal manifestations.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Lin BS, Chen YH, Hung CT. Pretibial myxedema: Paradoxical manifestation of thyroid dermopathy after I-131 ablation therapy. J Med Sci 2020;40:127-30.

Received: May 04, 2019; Revised: September 16, 2019; Accepted: October 21, 2019; Published: February 21, 2020
Corresponding Author: Dr. Chih-Tsung Hung, Department of Dermatology, Tri-Service General Hospital, No. 325, Sec. 2, Chenggong Rd., Neihu District, Taipei City 114, Taiwan. E-mail: barrypig72@hotmail.com



Figure 1: Clinical photograph of the patient showing extensively distributed cobblestone-like subcutaneous nodules over bilateral pretibial regions

Ophthalmopathy, dermopathy, and acropachy are the most common extrathyroidal manifestations, affecting 25%, 1.5%, and 0.3% of GD patients, respectively.³ Although PM is an uncommon extrathyroidal manifestations, it is even rare in male patients³ because PM most commonly influences middle-aged females who are 4 times more susceptible than males.⁴ Besides, there are several clinical variants of PM. The most common form is diffused, nonpitting edema, which affects 43% of the patients. Another is the plaque form, which manifests as bumped plaques on the surface of nonpitting edema, and it occurs in 27% of the patients. The nodular form has sharp, defined nodular or tubular lesions; it occurs in 18% of patients. Other forms, including elephantiasis, polypoid forms, or fungating forms, are rare.⁵ Besides, the treatment option of PM including topical and systemic steroids, oral octreotide, intravenous immunoglobulin, plasmapheresis, surgery, and compressive therapy.²

Although the development of PM is not related to thyroid function, and patients may be hyperthyroidism, euthyroid, or hypothyroidism at the time of presentation^{6,7} the onset of PM after treatment is rarely reported. In our case, a middle-aged man with nodule type PM, which occurred after I-131 ablation therapy, is quite uncommon. To the best of our knowledge, only three other cases of PM after I-131 ablation therapy for GD have been reported in the literature⁸⁻¹⁰ and our patient may be the first case of Chinese ethnicity.

The exact mechanism underlying this condition remains unknown because the condition of our case is quite contradictory to the previous studies. It is known that the high levels of thyroid autoantibodies,

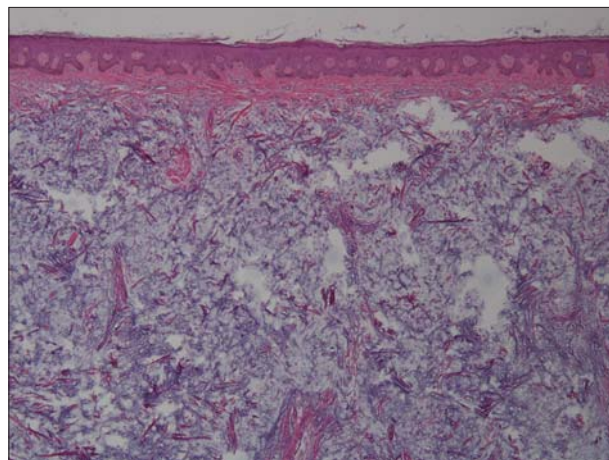


Figure 2: Histopathological photomicrograph showing the dermis was filled with basophilic mucinous material and haphazardly scattered collagen fibers

especially thyroid-stimulating hormone receptor (TSHR) antibodies (TRAb), are considered to be the main mechanism of GD and its extrathyroidal manifestations. TRAb can be stimulating, neutral or inhibiting and the stimulating antibody that binds to leucine-rich domain of the TSHR is considered to be the cause of GD.¹¹ Moreover, thus, most TRAb assays are separated into two categories. One is thyroid-stimulating immunoglobulin assay that detects TRAb in patients' serum by their affinity to the known TSHR ligand (TSH or monoclonal anti-TSHR antibody), and these assays cannot differentiate between stimulating, and nonstimulating antibody. Another one is TSH-binding inhibiting immunoglobulin assay, which detect cyclic adenosine monophosphate (cAMP) production in cells cultivated with patients' serum, and these assays identify only stimulating TRAb.¹² Besides, the level of thyroid autoantibodies is higher in the group with extrathyroidal manifestations.^{2,12}

In addition, the level of thyroid autoantibodies should subside after the treatment of GD, including antithyroid agents, surgery, or radioiodine therapy.^{12,13} However, our case developed PM after undergoing I-131 ablation therapy. Although there is the chance that TRAb may rebound and cause hyperthyroidism,¹³ our patient's TRAb was negative, and thyroid function was low (free T4 < 0.79 ng/dL) after the treatment. Additional factors other than the level of thyroid autoantibodies may be important to the development of pretibial myxedema.

McLachlan and Rapoport reported that the character of thyroid autoantibodies may change from stimulating

to inhibiting after the treatment of GD¹⁴ and may cause hypothyroidism. Thus, we can speculate that not only the titer but also the nature of the autoantibody can change during the therapy of GD, and this might trigger the onset of extrathyroidal manifestations. In addition, the coexistence of thyroid-stimulating autoantibodies, TSH blocking autoantibodies, is another hypothetical explanation.¹⁴ The levels of the two autoantibodies with contrasting functions may decrease and grow during the therapy and cause the transition from hyper- to hypothyroidism or vice versa.¹⁵ According to the aforementioned mechanisms, the onset of PM may indicate the possibility of relapse of hyperthyroidism and warrant continuous monitoring in the future.

CONCLUSION

We present a case with paradoxical manifestations of PM after I-131 ablation therapy. This case may reveal the potentially complex interaction of humoral and cellular immunity, which may be the cause of PM, but the mechanism of this phenomenon remains unclear and requires further investigation. In addition, it is recommended that physicians should be cautious of this rare condition; continuous monitoring of the thyroid function of these patients is warranted.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed. The study is approved by Institutional Review Board of Tri-Service General Hospital. The approval number is 2-108-05-188.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Anagnostis P, Adamidou F, Polyzos SA, Katargari S, Karathanasi E, Zouli C, *et al.* Predictors of long-term remission in patients with Graves' disease: A single center experience. *Endocrine* 2013;44:448-53.
2. Fatourehchi V. Pretibial myxedema: Pathophysiology and treatment options. *Am J Clin Dermatol* 2005;6:295-309.
3. Bartalena L, Fatourehchi V. Extrathyroidal manifestations of Graves' disease: A 2014 update. *J Endocrinol Invest* 2014;37:691-700.
4. Georgala S, Katoulis AC, Georgala C, Katoulis EC, Hatzilou E, Stavrianeas NG. Pretibial myxedema as the initial manifestation of Graves' disease. *J Eur Acad Dermatol Venereol* 2002;16:380-3.
5. Fatourehchi V, Pajouhi M, Fransway AF. Dermopathy of Graves disease (pretibial myxedema). Review of 150 cases. *Medicine (Baltimore)* 1994;73:1-7.
6. Anagnostis P, Artzouchaltzi A, Grekou A, Paschou SA, Gerou S, Tzalokostas V. Pretibial myxedema in a euthyroid patient. *Hormones (Athens)* 2018;17:133-5.
7. Ai J, Leonhardt JM, Heymann WR. Autoimmune thyroid diseases: Etiology, pathogenesis, and dermatologic manifestations. *J Am Acad Dermatol* 2003;48:641-59.
8. Harvey RD, Metcalfe RA, Morteo C, Furmaniak W, Weetman AP, Bevan JS. Acute pre-tibial myxoedema following radioiodine therapy for thyrotoxic Graves' disease. *Clin Endocrinol (Oxf)* 1995;42:657-60.
9. Kishimoto I, Chuyen NTH, Okamoto H. Annularly arranged nodular pretibial myxedema after 7-year treatment of Graves' disease. *J Dermatol* 2018;45:110-1.
10. Ponnusamy D, Pai RP. Nodular pretibial myxoedema after treatment of Graves disease with radioactive iodine ablation therapy. *BMJ Case Rep* 2014;2014. pii: bcr2013202530.
11. Sanders J, Chirgadze DY, Sanders P, Baker S, Sullivan A, Bhardwaja A, *et al.* Crystal structure of the TSH receptor in complex with a thyroid-stimulating autoantibody. *Thyroid* 2007;17:395-410.
12. Barbesino G, Tomer Y. Clinical review: Clinical utility of TSH receptor antibodies. *J Clin Endocrinol Metab* 2013;98:2247-55.
13. Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Tørring O. TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: A 5-year prospective randomized study. *Eur J Endocrinol* 2008;158:69-75.
14. McLachlan SM, Rapoport B. Thyrotropin-blocking

autoantibodies and thyroid-stimulating autoantibodies: Potential mechanisms involved in the pendulum swinging from hypothyroidism to hyperthyroidism or vice versa. *Thyroid* 2013;23:14-24.

15. Kraiem Z, Baron E, Kahana L, Sadeh O, Sheinfeld M.

Changes in stimulating and blocking TSH receptor antibodies in a patient undergoing three cycles of transition from hypo to hyper-thyroidism and back to hypothyroidism. *Clin Endocrinol (Oxf)* 1992;36:211-4.