BJCR
Brazilian Journal of Case Reports

PCAA
Publicações Científicas de Acesso Aberto

Case Report

Radioiodine Treatment and The Development of Pretibial Myxedema: A Series of Three Cases

Nicolas Perini [1,*], Camila Guidi Rossi [2], Gabriela Salles Martinez [2], Yedda Carolina Della Torre Rojas [2], Roberto Bernardo Santos [3], João Hamilton Romaldini [2], Danilo Villagelin [2]

[1] Postgraduate degree in Internal Medicine, State University of Campinas, Campinas, São Paulo, Brazil.
[2] Faculty of Medicine, School of Life Sciences, Pontifical Catholic University of Campinas (PUC – Campinas), Campinas, São Paulo, Brazil.
[3] Hospital of the Pontifical Catholic University of Campinas (PUC-Campinas), Campinas, São Paulo, Brazil.

* Correspondence: nicolas_perini@hotmail.com.

Abstract: Graves' disease presents itself clinically with signs of hyperthyroidism and autoimmune manifestations like Graves' dermopathy, mainly the pretibial myxedema, treatment for Graves' disease relies on the use of antithyroid medications and radioiodine treatment (RAI) in which case the thyroid cell destruction and subsequent antigen release aggravates the autoimmune response leading to TRAb mediated mucin and glycosaminoglycan deposition in the pretibial area. This report presents 3 cases of pretibial myxedema after radioiodine treatment for Graves' Disease combined with a brief literature review. This paper suggests that Graves' dermopathy could be due to an exacerbation of thyroid autoimmunity after RAI treatment. Physicians and patients' awareness of skin complaints or alterations play a key role in early diagnosis and treatment.

Keywords: Graves' Disease; Pretibial myxedema; Radioiodine therapy.

Citation: Perini N, Rossi CG, Martines GS, Rojas YCD, Santos RB, Romaldini JH, Villagelin D. Radioiodine Treatment and The Development of Pretibial Myxedema: A Series of Three Cases. Brazilian Journal of Case Reports. 2026 Jan-Dec;06(1):bjcr133.

https://doi.org/10.52600/2163-583X.bjcr.2026.6.1.bjcr133

Received: 24 September 2025
Accepted: 17 November 2025
Published: 21 November 2025

Copyright: This work is licensed under a Creative Commons Attribution 4.0 International License (CC BY 4.0).

1. Introduction

Graves' disease is the primary cause of hyperthyroidism in adults [1]. It is an autoimmune disease characterized by hyperthyroidism and extrathyroidal manifestations [1]. Graves' dermopathy generally occurs in the pretibial region known as pretibial myxedema (PM), however, Graves´ dermopathy can also manifest on the feet, elbows, and rarely the toes, and in severe cases, the entire lower leg might be affected [2]. The mechanisms involved in PM are unknown, but they may share a similar mechanism with Thyroid Eye Disease (TED), where TRAb binds to the TSH receptors in skin fibroblasts [2].

The skin manifestations presented in pretibial myxedema result from local inflammatory reactions producing fibroblast proliferation with glycosaminoglycans and mucin deposition in the lower extremities especially in the pretibial region [3]. The lesions' specific location relates to heat shock proteins in pretibial fibroblasts activated by high concentrations of serum TRAb [4]. This process leads to tissue edema and expansion, obstructing the local lymphatic circulation and causing a "peau d'orange" skin presentation that is intensified by local factors like the venous stasis in the lower extremities that stimulates mucin deposition, increasing the local edema and reducing the capacity of the lymphatic system to drain inflammatory factors [5].

Patients receiving RAI treatment for Graves' Disease are prone to thyroid cell destruction, with the release of thyroid antigens in the circulation, exacerbating the autoimmune response and possibly resulting in pretibial myxedema [6].

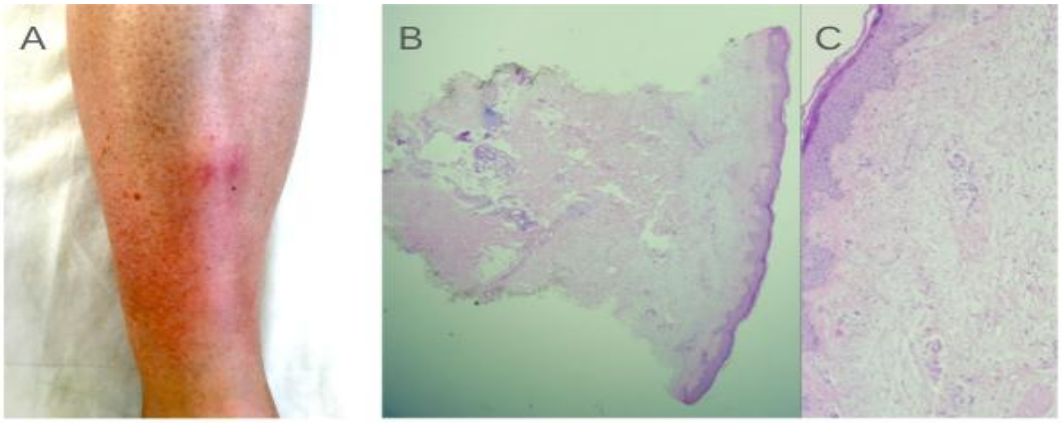
2. Case Report

2.1 Case 1

The first case is a 38-year-old female diagnosed with Graves' Disease and TED in initial evaluation with a CAS of 2 (eyelid edema and conjunctival hyperemia), proptosis of 20/20 mm, and eyelid measured 10/10 mm. Initial laboratory evaluation revealed a TSH of 0.01 mU/L, FT4 of 5.3 ng/dL, and positive TRAb. The thyroid ultrasound showed an enlarged diffuse goiter of 23 mL (standard value up to 16 mL). After 24 months of antithyroid drugs use with no disease remission, the patient was referred to RAI treatment.

The patient received a dose of 30 mCi of 131-I with euthyroidism achieved after four months and disease relapsed after ten months. Two years after RAI treatment, the patient developed hard pretibial edema associated with local hyperemia during this period. The patient presented clinical signs of TED during follow-up with persistently high serum TRAb levels. The diagnosis of PM was confirmed after a skin biopsy (Figure 1). After relapse, euthyroidism was reestablished and maintained using methimazole for an additional ten years.

Figure 1. A. Circumspect pretibial edema (right leg). B and C. Photomicrographs of skin specimens showing mucin deposition, edema, and fraying of connective tissue fibers.



2.2 Case 2

The second case is a 16-year-old male with a history of heart palpitations, weight loss and irritability in the last six months. Initial laboratory results were compatible with hyperthyroidism with serum TSH of 0.004 mUI/L, FT4 of 2.4 ng/dl, and positive TRAb levels. A thyroid ultrasound revealed an enlarged diffuse goiter. Physical examination showed a CAS of 2/1 (right eye/left eye - eyelid edema and conjunctival hyperemia), proptosis of 23/22 mm, and eyelid measurement of 11/10 mm, with no evidence of PM.

The patient started treatment with 30mg of methimazole, with no disease control after 18 months; thus, the patient was referred to RAI treatment. The patient received 15 mCi of 131-I associated with 20 mg daily of prednisone for 45 days to prevent orbitopathy deterioration; three months after RAI, the patient remained in hyperthyroidism, with physical examination revealing worsening of the orbitopathy with a CAS of 3/3 (right eye/left eye), proptosis of 24/24 mm, and eyelid measurement of 7/7mm and erythematous-infiltrated plaques and edema in both legs. The diagnosis of PM was confirmed by skin biopsy, as depicted in Figure 2.

2.3 Case 3

The third case is a 55-year-old female diagnosed with Graves' Disease initially treated with 15 mCi of 131-I followed by methimazole 20 mg daily. Five years after initial therapy, the patient relapsed. Upon initial evaluation, the patient presented with an enlarged goiter (18.9 mL on ultrasound) and symptoms of hyperthyroidism; physical examination

showed a CAS of 2 (eyelid edema and redness of the conjunctiva), proptosis of 19/19, eyelid measurement of 11/11 mm, with no diplopia. Laboratory examination was compatible with hyperthyroidism (TSH of 0.008 mU/L, FT4 of 1.72 ng/dl, and positive TRAb). The patient received a second dose of RAI (30 mCi) with euthyroidism achieved after six months. However, clinical examination showed hard, infiltrative, erythematous plaques on the right pretibial area and foot, and the left pretibial area. As shown in Figure 3, the skin biopsy confirmed the clinical diagnosis of PM.

Figure 2. The histopathologic features show the deposition of mucin (glycosaminoglycans) throughout the reticular dermis and with attenuation of collagen fibers.

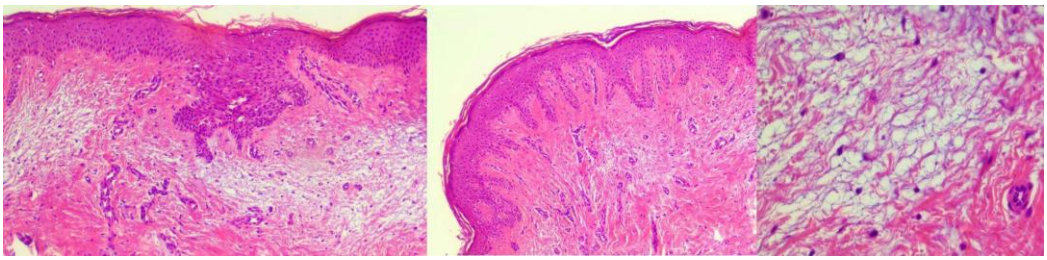
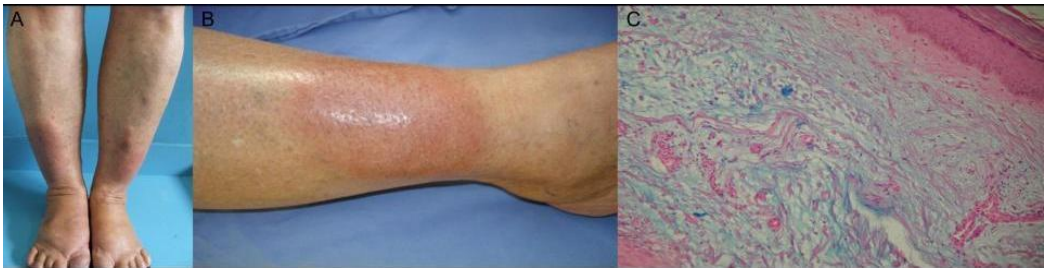


Figure 3. A and B. Figure demonstrated hard infiltrative erythematous plaques on the right pretibial area and foot as well as left pretibial area. C. The histopathologic features show edema and deposition of mucin throughout the reticular dermis.



3. Discussion

RAI treatment is a well-established therapy for Graves' Disease with adverse effects following the RAI administration deriving from both the radiation itself as well as the autoimmune exacerbation [7]. Laurberg and colleagues reported TRAb evolution in Graves' Disease treatment, with patients receiving antithyroid drugs and those subjected to surgery had a decline in serum TRAb levels during the first months and a negativation around the first year. In contrast, patients submitted to RAI treatment showed a significant increase in TRAb levels with a peak six months after 131-I administration, followed by a steady decrease with normalization only five years after treatment [7].

The evolution of TRAb levels after the RAI treatment might be responsible for some of the autoimmune adverse effects observed, such as worsening or onset of TED [1,8], as the physiopathological mechanism in both conditions bears significant similarities with tissue inflammation and glycosaminoglycans deposition mediated by TRAb in especial hyaluronic acid, expanding the upper dermis layer through water-binding and tissue edema [9], in the presented cases all the patients had varying degrees of TED. Given the autoimmune nature of both manifestations, these observations could indicate that patients with TED are at a higher risk of developing PM after RAI treatment, although no causality can be determined due to study limitations.

In this context persistently high levels of TRAb a known risk factor to TED worsening after RAI [10], TSH receptors are present in connective are potentially overexpressed in pretibial tissues of Graves' disease, patients as a result of inflammatory cytokines [11], these TSH receptors similarly to the orbital tissue present a cross talk with IGF1 receptors

intensifying the hyaluronic acid deposition and fibroblast differentiation [11], in the presented cases all patients had positive TRAb levels, although the serum levels could not be determined.

Tobacco use is a known risk factor for extrathyroid manifestation development in Graves' disease [12], with the literature postulating that the prolonged tissue hypoxia further stimulates the autoimmune process [12]. Although a definitive conclusion cannot be drawn, factors associated with TED worsening after RAI, such as uncontrolled hyperthyroidism, and persistently high TRAb levels, can be outlined [8], in the presented cases, all patients had positive TRAb prior to RAI administration, but only one patient was current smoker at the time, with thyroid function within the normal range for the three cases. This suggests that additional unknown factors may play a role in this rare phenomenon, such as genetic predisposition or environmental exposure. Patients' characteristics are depicted in table 1.

Table 1. Clinical characteristics of the three cases of pretibial myxedema.

Clinical Variables	**Case 1**	**Case 2**	**Case 3**
Gender	Female	Male	Female
Age (years)	38	16	55
Smoking	No	No	Yes
Thyroid volume (mL)	23.00	21.26	18.9
TSH (mU/mL)	0.01	0.004	0.008
Free T4 (ng/dL)	5.30	2.4	1.72
TRAb positive (%)	Positive	Positive	Positive
TPO positive (%)	Positive	Positive	Positive
CAS (initial)	2	2	2
Proptosis (mm)	20	23	19
Eyelid (mm)	10	11	11
Follow up (mean + SD months)	182	124	238
Time from RAI to developed PM	24 months	3 months	6 months

Regarding the treatment of PM after RAI therapy, there are no additional measures besides thyroid function control and topical steroids in mild to severe cases [2]. The patients in the study received intradermal (bethametasone 0.025% weekly for 4 weeks) and topical corticosteroids (2% fluocinolone acetonide cream applied directly to the affected area every night for 4 weeks) with satisfactory evolution. Patients presented improvement of peau d' orange aspect after a single corticosteroid course, with patients from case 3 still presenting local edema.

Given the limitations of this study, it is not possible to draw a precise conclusion on the causal effect of RAI treatment and pretibial myxedema, although the autoimmune exacerbation experienced in patients treated with RAI could play a crucial role in this phenomenon.

4. Conclusion

Pretibial myxedema following RAI treatment is a rare occasion but requires clinicians' vigilance to skin manifestations for prompt diagnosis. The mechanisms are not fully understood, demanding further research.

Funding: None.

Research Ethics Committee Approval: The patients provided written informed consent to participate in the study, which was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Acknowledgments: None.

Conflicts of Interest: All other authors declare no conflicts of interest.

References

1. Davies TF, Andersen S, Latif R, Nagayama Y, Barbesino G, Brito M, et al. Graves' disease. Nat Rev Dis Primers. 2020 Jul 2;6(1):52.
2. Fatourechi V. Pretibial myxedema: pathophysiology and treatment options. Am J Clin Dermatol. 2005;6(5):295–309.
3. Sendhil Kumaran M, Dutta P, Sakia U, Dogra S. Long-term follow-up and epidemiological trends in patients with pretibial myxedema: an 11-year study from a tertiary care center in northern India. Int J Dermatol. 2015 Aug;54(8):e280–6.
4. Peacey SR, Flemming L, Messenger A, Weetman AP. Is Graves' dermopathy a generalized disorder? Thyroid. 1996 Feb;6(1):41–5.
5. Bull RH, Coburn PR, Mortimer PS. Pretibial myxoedema: a manifestation of lymphoedema? Lancet. 1993;341:403–4.
6. Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. Endocr Rev. 2012 Dec;33(6):920–80.
7. 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 Jan;158(1):69–75.
8. Bahn RS. Graves' ophthalmopathy. N Engl J Med. 2010 Feb 25;362(8):726–38.
9. Kriss JP. Pathogenesis and treatment of pretibial myxedema. Endocrinol Metab Clin North Am. 1987;16(2):409-415.
10. Update on pathophysiology and treatment of pretibial myxedema: A comprehensive review of the literature Katsiaunis, Apostolos et al. JAAD Reviews, Volume 4, 116 - 122
11. Walsh HL, Shoji MK, Gallo RA, et al. Upregulation of insulin-like growth factor-1 receptor expression in pretibial myxedema: evidence for a treatment target. Am J Dermatopathol. 2024; 46(3):153-154. https://doi.org/10.1097/DAD.0000000000002597
12. Lan C, Hu L, Liao C, Shi Y, Wang Y, Cheng S, Huang W. Thyroid-Stimulating Hormone Receptor Autoimmunity and Local Factors in Multiple Risk Factors Are Mainly Involved in the Occurrence of Pretibial Myxedema. J Clin Med Res. 2020 Nov;12(11):711-723. doi: 10.14740/jocmr4352. Epub 2020 Nov 3. PMID: 33224373; PMCID: PMC7665869.