

Graves disease with atypical localization of dermatopathy and thyroid eye disease

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ABSTRACT

Background: Graves disease is an autoimmune condition. Simultaneous occurrence of Graves dermatopathy and thyroid eye disease is a rare extrathyroidal manifestation. Here, we present such a case and its improvement during the treatment.

Case Presentation: A 47-year-old woman with skin rash, pruritus, extremity swelling, tachycardia, and proptosis with worsening vision was previously examined by a dermatologist and was referred to an endocrinologist. She reported lesions on the lower and upper extremities. Laboratory findings revealed the following: suppressed thyroid-stimulating hormone, elevated free thyroxine, elevated anti-thyroid peroxidase antibodies, and markedly elevated thyrotropin receptor antibodies of >40 IU/L ($n \leq 1.75$ IU/L). Skin biopsy demonstrated histopathological findings consistent with thyroid dermatopathy. As a result of examination, she was diagnosed with Graves disease and was administered methimazole, pantoprazole, propranolol, and prednisolone. Smoking cessation was advised. 1 month after starting treatment, her symptoms had decreased. Among these, the swelling and lesions over the extremities resolved. Only exophthalmos persisted.

Conclusion: The report describes a rare presentation of Graves disease. Because of the atypical morphology and involvement of the forearms, skin biopsy was important in supporting the diagnosis and excluding alternative inflammatory or infiltrative dermatoses.

Keywords: Graves dermatopathy; thyroid eye disease; atypical localization; thyrotropin receptor antibodies; case report.

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Background

Graves disease is an autoimmune disease characterized by hyperthyroidism, goiter, thyroid eye disease (TED/ophthalmopathy), and dermatopathy (pretibial or localized myxedema). Approximately 25% of the patients have TED, whereas dermatopathy occurs in a smaller subset. Patients with ophthalmopathy report blurred vision, foreign body sensation, and discomfort in the eyes. Patients with dermatopathy may also have non-pitting edema, swelling, and cutaneous lesions on the extremities.

We present a patient with multiple manifestations of Graves disease, including ophthalmopathy and dermatopathy, with an atypical localization of the skin lesions over the forearms.

Case Presentation

A 47-year-old woman initially presented to a dermatologist with a 1-week history of skin rash and pruritus particularly at night. She also reported a several-month history of lower extremity swelling, bone and joint pain, fatigue, tachycardia, and unintentional weight loss of

8 kg over the previous 2 months ($BMI = 16.76 \text{ kg/m}^2$). She also complained of bulging of her right eye, which was insidious in onset and gradually progressive with difficulty in vision. Following physical examination, the dermatologist suspected Graves' disease, particularly in view of the patient's right-sided proptosis. The patient underwent diagnostic evaluation as recommended by the specialist: a complete blood count (CBC) was within normal limits, serum creatinine was $31.1 \mu\text{mol/L}$ (0.35 mg/dL) (reference range: $45\text{--}84 \mu\text{mol/L}$; $0.51\text{--}0.95 \text{ mg/dL}$), uric acid was $202 \mu\text{mol/L}$ (3.40 mg/dL) (reference range: $142\text{--}339.2 \mu\text{mol/L}$; $2.39\text{--}5.70 \text{ mg/dL}$), and fasting plasma glucose was 5.8 mmol/L (104.5 mg/dL) (reference range: $4.1\text{--}5.55 \text{ mmol/L}$; $73.9\text{--}100 \text{ mg/dL}$).

Her family history was notable for thyroid disease in her father. She was a current smoker. Consequently, she was referred to an endocrinologist for further investigation.

On examination, thyroid gland palpation revealed a nontender, diffusely enlarged thyroid gland. There was right-sided proptosis (right: 21 mm, left: 18 mm) and mild periorbital edema. Multiple pruritic,

erythematous-to-violaceous macules and slightly raised papules were present on the flexor surfaces of both shins and on both forearms (Figure 1 a–b). Some lesions coalesced into larger, ill-defined erythematous patches. Similar morphology was observed in the upper and lower extremities, with associated swelling and mild skin thickening of the lower extremities. A slight distal tremor was present. Blood pressure (BP) was 130/90 mmHg with a heart rate (HR) of 117 beats/min.

Investigation

Laboratory investigations revealed a suppressed thyroid-stimulating hormone (TSH) level of 0.00672 mIU/L (reference range: 0.27–4.2 mIU/L), an elevated free thyroxine (FT4) level of 6.34 ng/dL (81.6 pmol/L) (reference range: 0.92–1.68 ng/dL; 11.8–21.6 pmol/L), thyroid peroxidase antibody (anti-TPO) was positive at 40.9 IU/mL (reference range: <34 IU/mL), and TSH receptor antibodies (TRAb) were markedly elevated at >40 IU/L (reference range: ≤1.75 IU/L). The 25-hydroxyvitamin D [25(OH)D] level was profoundly low at <3 ng/mL (<7.5 nmol/L) (reference range: 30–100 ng/mL; 75–250 nmol/L).

A thyroid ultrasound demonstrated an enlarged, heterogeneous thyroid gland with increased vascularity. The right lobe measured $2.2 \times 2.2 \times 5.0$ cm (volume, 12.6 mL) and the left lobe measured $2.3 \times 2.0 \times 5.7$ cm (volume, 13.6 mL). The total thyroid volume was 26.2 mL. No thyroid nodules were identified.

On ophthalmological examination, decimal visual acuity was 0.6 in the right eye, improving to 1.0 with −1.50 D spherical correction, and 1.0 in the left eye. Intraocular pressures were 18 mmHg and 12 mmHg in the right and left eyes, respectively. There was right-sided proptosis (right: 21 mm, left: 18 mm) and mild periorbital edema. Right upper eyelid retraction was also noted. Right globe retropulsion was normal, and right extraocular motility was preserved in all directions, although accompanied by discomfort. The patient reported no diplopia. The right eyelid tissues and bulbar conjunctiva were otherwise clinically quiet. Both corneas and lenses were clear, and pupillary light responses were brisk bilaterally. Fundoscopy demonstrated pink optic discs with well-defined margins in both eyes, with no documented abnormalities of the central or peripheral retina. Formal CAS scoring and comprehensive optic neuropathy assessment were not documented, limiting standardized classification of TED activity and severity.

Because of the atypical morphology and distribution of the lesions, a punch biopsy was obtained from an active skin lesion on the forearm and shin. Histopathological examination revealed separation of collagen bundles, a mild perivascular lymphocytic infiltrate, and dermal mucin deposition highlighted by Alcian blue staining. In conjunction with the clinical findings and underlying

Graves disease, these features were considered supportive of thyroid dermopathy. However, they were not regarded as independently diagnostic, as similar findings may occur in other mucin-deposition disorders.

Treatment

Based on these initial findings, the following medications were prescribed for 1 month: pantoprazole 40 mg once daily, methimazole 10 mg three times daily, propranolol 10 mg twice daily, prednisolone 10 mg twice daily and cholecalciferol 5,000 IU daily. Prednisolone 20 mg/day was selected on an individualized basis, taking into account the intensity of symptoms associated with coexisting thyroid eye disease and dermopathy accompanied by pruritus and lower-extremity swelling. Clinical reassessment was planned after 4 weeks.

Outcome and Follow-Up

Four weeks after starting treatment, the patient's clinical symptoms and thyroid function test results improved: TSH was 0.1 mIU/L, FT4 decreased from 6.34 to 3.15 ng/dL (40.5 pmol/L), the 25-hydroxyvitamin D [25(OH)D] level was 57 ng/mL (142.5 nmol/L), and anti-TPO was 11.8 IU/mL. A favorable clinical evolution was observed. However, FT4 remained markedly elevated, indicating persistent biochemical hyperthyroidism. The skin lesions resolved completely within 4 weeks during combined treatment. As several interventions were initiated simultaneously, the improvement could not be attributed to any single therapy. The patient reported resolution of ocular discomfort, although proptosis persisted. She underwent a follow-up ophthalmological evaluation, and the ophthalmologist planned intravenous methylprednisolone pulse therapy for further management of TED. She gained 4 kg during this period. No adverse effects were reported during treatment. Accordingly, the treatment regimen was adjusted, the doses of medications were suppressed and prescribed: methimazole 10 mg twice daily for 5 days, then once daily 10 days, prednisolone 5 mg twice daily for 3 days, then 5 mg once daily for 3 days.

Discussion

The described patient presented with multiple manifestations of Graves disease, including hyperthyroidism, thyroid eye disease, and dermopathy. A notable feature was atypical localization of skin lesions over the forearms, as Graves dermopathy most commonly affects the pretibial region [1].

Pretibial myxedema with thyroid eye disease is a rare extrathyroidal feature. In a long-term outcome study of 178 individuals with Graves dermopathy, only 2 patients (1.1%) had lesions over upper extremities [2].

Graves dermopathy is strongly associated with thyroid eye disease and markedly elevated TRAb concentrations [3].



Figure 1. (a) Erythematous-to-violaceous macules and slightly raised papules on the forearm, with focal coalescence into larger, ill-defined patches. (b) Bilateral forearm involvement showing multiple erythematous-to-violaceous macules and papules with areas of coalescence.

Graves dermopathy results from the activation of fibroblasts by local cytokines and excessive accumulation of glycosaminoglycans (GAGs), especially hyaluronic acid, within the dermis. The cytokines are released as a result of lymphocytic inflammation [4].

TRAb plays an important role in the pathogenesis of TED by stimulating TSH receptors. TSHR and IGF-1R signaling pathways are connected and contribute to orbital inflammation, adipogenesis, and hyaluronic acid accumulation [5].

Smoking is associated with the development of Graves ophthalmopathy and higher TRAb levels. Smoking cessation is recommended because smoking may contribute to GAGs production and adipogenesis [6].

The treatment includes non-pharmacologic and pharmacologic approaches. First of all, risk factors should be reduced, particularly smoking. Thionamides are recommended to control hyperthyroidism, while beta-blockers provide symptomatic relief [7]. Glucocorticoids inhibit the conversion of T4 to T3 and are also used for treatment of TED [8].

In conclusion, the report describes a rare presentation of Graves disease. Because of the atypical morphology and involvement of the forearms, skin biopsy was important in supporting the diagnosis and excluding alternative inflammatory or infiltrative dermatoses.

List of Abbreviations

25(OH)D	25-hydroxyvitamin D
anti-TPO	Anti-thyroid peroxidase antibodies
BMI	Body mass index

BP	Blood pressure	204
CAS	Clinical Activity Score	205
CBC	Complete blood count	206
D	Diopter	207
FT4	Free thyroxine	208
GAGs	Glycosaminoglycans	209
HR	Heart rate	210
IGF-1R	Insulin-like growth factor 1 receptor	211
T3	Triiodothyronine	212
T4	Thyroxine	213
TED	Thyroid eye disease	214
TRAb	Thyrotropin receptor antibodies	215
TSH	Thyroid-stimulating hormone	216
TSHR	Thyroid-stimulating hormone receptor	217

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What Is New 224

- Graves disease with thyroid eye disease and dermopathy is a rare extrathyroidal manifestation. 225
- This patient presented with thyroid eye disease and dermopathy highlights the autoimmune nature of Graves disease. 226
- Smoking increases the risk of thyroid eye disease and is associated with poorer treatment response. Smoking cessation should be encouraged. 227

- Clinical improvement was observed after 1 month of treatment, especially the lesions were completely resolved.

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Summary of the case

1	Patient (gender, age)	Female, 47 years
2	Final diagnosis	Graves disease with thyroid eye disease and atypical thyroid dermopathy
3	Symptoms	Pruritic skin rash, lower-extremity swelling, tachycardia, weight loss, right-sided proptosis, and visual complaints
4	Medications	Methimazole, propranolol, prednisolone, pantoprazole, cholecalciferol
5	Clinical procedure	Skin biopsy
6	Specialty	Endocrinology