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Lower limb pain and edema due to thyroid dermopathy: an unusual presentation of Graves disease in an adolescent patient

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ABSTRACT

Graves disease is an immune-mediated process characterized by the presence of autoantibodies to thyrotropin receptors. Its stimulating action on the thyroid gland causes diffuse glandular growth and increased hormone production. Graves disease is characterized by a subacute onset of non-specific, neuromuscular, cardiovascular, gastrointestinal, and eye symptoms, sometimes followed by skin manifestations, such as thyroid dermopathy or myxedema. In pediatrics, Graves disease is rare (although it is the most frequent cause of hyperthyroidism). However, the chronology of symptom onset has been well described; the development of dermopathy in the absence of other symptoms of hyperthyroidism and without eye involvement is rare.

Here we describe the case of a 15-year-old female patient with thyroid dermopathy due to Graves disease without eye disease or other associated clinical symptoms of hyperthyroidism.

Key words: *hyperthyroidism; Graves disease; myxedema; pediatrics.*

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INTRODUCTION

Graves disease is an immune-mediated process in which autoantibodies bind to the thyrotropin (TSH) receptor in the thyroid gland, stimulating diffuse growth and hormone production. It is characterized by a subacute onset of general symptoms of clinical hyperthyroidism, with the following manifestations: non-specific (weight loss with increased appetite, heat intolerance, sweating, polydipsia), neuromuscular (tremor, nervousness, anxiety, fatigue, sleep disturbance, difficulty concentrating, hyperactivity, hyperreflexia, pelvic girdle and shoulder girdle weakness), cardiovascular (palpitations, tachycardia, systolic hypertension, arrhythmia), pulmonary (dyspnea, tachypnea), gastrointestinal (hyperdefecation, nausea, vomiting, abdominal pain), skin (sweating, hot and moist skin), and reproductive (menstrual disorders),[1] and disease-specific symptoms, such as Graves ophthalmopathy and thyroid dermopathy or myxedema.[2]

Thyroid dermopathy (TD) is an uncommon extrathyroidal manifestation of Graves disease with peak incidence in the sixth decade of life, rarely reported in children. It usually occurs in patients with a previous diagnosis of hyperthyroidism and established thyroid-associated ophthalmopathy.[3–8] In a case series published by Schwartz et al. in 2002 on 178 patients with TD, it was established that, prior to the diagnosis of dermopathy, 85% had a diagnosis of thyroid disease and 97%, significant eye disease.[9] In pediatrics, Kraus et al. described 2 patients with TD, both with clinical hyperthyroidism at diagnosis.[8]

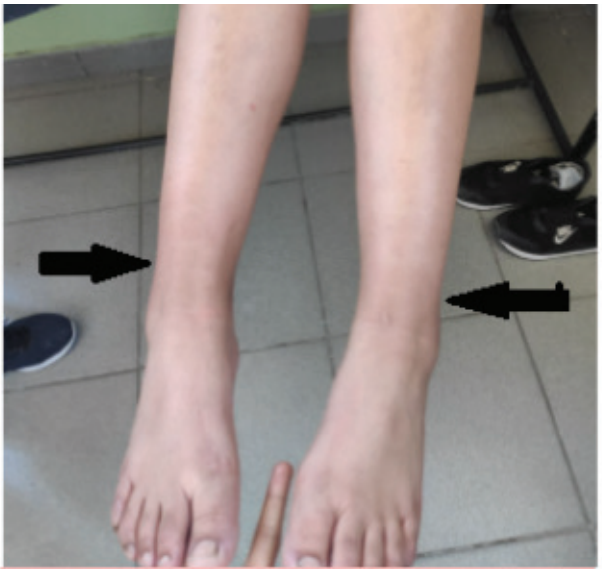
Here we describe the case of a previously healthy 15-year-old female patient with TD at onset of Graves disease without eye disease or other associated clinical symptoms of hyperthyroidism. In the bibliographic review performed to date, we found no similar cases published in the pediatric age group.

CASE REPORT

This was a 15-year-old female patient with no personal or family history of note, who presented with pain and edema of the lower limbs for the past month. She also reported asthenia, night sweats, and mild intermittent tension headache, but no recent history of trauma to the affected area.

She was in good general condition and had a normal body weight (body mass index: 27, stable in the past year). She had a normal heart assessment (heart rate: 90 bpm), normal blood pressure (BP: 120/80 mmHg, 50th percentile), no murmur, normal respiratory rate, soft and non-tender abdomen. She had marked pain to light touch in both pretibial areas, mild negative Godet's sign, increased temperature, and faint purplish color *(Figure 1)*. She did not show gait

Figure 1. Picture of pretibial area



Swelling and change in the color of the pretibial area of both lower limbs.

impairment and her neurological examination was normal. Palpation of the thyroid was difficult due to increased subcutaneous tissue caused by her overweight. Diuresis and purgation were normal; her date of last menstrual period was 10 days before and she had regular periods.

In order to rule out possible causes of edema (*Table 1*), general lab tests were done. Results were normal for blood count, kidney function, liver function, blood glucose, ionogram, urinalysis, total protein, and albumin. Results were pathological for the thyroid panel: increased thyroid hormones, suppressed TSH and positive anti-TSH receptor antibodies (TRAbs) (FT_4: 4.88 ng/dL [0.8–1.76], TSH: 0.015 µIU/mL [0.44–4], TRAbs: 10.26 U/L [NV up to 1.75]). The thyroid ultrasound showed diffuse enlargement of the thyroid gland and vascularization, without nodules (right lobe: 48 × 15 × 16 mm, left lobe: 48 × 11 × 19 mm). The Doppler ultrasound of the lower limbs was normal.

Based on the characteristic hormonal panel and goiter, Graves disease was diagnosed and the pretibial lesions were clinically assumed to be TD. Her eye examination showed a mild refractive error but no exophthalmos, chemosis, or ophthalmoplegia. She had a normal cardiovascular assessment, electrocardiogram, echocardiogram, and Holter ECG. The patient was started on methimazole 0.4 mg/kg/day and progressed with a decrease in free thyroxine (FT_4) level and clear symptom improvement. After 2 months, methimazole was reduced to 0.3 mg/kg/day. With this dose, she remained euthyroid at 7 months of follow-up; her last FT_4 value was 1.2 ng/dL.

DISCUSSION

Graves disease is the most common cause of hyperthyroidism in pediatrics and is rare, occurring with an annual incidence of 0.9 per 100 000 children under 15 years of age.[12] In addition to the signs and symptoms of clinical hyperthyroidism, extrathyroidal manifestations are described in the eyes (thyroid-associated ophthalmopathy) and skin (TD and clubbing). Skin manifestations occur very rarely in pediatric patients with an incidence of less than 5% for TD and less than 1% for clubbing.[2,6,8,9] According to the 2002 report by Schwartz et al. and other previously conducted studies, the mean age at the onset of TD is 53 years.[3,9] Another distinctive feature of extrathyroidal manifestations in the skin is that they usually occur within years of the diagnosis of thyroid disease and in patients with established eye disease.[3–7,13] It is worth noting that our patient was 15 years when she presented with TD due to Graves disease. The fact that this was the most important clinical manifestation at

Table 1. Causes of edema

Edema	
Bilateral	**Localized**
Heart disease (heart failure).	Venous insufficiency.
Kidney disease (acute glomerulonephritis, kidney failure, nephrotic syndrome).	Venous obstruction (deep vein thrombosis).
Liver disease (liver failure, cirrhosis).	Extrinsic venous compression (malignant, May Thurner syndrome, compartment syndrome).
Thyroid disease (hypothyroidism, hyperthyroidism).	Soft tissue injury (local infection, burn wound).
Primary lymphedema.	Secondary lymphedema.
Lipedema.	Type I complex regional pain syndrome (reflex sympathetic dystrophy).
Drugs (corticosteroids, AINEs, among others).	
Protein-losing enteropathy/malabsorption syndrome	
Protein malnutrition (kwashiorkor).	
Anaphylaxis.	
Pregnancy/pre-menstrual syndrome.	

Bilateral edema may or may not be generalized. If not generalized, it predominates in lower limbs or decubitus areas. Localized edema is usually unilateral, but depending on the etiology, in some cases it may be bilateral.[10,11]

the debut of the disease after 1 month of course, without associated eye disease, makes this case exceptional.

Hyperthyroidism in Graves disease is caused by the binding of stimulatory autoantibodies to the TSH receptor of the thyroid gland. The pathophysiology of extrathyroidal manifestations is more complex because, in addition to immunological factors, cellular, environmental, and mechanical factors are involved.[13] It is stated that the binding of these autoantibodies to connective tissue cells such as fibroblasts (with antigens similar to those found in thyroid tissue) stimulates the synthesis of glycosaminoglycans and cytokines. Some of these substances build up locally and promote fluid retention with subsequent expansion of the connective tissue.[5] Obstruction of the lymphatic microcirculation with local lymphedema could play some added role. In relation to the mechanical factors involved, the location of TD in the lower limb is probably related to the sloping position, with a slower lymph drainage and the possibility of more frequent trauma to that area.[5]

Clinically, TD is characterized by a localized and symmetrical thickening of the skin that is neither pruritic nor painful and, unlike our patient, whose cardinal symptom was pain in the affected area, which is usually asymptomatic and only of aesthetic importance.[6,13] Hyperkeratosis, hyperpigmentation, fissures, and a rough appearance due to the prominence of the hair follicles (*peau d'orange*) are frequently observed in the affected area. According to its clinical presentation, TD can be classified into 5 forms: non-pitting edema (43%), plaque (27.0%), nodular (18.5%), elephantiasic (2.8%), and unclassifiable (8.4%).[9] Most often, TD affects the pretibial area (99.4%), but in some cases it may involve the upper limbs, neck, trunk, and ears. When it occurs in these unusual locations, a history of trauma to the area is common.[6]

The diagnosis of TD is usually clinical, due to its characteristic clinical presentation in association with ophthalmopathy and/or hyperthyroidism.[7,13] In cases where the presentation is atypical or there is no ophthalmopathy/hyperthyroidism, the diagnosis is less clear and a skin biopsy of the area is recommended.[6] Our patient presented a typical lesion (due to its clinical characteristics and location), but she did not have a previous diagnosis of thyroid disease and did not show symptoms of eye involvement. Given that her baseline tests included a thyroid panel with pathological results, a biopsy was not required to reach the diagnosis.

The course of TD is unpredictable: it may resolve spontaneously or progress regardless of treatment for hyperthyroidism. In any case, treatment should be started as a first step in all cases.[7,8] Most of the time, TD resolves without requiring specific treatment. When this is not the case, topical corticosteroids (under occlusion or intralesional) may be administered in moderate cases and therapies with octreotide, intralesional hyaluronidase, IV immunoglobulin or plasmapheresis may be used in refractory patients.[6,7,9,13] Studies on the long-term effectiveness of these therapies are scarce.[13]

This case of Graves disease is of interest because of the atypical clinical presentation at debut. The cardinal symptoms were pain and non-pitting edema in the lower limbs (associated with TD), and not the typical symptoms of clinical hyperthyroidism. Our patient had TD without associated ophthalmopathy. Therefore, it is important to consider Graves disease in a patient with edema, even in the absence of ophthalmopathy or typical symptoms of hyperthyroidism. ■

REFERENCES

1. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet*. 2016; 388(10047):906-18.
2. Shroff A, Simpson G. Cutaneous manifestations of thyroid disease: a case of thyroid-induced myxedema. *Case Rep Dermatol Med*. 2011; 2011:386081.
3. Fatourechi V, Pajouhi M, Fransway AF. Dermopathy of Graves disease (pretibial myxedema). Review of 150 cases. *Medicine (Baltimore)*. 1994; 73(1):1-7.
4. Lohiya S, Lohiya V, Stahl EJ. Pretibial myxedema without ophthalmopathy: an initial presentation of Graves' disease. *Am J Med Sci*. 2013; 346(1):73-5.
5. Fatourechi V. Thyroid dermopathy and acropachy. *Best Pract Res Clin Endocrinol Metab*. 2012; 26(4):553-65.
6. Ansah-Addo S, Alexis AF. Pretibial Myxedema in a Euthyroid Patient. *J Clin Aesthet Dermatol*. 2021; 14(1):21-3.
7. Dhali TK, Chahar M. Thyroid dermopathy-a diagnostic clue of hidden hyperthyroidism. *Dermatoendocrinol*. 2015; 6(1):e981078.
8. Kraus CN, Sodha P, Vaidyanathan P, Kirkorian AY. Thyroid dermopathy and acropachy in pediatric patients. *Pediatr Dermatol*. 2018; 35(6):e371-4.
9. Schwartz KM, Fatourechi V, Ahmed DD, Pond GR. Dermopathy of Graves' disease (pretibial myxedema): long-term outcome. *J Clin Endocrinol Metab*. 2002; 87(2):438-46.
10. Trayes KP, Studdiford JS, Pickle S, Tully AS. Edema: diagnosis and management. *Am Fam Physician*. 2013; 88(2):102-10.
11. Flores-Villegas B, Flores-Lazcano I, Lazcano-Mendoza ML. Edema. Enfoque clínico. *Med Int Méx*. 2014; 30(1):51-5.
12. Williamson S, Greene SA. Incidence of thyrotoxicosis in

childhood: a national population based study in the UK and Ireland. Clin Endocrinol (Oxf). 2010; 72(3):358-63.

13. Fatourechi V. Pretibial myxedema: pathophysiology and treatment options. *Am J Clin Dermatol*. 2005; 6(5):295-309.