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CASE REPORT AND REVIEW

Hypothyroid Graves' disease complicated with elephantiasis nostras verrucosa (ENV): a case report and review of the literature

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Abstract Thyroid dermopathy is not a frequent feature of hyperthyroid Graves' disease, being present in less than 5% of the patients. Graves' disease has been shown to exist in euthyroid or hypothyroid forms in untreated patients. Here, we describe a case of hypothyroid Graves' disease with elephantiasis nostras verrucosa (ENV), which is an extreme form of thyroid dermopathy (TD). A 58-year-old female patient was admitted to the emergency department with somnolence, hypothermia, and bradycardia. Her mental status gradually worsened, resulting in a deep coma. She was intubated and followed in the intensive care unit, as she needed mechanical ventilatory assistance due to respiratory failure. She also had bilateral non-pitting edema, a cobblestone-like appearance, and hyperkeratotic greenish-brown-colored lesions in the pretibial and dorsal regions of the feet that were compatible with ENV. Hypothyroid Graves' disease is a very rare condition among autoimmune thyroid disorders, and ENV is an extremely rare form of TD. Here, we present a patient with hypothyroid Graves' disease and ENV.

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Introduction

Graves' disease is the most common cause of hyperthyroidism, with an annual incidence of 15–50/100,000 [1–3]. Thyroid swelling, ophthalmopathy, and dermopathy are classical manifestations of Graves' disease [1, 4]. Although pretibial myxedema (thyroid dermopathy) is almost unique to Graves' disease [5], it is the least common extrathyroidal manifestation, with a frequency of 0.5–4.3% [5, 6]. In general, patients who have all three manifestations of Graves' disease develop thyrotoxicosis first, then ophthalmopathy, and finally dermopathy [5, 7]. The diagnosis of TD without ophthalmopathy is questionable.

Pretibial myxedema rarely occurs in patients without thyroid dysfunction or in patients with hypothyroidism due to autoimmune thyroiditis. Graves' disease has been shown to exist in either euthyroid or hypothyroid forms in previously untreated patients. Reports of the hypothyroid form illustrate the multifaceted nature of this disorder, with thyrotoxicosis at one end of the spectrum and hypothyroidism at the other [8, 9]. Graves' ophthalmopathy and dermopathy may also develop in hypothyroid subjects, and is known as hypothyroid Graves' disease [8, 9]. The diagnosis of hypothyroid Graves' disease can be made on the basis of Graves' ophthalmopathy and/or dermopathy with permanent hypothyroidism in patients who have not had a previous diagnosis of or treatment for thyrotoxicosis [8, 9].

Here, we describe a case of hypothyroid Graves' disease with elephantiasis nostras verrucosa (ENV), an extreme form of thyroid dermopathy.

Case report

A 58-year-old female patient was admitted to the emergency room with confusion. On initial examination, somnolence was present. There was no localizing sign indicating a central nervous system accident. Cranial imaging was also obtained, and the results were normal. Her vital signs were abnormal. Her body temperature was below 36°C, her blood pressure was 130/97 mmHg, and her heart rate was below 60 beats/min. An electrocardiogram revealed sinus bradycardia (heart rate 48 beats/min) and decreased voltages. The chest X-ray study was normal. Her mental status gradually worsened, and she fell into a deep coma. Arterial blood gas analysis demonstrated moderate hypoxemia, hypercapnia, and respiratory acidosis. She was intubated and followed in the intensive care unit, as she needed mechanical ventilatory assistance due to respiratory failure. Liver and renal function tests in the patient were in the normal range. Thyroid function tests were reported as follows. TSH: 76.98 uIU/ml (normal range: 0.27–4.2 uIU/ml), freeT3: 0.725 pmol/l (normal range: 3.1–6.8 pmol/l), and freeT4: 0.646 pmol/l (normal range: 12–22 pmol/l). Thyroid autoantibodies were positive in low titers. Anti-thyroid peroxidase (TPO) antibody was 34 IU/ml (normal range: 0–30 IU/ml), anti-TSH receptor antibody was 9.8 U/l (normal range <9 U/l), and anti-thyroglobulin (TG) antibody was 166 IU/ml (normal range: 0–40 IU/ml). The hormonal profile and other laboratory findings were normal.

In addition to cardiovascular and respiratory supportive measures, treatment for myxedema coma was also immediately initiated with 300 μg levothyroxine/day. Due to hypothermia and her generally poor condition, the existence of an infection or sepsis could not be ruled out, and antibacterial therapy was initiated with a wide antibacterial spectrum agent. All of the cultures taken at the initial evaluation were negative. She was morbid obese and also had periorbital edema with puffiness of her face and extremities (Fig. 1). Her skin was dry, and her hair was coarse and thickened. She had 24 and 26 mm proptosis in her right and left eyes, respectively. A classification of ophthalmopathy by NOSPECS was grade 3b. Her thyroid gland was non-palpable. Thyroid ultrasound examination confirmed an atrophic thyroid gland with dimensions of $18 \times 11 \times 9$ and $20 \times 10 \times 9$ mm^3 for the right and left lobes of the thyroid, respectively. In addition to the aforementioned treatments, anticoagulant therapy was initiated due to the presence of obesity and a medical history of diabetes. ENV was diagnosed with the presenting features of bilateral non-pitting edema, a cobblestone-like appearance, and hyperkeratotic greenish-brown-colored lesions in the pretibial area and on the dorsum of the feet (Fig. 2). Smears from the lesions were negative for bacterial and fungal contamination. Color Doppler sonographic examination of her lower extremities was normal, and there was no osteomyelitis.

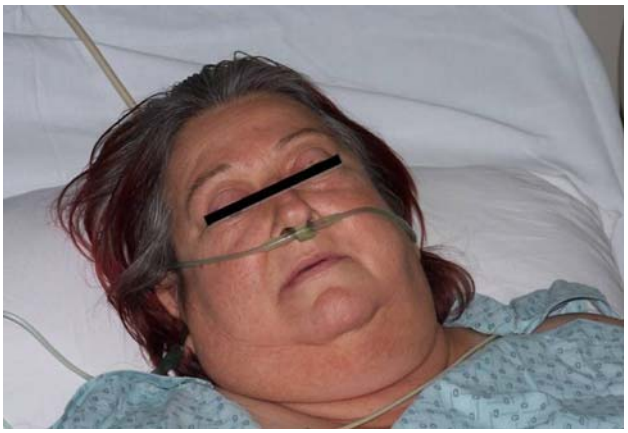

Fig. 1 She had morbid obesity and also periorbital edema with puffiness of her face

Her past medical history revealed that she had type 2 diabetes for 7 years and primary hypothyroidism for 4 years. She had never suffered from filariasis, and she did not have a family history of familial lymphedema (Milroy's disease). There was no evidence of congestive heart failure, liver or renal disease, allergy, or radiotherapy. She did not take any treatment for hyperthyroidism, and she had never been diagnosed with hyperthyroidism. Levothyroxine 200 μg/day had been recommended previously, but she was not compliant in taking the medication. She was on an oral anti-diabetic regimen with glimepride 2 mg/day and metformin 1,700 mg/day with moderate glycemic control (HbA1c: 7.5%). In the ICU, glycemic control was achieved by mini-insulin treatment.

During the follow-up in the ICU, the patient's vital signs, respiratory acidosis, and mental status normalized, and she was extubated after a successful weaning period. She was taken to the internal medicine ward for detailed evaluation and medical support.

For the treatment of ENV, salicylate vaseline and collagenase pomade were topically applied to soften the thickened upper epidermal layers, and the lesions were cleaned by daily brushing with soap and water. The thickened layers of the lesions were removed, and granulation tissue appeared. Now the patient is normoglycemic and euthyroid with appropriate treatments.

Discussion

Clinically, thyroid dermopathy presents in several forms, including non-pitting edema, nodules, plaques, elephantiasis, and unclassified [5]. The pathomechanism of thyroid dermopathy is unclear. In biological specimens, the

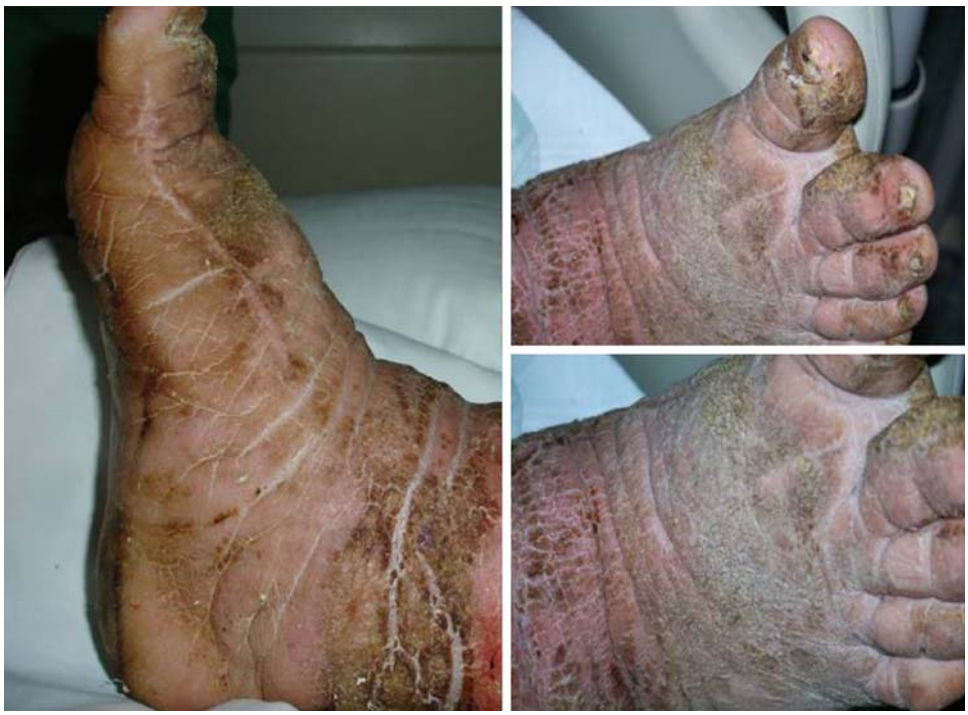

Fig. 2 Elephantiasis nostras verrucosa (ENV) was diagnosed with the presenting features of bilateral non-pitting edema, a cobblestone-like appearance, and hyperkeratotic greenish-brown-colored lesions in the pretibial area and on the dorsum of the feet

hallmark of thyroid dermopathy is increased levels of glycoaminoglycans (GAG) [6]. The hyaluronic acid levels are elevated 6–16 times in the reticular dermis compared to normal skin [10]. TSH receptor antibodies, heat-shock proteins, IL-1, and TGF-β probably play roles in the development of thyroid dermopathy [11–13]. Increased GAG production and accumulation lead to clinically recognized characteristics of thyroid dermopathy lesions. Also, increasing GAGs expand the dermoid tissue, causing compression and occlusion of small local lymphatics. Occlusion of small lymphatics leads to the accumulation of fluid, swelling, and dermal edema of the affected region. The pretibial area is most commonly involved (99% of the patients with thyroid dermopathy) [14]. In fact, GAG deposition occurs throughout the body without any clinical manifestation [15], but lesions are most often localized in the lower extremities. This localization is due to gravity and/or to site specific differences in fibroblasts [16]. If the dermopathy is seen in an unusual site of the body, a history of trauma should be questioned. ENV is an extreme form of thyroid dermopathy. It develops after periods of prolonged standing with dependent edema. In a recent study, Schwartz et al. [14] reported 150 patients with TD, 43.3% with non-pitting edema, 27% with plaques, 18.5% with nodules, 2.8% with elephantiastic morphologies, and 8.4% with an unclassified form. In this report, there were five patients with elephantiastic dermopathy. The majority of these patients had previously been treated for Graves' hyperthyroidism. There were very few patients with hypothyroidism and ENV in this report. In our case, the diagnosis of hypothyroid Graves' disease was based on the presence of Graves' ophthalmopathy and permanent hypothyroidism. Our patient had the elephantiastic form of TD. ENV is characterized by greatly thickened skin and a persistent swelling of one or both lower legs. Patients with pretibial myxedema have higher serum concentrations of TSH receptor (TSHR) antibodies than patients with fewer extrathyroidal manifestations of Graves' disease [5, 14]. In particular, patients with ENV have very high titers of TSHR antibodies. Normal skin can express TSH receptors, but if there are antigen specific T-cells and TSH receptor antibodies in the skin, these are the hallmarks of thyroid dermopathy [17]. This case had a history of longstanding autoimmune thyroiditis with hypothyroidism. The presence of ophthalmopathy and typical localization of the lesions led us to the elephantiastic TD diagnosis. A skin biopsy was neither needed, nor feasible, as the patient was on anticoagulant therapy.

Autoantibodies directed to thyrotropin receptors are the direct cause of the hyperthyroidism in Graves' disease, but the pathogenesis of extrathyroidal manifestations of Graves' disease, like ophthalmopathy and dermopathy, are not well understood. In the case of ophthalmopathy accompanied by low or negative TSH-R antibodies, just as in our hypothyroid Graves' patient, other factors implementing the pathogenesis of ophthalmopathy and dermopathy should be considered. The effects of TSH itself or of thyroid stimulating humoral factors were proposed [16]. Moreover, systemic low-grade connective tissue infiltration and the effects of superimposed local factors should also be

taken into account [16]. In our case, thyroid antibodies were positive in low titers, but TSHR antibodies could not be determined as TSH-blocking or stimulating antibodies. TSH-blocking antibodies are a significant cause of hypothyroidism in hypothyroid Graves' disease [8, 18]. In our case, we could speculate that the TSHR antibodies in this patient were blocking in nature due to the presence of the myxedemic coma and the un-palpable thyroid gland. Thyroid antibodies are detectable before hormonal failure. When 90% of the gland is destroyed, the secretion of T3 and T4 falls below normal ranges [1, 19]. TSH production increases, which normally leads to regrowth of the thyroid gland, but when the tropic actions of TSH are blocked by TSH blocking antibodies, then the thyroid cannot respond to high TSH levels [19]. The treatment of dermopathy is usually symptomatic. TD is generally a cosmetic concern and causes local discomfort. Therapy of TD has shown variable success. In local therapies, topical midpotency and high-potency steroids can be used [5]. Additionally, compression has been proven to be useful, especially when lymphatic involvement is suspected, as in ENV [20]. Surgical excision is not advised because of high rates of recurrence [21]. Systemic corticosteroids and cytotoxic therapy have also been tried for the treatment of TD [22, 23]. Because of their side effects, these agents are rarely used. Intravenous immunoglobulin treatment [22] and plasmapheresis [24, 25] have also been used to treat TD.

Hypothyroid Graves' disease is a very rare condition among autoimmune thyroid disorders. Also, ENV is an extremely rare form of TD. Here, we present a patient with hypothyroid Graves' disease and ENV as a result of TD. To our knowledge, this is the first case from Turkey, and one of only a few cases reported in the literature.

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