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CASE SERIES OF DERMOPATHY IN AUTOIMMUNE THYROID DISEASE

Abstract: Graves' disease (GD) is an autoimmune disease that can affect other tissues in addition to the thyroid gland. The clinical manifestations are a result of the impact of TSH receptor antibodies. Depending on the intensity of the immune response, in addition to hyperthyroidism, orbitopathy, dermatopathy and acropachy can also occur. Extrathyroidal manifestations of GD are most often the result of a more pronounced immune response. Dermatopathy is a rare extrathyroidal manifestation, with a prevalence of 0.5-4.3%, and when it occurs, it almost always accompanies orbitopathy (96%) and hyperthyroidism, while it is associated with a severe form of orbitopathy in 13-15% of cases. It is characteristic of long-standing disease and an intense autoimmune response. We present a case series of five patients with dysthyroid dermopathy. Our patients had different thyroid function disorders (hypo/hyperthyroidism), different forms of dermopathy, and varying times of onset during the disease. Association with orbitopathy and high TRAb concentrations were also present in all our patients. The effects of therapy applied for orbitopathy were monitored, which showed a favorable response on dermopathy, especially with the use of tocilizumab in some of our patients.

Keywords: dermopathy, orbitopathy, hyperthyroidism, Graves' disease, elephantiasis, pretibial myxedema, TRAb, glycosaminoglycans, thyroid gland

Introduction

Graves' disease is an autoimmune, multisystemic disorder that, in addition to hyperthyroidism caused by the stimulation of TSH receptor antibodies (TRAb),

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can lead to extrathyroidal manifestations, most commonly orbitopathy, followed by dermopathy, and rarely acropachy. We present a case series of five patients with dysthyroid dermopathy who were hospitalized at the Department of Thyroid Diseases, Clinic for Endocrinology, Diabetes, and Metabolic Diseases, Clinical Center of Serbia (UKCS) between 2020 and 2024. All patients, two women and three men aged 41 to 63, had thyroid function disturbances, either hypo- or hyperthyroidism, along with two extrathyroidal manifestations of the disease—orbitopathy and dermopathy.

Case 1

A 52-year-old patient presented with the simultaneous onset of dermopathy and orbitopathy in 2021, along with symptoms and signs of hypermetabolism. Dermopathy manifested as pronounced bilateral pretibial edema with skin redness and painful sensitivity, which progressively advanced to hard edema and a form of elephantiasis, with skin resembling orange peel and hyperpigmented deposits. In the later stages, a mild swelling of the hands also appeared. A skin biopsy of the lower leg revealed dermatitis with mucin deposition—pretibial myxedema. Orbitopathy, classified as severe and active (CAS 4), was treated in 2022 initially with a modified corticosteroid protocol due to the diagnosed papillophlebitis (cumulative dose of 5g methylprednisolone, followed by decreasing doses of prednisone), and later with the standard 12-week protocol. Following treatment, in addition to improvement in ocular findings, a positive effect was seen on dermopathy, partly due to significant weight loss of approximately 20 kg and better control of the previously unstable thyroid hormonal status. Leg swelling was significantly reduced, hyperpigmentation less pronounced, with the relief-like appearance of the skin still present.

Case 2

A 62-year-old female patient initially manifested Graves' disease with dermopathy in 2010, presenting as bilateral swelling of the lower legs and feet with skin hyperemia. One month later, ocular changes appeared, and the diagnosis of hyperthyroidism was established. Hyperthyroidism was initially treated with medication for two years, followed by total thyroidectomy. Over time, the swelling of the lower legs and feet gradually progressed into chronic lymphatic insufficiency with a resulting picture of elephantiasis, most pronounced in 2020, along with skin hyperpigmentation and hard, calcified subcutaneous changes. Radiographically, irregular calcific densities were observed in the soft tissues. Orbitopathy, with mild ocular changes, remained stable until 2021, when there was a sudden progression to active, severe orbitopathy. Treatment was initiated with corticosteroids, first following a medication-based decompression regimen (1g methylprednisolone on alternate days), and later continued

with the standard 12-week protocol. Throughout the corticosteroid therapy, the condition of the legs remained unchanged. Due to corticosteroid-resistant orbitopathy, treatment was switched to biological therapy with tocilizumab. Improvement in orbitopathy was accompanied by significant changes in dermopathy: reduction in leg edema, softening of the fibrous subcutaneous tissue, better skin hydration with reduced hyperpigmentation, increased joint mobility, and a reduction in lower leg circumference by over 10 cm.

Case 3

A 57-year-old female patient developed changes in the eyes, specifically exophthalmos, simultaneously with hyperthyroidism in 2015. After undergoing thyroidectomy in 2018 due to unstable disease progression, changes appeared on the lower legs in the form of erythematous plaques. A biopsy revealed cutaneous mucinosis—pretibial myxedema. A moderately severe form of orbitopathy with moderate clinical activity (CAS OU 3) was treated with corticosteroids in 2023. During this period, worsening of the dermopathy was noted, characterized by edema in the lower legs, dorsum of the feet, and both big toes, along with increased erythema and swelling of the old erythematous plaques. Further treatment of orbitopathy was continued with biological therapy (tocilizumab), which showed a favorable effect on dermopathy, resulting in reduced edema and less pronounced plaques.

Case 4

A 59-year-old male patient presented with orbitopathy in 2019, and hypothyroidism was diagnosed a year later. Moderately severe, active orbitopathy was treated on two occasions with pulse corticosteroid therapy (2020 and 2021). Changes in the legs appeared in 2022, presenting as edema of the lower legs and feet, followed by erythema, hyperpigmentation of the skin, and hypertrophic plaques. A biopsy confirmed the diagnosis of pretibial myxedema. During the continued treatment of orbitopathy with tocilizumab, partial improvement was observed in the condition of the legs, with reduced edema, especially with the use of compression stockings. However, the skin changes were slightly more pronounced.

Case 5

A 41-year-old male patient was diagnosed with hyperthyroidism in 2021, and two years later, extrathyroidal manifestations—orbitopathy and dermopathy—developed. Changes in the lower legs and ankle area presented as edema along with

erythematous plaques on the lateral sides of the lower legs. A biopsy of these lesions was performed, and the pathological findings confirmed the diagnosis of pretibial myxedema. The corticosteroid protocol, used in the treatment of moderately severe orbitopathy with moderate clinical activity, did not have a significant effect on the dermopathy. However, occasional improvement was observed with the use of local corticosteroid therapy.

Graves' disease (GD) is an autoimmune disorder that, in addition to affecting the thyroid gland, can also involve other tissues. Depending on the intensity of the immune response, alongside hyperthyroidism, orbitopathy, dermatopathy, and acropachy can occur. Extrathyroidal manifestations of GD are most often a result of a more pronounced immune response. The presence of dermopathy and acropachy is an indicator of the severity of the autoimmune process and a risk factor for severe orbitopathy. (1) Dermopathy is a rare extrathyroidal manifestation, with a prevalence of 0.5-4.3%. When it occurs, it almost always accompanies orbitopathy (96%) and hyperthyroidism, and is associated with a severe form of orbitopathy in 13-15% of cases. (2) Chronologically, hyperthyroidism and orbitopathy most often develop first, followed by dermopathy and acropachy; however, the order of appearance is not always the same. In two of our patients, dermopathy, in addition to appearing at the very onset of the disease, presented in its most severe form—elephantiasis. The onset of dermopathy is associated with the duration of the autoimmune disease and is less commonly seen today, as the diagnosis of GD is made earlier. It is more commonly observed in women (F:M=3.5:1) aged 40-60 years, although in our group, men were more prevalent, while the presentation occurred in the typical age range. (3,4)
Dysthyroid dermopathy is a diffuse mucinosis characterized by the typical accumulation of glycosaminoglycans in the dermis and hypodermis of the skin. The most common form is diffuse non-pitting edema (43.3%), followed by plaques (27%) and nodular changes (18.5%), while elephantiasis is rarer (2.8%). In our study, two patients presented with the rarest and most severe form—elephantiasis, while in the remaining three, dermopathy manifested in the more common form—edema with plaques. Clinically, it manifests as light red, sometimes yellow-brown skin lesions, often with an orange peel texture, usually in the pretibial region. Hyperpigmentation and hyperkeratosis may also occur. (5,6) On histopathological examination, in addition to mucin deposition among separated and fragmented collagen fibers, infiltration of lymphocytes in the perivascular space and mast cells can be observed. However, due to the significant presence of glycosaminoglycans, which make them difficult to detect, they are not considered diagnostic criteria. (5, 7) The pathogenesis of dermopathy is not fully understood, but it is believed that TRAb antibodies binding to receptors in connective tissue stimulate fibroblasts to produce large quantities of glycosaminoglycans. The presence of TSH receptors has been shown in orbital and pretibial fibroblasts in patients with Graves' orbitopathy

and dermopathy. Although dysthyroid dermopathy can occur in any skin region, the typical location is pretibial, likely due to the influence of local mechanical factors, trauma, and local hypoxia caused by arterial or venous insufficiency, edema, or smoking. It can also appear in other areas of the skin due to trauma, surgical interventions, or scars. The accumulation of glycosaminoglycans leads to fluid retention, expansion of connective tissue, and obstruction of lymphatic drainage. In the later stages of the disease, fibrosis develops, contributing to the progression of lesions and the development of elephantiasis. Smoking has been identified as a risk factor for a more severe clinical picture, and most of our patients were smokers (3/5), including both with the form of elephantiasis. (8, 9, 10) The diagnosis is based on the clinical presentation, association with hyperthyroidism and orbitopathy, serum analysis (TRAb), and histopathological findings. All of our patients had orbitopathy, with two cases of severe orbitopathy associated with the most severe and rarest form of dermopathy—elephantiasis. Most patients with dermopathy, as a marker of the severity of the autoimmune process, have significantly elevated TRAb concentrations, which were typically elevated in all of our patients. **Table 1.** (7, 11) Lesions are usually asymptomatic and primarily of cosmetic significance, often overshadowed by symptomatic orbitopathy. Most cases of dermopathy do not require any specific treatment. The first step is to reduce risk factors by quitting smoking, reducing body weight, and normalizing thyroid hormone status. (7) In milder forms, local corticosteroids applied under occlusion or intralesionally can be helpful. In more severe cases, systemic immunomodulation may be necessary (systemic steroids, pentoxifylline, octreotide, rituximab, plasmapheresis, intravenous immunoglobulins, teprotumumab, etc.). For significant edema and elephantiasis, local compressive therapy may also be beneficial. Surgical excision may be successful but is generally not recommended due to the risk of developing new lesions on injured skin. In mild cases that do not require treatment, 50% of patients achieve complete remission after several years. Severe cases treated with local or systemic therapy often do not have better outcomes than untreated mild cases, and there is a lack of convincing evidence for the long-term efficacy of these modalities. The likelihood of remission depends on the severity of the initial disease, rather than its treatment. Most often, dermopathy treatment is partially covered by systemic therapy given for orbitopathy, which was the case with our patients, as ocular symptoms were predominant. (12, 13, 14, 15)

The patients presented, who came to our hospital in a short period of time, had different forms and timings of dermopathy onset. Two patients had a severe form of dermopathy—elephantiasis—which occurred simultaneously with hyperthyroidism and orbitopathy in one patient, and with hyperthyroidism but before orbitopathy in the other. In the other two patients, dermopathy manifested as the third manifestation of Graves' disease, after hyperthyroidism and orbitopathy in one, and after

orbitopathy and hypothyroidism in the other. The fourth patient initially had orbitopathy, followed by a diagnosis of hypothyroidism a year later, and dermopathy appeared three years afterward. In the last patient, both extrathyroid manifestations occurred simultaneously, three years after the diagnosis of hyperthyroidism. The last three cases had a more common form, presenting as edema and plaques. In all patients, skin biopsy confirmed pretibial myxedema, except for the second patient, in whom no biopsy was performed due to the clear clinical presentation and the fact that tissue calcifications had already been present at the time of their visit due to the long duration of the disease.

Conclusion

Dermopathy is a rare manifestation of Graves' disease, typically associated with long-standing illness and an intense autoimmune response. It is less frequently seen today, which makes the occurrence of dermopathy in five patients within a short time period even more intriguing. Our patients had varying thyroid function disorders (hypo/hyperthyroidism), different forms of dermopathy, and different timings of its onset during the disease course. The association with orbitopathy and high TRAb concentrations were also present in all of our patients. The effects of therapy applied for orbitopathy showed a favorable response in treating dermopathy, particularly with the use of tocilizumab in some of our patients.

Table 1.

	Age (year)	Gender	TRAb (IU/L)	TPO-Ab (IU/mL)	TG-Ab (IU/mL)	Smoking
Patient 1	52	M	>40	11,0	17,0	Yes
Patient 2	63	F	>40	6,0	10,0	Yes
Patient 3	52	F	>40	X	X	Yes
Patient 4	59	M	105,3	2230	>4000	No
Patient 5	41	M	97.6	36.4	154	No

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