Tamara Janić[1], Mirjana Stojković[1,2], Bojan Marković[1], Ivana Đurković[1], Jovana Babić[1], Nata Joksimović[1], Biljana Nedeljković Beleslin[1,2], Jasmina Ćirić[1,2], Miloš Žarković[1,2]

SERIJA SLUČAJEVA DERMOPATIJE U AUTOIMUNOJ TIROIDNOJ BOLESTI

Sažetak: Grejvsova bolest (GB) je autoimuna bolest koja pored štitaste žlezde može zahvatiti i druga tkiva. Kliničke manifestacije su posledica uticaja TSH receptorskih antitela. U zavisnosti od intenziteta imunskog odgovora, pored hipertireoze mogu se javiti najčešće orbitopatija, zatim dermopatija i retko akropahija. Ekstratiroidne manifestacije GB su rezultat izraženijeg imunološkog odgovora. Dermatopatija je retka ekstratiroidna manifestacija, sa prevalencom 0.5–4.3%, kada se javi skoro uvek prati orbitopatiju (96%) i hipertireozu, dok je u 13–15% udružena sa teškom formom orbitopatije. Karakteristična je za dugotrajnu bolest i intenzivni autoimuni odgovor. Prikazali smo seriju slučajeva od pet pacijenata sa distiroidnom dermopatijom. Naši pacijenti su imali različit poremećaj funkcije štitaste žlezde (hipo/hipertireozu), različite forme dermopatije, kao i vreme njenog javljanja tokom bolesti. Udruženost sa orbitopatijom i visoke koncentracije TRAb bili su takođe prisutni kod svih naših pacijenata. Praćeni su efekti terapije primenjene za orbitopatiju koji su dali povoljan odgovor i na dermopatiju, kod dela naših pacijenata pre svega primena tocilizumaba.

Ključne reči: dermopatija, orbitopatija, hipertireoza, Grejvsova bolest, elefantijaza, pretibijalni miksedem, TRAb, glikozaminoglikani, štitasta žlezda

Uvod

Grejvsova bolest je autoimuna, multisistemska bolest, koja pored hipertireoze, usled stimulacije TSH receptorskim antitelima (TRAb), može dati i ekstratiroidne

[1] Tamara Janić, Klinika za endokrinologiju, dijabetes i bolesti metabolizma, Univerzitetski klinički centar Srbije, Odeljenje za bolesti štitaste žlezde

[2] Medicinski fakultet Univerziteta u Beogradu, Srbija

manifestacije, najčešće orbitopatiju, zatim dermopatiju i retko akropahiju. Prikazujemo seriju slučajeva od pet pacijenata sa distiroidnom dermopatijom koji su bili hospitalizovani na Odeljenju za bolesti štitaste žlezde Klinike za endokrinologiju, dijabetes i bolesti metabolizma UKCS u periodu od 2020. do 2024. g. Svi pacijenti, dve žene i tri muškarca starosti od 41 do 63 godine, su uz poremećaj funkcije štitaste žlezde u pravcu hipo- ili hipertireoze, imali i dve ekstratiroidne manifestacije bolesti – orbitopatiju i dermopatiju.

Slučaj 1.

Kod pacijenta starosti 52 godine bolest je počela 2021. g. istovremenom pojavom dermopatije i orbitopatije, uz simptome i znake hipermetabolizma. Dermopatija se prezentovala izrazitim obostranim pretibijalnim edemima sa crvenilom kože i bolnom osetljivošću, koji su vremenom progredirali do tvrdog edema i forme elefanijaze, sa kožom nalik pomorandžinoj kori i hiperpigmentovanim naslagama, a u kasnijem toku javio se i manji otok šaka. PH nalaz biopsije kože potkolenice pokazao je dermatitis sa deponovanjem mucina – pretibijalni miksedem. Orbitopatija klasifikovana kao teška, aktivna (CAS 4), lečena je 2022. g. najpre modifikovanim kortikosteroidnim protokolom zbog dijagnostikovanog papiloflebitisa (kumulativna doza 5 gr metilprednisolona, uz opadajuće doze pronisona), a zatim standardnim 12-nedeljnim protokolom. Na primenjenu terapiju, pored poboljšanja nalaza na očima, viđen je pozitivan efekat na dermopatiju, što je delom i posledica značajne redukcije telesne težine, za oko 20 kg, kao i bolje kontrole do tada nestabilnog tiroidnog hormonskog statusa. Otoci nogu su bili značajno redukovani, hiperpigmentacije manje izražene uz i dalje prisutan reljefni izgled kože.

Slučaj 2.

Kod pacijentkinje stare 62 godine Grejvsova bolest se inicijalno manifestovala dermopatijom 2010. g. u vidu obostranih otoka potkolenica i stopala sa hiperemijom kože, mesec dana kasnije javile su se promene na očima, kada je postavljena i dijagnoza hipertireoze. Hipertireoza je najpre lečena medikamentno dve godine, a zatim je učinjena totalna tiroidektomija. Tokom vremena otoci potkolenica i stopala postepeno su progredirali u hroničnu limfnu insuficijenciju sa posledičnom slikom elefantijaze, maksimalno izraženom 2020. g, uz hiperpigmentaciju kože i tvrde, kalcifikovane promene potkožno. Radiografski u mekim tkivima viđene su nepraavilne senke intenziteta kalcijuma. Orbitopatija, sa blagim očnim promenama, ostala je stabilna do 2021, kada je došlo do nagle progresije u aktivnu, tešku orbitopatiju. Lečena je KS najpre prema režimu medikamentne dekompresije (1 gr metilprednisolona alternativnim danima), a potom je nastavljeno lečenje standardnim 12-nedeljnim protokolom.

Sve vreme trajanja KS terapije nalaz na nogama bio je nepromenjen. S obzirom na kortnikorezistentu orbitopatiju, lečenje je nastavljeno biološkom terapijom – tocilizumabom. Poboljšanje orbitopatije pratile su i značajne promene u dermopatiji: smanjenje edema nogu, razmekšavanje fibroznog potkožnog tkiva, bolje hidrirana koža sa smanjenom hiperpigmentacijom, povećanje obima pokreta u zglobovima i smanjenje obima potkolenica za preko 10 cm.

Slučaj 3.

Kod pacijentkinje starosti 57 godina tokom 2015. g. istovremeno sa hipertireozom javile su se promene na očima u vidu egzoftalmusa. Nakon tiroidektomije 2018. g. učinjene zbog nestabilnog toka bolesti, razvile su se promene na potkolenicama u vidu eritematoznih plakova. Biopsijom je dobijen PH nalaz kutane mucinoze – pretibijalni miksedem. Srednje teška forma orbitopatije umerenog stepena kliničke aktivnosti (CAS 3) lečena je kortikosteroidima 2023. Tada je primećeno pogoršanje dermopatije u vidu pojave edema potkolenica, dorzuma stopala i oba palca, uz izraženiju hiperemiju i otok starih eritematoznih plakova. Dalje lečenje orbitopatije nastavljeno je biološkom terapijom (tocilizumab), koje je pokazalo povoljan efekat i na dermopatiju u vidu redukcije edema i manje izraženih plakova.

Slučaj 4.

Kod pacijenta starosti 59 godina bolest se manifestovala orbitopatijom 2019. g, a godinu dana kasnije verifikovana je hipotireoza. Srednje teška, aktivna orbitopatija lečena je u dva navrata pulsnom KS terapijom (2020. i 2021). Promene na nogama javile su se tokom 2022. g. sa slikom otoka potkolenica i stopala, a zatim i hiperemijom i hiperpigmentacijom kože uz hipertrofične plakove. PH nalaz biopsije potvrdio je da se radi o pretibijalnom miksedemu. U daljem toku lečenja orbitopatije primenom tocilizumaba registrovano je i delimično poboljšanje nalaza na nogama u smislu manjeg otoka, uz kompresivne čarape, dok su same kožne promene bile nešto izraženije.

Slučaj 5.

Pacijentu starosti 41 godina dijagnoza hipertireoze postavljena je 2021. g, a dve godine kasnije razvile su se i ekstratiroidne manifestacije – orbitopatija i dermopatija. Promene na potkolenicama i u predelu skočnih zglobova manifestovale su se otokom uz eritematozni plak na lateralnim stranama potkolenica. Učinjena je biopsija navedenih primena, a PH nalaz potvrdio je da se radi o pretibijalnom miksedemu. Na

kortikosteroidni protokol, primenjen u lečenju srednje teške orbitopatije umerenog stepena kliničke aktivnosti, nije bilo značajnijeg efekta na dermopatiju, dok je povremeno poboljšanje postajalo na primenu lokalne kortikosteroidne terapije.

Diskusija

Grejvsova bolest (GB) je autoimuna bolest koja, pored štitaste žlezde, može zahvatiti i druga tkiva. U zavisnosti od intenziteta imunog odgovora, pored hipertireoze, mogu se javiti orbitopatija, dermatopatija i akropahija. Ekstratiroidne manifestacije GB su najčešće rezultat izraženijeg imunološkog odgovora. Prisustvo dermopatije i akropahije je indikator težine autoimunog procesa i faktor rizika za tešku orbitopatiju. (1) Dermatopatija je retka ekstratiroidna manifestacija, sa prevalencom 0.5–4.3%, kada se javi skoro uvek prati orbitopatiju (96%) i hipertireozu, dok je u 13–15% udružena sa teškom formom orbitopatije. (2) Hronološki, najčešće se prvo razvija hipertireoza i orbitopatija, a zatim dermopatija i akropahija, međutim, redosled javljanja ne mora uvek biti takav. U dva naša pacijenta dermopatija, osim što se javila na samom početku bolesti, prezentovala se u svojoj najtežoj formi – elefantijazi. Pojava dermopatije povezana je sa trajanjem autoimune bolesti i danas se viđa ređe, jer se dijagnoza GB postavlja ranije. Češće se sreće kod žena (Ž:M=3,5:1) starosti 40–60 godina, mada su u našoj grupi bili brojniji muškarci, dok je ispoljavanje bilo u tipičnoj starosnoj dobi. (3, 4)

Distiroidna dermatopatija je difuzna mucinoza, sa tipičnom akumulacijom glikozaminoglikana u dermisu i hipodermisu kože. Najčešći oblik je difuzni netestasti edem (43.3%), zatim plakovi (27%) i nodozne promene (18.5%), a ređe elefantijaza (2.8%). Naša dva pacijenta su imala najređu i najtežu formu – elefantijazu, dok se u preostala tri dermopatija prezentovala češćim oblikom – edemom sa plakovima. Klinički se manifestuje kao svetlocrvena, ponekad žućkasto-braon lezija kože, često sa teksturom narandžine kore i uglavnom u pretibijalnom regionu. Mogu se javiti i hiperpigmentacija i hiperkeratoza. (5, 6)

Patohistološki, pored deponovanja mucina među razdvojenim i fragmentovanim kolagenim vlaknima, može se videti infiltracija limfocita u perivaskularnom prostoru i mastociti, međutim, zbog značajnog prisustva glikozaminoglikana koji otežavaju njihovo uočavanje, ne predstavljaju kriterijum za dijagnozu. (5, 7)

Patogeneza dermopatije nije sasvim poznata, ali se smatra da TRAb koja se vezuju za receptore u vezivnom tkivu stimulišu fibroblaste da proizvode veliku količinu glikozaminoglikana, a prisustvo TSH receptora pokazano je u orbitalnim i pretibijalnim fibroblastima pacijenta sa Grejvsovom orbitopatijom i dermopatijom. Iako se distiroidna dermopatija može javiti na bilo kojoj regiji kože, tipična lokalizacija je pretibijalna, verovatno kao posledica uticaja lokalnih mehaničkih faktora, povreda i lokalne hipoksije usled arterijske ili venske insuficijencije, edema ili pušenja. Na

drugim mestima na koži se može javiti kao posledica traume, hirurških zahvata ili ožiljaka. Nakupljanje glikozaminoglikana dovodi do zadržavanja tečnosti, širenja vezivnog tkiva i time opstrukcije limfne drenaže. U kasnijem toku bolesti dolazi do fibroze, što doprinosi progresiji lezija i razvoju elefantijaze. Pušenje se pokazalo kao faktor rizika za težu kliničku sliku, a većina naših pacijenta su bili pušači (3/5), uključujući oba sa formom elefantijaze. (8, 9, 10)

Dijagnoza se zasniva na kliničkoj slici, udruženosti sa hipertireozom i orbitopatijom, serumskim analizama (TRAb) i patohistološkom nalazu. Kod svih naših pacijenata postojala je orbitopatija, u dva slučaja teška forma orbitopatije udružena sa najtežim i najređim oblikom dermopatije – elefantijazom. Većina pacijenata sa dermopatijom, kao marker težine autoimunog procesa, ima značajno visoke koncentracije TRAb, koja su bila tipično povišena i kod svih naših pacijenata. Tabela 1. (7, 11)

Lezije su obično asimptomatske i imaju kozmetski značaj, a često su u senci simptomatske orbitopatije. Većina slučajeva dermopatije ne zahteva nikakvu terapiju. U prvom redu važno je smanjiti faktore rizika prestankom pušenja, redukcijom telesne težine i normalizacijom tiroidnog hormonskog statusa. (7) U blažim formama, lokalni kortikosteroidi pod okluzijom ili aplikovani intraleziono mogu biti korisni, dok u težim slučajevima može biti neophodna sistemska imunomodulacija (sistemski steroidi, pentoksifilin, oktreotid, rituksimab, plazmafereza, intravenski imunoglobulini, teprotumumab). Kod značajnog edema i elefantijaze lokalna kompresivna terapija takođe može biti od pomoći. Hirurška ekscizija može biti uspešna, ali se generalno ne preporučuje zbog rizika za razvoj novih lezija na povređenoj koži. U blagim slučajevima koji ne zahtevaju lečenje, 50% pacijenata postiže potpunu remisiju nakon nekoliko godina. Teški slučajevi tretirani lokalnom ili sistemskom terapijom često nemaju bolji ishod od nelečenih blažih slučajeva, odnosno nedostaju ubedljivi dokazi za dugoročnu efikasnost navedenih modaliteta. Verovatnoća remisije zavisi od težine početne bolesti, a ne od njenog lečenja. Najčešće, lečenje dermopatije je delom pokriveno sistemskom terapijom koja se daje zbog orbitopatije, što je bio slučaj i kod naših pacijenata, s obzirom na to da su dominantne bile očne tegobe. (12, 13, 14, 15)

Prikazani pacijenti koji su u kratkom roku došli u našu bolnicu imali su različite oblike i različito vreme nastanka dermopatije. Dva pacijenta su imala teški oblik dermopatije – elefantijazu, koja se javila istovremeno sa hipertireozom i orbitopatijom kod jednog pacijenta, i istovremeno sa hipertireozom, ali pre orbitopatije kod drugog pacijenta. U druga dva pacijenta dermopatija se prezentovala kao treća manifestacija GB, posle hipertireoze i orbitopatije kod jednog, i posle orbitopatije i hipotireoze kod drugog pacijenta. Četvrti pacijent je inicijalno imao orbitopatiju, posle godinu dana je dijagnostikovana hipotireoza, a dermopatija se pojavila tri godine kasnije. Kod poslednjeg pacijenta obe ekstratiroidne manifestacije javile su se istovremeno, tri godine nakon dijagnostikovane hipertireoze. Poslednja tri slučaja su imala češću formu u vidu otoka i plakova. Kod svih pacijenata je PH nalazom biopsije kože potvrđen

pretibijalni miksedem, osim kod druge pacijentkinje kod koje nije rađena biopsija s obzirom na jasnu kliničku prezentaciju i na to da su u trenutku javljanja kod nas već postojale kalcifikacije tkiva usled dugogodišnjeg trajanja bolesti.

Zaključak

Dermopatija je retka manifestacija GB i karakteristična je za dugotrajnu bolest i intenzivni autoimuni odgovor. Danas se ne viđa često, što pojavu pet pacijenata sa dermopatijom u kratkom vremenskom periodu čini dodatno zanimljivom. Naši pacijenti su imali različit poremećaj funkcije štitaste žlezde (hipo/hipertireozu), različite forme dermopatije, kao i vreme njenog javljanja tokom bolesti. Udruženost sa orbitopatijom i visoke koncentracije TRAb bili su takođe prisutni kod svih naših pacijenata. Efekti terapije primenjene za orbitopatiju dali su povoljan odgovor i na dermopatiju, kod dela naših pacijenata pre svega primena tocilizumaba.

Tabela 1

	Godine	Pol	TRAb (IU/L)	TPO-At (IU/mL)	TG-At (IU/mL)	Pušač
Pacijent 1	52	M	>40	11,0	17,0	Da
Pacijent 2	63	Ž	>40	6,0	10,0	Da
Pacijent 3	52	Ž	>40	X	X	Da
Pacijent 4	59	M	105,3	2230	>4000	Ne
Pacijent 5	41	M	97.6	36.4	154	Ne

Reference

1. Fatourechi V, Bartley GB, Eghbali-Fatourechi GZ, Powell CC, Ahmed DD, Garrity JA. Graves' dermopathy and acropachy are markers of severe Graves' ophthalmopathy. Thyroid. 2003 Dec; 13(12): 1141–4.
2. Fatourechi V, Garrity JA, Bartley GB, Bergstralh EJ, Gorman CA. Orbital decompression in Graves' ophthalmopathy associated with pretibial myxedema. J Endocrinol Invest. 1993 Jun; 16(6): 433–7.
3. Fatourechi V, Pajouhi M, Fransway AF. Dermopathy of Grave's disease (pretibial myxedema). Review of 150 cases. Medicine (Baltimore). 1994; 73: 1–7.
4. Beierwaltes WH. Clinical correlation of pretibial myxedema with malignant exophthalmos. Ann Intern Med 1954; 40: 968–84.

5. Schwartz KM, Fatourechi V, Ahmed DD, Pond GR. Dermopathy of Graves' disease (pretibial myxedema): long-term outcome. J Clin Endocrinol Metab. 2002 Feb; 87(2): 438–46.
6. Kriss JP. Pathogenesis and treatment of pretibial myxedema. Endocrinol Metab Clin North Am. 1987 Jun; 16(2): 409–15.
7. Fatourechi V. Pretibial Myxedema - Pathophysiology and Treatment Options. Am J Clin Dermatol. 2005; 6: 295–309.
8. Anderson CK, Miller OF 3rd. Triad of exophthalmos, pretibial myxedema, and acropachy in a patient with Graves' disease. J Am Acad Dermatol. 2003 Jun; 48(6): 970-2.
9. Chang TC, Wu SL, Hsiao YL, Kuo ST, Chien LF, Kuo YF, Change CC, Chang TJ. TSH and TSH receptor antibody-binding sites in fibroblasts of pretibial myxedema are related to the extracellular domain of entire TSH receptor. Clin Immunol Immunopathol. 1994 Apr; 71(1): 113–20.
10. Daumerie C, Ludgate M, Costagliola S, Many MC. Evidence for thyrotropin receptor immunoreactivity in pretibial connective tissue from patients with thyroid-associated dermopathy. Eur J Endocrinol. 2002 Jan; 146(1): 35–8.
11. Lan C, Wang Y, Zeng X, Zhao J, Zou X. Morphological Diversity of Pretibial Myxedema and Its Mechanism of Evolving Process and Outcome: A Retrospective Study of 216 Cases. J Thyroid Res. 2016; 2016: 2652174.
12. Volden G. Successful treatment of chronic skin diseases with clobetasol propionate and a hydrocolloid occlusive dressing. Acta Derm Venereol. 1992; 72(1): 69–71.
13. Ramos LO, Mattos PC, Figueredo GL, Maia AA, Romero SA. Pre-tibial myxedema: treatment with intralesional corticosteroid. An Bras Dermatol. 2015 May-Jun; 90(3 Suppl 1):143–6.
14. Varma A., Rheeman C., Levitt J. Resolution of pretibial myxedema with teprotumumab in a patient with Graves disease. JAAD Case Rep. Dec 2020; 6(12): 1281–1282.
15. Pingsmann A, Ockenfels HM, Patsalis T. Surgical excision of pseudotumorous pretibial myxedema. Foot Ankle Int. 1996 Feb; 17(2): 107–10.

Tamara Janić[1], Mirjana Stojković[1,2], Bojan Marković[1], Ivana Đurković[1], Jovana Babić[1], Nata Joksimović[1], Biljana Nedeljković Beleslin[1,2], Jasmina Ćirić[1,2], Milos Žarković[1,2]

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),

[1] Tamara Janić, Clinical Center of Endocrinology, Diabetes, and Metabolic Diseases, University Clinical Center of Serbia, Department of Thyroid Diseases.

2 Medical Faculty, University of Belgrade, Serbia

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

Reference

1. Fatourechi V, Bartley GB, Eghbali-Fatourechi GZ, Powell CC, Ahmed DD, Garrity JA. Graves' dermopathy and acropachy are markers of severe Graves' ophthalmopathy. Thyroid. 2003 Dec; 13(12): 1141–4.

2. Fatourechi V, Garrity JA, Bartley GB, Bergstralh EJ, Gorman CA. Orbital decompression in Graves' ophthalmopathy associated with pretibial myxedema. J Endocrinol Invest. 1993 Jun; 16(6): 433–7.
3. Fatourechi V, Pajouhi M, Fransway AF. Dermopathy of Grave's disease (pretibial myxedema). Review of 150 cases. Medicine (Baltimore). 1994; 73: 1–7.
4. Beierwaltes WH. Clinical correlation of pretibial myxedema with malignant exophthalmos. Ann Intern Med 1954; 40: 968–84.
5. Schwartz KM, Fatourechi V, Ahmed DD, Pond GR. Dermopathy of Graves' disease (pretibial myxedema): long-term outcome. J Clin Endocrinol Metab. 2002 Feb; 87(2): 438–46.
6. Kriss JP. Pathogenesis and treatment of pretibial myxedema. Endocrinol Metab Clin North Am. 1987 Jun; 16(2): 409–15.
7. Fatourechi V. Pretibial Myxedema - Pathophysiology and Treatment Options. Am J Clin Dermatol. 2005; 6: 295–309.
8. Anderson CK, Miller OF 3rd. Triad of exophthalmos, pretibial myxedema, and acropachy in a patient with Graves' disease. J Am Acad Dermatol. 2003 Jun; 48(6): 970-2.
9. Chang TC, Wu SL, Hsiao YL, Kuo ST, Chien LF, Kuo YF, Change CC, Chang TJ. TSH and TSH receptor antibody-binding sites in fibroblasts of pretibial myxedema are related to the extracellular domain of entire TSH receptor. Clin Immunol Immunopathol. 1994 Apr; 71(1): 113–20.
10. Daumerie C, Ludgate M, Costagliola S, Many MC. Evidence for thyrotropin receptor immunoreactivity in pretibial connective tissue from patients with thyroid-associated dermopathy. Eur J Endocrinol. 2002 Jan; 146(1): 35–8.
11. Lan C, Wang Y, Zeng X, Zhao J, Zou X. Morphological Diversity of Pretibial Myxedema and Its Mechanism of Evolving Process and Outcome: A Retrospective Study of 216 Cases. J Thyroid Res. 2016; 2016: 2652174.
12. Volden G. Successful treatment of chronic skin diseases with clobetasol propionate and a hydrocolloid occlusive dressing. Acta Derm Venereol. 1992; 72(1): 69–71.
13. Ramos LO, Mattos PC, Figueredo GL, Maia AA, Romero SA. Pre-tibial myxedema: treatment with intralesional corticosteroid. An Bras Dermatol. 2015 May-Jun; 90(3 Suppl 1):143–6.
14. Varma A., Rheeman C., Levitt J. Resolution of pretibial myxedema with teprotumumab in a patient with Graves disease. JAAD Case Rep. Dec 2020; 6(12): 1281–1282.
15. Pingsmann A, Ockenfels HM, Patsalis T. Surgical excision of pseudotumorous pretibial myxedema. Foot Ankle Int. 1996 Feb; 17(2): 107–10.