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TEŠKA FORMA DISTIROIDNE DERMOPATIJE KOD PACIJENTA SA HIPERTIREOZOM

Sažetak: Grejvsova bolest (GB) je autoimunski poremećaj u čijoj su osnovi patogenetskog mehanizma TSH receptorska antitela. Osim uobičajene kliničke slike hipertireoze, mogu biti prisutne i ekstratiroidne manifestacije. Distirodina dermopatija je jedna od njih i javlja se kod oko 0.5-4.3% slučajeva, uglavnom kod pacijenata sa već prisutnom distiroidnom orbitopatijom kao najčešćom ekstratiroidnom manifestacijom. Javlja se u različitim formama netestastih edema, plakova, čvorova i retko u obliku elefantijaza. Prikazali smo pacijenta sa tireotoksikozom na terenu GB kod kog je bila prisutna okularna ekstratiroidna manifestacija, kao i distiroidna dermopatija u obliku elefantijaze, koja je dokazana *punch* biopsijom. Na primenu kortikosteroidne terapije kod pacijenta je došlo do značajnog poboljšanja nalaza na očima, kao i poboljšanja dermopatije. Elefantijaza predstavlja najtežu formu ovog oboljenja i može biti rezistentna na bilo koji vid lečenja zbog čega predstavlja veliki terapijski izazov.

Uvod:

Distiroidna dermopatija, poznatija kao pretibijalni miksedem (PTM) zbog svoje lokalizacije, predstavlja retku komplikaciju autoimunske bolesti štitaste žlezde i najčešće je prisutna kod Grejvsove bolesti. Javlja se kod oko 0.5-4.3% slučajeva GB i gotovo uvek je udružena sa orbitopatijom.[1,2] Glavni patofiziološki supstrat je nagomilavanje glikozaminoglikana (GAG) u dermisu koje luče fibroblasti, stimulisani od strane TSH receptorskih antitela (*TRAb*).[1,3] Javlja se u različitim formama netestastih edema, plakova, čvorova i, retko, u obliku elefantijaze. Kod oko 20% pacijenata sa dermopatijom mogu biti zahvaćeni i vrhovi prstiju kada se radi o akropahiji.[1,4]

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Kod pacijenta muškog pola starosti 50 godina septembra 2021. godine su se javile tegobe u vidu edema potkolenica obostrano, sa crvenilom i bolnim senzacijama uz otežano kretanje, inicijalno okarakterisane kao celulitis, da bi potom došlo i do pojave edema šaka. Nakon dve sedmice javili su se obostrani otoci kapaka, hiperemija konjunktiva, iritativne smetnje i dvoslike u svim pravcima pogleda, uz istovremenu pojavu simptoma hipermetabolizma. Dijagnoza hipertireoze na terenu Grejvsove bolesti postavljena je decembra 2021. godine (fT4 34.07 pmol/L; fT3 14.3 pmol/L; TSH <0.002 mIU/L; *TRAb* >40 IU/L) kada je uvedena tireosupresivna terapija. Tokom hospitalizacije na Klinici za endokrinologiju, dijabetes i bolesti metabolizma UKCS maja 2022. godine učinjena su funkcionalna i morfološka ispitivanja Grejvsove bolesti sa ekstratiroidnim komplikacijama. U fizikalnom nalazu bili su prisutni obostrani otoci i hiperemija kapaka, crvenilo konjunktiva uz otok plika i karunkula (Clinical Activity Score - CAS 4), kao i blaga retrakcija kapaka i proptoza uz lagoftalmus 2 mm na desnom, a 4 mm na levom oku. Motilitet bulbusa bio je ograničen u svim krajnjim pozicijama, izraženije pri elevaciji obostrano i abdukciji desnog oka. Diplopije su bile prisutne u primarnom položaju i u svim pravcima pogleda. Palpatorno štitasta žlezda imponuje lako uvećana. Inspekcijom gornjih ekstremiteta uočeni su edemi i uvećanje šaka sa hiperpigmentovanim promenama i ograničenom pokretljivošću prstiju. Na donjim ekstremitetima uočeno je prisustvo obostranih edema donje trećine natkolenica, potkolenica i stopala nalik elefantijazi, palpatorno tvrde konzistencije sa hiperpigmentovanim poljima uz prisutne beličaste skvame (Slika 1 i 2).

Slika 1 i 2. Obostrani edemi donjih ekstremiteta nalik elefantijazi sa hiperpigmentovanim poljima

Na oftalmološkom pregledu verifikovana je uredna vidna oštrina (VOD cc suo 0.9-1.0, VOS cc suo 1.0) uz nalaz na fundusu OD koji odgovara papiloflebitisu (edem, hemoragije na rubu i peripapilarno, par cotton wool), kao i edem diskusa optičkog nerva i ređe plamenaste hemoragije na OS. Kompjuterizovanim vidnim poljem uočen je lučni skotom gore periferno na OD i nespecifični periferni ispadi sa proširenom slepom mrljom na OS. EHO orbita pokazao je zadebljale unutrašnje prave mišiće oba oka i donji pravi mišić desnog oka. Zbog subjektivnog pogoršanja vida učinjen je ponovni pregled oftalmologa kojim je registrovano pogoršanje vidne oštrine (VOD: cc suo 0.6 k.o. 0.8 VOS: cc suo 0.7 k.o. 1.0). U okviru ispitivanja dermopatije učinjena je *punch* biopsija promena na potkolenicama, a histopatološki nalaz je ukazao na elemente dermatitisa sa deponovanjem mucina, što bi moglo odgovarati pretibijalnom miksedemu (Tabela 1). Nativna radiografija šaka je bila uredna, dok je u projekciji lateralnog dela distalne falange prvog prsta levog stopala viđena koštana destrukcija. Inicijalno je razmišljano u pravcu akropahije koja je međutim isključena naknadnim dobijanjem anamneznog podatka o ranijoj mehaničkoj povredi.

Tabela 1. Histopatološki nalaz kože

Histopatološki nalaz	
Epiderm	pojačana pigmentacija bazalnog sloja
Derm	bledilo superficijalnih slojeva retkularnog derma
	između kolagenih vlakana superficijalnih slojeva retikularnog derma se uočava obilno deponovanje mucina

Slika 3 i 4. Donji ekstremiteti nakon terapije
(smanjenje otoka, manja izraženost hiperkeratoze i hiperpigmentacije)

Zbog GO udružene sa papiloflebitisom, a prema savetu od strane oftalmologa, primenjena je kortikosteroidna pulsna terapija metilprednizolonom (MP) u dozi od 1g u trajanju od 5 dana, a potom je uveden Pronizon u opadajućim dozama po shemi (60, 40, 20, 10 mg u trajanju od po 3 dana). Lokalno na donjim ekstremitetima je primenjena terapija topikalnim steroidima pod okluzijom uz pimekrolimus. Nakon inicijalne pulsne kortikosteroidne terapije (MP 5x1g) došlo je do značajnog poboljšanja papiloflebitisa (resorpcije edema i hemoragija uz smanjenje broja cotton wool), kao i diskretnog smanjenja očnih tegoba, dok su duple slike bile bez poboljšanja. Tada je zabeleženo i smanjenje otoka šaka i potkolenica. Tokom naredne hospitalizacije jula 2022. godine GO se prezentovala kao aktivna, srednje teška zbog čega je nastavljeno lečenje prema standardnom 12-nedeljnom kortikosteroidnom protokolu (MP 6x500mg + 6x250mg u nedeljnim intervalima). Na primenjenu terapiju beleži se poboljšanje očnih tegoba u smislu smanjenja otoka kapaka, crvenila konjunktiva i protruzije očnih jabučica uz povlačenje hemoze i otoka plika i karunkula (CAS 1-2), dok su duple slike zaostale. Uz značajnu redukciju telesne težine (maj 2022. godine 133 kg…novembar 2022. godine 109 kg) beleži se i poboljšanje dermopatije u vidu smanjenja otoka, manje izraženosti hiperkeratoze i hiperpigmentacije potkolenica (Slika 3 i 4), kao i bolje pokretljivosti u zglobovima.

Diskusija:

Grejvsova bolest je autoimunski poremećaj koji se karakteriše povišenim nivoom cirkulišućih autoantitela na TSH receptore (*TRAb*), pod čijim dejstvom tiroidna žlezda menja svoju morfologiju i funkciju. Osim uobičajene kliničke slike Grejvsove bolesti u vidu hipertireoze, mogu postojati i ekstratiroidni entiteti, kao što su orbitopatija i ređe, tiroidna dermopatija.[1,3]

Tiroidna dermopatija, poznata i kao pretibijalni miksedem, jeste retka ekstratireoidna manifestacija i gotovo uvek se javlja zajedno sa orbitopatijom.[3,5] Lezije na koži su okarakterisane kao hiperpigmentovane, sa hiperkeratoznim promenama, fisurama, ragadama, nepravilne su strukture, nalik na pomorandžinu koru (*peau d'orange*). Najčešće se javljaju bilateralno i dominantno u pretibijalnom regionu, neretko i sa zahvatanjem stopala, kao u slučaju našeg pacijenta. Ovakva lokalizacija se uglavnom vezuje za mehaničke faktore i javlja se pod dejstvom gravitacije, kao i usled dužeg stajanja. Međutim, ove promene se mogu javiti i na drugim mestima, najčešće na onim gde postoji istorija traume.[1-3,6] U težim slučajevima mogu biti zahvaćeni i vrhovi prstiju, kada govorimo o akropahiji, koja je prisutna kod 20% pacijenata sa dermopatijom, što se uglavnom vezuje za teže forme orbitopatije.[4] Pretibijalni miksedem se klasifikuje u 4 glavne forme: difuzni netestasti edem, plak, nodusi i forma nalik elefantijazi. Poslednji oblik viđen kod našeg pacijenta, ujedno i najteži, manifestuje se u vidu multiplih nodularnih formacija, masivnog edema sa

hiperpigmentacijom, dovodi do mehaničke i funkcionalne nesposobnosti i prisutan je kod samo 5% pacijenata sa PTM.[2,7]

U literaturi se spominje isti mehanizam nastanka obe ekstratireoidne manifestacije te da glavnu ulogu u nastanku i orbitopatije i dermopatije igraju *TRAb*. Ova antitela stimulišu fibroblaste da produkuju glikozaminoglikane (GAG), koji imaju sposobnost da vežu veću količinu vode dovodeći do edema. U slučaju dermopatije, GAG se akumuliraju u dermisu, dok se kod orbitopatije isti proces dešava u vezivnom tkivu i intersticijumu orbite.[1,2]

Biopsija predstavlja važnu dijagnostičku metodu kojom se uzimaju uzorci kože i boje hematoksilinom i eozinom. Ovom metodom mogu se vizualizovati histopatološke karkteristike dermopatije kao što su taloženje mucina u dermisu, fragmentacija dermalnih kolagenih vlakana, perivaskularna limfocitna infiltracija unutar dermisa uz pridruženu hiperkeratozu. Taloženje mucina se obično može i naknadno potvrditi specifičnim bojenjem (*alcian blue)*. Ponekad postavljanje dijagnoze može biti otežano ukoliko nisu prisutni svi histopatološki kriterijumi i u tom slučaju nalaz se korelira sa kliničkom slikom.[8,9]

PTM se najčešće javlja u blagoj asimptomatskoj formi koja teži spontanoj regresiji i rezoluciji kod polovine obolelih, i kao takav ne zahteva poseban tretman. Češće može predstavljati kozmetički problem i tada se pribegava primeni topikalnih kortikosteroida koji predstavljaju prvi oblik terapije i obično imaju povoljan efekat na tok bolesti.[2,3] U jednoj studiji sprovedenoj u Indiji[10] pokazano je da plakovi i nodusi predstavljaju forme koje najbolje reaguju na terapiju, kako topikalnim tako i intralezionim kortikosteroidima te se kod njih u velikom procentu slučajeva može očekivati potpuno izlečenje. Međutim, sa povećanjem težine bolesti, uspešnost ove terapije se smanjuje. U izuzetnim slučajevima dermopatija se može javiti i u obliku koji liči na elefantijazu, kao najteža forma bolesti koja predstavlja i funkcionalni i estetski problem za pacijenta, a ujedno je i najrezistentnija na terapiju. Kod ove forme najčešće se koristi lokalna kompresivna terapija (kompresivne čarape i zavoji), a nekada je potrebno pacijenta uputiti i na fizikalnu terapiju koja može dovesti do značajnog poboljšanja. Dobar rezultat može se postići i primenom sistemske imunomodulatorne terapije.[2,7,11]

Zaključak:

Prikazali smo pacijenta sa retkom ekstratiroidnom manifestacijom Grejvsove bolesti, tiroidnom dermopatijom u formi nalik na elefantijazu koja ujedno predstavlja i najtežu formu ovog oboljenja. Budući da često može biti rezistentna na bilo koji vid lečenja, predstavlja veliki terapijski izazov. U prikazanom slučaju nije došlo do potpunog izlečenja, tegobe kod pacijenta i dalje perzistiraju, međutim značajno su manjeg stepena u poređenju sa periodom pre započinjanja terapije.

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SEVERE FORM OF THYROID DERMOPATHY IN PATIENT WITH HYPERTHYROIDISM

Abstract: Graves' disease is an autoimmune disorder in which TSH receptor antibodies play the main pathogenic role. Besides the usual clinical presentation as hyperthyroidism, extrathyroidal manifestations can develop. Thyroid dermopathy is one of them and it is present in about 0.5-4.3% of cases, mostly in patients with thyroid orbitopathy as main extrathyroidal manifestation. Dermopathy can manifest in different forms: non-pitting edema, plaques, nodules and elephantiasis. We are reporting a case of a patient with thyrotoxicosis caused by Graves' disease with ocular extrathyroidal manifestation and dermopathy in elephantiasis form, confirmed by punch biopsy. Corticosteroid therapy significantly improved ocular manifestations, as well as skin lesions. Elephantiasis represents the most severe form of this disease and can be resistant to any treatment thus why it is a major therapeutic challenge.

Introduction:

Thyroid dermopathy, known as pretibial myxedema (PTM) is a rare complication of autoimmune thyroid disorder, and it is most often present in Graves' disease (GD). PTM is present in 0.5-4.3% cases of GD and it is almost always associated with orbitopathy.[1,2] Main pathophysiological substrate is accumulation of glycosaminoglycans (GAGs) in dermis, secreted by fibroblasts which are stimulated by TSH receptor antibodies (TRAbs).[1,3] Dermopathy can be manifested in different forms: non-pitting edema, plaques, nodules and elephantiasis. Fingertips can be affected in around 20% of dermopathy cases – a condition known as acropachy.[1,4]

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A 50 year old male patient in September of 2021. presented with bilateral edema of lower legs, with erythema and painful sensations, as well as walking difficulties, originally characterized as cellulitis. Swelling of the hands then developed as well. Bilateral swelling of the eyelids, conjunctival hyperemia, eye irritation and double vision appeared after two weeks. Symptoms and signs of hypermetabolism appeared simultaneously with eye problems. Diagnosis of hyperthyreosis caused by Graves' disease was made in December of 2021. (fT4 34.07 pmol/L; fT3 14.3 pmol/L; TSH <0.002 mIU/L; *TRAb* >40 IU/L) and treatment with thyroid hormone suppression therapy began. Functional and morphological examination of GD with extrathyroidal manifestation was conducted during hospitalization on Clinic for endocrinology, diabetes and metabolic diseases on University clinical centre of Serbia in May of 2022. On physical examination of the eyes the following was observed: bilateral edema and hyperemia of the eyelids, conjunctival hyperemia and swelling of the caruncle and plica (Clinical Activity Score - CAS 4), as well as mild retraction of the eyelids, proptosis and lagophtalmos (2mm on OD, 4 mm on OS). Restricted eye movement was present, especially during elevation of the eyes bilaterally and the right eye abduction. Double vision was present in primary position as well as in all positions of gaze. Palpatory, thyroid gland appeared slightly enlarged. Inspection of the upper extremities showed edema and enlargement of the hands with hyperpigmentation and limited finger movement. Bilateral elephantiasis like edema of lower third of the upper legs, lower legs and feet with palpatory hard consistency and hyperpigmentation was observed (Figure 1 i 2).

Figure 1 and 2. Bilateral elephantiasis like edema of lower extremities with hyperpigmentation

Eye exam showed normal visual acuity (VOD cc suo 0.9-1.0, VOS cc suo 1.0) with papillophlebitis on FOD (edema, peripapillar hemorrhages and cotton wool spots), as well as optic disc edema and flame shaped hemorrhages on FOS. Visual field test showed scotomas on both eyes. Orbital ultrasound showed internal rectus muscle thickening on both eyes and inferior rectus muscle thickening on OD. Subjective vision weakening lead to re-examination by ophthalmologist who diagnosed worsening of visual acuity (VOD: cc suo 0.6 k.o. 0.8 VOS: cc suo 0.7 k.o. 1.0). Dermopathy examination included punch biopsy of the lower leg skin lesions, and histopathological findings showed elements of dermatitis with mucin depositions, which could indicate pretibial myxedema (Table 1). Native radiography of the hands had no pathological findings, but bone destruction was seen in projection of lateral part of the first distal phalange of the left foot. Initially, we suspected of acropachy which was later excluded after getting information about mechanical trauma.

Table 1. Histopathological findings of the skin

Histopathological findings	
Epidermis	increased pigmentation of basal layer
Dermis	paleness of superficial layers of reticular dermis
	abundant mucin deposition between collagen fibers of superficial layers of reticular dermis

Figure 3 and 4. Lower extremities after treatment (reduction in edema, hyperkeratosis and hyperpigmentation)

Because of GO associated with papillophlebitis, and with the ophatlomogist's advice, we started corticosteroid therapy with methylprednisolone (MP) in a dose of 1g for 5 days, and then continued therapy with Pronison in gradual reduction of doses (60 mg x 3 days, 40 mg x 3 days, 20 mg x 3 days, 10 mg x 3 days). Lower extremities were treated with topical corticosteroids combined with occlusive therapy and pimecrolimus. After initial corticosteroid therapy with MP (5x1g) there was significant improvement of the papillophlebitis and slight improvement of eye problems, while double vision persisted. Improvement of hand and leg edema was also observed. During the next hospitalization in July of 2022. GO presented as an active, moderate to severe form which is why treatment was continued with 12-week corticosteroid therapy (MP 6x500mg + 6x250mg in weekly intervals). This treatment lead to improvement of the eye difficulties: decrease of the swelling of the eyelids, conjunctival redness and eye protrusion, and disappearance of chemosis and swelling of the caruncle and plica (CAS 1-2). Double vision persisted. With significant weight reduction (May of 2022. 133 kg….November of 2022. 109 kg), improvement of dermopathy was observed. There was a reduction in edema, as well as in hyperkeratosis and hyperpigmentation of the lower legs (Figure 3 and 4) and better joint mobility.

Discussion:

Graves' disease is an autoimmune disorder characterized by elevated levels of TSH receptor autoantibodies (TRAbs), causing changes in morphology and function of the thyroid. Besides the usual clinical presentation as hyperthyroidism, extrathyroidal manifestations of GD such as orbitopathy and dermopathy can be developed. [1,3]

Thyroid dermopathy, known as pretibial myxedema (PTM) is a rare extrathyroidal manifestation and it is almost always associated with thyroid orbitopathy.[3,5] Skin lesions are described as hyperpigmentations with hyperkeratosis, fissures, rhagades with irregular structure resembling an orange peel (*peau d'orange*). Usually, the skin changes are bilateral and dominantly in the pretibial region, often affecting feet, as in the case of our patient. This type of localization is often associated with mechanical factors and it is considered a consequence of the force of gravity, as well as being in standing position for a long period of time. However, these changes can be seen in other localizations, usually with a history of trauma.[1-3,6] Fingertips can be affected in more severe cases. This condition, present in around 20% of dermopathy cases, is called acropachy and it is usually associated with a more severe form of orbitopathy.[4] Pretibial myxedema is classified in 4 different forms: non-pitting edema, plaques, nodules and elephantiasis. Elephantiasis as the most severe form of PTM manifests in multiple nodular formations and massive

edema with hyperpigmentation. It can cause mechanical and functional disability and can be seen in 5% of patients with PTM.[2,7]

It is considered that TRAbs play the main role in pathophysiology of orbitopathy and dermopathy. These autoantibodies stimulate fibroblasts to produce GAGs, which can bind large amounts of water, causing edema. In case of dermopathy, GAGs are being accumulated in dermis, while in orbitopathy the same process happens in orbital connective tissue and interstitium.[1,2]

Biopsy is an important diagnostic method which consists of taking samples of the skin and hematoxylin and eosin staining. This method can help visualize histopathological characteristics of dermopathy such as mucin deposition in dermis, dermal collagen fibers fragmentation, perivascular lymphocyte infiltration in dermis and hyperkeratosis. Mucin deposition can be confirmed with specific staining (alcian blue). Making a diagnosis can be difficult in certain cases, especially if complete histopathological criteria is not present thus why it is important to correlate histopathological findings with clinical presentation.[8,9]

PTM usually manifests as a mild, asymptomatic form which can spontaneously regress and resolve itself in 50% of patients thus why it doesn't require any special treatment. However, more often it can represent a cosmetic problem for the patient in which case topical corticosteroids are the treatment of choice. They usually have positive effects on the course of the disease.[2,3] One study in India[10] showed that plaques and nodules are forms that usually react well to topical and intralesional corticosteroid therapy. However, with the increase of the disease severity, the success of this therapy decreases. Elephantiasis is the most extraordinary and severe form of PTM. It can cause functional and aesthetic problems for the patient and at the same time, it's the most resistant to therapy. Local compressive therapy is usually therapy of choice, and in certain cases physical therapy can lead to significant improvement. Systemic immunomodulatory therapy can give satisfactory results as well.[2,7,11]

Conclussion:

We showed patient with elephantiasic form of thyroid dermopathy as a rare extrathyroidal manifestation of GD, which is at the same time the most severe one. Considering that this form can usually be resistant to therapy, it stays a major therapeutic challenge. In this case, the complete resolvement of the disease was not achieved and skin lesions are still persistent. However, they are less extensive comparing to period before the initiation of therapy.

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