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Lichen planus in the lines of Blaschko – a case report

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VERSITA

Abstract

Lichen planus is an acquired inflammatory disease of the skin, mucous membranes and nails. It is characterized by pruritic polygonal livid papules. The disease was first described by Erasmus Wilson in 1869. It is primarily a disease of adults, and it usually occurs between the ages of 30 and 60, without gender predominance. The exact incidence and prevalence of this disease are unknown, but it is thought to affect less than 1% of the general population (0.14 to 0.80%) (1).

A 63-year old male patient was admitted to our Department with itchy erythematous papules and plaques which appeared a month before admission. On admission, numerous erythematous and livid papules and plaques of polygonal shape up to 5 mm in diameter were present in the lines of Blaschko, along the left lower extremity, left side of the trunk and the left upper arm (Figures 1-3), while mucous membranes, nails and scalp were spared.

Blaschko-linear distribution of skin lesions was first described by a German dermatologist Alfred Blaschko in 1901 in his work "The distribution of nerves in the skin and their relationship to diseases of the skin". In 1978, Happle first published that genetic mosaicism was the cause of these peculiar skin changes (1,4,6). Although knowledge of mosaicism in the skin was further elucidated in articles of several authors (Taieb in 1994, Bolognia in 1994, Heide 1996), the exact mechanism and molecular basis for the development of Blashcko linear distribution has not been fully clarified yet (5). Blaschko lines may be related to X-linked, congenital and inflammatory dermatoses, and they may be found in several skin conditions like segmental forms of atopic dermatitis, erythema multiforme, pemphigus vulgaris, vitiligo, and granuloma annulare. This is a case report of a patient with a rare form of lichen planus, with typical clinical manifestations and with Blaschko-linear distribution. Lichen planus in the lines of Blaschko was also described in several other dermatoses: lichen striatus, lichen sclerosus, morphea, porokeratosis of Mibelli, mucinosis follicularis and psoriasis vulgaris. The treatment included topical corticosteroids under occlusion, due to comorbidities, with satisfactory response. Other options include, topical calcineurin inhibitors, intralesional and systemic corticosteroids, retinoids, phototherapy and in resistant cases that severely affect the quality of life methotrexate, cyclosporine and thalidomide.

Key words

Lichen Planus; Signs and Symptoms; Administration, Topical; Adrenal Cortex Hormones; Retinoids; Phototherapy

Lichen planus is an acquired inflammatory condition of the skin, mucous membranes and nails. It is characterized by eruption of pruritic polygonal livid papules. It was first described by Erasmus Wilson in 1869. It primarily affects adults, usually between 30 and 60 years of age, without gender predominance. The exact incidence and prevalence of this disease is unknown, but it is thought to affect less than 1% of the general population (0.14 to 0.80%) (1).

Lichen planus is a polygenic disorder, but sometimes it may show a segmental distribution, as a result of postzygotic mutation at an additional predisposing gene locus. The loss of heterozygosity may occur from a mutation, deletion or DNA recombination, leading to the formation of a keratinocyte clone that is more susceptible to development of the disease. Linear lichen planus is a rare manifestation of this disease and occurs in less than 0.2% of all patients (1).

Case report

A 63-year-old man was admitted to our Department due to itchy erythematous papules and plaques which appeared a month before admission. On admission, the patient presented with numerous erythematous and livid papules and plaques of polygonal shape, up to 5 mm in diameter, in the lines of Blaschko, along the left lower extremity, on the left side of the trunk and on the left upper arm (Figures 1-3), while mucous membranes, nails and scalp were spared. In the past 15 years the patient was treated for diabetes mellitus with complications: microangiopathy, polyneuropathy, and hyperlipidemia. Diabetes was treated with insulin and metformin, hyperlipidemia with simvastatin, polyneuropathy with alpha-lipoic acid, and hypertension with fosinopril and furosemide. The regular therapy was not changed before the onset of the disease. Complications led to amputation of the fifth toe on both feet and malum perforans pedis on

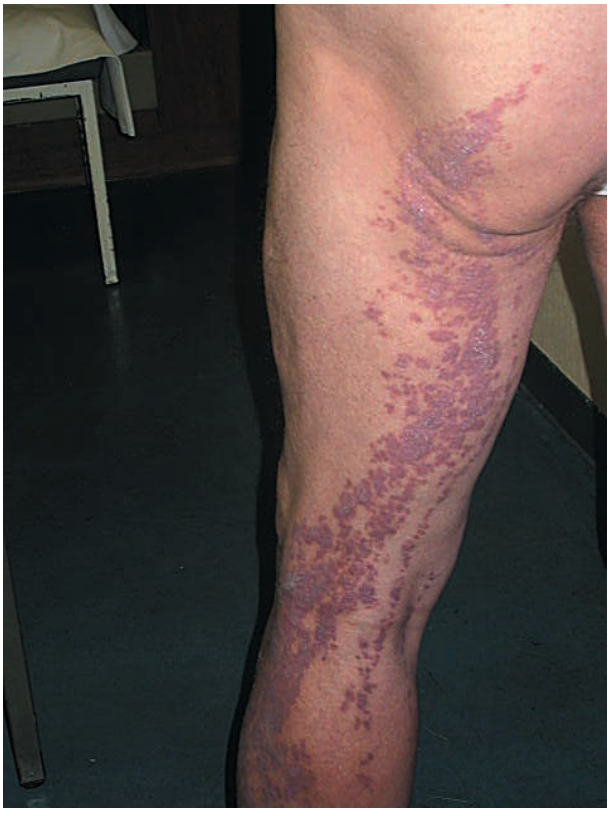

Figure 1. On admission, numerous erythematous and livid papules and plaques of polygonal shape up to 5 mm in diameter were present in the linear Blaschko distribution, along the left lower extremity

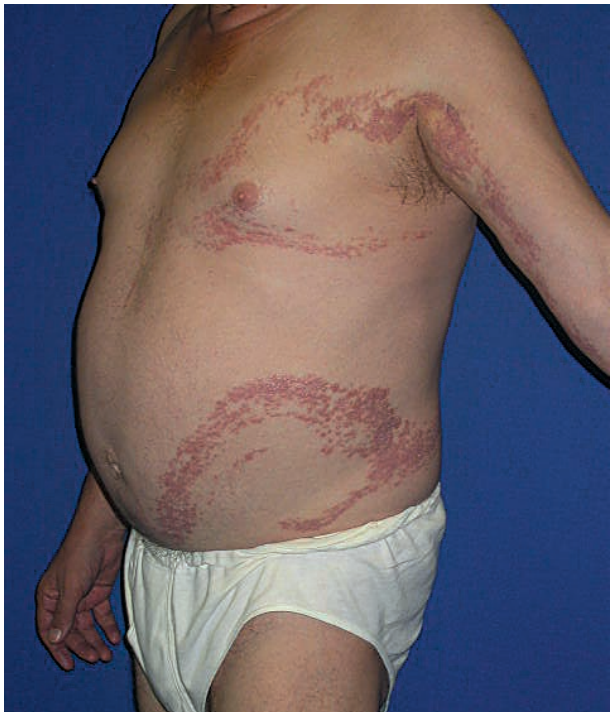

Figure 2. On admission, numerous erythematous and livid papules in the linear Blaschko distribution, along the left side of the trunk

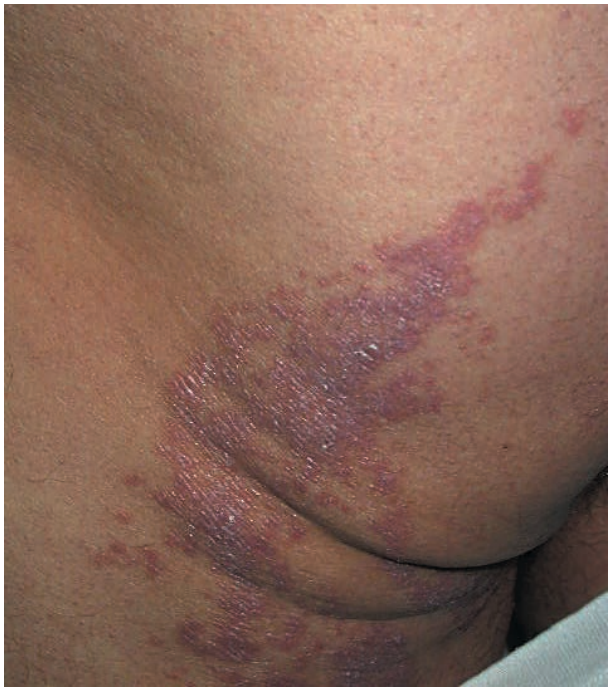

Figure 3. On admission, numerous erythematous and livid papules in the linear Blaschko distribution, along the left thigh

the left foot, with osteolysis of the phalanges up to the middle third of the fifth metatarsal bone.

Laboratory examination revealed increased sedimentation rate (51 and 33 mm/h), elevated CRP concentration (34,1 i 4,32 g/l), slight anemia with normal hemoglobin levels (RBC $3,95x10^{12}$/L), fasting blood sugar of 9.9 mmol/l, repeated 11.8 mmol/l, HbA1c 8,2%, while other parameters (CBC and DBC, AST, ALT, urea, creatinine, cholesterol, triglycerides, total bilirubin, albumin) were within normal range. Doppler ultrasonography of the lower extremities revealed diffuse metabolic changes on the large arterial vessel, but without stenoses or other hemodynamic changes, with arterial flow that could be traced to the distal parts with satisfactory perfusion. There were also no signs of venous insufficiency.

Biopsy of erythematous-livid papules was performed and histopathological analysis was consitent with lichenoid interface dermatitis, while direct immunofluorescence did not reveal deposits of immunoreactancts (immunoglobulins, complement or colloid boides) (Figure 4).

The long-term diabetes and its complications were relative contraindications for treatment with systemic corticosteroids, so therapy with potent topical steroids under occlusion (betamethasone dipropionate 0.05% ointment) was used leading to significant partial regression of lesions, with disappearance of itching after two weeks. Since the response to therapy was satisfactory at that point, the initially planned acitretin therapy was not introduced.

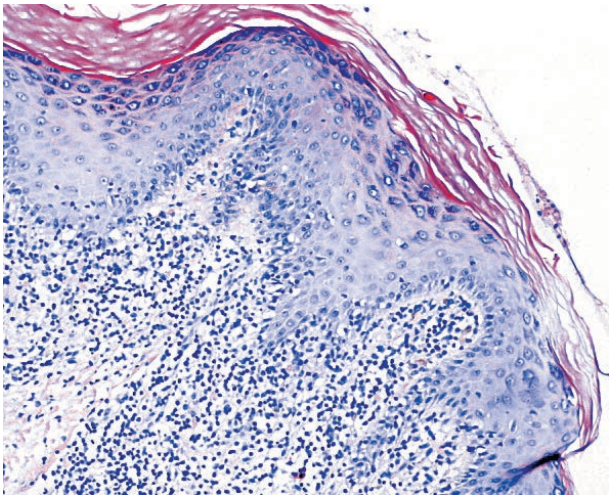

Figure. 4. Skin biopsy with hyperkeratosis, uneven hypergranulosis, moderate acanthosis and irregularly elongated epidermal ridges and signs of interface dermatitis (hematoxylin and eosin x 100)

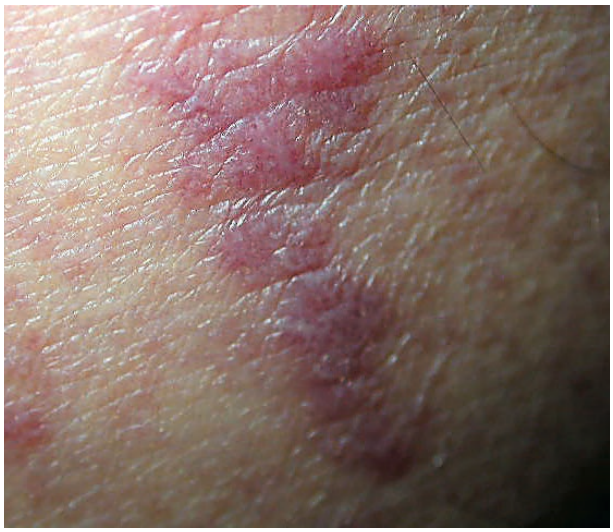

Figure 5. Numerous erythematous and livid papules of polygonal shape up to 5 mm in diameter in the linear Blaschko distribution

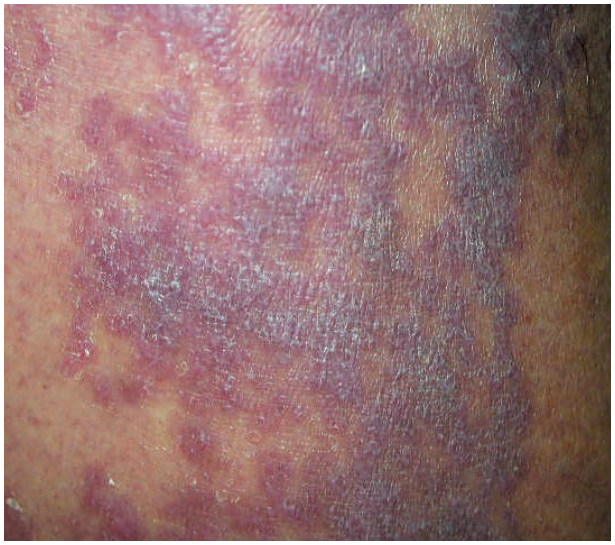

Figure 6. Numerous erythematous and livid papules of polygonal shape agglomerate to form a plaque

Discussion

Blaschko distribution of skin lesions was first described by the German dermatologist Alfred Blaschko in 1901 in his work "The distribution of nerves in the skin and their relationship to diseases of the skin". In 1978, Happle first reported that genetic mosaicism was the cause of these peculiar skin changes (1,4,6).

Although the knowledge of mosaicism in the skin was further elucidated in articles of several authors (Taieb in 1994, Bolognia in 1994, Heide 1996), the exact mechanism and molecular basis for the development of Blashcko distribution has not been fully clarified yet (5). Blaschko lines do not correspond to any known nervous, vascular or lymphatic structures, and they differ from other morphological lines like: Voight, Langer, embryonic cleavage and pigmentation demarcation lines. They are V-shaped on the upper back, inverted U-shaped on the upper chest, S-shaped on the abdomen, perpendicular on the extremities and never cross the center, but go along the central line of the trunk (2, 8). It is assumed that they represent the distribution of autonomous motor-visceral afferent nerve fibers, or are the result of stretching of the skin during embryogenesis. Blaschko lines may be related to X-linked, congenital and inflammatory dermatoses, and they are described in several skin conditions like segmental forms of atopic dermatitis, erythema multiforme, pemphigus vulgaris, vitiligo, and granuloma annulare (Table 1) (3).

Blaschko lichen planus was described in 0.2% of patients, resulting probably from postzygotic mutations, deletions or DNA recombination, in one of the genes that carry a predisposition to the development of the disease. Therefore, contrary to the generalized eruption to the yet unknown antigen, the reaction to the antigen manifests in a clone of keratinocytes susceptible to this disease.

In differential diagnosis, lichen striatus has similar clinical manifestations and distribution of skin lesions, but lichen striatus can be distinguished by its rapid development, generally after the fi rst year of life, thus being more common in children, the condition is often asymptomatic and usually self-limiting. Moreover, histopathological analysis in our patient was consistent with lichen planus. However, direct immunofluorescence was negative (which is not uncommon), probably due to the relatively short duration of the disease in our patient.

Table 1. Blaschko linear dermatoses and mosaicism*

X-linked mosaicism	Autosomal dominant mosaicism of non-lethal genes	Autosomal dominant mosaicism of lethal genes	Mosaicism of chromosomal abnormalities	Chimerism
Incontinentia pigmenti	Epidermolytic hyperkeratosis	Epidermal nevus	Hypomelanosis of Ito	Segmental hyperpigmentation
Goltz syndrome	Darier's disease	McCune-Albright syndrome		
Happle syndrome	Neurofibromatosis type I	CHILD syndrome		
Hypohydrotic ectodermal dysplasia	Gorlin syndrome	ILVEN		
	Comedo nevus	Proteus syndrome		
Menkes syndrome	Porokeratosis			
	Psoriasis			
	Lichen planus			
	Eczema (lichen striatus)			
	Vitiligo			

CHILD, congenital hemidyplasia with ichthhyosiform erythroderma and limb defects; ILVEN, inflammatory linear verrucous nevus.

The coexistence of lichen planus and diabetes mellitus has been described in the literature, and in one study around 50% of patients with lichen planus had glucose metabolism disorders and 25% had diabetes mellitus (9). In patients with lichen planus, levels of HbA1C, fasting glucose levels and insulin resistance were statistically higher than in the control group, and authors concluded that further studies are needed to examine this correlation, which can be explained by autoimmune etiopathogenesis of both diseases (9).

Conclusion

In conclusion, a patient with a rare form of lichen planus is described, with typical clinical manifestations of lichen planus but in the lines of Blaschko, which distribution is also described in several other dermatoses: lichen striatus, lichen sclerosus, morphoea, porokeratosis Mibelli, mucinosis follicularis and psoriasis vulgaris. The treatment included topical corticosteroids under occlusion, due to comorbidities, with a satisfactory response. Other options include topical calcineurin inhibitors, intralesional and systemic corticosteroids, retinoids, phototherapy and in resistant cases, that severely affect the quality of life, methotrexate, cyclosporine and thalidomide.

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Blaschko linearni lichen planus – prikaz slučaja

Sažetak

Uvod: Lihen planus (lat. *lichen planus*) predstavlja stečenu inflamatornu papuloznu pruritičnu dermatozu koja zahvata kožu, vidljive sluznice i nokte. Tačna incidencija i prevalencija ovog oboljenja i dalje je nepoznata, ali se može reći da bolest zahvata manje od 1% pripadnika opšte populacije.
Patofiziologija: U osnovi oboljenje se javlja kao posledica poligenskog poremećaja. U retkim slučajevima kliničkom slikom dominira segmentalni raspored promena za koji se pretpostavlja da predstavlja posledicu postzigotske mutacije na genskom lokusu koji je u klasičnim slučajevima odgovoran za povišenu prijemčivost za nastajanje oboljenja. Gubitak heterozigotnosti može nastati kao posledica mutacije, delecije ili DNA rekombinacije, a posledica je stvaranje klona keratinocita koji poseduje povišenu prijemčivost za lihenske promene. Linearni raspored lezija koji tom prilikom dominira kliničkim nalazom viđa se kod samo 0,2% svih pacijenata sa lihenom planus.
Prikaz slučaja: Prilikom prvog pregleda, odrastao muškarac, star 69 godina, u anamnestičkim podacima istakao je pojavu crvenih čvorića i ploča koji su se počeli pojavljivati u toku poslednjih mesec dana. Promene prati intenzivan svrab, a one zahvataju isključivo kožu. Od ranijih bolesti navodi šećernu bolest i povišene količine masnoća u krvi. Kliničkim nalazom prillikom prvog dermatološkog pregleda koji je urađen na prijemu u bolnicu, dominiralo je prisustvo mnogobrojnih eritematoznih i lividnih papula poligonalnog oblika oko 5 mm u prečniku koje su bile pojedinačne ili aglomerirane u manje plakove. Navedene promene su imale karakterističnu distribuciju po tzv. *Blaschko* linijama: duž levog donjeg ekstremiteta, na levoj strani trupa i duž leve nadlaktice; poglavina, nokti i sluznice bili su pošteđeni. Iz priložene dokumentacije zaključilo se da se bolesnik leči od dijabetesa melitus tokom poslednjih 15 godina i da su nastupile komplikacije: mikroangiopatija, polineuropatija i hiperlipidemija. Dijabetes je lečen insulinom i metforminom, hiperlipidemija simvastatinom, polineuropatija alfa lipoičnom kiselinom, a hipertenzija fosinoprilom i furosemidom. Navedena terapija nije menjana u periodu neposredno pre i za vreme pojave

promena na koži. Usled nastalih komplikacija izvršena je u prethodnom periodu amputacija malog prsta na oba stopala, razvio se malum perforans na levom stopalu, osteoliza falangi koja je zahvatila kost sve do srednje trećine pete metatarzalne kosti.

Relevantne analize: Laboratorijski nalazi, koji su odstupali od fizioloških, uključivali su povišenu sedimentaciju, povišenu koncentraciju C-reaktivnog proteina u serumu, blagu anemiju, povišenu vrednost glikemije od 9,9 mmol/l do 11,8 mmol/l. Vrednost hemoglobina A1c (HbA1c) iznosila je 8,2%. Prilikom ultrazvučnog dopler pregleda krvnih sudova donjih ekstremiteta, na arterijama nisu uočene stenoze, u arterijskom protoku nisu registrovani hemodinamički poremećaji, dok na venama nije bilo znakova insuficijencije.

Histopatotološka analiza: U isečku uzetom sa papulama zahvaćene kože, histološkom analizom dobijen je nalaz lihenoidnog *interface* dermatitisa, dok je direktna imunofluorescencija pokazala odsustvo depozita imunoglobulina, komplementa ili koloidnih telašaca.

Lečenje: Postojanje dijabetesa i razvoj njegovih komplikacija predstavljali su kontraindikaciju za lečenje sistemskim kortikosteroidima, tako da je terapija bila zasnovana na aplikaciji potentnih kortikosteroida za lokalnu primenu pod okluzijom (*bethamethasone dipropionate* 0,05% mast) što je izazvalo delimičnu ali značajnu regresiju promena i prestanak svraba nakon dve nedelje. S obzirom da je terapijski odgovor bio zadovoljavajući, odustalo se od ranije planirane sistemske primene acitretina.

Diskusija: *Blaschko* distribuciju kožnih promena prvi put je opisao nemački dermatolog Alfred Blaschko 1901. godine. Happle je 1978. godine prvi povezao postojanje genetskog mozaicizma sa karakterističnom distribucijom promena na koži. I pored brojnih ispitivanja, tačan mehanizam kojim nastaje *Blaschko* distribucija, ni do danas nije dovoljno razjašnjen na molekularnom nivou. Pružanje *Blaschko* linija ne prati raspored nervnih, vaskularnih niti limfatičnih struktura, a razlikuje se od svih ostalih poznatih morfoloških linija kao što su: *Voight*, *Langer*, embrionske pukotine i pigmentovane demarkacione linije. One su u obliku slova „V“, duž gornjih delova leđa, na gornjim delovima grudnog koša poprimaju oblik obrnutog „U“ slova, na abdomenu velikog slova „S“. Na ekstremitetima su perpendikularnog rasporeda, pri čemu nikada ne prelaze središnju liniju, za razliku od trupa na kome se mogu rasprostirati duž centralne linije. Pretpostavlja se da svojim oblikom prate distribuciju autonomnih motorno-visceralnih aferentnih nervnih vlakana, ili predstavljaju rezultat rastezanja kože za vreme embriogeneze. *Blaschko* linije se mogu javiti kod X-zavisnih naslednih poremećaja, kongenitalnih ili inflamatornih dermatoza, a opisuju se i kod segmentalnih formi atopijskog dermatitisa, multiformnog eritema, vitiliga, vulgarnog pemfigusa i anularnog granuloma. *Blaschko* linearni lihen planus je opisan kod svega 0,2% obolelih, i može se verovatno smatrati posledicom postzigotskih mutacija, delecija ili DNA rekombinacija u jednom od gena odgovornih za sticanje predispozicije za razvoj oboljenja. Za razliku od generalizovane erupcije, reakcija na nepoznati antigen se u tim slučajevima odvija samo u klonu keratinocita prijemčivih za nastanak lihena.

U diferencijalnoj dijagnozi značajno je isključiti postojanje strijatnog lihena koji nije praćen svrabom i koji, iako može imati identičnu kliničku sliku i distribuciju lezija, ima karakterističan tok: pojava u prvim godinama života, brza spontana regresija unutar nekoliko meseci do dve godine. Kod našeg bolesnika starog 69 godina, promene su bile praćene svrabom a patohistološka analiza je odgovarala lihenu planus. Direktnom imunofluorescencijom nisu uočeni imunodepoziti što nije neuobičajen nalaz kod lihena planus, a u našem slučaju on se može objasniti relativno kratkim trajanjem bolesti. Udruženost sa dijabetesom melitus dobro je poznata i ukazuje na moguću autoimunu etiologiju.

Zaključak: U radu je opisan slučaj lihena planus u kome su karakteristične lihenske papule i plakovi poprimili karakterističnu i retko, samo kod 0,2% oblelih, prisutnu *Blaschko* distribuciju. Navedenu distribuciju mogu poprimiti promene i u drugim, sa lihenom planus patogenetski nesrodnim dermatozama: lihen striatus, lihen sklerozus morfea, porokeratoza *Mibelli*, folikularna mucinoza i vulgarna psorijaza. Potentni kortikosteroidi primenjeni lokalno i pod okluzijom, dali su za kratak vremenski period zadovoljavajući efekat, te se iz tog razloga kao i zbog postojećeg komorbiditeta – insulin-zavisnog dijabetesa melitus, u terapiju nisu uključili sistemski retinoidi. Ostali terapijski modaliteti podrazumevaju lokalne pripravke inhibitora kalcineurina, intralezionu i sistemsku primenu kortikosteroida, retinoide, fototerapiju i u terapijski najrezistentnijim slučajevima, u kojima kvalitet života može biti teško narušen, metotreksat, ciklosporin i talidomid.

Ključne reči

Lichen planus; Simptomi i znaci; Topikalna primena lekova; Kortikosteroidi; Retinoidi; Fototerapija