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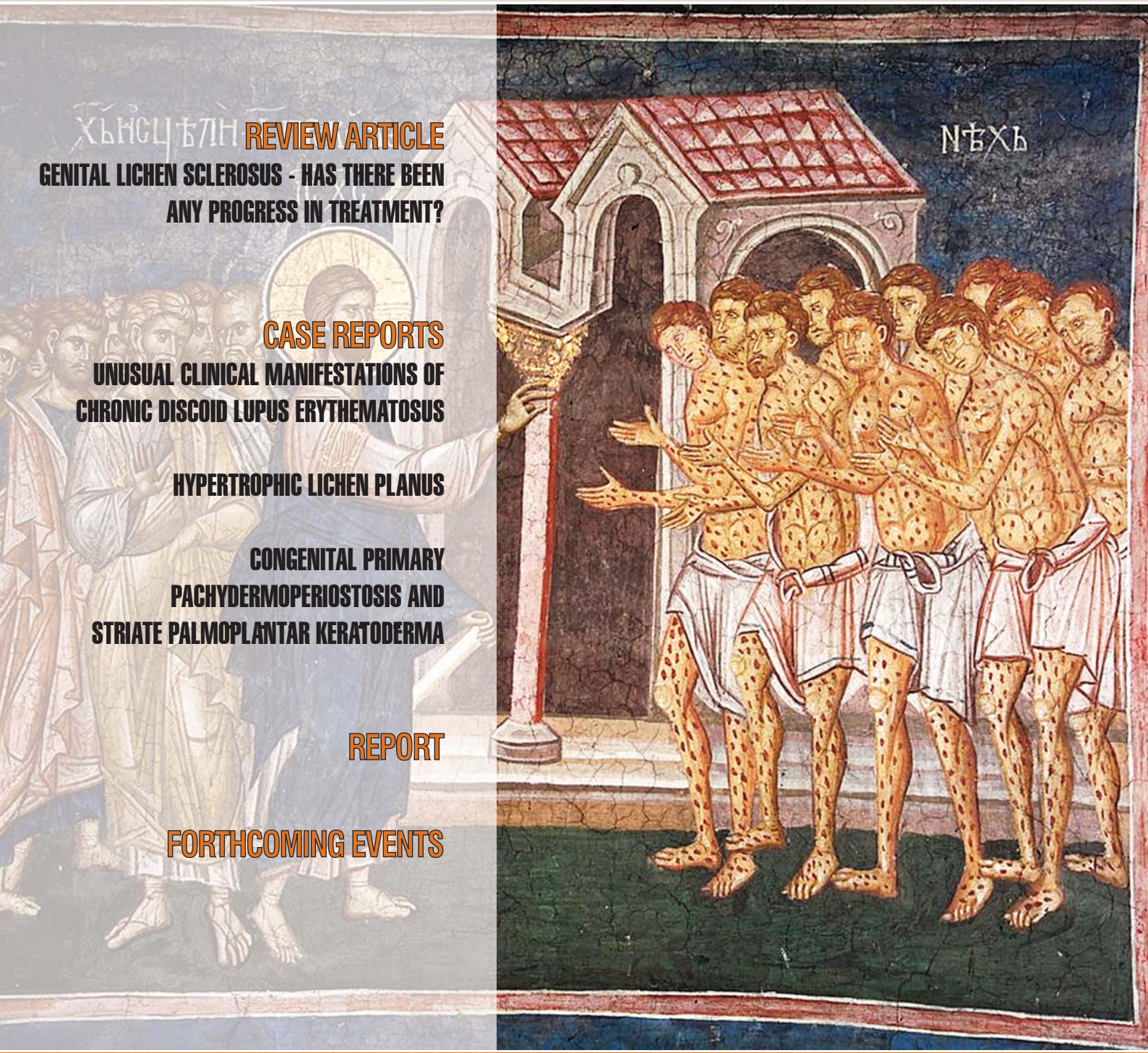

REVIEW ARTICLE

GENITAL LICHEN SCLEROSUS - HAS THERE BEEN ANY PROGRESS IN TREATMENT?

CASE REPORTS

UNUSUAL CLINICAL MANIFESTATIONS OF CHRONIC DISCOID LUPUS ERYTHEMATOSUS

HYPERTROPHIC LICHEN PLANUS

CONGENITAL PRIMARY PACHYDERMOPERIOSTOSIS AND STRIATE PALMOPLANTAR KERATODERMA

REPORT

FORTHCOMING EVENTS

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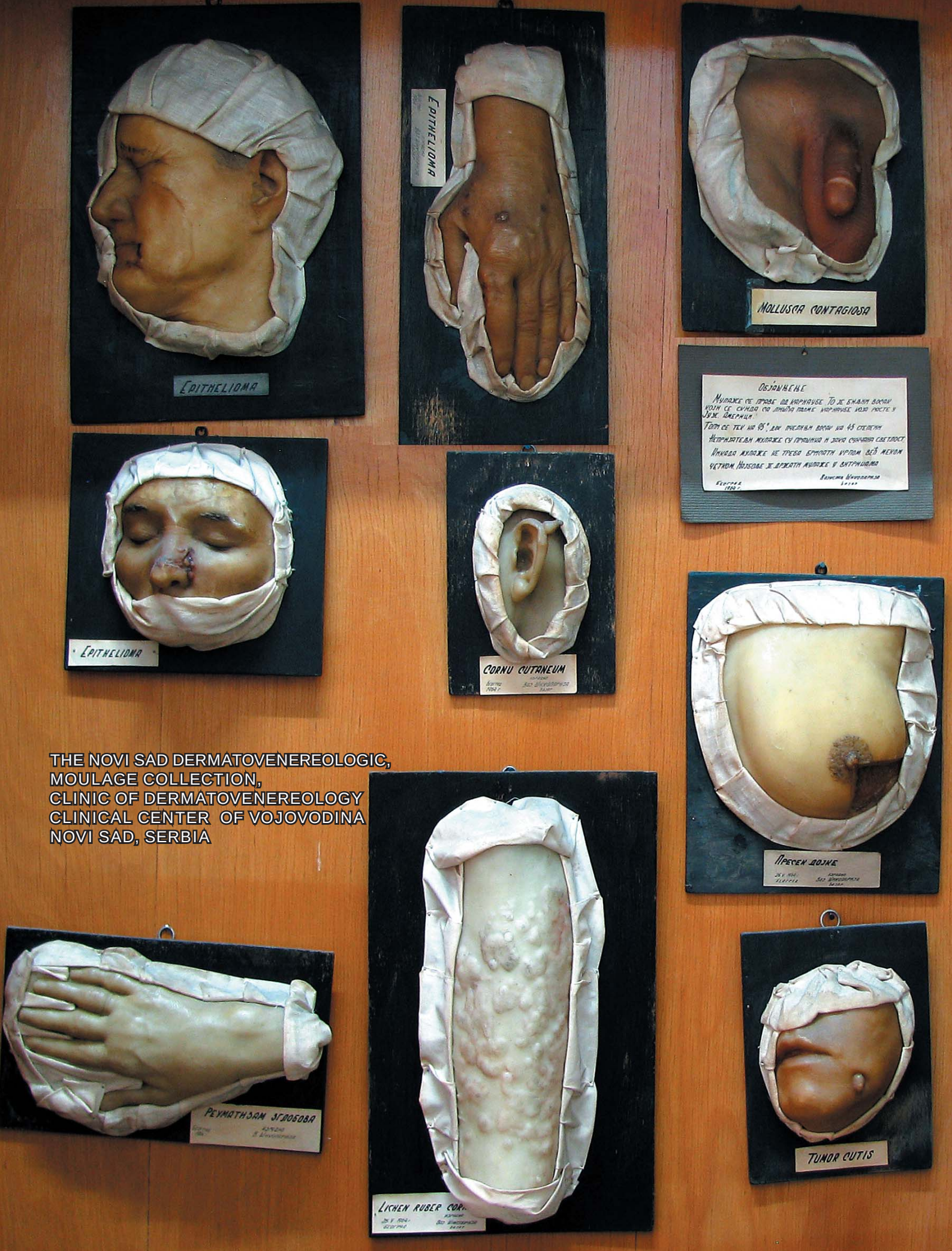

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Genital Lichen Sclerosus – Has There Been any Progress in Treatment?

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Abstract

Lichen sclerosus (LS) is a chronic inflammatory dermatosis localized mainly in the anogenital region, accompanied by itching, atrophy and sclerosis. Progressive destructive scarring in genital lichen sclerosus (GLS) may result in burying of the clitoris in females and phimosis in males. Affected persons have an increased risk of genital cancers. It is often unrecognized in everyday clinical practice due to undiagnosed squamous cell carcinoma at the site of lesions. Remissions are rare and the estimated remission rate is only 16%. GLS is a lifelong, incurable condition, but significant improvement can be achieved. Numerous therapeutic modalities have been used in GLS; unfortunately, the number of controlled studies is small and the results are mostly related to the management of symptoms, not the progression of the disease and destructive scarring. A systemic meta analysis of seven randomized controlled trials on local therapy of GLS was performed. It included a total of 249 patients treated with six topical agents: clobetasol propionate, mometasone furoate, testosterone, dihydrotestosterone, progesterone and pimecrolimus. Topical corticosteroids, clobetasol propionate 0.05% (highly potent) and mometasone furoate 0.05% (potent), showed to be significantly more efficient compared to placebo. Pimecrolimus 1% cream and clobetasol propionate 0.05% showed similar efficacy. Both agents have proven effective in the treatment of GLS: there was no statistically significant difference in relieving symptoms of pruritus and burning/pain. Tacrolimus 0.1% ointment also proved to be effective in the treatment of GLS. Topical androgens and progesterone did not show significant efficacy. Topical tretinoin and calcipotriol have been used with limited success, but they may induce irritation, so they are rarely used in the treatment of GLS.
Other therapeutic options for GLS include ultraviolet A1 (UVA-1) phototherapy, methotrexate, retinoids, cyclosporine, stanozolol, hydroxychloroquine, calcitriol, laser and photodynamic therapy, but the number of patients is small to allow for conclusive assessment. Surgery is not a standard therapeutic option for GLS.
In conclusion, treatment of GLS should be carried out in two phases: introduction of remission and maintenance of remission; topical therapy should include highly potent corticosteroids once daily during three months, followed by twice per week, or twice daily during 4 to 6 weeks, and then twice per week. There are different opinions regarding maintenance therapy: application of super potent or potent topical corticosteroids; these patients need long-term, several-year follow-up, although there is no agreement what parameters should be assessed; treatment efficacy is often reduced to monitoring GLS symptoms.

Key words

Lichen Sclerosus et Atrophicus; Meta-Analysis; Administration, Topical; Review; Dermatologi Agents; Clobetasol; Tacrolimus

Lichen sclerosus (LS) is a chronic inflammatory dermatosis, which primarily affects the anogenital region, and manifests with extensive sclerosis, atrophy and itching. Extragenital LS has milder symptoms; it is most common on the thighs, neck and trunk, and oral mucosa is rarely involved.

Genital lichen sclerosus

Women and girls with genital lichen sclerosus (GLS) present with postinflammatory scarring which may cause fusion of the labia minora, narrowing of the vaginal introitus, and burying of the clitoris, resulting in dyspareunia, sexual dysfunction, and anal or genital bleeding (Figures 1, 2, 3a-b) (1).

GLS in children is uncommon, so differential diagnosis in any pre-pubertal child presenting with chronic vulval symptoms is of great importance. The long-term prognosis is unknown, but assumptions that the condition will resolve at puberty may be incorrect (2).

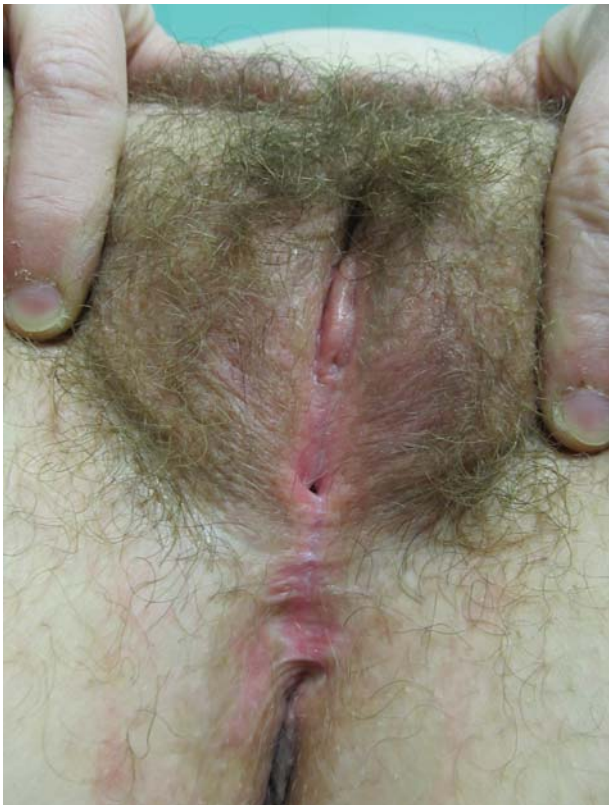

Figure 1. Vulval lichen sclerosus

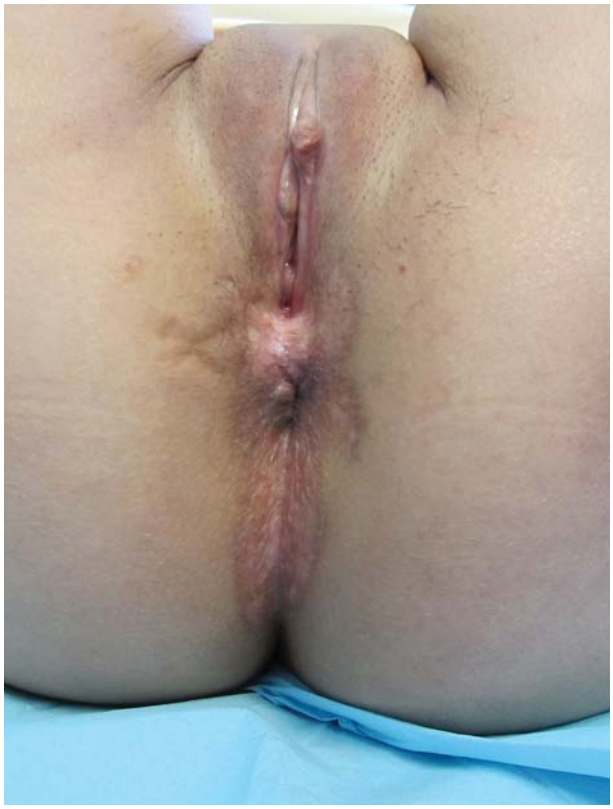

Figure 2. Vulval atresia

Vulval lichen sclerosus is associated with a significant risk for squamous cell carcinoma (SCC) of the vulva (3).

In men and boys, GLS is most common on the glans penis and prepuce (Figure 4), which may cause phimosis, paraphimosis, painful erection, and urethral meatal stenosis. The dermatological aspects of male genital lichen sclerosus (MGLS) have not received much prominence in the literature. Sexual morbidity appears under-appreciated: the relative places of topical treatment and circumcision are not established (4). Occluded contact with urine in males and reduced estrogen levels in females, are imortant factors in the etiopathogenesis of MGLS and VLS, respectively.

Prognosis in terms of sexual function, urination difficulties and penile cancer is uncertain (Figure 4).

The cause of LS is unknown, but there is strong association with autoimmune diseases, thyroid disease, pernicious anemia, diabetes mellitus, alopecia areata, vitiligo, and mucous membrane pemphigoid (5). Approximately 74% of patients with LS have an increased titer of circulating antibodies in the serum (6), and in 42% the titer is over 1:20 (5). The increased incidence of autoantibodies to extracellular matrix protein 1 (ECM-1) may point to its autoimmune pathogenesis (7).

Treatment

GLS requires long-term management; there is no cure, but significant improvement can be achieved. Unfortunately, the number of controlled studies is small and the results are mostly related to the management of symptoms, not the progression of the disease and destructive scarring (3).

Before starting treatment of LS, Bradford and Fischer (3) consider it necessary to answer a few questions:

1. Are there valid alternations to intermittent potent corticosteroids?
2. Should treatment be standardized or individualized?
3. Does treatment modify scarring, loss of vulval substance and risk of SCC?

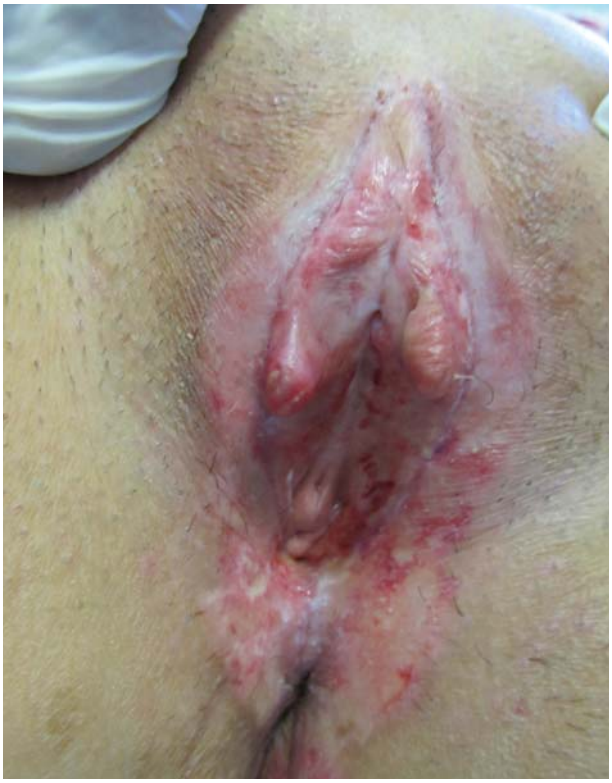

Figure 3a. Vulval lichen sclerosus with genital bleeding

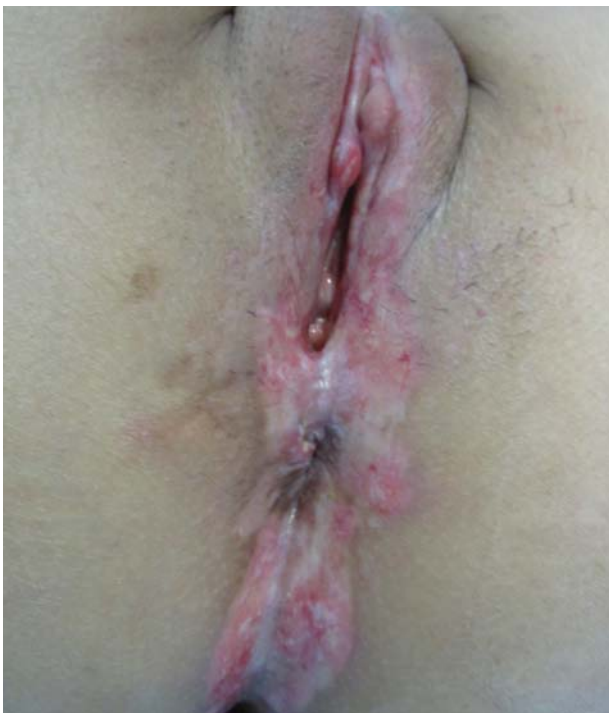

Figure 3b. Vulval lichen sclerosus with anal bleeding

Figure 4. Male genital lichen sclerosus

4. Are there risks of long-term potent corticosteroids on the vulva?
5. What should be the purpose and length of follow-up?

There are multiple treatment modalities for GLS, including topical and systemic agents (Table 1). Most authors agree that treatment of GLS should be carried out in two phases: introduction of remission and maintenance of remission.

Despite the use of numerous medications and topical agents in the treatment of GLS, there are few comparative studies of their effectiveness.

The Cochrane Library published a very good meta-analysis of randomized controlled trials on topical interventions for GLS by Ching-Chi and associates. It included 7 randomized controlled trials with a total of 249 participants covering 6 treatments (Table 2).

The aforementioned meta-analysis clearly shows the lack of standardized therapeutic procedures for the management of GLS, mostly due to the small number of respondents with a small number of studies meeting the inclusion criteria for meta-analysis (1).

Table 1. Treatment of genital lichen sclerosus (1)

Modality	Agent
Topical	Ultrapotent steroids (eg., clobetasol propionate 0.05%)
	Potent steroids (eg., mometasone furoate 0.05%)
	Calcineurin inhibitors (pimecrolimus tacrolimus)
Systemic	Retinoids (isotretinoin, acitretin, etretinate)
	Calcineurin inhibitors (cyclosporine)
	Androgens (stanazolol)
	Antimalarials (hydroxychloroquine)
	Corticosteroids (pulsed doses of methylprednisolone + methotrexate)
	Cytostatic drugs (methotrexate)
	Calcitriol
Surgical	Vulvectomy
	Circumcision
	Surgical dilatation + methotrexate
Light therapy	Phototherapy (UVA 1)
	Photodynamic therapy
	Laser (Carbon dioxide)

The lack of standardized protocols for the treatment of GLS may be partly explained by differences in the length of treatment, whereas in some studies the length of treatment was not indicated. However, in most studies the length of treatment was three months (Table 3).

Nevertheless, few studies compare the efficacy of several drugs, but rather their efficacy with placebo, which was also seen in Cochrane Library meta-analysis (1). However, this analysis provided significantly better insight into the effectiveness of drugs used in

Table 2. Cochrane library meta-analysis of randomized controlled trials on topical interventions for genital lichen sclerosus (Ching-Chi and associates) (1)*

Meta-analysis	Treatment options
	Clobestasol propionate
	Mometasone furoate
	Testosterone
	Dihydrotestosterone
	Progesterone
	Pimecrolimus

*, 249 participants covering 6 treatments

the treatment of local GLS. Cochrane Library meta-analysis clearly reported different effectiveness of drugs used in the treatment of genital lichen sclerosus (1).

Topical corticosteroids

A critical evaluation of clinical and histologic effects of topical, 3-months' treatment of VLS with clobetasol propionate versus placebo, showed that clobetasol was significantly more effective than placebo: participant-rated improvement/remission of symptoms: risk ratio 2.85 (95% confidence interval (CI) 1.45 - 5.61); investigator-rated global degree of improvement: standardized mean difference (SMD) 5.74 (95% CI 4.26 – 7.23) (1, 8).

When response of balanitis xerotica obliterans to mometasone furoate versus placebo in children with lichen sclerosus was assessed, after 5 weeks of therapy, the investigator-rated mean clinical grade of phimosis improved in the mometasone furoate group, but worsened in the placebo group (9). Potent topical steroids proved to be safe and effective in the treatment of childhood GLS (1), whereas early aggressive treatment gives the best therapeutic response (10).

Table 3. The length of treatment of genital lichen sclerosus

Trial	Duration
Clobetasol propionate versus placebo	3 months
Mometasone furoate versus placebo	5 weeks
Testosterone versus placebo	3 months; 1 year
Testosterone versus clobetasol propionate	3 months
Testosterone versus placebo as maintenance therapy after initial 24 week-treatment with clobetasol propionate 0.05% cream	Maintenance therapy

Topical androgens and progesterone

Topical androgens, testosterone propionate 2% cream and dihydrotestosterone 2% cream, were studied in five randomized clinical controlled trials on topical interventions for GLS (8, 11, 12, 13, 14). After 3 months of application (8) as well as after one year of aplication (11), there were no significant differences in therapeutic effects between testosterone and placebo in topical therapy of VLS (1, 8, 11). After 3 month of application, testosterone was significantly less effective than clobetasole propionate (1, 8).

No woman with VLS showed a significant improvement after a 3 month trial with dihydrotestosterone versus placebo (12). When comparing effects of topical testosterone to dihydrotestosterone in VLS, during 3 months without a washout period, there were no significant differences in efficacy between the two androgens (1, 13). When testosterone maintenance therapy effects on VLS treated with 0,05% clobetasole propionate were compared to placebo, testosterone worsened the symptoms, whereas placebo caused no change in symptoms or gross appearance (1, 14).

After 3 months of application, topical progesterone cream 2% showed no difference in efficacy compared to placebo in the treatment of of VLS (1, 8).

Topical calcineurine inhibitors

A double-blind randomized contolled trial tested effects of clobetasol versus pimecrolimus in patients with VLS: both pimecrolimus 1% cream and clobetasol propionate 0.05% cream were effective in relieving pruritus and burning pain after 3 months of application, there were no significant differences between pimecrolimus and clobetasol propionate relieving pruritus and burning pain; investigator global assessment showed both preparations were effective; clobetasol propionate was more effective than pimecrolimus in improving inflammation (15). Thus, investigator-rated global degree of improvement, measured by SMD, showed that pimecrolimus was less effective than clobetasol in improving gross appearance (1). Oskay et al. reported good effects of pimecrolimus 1% cream in the treatment of VLS in postmenopausal women (16). Kim et al. performed a prospective study investigating the efficacy of topical tacrolimus ointment in 16 patients with active lichen sclerosus. They found that tacrolimus ointment was a safe and effective treatment for GLS and that it should be used for long-term duration to prevent relapse (17). Similar findings were reported by Virgili et al. who treated VLS in 11 women with tacrolimus 0.1% ointment (18). However, there are authors who believe that topical corticosteroids may increase the risk for human papillomavirus (HPV) infection in men, and that they should not be treated by calcineurin inhibitors, except in resistant cases.

Others

Edmonds and associates estimated that circumcision is effective in 75% of men, and that it appears to abrogate the risk of squamous cell carcinoma; nevertheless, there are conflicting opinions.

Apart from topical tretinoin 0.025 and calcipotriol, which may induce improvement, but also irritation, thus they are rarely used in the treatment of GLS, other forms of LS treatment have shown benefits only in the open-label series or in individual cases: oral retinoids, methotrexate, cyclosporin, surgical therapy, cryotherapy, vulvectomy, carbon dioxide laser vaporisation, pulsed dye laser therapy, photodynamic therapy (19, 20).

Conclusions

In conclusion, we can say that: 1) topical clobetasol propionate, as well as other ultrapotent and potent steroids, such as mometasone furoate, are effective in treating vulval and penile GLS; 2) there is no consensus on how long treatment should last, but most authors agree that treatment of GLS should include highly potent topical corticosteroids once daily during 3 months, followed by twice per week, or twice daily during 4 to 6 weeks, and then, "if necessary" (a common term used in research), twice a week; 3) circumcision is effective in males; 4) topical pimecrolimus and tacrolimus are effective in eliminating subjective complaints of patients and lead to objective improvement; 5) there is no evidence supporting the use of topical androgens and progesterone; 6) long-term multi-year follow-up of patients is necessary, although there is no agreement on which parameters should be assessed; treatment efficacy is often reduced to monitoring GLS symptoms; 7) it still remains unknown wether effective

treatment can reduce the risk of genital squamous cell carcinoma.

Abbreviations

LS - lichen sclerosus
GLS – genital lichen sclerosus
UVA – ultra violet
VLS – vulval lichen sclerosus
SCC – squamous cell carcinoma
MGLS – male genital lichen sclerosus
ECM-1 – extracellular matrix protein-1
CI – confidental interval
SMD - standardized mean difference
HPV – human papillomavirus

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Genitalni lihen sklerozus – Ima li pomaka u terapiji?

Sažetak

Lichen sclerosus (LS) je hronična upalna dermatoza, lokalizovana uglavnom u anogenitalnoj regiji, praćena svrabom, atrofijom i sklerozom. Progresivno destruktivno ožiljavanje u genitanom lihenu sklerozus (GLS) može dovesti do prekrivanja klitorisa kod žena i fimoze kod muškaraca. Postoji povećan rizik za genitalni kancer. U praksi se dešavaju previdi zbog nedijagnostikovanja spinocelularng karcinoma na mestu lezija. Remisije su retke, kod lečenih do 16%. Lečenje GLS je dugotrajno, nema izlečenja, ali je moguće postići značajno poboljšanje. Brojna terapijska sredstva primijenjuju su za lečenje GLS, nažalost, broj kontrolisanih studija je mali a dobijeni rezultati se odnose na kontrolu simptoma, ali ne i na progresiju bolesti i pojavu ožiljavanja. Urađena je metaanaliza na sedam randomizovanih kontrolnih studija koje su se

odnosile na lokalnu terapiju GLS. Analiza je obuhvatila ukupno 249 lečenih pacijenata i šest lokalnih preparata: klobetazol propionat, mometazon furoat, testosteron, dihidrotestosteron, progesteron i pimekrolimus. Topijski kortikosteroidi, klobetazol propionat 0,05% (jako potentan) i mometazon furoat 0,05% (potentan), u odnosu na placebo pokazali su se značajno efikasnijim. Pimekrolimus 1% krem u komparaciji sa klobetazol propionatom 0,05%, pokazao je sličnu efikasnost. Oba preparata su se pokazala efikasnim u lečenju GLS: nije utvrđena statistički značajna razlika u njihovoj efikasnosti kada su kupiranje pruritusa i pečenja/bola u pitanju. Efikasnim u lečenju GLS pokazao se i takrolimus u obliku 0,1% masti. Topijski androgeni i progesteron nisu ispoljili značajnu efikasnost. Topijski tretinoin i kalcipotriol mogu dati poboljšanje, ali i iritaciju, pa se retko primenjuju u lečenju GLS. Druga terapijska sredstva koja se primenjuju u GLS su fototerapija (*UVA-1 rays*), metotreksat, retinoidi, ciklosporin, stanazolol, hidroksihlorokvin, kalcitriol, laseri i fotodinamička terapija, ali je broj lečenih ovim preparatima mali da bi se donosili temeljni zaključci. Hirurška intervencija kao primarni oblik lečenja GLS nije indikovana.

Zaključak. Lečenje GLS treba sprovoditi kroz dve faze, uvođenjem u remisiju i održavanjem postignutog efekta; u lokalnoj terapiji treba koristiti jako potentne kortikosteroide jedanput dnevno tokom tri meseca, zatim dvaput nedjeljno, ili dvaput dnevno 4 do 6 nedelja, a potom dvaput nedeljno. Da li u održavanju postignutog učinka treba primenjivati superpotentne ili potentne topijske kortikosteroide mišljenja su različita; potrebno je dugotrajno praćenje ovih bolesnika, više godina, mada ne postoji saglasnost koje parametre treba procenjivati; najčešće se procena efikasnosti leka svodi na praćenje simptoma.

Ključne reči

Lichen sclerosus et atrophicus; Meta analiza; Topijska primena; Pregled; Dermatološki preparati; Clobetasol; Tacrolimus

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Unusual Clinical Manifestations of Chronic Discoid Lupus Erythematosus

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Abstract

A 22-year-old woman with a 3-year history of discoid lupus erythematosus presented with two circumscribed patches of non-scarring alopecia, clinically simulating alopecia areata. Histopathological analysis of scalp lesions revealed discoid lupus erythematosus. Based on the clinical history, physical examination, and histological and immunological findings, we distinguished our case from a true combination of alopecia areata and typical chronic discoid lupus erythematosus.

Key words

Lupus Erythematosus, Discoid; Alopecia Areata; Comorbidity

Typical manifestations of chronic discoid lupus erythematosus (CDLE) of the scalp have been well described (1, 2). Any discrepancy warrants investigation. Other disorders, including alopecia neoplastica (cutaneous metastatic disease of the scalp) and alopecia areata, may require distinction (2, 3). We report a patient with CDLE clinically resembling alopecia areata.

Case report

A 22-year-old Caucasian woman was first seen with a 3-year history of gradually developing asymptomatic erythematous plaques located on her face and upper arms, associated with reversible patchy hair loss that appeared periodically, and had a self-limiting course. There was no history of an associated disorder and intake of medications. The possibility of drug-related hair loss and common causes of hair loss, such as androgenic alopecia, were excluded. Topical corticosteroid ointments were applied in short-term regimens.

Clinical examination revealed oval scaly erythematous plaques varying in size, from 2 to 3 cm, localized on the face, upper arms and the shoulder region. The plaques were well demarcated with peripheral spreading. Two round-to-oval denuded slightly erythematous patches with white hair regrowth were seen in the frontal scalp (Figure 1). Signs of atrophy were not detected. Oral and genital mucosa, were not involved.

Laboratory findings

The patient's complete blood count, erythrocyte sedimentation rate, C-reactive protein, urea, electrolytes, liver function tests, thyroid function, lipid profile, blood glucose and serum immunoglobulins were all normal. Antinuclear, anti-smooth muscle, SS-A antibodies were negative.

Histopathological analysis

Biopsy specimens from the scalp and arm revealed identical changes (Figure 2). Follicular hyperkeratosis and dense lymphocytic lichenoid infiltrates obscured the dermo-epidermal junction. Perifollicular and periadnexal lymphocytic infiltrations were present in the reticular dermis.

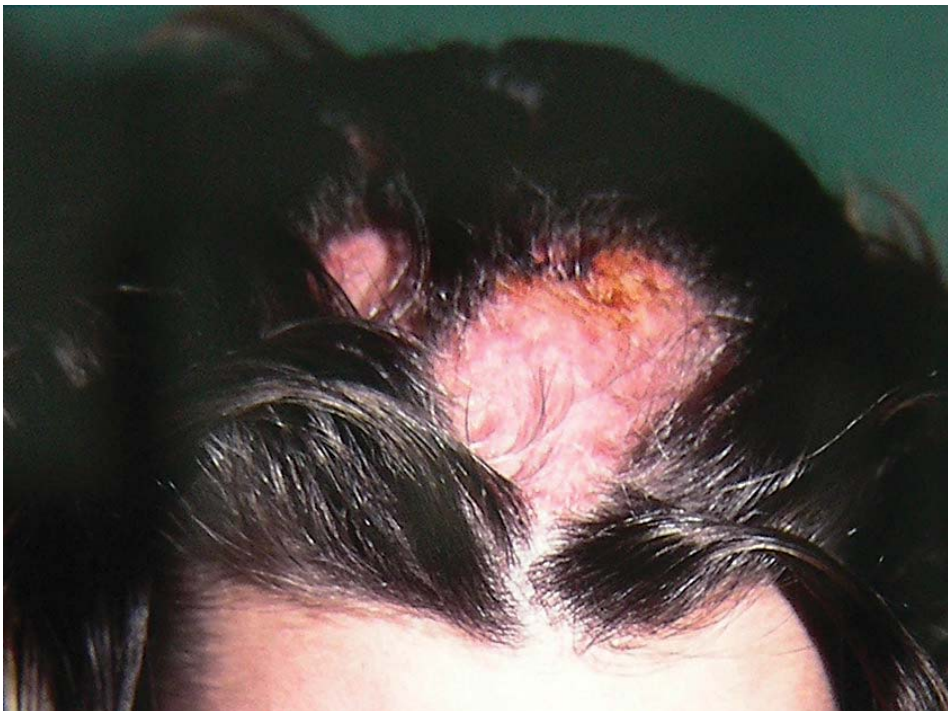

Figure 1. Two patches of circular, non-scarring alopecia on the scalp and a discoid plaque on the face

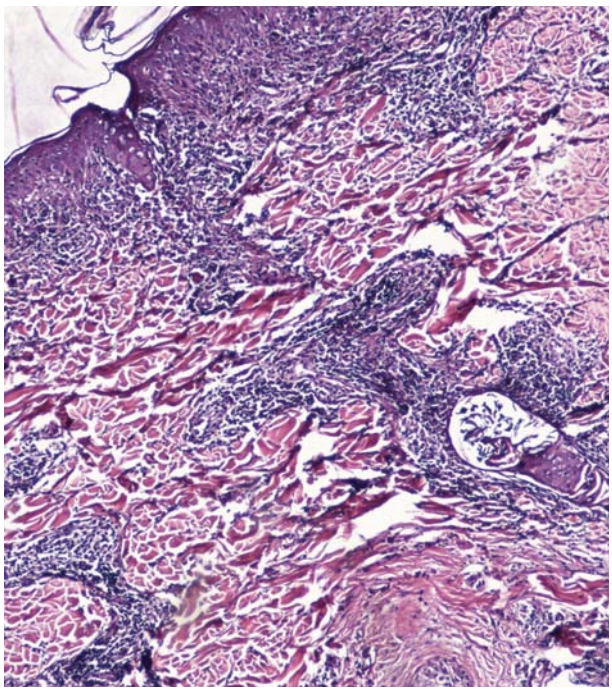

Figure 2. Follicular hyperkeratosis, vacuolar degeneration of the basal layer with obscured dermo-epidermal junction, lichenoid infiltration of the papillary dermis and dense perifollicular lymphocytic infiltrate in the deep dermis (hematoxylin and eosin, x 400).

Direct immunofluorescence of the scalp specimen and the plaque on the arm showed granular IgM, IgG and C3 deposits extending in a linear distribution along the dermo-epidermal junction.

Therapy

Chloroquine phosphate (250 mg daily) and a potent topical steroid ointment (twice daily) were initiated. At the 3-week follow-up visit, a significant improvement was observed. The cutaneous lesions resolved and alopecia plaques reduced in size. Stronger hair regrowth was evident.

Discussion

Clinical manifestations of chronic discoid lupus erythematosus (CDLE) are well recognized (4). Our case is interesting due to its unusual presentation. Most of the morphological signs of CDLE matched classical description. However, there were circumscribed patches of non-scarring alopecia on the scalp, closely resembling alopecia areata. Development of alopecia areata-like patches in patients with CDLE is distinctly unusual.

A characteristic cutaneous feature of CDLE of the scalp is scarring alopecia. Scalp involvement

occurs in 60% of CDLE patients and it is the only area involved in approximately 10% (5). Association of alopecia areata (AA) and CDLE has been reported anecdotally (6). In a cohort study of 736 AA patients, two had CDLE (7): two autoimmune disorders occurring together. More recent studies, performed by Kumar et al. (8), and Grandoflo et al. (9) also demonstrated a low incidence of CDLE in patients with AA, with only one of 104 patients affected and one of 68, respectively.

Systemic lupus erythematosus and lupus panniculitis may also induce non-scarring alopecia resembling AA (10, 11). A 27-year-old woman was described with a previous history of lupus erythematosus having slightly erythematous circumscribed patches of non-scarring alopecia closely simulating AA (11). The clinical history of scalp tenderness and histologic findings of predominantly subcutaneous and deep dermal lymphocytic infiltrates surrounding deep follicular segments and hair bulbs, as well as eccrine glands, were consistent with the diagnosis of lupus panniculitis and ruled out a true combination of AA and CDLE. Presumably, temporary hair loss, clinically simulating AA, was due to deeper lymphocytic inflammation that spared the hair bulbs and permanent stem cell-rich follicular segments (11, 12).

Based on the clinical and immunological findings, as well as histological changes observed in our patient, consisting of epidermal involvement with prominent vacuolar degeneration, upper dermis invasion by heavy, hugging type lymphocytic infiltrates and deep periadnexal inflammation, with granular IgM, IgG and C3 deposits extending in a linear distribution along the dermo-epidermal junction on direct immunofluorescence of the scalp specimen and the plaque on the arm, we believe she had true CDLE with hair involvement clinically resembling AA.

Conclusion

We report a patient with chronic discoid lupus erythematosus clinically resembling alopecia areata. In order to establish the diagnosis of scarring alopecia, scalp specimens should be divided into two vertical sections: one is used for direct immunofluorescence, the other for light microscopy.

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Atipične kliničke manifestacije hroničnog diskoidnog eritemskog lupusa

Sažetak

Uvod. Poznato je da se u hroničnom diskoidnom eritemskom lupusu mogu videti klinički tipične promene kako na koži lica, trupa i ekstremiteta, tako i u kosmatom delu glave. U diferencijalnoj dijagnozi alopecičnih promena, naročito u nekarakterističnim slučajevima, uprvom redu treba isključiti neoplazijsku

alopeciju (metastacka bolest kože poglavine) i alopeciju areatu.
Prikaz slučaja. U radu autori prikazuju slučaj dvadesetdvogodišnje osobe ženskog pola ,koja u svojoj anamnezi navodi da tri godine boluje od diskoidnog eritemskog lupusa. Na pregledu osim tipičnih promena na kože trupa, na koži kosmatog dela glave uočene su dva cirkumskriptna alopecična polja na kojima se nisu uočavali znaci atrofije ili ožiljavanja. Histopatološka i direktna imunofluorescentna analiza isečaka kože uzete sa promene na trupu i sa kože alopecičnog plaka na poglavini pokazale su identične promene, karakteristične za diskoidni eritemski lupus.
Zaključak: Autori prikazuju slučaj hroničnog diskoidnog lupusa na koži poglavine koji je klinički imponovao na alopeciju areatu.
U cilju dijagnostikovanja ožiljne alopecije, bioptat kože uzet sa kože skalpa uvek treba podeliti na dva vertikalna dela: jedan pripremiti za svetlosnu mikroskopsku analizu, a drugi za derektni imunofluorescentni pregled.

Ključne reči

Diskoidni eritemski lupus; Alopecia areata; Komorbiditet

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Hypertrophic Lichen Planus – a Case Report

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Abstract

Lichen planus is an immune, inflammatory reaction with characteristic clinical and histological lesions. It is a benign disorder, often chronic or recurrent, characterized by flat-topped, pink to purple, shiny pruritic polygonal papules on the skin, or milky white reticular papules on the visible mucous membranes.

Hypertrophic lichen planus is a chronic form of lichen planus with marked epidermal hyperplasia and intense pruritus. It is characterized by symmetrical hypertrophic plaques, usually located on the pretibial or perimalleolar regions. Lesions are often resistant to treatment.

This paper presents a patient with a giant form of verrucous lichen planus on the lower extremities, with a chronic course and resistance to various forms of therapy (keratolytics, local and intralesional corticosteroids, radiotherapy, systemic antibiotics, cryotherapy). Significant improvement was seen after 8-month treatment with etretinate (initial dose of 75 mg per day, with progressive reduction to 10 mg per day). Etretinate therapy resulted in a significant regression of the disease.

Key words

Lichen Planus + physiopathology + therapy; Etretinate; Treatment Outcome

Lichen planus is a rare, immune, inflammatory tissue reaction with characteristic clinical and histological lesions (1). Several other diseases, including graft-versus-host disease, may induce lichenoid tissue reactions. Lichen planus is the prototype of all lichenoid eruptions. Its prevalence in the general population ranges from 0.5% (6) to 1% (7), even to 4% (8). The disease is benign, often chronic or recurrent, and it is characterized by flat-topped, pink to purple, shiny, pruritic, polygonal papules on the skin or milky white reticular papules on the visible mucous membranes (2, 3). Some describe lichen planus with the six "Ps": planar, purple, polygonal, pruritic, papules and plaques (9).

Hypertrophic lichen planus is a less common form of lichen planus. It accounts for 4.7% of lichen planus cases, and 2.2% of all lichenoid tissue reactions (10). It is a chronic, hypertrophic form of the disease with severe epidermal hyperplasia and itching (7). It is characterized by symmetrical hypertrophic plaques, usually located on the pretibial or perimalleolar regions (4, 5). The disease has a chronic course, and it is often resistant to treatment. Upon remission, scarring, hypo-or hyperpigmentation may follow (7, 11).

This paper presents a patient with a giant form of verrucous lichen planus on the lower extremities, with favorable results after treatment with systemic etretinate.

Case report

We present a 47-year-old housewife in good general health, except for surgical treatment of uterine myomatosis and hypertension. At the beginning, the patient presented with itchy warty growths on the sides of the heels, rapidly growing and spreading to

other parts of the foot. They appeared on the front of the right lower leg 2-3 years later, at the site of a previous skin injury. There were no relatives with a similar disorder.

The patient was repeatedly treated at the Clinic for Skin and Venereal Diseases in Niš and once at the Military Medical Academy in Belgrade. She was treated with keratolytics, corticosteroids under occlusion and intralesional, cryotherapy with liquid nitrogen, radiotherapy (a total dose of 20 Gy, 10 sessions, two opposing fields), systemic antibiotics due to a secondary infection, sedatives, etc.), but without satisfactory long-term results. Therefore, systemic etretinate therapy was initiated.

Dermatological status before etretinate therapy

Tumor-like infiltrations, individual or confluent, were found on the sides and back of the heel, forming spur-like growths around the heels (Figure 1). Their surface was keratotic, verrucous, dark gray, and they were interspersed with rhagades producing hemorrhagic-purulent discharge under pressure. On the front right leg there was a tumor, 5 cm in diameter, with similar characteristics (Figure 2). The lesions were extremely pruritic, often painful, making everyday activities such as wearing shoes and walking difficult. There were no other changes on the skin and visible mucous membranes.

Laboratory tests

All required laboratory test results were within reference limits: erythrocyte sedimentation rate, complete blood count, hemoglobin, leukocyte count, urea, creatinine, liver scan, transaminases, protein electrophoresis, acid and alkaline phosphatase, lactate dehydrogenase, cholesterol, triglycerides, blood glucose, serum electrolytes; serological tests for adenoviruses, cytomegalovirus, herpes simplex virus, and Treponema pallidum. Staphylococcus aureus was isolated from the lesions, pointing to a secondary infection.

Histopathological analysis

Light microscopy of the affected skin biopsy samples showed: marked hyperkeratosis; sporadic involvement in the granular layer; uneven acanthosis, partly in the form of elongated epidermal ridges; moderate dermal infiltrations consisting mainly of lymphocytes and some histiocytes which mostly penetrated into the lower layers of epidermis, making the dermal-

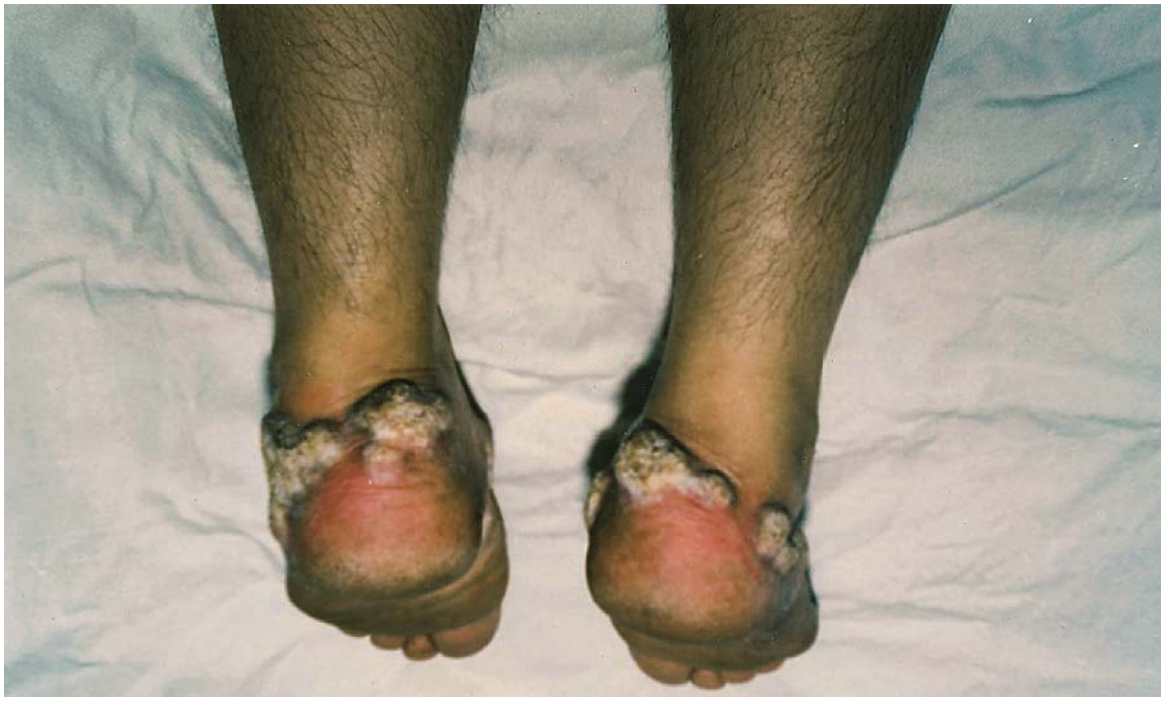

Figure 1. Spur-like lesions around the heels before etretinate therapy

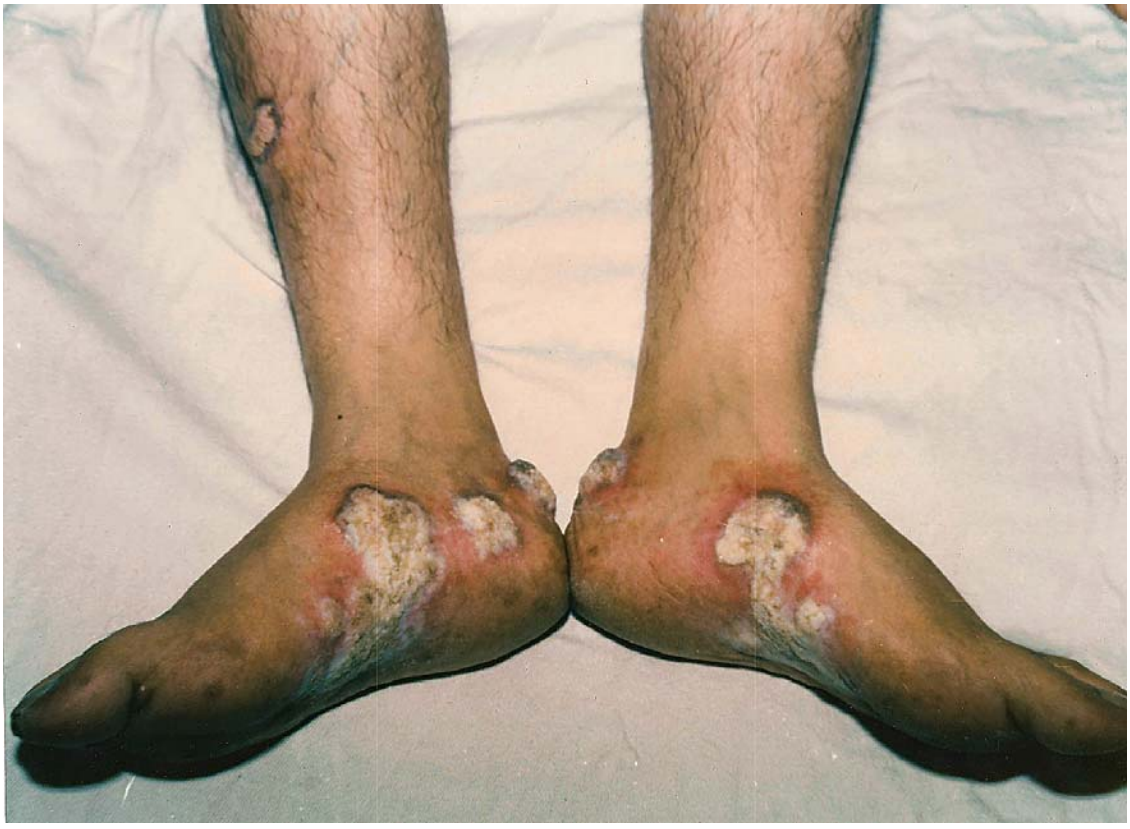

Figure 2. Skin lesions on the internal parts of the feet and on the right lower leg before etretinate therapy

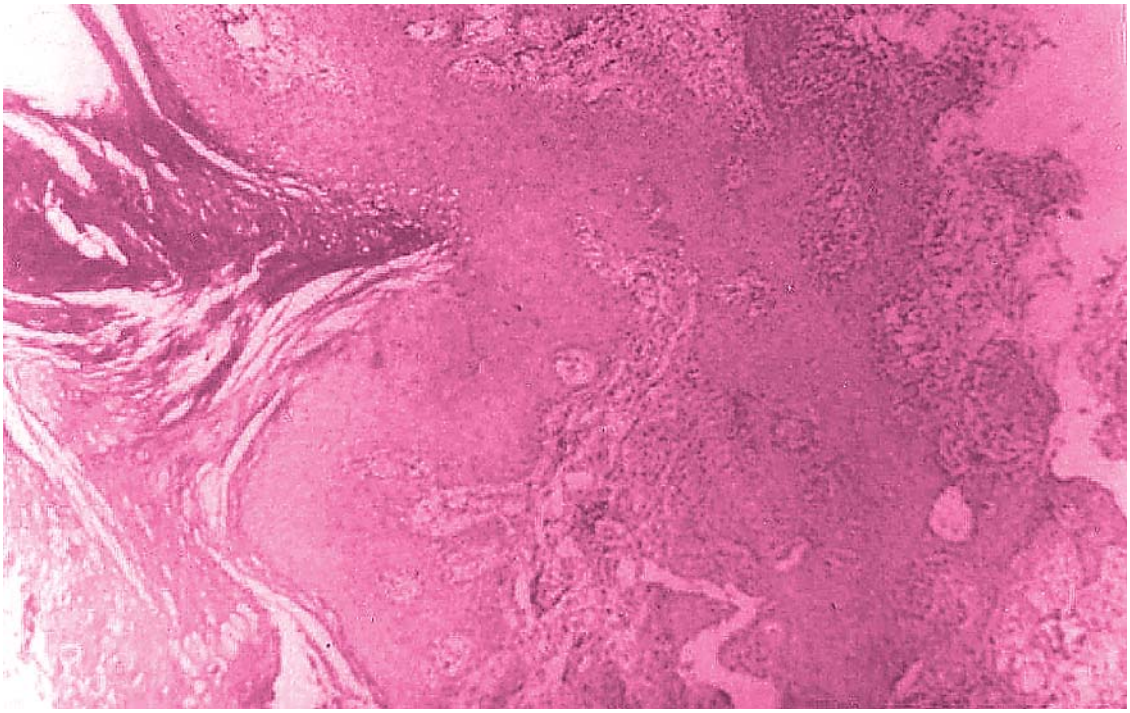

Figure 3. Histopathological finding (moth-eaten appearance)

epidermal border unclear (moth-eaten appearance) (Figure 3).

Direct immunofluorescence analysis

Direct immunofluorescence showed findings typical for lichen palnus: fibrinogen deposits with rough jagged edges along the epidermal-dermal junction and in the blood vessel walls in the papillary dermis; multiple clustered colloid bodies (IgM) beneath the dermal-epidermal border; lines of fibrinogen deposits in the border area between the dermis and epidermis.

Treatment

Etretinate was initiated at a dose of 75 mg per day (3 x 25 mg, ie. 1 mg/kg/day, with a gradual decrease to 10 mg per day). Topical keratolytics were used with boric lotion. The treatment lasted for 8 months. The patient reported the following side effects at the beginning of treatment: dry mouth, increased desquamation of the palms and soles, transient elevation of serum triglycerides, which was normalized after dose reduction. The therapeutic effects on skin lesions were remarkable (Figures 4 and 5). The tumefaction decreased, the heels regained nearly normal size, the patient could wear shoes, there were no secondary infections and relief of itching was significant.

During the further course of the disease, the patient suffered from a mild recurrence in the following year, so etretinate was initiated again at a dose of 0.5 mg/kg bw/day with a gradual reduction to a maintenance dose of 10 mg every other day. In the last two years, the patient's condition remained unchanged, and her quality of life has improved. Currently, the skin lesions are located at the same sites as during the worst stage of the disease, but the infiltrates are less prominent, clearly demarcated, uneven keratotic lesions, with scattered atrophic areas circumscribed by hyperpigmentation.

Discussion

Lichen planus usually occurs between 30 and 60 years of age (1), more frequently in women. It is a chronic mucocutaneous T-cell-mediated disease, the cause of which remains unknown (12). According to Boyd and Neldner (13), there are two main types of lichen planus: "classical" idiopathic type, and lichenoid reaction

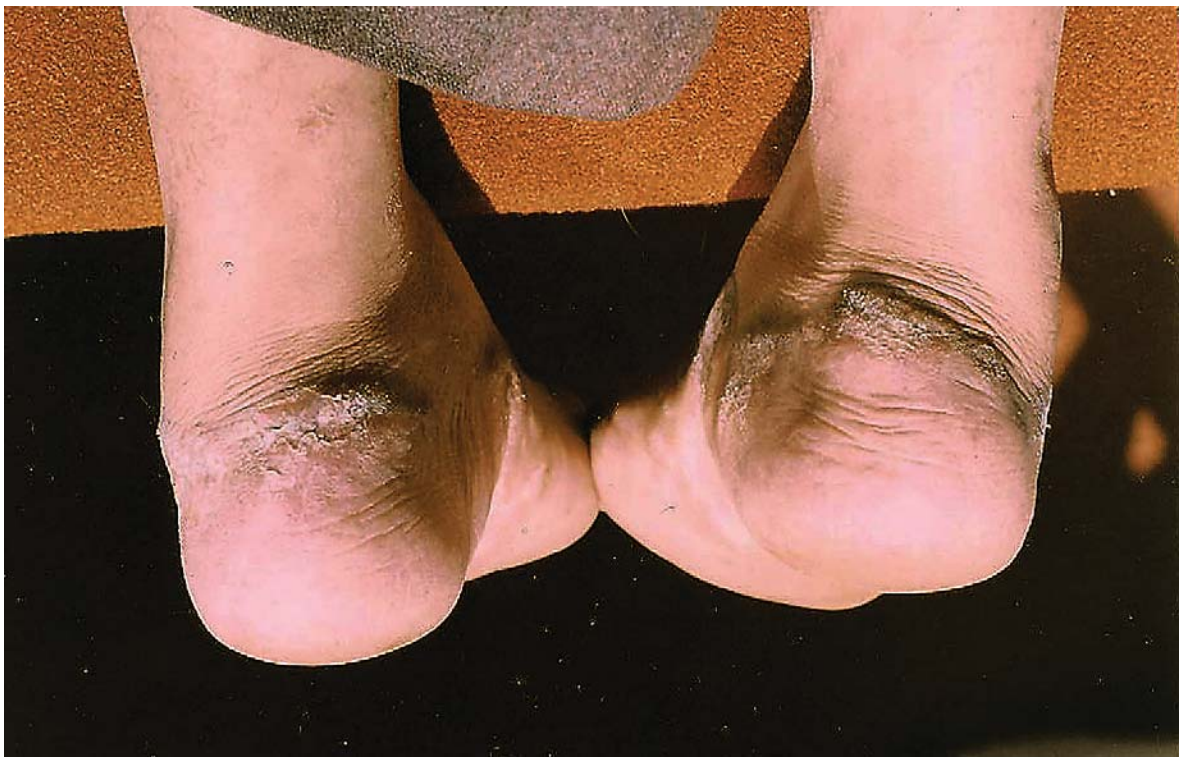

Figure 4. Regression of lesions on the heels after etretinate therapy

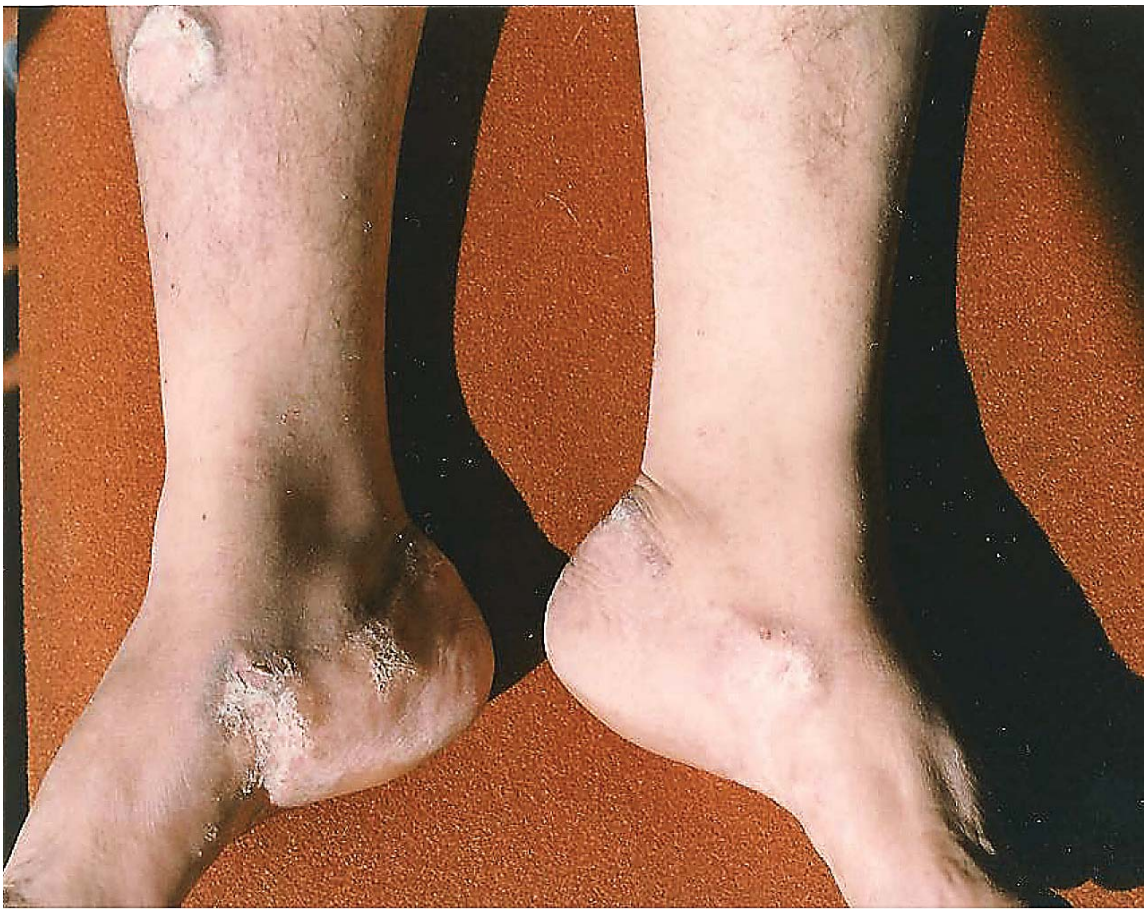

Figure 5. Regression of lesions after etretinate therapy

induced by various stimuli. The classical, idiopathic form is clinically identical to the familial form: it tends to be a severe, long-term condition, with erosive, linear or ulcerative lesions, dissemination and generalization. Genetic predisposition to the disease is associated with HLA antigens: HLA-B7,-AW19 - B18,-CW8 were found in cases of familial lichen planus, while HLA-A3,-A5,-B8,-BW35 were found in non-familial cases. Oral lichen planus is associated with HLA-B8, whereas HLA-BW35 is prevalent in cutaneous forms.

There are several hypotheses on the etiopathogenesis of lichen planus (3): metabolic (decreased enzyme activities in the epidermis) (14), neurogenic and psychogenic (zosteriform pattern, association with paravertebral tumors, emotional stress, especially in emotionally labile persons) (15), and autoimmune (lichenoid eruptions with graft rejection, concomitant systemic lupus erythematosus, bullous pemphigoid eruption in generalized lichen) (16, 17). Viruses, bacteria, hormones, metal ions, drugs and physical factors are considered to be potential triggers (18, 19). The most accepted theory is that it is a cellular autoimmune response to a viral infection (20, 21). Cellular components of the immune system induce epidermal reactions, injury to basal keratinocytes, and secondary inflammatory reactions (22, 23, 24). In lichen planus lesions, CD8 + T cells infiltrate the epidermis while T cells, both CD4 + and CD8 +, accumulate in the dermis. It has been suggested that CD8+ cytotoxic T cells recognize an antigen (currently unknown) associated with the major histocompatibility complex (MHC) class I on lesional keratinocytes and lyse them (24).

Malignancy developing in lesions of lichen planus is a rare phenomenon, except in oral lichen planus (chronic inflammation and accelerated cellular turnover in erosive lesions) (25), where the risk is estimated to range from 1.1 to 3.5% (26, 27, 28), which is the reason

why the WHO defines it as a pre-cancerous conditions (29). Among other localizations and clinical forms being complications of hypertrophic lichen planus of the lower extremities, the most common are neoplastic transformations and squamous cell carcinoma with a risk of metastasis (30), (25, 31, 32, 33, 34).

The diagnosis is made through clinical and histopathological findings. Differential diagnosis of various forms of lichen includes several conditions (lichenoid eruptions induced by drugs or color developer, eczematous eruptions with lichenification from scratching, lichen amyloidosis), whereas in hypertrophic lichen planus, chronic lichen simplex must be excluded (19).

The choice of treatment mainly depends on the clinical type of lichen planus and its localization. According to Oliver et al (1), general principles of treatment include rest, dressings, topical steroids (mild or potent), retinoids, treatment of oral lesions and treatment of secondary or primary infections. Topical calcineurin inhibitors, such as tacrolimus (35, 36), pimecrolimus (37) and cyclosporine (38) are second-line therapies. Hypertrophic lesions are treated with intralesional corticosteroids. Systemic therapy includes corticosteroids, cyclosporine, dapsone, retinoids (etretinate, acitretin, isotretinoin), and PUVA therapy. If necessary, surgical treatment is performed.

Due to various mechanisms of action (39), retinoids may exhibit beneficial effects on the pathogenesis of lichen planus. The immunomodulatory effect is probably achieved by restoring balance between T helper and T suppressor cells. The anti-inflammatory effect is mainly due to the inhibition of inflammatory mediators. It is believed that their specific effect is to stimulate proliferation of normal epithelial cells. On the other hand, their antiproliferative activity is based on the reduction of DNA synthesis. It is known that in healthy skin, retinoids increase the activity of glucose-6-phosphate dehydrogenase, so this mechanism of action may be involved in the pathogenesis of cutaneous lichen planus.

Our patient showed a significant improvement after etretinate therapy. Jerne et al, reported about excellent therapeutic response to acitretin in disseminated hypertrophic lichen planus (5). Recent literature has reported on the application of alitretinoin (9-cis retinoic acid) in the treatment of several cutaneous forms of lichen planus (6, 40, 41).

Conclusion

This case report describes a patient with a rare form of verrucous lichen planus on the lower extremities. Although lesions were resistant to treatment, systemic etretinate therapy resulted in a significant regression of the disease, leading to better quality of life.

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Hipertrofični lihen planus – prikaz slučaja

Sažetak

Uvod. Lichen planus je inflamatorna imunska reakcija sa karakterističnim kliničkim i histološkim lezijama. Bolest je benignog, često hroničnog ili recidivantnog toka, a karakterišu je zaravnjene ružičaste do ljubičaste sjajne pruritične poligonalne papule na koži ili mlečnobele retikularne papule na vidljivoj sluzokoži.

Lichen planus hypertrophicus je hronična hipertrofijska forma bolesti, sa naglašenom epidermalnom hiperplazijom i jakim svrabom. Karakterišu je simetrični hipertrofični plakovi, najčešće lokalizovani pretibijalno i perimaleolarno. Lezije su često rezistentne na terapiju.

Prikaz slučaja. Prikazuje se 47 godina stara domaćica, dobrog opšteg stanja: osim operativnog lečenja miomatoznog uterusa i hipertenzije u prošlosti nije bilo drugih oboljenja; bolest je počela na bočnim stranama peta u vidu bradavičastih izraslina praćenih svrabom koje su se brzo povećavale i širile na susedne delove stopala: na prednjoj strani desne potkolenice nastale su 2-3 godine kasnije i to na mestu prethodne povrede kože; u porodici nije bilo obolelih srodnika.

Bolesnica je u više navrata lečena na Klinici za kožne i polne bolesti u Nišu i jednom na Vojnomedicinskoj akademiji u Beogradu. Primenjena terapija (keratolitici, kortikosteroidi pod okluzijom i intraleziono, krioterapija

tečnim azotom, zračna terapija X-zracima – ukupna primljena doza od 20 Gy data u 10 seansi na dva suprotna polja, sistemski antibiotici prema antibiogramu zbog sekundarne infekcije, sedativi, itd.) nije dala zadovoljavajuće i trajnije rezultate. Zbog toga je odlučeno da se primeni etretinat u obliku kapsula.

U momentu pregleda, na bočnim i zadnjim stranama peta bili su prisutni infiltrati tumoroznog izgleda, pojedinačni ili sliveni, koji su davali izgled mamuza oko peta. Površina im je bila keratotična, verukozna, sivkasto mrko prebojena, ispresecana ragadama, iz kojih se na pritisak cedio hemoragično purulentan sadržaj. Na prednjoj strani desne potkolenice bio je prisutan tumefakt oko 5 cm u prečniku, sličnih osobina. Promene su bile jako pruritične, često bolne, onemogućavale su nošenje obuće i otežavale hod. Drugih promena na koži i vidljivim sluzokožama nije bilo.

Sve tražene laboratorijse analize su bile u granicama referalnih vrednosti: sedimentacija eritrocita, kompletna krvna slika, hemoglobin, leukocitarna formula, urea, kreatinin, hepatogram, transaminaze, elektroforeza proteina, kisela i alkalna fosfataza, laktat-dehidrogenaza, holesterol, trigliceridi, glikemija, elektroliti u serumu; serološke reakcije na adenoviruse, citomegalovirus, herpes simpleks virus i *Treponema pallidum*. *Staphylococcus aureus* je bio izolovan iz lezija koje su pokazivale znake sekundarne infekcije.

Svetlosnom mikroskopskom analizom bioptiranog uzorka promenjene kože uočeno je sledeće: veoma izražena hiperkeratoza; granulozni sloj samo mestimično naznačen; nejednako izražena akantoza, delimično u vidu epidermalnih produžetaka; umereno gust infiltrat u dermisu, sastavljen najvećim delom od limfocita i ređih histiocita koji u većem delu preparata prodire i u donje slojeve epidermisa, te je epidermo-dermalna granica nejasna – kao izjedena moljcima).

Direktnom imunofluorescencijom je dobijen nalaz koji je ukayivao na lihen palnus: depoziti fibrinogena u vidu grube nazubljene trake duž epidermo-dermalne granice i u zidovima krvnih sudova papilarnog dermisa intenzivne fluorescencije; brojna koloidna tela klase IgM u većim grupama ispod epidermo-dermalne granice; trakasti depoziti fibrinogena na graničnom delu između epidermisa i dermisa.

Terapija. Lečenje etretinatom započeto je dozom od 75 mg na dan (3 puta 25 mg, tj. oko 1 mg na kg na dan, sa postepenim smanjivanjem na 10 mg na dan). Lokalno su primenjivani keratolitici u bornom kremu. Kura je trajala 8 meseci. U početku lečenja od neželjenih efekata javila se suvoća usta, pojačana deskvamacija dlanova i tabana, prolazno povišenje triglicerida u serumu koje se normalizovalo sa smanjenjem doze. Efekat terapije na promene na koži je bio izvanredan. Došlo je do izravnavanja tumefakta, pete su dobile skoro normalan obim, bolesnica je mogla da nosi cipele, nije bilo sekundarne infekcije i bitno je smanjen svrab.

Diskusija. Izbor terapije za lihen planus zavisi od kliničke forme i lokalizacije promena. Prema Oliveru i saradnicima, opšti principi lečenja lihena obuhvataju: odmor, previjanje, topikalne steroide (srednji ili potentni), retinoide, lečenje oralnih lezija i tretman sekundarne ili primarne infekcije. Lokalno se mogu primeniti i inhibitori kalcineurina, kao što je takrolimus, pimekrolimus i ciklosporin. Kod hipertrofijske forme kortikosterodi se aplikuju intraleziono. Sistemski se primenjuju kortikosteroidi, ciklosporin, dapson, retinoidi (etretinat, acitretin, isotretinoin), PUVA terapija. Po potrebi se mogu koristiti i hirurške metode.

Retinoidi, zbog svojih raznovrsnih mehanizama dejstva mogu da deluju na različitim nivoima u patogenezi lihena planus. Imunomodulatorno dejstvo se najverovatnije ostvaruje uspostavljanjem ravnoteže između T-pomažućih (helper) i T-supresorskih limfocita. Antiinflamatorni efekat je uglavnom posledica inhibicije medijatora inflamacije. Smatra se da je specifično dejstvo retinoida da stimulišu proliferaciju normalnih epidermalnih ćelija. S druge strane, njihovo antiproliferativno dejstvo zasniva se na redukciji sinteze DNA. Poznato je da retinoidi u zdravoj koži povećavaju aktivnost glukoza 6 fosfat-dehidrogenaze, pa bi i ovaj mehanizam dejstva mogao biti uključen u patogenezi lihenskih promena.

Kod naše bolesnice do bitnog poboljšanja došlo je tek posle primene etretinata. Džeme (Jeme) i saradnici navode odličan terapijski odgovor na acitretin ostvaren kod diseminovanog hipertrofijskog lihena. U novijoj literaturi ima više izveštaja o primeni alitretinoina (9-*cis* retinoic acid) u lečenju nekoliko kutanih oblika lihena.

Zaključak. Prikazana je bolesnica sa retkom formom verukoznog lihena sa lokalizacijom na donjim ekstremitetima, sa rezistencijom na bilo koju terapiju do sistemske primene retinoida, etretinata. To je znatno olakšalo stanje bolesnice i dovelo do poboljšanja kvaliteta njenog života.

Ključne reči

Lichen planus + fiziopatologija + terapija; Etretinat; Ishod lečenja

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Congenital Primary Pachydermoperiostosis and Striate Palmoplantar Keratoderma - a Case Report

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Abstract

The authors present a rare case of congenital pachydermoperiostosis associated with striate palmoplantar keratoderma in a 55-year-old female. Pachydermoperiostosis (PDP) is a heterogeneous syndrome characterized by hypertrophic changes involving predominantly the skin and bones of the extremities: pachydermia, clubbing of the fingers and toes, and hypertrophic osteoarthropathy. Primary pachydermoperiostosis (Touraine–Solente–Gole syndrome) (PPDP) or primary hypertrophic osteoarthropathy (PHO) is a rare congenital disorder and is one of two types of hypertrophic osteoarthropathy. In addition to the three main criteria, which are confirmed clinically, histologically, and by X-ray, there may be other additional clinical features. Hyperhidrosis of the hands and feet may be troublesome. The skin of the face, forehead and scalp becomes grossly thickened and thrown into folds. The folding of the scalp produces a form of cutis verticis gyrata. Additional clinical features include hypohidrosis, seborrhea, sebaceous gland hyperplasia and folliculitis, carpal and tarsal tunnel syndrome, chronic leg ulcers and calcification in the Achilles tendon. Our patient presented with most of these additional clinical features, such as acro-osteolysis of the fingers and toes, which generally occurs occasionally. In regard to palmoplantar keratoderma, we have not found reports of its association with PPDP in the available literature.

Unlike PPDP, secondary pachydermoperiostosis (secondary hypertrophic osteoarthropathy -SHO) occurs in association with severe pulmonary disease such as bronchiectasis, abscess, bronchial carcinoma, pleural mesothelioma, or thymic, esophageal or stomach cancer, which were all excluded in our patient.

In conclusion, this paper presents a congenital form of pachydermoperiostosis in a female also suffering from striate keratoderma. According to the available literature, this is the first case report of comorbidity between these two dermatoses.

Key words

Osteoarthropathy, Primary Hypertrophic; Keratoderma, Palmoplantar; Diagnosis; Signs and Symptoms; Comorbidity

Pachydermoperiostosis (PDP) is a heterogeneous syndrome characterized by hypertrophic changes involving predominantly the skin and bones of the extremities: pachydermia, clubbing of the fingers and toes and hypertrophic osteoarthropathy (1, 2). Primary pachydermoperiostosis (Touraine-Solente-Gole syndrome) (PPDP) or primary hypertrophic osteoarthropathy (PHO) is a rare inherited disorder with no hard evidence of inheritance related to X chromosome: in some families, autosomal dominant inheritance with incomplete penetrance and variable expressivity was detected, while in other families, autosomal recessive inheritance has been demonstrated (1, 3). In 2008, the primary genetic defect in this disease was mapped to chromosome 4q33-q34 identifying mutations in the HPGD gene, encoding the NAD+dependent 15-hydroxyprostaglandin dehydrogenase (3). This is the main enzyme of prostaglandin degradation, so homozygous individuals with truncating mutations of HPGD may also have persistent patent ductus arteriosus, secondary to the elevated levels of prostaglandin, while mild clubbing of the digits can be present in heterozygous carriers of HPGD mutations (3).

The three major criteria of this syndrome include pachydermia (thickening of the skin), hypertrophic osteoarthropathy with periostitis (excessive bone formation) and the so-called "clubbing" (swelling of the soft tissues of the terminal phalanx of a digit that obliterates the angle between the base of the nail and the digit) with idiopathic acromegaloid features (1, 4). It has a marked predominance in males (5).

The authors present a rare case of congenital pachydermoperiostosis associated with palmoplantar keratoderma in a 55-year-old female.

Case report

A 55-year-old female with a lifelong history of clubbing of the fingers and a diagnosis of congenital pachydermoperiostosis was first referred to our Clinic in 2011. The diagnosis was made in childhood by a physiatrist, based on x-rays, but since then the patient was not treated or examined thoroughly. On admission, she complained of pain in muscles and joints, especially in the small joints of the hands and feet, as well as of toenail changes and inability to stand on a flat surface, forcing her to wear high heels. Over the last ten years she noticed yellowish thickening of the skin on the palpms and feet with nail damage and deformities of the fingers and toes. She experienced walking difficulties and pain in the joints of knees, feet, and along the lumbosacral spine.

History data showed that during childhood the patient was admitted to the Endocrinology Department of the Institute for Mother and Child Health Care in Novi Sad on two occasions, and at the Institute of Internal Medicine in Novi Sad 20 years ago.

Based on the submitted data, we learned that she underwent benign breast tumor surgery in 2003, and had regular 6-month check-ups with her oncologist: an intraductal papilloma was removed from the left, and an atheroma from the right breast. The following check-ups indicated removal of new tumors in both breasts, and after magnetic resonance imaging and histopathological analysis, the diagnosis of fibro-micro-cystic dysplasia/ adenosis without extensive changes was made; 6-month check-ups with her oncologist continued.

Patient data also revealed that a tumor was removed from the palm of her right hand in 2008, histologically consistent with intradermal pigmented nevus and syringoma. Due to a reduced passive and active mobility of the right hand, electromyography test showed: axonal moderate to severe lesion of the C8, Th1 right-sided miotomes; no signs of acute injury, corresponding to radicular syndrome. X-ray examination showed diffuse osteoporosis of the hands, feet and knee joints. Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DEXA) and spinal osteoporosis was excluded.

Apart from this, it was found that the patient was treated by a cardiologist for compensated cardiomyopathy.

The family history revealed that her father's mother suffered from "arthritis" and changes similar to hers, and that her father died of a myocardial infarction.

On the first visit, general physical examination showed that the patient was in good general condition, but having mobility difficulties. The pertinent findings were confined to the skin of palms and soles, fingers, toes and nails as well as bones and joints on the hands and feet: hyperkeratosis on the palms and soles with a clinical picture of palmoplantar striate keratoderma (Figures 1,2); signs of hypertrophic osteoarthropathy on the fingers with clubbing of the nails (Figure 3); subungual hyperkeratosis of the toenails and hands with thickened, dystrophic dark yellow nail plates and onycogryphosis (Figure 4); inguinal follicular hyperkeratosis; keratotic - thickened skin around the Achilles tendons and swelling of the ankles.

Investigations

Laboratory tests revealed the following abnormal test results: sedimentation rate 44/74 mm/h, red blood cell count 3.19 x1012/L, hemoglubin: 10.5 g/L, osteocalcin: 54.3 ng/ml (normally 12-41 ng/ml), Cross Laps: 572 pg/ml (normally 162-436 pg/ml).

Affected skin samples were positive for: *Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Stenotrophomonas maltophiia*, which are sensitive to several antibiotics.

Mycological examination: Candida albicans was isolated between the toes of both feet.

Oncomarkers: The following serum levels of tumor markers were estimated: carcinoembryonic antigens (CEA) **9,**7 ng/ml (normally < 5,0 ng/ml), alpha fetoprotein antigens (AFP), CA 19-9 carbohydrate antigen, CA 15-3 carbohydrate antigen, and CA 125 carbohydrate antigen were all within normal levels.

X-ray of the hands, feet and long bones: Prominent diffuse osteoporosis. Hand X-ray: bilateral narrowing of the proximal interphalangeal joint space, pronounced on the third, fourth and fifth fingers on the right hand, and

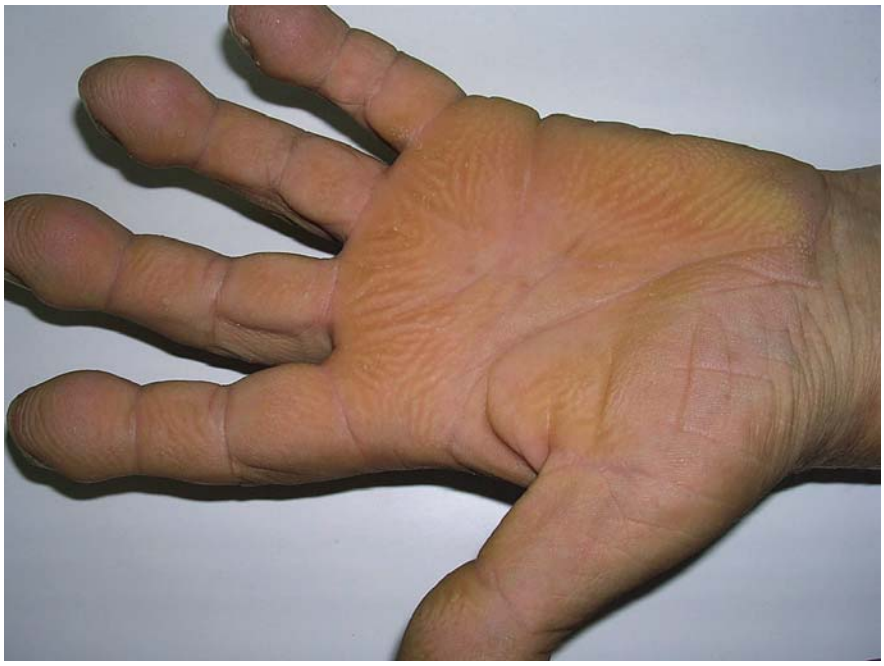

Figure 1. Striate palmar keratoderma with pachyonyichia

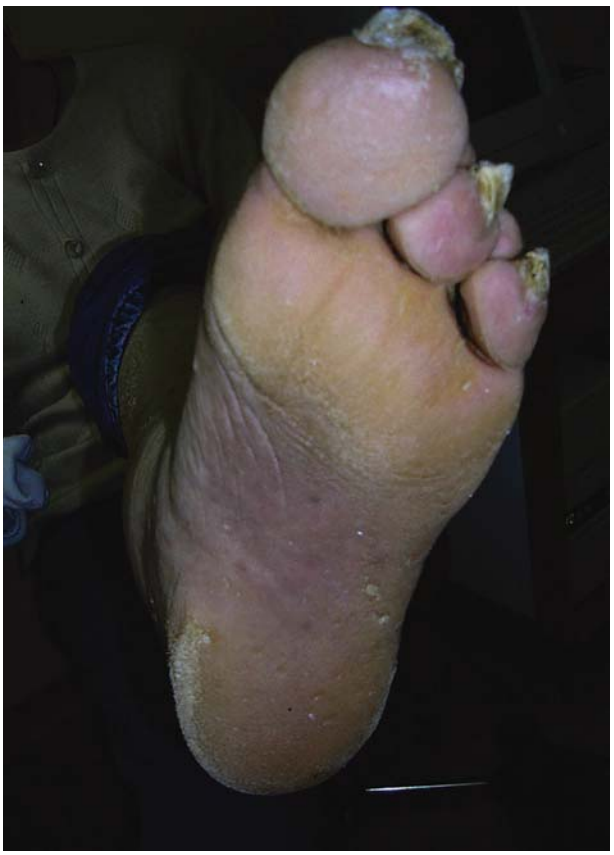

Figure 2. Plantar keratoderma with subungual hyperkeratosis and onychogryphosis

on the fift finger on the left hand; marked narrowing of the distal interphalangeal joint space, with subluxation of the distal phalanges of the fifth finger of the right hand; acro-osteolysis of distal phalanges present on all fingers, with almost complete lysis of the distal phalanges of the fifth finger of the left hand; edema of the surrounding soft tissue - clubbing fingers (Figure 5).

X-ray of the feet: Bilateral talocrural joint and metatarsophalangeal joint space narrowing of the first toe; acro-osteolysis of distal phalages present on all toes, with nearly complete lysis of ditstal phalanges of the fifth, third toes of the left foot, and on the third, fourth and fifth toes of the right foot; bilateral periosteal reaction of the calcaneus and the first metatarsal bone, more prominent on the right foot; rough exostoses on the distal heads of the first metatarsal bone of both feet; bilateral calcaneal spurs at the site of the insertion of the plantar aponeurosis of the Achilles tendon, more pronounced on the right foot (Figure 6).

X-ray of long bones: Bilateral periosteal reaction in the tibia, fibula with bone bridge formation (Figure 7).

X-ray of the knee and long bones: Marked diffuse osteoporosis; bilateral asymmetric narrowing of the joint space of the tibiofemoral joint, prominent laterally with a lateral notch, and intercondylar eminences and subchondral sclerosis of the articular surfaces; periosteal reaction of both the femur(with a

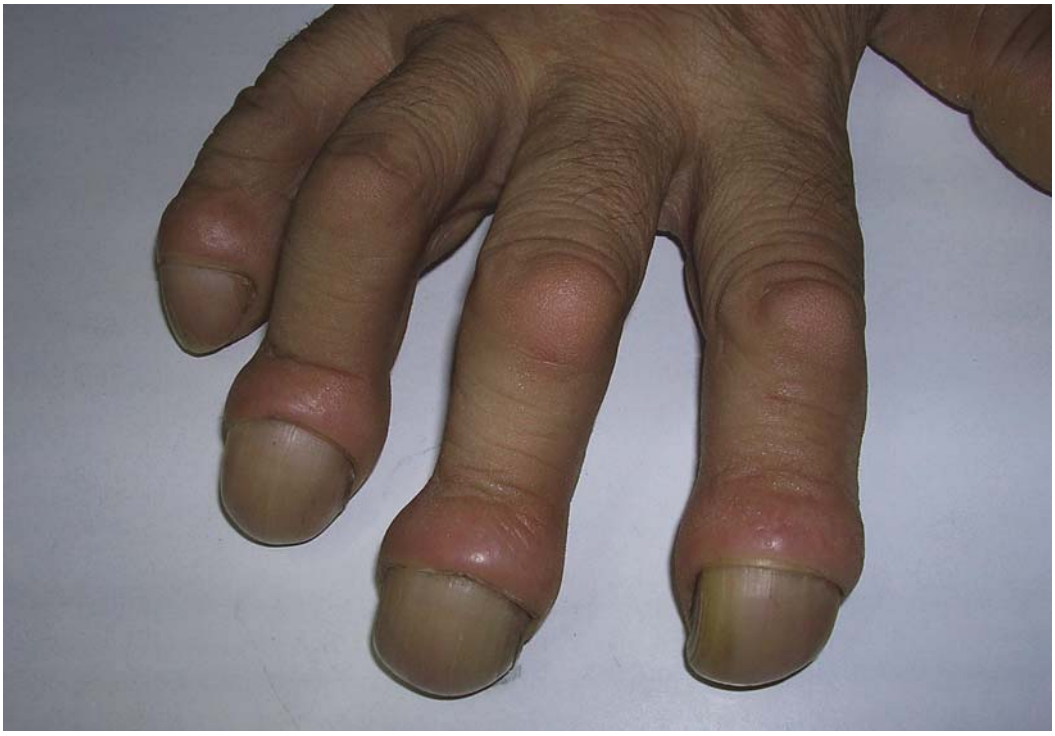

Figure 3. Clubbed fingers (digiti hippocratici) with osteohypertrophic arthropathy

"sunburst" appearance), including the tibia and fibula; calcification in the knee pits; bilateral narrowing of the patellofemoral joint (Figure 8).

Lumbosacral spine X-ray: Corrected physiological lordosis of the lumbar spine, with a sharp transition – sacrum acutum; intervertebral disc space height and configuration of the lumbar spine preserved. Incidental finding: abdominal aortic calcification; calcified fibroid in the small pelvis.

Mammography in two directions: Predominantly

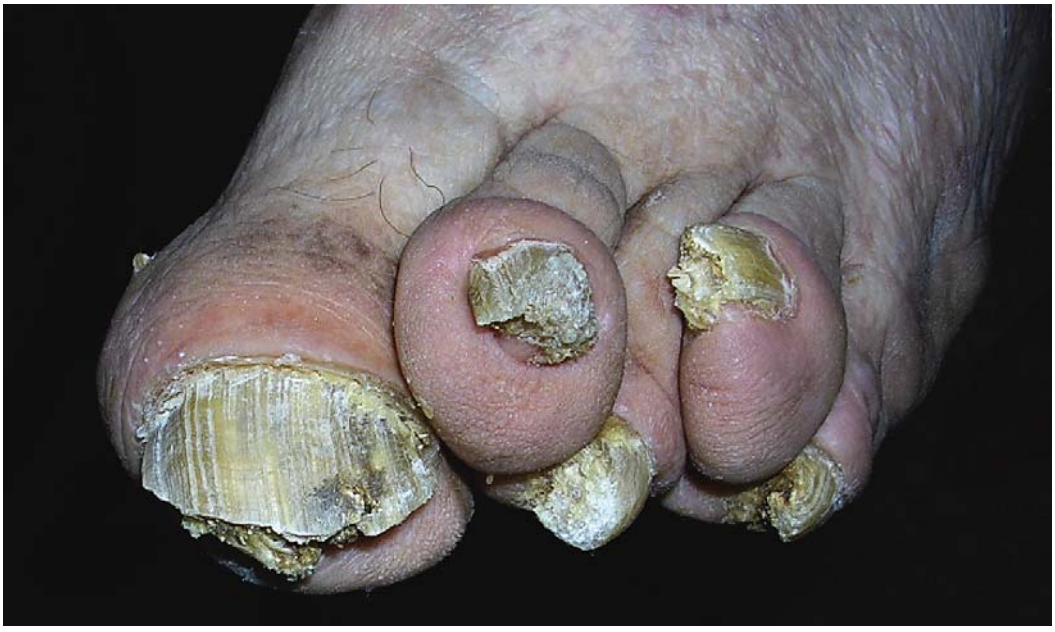

Figure 4. Subungual hyperkeratosis with onychogryphosis and osteoarthropathic foot deformity

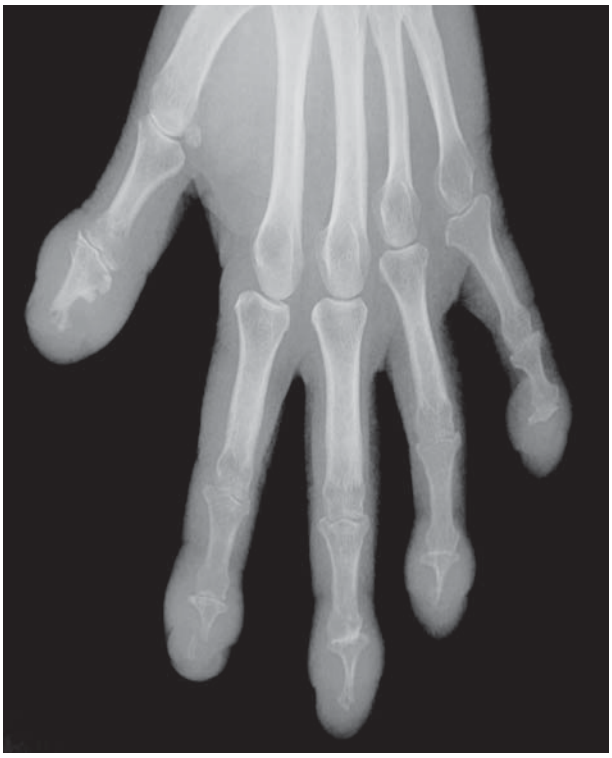

Figure 5. X-ray of the left hand: clubbing of the digits with acrolysis of the distal phalanges; distal phalange of the fifth finger with prominent lysis; visible bone fragments in the soft tissue of the second finger after acrolysisdeformity

fibroglandular tissue in both breasts; perimammilar area of the left breast presents with thickened skin, while grouped polymorphic microcalcifications are present in the retromammary region; oval, vaguely demarcated condensed parenchyma observed in the

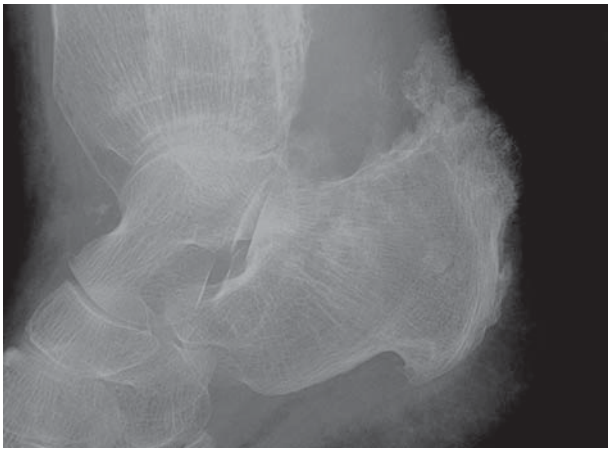

Figure 6. X- ray of the right calcaneus: rough periosteal bone deposits along the edge of the calcaneus

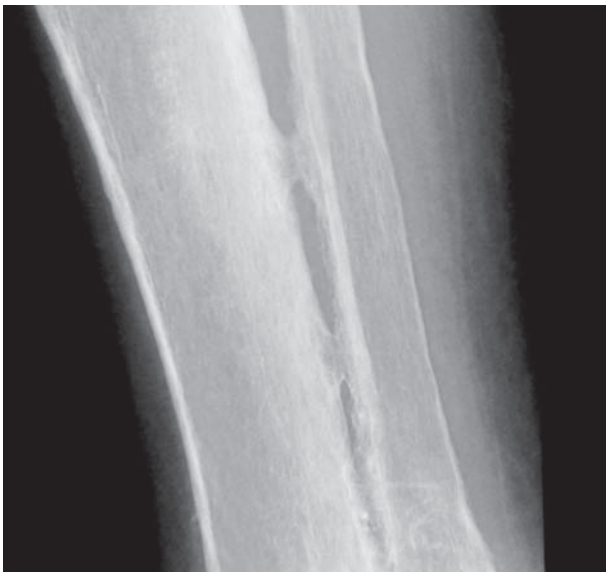

Figure 7. X-ray of the left calf: pronounced periosteal deposits on the tibia and fibula with bone bridge formation

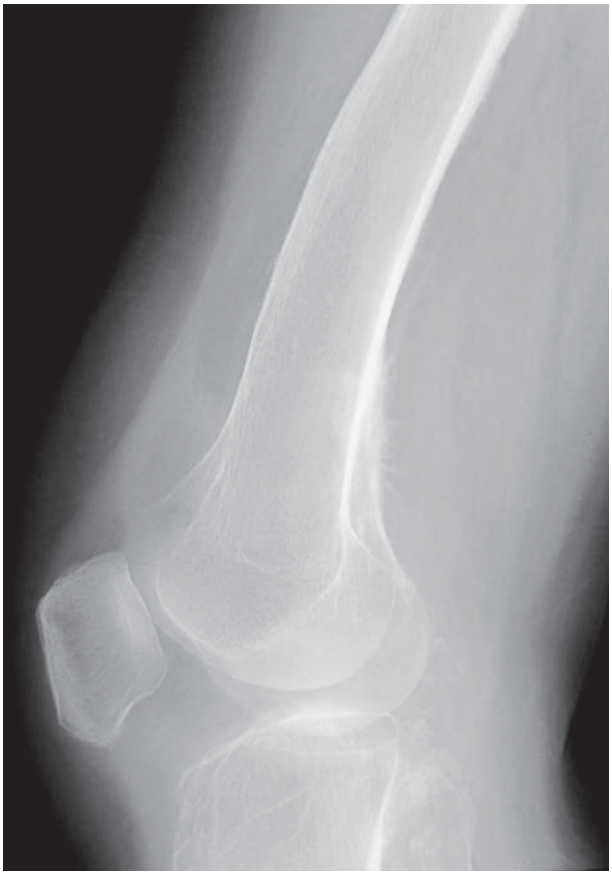

Figure 8. X-ray of the right femur: a periosteal reaction with a "sunburst" appearance

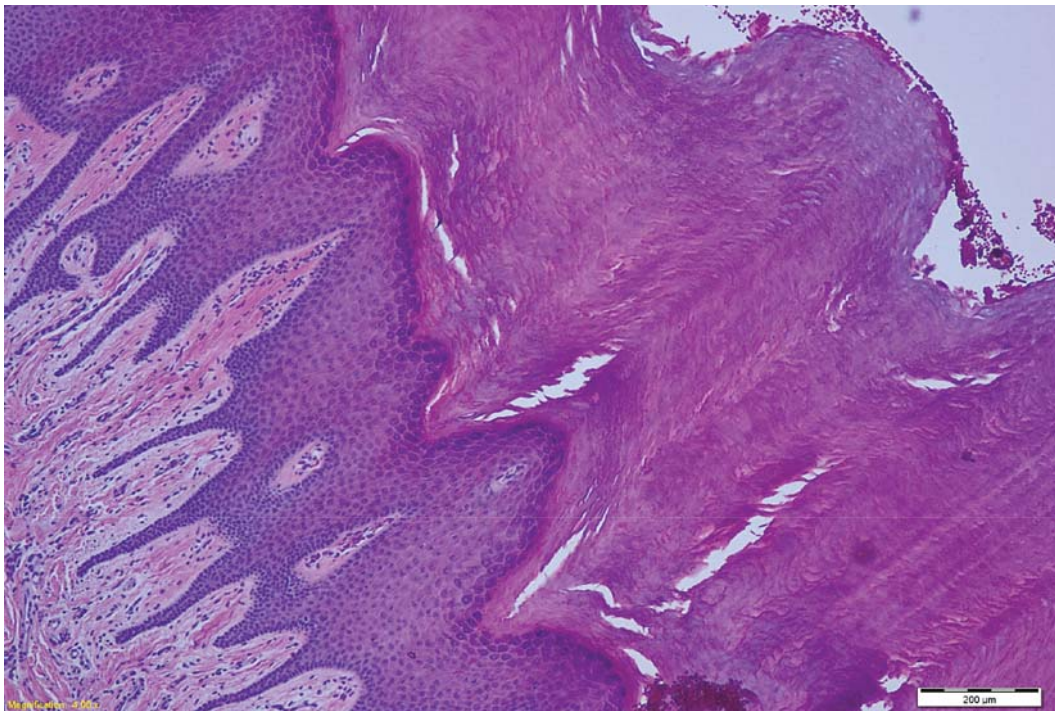

Figure 9. Photomicrograph of the skin with a thick keratotic layer, moderately thick granular layer of the epidermis and mild acanthosis and papillomatosis (HE x 40)

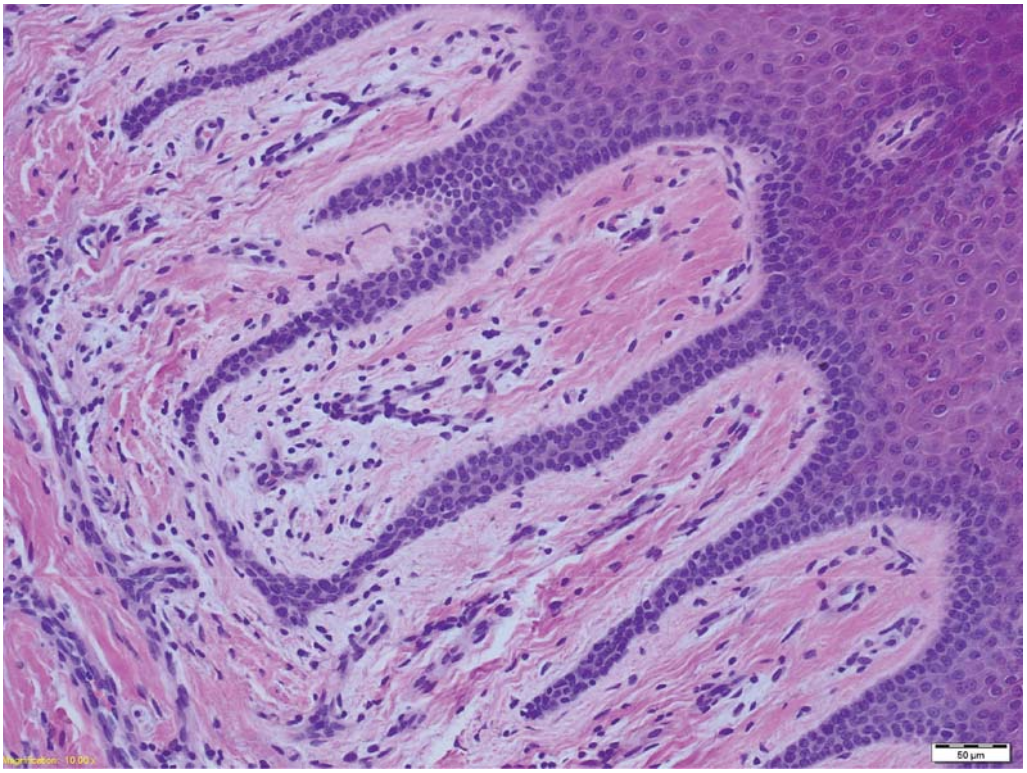

Figure 10. Photomicrograph of a skin biopsy specimen with moderately elongated epidermal papillae and thickened collagen fibers in the papillary dermis (HE x 100)

center line requiring ultrasound evaluation; there are no tumor shadows in the right breast, nor pathognomonic microcalcifications; no visible axillary node enlargement.
Breast ultrasound: A round cyst 14x9 mm, along with a smaller one 6 mm in diameter, were found in the retroareolar region of the left breast; moderate duct ectasia; no visible signs of pathological condensation of breast parenchyma; the right breast presented with sporadic microcysts up to 5 mm in diameter; axillary fibrolipomatous lymph nodes.
Chest X-ray finding (PA): Normal.
Gastroduodenal X-ray finding: Normal.
Upper abdomen X-ray: Signs of gallbladder polyps and cholesterolosis. Uterus myomatosus was an incidental finding. Findings on the liver, pancreas, and kidneys were normal.
Thoracic CT (native): Normal.
Arterial and venous duplex ultrasound of the lower extremities: Normal findings on the arteries and veins, with a slightly pronounced Cockett's perforator on the left leg; enlarged lymph nodes visible bilaterally in the proximal part of the thigh; distal soft tissue swelling below the knee, more pronounced on the left leg.
Histological findings of palmar keratoderma (thenar of the left hand from May 27, 2011; PH finding no.13072/11): pronounced hyperkeratosis of the epidermis with acanthosis (Figure 9); a prominent granular layer and regularly elongated rete ridges; moderate edema of the papillary dermis; collagen fibers are tough and the dermis is slightly thickened (Figure 10); septa of the subcutaneous adipose tissue are extremely visible and thick; sweat glands are normal. Conclusion: Cutaneous and subcutaneous changes are consistent with pachydermoperiostosis.
Specialist consultations: Otorhinilaryngologist, dentist, gynecologist, gastroenterologist, cardiologist, ophthalmologist, pulmonologist, physiatrist.
Otorhinolaryngologist: Hypoacusis mixta gradus levis. No focus. Bilateral light mixed hearing loss - 25 dB.
Gynecologist: Menopause - the last cycle in 2009. Postmenopause. Myoma uteri. Other findings – normal.
Dentist: Periodontal disease.
Ophthalmologist: Normal.
Endocrinologist: Dual-energy X-ray absorptiometry (DEXA) - indicates left hip osteoporosis.
Vascular surgeon: Feet problems are not vascular in nature.
Orthopedic surgeon: contractura genus bilateralis gravis.
Cardiologist: Chronic cardiomyopathy.
Pulmonologist: No pulmonary fibrosis. Recommendation – 6-month check-up.
Radiologist: Skeletal X-rays revealed changes, predominantly in the long bones, hands and feet consistent with severe pachydermoperiostosis.
Physiatrist: Orthopedic shoes with a platform are recommended. Postural imbalance is part of the underlying disease; clubbing fingers - functional. Scoliosis - T4L, the right leg is longer, the right hip is higher set; contracture of the right knee, swelling of both lower legs; impaired walk.

Therapy

The proposed treatment with systemic and local retinoids was rejected by the patient. After the potential chronic and malignant causes of secondary hypertrophic osteoarthropathy were excluded, nonsteroidal antiinflammatory drugs (NSAID) and local keratolytic treatment was initiated, as well as Tamoxifen, an anti-oestrogenic drug which may be useful in the treatment of fibrocystic disease of the breast, prescribed by the gynecologist.

Discussion

Primary pachydermoperiostosis (PPDP), or primary hypertrophic osteoarthropathy (PHO), is a rare inherited disorder with a characteristic triad: clubbing of the fingers and toes, periostosis, and pachydermia (1, 3), as well as elevated levels of prostaglandin E2 (PGE2) , which can be considered as a consequence of cytokine-mediated tissue remodeling and vascular stimulation. In PHO, these effects are associated with hyperhidrosis, acroosteolysis, pachydermia, periostosis and arthritis (6,7). PGE2 may affect the activity of osteoblasts and osteoclasts (ie promote osteoclasia). For these reasons, acroosteolysis and periosteal new bone formation are explained by effects of PGE2 (8). Moreover, PGE2 has vasodilator effects, which is consistent with prolonged local vasodilation in clubbing fingers (8). Apart from elevated levels of PGE2, studies including patients with PDP showed increased plasma levels of several other mediators, such as von Willebrand factor, and vascular endothelial growth factor (VEGF) (1, 9). These mediators play a significant role in PDP progression and periosteal proliferation (1). Unlike mutations in 15-hydroxyprostaglandin dehydrogenase (HPGD), mutations in the genes encoding synthesis of these factors have not been established so far (1, 9).

PPDP is one of the two types of hypertrophic osteoarthropathy. It represents approximately 5% of

the total hypertrophic osteoarthropathy cases with a prevalence of 0.16% (4, 10). Contrary to PPDP, secondary pachydermoperiostosis (secondary hypertrophic osteoarthropathy - SHO) occurs in patients with severe pulmonary diseases such as bronchiectasis, lung abscess, bronchial carcinoma, pleural mesothelioma, or thymic, esophageal and stomach cancer. The bone changes are often painful, develop rapidly and are usually presented as a pertinent finding. Skin changes may be absent or mild. The bone and skin changes regress after appropriate treatment of the primary disease (2). Our case report is about a patient with a congenital hypertrophic osteoarthropathy, without signs of malignancy or cardiopulmonary conditions that might have caused it.

Based on the phenotypic expression, three clinical subtypes of PDP have been proposed: 1) a complete form, presenting the full-blown phenotype which includes all thus far described signs ad symptoms of PDP, but necessarily pachydermia, periostosis and clubbing fingers; 2) an incomplete form, accounting for 54% of cases with isolated bone involvement, limited skin changes, while pachydermia is less pronounced; 3) a fruste form, which accounts for only 6% of cases with pachydermia and minimal or absent periostosis (1). The cause of different forms of the disease is unknown (1). In our case, it was a complete phenotype associated with striate palmoplantar keratoderma. Pachydermoperiostosis has a familial aggregation in 25 to 38% of cases (5), but it has not been verified in our case. Autosomal dominant model with incomplete penetrance, with extremely variable expression, has been proved in about half of the families with incomplete type of the disease (1). Several families with confirmed autosomal recessive model of inheritance, presented with a complete phenotype with severe osteo-skeletal and cutaneous manifestations. Considering the fact that medical history data indicated the existence of the disease only in her father's mother, our patient can be included in the group with a recessive model of inheritance.

Pachydermoperiostosis is clinically diagnosed if the following symptoms are present: pachydermia, clubbing of the fingers and toes, and periostosis (predominantly affecting the distal ends of long bones) (1, 12, 13). New bone formation is seen on long bone X-rays as symmetrical, irregular periosteal ossifications (13). Digital clubbing is associated with cylindrical thickening of the legs and forearms. Acroosteolysis of the fingers and toes, which may occasionally occur, was also present in our patient. The skin of the hands and feet is also thickened, but usually not folded. Hyperhidrosis of the hands and feet may be troublesome. The skin of the face, forehead and scalp becomes grossly thickened and thrown into folds. The folding of the scalp may produce one of the forms of cutis verticis gyrata. Additional clinical features include hypohidrosis, seborrhoea, sebaceous gland hyperplasia and folliculitis, carpal and tarsal tunnel syndrome, chronic leg ulcerations and calcification in the Achilles tendon. Our patient presented with most of the additional clinical features.

Skin biopsy is another way to diagnose PDP. Histology shows cutaneous sclerosis and hyalinosis, with perivascular infiltration of lymphoid cells in the dermis (5); apart from hypertrophy of collagen and epidermal appendages, an increase of acid mucopolysaccharides may also be seen (2). However, it is not an absolutely specific finding, because changes similar to those in PDP may be found in some other diseases such as myxedema, hypothyreoidism, acromegaly (4). However, skin biopsy helps to diagnose PDP in patients with skin manifestations (4, 14). Histological tests of skin samples taken from palms with changes in the dermis and subdermis that match pachydermoperiostosis confirmed the clinical diagnosis of palmoplantar keratodrma and pachydermoperiostosis.

In order to diagnose PPDP, other diseases often need to be excluded. For example, secondary hypertrophic osteoarthropathy must be excluded, as well as cardiovascular, pulmonary, hepatic, intestinal and mediastinal diseases (12). In differential diagnosis, detailed hormone tests are necessary (eg. thyrotropin and growth factor levels), and they were carried out in our patient. In our case thyroid gland disorders were excluded.

In regard to the course and prognosis of PPDP, skin and bone manifestations tend to progress for 5–20 years before stabilizing. Life expectancy may be the same, regardless of the fact that many patients have functional and esthetic complications, including restriction of movements, neurological manifestations and the lion-like appearence with facial folds (leonine facies) (1, 15).

Non-steroidal anti-inflammatory drugs (NSAID) are employed as symptomatic treatment, while corticosteroids are used to relieve inflammation and pain. By inhibition of cyclooxygenase enzymes, NSAIDS reduce prostaglandin levels. Other medications are used to improve skin manifestations of patients with PPDP (5). Retinoids are preferably used to improve skin lesions (5). By their systemic action on nuclear receptors of

skin cells and sebaceous glands, retinoids regulate gene transcription resulting in the following: apoptosis in sebaceous glands (isotretinoin shows favorable cosmetic results) (16), and inhibition of connective tissue and sebaceous glands hyperplasia (17). Retinoids have been shown to reduce procollagen production by diminishing procollagen mRNA in fibroblasts, thus inhibiting the production of collagenase and improving skin lesions in pachydermia: fibroblast biosynthetic activity in the skin lesions of pachydermoperiostosis demonstrates an alteration which may be responsible, at least partly, for the patient's phenotype (1a). Infliximab, tumor necrosis factor alpha (TNF-alpha) inhibitor, may be effective in the resorption of newly formed bones (18). Surgical treatment has been mainly focused on cosmetic and functional improvement (19).

As far as palmoplantar striate keratoderma is concerned, we have not found its association with PPDP in the available literature. Barraud-Klenovsek et al. reported a case of a 30-year-old woman with palmoplantar keratoderma and clubbing of the fingers in 1997 (20). Recently, Perić et al, reported a case of pachydermoperiostosis in a patient with psoriasis (21).

Conclusion

This paper presents a congenital form of pachydermoperiostosis in a female patient who developed striate keratoderma. According to the available literature, this is the first case report of comorbidity between these two dermatoses.

Abbreviations

PDP - pachydermoperiostosis
PPDP - primary pachydermoperiostosis
PHO - primary hypertrophic osteoarthropathy
SHO - secondary hypertrophic osteoarthropathy
CEA - carcinoembryonic antigen
CA - carcino antigen
NAD - nicotinamide adenine dinucleotide
BMD - bone mineral density
DEXA - dual-energy X-ray absorptiometry
NSAID - nonsteroidal antiinflammatory drugs
PGE2 - prostaglandin E2
VEGF - vascular endothelial growth factor
TNF-alpha - tumour necrosis factor alpha

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Kongenitalna primarna pahidermoperiostoza udružena sa strijatnom keratodermijom – prikaz slučaja

Sažetak

Uvod. Pahidermoperiostoza (PDP) predstavlja heterogeni sindrom za koji su karakteristične hipertrofične promene prvenstveno kože i kostiju ekstremiteta: pahidermija, klabing (clubbing) prstiju šaka i stopala i hipertrofična osteoartropatija. Primarna pahidermoperiostoza – sinonim Turen–Solent–Goleov sindrom (Touraine–Solente–Golé) (PPDP), ili primarna hipertrofična osteoartropatija (PHO), redak je nasledni poremećaj i predstavlja jedan od dva tipa hipertrofične osteoartropatije.

Za razliku od PPDP, sekundarna pahidermoperiostoza (sinonim sekundarna hipertrofična osteoartropatija – SHO) javlja se u sklopu teških bolesti pluća (karcinom, bronhiektazije, apsces), pleuralnog mezotelioma, ili karcinoma timusa, ezofagusa ili želuca.

Primarna pahidermoperiostoza (PPDP) ili primarna hipertrofična osteoartropatija (PHO) redak je genetski poremećaj koji pogađa i kosti i kožu, sa nesigurnim načinom genetskog prenosa (autozomnodominantnim ali i autozomnorecesivnim), bez sigurnih dokaza o X-hromozom vezanom nasleđivanju. Primarni genetski defekt kod ove bolesti je 2008. godine mapiran na 4q33-q34.15 pri čemu je identifikovna mutacija na genu HPGD koji kodira hidroksiprostaglandin-dehidrogenazu, glavni enzim degradacije prostaglandina. Jedna od glavnih karakteristika bolesti je uglavnom pahidermija (zadebljanje kože), upala pokosnice (prekomerno formiranja kosti) i tzv. klabing (oticanje tkiva sa gubitkom normalnog ugla između noktiju i nokatnog ležišta), sa idiopatskim akromegaloidnim promenama udruženim sa hipertrofičnom osteoartropatijom.Češće obolevaju muškarci.

Prikaz slučaja. Bolesnica starosti 55 godina, sa dugogodišnjiim prisustvom maljičastih prstiju i dijagnozom kongenitalne pahidermoperiostoze, koju je postavio fizijatar na osnovu ogovarajućih RTG snimaka još u detinjstvu, prvi put nam se javila 2011. godine; nije se do tada ozbiljnije lečila i ispitivala. Na prijemu je imala bolove u mišičima i zglobovima posebno u predelu malih zglobova šaka i stopala, promene na noktima prstiju stopala i nemogućnost stojanja na ravnoj podlozi, što je primoravalo da nosi samo obuću sa potpeticama. Primetila je tokom poslednjih desetak godina žućkaste deblje naslage na dlanovima i stopalima sa oštećenjem noktiju i deformitetima na prstima šaka i stopala. Takođe, imala je i otežan hod i osećaj bolova u zglobovima kolena, stopala, duž lumbosakralne kičme. Na osnovu priložene dokumentacije došlo se do podatka da je operisala benigne tumore na obe dojke 2003. godine, da se od tada redovno kontrolisala na 6 meseci kod onkologa; iz leve dojke odstranjen je intraduktalni papilom, a iz desne dojke aterom. Tokom narednih kontrola kod onkologa indikovano je odstranjenje novih tumorskih formacija na obe dojke, te je nakon snimanja magnetnom rezonanicijom i histopatološke analize postavljena dijagnoza fibromikrocistične displazije/adenoze, bez prisustva ekspanzivnih promena i indikovane šestomesečne kontrole kod onkologa.

Na osnovu priložene dokumentacije takođe se saznalo da je 2008. godine odstranjena tumorska promena na dlanu desne šake koja je po patohistološkoj analizi odgovarala intradermalnom pigmentnom nevusu i siringomu. Zbog redukovane pasivne i aktivne pokretljivosti desne šake u celini, tada je indikovan i elektromiografski pregled desne ruke: lezija aksonskog tipa srednjeg do težeg stepena mišića C8, Th1 miotoma desnostrano, bez znakova aktuelizacije, što odgovara radikularnom sindromu. Pomoću RTG pregleda utvrđena je difuzna osteoporoza šaka, stopala i kolenih zglobova. Na osnovu merenja mineralne gustine kostiju (BMD) aparatom DEXA (eng. Dual Energy X-ray), isključena je osteoporoza kičmenog stuba.

Iz porodične anamneze saznalo se da je očeva mati bolovala od „kostobolje“ sa promenama i tegobama koije su slične njenim, a da je otac umro od infarkta miokarda. Na prvom pregledu, objektivni fizički nalaz je pokazao da je bolesnica bila u dobrom opštem stanju, ali teško pokretna. Relevantni zaključci su ograničeni na kožu dlanova i tabana, prste i nokte, kao i kosti i zglobove

na rukama i nogama: hiperkeratoza na dlanovima šaka i tabanima sa kliničkom slikom palmoplantarne keratodermije strijatnog tipa; znaci osteoartropatije hipertrofičnog tipa na prstima šaka sa slikom maljičastih prstiju; subungvalna hiperkeratoza na noktima stopala i šaka sa zadebljalim delom, distrofičnim nokatnim pločama žutomrke boje sa pojavom slike onihogripoze – kandžasti nokti; ingvinalna folikularna hiperkeratoza; keratotična i zadebljala koža oko Ahilovih tetiva i na skočnim zglobovima sa otokom skočnih zglobova.

Laboratorijski i drugi nalazi. Imala je abnormalne nalaze: sedimentacija 44/74 mm/h, broj eritrocita 3,19 x 10^{12}/L, hemoglobin: 10,5 g/L, osteokalcin: 54,3 ng/ml (normalno 12–41ng/ml), crossLaps: 572 pg/ml (normalno 162–436 pg/ml). CEA karcinoembrioni antigen 9,7 ng/ml (normalno < 5,0 ng/ml).

RTG snimak šaka i stopala i dugih kostiju: Izražena difuzna osteoporoza snimljenih koštanih struktura. Radiografija šaka: obostrano prisutno suženje proksimalnih interfalangealnih zglobnih prostora, izraženije na III, IV i V prstu desno, kao i na V prstu levo; izrazito suženje svih distalnih interfalangealnih zglobnih prostora, uz subluksaciju distalne falange V prsta desno; na svim prstima pisutna je akroosteoliza distalnih falangi, uz gotovo potpunu lizu distalne falange V prsta leve šake; prisutan otok okolnih mekih tkiva – batičasti prsti. Radiografija stopala: obostrano prisutno suženje talokruralnog zgloba kao i metatarzofalangealnih zglobnih prostora I prsta; na svim prstima je prisutna akroosteoliza distalnih falangi, uz gotovo potpunu lizu distalne falange V, III prsta levog stopala, kao i III, IV i V prsta desno; obostrana periostalna reakcija na kalkaneusu, I metatarzalnoj kosti, izraženije desno, u vidu grubih egzostoza na distalnim glavicama I metatarzalne kosti oba stopala; spina kalkanei obostrano u projekciji plantarne aponeuroze i Ahilove tetive, masivnije desno.

Rtg snimak dugih kostiju: obostrana periostalna reakcija na tibiji, fibuli.

RTG snimak kolena i dugih kostiju: izražena difuzna osteoporoza snimljeih koštanih struktura, obostrano prisutno asimetrično suženje zglobnog prostora tibiofemoranlnog zgloba; periostalne reakcije oba femura i snimkom obuhvaćene tibije i fibule; kalcifikacije u zatkolenim jamama; suženja patelofemoralnog zgloba obostrano.

Mmamografija i UZ dojku: promene odgovaraju fibrocistično izmenjenim dojkama

Rtg srca i pluća u PA pravcu: uredan.

Rtg gastroduodenuma: uredan.

UZ gornjeg abdomena: znaci polipoze i holesteroloze holeciste. Uterus miomatozus je uzgredan nalaz. Nalaz na jetri, pankreasu, bubrezima uredan.

CT toraksa nativno: uredan.

Dupleks sken vena i arterija donjih ekstremiteta: uredan nalaz na arterijama uz nalaz na venama, jedino nešto naglašenijeg Koketovog (Cockett) perforatora levo; u proksimalnom delu natkolenice, femoralno obostrano su vidljivi po jedan uvećan limfni nodus; evidentan je otok mekih tkiva distalno potkoleno, izraženije levo.

Histološki nalaz biopsije sa keratodermijskih promena na dlanovima šaka (tenar leve šake od 27.05. 2011. PH nalaz br.13072/11): epidermis je naglašeno hiperkeratotičan, prominentnog granularnog sloja, izduženih epidermalnih prečki; papilarni dermis je umereno edematozan; kolagena vlakna su grublja i demis je blago povećane debljine; u supkutanom masnom tkivu septa su naglašena i deblja; znojne žlezde su pravilne. Zaključak: promene u dermisu i subdermisu odgovaraju pahidermoperiostozi.

Specijalističke konsultacije: ORL, stomatolog, ginekolog, gastroenterolog, kardiolog, oftalmolog, pulmolog, fizijatar

Radiolog: na osnovu RTG pregleda skeleta, nađene promene na skeletu predominantno na dugim kostima, šakama i stopalima definišu izraženu formu pahidermoperistoze.

Fizijatar: Dolazi u obzir prepisivanje ortopedske obuće po meri sa povišicom. Postoji posturalni disbalans u sklopu osnovne bolesti, maljičasti prsti sa očuvanom funkcijom. Skolioza T4L, desna noga duža, desni kuk višlje postavljen, kontraktura desnog kolena, otoci potkolenica obe noge. Hod izmenjen.

Terapija. Predloženu terapiju sistemskim i lokalnim retinoidima pacijentkinja je odbila. Nakon što su isključeni mogući hronični ili maligni uzroci za sekundarnu hipertrofičnu osteoartropatiju, u terapiju je, pored NSAID i lokalne terapije keratoliticima, uključen tamoksifen (prepisao ginekolog), antiestrogeni lek koji bi mogao biti koristan u tretmanu cistične fibroze dojke i prevenciji karcinogeneze.

Diskusija. Primarna pahidermoperiostoza (PPDP) ili primarni oblik hipertrofične osteoartropatije (PHO), predstavlja retku naslednu bolest za koju je karakteristična trijada: maljičasti prsti na šakama i palčevima stopala, periostoza i pahidermija, kao i povišen nivo prostaglandina E2 (PGE2), što se može smatrati posledicom delovanja citokina na tkiva i krvne sudove. Kod PHO se ova dejstva povezuju sa pojavama hiperhidroze, akroosteolize, pahidermije, periostoze i artritisa. PGE2 može uticati na aktivnost osteoblasta i osteoklasta (odnosno izgradnju i osteoklaziju koštanog tkiva). Iz ovih razloga se akroosteoliza i periostalno

obrazovanje kostiju objašnjavaju dejstvom PGE2. Štaviše, PGE2 ima vazodilatorne efekte, što je u skladu sa produženom lokalnom vazodilatacijom prisutnom u maljičastim prstima. Osim povišenog nivoa PGE2, studije o bolesnicima sa PDP pokazale su i povećane nivoe u plazmi nekoliko drugih mdijatora, kao što su Von Vilebrandov (Von Willebrand) faktor i vaskularni endotelni faktor rasta (VEGF). Ovi medijatori bi mogli imati značajnu ulogu u progresiji i širenju PDP (1). Za razliku od HPGD mutacija, nije do sada utvrđeno postojanje mutacija na genima koji kodiraju sintezu navedenih faktora.

Na osnovu fenotipske ekspresije, razlikuju se tri podtipa PDP: 1) kompletan fenotip, koji u 40% slučajeva može uključivati sve do sada opisane simptome i znake PDP, ali obavezno pahidermiju, periostozu i maljičaste prste, što je puni fenotip bolesti; 2) Nepotpuni fenotip se javlja u 54% slučajeva, a karakterišu ga uglavnom koštane i skeletne promene, dok je pahidermija slabije izražena; 3) frusta fenotip javlja se u samo 6% slučajeva; kliničkom slikom dominiraju promene na koži sa manje izraženim skeletnim promenama i ograničenom periostozom (1). Nepoznat je uzrok nastanka ovako različitih formi bolesti (1). U našem slučaju se radilo o kompletnom fenotipski ispoljenom obliku bolesti udruženom sa palmoplantarnom keratodermijom strijatnog tipa. U 25–38% slučajeva, pacijenti imaju familijarnu pojavu PDP (4), što nije siguran podatak u našem slučaju. Autozomnodominantni model nasleđivanja, sa izrazitom penetrantnošću i varijabilnošću, potvrđen je kod oko polovine porodica sa nepotpunim oblikom bolesti (1). Nekoliko porodica, sa poznatim autozomno recesivnim modelom nasleđivanja, imalo je kompletno fenotipski ispoljen oblik bolesti sa izraženim koštano-skeletnim i kožnim oblikom bolesti. S obzirom na postojanje samo anamnestičkih podataka o pojavi oboljenja samo kod očeve majke, i naša bolesnica mogla se ubrojati u ovu grupu sa recesivnim modelom nasleđivanja PDP.

Biopsija kože predstavlja još jedan način da se dijagnostikuje PDP. Histologija otkriva kutanu sklerozu, hijalinozu, perivaskularni infiltrat limfoidnih ćelija; takođe mogu biti prisutni hipertrofija kolagena i epidermisa i epidermalnih adneksa, kao i povećanje nivoa kiselih mukopolisaharida. Međutim, to nije apsolutno specifičan nalaz, jer se i kod drugih bolesti mogu u koži ispoljiti slične promene kao kod PDP, npr. kod miksedema, hipotireoze, akromegalije. Međutim, biopsija kože pomaže postavljanju dijagnoze PDP u nejasnim slučajevima. Histološki, analiza kože uzete sa keratodermijskih promena na dlanovima šaka kod naše pacijentkinje, zajedno sa promenama u dermisu i subdermisu, koje odgovaraju pahidermoperiostozi, potvrdila je kliničku dijagnozu palmoplantarne keratodermije u sklopu pahidermoperistoze.

Radi postavljanja dijagnoze PPDP, često moraju biti isključene druge bolesti. Na primer, isključuje se sekundarna hipertrofična osteoartropatija u sklopu kardiovaskularnih, plućnih, jetrenih, crevnih i medijastinalnih bolesti. Radi postavljanja diferencijalne dijagnoze, potrebna je detaljna hormonalna pretraga (npr. tirrotropni i nivo hormona rasta) što je je sprovedeno kod naše bolesnice. U našem slučaju isključene su endokrinološke abnormalnosti štitne žlezde.

Kada govorimo o toku i prognozi bolesti, PPDP obično napreduje tokom 5 do 20 godina, dok tok ne postane stabilan. Očekivano trajanje života može biti nepromenjeno, bez obzira na to što bolesnici imaju mnogo funkcionalnih i estetskih komplikacija, uključujući ograničeno kretanje, neurološke manifestacije i „lavlje lice“ sa naborima (*facies leontina*).

Konvencionalna terapija PPDP je u osnovi simptomatska, najčešće se bazira na nesteroidnimantiinflamatornim lekovima (NSAIL) i kortikosteroidima koji se daju sa ciljem smanjenja upale i bola. NSAIL inhibicijom enzima ciklooksigenaze smanjuju nivo prostaglandina. Drugi lekovi se koriste kod bolesnika sa PPDP sa ciljem delovanja na kosti i promene na koži. Retinoidi se koriste prvenstveno za poboljšanje kožnih promena. Infliksimab, biološki inhibitor faktora tumorske nekroze alfa (TNF-alfa) može biti efikasan u resorpciji novostvorene kosti. Hirurški tretman služi za poboljšanje estetskih i funkcionalnih sposobnosti obolelih.

Kada je palmoplantarna strijatna keratodermija u pitanju, do sada nismo našli, u nama dostupnoj literaturi, njenu udruženost sa PPDP. Baro–Klenovsek (Barraud–Klenovsek) objavili su slučaj 30-godišnje žene sa palmoplantarnom keratodermijom i maljičastim prstima 1997. godine. Nedavno, Perić i saradnici, objavili su slučaj pahidermoperiostitisa kod bolesnika sa psorijazom.

Zaključak. U radu je prikazan kongenitalni oblik pahidermoperiostoze kod ženske osobe kod koje se tokom života razvila strijatna keratoderma. Prema nama dostupnoj literaturi, ovo bi bio prvi objavljeni slučaj udružene pojave ove dve dermatoze.

Ključne reči

Primarna hipertrofična osteoartropatija; Palmoplantarna keratodermija; Dijagnoza; Znaci i simptomi; Komorbiditet

A Report on the American Academy of Dermatology 72nd Annual Meeting 2014, Denver, Colorado

More than 14.000 dermatologists from all over the world gathered at the 72nd Annual Meeting of American Academy of Dermatology which took place in Denver, Colorado, USA, from March 21 – 25, 2014. The Academy, with over a 75-year tradition and a membership of over 17.000 dermatologists from the USA and its international affiliates, made it possible for the participants to share the latest news in the field of dermatology.

More than 200 sessions and lectures were given during the five-day event at the Colorado Convention Centre, which is one of the biggest in the USA. Many interesting lectures and novelties in the fields such as allergology, dermatopathology, dermoscopy, dermatooncology, dermatosurgery, pediatric dermatology and aesthetic dermatology were presented.

During the congress, many specialized societies, both American and European, such as International Dermoscopy Society, International Society of Atopic Dermatitis, Society for Investigative Dermatology, Society for Pediatric Dermatology and many others, had their own meetings with their own board members. The International Dermoscopy Society held a joint meeting with the Confocal Group and the Society for Skin Imaging in Sheraton Hotel in Denver on the 22nd of March.

Figure 1. Dr. Danica Tiodorović-Živković in front of the Colorado Convention Center in Denver, Colorado

Figure 2. Dr. Danica Tiodorović-Živković giving a lecture "What's New in the Diagnosis of Lentigo Maligna

Danica Tiodorović-Živković, who is an International Dermoscopy Society Board member and an International Dermoscopy Society representative of Serbia, delivered a lecture titled "What's New in the Diagnosis of Lentigo Maligna". The lecture presented the latest research on lentigo maligna which included more than 200 patients from 4 different countries.

In the field of dermoscopy many interesting lectures were given, including basic and advanced courses on dermoscopy. Numerous interesting dermoscopic case sessions were presented covering pigmented and nonpigmented skin lesions, as well as applicability of dermoscopy in general dermatology.

The next Summer American Academy Meeting will be held in Chicago, from August 6 – 10, 2015.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2014

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
18-20 July, 2014	10th World Congress of the International Academy of Cosmetic Dermatology; Rio de Janeiro, Brazil	No abstract submission	www.iacdrio2014.com.br
3-6 September, 2014	15th World Congress on Cancers of the Skin; Edinburgh, UK	31 March, 2014	www.wccs2014.org
3-6 September, 2014	5th International Conference LaserInnsbruck 2014; Innsbruck, Austria	No abstract submission	www.laserinnsbruck.com
4-7 September, 2014	22nd International Pigment Cell Research Congress 2014**;** Singapore, Singapore	20 June, 2014	www.ipcc2014.org
10-12 September, 2014	35th Symposium of the International Society of Dermatopathology; Jerusalem, Israel	1 July, 2014	www.isd2014.com
18-20 September, 2014	5th World Congress of Teledermatology; Barcelona, Spain	15 July, 2014	www.teledermatology2014.com
18-20 September, 2014	EAACI Skin Allergy Meeting; Krakow, Poland	30 June, 2014	www.eaaci-sam.org
18-20 September, 2014	28th IUSTI Congress Europe 2014; St Julian s, Malta	3 July, 2014	www.iustimalta2014.org
18-21 September, 2014	1st Euro-Asian Melanoma Congress; Sarajevo, Bosnia & Herzegovina	15 June, 2014	www.melanoma.ba
19-20 September, 2014	Perspectives in Melanoma XVIII; Dublin, Ireland	7 August, 2014	www.imedex.com/perspectives-melanoma-conference/
8-12 October, 2014	23rd EADV Congress Amsterdam, Netherlands	7 April, 2014	www.eadvamsterdam2014.org
17 October, 2014	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Novi Sad, Serbia	No abstract submission	www.sld.org.rs
22-24 October, 2014	35th Annual Meeting of the International Society for Dermatologic Surgery'; Jerusalem, Israel	30 June, 2014	www.isdsworld.com
31 October, 2014	Scientific Meeting of the Academy of Medical Science of the Serbian Medical Society; Belgrade, Serbia	No abstract submission	www.sld-rs.org
13-16 November, 2014	11th International Congress of the Society for Melanoma Research; Zurich, Switzerland	19 June, 2014	www.melanomacongress.com

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AUTHOR GUIDELINES

Serbian Journal of Dermatology and Venereology is a journal of the *Serbian Association of Dermatologists and Venereologists*. The journal is published in English, but abstracts will also be published in Serbian language. The journal is published quarterly, and intended to provide rapid publication of papers in the field of dermatology and venereology. Manuscripts are welcome from all countries in the following categories: editorials, original studies, review articles, professional articles, case reports, and history of medicine.

Categories of Manuscripts

1. Editorials *(limited to 5 pages) generally provide commentary and analyses concerning topics of current interest in the field of dermatology and venereology. Editorials are commonly written by one author, by invitation.*

2. Original studies *(limited to 12 pages) should contain innovative research, supported by randomized trials, diagnostic tests, outcome studies, cost-effectiveness analysis and surveys with high response rate.*

3. Review articles *(limited to 10 pages) should provide systemic critical assessment of literature and other data sources.*

4. Professional articles *(limited to 8 pages) should provide a link between the theory and practice, as well as detailed discussion or medical research and practice.*

5. Case reports *(limited to 6 pages) should be new, interesting and rare cases with clinical significance.*

6. History of medicine *(limited to 10 pages) articles should be concerned with all aspects of health, illness and medical treatment in the past.*

7. Short Communications *(limited to 3 pages) should disseminate most current results and developments in the shortest possible time. They will be reviewed by expert reviewers and evaluated by the Editor.*

The journal also publishes book reviews, congress reports, as well as reports on local and international activities, editorial board announcements, letters to the editor, novelties in medicine, questions and answers, and "In Memoriam". All submitted manuscripts will undergo review by the editor-in-chief, blind review by members of the manuscript review panel or members of the Editorial Board. Manuscripts submitted to this journal must not be under simultaneous consideration by any other publisher. Any materials submitted will NOT BE RETURNED to the author/s.

All manuscripts should be submitted to the **Editor in Chief: Prof. Dr. Marina Jovanović***, Clinic of Dermatovenereologic Diseases, Clinical Center of Vojvodina, Hajduk Veljkova 1-3, Novi Sad, Serbia, by mail to: serbjdermatol@open.telekom.rs.*

Manuscripts for submission must be prepared according to the guidelines adopted by the International Committee of Medical Journal Editors (www.icmje.org). Please consult the latest version of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

1. Manuscript Preparation Guidelines

The manuscript should be written in English, typed in double spacing throughout on A4 paper, on one side only; Use Times New Roman, font size 12, with 30 lines and 60 characters per line. Articles must be written clearly, concisely and in correct English. Accepted manuscripts in need of editing will be returned after editing to the corresponding author for approval. When preparing their manuscripts, authors should follow the instructions given in the *Categories of Manuscript:* the number of pages is limited (including tables, figures, graphs, pictures and so on to 4 (four)), and all the pages must be numbered at the bottom center of the page.

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

- The title of the article, which should be informative, without abbreviations and as short as possible;

- A running title (limited to 30 characters);

- Authors' names and institutional affiliations;

- The name, mailing address, telephone and fax numbers, and email of the corresponding author responsible for correspondence about the manuscript. Furthermore, authors may use a footnote for acknowledgements, information and so on.

1.2. Abstracts

A structured abstract in English *(limited to 150 words) should follow the title page. The abstract should*

provide the context or background for the study, as well as the purpose, basic procedures, main findings and principal conclusions. Authors should avoid using abbreviations.

- An **abstract in Serbian language***, (limited to 150 words) should follow the second page. It should contain a briefing on the purpose of the study, methods, results and conclusions, and should not contain abbreviations.*

1.3. A list of abbreviations

Use only standard abbreviations, because use of non-standard abbreviations can be confusing to readers. Avoid abbreviations in the title, abstract and in the conclusion. A list of abbreviations and full terms for which they stand for should be provided on a separate page. All measurements of length, height, weight, and volume should be reported in the metric units of the International System of Units – SI, available at http://www.bipm.fr/en/si/.

1.4. Cover Letter

Manuscripts must be accompanied by a cover letter, which should include a date of submission, statement that the manuscript has been read and approved by all the authors and that the authorship requirements have been met. It should also include the name, address, and telephone number of the corresponding author, who is responsible for communicating with other authors about revisions and final approval of the proofs. The original copy of the cover letter, signed by all authors, should be enclosed with the manuscript.

2. Tables and illustrations

Tables *should capture information concisely and precisely. Including data in tables, rather than in the text, reduces the length of the article itself.*

- Submit tables in separate files, not included in the manuscript. Tables are to be double spaced and numbered sequentially, with Arabic numbers (Table 1, Table 2, etc.), in order of text citation. Each column, including the first, must have a heading. Provide a brief title for each table. Put all explanatory matter in footnotes, including any nonstandard abbreviations used in the table.

- **Figures** should be submitted in a separate file, not included in the manuscript document. Cite figures consecutively, as they appear in the text, with Arabic numbers (Fig. 1, Fig. 2, Fig. 3, etc.). Each figure must be assigned a title, as well as a legend. Legends should appear on a separate page, not with each figure. The **Legend Page** is to be numbered in sequence after the last page of the references list. Figures should be professionally drawn, as sharp black-and-white or color photographs. If photographs of persons are used, either the subjects must not be identifiable, or their pictures must be accompanied by written permission to use them.

3. References

References in the text, tables and legends should be identified by Arabic numerals in parentheses. Number references consecutively in the order in which they are first mentioned in the text. The *Vancouver System* of referencing should be used. List each author's last name and initials; full first names are not included. List all authors, but if the number exceeds six, give the first six followed by „et al." National journals, which are not indexed in *Index Medicus*, should be abbreviated according to the style in the *List of Abbreviated Titles of Yugoslav Serial Publications* available on http://vbsw.vbs.rs. For further information please visit www.ICMJE.org.

4. Additional information

Accepted manuscripts are edited and returned to the corresponding author for approval. Then a final version of the manuscript will be requested in a defined period of time. Authors will be notified of acceptance or rejection by email, within approximately 4 weeks after submission.

- Open access: Every article published in the **Serbian Journal of Dermatology and Venereology** will immediately be accessible on **www.udvs.org** to everyone at no charge.

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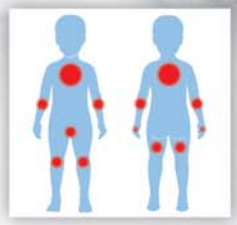

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Cover figure: Christ Healing Ten Lepers, Christ's Miracles, 14th century, The monastery Visoki Dečani, Serbia, Kosovo

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