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 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 planus: 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
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 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).
... 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, dapson, 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.

References
Hipertrofični lihen planus – prikaz slučaja

Sažetak


Lichen planus hypertrophicus je hipertrofična forma bolesti, sa naglašenom epidermalnom hiperplazijom i jakim svrabom. Karakterišu je simetrični hipertrofični plakovi, najčešće lokalizovani pretibijalno i perimaleolarno.

Prikaz slučaja. Prikazuje se 47 godina stara domaćica, sa dobrom opštem stanju; 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, a 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 dubine bolesti u Nišu i jednom na Vojnomedicinskoj akademiji u Beogradu. Primerjena terapija (keratolitici, kortikosteroidi pod okluzijom, retikularne papule na vidljivoj sluzokoži, pruritične poligonalne papule na koži ili mlečnobele lezije su često rezistentne na terapiju. Prikaz slučaja. Prikazuje se 47 godina stara domaćica, dobrog opštem stanju; 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, a kasnije i to na mestu prethodne povrede kože; u porodici nije bilo obolelih srodnika.

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Lichen planus hypertrophicus

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Ključne reči
Lichen planus + fiziopatologija + terapija; Etretinat; Ishod lečenja