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Balneotherapy of Psoriasis

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Abstract

Application of different kinds of mineral waters and peloids on the skin exerts mechanical, thermal and chemical effects. Significant reduction of inflammation and increased differentiation of keratinocytes may explain why balneotherapy has positive clinical effects in psoriatic patients. In vitro models have shown that thermal water stimulates interleukin-2 production after cell stimulation by staphylococcal enterotoxin B, and reduces interleukin-4 secretion. After balneotherapy, a significant decrease in Psoriasis Area Severity Index (PASI), associated with a significant reduction of interleukin-8, Staphylococcus aureus colonization and enterotoxin N, have been reported in patients with psoriasis. Mineral water was found to have inhibitory in vitro effects on substance P, TNF-α release and antigen-induced cell degranulation. Immunomodulatory effects of water depend on its content. Sulfur waters have beneficial anti-inflammatory, keratolytic, and antipruriginous effects and also possess antibacterial and antifungal properties. The effectiveness of balneotherapy in the treatment of psoriasis has been reported in many studies conducted all over the world. The majority of studies were conducted at the Dead Sea coast. Investigations showed that balneotherapy factors are important therapeutic factors in the treatment of psoriatic patients. The first and only comparable study of this kind in Serbia, was conducted in Prolom Spa with satisfactory therapeutic results.

Key words

Balneology; Psoriasis; Mineral Waters; Treatment Outcome; Hydrotherapy; Review

Since the beginning of the time, man has searched for cures for diseases in nature. At first, he empirically came to the conclusion what types and mechanism of action natural factors have on human beings, noticing that not all types of water, air and soil have equal curative effects. Over the time, newer scientific disciplines emerged, studying and comparing different effects of natural, environmental, physical and chemical factors affecting human health. Balneology and balneoclimactology are among them.

Historical Review

The pioneer of modern dermatology, Ferdinand von Hebra (1816 - 1880), Austrian dermatologist, was the first to notice the benefits of mineral water on the psoriatic skin. However, at the same time he became aware that there was no place on Earth that would have a permanent reputation as highly effective in the management of diseases (1). Louis Duhring (1845 - 1913) also discussed the importance of water baths in the treatment of ichthyosis and pemphigus. There are written documents about beneficial effects of sulphur and alkaline waters in the treatment of psoriasis and eczema (2).

Almost all important mineral springs in Serbia have been used since Roman times. Upon their arrival to the Balkan peninsula, the Slavs inherited the practice of using the benefits of mineral springs and great majority of monasteries were founded by the rulers of that time in the vicinity of hot springs. There are not many data about the use of mineral waters in central and southern Serbia in the period of Turkish rule. Immediately after the liberation from the Turks rule, studies on mineral springs in Serbia began once again. In the early 1834, Prince Miloš issued a written notice “to all officers of arms at whose territories there
were mineral springs” to fill a number of jugs and send them to him in Kragujevac, whereby they would be sent to Vienna for analysis. These mineral waters were from Ribarska, Jošanička, Brestovačka, Višnjička and Palanačka spas. In 1851, Prince Aleksandar Karadžorđević formed a Committee for Water Analysis and on its Application for therapeutical purposes. The task of this Committee was to visit and explore mineral springs, their therapeutic properties and write down what diseases they could cure, as well instructions for patients. Increased attention was given to spas by Austria-Hungary, as first descriptions and analyses of peloids originate from these territories in the second half of the 19th century (3). The first law on spas, on mineral and thermal waters was passed in 1914, but due to the war it was put in action 15 years later. After the World War II, the position of spas and health resorts was regulated by the Health Protection Act, thereafter recognized as special health facilities. The first extensive report on the effects of balneotherapy on psoriasis in Serbia was done by Paravina et al. (4).

**Balneotherapy - nomenclature**

In order to avoid inconsistencies in the nomenclature and definitions of terms found in scientific literature referring to balneotherapy, Gomes et al. proposed a glossary that improves scientific communications (5):

Balneotherapy represents a set of methods and practices (bathing, drinking, inhalation, etc.), which use medical mineral waters, medical peloids and natural gases for therapeutic purposes inside the facilities of the Health Resort Medicine Centers;

Hydrotherapy includes use of plain water (tap water) for therapy, through the external application of water and benefiting from its physical properties such as temperature, hydrostatic pressure, viscosity and electric conductivity; bathing, showers, water jets, underwater exercises, and body wraps are some methods of water application; hydrotherapy is commonly used along with pelotherapy;

Medical mineral waters are a group of underground waters, with special physical and chemical properties favorable to the human body, which can be used for prophylaxis and treatment. Mineral water is medically recognized by its special therapeutic properties, or simple health benefits that result from its mineral nature and content in oligoelements or other bio-essential elements;

Thermal waters are currently defined as mineral waters whose temperature, measured at the emergence site, exceeds in 4 °C the mean local air temperature. The terms hyperthermal (>38 °C), mesothermal (36–38 °C) and hypothermal (<36 °C) are used when the temperature of water exceeds 38°C, ranges between 36-38°C, is lower than 36°C, respectively. Nowadays, the concept of thermal water is extended to all mineral waters which independently of the temperature at their emergence sites occur inside the area of the thermal resort and can be used for therapeutic purposes and consumed in the spa of the thermal resort. For therapeutic applications the temperature of mineral water is less important than its chemistry, since mineral water temperature is much more easily changed and controlled, particularly inside the spa;

Peloid is a maturated mud with healing and/or cosmetic properties; peloids are natural products which are a mixture of mineral waters and fine-grained organic and inorganic materials formed under the influence of geological, physical and/or biological and other processes which are used for therapeutic purposes as baths and packs; medical peloids are peloids with specific therapeutic properties recognized by national authorities who approve medicines or drugs based upon epidemiological studies, carried out by physicians specialized in medical hydrology and physiotherapy; medical peloids, hot or cold, should be applied under medical prescription and supervision, depending on the pathology that should be treated; Peloids are two-component systems, comprising a solid phase (inorganic/organic) and a liquid phase (mineral or sea water), the last sometimes including a gas phase (natural gases, SH₂, CO₂, radon). Apart from dermatological diseases, peloid therapy is indicated for chronic rheumatic processes, degenerative osteoarthrosis, sequelae of osteo-articular injuries, fractures, dislocations, disorders following vasculopathies;

Thalassotherapy includes different medical preventive or curative benefits in marine or in high-saline lake environments, including practices such as: heliotherapy (controlled exposure to the sun), psammotherapy (controlled bathing in warm special sands, such as volcanic sand and biogenic carbonate sand) and algotherapy (controlled use of special marine algae), mud therapy (controlled external application
of marine natural peloids), sea bathing, and any other substances of marine origin; peloids containing sea water are also used.

**Impact of balneotherapy factors on the skin**

It is known that application of mineral waters and peloids on the skin exerts mechanical, thermal and chemical effects. It reduces the thickness of the stratum corneum and stratum lucidum of the epidermis, increases the number of lymphocytes, histiocytes and eosinophilic granulocytes, increases skin permeability, reduces inflammation, improves microcirculation and immunity (3).

Thermal water can modulate cell membrane fluidity. Thus, a significant increase in membrane fluidity of fibroblasts, evidenced by decrease in fluorescence anisotropy, is observed. This property may be of interest because membrane fluidity has a significant impact on receptor expression, enzyme activity, pinocytosis, cell migration and cell transport processes (6). In vitro models have shown that thermal water stimulates interleukin-2 production after cell stimulation by staphylococcal enterotoxin B, and reduces interleukin-4 secretion. It has also been demonstrated that thermal water induces secretion of interferon γ after cell treatment with anti CD3 monoclonal antibodies (7). A significant reduction of inflammation has been attributed to balneotherapy: inhibitory in vitro effects on substance P, antigen-induced cell degranulation, as well as TNF-α (8, 9). Some data suggest that thermal water mediates inhibition of TNF-α induced E-selectin and ICAM-1 expression. The inhibition of such adhesion molecules is mediated by suppression of nuclear factor-κB transcription factor, as it has been shown by in vitro model (10).

A study was conducted to evaluate effects of thermal water on keratinocyte differentiation. Three major findings were observed: water accelerates differentiation of normal human keratinocytes, increases expression of differentiation markers and formation of the upper layer; molecular mechanism responsible for mineral water effects on normal human keratinocytes was mediated by enhanced constitutive calcium cell entry that resulted in increased expression of involucrin and cytokeratins 1 and 10; this entry was due to overexpressed activated membrane receptor called transient receptor potential vanilloid 6 calcium channel (TRPV6). By accelerating differentiation and barrier restoration, this channel becomes a target responsible for beneficial effects of balneotherapy on skin lesions, such as psoriasis or atopic dermatitis (11).

After hydrotherapy, a significant decrease in Psoriasis Area Severity Index (PASI) was detected, associated with significant reduction of interleukin-8, enterotoxin N and colonization of Staphylococcus aureus (12).

The immunomodulatory effects of mineral waters depend on their composition. Waters with high contents of sodium bicarbonate and silicon dioxide reduce degranulation of basophils with suppressive effects on cytokine production. These in vitro immunomodulatory effect attributed to selenium, zinc and copper, may be compared with pharmacological effects of local immunomodulators such as imiquimod (13).

Sulfur waters may comprise various combinations of sulfur ions, water, and other ions. Sulfur waters exert beneficial anti-inflammatory, keratoplastic, and antipruritic effects and also possess antibacterial and antifungal properties. The therapeutic action of sulfur water is related to sulfur’s keratolytic effect, resulting in peeling (14). On the immunologic level, sulfur-containing waters have inhibitory effecting on T-lymphocyte proliferative response to mitogens. It has been shown that sulfur waters inhibit the production and release of cytokines in human skin, such as IL-2 and IFN-gamma. According to some authors, these types of waters act mainly on the T-memory cells subset (15). Sulfur mineral waters, used for drinking, have antioxidant properties (16). It has been shown that exogenous hydrogen sulphide reduces clonal growth, cell proliferation and cell adhesion of human keratinocytes in psoriasis, but the role of endogenous sulfur in psoriasis is not well clarified, since reduced level has been reported in patients with psoriasis as compared to normal subjects (17). Results obtained in experimental mouse model proved that hydrogen sulphide in sulfur mineral waters significantly reduces edema, inhibits the vascular phase of allergic contact dermatitis and increases plasma concentration of somatostatin. Since somatostatin is an anti-inflammatory neuropeptide, Boros et al. showed that somatostatin plays an important role in the
Clinical effectiveness of balneotherapy in psoriasis

Psoriasis is among the diseases that are successfully treated with balneotherapy, and its therapy is still the object of numerous studies, particularly those that combine balneotherapy with other therapeutic modalities, eg. phototherapy (13). The effectiveness of balneotherapy in the treatment of psoriasis has been reported in many studies conducted in the world. One study was conducted in Prolom Spa (Serbia), with satisfactory therapeutic results. The study included 35 patients. After one week of using mineral waters and peloids, the PASI score improved by 26.69%, after 2 weeks by 28.60%, after 3 weeks by 38.75% and after 4 weeks by 46.42%; erythema persisted during the first week; significant improvement was noticed after 4 weeks treatment, when PASI was reduced by 41.05%. The effects of treatment on infiltration was noticed after the first and the second week when PASI was reduced by 26.13% and 27.51%, respectively, and it improved as treatment went on; desquamation was significantly decreased after seven days of treatment by 38.26%; females showed better response to therapy and improvement of PASI in the first two weeks of treatment, whereas males responded better in the second two weeks. Prolom water is in the category of sodium hydrocarbonate, silicon, alkaline, oligomineral and hypothermic waters (4).

In Argentina, 55 patients with psoriasis were treated with mineral baths, peloids and/or algae at the Copahue Thermal Complex. The patients took mineral baths twice a day, during 10 days on average. They showed improvement in terms of reduced erythema and desquamation, which was confirmed anti-inflammatory mechanism of action of sulfur medicinal water. In response to 21-day treatment of patients with psoriasis with sulfur medicinal water, dermal pool of dendritic cells almost disappeared and the epidermal populations of Langerhans cells showed normal distribution. Plasma concentration of somatostatin in psoriatic patients was higher than in healthy volunteers, and its level showed a further increase in response to bath treatment (18).

In the treatment of psoriasis, a combination of two balneotherapeutic active principles, namely mineral waters and peloids, is frequently used. Thus, Figures 1 and 2, show our patient after three weeks of treatment in Rusanda Spa (19).

Figure 1. Our patient before treatment in Rusanda Spa
Beneficial effects of balneotherapy have been reported in Bulgaria, with hypothermal water: in Jagoda Spa 54 patients with vulgar psoriasis underwent a combination of balneotherapy, topical dithranol and phototherapy (20-minute baths, then 1.5 to 3% dithranol for 10 to 30 minute and exposure to UV rays with wavelengths of 300 - 340 nm from 1 to 20 minutes); three weeks later, 73.3% of patients showed a significant improvement of skin lesions (21). A study conducted in Marikostinovo Spa included 100 patients treated with a combination of mineral water and sulfide peloids; both procedures lasted 10 to 20 minutes daily, during three weeks; 3% of respondents showed complete regression of skin lesions, in 5% there was a significant improvement, 83% showed moderate improvement, in 5% the therapy showed no effects and in 4% of patients the condition got worse (22).

A large number of investigations worldwide have led to the recognition of beneficial effects of balneotherapy and heliotherapy for chronic stationary psoriasis. The best results were achieved at the Dead Sea in Israel, which is characterized by high salinity (about 30%), high concentration of minerals in the air (magnesium, bromide and other minerals) and more than 330 sunny days per year. The most comprehensive study at the Dead Sea was conducted in 1995, including 1,448 patients with psoriasis. After four weeks of bathing in sea water and sun exposure, 88% of patients showed improvement. The degree of improvement varied from 80% to 100% reduction in PASI score (23). Another prospective study at the Dead Sea included 100 patients with psoriasis, who were treated during four weeks; in 75% of patients there was a complete regression of skin lesions; after the end of therapy, 68% of these patients were in complete remission during the next four months, 43% of patients were in remission after six months, and in 10% of patients complete remission lasted for eight months after the treatment. By monitoring the length of remission after the treatment, it was observed that this period was shorter than after some other forms of therapy, such as cyclosporine or PUVA. Moreover, the efficacy of heliotherapy during four weeks was higher than with UVB phototherapy (24). In patients who bathed in Dead Sea and underwent narrow-band UVB (wavelengths of 311 nm), phototherapy three to five times per week, after 35 treatments, PASI score decreased from 17.7 to 5.2; the most common side effect of this therapy was rash, found in 87% of patients.
patients; after the treatment, 55% of patients had recurrence after six months, and 68% of patients after one year (25). Using retrospective data, David et al. concluded that guttate and chronic plaque psoriasis showed the highest benefit from balneotherapy at the Dead Sea; moderate improvement was seen in flexural psoriasis and palmar-plantar psoriasis; scalp and erythrodermic psoriasis were mostly unresponsive, whereas in generalized pustular psoriasis balneotherapy was contraindicated (26).

Harari et al. conducted a prospective non-randomized study on the efficiency of balneotherapy at the Dead Sea including 740 psoriatic patients. Complete clearance after 4 weeks of natural balneotherapy and heliotherapy (controlled exposure to sun) was reported in 70% of patients (27). A retrospective analysis included 605 patients treated at the Dead Sea for plaque psoriasis. Patients with early-onset of psoriasis (under 40 years of age), achieved better results following Dead Sea climatotherapy (28).

A prospective non-randomized study on the efficacy of climatotherapy at the Dead Sea for pediatric-onset psoriasis vulgaris, studied 17 children between 10 and 18 years of age; six months after the treatment period, 12 patients were relapse-free, and five had a mild relapse; improvement in PASI score over 75% and between 50% and 75% was noted in 35.3% and 29.4% of patients, respectively (29). Studying skin biopsies of psoriatic patients before and after climatotherapy at the Dead Sea coast, Hodak et al. reported significant reduction in the number of activated T-lymphocytes in the epidermis (depletion of more than 90% of CD3+ and CD25+ cells) and in the dermis (depletion of 69.4% of CD3+ and of 77.4% CD25+ cells); there was also a marked reduction in HLA-DR expression in keratinocytes (30).

A combination of three beneficial factors for psoriasis: sun, sea water and air, has been studied in patients with psoriasis at the Black Sea in Bulgaria. In a group of 177 patients, the therapy lasted 20 days and covered sun exposure of 5 - 6 hours and bathing in the sea water from 5 - 15 minutes a day; complete regression of skin lesions was found in 68.9% of patients, significant improvement in 17.1% and moderate improvement in 9.5% of patients; only 4.5% of patients did not respond to the therapy: patients with acute guttate type improved more quickly compared to those with other types of psoriasis (plaque, geographical, palmo-plantar, inversa and inveterata) (31).

In German rehabilitation centers, balneophototherapy is a phototherapeutic modality, a combination of salt water baths and artificial UV radiation. A prospective, randomized, blind, right/left comparison investigating the efficacy of balneophototherapy in psoriasis with highly concentrated salt water versus tap water, was performed in patients with chronic plaque psoriasis: one elbow was soaked in 24% NaCl solution and the other in tap water, subsequently, broadband UVB irradiation was administered on both. Balneophototherapy was performed 4 times weekly with a total of 30 treatments; a highly significant (p<0.001) decrease of the baseline score was observed after 30 treatments; however, there was no significant (p>0.5) difference in clearance of lesions between sites soaked in salt water and tap water (32).

During balneotherapy of psoriasis, some studies have investigated the influence of natural factors on psychosomatic and somatopsychological factors of patients with psoriasis. About 45% of psoriatic patients feel inadequate and are socially isolated (p<0.001). Depressive disorders were detected in 66% of patients with psoriasis prior to a 20-day thalassotherapy at the Bulgarian Seaside. Common complaints among patients with different levels of depression were the following: fatigue (57%), bitterness (50%) and sleeping disorders (46%). After the course of treatment, 63.6% of patients with depression showed no psychological abnormalities (euthymic state) (33).

Conclusion

Due to the multidisciplinary character of balneotherapy and its applications in patients with psoriasis, it is necessary to consider therapeutic methods used in balneotherapy complementary to the well known methods used in health resorts. The best effects are achieved when these methods are combined. Further controlled studies are required to ascertain the best treatment regimens and duration of their administration.

Abbreviations

PASI - Psoriasis Area Severity Index
TNF-α - tumor necrosis factor-alpha
References


Balneoterapija psorijaze

Sažetak


Uticaj balneoterapijskih činilaca na kožu. Poznato je da mineralne vode i peloid aplikovani na kožu ispoljavaju mehaničko, termičko i hemijsko dejstvo. Rezultati dosadašnjih istraživanja pokazali su da primena mineralnih voda i peloida smanjuje debljinu stratuma korneuma i stratuma luciduma u epidermisu, povećava broj limfocita, histiocita i eozinofilskih granulocita, povećava permeabilnost kože, redukuje aktivnost zapaljenskih procesa, poboljšava mikrocirkulaciju i povoljno deluje na imunske procese. Uticaj na diferencijaciju keratinocita objašnjen je istraživanjima koja su vršena u poslednjih nekoliko godina. Značajno smanjenje PASI (Psoriasis Area Severity Index) skora kod bolelih od psorijaze povezuje je sa značajnim smanjenjenjima nivoa intreleukina 8, kolonizacije bakterijom Staphylococcus aureus i endotoksina N posle balneoterapije. Imunomodulirajući efekat mineralnih voda zavisi od njihovog sastava, a posebno mesto imaju sumponne vode koje deluju antiinflamatorno, keratolitički, antiruriginozno, antibakterijski i antifungalno.


Ključne reči

Balneologija; Psorijaza; Mineralne vode; Ishod lečenja; Hidroterapija; Pregled literature
Cutaneous Manifestations of Toxoplasmosis: a Case Report

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Abstract

Although toxoplasmosis is one of the most widely spread infections in the world, types that involve the skin are extremely rare. However, skin lesions are not specific; moreover, they are quite diverse, which makes the diagnosis of cutaneous toxoplasmosis rather difficult. Thus, differential diagnosis should include a number of other diseases. We present a case of a 43-year-old immunocompetent man with multiple livid erythematous papules and nodules with yellowish discharge that involved the skin of the body and the extremities. By using electro-chemiluminescence immunoassay, immunoglobulin G antibodies to Toxoplasma gondii were detected in the serum, confirming the diagnosis of toxoplasmosis. The treatment with pyrimethamine and trimethoprim-sulfamethoxazole led to complete resolution of skin lesions. In conclusion, although rare in the dermatological practice, cutaneous toxoplasmosis should be considered in all patients presenting with lymphadenopathy, non-specific skin eruptions, especially nodular and colliquative, blood eosinophilia and histological findings revealing abundant eosinophilic infiltrations.

Key words

Toxoplasmosis; Signs and Symptoms; Skin Manifestations; Pyrimethamine; Trimethoprim-Sulfamethoxazole Combination; Treatment Outcome

Toxoplasmosis is a parasitic disease caused by the protozoan Toxoplasma gondii, a tiny crescent shaped parasite (1). There are 3 genotypes of T. gondii, which cause different clinical manifestations and distribution. The main reservoirs are Toxoplasma cysts found in the cat feces. However, other mammals including humans, can also be infected. The main mechanisms of transmission to humans include consumption of infected undercooked meat or ingestion of ova via contaminated food or water. Other possible mechanisms of transmission are via organ transplantation (2, 3), blood transfusion (4) and transplacental transfer. The parasites form cysts, usually found in the muscles, heart and brain. They also invade the reticuloendothelial system, as well as the endothelium of blood vessels where they form granulomas and later necrosis.

There are three main types of toxoplasmosis in humans:

1. Fetal infection - which may result in severe brain damage, chorioretinitis or stillbirth;

2. Acquired infection - which is asymptomatic in up to 90 % of patients. Cutaneous manifestations are very rare. A small number of patients present with cervical lymphadenopathy and flu-like symptoms. It is estimated that approximately one third of the world population is infected with T. gondii. Ocular disease, is usually due to reactivation of fetal infection (1).

3. Toxoplasmosis in immunocompromised patients - which is often a result of activation of a latent disease and clinical manifestations include papular and nodular eruptions as well as encephalitis. It usually occurs in patients with defects of T-cell–mediated immunity, including patients with hematologic malignancies and transplantations, as well as human immunodeficiency virus (HIV)-infected patients who often develop encephalitis (1).

Case Report

A 43-year-old man complained of skin eruptions which appeared 3 years earlier. He noticed livid spots
and nodules on the skin of the lower extremities with subsequent spreading to the skin of the body and arms, accompanied by moderate itching.

The patient was in good health, afebrile, and physical examination revealed no abnormalities.

Multiple livid erythematous papules with peripheral scaling and livid nodules, some with central depression expressing yellowish discharge, were observed on the skin of the ears, body and upper and lower extremities (Figures 1-3). Postlesional hyperpigmented macules were also present. Two non-tender, soft lymph nodes 1.5 cm in diameter were palpable in the inguinal regions.

Routine laboratory and other relevant tests were within normal limits, except for the white cell count which showed leukocytosis with eosinophilia: total white blood count 23.84 x10^9/L, with a differential of: neutrophils 28%, lymphocytes 45.5%, eosinophils 19.2% (4.6 x10^9/L), monocytes 3.4%, basophils 1.5%.

A punch biopsy was performed and histological examination revealed: hyperkeratosis, hypergranulosis, and acanthosis of the epidermis (Figure 4a); in the dermis and upper hypodermis, there was a thick infiltrate, pronounced in the deep dermis (Figure 4b);
deep dermal infiltrate with numerous eosinophils, histiocytes, lymphocytes, plasmocytes and foreign-body giant cells was also observed (Figure 4c); dermal collagen appeared rough and fibrotic (Figure 4d), and a scaring tissue was present as well. However, *T. gondii* zoites were not found.

Due to the finding of a dense eosinophilic infiltrate and an increased number of eosinophils in the blood, the patient was examined by a hematologist and bone marrow examination was performed. The bone marrow was normocellular with a myeloid to erythroid ratio of 3:1; granulocytes of all stages maturation were seen; the blast cell count was under 5%; the eosinophil count was 5%; the megakaryocyte count was slightly increased. According to the hematologist, there were no abnormalities suggesting a lymphoproliferative process. Taking into account the patient’s complaints, the appearance of lesions and laboratory test results,
a parasitic disease was suspected. No intestinal parasites were detected. Serologic testing for *Echinococcus granulosus* antibodies was negative. However, by using ECLIA (electro-chemiluminescence immunoassay), immunoglobulin G (IgG) antibodies to *Toxoplasma gondii* were detected in the serum with an elevated titer of 598 IU/ml (normally < 1 IU/L). HIV testing was negative. After consulting a parasitologist, treatment with Daraprim® tbl (pyrimethamine) 2 x 25 mg/d and Biseptol® (trimethoprim-sulfamethoxazole) 2 x 960 mg/d p.o. were initiated in three courses of 5 days with 14-days intervals between them. The eruptions resolved completely leaving scars and postinflammatory hyperpigmented macules (Figures 5-12). One month later, the titer of antibodies decreased significantly to 1:80.

**Discussion**

Although toxoplasmosis is a common infection, affecting about 1/3 of the world population, it is asymptomatic in most cases. *T. gondii* was first observed by Nicolle and Manceaux in 1908 in a North African rodent, *Ctenodactylus gondii* (5). In 1939, it was identified as the cause of severe congenital syndrome by Wolf, Cowan, and Paige (6).
Cutaneous toxoplasmosis is usually found in patients with a compromised immune system, such as transplanted patients or patients having acquired immunodeficiency syndrome (AIDS). Cutaneous lesions are rarely observed in immunocompetent patients. In 2002, Bossi described acute disseminated toxoplasmosis in 3 patients with normal immune system with maculo-papular rash and systemic symptoms (18).

Although demonstration of the organism in biopsy of lymph node, liver or spleen, bone marrow, or in cerebrospinal and ventricular fluid confirms toxoplasmosis, the diagnosis is usually based on clinical evidence, and confirmed serologically (1).

Up to now, only few cases of disseminated cutaneous nodular toxoplasmosis in immunocompetent patients have been described in the
literature. We report a case of nodular cutaneous toxoplasmosis in a young patient without concomitant diseases. The diagnosis was confirmed serologically. The patient was treated with sulphonamides and pyrimethamine (Daraprim) which as it has been reported act synergistically and are effective (1).

**Conclusion**

Although rare in the dermatological practice, cutaneous toxoplasmosis should be considered in all patients presenting with lymphadenopathy, non-specific skin eruptions, especially nodular and colliquative, blood eosinophilia and histological findings of abundant eosinophilic infiltrations.

**Abbreviations**

- HIV - human immunodeficiency virus
- CRP - C-reactive protein
- ECLIA - electro-chemiluminescence immunoassay
- IgG - immunoglobulin G
- AIDS - acquired immunodeficiency syndrome

References

Keratosis Lichenoides Chronica – a Case Report and Literature Review

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Abstract

Keratosis lichenoides chronica represents a distinct entity, a rare disease of unknown etiology and pathogenesis, with clinical manifestations which, although typical, require extensive differential diagnosis. The course of the disease is chronic, progressive, and it is resistant to various treatment options, so despite variations in the clinical picture it is really easier to diagnose than to treat. This is a case report of a male patient in whom the diagnosis of keratosis lichenoides chronica was based on typical clinical picture, repeated biopsies and histopathological findings, course of the disease and poor response to any therapy.

Key words
Keratosis; Lichenoid Eruptions; Signs and Symptoms; Disease Progression; Diagnosis; Diagnosis, Differential; Treatment Outcome; Review

The idea for this paper on keratosis lichenoides chronica (KLC) was born after the first visit of a patient with an unusual clinical picture resembling both psoriasis and lichen planus, but also distinct from them, posing a diagnostic and therapeutic dilemma. After a consultation with Prof. Danilo Stevanović, whom we hereby wish to thank, and repeated histopathological examinations, the diagnosis of keratosis lichenoides chronica was confirmed. Papers of Böer (1), Massi et al. (2) and Ackerman et al. (3) have encouraged us to continue our analysis of published papers.

Case report
Case history
We report a 40-year old man who developed skin lesions on the trunk and extremities more than 10 years earlier: asymptomatic, symmetrically distributed linear and reticular red to purple papules with white scaly surface. Before the appearance of skin lesions, the patient's history was unremarkable and he denied taking any medications. He was treated under the diagnosis of psoriasis vulgaris, and lichen verrucosus. In 2014, he underwent phimosis surgery. There was no family history of skin conditions.

Examination
On admission, the patient presented with symmetrical generalized eruptions of erythemolivid to dark livid papules and nodules with a keratotic surface, in a solitary, linear or reticular pattern on the lower lateral parts of the trunk and along the extremities (Figures 1-3); the infiltrated lesions were prominent, verrucous and hyperkeratotic. Mild erythematousquamous lesions were present on the face. Solitary erythematous papules on erythematous base...
were seen on the dorsal aspects of the feet (Figure 4), as well as palmoplantar focal hyperkeratosis. Hyperkeratotic papules were found on the preputium and scrotum preventing normal retraction over the glans (Figures 5-7).

**Laboratory and histopathological tests**
Relevant laboratory tests, including serologic tests for human immunodeficiency virus type 1 (HIV-1), hepatitis viruses and syphilis were within normal limits.

**Figure 1.** Skin lesions on the trunk and arms

**Figure 2.** Lesions on the lateral aspects of the trunk

**Figure 3.** Lesions on the posterior aspects of lower extremities

**Figure 4.** Lesions on the dorsal surface of the feet
Histopathological analysis of skin specimens was repeated several times: in 2004, findings pointed to psoriasiform dermatitis and later to lichenoid dermatitis; in 2009, they pointed to hypertrophic lichen planus, and in 2010 to pityriasis lichenoides. Histopathological analysis of the lower limb skin specimens performed in 2009 showed: irregular epidermal acanthosis, variable atrophy, moderate ortho-parakeratosis; telangiectasias and both superficial and deep inflammatory infiltrates in the dermis (Figure 8). Higher microscopy magnification showed vacuolar degeneration of the basal layer and distinct hyaline bodies ("civatte bodies") (Figure 9). Histopathological analysis of the preputium tissue was performed in 2014: epidermis showed irregular acanthosis, hyperkeratosis and focal parakeratosis; telangiectasia and abundant inflammatory infiltrates in the dermis (Figure 10). Higher magnification revealed irregular acanthosis, hyperkeratosis and focal follicular parakeratosis, vacuolar alteration of the basal layer of the epidermis with telangiectasia and abundant inflammatory infiltrates including lymphocytes and plasma cells in the upper dermis (Figures 11, 12).

**Diagnosis and therapy**

The diagnosis of keratosis lichenoides chronica was based on typical clinical picture, repeated biopsies and histopathological findings, course of the disease and poor response to any therapy. Systemic corticosteroid therapy, UVB irradiation, topical corticosteroids and salicylic acid did not provide satisfactory results. The use of acitretin, at an initial dose of 0.3 mg/kg/bw which was increased to 1 mg/kg/bw, showed minimal therapeutic effects (Figures 13, 14).

**Literature review**

Keratosis lichenoides chronica is a rare, chronic, and progressive dermatosis of unknown origin (4, 5), characterized mostly by asymptomatic, papular or nodular lesions, in a linear or reticular pattern, symmetrically distributed on the trunk and extremities; facial lesions resemble seborrheic dermatitis or rosacea, but they may involve palms, soles, nails as well as oral, pharyngeal, laryngeal, ocular and genital mucous membranes (6 - 13).
The first description of a patient with the clinical picture of KLC was given by Kaposi in 1886 (14) under the diagnosis of "lichen ruber moniliformis". However, in 1895, two patients with similar lesions were diagnosed with "lichen ruber acuminatus (verrucosus et reticularis)" (15). Further confusion
over the name of the disease occurred in 1938 (16) when Nekam reported Kaposi’s case from 1895 as “porokeratosis striata lichenoides.” Since 1972, the term “keratosis lichenoides chronica”, suggested by Margolis (17) for patients with a typical clinical picture, has been generally accepted for this condition, but in the meantime there were new terms as well. There are papers with terms "lichenoid trikeratosis” (18) ”keratosis lichenoides striee” (19), and ”dermatose papulohyperkeratosic en striée” (20).

Papers published on keratosis lichenoides chronica or synonyms from 1886 to 2014

To the best of our knowledge, in the last 128 years (1986 - 2014), 120 papers were published with keratosis lichenoides chronica or its synonyms as a topic (Table 1) (14 - 123).

In seven papers (26, 27, 29, 30, 60, 75, 93) KLC is referred to as Nekam’s disease.

The etiology of the disease has not yet been identified. Mode of inheritance, influence of any other genetic alteration, relationship with any drugs or infection, has not been defined (1). The most common factors causing KLC as a variant of lichenoid drug eruption are antimalarials, antituberculosis agents (11, 20, 123), and tetanus antiserum (18); KLC may also be induced by mechanical skin damage, for example after trauma or skin transplantation (50, 84), or it is a cutaneous manifestation of toxoplasmosis (27).

The pathophysiology of KLC is not known (110). Some conditions associated with KLC, mentioned in the literature thus far, include appearance after drug-induced erythroderma (82), prolonged exposure to a source of heat (infrared radiation) (95); association with multiple eruptive keratoacanthoma-like lesions in patients with multiple myeloma (100), in patients with atypical sarcoidal granulomatous inflammation (107), or hypothyroidism (89), tuberculosis (10), kidney diseases, diabetes, lymphoma (81), toxoplasmosis (27), mycosis fungoides (78), multiple sclerosis (68) hepatitis (57, 70), lesions mimicking verrucous secondary syphilis (91), primary cutaneous anaplastic large cell lymphoma (122), atopic dermatitis (5, 10), allergic rhinitis, (3), and neurological diseases (11). However, significant association between KLC and internal diseases has not been established (87).

It has been a subject of controversy whether KLC is a distinctive inflammatory disease of the
skin or whether it represents a manifestation of another well-known disease, such as lichen planus, lupus erythematosus, or lichen simplex chronicus. These dilemmas have existed for years: whether KCL represents an inherited type of epidermolysis bullosa (54), a disseminated variant of inflammatory linear verrucous epidermal nevus (ILVEN) (71), a variant of lichen planus (10, 41, 50, 74, 77, 86, 99, 107), or a transition of lichen planus to KLC, due to an increase in the number of focuses (109). Strong similarity between KLC and lupus erythematosus has been established (120). Basically, the condition may have an authentic disease underlying, such as lichen planus, lupus erythematosus, pityriasis vulgaris, or pityriasis rubra pilaris, which explains variations of histopathological findings (3).

However, it is an authentic pathological process (71), a distinct entity (1, 11), which is characterized by linear lesions, absence of Wickham’s striae, long-term evolution, lack of response to corticosteroids (9), and differs from lichen planus, lupus erythematosus, pityriasis lichenoides, pityriasis rubra pilaris, psoriasis vulgaris, porokeratosis, mycosis fungoides, and porokeratosis variegata. KLC is generally considered a distinct dermatologic disease due to typical clinical and histopathological features (13).

Differential diagnosis includes lichen planus and lichen planopilaris, lupus erythematosus, pityriasis lichenoides, pityriasis rubra pilaris, psoriasis vulgaris, mycosis fungoides (78), lichenoid drug reactions (18), lichen hypertrophicus, parapsoriasis variegata, keratosis follicularis, epidermolysis bullosa pruriginosa, Reiter's and Kyrle's disease (5, 11, 53, 58, 98, 105, 117).

A full description of histopathological features of KLC was given by Böer (1): vacuolar alteration of keratinocytes along the dermo-epidermal junction;

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of papers</th>
<th>Time period</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichen ruber moniliformis</td>
<td>4</td>
<td>1886-1955</td>
<td>14, 21-23</td>
</tr>
<tr>
<td>Lichen ruber acuminatus</td>
<td>1</td>
<td>1895</td>
<td>15</td>
</tr>
<tr>
<td>(verrucosus et reticularis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lichen verrucosus et reticularis</td>
<td>5</td>
<td>1944-1984</td>
<td>24-28</td>
</tr>
<tr>
<td>Porokeratosis striata</td>
<td>3</td>
<td>1938-1983</td>
<td>16, 29, 30</td>
</tr>
<tr>
<td>Lichenoid trikeratosis</td>
<td>1</td>
<td>1974</td>
<td>18</td>
</tr>
<tr>
<td>Keratosis lichenoides striata</td>
<td>9</td>
<td>1974-1989</td>
<td>19, 31-38</td>
</tr>
<tr>
<td>Dermatose papulohyperkeratotic en striaes</td>
<td>1</td>
<td>1970</td>
<td>20</td>
</tr>
<tr>
<td>Keratosis lichenoides chronica</td>
<td>89</td>
<td>1972-2014</td>
<td>1-4, 6, 9-13, 17, 39-123</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>1886-2014</td>
<td>14-123</td>
</tr>
</tbody>
</table>
numerous necrotic keratinocytes, sometimes in clusters, in surface epidermis and infundibular epidermis, especially in the lower parts; atrophy and sometimes erosion of epithelium in foci where there are many necrotic keratinocytes; irregular focal acanthosis; infundibular keratotic plugs of hair follicles and around acrosyringia; parakeratosis in staggered fashion; remnants of neutrophils in zones of parakeratosis; hypogranulosis beneath zones of parakeratosis; plasma cells in the infiltrate zones adjacent to erosions. Lichenoid infiltrate is found under the epidermis, often centered around an infundibulum or an acrosyringium; foreign body reaction is consequent to rupture of dilated infundibula and spewing of their contents into the dermis. Basically, it is a lichenoid dermatosis with irregular acanthosis, focal parakeratosis, variable atrophy, vacuolar degeneration of the basal layer and keratinocyte necrosis, chronic inflammatory infiltrate in the papillary dermis consisting lymphocytes, histiocytes, plasma cells and eosinophils and colloid bodies (“Civatte bodies”) (67, 82, 86, 101, 107, 108, 110, 111, 113, 115, 120, 122).

KLC should be differentially distinguished from hypertrophic lichen planus: KLC is characterized by mild papillomatosis, focal parakeratosis, variable atrophy and epidermal acanthosis, vacuolar basal cell degeneration, superficial dermal telangiectasias; hyperkeratotic lichen (lichen verrucosus) is found in the epidermis and it is associated with compact orthokeratosis, papillomatosis, prominent irregular acanthosis and vacuolar basal cell degeneration.

In our patient, histopathological findings were consistent with KLC.

Due to a large number of conditions considered in the differential diagnosis and a possibility of comorbidity of two or more dermatoses (3), it sometimes happens that the patient actually suffers from a dermatosis other than KLC (1).

Patients reported under a controversial diagnosis of keratosis lichenoides chronica (KLC)/or synonyms in the period 1886 - 2005

After analyzing the available literature, Böer (1) wrote a critical review of studies published in the period from 1886 to 2005. He found that a certain number of patients included in these studies should have been diagnosed with keratosis lichenoides chronica, no matter if they had characteristics of other similar diseases or if there was a lack of evidence for a reliable diagnosis (Table 2). According to Böer, out of the total number of patients reported from 1886 - 2005 under the controversial diagnosis of KLC or its synonym, there were 23 (34.33%) who suffered from other diseases, 20 (29.85%) with a lack of evidence for the diagnosis, while 24 (35.82%) patients suffered from keratosis lichenoides chronica, more or less certainly (Table 2) (1).

In his analysis, Böer argued that the diagnosis of KLC should be made only for patients presenting with at least two clinical and one histological feature: 1. chronic facial lesions reminiscent of seborrhoeic dermatitis; 2. tiny papules on the trunk and extremities, which assumed linear and reticulate shapes by way of confluence of lesions, with infundibulocentric papules and papules around acrosyringia; 3. histological feature: lichenoid dermatitis with numerous necrotic keratinocytes and parakeratosis. Among other characteristics, there may be mucosal involvement, including conjunctival hyperemia, but they are not indicative (1).

According to the findings of Böer (1), KLC affects men and women equally, mostly adults. Anamnestic data show that lesions often persist for years before diagnosis. The lesions are found on the face, extremities, especially on the acral regions, less often on the trunk, while mucous membranes are affected in 25% of patients. The lesions may be discrete, individual, linear or circular, atrophic, with erosions or crusts, forming keratotic papules or plaques. Pruritus is present in less than 20% of patients. Deviations from laboratory findings are nonspecific and are of no diagnostic value. The course of the disease is protracted, while complete resolution has never been reported.

Patients reported under a controversial diagnosis of keratosis lichenoides chronica (KLC)/or synonyms in the period 1886 - 2014

Although a review of the available literature revealed about 120 papers on KLC, certainly with a larger number of patients, Böer’s analysis (1) shows that the actual number of patients suffering from KLC in the period from 1886 to 2014 cannot be determined with certainty.

In order to get information about the patients and characteristics of KLC, we have reviewed 98
Table 2. Patients reported under a controversial diagnosis of keratosis lichenoides chronica (KLC)/or synonyms in the period 1886 – 2005*

<table>
<thead>
<tr>
<th>Diagnosis*</th>
<th>References</th>
<th>Time period</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis atopica</td>
<td>70</td>
<td>1996</td>
<td>1</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>57, 80, 84, 95, 97</td>
<td>1989-2005</td>
<td>5</td>
</tr>
<tr>
<td>Porokeratosis</td>
<td>18</td>
<td>1974</td>
<td>1</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>27, 28</td>
<td>1976, 1984</td>
<td>2</td>
</tr>
<tr>
<td>Lichen simplex</td>
<td>27, 43, 89</td>
<td>1976-2002</td>
<td>3</td>
</tr>
<tr>
<td>Subepidermal bullous dermatosis</td>
<td>54</td>
<td>1986</td>
<td>1</td>
</tr>
<tr>
<td>Unclarified diagnosis</td>
<td>11, 13, 25, 27, 29, 49, 58, 62, 71, 72, 74, 76, 86, 94,</td>
<td>1954-2004</td>
<td>16</td>
</tr>
<tr>
<td>Keratosis lichenoides chronic (KLC)</td>
<td>24, 31, 45, 48, 73, 77, 79, 96</td>
<td>1981-1999</td>
<td>8</td>
</tr>
<tr>
<td>Possible KLC</td>
<td>20, 38, 97</td>
<td>1970-2005</td>
<td>3</td>
</tr>
<tr>
<td>Probable KLC</td>
<td>16, 17, 18, 26, 27, 41, 47, 71, 91</td>
<td>1938-2003</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis atopica</td>
<td>15</td>
<td>1895</td>
<td>1</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>12, 81, 85</td>
<td>1982/2001</td>
<td>3</td>
</tr>
<tr>
<td>Lupus erythematodes</td>
<td>46, 59</td>
<td>1981, 1993</td>
<td>2</td>
</tr>
<tr>
<td>Subepidermal bullous dermatosis</td>
<td>40</td>
<td>1976</td>
<td>1</td>
</tr>
<tr>
<td>Lichen simplex</td>
<td>33</td>
<td>1997</td>
<td>1</td>
</tr>
<tr>
<td>Verrucae vulgaris</td>
<td>41</td>
<td>1995</td>
<td>1</td>
</tr>
<tr>
<td>ILVEN</td>
<td>71</td>
<td>1997</td>
<td>1</td>
</tr>
<tr>
<td>Unclear</td>
<td>44, 60, 71</td>
<td>1973-1993</td>
<td>4</td>
</tr>
<tr>
<td>KLC</td>
<td>59, 71</td>
<td>1993, 1997</td>
<td>2</td>
</tr>
<tr>
<td>Probable KLC</td>
<td>69</td>
<td>1996</td>
<td>1</td>
</tr>
<tr>
<td>Possible KLC</td>
<td>34</td>
<td>1983</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Adults + children</td>
<td></td>
<td></td>
<td>67</td>
</tr>
</tbody>
</table>

* Böer A. 2006 (1); KCL, keratosis lichenoides chronica; ILVEN, inflammatory linear verrucous epidermal nevus
papers published in the available literature in the period from 1886 to 2014, including a total of 115 patients (Table 3). Adult patients in whom the disease began in childhood were grouped as children. The disease is more common in males. The male to female ratio was around 1.97: 1 with male predominance (in children and adults, the ratio was 1.62:1 and 2.17:1, respectively). According to our analysis, the average age of KLC onset was 37 years (in children and adults it was 15 and 47 years, respectively). According to data from 1995 (10), KLC was also more common in males (the male to female ratio was 1.35:1), usually affecting people aged between 20 and 40 years of age, with an average age of onset of 28.5 years (10). According to data from 2010, the age of disease onset was between the ages of 20 to 50 years (110). Clinical signs of the disease are most typical among adolescents and young adults (107). The fact that KLC is uncommon in pediatric population (63, 66, 90) is not fully in agreement with our findings. It would be more precise to claim that it is less common in children, considering the fact that in 31.48% of patients the onset of the disease was in childhood. The rarity of pediatric cases may be due to late diagnosis, rather than actual low incidence among children (90). KLC rarely affects several persons from the same family (59, 106); only 10 (8.70%) cases have been reported so far, all being affected in childhood, while congenital cases were described only in 4 (3.48%) patients (Table 3).

Table 3 shows that KLC lesions are most commonly found on the extremities, both in children and adults, whereas 40% of patients present with palmoplantar hyperkeratosis; facial lesions are more common in adults than in children; nail lesions are more common in adults, affecting over 30% of patients, presenting as yellow discoloration, thickening and longitudinal ridging of the nail plate and nail bed hyperkeratosis; oral lesions are more common in adults than in children; ocular lesions include blepharitis, conjunctivitis, anterior uveitis and iridicyclitis which affect both children and adults; genital lesions, including keratotic papules on the scrotum and penis, chronic balanitis and phimosis, have been reported in 9.88% of adults, but in children they have not been described; pruritus occurs in less than 20% of patients, both in children and adults (Table 3).

Facial reticular lichenoid eruptions (121), vascular variant of the disease with telangiectasia (57, 89), purpura (111), as well as unilateral distribution of lesions (64) have been reported in the literature, although less commonly (124).

Based on the analysis of reported cases of KLC in adults and children, Ruiz-Maldonado et al. (9) pointed out clearly defined several characteristics of the disease that only occur in patients in whom the disease started in childhood: occurrence of the disease in members of the same family (autosomal recessive inheritance); in children, lesions including erythematous purpuric macules always appear first on the face with subsequent hyperpigmentation; alopecia has only been described in children.

The disease proved to be resistant to various therapeutic regimes, both topical and systemic (107). The following therapeutic modalities proved to be inefficient: systemic and topical corticosteroids, systemic antimalarials, diaminodiphenylsulfone, tetracyclines, cyclosporine, methotrexate (90, 91). Various results were obtained with systemic administration of acitretin, isotretinoin, etretinate, psoralen ultraviolet A radiation (PUVA), retinoids combined with PUVA or with narrow-band ultraviolet B radiation (NB-UVB) (4), as well as topical calcipotriol (89, 98) and NB-UVB monotherapy (106). NB-UVB has proven more effective in the treatment of children than adults (117). Significant improvement has been achieved with photodynamic therapy (104) and treatment with efalizumab (107). According to Ghislain (87), PUVA therapy is the first line therapy for this rare disease. There are also reports on spontaneous improvement or complete spontaneous remission (62, 63). Table 4 shows results of treatment using various medications and physical therapeutic procedures in the period from 1886 - 2014.

In 1938, Nekam (16) described a patient who had been reported by Kaposi in 1895 (15), even suggesting another term for the condition. We report a patient treated at our clinic since 2004 (119). He presented with genital lesions in 2014, and they were surgically resolved.

**Conclusion**

In our patient the diagnosis was based on typical clinical picture, repeated biopsies and histopathological findings, course of the disease and poor response to any therapy. Keratosis lichenoides chronica represents a distinct entity, a rare disease of unknown etiology.
Table 3. Patients reported under a controversial diagnosis of keratosis lichenoides chronica (KLC) or synonyms in the period 1886 - 2014

<table>
<thead>
<tr>
<th>Keratosis lichenoides chronica</th>
<th>Children</th>
<th>Adults</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of papers</td>
<td>25 (25.51%)</td>
<td>73 (74.49%)</td>
<td>98 (100%)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>34 (29.57%)</td>
<td>81 (70.43%)</td>
<td>115 (100%)</td>
</tr>
<tr>
<td>Males</td>
<td>21 (61.76%)</td>
<td>50 (68.49%)</td>
<td>71 (66.36%)</td>
</tr>
<tr>
<td>Females</td>
<td>1 (38.24%)</td>
<td>23 (31.51%)</td>
<td>36 (33.64%)</td>
</tr>
<tr>
<td>Unrecorded sex</td>
<td>8 (6.96%)</td>
<td>8 (6.96%)</td>
<td>16 (14.64%)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>1.62</td>
<td>2.17</td>
<td>1.97</td>
</tr>
<tr>
<td>Median age (y)</td>
<td>15</td>
<td>47</td>
<td>37</td>
</tr>
<tr>
<td>Median age at onset (y)</td>
<td>1</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>Range of age at onset (y)</td>
<td>Birth - 16</td>
<td>18 - 80</td>
<td>Birth - 80</td>
</tr>
<tr>
<td>Median duration of disease (y)</td>
<td>11</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Range of disease duration (y)</td>
<td>0.3-49*</td>
<td>0.01-48</td>
<td>0.3-49</td>
</tr>
<tr>
<td>Congenital cases</td>
<td>4 (11.76%)</td>
<td>0 (0.00%)</td>
<td>4 (3.48%)</td>
</tr>
<tr>
<td>Familial cases</td>
<td>10 (29.41%)</td>
<td>0 (0.00%)</td>
<td>10 (8.70%)</td>
</tr>
<tr>
<td>Initial site</td>
<td>Face</td>
<td>Extremities</td>
<td></td>
</tr>
<tr>
<td>Facial lesions</td>
<td>Erythematous/purpuric</td>
<td>Seborrheic-like/roacea like</td>
<td></td>
</tr>
<tr>
<td>Face</td>
<td>30 (88.24%)</td>
<td>31 (38.27%)</td>
<td>61 (53.04%)</td>
</tr>
<tr>
<td>Extremities</td>
<td>19 (55.88%)</td>
<td>66 (81.48%)</td>
<td>85 (77.27%)</td>
</tr>
<tr>
<td>Trunk</td>
<td>9 (26.47%)</td>
<td>32 (39.51%)</td>
<td>41 (35.65%)</td>
</tr>
<tr>
<td>Dissemination</td>
<td>5 (14.71%)</td>
<td>8 (9.88%)</td>
<td>13 (11.30%)</td>
</tr>
<tr>
<td>Ocular lesions</td>
<td>4 (11.76%)</td>
<td>7 (8.64%)</td>
<td>11 (9.57%)</td>
</tr>
<tr>
<td>Oral lesions</td>
<td>4 (11.76%)</td>
<td>22 (27.16%)</td>
<td>26 (22.61%)</td>
</tr>
<tr>
<td>Genital lesions</td>
<td>0 (0.00%)</td>
<td>8 (9.88%)</td>
<td>8 (6.96%)</td>
</tr>
<tr>
<td>Nail lesions</td>
<td>1 (2.94%)</td>
<td>29 (35.86%)</td>
<td>30 (26.09%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5 (14.71%)</td>
<td>0 (0.00%)</td>
<td>5 (4.31%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7 (20.59%)</td>
<td>10 (12.35%)</td>
<td>17 (14.78%)</td>
</tr>
</tbody>
</table>

Y, year; *, Adults with childhood onset were included in the group of children
Table 4. Treatment effects in patients with KLC treated in the period 1886 - 2014

<table>
<thead>
<tr>
<th>Treatment effects</th>
<th>Therapy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No response</td>
<td>X rays, Vitamin A</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Topical steroids/retinoids/tar</td>
<td>6,45, 62,99,102, 108, 111, 117</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous</td>
<td>11, 107,120</td>
</tr>
<tr>
<td></td>
<td>Dapsone, Calcipotriol</td>
<td>93, 106</td>
</tr>
<tr>
<td></td>
<td>Acitretin, Griseofulvin, Corticosteroids</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>Topical and systemic steroids and PUVA</td>
<td>55</td>
</tr>
<tr>
<td></td>
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and pathogenesis, with clinical manifestations which, although typical, require extensive differential diagnosis. The course of the disease is chronic, progressive, and it is resistant to various treatment options, so despite variations in the clinical picture it is really easier to diagnose than to treat.

Abbreviations
- KLC - keratosis lichenoides chronica
- HIV-1 - human immunodeficiency virus type 1
- ILVEN - inflammatory linear verrucous epidermal nevus
- PUVA - psoralen ultraviolet A radiation
- NB-UVB - narrow-band ultraviolet B radiation

Acknowledgement
With great pleasure, we acknowledge our gratitude to Prof. Dr. Danilo Stevanović, who helped us a great deal with the terminology used.

References
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Hronična liheoidna keratoza – prikaz bolesnika iz sopstvene prakse i pregled literature

Sažetak

Uvod. Ideja za ovakav pristup liheoidnoj hroničnoj keratozi (keratosis lichenoides chronica), rodila se kao rezultat prvog susreta sa bolesnikom koji je imao neobičnu kliničku sliku koja je asociirala na lihen ili psorijazu, ali se ipak razlikovala od njih, što je dovelo do dileme oko dijagnoze i lečenja. Konsultacija sa profesorom Danilom Stevanovićem, kome ovom prilikom zahvaljujemo, i više puta urađen patohistološki pregled konačno su potvrdili dijagnozu: keratosis lichenoides chronic (KLC).


Pri pregledu, na donjoj polovini i bočnim stranama trupa i duž ekstremiteta, registruje se simetrična generalizovana erupcija od eritemolividnih do tmnolividnih papula i nodusa sa keratotičnom površinom, pojedinačnih ili u linearnom i retikularnom rasporedu (slike 1–3); lezije su infiltrirane, prominentne, često verukoznog izgleda i hiperkeratotične; na licu prisutni blago izraženi eritemoskvamozni plakovi, blagog intenziteta; na dorzalnim stranama stopala vidljive pojedinačne eritematozne papule na eritematoznoj osnovi (Slika 4); palmoplantarno prisutna fokalna hiperkeratoza; na prepučiju i skrotumu pojedinačne hiperkeratotične papule sa otežanim prevlačenjem preko glansa (slike 5–7).

Relevantne laboratorijske analize, uključujući i serološke reakcije na HIV-1 (eng. human immunodeficiency virus type 1), viruse hepatitisa i sifilis, bile su u granicama fizioloških vrednosti. Patohistološka analiza isečka kože radena je u više navrata, od 2004. godine kada je napravljena na psorijazi-formirnom dermatitis, potom lihenoidni dermatitis, 2009. godine na hipertrofični lihen planus, a 2010. godine pityriasis lichenoides. Patohistološka analiza isečka kože sa ekstremiteta radena je u 2009. godine: epidermis pokazuje irregularnu akantozu, varijabilnu atrofiju, umerenu ortoparakeratozu; telegiektazije i superfijijalni i dublje lokalizovan inflamatorni čelijski infiltrat u dermusu (Slika 8); na većem mikrokskopskom povećanju prisutni su vakuolarna degeneracija bazalnog sloja i apandiljiva hijalina tela (civatte body) (Slika 9). Patohistološka analiza isečka kože prepučijama radena je u 2014. godine: irregularna akantozan, hiperkeratoza i fokalna parakeratoza u epidermisu; telegiektazije uz inflamatorni infiltrat u dermusu (Slika 10); na većem uveličanju vide se irregularna parakeratoza, fokalna folikularna hiperkeratoza i parakeratoza, vakuolna degeneracija čelija bazalnog sloja epidermis-a uz telegiektazije i inflamatorni infiltrat sastavljen od limfocita i plazma čelija (slike 11 i 12). Dijagnoza KLC je postavljena na osnovu tipične kliničke slike i pravilnoj analizi, uključujući i serološke reakcije na HIV-1, viruse hepatitisa i sifilis. Radi izraženih atrofija i irregularnih akantoznih lezija, dijagnoza KLC je potvrđena u više navrata, po komponentima Hronične liheoidne keratoze, sa karakterističnim pravilima rasta i otežanim prevlačenjem preko glansa, kao i svezom i retikularnom raspoređenju lezija.
Diferencijalno-dijagnostički dolaze u obzir: *lichen planus* i *lichen planopilaris*, *lupus erythematosus*, *pityriasis lichenoides*, *pityriasis rubra pilaris*, *psoriasis vulgaris*, *mycosis fungoides*, lihenoidna reakcija na lekove, *lichen hypertrophicus*, *parapsoriasis variagata*, *keratosis follicularis*, *epidermolysis bullosa pruriginosa*, Rajterova bolest, *morbus Kyriele*. Opsežan opis patohistoloških karakteristika dao je Ber (Böer): prisustvo vakuularne degeneracije keratinocita na dermoepidermalnoj granici; brojni nekrotični keratinociti ponekad u satima, u površnom epidermisu i infundibularnom epidermisu, naročito u nižim delovima; atrofi ja i nekrozom keratinocita, hroničnim varijabilnom atrofi jom, vakuolarnom degeneracijom, iregularnom akantozom, fokalnom parakeratozom, u osnovi, radi se o lihenoidnoj dermatozi sa infundibula i izbacivanja njihovog sadržaja u dermis.

Prema nalazima Bera odstupanja u infundibulumu folikula dlake i oko akrosiringa; centar papula nalazi u infundibulumu ili u akrosiringu; 3. histološki: lihenoidni dermatitis sa mnogobrojnim nekrotičnim keratinocitima i parakeratozom. Od ostalih znakova, može se javiti mukozno zahvatanje, uključujući konjunktivalnu hiperemiju, ali ono nije karakteristično. Prema nalazima Ber a odstupanja u laboratorijskim nalazima su nespecifična i nemaju dijagnostički značaj. Tok je protrahiran, kompletna rezolucija promena nije nikada opisana.

Radeći ovu analizu Ber je zastupao stav da se KLC može dijagnostikovati samo ako su prisutna najmanje dva klinička i jedan histološki kriterijum: 1. hronične rasprostranjenje erupcije koje zahvataju lice, slične seboroičnom dermatitisu; 2. papularna erupcija sa karakterističnim linearnim i retikularnim rasporedom na trupu i ekstremitetima, pri čemu se centar papula nalazi u infundibulumu ili u akrosiringu; 3. histološki: lihenoidni dermatitis sa mnogobrojnim nekrotičnim keratinocitima.

Diferencijalno-dijagnostički dolaze u obzir: *Kaposi prikazao 1895. godine i čak predlozio drugi broj bolesnika obuhvaćenih ovom analizom trebalo bi da bude postavljena dijagnoza *keratosis lichenoides chronica*, bilo da ima karakteristike drugog sličnog oboljenja ili da nema dovoljno podataka kliničkih ili patohistoloških za postavljanje sigurne dijagnoze (Tabela 2).
koje su se pojavile 2014. godine a koje su morale biti
hirurškim putem rešene.
Zaključak. Dijagnoza je kod pacijenta koga smo
prikazali postavljena na osnovu tipične kliničke
slike, na osnovu više puta ponovljene biopsije i
patohistološkog nalaza, toka bolesti i slabog odgovora
na bilo koji vid terapije. Tok bolesti je inače hroničan,
progresivan sa rezistencijom na razne vrste terapije,
tako da je i pored varijacija u kliničkoj slici zaista lakše
postaviti dijagnozu bolesti nego je lečiti.

Ključne reči
Keratoza; Lihenoidne erupcije; Znaci i simptomi; Tok bolesti; Dijagnoza; Diferencijalna dijagnoza; Ishod terapije;
Pregled literature
Cutaneous Sarcoidosis Associated with Vitiligo and Autoimmune Thyroiditis – a Case Report

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Abstract

Sarcoidosis is a multisystem granulomatous disease and approximately one third of patients with the systemic form develop skin lesions. We present a case of cutaneous sarcoidosis associated with autoimmune thyroiditis and vitiligo. Although this association is rare by itself, it imposes the theory of autoimmune etiology of sarcoidosis. Moreover, our patient presented with elevated levels of serum chitotriosidase, a known biomarker in the activity of systemic sarcoidosis. To the best of our knowledge, there are no reports of chitotriosidase in isolated cutaneous sarcoidosis, raising a possible field for future research.

Key words

Sarcoidosis; Skin Diseases; Thyroiditis, Autoimmune; Vitiligo; Comorbidity; Hexosaminidases

Sarcoidosis is a multisystem granulomatous disease characterized by hyperactivity of the cell-mediated immune system. Cutaneous sarcoidosis can be isolated, or it can be a part of a systemic sarcoidosis (approximately one third of all patients with systemic form develop cutaneous sarcoidosis) (1).

Case report

We present a case of a 53-year-old woman with autoimmune thyroiditis and vitiligo (stable in the past 4 and 10 years, respectively), involving 20% body surface, who developed multiple, asymptomatic, erythematous papules and nodules over the sun-exposed areas (nose, lateral sides of her arms, elbows, shins and dorsal feet) in the year preceding the examination (Figures 1, 2, 3). Some of these lesions were localized on areas affected by vitiligo, especially on the elbows and dorsal feet (Figures 2, 3).

A skin biopsy of a papule on the elbow and histopathological analysis revealed non-caseating, well-defined, naked granulomas in the dermis consistent with sarcoidosis (Figure 4). Mycological and mycobacterial cultures of skin biopsies were negative. A chest X-ray did not reveal any signs of hilar lymphadenopathy or interstitial infiltrate. Also, serum levels of angiotensin-converting enzyme (ACE) were normal, and there was no increase in 24 hour calciuria.

Laboratory tests showed elevated erythrocyte sedimentation rate (30 mm/h), slightly lower levels of hemoglobin - 115.9 g/L (reference values 122-155 g/L), whereas the rest of laboratory findings were within normal ranges – complete blood count with differential, urinalysis, lipid status, renal and liver biochemistry, serum levels of amylase, lipase, lactate dehydrogenase; tumor markers - carcinoembryonic antigens (CEA), alphafetoprotein antigens (AFP), carbohydrate antigen (CA 19-9). The thyroid function test showed elevated levels of thyreo-stimulating hormone - 7.32 mIU/L, anti-thyroglobulin (Tg)
antibodies - 350.83 IU/mL, and anti-thyroperoxidase (TPO) antibodies - 517.24 IU/mL, verifying the diagnosis of chronic autoimmune thyroiditis. Also, elevated levels of serum chitotriosidase - 180 nmol/mL/h (normally 1.80-146.6 nmol/mL/h) was noted. Antinuclear antibodies, of a homogenous type, were present in the patient's serum at a titer of 1:40. ENA screen was within reference values, while anti-dsDNA antibodies and rheumatoid factor were negative.

**Discussion**

An association of sarcoidosis with autoimmune diseases has been recognized in the past, especially with lupus erythematoses (2) and autoimmune thyroiditis (3). Nevertheless, there are few reports of patients with sarcoidosis, autoimmune thyroiditis and vitiligo (4, 5, 6).

The exact etiopathogenesis of sarcoidosis is still not elucidated, even though it is widely accepted that an unrecognized antigen is responsible for the cascade of non-caseating granuloma formation. This hypothesis would be confirmed by the development of characteristic skin granulomas after injecting Kveim-Siltzbach's antigen (sarcoid tissue prepared from the spleen) (7).

Both vitiligo and autoimmune thyroiditis are considered to be a result of self-intolerance, with the development of autoantibodies against thyreocytes and melanocytes (8, 9). In cases of cluster autoimmunity, as in our patient, the bigger issue is if this hyperreactivity
leads to the development of immunological response to a still undefined antigenic stimulus (10). Another question is the nature and origin of the presumptive antigen: is it from the environment, continuously present, or perhaps antigen preexisting in the organism but not recognized by the immune system.

In cases of vitiligo associated with sarcoidosis reported in the literature, sarcoïdal lesions sporadically appear on vitiligo macules. This was also the case in our patient. Some authors postulate that photodamage within the vitiliginous skin may alter the expression of antigens identified by T-cell, such as the case of lichen planus and psoriasis confined to vitiligo lesions (11, 12). Julian et al. proposed that some kind of cellular injury in vitiliginous skin might lead to an immune mechanism causing Koebner’s phenomenon (13).

Taking into consideration that our patient had autoimmune thyroiditis and vitiligo, we believe that she should be monitored for diabetes mellitus, since by some authors sarcoidosis can be related to various polyglandular autoimmune syndromes (6, 14, 15).

Human chitotriosidase (HC) has proven to be a biomarker with high sensitivity and specificity in the detection of systemic sarcoidosis (16,17). Sensitivity is estimated to about 90%, which exceeds the sensitivity of commonly used biomarker ACE of about 60% (18,19). Even though our patient did not have x-ray findings consistent with pulmonary sarcoidosis, she

![Figure 2. Erythematous papules and small nodules on vitiligo macules](image)

![Figure 3. Erythematous papules and small nodules on unaffected skin](image)

![Figure 4. Non-caseating, well-defined, naked granulomas in the dermis (Hematoxylin-Eosin, x40)](image)
Presented with elevated levels of serum HC. In the available literature, there is no evidence about the activity of HC in cutaneous sarcoidosis. We believe that further investigations are required to reveal if levels of serum HC in cutaneous sarcoidosis may be a prognostic factor in the development of systemic sarcoidosis, or a good biomarker of isolated cutaneous sarcoidosis.

Conclusion

In conclusion, we present a case with a rare clustering of autoimmune diseases: autoimmune thyroiditis, vitiligo and cutaneous sarcoidosis. To date, there have been no reports of isolated cutaneous sarcoidosis with such clustering. Moreover, elevated HC serum levels may implicate that our patient’s sarcoidosis may progress to a pulmonary disease. This hypothesis, however, needs to be explored in further investigations.

Abbreviations

ACE - angiotensin-converting enzyme
CEA - carcinoembryonic antigen
AFP - alphafetoprotein antigens
CA - carbohydrate antigen
Tg - thyroglobulin
TPO - thyroperoxidase
ENA- extractable nuclear antigens
anti-dsDN - anti-double-stranded desoxyribonucleic acid
HC - human chitotriosidase

References

Kutana sarkoidoza udružena s vitiligom i autoimunim tiroiditisom – prikaz slučaja

Sažetak
Sarkoidoza predstavlja multisistemsko granulomatozno oboljenje u kome je zahvaćena i koža kod trećine pacijenata. Naš prikaz je pacijent sa kutanom formom sarkoidoze udruženom sa autoimunim tiroiditisom i vitiligom. Ova asocijacija (povezanost ili komorbiditet) sam po sebi je redak i implicira na autoimunu etiologiju sarkoidoze. Naš pacijent je imao i povišene nivoe serumske hitotriozidaze, prepoznatog biomarkera aktivnosti sarkoidoze. Pretaživanjem literature nismo došli do podataka o nivoima serumske hitotriozidaze kod izolovane kutane sarkoidoze, otvarajući potencijalne sferе daljeg naučnog istraživanja.

Ključne reči
Sarkoidoza; Kožne bolesti; Autoimuni tiroiditis; Vitiligo; Komorbiditet; Heksosaminidaze
Atlas of Skin and Venereal Diseases of the Male Genital Region - Book review
by Milan Bjekić
Ljiljana Medenica

Atlas of Skin and Venereal Diseases of the Male Genital Region, published by the Textbook Publishing Institute, Belgrade, is a collection of texts and pictures of venereal and non-venereal diseases of the male genital region.

The book has 88 pages, 287 photographs and is divided into 7 chapters: anatomy and physiology of the male genital region; diagnosis of genital dermatoses and sexually transmitted infections; sexually transmitted infections; non-venereal skin and mucous diseases of the male genitalia; other dermatological diseases of the male genital region; other conditions and diseases of the male genital region; benign neoplasms and hyperplasias, precancerous lesions and malignancies.

The first chapter describes the anatomy of the male external genitalia and physiological phenomena important to distinguish physiological variations from disease of this region. This chapter is, as well as the whole book, richly illustrated by 18 photographs.

The second chapter describes the signs and symptoms of sexually transmitted infections. It describes: history taking, physical examination and efflorescence of the skin and mucous membranes of the genital region, with photographs and tables, being an excellent base for medical students studying dermatovenereology and urology.

The third chapter is one of the most important in the book and it includes a test and the clinical picture of sexually transmitted infections. It reviews different clinical manifestations, making this chapter a rarely valuable material that is hard to find even in foreign medical literature.

The fourth chapter presents common non-venereal diseases such as balanitis, balanoposthitis, phimosis and paraphimosis.

The fifth chapter includes pictures which show the extent to which genital region is important in the diagnosis of other dermatological diseases, such as psoriasis vulgaris, seborrheic dermatitis, lichen planus, atopic dermatitis, contact dermatitis, lichen sclerosus,
Reiter’s syndrome, viral and fungal diseases, artificial dermatoses, etc.

The sixth chapter deals with other conditions and diseases (hypospadia, induratio penis plastica, venous circulation disorders).

The last chapter illustrates various tumor lesions of the anogenital region: nevuses, blood vessel neoplasms, cysts, precancerous and carcinomas.

This Atlas is the first richly illustrated book on male anogenital skin and venereal diseases in Serbian medical literature. It shows many years of hard work and dedication put in by its authors, primarily regarding collection of photographs from medical practice. *Atlas of Skin and Venereal Diseases of the Male Genital Region* is meant for students, medical interns, general practitioners and dermatovenereologists, to get to know this field of medicine, which may represent a diagnostic and therapeutic challenge in everyday practice.

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INOVACIJA PROIZAŠLA IZ 25 GODINA ISTRAŽIVANJA

**LIPIKAR BAUME AP+**
Sa termalnom vodom La Roche-Posay

**Pomaže u prevenciji relapsa i proređuje faze pogoršanja veoma suve kože**

2x manji rizik od ponovnog nastupanja faze pogoršanja kod osoba sklonim atopijskom dermatitisu*

**KLINičKI DOKAZANA EFIKASNOST**

---

**NOVA FORMULA SA JEDINSTVENOM SINERGIJOM AKTIVNIH SASTOJAKA**

[AQUA POSAE FILIFORMIS]
Pomaže u delovanju na odlučujuće faktore kod veoma suve kože sklonog atopijskom dermatitisu:
- ponovno uspostavljanje ravnoteže i raznolikosti kožnog mikrobioma,
- protivupalno delovanje.

[KARITE MASLAC I ULJE KANOLE] Obnova hidrolipidnog filma.

[GLICERIN] Vraćanje elastičnosti i mekoću koži.

[NIACINAMID] Delovanje protiv svrabe i obnova zaštitne kožne barijere. 24h učinkovitost protiv svrabe.

[LA ROCHE-POSAY TERMALNA VODA] Umiravanje nadražene kože.

---

**Tekstura koja omogućava oblačenje odmah nakon nanošenja**
- Nemasna. Nelepšiva.
- Balzam sada u laganoj teksturi poput mleka.

**Indikacije:**
- Veoma suva i nadražena koža, sklona atopijskom dermatitisu kod beba, dece i odraslih.

**Upotreba:**
- Jednom ili dva puta dnevno.

**Tolerancija testirana na koži sklonoj atopijskoj i osjetljivoj koži.**

---

*Klinička studija, 94 pacijenata sa suvom kožom sklonom atopijskom dermatitisu, starosti od 6 meseci i više. Ocena nakon 4 nedelje svakodnevne upotrebe Lipikar Baume AP+ nasuprot drugog emoljensa.*
Dr. Bosiljka Lalević-Vasić was a professor of dermatology at the School of Medicine, University of Belgrade, head of the Department of Dermatology at the Clinic of Dermatovenereology in Belgrade, president of the Dermatovenereology Section of the Serbian Medical Society and an internationally renowned dermatovenereologist, especially in the field of hair shaft defects.

She was born in Peć, in 1928. Her father, Miodrag S. Lalević, was a well known professor of
Serbian language and literature and her mother, Danica, was a schoolteacher.

She completed her elementary and high school education in Belgrade and graduated from the School of Medicine in Belgrade in 1952. She completed her residency training in dermatovenereology at the Clinic of Dermatovenereology in Belgrade, learning from the eminent dermatologists of the Belgrade Dermatology School, professors Sima Ilić and Milorad Manok, as well as from the first Serbian pediatric dermatologist, a consultant dermatologist, Dr. Kosara Pavlović. She became a Board Certified Dermatologist in 1960, at the School of Medicine, University of Sarajevo, passing the exam with the world famous Professor Tibor Šalamon. She received her Masters Degree in 1970 and PhD in 1975, at the School of Medicine, University of Belgrade.

In the period 1960 - 1964, she worked at the City Institute for Skin and Venereal Diseases in Belgrade, mostly at the Pediatric Department. In 1964, she was elected an Instructor in Dermatology at the School of Medicine in Belgrade. In 1976, she became an Assistant Professor, in 1983 an Associate Professor and in 1990 a Full Professor of Dermatovenereology.

At dermatology departments in Lyon and Amsterdam she studied immunofluorescence techniques important in the diagnosis of skin diseases.

For many years she was the Head of the First Department for female patients at the Clinic of Dermatovenereology of the Clinical Center of Serbia. Her specific fields of interest were hair diseases, especially hair shaft defects. She was also active in the field of immunopathology and history of medicine.

She authored or co-authored more than 160 papers, of which more than 40 in peer-reviewed journals. Her articles in the field of hair diseases represented original scientific contributions and were cited in major medical journals and textbooks.

She was the principal investigator in scientific projects supported by the Ministry of Science of the Republic of Serbia for 10 years, and a mentor to several graduate students doing their masters theses and doctoral dissertations.

Her major contribution was *Dermatovenereology with Propedeutics*, representing the first comprehensive dermatology textbook for medical students in Serbia, which she wrote with her closest associates (first published in 1997, with five editions by 2010). This textbook has been used not only by students at the University of Belgrade, but also by students at the Universities of Novi Sad, Niš, Kragujevac, Priština, and Banja Luka.

Professor Lalević-Vasić was the initiator and the first president of the Belgrade Dermatological Days (BDD). Since 1994, BDD are regularly held as the central annual meeting of dermatologists of Serbia, with a large number of participants and lecturers from Serbia, neighboring countries and Europe.

She was a member of several national and international scientific societies.

Prof. Lalević-Vasić retired in 1993. After retirement, she dealt mostly with the history of medicine and dermatology and published a number of important papers in the *Serbian Journal of Dermatology and Venereology* and other journals. Her work has shed light on, and saved people and events of special importance for Serbian medicine from oblivion.

Professor Bosiljka Lalević-Vasić was a highly moral person, and an outstanding scholar. Numerous generations of students and dermatologists are indebted to her as she contributed to the promotion of Serbian dermatology in Europe and in the world. She will also be remembered by her patients and their families.

She died in Bar (Montenegro), on July 15, 2014. She was buried in the New Cemetery in Belgrade.

Miloš NIKOLIĆ*
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Dr. Sava Konstantinović was born in Belgrade in 1926, where he completed his education and finished his working life as a professor at the Department of Dermatovenerology, School of Medicine, University of Belgrade. He graduated from medicine in 1954, and was elected an assistant in 1959. He received his PhD degree in 1969, from the School of Medicine, University of Belgrade, with thesis “The Role of Skin pH in the Development of Pathogenic Fungal Diseases”. In 1970, he became an
Assistant Professor, afterwards, Associate Professor in 1976, and in 1983 he was promoted to a Full Professor. He retired in 1991. During his prolific teaching career at the School of Medicine, University of Belgrade, at the School of Dentistry in Belgrade, as well as at School of Medicine in Kragujevac, he worked tirelessly with students and doctors specializing in various professional committees, mentoring graduate and postgraduate students obtaining masters and doctoral degrees.

As a respected organizer, he improved the work of the Department of Physical Therapy, as well as other departments of the Clinic, showing his remarkable ability to adapt. He demonstrated his organizational and technical skills related to the profession as a secretary and later the president of the Dermatology Section of the Serbian Medical Association. He was also the Editor-in-Chief of the national journal Acta Dermatovenerologica Jugoslavica, and a member of the Editorial Board of the Serbian Archives of Medicine (Srp Arh Celok Lek). He actively participated in all professional events in the country and abroad. He was the organizer and the president of the 15th Congress of Dermatovenereologists of Yugoslavia. In 1990, he was elected a member of the Academy of Medical Sciences of the Serbian Medical Association, and organized a number of symposia bringing innovations in the field.

His interest in sports medicine inspired his active work at the Sports Section of the Serbian Medical Association. He organized several international symposia within the European and World championships in boxing and ice hockey. He participated in many internships abroad, in Vienna, Paris and Amsterdam. He was invited to the United States of America to give lectures on his results in the treatment of skin diseases with retinoids, at that time still not introduced in the US. The lectures were held at nine most distinguished American departments of dermatology.

He participated in numerous conferences abroad: Stockholm, Munich, Venice, Tokyo, Mexico, Verona, Graz, Geneva, Turin, Italy, Tunisia, Rome, Brazil, Brussels, Athens, Lisbon, etc. It is needless to say that he did not miss a single professional event in our country.

Professor Sava Konstantinović published 157 scientific papers. He authored 5 books and 6 monographs. All these textbooks are used by physicians and residents to learn the essence of dermatovenereology.

He was also a member of international dermatological societies and sections in France, Greece, Germany and Romania.

Professor Sava Konstantinović was honoured with a number of professional acknowledgments, but besides that, he was also a very interesting person who magically, easily and quickly made friends and professional relationships.

Aside from being witty and charming, he was an unparalleled speaker, who was always welcomed everywhere, both at home and abroad. Many friendships, carefully nourished, will for sure keep him from falling into oblivion.

Jovan LALOŠEVIĆ*
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## FORTHCOMING EVENTS
Dermatology and Venereology Events 2014 & 2015

<table>
<thead>
<tr>
<th>DATE</th>
<th>MEETINGS, CONGRESSES, SYMPOSIA</th>
<th>ABSTRACT SUBMISSION DEADLINE</th>
<th>MORE INFORMATION AT</th>
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<tr>
<td>8-12 October, 2014</td>
<td>23rd EADV Congress Amsterdam, The Netherlands</td>
<td>7 April, 2014</td>
<td><a href="http://www.eadvamsterdam2014.org">www.eadvamsterdam2014.org</a></td>
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<tr>
<td>17 October, 2014</td>
<td>Meeting of the Serbian Medical Society’s Section of Dermatology and Venereology, Novi Sad, Serbia</td>
<td>No abstract submission</td>
<td><a href="http://www.sld.org.rs">www.sld.org.rs</a></td>
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<tr>
<td>24-26 October, 2014</td>
<td>World Congress of Cutaneous Lymphoma, Paris, France</td>
<td>No deadline information</td>
<td><a href="http://www.eortcparis2014.com">www.eortcparis2014.com</a></td>
</tr>
<tr>
<td>29-31 January, 2015</td>
<td>3rd European School of Dermato-Oncology, Berlin, Germany</td>
<td>No abstract submission</td>
<td><a href="http://www.dermato-oncology2015.org">www.dermato-oncology2015.org</a></td>
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<tr>
<td>29 January - 1 February, 2015</td>
<td>IMCAS World Congress, Paris, France</td>
<td>No deadline information</td>
<td><a href="http://www.imcas.com">www.imcas.com</a></td>
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<tr>
<td>4-7 February, 2015</td>
<td>EUROGIN 2015 Congress, Sevilla, Spain</td>
<td>1 October, 2014</td>
<td><a href="http://www.eurogin.com">www.eurogin.com</a></td>
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<tr>
<td>7-9 April, 2015</td>
<td>Dubai World Dermatology and Laser Conference, Dubai, UAE</td>
<td>31 December, 2014</td>
<td><a href="http://www.dubaiderma.com">www.dubaiderma.com</a></td>
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<tr>
<td>16-18 April, 2015</td>
<td>4th World Congress of Dermoscopy and Skin Imaging, Vienna, Austria</td>
<td>5 December, 2014</td>
<td><a href="http://www.dermoscopy-congress2015.com">www.dermoscopy-congress2015.com</a></td>
</tr>
<tr>
<td>28 July - 1 August, 2015</td>
<td>4th International Summer Academy of Practical Dermatology, Munich, Germany</td>
<td>No deadline information</td>
<td><a href="http://www.isa2015.com">www.isa2015.com</a></td>
</tr>
<tr>
<td>24-26 September, 2015</td>
<td>29th European Conference on Sexually Transmitted Infections, Barcelona, Spain</td>
<td>No deadline information</td>
<td><a href="http://www.iusti2015.com">www.iusti2015.com</a></td>
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Prepared by: Dr. Tatjana Roš, Clinic of Dermatovenerology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia, E-mail: t.rosh@nscable.net
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 authors.

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.

For further information please contact the Editorial Office (Tel: +381 21/484 35 62) or visit our web site: www.udvs.org.
KOMPONENTARNA MEDICINSKA NEGA KOJA DELUJE NA SVA 4 UZROKA ZBOG KOJIH NASTAJU AKNE

Eucerin istraživački tim formulisao je jedinstveni, patentom zaštićeni kompleks aktivnih principa koji deluju na glavne uzroke nastanka akni: L-karnitin reguliše produkciju sebuma Dekandiol deluje antibakterijski Likokalkon A deluje antiinflamatorno

U saradnji sa dermatolozima, formulisana je dnevna krema koja rešava probleme koji se često javljaju kao posledica medicinskog tretmana akni, a to su dehidrirana koža i fotosenzitivnost.

Eucerin DermoPURIFYER komplementarna hidratantna krema SPF 30

Osim patentom zaštićenog kompleksa protiv akni ova krema sadrži:

- Gliko-glicerol koji stimulise stvaranje akvaporin kanala i obezbeđuje dubinsku hidrataciju kože
- Visoku UVA/UVB zaštitu

Efikasnost i veoma dobra podnošljivost na koži dokazana je kliničkom studijom. Klinička studija Eucerin DermoPURIFYER Komplementarna hidratantna krema:

- Procena podnošljivosti od strane lekara i pacijenata: veoma dobra
- Preporuka (od strane lekara): 93%
- Želja za ponovnim korišćenjem (pacijenti): 85%

Eucerin DermoPURIFYER preparati mogu da se koriste zajedno sa uobičajenim medicinskim tretmanima akni. Svi preparati su nekomedogeni i pogodni su za svakodnevnu upotrebu.