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E-mail: serbjdermatol@nadlanu.com, Tel: +381 21 484 3562; +381 21 451 781.

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Treatment of venous leg ulcers with an ointment containing yarrow (*Achillea millefolium*) extract

Milan MATIĆ[1], Verica ĐURAN[1], Marina JOVANOVIĆ[1], Zorica GAJINOV[1], Aleksandra MATIĆ[2], Branislav ĐURAN[3], Boža PAL[4] and Neda MIMICA-DUKIĆ[5]

[1] Clinical Center of Vojvodina, Clinic of Dermatovenereology, Hajduk Veljkova 1, Novi Sad, Serbia
[2]Pediatric Clinic, Institute of Child and Youth Health Care of Vojvodina, Hajduk Veljkova 10, Novi Sad, 21000, Serbia
[3]Radiology Department, Institute of Oncology Sremska Kamenica, Sremska Kamenica, Serbia
[4]Institute of Biology, Faculty of Natural Sciences, University of Novi Sad, Serbia
[5]Institute of Chemistry, Faculty of Natural Sciences, University of Novi Sad, Serbia
Correspondence: Milan Matić, E-mail: mamatic@nadlanu.com

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Abstract

Traditional medicine credits yarrow (*Achillea millefolium*) with the ability to accelerate wound healing. The purpose of this research was to determine the effects of yarrow on the epithelization of the lower leg venous ulcers. The study included 39 patients with venous leg ulcers. They were divided into two groups: the first (experimental) group of patients were treated with an ointment containing 7.5% of yarrow extract. In the second (control) group, saline solution dressings were applied to ulcers, within the period of three weeks. In the experimental group, at the beginning of the therapy, the total surface of all the ulcers was 44736 mm^2. After three weeks, the total surface of all the ulcers was 27000 mm^2 (a decrease of 39.64%). In the control group, at the beginning of the therapy, the total surface of all the ulcers was 46116 mm^2. At the end of the study (21 days) the total surface of all the ulcers was 39153 mm^2 (a decrease of 15.1%). Herbal preparations are suitable for application in the therapy of venous ulcers, but their efficiency in wound healing is still to be investigated.

According to the World Health Organization statistics, disorders of the venous circulation are among the most frequent diseases affecting the world population. It is estimated that 15% of the whole adult population has some type of chronic venous insufficiency (1, 2, 3). According to various epidemiological studies, it is evaluated that the prevalence of lower leg ulcers in adult population is about 2%. The etiological factor of the vast majority (70-90%) of these ulcers is chronic venous insufficiency (4, 5).

Any topical preparation that accelerates wound healing is of great help. Because of this, modern medicine is frequently using traditional methods.

Yarrow (*Achillea millefolium* L., Asteraceae) is a widely distributed medicinal plant. The herbal drug (*Millefolii* herba) is believed to possess antiphlogistic, spasmolytic, stomachic, carminative and cholagogue activities. Topically, it is used in the treatment of skin disorders, especially inflammation of skin and mucous membranes, as well as a trophic protective agent (6). Recent investigations also point to the antimicrobial (7, 8, 9) and antioxidant activities (8) of yarrow. Yarrow is also well known for its wound healing properties, particularly in staunching blood flow. An infusion of the leaf, stems, and flowers will speed the healing of rashes, hemorrhoids, and skin ulcers (10).

Its pharmacological activity is attributed to particular plant constituents. *A. millefolium* contains essential oil which, depending on the origin, contains no, or up to 50% of chamazulene (produced during the distillation process of proazulene). The presence of prochamazulene is correlated with the chromosome number in the plant. Only tetraploid plants contain prochamazulene and blue sesquiterpene (chamazulene) in essential oil. Most

common oil compounds are camphor, sabinene, 1,8-cineole, etc. The plant contains several classes of sesquiterpene lactones: guaianolides, germacranolides, dihydroparthenolides. These substances have been proven to take part in the antiseptic and antiphlogistic action of yarrow. However, although *Millefolii* herba is widely used in phytotherapy, its use is sometimes restricted, because it may cause allergic contact dermatitis (11, 12). Guaianolide peroxides and sesquiterpene lactones, and with azulenes in the essential oil, are believed to be responsible for itching and inflammatory skin changes with formation of vesicles (11). Beside terpenoids, yarrow contains considerable amount of plant phenolic compounds, of which the most important are flavonoids: apigenin, luteolin and their 7-O-glycosides, 6-methoxylated or di- and trimethylated flavonols (pectolinarigenin, 3-methylbetuletol, etc). Flavonoids are presumed to be responsible for the well-known anti-inflammatory effects of yarrow`s herbal medicines (13).

Purpose

The aim of this research was to determine the therapeutic efficiency of yarrow (*Achillea millefolium*) extract on the epithelization of the lower leg venous ulcers.

Material and methods

The experiment was carried out on 39 patients with venous leg ulcers. All patients were treated at the Clinic of Dermatovenereology Diseases of the Clinical Center of Vojvodine in Novi Sad, Serbia. All patients were randomly assigned into the investigation in regard with their arrival to the Clinic. Arterial etiology of ulcers was excluded by measuring the ankle-brachial pressure index (ABPI). The average value of ABPI was 0,98. Prior to being included into the study, all patients were tested with originally made 1%, 3% or 10% ether extract of yarrow, in order to exclude contact sensitivity due to previous sensitization to compositae-containing herbal remedies and cosmetics (14). Patch tests were performed according to international guidelines (15). They were applied to the patients' back using Curatest® (Lohmann-Rauscher, Neuwied, Germany). All patients were divided into two groups.

Potential adverse effects of the therapy were explained to all patients in detail, and all signed a written consent form for participation in the research.

Experimental group

In the first group, patients were treated with an ointment with yarrow extract.

Plant material

The herbaceous part of the cultivated *Achillea millefolium* L. (Asteraceae) was collected in June of 2003, in the Province of Vojvodina. Voucher specimens were confirmed and deposited at the Herbarium of the Botany Department, Faculty of Sciences, University of Novi Sad.

Plant extract preparation

Sixty-five grams of dry plant material was subjected to the Soxhlet extraction with absolute ethanol for 3 hrs. After that, the solvent was evaporated under vacuum, and the obtained dry residue (4 g) was subsequently dissolved in propylene glycol. A 7.5% concentration of yarrow extract was added to a neutral basis, Galsana® (Galenika, Belgrade, Serbia).

Treatment protocol

The first group, included a total of 20 patients: 6 males and 14 females, of an average age of 63.05, with a total number of 32 venous ulcers. Local therapy was applied twice a day, for three weeks.

Control group

The second group was the control group. It included 19 patients, 15 females and 4 males, of an average age of 68.35, with a total number of 31 venous ulcers. This group was treated with saline solution dressings which were applied to ulcers, for the period of three weeks.

Results were recorded by measuring the ulcer area, as well as semi-quantitative parameters (granulation, epithelization and dermatitis) once a week, throughout the treatment.

The study was approved by the Institutional Review Board and the Ethics Committee of the University of Novi Sad and the Ministry of Science and Environment Protection of the Republic of Serbia.

Results

At the beginning of the therapy the total surface of all ulcers in the experimental group (treated with ointment containing yarrow extract) was 44736 mm^2, that is 1398 mm^2 on average. After the first week there was a 14.07% decrease of ulcer size, 26.80% after the

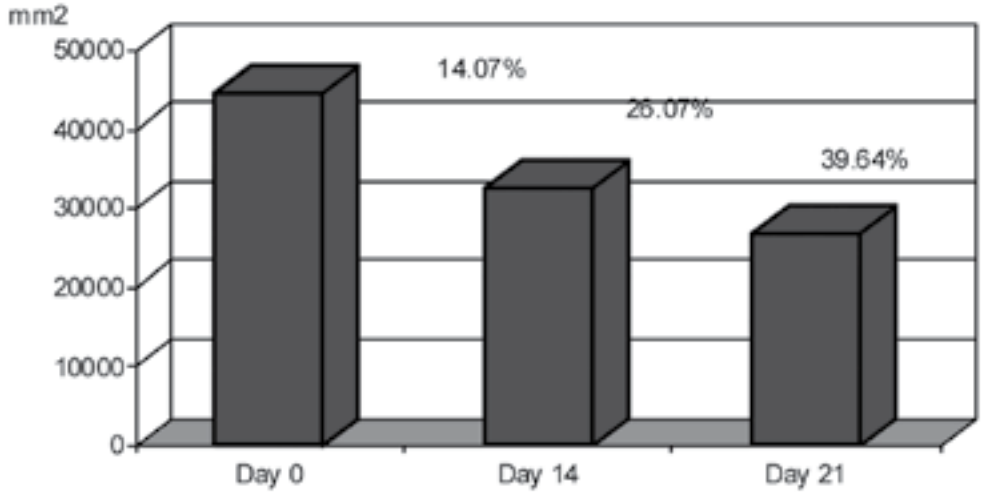

Figure 1. Decrease in total ulcer surface in patients treated with topical preparation with yarrow extract

second and after the third week the total surface of all ulcers was 27000 mm^2 (a decrease by 39.64%) (Figure 1). In 3 cases a complete epithelization was achieved (Figure 2, Figure 3).

All of the registered semi-quantitative parameters (granulation, epithelization and dermatitis) were significantly improved when compared to the beginning of the treatment. During the experiment, there were no systemic or local side effects.

In the control group, at the beginning of the therapy the total surface of all ulcers was 46116 mm^2, 1487 mm^2 on average. After 7 days, a 3.93% decrease was established, 10.11% after 14 days, and at the end of the experiment (21 days) the total surface of all

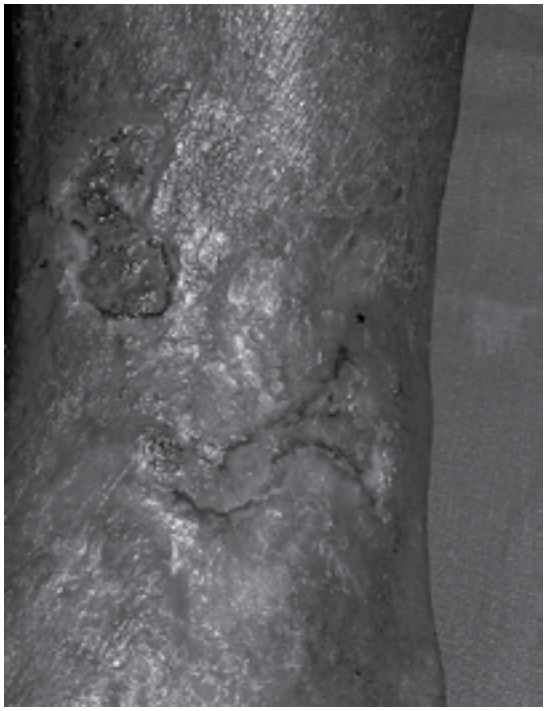

Figure 2. Before treatment

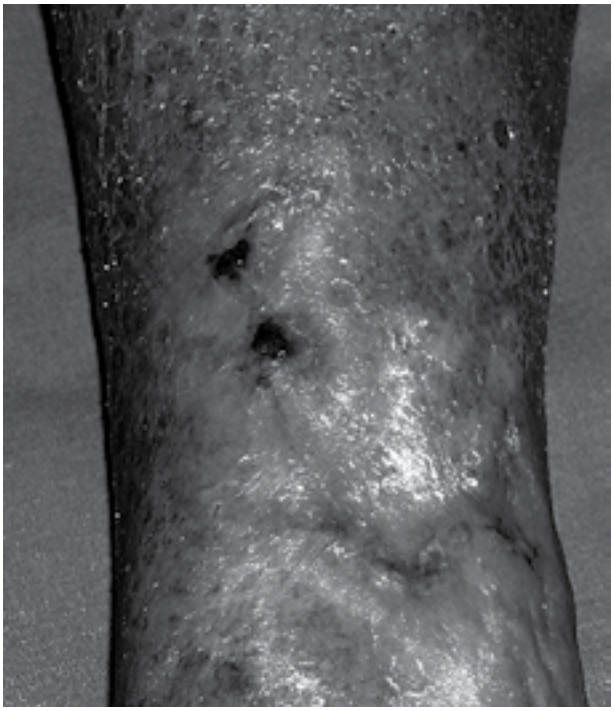

Figure 3. After treatment

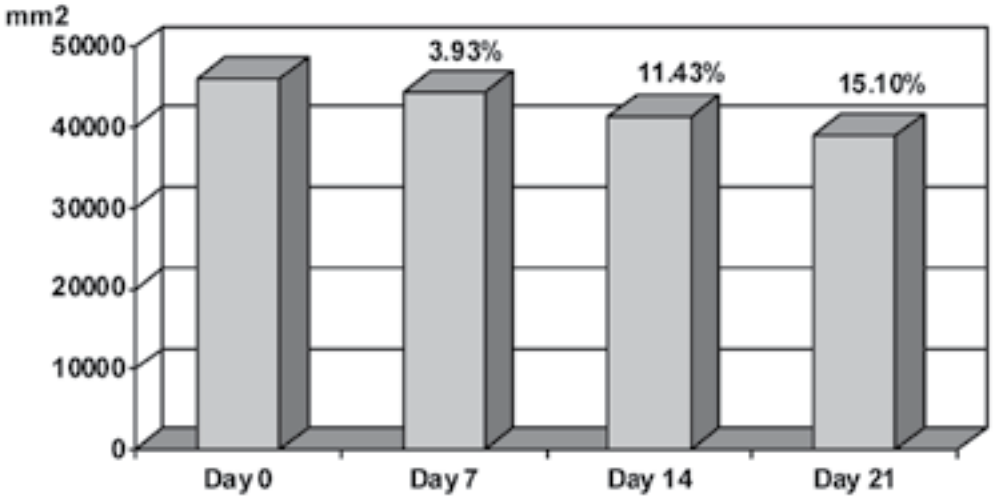

Figure 4. Decrease in total ulcer surface in the control group

ulcers was 39153 mm^2 (a 15.10% decrease) (Figure 4). In 4 cases a complete epithelization was achieved.

After statistical evaluation (student t-test) of results between the experimental and control groups, the group treated with ointment containing yarrow extract showed no statistically significant acceleration of wound healing ($p>0.05$) (Figure 5).

Discussion

In contemporary literature, no previous researches concerning the effects of yarrow preparation on venous ulcers healing were found. In general, there are very few controlled clinical studies concerning the effects of medicinal plants on wound healing.

The obtained results of the study point to a faster epithelization of venous ulcers after the application of the cream with yarrow extract, in comparison with the control group (decrease of ulcer surface by 39.64% in comparison with 16.75%), although without statistical significance.

However, the previous investigation, in which we analyzed the influence of the cream with 7.5% marigold extract on the healing of venous ulcers, a statistically significant acceleration of the healing process ($p<0.05$) was established (16).

Nevertheless, the evaluation of semi-quantitative parameters (granulation, epithelization and dermatitis) showed better results in the group treated

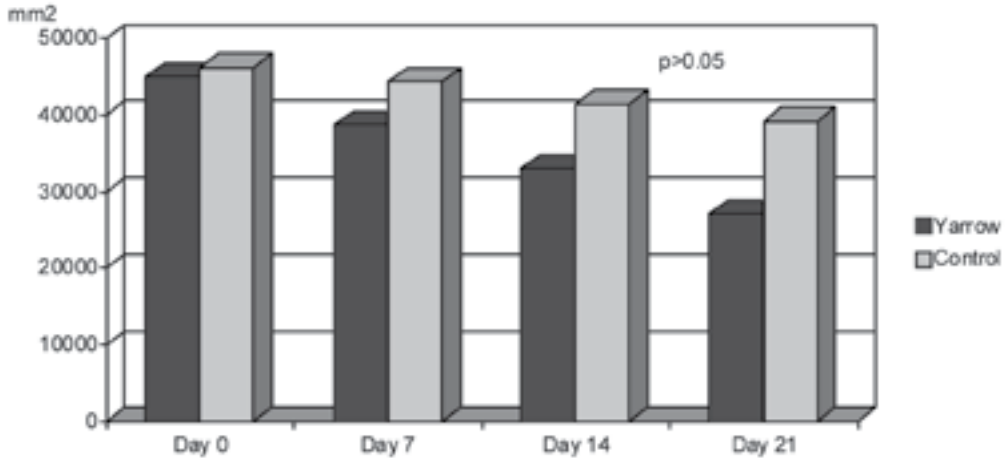

Figure 5. Decrease in the wound surface during the study in experimental and control groups (comparative review)

with yarrow extract, especially concerning reduction of dermatitis. On the basis of these findings, one can conclude that, even though both of these plants are known for their capacity to accelerate wound healing, their effects are achieved at different levels. Therefore, a combination of several medicinal plants probably exerts a synergistic effect. This is in accordance with yet another of our previous investigations, in which a preparation containing 4 different medicinal herbs (*Calendula officinalis, Achillea millefolium, Symphytum officinale, Salvia officinalis*) showed the best results (17). In this investigation we treated 40 patients with a total number of 66 venous ulcers. After a 3-week therapy, a 58.55% decrease of ulcer surface was established. A complete epithelization was recorded in 22 ulcers.

Conclusion

Our investigation showed no significant acceleration of wound healing after application of cream with yarrow extract. However, based on this research and our previous investigations, we can conclude that herbal preparations are safe and suitable for application in the therapy of venous ulcers. Better results may be achieved by appropriate combination of different medicinal herbs and by utilization of their synergistic effect. Yet, this calls for good knowledge of herbal medicines and venous pathology.

Acknowledgement

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References:

1. Beebe-Dimmer JL, Pfeifer JR, Engle JS, Schottenfeld D. The epidemiology of chronic venous insufficiency and varicose veins. Ann Epidemiol 2005;15(3):175-84.
2. Fowkes FG, Evans CJ, Lee AJ. Prevalence and risk factors of chronic venous insufficiency. Angiology 2001;52(Suppl 1):S5-15.
3. Browse NL, Burnard KG, Thomas ML. Diseases of the veins: pathology, diagnosis and treatment. Baltimore: Edward Arnold; 1988:445-6.
4. Baker SR, Stacey MC, Jopp-McKay AG, Hoskin SE, Thompson PJ. Epidemiology of chronic venous ulcers. Br J Surg 1991;78(7):864-7
5. Lopez AP, Phillips TJ. Venous ulcers. Wounds 1998;10:149-57.
6. Bruneton J. Pharmacognosy: phytochemistry of medicinal plants. Paris: Lavoisie Publishing; 1995:337-9.
7. Barbour EK, Sharif MA, Sagherian VK, Habre AN, Talhouk RS, Talhouk SN. Screening of selected indigenous plants of Lebanon for antimicrobial activity. J Ethnopharmacol 2004;93:1-7.
8. Candan F, Unlu M, Tepe B, Daferera D, Polissiou M, Sokmen A, et al. Antioxidant and antimicrobial activity of the essential oil and methanol extracts of Achillea millefolium subsp. millefolium Afan. (Asteraceae). J Ethnopharmacol 2003;87:215-20.
9. Stojanović G, Radulović N, Hashimoto T, Palić R. In vitro antimicrobial activity of extracts of four Achillea species: the composition of Achillea clavennae L. (Asteraceae) extract. J Ethnopharmacol 2005;101:185-90.
10. Gale T. Yarrow: encyclopedia of alternative medicine, 2006. eNotes.com. 2006. 26 Jan, 2007. Available from: http://health.enotes.com/alternative-medicine-encyclopedia/yarrow
11. Bisset NG, Wichtl M, eds. Herbal drugs and phytopharmaceuticals. Boca Raton: CRC Press; 2001:342-4.
12. Blumenthal R. The complete German commission E monographs. Austin: American Botanical Council; 1999:233-4.
13. Wichtl M. Herbal drugs and phytopharmaceuticals. Boca Raton: CRC Press; 1994:342-7.
14. Paulsen E. Contact sensitization from Compositae-containing herbal remedies and cosmetics. Contact Dermatitis 2002;47:189-98.
15. Lachapelle JM, Maibach HI. Methodology of patch testing. In: Lachapelle JM, Maibach HI, eds. Patch testing Prick testing: a practical guide (official publication of ICDRG). Berlin: Springer; 2003:27-49.
16. Đuran V, Matić M, Jovanović M, Mimica N, Gajinov Z, Poljački M, et al. Results of the clinical examination of an ointment with the marigold (Calendula officinalis) extract in the treatment of venous leg ulcers. Int J Tissue React 2005;27(3):101-6.
17. Đuran V, Matić M, Zrnić B, Poljački M, Jovanović M, Dimoski A. Rezultati kliničkog ispitivanja Plantoderm masti u bolesnika sa venskim ulceracijama donjih ekstremiteta. Arh Farm 1997;5:526-7.

Primena preparata sa ekstraktom hajdučke trave (*Achillea millefolium*) u lečenju venskih ulkusa potkolenice

Sažetak

Uvod: U Tradicionalnoj medicini hajdučka trava (*Achillea millefolium*) je dobro poznata po svojoj sposobnosti da ubrzava zarastanje rana.

Cilj: Cilj ovog istraživanja bio je da ispitamo uticaj hajdučke trave na zarastanje venskih ulkusa potkolenice.

Materijal: U našem istraživanju lečeno je ukupno 39 pacijenata sa venskim ulkusima. Bili su podeljeni u dve grupe. U prvoj (eksperimentalnoj grupi) pacijenti su lečeni preparatom u obliku krema koji je sadržao 7,5% ekstrakta hajdučke trave. U drugoj (kontrolnoj) grupi su na ulkuse primenjivani oblozi fiziološkog rastvora, tokom perioda od 3 nedelje.

Rezultati: Na početku ispitivanja u eksperimentalnoj grupi ukupna površina ulkusa iznosila je 44 736 mm^2. Posle tri nedelje terapije ukupna površina ulkusa bila je 27 000 mm^2 (smanjenje za 39,64%). U kontrolnoj grupi ukupna površina ulkusa na početku eksperimenta je bila 46116 mm^2. Na kraju ispitivanja (21 dan) ukupna površina ulkusa bila je 39 153 mm^2 (smanjenje za 15,1%).

Zaključak: Primena biljnih preparata pogodna u terapiji venskih ulkusa, ali efikasnost njihovog dejstva na zarastanje ulkusa tek treba da bude detaljnije ispitana.

Genital warts: New approaches to the treatment

Zoran GOLUŠIN*

Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad
*Correspondence: Dr Zoran Golušin, E-mail: zgolusin@eunet.yu

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Abstract

Genital warts are one of the most common sexually transmitted infections caused by the human papilloma virus. Persons with genital warts may be infected by several types of human papilloma viruses: various types may have antagonistic or synergistic interactions, causing regression or recurrence of the existing lesions. No specific antiviral therapy is currently available. The treatment includes removal of symptomatic lesions on the skin and mucous surfaces. Apart from classical surgical procedures, local destruction of lesions is performed using various chemical and physical agents, whereas systemic therapy includes administration of agents promoting the immune system. The efficacy of treatment is not identical in all cases, and relapses are still inevitable. Combination therapy is often an alternative to monotherapy, while vaccine has an important role in prevention of genital warts.

Genital warts (GWs) (lat. *Condylomata acuminata*) are visual manifestations of genital human papilloma virus (HPV) infection, and they are among the most common sexually transmitted diseases (STDs) in developed countries. Due to their high prevalence, viral etiopathogenesis and still inefficient therapy, GWs represent a complex clinical problem in dermatology and venereology.

Epidemiology

Genital warts are a clinical manifestation of HPV infection in 1% of the sexually active population. The incidence of GWs is around 2,4 per 1000 inhabitants of Western Europe, and 8 per 1000 females in North America. The incidence is ten times higher among HIV (eng. Human Immunodeficiency Virus) positive individuals (1, 2). Genital warts are the most common viral sexually transmitted infection in the Great Britain (3). The highest prevalence of GWs is established among people from 20 – 24 years of age, and it is around 0.6 to 1.2% in both sexes (1, 4). In 2000, it was estimated that in the US, 6.2 million people, aged 15 – 44 years, are infected with GWs (5). The infection affects men and women equally, but it is also seen in the pediatric population. Vertical transmission and sexual transmission are the main routes of acquisition at an early age (6).

Etiology and immunology

The viral etiology of GWs was recognized in 1907 (7), whereas HPV was identified as the virus responsible for GWs in the mid-seventies of the last century (8). This group of viruses of epithelial epidermotropic nature may invade various parts of the body, including the skin, mucosal surfaces of the mouth, larynx, esophagus, and of the anogenital tract. More than 120 types of HPV have been identified, and approximately 30 of them have been associated with genital epithelial infection (HPV-type 6, 11, 16, 18, 31, 33, 35, 42, 43, 44, 45, 51, 52, 53, 55, 56, 57, 58, 59, 68…) (9). HPV-16 and HPV-84 are the most commonly detected types in men (10).

The cellular immune system plays a major role in the regression of HPV-induced genital diseases. Spontaneous regression of GWs is associated with significant increase in CD4+ T-lymphocytes in the dermis and epidermis. Anti-HPV antibodies are detected in the sera of patients with GWs (9). Immunosuppression is considered a condition sine qua non, especially in HIV-positive patients, who are 10 times more susceptible to genital warts (1, 2). However, the highest incidence of genital warts is observed among adolescents (1, 4). In the United States, it has been established that 3 million cases of sexually transmitted infections (STI) occur in

adolescents each year and that every fourth sexually active adolescent gets a STI before the age of 18 (11). Taking into consideration the threatening results of the research performed among high-risk teenagers in the United States, revealing a significant immune deficiency even in HIV-negative persons, it is obvious that immune deficiency is directly associated with high prevalence of STI in this age group (12).

Patients with GWs may be infected with various types of HPV at the same time (13). It has been established that during infection different types of viruses may have antagonistic or synergistic effects on other types of HPV, which can be an explanation for frequent spontaneous regression and recurrence of skin and mucous lesions (14). Spontaneous regression of GWs occurs in up to 30% of affected patients during a 4-month period (9).

Risk factors

Studies have shown that the association between HPV genital infection and promiscuity significantly increases the risk of GWs in women in regard to men. Other risk factors include lack of condom use and immunosuppression (15). HPV is transmitted by direct skin-to-skin and mucous membrane contact. Cervical infection may be caused by HPV transmitted from the external genitalia (16). Transmission of HPV through routes other than sexual is also possible, and it must not be forgotten. HPV was detected on the fingers of persons with GWs (17). Transmission is possible by using sexual aids as well. Moreover, HPV infection was found in 6.1% of women who have never had sexual intercourse (18). The incubation period of genital HPV infections is rather long, from 2 to 9 months, although there are data about the possible range of incubation from 6 weeks to several years (21). Most infected individuals remain asymptomatic; on average, the infection lasts from several months to 2 years, while the final stage of infection is also asymptomatic. The virus is detected only by HPV DNA testing (19, 20).

There is strong evidence for an association between HPV infection and anogenital cancers. HPV can be identified in 93% of invasive cervical cancers, primarily HPV type 16 (21). HPV is also diagnosed in 42% of patients with penile carcinomas; while HPV type 16 is also most frequent (22, 23, 24).

Clinical manifestations

Genital warts are the most common clinical manifestation of genital HPV infection. They are warty, flat, dome-shaped, papillomatous, filiform, keratotic growths of normal skin color; rarely they are inflamed or hyperpigmented, and may affect any part of the skin or exposed mucous surfaces. Genital warts are most frequently found inside the preputium and frenulum, glans and coronary sulcus, on scrotum, inguinal folds, vulva, perineum, perianal and intraanal region, the vagina, cervix and urethra. More than 50% of women with GWs on the external genitalia have the same lesions in the vagina, whereas 20% of men with external lesions have intraurethral warts. Genital warts are frequently multifocal, especially in the intertriginous areas (madidation and maceration) (25, 26). A study of recent literature indicates a special entity - flat condyloma (lat. *Condylomata plana*), which used to be described as a clinical form of genital warts. They are commonly caused by HPV types 16, 18, 31, and 33. They are considered as an entity due to their higher oncogenic potential in regard to GWs (27, 28). Giant condyloma, or Buschke-Lowenstein tumor, is a massive timorous lesion of the anogenital region, the size of a fist. Despite the impressive clinical picture, malignant transformations are rare. They are commonly caused by HPV types 6 and 11. It is believed that immunosuppression plays an important role in the pathogenesis of giant condylomas. In cases of clinical and histological malignancy, HPV types 16 and 18 were identified (29, 30, 31).

Another clinical manifestation of genital HPV infection also includes Bowenoid papulosis. This disease manifests as multiple hyperpigmented or hypopigmented papules, with histological signs of cellular atypia (similar to: Morbus Bowen; spinocellular carcinoma in situ). Lesions commonly contain HPV type 16 (29, 30, 31). Although usually asymptomatic, due to their location and size, GWs may cause pain, itching, urethral and vaginal bleeding, as well as urinary obstruction (25).

Diagnosis and differential diagnosis

The diagnosis of GWs is based on the clinical presentation. A biopsy may be indicated if genital warts cannot be easily identified, in immunosuppressed patients, when response to therapy is unsatisfactory,

in cases when warts are pigmented, indurated, fixed, and ulcerated, but also in cases of high risk of malignancy (chronic GWs or positive Pap test) (32, 33). HPV infection is determined only by HPV DNA detection. The diagnosis is also made by polymerase chain reaction (PCR) and hybrid capture test (HC2). Serological tests with low sensitivity are useless (34). Application of 3-5% acetic acid is not recommended any more (false positive results) (9).

The differential diagnosis includes the following diseases and conditions: *condylomata lata,* seborrheic keratosis, dysplastic and benign nevi, *molluscum contagiosum*, *papillae coronae glandis*, Crohn's disease, lichen planus, *lichen nitidus* and malignant skin diseases (35).

Therapy

There is no specific antiviral therapy for GWs. The therapy primarily involves the removal of visible lesions on the skin and mucous areas. If untreated, genital warts may grow larger and multiply, and about 95% of patients wish to undergo therapy. It is believed that therapy may induce natural regression of GWs. It remains unclear to what extent immunologic response affects and modifies the treatment, so it is impossible to predict relapses in treated patients. There is still no evidence that the treatment of GWs decreases the contagiousness of treated patients (36, 37). The matter of contagiousness opens another question: if subclinical infections should be treated or not. Clinical studies have shown that after laser therapy of subclinical infections, in women diagnosed by colposcopy, relapses occur in 88% of cases (38). It is still unclear whether patients with subclinical infections are as contagious as patients with clinical infections, but there is evidence that in many cases transmission to the partner occurs when there are no clinical signs or symptoms. According to the traditional clinical approach, treatment of genital warts in one partner does not affect the treatment outcome in the other (37).

Treatment of genital warts mostly includes medications and procedures targeting lesions and the immune system: 1) chemical agents (podophyllin, podophyllotoxin, imiquimod, trichloroacetic acid, 5-fluorouracil, interferon, cidofovir); 2) cryotherapy (liquid nitrogen or carbon dioxide snow); 3) CO_2 laser; 4) photodynamic therapy; 5) surgical treatment (curettage, excision, electrocauterization, circumcision); 6) systemic and intralesional interferon therapy.

Topical chemical agents

Podophyllin

Podophyllin is a crude plant extract prepared by extracting the resin from the rhizome of Indian *Podophyllum emodi* or American *Podophyllum pelatum*. It induces tissue necrosis by blocking the cell mitosis. It is applied to genital warts as a 10-25% suspension in tincture, and it is removed by washing after 1 - 4 hours. It is usually applied once a week for at least 6 weeks. Due to its potential systemic toxicity causing bone marrow depression, its application is limited to less than 0.5 ml per less than 10 cm^2. Podophyllin has teratogenic effects, whereas relapses occur in 40% of treated patients. It is least effective on the frenulum, scrotum and labia major in women (39). Studies also show that podophyllotoxin, a crude alcohol extract and a biologically active component in the podophyllum resin, is more effective than podophyllin and that it is taking its place in the treatment of GWs.

Podophyllotoxin

Podophyllotoxin causes both epidermal and dermal necrosis by binding to cellular microtubules and by blocking mitotic activity in the metaphase. Podophyllotoxin is contraindicated in pregnancy. It is applied twice a day, three times a week, during 2 – 6 weeks. It is available in a 0.5% solution, cream or gel. In clinical practice, podophyllotoxin solution is used for penile lesions, while cream is used in women and for anal lesions. The maximum treatable surface area should not exceed 10 cm^2. A complete remission is reported in 75% of cases treated with podophyllotoxin solution, and in 64.6% of cases treated with cream (8). Relapses occur in one third of patients after one month. Topical application of podophyllin and podophyllotoxin is associated with possible local adverse effects such as itching, pain, inflammation, edema and ulcerations (37, 39).

Imiquimod

Imiquimod modifies the immune response and increases cellular indirect antiviral activity. However, imiquimod has no direct antiviral effects. Its effects proved better in women than in men, with complete

remission in 72% of treated women. Imiquimod 5% cream is used three times per week, during a 16 week period. The most frequent local adverse reaction is erythema (40). The reported relapse rate is lowest after three months – 9%, and highest after six months – 23% (41).

Trichloroacetic acid

Trichloroacetic acid is used in an 80 – 90% solution. It has no systemic effect and it is safe for use during pregnancy. It is applied once a week. Its remission rate after six applications is 70%, while relapses occur in 36% of patients (42).

5-Fluorouracil

5-Fluorouracil inhibits the nucleic acids synthesis. Due to its teratogenic effects, it is contraindicated during pregnancy. It is applied as a 5% cream on vulvar, perianal, penile and intrameatal genital warts. It is used 1 – 3 times a week, during 3 – 10 hours. It often causes local irritation (36, 39). Complete remission is reported in 41% of patients after 3 months, while relapses occur in 50% (43).

Interferon

Interferon is a proinflammatory cytokine with antiviral effects. When combined with surgical or laser therapy, it causes complete remission of GWs in 54 – 62% of treated patients (44).

Cidofovir

Cidofovir is a medication which was used for the treatment of cytomegalovirus and herpes virus infections, and later for GWs in HIV-positive patients. 1% cidofovir gel is applied once a day, for 5 days, during 6 two-week cycles. In immunocompetent patients complete remission is reported in 47% (44).

Cryotherapy

Cryotherapy is a procedure in which a chemical, usually nitrous oxide or liquid nitrogen is used to freeze off genital warts. It causes both epidermal and dermal cellular necrosis, consequently leading to cessation of circulation in the tissues and edema. Cryotherapy is an effective and inexpensive method which is safe for use during pregnancy. Cryotherapy with liquid nitrogen is the most widely used method and it is applied with a cryo-spray. Another method includes application of liquid nitrogen or carbon dioxide snow using a cryo-probe for 10 – 20 seconds, freezing a wart and a margin of healthy skin. Generally, three sessions are required, at intervals of 1 to 2 weeks. Anesthesia is rarely required for cryotherapy. Complete wart removal occurs in 79 – 88% of cases, while relapses occur in 25 – 39% (37, 39).

Laser therapy

CO_2 laser therapy provides precision preserving the healthy tissue, especially in the treatment of extensive genital warts. It is used in the treatment of penile, anorectal and urethral GWs in men, and flat vaginal condylomas in women. It is safe to use during pregnancy. However, anesthesia is necessary. Complete wart clearance after CO_2 laser surgery has been reported in 23 – 52% of patients, while relapses occur in 60 – 77% of cases (36, 37, 39).

Photodynamic therapy

By photodynamic (photochemical) therapy, 5-aminolevulinic acid is selectively accumulated in neoplastic and HPV-infected tissues and then activated by a red laser light. The result is tissue destruction (37).

Surgical treatment

Surgical removal of GWs can be performed with a scalpel, scissors (scissor excision was first used for perianal and anal condylomas in 1978), or a curette in local anesthesia. It can be used during pregnancy, but there is a risk of infection. Regression occurs in 35 – 93% of patients, while relapses are reported in 19 – 29% (36, 37, 39). Electrosurgery is associated with a regression of 61 – 94%, whereas relapses occur in 14 – 22% of patients (45). In extensive and long-term GWs on the preputium, circumcision may be performed (45).

Systemic and intralesional interferon therapy

Due to its high cost, bone marrow suppression, anaphylaxis, bronchospasm, fever, headache and myalgia, systemic use of interferon (3 million U sc or im 3 times/wk for 6 weeks) is neither primary, nor adjuvant therapy for GWs. Its efficacy varies from 7 – 82%, while relapses occur in 23% of treated patients (36, 39). Administration of intralesional interferon is associated with pain, because interferon is injected directly into the wart. Regression occurs in 35 – 53% of treated patients, whereas relapses occur in 21 – 25% of cases (39). Spontaneous resolution of genital warts in children is reported in more than 50% of cases. Drugs of choice are podophyllotoxin and imiquimod (46, 47).

Combination therapy

High recurrence rate reported for monotherapy led to use of combination therapy (simultaneous or sequential application of two or more methods) with: CO_2 laser surgery and intralesional interferon therapy or imiquimod cream (48), intralesional interferon alpha 2b and podophyllin (49), electrocoagulation and 1% cidofovir gel (in HIV-positive patients) (49); trichloroacetic acid and podophyllin; trichloroacetic acid and cryotherapy; cryotherapy and podophyllotoxin; cryotherapy and imiquimod; surgical and imiquimod; podophyllin and imiquimod; trichloroacetic acid and podophyllin and cryotherapy; trichloroacetic acid and podophyllin and podophyllotoxin; trichloroacetic acid and podophyllin and imiquimod (3).

Although there are no sufficient data to make any conclusions, a combination therapy with podophyllin and cryotherapy induces complete clearance of GWs in 72.5% of patients after two treatment cycles, while after the same period of time combination of trichloroacetic acid and podophyllin shows regression of GWs in 62.3% of patients (Table 1) (50-53).

According to a recent cross-sectional survey, only 11% of all treatments involved a combination of two or more agents. However, the following combinations proved to be the most frequent initial choice of treatment: trichloroacetic acid and podophyllin, trichloroacetic acid and cryotherapy, cryotherapy and podophyllotoxin, cryotherapy and imiquimod (3).

Prevention of HPV infections is of great importance, not only to avoid transmission, but also to prevent HPV associated diseases, primarily cervical cancer. Considering the fact that prevention strategies are still not available, sexual abstinence is believed to be the only absolute primary prevention. Taking into account the above-mentioned HPV susceptibility to latent infection, secondary preventive strategies, such as treatment of GWs and cervical displasias, have not been found to be helpful. Complete protection from HPV infection is not possible, because infections may occur on sites not covered by the condom (54).

The quadrivalent prophylactic vaccine against HPV types 6, 11, 16 and 18 is the first successfully applied vaccine (55). Vaccination of children of both sexes, aged 10 – 13, would directly protect the immunized individuals, and indirectly protect their partners (56). Although this vaccine is not intended for treatment of GWs, the therapeutic vaccine HspE7, which consists of a fusion of the well known stimulator of cellular immunity, heat shock protein from *Mycobacterium bovis* and HPV 16E7 oncoprotein, given to patients with anal dysplasia, showed complete remission of GWs in 73% of patients 18 months after the first injection (57).

Conclusions

Genital warts infection commonly occurs early in the sexual life of men and women. There is a strong relationship between GW infection and development

Table 1. Summary of reported results of combination therapy of genital warts

Treatment	Wart clearance	Recurrence	Reference
Trichloroacetic acid and podophyllin	53/85 (62.3%)	Not reported	Sherrard et al [50]
Podophyllin and cryotherapy	55/76 (72.5%)	Not reported	Sherrard et al [50]
Intralesional interferon and podophyllin	25/41 (61%)	67%	Douglas et al [51]
Systemic interferon and isotretinoin	40/44 (90.9%)	0%	Cardamakis et al [52]
Electrocauterization and cidofovir gel	19/19 (100%)	27%	Orlando et al [53]

of precancerous and cancerous lesions. There is no consensus about the treatment of GWs and there are many therapeutic options, but unfortunately no cure yet exists to prevent relapses. Vaccine has an important role in the prevention, and its application provides encouraging results in developing immunization strategies worldwide. A systematic and effective use of HPV vaccine should facilitate the implementation of universal immunization of persons of both sexes at the earliest age, not only of groups at risk. Until then, our task is to determine and apply the most effective methods of prophylactic treatment.

References

1. Persson G, Andersson K, Krantz I. Symptomatic genital papillomavirus infection in a community: incidence and clinical picture. Acta Obstet Gynecol Scand 1996;75:287-90.
2. Chirgwin KD, Feldman J, Augenbraun M, Landesman S, Minkoff H. Incidence of venereal warts in HIV-infected and unifected women. J Infect Dis 1995;172:235-8.
3. McClean H, Shann S. A cross-sectional survey of treatment choices for anogenital warts. Int J STD AIDS 2005;16:212-6.
4. Lacey CJN, Goodall RL, Ragnarson Tennvall G, Maw R, Kinghorn GR, Fisk PG, et al. Randomised controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream and podophyllin in the treatment of genital warts. Sex Transm Infect 2003;79:270-5.
5. Weinstock H, Berman S, Cates W. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. Prospect Sex Reprod Health 2004;36(1):6-10.
6. Shelton TB, Jerkins GR, Noe HN. Condylomata acuminata in the pediatric patient. J Urol 1986;135(3):548-9.
7. Ciuffo G. Inesto positiv con filtrado di verrucae volgare. G Ital Mal Venereol 1907;48:12-7.
8. Zur Hansen H. Condyloma acuminata and human genital cancer. Cancer Res 1976;36:530.
9. Scheinfeld N, Lehman DS. An evidence-based review of medical and surgical treatments of genital warts. Dermatol Online J 2006;12(3):5.
10. Nielson CM, Flores R, Harris RB, Abrahamsen M, Papenfuss MR, Dunne EF, et al. Human papillomavirus prevalence and type distribution in male anogenital sites and semen. Cancer Epidemiol Biomarkers Prev 2007;16(6):1107-14.
11. Ciconte A, Campbell J, Tabrizi S, Garland S, Marks R. Warts are not merely blemishes on the skin: a study on the morbidity associated with having viral cutaneous warts. Aust J Dermatol 2003;44:169-73.
12. Futterman DC. HIV and AIDS in adolescents. Adolesc Med 2004;15:369-91.
13. Brown DR, Schroeder JM, Bryan JT, Stoler MH, Fife KH. Detection of multiple human papillomavirus types in Condylomata acuminata lesions from otherwise healthy and immunosuppressed patients. J Clin Microbiol 1999;37:3316-22.
14. Elbasha EH, Galvani AP.Vaccination against multiple HPV types. Math Biosci 2005;197:88-117.
15. Partridge JM, Koutsky LA. Genital human papillomavirus infection in men. Lancet Infect Dis 2006;6:21-31.
16. Moscicki AB. Impact of HPV infection in adolescent populations. J Adolesc Health 2005;37:S3-S9.
17. Sonnex C, Strauss S, Gray JJ. Detection of human papillovirus DNA on the fingers of patients with genital warts. Sex Transm Infect 1999;75:317-9.
18. Marrazzo JM, Koutsky LA, Kiviat NB, Kuypers JM, Stine K. Papanicolaou test screening and prevalence of genital human papillomavirus among women who have sex with women. Am J Public Health 2001;91:947-52.
19. Obalek S, Jablonska S, Orth G. Warts and HPV-related squamous cell tumors of the genitoanal region in children. In: Gross G, von Krogh G, eds. Human papillomavirus infections in dermatovenerology. Bocca Raton: CRC-Press; 1997:305-14.
20. Moscicki AB, Shiboski S, Broering J, Powell K, Clayton L, Jay N, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. J Pediatr 1998;132:277-84.
21. Bosch FX, Manos MM, Munoz N, Sherman M, Jansen AM, Peto J, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. J Natl Cancer Inst 1995;87(11):796-802.
22. Rubin MA, Kleter B, Zhou M, Ayala G, Cubilla AL, Quint WG, et al. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. Am J Pathol 2001;159:1211-8.
23. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in situ and invasive disease. Int J Cancer 2005;116:606-16.
24. Strickler HD, Schiffman MH, Shah KV, Rabkin CS, Schiller JT, et al. A survay of human papillomavirus 16 antibodies in patient with epithelial cancers. Eur J Cancer Prev 1998;7:305-13.
25. Dupin N. Genital warts. Clin Dermatol 2004;22:481-6.
26. Giuliano AR, Nielson CM, Flores R, Dunne EF, Abrahamsen M, Papenfuss MR, et al. The optimal anatomic sites for sampling heterosexual men for human papillomavirus (HPV) detection: the HPV detection in men study. J Infect Dis 2007;196(8):1146-52.
27. Skerlev M, Grce M, Sirotković-Skerlev M, Husnjak K, Lipozenčić J. Human papillomavirus male genital infections: clinical variations and the significance of DNA typing. Clin Dermatol 2002;20:173-8.
28. Aynaud O, Ionesco M, Barrasso R. Penile intraepithelial neoplasia: specific clinical features correlate with histologic and virologic findings. Cancer 1994;74:1762-7.
29. Noel JC, Vandenbossche M, Peny MO, Sassine A, de Dobbeleer G, Schulman CC, et al. Verrucous carcinoma of the penis: importance of human papillomavirus typing for diagnosis and therapeutic decision. Eur Urol 1992;22:83-5.
30. Trombetta LJ, Place RJ. Giant condyloma acuminata of the anorectum: trends in epidemiology and management: report of a case and review of the literature. Dis Colon Rectum 2001;44:1878-86.
31. Antony FC, Ardern-Jones M, Evans AV, Rosenbaum T,

Russell-Jones R. Giant condyloma of Buschke-Loewenstein in association with erythroderma. Clin Exp Dermatol 2003;28(1):46-9.
32. Sexually trasmitted diseases treatment guidelines 2002. Center for Disease Control and Prevention. MMWR Recomm Rep 2002;51:1-78.
33. Kodner CM, Nasraty S. Management of genital warts. Am Fam Physician 2004;70:2335-42.
34. Chan EL, Kingston MA, Carlin EM. The laboratory diagnosis of common genital viral infections. J Fam Plan Reprod Health Care 2004;30(1):24-5.
35. Dunne EF, Burstein GR, Stone KM. Anogenital human papilomavirus infection in males. Adolesc Med 2003;14(3):613-32.
36. Wiley DJ, Douglas J, Beutner K, Cox T, Fife K, Moscicki AB, et al. External genital warts: diagnosis, treatment and prevention. Clin Infect Dis 2002;35(Suppl 2):210-24.
37. Lacey CJN. Therapy for genital human papillomavirus-related disease. J Clin Virol 2005;32S:S82-S90.
38. Riva JM, Sedlacek TV, Cunnane MF, Mangan CE. Extended laser vaporization in the treatment of subclinical papillomavirus infection of the lower genital tract. Obstet Gynecol 1989;73:25-30.
39. Beutner KR, Ferenczy A. Therapeutic approaches to genital warts. Am J Med 1997;102(5A):28-37.
40. Gupta AK, Cherman AM, Tyring SK. Viral and nonviral uses of imiquimod: a review. J Cutan Med Surg 2004;8(5):338-52.
41. Garland SM, Sellors JW, Wikstrom A, Petersen CS, Aranda C, Aractingi S, et al. Imiquimod 5% cream is a safe and effective self-applied treatment for anogenital warts: results of an open-label, multicentre phase IIIB trial. Int J STD AIDS 2001;12:722-9.
42. Abdullah AN, Walzman M, Wade A. Treatment of external genital warts comparing cryotherapy (liguid nitrogen) and trichloracetic acid. Sex Transm Dis 1993;20:344-5.
43. Krebs HB. Treatment of extensive vulvar condylomata acuminata with topical 5-fluorouracil. South Med J 1990;83:761-4.
44. Snoeck R, Bossens M, Parent D, Delaere B, Degreef H, Van Ranst M. Phase II double-blind, placebo-controlled study of the safety and efficacy of cidofovir topical gel for the treatment of patients with human papillomavirus infection. Clin Infect Dis 2001;33:597-602.
45. Dogra S, Kumar B. Circumcision in genital warts-lets us not forget! Sex Transm Infect 2003;79:265.
46. Moresi JM, Herbert CR, Cohen BA. Treatment of anogenital warts in children with topical 0,05 podofilox gel and 5% imiquimod cream. Pediatr Dermatol 2001;18(5):448-50.
47. Schaen L, Mercurio MG. Treatment of human papilloma virus in a 6-month-old infant with imiquimod 5% cream. Pediatr Dermatol 2001;18(5):450-2.
48. Gunter J. Genital and perianal warts: new treatment opportunities for human papillomavirus infection. Am J Obstet Gynecol 2003;189:S3-S11.
49. Lipke MM. An armamentarium of warts treatments. Clin Med Res 2006;4 (4):273-93.
50. Sherrard J, Riddell L. Comparison of the effectiveness of commonly used clinic-based treatments for external genital warts. Int J STD AIDS 2007;18:365-8.
51. Douglas JM, Eron LJ, Judson FN, Rogers M, Alder MB, Taylor E, et al. A randomized trial of combination therapy with intralesional interferon alpha 2b and podophyllin versus podophyllin alone for the therapy of anogenital warts. J Infect Dis 1990;162(1):52-9.
52. Cardamakis E, Kotoulas IG, Relakis K, Metalinos K, Michopoulos J, Stathopoulos E, et al. Comparative study of systemic interferon alpha-2A plus isotretinoin versus isotretinoin in the treatment of recurrent condyloma acuminatum in men. Urology 1995;45(5):857-60.
53. Orlando G, Fasolo MM, Beretta R, Merli S, Cargnel A. Combined surgery and cidofovir is an effective treatment for genital warts in HIV-infected patients. AIDS 2002;16:447-50.
54. Castellsague X, Bosch FX, Munoz N, Meijer CJ, Shah KV, de Sanjose S, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med 2002;346:1105-12.
55. Skjeldestad FE, et al. Prophylactic quadrivalent human papillomavirus (HPV) (types 6,11,16,18) L1 virus- like particle (VLP) vaccine (GardasilTM) reduces cervical intraepithelial neoplasia (CIN) 2/3 risk [Abstract] 43rd Annual Meeting of Infectious Diseases Society of America; October 2005, San Francisco, CA, USA.
56. Tjalma WAA, Van Damme P. Who should be vaccinated against human papillomavirus? Int J Gynecol Cancer 2006;16:1489-99.
57. Goldstone SE, Palefsky JM, Winnett MT, Neefe JR. Activity of HspE7, a novel immunotherapy, in patient with anogenital warts. Dis Colon Rectum 2002;45:502-7.

Genitalne bradavice - novi pristupi u lečenju

Sažetak

Epidemiologija: Genitalne bradavice su klinička manifestacija infekcije humanim papilomavirusima sa prevalencijom od 1% kod seksualno aktivne populacije.
Etiologija i imunologija: Humani papilomavirusi su epitelio-epidermotropni. Ćelijski imunološki sistem ima glavnu ulogu u regresiji oboljenja uzrokovanih ovim virusima.
Kliničke manifestacije: Najčešća klinička manifestacija genitalne infekcije humanim papilomavirusima su genitalne bradavice. Ispoljavaju se u vidu bradavičastih formacija koje mogu biti: šiljaste (condylomata

acuminata), karfiolaste (eng. couliflower-shaped), kupaste (eng. dome-shaped), zaravnjene (condylomata plana) ili viseće (eng. peduculated).

Dijagnoza i diferencijalna dijagnoza: Dijagnoza se najčešće postavlja na osnovu kliničke slike. Neposredno prisustvo virusa može da se dokaže jedino detekcijom HPV DNK.

Terapija: Za sada ne postoji specifično antivirusno lečenje. Terapija podrazumeva uklanjanje vidljivih promena sa kože i sluznica. U lokalnoj destrukciji lezija, pored klasičnih hirurških metoda, primenjuju se različiti hemijski i fizički agensi, a u sistemskoj terapiji agensi koji deluju na imunološki sistem. Lečenje nije u svim slučajevima jednako efikasno i recidivi su za sada neizbežni. Alternativu monoterapiji čini, sve češće, kombinovana terapija. Važnu ulogu u prevenciji ima vakcina.

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Erythrodermic cutaneous T-cell lymphoma: Two case reports

Miroslav Ž. DINIĆ[1]*, Lidija KANDOLF-SEKULOVIĆ[1],
Tomislav MLADENOVIĆ[1] and Radoš D. ZEČEVIĆ[1]

[1]Department of Dermatology and Venereology, Military Medical Academy, Belgrade
*Correspondence: Miroslav Ž. DINIĆ, E-mail: miroslavdinic@hotmail.com

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Abstract

Primary cutaneous T-cell lymphomas (CTCLs) are Non-Hodgkin lymphomas where skin may be the only involved organ for a long time. The erythrodermic form of CTCL, including Sezary syndrome, with increased IgE concentration, eosinophilia and intense pruritus, may suggest atopic dermatitis, in the lack of evidence for diagnosis of T-cell lymphoproliferative disorder. After vigorous research, two patients with erythroderma, increased IgE and eosinophilia, were not diagnosed with CTCL. Adult atopic dermatitis was diagnosed, based on clinical examination and histopathologic analysis of the skin sample. Therapy with oral cyclosporin A (CsA) and systemic corticosteroids were initiated, but the improvement was minimal and short-lived. Disease progression was noted in both patients, after a month of cyclosporine therapy: malaise, subfebrile and febrile temperatures, and development of generalized skin nodules were evident. In the first patient (aged 30) repeated examinations confirmed presence of Sezary cells in peripheral blood samples, dominant T-cell clone in the skin, peripheral blood and bone marrow, whereas the last repeated histopathologic analysis revealed T-lymphoproliferative skin disorder. In the second patient, (aged 44) primary cutaneous CD30+ T-cell lymphoma was diagnosed, based on histopathologic analysis of the newly appearing skin nodule. Differential diagnosis of erythroderma is always difficult, since clinical, histopathologic and immunophenotypic findings are frequently insufficient to differentiate between inflammatory and lymphomatous erythroderma. Treatment with cyclosporin A always demands carefull evaluation of the course of the disorder.

Erythroderma (erythema of at least 90% of the body skin surface) is a rare, but severe skin manifestation of several cutaneous disorders including psoriasis, atopic dermatitis, pityriasis rubra pilaris and cutaneous T-cell lymphoma (CTCL). CTCLs are Non-Hodgkin lymphomas where skin may be the only involved organ for a long time. Erythrodermic CTCLs most often include erythrodermic mycosis fungoides and Sezary syndrome. The erythrodermic form of CTCL, including Sezary syndrome, with increased IgE concentration, eosinophilia and intense pruritus, may be mistaken for atopic dermatitis in the lack of evidence for diagnosis of T-cell lymphoproliferative disorder. We report two patients with erythroderma, increased IgE and eosinophilia in whom, after vigorous research, the diagnosis of CTCL was not established, and adult atopic dermatitis was diagnosed. The therapy with cyclosporine A was initiated and after a month of therapy, which showed to be ineffective, repeated clinical examination and histopathological, immunohistochemical and gene rearrangement analyses, revealed existence of T-cell cutaneous lymhoma in both patients.

Case 1

A male patient, aged 30 years, was admitted to our Department with extremely itchy erythroderma with generalized peripheral lymphadenopathy and hyperkeratosis of the palms and soles, that lasted for two months (Figure 1). During the previous year he received therapy for dry, red and scaly erythematous macules in the skin folds, with topical and systemic corticosteroids and topical pimecrolimus, without improvement. A short course of P-UVA phototherapy led to minimal improvement.

Laboratory analyses revealed leukocytosis $16{,}65 \times 10^9$/L, and eosinophilia 8,5%, as well as elevated lactate dehydrogenase (LDH) of 559 U/L

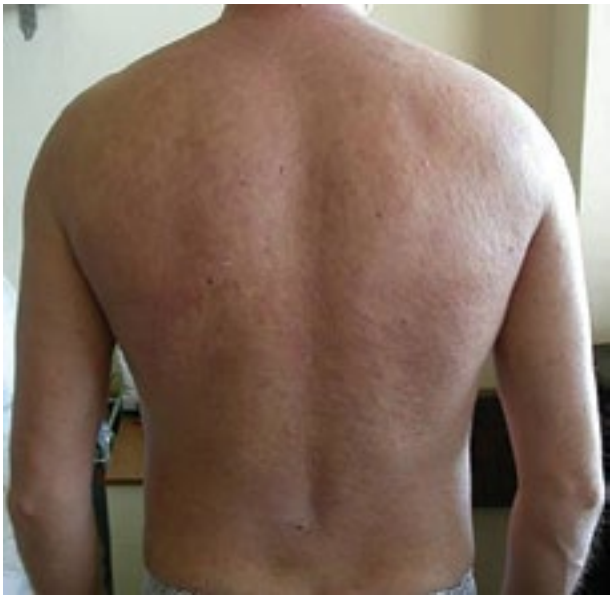

Figure 1. Erythroderma involving the back and upper arms in the first patient

and increased IgE concentration - 5650 IU/L. Other complete blood count (CBC) parameters, electrolytes, urea, creatinine, total bilirubine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gama glutamyl transpeptidase (γGT), IgG, IgA, IgM, were within normal range. ELISA HIV test was negative. Increased number of leukocytes was evident ($14x10^9$/L), in the peripheral blood smear, but Sezary cells were not found. Chest X-ray findings and abdominal and pelvic ultrasounds were normal. Histopathologic analysis of the skin sample specimens revealed immune inflammatory response and secondary neutrophilic spongiosis consistent with non-specific inflammatory dermatosis. Cytologic analysis of the left supraclavicular enlarged lymph node smear revealed a non-specific lymphoid hyperplasia. T-cell receptor-γ gene rearrangement analysis of skin and blood specimens showed polyclonal T-cell population. Due to lack of evidence for the diagnosis of T-cell lymphoproliferative disorder, the diagnosis of adult atopic dermatitis was established, and therapy with cyclosporin A (CsA) oral solution (5 mg/kg/bw), and methylprednisolone 40 mg/d i.v. was initiated, with chloropyramine i.m. and topical corticosteroid therapy.

Three weeks later, the patient referred for check-up with signs of disease progression: malaise, more enlarged peripheral lymph nodes, fever (39.1°C) generalized erythemolivid nodules, with more intense erythroderma. Repeated peripheral blood smear revealed younger lymphatic cells (5% were suspicious for Sezary cells). In the peripheral blood and skin, a dominant T-cell clone was detected by T-cell receptor-γ gene rearrangement analysis. A dominant T-cell clone was also detected in the bone marrow. CD4/CD8 ratio was increased to 7.8. Chest and abdominal multi-slice computed tomography (MSCT) revealed axillary lymphadenopathy up to 3.5 cm in diameter, while chest and retroperitoneal lymph nodes were not enlarged. Repeated skin biopsy was performed, and histopathological analysis was consistent with T-lymphoproliferative disorder - Sezary syndrome (Figure 2.). Based on repeated hemoculture test, staphylococcal sepsis was also diagnosed, so intravenous sulfametoxazol trimetoprim was administred. Based on these fingdings, diagnosis of Sezary syndrome was established in stage IIIB: T4 (confluence of erythema covering ≥80% body surface area) N1 (clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1) M0 (no visceral organ involvement) B2 (high blood tumor burden: positive clone, increased CD4/CD8), according to revised classification of mycosis fungoides/Sezary syndrome (1). The patient was reffered to a hematologist for

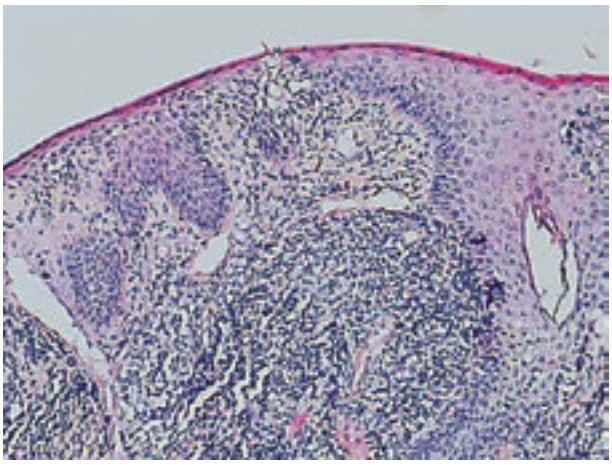

Figure 2. Focal parakeratosis, acanthosis and hypogranular epidermal basal layer are evident. In the superficial dermis, perivascular aggregation of lymphocytes is present, and in one follicle intraepidermal grouping of lymphocytes forming Pautrier's abscess is evident; subepidermal infiltration of eosinophils is evident, rare eosinophils are present intraepidermally (hematoxylin and eosin, x100)

polychemotherapy. He was treated with four cycles of cyclophosphamide, doxorubicine, vincristine, prednisolone (CHOP) chemotherapeutical protocol, that led to regression of erythroderma, but lymphadenopathy still remained unchanged, so treatment with second-line therapy with cytarabine, cisplatin, etoposide and methylprednisolone, was in course at the last follow-up.

Case 2

A male patient, aged 44, was admitted to our Department with generalized dry, scaly and itchy livid skin, and lichen ification on the elbows, knees and ankles. At the age of 26, his skin turned dry, scaly and itchy, and at the age of 39 his skin condition worsened, with pronounced livid erythema and scaling of over 95% of the skin surface. He was treated by several dermatologists for generalized ichthyosis of unknown cause. Repeated histopathologic findings, in the last 15 years, were non-specific and inconclusive. There was no other evidence of atopy in personal and family history. Topical corticosteroid therapy and emollients showed no benefit. The patient turned chronically subfebrile 4 months before admission, and generalized peripheral lymphadenopathy occured.

On admission, increased erythrocyte sedimentation rate (ESR) 38 mm/h, leukocytosis 13.91x10^9/L, eosinophilia 8.9%, thrombocytosis 604x10^9/L, and increased concentration of IgE (3200 IU/L) were established. Other parameters of CBC, blood biochemistry, AST, ALT, γGT, LDH, carcinoembrionic antigens (CEA), alpha fetoprotein antigens (AFP), amylase and immunoglobulins (G, A, M) were within normal range. ELISA tests for anti-HIV and anti-Borrelia burgdorferi antibodies were negative. Chest X-ray and abdominal and pelvic ultrasound findings were normal. Histopathologic analysis of skin specimens and hyperkeratotic skin specimens revealed chronic inflammation and reparative changes suggestive of hypersensitive reaction. Histopathological analysis of the enlarged right axillary lymph node specimen was consistent with dermatopathic lymphadenopathy. Examinations to establish a lymhoproliferative disease, including bone marrow biopsy, histopathological analysis, peripheral blood smear, T-cell receptor-γ gene rearrangement analysis of the skin, peripheral blood and bone marrow specimens, immunophenotypization of peripheral blood lymphocytes were done, but the nature of the presenting erythroderma was not elucidated. Due to the lack of evidence for diagnosis of T-cell lymphoproliferative disorder, it was concluded that the diagnosis could be an adult form of atopic dermatitis, so a trial of CsA oral solution (5 mg/kg/bw) with methylprednisolone (40 mg/d) i.v. was commenced, with systemic antihistamine and topical corticosteroids and emollients.

Three weeks later, the patient became febrile (38°C), with worsened peripheral lymphadenopathy (enlarged lymph nodes in the right groin were evident). Also, disseminated livid papules up to 5 mm in diameter, some with necrotic surface appeared, while erythroderma aggravated during the second admission (Figures 3a and 3b). Leukocytosis (14.51x10^9/L) and eosinophilia (9%), with platelets count of 590x10^9/L and ESR 67 mm/h were also present. The chemocultures remained sterile. The repeated peripheral blood smear confirmed leukocytosis and eosinophilia, while on flow-cytometry, CD4/CD8 index was within normal range. Histopathologic analysis of the enlarged lymph node specimen in the right groin revealed dermatopathic lymphadenopathy again. However, histo- pathologic analysis of the livid papule with necrotic surface led

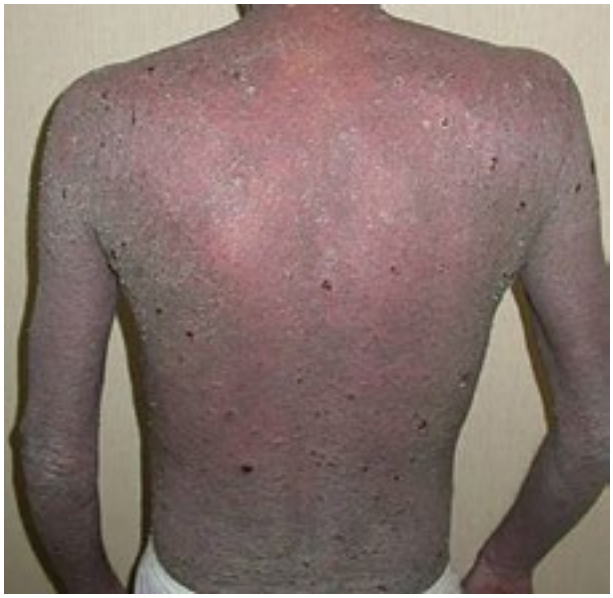

Figure 3.a. Erythemolivid skin color of the back and upper arms, with numerous necrotic papules in the second patient.

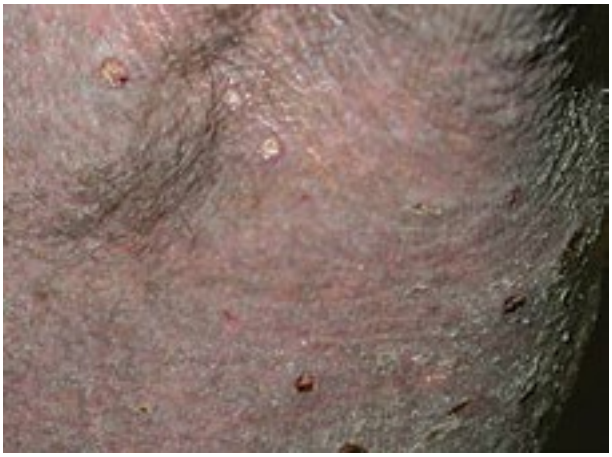

Figure 3.b. Close-up view at livid, scaly skin of the abdomen, with erosions at places of previous necrotic papules

to the following diagnosis: primary cutaneous CD30+ T-cell lymphoma (Figures 4a and 4b). The patient was referred to a hematologist who prescribed bleomycine, cyclophosphamide, doxorubicine, vincristine, prednisolone (B-CHOP) polychemotherapy. After six cycles of (B-CHOP) polychemotherapy, the skin lesions regressed, as well as lymphadenopathy, but the peculiar livid color of the skin was still evident on the last follow-up (Figure 5).

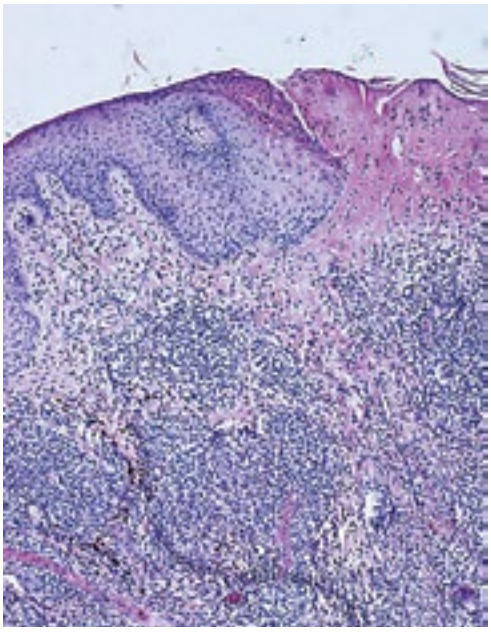

Figure 4.a. Superficial diffuse and pseudonodular deep dermal infiltration with superficial necrosis. The infiltrate consists of medium-sized cells, with one or several nucleoli; mitoses are evident. Eosinophils are present at the periphery (hematoxylin and eosin, x100);

Disscusion

Erythroderma is defined as an erythematous dermatitis involving of at least 90% of the cutaneous surface. It is a severe skin manifestation of several cutaneous disorders, including cutaneous T-cell lymphoma (CTCL). If the

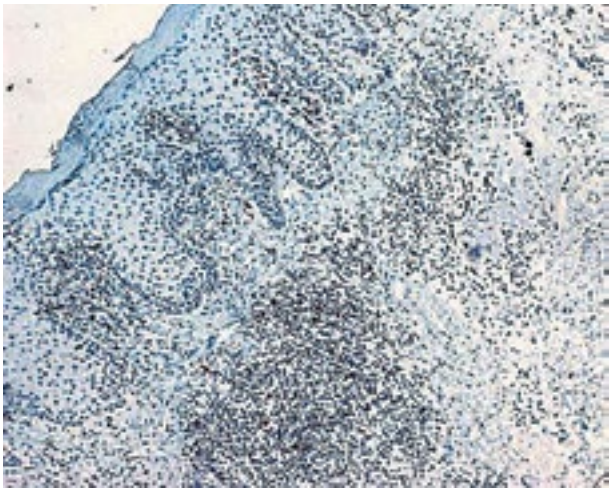

Figure 4. b. At least 20% of cells are CD30+ large cells with polymorphic nuclei and small nucleoli (immunoperoxidase staining, DAB chromogen, contrastained with hematoxylin, x100)

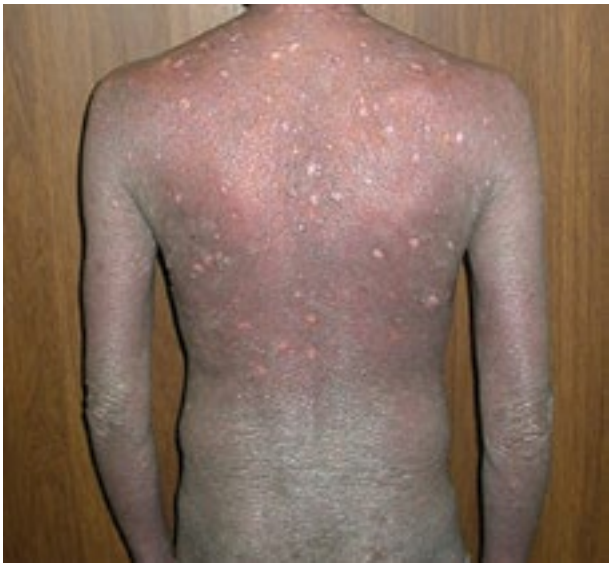

Figure 5. Regression of papulonecrotic lesions, with remaining of livid color of the skin in the second patient

diagnosis of a preexisted skin disorder was previously established, such as psoriasis, atopic dermatitis and pityriasis rubra pilaris, there are no doubts about the nature of erythroderma or its treatment. Considering the fact that CTCL is a slow-developing disorder, evolving skin changes and, often repeated, histopathologic findings of erythrodermic skin may lead to the diagnosis. In some cases, there are difficulties to differentiate between inflammatory dermatosis and skin lymphoma by clinical and histopathological features. Thus correlation of clinical appearance, immunohistochemistry and T-cell receptor-γ gene rearrangement analyses are needed (2). Sometimes, even that is not enough, so regular follow-ups and repeated analyses are necessary to detect the true nature of erythroderma and other skin changes of CTCL. It can be said that the final diagnosis of CTCL is possible during the course of the disease, when the tumor load is sufficient to be detected by vigorous research.

In the first patient, the diagnosis of Sezary syndrome, the most frequent form of erythrodermic CTCL, was diagnosed only after repeated analyses to identify the cause of erythrodrma, one month after the initiation of cyclosporine treatment. The other patient was diagnosed with primary cutaneous CD30+ T-cell lymphoma which manifested with erythroderma and necrotic skin nodules that appeared late during the course of the disease. Primary CD30+ CTCL are most frequently manifested as primary cutanous CD30+ anaplastic large cell lymphoma (ALCL), lymphomatoid papulosis, or borderline cases. Primary cutaneous CD30 + ALCL is manifested with multiple, often ulcerating, skin papules and nodules, like in our patient. On histopathological analysis, the majority of cells have anaplastic appearance, but in 20-25% cases non-anaplastic cells are present, which was the case in our patient (3). Erythroderma is not a typical feature of primary cutaneous CD30 + CTCL. In our patient, the preexisting, long-lasting erythroderma may be considered as secondary to the slowly developing T-cell dyscrasia, that could not be detected earlier by repeated histopathological analyses. Previously published cases of primary cutaneous ALCL with prolonged erythrodermic prodrome support this observation (4, 5).

Administration of CsA demands careful evaluation of the course of the disease. There is no evidence that CsA, used for the treatment of erythrodermic adult atopic dermatitis, caused lymphoproliferative disorders in these two cases, because the therapy lasted only a few weeks. According to previous reports, in adult atopic dermatitis patients, lymphoproliferative disease developed after at least 6 months of cyclosporine A treatment (6, 7). Also, in a large study, CTCL was not found to be more frequent in patients with atopic dermatitis, although in another study increased prevalence of lymphoma (especially cutaneous lymphoma) was found among patients with atopic dermatitis treated with topical corticosteroids (8, 9). Published case reports suggest that in rare cases CTCL may develop in atopic dermatitis patients who never received cyclosporine A therapy (10).

In conclusion, correlation of the clinical appearance, and, often repeated, histopathologic analysis of the skin, enlarged peripheral lymph nodes and bone marrow, together with peripheral blood smears, T-cell receptor-γ gene rearrangement analysis of the skin, peripheral blood and bone marrow specimens and immunophenotypization of peripheral blood lymphocytes, are useful in the diagnosis of patients with erythroderma without previously existing dermatosis, because the lymphomatous nature of presenting erythroderma may be elucidated (2).

References:

1. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1713-22.
2. Kandolf-Sekulović L, Cikota B, Dinić M, Škiljević D, Medenica Lj, Magić Z. T-cell receptor-γ gene rearrangement analysis in the diagnosis of patients with erythroderma. Serb J Dermatol Venereol 2009;1:17-26.
3. Willemze R, Jaffe E, Burg G, Cerroni L, Berti E, Swerdlow S, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-85.
4. Goyal S, Brinster NK, Goyal S. Ki-1(CD30) positive anaplastic large cell lymphoma: primary nodal disease relapsing as erythroderma. J Am Acad Dermatol 2002;47:S201-4.
5. Denton K, Wilson CL, Venning VA. Primary cutaneous anaplastic large-cell lymphoma with a prolonged erythrodermic prodrome. Br J Dermatol. 1992;126:297-300.
6. Mougel F, Dalle S, Balme B, Houot R, Thomas L. Aggresive CD30 large cell lymphoma after cyclosporine given for putative atopic dermatitis. Dermatology 2006;213:239-41.

7. Laube S, Stephens M, Smith AG, Whitaker SJ, Tan BB. Lymphomatoid papulosis in a patient with atopic eczema on long-term cyclosporine therapy. Br J Dermatol 2005;152: 1346-1348.
8. Mehrany K, El-Azhary RA, Bouwhui SA, Pittelkow MR. Cutaneous T-cell lymphoma and atopy: is there an association? Br J Dermatol 2003;149:1013-7.
9. Arellano F, Arana A, Wentworth C, Fernandez-Vidaurre C, Schlienger R, Conde E. Lymphoma among patients with atopic dermatitis and/or treated with topical immunosuppressants in the United Kingdom. J Allergy Clin Immunol 2009;123:1111-6.
10. Meyer N, Mazereeuv-Hautier J, Launay F, Lamant L, Paul C. CTCL complicating severe atopic dermatitis. Dermatology 2009;218:168-71.

Eritrodermalni kutani limfom T-ćelija - prikaz dva slučaja

Sažetak

Uvod: Primarni kutani limfomi T-ćelija su Non-Hočkinovi limfomi kod kojih koža može biti dugo jedini zahvaćeni organ. U nedostatku nalaza koji bi potvrdili limfoproliferativno oboljenje T-ćelija, eritrodermijski oblik ovih limfoma (uključujući i Sezarijev sindrom), uz visoke koncentracije IgE, eozinofiliju i izrazit svrab može da podseća na atopijski dermatitis.

Prikaz slučaja: Dva bolesnika, hospitalizovana zbog eritrodermije, kod kojih opsežnim ispitivanjima nije dokazano limfoproliferativno oboljenje, pod dijagnozom eritrodermijskog adultnog atopijskog dermatitisa lečeni su oralnim ciklosporinom uz sistemske kortikosteroide, sa privremenim i minimalnim poboljšanjima. Bolest je kod oba bolesnika progredirala u vidu pogoršanja opšteg stanja, febrilnosti i pojave generalizovanih eritemolividnih nodusa. Kod prvog bolesnika ponovljenim ispitivanjima postavljena je dijagnoza Sezarijevog sindroma na osnovu histopatološkog nalaza kože koji je upućivao na T-limfoproliferativno oboljenje, nalaza Sezarijevih ćelija u razmazu periferne krvi i nalaza monoklonske populacije T-limfocita u koži, perifernoj krvi i kostnoj srži. Kod drugog bolesnika histopatološkom analizom jednog od novonastalih nodusa detektovan je periferni T-ćelijski limfom.

Zaključak: Diferencijalna dijagnoza između inflamatorne dermatoze i eritrodermijskog primarnog T-ćelijskog limfoma uvek je teška i zahteva ponavljana ispitivanja sa ciljem dokazivanja mogućeg limfoma. Primena ciklosporina u terapiji uvek zahteva pažljivo praćenje toka bolesti.

THE NOVI SAD DERMATOVENEREOLOGIC MOULAGE COLLECTION,
CLINIC OF DERMATOVENEREOLOGY, CLINICAL CENTER OF VOJVODINA, NOVI SAD, SERBIA
VOJISLAV ŠIKOPARIJA, SCULPTOR DONATES HIS MOULAGES TO THE FACULTY OF MEDICINE IN NOVI SAD, BELGRADE, 1964

History of dermatology and venereology in Serbia - part III/1: Dermatovenereology in Serbia from 1881 - 1918

Bosiljka M. LALEVIĆ-VASIĆ*

Institute of Dermatology and Venereology, Clinical Center of Serbia, Belgrade, Serbia
*Correspondence: Bosiljka LALEVIĆ-VASIĆ, E-mail: labuba@eunet.rs

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Abstract

This paper deals with the period from 1881 to 1918, when the following Sanitary Laws were passed: *Law on the Organization of the Sanitary Profession and Public Health Care* (1881), which implemented measures for protection from venereal diseases, as well as restriction of prostitution; *Public Sanitary Fund* (1881), with independent budget for health care; *Announcement on Free of Charge Treatment of Syphilis* (1887). Dermatovenereological Departments were also founded: in the General Public Hospital in Belgrade (1881), and in the General Military Hospital (1909). The Hospital in Knjaževac for Syphilis was reopened (1881), as well as mobile and temporary hospitals for syphilis, and a network of County and Municipality hospitals. The first Serbian dermatovenereologist was Dr. Jevrem Žujović (1860 – 1944), and then Dr. Milorad Savićević (1877 – 1915). Skin and venereal diseases were treated by general practitioners, surgeons, internists and neurologists. Although Dr. Laza Lazarević (1851 – 1890) was not a dermatologist, but a physician and a writer, he published three papers on dermatovenereology, whereas Dr. Milorad Godjevac (1860 – 1933) wrote an important study on endemic syphilis. From 1885 to 1912, organization of dermatovenereology service has significantly improved. Considering the fact that archive documents are often missing, only approximate structure of diseases is specified: in certain monthly reports in Zaječar, out of all the diseased persons, 45% had skin or venereal diseases, while in Užice the number was 10.5%, which points to different distribution of these diseases. High percentage of dermatovenereology diseases was caused by high frequency of venereal diseases and syphilis. During the war: 1912 – 1918, the military medical service dominated, and in 1917 *Prince Alexander Serbian Reserve Hospital was founded in Thessaloniki* with a *Department for Skin and Venereal Diseases*. During this period, work of the Civilian Health Care Service was interrupted, consequently leading to a considerable aggravation of public health.

This chapter focuses on the period from 1881, when the health care service was legally regulated, to 1918, when the First World War ended. After the Serbian-Bulgarian War (1885), being on the crossroads of Turkish, Austrian and Russian interests for a long time, Serbia entered a period of peace, which lasted about 25 years. Despite the political turmoil in the country, it contributed to progress in every aspect. After this period, the country entered yet another period of war (1912 – 1918), and the newly established Sanitary Service was shut down. The number of military physicians, insufficient during the peace, became even more apparent during the war, so that civilian doctors were recruited to the army (1), whereas the Sanitary Service was almost completely transformed into a Military Sanitary Service. The consequences were to be distressing and long lasting.

Legislation and organization of the dermatovenereology service

After the wars which led to the liberation of Serbia (1876 – 1878), things which happened before, occurred again, like in similar situations in the past: the major health problem was the spread of communicable diseases, while their occurrence was associated with historical ups and downs of the country. Apart from venereal diseases, skin diseases spread as well, due to lack of health care, but also due to low life and hygiene standards. Although syphilis remained a dominant health concern, dermatology gained recognition in the frame of general health care.

This period was characterized by establishment of sanitary laws (2), under the authorization of Dr. Vladan Đorđević, the chief of the Sanitary Department

of the Ministry of Internal Affairs - MIA (1879 – 1884) (3). In 1881, on his initiative, a *Public Sanitary Fund* was established, which provided an independent sanitary budget (2, 3). Dr. Vladan Đorđević created a *Law on the Organization of the Sanitary Profession and Public Health Care* (hereinafter: *Sanitary Law*), which was also adopted in 1881 (4). World experts found it to be one of the best and most contemporary laws in Europe (5).

Of the general *Sanitary Law* regulations, which applied to all sanitary districts, two were significant for the development of the dermatovenereology service:

- Foundation of district and county hospitals over the whole country during a 10-year-period (6);
- Submission of formal reports on the public health on regular basis (7, 8).

Certain law articles concerned organization and development of the dermatovenereology profession:

- Measures for the prevention of multiplication and spread of venereal diseases (9);
- Suppression of wanton and all that provoked it (8).

In the same year, *Prostitution Regulations* (10) and *Regulations of the Hospital Funds gained for Prostitutes* were passed. These funds were used for medical check-ups and hospital treatment of prostitutes (11).

The *Announcement dated 1887*, was of utmost importance for the dermatovenereology service. According to the *Announcement*, treatment of syphilis was free of charge for peasants and workers, regardless of their financial status. In 1895, this privilege was exercised by all patients with sexually transmitted diseases, as well as by railway "guardians" and low-paid railway staff (12).

The main obstacles for the enforcement of these laws included lack of physicians, lack of specialists and hospitals, and that is why special attention was paid to the above mentioned.

Hospitals

The Sultan's Edict ("Hatiserif") from 1830 (12), allowed building of hospitals in Serbia, but they were mostly organized in unsuitable buildings for their purpose, whereas their number and equipment were rather deficient. The conclusions of the *Medical Board for the investigation of "frenga"* in 1846 (see part II), according to which syphilis was to be treated in hospitals, was extremely important. The new *Sanitary Law* intended development of a hospital network, as well as reorganization of the existing hospitals, defining eradication of venereal diseases as one of the greatest problems.

By the *Sanitary Law*, the previous *County and Belgrade City Hospital* was transformed into the *General Public Hospital* (GPH), with five departments, one of them being the *Department for Skin Diseases and Syphilis*. It was the first dermatovenereology department in Serbia, and it had separate sections for male and female patients (5, 6).

A Department for Skin and Venereal Diseases was also founded in the frame of the General Military Hospital (GMH), after a new hospital was built in the western part of Vračar, in 1909. The acting chief of the Department was Captain First Class, Dr. Milutin Pop Jovanović (13).

The Knjaževac *Hospital for Syphilis*, burnt down in 1876 in the Serbian – Turkish war (see part II), was reopened in 1881, in a private residence. It remained there for ten years to come, but after that it was moved into a restored, old hospital (14).

The County and District General Hospitals also represented important centers for the treatment of skin and venereal diseases.

Apart from these, in regions with a great number of patients suffering from syphilis, in 1882 a new way of treatment was organized: *two mobile hospitals,* which were active till 1885, with some interruptions. The treatment took place at a person's residence, under the supervision of a doctor, and it lasted for months, even after the end of treatment (12, 14).

For the same reasons, in 1894, three *temporary hospitals for syphilis* were founded: in *Vitkovo, Krupanj and Soko Banja*, as well as a *Hospital for the Treatment of Syphilis* in Boljevac (15).

These kinds of hospitals were possibly organized in other areas with a great number of diseased.

This extraordinarily long period of peace allowed good organization of an antivenereal service, decreasing the number of patients with syphilis. In 1912, a war period started, and lasted till 1918. At that time, the total number of physicians in Serbia was 370, out of which 296 were recruited into the

army, whereas 57 physicians capable of work were left behind (16). It affected the public health a great deal, causing spread of venereal and skin diseases once again. During the war period, a military sanitary network was reorganized, and on March 16, 1917, the *"Prince Alexander Serbian Reserve Hospital"* (PASRH) was founded in Thessaloniki. It was the Central Military Hospital of the Serbian Army in exile; it included a *Department for Skin and Venereal Diseases*, and its chief was Major Dr. Dušan Kopša (17).

In this way, organization of dermatovenereology service gained its position both in peace and in war. However, the discontinuity, which goes hand-in-hand with the Serbian history through centuries, this time, also stopped the progress of the sanitary service.

Physicians

One of the reasons which made enforcement of the *Sanitary Law* extremely difficult was lack of physicians in Serbia: in 1895 there were 150, in 1900 there were 200, and in 1908 there were 288 physicians. Before the outbreak of the Balkan Wars, in 1912, there were 370 physicians in Serbia. Although the law required medical specialists for some positions, with the exception of surgeons (there were 30 surgeons at the end of the 19th and at the beginning of the 20th century) (3), they were extremely scarce. Until the twentieth years of the 20th century, dermatovenereologists were really rare. That is why implementation of the *Sanitary Law* took a long time.

Dr. Jevrem Žujović (1860 – 1944) was the first educated Serbian dermatovenereologist (Figure 1). He studied medicine in France, and specialized in dermatovenereology at the St. Louis Hospital in Paris with Professor A. Fournier, a specialist in syphilisology of worldwide reputation (18). He became a Head of the *Department of Skin Diseases and Syphilis* at the GPH in 1889 (19). He implemented modern dermatology doctrine in the whole country, organized struggle against syphilis and surveillance of prostitution, and also studied leprosy. He introduced arsenic into the treatment of syphilis, while in 1909 he organized a laboratory for the Wassermann reaction test and microscopic detection of *Treponema pallidum* in skin lesions (20). He translated a book by A. Fournier: "Syphilis and Marriage". Together with M. Jovanović-Batut, he wrote "Instructions on Syphilis" according to the decision of the Serbian Medical Society (21). He was also the first President of the Yugoslav Dermatology Association.

Figure 1. Jevrem M. Žujović

Dr. Milorad Savićević (1877 – 1915) was a Vienna medical student who specialized in dermatovenereology with Professor Dr. E. Finger. From 1908, he was a secondary physician at the GPH. He died from spotted typhus in 1915 (21). During his short life he had built up an enviable bibliography. Apart from several professional and scientific papers, he wrote the following books: "Venereal Diseases", "Venereal Diseases and their Effects on Marital Life and on the Offspring", "Prostitutes", "Who May get Married", "Sexual Life and its Consequences", "Physicians and the Audience". "The Beauty of the Body, its Care and Cosmetology" is probably our first book in cosmetology. He also translated several books on syphilis (22). His early death was a great loss for Serbian dermatovenereology.

Dr. Filip Tajsić, a Sanitary Colonel, was a Vienna student; he specialized in dermatovenereology for 11 months in Paris, but he never practiced it. After his return to the country, he joined the army where he

mostly held leading position in the Military Medicine (21).

The above mentioned doctors, *Milutin Pop-Jovanović* (GMH) and *Dušan Kopša* (PAH) were educated dermatovenereologists as well. The former one died in 1914, from sepsis (23).

According to the documents and reports of the Serbian Medical Society, as well as of the Serbian Archive for General Medicine, skin and venereal diseases were mostly treated by general practitioners, surgeons, internists and neurologists. Some of them attracted special attention.

Dr. Laza Lazarević, (1851 – 1890), was a writer, creator of the genre of realistic story, "our first clinician, first scientist and first philosopher-physician" (21). During his short life he left his mark in dermatology as well. He graduated from medicine in Berlin in 1879, with a thesis entitled "Effects of Mercury on Rabbit Tissues" (24). He also published the following papers: "A Contribution on Latent Syphilis" (25); "Two Rare Cases of Erythema Nodosum" (26); "Exanthem – Variola – Syphilitic Exanthem" (27).

Dr. Milorad Gođevac (1860 – 1933), was a physician in Belgrade municipality (21). He spent three years in Knjaževac (1890 – 1893) on a "special mission" by the order of the MIA, in order to study endemic syphilis and suggest solutions for its eradication. After this mission, he published a monograph which remained a valuable document on all circumstances in the region (28).

In this period, *Vojislav Mihailović* (Graz, 1904), (29), *Ivan Marković* (Vienna, 1914), and *Miloš Đorić* (Nancy, 1914) (30), were among our students of medicine who later became eminent dermatovenereologists.

(To be continued in the next issue)

References:

1. Stanojević Vl. Rad našeg saniteta u Balkanskom ratu 1912. i 1913. godine [Our sanitary service during the Balkan wars, in 1912 and 1913]. U: Gvozdenović N, Stanojević L, urednici. 700 godina medicine u Srba [700 years of Medicine in Serbs]; Beograd: SANU; 1972. str. 218-26.
2. Milovanović V, urednik. Medicinski godišnjak Kraljevine Jugoslavije. Ministarstvo socijalne politike i narodnog zdravlja br. 15080 [Medical almanac of the Kingdom of Yugoslavia. Ministry of social policy and public health, No: 15080]. Beograd: Jugoreklam; 1933.
3. Đokić D, Dovijanić P. Osamdeset godina u službi zdravlja naroda. 2. izd. [Eighty years of the public health service, 2nd ed]. Beograd: Institut za zaštitu zdravlja Srbije "dr Milan Jovanović Batut"; 2000.
4. Garašanin M. Raspis svim Načalstvima, upravi varoši Beograda i gospodinu Ministru finansija [Circular announcement to all executives, city administration of Belgrade and mr. ministry of finance]. Nar Zdrav 1882;1:13.
5. Gjorgjewitj V. Entwicklung der oeffentlichen Gesundheitspflege im Serbischen Königreiche von XII Jahrhundert an bis 1883. Berlin: Max Pasch; 1883.
6. Zakon o uređenju sanitetske struke i o čuvanju narodnog zdravlja [Law on the organization of the sanitary profession and public health care]. Srp Novine. 1881 Apr.10;49(80).
7. Zakon o uređenju sanitetske struke i o čuvanju narodnog zdravlja [Law on the organization of the sanitary profession and public health care]. Srp Novine. 1881 Apr. 6;49(76).
8. Zakon o uređenju sanitetske struke i o čuvanju narodnog zdravlja [Law on the organization of the sanitary profession and public health care]. Srp Novine 1881 Apr. 4;49(75).
9. Zakon o uređenju sanitetske struke i o čuvanju narodnog zdravlja [Law on the organization of the sanitary profession and public health care]. Srp Novine 1881 Apr. 9;49(79).
10. Garašanin M. Pravila o regulisanju prostitucije [Prostitution regulations]. Nar Zdrav 1882;1:10-3..
11. Pravila o rukovanju sa bolničkom kasom prostitucijanih [Regulations of the hospital funds for prostitutes]. Nar Zdrav 1881;1(31):385-6.
12. Mihajlović V. Istorija polnih bolesti u Srbiji do 1912. godine [The history of venereal diseases in Serbia up to 1912]. Beograd: Štamparija Centralnog higijenskog zavoda 1931;7.
13. Stojiljković MP, Zeljković J, Tadić V. Iz istorije Vojnomedicinske akademije: I Vojne bolnice u Beogradu od 1836. do 1838. godine [Out of the history of the military medical academy: the first military hospitals in Belgrade, from 1836 to 1838]. Vojnosanit Pregl 2002;59(3):329-33.
14. Ivanović-Šakabenta D. 150 godina bolnice u Knjaževcu [150th anniversary of the Knjaževac hospital]. Knjaževac: Zdravstveni centar; 2001.
15. Kalendar sa šematizmom Knjaževstva Srbije za godinu 1894. [A schematic calendar of the Serbian principality for 1894]. Beograd: Državna štamparija; 1894.
16. Ignjatović M. Istorija vojne hirurgije u Srbiji (do Drugog svetskog rata) [The History of the military surgery in Serbia (till the second world war)]. U: Čolović RB, urednik. Hronika hirurgije u Srbiji (Annals of surgery in Serbia). Beograd: Prosveta; 2002. str.143-98.
17. Nedok AS. Reorganizacija vojnog saniteta u 1916. godini [Reorganization of the military sanitary service in 1916]. U: Nedok AS, Dimitrijević B, urednici. Srpski vojni sanitet u 1916. godini [The Serbian military sanitary service in 1916]. Beograd: Akademija medicinskih nauka SLD; 2007. str. 11-42.
18. Žujović J. Curriculum vitae. Arhiv Muzeja SLD.
19. Kalendar sa šematizmom Knjaževstva Srbije za godinu 1889. [A schematic calendar of the Serbian principality for 1889].

Beograd: Državna štamparija; 1889.
20. Žujović J. Rapport de la Société de la Croix-Rouge des Serbes, Croates et Slovènes à la conférence régionale de l'Europe orientale sur les maladies vénériennes. Décembre 1921, Prague. (Rukopis). Beograd: Arhiv Muzeja SLD ; 1921.
21. Stanojević V. Likovi i dela istaknutih lekara od osnivanja Srpskog lekarskog društva do danas [Lives and work of outstanding physicians from the foundation of the Serbian medical society till present]. U: Đurić D, i dr.urednici. Srpsko lekarsko društvo 1872-1972: spomenica. Beograd: SLD; 1972. str.159-234.
22. Stanojević S, urednik. Savićević dr Milorad. U: Narodna enciklopedija srpsko-hrvatsko-slovenačka [National encyclopedia of Serbo-Croats and Slovenes]. Zagreb: Bibliografski zavod d.d; 1928.
23. Nedok AS. Personalna istorija srpskog vojnog saniteta [Personal history of the Serbian military sanitary service]. U rukopisu (A manuscript).
24. Lešić A, Bumbaširević M. Dr Laza K. Lazarević - književnik i lekar (1851-1890) [Dr. Laza K. Lazarević, a writer and a physician]. Srp Arh Celok Lek 2005;133(1-2):106-9.
25. Lazarević LK. Jedan prilog za latentnu sifilidu [A contribution on latent syphilis]. Srp Arh Celok Lek. 1881; 2-4.
26. Lazarević LK. Dva retka slučaja erythema nodosum [Two rare cases of erythema nodosum]. Srp Arh Celok Lek 1883:97-103.
27. Lazarević LK. Egzantem-variola-sifilisni egzantem: saopštenje na 13. redovnom sastanku SLD [Exanthem – variola – syphilitic exanthem: announcement]. Beograd: SLD; 1887.
28. Gođevac M. Sifilis u Timočkoj krajini. Način kako da se stane na put širenju te zaraze [Syphilis in the Timok region. modalities for stopping the spread of the infection]. Beograd: Parna radikalna štamparija; 1893.
29. Kalendar sa šematizmom Knjaževstva Srbije za godinu 1904. [A schematic calendar of the Serbian principality for 1904]. Beograd: Državna štamparija; 1904.
30. Kalendar sa šematizmom Knjaževstva Srbije za godinu1914. [A schematic calendar of the Serbian principality for 1914]. Beograd: Državna štamparija; 1914.

Abbreviations

MIA: Ministry of Internal Affairs
GPH: General Public Hospital
GMH: General Military Hospital
PASRH: Prince Alexander Serbian Reserve Hospital

Prof. Dr. Mirjana Poljački
1949 – 2009

Professor Dr. Mirjana Poljački was born on August 9, 1949 in Sombor. She received her education in Novi Sad and graduated from the Faculty of Medicine as an excellent student.

Prof. Dr. Mirjana Poljački started her teaching, scientific and professional career in 1976. As a physician specializing in dermatovenereology, she was granted the position of a research assistant in dermatovenereology. Gradually, she passed from one position to another, both at the Faculty of Medicine and Clinic of Dermatovenereology in Novi Sad: from a research assistant to a full professor and a Head of the Department of Dermatovenereology, from a specializing student to the Head of the Clinic of Dermatovenereology. Prof. Dr. Mirjana Poljački acquired a rich teaching, research and professional experience.

After becoming an associate professor in 1997, and a full professor in 2002, Professor Dr. Poljački was included in all the teaching activities at the Department of Dermatovenereology. Apart from taking part in the teaching process for students of medicine and dentistry, for physicians specializing in dermatovenereology, general medicine, occupational medicine and emergency medicine, Prof. Dr. Mirjana Poljački was the Chair of the Commission for Specialist's Exam in Dermatovenereology for years.

As a distinguished educator she contributed to the establishment of higher standards of the teaching process of dermatovenereology. She published and edited "Test Questions in Dermatovenereology", using tests as a contemporary means for student knowledge assessment. She edited a monograph "Basocellular and Spinocellular Skin Cancers" and was a coauthor of a textbook for students of medicine and dentistry "Selected Chapters in Skin Pathology" and "Dermatology", which was published in 2000.

She mentored three students writing scientific papers, a few graduate students obtaining their master's degrees, and one postgraduate student defending his PhD thesis. She published numerous scientific and professional papers, as an author and a coauthor, in international and national journals, and took part in international and national meetings. Prof. Dr. Mirjana Poljački received a great number of awards for her research and professional practice. She participated in three scientific projects, of special value for the development of scientific disciplines, and she was a principal investigator of one research project. She was a member of many associations.

Her main professional interest was in allergology and immunology in the field of dermatovenereology. Apart from these activities, Prof. Dr. Mirjana Poljački founded a Service for Radiation Therapy for Skin Cancer.

Unfortunately, before her full retirement, in December 2008, she fell ill with a severe, incurable illness.

In the end, I should like to point out that using her creative and positive attitude, Prof. Dr. Mirjana Poljački showed an outstanding ability in developing young scientists and professionals, for which we are deeply grateful.

Prof. Dr. Verica ĐURAN

Clinic of Dermatovenereology Diseases,
Clinical Center of Vojvodina, Novi Sad, Serbia
*Correspondence: Prof. Dr. Verica ĐURAN
E-mail: angiologija@nadlanu.com

A report on the 6th Spring Symposium of the European Academy of Dermatology and Venereology

After Malta, Budapest, Lapland, Sofia and Istanbul, the 6th EADV Spring Symposium was held in Bucharest, Romania, from April 23-26, 2009. The Chair of the Local Organizing Committee was Dan Forsea, and Vice-Chair was Virgil Feier. The Spring Symposium of EADV is a beautiful tradition, bringing together Dermatologists from all parts of Europe and beyond. The concept of the Symposium was "Endless Dermatology", inspired by the famous work of the world-wide known Romanian sculptor, Constantin Brancusi. His sculpture, "The Endless Column", stands as the logo of the Symposium, as a symbol of the endless passion to learn, to understand in depth and to strive higher, but also to develop and to perfect our science and our art - Dermatology.

Dermatologists from Serbia were also present in Bucharest. Professor Ljiljana Medenica was the Co-Chair in workshops: "The Burden of Ageing Skin", and she delivered her lecture "Rejuvenation of the Ageing Skin". An oral presentation was held by Dr. Javorka Delić and Dr. Milutin Delić: "*Ulcus Cruris venosum* - Impact on the Quality of Life" and Dr. Jadranka Krstić and Dr. Spasoje Radovanović: "Nail Plate Dermatoscopy - a Two Year Study". Eleven posters were exhibited from Serbia.

Figure 1. Prof. Dr. Mirjana Paravina - Niš, Prof. Dr. Virgil Feier - Timisoara, Prim. Dr. Zoran Nedić - Pančevo i Prim. Dr. Josa Lotrean - Alibunar

Six plenary lectures were also presented: Placing Quality of Life in Dermatology Care, Prevention Strategies in Skin Cancer, Advantages and Pitfalls of Biologics in Psoriasis, The Role of Dermato(patho) logy in Composite Tissue (hands and face) Allografts, Kaposi Sarcoma - an Enigma Solved?, and Climate Change and Human Skin Cancer. Seventeen symposia, 17 workshops and 8 focus sessions, along with forums, poster discussions, free communication sessions and satellite symposia, have given the opportunity to physicians and scientists to meet and share their experiences with the skin.

Figure 2. Prof. Dr. Mirjana Paravina - Niš, Prim. Dr. Zoran Nedić - Pančevo, Dr. Danijela Čoloka - Vršac, Dr. Persa Ghitulesku - Timisoara and Dr. Daniela Zaharia - Timisoara

The next EADV Spring Symposium will be held in Cavtat (Croatia) in May, 2010.

Zoran NEDIĆ
Medical Center "South Banat",
Department of Dermatovenereology
*Correspondence: Zoran NEDIĆ
E-mail: nedicz@panet.co.rs

FORTHCOMING EVENTS

Dermatology and Venereology Events 2009-2010

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
17-19 September, 2009	8th Congress of the Baltic Association of Dermatovenereologists Vilnius, Lithuania	31 July, 2009	www.badv2009.com
18-19 September, 2009	Photodermatology Meeting & Photopatch Test Course Krakow, Poland	No abstract submission	www.photopatch.eu
23-26 September, 2009	4th Congress of the Dermatovenereologists of Macedonia, Ohrid	15 June, 2009	www.unet.com.mk/dermatology/
7-11 October, 2009	18th EADV Congress, Berlin, Germany	4 March, 2009	www.eadvberlin2009.com
9-12 November, 2009	11th IUSTI World Congress Spier Wine Estate, Cape Town, South Africa	1 June, 2009	www.iusti.co.za
11-14 November, 2009	12th European AIDS Conference Cologne, Germany	1 July, 2009	www.eacs-conference2009.com
12-14 November, 2009	2nd IDS Congress Barcelona, Spain	15 July, 2009	www.idsdermoscopycongress2009.com
17-20 November, 2009	11th World Congress of Pediatric Dermatology, Bangkok, Thailand	7 July, 2009	www.kenes.com/wcpd
21-23 January, 2010	International Congress of Aesthetic Dermatology, Bangkok, Thailand	20 September, 2009	www.euromedicom.com/index.php
26-28 March, 2010	Hair and Scalp Diseases in Clinical Practice, Warsaw, Poland	Under construction	www.spederm.eu
13-16 May, 2010	7th EADV Spring Symposium Cavtat, Croatia	Under construction	www.eadv.org/eadv-meeting
1-4 July, 2010	Congress of the Psoriasis International Network, Paris, France	15 February, 2010	www.pso2010.com
9-11 September, 2010	40th Annual ESDR Meeting, Helsinki, Finland	Under construction	www.esdr.org/index.php
15-18 September, 2010	10th Congress of the European Society of Contact Dermatitis, Strasbourg, France	March, 2010	www.escd-gerda2010.com
6-10 October, 2010	19th EADV Congress Gothenburg, Sweden	Under construction	www.eadv.org/eadv-meeting
4-7 November, 2010	1st World Congress on Controversies in Plastic Surgery and Dermatology, Barcelona, Spain	4 September, 2010	www.comtecmed.com/coplasdy/2010

Prepared by: Dr. Tatjana Roš, Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia

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.*

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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.*

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

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

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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/.

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