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A word of introduction

After a period of over 80 years of existence, the Association of Dermatovenereologists of Yugoslavia, established on December 17th, 1927 in Belgrade, has changed its official name to the Serbian Association of Dermatovenereologists, proposed by General Assembly of the Association of Dermatovenereologists of Yugoslavia on February 17th, 2007 in Belgrade.

Founding of the journal of the Association of Dermatovenereologists of Yugoslavia was realized through the efforts of three Slovenian dermatologists: J. Fettich, A. Kansky and S. Bunta. In 1974, they launched a journal *Acta dermatovenerologica Iugoslavica (Acta Derm Iug)*, published by the Association of Dermatovenereologists of Yugoslavia. *Acta Derm Iug* was published for 18 years, four times a year (except in the period 1985 – 1986, when volumes 12 and 13 were not available) in Serbian and Croatian languages. The Editors-in-Chief, from 1974-1991, were dermatologists from former Yugoslavia: J. Fettich (1974–1983) from Ljubljana; J. Lalošević (1984-1987) from Belgrade and A. Kansky (1988–1991) from Zagreb. After the outbreak of civil war in former Yugoslavia, the Editor-in-Chief of the *Acta Derm Iug,* A. Kansky, transferred the Editorial Office from Zagreb to Ljubljana, and continued with publishing of *Acta Derm Iug* (YU ISSN 0302-4466).

Editor-in-Chief of *Acta Derm Iug,* A. Kansky, changed the name and renewed the registration of the *Acta Derm Iug* in 1992, to *Acta dermatovenerologica Alpina, Pannonica et Adriatica (Acta Dermatovenerol Alp Panonica Adriat)*. The dermatological journal *Acta Dermatovenerol Alp Panonica Adriat* (ISSN: 1318-4458) published by Dermatovenereologic Society of Slovenia, started to appear in 1992 in Ljubljana and thus continued *Acta Dermatovenerologica Iugoslavica* (1).

Nevertheless, in the 1992, the Association of Dermatovenereologists of Yugoslavia still existed, even during the turbulent times and the isolation in ninth decade of the XX century, due to great efforts of dermatovenereologists from Serbia. However, after the outbreak of the civil war in former Yugoslavia, due to financial and technical difficulties, publishing of *Acta Derm Iug* was stopped.

After a 4-year-pause, *Acta Derm Iug* published by the Association of Dermatovenereologists of Yugoslavia, appeared again in 1996. The Editor-in-Chief was I. Dostanić. *Acta Derm Iug*, volume 19, issue No 1 was published (YU-ISSN 0345-7558) (2), but during the following year, lack of adequate regard interrupted its regular publication again.

During the 15th Congress of the Association of Dermatovenereologists of Yugoslavia, which took place in Belgrade in 1996, General Assembly of the Association elected a new Editor-in-Chief of *Acta Derm Iug*, M. Nikolić from Belgrade. In 1997 the Editorial Board was moved to the Institute of Derma-

tovenereology in Belgrade. *Acta Derm Iug* volume 20 , issues No 1 (YU-ISSN 0345-7558) and 2 (YU-ISSN 0345-7558) were published (3,4). Soon after that, publishing activities of the Association of Dermatovenereologists of Yugoslavia ended.

With the aim to acquaint the medical and wider community with its activities, the Serbian Association of Dermatovenereologists started to organize and establish publishing activities once again. These activities are initiated with the aim of satisfying scientific, professional, educational, health-pedagogical and other needs of the Association members, wider medical community, as well as other citizens.

General Assembly of the Serbian Association of Dermatovenereologists which took place in Belgrade, on April 11th, 2008, decided to establish a new scientific-professional journal of the Association titled *Serbian Journal of Dermatology and Venereology* (*Serb J Dermatol Venereol*).

Serb J Dermatol Venereol (ISSN 1821-0902), will be published quarterly by the Serbian Association of Dermatovenereologists, in English language. Contents of the *Serb J Dermatol Venereol* is as follows: editorial, original studies, review articles, professional articles, case reports, letters, conference/congress/symposium reports, in memoriam and forthcoming events. Beside a hard copy of the Journal, electronic version will also be available (www.udvs.org).

We hope, that *Serb J Dermatol Venereol* will attract authors all over the world willing to share their expeirence and knowledge in the field of basic and clinical dermatology and venereology. The Editorial Board of the Serb J Dermatol Venereol plans and expects strong impact and international affirmation of the Journal.

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Evaluation of clinical diagnostic tests in dermatology

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Dermatology is primarily a visual discipline (1,2). For example, a group of students can easily be recognized holding their hands behind their backs when examining a patient from a distance. When faced with dermatological conditions they are not familiar with, non-specialists prefer a tool that helps them to search for images of skin conditions by body region or morphology, rather than by the condition's name. Using the Map of Dermatology, non-specialists can achieve a diagnosis or differential diagnosis by browsing the resultant image sets and compare them to the clinical presentation at hand (2). Teledermatology techniques can be reliably applied even to retrospective diagnosis (3,4). However, although the vast majority of dermatologic conditions are accessible for examination by visual inspection, dermatologists also touch and sometimes smell the skin as well as look at it (1). The fundamental point that palpation in itself has diagnostic utility in dermatologic diagnosis, even when the visual stimulus is absent, has recently been confirmed. This may explain some of the reservations regarding teledermatology (1). Often being the sole diagnostic tool in patients care, clinical examination has a crucial role in dermatology. Moreover, without clinicopathologic correlation, the histopathologic diagnosis would extremely be limited (5).

Issues

So, what do we do now? A patient has a di-sease, but experiences an illness. We need to determine how often the medical history and physical examination provide a highly accurate diagnosis. We also have to determine whether specific historical or physical examination findings exist, and whether they can predict the disease (6). If a disease is characterized by more than one basic lesion, only consideration of other criteria will permit us to consider the right diagnosis. For example, when patients with atopic dermatitis present with plaques, papules, vesicles, pustules, excoriations, or various combinations of these lesions, pruritus, although nonspecific, will probably be the best diagnostic symptom of atopic dermatitis (4). Thus, better and more comprehensive maps should be developed, based on differential diagnosis algorithms/trees, taking into consideration many other aspects of patients and their lesions, in addition to images (2,7). The Decision Tree is one among different approaches to create a classification model as an optimal predictive model that will further be a referential diagnostic tool for physicians. Data mining is an important part of this information technology (7).

Classification of clinical signs and symptoms

Medical diagnosis may be considered as a categorization task. At least 2 different processes, by which this categorization task may be accomplished, are operative. In ”analytic processing” the clinician reaches a diagnosis by identifying and combining clinical signs and symptoms. The diagnosis is made after careful evaluation of all clinical parameters exhibited in a particular case. This strategy has traditionally been strongly proposed and considered as an expert diagnostic hallmark. Instructions aimed at advancing the ”analytic processing” can improve the accuracy of typical cases. On the other side, ”nonanalytic prossesing” makes use of the similarity between previously encountered examples and the present case. As clnicians gain experience, they rely less on ”analytic processing” and more on ”similarity-based processing”. Thus, analityc approach to diagnosis is replaced by a more holistic or similarity-based approach, as one gains significant clinical experience. If reliance on prior examples is related to the expertise level of the participants, one might find a greater reliance on rules or less reliance on similarity to prior cases with less expert participants or beginners. Instructions that foster ”analytic processing” would have little effect on

the performance of inexperienced participants, since they are already inclined toward this strategy. However, instructions fostering a similarity-based approach, would have positive effects on their performance. Thus, inexperienced participants who are encouraged to use a similarity-based approach would exhibit a higher rate of accuracy for similar cases, regardless of typicality (8).

Assessment of clinical examination

Clinical examination can and should be assessed as a diagnostic test within the discipline of clinical epidemiology. The main strategy of this discipline is improving the patient-clinician interaction (6). It is important in dermatology, especially regarding precision, accuracy and utility of alternative diagnostic strategies, such as epiluminescence and digital imaging, as well as differences in practice patterns between dermatologists and nondermatologists.

All diagnostic tests, including clinical examinations in dermatology, need high quality evidence about the level of precision and accuracy. Precision (reliability, reproducibility, repeatability) refers to agreement. When related to clinical examination, it is called ”observer agreement”. Intraobserver agreement refers to the agreement the same observer has at 2 different evaluations of the same patient. ”Interobserver agreement” refers to the agreement between 2 different observers, who independently (blinded), within minutes or at most hours, examine the same patient. If the same diagnosis is obtained, then it is precise, if not, the diagnosis is imprecise. ”Accuracy” answers whether the diagnosis is correct or incorrect, by correlating or not with the truth. Imprecise diagnoses (at least one) will inherently result in inaccuracy, though inaccuracy cannot be predicted from precision estimates alone (6).

We cannot always know the truth regarding the status of the disease. A ”gold standard” or reference standard test should be chosen to represent the truth. It will be the best test available. A good example of a gold standard is biopsy specimen for histologic evaluation to diagnose skin cancer. The accuracy of the test (diagnosis) is measured with its sensitivity (a proportion of patients that will have a positive test among patients who actually have the disease), specificity (a proportion of patients that will not have a positive test among patients who do not have the disease), positive predictive value (the proportion of patients with positive test results, who are correctly diagnosed) and negative predictive value (the proportion of patients who do not have the disease, if they do not have positive test results). The positive predictive value will increase, while the negative will decrease as the prevalence of disease in the study population increases. Likelihood ratio is derived not from the prevalence, but from sensitivity and specificity, and expresses the odds that the diagnostic test (diagnosis) has in a patient with the disease, as opposed to a patient without the disease (6).

If examinations performed by different examiners are imprecise, then the diagnosis is examiner-dependent. The patient's treatment depends on who performs the examination. On the other side, inacuracy will result in misdiagnosis and affect management and treatment outcome. Precision, clinical agreement, namely consensus, may be necessary more than application of a gold standard, if a gold standard does not exist, or the diagnostic test (clinical examination) and the gold standard are the same. For example, if dermatologists gain consensus, the results of their highly precise examinations can be used to categorize the disease. Ideally, data are categorized as present or absent, then chance-corrected measures of agreement can be used, e.g., k- statistics (k values the range from -1 representing complete disagreement, 0, agreement by chance alone, and 1 - complete agreement). Clinical follow-up is another strategy that can overcome the difficulty in applying the gold standard. Clinical follow-up is the main strategy that should be used in patients with negative results of examinations. Reexaminations should be done in reasonably short periods. Moreover, it is worth knowing that the small number of incorrectly categorized misdiagnoses can dramatically affect sensitivity rates (6).

Diagnostic skills in dermatology

There is a continuing trend of non-dermatologists to treat skin diseases. A recent study assessed the accuracy of clinical diagnoses made by physicians, not specifically trained in dermatology, and by dermatologists using histopathological diagnosis as the ”gold standard” (5). The results clearly demonstrated that dermatologists diagnosed twice as many cases correctly, compared with non-dermatologists. Family practitioners recognized only 26% of all biopsed neoplastic and cystic skin lesions correctly, compared with 75%, recognized by dermatologists. Plastic surgeons were also considerably behind dermatologists, since they recognized correctly 45% of these lesions.

When examined separately, premalignant and malignant lesions were diagnosed correctly by dermatologists in 67% of cases, versus 11% and 44% diagnosed by family phisicians and plastic surgeons, respectively. All the differences were statistically significant (5). A study from Australia showed that general practitioners agreed with dermatologist in 63% of cases in diagnosing benign nevi, but had a lower concordance rate in diagnosing melanomas and seborrhoic keratoses (38% and 24%, respectively). Overall, dermatologists made correct diagnosis in 77% of cases prior to biopsy, and general practitioners made correct diagnosis in 24% of cases prior to biopsy. Diagnoses made by dermatologists, did not match the histology mostly in skin tumors and skin condtions where clinical diagnosis was not always possible or reliable. This extremely low level of agreement suggests a need for improving general practicioners' skills for recognizing dermatological conditions, especially in diagnosing skin cancer, through both undregraduate and postgraduate education (9). However, it is not determined whether further general practitioners' education will reduce the health-care costs. The increased costs, due to higher professional fees, is counterbalanced by greater laboratory costs, more misdiagnoses, subsequent return visits and/or referrals by family physicians.

Since the 1980s, there have been dedicated Pigmented Lesion Clinics (PLCs) in the UK, aimed to provide general practitioners (GPs) with a rapid referral system for lesions clinically suspected of being malignant melanomas (MMs). The time interval between GP referral and attendance at the clinic, diagnostic accuracy, and the time interval to definitive surgery, are the most important measures when comparing the efficacy of a referral system. The false negative rate (FNR), defined as the ratio between the number of false-negative clinical diagnoses to the number of histologically diagnosed MMs, represents a particularly important measure of diagnostic accuracy, being responsible for a significant delay in lesion excision. The accuracy of clinical diagnosis of MMs has been reported to increase with level of experience. Thus, it is not surprising that the FPR was significantly lower in Pigmented Lesion Clinics, staffed by dermatologists, particularly experienced in clinical diagnosis of pigmented lesions, then in General Dermatology and Plastic Surgery Clinics. Dermoscopy was not used in any of the clinics (10). However, when interobserver agreement of PLs malignancy risk was made by a pigmented lesion specialist (dermoscopy-experienced dermatologist) and an arteficial computer algorithm-based automated digital dermoscopy system, a low agreement was found. While digital dermoscopy confirmed its advantages, the computer-based algorithm requires futher development and validation. From a clinical point of view, the main advantages of digital dermoscopy were high quality dermoscopic images, that allowed for enhanced patient education of clinical atypical nevi and melanoma warning signs (11).

In a study comparing self-reported and dermatologists' diagnoses, a low agreement was observed for five chronic skin diseases: acne, eczema, fungal infections, psoriasis and seborrhoic dermatitis (12). Self-reports underestimated the actual prevalence of four of five diseases. Many cases of chronic skin diseases were diagnosed in patients who did not report them. Diagnostic knowledge was poorer in those above 54 years of age, and better in patients treated for the condition and those with impairment of social life. The results showed a need for dermatologists to explain to the population what these five diseases really are (12).

Case mix and diagnosis-related groups

The changing healthcare environment world-wide is leading to extensive use of so called "per case" payment systems. Currently, these systems are based on diagnosis-related groups. Diagnosis-related groups (DRGs) are primarily formed based on the patients primary diagnosis. Case mix refers to the number and types of patients treated, classified by diagnosis in the DRGs (13). It can be used for different purpuses, but the main aim of DRG implementation was cost control, by setting hospital payments for all payers at a fixed DRG rate per admission. Thus, the future of inpatient dermatology is depiction of well-established diagnostic and treatment standards (14).

One of the main difficulties in dermatology is the problem how to offer highly specialized and extensive inpatient care. Patients with skin diseases remain difficult to categorize and to depict in patient classifications and case mix systems. The success of DRGs depends on the ability to distinguish severe and costly cases and less complex cases. If solutions are not found, dermatologists will be tempted to reduce their services or take action on early discharge and new admission (14). Many hospitals rely on other physicians, non-dermatologists, to care for dermatology inpatients. However, it should not be ignored that improvement in the quality of medical care will, and must be conceptually defined and implemented.

Conclusions

Since the ability of non-dermatologists, including internists and general practitioners, to make accurate diagnosis of some skin disorders, does not differ from that of undergraduate medical students, with no previous dermatologic experience, their diagnostic skills, especially in the area of skin cancers, need further improvement. Meanwhile, in order to minimize adverse treatment outcomes, and to decrease health-care costs, a low threshold for dermatology specialists referral should be encouraged. When comparing response rates for various modalities, one should bear in mind that the best interest of most inpatients with skin diseases is to be cared for by dermatologists in adequate clinical conditions.

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Tinea capitis in Belgrade 1998-2002

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Abstract

Tinea capitis (TC) is a worldwide health problem and a specific therapeutic challenge. The objective of this study was to establish the causative agents and clinical types and to present management options for TC. From 1993 to 2002, we treated 354 children (61% were boys) with TC. The data for the period 1998-2002, were analyzed in detail. After clinical and Wood's light examination, specimens were directly microscopically analyzed and cultivated. Superficial TC was diagnozed in 230 (65%), and kerion in 124 patients (35%), respectively. Of 51 kerion patients, 3 children (6%) had erythema nodosum. Griseofulvin was given at a dose of 15 to 25 mg/kg (average: 18 mg/kg). A 100% cure rate was achieved. In the period 1998-2002, M. audouinii was predominantly found in superficial TC. Oral griseofulvin therapy should be accompanied by shaving the hair from the scalp and topical imidazole creams, which provides 100% cure rate of superficial TC (in 6.5 weeks) and of kerion (in 5.4 weeks).

Tinea capitis (TC) is a fungal infection of the scalp, hair follicles and the surrounding skin caused by dermatophytes, usually species in the genera *Microsporum* and *Trichophyton*. TC is predominantly an infection of children. The prevalence of tinea capitis remains low in developed countries, but on the contrary, it is endemic in many developing countries, especially in Africa, making it a significant infectious dermatological disease (1). *Microsporum canis* is the predominant pathogen worldwide, except in the United Kingdom and North America, where *Trichophyton tonsurans* is the most prevalent (2,3). Oral griseofulvin has been, and still is, the treatment of choice for most cases of tinea capitis (4, 5). This study assesses the freqency, causative species, clinical types and management of tinea capitis in Belgrade.

Subjects and methods

This retrospective study covered the period between 1993 and 2002. During this time, 354 children with TC were treated at the Pediatric Dermatology Unit of the Institute of Dermatovenereology, University Clinical Center, Belgrade. The authors of the study treated and followed-up the patients. The data for the period 1998-2002, were analyzed in detail.

The diagnosis was based on clinical signs and symptoms, Wood's light examination and mycological examinations. Hair stumps, skin scrapings and scales were taken using sterile scalpel blades. Each sample was subjected to direct microscopic examination using 30% potassium hydroxide solution, and cultivated on Sabouraud's dextrose agar, at 25 °C. Dermatophytes were detected by colony morphology and microscopic appearance. Wood's light examination was done on admission, during the treatment and at the end of treatment. Patients were divided into two clinical types: those with superficial TC, and those with kerion celsi.

Results

Of 354 patients, 215 (61%) were boys. The youngest patient was a 3-month-old infant, whereas the eldest patient was a 16-year-old girl. In all age groups, boys had a higher incidence of infection (boys : girls=1.6: 1). Majority of infected children were aged from 4 to 12 (71%) (Table 1).

Superficial TC was more frequent, found in 230 patients (65%), while kerion celsi was diagnozed in 124 children (35%).

The data for the period between 1998 and 2002 were analyzed in detail. In this period 176 children with TC were treated. Mycological cultures revealed the predominance of *Microsporum* species (81%). *M. audouinii* infection was found in 53% of patients, *M. canis* in 27%, *T. mentagrophytes var. granulare* in 13% and *T. rubrum* in 4%. Superficial TC was most frequently caused by Microsporum species, while kerion celsi was most frequently caused by *Trichophyton species*. Mycological cultures were positive in 122/176 (69%) patients with TC. Of these, mycological cultures were positive in 102/125 (82%) of patients with superficial TC, and only in 20/51 (39%) of kerion celsi patients. The correlation between the clinical types and isolated dermathophytes is shown in Table 2.

A very interesting change in the epidemiological profile was established in the period 1993-2002. While *M. canis* was the predominant pathogen between 1993 and 1997 (99%), in the period 1998-2002, *M. audouinii* became the first causative agent of TC: *M. audouinii* was found only in one patient in 1997, while in 2002 there were 14 cases of TC (Fig. 1).

Of 51 patients with kerion celsi, 3 patients (6%) had concomitant sings and symptoms of erythema nodosum. *T. mentagrophytes var. granulare* was isolated in all these patients.

Griseofulvin (microcrystalline) was the mainstay of therapy. Between 1998 and 2002, griseofulvin was used in 162/176 (92%) patients. It was not used

Table 1. Tinea capitis in Belgrade, age and sex distribution (1993-2002)

	Number of patients			
Age (years)	Boys	Girls	Total	%
0-3.9	50	32	82	23.2%
4-7.9	96	67	163	46.0%
8-11.9	52	35	87	24.6%
12-15.9	17	5	22	14.4%
Total	215	139	354	100.0%

Table 2. Tinea capitis in Belgrade, clinico-etiologic correlations (1998-2002)

	Clinical variety			
Etiologic agent	**Superficial TC**	**Kerion celsi**	**Total**	**%**
M. audouinii	64	0	64	52.5%
M. canis	26	7	33	27.0%
M. persicolor	1	0	1	0.8%
M. gypseum	0	1	1	0.8%
T. mentagrophytes	6	10	16	13.1%
T. rubrum	3	2	5	4.1%
T. violaceum	1	0	1	0.8%
Trichophyton spp.	1	0	1	0.8%
Total	102	20	122	100.0%

only in case of drug shortages, or some adverse effects (exanthema, urticaria). Terbinafine was used in 11 patients, itraconazole in 2, and ketoconazole in 1 patient. In all patients, topical antimycotics (imidazole creams, twice a day, after a thorough wash) were used together with systemic therapy. The infected area or the whole scalp was shaved (in disseminated /diffuse forms) at the beginning of treatment and 2-3 weeks later. With such a treatment a 100% cure rate was achieved. Patients were followed-up for clinical and mycological response. Patients were considered cured if the clinical presentation was unremarkable, Wood's light examination negative (in *Microsporum spp*.) and mycological cultures negative.

Griseofulvin was given at a dose of 15 to 25 mg/kg, the average dose was 18 mg/kg, but 77% of patients were treated with 15 to 20 mg/kg, while 23% of patients were treated with doses above 20 mg/kg. In patients with superficial TC, the average treatment duration was 6.5 weeks, and in kerion patients 5.4 weeks.

Apart from oral antimycotic therapy, patients with kerion, were concomitantly treated with oral antibiotics and some with oral corticosteroids. All patients with kerion received oral antibiotics (cephalexin or erythromycin). 10/51 (~20%) patients with kerion (the most severe cases) received prednisone, beginning with 0.5 to 1 mg/kg (an average dose of 0.85 mg/kg). The dose was gradually tapered and discontinued after 10 to 14 days (12 days on average).

Griseofulvin adverse efects were noted in 5/162 patients (3%). Elevation of transaminases was registered in 3 patients (1.9%), one patient (0.6%) developed urticaria and one patient (0.6%) presented with exanthematous rash. In patients with urticaria or exanthema, griseofulvin treatment was stopped, and another oral antimycotic was introduced. In children with abnormal liver function tests, transaminase levels were approximately twice the level. Following the advice of the pediatrician, the treatment was continued and patients were closely monitored. At the end of treatment, the levels showed spontaneous normalization.

Discussion

The results of this study point to the high incidence of tinea capitis among examined children between 4

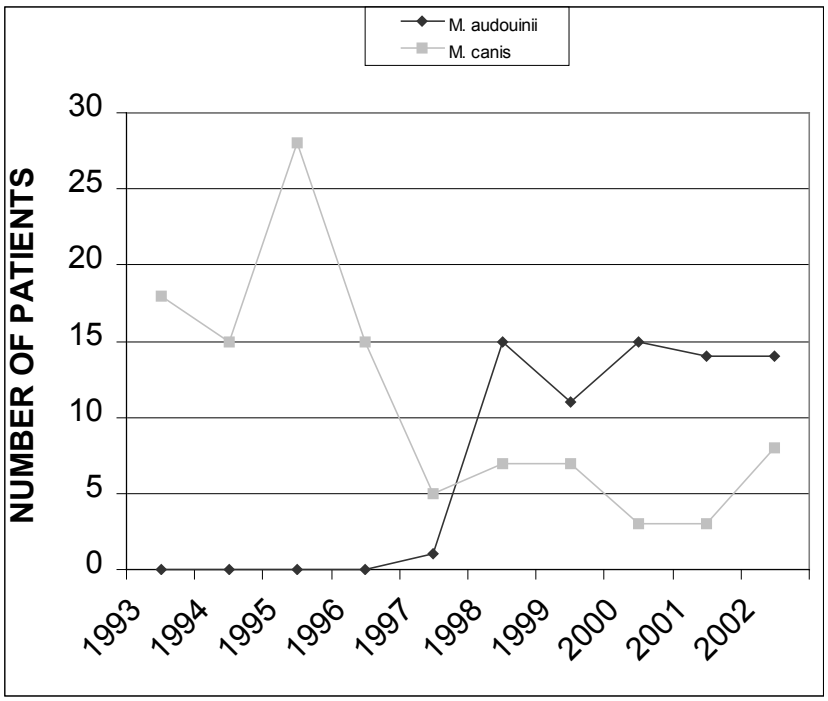

Figure 1. Tinea capitis caused by Microsporum spp.: epidemiology

and 12 years, 70% of all cases being from this group. This observation is in accordance with other reports (6-8). The patients with TC were mostly from rural areas, surrounding Belgrade. The peak incidence was between 4 and 8 years of age; TC was twice as frequent among children between 4 and 8, than among younger (0-4 years old) and older (8-12 years old) children. There are at least two explanations: (a) children aged 0 to 4 are more attentively cared for, and (b) after the age of 12, sebum production is higher, reducing the risk of infection.

Boys were affected more frequently than girls; male domination was found in all our age groups (boys : girls = 1.6 : 1). Such a domination could have been caused by several reasons: (a) boys have shorter hair than girls, (b) sexual maturation and sebum production begin earlier in girls than in boys (c) generally, boys spend more time outside than girls, and they are at higher risk for getting an infection.

During the 1960s, in our country, mycotic infections of the scalp were most frequently caused by *Trichophyton spp*. The first cases of infection caused by *Microsporum* canis were diagnozed after transmission of this species by people working in Austria or Germany (9). During the last 10-year period, the majority of infections were caused by *Microsporum species* - 81%, while *M. audouinii* infection was present in 53%. Changes in the epidemiologic profile of TC infection is also found in other countries: in the USA, for example, M. audouinii was the primary causative agent of TC up to the 1950s, when increased Hispanic immigration introduced *Trichophyton tonsurans* to the USA (5). Today, *M. canis* is the predominant pathogen worldwide, except in the United Kingdom and North America, where *Trichophyton tonsurans* is prevalent (2,3). In countries close to Serbia and Montenegro, like Greece and Bosnia and Herzegovina, the infection is predominantly caused by *M. canis* (2,10). The epidemiologic profile of TC and its causative agents is not static, and a change was recently noted: *M. canis* was predominant up to 1997, and afterwards *M. audouinii* took the first position.

Although in our opinion erythema nodosum induced by kerion celsi of the scalp is not so exceptional, a detailed review of international literature surprisingly shows only nine published cases (11-16). Of these, *T. mentagrophytes* was identified in 7/9 cases, *T. gypseum* and *T. sulphureum* were isolated in two other patients (11-16). In our series, of 51 patients with kerion, there were 3 cases (6%) of erythema nodosum. *T. mentagrophytes var. granulare* was isolated in all these patients. Although *T. mentagrophytes* is not the most common etiological agent for kerion or superficial TC, it was detected in all patients with kerion associated with erythema nodosum. During treatment of kerion, erythema nodosum gradually disappeared.

Griseofulvin is a fungistatic agent that inhibits nucleic acid synthesis which arrests cell division at metaphase and impairs fungal cell wall synthesis. It demonstrates less drug interactions, than other antimycotic agents. Its advantages are that it is: licensed, inexpensive, syrup formulation, while prolonged treatment course is its main disadvantage. Griseofulvin was introduced in 1958 (17) and it represents the only agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of tinea capitis in children (4). Our results show that all patients treated with griseofulvin, which was used in 162 patients, at a dosage of 15 to 25 mg/kg (18 mg/kg on average), during 4 to 8 weeks were cured. This observation is in accordance with other reports (4, 5, 6). In a study about dermatophytes and their in vitro antifungal sensitivity, griseofulvin proved to be the best drug with a sensitivity of 94.4% of isolates, followed by miconazole (a sensitivity of 75% of isolates) (18).

Many studies compared effects of griseofulvin (6-8 weeks) and terbinafine (3-4 weeks) in the treatment of TC. These studies showed that: (a) in case of *Trichophyton* infection the results were at least the same, comparing griseofulvin and terbinafine, (b) in case of *Microsporum* infection, the results were worse in patients receiving terbinafine (19,20). Today, terbinafine is the drug of second choice in the treatment of tinea capitis (4), but the drug of first choice in onychomycosis treatment (17,21). Recent studies on TC showed that the cure rate of 2% ketoconazole shampoo, as a monotherapeutic agent, was 33% (22). It is possible that the combination of 2% ketoconazole shampoo with oral griseofulvin, might decrease the treatment time for TC (5).

In our opinion, based on experience including 354 TC patients during the last ten years, and on international literature, griseofulvin is definitely the first choice drug for treatment of TC in children, especially in patients with *Microsporum* infection which is found in 81% of patients in our country. Our experience and published literature data show that the dose of microcrystalline griseofulvin necessary to cure children with TC, is 15 to 25 mg/kg, not 10 mg/kg, recommended by British National Formulary (BNF) and some other books.

Some studies show that the efficacy of griseofulvin in the treatment of TC during 12 weeks was 88%, but without mentioning concomitant topical antimycotic treatment (23). In our study, systemic antimycotic therapy was always given with topical antimycotics, after shaving of the scalp, and the cure rate was 100%, in 6.5 weeks (on average) for superficial TC, and in 5.4 weeks in patients with kerion. Generally, the importance of topical adjunctive measures in the treatment of TC is not adequately emphasized in the literature. We consider that shaving of the affected areas, of the scalp, if the affection is disseminated/ diffuse, together with topical application of imidazole creams twice a day, are useful measures that reduce the treatment time.

Of 51 patients with kerion celsi, 10 children (~20%) were treated with griseofulvin and oral prednisone. In our series, prednisone was given at 0.5 to 1 mg/kg. The dose was gradually reduced and discontinued 10 to 14 days later (12 days on average). One study has shown that combination of oral prednisolone and griseofulvin does not result in additional objective or subjective improvement, compared to griseofulvin alone, in cases with kerion celsi (24). Our results showed that patients were cured without oral corticosteroids, but the period of inflammation was shorter in patients with prednisone, than in patients without it.

Tinea capitis is still a significant health problem in developing countries. However, the epidemiological profile in Serbia is changing now. *M. audouinii* is the predominant causative agent and similar change might take place in the surrounding countries as well as in other parts of Europe. Griseofulvin is a very effective therapy and we sugest that the treatment should be accompanied by local measures including shaving the scalp and use of topical imidazole creams. Such a combination offers a 100% cure rate of superficial TC in 6.5 weeks and in 5.4 weeks in patients with kerion.

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Tinea capitis u Beogradu 1998-2002. godine

Sažetak

Tinea capitis (TC) predstavlja zdravstveni problem koji se sreće u celom svetu i koji nameće specifične terapijske izazove.
Ciljevi: Ustanoviti učestalost, uzročne agense, kliničke tipove TC i predstaviti terapiju TC.
Metode: Od 1993. do 2002. godine, lečili smo 354 dece sa TC. Podaci za period 1998-2002. godine detaljno su analizirani. Pacijenti su pregledani klinički i pod Woodovom lampom, a uzorci mikroskopski i kultivisani na Sabouraudovom agaru.
Rezultati: 215 pacijenata (61%) bili su dečaci. Odnos dečaci : devojčice bio je 1,6 : 1. 71% pacijenata bilo je u uzrastu 4 do 12 godina. Superficijalna TC je dijagnostikovana kod 230 (65%), dok je kerion celsi dijagnostikovan kod 124 pacijenta (35%). U periodu 1993-2002. godine dominirali su uzročnici iz roda *Microsporum* (81%). U periodu 1993-1997. godine, *M. canis* je bio predominantni uzročnik, dok je od 1998. do 2002. godine predominantan *M. audouinii*. Od 51 deteta sa dijagnozom kerion celsi, 3 pacijenta (6%) imala su erythema nodosum i kod sva tri je izolovan *T. mentagrophytes var. granulare*. Grizeofulvin je bio osnovni lek i primenjivan je u dozi od 15 do 25 mg/kg tt (prosečno 18 mg/kg tt). Postizali smo izlečenje kod 100% pacijenata. Kod 10/51 dece sa kerionom, primenjivan je i prednizon per os, zajedno sa antimikotikom.
Zaključak: U periodu 1998-2002. godine *M. audouinii* je bio predominantan izazivač superficijalne TC. Sugerišemo da peroralna antimikotska terapija treba da bude praćena brijanjem kapilicijuma i topikalnom terapijom imidazolima, što omogućava izlečenje 100% pacijenata: superficijalne TC u proseku za 6,5 nedelja, a keriona u proseku za 5,4 nedelja.

T-cell receptor-γ gene rearrangement analysis in the diagnosis of patients with erythroderma

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Abstract

The diagnosis of erythroderma is challenging, since clinical, histopathological and immunophenotypic findings are insufficient to differentiate between inflammatory and lymphomatous erythroderma. Thus, multiplex PCR was used for T-cell receptor-γ gene rearrangement analysis, in the skin and peripheral blood samples of 24 patients (20 men and 4 women) with erythroderma of varying origin, in order to estimate its diagnostic value. Cutaneous T-cell lymphoma was confirmed in 9, benign inflammatory dermatosis in 12, and idiopathic erythroderma and clonal dermatitis in 3 patients. In the group of patients with erythrodermic cutaneous T-cell lymphoma, the dominant clone was detected in the skin of 8/9, and in none of the patients with inflammatory dermatoses. A dominant clone was found in peripheral blood of 5/6 samples of patients with erythrodermic cutaneous T-cell lymphoma, and in 2/12 patients with inflammatory dermatosis. T-cell receptor-γ gene rearrangement analysis is valuable in differentiation between inflammatory and lymphomatous erythroderma, thus substantially improving the diagnosis of patients with erythroderma.

Erythroderma, or exfoliative dermatitis, is a rare, but severe skin manifestation, involved in several skin disorders. The patient is presenting with erythema of at least 90% of the body skin surface, and varying degree of scaling. In addition, hyperkeratosis of the palms and soles, alopecia and severe pruritus may develop, and vital functions are compromized, due to increased cardiac output, hypoalbuninemia, fever and susceptibility to sepsis, since the skin barrier function is seriously compromised.

At first, the treatment of patient is symptomatic, (correction of electrolyte disbalance and hypoalbuminemia, prophylaxis of the secondary infections, antiinflammatory treatment), but precise diagnosis of the cause of erythroderma is mandatory for proper final treatment.

The etiological diagnosis of erythroderma can often be difficult, bearing in mind that clinical presentation is often non-specific. Psoriatic erythroderma, erythrodermic pityriasis rubra pilaris and erythrodermic cutaneous T-cell lymphoma (CTCL) have their specific features, but sometimes are indistinguishable. Moreover, it is particularly difficult to differentiate between erythrodermic dermatitis (atopic, contact etc.) and cutaneous T-cell lymphoma, which can clinically look alike. In addition, although patch and plaque stage mycosis fungoides have clear histologic criteria, their erythrodermic stages of histopathological features are often non-diagnostic, so the diagnosis of erythrodermic CTCL can be especially challenging. Histopathological analysis can reveal diagnosis of erythroderma in only 50% of patients (1). Immunohistochemical analysis of the cellular phenotype is

also, in most cases, of little help, since the erythrodermic CTCL is a malignancy of mature T-cells, and often there is no detectable loss of T-cell antigens (2).

Molecular genetic studies, based on the T-cell receptor-γ (TCR-γ) gene rearrangement analysis, became the standard in diagnosis of systemic and cutaneous lymphomas and leukemias. TCR gene rearrangement analysis detects T-cell clonality in cellular infiltrates. Detection of the dominant clone in skin infiltrate (monoclonal pattern) reflects the fact that the majority of T-cells in the lymphocyte infiltrates in patient's skin, belongs to the same clone, i.e. derives from the single cell. Rearrangement analysis of the γ chain of the TCR gene is most frequently used, since it is rearranged in all T-cells, irrespective of the final T-cell phenotype (αβ or γδ) (3).

T-cell clonality detection proved to be very useful in early diagnosis of mycosis fungoides, especially when the clinical and histopathological features are non-diagnostic (4-6). In addition, the detection of the dominant clone in the peripheral blood was found to be an independent prognostic factor in patients with mycosis fungoides (7). It is, also, an established criterion for the diagnosis of Sezary syndrome and erythrodermic cutaneous T-cell lymphoma (4, 8). Most of the available studies on TCR gene rearrangement analysis, in skin samples of patients with erythroderma, included patients with Sezary syndrome, or pseudolymphoma (7-9). There are only few studies available on the role of TCR-γ gene rearrangement anaysis in patients with erythroderma of varying origin, and the way it can aid the etiologic diagnosis (10, 11).

In this study, a PCR-based TCR-γ gene rearrangement analysis was used for detection of clonality of T-cells in skin infiltrates and peripheral blood of patients with erythroderma of varying origin treated in two dermatologic refferal centres in Serbia from 2001 to 2008.

T-cell clonality analysis results were correlated with clinical data, histopathological results and follow-up data, in order to establish an etiologic diagnosis of the disease. The aim of the study was to examine if the T-cell clonality analysis can help in distinguishing inflammatory erythroderma and erythroderma due to the lymphoma.

Patients and methods

Patients: Twenty-four patients were enrolled in the study. The patients were treated in two refferal dermatologic centers in Serbia: Department of Dermatology, Military Medical Academy and Institute of Dermatovenereology, Clinical Centre of Serbia, from 2001 to 2008. The inclusion criteria were: 1) clinical manifestation of erythroderma; 2) clinical suspicion of lymphoma; 3) skin samples available for histopathological, immunohistochemical and molecular genetic testing. The patients with preexisting skin diseases were excluded from the study, as well as patients with drug-induced erythroderma, in whom the diagnosis was confirmed by acute onset of erythroderma after ingestion of drug and resolution of the erythroderma after drug withdrawal. Five patients presented with erythroderma and plaques and/or tumors corresponding to mycosis fungoides. Final diagnosis of erythroderma was made by correlating clinical, histopathological and immunohistochemical data, and in cases of erythroderma due to the lymphoma - according to the WHO-EORTC classification of cutaneous lymphomas (4). All patients underwent, routine investigations needed for evaluation of patients with erythroderma as follows (12, 13): sedimentation rate, CRP, CBC, DBC, routine biochemistry, urinalysis, liver enzymes, peripheral blood smear, peripheral blood lymphocyte immunophenotype analysis in selected cases, skin biopsy for histopathological analysis, immunohistochemistry and TCR-γ gene rearrangement analysis, abdominal ultrasound, chest radiography, CT scan of chest and abdomen as indicated, cytological analysis of lymph nodes and/or lymph nodes biopsy in cases with lymphadenopathy, bone marrow biopsy as indicated by consultant hematologist and testing for HIV infection.

Informed consent was obtained from patients enrolled in the study. There were 20 men and 4 women, aged 31-85 years (median 63 years). Median duration of follow up period was 2 years (1-8 years).

Samples

From 2001 to 2008, 24 skin and 20 peripheral blood samples were analyzed. The samples were taken at the time of diagnosis, or during the relapse of disease after therapy, with excisional or shave biopsy. Half of the samples were placed in 10% formaldehyde for further

histopathological analysis, and the other half were frozen and stored at -20 °C for DNA extraction and further DNA analysis. The blood samples were taken by venepuncture and used for DNA extraction and further analysis.

TCR-γ gene rearrangement analysis

DNA was isolated by phenol: chloroform/isoamyl alcohol extraction (14).

PCRs were performed in a 50 μL reaction mixture containing 400-600 ng of gDNA (Master Mix, Applied Biosystems). For amplification of the hypervariable region of rearranged TCR-γ chain gene, 0.2 μM/L of each oligonucleotide primer was used (Table 1.).

Results

Patients with confirmed cutaneous T-cell lymphoma

After the completion of all investigations needed for evaluation of patients with erythroderma, cutaneous T-cell lymphoma was diagnosed in 9 patients. Three patients fulfilled the criteria for Sezary syndrome, and 6 were diagnosed with erythrodermic mycosis fungoides.

Table 2. presents clinical data, histopathological analysis and TCR gene rearrangement analysis of skin samples of patients with confirmed cutaneous T-cell lymphoma (CTCL).

Table 1. Primer sequences for amplification of TCR-γ gene hypervariable region

Gene	Region	Nucleotide sequence
		5'-C TTC ACT CAG ATG TCA CCT ACA ACT CCA AGG TTG-3'
		5'-C TTC CTG AAG ATG ACG CCT CCA CCG CAA GGG ATG-3'
		5'-C TTC CTG GGA ATG ACT ACC ACA CCT CCA GCG GTT-3'
		5'-C TTC CTG ATG GTA ACT CCT ACA ACT CCA GGG TTG-3'
TCR-γ	*V-J*	5'-GGNA CTG CAG GAA GGC AAT GGC GCA TTC CG-3'
		5'-GGNA AAA CAG GAA AGG AAT CTG GCA TTC CG-3'
		5'-AAG TGT TGT TCC TAC GCC TTT-3'
		5'-AGT TAC TAT TCT CCT AGT CCC-3'
		5'-TGT AAT GAT GGA CTT TGT TCC-3'

The PCR protocol included 40 repeats of the basic cycle (94°C for 40 seconds, 56°C for 1 minute, 72°C for 1 minute). The uniformity of rearranged TCR-γ genes was analyzed on 10% polyacrylamide gel (PAGs) electrophoresis after staining with silver nitrate (15).

To ensure that DNA was amplifiable, all samples were amplified with commercial primers for the P53 exon 4. In order to avoid false–positive results, negative controls, containing no template DNA, were subjected to the same procedure. PCR products were considered to be monoclonal only if one or two discrete band within the expected size range (~200 bp) was observed on the gel after electrophoresis.

In two patients, pathohistological analysis of skin samples was non-specific: in one, chronic inflammatory lymphocyte infiltrate was accompanied by a prominent eosinophilic infiltration, and the other presented with features of subacute dermatitis.

Patients with erythroderma due to benign inflammatory dermatoses

In 12 patients, clinical features and histopathological analysis of the skin samples were consistent with inflammatory dermatoses: 4 presented with adult-onset atopic dermatitis, 3 were diagnosed with disseminated eczema, 3 with senile erythroderma (after exclusion of paraneoplastic disease), 1 with pityriasis rubra pilaris, and 1 with paraneoplastic erythroderma accompanied by low-grade B-cell leukemia (Table 3). In this

Table 2. TCR-γ gene rearrangement in the skin samples of patients with confirmed CTCL

No.	Age/ Gender	Clinical diagnosis	Histopathological diagnosis		TCR-γ gene rearrangement (skin)	Final diagnosis
			First (date)	*Diagnostic (date)*		
1	75/M	Paraneoplastic erythroderma. CTCL in obs.	Subacute dermatitis (2000)	CTCL (2001)	Monoclonal	Sezary syndrome
2	63/M	Paraneoplastic erythroderma. CTCL in obs.	CTCL (2003)	CTCL (2003)	Monoclonal	Erythrodermic mycosis fungoides
3	49/F	Mycosis fungoides in bs. Erythroderma.	Mycosis fungoides (2003)	Mycosis fungoides (2003)	Polyclonal	Erythrodermic mycosis fungoides
4	48/M	Paraneoplastic erythroderma. CTCL in obs.	CTCL (2003)	CTCL (2003)	Monoclonal	Erythrodermic mycosis fungoides
5	66/M	Mycosis fungoides in obs. Erythroderma.	Parapsoriasis en plaque (1999)	Mycosis fungoides (2001)	Monoclonal	Erythrodermic mycosis fungoides
6	62/M	Paraneoplastic erythroderma. CTCL in obs.	Mycosis fungoides (2001)	Mycosis fungoides (2001)	Monoclonal	Erythrodermic mycosis fungoides
7	57/M	Mycosis fungoides Erythroderma.	Mycosis fungoides (2001)	Mycosis fungoides (2001)	Monoclonal	Erythrodermic mycosis fungoides
8	46/F	Adult onset atopic dermatitis. CTCL in obs.	Subacute dermatitis (2006)	Chronic nonspecific dermatitis (2007)	Monoclonal	Sezary syndrome
9	31/M	Adult onset atopic dermatitis. CTCL in obs.	Chronic nonspecific dermatitis (2007)	Chronic nonspecific dermatitis (2008)	Monoclonal	Sezary syndrome

Obs. – Abbreviated from: Observed and expected

patient, monoclonal pattern was found in the skin, blood and bone marrow in B-cell receptor (immunoglobulin gene) rearrangement analysis, while the polyclonal pattern was found in the skin sample for TCR-γ gene rearrangement analysis.

T-cell clonality analysis in all our patients with inflammatory dermatoses revealed a polyclonal pattern.

Patients with idiopathic erythroderma and clinical suspicion of lymphoma

In three patients, in spite of vigorous researches, the true nature of presenting erythroderma was not elucidated (Table 4).

Two patients presented with generalized redness and lymphadenopathy, diffuse alopecia, fever and prominent weight loss during the previous months.

Table 3. TCR-γ gene rearrangement in patients with inflammatory dermatoses

No.	Age/ Gender	Clinical diagnosis	Histopathological diagnosis	TCR-γ gene rearrangement (skin)	Final diagnosis
1	80/M	Disseminated eczema. CTCL in obs.	Eczematoid dermatitis	Polyclonal	Disseminated eczema
2	85/M	Paraneoplastic erythroderma. CTCL in obs.	Superficial perivascular dermatitis	Polyclonal	Senile erythroderma
3	71/F	Adult onset atopic dermatitis. CTCL in obs.	Chronic spongiform dermatitis	Polyclonal	Adult onset atopic dermatitis
4	63/M	Pityriasis rubra pilaris in obs. CTCL in obs.	Pityriasis rubra pilaris	Polyclonal	Pityriasis rubra pilaris
5	59/M	Adult onset atopic dermatitis. CTCL in obs.	Chronic spongiform dermatitis	Polyclonal	Adult onset atopic dermatitis
6	73/F	Adult onset atopic dermatitis. CTCL in obs.	Chronic spongiform dermatitis	Polyclonal	Adult onset atopic dermatitis
7	61/M	Adult onset atopic dermatitis. CTCL in obs.	Acute spongiform dermatitis	Polyclonal	Adult onset atopic dermatitis
8	82/M	Erythrodermia paraneoplastica seu senilis. CTCL in obs.	Superficial perivascular dermatitis	Polyclonal	Senile erythroderma
9	64/M	Paraneoplastic erythroderma. CTCL in obs.	Superficial perivascular dermatitis	Polyclonal	Paraneoplastic Erythrodermia (low-grade B-cell leukemia)
10	68/M	Disseminated eczema. CTCL in obs.	Chronic spongiform dermatitis	Polyclonal	Disseminated eczema
11	54/M	Disseminated eczema. CTCL in obs.	Chronic spongiform dermatitis	Polyclonal	Disseminated eczema
12	83/M	Paraneoplastic erythroderma. CTCL in obs.	Chronic dermatitis with prominent eosinophilic infiltration	Polyclonal	Senile erythroderma

Obs. – Abbreviated from: Observed and expected

Protracted erythroderma was resistant to corticosteroid therapy, which only temporarily and in medium doses controlled the signs and symptoms of the disease. In the first patient, the disease was present for 8 years, with partial remissions and exacerbations, and repeated histopathological analyses revealed chronic dermatitis, with spongiform features. However, by repeated TCR-γ gene rearrangement analysis of the skin and peripheral blood samples, at the last control, detected a dominant clone, and immunophenotype analysis of peripheral blood lymphocytes detected significant predominance of CD4+ T-cells, with increased CD4/CD8 index. Since atypical lymphocytes were not detected by histopathological analysis and in peripheral blood smears, these criteria were considered insufficient for diagnosis of Sezary syndrome. Acitretin was introduced, with slow tapering from systemic corticosteroids, and the patient should be further followed-up for final diagnosis. In the second patient erythroderma lasted for 2-years and it was accompanied by fever, severe pruritus and lichenification, diffuse alopecia, 10 kg weight loss in 2 months, and axillary and inguinal lymphadenopathy (up to 3 cm in diameter and in packages). Although clinical features were highly suspicious for lymphoma, histopathological analysis of the skin and lymph node samples, peripheral blood smears and immunophenotype analysis, radiographic studies and searches for neoplasia did not reveal any signs of a malignant (hematologic or other) disease. However, repeated TCR-γ gene rearrangement analysis, detected a dominant clone in the skin and peripheral blood sample. The patient was treated with systemic corticosteroids and should be followed-up. In cases with idiopathic erythroderma, cutaneous T-cell lymphoma, atopic dermatitis and drug reactions were found to be the most common causes, during the follow up, in one study, and in the other, CTCL was the most common diagnosis during the follow-up of patients with idiopathic erythroderma (11, 16).

Table 4. TCR-γ gene rearrangement in patients with idiopathic erythroderma

No.	Age/ Gender	Clinical diagnosis	Histopathological diagnosis	TCR-γ gene rearrangement (skin)	Final diagnosis
1	65/M	Paraneoplastic erythroderma. CTCL in obs.	Chronic dermatitis	Monoclonal	Idiopathic erythroderma. Sezary syndrome in obs.
2	63/M	Paraneoplastic erythroderma. CTCL in obs.	Superficial perivascular dermatitis	Monoclonal	Idiopathic erythroderma. CTCL in obs.
3	59/M	Mycosis fungoides in obs Erythroderma.	Chronic spongiform dermatitis Diffuse T-cell hyperplasia	Monoclonal	Erythroderma sec. CTCL in obs.

Obs. – Abbreviated from: Observed and expected

The third patient was admitted to our Department with erythroderma and tumorous lesions on the chest, arms and legs. Clinical diagnosis of erythrodermic mycosis fungoides was highly probable. However, histopathological analysis of one skin sample was consistent with spongiform dermatitis while in the tumorous lesion, diffuse T-cell hyperplasia was found, but with no signs of lymphocyte atypia and loss of T-cell markers (CD5, CD7). Nevertheless, dermopathic lymphadenopathy was found in lymph node biopsy, CT scan of the chest and abdomen did

not reveal any signs of systemic lymphadnopathy and hepatospleno-megaly. Bone marrow histopathological analysis was also normal. However, TCR-γ gene rearrangement analysis detected a dominant clone in the skin and polyclonal pattern in peripheral blood. Infectious etiology of the disease, and presence of other malignant disease were also excluded. Since there were insufficient criteria for diagnosis of cutaneous T-cell lymphoma, therapy with acitretin and systemic corticosteroids and close follow-up was indicated.

TCR-γ gene rearrangement analysis in peripheral blood samples

In patients with erythroderma and confirmed cutaneous T-cell lymphoma, a dominant T-cell clone was detected in peripheral blood of 5 patients. In one patient polyclonal pattern was found in peripheral blood, and in three the analysis was not performed. In patients with inflammatory dermatoses, a dominant clone was found in peripheral blood in one patient with senile erythroderma (a dominant clone was not found in the skin), and in one patient with erythroderma accompanying low-grade B-cell leukemia. Of 3 patients with idiopathic erythroderma, a dominant clone was found in 2 patients: in both in the skin and in peripheral blood.

Discussion

The incidence of erythroderma (or exfoliative dermatitis) was estimated to be 35 per 100.000 of dermatotological outpatients in one study, but there are no data on overall incidence (17). The causative factors are previous dermatoses, drug reactions, malignancy, infections and idiopathic erythroderma. The 4 most common causes are: adult atopic dermatitis, drug reactions, cutaneous T-cell lymphoma (CTCL) and paraneoplastic erythroderma (12, 13, 16, 18, 19). In our study, drug reactions and previous dermatoses were excluded, and there were 9 patients with erythrodermic CTCL, 3 with idiopathic erythroderma (and probable prelymphomatous eruption), 8 with adult onset atopic dermatitis and disseminated eczema, 2 patients with senile erythroderma, 1 patient with pityriasis rubra pilaris, and 1 with paraneoplastic erythroderma. This is in concordance with other studies of patients with erythroderma, where these entities are the most common (apart from previous dermatoses and drug eruptions). In our patients, male to female ratio was 5:1, and the mean age of presentation 63 years, similar to other studies (12).

Histopathological analysis of skin samples can be a diagnostic criterion in up to 50% of patients, but usually after repeated biopsies (1). In our patients, histopathological analysis was diagnostic in 13 of 24 patients (54.1%), which corresponds with the data from other studies. In patients with inflammatory dermatoses, specific features were found in 8 of 12 patients (7 with eczema and 1 with pityriasis rubra pilaris) while in the other 4, nonspecific perivascular superifical dermatitis with varying presence of eosinophils was found. In patients with erythrodermic CTCL, the first pathological analysis was diagnostic in 5 of 9 patients, and in repeated biopsies in 7 of 9 patients. In two patients, histopathological features of skin sample analysis remained non-specific, but patients fullfilled criteria for Sezary syndrome: presence of Sezary cells $\geq 1000/mm^3$ in peripheral blood, immunophenotype abnormalities with loss of T-cell antigen markers, and dominant T-cell clone in peripheral blood (4, 8).

In patients with erythrodermic CTCL, TCR-γ gene rearrangement analysis detected a dominant clone in 8 of 9 patients (88.8%). In other studies, a dominant clone was found in erythrodermic CTCL in up to 83% of patients, which is in concordance with our results (7, 10, 20). In 1 patient with erythrodermic mycosis fungoides, a dominant clone was not detected. In the late stages of the disease, there is a possibility of TCR gene deletion only during malignant transformation (21). Also, this can be a false-negative result, due to poor sampling, i.e. taking the skin sample with small number of malignant T-cells, and there is a possibility that primers used in this study did not cover all possible TCR-γ gene rearrangements (5, 21, 22).

In contrast, in the group of erythroderma due to inflammatory dermatoses, a dominant clone was not detected in any of the samples. This clearly demonstrates that in patients with erythroderma, TCR-γ gene rearrangement analysis is a useful adjunct to diagnosis, since it can differentiate between polyclonal (e.g benign), and monoclonal (e.g lymphomatous) T-cell population in the cellular infiltrate. Cherny et al., in their series of 16 patients with erythroderma

found that finding of a dominant clone was specific for lymphomatous erythroderma (11). Cordel and co-authors found a dominant clone in the skin samples of 7 patients with suspected lymphoma and in none of 16 patients with probable inflammatory dermatoses (as determined by the dermatopathologist) (10). TCR-γ gene rearrangement analysis mainly increased the sensitivity of diagnosis of erythrodermic mycosis fungoides in the other study: the sensitivity was 62% with histopathological analysis, and 87% with a combined histopathological analysis and T-cell clonality analysis (9).

However, it should be noted that the finding of a dominant clone does not imply malignancy in every case. There is a possibility of „false-positive" results, in cases where more than 1% of reactive benign lymphocytes of the same clone is present in the cutaneous infiltrate. In these cases, monoclonality is detected, but is not a sign of malignancy.

In our study, three patients were present with so-called „clonal dermatitis", i.e. finding of non-specific dermatitis by histopathological analysis and a dominant clone by PCR. Patients with «clonal dermatitis» require close follow-up and repeated biopsies, because of a possible underlying lymphoproliferative disorder, not recognized at the beginning of signs and symptoms of the disease (23).

One patient with „clonal dermatitis", presented with two criteria for Sezary syndrome (SS). The International Society for Cutaneous Lymphomas (ISCL) recommendation criteria for the diagnosis of SS include one or more of the following: an absolute Sezary cell count of at least 1000 cells/mm^3; demonstration of immunophenotypical abnormalities (an expanded CD4$^+$ T-cell population resulting in a CD4/CD8 ratio over 10, loss of any or all of the T-cell antigens CD2, CD3, CD4, and CD5, or both); or demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods (8). In addition, if the skin and lymph node studies are showing non-specific features and are not diagnostic, additional evidence of malignancy are required for final diagnosis of Sezary syndrome, such as: presence of large Sezary cells, presence of the same dominant clone in the skin and blood, or aberrant expression of T-cell markers (8). Since the clinical validity of these criteria has not yet been established in a large study, WHO-EORTC believe that finding of a dominant T-cell clone in the peripheral blood (preferably the same as in the skin) together with one of the cytomorphologic or immunophenotypic criteria, should be a minimum for diagnosis of Sezary syndrome. In our patient, two ot the minimum criteria were met, and the patient was closely followed-up to confirm these findings in repeated analyses. In the meanwhile, therapy with acitretin and slowly tapered systemic corticosteroids was introduced, with satisfying results. In the second patient, a dominant clone in the skin and the peripheral blood was found, but the cytomorphologic and immunophenotypic criteria were not detected, so the patient was closely followed-up. In the third patient with "clonal dermatitis", clinical features with erythroderma and tumorous lesions pointed out to the erythrodermic mycosis fungoides, but repeated histopathological analyses were non-diagnostic. A dominant clone was repeatedly found in the skin (not in the blood), and in one sample, T-cell diffuse hyperplasia was found but with no signs of lymphocyte atypia. In this case, acitretin and systemic corticosteroids were introduced with good effects, and close follow-up was also necessary for final diagnosis.

On the other hand, in two patients with benign inflammatory dermatoses (aged 85 and 65), a dominant clone was found in peripheral blood samples, but not in the skin. The significance of the isolated finding of peripheral blood monoclonality is not yet established. It can be found in healthy subjects older then 80 years, and also in patients with certain autoimmune disorders (24, 25). In this study, a dominant clone was found in one patient aged 85 years, with senile erythroderma, and it was not found in the skin sample, but non-specfic dermatitis was found by histopathological analysis. Search for internal malignancy, bone marrow biopsy, and lymph node biopsy, among other investiagations, did not reveal any signs of malignant disease, and the patient was diagnosed to have senile erythroderma. Senile erythroderma is most commonly manifested by previous eczema or atopic dermatitis, with persistent course and nonspecific features by histopathological analysis, elevated IgE and LDH and variable presence of eosinophils in the skin biopsy (16). In the other patient, aged 65, a dominant T-cell clone was found only in the peripheral blood, while a dominant B-cell clone was found in the bone

marrow, peripheral blood and skin samples. This patient was diagnosed to have low-grade B-cell leukemia (the bone marrow histopathological analysis was diagnostic), and the finding of a dominant T-cell clone and erythroderma, can point to possible false-positive result due to existence of more than 1% of reactive T-cells, which were activated by malignant B-cell clone during the course of the disease. There is a possibility that these T-cells were responsible for erythroderma, which is not an usual manifestation of low-grade B-cell leukemia. Less probable is a possibility of composite B- and T-cell lymphoma (yet not fully developed) which is very rare (26).

In the group of patients with erythrodermic CTCL, a dominant clone was found in 5 of 6 patients in whom analysis was performed. The finding of the same dominant clone in peripheral blood and in the skin sample (and/or lymph node) may be a disease manifestation, and in this case represents an independent factor of poor prognosis (7, 27, 28). In our previous study, presence of a dominant clone, both in the skin and peripheral blood of patients with mycosis fungoides, was detected in 7/16 (43.8%) of patients with end-stage disease, while in patients with early-stage disease, it was present in 1/7 patients (14.2%) (29). In 3/4 (75%) of patients with disease, a remission of polyclonal pattern was detected, while in patients with stable disease and disease progression, polyclonal pattern in skin/blood was present in only 3 of 14 patients (21.4%). Also, a trend toward shorter time to progression was found in patients with a dominant clone, both in the skin and peripheral blood, in comparison to patients in whom a dominant clone was not found (29). Although these differences were not statistically signficant, they may have a prognostic importance of a dominant clone in the skin/peripheral blood, which was found in other studies (7, 27, 28).

In conclusion, TCR-γ gene rearrangement analysis was found to be useful in diagnosis of patients with erythroderma. Findings of a dominant clone in the skin and peripheral blood should be correlated with the clinical, histopathological and immunophenotypical features, for the final diagnosis, and proper treatment of patients with erythroderma.

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Dijagnostički značaj analize preuređenja gena gama lanca T-ćelijskog receptora kod pacijenata sa eritrodermijom

Sažetak:

Uvod: Etiološka dijagnoza eritrodermije, predstavlja veliki izazov, s obzirom da kliničke manifestacije, histopatološka analiza i imunofenotipizacija ćelijskog infiltrata kod mnogih bolesnika nije dovoljna za diferencijalnu dijagnozu inflamatorne eritrodermije i eritrodermijskog kutanog T-ćelijskog limfoma. U ovoj studiji, klonalnost T–limfocita ispitana je analizom gena za γ-lanac T-ćelijskog receptora u uzorcima kože i periferne krvi pacijenata sa eritrodermijom različitog porekla, radi ispitivanja značajnosti ove analize u dijagnostici eritrodermije.

Metodi: Uzorci kože i periferne krvi su uzeti kod 24 pacijenata sa eritrodermijom, lečenih od 2001 do 2008 u Klinici za kožne i polne bolesti Vojnomedicinske akademije i Instituta za dermatovenerologiju Kliničkog centra Srbije. Multipleks PCR korišćen je za analizu rearanžmana gena za γ–lanac T-ćelijskog receptora.

Rezultati: 20 muškaraca i 4 žene bilo je uključeno u ispitivanje. Dijagnoza eritrodermijskog primarnog kutanog T-ćelijskog limfoma postavljena je kod 9 bolesnika, dok je 12 pacijenata dijagnostikovana neka od inflamatornih dermatoza. U grupi pacijenata sa eritrodermijskim kutanim T-ćelijskim limfomom, kod 8 od 9 pacijenata (88.8%) detektovan je dominantni klon u uzorku kože, i u 5 od 6 uzoraka periferne krvi. U grupi inflamatornih dermatoza, dominantni klon nije nađen ni u jednom uzoraku kože, dok u perifernoj krvi nađen u 2 od 12 uzoraka. Kod 3 pacijenta uprkos iscrpnim ispitivanjima uzrok eritroderme nije utvrđen, a u uzorcima kože je viđen tzv. «klonski dermatitis», te su savetovane česte kontrole i ponavljane biopsije, zbog moguće dijagnoze limfoproliferativnog oboljenja.

Zaključak: Detekcija T-ćelijske klonalnosti analizom gena za γ-lanac T-ćelijskog receptora značajno doprinosi diferencijalnoj dijagnozi inflamatornih eritrodermija i eritrodermijskog primarnog kutanog T-ćelijskog limfoma.

Actinic keratosis: a new approach to the treatment

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Abstract

Actinic keratosis is an intraepidermal proliferation of transformed, atypical keratinocytes, induced by exposure to solar ultraviolet radiation. Many authors believe that it is the earliest form of squamous cell carcinoma. More than 40% of all metastatic squamous cell carcinomas develop from actinic keratosis. The clinical, histological and molecular characteristics of actinic keratosis are those of squamous cell carcinomas. Since it can be extremely hard to distinguish actinic keratosis from some squamous cell carcinomas, treatment can be rather difficult. The best treatment of actinic keratosis is its prevention. The main reason for therapy which is universally accepted, is prevention of squamous cell carcinoma. A number of options are available, but when considering the efficacy, invasive procedures remain the standard treatment. Treatment of individual lesions may prevent further progression of actinic damage present in the surrounding skin.

Actinic keratosis (AK) is an intraepidermal proliferation of transformed, atypical keratinocytes induced by exposure to ultraviolet (UV) solar radiation. The most common synonyms are "solar keratosis" and "senile keratosis". In regard to the precision of the term: ''solar'' may be more preferable, but the lesions can be produced by all types of radiation, including radioactive, x-rays, and sun (1).

Current concepts

Many authors share different opinions about the real nature of AK. Some of them think that AK is a ''premalignant'', or ''precancerous'' disease, because the lesions are confined to the epidermis, without a metastatic involvement. Other authors believe that actinic keratosis is a squamous cell carcinoma, or squamous cell carcinoma in progress, or incipient intraepidermal squamous cell carcinoma (2-4). ''*AKs are malignant in the same sense as Bowen's disease (squamous cell carcinoma in situ), intraepithelial Merkel cell carcinoma, intraepithelial sebaceous carcinoma, intraepithelial melanoma (melanoma in situ), extramammary Paget's disease, and cervical intraepithelial neoplasms (CIN)*" (4).

Epidemiology

After acne vulgaris and nonspecific dermatitis, AK is the third most common reason for visiting a dermatologist. The prevalence rates vary substantially in different geographic areas, from 11 to 40% (5,6). The development of AKs depends on many variables, such as: age, sex, race, place of birth, ethnic origin, place of living, occupation, socio-economic status, and skin type. In the third decade of life a prevalence of less than 10% has been reported, increasing to over 80% in light-complexioned individuals aged 60-69 years (6). Men are more susceptible to develop AKs than women, mostly because they get more sun exposure.

Cumulative, lifetime exposure to UV radiation and, recent intense exposure, are other major risk factors responsible for the development of AK. More than 80% of all AKs are localized on chronically sun

exposed skin, such as the scalp, head, neck, forearms, and on the dorsal aspects of hands. The age at which a person experienced the highest level of exposure to UV radiation, and at which sun burns occurred, is another major risk factor for developing AK. Exposure during childhood is associated with the greatest risk. Thus, Kennedy assessed the effects of painful sunburns and lifetime sun exposure on the risk of AKs and seborrheic warts in relation to the development of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) in 966 individuals. Painful sunburns before the age of 20 years were associated with an increased risk for SCC, BCC and AKs (7).

Etiology and pathogenesis

The aim of some recent studies was to assess the effects of UV light and oncogenes on the induction and progression of AKs (8-10). High frequency loss of heterozygosity on several chromosome arms (17p, 17q, 9p, 9q, 13q) has been commonly found in AK. The most common genetic alteration found in AK and SCC is a mutation in the p53 tumor suppressor gene. Located on chromosome 17p, this gene functions in DNA protection and may account for tumor progression. The frequency of p53 mutation in patients with AK has been estimated to be about 75-80%. The progression of AK into a SCC of the skin, also correlates with deletion of 9p21 region which encodes a p16INK4a tumor suppressor (11). The development of SCC and BCC is the result of a complex sequence of events, initiated by exposure to UV light. The initial damage takes place in the DNA, and most of the UV-induced lesions in the DNA are repaired (23). The progression from stimulus to neoplastic transformation and to metastasis is presented in Fig. 1. (4). Tenascin (extracellular matrix protein) expression in AKs is related to the stage of dysplasia and plays a role in neoplastic progression working as an anti-adhesive factor (13).

Thomas and associates believe that keratinocytes in hypertrophic AK live longer and probably have higher propensity for additional mutations and conversion to overt SCC (14).

Histopathology

Microscopic changes are confined to foci in the epidermis with atypical aggregates and pleomorphic keratinocytes at the basal cell layer, which may extend to the granular and cornified layers. The epidermis demonstrates an abnormal architecture because of irregular acanthosis. In the basal cell layer, nuclei may be clustered with atypical keratinocytes forming buds or pseudo ducts in the papillary dermis. The basal cell layer appears more basophilic, because of

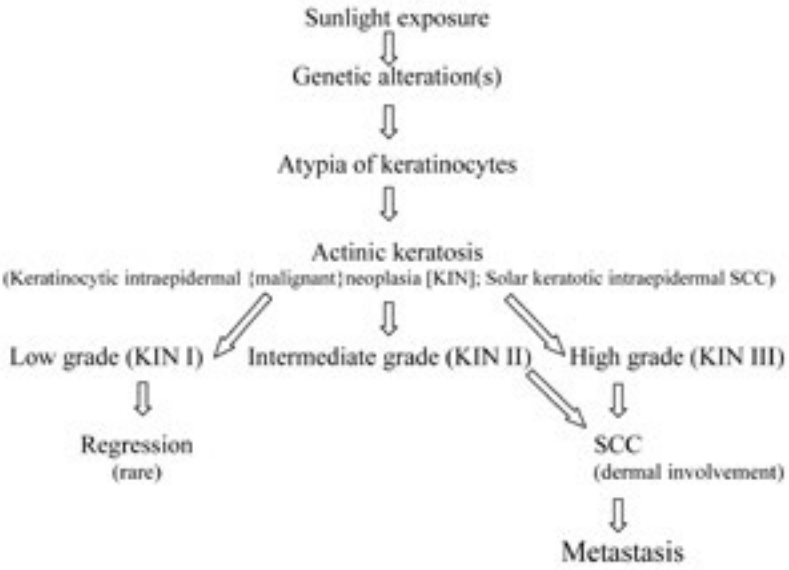

Figure 1. Postulated steps in the pathogenesis of squamous cell carcinoma (SCC) induced by ultraviolet rays (4)

the crowding of atypical keratinocytes. Dyskeratotic, even multinucleated or vacuolated cells may also be found. The adnexal epithelium is spared, with orthokeratosis overlying these structures, giving rise to the characteristic pattern of alternating orthokeratosis (or hyperkeratosis) and parakeratosis („flag sign") (15).

AK is almost always associated with solar elastosis in the dermis, and lack of solar elastosis should cause reconsideration of the diagnosis unless the patient has genodermatosis with abnormal DNA repair (4). Several histological, with corresponding clinical types have been described: pigmented, hypertrophic, atrophic, bowenoid, epidermolytic, lichenoid.

The relationship between AK and Scc

The pleomorphic and atypical keratinocytes are covered with an abnormal, parakeratotic cornified layer that is rough and appears as a crust of a horn-like texture. Though many factors can affect its further course, the crucial role depends on the host immune response. These lesions may either remain stable or enlarge and extend into the dermis. Once neoplastic cells grow into the dermis, they are referred to as SCC (4).

Clinical features

Actinic keratosis has several clinical variations: erythematous, hypertrophic, keratotic papular, verrucous, pigmented, actinic cheilitis, cutaneous horn, acantholytic, solitary lichenoid, proliferative multiple, atrophic, and spreading pigmented.

Cutaneous horn represents a hypertrophic type of AK and 15.7% of these cutaneous horns are SSC (16). There is no way to distinguish cutaneous horn, a type of AK, from SSC without skin biopsy. Pigmented AK can resemble scaling lentigo, which has histological features of AK. Conjunctiual actinic keratosis is termed pinguecula or pterygium.

Definitiely, there is no way to distinguish AK from SCC without performing a biopsy. An increase in thickness, redness, pain, ulceration and size, may suggest a progression to SCC, but these are not absolutely reliable criteria (4).

Treatment

Generally, since there is no way, neither clinical nor histological, to determine which lesion will progress, invade the dermis or even metastasize, every AK has to be treated (17).

There are many treatments that are highly effective for AK (Table 1). Cure rates over 90% are not unusual. When deciding what therapeutic modality should be used, final decision should be based on the following aims: prevention of progression and metastasis; cosmetic results; and symptom relief.

Table 1. Treatment modalities of Actinic keratosis

Modalities	
Cryosurgery	Excisional surgery
Curretage with and without electrosurgery	Oral retinoids
Topical 5-fluorouracil	Interferon
Imiquimod	Photodynamic therapy
Cryosurgical peel	Topical tubercidin
Laser	Solasodine glycosides
Dermabrasion	Calcitriol and isotretinoin
Tretinoin and other topical retinoids	Diclofenac in hyaluronic acid gel
Chemical peel	

Although a number of different options are available, they are not equally effective in all patients. Actinic keratosis has a wide range of clinical presentations and every individual patient is unique (18,19).

The best treatment is prevention, because the primary cause of AK is excessive exposure to UV light rays. Thus, with reduced sunlight exposure in childhood, one can substantially decrease the incidence of AKs and SSCs in later life. Sun protective clothing, sun screens (applied twice daily for 7 months) and avoidance of sunlight, can protect patients from UV light and prevent formation of AK. However, there are several factors affecting which therapy should be chosen, such as: the patient himself, type of lesion, physician's experience with a certain option, and availability of different treatment alternatives.

According to Dienhart, all treatments for AK can be divided, due to their utilization, into common, less common and uncommon (18).

Cryosurgery

In many countries cryosurgery is the most common treatment method of AK and liquid nitrogen is the most widely used cryogen. Basically, it is a invasive method of treatment, which is relatively easy to perform (both single and double freeze-thaw cycles can be used). The cure rate is higher than 95%. Sometimes it is associated with blistering, crusting, hypo- or hyperpigmentation and even scarring of the treated area. Pretreatment with topical 5-fluorouracil may enhance its efficacy and reduce the duration of treatment as well as side effects of both techniques. Extensive cryosurgery, known under the term cryopeeling, can be used for treating fields of AKs.

Curettage

Curettage is another effective treatment of AK. This technique is very suitable for patients with a few lesions, for lesions left after biopsy, as well as for hypertrophic AKs. Curettage may be followed by electrosurgery which will destroy atypical cells and provide hemostasis. Minimal use of cautery enhances the final cosmetic result. Whenever precise histological evaluation is needed, curettage or excisional surgery are of value.

Topical chemotherapy

Topical chemotherapy with 5-fluorouracil is frequently used in the treatment of AK. The efficacy and tolerability of 5% 5-FU cream and 5% imiquimod cream (not licensed for AKs) were compared in one 2007 study, and the authors concluded that 5% of 5-FU remains the gold standard therapy of extensive AKs (20). It blocks the methylation reaction of deoxyuridylic acid to thymidylic acid and thus interferes with DNA and RNA synthesis (21). The standard method consists of 5-FU application to the affected region twice-daily during 2-4 weeks. Pretreatment or concurrent treatment with topical tretinoin of AKs localized on forearms and dorsal aspects of hands represents a more effective method than application of 5% of 5-FU cream alone (15).

Less common treatments of AK include dermabrasion, chemical peels (35% of tri-chloroacetic acid alone, or combined with 70 % glycolic acid) or dermabrasion, cryopeels, laser therapy, photodynamic therapy, salicylic acid ointment and masoprocol cream.

Photodynamic therapy

Photodynamic therapy (PDT) is also an invasive procedure with some specificity for malignant cells. PDT involves application of topical 5-aminolevulinic acid (5-ALA), which accumulates preferentially in dysplastic cells, in combination with light therapy. Exposure to light of appropriate wavelength generates oxygen free radicals, causing cell death. Some studies have shown that if patients with AKs were to choose between methyl aminolevulinate-photodynamic therapy (MAL-PDT) and cryotherapy (which seems to be more superior for thicker lesions), they would significantly prefer MAL-PDT, because it is a more attractive option with comparable efficacy and superior cosmetic outcome (22). Response rates to two cycles of PDT, predominantly on the scalp and face, range from 69% - 91%. The cost-effectiveness is not established. PDT is of value in treating multiple AKs, or those situated on the lower legs or other sites of poor healing (23).

Laser therapy

Resurfacing of the skin, by use of CO2 or erbium laser, removing the skin surface, can remove nonspecifically

dysplastic cells within the epidermis as well. When treating more aggressive lesions which invade the follicular epithelium, scarring and prolonged redness may appear.

Retinoids

Retinoids normalize abnormal keratinization by inducing terminal differentiation or apoptosis in abnormal keratinocytes. Unfortunately, monotherapy with retinoids failed to be successful for AKs. A dose-related response has been reported.

Use of systemic retinoids may be justified in organ transplant recipients, since it has been presumed that these patients are at high risk of progression from AK to SCC (23).

Topical diclofenac

Three percent topical diclofenac in a 2.5% hyaluronic acid gel is a relatively new option in the treatment of AKs. It should be applied on the target lesions twice daily during 60-90 days. According to Karadaglić (Karadaglić Đ, unpublished data), this therapy has limited efficacy. However, in Merk's opinion, 3% diclofenac is a rational choice for early treatment since it minimizes any possibility for progression to SCC (24).

Other therapeutic options include interferon, topical immune response modifiers (IRMs), alpha-hydroxy acids, salicylic acid (2% ointment for its emollient and mild keratolytic effects, either alone or as a pretreatment for topical 5-FU).

Topical immune response modifiers

Topical immune response modifiers (IRMs) alter the skin immune system and stimulate the innate and adaptive mechanisms capable to clear precancerous and even some fully transformed malignant keratinocytes (25). Imiquimod, a 5% cream-based IRM compound, is an immune potentiator with clearly defined immunologic parameters.

Standard protocol in the treatment of AKs includes application of 5% imiquimod cream, twice or three-times weekly, during 4 weeks. After a week-rest-period, the therapy can be repeated completely, if lesions still persist. Complete clearance occurred in 50 % of all patients treated in such way (26).

Retinoic acid, applied 1-2 weeks prior to imiquimod therapy, should enhance the results.

Guidelines

The main reason for treating AKs, which is universally required, is prevention of SCC. Treatment of individual lesions may prevent further progression of actinic damage already present in the surrounding skin (23).

There are several therapeutic guidelines for AKs, but even though new topical treatments still evolve, if we consider the frequency of use, efficacy and benefits against side-effects, as well as cost control, invasive procedures remain the standard of care (27).

It is very important for clinicians to know the indications for biopsy. Bleeding, induration, rapid growth and pain, are highly suggestive of progression to SCC (18). Progression to SCC is more likely if unresponsiveness to standard treatments for AK occurs. Such lesions should be treated as SCC, and not as AKs (18).

There are evidences that at least 40% of all metastatic SCC begin as AK (28). The prevalence of 82.4% of prevalence of concomitant AK and cutaneous SCC in Mittelbronn's and associates biopsy-population, suggest a strong correlation between the two lesions. In 26.7 % of these lesions, SCC arose from AK (29). Variable rates of progression to invasive SCC were reported, the prevalence between 10% - 15% reached the consensus (30). Since there is no way to predict which lesion will progress to SCC, with a 100% accuracy, the treatment of all lesions is strongly recommended. The failure to treat AK may have serious consequences for the patient. In a state of continual flux, even when clinically unapparent after immune rejection or because of scraped surface, if untreated, it may still become an invasive SCC (30). Clinical, histological and molecular features of AK are those of SCC. AK is the earliest manifestation of this malignancy (3). Evans and Cockerell wrote: „Actinic keratosis: time to call a spade a spade" (31).

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Aktinična keratoza: novi pristup lečenju

Sažetak

Savremeni koncept: Aktinična keratoza je neoplazma sastavljena od proliferacije aberantnih keratinocita, ograničena na epiderm. Mnogi autori je smatraju početnim spinocelularnim karcinomom. Više od 40% metastaza spinocelularnog karcinoma počinje kao aktinična keratoza.

Učestalost: Javlja se često, čak 11-25% stanovništva oboleva od nje. Prevashodno su zahvaćene osobe stare 60-69 godina, iako, do 10%, mogu oboleti osobe stare 20-29 godina.

Etiologija i patogeneza: Za nastanak oboljenja značajni su dugotrajno izlaganje suncu, imunosupresija i genetski faktori.

Klinička slika: Znaci i simptomi variraju ne samo po izgledu već i po lokalizaciji (usne, koža, konjuktive, sa ili bez ulceracije itd). Postoji više tipova aktiničnih keratoza.

Patohistologija: Kliničke, histološke i molekularne karakteristike su kao i kod nekih spinocelularnih karcinoma.

Lečenje: Glavni razlog zašto svaku aktiničnu keratozu treba lečeti je prevencija spinocelularnih karcinoma. Pošto ih je nekada teško razlikovati, lečenje može biti otežano. Najuspešnije lečenje aktiničnih keratoza je njihova prevencija. Primenjuju se i brojne metode koje se smatraju uobičajenim (kriohirurgija, kiretaža sa ili bez elektrohirurgije, topijski 5-fluorouracil), manje uobičajene (dermoabrazija, hemijski ili kriohirurški piling, laser, tretinoin, alfa hidroksikiseline) i ređe (ekscizija, oralni retinoidi, fotodinamička terapija, diklofenak).

Zaključak: Destruktivne procedure ostaju standard u terapiji aktiničnih keratoza. Lečenje mora biti efikasno, kako bi se zaustavila njihova progresija. Lečenjem individualne promene, može se zaustaviti progresija aktiničnog oštećenja okolne kože.

Myofibroblastic dermatofibroma: an unusual variant

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Abstract

Myofibroblastic dermatofibroma (MFD) is an unusual neoplasm characterized by a predominance of myofibroblastic differentiation. It is extremely rare and it is not well described. Expressions of smooth muscle actin, CD34, S-100, desmin, CD31, and Factor XIIIa were evaluated along with hematoxylin-eosin and trichrome staining of fixed tissue specimens from a fibrohistiocytic neoplasm. The neoplasm demonstrated a storiform pattern characteristic of fibrohistiocytic origin. It was strongly and diffusely positive for smooth muscle actin and vimentin, and negative for all other stains performed. A trichrome stain showed the entire tumor to be blue, demonstrating the collagenous and fibrous tissue to a marked degree. MFD is a distinct variant of dermatofibroma characterized by a predominance of myofibroblastic differentiation.

Myofibroblastic Dermatofibroma (MFD) is thought to be an unusual variant of dermatofibroma (1). It shares features of intranodal myofibroblastoma. All reported lesions show immunohistochemical staining for smooth-muscle actin and vimentin, supporting myofibroblastic differentiation. We described a 31-year-old male with MFD with review of the literature.

Case report

Clinical features

A 31-year-old man initially presented to the Dermatology Department of the University of Medicine and Dentistry of New Jersey with a six-month history of a pink pruritic nodule on the nose, which started as a "pimple". There was a history of occasional painless bleeding. He had a one-year history of diffuse scaling and erythema on the dorsum of the hands and lateral fingers. The family history was negative for similar conditions or skin disorders. The patient had no other significant medical history and no known drug allergies. Physical examination revealed a firm, pearly pink nodule measuring 0.5 x 0.5cm in diameter. The clinical impression was of a possible basal cell carcinoma or dermatofibroma. A shave biopsy was performed.

Histopathology

The epidermis was without significant pathology and no psuedoepitheliomatous hyperplasia was evident. There was a Grenz zone in the superficial dermis, between the epidermis and a nodular dermal neoplasm. This nodule showed a network of short, ovoid cells intimately intertwined with longer cells with tapered nuclei, suggestive of myofibroblastic differentiation (Figure 1). Areas of the tumor show a storiform pattern characteristic of a fibrohistiocytic lesion (Figures 2 and 3). Immunohistochemical stains, including smooth muscle actin, CD34, S-100, desmin, CD31, and Factor XIIIa were performed. The lesion was strongly and diffusely positive for smooth muscle actin and vimentin and negative for all other stains performed (Figure 4). A trichome stain was also performed and stained the entire lesion blue, demonstrating the collagenous/

fibrous nature of the tumor. The diagnosis of myofibroblastic dermatofibroma was rendered.

Discussion

Fibroblasts are activated fibrocytes that are similar in morphology to macrophages, Langerhans cells and other epithelioid cells and are immunohistochemically positive for vimentin (2). In contrast to fibroblasts, myofibroblasts display a number of heterogeneous cytoskeletal immunophenotypes and actin isoforms; some combinations include vimentin with alpha-smooth muscle actin, desmin, or both or neither, and myosin (3,4).

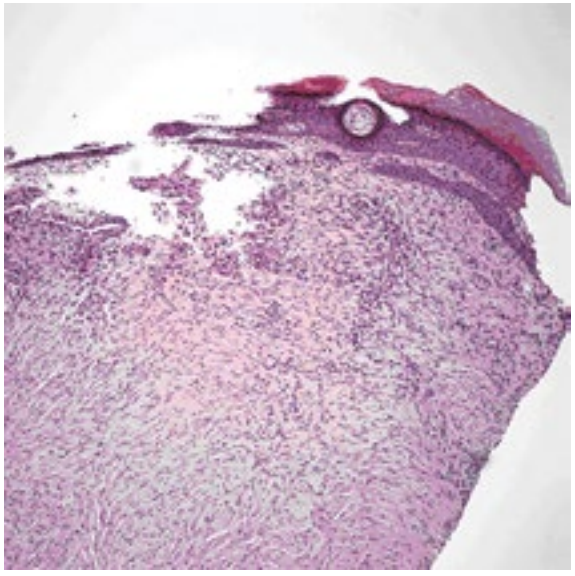

Figure 1. Low power view of the spindle cell dermal lesion (hematoxylin and eosin, x10).

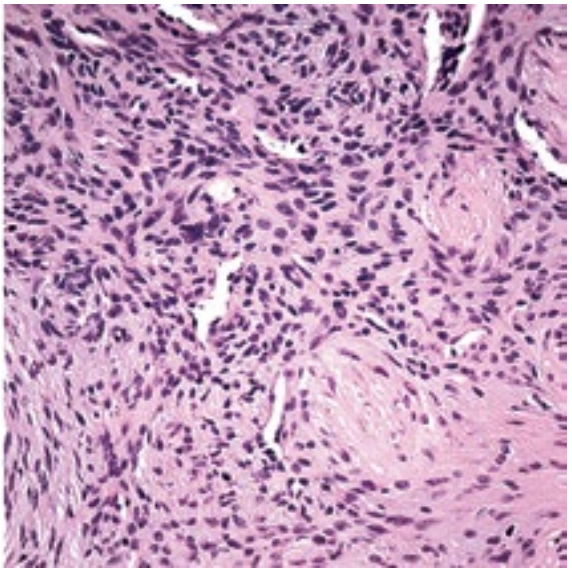

Figure 2. High power view of the tumor with smooth muscle appearing areas and a fascicular pattern (hematoxylin and eosin, x40).

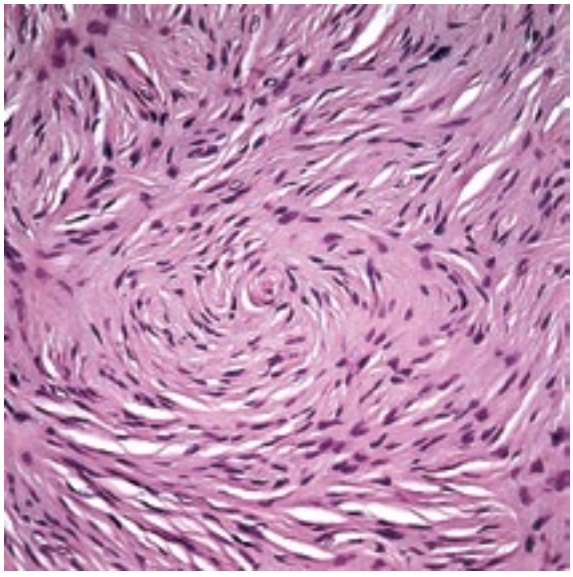

Figure 3. High power view of spindled areas of the lesion with storiform architecture (hematoxylin and eosin, x40).

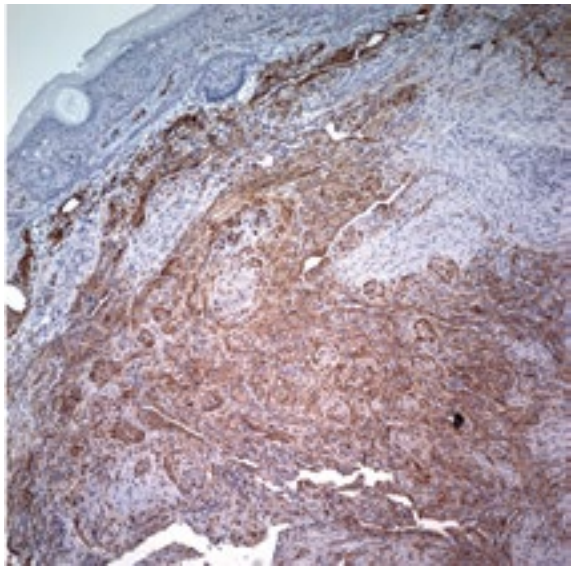

Figure 4. Tumor staining positive for smooth muscle actin, low power (smooth muscle actin, x10).

Fibroblastic tumors include histiocytic and fibrohistiocytic tumors; adipocytic and lipogenic tumors; and myofibroblastic tumors (5). Myofibroblastic tumors consist of modified fibroblasts that form the primary structure of multiple reactive and benign soft tissue lesions; the cells may be stellate or bipolar with nuclei elongated and tapered as seen in fibroblasts, or short, oval, and pale staining cells with distinct, punctuate nucleoli (4,6,7).

Dermatofibroma, or benign fibrous histiocytoma, is a fibrosing dermatosis with a significant number of dermal fibrocytes with variable number of histiocytes, lymphocytes, and multinucleated giant cells; and an overlying psuedoepitheliomatous hyperplasia is often present (2,8,9).

The epidermal hyperplasia may be so intense as to mimic basal cell carcinoma. It is unclear whether dermatofibroma is a neoplastic or reactive process (2,8,10).

MFD is a distinct variant of dermatofibroma characterized by a predominance of myofibroblastic differentiation (2,3). It is extremely rare and is not well described in the medical literature. Zelger and Zelger (1,11) described three cases in the neck and shoulder region of male adults. They described cells that were densely packed, slender and spindle shaped with strong immunoreactivity for vimentin, smooth muscle actin and CD57. Our case showed strong immunoreactivity for vimentin and smooth muscle actin, without staining for CD57, but showed all other characteristic histopathological features. The storiform architecture and tapered nuclei in some areas of the tumor argue against the diagnosis of leiomyoma.

MFD may be related to intranodal myofibroblastoma (1,12). Intranodal myofibroblastoma is a rare primary spindle cell tumor of lymph nodes, which is vimentin- and smooth muscle actin- positive, with proliferative spindle cells giving a striking histopathological resemblance to myofibroblastic dermatofibroma (12,13). MFD may also be mistaken for other spindle cell neoplasms such as dermatofibrosarcoma protuberans and can lead to unnecessary wide excisions and investigations (14).

In our patient, the lesion was on the left dorsum of the nose, a location not previously reported. Myofibroblasts occur most commonly in adults, in the periodontal ligament and around testicular seminiferous tubules; in addition, they are a major constituent of inflammatory and granulation tissue (4,13). They may not show predilection for a particular part of the body and more cases will need to be examined in order to develop definitive epidemiological data.

MFD is currently viewed as a benign tumor with limited clinical behavior (2). Appropriate investigations will prevent clinical mismanagement of this rather benign process.

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Miofibroblastni dermatofibrom: neuobičajena varijacija

Sažetak

Uvod: Miofibroblastni dermatofibrom (MFD) neobičan je tumor karakterističan po tome što kod njega preovladava miofibroblastna diferencijacija. Veoma je redak i nedovoljno opisan u literaturi.

Metode: Ispitivanje je obuhvatilo ekspresiju aktina glatkih mišića, CD34, S-100, dezmin, CD31 i faktor XIIIa, kao i histopatološke analize hematoksilin-eozin i trihromnim bojenjem fiksiranih uzoraka tkiva fibrohistiocitnih tumora.

Rezultati: Histopatološki, tumor se sastojao od vretenastih ćelija, karakterističnih za fibrohistiocitno poreklo. Imunohemijskom analizom dobijena je pozitivna reakcija na aktin i vimentin glatkih mišića, dok je na ostala bojenja reakcija bila negativna. Trihromnim bojenjem dobijena je potpuna obojenost tumora plavom bojom, što je do određene granice demonstriralo i kolagenozno i fibrozno tkivo.

Zaključak: MFD je posebna varijanta dermatofibroma sa karakterističnim prisustvom miofibroblastne diferencijacije.

History of dermatology and venereology in Serbia - part I: Medieval dermatovenereology

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Abstract

Medieval medicine in Serbia used to be the scientific medicine of that time. It included dermatology and venereology, which developed into an independent discipline in the second half of the 19th century. The most relevant sources for studying dermatology and venereology are Serbian medieval medical and therapeutic codices. The terms used in the manuscripts report about the diseases people in Serbia suffered from and were treated for in the Middle Ages. The following diseases were reported: scabies, leprosy, fungal scalp infections, as well as psoriasis, crusts (pyococcal ulcers), granulation, baldness, excessive body hair, leg wounds and old wounds, facial spots, unspecified skin diseases, urethritis and syphilis. Special attention was also given to cosmetics. Topical remedies were applied – various herbs, sulphur, mercury, tar, pyrethrum, plasters, ground glass, auripigment – in the form of a powder, liniment, ointment or plaster.

The history is one and indivisible, and all events in the development of humankind or a nation together create a real totality. The segments of its overall course, neither can be viewed in isolation, nor can individual courses within a period be separated and observed outside the period. The history of medicine thus cannot be separated from the political history. The turbulent history of Serbia, with its upturns and downturns, caused a lot of discontinuity in the development of overall Serbian medicine. The history of Serbian medicine is, hence, despite numerous similarities, in many aspects different from that of nations with the continual cultural development.

It should be kept in mind that in the Middle Ages dermatology and venereology did not exist in the present sense. Even in Europe, significant articles and reports on skin diseases, written by authors today called protodermatologists, did not appear before the 18th century, while scientific dermatology emerged as "an era of disease description and classification" in the late 18th and early 19th century (1). Similar developments followed in Serbia, although under different circumstances, and to a different extent, later and slower. It is only through the overall history of medicine, hence, that we can observe the development of dermatology and venereology in Medieval Serbia. Our profession here only started evolving into a separate specialty in the 19th century, after the liberation wars.

Considering these facts, as well as important dates in the development of health care in Serbia, this review will be divided into the following sections:

- Medieval dermatology and venereology in Serbia (12th-18th century);

- Dermatology and venereology in Serbia from 1804 to 1880;

- Dermatology and venereology in Serbia from 1881 to 1918, and

- Dermatology and venereology in Serbia from 1919 to 1945.

Medieval medicine: dermatology and venereology in Serbia

Medieval medicine in Serbia refers to the period of the reign of the Nemanjić dynasty and subsequent invasion of the Ottoman Turks, lasting from the 12th to 18th century, and in some areas extending to the 20th century.

The origin of medieval medicine in Serbia

Contrary to previous opinions that medical culture in Medieval Serbia developed on the foundations of folk empiricism, its substantial part was actually based on scientific medicine of that time (2). Early Serbian medicine, in the Middle Ages, was a synthesis of Byzantine and Western European medical schools that dominated the scientific medical thought of the time. Byzantine medicine originated in antique sources and it was through Byzantine medicine that the teaching of ancient authors reached our profession (3). It was passed on by our people, monks from Serbian or Byzantine monasteries on Mount Athos. In this way, our people learned about medical sciences, but not about art of practicing medicine (3,4). The first translations of Medieval Western European medical writers, from medical schools of Salerno and Montpellier, appeared in Serbia in the late 13th and early 14th century, brought by erudite Italian physicians and pharmacists who lived and worked in Serbia (4). It was recorded, for example, that Tsar Stefan Dusan's physician Antonio, left two chests full of books in Serbia when leaving for Dubrovnik. Marital relationships between Serbian rulers and Western princesses were also significant. Influences of these schools in Medieval Serbia were so prevailing in both practicing medicine and pharmacotherapy and so widely present among our people that Salerno-Montpellier medicine was considered to be folk medicine (2). At the time, central Serbia was mainly under the influence of Byzantium, while coastal areas were more influenced by Western countries (5), which resulted with fusion of the two doctrines. The invaluable study of R. Katić is essential for our understanding of the period.

In addition to these influences, Serbian medieval medicine also included papers, i.e. ritual books, about magical-religious medicine of Byzantine origin (6). These books and their practical application found their place in our Medieval Medicine, including dermatology. There was a similar situation in Italy and France, where the first medical schools were founded (4). However, the writings presented only general therapeutic procedures, with little information about skin and venereal diseases and, according to our sources, were of little importance for the study of medieval dermatology and venereology. Therefore we will make only occasional reference to them.

Medicine in Serbia during the rule of the Nemanjić dynasty and the Turkish occupation (12th – 18th century)

European medicine was first introduced into Serbia in the 12th century, when the Serbian political scene stabilized and our culture got defined national characteristics (3,7). It was during the period of the rule of the Nemanjić dynasty, which lasted for 205 years (1166 -1371), described by Jirecek as the golden period in Serbian history (8). One of the first members of the Nemanjić family - St. Sava, was the founder of the Serbian Medieval culture, as well as of the Serbian scientific medicine (7). He built the first Serbian hospitals, first in the Hilandar Monastery (1199-1200), and then in the Studenica Monastery (1208); he wrote our first manuscripts about hospital organization (9), and fought against quackery (7). His activity undoubtedly encouraged translation of significant contemporary medical writers. The succeeding members of the Nemanjić family also founded monastery hospitals. In 1308, King Milutin founded a Serbian hospital in Constantinople, in the Prodrom Monastery complex with a medical school which was being considered the nucleus of our Medical Faculty (10). In the 14th century, King Stefan Dečanski, built a hospital in the Dečani Monastery, and Tsar Dušan, another in Monastery of Holy Archangels near Prizren, both in Kosovo (3).

In the Middle Ages in Serbia, like in other European countries, along with trained physicians and surgeons, medicine was practiced by empiricist physicians, self-taught people and other unskilled persons, including quacksalvers. Trained physicians lived and worked mostly in towns, more frequently in the coastal area (Primorje which literally means “by

the sea"), a Serbian region at the time, but sometimes in continental towns as well. They were mostly Italians, and this was the case in almost all Europe, because the majority of medical schools were located in Italy. There is no data as to whether any Byzantine physicians practiced medicine in our regions. (2).

During the 14th and 15th centuries, Serbian medicine was advancing along with the overall cultural growth. Translations of medical and biological manuscripts from Latin and Greek resulted in a compilation of the Serbian Medieval medical terminology (11), including the dermatological terminology in which the terms were based mainly on the external appearance of skin changes and subjective complaints.

Following the fall of the Serbian Medieval state under the Turkish rule (14th-15th centuries) the Serbian overall development was disrupted and practical medicine kept its medieval characteristics until the national liberation of the Serbian country (3). Therefore, as R. Katić observed, when we speak of Medieval medicine in Serbia, we cannot limit it to the period of Middle Ages only, but rather observe the actual duration of Medieval medical practice in Serbia (2). Including structural changes in the population and migrations, many important factors affected the overall social and cultural development, as well as health care, which clearly contributed to the occurrence and spread of diseases, especially contagious ones. In the wars against the Turks, the old Serbian nobility was killed or driven into exile in Austria. The remaining Serbian population lived in scattered mountainside villages away from main roads, which at least partially protected them from the conquerors, as well as diseases. Regarding medical treatment, people had to rely exclusively on folk physicians. In contrast, the towns were populated by Turks – conquerors, land owners and warriors - who had better health care provision, but also caught infectious diseases considerably more frequently due to communication and dissolute lifestyle (12).

In the region of today's Vojvodina, the situation was different. After the Turks started spreading out over the Balkan Peninsula, the Serbian population started migrating towards southern Austrian provinces, which went on for several centuries. As the local population retreated from Turks to the north, Serbs gradually became the majority population in these regions. They created a "Military Frontier" against the Turkish invasion towards Austria and protected spreading of epidemics from the east. In these regions Serbian culture was preserved in newly-founded monasteries in Mt. Fruška Gora. It was in this social and cultural milieu in the late 18th century that a revival of Serbian culture, including medicine, began. The first Serbian hospitals were established in Novi Sad (1730), Zemun (1758) and Vršac (1799). These hospitals employed our first trained physicians - Jovan Apostolović and Petar Miloradović, who both studied medicine in Halle, and worked in Vojvodina. Petar Miloradović wrote a dissertation on syphilis, the first manuscript in our profession written by a Serb (see Venereal diseases) (3). These physicians and their successors represent the nucleus from which our modern medicine has developed.

Meanwhile, there was a renaissance of medicine in Europe, which continued throughout the Middle Ages, influencing revival of medical thought.

Relevant sources for studying Serbian Medieval medicine and dermatology

The basis for studying our Medieval medicine and dermatology are the codices, i.e. therapeutic collections - our oldest medical written documents. Of particular interest for our profession are parts that concern practical medicine and pharmacotherapy, which are mostly translations of the document of the Salerno-Montpellier School (4). Most also include data from Byzantine and astrological texts, as mentioned earlier. The following are the most important (5):

The Codex of Hodoš (CHO) was written in 1369 (4). With regard to the number of diseases covered, it is our most comprehensive medicinal collection (3). The Hilandar Science About Curing All Diseases (HSACAD) originated in the 14th century (4). The Medical Codex of Hilandar (MCOH) No 517 laid the foundations of the Serbian medical terminology. The transcript saved to date was put together in the first half of the 16th century (6). Somewhat less significant, but also important for the general knowledge about medieval skin diseases and their treatment in Serbia are our other medieval codices. They were written according to the oldest Serbian documents, reflecting

the scientific European medicine of that time. They were the most widely used medieval medical sources that our people turned to for treatment up to the recent time (2,5). Due to their widespread use, they acquired the character of folk medicine and were mistakenly regarded as ethnomedicine. They were frequently rewritten by folk physicians and inevitably changed during the process; consequently, the copies made in the 17th and 18th centuries often included prescriptions from Turkish or Serbian empirical medicine (4).

Most of these collections are comprised in Katić's Terminological Dictionary of Serbian Medieval Medicine (11).

By the terms used in these old books, one can conclude what diseases people suffered from and how they used to treat them at the time. The first occurrence and spreading of diseases will be considered within the scope of available relevant data.

Skin diseases and sexually transmitted diseases in Medieval Serbia

Research, identification and interpretation of skin diseases and sexually transmitted diseases (STD), according to medieval documents, is very difficult, for several reasons. Firstly, as skin diseases were not fatal, they were often neglected. Further, the terminology related to skin diseases was vague, descriptions inadequate, and translations from Latin and Greek sometimes incorrect. Even in the 18th century, in the era of protodermatologists, a number of dermatological diseases were lumped together, or subdivided arbitrarily (1). Another confounding factor is that these sources contain mainly pharmacological and therapeutical and less frequently clinical data. This is, for the most part, the case with STDs, as well.

In the present paper we are using mainly the terminology of Katić's translations from the Old Serbian language used in codices on which our work was based on.

Scabies is among the earliest reported skin diseases in Serbia. In the 12th century, Nemanja's contemporary, the chronicler Nicetas Choniates, in his "Historia" noted that the King Stefan Prvovenčani's first wife, Eudokia, suffered from "uncontrollable itching caused by scabies"[1] (13). However, it is more likely that it was not scabies in the present sense of the term at all, but another disease, since there is no data that King Stefan Prvovenčani himself suffered from any kind of dermatosis. This is a good example of how ignorance, along with incorrect translation and transcription, contributed to confusion. In the Latin translation of Nicetas Choniates's Greek text, the word "incontrollable" was ascribed to Eudokia's behavior, not the disease, suggesting that the reason for the separation between Stefan Prvovenčani and his wife was infidelity - although from a historical perspective the reason appears to be political (13). Scabies is included in almost all our medicinal collections, which indicates that it was very widely spread. The MCOH lists several medications. Of greatest importance for us is *sulphur* (5,11), still used today. The following is also recommended: *mercury ointment* (14); a very complicated *lemon ointment* made of borax, white marble powder, frankincense/ olibanum and several other ingredients; *emplastrum* (plaster) for scabies, with no information about its composition (6); saltpeter/potassium nitrate with olive oil or soap in the form of ointment; *resin, tar* in the form of liniment with soap; glass ground into powder mixed with turpentine/terebinth and olive oil, with a note that exanthema should first be well scratched; several herbs in the form of liniment or oil, and even *rose oil. Pyrethrum* is listed in the MCOH, although not as a medicine for scabies (11).

In the Medieval Serbia, *leprosy* was called black death up to the 14th century, and afterwards the term was used to refer to all serious and chronic skin diseases (11). The earliest known record of leprosy in Serbia was found in the biography of Stefan Nemanja (1166-1196) (15). Stefan Decanski (14th century) also built a shelter for the leprous near the Dečani Monastery, and among the leprous was the painter of famous icons, zoographer Longin. Another leprosy shelter was founded in the Hilandar Monastery, and leprosy was recorded also in the period of Despot Stefan Lazarević (1389-1427) (14). There is a record from the early 15th century about leprosy and a leprosy Hospital in Kotor, the greatest sea port in the Old Serbian state (3). However, there is a little data about the clinical picture of leprosy. St. Constantine the Philosopher wrote that

[1] Serbian translation from Greek by Professor Vojislav Jelić, Department of The Humanities, Faculty of Philosophy, Belgrade

Figure 1. Christ Healing Ten Lepers, taken from the Fresco Collections: Christ's Miracles, XIVth century. The monastery Visoki Dečani, Serbia, Kosovo

people with leperosy had "rotten face with flesh falling off the bones", and the zoographer Longin describing his own disease spoke of pus-filled crusts "that hurt bitterly" (14). Healing of the leprous was among the favorite motives in Serbian Medieval frescoes (3) (Fig. 1). Yet, there is little data about actual treatment of leprosy in our medical collections, probably because it was incurable. The CHO recommends bloodletting, particularly in the middle of March, April and May, indicating evident effects of ancient, and astrological medicine. Crushed cinnamon with honey and wine was also advised (4). MCOH recommended: *laurel oil* (11).

Fungal diseases of the head probably included: crusts on the head in children according to CHO (4), "evil crusts on the head" according to MCOH (6) and "crusts on the head" in the Dečani Codex in the 16th century, as well as in the Codex of Grigorović (CGRI) in the 17th century (2,5). Most likely, these correspond to fungal diseases of the scalp, although psoriasis cannot be ruled out definitely. Treatment by (CHO): haircut, hair wash using a mixture of boiled blackberry leaves and wine, compression with lentils boiled in a mixture of wine and water, application of a mixed burnt cotton paper, wine and mercury. Bloodletting was obligatory (4). The CGRI lists *lichen* (probably mycosis, eczema or psoriasis), for which crumbled *cucullus* (Latin) known as a hood, with vinegar and *sulphur* was prescribed (5).

Crusts (pyococcal skin lesions): HSACAD and CHO advised application of *sulphur and vinegar* ointment (4). *Vinegar* was used as a disinfectant at that time (14); CHO: a mixture of *almond oil and cow's butter*; juice squeezed from *ivy leaves*, salt, wine and oil; Russian oil (Latin: *Elaeagnus angustifolia*) (4).

Nicina (CHO): refers to a purulent wound (11).

Skin Rashes: According to CHO, the main treatment is a special diet – the food must not be hot (spicy), but fresh and include bread made of pure

flour, soft-boiled eggs, warm sheep's milk, fresh meat and fish (4) (Urticaria and Exanthema are probably synonyms for rash).

Unspecified *skin diseases:* MCOH: general medications for skin diseases are horse *radish ointment* (6); *Lapsana Communis* (Latin) common nipplewort used against bites and abscesses in the form of liniment (11,16).

Extensive Hairiness: orpiment (Latin: *auri-pigmentum*) is a mineral (arsenic sulphide) medicine (6, 17) which was used for depilation. In order to check its efficacy, it was recommended to dip a feather into the solution to determine the activity of the medicine (4).

Proliferated tissue: Procedures for tissue reduction are described. The MCOH lists mostly plants or their resins (5, 11), and *emplastrum* (Latin), the composition of which is unknown (11).

Baldness (hair loss) is frequently included in these old books. CHO: a donkey's hoof should be burnt, then (unclear in the original manuscript....) should be made, and applied on the areas where the hair has fallen out, and it will soon grow again. Other medicines are herbal, often prepared in strong red wine (4, 5).

Old wounds (any incurable wound) CHO: A new sea sponge should be soaked in vinegar and tied to the wound; *sulphur* dissolved in white vinegar (4). In order to drain pus from the wound: *black ointment* made of colophony and frankincense (6); MCOH: iris ("herb") should be used in the form of powder (11).

Leg wounds: CHO: Wash the wound with a sponge soaked in vinegar, bind it up until it heals (4); MCOH: *basilicon ointment* made of sweet basil (Latin: *Ocimum basilicum*), a plant used against burns, frankincense, tar, wax and (animal) fat, as well as *emplastri* (juice made of several plants) (6,16). Therapeutic effects of tar in dermatology are accepted to date, although for different indications. According to Gilje, application of plasters can be compared to the ulcer treatment.

Non-healing wounds, chronic purulent wounds, suppurative eczemas: MCOH: *antimonium* ground into powder and mixed with dissolved soap (11).

Decubitus: anise butter (MCOH), made of anise, wormwood/absinthe and olive oil (11).

Facial spots (probably acne): CHO: local application of marble powder and egg white; finely chopped lily root with vinegar, as well as mixture of alder (Lat: *Rhamnus*), a herb used as a remedy against itch (11,16) and dried swallow dung (4).

Facial treatment: cosmetics was important in Medieval Serbia. CHO: horse bean flour, goose fat with sesame oil (4); MCOH: *lemon ointment* (see Scabies), for facial skin whitening (2,6); mercury ("for whitening/bleaching"), which was used until the first decades of the 20th century; honey and *camphor; saltpeter* with honey for fading facial freckles; various herbs, sometimes mixed with rose water (11).

Flea treatment: soak a broom with a black male goat's blood, leave it overnight in the middle of the room and remove it the next morning; fleas will be collected on it (4). This recipe was very important, because of plague transmission by fleas raging throughout the Middle Ages (14).

Lice infestation: MCOH: use *saltpeter* (potassium nitrate) with olive oil or soap in the form of ointment (11); or *mercury* (14). These recipes were important because lice were a common part of general hygienic conditions in which our people lived under Turks, causing epidemics of louse-borne typhus. The situation was similar in other countries, and there are records from the 16th century, stating that "men and women, even the most distiguished ones, were full of fleas and lice" (18).

Syphilis: there are no traces of the existence of this disease in Serbia before the 15th century (14). Syphilis spread to the Balkan Peninsula during the Turkish invasion (2); However, The Codex of Bosnia first mentions it in the 17-18th centuries; CGRI (16th century) provides a brief description that may correspond to "Ulcus molle" or "Ulcus durum" ("when men contracted the disease from immoral women") (5). Syphilis was brought to Serbia from Italy through coastal towns of Dalmatia, while from the north it was spread by Austrian soldiers, who fought against the Osmanli Army on the territory of Serbia (14); migrations from Romania in the 18th century also contributed to its spreading (19). In our regions, a great epidemic was recorded in Banat, and consequently a hospital for venereal diseases was founded in Vršac in 1799. The treatment included "placement of calomel and mercury solution, followed by nitric acid and mercurius corrosivus" (3). Syphilis was common in towns, populated mainly by Turks, while

it was rarely found in villages, populated exclusively by Serbian people. As mentioned earlier, the first manuscript in our profession written by a Serb was Petar Miloradović's doctoral dissertation on syphilis (De innocendi infectione venerea, 1768). His work was theoretical, but the ways of infection transmission are still valid (14). It seems that in that period, syphilis was more frequent in the Northwestern than in the central parts of Serbia (5).

Urethrites were known since ancient history; they were usually named by symptoms, and it was emphasized that they were transmitted through sexual intercourse (20). Although our medieval sources do not analyze these diseases specifically, MCOH contains a part on uroscopy, and sections about milk-like urine or yellow-green discharge (6). It seems likely that at least some of these cases were gonorrhea or non-gonorrheal urethritis.

There are also a few documents about the treatment of sexually-transmitted diseases, and it should be kept in mind that the belief that syphilis and gonorrhea were the same disease, was still common in Europe in the 18th century (20). The MCOH lists *letargiro* (lead oxide) for the treatment of venereal diseases, as well as *mercury*, mainly for genital infections in men (11), but emphasizing that both substances are toxic (5). It is not specified what types of venereal diseases these are, though. According to the CGRI, the wound should be dressed with crushed rose hip (5). In relation to the ways of transmission of STDs, they are said to be caused by too frequent sexual intercourses - "of spending too much time with women" (2).

With regard to venereal diseases, maybe it might be appropriate to discuss the appearance of prostitution in our medieval state. For the majority of our rural population this problem in fact did not exist. It was a problem in our towns. (3). However, it is known that prostitution was spread in the coastal towns in Medieval Serbia. In Budva, whores started wearing head-coverings. Prostitution was present in Belgrade as well, and in 1643 it was recorded that people used to throw innkeepers and prostitutes in the river Sava, believing that their shameful lifestyle was the cause of frequent outbreaks of plague (3). In addition, Turkish soldiers used to rape women in the conquered Serbia, which represented a special form of promiscuity. Other contributing factors were other armies passing through Serbia over the period (14). Prostitution came to the coastal parts of Serbia from Italy, and to the northern parts from Austria (3).

Finally, it is necessary to point to two substances, which are not medicines:

Violet: (MCOH) with no medicinal value, but highly improving in preparation of various oils called "djulat" (11).

Tow was used instead of cotton (4).

In conclusion, we would like to emphasize that our Medieval codices recorded not only medicines and minerals used in the scientific medicine of that time, but also animal products. Plants ("herbs") were almost always present in the treatment of skin diseases. The substances were applied in the forms of powder, ointment, liniment or plaster, and herbs were mixed with wine, vinegar and honey. Sometimes their usage was fantastic and illogical (3) and sometimes justified. There were also medicines, which are used to date, such as sulfur, pyrethrum, tars and resins, and until recently used mercury. However, they were not always used for indications like today. The most frequently reported dermatological and venereological diseases were those caused by infections. One more field of interest in medieval medicine we would like to point out is cosmetic defects and their treatment.

Following the liberation from the centuries-long Turkish occupation, together with the revival of the Serbian state, there began the development of modern medicine in Serbia.

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Abbreviations

MCOH - Medical Codex Of Hilandar
STD - Sexually Transmitted Diseases
CHO - The Codex of Hodos
CGRI - The Codex of Grigorović
HSACAD - The Hilandar Science About Curing All Diseases

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With great pleasure, we acknowledge our gratitude to Prof. Dr. Boža Pal, who helped us a great deal with the terminology used for herbs and remedies in Medieval Serbia.

Istorija dermatovenerologije u Srbiji - I deo: Srednjovekovna dermatovenerologija

Sažetak

Dermatovenerologija kao samostalna disciplina u Srbiji stvara se tek u drugoj polovini XIX veka, tako da se njen rani razvoj proučava u okviru srednjovekovne medicine, koja je bila naučna medicina toga doba i predstavljala je sintezu vizantijske i zapadnoevropske nauke.
Izvori za proučavanje srednjovekovne dermatovenerologije u Srbiji su naši medicinski i terapijski zbornici toga doba. Iz termina i opisa bolesti upotrebljenih u njima vidi se od čega su naši ljudi u srednjem veku bolovali i kako su se lečili.
"Šuga" je prva bolest kože koja se pominje, a u lečenju se primenjivao sumpor, živina mast, katran sa sapunom, istucano staklo u ulju.
Lepra je bila poznata od davnina, ali se kod nas nalazi tek u biografijama Nemanjića (XII), a često je prikazivana i na freskama srpskih manastira.
Za lečenje gljivičnih obljenja kapilicijuma (ili psorijaza), savetuje se šišanje kose i biljni melemi; za kraste (piokokna oboljenja?) – sumpor; granulacije na ranama - specijalna smola u medu i sirćetu i emplastri; ćelavost - biljni preparati; dlakavost – auripimentum; ospe, oboljenja kože - biljni linimenti; lišaj (psorijaza, mikoza); rane na nozi - katran i emplastrum (Gilje!), stare rane - katran; sifilis se pominje tek od XV veka, a nailazi se i na oboljenja s abnormalnim uretralnim sekretom (uretritisi).
Negovana je kozmetika: za pege je davana limunska mast i živa, a za negu lica guščije salo sa susamovim uljem, brašno od boba.
Protiv insekata (vaši, buve) pored određenih postupaka, davana je i živa. Kao što se vidi, terapija je bila lokalna, a upotrebljavani su biljni lekovi, ali i hemijske supstancije. Neki lekovi mogu naći svoj ekvivalenat i u današnje vreme.

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Spectrum of histamine-mediated allergic disease summit 2008, Lisbon Aerius summit

From February 7-10th, Lisbon welcomed 292 Physicians from 39 different countries and 5 internationally recognized speakers, in order to provide new discussion on antihistamine therapy in chronic urticaria (CU) and allergic rhinitis (AR).

This 2-day meeting overviewed the following current topics:

- Core Facets of Histamine-Mediated Allergic Disease
- Living with Allergies: Impact on Quality of Life
- Management Considerations for Allergic Rhinitis
- Contemporary Understanding of Chronic Urticaria Management
- Comparative Pharmacology of Antihistamines

Apart from this, 8 oral posters were presented by attendees.

Professor Marina Jovanović, Clinical Center of Vojvodina, Republic of Serbia, presented an original study "Contact Urticaria in Patients with Chronic Urticaria, Allergic Contact or Atopic Dermatitis: The Effects of Oral Antihistamines."

Antihistamines are widely used as a first-line therapy for chronic urticaria, because of demonstrated efficacy in the treatment of this disease. Second-generation antihistamines provide efficacy with fewer side effects, including lower rates of sedation, drug-drug interactions and anticholinergic effects.

The most important clinical data about superior efficacy and safety of antihistamine desloratadine was also presented in the Summit.

Desloratadine is a second generation antihistamine, with wide range of clinical data confirming its superior effects in CU.

Pharmacology of desloratadine

The highest H1-receptor affinity among second-generation antihistamines and slow dissociation from H1 receptor, provide a reliable 24-hour duration of action.

Desloratadine shows no antimuscarinic effects at clinical doses. In addition to blocking histamine-induced production of inflammatory mediators, it also in vitro inhibits the production of inflammatory mediators in the absence of histamine, providing potential additive antiallergic activities. There is no interaction between desloratadine and intestinal P-glycoprotein and organic anion transporting polypeptide (OATP) transport pathways. Absorption and metabolism are also unaffected by age, gender or race. Desloratadine is not metabolized by the liver cytochrome P450 3A4 pathways. It has no relevant drug-drug interactions. It causes no sedation, due to its high lipophilicity, low active uptake, and high efflux from the CNS by P-glycoprotein transporters.

Desloratadine was evaluated in several placebo-controlled trials of patients with CU. In a large, multicentre, randomized, double-blind trial, 190 patients with moderate pruritus associated with CU were randomized to once-daily dosing of desloratadine: 5mg or placebo for 6 weeks. Compared with placebo, desloratadine significantly ($p<0.001$), for all comparisons) reduced morning signs and symptoms of CU, including pruritus, the number of hives, and the size of the largest hive, after only 1 dose, and these benefits were maintained over the 6-week duration of the study. Desloratadine has improved sleep quality ($p<0.03$) and reduced interference with daily activities ($p<0.001$). In another multicentre trial, 226 patients with CU were randomized to receive 5mg desloratadine, or placebo for 6 weeks. Once-daily desloratadine has significantly improved the morning signs and symptoms of CU after 1 dose, compared with placebo ($p<0.005$), and this advantage was maintained for the entire duration of the study ($p<0.01$). The efficacy of desloratadine was also evaluated in community practice settings. In a study of 9246 chronic idiopathic urticaria patients performed in Germany, over two-thirds of patients reported improvement in sleep ($p<0.0001$) and daily activities ($p<0.0001$), and nearly 90% of patients reporting complete or significant relief of signs and symptoms. Global efficacy and safety were rated as excellent/good by the vast majority of both patients

and physicians. So, we can definitely draw an obvious conclusion that desloratadine improves quality of life of patients with CU.

All the data that were reported in the Summit indicate that nonsedating desloratadine is safe and effective as a first-line therapy option for chronic urticaria.

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Euromelanoma Campaign in Serbia 2008

For years, dermatologists from European countries have been actively involved in the Euromelanoma Task Force of the European Academy of Dermatology and Venereology – a prevention campaign against melanoma entitled the Euromelanoma Day. The number of participating countries in this, above all, a humanitarian, prevention campaign, has increased from less than 10, in the first years, to 25 in 2008.

From year to year, Euromelanoma Day takes place in May, usually on Monday. This year Euromelanoma Monday was set for May 5th 2008.

The motto for all European countries included in the campaign was: "Check your moles regularly; catch melanoma early!"

Euromelanoma Day Campaign in Serbia 2008 was organized by Serbian Association of Dermatovenereologists and European Academy of Dermatology and Venereology (EADV), Euromelanoma Task Force of the EADV, under the protection of the Ministry of Health of the Republic Serbia, sponsored by Beiersdorf Eucerin Company, dedicated to dermatology.

The aim of the Campaign was to identify as many people as possible, at risk for skin cancer and at early stage, provide information about risk factors and symptoms of the melanoma in early stages and alert the public to dangers of the sun exposure.

The Campaign was promoted by various means: a press release held on March 14th 2008 announced on all national televisions, through a media campaign in newspapers, radio and TV; a poster advertisements and an open line center for information on participating dermatologists, addresees and so forth. Website: www.udvs.org provides basic information about the prevention, screening, diagnosis and treatment of melanoma and other skin cancers.

In order to take part in Campaing, people could get information on participating dermatologist (their addresses and phone numbers) and make appointments throught free of charge phone calls (from April 14th to 20th, 2008, call center: 0800 222 888 from 08:00-20:00), which was organized by the Sponsor.

Professor Andreas Katsambas, EADV President, has welcomed the Serbian campaign and joining the Euromelanoma Day using a unique European questionnaire on melanoma. Euromelanoma questionnaire was translated into Serbian and sent to the participating dermatologists after the list of appointments was closed.

Before the Campaign started, informative posters were distributed to the patricipating dermatological institutions, private practitioners, pharmacists...

Dermatologists all over Serbia (from Belgrade, Novi Sad, Niš, Pančevo, Kragujevac, Kraljevo, Čačak, Užice, Valjevo, Požarevac, Kikinda, Sremska Mitrovica, Kosovska Mitrovica) participated in the Euromelanoma Campaign. 114 dermatologists (~ 50 % of all dermatologists from the Serbian Association of Dermatovenereologists) undertook skin screening of patients on their list; there were 106 dermatologists from Public hospitals and 9 dermatologists from private practice. Free-of-charge screening was performed in 1392 subjects. The screening took place at Dermatology Clinics of Medical Centers, Outpatient Clinics or at Private Offices.

All of the screened subjects received a Patient Information Leaflet containing answers to the questions: What is malignant melanoma? What causes malignant melanoma? Risks factors for developing melanoma? A need for self-examination because melanoma follows the ABCDE rule. What can I do to avoid another melanoma? Dangers of the sun exposure? Information about sun protection.

Euromelanoma Day Campaign team from Serbia was presented by: Prof. Lj. Medenica, Ass. Prof. D. Škiljević, Ass. Prof. D. Živanović, Mrs. N. Miletić-Nevajda (Beiersdorf - Eucerin). Results from the Euromelanoma Day Campaign in Serbia 2008 were presented on the Euromelanoma Meeting at the 17th EADV Congress, in September 16-20, 2008.

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A report on the 5th EADV Spring Symposium 2008, Istanbul

Istanbul, the largest town in Turkey, and the only metropolis situated on two continents, was the host of the 5th EADV Spring Symposium 2008. The symposium was organized from 22-25 May, 2008, in the „Istanbul Lütfi Kirdar" Congress and Exhibition Centre. „Dermatology Bridging the Continents" was the main theme of this symposium, showing that dermatology connects East and West, Asia and Europe, past and future. The program consisted of 68 sessions, 210 chairs, co-chairs and speakers who took part in the symposium and there were much more registered participants. Three plenary sessions, 18 symposia, 16 workshops, 6 lunch sessions and 4 satellite symposia were organized. There were 707 accepted abstracts, 139 for oral presentation in 18 different sessions, and there were 568 abstracts for poster presentation. Laser dermatology attracted special attention, as well as dermatoscopy, melanoma, autoimmune bullous diseases, atopic dermatitis, pediatric dermatology... During the workshop „Traditional Dermatologic Therapies From the East to the West", there was a discussion about an original Bulgarian method for treatment of psoriasis, about traditional therapies in Turkey and Nordic countries, and German traditional therapies of acne and rosacea.

Participation of dermatovenereologists from Serbia was well appreciated, because most of the 50 participants from our country had presentations. The oral presentations were: „Bipolar aphthosis and its relation to Behcet's disease" by Miloš Nikolić, who was also a lecturer by invitation and a co-chair over the symposium on Behcet's disease; „Behcet's disease: an analysis of 13 patients" by Kristina Kostić, Lidija Kandolf-Sekulović and Radoš Zečević; „Pimecrolimus 1% cream for treatment of Granulomatous cheilitis" by Vesna Mikulić; „Skin and lung sarcoidosis, unusual clinical presentation" by Mirjana Milinković, Danijela Milčić, Sonja Vesić, Violeta Vučinić and Ljiljana Medenica"; „Papular mucinosis (Scleromyxoedema) - Case Report" by Danijela Milčić, Dušan Škiljević, Maja Tomović, Mirjana Popadić and Mirjana

Milinković; „Blood vessels in trombosis patients with vasculitis“ by Javorka Delić and Zagorka Jovanović.

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Spring Meeting of the Section of Dermatovenereologists of the Serbian Medical Society in Prolom Banja

Since 2001, the Dermatovenereology Section of the Serbian Medical Society's Branch in Niš, and the Clinic of Skin and Venereal Diseases in Niš, traditionally organize a Spring Meeting in Prolom Banja.

The last meeting was held from 9th to 11th May, 2008. There were more than 100 participants, not only from Serbia, but also from Bulgaria and Macedonia. The main program included presentation of 14 interesting case reports, as well as 2 plenary sessions. Prof. Dr. Mirjana Paravina gave a lecture on spa-therapy of different dermatoses by using spa resources of Prolom Banja. Prof. Dr. Dragan Jovanović presented the most common transient neonatal skin changes. During the meeting, participants also had many social activities, including a visit to a unique, picturesque and true wonder of nature, Đavolja Varoš ("Devil's Town").

The Dermatovenereology Section of the Serbian Medical Society's Branch in Niš was founded 27 years ago, on 29th of May, 1981. It was founded at a Meeting of Dermatovenereologists of South-East of Serbia, held in the Dermatovenereology Clinic in Niš (today Clinic of Skin and Venereal Diseases, Clinical Centre Niš), under the initiative of Prof. Dr. Snežana Vojinović-Jovanović, who was elected for the first President of the Section.

At the moment, the president of the Dermatovenereology Section of the Serbian Medical Society's Branch in Niš is Prim. Dr. Milanka Ljubenović.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2009

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
16 January, 2009	Scientific meeting: "Disorders of the hair and nails" Academy of Medical Sciences Serbian Medical Society, Belgrade, Serbia	No abstract submission	www.sld.org.rs
2-5 April, 2009	2nd Winter Academy of Dermatology St. Moritz and Pontresina, Switzerland	31 January, 2009	www.winteracademy.net
23-26 April, 2009	6th EADV Spring Symposium - Bucharest, Romania	28 November, 2008	www.eadv.org/bucharest2009
3-6 May, 2009	12th World Congress on Cancer of the skin 2009, Tel Aviv, Israel	5 January, 2009	www.kenes.com/wccs2009
12-16 May, 2009	7th World Congress on Melanoma and 5th Congress of the EADO, Vienna, Austria	31 January, 2009	www.worldmelanoma2009.com
20-24 May, 2009	10th International Congress of Dermatology Prague, Czech Republic	30 October, 2008	www.icd2009.com
4-6 June, 2009	18th Congress of Dermatologists of Serbia, Sava Center, Belgrade, Serbia	In construction	www.udvs.org
6-10 June, 2009	27th EAACI Congress, Warsaw, Poland	14 January, 2009	www.eaaci2009.com
14-17 June, 2009	Occupational and Environmental Exposure of Skin to Chemicals, Edinburgh, Scotland	1 Novembar, 2008	www.oeesc2009.pwp.blueyonder.co.uk
18-23 June, 2009	15th International Congress on Photobiology, Duesseldorf, Germany	In construction	www.iuf.uni-duesseldorf.de/ICP2009
24-28 June, 2009	2nd World Psoriasis and Psoriatic Arthritis Conference, Stockholm, Sweden	1 March, 2009	www.ifpa-pso.org
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
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
12-14 November, 2009	2nd IDS Congress, Barcelona, Spain	In construction	www.idsdermoscopycongress2009.com

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.*

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

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

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

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

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

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.*

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

1. Manuscript Preparation Guidelines

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

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

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

- A running title (limited to 30 characters);

- Authors' names and institutional affiliations;

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

1.2. Abstracts

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

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

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

1.3. A list of abbreviations

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

1.4. Cover Letter

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

2. Tables and illustrations

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

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

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

3. References

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

4. Additional information

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

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