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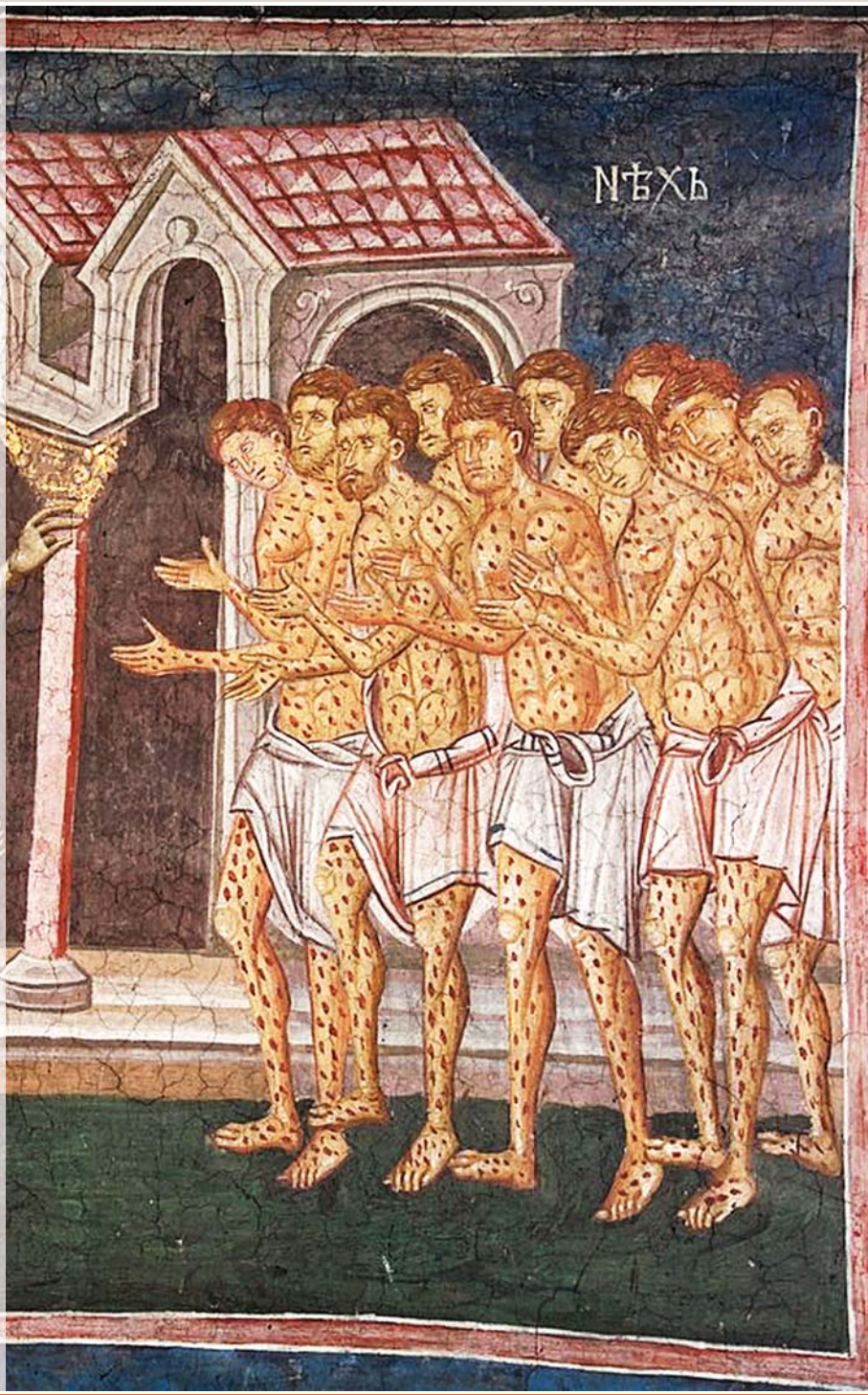

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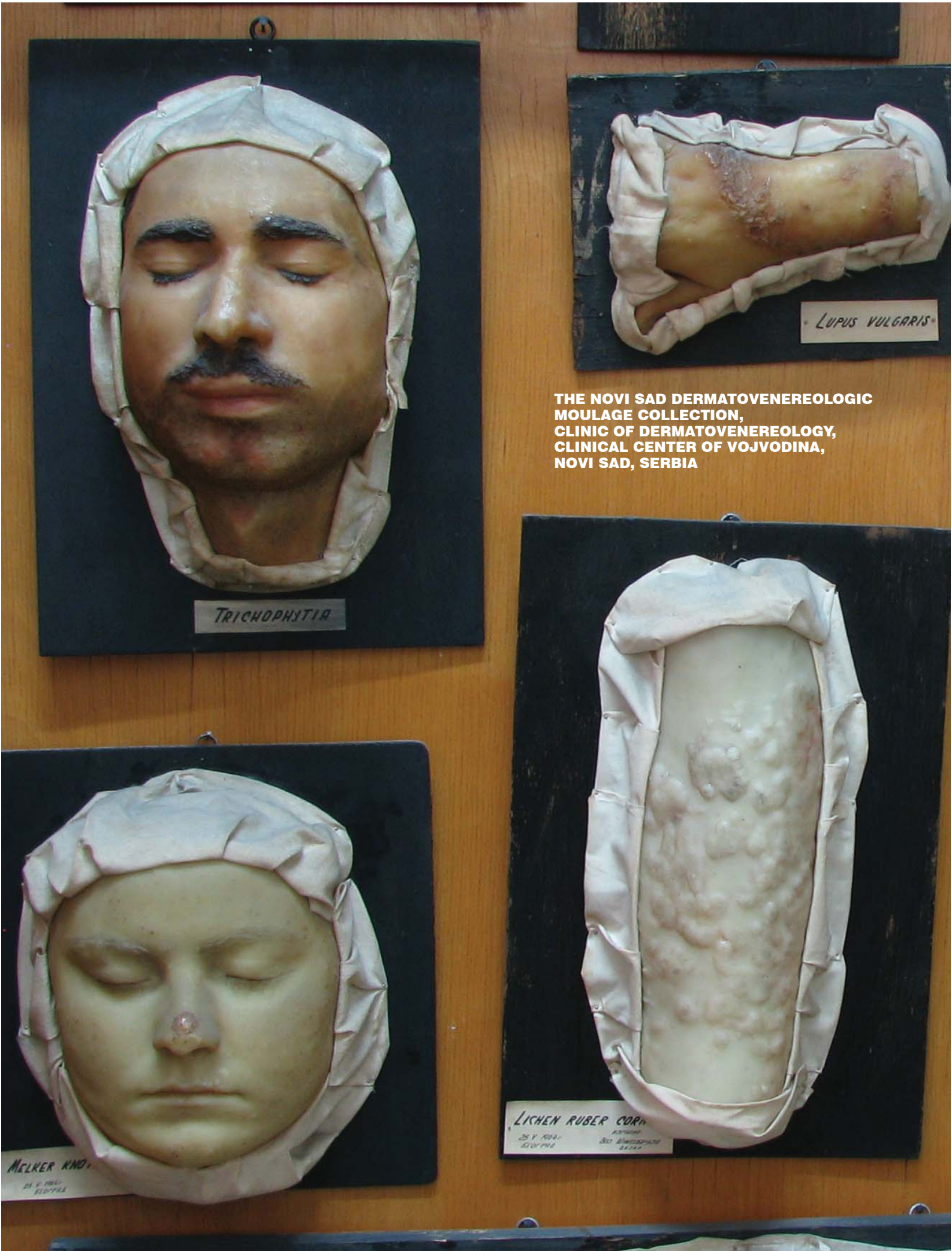

THE NOVI SAD DERMATOVENEREOLOGIC MOULAGE COLLECTION, CLINIC OF DERMATOVENEREOLOGY, CLINICAL CENTER OF VOJVODINA, NOVI SAD, SERBIA

Cardiovascular and Metabolic Comorbidities in Patients with Plaque-Type Psoriasis Never Treated with Systemic Antipsoriatic Drugs: a Case-Control Study

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Abstract

Previous studies have shown a higher prevalence of cardiometabolic diseases among patients with psoriasis compared to non-psoriatics. However, little attention has been paid to the effects of systemic antipsoriatic drugs. The aim of this study was to investigate the association between psoriasis and these comorbidities, comparing untreated patients with psoriasis and population-based control non-psoriatic patients.

A hospital-based case-control study included 122 patients with plaque-type psoriasis and 122 age- and gender-matched controls. Patients who ever received systemic antipsoriatic drugs were excluded.

There were no significant differences between psoriatic patients and controls regarding the prevalence of hypertension (p=0.311), coronary heart disease (p=0.480), diabetes (p=0.641), myocardial infarction (p=0.71), stroke (2.4% vs. 2.4%, p=1.00) and metabolic syndrome (p=0.764). The prevalence of hypertriglyceridemia in patients with psoriasis and controls was 41.8% and 28.7%, respectively (OR 1.78, 95% CI 1.04-3.04, p=0.032). Furthermore, significant differences were observed in mean triglyceride levels (p=0.013). Smoking was significantly more often reported in psoriatic patients compared to controls. Patients with psoriasis also had a higher mean BMI (26.24, SD 4.42) compared with controls (24.73, SD 3.86), p=0.005. Psoriasis showed a statistically significant association with BMI obesity classification [$\chi 2(4)=11.560$, p=0.02].

The prevalence of cardiovascular and metabolic comorbidities was not significantly higher in patients with plaque-type psoriasis who were never treated with systemic antipsoriatic drugs, compared to population-based non-psoriatic controls. Our data suggest that systemic antipsoriatic drugs may play an important role in the development of these comorbidities. However, this study confirms that untreated psoriasis patients have three major modifiable increased cardiovascular risk factors, such as smoking, obesity and hypertriglyceridemia.

Key words

Psoriasis; Comorbidity; Cardiovascular Diseases; Diabetes Mellitus, Type 2; Metabolic Syndrome X; Smoking; Risk Factors

Psoriasis is a chronic, relapsing, inflammatory skin disease with an estimated prevalence worldwide ranging from 0.91% (USA) to 8.5% (Norway) (1). The most common type of psoriasis is plaque psoriasis, accounting for around 80% of cases. Approximately 20% of affected individuals have moderate-to-severe psoriasis (2). The traditional belief about psoriasis is that it is a skin disease without visceral involvement. However, by the end of the 20th century, the psoriasis model had evolved to become a disorder of the skin and joints. Nevertheless, this concept has been challenged in recent years. Currently, psoriasis is considered to be a Th1/Th17-mediated inflammatory disease, characterized by chronically elevated levels of proinflammatory cytokines (3). Recently it has been classified as an immune-mediated inflammatory disease (IMID) with high risk of systemic comorbidities (4).

Comorbidity in psoriasis has become one of the most engrossing topics in dermatology in the past five years. A mere search of the terms "psoriasis and comorbidities" in Pubmed shows more than 300 articles published over the last decade.

In 2011, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) identified comorbidities as one of three priority research areas in psoriasis and psoriatic arthritis (5). Traditionally, comorbidity has been defined as the presence of two or more diseases or conditions in the same individual at the same time (6). Klein et al. argue that comorbidity may occur for a variety of reasons. There is a possibility that comorbitity occurs due to the following: conjuction of independent risk factors; shared or overlapping risk factors; one disorder causes another; variable expression of one disorder; independent coincidence (7).

There is a growing evidence that psoriasis is associated with a number of systemic comorbidities, including psoriatic arthritis (PsA), obesity, hypertension, diabetes mellitus, hyperlipidemia, metabolic syndrome, cardiovascular disease (CVD), Crohn's disease, lymphoma, malignancies and multiple sclerosis, as well as mental health comorbidity including anxiety, depression, smoking, alcoholism, and eating disorder (8-15). However, the exact mechanisms standing behind these associations are still uncertain.

The relationship between psoriasis and CVD is probably associated with the underlying chronic inflammation that exists in psoriasis, as a consequence of increased levels of proinflammatory cytokines (16). The elevated tumor necrosis factor-alpha (TNF-α) levels have been found in the skin lesions and sera of patients with psoriasis and increased serum levels have been shown to correlate with disease activity (17). The relationship between psoriasis and associated diseases is complex, making it difficult to identify direct relationships (Figure 1). Life style factors, impaired health-related quality of life, depression, and therapeutic interventions, may be confounding. Also, several biases, such as detection bias, may affect observational study results (18).

There is little information available on the effects of drugs on comorbidities. Drugs used in the treatment of psoriasis, such as acitretin, cyclosporine, and methotrexate, may adversely affect independent

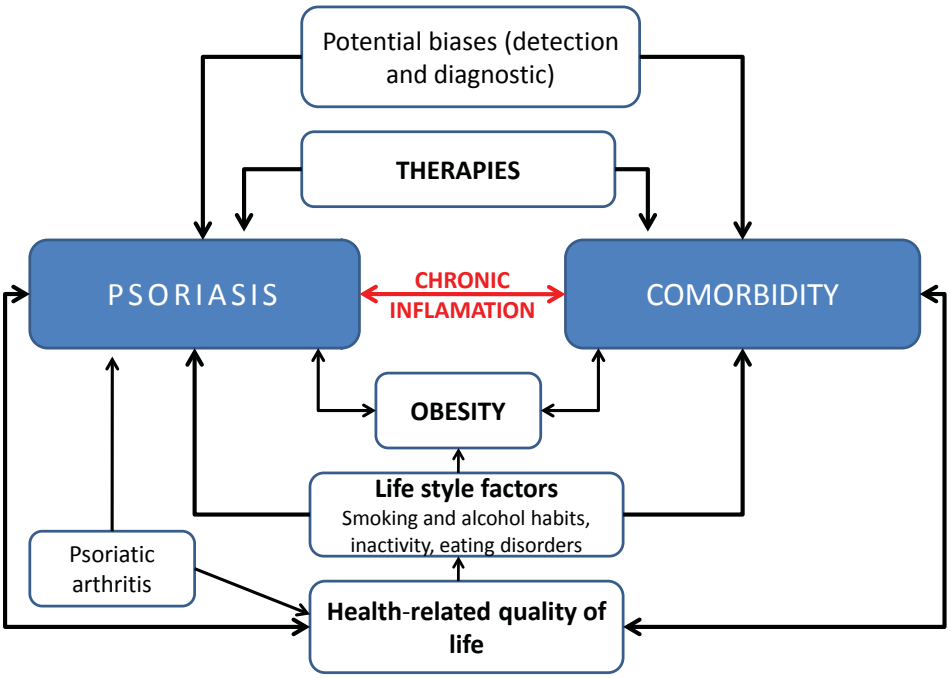


Figure 1. The complex relationship between psoriasis and comorbidity [Adapted from Wakkee et al, (18)]

cardiovascular risk factors such as blood pressure and lipid levels. Methotrexate increases homocysteine levels (19), whereas cyclosporine and acitretin induce hyperlipidemia (20). Thus, high prevalence of some comorbidities in patients with psoriasis may be, at least partly, due to systemic antipsoriatic drugs. Wakkee at al. argue that effects of systemic drugs on the cardiovascular risk represent a sum of anti-inflammatory effects and atherogenic side effects (18).

The objective of this study was to determine the prevalence of comorbidities in patients with psoriasis never treated with any systemic antipsoriatic drugs.

Material

Patients

One hundred and twenty two patients with plaque-type psoriasis and 122 age and sex-matched controls participated in the study. The group of psoriatic patients included 44 inpatients (36.1%) and 78 outpatients (63.9%), who were consecutively recruited from the University Clinic of Dermatology, at Skopje Medical Faculty from September 2011 to April 2012. The inclusion criteria were age > 18 years and clinical diagnosis of plaque-type psoriasis lasting at least six months. The study included only systemically untreated patients. Thus, patients who received systemic antipsoriatic drugs, (eg. acitretin, cyclosporine, methotrexate, ultraviolet therapy, corticosteroids) or biologics, were excluded. In addition, patients with other types of psoriasis (guttate, erythrodermic and pustular psoriasis), history of SLE, RA and other autoimmune disorders were also excluded. The control group was selected from patients from the same geographic region, who were consecutively admitted/visited the Public Health Center "13 Noemvri", during the same period. Each control was matched to a case according to age (+/-1 year) and sex. Controls visited general practitioners for: routine control (59 patients), viral infection (15 patients), bacterial infection (11 patients) and hypertension (10 patients), dermatologic condition other than psoriasis (8 patients), cardiomyopathy (8 patients), diabetes (4 patients), urology problems (3 patients), gastroenteritis (2 patients), and trauma (2 patients).

The study was conducted through a structured face-to-face interview and examination, and it was approved by the Ethics Committee of the Medical Faculty. All participants signed an informed consent.

Methods

Severity of psoriasis

The severity of psoriasis was assessed using the Psoriasis Area and Severity Index (PASI) and Body Surface Area (BSA). A PASI score ≤10 defines psoriasis as mild, whereas scores above 10 classify it as moderate or severe. Patients were classified in regard to the age of onset of psoriasis; type 1: onset before the age of 40 years, and type 2: onset after the age of 40 years (22). The diagnosis of psoriatic arthritis (PsA) was made using Moll and Wright criteria (23).

Comorbidity data

A list of clinically-relevant comorbidities was derived from diagnoses included in the Charlson Comorbidity Index (21). Chronic conditions were classified using diagnoses at discharge or drug prescriptions, for example: diabetes - if use of antidiabetic drugs was registered; hypertension - if BP ≥140/90 mmHg was found, and/or current use of an antihypertensive.

Metabolic syndrome

Metabolic syndrome was diagnosed by the presence of three or more of the following criteria of the National Cholesterol Education Programme's Adult Treatment Panel III (ATP III): waist circumference > 102 cm in men and > 88 cm in women; hypertriglyceridemia > 1.7 mmol/l (150 mg/dl) or ongoing drug treatment for elevated triglycerides; high density lipoprotein (HDL) cholesterol < 1.0 mmol/l (40 mg/dl) in men and < 1.3 mmol/dl (50 mg/dl) in women or ongoing antilipidemic treatment; blood pressure > 130/85 mmHg, or ongoing antihypertensive treatment; fasting plasma glucose > 6.1 mmol/l (100 mg/dl) or ongoing antidiabetic treatment (24).

Body mass index

The body mass index (BMI) was calculated as weight in kilograms divided by height in meters^2 and patients were classified as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30.0 kg/m^2).

Blood pressure
Blood pressure (BP) was measured in sitting position using a standard mercury sphygmomanometer.

Smoking
Smoking habit was classified into two categories of never smokers and ex-smokers/current smokers.

Alcohol consumption
Alcohol consumption was classified into two categories of none/low/moderate: up to three alcoholic drinks per week, and regular/heavy: ≥ 4 alcoholic drinks per week.

Statistical analysis
Categorical variables were expressed as frequencies and percentages, and numerical variables as means, range and standard deviations (SD). Odds ratios (OR) were estimated using logistic regression models with conditional 95% confidence intervals (CI). The proportion of comorbidities in psoriatic patients was compared with their matched non-psoriatic controls. Comparisons were made by using the Student's t-test for parametric continuous variables, Mann-Whitney U test for nonparametric continuous variables and Chi-square test for qualitative variables. The limit for statistical significance was set at $p \leq 0.05$. The SPSS version 10 statistical software (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis.

Results

Baseline characteristics of the study group are shown in Table 1. One hundred and twenty-two patients with psoriasis (52 male and 70 female, the mean age 51.52 years, SD 15.56, range 19 -80 years), and 122 age- and gender-matched controls (52 males and 70 females, the mean age 51.98; years, SD 15.72, range 19 - 79 years, participated in the study. Figure 2 shows their age and sex distribution. A close match between the groups can be seen. No statistically significant difference was noted in the mean age and sex ratio between the groups (p=0.82 and p=1.00, respectively).

Disease characteristics
Type 1 psoriasis was found in 78 patients (63.9%). The mean age of psoriasis onset was 33.34 years (SD 17.14, range 1 - 76). The mean duration of psoriasis was 17.9 years (SD14.21, range 1 – 65 years). Psoriatic arthritis was present in 16 patients (13.1%). The mean age of PsA onset was 39.2 years (range 27 - 59). The mean interval between the onset of psoriasis and onset of PsA was 6.67 years (SD 6.6). In 2 patients, arthritis developed before psoriasis was diagnosed. A positive family history of psoriasis was reported by 21 patients (17.21%), with a 92% incidence in first-degree relatives.

PASI scores ranged from 2.4 to 62,0 (mean 14.75, SD 12.78) and 56 patients (45.9%) had moderate to severe psoriasis (PASI>10). BSA ranged

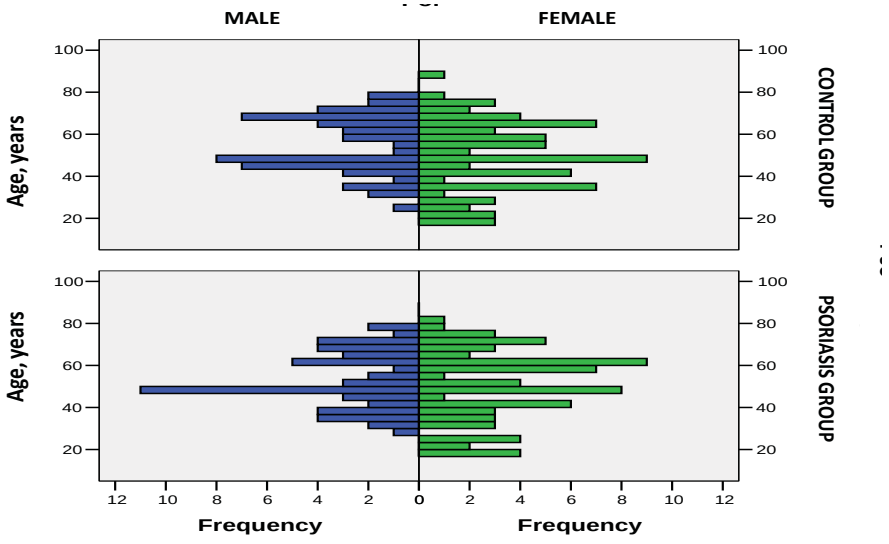


Figure 2. Age and sex distribution of patients with plaque psoriasis and controls

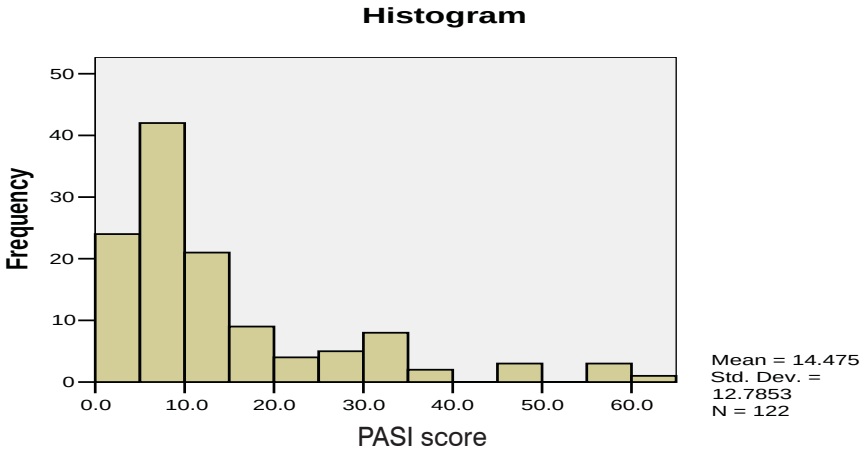


Figure 3. Distribution of patients with plaque psoriasis according to PASI scores

from 2% to 85% (mean 15.23, SD 13.09), while 55 (45.1%) patients had > 10% of body surface area involved. Figure 3 shows distribution of patients according to the PASI score.

The prevalence of cardiovascular and metabolic comorbid conditions

There were no significant differences in the prevalence of hypertension (29.5% vs. 23.7%, p=0.311), coronary heart disease (13.9% vs. 17.2%, p=0.480), diabetes (9.0% vs. 7.3%, p=0.641), myocardial infarction (3.2% vs. 2.4%, p=0.71), stroke (2.4% vs. 2.4%, p=1.00) and metabolic syndrome (24.6% vs. 22.9%, p=0.764), between cases and controls (Table 2), (Figure 4).

The prevalence of hypertriglyceridemia in patients with psoriasis and controls was 41.8% and 28.7%, respectively (OR 1.78, 95% CI 1.04-3.04, p=0.032) (Table 2), (Figure 4). Furthermore, a significant difference was found in mean triglyceride levels of patients and controls (170.19±67.84 mg/dL vs. 149.27±81.15 mg/dL, p=0.013).

Lifestyle factors

Smoking was significantly more prevalent in psoriasis patients compared to controls (58.1% vs. 44.2%, OR 1.813, 95% CI, 1.091-3.013, p=0.021) (Table 1).

Regular and heavy alcohol consumption was infrequent and of similar prevalence in psoriasis cases and controls: 20.5% vs. 17.2%, p=0.513 (Table 1).

Patients with psoriasis had a higher mean BMI (26.24, SD 4.42) compared to controls (24.73, SD 3.86), p=0.005 (Table 1), (Figure 5). Furthermore, psoriasis showed a statistically significant association with BMI obesity classification [$\chi^2(4)=11.560$, p=0.02].

Discussion

Psoriasis and cardiovascular risk

The relationship between psoriasis and increased risk of CVD remains controversial (25). In general, most of the previous studies suggest that people with psoriasis are at increased risk of CVD (8-10, 16, 20, 26-28). This was not confirmed in a large prospective cohort study conducted by Stern and Lange (29). Furthermore, two recent studies of general population (30, 31) demonstrated that the relationship between psoriasis and cardiovascular risk (CVR) is insignificant, and that traditional cardiovascular risk factors are significantly associated with cardiovascular risk in psoriasis (30, 31). Moreover, two population-based database studies that included pharmaceutical data did not confirm the association between psoriasis and treatment of CVD (32, 33). Mallbris et al. found a 50% greater risk of death from CVD among psoriatic inpatients, compared with the general population. In contrast, the overall risk of cardiovascular death was slightly decreased among outpatients with psoriasis (27).

A recent meta-analysis of cardiovascular risk confirms that psoriasis is related with an increased risk of cardiovascular mortality (28). However, it remains unclear whether cardiovascular risk in

Table 1. Baseline characteristics of the study group

Baseline characteristics	Psoriatics (n=122)	Controls (n=122)	OR (95% CI)	p
Mean age (SD), years	51.52 (15.56)	51.98 (15.72)	NA	0.82
Sex M/F	52/70	52/70	NA	1
Smoking habit				
Current +ex-smoker, n (%)	51+21=72 (58.1)	42+12=54(44.2)	1.81 (1.09-3.01)	0.021
Never smoker	50 (41.8)	68 (55.7)		
Alcohol consumption, n (%)				
Moderate	97 (79.5)	101 (82.7)		
Regular/heavy	25 (20.5)	21 (17.2)	1.24 (0.65-2.35)	0.513
BMI obesity classification n (%)				
Underweight	4 (3.3)	5 (4.1)		
Normal	49 (40.2)	74 (60.7)		
Overweight	44 (36.1)	29 (23.8)	NA	0.02
Obese	20 (16.4)	12 (9.8)		
Severe obesity	5 (4.1)	2 (1.6)		
BMI, mean (SD), kg	26.24 (4.42)	24.73 (3.86)	NA	0.005

SD - standard deviation; OR - odds ratio; NA - not applicable; BMI - body mass index

psoriasis is increased beyond that conferred by traditional cardiovascular risk factors. Samarasekera et al. evaluated 15 cohorts and meta-analyses of the magnitude of CVD risk for the primary outcomes of CVD mortality, stroke and myocardial infarction and identified increased CVD risk only in people with severe psoriasis (defined as requiring systemic therapy or hospital admission). They detected that majority of studies failed to adequately adjust for key traditional risk factors (25).

In this matched case-control study, we found no differences between subjects with and without psoriasis, in regard to cardiovascular disease and major cardiovascular risk (CVR) factors.

Our study showed no significant difference in the prevalence of coronary heart disease (CHD) (p=0.48), hypertension (p=0.31), myocardial infarction (p=0.71), stroke (p=1) and metabolic syndrome (p=0.76), between patients with psoriasis and controls.

Psoriasis and diabetes

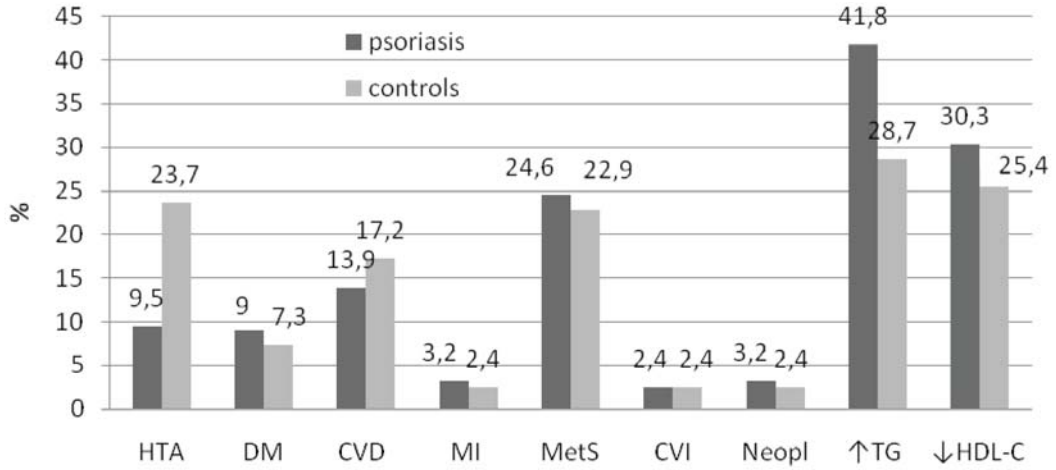
In recent years it has been recognized that patients with psoriasis carry an increased risk of type 2 diabetes. Two meta-analyses have examined diabetes in psoriatic patients. Armstrong et al. conducted a meta-analysis of 27 observational studies and found that psoriasis is associated with a relative risk of 1.27 (95% CI 1.16

Table 2. Prevalence of cardiometabolic comorbidity conditions in psoriatics and controls

	Psoriatics N=122	Controls N=122	OR	95% CI	*p*
Hypertension	36 (29.5)	29 (23.7)	1.342	0.759-2.374	p=0.311 χ^2 =1.029
Diabetes	11 (9.0)	9 (7.3)	1.244	0.496-3.119	p=0.641 χ^2 =0.218
Coronary heart disease	17 (13.9)	21 (17.2)	0.779	0.388-1.561	p=0.480 χ^2 =0.499
Myocardial infarction	4 (3.2)	3 (2.4)	1.345	0.295-6.138	p=0.71 χ^2 = 0.147
Metabolic syndrome, n (%)	30 (24.6)	28 (22.9)	1.09	0.61-1.97	0.764 χ^2 =0.090
Stroke	3 (2.4)	3 (2.4)	1.0	0.198-5.055	p=1 χ^2 = 0.0
Dyslipidemia, n (%)					
↑TG	51(41.8)	35 (28.7)	1.78	1.04-3.04	0.032
↓HDL-C	37 (30.3)	31 (25.4)	1.27	0.73-2.24	0.392

TG - Triglyceridemia > 1.7 mmol/L; HDL-C - high-density lipoprotein cholesterol < 1.0 mmol/L (Male) or < 1.3 mmol/L (Female)

- 1.40) for developing diabetes (34). Findings from a meta-analysis conducted by Cheng et al. suggested that individuals with psoriasis may have a slightly increased risk of diabetes (OR 1.42, 95% CI 1.40 - 1.45) (35). A cross-sectional study of Shapiro et al. performed using a database of a large health provider in Israel, showed that the incidence of diabetes was significantly higher in psoriasis patients in comparison with the control group (OR 1.27, 95% CI 1.1 - 1.48) (36). Interestingly, authors found an association between diabetes and multiple use of very potent topical steroids (P < 0.05) or systemic medications for psoriasis (methotrexate, cyclosporine or acitretin) (P < 0.001) (36). Brauchli et al. conducted a follow-up study with a nested case-control analysis within the UK-based General Practice Research Database. They found that the risk of incident DM increased with psoriasis duration and severity (37). It is well known that chronic systemic inflammation of psoriasis induces endothelial dysfunction, altered glucose metabolism, and insulin resistance which all together play a significant role in the development of obesity, diabetes mellitus, dyslipidemia, and cardiovascular disease (38). It is also possible that patients with psoriasis use topical corticosteroids for long periods of time, which are systemically absorbed and contribute to the development of diabetes (37, 39). However, several studies, failed to establish such a relationship



HTA - hypertension; DM - diabetes mellitus; CVD - cardiovascular diseases; MI - myocardial infarction; MetS - metabolic syndrome, CVI - cerebrovascular insult; TG - Triglyceridemia > 1.7 mmol/L; HDL-C - high-density lipoprotein cholesterol < 1.0 mmol/L (Male) or < 1.3 mmol/L (Female)

Figure 4. Prevalence of comorbid conditions in patients with plaque psoriasis and controls

(40). In this case-control study, we found no differences between subjects with and without psoriasis in regard to diabetes (9.0% vs. 7.3%, p=0.641).

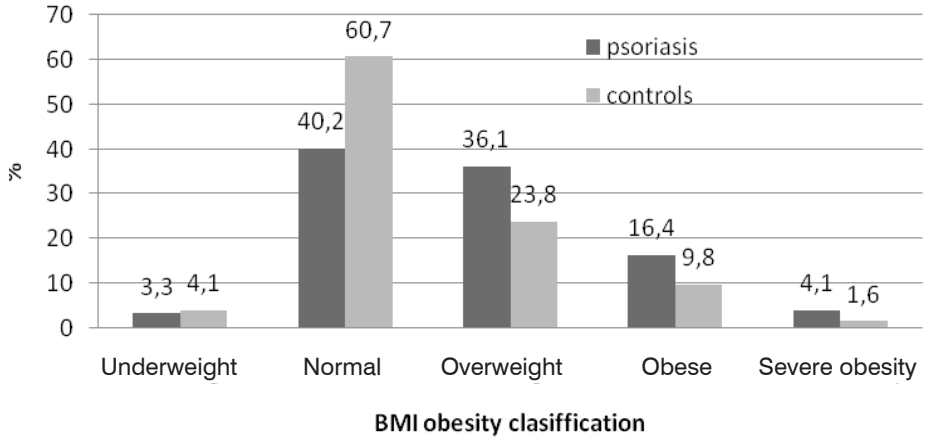
There are several possible explanations for the diversity of findings. Some studies are associated with high risk of selection and detection bias, due to the use of hospital records/administrative databases, and hospital/registry controls. Differences in various exposure factors, such as geographic-regional and ethnic, in genetic susceptibility and nutritional habits among different populations may affect the prevalence of cardiovascular diseases and diabetes. Thus, the prevalence of diabetes in the Macedonian population is considered to be about 7.7%, which is similar to our findings (41).

Finally, selection of untreated patients with psoriasis eliminates the influence of systemic antipsoriatic drugs on cardiovascular risks. To our knowledge, this is the first case-control study on comorbidities in untreated patients with psoriasis. Only few studies considered drugs as a factor contributing to the development of CVD (42). Gissondi et al. (42) and Nisa and al. (43) did not include patients receiving any systemic antipsoriatic treatment for at least one month before enrolment. Several other studies analyzed patients with new diagnosis of psoriasis (27, 44). On the contrary, some studies used systemic treatment as a measure of disease severity (45, 46). Traditional systemic therapies for psoriasis may aggravate cardiovascular risk factors (19, 20). Thus, high prevalence of CVD may be in part due to systemic antipsoriatic therapy. It is rather difficult to assess the independent contribution of systemic antipsoriatic drugs on the development of CVR in patients with psoriasis, since a certain number of concurrent factors, such as lifestyle factors, as well as other systemic drugs such as NSAIL, antidepressants and diuretics, needs to be taken into consideration, as these drugs are widely prescribed for patients with psoriasis (47).

Psoriasis and traditional cardiovascular risk factors

Our study confirms that psoriasis patients have three lifestyle/classic risk factors for CVD more frequently compared to controls: smoking, obesity and hypertriglyceridemia. The prevalence of smoking was higher in patients with psoriasis (41.8%) than in the control group (34.4%), and higher than in general population in Macedonia (35%) (48). Psoriasis showed a statistically significant association with BMI and obesity classification. This finding is in agreement with most of the previously published studies.

The major weakness of our study is its sample size, while its strength is its matched case-control design which controlled fundamental confounders of age and gender. Besides, both case and control subjects were selected from the same source population. All data



BMI - body mass index

Figure 5. BMI obesity classification among patients with plaque psoriasis and control group

were collected through interviews and measurements of disease activity were performed by an experienced dermatologist.

Conclusion

In conclusion, our data suggest that systemic antipsoriatic drugs may exert an important influence on the prevalence of cardiometabolic comobidity in patients with psoriasis. Furthermore, our study confirms that untreated psoriatic patients have three major increased lifestyle cardiovascular risk factors: smoking, obesity and hypertrigliceridemia. Further research will explore the effects of systemic antipsoriatic drugs on these comorbid conditions in psoriasis.

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Abbreviations

IMID - immune-mediated inflammatory disease
CVD - cardiovascular disease
TNF-α - tumor necrosis factor-alpha
UV - ultraviolet rays
GP - general practitioner
BMI - body mass index
BP - blood pressure
PASI - Psoriasis Area and Severity Index
BSA - body surface area
NCEP - National Cholesterol Education Program
ATP III - Adult Treatment Panel III
HDL - high density lipoprotein
SD - standard deviations
OR - odds ratios
CI - confidence intervals
PsA - psoriatic arthritis
CVR - cardiovascular risk
CHD - coronary heart disease
NA - not applicable
TG - triglyceridemia
MI - myocardial infarction
MetS - metabolic syndrome
CVI - cerebrovascular insult

Kardiovaskularni ili metabolički komorbiditet kod osoba sa plak-tipom psorijaze koje nikada nisu dobijale sistemsku terapiju za psorijazu: analitička studija slučaja

Sažetak

Uvod: Komorbiditeti su bolesti koje koegzistiraju sa bolešću koja je cilj ispitivanja; u ovom radu to je psorijaza. Sve su brojniji radovi u svetskoj literaturi koji doprinose stavu da je psorijaza značajno povezana sa nizom komorbiditeta kao što su psorijatični arthritis, debljina, hipertenzija, dijabetes, hiperlipidemija, metabolički sindrom, kardiovaskularne bolesti (KVB), Kronova bolest, limfomi, neoplazije i multipla skleroza, kao i anksioznost, alkoholizam, pušenje i neravnoteža u ishrani. Nije poznat tačan mehanizam odgovoran za ovu udruženost ali se ne može zanemariti direktni uticaj hronične inflamacije i povećani nivo TNF-α. Niz drugih faktora utiču na tu asocijaciju) (Shema 1). Malo je radova koji se odnose na uticaj lekova za sistemsko lečenje psorijaze na komorbiditete, ali je dobro poznato da metotreksat povećava vrednosti homocisteina u serumu, a ciklosporin i acitretin uzrokuju povišeni krvni pritisak i hiperlipidemiju.

Cilj: Ovo istraživanje je obavljeno sa ciljem procene prevalencije kardioloških i metaboličkih komorbidnih stanja kod bolesnika sa hroničnom plak-psorijazom koji nikada nisu lečeni antipsorijaticima za sistemsku primenu. Istraživanje je sprovedeno kao studija slučajeva – kontrola, a uparivanje kontrolne grupe po polu i uzrastu omogućilo je eliminaciju uticaja ovih kovarijabli na rezultate istraživanja.

Rezultati: Demografske i osnovne karakteristike ispitivane populacije su prikazane u tabeli 1. i shemi 2. Stepen težine psorijaze grafički je prikazan shemom 3. Prevalencije ispitivanih komorbiditeta date su u tabeli 2 i shemama 4 i 5. Nije utvrđena signifikantna razlika u odnosu na prevalenciju hipertenzije (29,5% vs. 23,7%, p = 0,311), koronarne bolesti srca (13,9% vs. 17,2%, p = 0,480), dijabeta (9% vs. 7,3%, p = 0,641), infarkta miokarda (3,2% vs. 2,4%, p = 0,71), cerebrovaskularnog inzulta (2,4% vs. 2,4%, p = 1) i metaboličkog sindroma (24,6% vs. 22,9%, p = 0,764), između ispitanika sa psorijazom i kontrolnih ispitanika. Prevalencija hipertrigliceridemije kod bolesnika sa psorijazom iznosila je 41,8%, za razliku od kontrolnih ispitanika kod kojih je iznosila 28,7% (p = 0,032). Značajna razlika utvrđena je i u odnosu na srednje vrednosti triglicerida (170,19 ± 67,84 mg/dl vs. 149,27 ± 81,15 mg/dl, p = 0,013). Pušenje je bilo češće kod bolesnika sa psorijazom (58,1% vs. 44,2%, p = 0,021). Osim toga, pacienti sa psorijazom imali su veći prosečni indeks telesne mase, BMI (eng. *body mass index*) (26,24 vs. 24,73, p = 0,005) (Tabela 1).

Zaključak**:** Istraživanje je pokazalo da pacijenti sa plak psorijazom koji nikada nisu lečeni od psorijaze sistemskim lekovima nemaju statistički značajno češću pojavu kardiovaskularnih i metaboličkih komorbidnih stanja u odnosu na kontrolnu grupu. Sistemski antipsorijatični lekovi mogu uticati na pojavu ovih komorbiditeta. Ipak, ova studija je pokazala da bolesnici sa psorijazom imaju povišena tri važna faktora rizika za nastanak kardiovasklarnih bolesti – pušenje, debljinu i hipertrigliceridemiju.

Ključne reči

Psorijaza; Komorbiditet; Kardiovaskularne bolesti; Dijabetes melitus tip 2; Metabolički sindrom X; Pušenje; Faktori Rizika

An Outbreak of Early Syphilis in Patients Registered at the City Institute for Skin and Venereal Diseases in Belgrade from 2010 to 2012: a Case Series of 86 Patients

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Abstract

The purpose of this study was to analyze the characteristics of an outbreak of early syphilis registered at the City Institute for Skin and Venereal Diseases in Belgrade, during the period from 2010 to 2012. The study was designed as a case-note review. In a three-year-long period, a total of 86 patients with early syphilis were registered: 33 cases of primary, 31 of secondary and 22 cases of early latent syphilis. Sixty-five (76.5%) of all patients were men who have sex with men, 15 were heterosexual men and 6 were women. The majority of patients were infected in Belgrade, and in 51/86 cases oral sex was the only risk factor. There were 13 HIV-positive patients, all men who have sex with men. Thus, 20% of men who had sex with men in this study were co-infected with HIV.

In conclusion, this outbreak of early syphilis in Belgrade, in which more than two thirds of all patients were men who have sex with men, of whom 20% were HIV-infected, shows the need for: 1) enhanced prevention efforts targeting this group more important than ever, with education and condom use for oral sex as an important part of patient counseling; 2) coordinated and expeditious surveillance, partner services, screening among population at-risk, as well as early diagnosis and treatment.

Key words

Syphilis; Sexual Behaviour; Homosexuality, Male; HIV; Sexual Partners; Disease Transmission, Infectious

In North America and developed countries of northern Europe, by the 1970s, syphilis had become predominantly a disease of men who have sex with men (MSM) (1). However, during the late 1980s, there were renewed outbreaks of heterosexual and congenital syphilis in North America. The outbreaks were mainly observed in commercial sex workers, in whom it was often associated with selling sex for drugs (especially cocaine), and in other persons of lower socioeconomic status.

The incidence of primary and secondary syphilis among MSM is increasing again in many countries. Although the incidence of infectious syphilis in the UK was only 0.3 cases per 100.000 people in 1998, since then, there have been outbreaks in several cities with a previous low prevalence leading to more than 10-fold increase in national incidence rates by 2005. The outbreaks were associated with high rates of partner change, travel or migration links and an increasing predominance of homosexual transmission with a high proportion of human immunodeficiency virus (HIV) co-infection among incident cases. Furthermore, there was a similar trend in increasing number of men who have sex with men who acquired syphilis engaging in unsafe sex in Western Europe [1].

Generally, syphilis is classified as acquired or congenital. Acquired syphilis is divided into early and late syphilis. Early syphilis is defined as any of the first three stages of syphilis: primary, secondary and early latent syphilis. Guidelines of Centers for Disease

Control and Prevention (CDC) and European Guidelines, define early latent syphilis as that acquired within the previous year. According to Guidelines of the World Health Organization (WHO) it is defined as syphilis acquired less than 2 years before referral [2, 3]. Early syphilis is considered infectious, with an estimated risk of transmission of around 60% per partner [4]. Direct contact with lesions of primary and secondary syphilis possess: the greatest risk of transmission. Early latent syphilis is considered infectious because of the 25% chance of relapse to secondary stage [5].

The purpose of this study was to analyze an outbreak of early syphilis registered at the City Institute for Skin and Venereal Diseases in Belgrade (CISVD), from 2010 to 2012, where more than two thirds of all affected patients were men who have sex with men, 20% of whom were HIV-infected. To the best of our knowledge, it was the first reported outbreak of early syphilis among MSM that has occurred in the capital of Serbia.

Methods

A case-note review of patients with primary, secondary or early latent syphilis was undertaken in the City Institute for Skin and Venereal Diseases (CISVD) in Belgrade. The diagnosis of primary and secondary syphilis were made by clinical features and/or positive dark ground microscopy of scrapings and positive serology tests (Venereal Disease Research Laboratory and *Treponema Pallidum* Haemagglutination Assay). The diagnosis of early latent syphilis was made if any of the following criteria were present in the preceding year: a documented seroconversion; 4-fold rise in non-treponemal (reaginic) serum antibody titre in properly treated patients; a history of unequivocal symptoms of primary or secondary syphilis; a sex partner documented to have primary, secondary or early latent syphilis.

Results

From 2010 to 2012, a total of 86 cases of early syphilis were identified at the CISVD (Figure 1) (Table 1). There were 80 male patients, among whom 65 were men who have sex with men (MSM), and 6 female patients among whom 3 were sex workers. The patients' average age was 31 years (range 17 - 58). There were 33 (38.4%) patients with primary syphilis (PS): 31 male patients including 1 with overlapping clinical stage [6], as well as 2 female patients, both with vulvar primary lesions. Twenty eight patients had penile lesions associated with non-tender regional

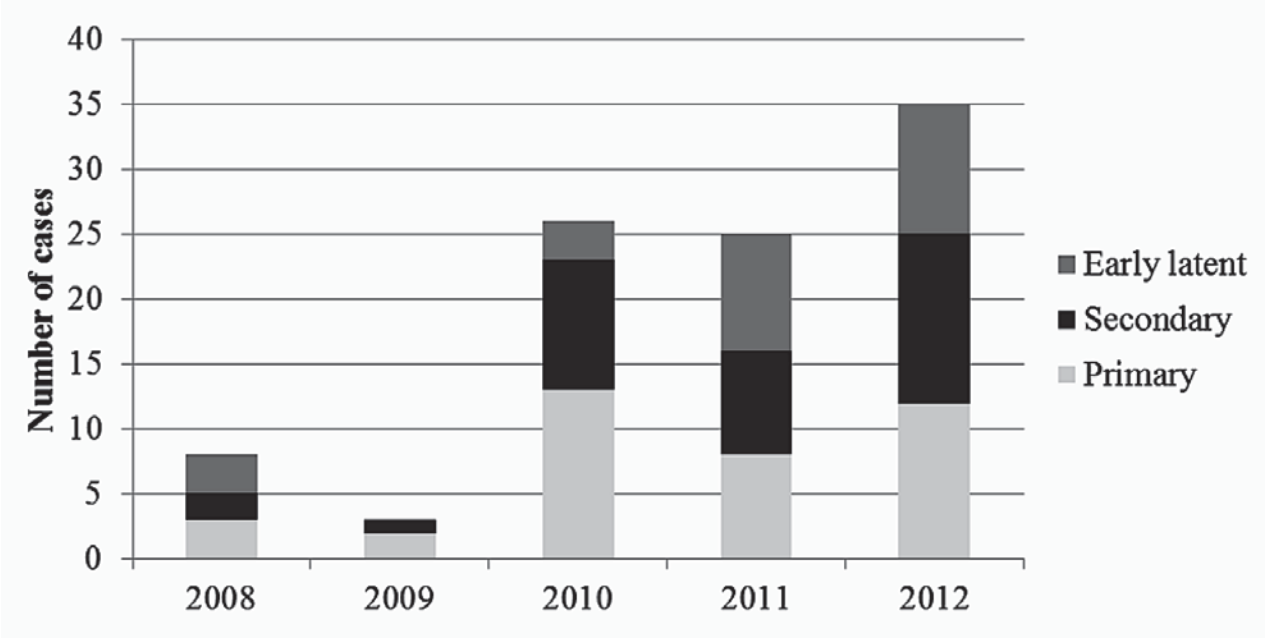

Figure 1. Annual distribution of early syphilis diagnosed at the City Institute for Skin and Venereal Disease, in Belgrade from 2008 to 2012

Table 1. Annual distribution of patients with early syphilis diagnosed at the City Institute for Skin and Venereal Diseases, in Belgrade from 2008 to 2012 classified by the stage of the disease

Year	Patients with primary syphilis (n)	Patients with secondary syphilis (n)	Patients with early latent syphilis (n)	Patients with early syphilis (n)
2008	3	2	3	8
2009	2	1	0	3
2010	13	10	3	26
2011	8	8	9	25
2012	12	13	10	35

n - number of patients

lymphadenopathy while only seven presented with a typical chancre. Anal chancres were found in three cases. Furthermore, atypical presentations of PS were seen in 4/5 of patients as: multiple chancres, painful ulcers resembling genital herpes, nodular lesion and lichen planus-like lesions. All PS cases with penile lesions reported unprotected insertive oral sex with unknown partners one-month before referral to our Institute.

Thirty one patients (36.05%) presented with secondary syphilis (SS). All patients with SS were men who have sex with men: 27 (87.10%) presented with rash, 3 (9.68%) with alopecia syphilitica [7, 8], and 1 (3.22%) with a mucous patch on the tongue as an isolated manifestation of the secondary stage of syphilis [9]. The risk factor for SS was unprotected oral sex alone in 21 cases, and unprotected oral and anal sex in 10 cases.

Primary or secondary syphilis was diagnosed in 64 (74.42%) patients, and among them, there were 3 patients with reinfection. All of them were men who have sex with men in whom reinfection occurred within the past 3 years.

There were twenty two (25.58%) patients with early latent syphilis at the referral: 18 men and 4 women.

Among all 86 patients with early syphilis in this outbreak, there were: 13 HIV-positive, 55 HIV-negative and 16 patients declined testing. All 13 HIV-positive patients were men who have sex with men and 11 (84.61%) were on antiretroviral therapy.

The majority of patients reported to have acquired syphilis in Belgrade. Actually, only 8 patients were infected abroad. Out of all 86 patients, 21 (24.42%) were referred to our Institute due to information provide by their sexual partners.

Almost all patients were treated with a single intramuscular dose of 2.4 million units of benzathine penicillin G, except seven penicillin-allergic patients, who were treated with 14-day course of oral doxycycline (100 mg twice a day).

Discussion

The overall incidence of syphilis in Serbia showed some variations during the last three decades with a peak incidence in 1995 and 2001 [10]. The first increase may be attributed to changes in the country caused by the war, the breakup of former Yugoslavia, economic sanctions and the resulting socioeconomic difficulties as well as the importation of syphilis from the countries of the former Soviet Union [11]. The second peak was in 2001, due to an outbreak of early syphilis in the Institution for Care for Adults with Mental Disorders [12]. Furthermore, since 2010, the incidence showed an increasing trend (Figure 2).

At the beginning of a new millennium, the incidence of syphilis has been increasing worldwide, primarily among MSM. Outbreaks of syphilis in this population have been reported in several European cities [13, 14, 15, 16]. Since 1998, the resurgence of syphilis led to a 25-fold increase in cases of early syphilis among MSM in the United Kingdom [17].

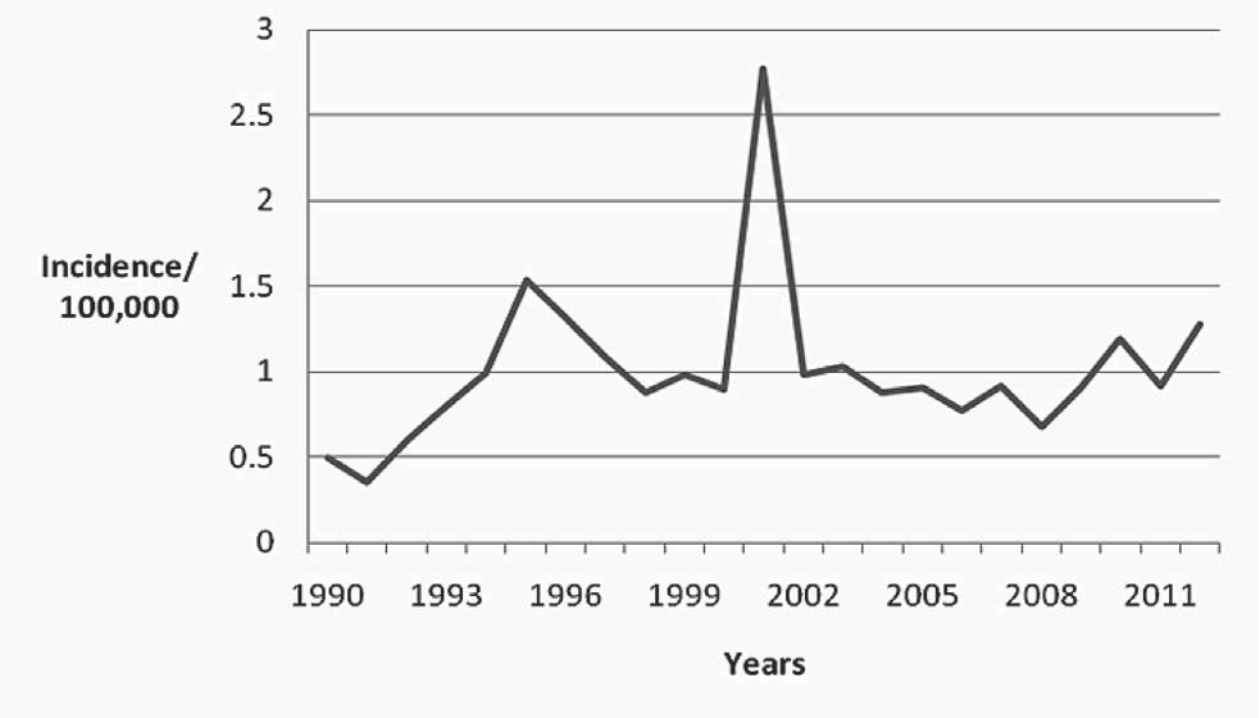

Figure 2. The incidence of syphilis in Serbia from 1990 to 2012

The outbreaks were characterized by rapid increase in homosexual transmission networks, high proportion of HIV coinfection, male to female case ratio of 8:1 and highest rates occurring in men aged 35–44 years and women aged 20–24. Moreover, there was a similar trend in the increasing numbers of men who have sex with men engaging in unsafe sex who acquired syphilis and other bacterial sexually transmitted infections in Western Europe [1]. Thus, during the outbreak of early syphilis in Denmark, 78% of registered cases were MSM, and 37% of them were known to be HIV-positive [18]. According to our results, more than two thirds of all patients (76.5%) with early syphilis in this study were men who have sex with men, and 20% of them were known to be HIV-positive. This is the first reported outbreak of early syphilis among MSM in the capital of Serbia.

Recently described outbreaks of syphilis among MSM revealed that unsafe sex was frequent in this population, with a growing number of casual and anonymous sexual partners and lack of consistent use of condoms. Moreover, increase in syphilis cases may be due to an increased number of psychoactive substance users or because of decreased concern about HIV infection in the era of antiretroviral therapy [19]. The rate of HIV infection is high in patients with syphilis. According to the report of Blocker et al. conducted in 2000, the median HIV-seroprevalence in men and women infected with syphilis in the United States was 15.7 % and seroprevalence among MSM and injecting drug users ranged from 64.3% to 90% and 22.5% to 70.6%, respectively [20]. These data indicate that HIV-infected patients with syphilis may be among the most important transmitters of HIV infection based on their continuous risky behavior as well as well-known biologic effects of genital ulcerations.

The majority of our patients (59.3%) acquired syphilis infection through unprotected oral sex. MSM have low awareness of transmission of other sexually transmitted infections due to diverse types of sexual behavior other than anal intercourse. Oral sex is usually mistaken for "safe" sexual behavior. Moreover, it seems obvious that male patients in this study who had sex with men did not identify oral insertive intercourse as the route for acquiring syphilis, despite the well-known highly contagious oral lesions. These data correlate with other reported outbreaks of syphilis

such as the ones reported in Brighton and Manchester, United Kingdom, where one third of MSM included in the study acquired syphilis through oral sex [21].

Lesions of PS develop after an incubation period of 10 to 90 days (usually 3 weeks). Primary lesions usually last 3 weeks and resolve without treatment. The onset of SS occurs from 2 weeks to 6 months after the resolution of the primary stage (usually 4 weeks). Secondary syphilis lasts 4 weeks, and like primary resolves spontaneously without treatment.

In this study the majority of patients with PS presented with multiple genital ulcers clinically resembling herpes simplex virus infection (22). Similarly, only 31% of males presented with classical manifestations of primary syphilitic chancre in the study of DiCarlo & Martin [23]. These may cause a serious differential diagnostic confusion with other genital ulcers, especially among inexperienced physicians and/or in countries with low incidence of syphilis. The lack of sensitivity of treponemal serologic tests in PS, accentuates the importance of dark ground microscopy, which, if applicable, represents a highly sensitive diagnostic tool in hands of a trained physician, thereby facilitating early diagnosis and intervention [24].

Acquisition of syphilis in this report mainly occurred in Belgrade, the largest city in Serbia, with approximately 2 million citizens. MSM choose to live in large cities which provide more anonymity, less stigma and more meeting places (i.e. sex venues such as parks, bars, public toilets) for sexual contacts [15]. All of the mentioned facilitates spread of sexually transmitted infections.

Contact tracing of sexual partners and treatment of sexual partners affected by sexually transmitted infections, has historically been regarded as an important control measure for syphilis [25]. However, contact tracing is effective only if infected persons are able and willing to cooperate and give information regarding sexual partners. In this report, twenty one persons were identified by their sexual partners. In this outbreak, identification of potentially infected persons by their sexual partners was of a limited contribution to epidemiological data, because majority of partners were casual, anonymous or untraceable. Moreover, patients with diagnosed syphilis were reluctant to identify their partners, despite knowing the importance of their information.

In order to identify other persons at risk of getting syphilis, infected patients were asked to reveal the number of sexual partners they had during the period when they were infectious and to give further information about their partners. The infectious period was estimated on the stage of syphilis: 3 months before the diagnosis for PS, 6 months before the diagnosis for SS, and 1 year before the diagnosis for early latent syphilis.

Conclusion

In summary, the outbreak of early syphilis in Belgrade was mainly transmitted among men who have sex with men. The increasing coinfection with HIV in this population underlines the need for enhanced screening and preventive programs. Risk reduction messages are more important than ever for targeting this group, and condom use for oral sex should be an important part of patient counseling. This outbreak of syphilis also pointed to the need for coordinated and expeditious surveillance, partner services, screening of population at-risk, as well as early diagnosis and treatment.

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Abbreviations

MSM - men who have sex with men
HIV - human immunodeficiency virus
CDC - Centers for Disease Control and Prevention
WHO - World Health Organization
CISVD - City Institute for Skin and Venereal Diseases in Belgrade
PS - primary syphilis
SS - seondary syphilis

Povećan broj pacijenata s ranim sifilisom koji su registrovani u Gradskom zavodu za kožne i polne bolesti u Beogradu u periodu 2010–2012. godine – prikaz serije od 86 slučajeva

Sažetak

Cilj: U ovom radu, osnovni cilj bio je da se analizira povećan broj slučajeva ranog sifilisa koji je registrovan u Gradskom zavodu za kožne i venerične bolesti u Beogradu u periodu 2010–2012. godine.

Materijal i metode: U seriji slučajeva prikazani su podaci prikupljeni od pacijentima sa sifilisom čija je dijagnoza postavljena u Gradskom zavodu za kožne i venerične bolesti u periodu 2010–2012. godine. Sifilis je dijagnostikovan na osnovu kliničke slike i/ili nativnog pregleda u tamnom polju i reaktivnih seroloških testova.

Rezultati: U navedenom trogodišnjem periodu dijagnostikovano je 86 pacijenata sa ranim sifilisom. Trideset tri (38,4%) osobe imale su primarni sifilis, 31 (36%) sekundarni, a kod 22 (25,6%) osobe dijagnostikovan je rani latentni sifilis. Šezdeset pet osoba (76,5%) pripadalo je populaciji muškaraca koji imaju seksualne odnose sa muškarcima a ostalih 15 muškaraca bilo je heteroseksualne orijentacije. Šest

obolelih osoba bilo je ženskog pola. Kod 13 muškaraca koji su imali seksualne odnose sa muškarcima postojala je udružena infekcija HIV-om. Većina obolelih inficirala se u Beogradu, a 51 osoba (59,3%) infekciju je dobila isključivo nezaštićenim oralnim seksom.
Zaključak: Povećan broj registrovanih slučajeva ranog sifilisa u Beogradu, u kojem su više od dve trećine obolelih bili muškarci koji imaju seksualne odnose sa muškarcima od kojih je najmanje 20% bilo inficirano HIV-om, ukazao je na neophodnost promocije bezbednog seksualnog ponašanja, a posebno upotrebe kondoma tokom oralnih seksualnih odnosa. Rana dijagnostika i lečenje sifilisa čine nadasve neophodne preventivne mere u ovoj vulnerabilnoj populaciji.

Ključne reči

Sifilis; Seksualno ponašanje; Homoseksualnost kod muškaraca; Seksualni partneri; Prenošenje infektivnih bolesti

NAUČNICI SU PREŠLI NOVI PRAG U BRIJANJU

Već skoro čitav vek naučnici pokušavaju da unaprede iskustvo brijanja popravljanjem formulacije gelova, balzama i krema za brijanje, ali i povećanjem efikasnosti i komfora samog brijača. Danas na tržištu postoji veliki broj različitih vrsta brijača. Šta bi potrošač trebalo da izabere, odnosno, da li zaista postoje razlike između jedne, tri i pet oštrica? Naučnici kažu da postoji.

Jedan pronalazač je još 1929. godine, težeći ka savršenom brijanju, uočio prednosti brijača sa 5 oštrica i patentirao ga. Međutim, pronalazak nije dospeo do javnosti jer je brijač sa pet oštrica iritirao kožu i izazivao posekotine. U toku narednih nekoliko decenija brijač sa jednom oštricom je predstavljao zlatni standard, sve do 1971. godine kada su Gillette-ovi naučnici uspešno kreirali brijač sa 2 oštrice koji je demonstrirao preciznije i komfornije brijanje nego dotadašnji brijači. 1998. godine je predstavljen i brijač sa 3 oštrice, napravljen na osnovu poboljšanja brijača sa 2 oštrice.

Istraživanje je pokazalo korist od brijača sa više oštrica. Prva oštrica podiže dlaku i izvlači je iz folikula tako da sledeća oštrica, ukoliko je pravilno pozicionirana, seče dlaku nisko u stablu, pre nego što se ona potpuno vrati u ušće folikula. Brijač sa više oštrica ponavlja ovaj proces i daje značajno preciznije brijanje, ali takođe stvara i nove izazove. Studije su pokazale da, kada se koriste brijači sa više oštrica, koža između oštrica se podiže i stvara mala ispupčenja. Ona mogu izazvati trenje i nelagodnost i napraviti iritaciju kože.

Naučnici su otkrili da, smanjujući međusobno rastojanje između oštrica, ispupčenje kože biva značajno niže, te da na taj način pritisak na kožu biva više uniforman, omogućavajući manju frikciju i sigurnije i komfornije brijanje. Gillette naučnici su takođe došli do značajnog napretka u kvalitetu nerđajućeg čelika za oštrice. Ove oštrice, koje su oštrije od hirurškog skalpela, ojačane su posebnim omotačem, koji dramatično poboljšava funkciju oštrice sa manje povlačenja kože i više komfora. Ali, pred naučnicima je još jedna prepreka. Premda blizu postavljene oštrice obezbeđuju bolje brijanje, one takođe izazivaju i zapušenje brijača. Ovaj problem je rešen smanjenjem dimenzije nosača oštrica. Stavljanjem tanjeg materijala ispod oštrica stvoreno je više prostora da se gel i dlake isperu.

Koristi od brijača sa više oštrica su otkrivene krajem šezdesetih godina dvadesetog veka. Korišćenjem ovog brijača dlaka prolazi kroz fizički proces nazvan "hysteresis" kod koga prva oštrica u brijaču izvlači dlaku iz folikula omogućavajući narednoj oštrici da niže seče stablo dlake, pre nego što se dlaka potpuno vrati u folikul. Ovo obezbeđuje preciznije brijanje koje duže traje. Što se više oštrica doda brijaču, verovatnoća ovog procesa se povećava. Međutim, razmak između oštrica je jednako važan kao i njihov broj. Pritisak brijača na kožu izaziva njeno ispupčenje između oštrica. Stavljajući više oštrica u brijač i smanjujući njihov međusobni razmak stvara se relativno podjednak pritisak na kožu, te su ispupčenja kože značajno manja, dovodeći do sigurnijeg i komfornijeg brijanja.

Širom sveta milioni ljudi, različitih etničkih i kulturnih zaleđa, se redovno briju. Ovi muškarci imaju kožu različite osetljivosti, različit tip dlake, različitu veličinu šake i posebne tehnike brijanja. Dok su sve ove osobine različite, cilj je isti; većina muškaraca želi preciznije i komfornije brijanje. Kao pripremu za ispit zrelosti, muškarce brijanju obično uče prethodne generacije stvarajući im uverenje da postoji samo jedan način brijanja - onako kako su naučeni.

Način brijanja dolazi od različitih izvora i uključuje različite proizvode. Prenoseći se kroz generacije, diskutujući o njima u školskim svlačionicama, spavaonicama i teretanama širom zemlje, načini brijanja su različiti koliko i muškarci koji ih upražnjavaju.

Premda većina muškaraca nema posebnih medicinskih problema povezanih sa brijanjem, postoji veliki broj izveštaja o pojavi osetljivosti kože tokom ili nakon brijanja. Da bi izbegli iritaciju neki muškarci su spremni na ekstreme dok su se, sa druge strane, brojni muškarci pomirili sa načinom brijanja koji je potencijalno štetan za kožu samo zato što im je blizak.

Muškarci i žene imaju veoma različite potrebe u pogledu nege kože i brijanja, tako da je svaki brijač dizajniran imajući u vidu određene potrebe. Stoga se uvek preporučuje da muškarci koriste proizvode koji su dizajnirani za njih.

Razmislite o ovome: većina muškaraca brije samo jedan deo kože - lice, relativno malu površinu. Nasuprot tome, površina koju žena mora da tretira je daleko veća (oko 18 puta veća), a većina regiona kao što su članci, zadnja strana potkolenica, kolena i natkolenice je teško dostupna.

Koža na nogama kod žena je relativno suva u poređenju sa licem muškarca jer ima značajno manje lojnih žlezda. Suva koža sa skvamom stvara neravnu površinu za brijač, te je efikasna lubrikacija vrlo značajna. Nadalje, dlaka na licu kod muškarca je većeg prečnika i nepravilnijeg oblika od dlake žena, koje su uniformnije i primarno ovalnog oblika. Međutim, iako je dlaka kod žena tanja nego kod muškaraca, ona je, kada je suva, i dalje jaka kao bakarna žica iste debljine.

Naučnik Gillette-a proučava kožu lica i dlaku brade koristeći video mikroskop velikog uveličanja

Muška koža u detaljima

Posebni problemi kože

- Koža kod muškarca je deblja i masnija od kože žena.
- Muškarci žele proizvode koji se brzo apsorbuju i ne ostavljaju lepljive tragove.

KOŽA: veća proizvodnja sebuma (masnija koža)

DLAKA:

- 50-60% većeg prečnika
- ~8x više dlaka/cm2
- Brža stopa rasta
- Iregularnijeg oblika
- Rast u svim pravcima

Posebna oštećenja

- Brijanje i pranje jakim surfaktantima može dovesti do oštećenja barijerne funkcije kože putem uklanjanja ćelija kože i prirodnih lipida kornealnog sloja. Ovo može dovesti do suvoće kože i okinuti negativnu kaskadu inflamacije i iritacije.

Posebni neprijatni simptomi

- Mnogi muškarci osećaju zatezanje kože, iritaciju i osećaj pecka-nja nakon brijanja

Ekstenzivna istraživanja fiziologije rasta dlake kod muškaraca i žena u kombinaciji sa razlikama između njihovih navika i stavova koji se tiču brijanja čine nauku koja stoji iza Gillette-a.

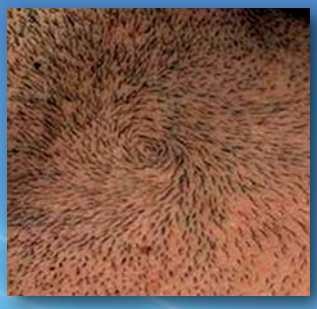
Zdravlje kože je izuzetno važno, a mnogi muškarci se bore sa čestim stanjem kože koje se karakteriše lezijama nakon brijanja i naziva se pseudofolliculitis barbae (PFB). Javlja se kada urasla dlaka na licu i vratu izazove inflamatorni odgovor oko stranog tela. Podaci iz skorijih kliničkih studija odbacuju mit da svakodnevno brijanje brijačem sa više oštrica (koji obezbeđuje preciznije brijanje) pogoršava PFB. Rezultati zapravo pokazuju da je moguće postići malo, ali značajno smanjenje broja lezija PFB nakon svakodnevne upotrebe brijača sa 5 oštrica u toku 8 nedelja, u poređenju sa običnim brijačima i uobičajenom učestalošću od 2-3 brijanja nedeljno tokom 8 nedelja. Nadalje, klinički rezultati dozvoljavaju zaključak da svakodnevno brijanje neposredno blizu površine kože nema uticaj na PFB. Istraživanje Gillette®-a je takođe otkrilo da postoje strategije koje mogu pomoći mu-škarcima u borbi sa PFB, kao što je regularna nega emolijentnim kremovima i korišćenje adekvatnih tehnika brijanja.

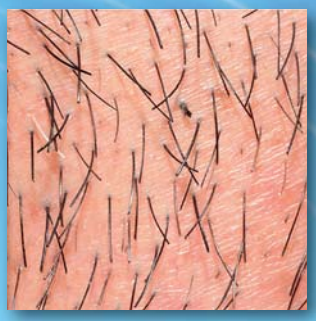
Studije pokazuju da je potrebno održati pažljivu ravnotežu između brijanja tvrde dlake koja usađena u meku kožu i ostavl-janja kože bez oštećenja. Gillette® je razvio proizvode koji popra-vljaju kvalitet i komfor brijanja vodeći računa o koži pre, u toku i nakon brijanja.

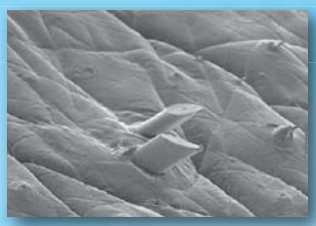
Nadalje, Gillette® je nedavno sproveo nekoliko kliničkih studija koje su pokazale koristi naprednog režima brijanja u 3 koraka. Rezulati konzistentno pokazuju da ovaj režim u 3 koraka dovodi do optimalne hidratacije kože dovodeći do, kako ispitanici sami prijavljuju, glatkog i komfornog brijanja. Ovo je pokazano čak i kod muškaraca koji imaju osetljivu kožu u kliničkoj studiji u kojoj su učestvovali i dermatolozi.

Kombinujući sedam novih tehnoloških napredaka u izvođenju i komforu brijanja, Gillette® je razvio Fusion® ProGlide™ i Fusion® ProGlide™ Power. Novi napreci se odnose na izazove koje pacijenti imaju u vezi sa negom kože, kao što su iritacija i nelagodnost izazvani povlačenjem kože. Ovi napreci popravljaju komfor, poverenje i spremnost pacijenata da se povinuju preporukama dermatologa. Fusion ProGlide je dizajniran da pruži precizno, komforno brijanje bez obzira na karakteristike kože i dlake muškarca, veličinu i konturu lica, tehniku brijanja ili životni stil.

Da bi postigao krajnji cilj preciznog i komfornog brijanja sa minimalnom iritacijom, brijač mora biti sposoban da optimalno klizi i istovremeno vodi računa o koži, bez obzira na različite tipove kože i navike brijanja. Sa ovim ciljem, Gillette je sproveo rigorozne protokole testiranja koji su uključili više od 30000 muškaraca, da bi razvio brijač sa naprednom tehnologijom za komforno brijanje.







Skening elektronska mikroskopija stabla dlake na bradi na nepraviloj površini muškog lica.

7 prednosti

- Oštrice koje seku dlaku niže
- Stabilizator oštrice
- Zaštitna krilca sa prorezima
- Unapređena indikator traka sa lubrikatorom
- Poboljšan trimer
- Novi vodeći mikročešalj (samo Power)
- Redizajnirana ergonomska drška.

Pripremio: Ass. dr. Dušan Škiljević

Gillette® Fusion PROGLIDE™

Langerhans Cell Histiocytosis: a Case Report

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Abstract

Langerhans cell histiocytosis is a disease which results from accumulation or proliferation of a clonal population of cells with the phenotype of Langerhans cells arrested at an early stage of activation that are functionally deficient. The etiology and pathogenesis of the disorder are still unknown. There are ongoing investigations to determine whether it is a reactive or a neoplastic disease. The fact is that neoplastic and reactive processes may have many clinical and pathological similarities. Some emphasize the role of "cytokine storm" in Langerhans cells. Further studies are necessary in all areas, from the etiology and pathogenesis to diagnosis and therapy.

Langerhans cell histiocytosis primarily affects bones, but less commonly it may involve other organ systems, or present as a multisystem disease. The clinical course is variable, from benign forms with spontaneous resolution, to chronic disseminated forms with fatal outcome.

This is a report of a 29-year-old man with Langerhans cell histiocytosis with an onset at the age of 8, which later progressed to a multisystem disease. Apart from lesions on the skin and exposed mucous membranes, the patient also presented with: diabetes insipidus, granuloma of the right femur and slight bulbar protrusion of the right eye. The patient experienced spontaneous pneumothorax on two occasions. The diagnosis of Langerhans cell histiocytosis was histologically confirmed using electron microscopy by presence of Birbeck granules in the histiocytes. A favorable therapeutic response was obtained after systemic corticosteroid therapy.

Key words

Histiocytosis, Langerhans-Cell; Diabetes Insipidus; Eosinophilic Granuloma; Pneumothorax; Treatment Outcome

Langerhans cell histiocytosis (LCH), also known as histiocytosis X, is a rare disease characterized by an accumulation of cells with Langerhans cell phenotype in a variety of tissues causing their damage (1). In 1987, the Writing Group of the Histiocyte Society defined it as "accumulation or proliferation of a clonal population of cells with the phenotype of Langerhans cells (LCs) arrested at an early stage of activation and functionally deficient" (2, 3). Other authors believe that LCH is caused by: primary antigen-presenting cells (4); oligoclonal accumulation of LCs (5), or phenotypically immature CD1a + LC (6, 7, 8).

LCH primarily affects bones, but rarely it may involve other organ systems as well (skin, lymph nodes, pituitary, nervous system, lungs, spleen), or it presents as a multisystem disease (9). The clinical course is variable, from benign forms with spontaneous resolution (10, 11), to chronic disseminated forms which may be aggressive with fatal outcome (12, 13). In 1987, the Histiocyte Society (2) classified histiocytoses into three major categories: 1. Langerhans cell histiocytosis (Letterer Siewe disease, Hand-Schuller-Christian disease, eosinophilic granuloma, congenital self-healing reticulohistiocytosis of Langerhans cells, and undetermined cell histiocytosis); 2. Non-Langerhans cell histiocytosis and 3. Neoplastic (malignant) histiocytoses.

In 1997, the Histiocyte Society revised the earlier classification. According to the revised classification, there are two categories: disorders of varied biological

behavior and malignant disorders. The first category included two groups of diseases: 1. Dendritic cell or related disorders (Langerhans cell histiocytosis, juvenile xanthogranuloma and related disorders, solitary histiocytoma with dendritic cell phenotypes and secondary dendritic cell disorders); 2) Macrophage or related disorders (primary and secondary hemophagocytic syndromes, Rosai-Dorfman disease, solitary histiocytoma with macrophage phenotypes, multicentre reticulohistiocytosis, generalized eruptive histiocytoma. The second category includes malignant disorders: monocytic leukemia, monocytic sarcoma, histiocytic sarcoma with dendritic cell phenotype and macrophage phenotype (14).

LCH commonly occurs in childhood. The annual incidence of LCH in Denmark is reported to be 5.4 per million children (15). The German Registry for Childhood Cancer shows that the incidence of LCH in Germany is 6.0 per million children (16), while the Hungarian National Cancer Registry shows an incidence of 2.2 per million individuals under the age of 18 years (17). The Manchester Children's Tumor Registry shows that 101 children have been treated for LCH during 45 years with an annual incidence of 2.6 cases per million children: in children under the age of 12 months the annual incidence was 9.0 and in children from 10 to 14 years of age it was 0.7 cases per million children (18). A French study showed an annual incidence of 4.6 cases per million children under the age of 15, ranging from 15.3 per million children under the age of 2, to 2.0 cases per million children over the age of 10 (19). The incidence of LCH among adult population has not been precisely defined: it is assumed that 30% of all patients are adults (20).

Case Report

A 29-year-old man, a traffic technician out of job and a father of two children, on his first visit complained about the following: increased fluid intake, constant thirst and frequent urination, pain in the muscles of the lower extremities and painfull and difficult walking. His history showed that at the age of 8 he noted excessive thirst and fluid intake, frequent urination and weight loss. At the age of 12 he presented with red squamous skin lesions on the scalp and had problems with fast tooth loss. He had spontaneous pneumothorax twice, at the age of 21 and 24, and was treated with pronisone and eutisone (supposedly due to sarcoidosis, but there is no written evidence about it). The skin lesions got worse and spread over the folds of large joints, chest and face. The patient's history shows that his father died of liver cancer and his father's sister had diabetes mellitus.

On his first visit the patient was in good general condition, presenting with skin and mucous membrane changes: erythematous infiltrated plaques partly covered with vegetant proliferative yellowish squames; dense erythematous papules, the size of a lens, somewhat eroded and covered with yellowish squames, were found on the face, mostly on the forehead (Figure 1), on the nasolabial folds, in the retroauricular region (Figure 2), on the chin (Figure

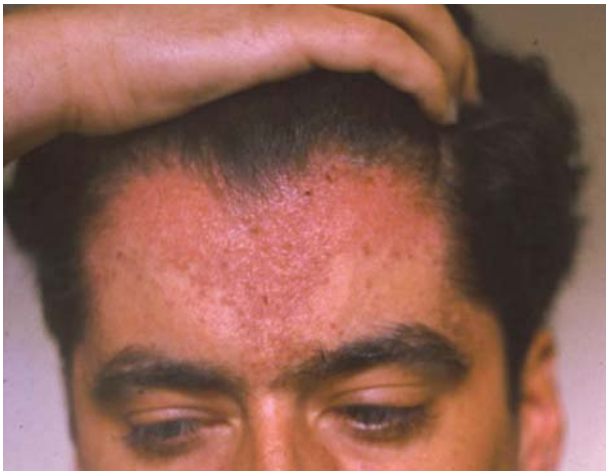

Figure 1. Great part of the forehead affected by erythema, eroded papules and squames

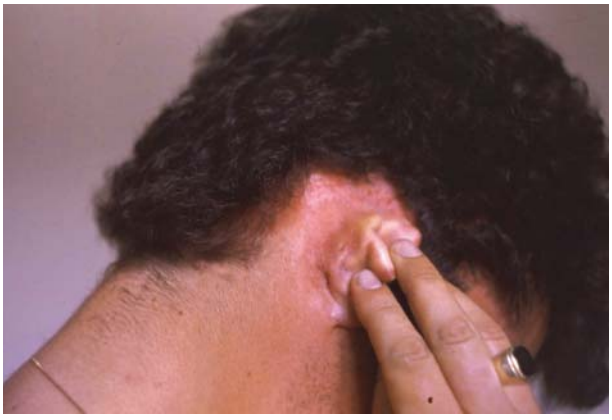

Figure 2. Retroauricular area with papular and squamous lesions on erythematous base

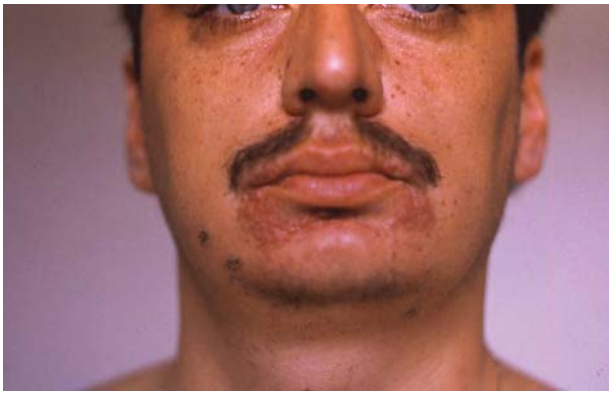

Figure 3. Lesions on the chin similar to those on the forehead

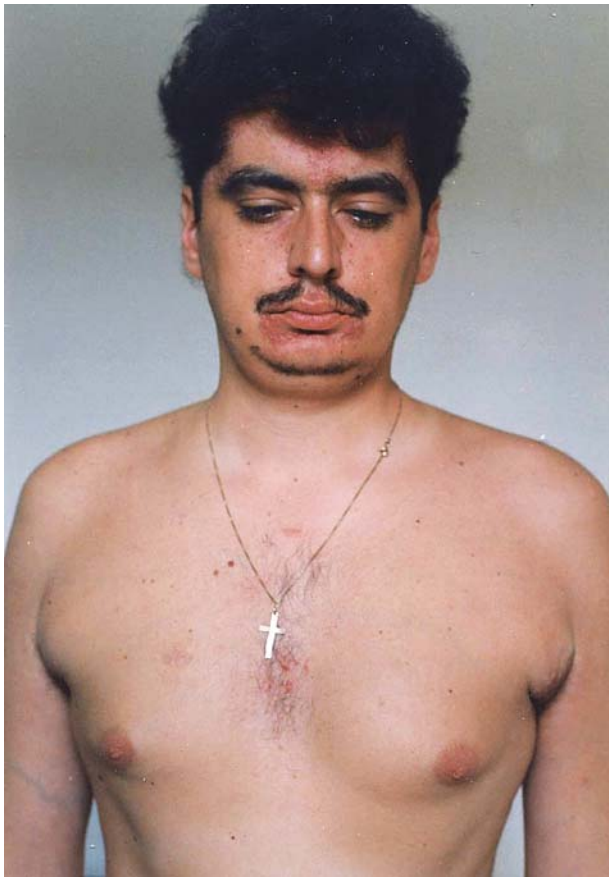

Figure 4. Presternal area with dense erythematous papules, the size of a lens, covered with yellowish squames; Plaques of partly eroded papules on the face

3), as well as on the trunk, especially on the presternal (Figure 4) and intercapular regions; erythematous vegetant proliferations with erosions and effusion of

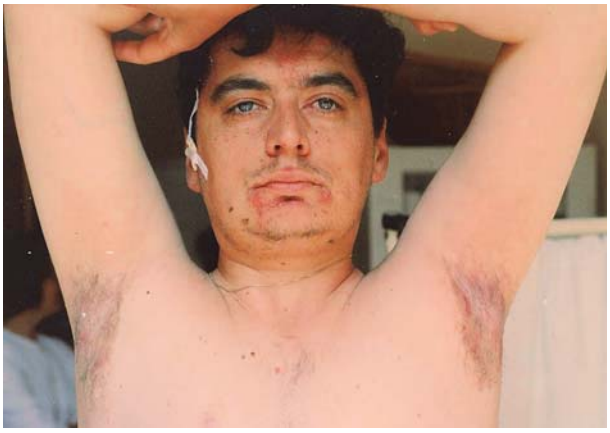

Figure 5. Axillary folds with vegetant erythemas and moist erosions

putrid, bad odor were found in the axillary (Figure 5), groin (Figure 6) and intergluteal areas; the intergluteal area presented with several wet fistula canals and macerated surrounding skin; protrusions about the size of a grain of rice were found on the hard palate mucosa; fibrinoid pseudomembranes were present in the hypertrophic gingival area; the teeth were affected by caries, a great number were missing; exophthalmos was noted in both eyes.

Laboratory test results, including erythrocyte sedimentation rate, complete blood count, basic biochemical, endocrinology and immunology tests, were within normal physiological limits.

Microbiology specimens were collected from the affected lesions and *Staphylococcus aureus*, susceptible to penicillin, erythromycin and ciprocinal, was isolated.

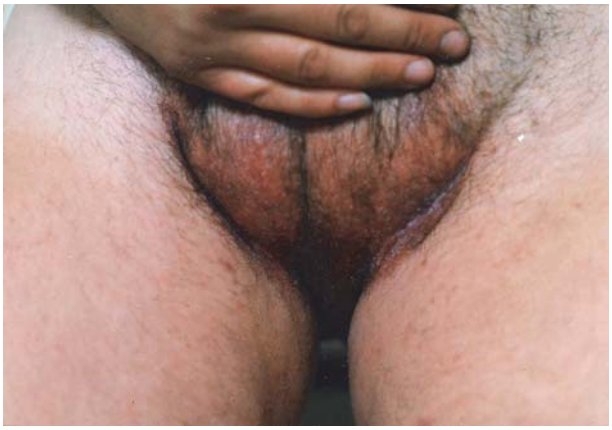

Figure 6. The groins and intergluteal folds affected by intensive exudation with a few fistula canals

Ultrasonography of the upper abdomen, thyroid gland and breasts showed no abnormalities.

X-ray of the heart and lungs showed no pathological findings. There were no osteolytic lesions on the bones of the head; sella turcica presented with normal physiological findings; paranasal sinuses showed no pathological changes. In the lower end of the right femoral diaphysis a small lytic lesion of irregular shape was found (Figure 7).

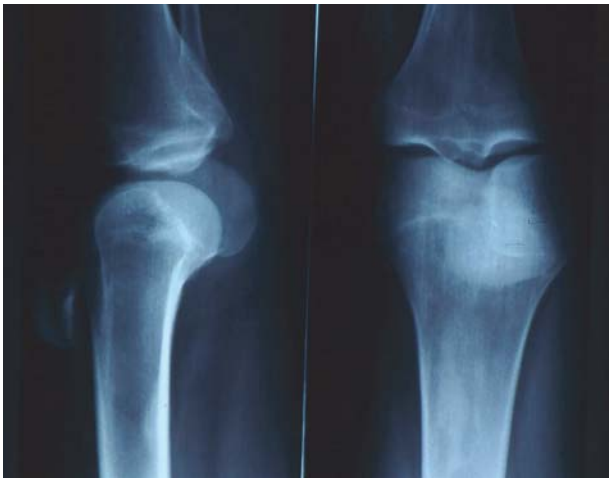

Figure 7. X-ray of the lower end of the right femur shows a lucent area of irregular shape

Static bone scintigraphy (anterior skull projection) showed a physiological distribution of radio-opacity (Figure 8). There was an increased focal accumulation in the lower end of the right femur (Figure 9).

Fistulography was carried out using a cannula and it revealed a great number of pseudofistulous canals with uneven walls and purulent discharge.

Histopathological analysis of skin biopsy specimens showed: severe epidermal atrophy; dense histiocyte infiltrations, sparse eosinophils and erythrocyte extravasation in the dermis invading epidermis on several sites; numerous sebaceous glands near the atrophic epidermis. These findings supported the conclusion about Hand-Schuller-Christian disease.

Electron microscopy analysis of skin biopsy showed Birbeck granules in histiocytes (Figure 10).

Specialist consultations established the following pathological conditions: borderline (partial) diabetes insipidus requiring no medication therapy;

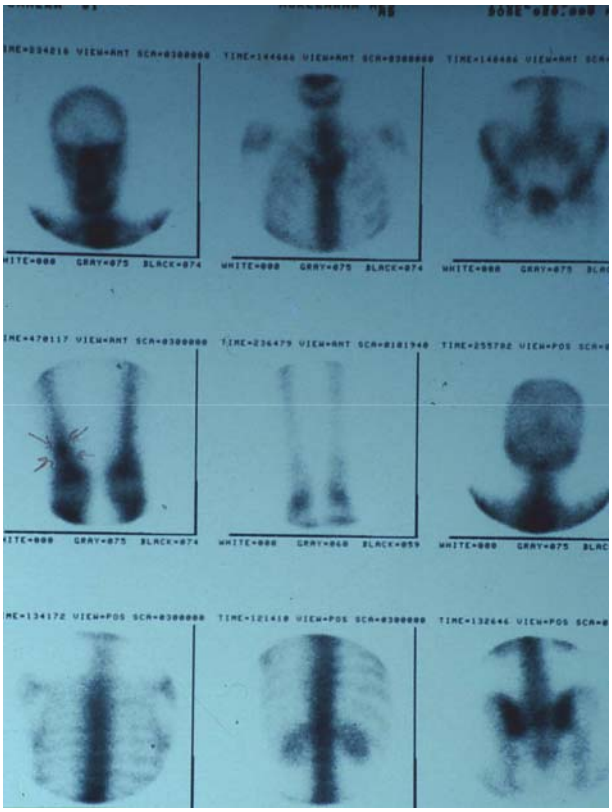

Figure 8. Static bone scintigraphy shows a physiological distribution of radio-opacity, except on the lower end of the right femur

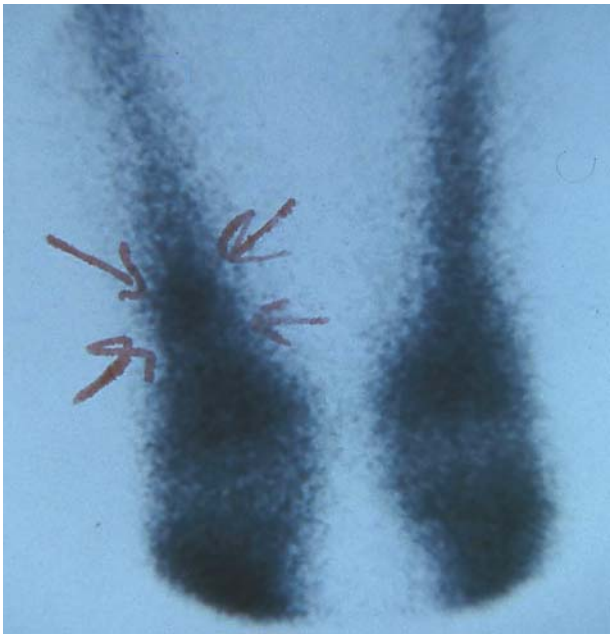

Figure 9. Increased focal accumulation in the lower end of the right femur

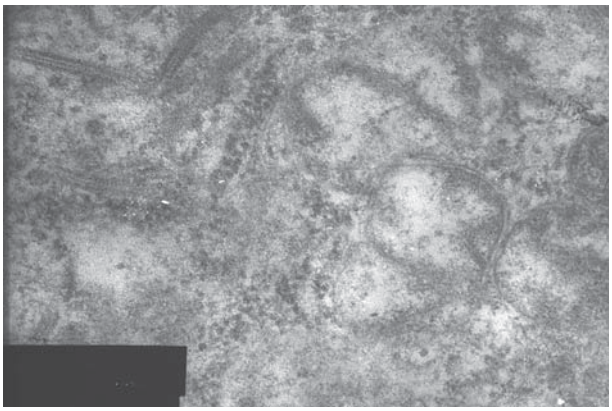

Figure 10. Electron microscopy shows Birbeck granules in histiocytes

periodontal disease; right eye protrusion (Hertel 110: OD 21, OS 19); nasal septal deviation.

The treatment started with systemic parenteral prednisone (initial dose of 1 mg/kg/bw per day, which was gradually reduced), systemic antibiotics, topical corticosteroid and antibiotic preparations and cryotherapy.

Discussion

Langerhans cell histiocytoses include a group of rare diseases that may develop at any age, most commonly in childhood. They are characterized by unpredictable course and variable prognosis, from self-healing to fatal outcome.

The etiology of LCH remains unknown (1) despite numerous studies over the past decades. Various factors have been indicated, such as tuberculosis, lipid metabolism disorders, infections and immunity disorders, genetic and environmental factors. Although some studies established an association between human herpesvirus type 6 (HHPV6) (21) and LCH, others failed to prove increased prevalence of HHPV6 in the tissues of patients with LCH in regard to healthy population (22). It was also found that there was no causal role for HHV8 in the etiology of LCH (23), as well as the other eight viruses (24): herpes simplex virus, cytomegalovirus, Epstein Barr virus, adenoviruses, T-cell lymphotropic type I and type II virus, human immunodeficiency virus (HIV) and parvovirus. Huang and Arceci (12) indicated authors who suggested that development of LCH was associated with several apparently unrelated factors, including maternal urinary infection and nutritional problems, use of medications, blood transfusion during the first six months of life (25). An association was also established with personal or family history of patients, thyroid disease and postnatal infection, vomiting, diarrhea and drug use (26).

The pathogenesis of the disease is also unclear. There is a long standing dispute whether LCH is a reactive or a neoplastic disorder (9, 13, 27, 28, 29). Egeler and associates (30) tried to elucidate this dilemma in their paper. The fact is that neoplastic and reactive disorders may have many clinical and pathological similarities, making their differentiation more difficult. Neoplasms are caused by proliferation of genetically abnormal progenitor cells, while in reactive disorders genetically normal cells multiply and accumulate under some other stimuli. Neoplastic processes are associated with inflammatory responses inducing accumulation of adjacent cells, and contrary to this, some reactive immune diseases are characterized by the accumulation and sequestration of activated white blood cells, which occasionally form lesions similar to neoplastic tumors. Some emphasize the role of "cytokine storm" in Langerhans cells (28). Cytokines provide an optimal microclimate for survival of interactive inflammatory cells by creating autocrine or paracrine mechanisms. They also affect differentiation of precursor cells. Some cytokines may stimulate development of macrophages, Langerhans cells and other types of dendritic cells from CD34+ stem cells, or by sequestrating of circulating (peripheral) monocytes from the blood to affected tissues. Arguments supporting the neoplastic or reactive process that results of numerous studies are given in Table 1 (30-37).

Given the existence of this dilemma, the third edition of the International Classification of Diseases for Oncology differentiates three groups of LCH: unifocal and multifocal variants which are considered to be neoplastic diseases, and disseminated LCH, considered as a malignant disease (19, 38). The most important characteristics of this disease are given in Table 2 (39, 40).

In our 29-year-old patient, the onset was at the age of 8, with symptoms of diabetes insipidus, associated with skin and oral lesions, involvement of lungs (spontaneous pneumothorax at the age of 21 and 24), whereas in the last 5 years the leading

Table 1. Langerhans cell histiocytosis: a neoplastic or reactive disease? [Adapted from Egeler et al, (30)]

Neoplastic	Reactive
Clonality of LC cells in all studied cases of non-pulmonary LCH	Non-clonality of pulmonary LCH, related to smoking
Recurrent genetic abnormalities, including deletion of chromosome segments in 7 patients	No gross genetic abnormalities observed in 72 patients No mutation in genetic master switch p53 gene
More extensive and higher-risk forms of LCH have evidence of more mutational events at tumor suppressor genes	
Rare cases of familial clustering with high concordance between monozygotic twins	Sporadic disease in vast majority of cases
Clinically aggressive behavior of some LCH forms	Indolent, clinically benign behavior of most LCH cases, sometimes involving: Spontaneous remissions; "Flare up" when patients develop a cold or other infectious process; Faborable response to antibiotic treatment
Apparent maturation arrest of LCH cells *in vivo*	Immature LCs may accumulate in inflammatory processes, e.g. in lymph nodes that drain chronically inflamed skin
	LCH cells cannot be maintained *in vitro* or *in vivo* in humanized mouse models
	LCH cells are cytologically benign
	Granulomatous compositions of apparently immune-activated cells

LCH, - Langerhans cell histiocytosis; LCs- Langerhans cells

symptoms included cutaneous-mucosal lesions. Right eye protrusion and right femoral granuloma developed as well. Histological examination showed histiocytic infiltration, and electron microscopy showed Birbeck granules in the histiocytes. The dominant clinical symptoms corresponded with those typical for Hand-Schuller-Christian disease and for eosinophilic granuloma, making differentiation between diseases difficult. Given that this is a common problem, all the above-mentioned diseases are grouped under the common term Langerhans cell histiocytosis, or after Lichtenstein, histiocytosis X (41). In 1997, authors from Novi Sad reported a case of a patient with hyperthyroidism and LCH, but also presenting with symptoms found in our patient: diabetes insipidus, pneumothorax and skin lesions (42). A retrospective study conducted by the Mayo Clinic included 265 patients with LCH aged from 2 months to 71 years demonstrated the following: the sex ratio was 1,6 : 1,0 in favor of male patients; the most common signs and symptoms were pain, bone defects, soft tissue swelling, tooth loss, oral ulcerations, and diabetes insipidus (43). One study of adult patients with LCH reported that the most common sites of involvement were skin, lungs and bones, and then the lymphoproliferative system (20). The disease may develop in the CNS

Table 2. Langerhans cell histiocytosis (LCH)

Characteristics	Letter-Siwe disease	Hand-Schuller Christian disease	Eosinophilic granuloma	Congenital self-healing histiocytosis	Undetermined cell histiocytosis
Onset	First year of life	Rare in childhood Adult	Older children Adult	At birth	Adult
Course	Acute (disseminated)	Acute-chronic to progressive	Chronic and localized	Subacute	Subacute
Prognosis	Unfavorable	Favorable	Good	Self-healing	Poor
Systemic symptoms	Septic fever Weight loss Limphadenopathy Hepatosplenomegaly Lungs Anemia Eosinophilia	Classical triad: lytic bone lesions, exopthalmos, diabetes insipidus Infantility Otitis media Lymphadenopathy, Hepatosplenomegaly Lungs	Bone tumors Lymphadenopathy Hepatosplenomegaly		No
Skin	Papulopustular lesions Papulovesicular lesions, Erosions Mucosal petichias	Papules Xanthomas	Granulomas	Papules Nodules Crater-shaped ulcers	Papules Nodules Tumors
Mucous membranes	Yes	Yes	Yes	Yes/No	Yes/No
Bone lesions	Sometimes	Multifocal	Solitary or sparce	No	No
Histology	Proliferative reaction Histiocytic LC infiltrations	Xanthomatous reaction	Granulomatous reaction	Proliferative reaction	Proliferative reaction
Antigenic markers	S-100+, CD1a+, Birbeck granules +	S-100+, CD1a+, Birbeck granules +	S-100 +, D1a+, Birbeck granules +	S-100+, CD1a+, Birbeck granules +	S-100+,CD1a+ Birbeck granules

LC - Langerhans cell

(4%), while diabetes insipidus in a wide range of 10 – 50% of patients (44, 45).

According to the International Langerhans Cell Histiocytosis-2 (LCH2) study, LCH has three stages: the first stage is unifocal, the second multifocal – without spleen, liver, lung or bone involvement in patients over the age of 2 years, whereas the third stage is characterized by involvement of the liver, spleen, lungs and bone marrow in patients under the age of 2 years (44).

The diagnosis is based on anatomical and pathological signs and symptoms. In 1987, the Writing Group of the Histiocytic Society identified three levels of confidence in the diagnosis of LCH (2): presumptive diagnosis is based on histological findings; the diagnosis is established when the histology is consistent with LCH and lesional cells are shown to express S 100 protein, peanut agglutinin and alpha-D-mannosidase activity; a definite diagnosis is made if the histology is consistent with the diagnosis of LCH and the lesional cells are shown to express CD1 complex or to have intracytoplasmic Birbeck granules on electron microscopy. In the early days, a definitive diagnosis was the ultrastructural proof of Birbeck granules (BGs), now it can immunohistologically be recognized by the expression of langerin in the histiocytic cells (46). Langerin (CD207 antigen) is a mannose-specific lecitin endocytic receptor that induces formation of Birbeck granules (47). The induction of BGs appears to be the consequence of antigen-capture function of langerin, allowing routing of antigen into these organelles. Langerin, as a type of transmembrane cell surface glycoprotein is involved in the formation of BGs by limiting cell membranes (48, 49, 50). Using langerin, BGs provide sequestrial selection of antigens, which may be important in migration of LC into epidermis (51). The significance of langerin in BGs is obvious from the definition of LCH as accumulation of langerin + dendritic cells (DCs) in the skin, bones and other tissues (52). Although langerin, as an intracellular component is associated with BGs in 100% of cases (52, 53), its diagnostic specificity has not been established yet, which points to the necessity of further investigations. Thus, langerin is an additional marker for identification of LCH (48).

Three types of histological reactions have been described in LCH: proliferative, granulomatous and xanthomatous (54, 55). These reactions may be considered *sui generis*; they may develop at sites of previous lesions, may simultaneously exist, or heal in any of these types. Various types of histological reactions may be found in one patient (56). No association has been established between the histological type and severity of illness, morbidity or mortality (1).

The differential diagnosis includes: seborrheic dermatitis, Darier's disease, Hailey-Hailey disease, purpura, scabies, cutaneous tuberculosis, hematological diseases, malignant neoplasms, leukemia, lymphomas, multiple myeloma, disseminated xanthomas with diabetes insipidus and non-Langerhans cell histiocytosis (57).

Therapeutic options depend on the clinical presentation of the disease (unifocal, multifocal, disseminated (19, 38), and the disease status (inactive or active) (58). LCH may be: inactive – if there is no evidence of the disease (due to resolution of all signs and symptoms) and active. The activity may lead into three directions: regression of signs or symptoms without new lesions; persistence of signs and symptoms without new lesions; progression of signs and symptoms and/or development of new lesions (58). Progression and reactivation of the disease indicate a chronic clinical course (59). There is a variety of therapeutic options: local curettage, radiotherapy, use of mechlorethamine (60), combination of mechlorethamine and PUVA (psoralen ultraviolet A) therapy (61), local corticosteroid therapy, antibiotics, systemic corticosteroids and cytostatic agents (methotrexate, cyclosporine, azathioprine), various protocols of chemotherapy and immunosuppressive treatment. According to LCH I protocol in the treatment of LCH, patients with multisystem disease receive vinblastine or etoposide during 6 months with an initial dose of methylprednisolone (62). Etoposide proved to be more effective than vinblastine (14, 63), but may induce significant leukemoid reactions (20, 64). According to LCH II protocol, vinblastine is combined with etoposide (65). The LCH-S-98 protocol includes 2-chlorodioxyadenosine (58). Immunotherapy is associated with bone marrow transplantation, and if the donor is not compatible, antithymocyte globulin + prednisone + cyclosporine A are used (66). Etanercept also proved to be successful in the treatment of multifocal LCH (67).

The course and prognosis depend on the age of patients, number of involved organs and the degree of organ dysfunction, as well as on the applied treatment. The prognosis is better if only the skin and bones are involved, and if the onset is from birth. The prognosis is favorable if there is bone involvement without diabetes insipidus. Diabetes insipidus in children is associated with high risk for chronic disease, but not for mortality. Permanent consequences

are rather common and they significantly reduce patients' quality of life (68, 69). A study conducted by 12 oncology centers and 9 institutions included 201 children with LCH. Endocrine problems were reported (diabetes insipidus in 24% and growth disorders in 9% of cases), neurological consequences in 11% (cerebellar symptoms and psycho-intellectual problems), orthopedic abnormalities in 20%, hearing loss in 13%, ophthalmological problems in 8%, skin problems in 2%, pulmonary fibrosis in 4%, secondary carcinoma in 4 patients: 3 cases with acute myeloid leukemia and 1 case with thyroid carcinoma (68).

Increased risk of mortality is associated with: early onset, hepatosplenomegaly, thrombocytopenia and polyostotic bone diseases (43). Disseminated forms may also be related to the development of lymphomas, leukemias and tumors. It is a fact that LCH may precede malignancies; the fact that it occurs simultaneously or after the development of malignancies, suggests the same etiological factors (20). Fatal outcome accounts for 10% of cases, remission occurs in 30%, while 60% of cases have a chronic course. However, with adequate treatment the survival rate is believed to be 80% (64).

Conclusion

In conclusion, this is a case report of a patient with a very rare disease, multisystem Langerhans cell histiocytosis, but with a relatively favorable course and good response to systemic corticosteroid therapy. Langerhans cell histiocytosis is a disease with many unknown factors which remain to be further studied in all aspects, from the etiology and pathogenesis, to diagnosis and therapy.

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Abbreviations

LCH - Langerhans cell histiocytosis
LCs - Langerhans cells
OD - oculus dexter
OS - oculus sinister
HHPV6 - human herpesvirus type 6
HIV - human immunodeficiency virus
BGs - Birbeck granules
DCs - dendritic cells
PUVA - psoralen ultraviolet A

Histiocitoza Langerhansovih ćelija – prikaz slučaja

Sažetak

Uvod: Histiocitoza Langerhansovih ćelija (eng. *Langerhans cell histiocytosis* – LCH) ili histiocitoza X (eng. *histiocitosis X*) bolest je koja se retko javlja i kod koje se ćelije sa fenotipom Langerhansovih ćelija (eng. *Langerhans cells* – LCs) akumuliraju u različita tkiva i izazivaju oštećenja tih tkiva. *Writing Group of the Histiocyte Society* je 1987. godine dala sledeću definiciju: „Akumulacija ili proliferacija klonalne populacije sa fenotipom Langerhansovih ćelija koje su zaustavljene u ranom stadijumu aktivacije i funkcionalno su deficijentne". LCH je bolest koja primarno zahvata kosti, ali u retkim slučajevima može takođe da zahvati i druge organske sisteme (koža, limfni čvorovi, hipofiza, nervni sistem, pluća, slezina), ili da se prezentuje kao multisistemska bolest. Kilnički tok je varijabilan, od benignih formi sa spontanom rezolucijom do hroničnih, diseminovanih formi, agresivne bolesti koja može imati smrtni ishod).

Prema klacifikaciji *Writing Group of the Histiocyte Socity* iz 1987. Godine, kod histiocitoza se razlikuju tri velike grupe bolesti: 1) histiocitoze Langerhansovih ćelija (*Morbus. Leterer Siwe*, *Morbus Hand-Schuller-Christian*, eozinofilni granulom, kongenitalna samozaceljujuća histiocitoza Langerhansovih ćelija i histiocitoza nedeterminisanih ćelija); 2) ne-X histiocitoze (histiocitoze ne-Langerhansovih ćelija) i 3) neoplastične histiocitose.

Prema studiji iz Francuske, godišnja incidencija LCH je 4,6 na milion dece mlađe od 15 godina i to 15,3 na milion pre prve godine do 2 na milion posle 10. godine života. Tačna incidencija među odraslima je nepoznata – pretpostavlja se da 30% svih obolelih čine odrasli.

Prikaz slučaja: Muškarac star 29 godina još u osmoj godini života primetio je da je često žedan, često mokri i gubi na težini. U 12. godini javile su mu se prve promene na koži u vidu crvenila i naslaga skvama u kosmatom delu glave. Od tada nastaju problemi sa

zubima (klate se, ispadaju, kariozni su). U 21. i 24. godini nastupio je spontani pneumotoraks. Promene na koži se šire i zahvataju lice, grudni koš i pregibe velikih zglobova.

Opšte stanje pacijenta na prijemu je bilo u fiziološkim granicama, bez limfadenopatije i hepatosplenomegalije. Od tegoba naveo je povećan unos tečnosti, učestalo mokrenje, bolove u listovima i butinama i kod jače izraženih promena u pregibima, smanjenu pokretljivost i bol.

Dermatološki status je ukazao na prisustvo: u kosmatom delu glave eritemne, infiltrovane, mestimično vegetantne plaže sa naslagama žućkastih skvama; na čelu, u nazolabijalnim brazdama, na bradi, retroaurikularno, presternalno i interskapularno gusto zbijene eritemne papule do veličine sočiva, mestimično erodovanih površina, pokrivenih žućkastim skvamama; u aksilama i preponama i interglutealno eritemne vegetacije, sa erozijama i vlaženjem, putridne; interglutealno vlaženje intenzivno sa nekoliko fistuloznih otvora; u predelu tvrdog nepca veći broj prominencija veličine zrna pirinča, gingive hipertrofične, pokrivene belim naslagama, zubi kariozni ili nedostaju; oči krupne, lako egzoftalmične. Laboratorijske analize uključujući hematološke, osnovne biohemijske i imunološke, kao i ehosonografski pregled gornjeg abdomena, štitne žlezde i dojki bili su u fiziološkim granicama. Sa promena na koži izolovan je *Staphylococcus aureus.*

Radiološki nalazi na plućima, srcu, prednjim paranazalnim šupljinama, kraniogram, kao i *sela turcica* u fizioloskim granicama. Rendgenografski pregled butne kosti otkriva u donjem okrajku desne butne kosti rasvetljenje nepravilnog oblika. Fistulografija ukazuje na prisutnu pseudofistulu.

Patohistološki nalaz isečka uzetog sa promenjene kože pokazao je atrofiju epidermisa, gust infiltrat sa mnoštvom histiocita, retkim eozinofilima i retkim ekstravazatima eritrocita u dermisu, koji na više mesta invadira epidermis. Zaključak, u preparatu ima mnogo elemenata koji ukazuju na Hant-Šiler-Kristijanovu bolest (*Morbus Hand-Schuller-Christian)*.

Elektronska mikroskopija ukazala je na postojanje Birbekovih granula u histiocitima. Statička scintigrafija kostiju (ciljano je rađena scintigrafija lobanje u anteriornoj projekciji) ukazala je na fiziološku distribuciju radiorazređivača, ali je na donjem okrajku desnog femura utvrđeno pojačano fokalno nakupljanje.

Na osnovu konsultativnih specijalističkih pregleda, utvrđeno je prisustvo graničnog (parcijalni) insipidnog dijabetesa (koji aktuelno nije zahtevao medikamentnu terapiju), paradontopatija, laka protruzija desne očne jabučice, devijacija nosne pregrade, hronični faringitis, u spoljnom ušnom kanalu promene kao na koži. Audiometrija je bila u granicama normale.

Lečenje je započeto sa parenteralnim davanjem prednizona u početnoj dozi od 1 mg/kg/TT dnevno, sistemskom primenom antibiotika i lokalnom primenom kortikosteroidnih i antibiotskih preparata uz krioterapiju.

Diskusija: Etiologija LCH je nerazjašnjena: navode se razni faktori kao što su tuberkuloza, lipidne abnormalnosti, infekcija, imunološki poremećaji, genetski i faktori okoline. Patogeneza bolesti takođe nije jasna. Vode se rasprave da li je to reaktivna ili neoplazijska bolest. Veliki značaj pridaje se „citokinskoj oluji" u LCH ćelijama. Poznato je da neoplazijski i reaktivni poremećaji mogu imati mnogo kliničkih i patoloških sličnosti, što otežava njihovo razumevanje. Upravo zbog ove dileme, treća verzija *International classification of Diseases for Oncology* kodira tri glavna klinička podtipa LCH: unifokalna i multifokalna varijanta koja se smatraju neneoplastičnom/neoplastičnom reaktivnom bolešću i diseminovana LCH, označena kao maligna bolest. Najvažnije osobine ove grupe bolesti prikazane su u Tabeli 2.

Kod našeg 29-godišnjeg bolesnika bolest je počela u osmoj godini života simptomima insipidnog dijabetesa, potom su se javile promene na koži i u usnoj duplji, na plućima (spontani pneumotoraks u 21. i 24. godini), da bi poslednjih 5 godina vodeća bila kutano-mukozna simptomatologija. Došlo je do razvoja i lake protruzije desnog bulbusa i granuloma na desnom femuru. Histološki je u bioptatu uzetom sa promene na koži utvrđen histiocitni infiltrat a elektronskom mikroskopijom Birbekove granule u histiocitima. Istovremeno prisustvo simptoma i znakova tipičnih za Hant-Šiler-Kristijanovu bolest i eozinofilni granulom otežalo je kod bolesnika prikazanog u ovom radu, diferencijaciju prema jednoj od ovih bolesti. Kako je to česta pojava, sve navedene bolesti su obuhvaćene zajedničkim nazivom histiocitoza Langeransovih ćelija

ili po Lihtenstejinu, histiocitoza X.

Na osnovu podataka iz literature, LCH najčešće zahvata kožu, pluća i kosti, zatim limfoproliferativni sistem CNS u 4% slučajeva a u 10–50% slučajeva prisutan je insipidni dijabetes.

LCH je klasifikovana prema *International Langerhans Cell Histiocytosis* – 2 (LCH2) studiji u tri stadijuma: 1) unifokalni, 2) multifokalni bez zahvtanja slezine, jetre, pluća ili kostne srži kod osoba starijih od 2 godine i 3) diseminovani stadijum sa zahvatanjem jetre, slezine pluća i kostne srži kod osoba mlađih od 2 godine. Dijagnoza LCH se postavlja na osnovu kliničke slike i anatomopatoloških znakova. Prema Udruženju za histiocitoze, postoje tri nivoa dijagnostičke sigurnosti: 1) verovatni, kada je dijagnoza postavljena histološkim nalazom; 2) viši, ako se pomoću markera otkrije da su ćelije pozitivne na S 100 protein, aglutinin kikirikija i alfa D-manozidozu; 3) definitivan, ako ćelijske lezije produkuju CD1 kompleks ili se na elektronskom mikroskopu nađu Birbekove granule. I dok je u početku za definitivnu dijagnozu bio potreban ultrastrukturni dokaz Birbekovih granula (BG), sada se BG mogu demonstrirati imunohemijski ekspresijom langerina. Langerin (CD207) je manoza specifični lecitin, endocitni receptor, koji utiče na formiranje BG. Iako se langerin, kao intraćelijska komponenta, dovodi u vezu sa BG u 100% slučajeva pa se čak LCH definiše kao akumulacija langerina + dendritičnih ćelija u koži, kostima i ostalim tkivima, dijagnostička specifičnost langerina još nije utvrđena, što zahteva dodatna istraživanja. Tako je langerin samo dodatni marker za identifikaciju LCH.

Histološki se u LCH razlikuje nekoliko tipova reakcija: proliferativni, granulomatozni i ksantomatozni. Oni mogu nastati kao takvi, proisteći iz prethodnih, biti prisutni u lezijama drugih i zaceliti u bilo kom tipu.

Diferencijalna dijagnoza uključuje seboroični dermatitis, *Morbus Darier*, *Morbus Hailley-Hailey*, purpuru, skabies, kutanu TBC, hematološka oboljenja, maligne neoplazme, leukemiju, limfome, multipli mijelom, diseminovane ksantome sa insipidnim dijabetesom i kandidozu.

Izbor terapije zavisi od kliničkog oblika bolesti (unifokalni, multifokalni, diseminovani) i aktivnosti (neaktivna ili aktivna). Postoje različite mogućnosti lečenja od lokalne primene kiretaže, radioterapije, kortikosteroida, mehloretamina, kombinacije mehloretamina i PUVA terapije, po potrebi antibiotika, do sistemske imunosupresivne terapije primenom kortikosteroida i citostatika (metotreksat, ciklosporin, azatioprin).

Ishod bolesti zavisi od starosti bolesnika, broja zahvaćenih organa, stepena njihove disfunkcije i od primenjene terapije. Prognoza je bolja kada su zahvaćeni samo koža i kosti i kad bolest počinje od rođenja. Prisustvo insipidnog dijabetesa kod dece povećava rizik za hroničnu bolest, ali ne i smrtnost. Prognoza bolesti kod zahvaćenosti kostiju bez dijabetesa je izvrsna.

Trajne posledice su relativno česte, npr. endokrini problemi, neurološke konsekvence, ortopedske abnormalnosti, gubitak sluha, oftalmološki problemi, kožne promene, fibroza pluća, sekundarni kanceri (akutne mijeloidne leukemije i tiroidni karcinom). Faktori koji predstavljaju povećani rizik za smrtni ishod su: početak u prvim godinama života, hepatosplenomegalija, trombocitopenija i poliostitične promene na kostima. Kod diseminovanih formi postoji mogućnost nastanka limfoma, leukemija i tumora. Smrtni ishod nastaje u 10% slučajeva, kod 30% nastaje remisija a 60% slučajeva bolest dobija hronični tok.

Zaključak: U radu je prikazan bolesnik sa vrlo retkom bolešću, histiocitozom Langerhansovih ćelija, sa multisistemskim lokalizacijama, ali sa relativno povoljnim tokom bolesti i reakcijom na sistemsku kortikosteroidnu terapiju. Bolest podrazumeva postojanje mnogih nepoznanica koje zahtevaju dalja istraživanja na svim poljima, od etiologije i patogeneze do dijagnostike i terapije.

Ključne reči

Hisiocitoza Langerhansovih ćelija; Dijabetes insipidus; Eozinofilni granulom; Pneumotoraks; Ishod lečenja

Multiple Reticulohistiocytomas in an 88-year-old Man: a Case Report

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Abstract

Solitary and multiple reticulohistiocytomas, often referred to as diffuse cutaneous reticulohistiocytosis, that are generally restricted to skin, must be differentiated from multicentric reticulohistiocytosis. Multicentric reticulohistiocytosis is a rare histiocytic proliferative disease affecting joints, skin and mucous membranes, while arthropathy usually precedes skin and mucosal involvement. Other organs may also be involved, and 20% of patients have an associated internal malignancy. Multicentric reticulohistiocytosis has been reported to be associated with autoimmune diseases and malignancies.

We present an 88-year-old man, with a sudden eruption of asymptomatic, firm, skin to brown colored papules and nodules, 6 to 17 mm in diameter, localized on forehead, arms, legs, and buttocks. There were no symptoms of joint or other organ involvement. Clinical and dermoscopic characteristics pointed to reticulohystiocytomas. Multiple excision biopsies of different tumors were performed and histopathology reports confirmed the diagnosis. In the case presented, reticulohistiocytosis was limited to the skin, exhibiting multiple reticlohistiocytomas with typical clinical, dermoscopic and rather peculiar histopathology presentation. Apart from this, some histologic features were seen in early lesions of multicentric reticulohistiocytosis, such as multinuclear cells dissociating collagen fibers with pale eosinophilic and foamy cytoplasm. Besides surgical excisions, no other treatment options were done. Laboratory and other tests showed no presence of extracutaneous illness, and no autoimmune or paraneoplastic processes. At one year follow up, the remaining tumors were of the same size, but there were no recurrences at excision sites, no signs of disease progression or systemic involvement. Since diffuse cutaneous reticulohistiocytosis without arthropathy as well as isolated reticulohistiocytomas have been described, in some cases of multiple reticulohistiocytomas even without systemic symptoms and signs, multicentric reticulohistiocytosis should be considered with an appropriate follow up. In such cases, skin lesions have the same histological features as lesions in multicentric reticulohistiocytosis, but they are not associated with joint problems or neoplasms.

Key words

Histiocytosis, Non-Langerhans-Cell; Dermoscopy; Histology; Signs and Symptoms; Aged, 80 and over

The histiocytoses are a group of proliferative disorders that have a common progenitor cell in the bone marow. In general, these disorder are broadly devided into Langerhans cell and non-Langerhans cell histiocytosis (1, 2). Reticulohistiocytoma is a non-Langerhans cell histiocytosis also involving cells other than dermal dendrocytes, which is a rare, generally solitary and asymptomatic skin tumor of unknown etiology. Solitary and multiple reticulohistiocytomas RHs, often referred to as diffuse cutaneous reticulohistiocytosis are: generally restricted to skin neither associated with arthropathy nor internal malignancy; must be differentiated from multicentric reticulohistiocytosis (MRH). Multicentric reticulohistiocytosis is a rare histiocytic proliferative disease affecting joints, skin and mucous

membranes, while arthropathy usually precedes skin and mucosal involvement. Other organs may also be involved, and 20% of patients have an associated internal malignancy. MRH has been reported to be associated with autoimmune diseases and fatal cardiac involvement, and widespread systemic involvement (3). Constitutional symptoms commonly include fever, malaise, weakness and weight loss.

Multiple cutaneous RHs rarely present without any evidence of systemic disease (1, 2), and it has been suggested that in such cases extracutaneous features may develop at any time (4). We present an 88 year-old patient who developed multiple cutaneous RHs and remained systemic disease-free after a year follow-up.

Case report

An 88-year-old man, a retired lawyer, who was referred to our Clinic with earlyer medical history of benign prostatic hyperplasia and cerebrovascular insult, presented with a sudden onset of widespread asymptomatic cutaneous eruption of papules and nodules, gradually progressing within the following 3 months. There were no mucosal lesions, no history of joint diseases, or constitutional symptoms. Complete skin examination revealed firm, round, well-circumscribed, skin to brown colored papules and nodules, 6 -17 mm in diameter, affecting the patient's forehead, arms, legs and buttocks (Figures 1 and 2). The rest of the systemic examination was normal.

Dermoscopy of forehead lesions revealed a homogeneous yellow pattern with central white scar-like streaks (Figure 3a); the same appearance was seen on the right and left upper arms, with an erythematous, slightly brownish halo and some vessels on the periphery (Fiugres 3b, c); a central homogeneous yellow pattern with whitish scar-like streaks and a bright to dark livid halo with brown linear and reticular structures at the periphery were seen on the four different lesions on the lower limbs (Figures 4a - d).

Multiple excision biopsies from the forehead, both arms, and buttocks were performed and histopathological examination revealed and confirmed RHs.

Histopathology of four exhcised nodules exibited similar characteristics: the epidermis was centrally slightly distended over the lesion, but preserved over the dermal infiltrate (Figure 5a); diffuse infiltrates of histiocytes involved the whole dermis showing areas of storiform pattern (Figure 5b); the infiltrates consisted of some lymphocytes and eosinophilic granulocytes as well as broad thick collagen bundles (Figure 5c); histiocytes were mostly mononuclear, but a few were

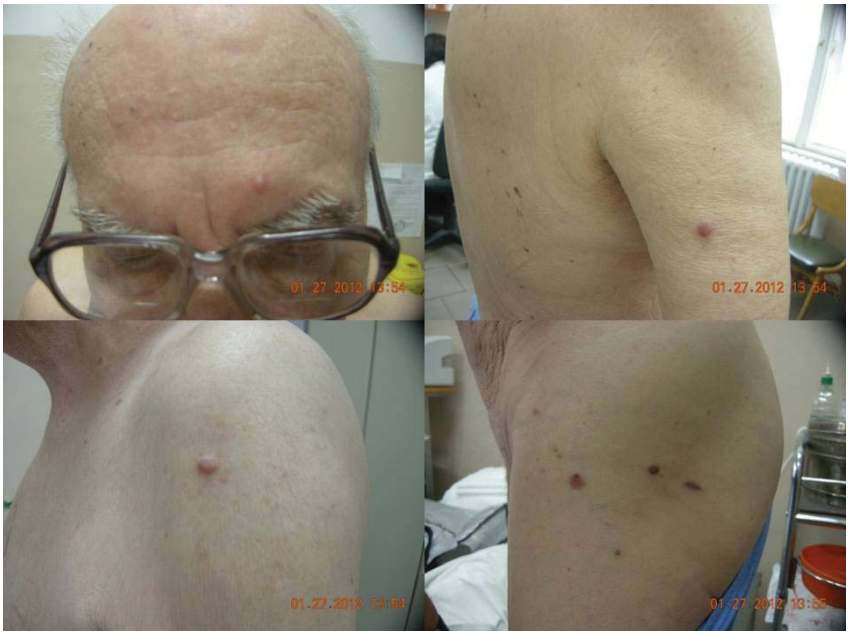

Figure 1. Skin colored to brownish nodules located on the forehead, right and left arm and the buttocks

Figure 2. Brownish nodules on the lower legs

multinuclear, the cytoplasm was pale, eosinophilic and foamy; the staining with CD34 and S-100 was negative, but with CD68 – it was diffusely positive (Figure 5d).

Laboratory tests were within normal values including: erythrocyte sedimentation rate, complete blood count with differential, urinanalysis, lipid status, renal and liver biochemistry, serum levels of amylase, lipase, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transpeptidase, tumor markers such as carcinoembryonic antigens (CEA), alpha fetoprotein antigens (AFP), carbohydrate antigen (CA 19-9) and prostate serum antigens (PSA), as well as immunology parameters such as rheumatoid factor, antinuclear antibodies, cold agglutinins and cryoglobulins.

Chest X-ray and abdominal ultrasound showed no signs of MRH or malignancies. Plain x-ray showed marked osteoporosis of the hands and feet and mild narrowing of proximal interphalangeal space of the fifth finger of the right hand.

Annual follow up showed that RHs persisted in number and size, but there was no systemic disease and no new RHs developed.

Discussion

Solitary RHs are confined to the skin, but when multiple tumors develop they usually represent an introduction into a rare systemic disease – MRH. The etiopathogenesis of MRH remains unknown. It has been suggested that a yet unidentified stimulus may trigger proliferation of reactive histiocytes (1), and that destructive, mainly osteolytic lesions are due to the action of protease released by infiltrating cells as well as proinflammatory cytokines, TNF-α and IL-1, in inducing osteoclastic activity (3, 5).

Multiple reticulohistiocytosis predominantly affects Caucasians, and three times more frequently women than men. The mean age of onset is in the fourth decade of life, although it may also affect children, adolescents and the elderly (4). As a systemic form of reticulohistiocytosis, MRH usually has a sudden onset. In 30% of cases it begins with skin manifestations, in nearly 40% with joint symptoms and in 29% of cases with both joint and skin symptoms (5). Skin manifestations have very similar clinical and histological features in all forms of reticulohistiocytosis. Lesions consist of papules and nodules, a few millimeters to 20 mm in diameter, pink, yellow, brown or gray in color, and are localized on hands, face, arms, trunk, legs, ears and neck (1, 5). Although they are usually asymptomatic, one third of patients report pruritus associated with skin lesions (6).

Radiographs of MRH with erosive polyarthritis commonly show well circumscribed periarticular "punched out" lesions and resorption of the juxtaarticular zone, but without periarticular osteopenia typical in rheumatoid arthritis, or heterotrophic new bone formation typical in the spondylarthritides and gouty arthritis (7). Distal interphalangeal joints are most frequently involved (in 75% of patients) and are one of defining characteristics of MRH (4). Even though arthritis has a tendency to wax and wane, it progresses into disabling mutilating arthritis in almost 50% of patients (6).

Besides skin and joint involvement, MRH can also affect other organs: mucous membranes in almost half of patients (6), lungs in 20% of cases, less frequently thyroid, salivary glands, heart, kidney, liver

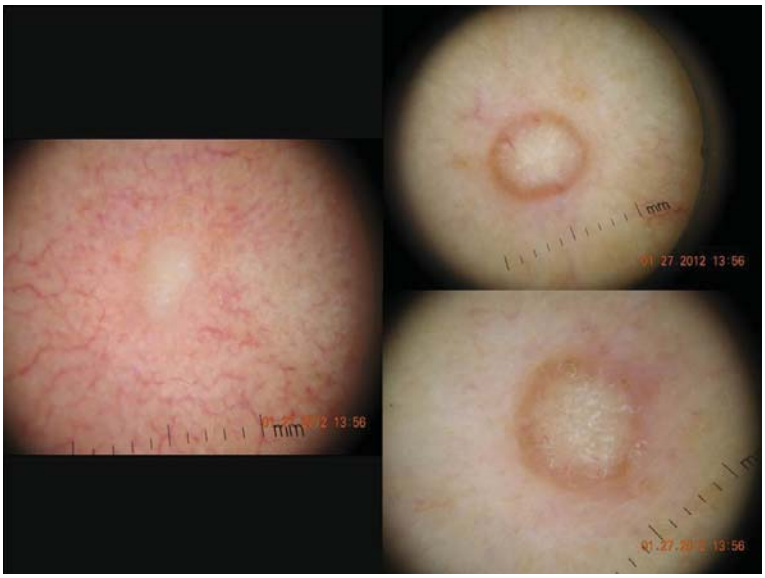

Figure 3. Dermoscopic findigs: forehead lesions showing a homogeneous yellow pattern with central white scar-like streaks (a); right and left upper arm lesions showing the same appearance with an erythematous, and a slightly brownish halo and some vessels at the periphery (b and c)

and gastrointestinal tract (7). In 15% of cases MRH was reported to be associated with autoimmune diseases: hypothyroidism, Sjögren`s syndrome, diabetes mellitus, primary biliary cirrhosis, systemic sclerosis, idiopathic inflammatory myopathy and systemic lupus erythematosus (7). Associations of MRH with various malignances have been reported in 25 - 30% of cases (8).

There are no specific laboratory tests for diagnosing MRH. Elevated erythrocyte sedimentation rate and anemia are seen in about half of all patients. About one third of patients may have hyperlipidemia. Less commonly, positive rheumatoid factor, antinuclear antibodies, cold agglutinins and cryoglobulinemia are present (1, 4). As a noninvasive diagnostic tool, dermoscopy is useful in evaluation of reticulohistiocytomas. Previously described as the "setting sun" pattern, in combination with brown reticular structures and whitish streaks, seen in xanthogranulomas and reticulohistiocytomas, it corresponds with dermoscopy findings in our patient (2, 9).

Histopathology findings often show dermal nodular infiltrates composed mainly of histiocytes dissociating collagen fibers. The infiltrates consist of multinucleated giant cells and lipid-laden histiocytes containing an eosinophilic, granular "ground glass" material inside their cytoplasm, also lymphocytes, plasma cells, eosinophils and fibroblasts. Most studies have reported immunoreactivity with CD68 and CD45, suggesting a monocyte-macrophage origin; immunoreactivity with TRAP (tartrate - resistant acid phosphatase) and cathepsin K, suggesting osteoclastic origin of multinucleated cells (7, 8). Negative staining with S-100 and CD1a support a non-Langerhans cell histiocytic origin (4), whereas negative staining with CD34 excludes dermatofibrosarcoma protuberans (10). Based only on histopahology, in most cases MRH cannot be differentiated from purely cutaneous forms of reticulohistiocytosis, in which histology shows nodules of epithelioid histiocytes, CD68 positive and generally CD1a and S100 negative (3, 4, 5, 11).

Clinical differential diagnosis includes sarcoidosis, xanthoma, xanthogranuloma, fibroxanthoma, lymphoma, lipoid proteinosis, Farber's disease, hystiocytosis X, eruptive histiocytomas. Histology is essential for accurate diagnosis (4, 5).

MRH has a tendency to spontaneously and slowly resolve after 5 - 8 years (6), leaving a variable degree of permanent joint and other involved tissue damage, depending on the course of the disease and time of appropriate treatment initiation.

There are no guidelines for the management of MRH or multiple RHs. Treatment of the primary

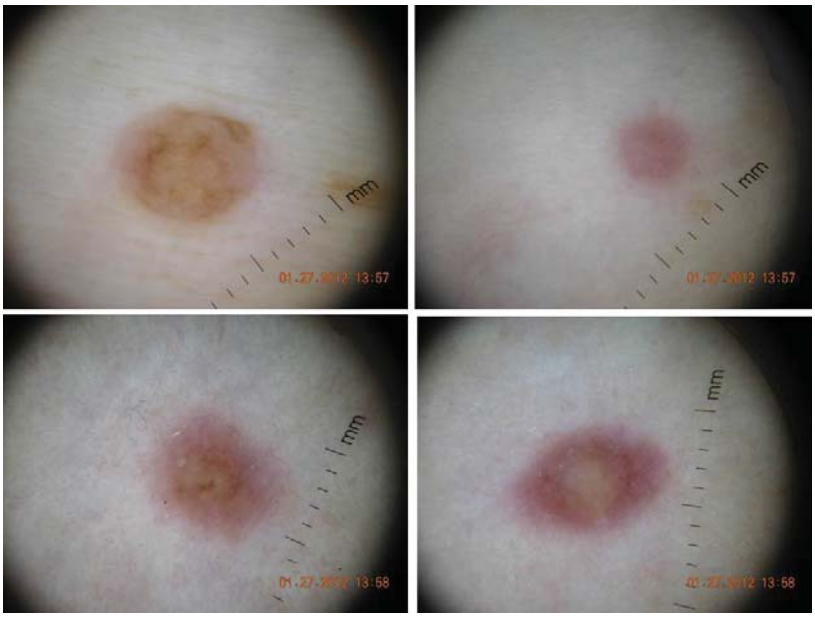

Figure 4. Dermoscopic findings: central homogeneous yellow pattern with whitish scar-like streaks and a bright to dark livid halo with brown linear and reticular structures at the periphery on four different lesions on the lower limbs (a - d).

malignancy, when associated with MRH, results in complete remission only in few cases. Successful treatment of arthritis has been reported with methotrexate, cyclophosphamide, chlorambucil, alone or in combination with systemic steroids, bisphosphonates (alendronate, zoledronate), TNF-α inhibitors (infliximab, etanercept) (4, 8, 12). Surgical excision is a therapeutic procedure for individual lesions of solitary or multiple RHs. confined to the skin (1).

Since diffuse cutaneous reticulohistiocytosis without arthropathy as well as isolated reticulohistiocytomas have been described, in some cases of multiple RHs even in the absence of systemic signs and symptoms, MRH should be considered with an appropriate follow-up. In these cases, skin lesions have the same histology as lesions in (MCH), but they are not associated with joint problems or neoplasms. In this case report reticulohistiocytosis was limited to the skin, exhibiting multiple RHs with typical clinical features, characteristic dermoscopy and rather peculiar histopathology presentation, showing features seen in early lesions of (MCH), such as multinuclear cells dissociating collagen fibers with pale eosinophilic and foamy cytoplasm. Apart from surgical excisions, no other treatment options were performed.

Conclusion

To our knowledge, this is the oldest patient reported to have developed multiple isolated reticulohisiocytomas. The follow up period for these patients has not been precisely established. Our patient was informed about the nature of his condition and he is being followed up at three month intervals.

Abbreviations

RHs - Reticulohistiocytomas
MCH - multicentric reticulohistiocytosis

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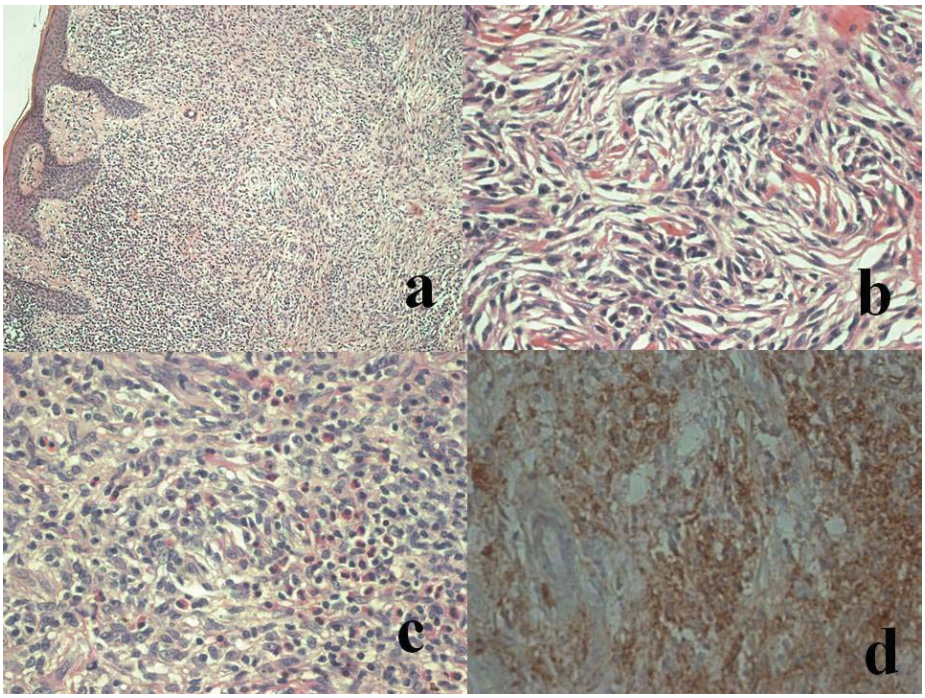

Figure 5. Histopathology of the four excised nodules exhibiting similar characteristics: preserved epidermis over the dermal infiltrate (a) (HEx100); diffuse infiltrates of histiocytes involving the whole dermis showing areas of storiform pattern (b) (HEx400); the infiltrate consisting of some lymphocytes and eosinophylic granulocytes (c) (HEx400); the staining diffusely positive with CD68 (d) (CD68x400)

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Multipli retikulohistiocitomi kod osobe stare 88 godina – prikaz slučaja

Sažetak

Uvod: Retikulohistiocitoze su poremećaji histiocita koje nisu Langerhansovog tipa, nepoznate su etiologije. Javljaju se kao izolovano oboljenje kože u vidu tumora – retikulohistiocitoma (RH), koji mogu biti solitarni ili multipli, neretko difuzno raspoređeni, kada govorimo o difuznoj retikulohistiocitozi kože.

Prikaz slučaja : Prikazujemo pacijenta starosti 88 godina, kod kojeg se javila nagla asimptomatska erupcija čvrstih papula i nodula, smeđih i boje kože, prečnika 6 – 17 mm lokalizovanih na čelu, rukama, nogama i glutealnoj regiji. Višestruke ekscizione biopsije sa histopatološkom analizom potvrdile su postavljenu dijagnozu. Nakon jednogodišnjeg praćenja, preostale kožne lezije su ostale iste veličine, a na mestima ekscizije nije bilo znakova recidiva, niti znakova progresije bolesti ili sistemskog zahvatanja.

Diskusija: Multipli RH kao multipli tumori kože uglavnom su manifestacija sistemske bolesti – multicentrične retikulohistiocitoze (MRH), koju karakteriše zahvatanje kože i erozivni artritis, najčešće distalnih interfalangealnih zglobova, ali mogu biti zahvaćeni i drugi organi i sluznice, kao što se mogu registrovati i opšte tegobe. Registrovana je udruženost MRH sa hiperlipidemijom, kod oko trećine obolelih, sa različitim malignitetima i sa autoimunim oboljenjima. Klinička diferencijalna dijagnoza multiplih RH obuhvata sarkoidozu, ksantome, ksantogranulome, fibroksantome, limfome, lipoidnu proteinozu, Farberovu bolest, eruptivne histiocitome, histiocitozu X.

Kod RH dermoskopski se opisuje obrazac „zalazećeg sunca“, u kombinaciji sa smeđim mrežastim strukturama i beličastim žiličastim strukturama, ali se radi o malom broju za sada objavljenih slučajeva.

Histološki, promene na koži u MRH predstavljene su dermalnim nodularnim infiltratima sačinjenim od multinuklearnih džinovskih ćelija i brojnih histiocita sa eozinofilnom sitno zrnastom citoplazmom izgleda „brušenog stakla“. Imunohistohemijski profil infiltrata je: CD68+ i CD45+ što govori o monocitno-makrofagnom poreklu, a S100- i CD1a- govore o histiocitima porekla ne-Langerhansovih ćelija. Negativno bojenje sa CD34 isključuje dermatofibrosarkom protuberans. U najvećem broju slučajeva, diferencijalna dijagnoza MRH u odnosu na izolovane kutane forme retikulohistiocitoza ne može biti zasnovana isključivo na histopatološkim karakteristikama. U izolovanim, solitarnim kutanim RH, nodularni infiltrati sačinjeni su od epteloidnih histiocita. Multipli kutani RH retko se javljaju izolovano, ali se i u takvim slučajevima može očekivati naknadni razvoj sistemske bolesti ; tada histološke karakteristike kožnih promena pokazuju osobine karakteristične za MRH, ali nisu udružene sa zglobnim promenama ni malignim neoplazmama.

Solitarni i multipli RH leče se hirurškom ekscizijom, dok su pozitivni rezultati u lečenju artritisa postignuti metotreksatom, ciklofosfamidom i hlorambucilom, samostalno ili u kombinaciji sa sistemskim steroidima, kao i bifosfonatima (alendronat, zoledronat) i inhibitorima TNF-α (infliksimab, etanercept). U nekim slučajevima udruženim sa malignim oboljenjima, lečenjem maligniteta dolazi do kompletne remisije MRH.

Zaključak: U svim slučajevima multiplih retikulohistiocitoma, čak i u odsustvu sistemskih znakova bolesti, neophodno je misliti na multicentričnu retikulohistiocitozu i redovno pratiti pacijenta. Autori prikazuju slučaj do sada najstarijeg pacijenta sa multiplim retikulohistiocitomima sa histološkim osobinama karakterističnim za rane lezije multicentrične retikulohistiocitoze kod koga se u toku dvogodišnjeg praćenja nije razvila sistemska bolest.

Ključne reči

Non-Langerhans histiocitoza; Dermoskopija; Histologija; Simptomi i znaci; Osobe starije od 80 godina

Pigmented Skin Tumors – Noninvasive Diagnosis and Preoperative Evaluation of Melanoma Thickness

by
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Publisher: Zadužbina Andrejević, Belgrade, 2012.

The book Pigmented Skin Tumors – Noninvasive Diagnosis and Preoperative Evaluation of Melanoma Thickness is the result of the author's successfully defended doctoral thesis entitled: "Digital Dermoscopy in the Diagnosis of Pigmented Skin Tumors – Evaluation of Different Algorithms" at the School of Medicine of the University of Belgrade in 2010. The dissertation and this monograph are the result of many years of hard work and commitment.
This is an original contribution to the diagnosis of malignant and benign skin tumors in our scientific and professional circles. It is also a serious basis for further research in this ever increasing health problem. The book has 118 pages and it presents results of independent and original research as well as useful conclusions in the science and practice. The originality of this book is that it deals with the evaluation of melanoma thickness by digital dermoscopy, whereas there are only a few studies about it in the world.
The author recommends digital dermoscopy (epiluminiscence microscopy) as a fast, inexpensive, available and reliable method in the diagnosis of pigmented skin lesions.

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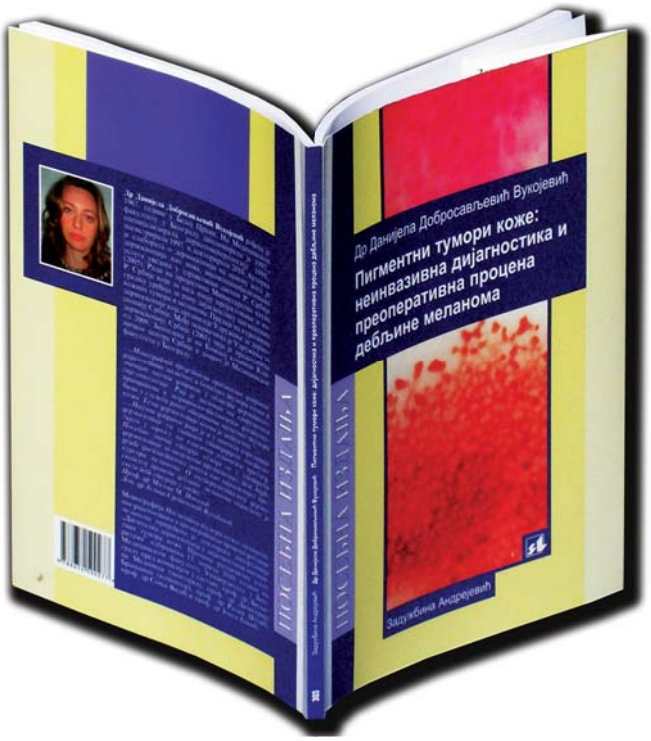

When I say: "Books, my friends, books, not bells and chimes! They rule the lands and seas and they bring wise laws! They fight, and they win!", you will remember that these are the words of Dositej Obradović. Isn't it still so?

Reading is not learning; reading is a pleasure, and learning is an effort; everybody reads, but not everybody learns (Edmondo de Amicis).

The book of Assoc. Prof. Danijela Dobrosavljević-Vukojević, an outstanding dermatovenereologist *Pigmented Skin Tumors – Noninvasive Diagnosis and Preoperative Evaluation of Melanoma Thickness* provides both – reading and enjoyment while expanding your knowledge about the most malignant human tumors today. A good book makes its way where even water cannot reach (Russian saying).

The book of Assoc. Prof. Dobrosavljević-Vukojević, skillfully written, is a wise comprehension of science. At a time when skin tumors are on a rise and threaten human life as well as malignant tumors of any other organ, non-invasive diagnosis, that is observation of skin lesions in vivo, is of utmost importance. Furthermore, unlike other organs, the skin is easily accessible, making the diagnosis of skin changes easier. However, the incidence of these changes is higher and higher, often as a result of action and reaction of genetic predispositions and environmental factors. The skin is a mirror of systemic disorders – infectious, metabolic, endocrine, hematological or immune. A great number of autoimmune diseases may manifest on the skin as a primary site, or reflect activity of the main target organ. That is why dermatologists must have a good knowledge of internal medicine as well as about numerous environmental factors which may cause skin diseases and disorders – effects of chemical agents, plants, animals, parasites, microorganisms, radiation and climate.

Skin conditions may cause depression, but psychological disorders of other origin may lead to aggravation of skin disorders. There are persons with "skin conditions", although they do not manifest on the skin. It is in fact a cry for help due to other issues: social, marital and so on.

Skin is the mirror of our health. Lao Tzu said: "One who wants to live without worries should

give up on science". Fortunately, Assoc. Prof. Dobrosavljević-Vukojević likes the science and she did her best to reveal the importance, possibilities and limitations of digital dermoscopy (the so called epiluminiscence microscopy). Not only has she done it successfully, she has done it at the time when similar studies are being performed in dermatology research units worldwide. Like any scientific study worthy of interest, this book shows advantages and disadvantages of dermoscopy compared with methods used so far, primarily histopathological diagnosis. The sensitivity and specificity of this method have been correctly estimated. An important segment of this book is assessment of histological correlates of dermoscopic structures regarding the thickness of melanomas, being among the most malignant human cancers. Unfortunately, many people still believe that melanomas should not be removed.

The major contribution of the author is analysis of recognized dermoscopic algorithms. Owing to her efforts and efforts of Prim. Dr. Jadran Bandić and associates, dermoscopy has been introduced in the health care system of the Republic of Serbia as a highly specialized service. This research and presented images are original by all means.

There are books that do not deserve to be forgotten; none of them is remembered without good reason. I assume this one will be remembered, and it will certainly not vanish into oblivion.

Assoc. Prof. Dobrosavljević-Vukojević showed that the diagnosis of pigmented skin lesions has been significantly improved by dermoscopy in only two steps. She recommends digital dermoscopy as an available, precise and fast method in the diagnosis of pigmented skin tumors. Personally, I wish her to continue her research, but also to remain a fine dermatovenereologist and never to forget that the wind always blows harder on the top of the mountain and, as players of Preferans say – the hat can easily drift off.

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Atlas of Dermatoscopy: Melanoma and Other Pigmented Skin Lesions

by
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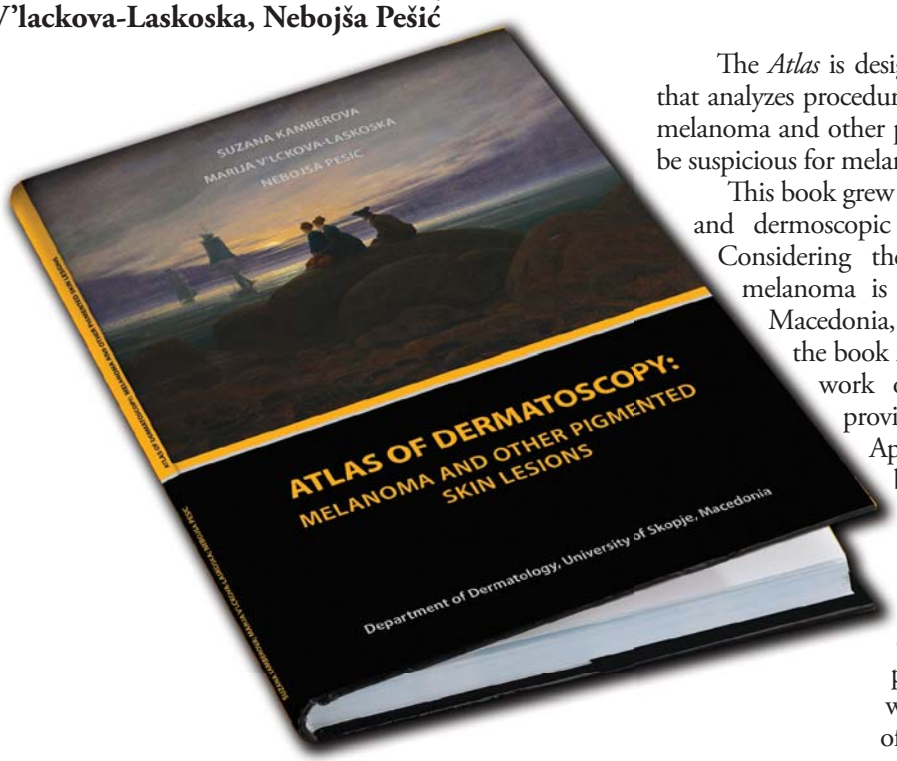

This book is an up-to-date publication of three dermatologists from Skopje, Republic of Macedonia, which comes as a result of a multiyear successful work. The *Atlas* contains 160 pages and offers a wide variety of original 450 high quality photographs. All photographs are digital microphotographs of the clinical and dermatoscopical appearance of pigmented skin lesions.

The *Atlas* is designed as a comprehensive source that analyzes procedures used in the early detection of melanoma and other pigmented skin lesions that may be suspicious for melanoma.

This book grew out of the need to clarify clinical and dermoscopic characteristics of melanomas. Considering the fact that the incidence of melanoma is increasing in the Republic of Macedonia, but also in the region of Serbia, the book is a real contribution to the daily work of dermatologists in order to provide early and accurate diagnosis. Apart from dermatologists, this book is aimed at the education of oncologists dealing with skin tumors, but also of general practitioners, because the skin is easily accessible to any routine examination for diagnostic purposes. Although the book is written in English, a large number of high quality images allows its extremely broad application.

Book address on Facebook:
https://www.facebook.com/pages/Atlas-of-dermatoscopy-melanoma-and-other-pigmented-skin-lesions/

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A Report on the 10th EADV Spring Symposium, Cracow 2013

The 10th Spring Symposium was held from 23 - 26 May, 2013 in Cracow (Poland). The main theme of the Symposium was "The Burden of Skin Diseases". This concept was not only dealing with skin diseases, but also their impact on the patients psyche and family.

Plenary Lectures were given on: links between neuroendocrinology and skin, pediatric dermatology, vitamin D deficiency, hair research, aging of the skin and economic consequences of dermatological diseases.

In the scientific program, Professor Miloš Nikolić, was the chair of the Symposium "Vasculitis: Clinico-pathological features", and held lectures "Introductions on vasculitis and vasculopathy and clinico-pathological and laboratory features of propylthiouracil-induced necrotising cutaneus vasculitis with cryoglobulins and multispecific ANCA". In the same Symposium, Danijela Dobrosavljević presented a lecture "Cutaneus vasculitis in systemic lupus erythematosus".

In the Free Communications Session on "Inflammatory diseases" Mirjana Milinković was a co-chair. On the closing ceremony of the Spring Symposium Professor Ljiljana Medenica was one of chairs in the session "What's new". Authors from Serbia had 11 E-Poster presentations.

The next Spring Symposium will be held in Belgrade (22 - 25 May, 2014.)

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Figure 1. Mirjana Milinković (Serbia) and A. Zelewska (Poland) holding a session "Inflammatory diseases"

Figure 2. Miloš Nikolić presenting his paper

Figure 3 Danijela Dobrosavljević's invitation for the next Spring Symposium which will be held in Belgrade

Figure 4 Exibiton area and the announcement of the next host of Spring Symposium

Announcement of the 11th EADV Spring Symposium, Belgrade, Serbia 22 - 25 May, 2014

Belgrade was chosen to host the EADV Spring Symposium in 2014, in Verona in 2012, and for the first time in the history of dermatology this region will host a large European and global dermatology meeting.

The EADV Spring Symposium will be held from 22 - 25 May 2014, under the motto "Tradition and Innovation".

The 2014 EADV Spring Symposium will address the following areas:

- Dermatology and internal medicine: Cutaneous signs of internal diseases (e.g. diagnostic algorithm and management of vasculitis, connective tissue disorders, granulomatous disease, skin signs of hematologic, gastrointestinal and metabolic disorders);
- Pediatric dermatology (common diseases in the newborn and early childhood period, red flags, febrile rashes, management of eczema and viral diseases);
- Nail and hair diseases (diagnosis, workup, biopsy techniques, dermoscopy, surgery);
- Sexually transmitted diseases (review of novel diagnostic tests and advances in management);
- Dermatological surgery (common pitfalls, complications, anesthesia, intermediate and advanced surgery, reconstruction techniques, flaps, Mohs surgery).

Figure 1. From left to right: Dušan Škiljević - 11th EADV Spring Symposium Secretary, Miloš Nikolić - 11th EADV Spring Symposium Vice-Chair, Ljiljana Medenica - 11th EADV Spring Symposium Chairwoman, Jana Hercogová - EADV President, Jacek Szepietowski - 10th EADV Spring Symposium Chairman, Adam Reich - 10th EADV Spring Symposium Secretary

Figure 2. From left to right: Dušan Škiljević - 11th EADV Spring Symposium Secretary, Miloš Nikolić - 11th EADV Spring Symposium Vice-Chair, Ljiljana Medenica - 11th EADV Spring Symposium Chairwoman, Jana Hercogová- EADV President, Jacek Szepietowski - 10th EADV Spring Symposium Chairman

The topics were selected by compiling our evaluation forms. These topics, which have always raised a lot of interest at our previous meetings, will be concluded with the popular *Test Yourself* and *What's New* Sessions.

The program will also include the most successful EADV courses, including dermoscopy, lasers, corrective aesthetic and cosmetic dermatology, and acne/rosacea.

According to Prof. Ljiljana M. Medenica MD, PhD, the Spring Symposium Chairwoman, the 11th EADV Spring Symposium will be completely different from the previous Spring EADV events. For the first time, the EADV Spring Symposium will be compact and focused on a selected number of important practical areas with reviews and updates.

The EADV Scientific Programming Committee, under the chairmanship of Prof. Luca Borradori, has made major efforts to select experts able to deliver lectures in a clear, concise and engaging way. The aim and challenge is simply to provide "The Best and the Latest in Dermatology and Venereology".

Belgrade, recently referred to as the "New Capital of Cool", is the cultural and administrative capital of Serbia, well-known for its lifestyle, famous restaurants, as well as its many unique floating restaurants, lively nightlife, excellent national cuisine, and numerous museums, cultural and historical heritage sites. It will be a great honor to host several distinguished experts in dermatology and venereology, motivated lecturers and participants, and do everything feasible to provide proper environment for acquiring new

knowledge, sharing ideas and promoting exchange among colleagues - dermatologists and venereologists.

The program includes the following sessions:

Thursday 22 May
The session will include the following topics: Acne, rosacea, red face: spectrum and management; Corrective esthetic and cosmetic dermatology: pitfall; Lasers; Dermoscopy: intermediate and advanced refresher course; Mycoses of the hair, nails, skin and mucosae: advances and management.

Opening Plenary Lecture will start at 17h.

Friday 23 May
The program will start with free communications, and continues with many workshops: „How to deal with children with a febrile rash", "Anatomy and dangerous zones", "Clinical evaluation and diagnosis in hair and nail diseases", "Skin manifestations of systemic diseases (hematological, rheumatological and gastrointestinal diseases)", "Infection or inflammation in anogenital skin?", "How not to miss STIs in any clinical setting", "Surgery or no surgery, that is the question!", "Hair: Clinical features and spectrum", "How to deal with the blistering neonate and child", "Granulomatous diseases: spectrum and work-up", "New tests for easier patient care in STIs", "Basic principles and pitfalls in anesthesia and tumor excision", "Hair diseases and management", "Melanocytic naevi in children: what the practitioner needs to know", "Connective tissue disease: practical and evidence-based management", "Anatomy and nail pathology: the essentials" etc.

Saturday 24 May
Workshops: How to deal with the scaly baby: from differentials to treatment; What not to do in venereology; How do I treat severe skin diseases?; Red flags in pediatric pharmacotherapy,….

Test Yourself Session will include the following topics: How would you operate?; STI; Hair and nail diseases; Skin and internal medicine; Pediatric dermatology.

What's New Session at the end of the symposium: Therapy for STIs; Hair and nails; Pediatric dermatology; Skin and internal medicine; Mohs and slow Mohs surgery.

Abstract submission deadline: January 11, 2014

Early bird registration deadline: January 22, 2014

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2013/2014

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
4-7 July, 2013	4th International Congress of Psoriasis 2013, Paris, France	15 February, 2013	www.pso2013.com
18-20 July, 2013	8th World Congress of Melanoma, Hamburg, Germany	24 March, 2013	www.worldmelanoma2013.com
21-26 July, 2013	3rd International Summer Academy of Practical Dermatology, Munich, Germany	No abstract submission	www.isa2013.com
29-31 August, 2013	34th Annual Meeting of International Society for Dermatologic Surgery, Dubrovnik, Croatia	No abstract submission	www.isdsworld.com
25-27 September, 2013	12th World Congress of Pediatric Dermatology, Madrid, Spain	01 May, 2013	www.wcpd2013.com
2-6 October, 2013	22nd EADV Congress, Istanbul, Turkey	24 April, 2013	www.eadvistanbul2013.org
18 October, 2013	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Vojvodina, Novi Sad, Serbia	No abstract submission	www.sld.org.rs
8 November, 2013	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Kragujevac, Serbia	No abstract submission	www.sld.org.rs
17-20 November, 2013	10th International Congress of the Society for Melanoma Research, Philadelphia, United States	03 July, 2013	www.melanomacongress.com
4-6 December, 2013	21st COSMODERM - Congress of the European Society of Cosmetic and Aesthetic Dermatology, Bratislava, Slovakia	No abstract submission	www.escad.org
4-7 December, 2013	11th International Congress of Dermatology, New Delhi, India	31 May, 2013	www.icddelhi2013.com
22-25 May, 2014	11th EADV Spring Symposium, Belgrade, Serbia	11 January, 2014	www.eadv.org
12-14 June, 2014	12th European Congress of the Society for Pediatric Dermatology, Kiel, Germany	Under construction	www.espd2014.com
14 June, 2014	12th Congress of the European Society for Contact Dermatitis, Barcelona, Spain	Under construction	www.escd2014.com
18-20 July, 2014	10th World Congress of the International Academy of Cosmetic Dermatology, Rio de Janeiro, Brazil	Under construction	www.iacdrio2014.com.br
3-6 September, 2014	15th World Congress on Cancers of the Skin, Edinburgh, UK	Under construction	www.wccs2014.org

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AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

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

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

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

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

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

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

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

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

1. Manuscript Preparation Guidelines

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

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

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

- A running title (limited to 30 characters);

- Authors' names and institutional affiliations;

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

1.2. Abstracts

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

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

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

1.3. A list of abbreviations

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

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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.

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

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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

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