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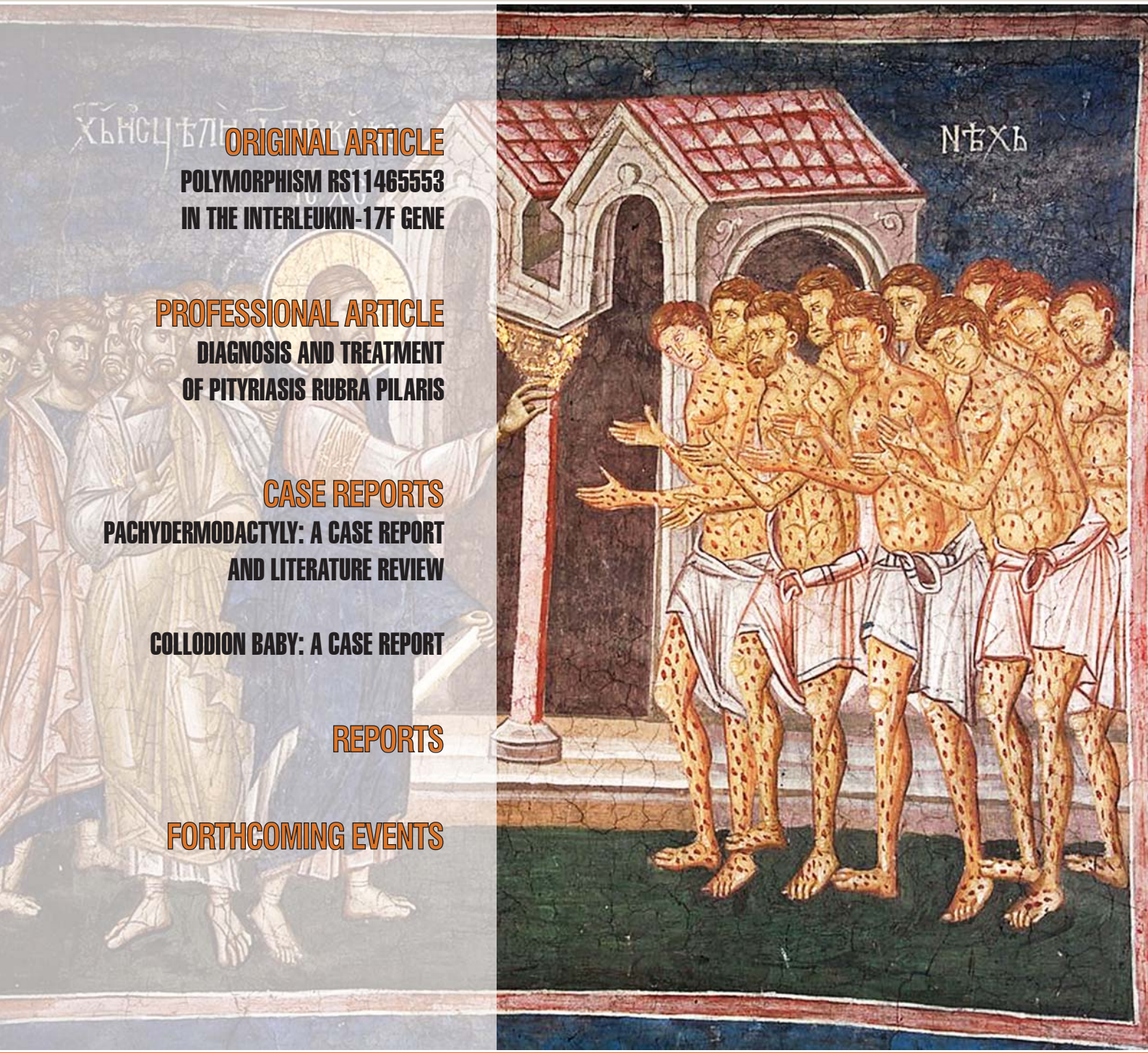

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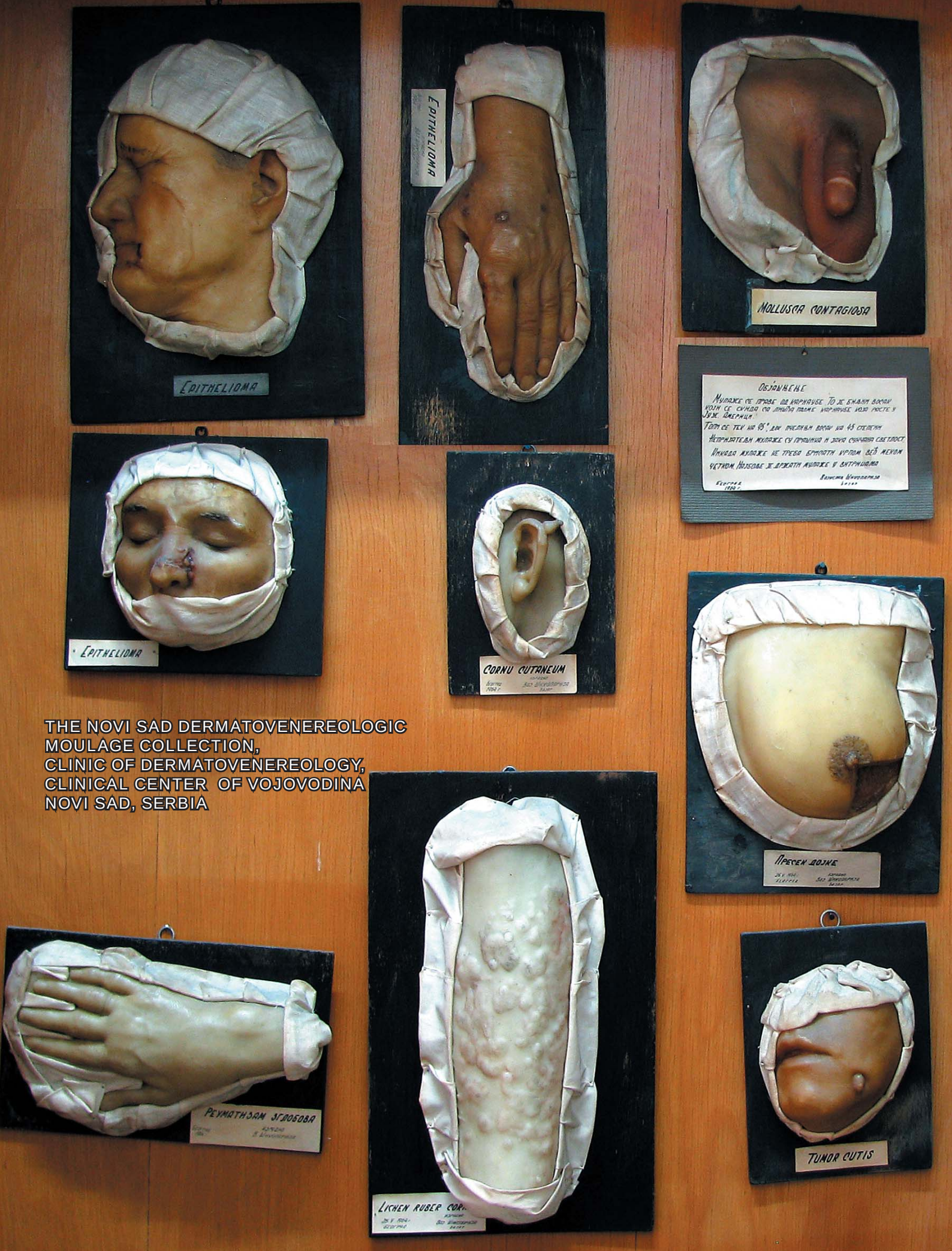

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Polymorphism rs11465553 in the Interleukin-17F Gene in Serbian Patients with Psoriasis and Healthy Controls

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Abstract

We examined single nucleotide rs11465553 polymorphism in the interleukin-17F gene causing valine to isoleucine substitution at the position 155 in the third exon of IL17F gene in Serbian patients with psoriasis and healthy blood donors. For the first time we found rs11465553 G (valine) and A (isoleucine) allele frequency in healthy Serbian population and in psoriasis patients, but without statistically significant difference between the two groups.

Key words

Interleukin-17; Polymorphism, Single Nucleotide; Psoriasis; Arthritis, Psoriatic; Blood Donors; Valine; Isoleucine; Real-Time Polymerase Chain Reaction

Psoriasis vulgaris (PsV) is a common chronic inflammatory skin disease affecting approximately 2-4% of the general population, with significant ethnic and geographic variations. Psoriasis is characterized by cutaneous inflammation and keratinocyte hyperproliferation that may be accompanied by severe complications, such as psoriatic arthritis (PsA), a debilitating inflammatory joint disease (1). Based on the time of onset, psoriasis is divided into type 1 - early onset psoriasis (disease starts before the age of 30) and type 2 – late onset psoriasis, which appears later in life (2). Type 1 psoriasis affects approximately 65% of psoriasis patients and it is usually associated with progressive course of the disease. Disease severity and activity is usually measured by Psoriasis Area and Severity Index (PASI) (3, 4).

Substantial evidence supports a central role of interleukin-17 (IL17) - producing T cells (Th17) dysregulation resulting in psoriasis (1). The recent development of biological drugs that target cytokines secreted by Th17 has confirmed the importance of this subpopulation in the initiation/maintenance of inflammatory processes in psoriatic skin and yielding potent therapies in the treatment of PsV (5). Induction of Th17 response leads to release of proinflammatory IL17 family cytokines such as IL17A and IL17F from Th17 and γδ T-cells which further influence keratinocyte activation (6). IL17F induces release of proinflammatory and neutrophil-mobilizing cytokines such as IL-6 and IL-8 (7), which enhance skin inflammatory pathways and further development of skin lesions in psoriasis (8). IL17F in psoriatic lesions is produced by neutrophils and mast cells (9).

Previous studies have shown that psoriasis belongs to so-called complex genetic diseases, in which the risk of inheriting the disease appears to be determined by interaction of multiple genes. *IL17F* is a gene located on the short arm of the chromosome 6 (6p12) and represents an interesting area in the investigation of chronic inflammation pathways. Some single nucleotide polymorphisms (SNPs) in *IL17F*,

such as rs763780 T/C which represents a substitution of histidine at position 161 to arginine in *IL17F*, are associated with ulcerous colitis, a typical Th17 disease (10), but also bronchial asthma, a typical Th2 disease (7). However, association of SNPs in *IL17F* and PsV susceptibility is still unclear due to small number of studies and insufficient data. A recent study in Japan showed that rs763780 polymorphism is not associated with an increased susceptibility to PsV (11).

Bearing in mind the important role of IL17 cytokines in psoriasis, ethnic differences, and the lack of clearly defined polymorphisms of *IL17F,* which may be considered biomarkers of PsV susceptibility, we investigated whether rs11465553 G/A polymorphism, causing valine to isoleucine substitution at the position 155 in the *IL17F,* can be used as a potential biomarker of susceptibility to PsV.

Patients and methods

The study included 130 patients with PsV treated at the Clinic of Dermatovenereology, Clinical Center of Serbia. Demographic and clinical data are given in Table 1. Patients were classified according to the time of PsV onset, while presence of PsA was confirmed by an experienced rheumatologist. Blood samples from 305 healthy blood donors were obtained from the National Blood Transfusion Institute of Serbia. Informed written consent was obtained from all individuals before blood sampling, and this study was approved by the ethics committees of the School of Medicine, University of Belgrade, Clinical Centre of Serbia and National Blood Transfusion Institute in accordance with Helsinki Declaration.

Genomic DNA was isolated from peripheral blood EDTA samples, using GeneJET whole blood genomic DNA purification mini kit (Fermentas Thermo Fisher Scientific Inc, Vilnius, Lithuania). Detection and analysis of *IL17F* polymorphism (rs11465553), was performed with commercial TaqMan genotyping assay (PE, Applied Biosystems Inc, Foster City, CA., USA.) with Maxima Probe qPCR Master Mix, (Fermentas Thermo Fisher Scientific Inc, Vilnius, Lithuania) using the RealPlex^2 (Eppendorf AG, Hamburg, Germany) under cycling conditions as recommended by manufacturer of oligonucleotide mixture.

Hardy–Weinberg equilibrium of rs11465553 *IL17F* genotypes was tested by online calculator available at http://www.oege.org/software/hwe-mr-calc.shtml. Comparison between genotype and allele frequencies in different groups was performed using the Pearson Chi-square test or Fisher's exact probability test, when applicable.

Results

Genotype frequencies were in Hardy–Weinberg equilibrium for healthy controls and patients. X^2 values were 3.15 for healthy blood donors and 0.07 for patients (<3.84 which is a threshold of significance at the level of 0.05) (Table 2), suggesting that a sufficient number of subjects were analyzed in each group, and that G and A alleles were inherited in accordance with Mendel's laws. The results of genotyping for patients with PsV and healthy controls along with p values, odds ratios and confidence intervals are presented in Table 3. The allele frequencies and genotype distribution for rs11465553 *IL17F* polymorphism

Table 1. Characteristics of 130 PsV patients

	Number	Percentage
Gender (male/female)	93/37	71.3/28.7
Type 1 psoriasis (age at onset <30 y)	62	48.1
Type 2 psoriasis (age at onset >30 y)	68	51.9
Psoriatic arthritis	26	20.2

PsV, Psoriasis vulgaris; y, years

Table 2. Hardy–Weinberg equilibrium for rs11465553 genotype frequencies

IL17F rs11465553		Controls	PsV	Total
Genotype	GG	279	124	403
	GA	24	6	30
	AA	2	0	2
Total		305	130	435
HWE		X^2= 3.15*	X^2= 0.07*	X^2= 2.91*

PsV, Psoriasis vulgaris; HWE, Hardy-Weinberg equilibrium; *not statistically significant, p>0.05 (3.84 is the X^2 threshold for statistical significance at the level p=0.05)

did not show significant difference between patients and controls, although A allele frequency was lower in patients with psoriasis and accordingly, A allele carriers, were underrepresented among patients with psoriasis. None of the 26 PsA patients was an A-allele carrier (Table 3). The frequencies of G and A alleles in subgroups of patients with early disease onset (psoriasis type 1) and late onset (psoriasis type 2) were similar, and did not reach the level of statistical significance compared to control subjects (data not shown).

When we stratified rs11465553 G and A allele carriers according to disease severity measured by PASI, we found no statistical significance between tested groups, although a trend toward higher percentage of A allele carriers (p=0.086) was observed in the group of patients with lower disease severity (Table 4).

Table 3. rs11465553 allele, genotype and carrier counts and frequencies, along with statistical analysis of patients with PsV and PsA compared to healthy controls

IL17F rs11465553		Control		PsV (total)		PsA		PsV (total) vs. controls		PsA vs. controls	
		n	f	n	f	n	f	p	OR (95% CI)	p	OR (95% CI)
Alleles	G	582	0,954	254	0,977	52	1,000	0,112	2,037 (0,83–4,98)	0,157†	NA
	A	28	0,046	6	0,023	0	0,000		0,491 (0,20–1,20)		NA
Genotypes	GG	279	0,915	124	0,954	26	1,000	0,153	1,926 (0,77–4,80)	0,151†	NA
	GA	24	0,079	6	0,046	0	0,000	0,221	0,567 (0,23–1,42)	0,237†	NA
	AA	2	0,007	0	0,000	0	0,000	0,580†	NA	1,000†	NA
Carriers	G	303	0,993	130	1,000	26	1,000	0,580†	NA	1,000†	NA
	A	26	0,085	6	0,046	0	0,000	0,153	0,519 (0,21–1,29)	0,151†	NA

PsV, psoriasis vulgaris; PsA, psoriatic arthritis; n, number; f, frequency; p, level of statistical significance; OR, odds ratio; CI confidence interval; † Fisher's exact probability test, NA, not applicable

Table 4. rs11465553 carriers classified according to PASI

IL17F rs11465553	Low PASI	Moderate PASI	Severe PASI	p
Carriers				
G (GG+GA)	12 (100.0%)	63 (100.0%)	55 (100.0%)	1,000
A (GA+AA)	2 (16.7%)	3 (4.8%)	1 (1.8%)	0,086

PASI, Psoriasis Area and Severity Index; G carrier, an individual with GG or GA genotype; A carrier, an individual with GA or AA genotype

Discussion

Our study is the first study demonstrating rs11465553 G/A allele distribution in the third exon in *IL17F* gene, (corresponding to the position 534G/A in IL17F gene transcript and leading to Val 155 Ile substitution) in Serbian patients with PsV and healthy controls. A review of the available literature shows only two papers on rs11465553 distribution of alleles and genotypes. In Saudi Arabia, there was no association between rs11465553 and asthma susceptibility (12), while in South Korean patients rs11465553 was not associated with Behçet disease, another neutrophils mediated disease (13).

The main limitation of our study is the limited number of patients, precluding more general conclusions. Although in our study the frequency of A alleles was twice higher in controls than in patients with psoriasis, a small total number of A alleles resulted in failure to demonstrate significant differences in the distribution of alleles and genotypes between PsV patients and controls. A gradual decline of A allele frequency with the increase of PsV severity was also not statistically significant. Similarly, although we could not demonstrate presence of A allele in any of 26 patients with PsA, the difference was not statistically significant. However, these data may indicate that a study involving more PsV and PsA patients is warranted to demonstrate potentially protective effect of rs11465553 A allele in PsV and PsA.

Comparing the frequency of A allele in healthy Serbian, Saudi Arabian and South Korean population, we found that A allele is more frequent in Serbian population compared to both other populations.

Despite its limitations, our study is the first study that demonstrates distribution of *IL17F* SNP rs11465553 in Serbian psoriasis patients and healthy controls. Also, our results are relevant because they represent the first report that reveals the allele and genotype distributions of rs11465553 single nucleotide polymorphism in one European population. Therefore, we believe that the results of this study will expand genetic knowledge considering the significance of *IL17F* polymorphisms in psoriasis that may prove valuable for future meta-analyses. Furthermore, this study will provide data for rs11465553 alleles and genotypes distribution in healthy Serbian population, which may facilitate studies of this SNP in patients suffering from other diseases in Serbia and neighboring countries.

Acknowledgment

This study was supported by the Fund of The Serbian Ministry of Education and Science (Grant No. 175038).

Abbreviations

PsV - psoriasis vulgaris
PsA - psoriatic arthritis
PASI - Psoriasis Area and Severity Index
Th17 - interleukin-17 (IL17) - producing T cells
6p12 - short arm of the chromosome 6
EDTA - ethylenediamine tetra-acetic acid
SNPs - single nucleotide polymorphisms
Val – valine
Ile - isoleucine

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Polimorfizam interleukina 17F gena- rs11465553 kod srpskih pacijenata sa psorijazom i zdravih osoba

Sažetak

Uvod. Novija saznanja ukazuju na značaj proinflamatornih IL-17 citokina, u prvom redu IL17A i IL17F u patogenezi psorijaze. Ispitivali smo kod pacijenata sa vulgarnom psorijazom i kod zdravih osoba (dobrovoljni davaoci krvi) u Srbiji, polimorfizam pojedinačnog nukleotida koji se nalazi na *IL-17F* genu odgovornom za sintezu interleukin 17F. Ispitivali smo *rs11465553* G/A polimorfizam koji se odnosi na supstituciju valina (G) sa izoleucinom (A) na poziciji 155 na trećem eksonu gena *IL-17F.*

Cilj ispitivanja se sastojao u određivanju učestalosti dva alela, G (valin) i A (izoleucin) ovog polimorfizma i distribucije njihovih genotipova kod pacijenata obolelih od vulgarne psorijaze i zdravih, kontrolnih osoba

Materijal imetode. Studijom je obuhvaćeno 130 pacijenta sa vulgarnom psorijazom lečenih na Klinici za dermatovenerologiju KCS i 305 zdravih davaoca krvi (materijal dobijen iz Zavoda za transfuziju krvi Srbije). DNK je izolovana iz periferne krvi a detekcija i analiza ispitivanog polimorfizma urađeni su TaqMan esejom za genotipizaciju (PE, Applied Biosystems Inc, Foster City, CA., USA.) sa Maxima Probe qPCR Master Mix-om (Fermentas Thermo Fisher Scientific Inc, Vilnius, Lithuania) pomoću RealPlex^2-a (Eppendorf AG, Hamburg, Germany), a prema preporukama proizvođača mešavine oligonukleotida.

Testirani uzorci bili su u Hardy–Weinberg ravnoteži a poređenje frekvencija alela između različitih grupa obavljano je $\chi 2$ testom ili Fišerovim testom tačne verovatnoće.

Rezultati. Urađena je analiza polimorfizma *rs11465553.* Nije ustanovljena statistički značajna razlika u frekvenciji alela kao ni u frekvenciji genotipova između pacijenata obolelih od vulgarne psorijaze i zdravih kontrolnih osoba, iako je primećeno da je frekvencija A alela bila viša kod zdravih, kontrolnih osoba u odnosu na obolele odpsorijaze..

Diskusija. Naša studija je prva studija kojim je ustanovljena distribucija G i A alela u trećem eksonu gena za IL17F kod zdravih osoba i pacijenata sa vulgarnom psorijazom u Srbiji. U poređenju sa rezultatima drugih studija u kojima je analiziran ovaj polimorfizam, ustanovljeno je da je frekvencija A alela u zdravoj populaciji Srbije češća u odnosu na frekvenciju A alela u zdravim populacijama Koreje i Saudijske Arabije.

Zaključak. Po prvi put je u Srbiji analiziran polimorfizam *rs11465553*. Rezultati naše studije predstavljaju istovremeno i prvu publikaciju u kojoj je sa aspekta polimorfizma pojedinačnih nukleotida, opisana distribucija alela i genotipova *rs11465553 polimorfizma* u jednoj evropskoj populaciji. Odgovor na pitanje da li A alel ima protektivnu ulogu u odnosu na oboljevanje od psorijaze pružiće buduća istraživanja sprovedena na većem broju obolelih.

Ključne reči

Interleukin-17; Polimorfizam pojedinačnih nukleotida; Psorijaza; Psorijatični artritis; Davaoci krvi; Valin; Izoleucin; Lančana reakcija polimeraze u stvarnom vremenu

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Diagnosis and Treatment of Pityriasis Rubra Pilaris

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616.511:615.262

Abstract

The article deals with clinical diagnosis and treatment of pityriasis rubra pilaris (PRP). The authors analyze the diagnostic errors, present literature review, and their own observations. The clinical study included 23 patients with pityriasis rubra pilaris: 18 women and 5 men, average age of 54 ± 7.2. The clinical diagnosis of all examined patients was subsequently confirmed by histological analysis of the skin. The primary clinical diagnosis was psoriasis in 15 (65.2%) patients, 6 (26%) patients received treatment for toxic exanthema, and only 2 (8.8%) patients were presumptively diagnosed with pityriasis rubra pilaris. In conclusion, pityriasis rubra pilaris was initially misdiagnosed in 91.2% of patients. Considering the great number of diagnostic errors, we analyzed the main diagnostic and differential diagnostic features of PRP. The most effective of all synthetic retinoids in PRP treatment is acitretin. Although symptomatic improvement in PRP occurs within a month, substantial improvement, even clearing is possible within 4 - 6 months.

Key words

Pityriasis Rubra Pilaris; Diagnosis; Diagnosis, Differential; Diagnostic Errors; Acitretin; Treatment Outcome

Pityriasis rubra pilaris (PRP) is a heterogeneous group of chronic skin conditions including familial forms, inherited in an autosomal dominant fashion, transplacental transmission, and sporadic acquired forms (1-4).

Introduction

Pityriasis rubra pilaris was first described by Claudius Tarral in 1828 (5). He noted isolated scaly asperities, round-shaped, in the middle of which a hair breaks through; to the touch a solid roughness is felt (1-3,5).

PRP is a rare condition which accounts for 0.03% of all skin diseases. The etiology and pathogenesis are still poorly understood, and the opinions of contemporary authors are controversial. The theory of genetic predisposition prevails. PRP affects both males and females equally. The age of disease onset has three peaks: 1st, 2nd and 6th decades. The course of the disease is chronic, sometimes it lasts for decades and it is not season related (1).

In 1980 Griffiths described 5 clinical subtypes of PRP (6): classic adult type; atypical adult type; classic juvenile type; circumscribed juvenile type, and atypical juvenile type.

In contemporary dermatology it is widely accepted that classic adult type and classic juvenile type have similar clinical features and differ only in the age of onset. Therefore, today PRP is classified into three clinical subtypes: classic type; circumscribed juvenile type, and HIV-associated type (1).

The diagnosis of PRP is difficult, especially in the initial stage, as the typical clinical picture develops slowly. It includes rash, circumscribed follicular keratoses, branny scales with perifollicular orange-red erythema, and palmoplantar keratoderma. Follicular papules are cone-shaped with typical spinulose appearance – "cones of Besnier" (2,7,8). These cones produce a "grater" effect, and the skin may feel rough to touch (Figure 1). In the literature, follicular

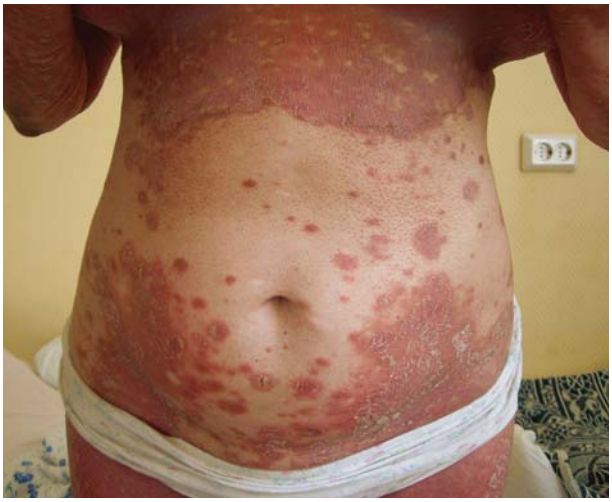

Figure 1. Pityriasis rubra pilaris (PRP)

hyperkeratosis on the dorsal aspects of the I-II finger bones is known as the "symptom of Besnier". The color of eruptions is brick-red or yellowish red, that is typical for PRP. It may have a sudden or gradual onset. PRP usually starts with erythematous patches or with a single erythematous plaque and then spreads (Figures 2, 3). The first onset is associated with erythematosquamous lesions on the face and pityriasis capitis (dandruff) on the scalp, which are accompanied by itching of different intensity and may resemble seborrheic dermatitis. Over time the clinical picture changes; the disease spreads and gradually gets features of diffuse erythroderma due to the fusion of erythematosquamous plaques; the hallmark of this condition is the presence of "islands of unaffected skin" within generalized erythroderma (Figures 4, 5). The presence of discoid-shaped islands of unaffected skin is very important for the detection of PRP and sometimes it is one of the most important distinctive features. The islands are usually one centimeter in diameter, and remain scattered over the erythema on any part of the skin. The scaling is heterogeneous: scales on the upper part of the body are small, whereas on the lower part of the body scales are mostly large, lamellar. These clinical features together with follicular hyperkeratosis on the back side of finger bones ("symptom of Besnier") are observed in 50% of cases. The palmoplantar hyperkeratosis appears

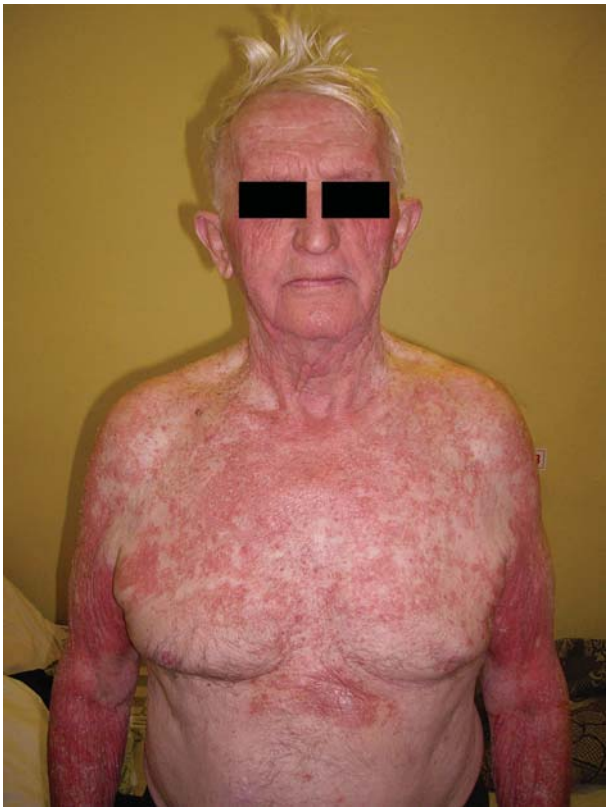

Figure 2. A 72-year-old male with PRP at the onset of disease

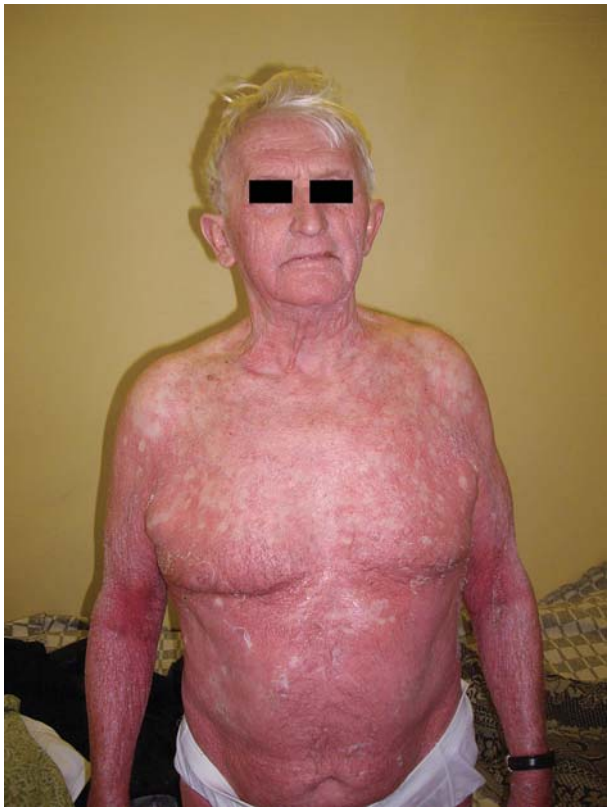

Figure 3. A 72-year-old male with PRP, 2 weeks after the onset of disease

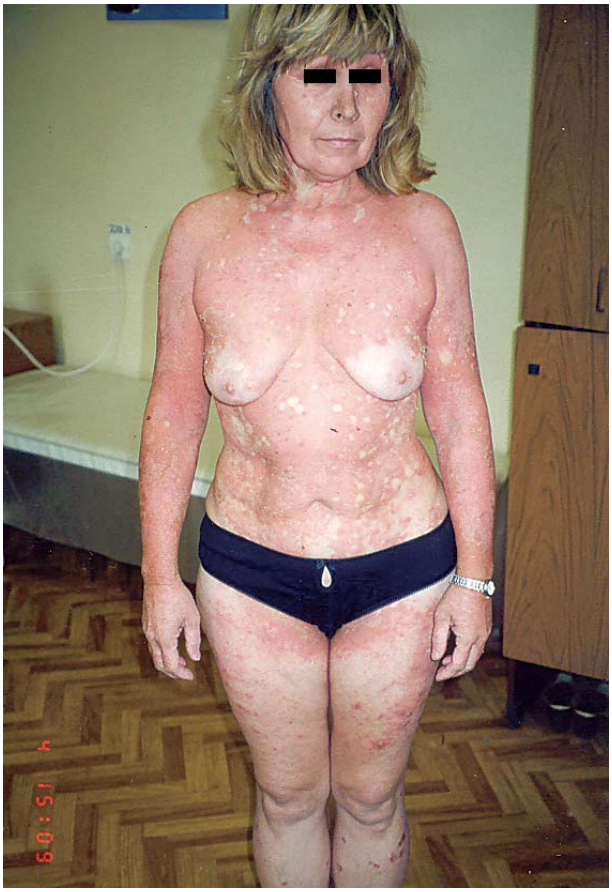

Figure 4. "The islands of unaffected skin" on the background of erythroderma in PRP

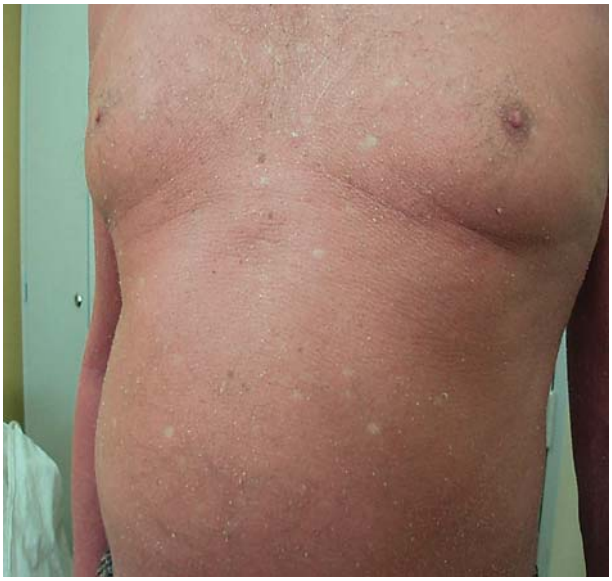

Figure 5. "The islands of unaffected skin" on the background of erythroderma in PRP

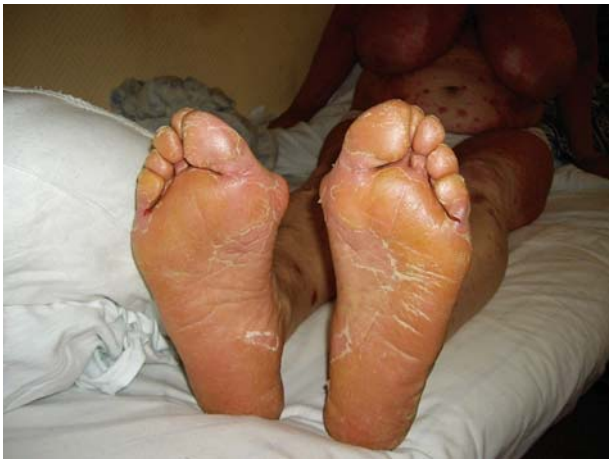

Figure 6a. The patient with PRP: plantar hyperkeratosis

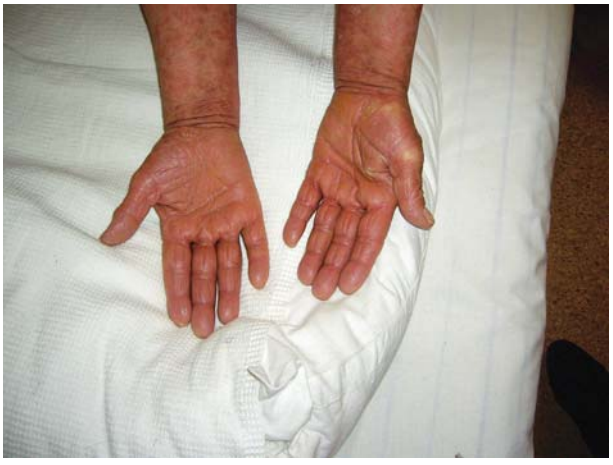

Figure 6b. The patient with PRP: palmar hyperkeratosis

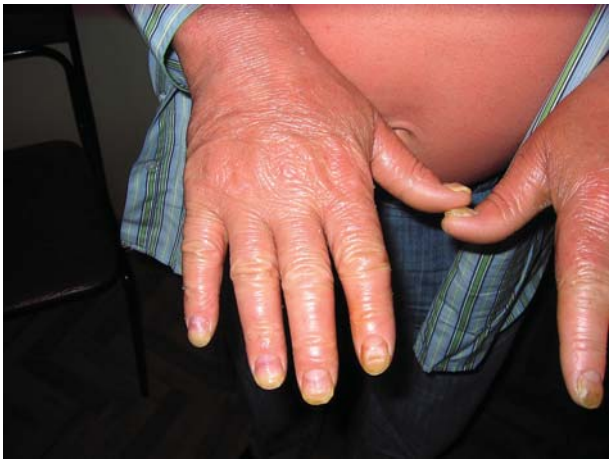

Figure 7. Regrowth of healthy nails in PRP after acitretin therapy 30 mg/aday within 4 months

simultaneously with the disease onset or later (Figure 6) (1,2,3,7).

Nail plates are frequently affected; they are yellowish in color, and striated with longitudinal or transversal sulci and subungual hyperkeratosis that appears quite often. In some cases onychogryphosis develops.

The diagnosis is based on clinical findings: perifollicular papules with a central keratotic acuminate plug, producing a "grater" effect; perifollicular erythema with a tendency to fusion; "islands of unaffected skin" within generalized erythroderma; brick-red color of the skin; palmoplantar hyperkeratosis; nail alterations; "symptom of Besnier" (1,4).

However, eruptions of PRP and diffuse erythema, in the form of exfoliative dermatitis, very often resemble psoriasis (4).

Case series

The clinical study included 23 patients with PRP: 18 women and 5 men, average age of 54 ± 7.2. The clinical diagnosis of all examined patients was confirmed by histological analysis of the skin.

The primary diagnosis was psoriasis in 15 (65.2%) patients, 6 (26%) patients received treatment for toxic exanthema, and only 2 (8.8%) patients were presumptively diagnosed with PRP. Considering the great number of diagnostic errors, we analyzed the main diagnostic and differential diagnostic features of PRP.

Firstly, the general condition was not disturbed in any of the patients with PRP and it remained the same, even in patients with diffuse lesions (Figures 1 - 5), which was in contrast with patients with psoriatic erythroderma, who complained about prodromal symptoms, subfebrile fever and fatigue. The pertinent complaints of PRP patients included the skin lesions, feeling of tightness and dryness.

In differential diagnosis of PRP, special attention was paid to typical signs of the disease - "islands of unaffected skin" (Figures 1, 5). All supervised patients had this feature. It is easy to distinguish this feature from areas of uninvolved skin in psoriatic erythroderma if we bear in mind that "islands of unaffected skin" in PRP do not exceed 1.5 cm in diameter (Figure 5), have well defined clear round ring-shaped borders, and are located within generalized erythroderma (Figure 5). In the diagnosis of PRP, the first presentation is papule with a hair in its center. However, follicular form of psoriasis should not be forgotten, when patients also present with pink papules with a hair in the center. In such cases, it is quite complicated to distinguish the two diseases, but typical psoriatic plaques affect specific locations: scalp, extensor surface of the limbs. A dynamic supervision of patients allows correct diagnosis. Psoriatic papules always have an inclination to peripheral growth and fusion due to skin infiltration, in contrast to PRP where diffuse erythroderma is formed due to an ongoing erythematosquamous process. The absence of infiltration, lichenification, and profuse lamellar scaling, essential for psoriasis, counted in favor of PRP.

In 7 patients (30.4%) the skin color was carrot-orange and 16 (69.6%) had a brick-red skin tone. However, 19 (82.6%) patients had palmoplantar hyperkeratosis, with yellow-orange color (Figures 6a and 6 b). Though 18 (78.2%) patients had nail disorders, we would like to note that this feature most likely depends on remoteness of the disease, since the rate of the nail plate growth is much slower than the pathologic process.

Our observations have confirmed that: disease duration in patients with nail disorders varied from 4 to 10 months. Nail plate changes were characterized by subungual hyperkeratosis, discoloration, and longitudinal or transverse striations (Figure 7). However, none of the patients had onycholysis, typical for psoriasis.

After the diagnosis was established and hystopathologically confirmed, acitretin was initiated at a dose of 0.5 - 0.7 mg/kg/day. Therapy analysis of PRP patients revealed that the most frequent side-effects were present in all 23 patients including dry lips, cheilitis (particularly angular cheilitis), skin dryness with skin exfoliation and xerostomia (n=23; 100%); alopecia (n=12; 52%); thirst and dry mouth (n=5; 21.7%); less common were intolerance to contact lenses in 3 patients (13%), conjunctivitis and stomatitis, each in 2 patients (8.6%), nosebleed, rhinitis and change in taste sense, each in 1 patient (4.3%).

The medium duration of treatment was 9 months, whereas the nail condition improved faster than the skin condition (Figure 7).

Disscusion

As it has already been mentioned above, PRP was initially misdiagnosed in 91.2% of patients. Most of them were treated with antihistamines. In 15 patients (65.2%) prolonged therapy with systemic steroids was commenced, without any improvement. This fact confirms once more that PRP is resistant to usual therapy.

Summarizing the aforesaid, we can outline the main differential and diagnostic features which distinguish pityriasis rubra pilaris from psoriasis:

- the general health of PRP patients remained good in contrast to psoriatic, even if their skin was diffusely affected;
- "islands of unaffected skin" was a typical feature;
- the primary lesion presents with plaques and follicular involvement;
- brick-red or carrot-orange color of the skin;
- the absence of infiltration, lichenification, and profuse lamellar scaling which are essential for psoriasis;
- the absence of onycholysis which is typical for psoriasis;
- palmoplantar hyperkeratosis, yellow-orange in color, without infiltration;
- ineffective, antihistaminic and hormonal treatment.

Today, retinoids appear to affect the processes of keratinization. In 1930, Moore first synthesized retinol from carotenoid and began studying its systemic action (9). The most effective of all synthetic retinoids in PRP treatment is acitretin at a dose of 1.0 - 1.5 mg/kg/day. The average daily dose varies between 25 - 50 mg per day (1-3,7,10). However, one should not count on fast clinical effects in the treatment of PRP, especially in adults. Our opinion coincides with the opinion of other authors that symptomatic improvement in PRP occurs within a month, but substantial improvement, even clearing is possible within 4 - 6 months (1-3, 7, 10). According to some data the average length of treatment is about 4 years (1). In our PRP patients the medium duration of treatment was 9 months, and the nail condition improved faster than the skin condition (Figure 7).

Acitretin is known to have strong teratogenic effects. The risk for birth defects is very high, especially if acitretin is taken before or during pregnancy, no matter for how long or at what dosage. Acitretin is a US FDA Pregnancy Category X medication that should not be administered during pregnancy and 3 years after discontinuation (11).

It is well known that the majority of patients receiving acitretin have side-effects. These side-effects usually disappear after dose reduction or drug withdrawal (1, 10, 12). It is significant that aggravation of symptoms is usually observed at the beginning of the disease.

Liver function tests need to be performed before the initiation of acitretin, every 1 - 2 weeks within the first month, and then every 3 months during maintenance therapy. During treatment with high doses of acitretin, reversible triglyceride and cholesterol elevation is possible, especially in patients with lipid disorders, diabetes, obesity, or alcohol abuse (12, 13). If hepatic function fails to return to normal, acitretin should be widthrown. In such cases, it is advisable to continue monitoring the hepatic function for at least three months. In diabetic patients retinoids can alter glucose tolerance, therefore in the early stages of treatment blood sugar levels should be checked more often than usual. There are a few articles about the appearance of diffuse oedema during acitretin therapy (14).

According to some authors, methotrexate (MTX) may be an alternative therapy at a dose of 15 - 25 mg/week. In a recent report it has been observed that adding MTX (5–30 mg/week) to oral retinoids during 16 weeks increased the positive therapeutic response by more than 50% in 8 of 11 patients, but the combination may lead to increased hepatotoxicity (1, 15).

Although regarded only as adjuvant, topical treatment during retinoid therapy significantly improves the general state of patients and their quality of life. Moisturizing creams, ointments with salicylic acid 2 - 5%, urea 10%, malic acid 1 - 20% should be prescribed in the treatment of palmoplantar hyperkeratosis.

The use of ultraviolet irradiation is inadvisable in PRP patients (1,16). According to our observations, all examined patients had acute exacerbation after ultraviolet irradiation or insolation. In severe cases, antagonists of tumor necrosis factor-alpha are an effective treatment option (17) .

Conclusion

Recent scientific discoveries have greatly improved the understanding of clinical and genetic polymorphism of hereditary skin diseases; knowledge in pathomorphology and immunomorphology has significantly advanced and in turn increased the possibility of accurate diagnosis of PRP. The use of synthetic retinoids has increased treatment efficiency in these patients. However, the treatment of PRP is long and challenging due to side-effects, contraindications in elderly people and in patients with a disease burden.

Abbreviations

PRP - pityriasis rubra pilaris
HIV - human immunodeficiecy virus
US FDA – United States Food and Druf Agency
MTX - methotrexate

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Dijagnoza i lečenje pitirijaze rubra pilaris – prikaz serije slučajeva

Sažetak

Uvod i cilj. U radu autori na osnovu podataka iz literature i sopstvenog iskustva, analiziraju klinički zasnovane kriterijume za postavljanje dijagnoze i lečenje pitirijaze rubra pilaris (PRP), ističu moguće greške, odnosno izazove u postavljanju dijagnoze ove heterogene grupe dermatoza.

Serija slučajeva. U radu su analizirane 23 osobe kod kojih je postavljena klinička dijagnoza. Ukupno je bilo 18 žena i 5 muškaraca, prosečna starost iznosila je 54 ± 7,2 godine. Klinička dijagnoza je kod svakog pacijenta potvrđena patohistološkom analizom isečka uzetog sa promenjene kože. Prvobitno je postavljena dijagnoza psorijaze kod 15 (65,2%) pacijenata, 6 (26%) je lečeno pod dijagnozom toksičnog egzantema, a samo je kod 2 (8,8%) postavljena dijagnoza pitirijaze rubre pilaris. U 91,2% slučaja, postavljena je pogrešna dijagnoza.

Diskusija. Uzimajući u obzir brojne izazove i učinjene greške, analizirani su glavni dijagnostički i diferencijalno-dijagnostički kriterijumi, što je autorima omogućilo da razlikuju pitirijazu rubra

pilaris od psorijaze:

- Dobro opšte stanje kod pacijenata sa PRP koje za razliku od obolelih od psorijaze ostaje nepromenjeno čak iako je koža difuzno zahvaćena eritrodermijom;
- Tipično za PRP je zaostajanje ostrvaca klinički nepromenjene kože;
- Primarnu leziju PRP predstavlja papula iz čijeg centra izrasta dlaka;
- Oranž boja kože u PRP poredi se sa bojom cigle, odnosno mrkve;
- Odsustvo infiltrata, lihenifikacije, velikih lamelarnih skvama u PRP, koji su svi ključni za postavljanje dijagnoze psorijaze;
- Odsustvo u PRP oniholize, koja je tipična za psorijazu;
- Palmoplantarna hiperkeratoza u PRP pokazuje karakterističnu žućkastooranž boju i odsustvo infiltracije;
- Hormonska terapija u PRP, u prvom redu kortikosteroidima ostaje bez željenog efekta.

Analizom postignutih terapijskih rezultata, u grupi sintetskih retinoida najveću efikasnost ispoljio je acitretin. Iako je simptomatsko poboljšanje nastupalo unutar prvih mesec dana, do značajnijeg poboljšanja ili izlečenja dolazilo je tek nakon ~~4,6~~ 4-6 meseci.

Zaključak. Za postavanje dijagnoze pitirijaze rubra pilaris značajnu ulogu ima dobro poznavanje kliničkih osobina oboljenja, dok za postizanje punog terapijskog efekta retinoidima treba ostaviti duže vreme – čak i više meseci.

Ključne reči

Pityriasis Rubra Pilaris; Dijagnoza; Diferencijalna dijagnoza; Dijagnostičke greške; Acitretin; Ishod terapije

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Pachydermodactyly: a Case Report and Literature Review

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Abstract

Pachydermodactyly is a rare, benign form of digital fibromatosis, characterized by asymptomatic and progressive, periarticular and usually symmetrical soft tissue finger swelling, specifically on the lateral aspects of the proximal interphalangeal joints mainly of the second, third, and fourth fingers; it mostly affects young adolescents and is probably due to repeated mechanical injury of the skin (such as repeated clasping or rubbing of crossed fingers), sometimes as a result of obsessive-compulsive disorder, which must be distinguished from obsessive "chewing pads". This paper presents a male patient aged 19, who presented with first symptoms at the age of 12, and was diagnosed with periarticular hypertrophy: localized soft tissue thickening around the proximal interphalangeal joints of all fingers except the thumbs; slight hypertrophy of the skin; absence of subjective complaints; normal joint function. Dermatological status on admission revealed: symmetrical soft tissue swelling of all fingers of both hands except the thumbs at the level of the proximal interphalangeal joints; normal appearance of the distal parts of all fingers; thickening at the level of the proximal interphalangeal joints, bilateral, almost symmetrical hypertrophy (ulnar and radial) of phalanges of the affected fingers except both index fingers, affecting only the ulnar side. The skin lesions were pain-free on palpation, with homogeneous texture and elastic consistency, freely movable over underlying structures. The affected joints showed no functional deficit. The test results, sonography, radiography and histopathology confirmed our clinical diagnosis - pachydermodactyly. The review of the currently available literature, published between 1973 and 2014, including 99 papers and 160 patients, provided important insight into the characteristics and variations of the disease.

Key words

Fibroma; Hand Dermatoses; Hand Deformities; Fingers; Soft Tissue Neoplasms; Cumulative Trauma Disorders

Pachydermodactyly (PDD) is a benign digital fibromatosis characterized by asymptomatic and progressive, periarticular and usually symmetrical soft tissue finger swelling, specifically on the lateral aspects of the proximal interphalangeal joints mainly of the second, third, and fourth fingers: thus, it produces a symmetrical, diffuse swelling of the skin around the dorsal and lateral aspects of the proximal phalanges of the index, ring and middle fingers (1).

It particularly affects young adolescents and is probably due to repeated mechanical skin injury, sometimes as a result of obsessive-compulsive disorder, which must be distinguished from obsessive "chewing pads" (1, 2, 3). Diffuse swelling of the digits, which includes the dermis as well as epidermis, clearly distinguishes PDD from "knuckle pads", calluses, occupational callosities, etc. Affected families have been reported, and pachydermodactyly and knuckle pads may coexist (1).

Pachydermodactyly was first described by Bazex et al. in 1973 as "pachydermie digitale" (4). Verbov named this entity as pachydermodactyly from the Greek pachy (thick), dermo (skin), and dactyly (finger) in 1975 (5).

Case Report

This paper presents a male student aged 19, who developed thickening of the third and fourth fingers of the left hand at the age of 12. By the age of 14, he presented with the same changes on all fingers except the thumbs, and since then the condition has not changed. He associated these changes with hitting the ball, as well as with the habit of repeated clasping or rubbing the fingers. After he underwent evaluation by an orthopedist, physiatrist and rheumatologist, he was referred to our Clinic with the diagnosis of periarticular arthropathy in order to exclude psoriasis and/or seborrheic scalp dermatitis. On admission, the patient denied any other disease or a family history.

On admission, the patient's general condition was good. Dermatological examination revealed: symmetrical soft tissue swelling of all fingers of both hands except the thumbs at the level of the proximal interphalangeal joints; normal appearance of the distal parts of all fingers; thickening at the level of the proximal interphalangeal joints, bilateral, almost symmetrical hypertrophy (ulnar and radial) of phalanges of the affected fingers except both index fingers, affecting only the ulnar side (Figure 1). The skin lesions were pain-free on palpation, with homogeneous texture and elastic consistency, freely movable over underlying structures. The affected joints showed no functional deficit.

Laboratory and other test results

All relevant laboratory test results were within reference values, including factors of inflammation, serum levels of immunoglobulins, C3 and C4 complement components, presence of antinuclear antibodies and immunoglobulins.

Ultrasonography of the hand joints: osteoarticular surfaces without signs of defects; there are no periarticular focal lesions, except for imbibition of the soft tissues; synovial thickening of the medial interphalangeal joints; intra-articular synovial fluid volume is increased.

X-rays of the hands (both directions) did not reveal any involvement of the bones structures (Figure 2).

Histopathological findings: severe epidermal hyperkeratosis and acanthosis; dermoepidermal junction is flat; dermis is thickened and hypocellular,

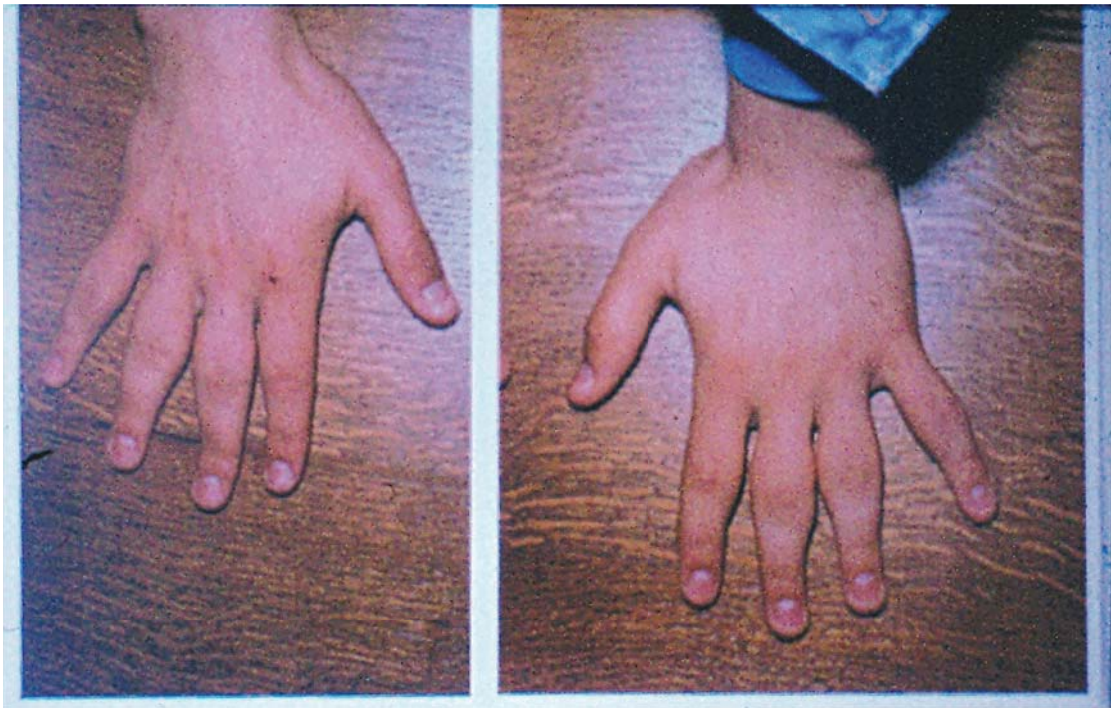

Figure 1. A symmetrical, diffuse swelling around both lateral (ulnar and radial) aspects of the proximal phalanges of the small, ring and middle fingers; proximal phalanges of both index fingers affected only around the ulnar aspects; distal parts without involvement

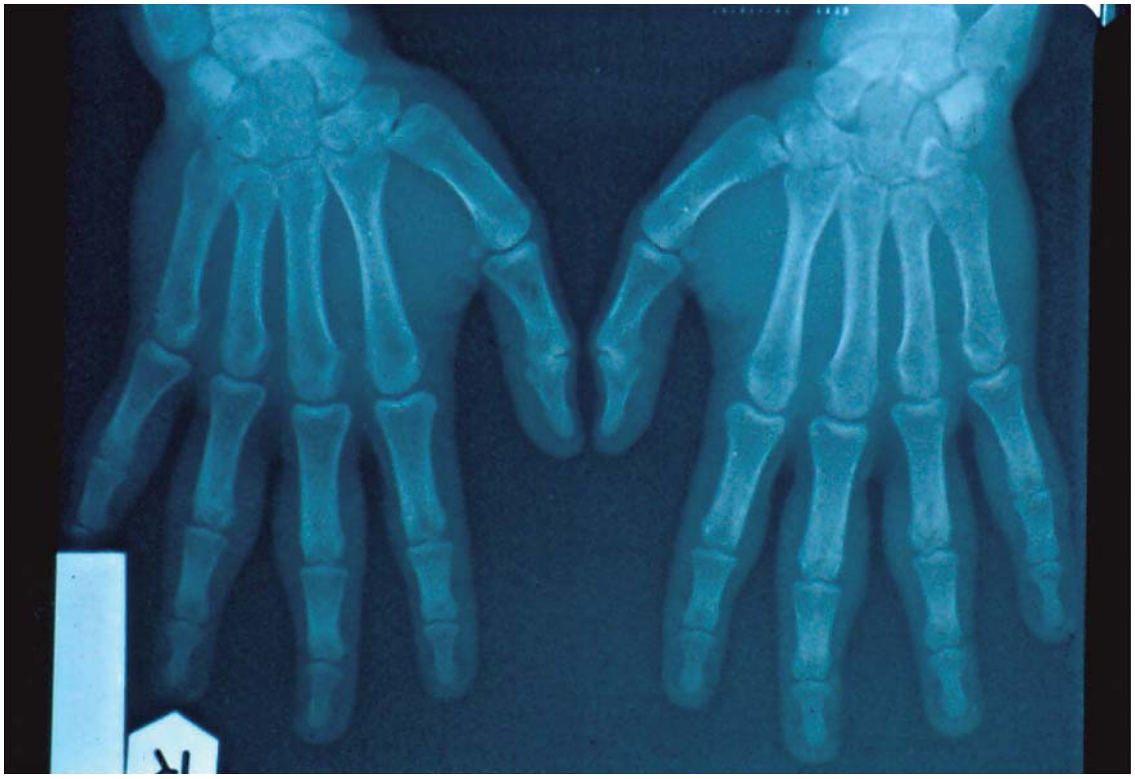

Figure 2. Hand x-ray: preserved bone structure

rare fibroblasts accompanied by hyalinized collagenous stroma; absence of adnexal skin structures.

Therapy

Intralesional triamcinolone solution injections during three months resulted in slight reduction of swelling of the treated finger. The patient was advised to avoid mechanical trauma, rubbing and cracking of the fingers.

Discussion and literature review

Pachydermodactyly is a condition which mostly occurs in adolescents and is characterized by asymptomatic soft tissue swelling, specifically on the lateral aspect of the proximal interphalangeal (PIP) joints of the hands, and skin lesions. Its diagnosis and treatment requires expertise of various health professionals (rheumatologists, orthopedic surgeons, pediatricians, dermatologists, surgeons). Papers on PDD are published in journals that are not exclusively focused on dermatology, probably because patients with PDD require a multidisciplinary approach (Table 1). Two papers represent a comprehensive analysis of previously published papers: the first published in 2009 by Beltraminelli et al. (2), and the second published in 2014 by Dallos et al. (3). The first paper analyzed 55 papers including 88 patients, while the other included 17 more papers, with a total of 121 patients reported until then. Our research found 27 more papers (41, 46, 48, 49, 54, 55, 57, 59, 62, 69, 70, 73, 74, 78, 79, 83, 85, 86, 88, 89, 92, 93, 95-98, 100) including 39 patients. So, since Bazex and associates to date, at least 99 papers including 160 patients have been published on PDD. Our case report is the 100rd, and our patient the 161st. These papers are listed in the references, mostly in order of publication, except for authors from the beginning of this paper.

The characteristic features of the disease, described in certain number of patients, are shown in Table 2, based on the table of Dallos et al. (3). Although PDD may be considered a rare condition, one must not neglect clinical features that are at the same time factors responsible for not recognizing the disease (62), such as the absence of subjective symptoms, self limiting course, regression during adolescence, absence of permanent sequelae. For this

Table 1. Types of journals reporting patients with pachydermodactyly

Journal	No. of reports	References
Dermatology	60	2, 4-62
Rheumatology	18	3, 63-79
Surgical	4	80-83
Pediatric	6	84-89
Orthopedic	3	90-92
Other	8	93-100
Total	99	2-100

reason, the actual prevalence of PDD is estimated to be much higher (2, 3).

The disease commonly affects boys around puberty, as in our patient (2, 44, 76); PDD at older age may be due to non-recognition of the disease (3). The medical literature describes two cases of PDD since birth (13, 27), and only four cases in the elderly (36). The condition occurs sporadically, but familial cases have also been reported (8, 21, 24, 36, 42, 93), and in three cases it was a transgradient form of PDD (14, 19, 36).

The exact etiology of pachydermodactyly is unknown; it may include genetic predisposition, probably essential, associated with precipitating factors (3). It is probably due to repeated mechanical injury such as tics, stretching, rubbing or cracking of the fingers, both in healthy or people with obsessive-compulsive disorders (19, 20, 26, 35, 38 , 39, 47, 51, 62, 84, 85, 96). PDD may occur due to repeated mechanical trauma in poultry processing workers, farm workers, those whose work is computer-related (52, 56, 58, 77); in athletes (football, handball, fencing) (61, 71), or musicians playing the guitar or flute (69); excessive use of computers by adolescent boys also contributes to appearance of PDD (53, 76). However, there are reports on patients with PDD unpreceded by friction or trauma (8, 10, 49, 74, 100). PDD is significantly more common in boys at the beginning of puberty compared to females and older children, supporting the role of androgen hormones in its pathogenesis; the possible impact of the growth hormone and hypothyroid function should not be excluded (3).

Due to frequent occurrence of PDD in persons with obsessive compulsive and neurological disorders, there are authors who think that PDD should be on the list of skin manifestations of psychological problems (2, 26, 51). Our patient presented with a habit of rubbing and cracking of fingers, but had no psychological disorders.

Although a typical clinical picture includes benign asymptomatic soft tissue thickening on the lateral (ulnar and radial) proximal interphalangeal joints of the II, III and IV fingers of both hands, there are deviations, as in our patient whose both little fingers were affected, as well as the ulnar sides of both index fingers. Dorsal and/or ventral sides of fingers can also be affected (23, 29, 31, 94). Distal involvement has also been described affecting distal phalanges (37, 42, 45), as well as metacarpophalangeal joints (16, 40), with fibromatous thickening or rigid nodes (83). These lesions are usually symmetrical (88), but may be asymmetrical to a certain point, varying in the number and extent of affected joints on the left and right hand (76, 97) or affecting only some joints, the so-called localized form of PDD (13). There are reports on the monoarticular form of PDD (32, 65). The thumbs and fifth fingers are rarely

Tabela 2. Reported patients with pachydermodactyly

Reference	Dallos T, et al. (3)	Current review
Demographic data		
No. of patients	n=121	n=31
male/female	(79)/(21)	26 (84)/5 (16)
Disease characteristics		
No. of patients	n=121	n=22
Disease onset: median age (y) (range)	14 (5-74)	13 (4-20)
Course of disease: median (y) (range)	2.5 (0.25-15)	3.5 (1-12)
Clinical signs and symptoms		
No. of patients	n=121	n=22
Thickening: n (%)	121 (100)	31 (100%)
Restriction of movement (n (%)	(2.5)	0 (0)
Subjective complaints: n (%)	(5)	0 (0)
Itching: n (%)	(2.5)	0 (0)
Pain: n (%)	NA	0 (0)
Etiology		
No. of patients	n=121	n=31
Identified mechanical injury: n (%)	(44)	12 (39)
Psychological and/or psychiatric diseases: n (%)	(15)	8 (26)
Positive family history: n (%)	(5)	0 (0)

n, number of patients; y, year; NA, not available

affected (6, 8, 21, 50, 80, 99). Toes are never affected, whereas plantar pachydermia was described in a patient with PDD and acrocyanosis (39). Sometimes the skin shows lichenification, fine desquamation or hyperkeratosis, even moderate erythematosis (27), but it is rarely painful (9, 10, 17). No cases with hypersensitivity, itching, burning, morning stiffness or reduced mobility have been reported (3, 48, 73, 91). Only one case of deforming PDD was reported with nonerosive interphalangeal joint subluxation

(72). Our patient presented with involvement of both lateral aspects, ulnar and radial parts of the proximal interphalangeal joints and proximal phalanges of the II, III, IV and V fingers of both hands, except the index fingers, where only ulnar sides were affected. The skin surface was slightly hyperkeratotic. He had no pain or functional limitations.

Pachydermodactyly has been described in association with Dupuytren's contracture (90), Asperger syndrome (38), Ehlers-Danlos syndrome (33), carpal tunnel syndrome and tuberous sclerosis (13, 33, 36), gynecomastia (10), foot syndactyly (2), acute atrophia maculosa varioliformis (25), and Tourette's syndrome (59).

Due to the heterogeneous clinical picture and described familial cases, a classification with five different forms was proposed (36):

1. classical pachydermodactyly (several proximal interphalangeal (PIP) joints affected, frequently associated with mechanical trauma)

2. localized (one joint affected - mono-pachydermodactyly)

3. transgrediens pachydermodactyly (extension to the palms or metacarpophalangeal joints)

4. familial pachydermodactyly (affecting several family members)

5. pachydermodactyly associated with tuberous sclerosis.

Diagnosis

Laboratory findings show no specific changes. Plain radiography shows soft tissue thickening, without bone, tendon or capsular changes such as periostosis, periarticular osteoporosis, erosions, cysts or osteophytes (3, 55). Magnetic resonance imaging reveals only soft tissue swelling, and typical fusiform swelling (without effusion, synovitis, tendonitis, hypervascularization and without bone involvement) (53, 57, 68, 70, 71).

Histologically, there is hyperkeratosis, acanthosis, thickening of the dermis, increase in fibroblasts and collagen deposits; increase in the thickness of basal membrane and of eccrine sudoriparous glands, intense deposition of mucopolysaccharides, poor demarcation between the papillary and reticular dermis, mucin deposition between collagen fibers (7, 11, 30, 34, 43, 53, 60, 70, 82, 83, 90, 95, 96). Types III and V collagen are increased with a reduction of collagen type I. Electron microscopy shows an increased number of fine-diameter collagen fibers (21, 30, 34, 36), less uniform (12, 64). Some authors believe that histology is not mandatory for diagnosis (55), as well as many useless and expensive diagnostic tests (54, 89).

Chen and associates (99) proposed the following diagnostic criteria:

- the patient has no symptoms
- morning stiffness is absent
- pain on motion and tenderness to palpation is absent
- finger swelling is radial or ulnar in location, rather than circumferential
- laboratory test results are unremarkable
- plain radiographs show only soft tissue swelling.

With these typical findings, additional investigations, such as MRI or skin biopsy, are rarely needed to establish a diagnosis of PDD.

It is of great importance to distinguish PDD from other diseases of this localization. Differential diagnosis should include: rheumatic diseases, primarily juvenile idiopathic arthritis, rheumatoid arthritis, rheumatoid nodules; bone diseases such as secondary pachydermoperiostosis, ostitis cystoides multiplex Jüngling, spina ventosa; skin diseases, often knuckle pads with circumscribed keratoses that overly the finger joints with highly hyperkeratotic epidermis and hyperplastic dermal connective tissue, pseudo knuckle pads, foreign-body granulomas, collagenous plaques of the hands, infantile or juvenile digital fibromatosis, progressive nodular skin fibrosis, psoriatic acropachydermodactyly, connective tissue nevi; endocrine disorders, thyroid acropachy, acromegaly; tumors, primarily fibromas, sarcomas, paraneoplastic acropachydermodactyly; hereditary diseases, such as tuberous sclerosis, primary pachydermoperiostosis, Thiemann disease (3, 41, 55, 66, 67). PDD is commonly misdiagnosed as a rheumatologic condition (100), namely juvenile idiopathic arthritis (63, 69, 70, 78, 89, 86), which may lead to unnecessary treatment (78). Pereira and associates discussed similarities (mechanical irritation, favorable effects of intralesional triamcinolone injections) and differences (epidermal and dermal response) between knuckle pads and PDD (41).

Treatment

There is no effective medical treatment for PDD at this time (2, 25). Surgical excision of fibrous tissues may be a good therapeutic option (3, 46, 80) without recurrence (75). Good results are obtained using intralesional triamcinolone injections (10, 22, 100), while topical therapy with corticosteroids is mostly ineffective. Higuchi reported good therapeutic results after using tranilast, an anti-allergy agent which inhibits collagen synthesis in human skin fibroblasts (300 mg daily for 6 months) (92). Elimination of mechanical irritation may lead to spontaneous regression (2, 15, 18, 20, 71, 81, 91, 99). Patients with PDD should avoid mechanical irritation, receive adequate care and monitoring, whereas invasive procedures are not recommended (3, 74). Protective gloves and bandages are proposed to prevent mechanical irritation (44). Patients with obsessive compulsive disorders may need psychiatric help.

Pachydermodactyly is a benign condition with a chronic course. The prognosis is variable. After long-term progression, regression may occur at a later age (97).

Conclusion

We report a case of a male patient who developed symptoms of pachydermodactyly around puberty as a progressive soft tissue thickening around the proximal interphalangeal joints of all fingers except the thumbs probably due to stretching, rubbing or cracking of the fingers. There was no family history. Intralesional triamcinolone solution injections during three months resulted in slight reduction of swelling of the treated finger. The patient was advised to avoid mechanical trauma, rubbing and cracking of the fingers. A review of the available literature from 1973 to 2014 provided important insight into the characteristics and variations of the disease.

Abbreviations

PDD - pachydermodactyly
PIP - proximal interphalangeal
MRI - Magnetic resonance imaging

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Pahidermodaktilija – prikaz slučaja i pregled literature

Sažetak

Uvod. Pahidemodaktilija (PDD) je benigna digitalna fibromatoza za koju je karakteristično asimptomatsko progresivno lateralno zadebljanje periartikularnog mekog tkiva, obično simetrično lokalizovanog oko proksimalnih interfalangealnih zglobova (PIP) drugog, trećeg i četvrtog prsta ruku: tako dolazi do simetričnog, oticanja kože dorzalnih i lateralnih strana proksimalnih falangi kažiprsta, srednjeg prsta i domalog prsta. Najčešće se javlja kod mladih adolescenata i verovatno je posledica ponovljene mehaničke stimulacije; nekad se javlja i kao posledica opsesivno-kompulzivnog poremećaja, ali se mora razlikovati od obsesivnog 'chewing pads' (eng. grickanje prstiju). Difuzno oticanje zahvaćenog prsta koje uključuje dermis pored epidermisa, jasno odvaja PDD od 'knuckle pads' (bokserski jastučići), kalusa, profesionalnih kalozita, itd. Opisani su slučajevi u kojima su oboleli članovi unutar iste porodice, PPD i "knuckle pads" mogu biti istovremeno prisutni kod jedne iste osobe.

Prvi opis bolesti dali su Baseks (Basex) i saradnici 1973. kao pachydermie digitale. Termin pachydermodactyly predložio je Verbov 1975. i potiče od grčkih reči pachy (thick – zadebljanje), dermo (koža) i dactilos (prst).

Prikaz slučaja. U radu je prikazan muškarac star 19 godina, po zanimanju student, koji je u 12. godini života primetio povećanje obima trećeg i četvrtog prsta leve ruke. Do kraja 14. godine bili su izmenjeni svi prsti sem palčeva na obema rukama i od tada je stanje uglavnom ostalo isto. Pojavu ovih promena povezao je sa udaranjem lopte, kao i sa tim da ima običaj da trlja i „lomi" prste. Nama je upućen sa uputnom dijagnozom periartikularne artropatije posle pregleda ortopeda, reumatologa i fizijatra, a radi isključenja psorijaze i/ili seboroičnog dermatitisa kapilicijuma. Pacijent je na prijemu negirao postojanje drugih oboljenja i izjavio da u porodici nije bilo obolelih srodnika.

Opšte stanje pacijenta na prijemu bilo je u fiziološkim granicama. Dermatološki status je ukazao na: izmenjen oblik i obim svih prstiju obe šake, osim oba palca, u nivou proksimalnih falangi; normalan izgled distalnih delova svih prstiju; u nivou prvih interfalangealnih zglobova zadebljanje; hipertrofija, skoro simetrična na obe lateralne strane (ulnarna i radijalna) falangi svih zahvaćenih prstiju, osim oba kažiprsta, gde je hipertrofija zahvatila samo ulnarnu stranu (Slika 1). Palpatorno, promenjeni delovi su bili bezbolne, homogene teksture i elastične konzistencije, pokretni u odnosu na susedne koštane strukture. Svi zglobovi su pokazivali nepromenjenu funkciju.

Svi ispitivani relevantni laboratorijski parametri pokazali su vrednosti koje su bile u granicama referalnih vrednosti, uključujući faktore inflamacije, serumski nivo imunoglobulina, C3 i C4 komponente komplementa, prisustvo antinuklearnih antitela i imunoglobulina.

Ehosonografija zglobova šaka: osteoartikularne površine bez ehosonografskih znakova za defekte; ne uočavaju se periartikularne fokalne promene, osim inbibicije mekih tkiva; sinovije medijalnih interfalangealnih zglobova zadebljane; povećanje intraartikularne sinovijalne tečnosti.

RTG šaka u oba pravca: koštana građa prvog reda očuvana (Slika 2).

Patohistološki nalaz: u epidermisu izražena hiperkeratoza i akantoza; epidermo- dermalna granica zaravnjena; dermis zadebljao, hipocelularan, retki fibroblasti okruženi su širokim hijalinizovanim trakama kolagene strome; adneks kože odsutan.

Intraleziono ubrizgavanje rastvora triamcinolona u toku tri meseca dovelo je do neznatnog smanjenja obima tretiranog prsta. Savetovali smo pacijenta da izbegava mehaničke traume, trljanja i „pucanja" prstiju.

Diskusija i pregled literature. Kako je PDD oboljenje koje se javlja u pubertetu i manifestuje se uglavnom asimptomatskim promenama u predelu proksimalnih interfalangealnih zglobova (PIP) ruku u vidu uvećanja tkiva oko zglobova, sa mogućim promenama na koži, to su u dijagnostiku i lečenje uključeni lekari različitih specijalnosti (reumatolozi, ortopedi, pedijatri, dermatolozi, hirurzi). Radovi koji se odnose na PDD, objavljivani su i u časopisima koji nisu isključivo usmereni samo na dermatologiju, a to se može tumačiti multidisciplinarnim pristupom obolelima (Tabela 1). Dva rada predstavlju opsežne analize do tada objavljenih radova: prvi iz su 2009. objavili Beltramineli (Beltraminelli) i saradnici, a drugi su

2014. godine objavili Dalos (Dallos) i saradnici. U prvoj studiji izvršena je analiza 55 radova sa 88 bolesnika, dok je druga obuhvatila još 17 objavljenih radova, sa ukupno 121 bolesnikom registrovanim do tada. Novim pretraživanjem registrovali smo još 28 radova sa 45 obolelih. Znači, od Baseksa i saradnika do danas, objavljeno je o PDD najmanje 100 radova u kojima je prikazano 165 bolesnika. S našim prikazom, to bi bilo 101 rad sa 166 bolesnika.

Odsustvo subjektivnih tegoba, samolimitirajući tok, zaustavljanje progresije oboljenja u adolescentnom dobu, odsustvo trajnih sekvela, predstavljaju faktore zbog kojih se pretpostavlja da je stvarna prevalencija PDD realno viša, te da PDD nije tako retka. Bolest se najčešće javlja u ranom pubertetu kod osoba muškog pola, kao što je to slučaj kod našeg pacijenta: u starijem uzrastu, može biti posledica neprepoznavanja oboljenja. U literaturi su opisana dva slučaja bolesti od samog rođenja i samo četiri slučaja kod starih osoba. Bolest se javlja sporadično, ali su opisani i familijarni slučajevi, a u tri slučaja se radilo o transgredijentnoj formi PDD.

Etiologija bolesti nije u potpunosti razjašnjena: na moguću individualnu genetsku predispoziciju, koja je verovatno esencijalna, nadovezuje se više precipitirajućih faktora. Najznačajnja je ponavljana mehanička trauma usled pokreta sličnih tikovima, kao što je istezanje, trljanje ili „pucketanje“, „lomljenje“ prstiju, bilo da se radi o zdravim osobama ili onima sa opsesivno-kompulzivnim poremećajem. U literaturi su objavljeni slučajevi PDD čijoj pojavi nisu prethodile ni trauma ni frikcija. Značajno češća pojava PDD kod dečaka na početku puberteta u odnosu na osobe ženskog pola i starijeg uzrasta, ukazuje na patogenetske uloge androgenih hormona; ne isključuje se i mogući uticaj hormona rasta i tiroidne hipofunkcije). Zbog česte pojave PDD kod osoba sa opsesivno-kompulzivnim i neurološkim poremećajima postoje zagovornici da se PDD stavi na listu kutanih manifestacija psiholoških poremećaja. Kod našeg pacijenta je postojala navika da trlja i „lomi“ prste, ali nije imao nikakve psihogene poremećaje.

Pored tipične kliničke slike, mogu biti zahvaćene i dorzalne i/ili ventralne strane prstiju. Opisana je i distalna varijanta, sa zahvatanjem distalnih falangi i metakarpofalangealnih zglobova, sa fibromatoznim zadebljanjem ili sa čvrstim nodusima. Promene su obično simetrične, ali mogu biti asimetrične u raznom stepenu, od različitog broja i stepena zahvaćenih zglobova na levoj i desnoj ruci do zahvatanja samo pojedinih zglobova u tzv. lokalizovanoj formi PDD. Opisana je i monoartikularna varijanta PDD. Peti prst i palac su retko zahvaćeni; prsti nogu nikada nisu zahvaćeni, a plantarna pahidermija je opisana kod bolesnika sa PDD koji je imao akrocijanozu. Koža na obolelim prstima može biti lihenificirana, sa lakom deskvamacijom ili hiperkratozom, nekad i umereno eritematozna, retko bolna. Nije registrovana pojačana osetljivost, svrab, žarenje jutarnja ukočenost ili redukovana pokretljivost. Objavljen je samo jedan deformantni slučaj PDD sa neerozivnom subluksacijom interfalangealnog zgloba. Kod prikazanog bolesnika bila su zahvaćena oba lateralna aspekta, ulnarni i radijalni delovi kože proksimalnih interfalangealnih zglobova i proksimalnih falangi II, III, IV i V prsta obeju ruku, sem kažiprsta, gde su promene bile samo na ulnarnim stranama. Površina kože je bila lako hiperkeratotična. Nije imao poremećaj funkcije, niti bolove.

Zbog heteregenosti kliničke slike i opisanih familijarnih slučajeva, izvršena je klasifikacija bolesti na pet tipova: 1. klasični tip (zahvaćeno više PIP kao posledica mikrotraume); 2. lokalizovani tip (zahvaćen jedan zglob); 3. transgredijentni (zahvata metakarpofalangealnu regiju); 4. familijarni (zahvaćeno više članova iste porodice) i 5. udružen sa tuberoznom sklerozom.

Prema Čenu (Chen), dijagnostički kriterijumi su: pacijent je bez simptoma; jutarnja ukrućenost je odsutna; bol pri pokretima i osetljivost na palpaciju su odsutni; zadebljanje prsta je radijalno ili ulnarno, retko cirkumskriptno; laboratorijski testovi nisu značajni; radiografski se nalazi samo zadebljanje mekog tkiva. Sa ovim tipičnim nalazom dodatna istraživanja retko su potrebna za postavljanje dijagnoze PDD.

U lečenju PDD nema efikasnog medikamentnog tretmana. Operativnom resekcijom fibroznog tkiva postignuti su dobri rezultati bez recidiva. Dobre rezultate dala je i intraleziona aplikacija triamcinolona, dok su pokušaji lokalne aplikacije topikalnih kortikosteroida uglavnom ostali bezuspešni. Higuči (Higuchi) je objavio dobre rezultate posle primene antialergijskog leka tranilasta, koji izaziva inhibiciju sinteze kolagena u koži, u dozi od 300 mg dnevno u toku 6 meseci. Eliminacija mehaničke stimulacije može dovesti do spontane regresije. Bolest je benignog karaktera sa hroničnim tokom. Prognoza je varijabilna.

Moguća je stabilizacija u kasnijim godinama posle višegodišnje progresije.
Zaključak. Prikazana je osoba muškog pola kod koje se pahidermodaktilija manifestovala na proksimalnim falangama svih prstiju osim palčeva obe šaka kao posledica trljanja i „pucketanja“ zglobova prstiju. U porodici nije bilo obolelih. Intralaziona aplikacija triamcinolona na jednom prstu dovela je do poboljšanja. Dat je savet da se prekine sa mehaničkom traumom. Pregled dostupne literature od 1973. do 2014. godine omogućio je bolje sagledavanje kliničkih varijanti oboljenja.

Ključne reči

Fibrom; Dermatoze šake; Deformiteti šake; Prsti; Neoplazme mekih tkiva; Kumulativni traumatski poremećaj

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Collodion Baby - a Case Report

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Abstract

Colloidon baby describes a highly characteristic clinical entity in newborns encased in a yellowish translucent membrane resembling collodion. In most cases the condition either precedes the development of one of a variety of ichthyoses, the commonest of which are lamellar ichthyosis and non-bullous ichthyosiform erythroderma, or occasionally represents an initial phase of other ichthyoses such as ichthyosis vulgaris. In at least 10% of all cases of collodion baby, the condition is followed by a mild ichthyosis of lamellar type, so mild as to be considered more or less normal, so-called self-healing collodion baby or 'lamellar ichthyosis of the newborn'. In this report we present a rare case of collodion baby in whom, after collodion membrane peeled-off, the skin retained normal appearance.

Key words

Ichthyosis, Lamellar; Newborn Diseases; Skin Diseases; Treatment Outcome; Signs and Symptoms; Diagnosis

The term colloidon baby (CB) (lamellar desquamation/exfoliation of the newborn), describes a highly characteristic clinical entity in newborns encased in a yellowish translucent membrane resembling collodion. In most cases the condition either precedes the development of one of a variety of ichthyoses, the commonest of which are the autosomal recessive, rarely autosomal dominant forms of lamellar ichthyosis and non-bullous ichthyosiform erythroderma, or occasionally represents an initial phase of other ichthyoses such as ichthyosis vulgaris, X-linked ichthyosis, Netherton's syndrome, neutral lipid storage disease or the Sjögren–Larsson syndrome. In at least 10% of all cases, the collodion baby phase is followed by a mild ichthyosis of lamellar type, so mild as to be considered more or less normal, so-called self-healing collodion baby or 'lamellar ichthyosis of the newborn' (1). Although self-healing collodion baby was firstly thought to be an autosomal recessive condition, it is most likely genetically heterogeneous (1).

Since 1884, when Hallopeau used the term collodion baby for the first time, about 270 cases have been sporadically reported including familial, self-healing cases and localized forms (2, 3, 4, 5, 6, 7). In this report, a case of a self-healing collodion baby is presented.

Case report

We present a child, born as a result of the first, controlled and uneventful, consanguineous pregnancy. A female infant was born at 37 weeks of gestation. The 1- and 5-minute Apgar scores were 9, respectively. The newborn's birth weight was 3570g (90th centile), birth length 49 cm (98th centile) and head circumference 35cm (91st centile). From the regional maternity ward the baby was transferred to the Neonatal Intensive Care Unit (NICU) of our Institute.

On admission, the newborn presented with normal vital signs, generalized edema, anxiety, Douleur Aigue du Nouveau-né (DAN) of 5 (8). DAN scale is a

behavioral scale developed to rate acute pain in term and preterm neonates, scores range from 0 (no pain) to 10 (maximum pain); It evaluates three items - facial expressions, limb movements, and vocal expression (8). Whole body surface was covered with a yellowish membrane with laminar cracks especially on the neck. The eyelids were edematous with profuse mucus secretion. The earlobes were deformed by swelling and tension of the skin, the lips were everted showing eclabion (Figure 1). Due to the collodion membrane limited range of motion in all joints was present. The result of physical assessment was otherwise normal.

During the first week of life, laboratory findings such as sedimentation rate, C-reactive protein, complete blood count as well as other relevant biochemical findings were in normal ranges. Ultrasound findings of the upper abdomen, head and echocardiography were normal. TORCH (serological analysis for toxoplasmosis, rubella, cytomegalovirus, herpes simplex) IgM was negative. Karyotype showed 46, XX (normal). Since septicemia is a common complication, regular skin, eye, ose, external ear canal and throat swabs, as well as blood, stool and gastric aspirate cultures, were done for bacteria and candida, and they were all negative.

Upon admission, parenteral administration of antibiotics (ampicillin, gentamicin) and analgesics (paracetamol, fentanyl) was initiated. The baby was

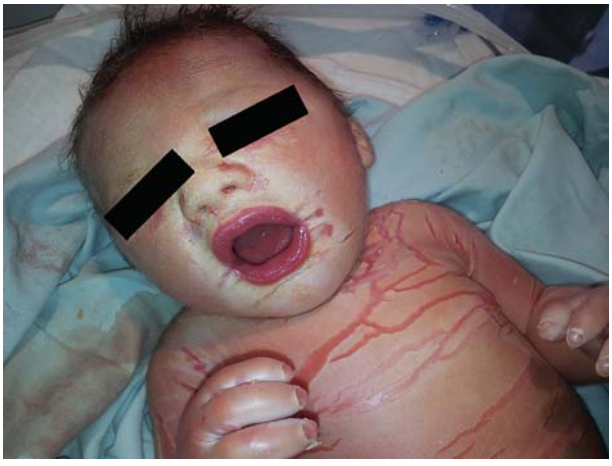

Figure 1. Collodion baby at birth: whole body is covered with yellowish membrane with laminar cracks; edematous closed eyelids with profuse mucus secretion; earlobes deformed by swelling and membranes; eclabium (eversion of the lips)

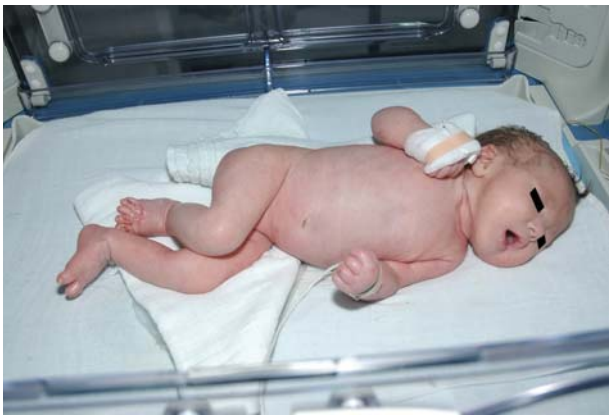

Figure 2. Four weeks after birth: baby`s skin is smooth and pink, retaining normal appearance

nursed in humidified incubator (60 to 70%), with close monitoring of body temperature. The skin was treated with emollients every 4 hours during the first days of life. After the first week of life, when almost all the membrane has desquamated (except on the palms and soles), emollients were applied twice a day. A prophylactic, topical antibiotic cream was applied on fissures and bare skin. Artificial eye drops were initiated (ectropion from the 2nd day of life) and periorbital area was treated with Solcoseryl® cream (deproteinized dialysate of calfs blood). During the second week of life, the level of acute phase reactants increased and *Acinetobacter* spp. was isolated from blood cultures and swabs of skin fissures. The antibiotic therapy was modified and colistimethate sodium was introduced parenterally; the subsequent cultures were all negative. Enteral feeding was started on the 1st day of life, initially via nasogastric tube, later by bottle. Due to high transdermal fluid loss, intravenous fluid, 250 ml/kg/day, and nasogastric fluid supplementation were commenced. One episode of hypernatremia was registered, probably as a result of technical incident (isolete malfunction and inappropriate humidification). During hospitalization, episodes of hyper - or hypothermia were not recorded. In the 3rd week of life, most of the membrane on palms and soles peeled-off. The skin became hyperemic, dry and scurfy. During the 4th week of life, the baby`s skin became smooth and pink and subsequently looked normal (Figure 2). After discharge from the hospital, the child is regularly monitored by a dermatologist. Last control at the age of 1,5 years revealed clinical symptoms that corresponds to a very mild form of ichthyosis vulgaris.

Discussion

Collodion membrane is a result of disturbed epidermal lipid and protein homeostasis. It has the same etiopathogenesis as ichthyosiform erythroderma, which develops in the majority of collodion babies. Most of collodion babies have autosomal recessive congenital ichthyosiform erythrodermas as a result of functional mutations in transglutaminase 1 - TGM1, ALOXE3 or ALOX12B genes, ABCA12, HIPAL4/ ichthyin, ABHD5 or other genes responsible for aforementioned epidermal homeostasis (5, 9). Most cases develop ichtyosis, ichtyosis-like conditions or other keratinization disorder. Most cases, approximately 75% will go on to develop autosomal recessive congenital ichtyosis, either lamellar ichthyosis or congenital ichthyosiform erythroderma - particularly non-bullous. After shedding the collodion membrane, the skin, especially on the trunk, usually remains dry and resembles a mild form of ichtyosis vulgaris. Only 10% of cases eventually develop normal skin. This is known as self-healing collodion baby (2, 7, 10). Self-healing collodion baby is caused by compound heterozygous mutations which *in utero* render the transglutaminase 1 inactive *cis* form; after delivery, a normal phenotype develops, since in the extrauterine environment the enzyme isomerizes back to its active *trans* form (7). About 15% of cases are caused by different conditions which include keratinization disorders, such as ichthyosis vulgaris and trichothiodystrophy–ichthyosis syndrome, Sjogren-Larsson syndrome, ichthyosis variegata, palmoplantar keratoderma with anogenital leukokeratosis, as well as non-syndromic autosomal dominant loricrin keratoderma, anhidrotic ectodermal dysplasia etc. (3, 7).

Collodion babies are often born prematurely (between 32 and 36 weeks of gestation) and are small for gestational age. However, premature delivery is not usually a significant problem (7). Our patient was born in term, with normal somatometric parameters.

During the first weeks of life, the diagnosis is unmistakable (1). Collodion baby is a syndrome in which a bright red newborn is encased in a taut, shiny, yellowish translucent membrane resembling collodion, known as collodion membrane. This extra layer of skin usually covers the whole body and looks tight; it may be described as 'plastic skin', 'parchment-like' or 'as if dipped in hot wax' (2, 3, 4, 5, 6, 7). The whole body surface is covered by armor-like plates. The face appears immobilized. Tension around the eyes and the mouth results in: ectropion and eversion of the lips (eclabion) as in our patient, producing a rather fish-like appearance of the mouth, and effacement of the nose and ears. The nostrils may be blocked (1). Since the baby's eyes and mouth are forced opened, if appropriate treatment is not started, keratitis due to xerophthalmia and subsequent blindness may occur (2, 11). Severe tightness of the skin on the thorax may interfere with respiration, and very occasionally, respiratory distress may be caused by nasal obstruction, such as impaired feeding and breathing. Since respiration can be also compromised during delivery, due to aspiration of amniotic fluid with squamous debris, this can be seen on fetal ultrasound and early delivery by caesarean section can prevent this complication. The membrane may cause physical constraints of underlying tissues with development of constriction bands with subsequent reduction of local blood supply and swelling of extremities (2, 12, 13).

Awareness of potential complications is of utmost importance. The baby should be nursed in an incubator at high humidity, with constant monitoring of body temperature. High humidity (40 - 100%) is exceptionally important in order to decrease the level of transepidermal fluid loss, that is 6 to 7 folds increased in these newborns (14). On the other hand, high humidity increases the risk of skin colonization with different pathogens. Other supportive measures include maintenance of fluid and electrolyte balance. In severe cases, intravenous fluid therapy in indicated, but in less severe cases oral or nasogastric fluid supplementation is recommended. Peritoneal dialysis may be indicated if renal failure occurs. The skin should be maintained soft in order to decrease scaling. Other treatment options include pain alleviation (for example paracetamol or opioids), as well as use of emollients and mild topical steroids in order to decease inflammation, and application of artificial tear drops. Use of emollients is contradictory (2, 15). The collodion membrane should not be peeled-off roughly. Bands of tight skin constricting digits, hands or feet may occasionally require surgical division.

Our patient was initially treated with emollients 6 times a day, and twice a day after the first week of life.

In collodion babies with localized lesions, local use of retinoic acid and calcipotriol is a good treatment option. Also, introduction of systemic retionids in the treatment of generalized lesions was highly successful leading to significant decrease in mortality, from 50% in the 1960s to 11% in 1986, and less than 5% nowadays (14).

As large transepidermal fluid loss results in high metabolic demands, supplementation of calories is mandatory in early phases of treatment in order to maximize the growth potential. Therefore, as a result of sucking difficulties due to eclabium, feeding via nasogastric tube is initially recommended (3).

In most cases, the membrane starts to dry and breaks within the first 48 hours of life and usually peels off completely in two to four weeks like in our case, but may reform several times. Subsequently, the typical features of one of several above mentioned varieties of ichthyosis gradually develop over a period of weeks or months, but it was not the case in our patient in whom, after the collodion membrane peeled off, the skin became smooth, pink and without scales. Although the necessity for intensive care depends on the baby's condition, most are discharged within the first 4 weeks, once the membrane completely peels off. No correlation between the severity of ichthyosis that follows and the initial severity in a collodion baby has been reported (1). Since on light microscopy histopathological findings of skin biopsy within the first weeks are identical, regardless if severe ichthyosis will develop or not, and cannot distinguish which disturbance will develop, the diagnosis of collodion baby is clinical. Apart from orthokeratotic stratum corneum, light microscopy of the skin shows normal epidermis and dermis. Regardless of the clinical status which may still be indistinguishable, it is possible to make a prediction on histological grounds at about 15 days (1), but the best option is to perform skin biopsy after the collodion membrane is peeled off (2). Electron microscopy features vary in the early neonatal phase and may persist for several months with no predictive value (5). Although skin biopsy was not performed in our patient, because the parents have not consented to the intervention, based on visible characteristics of the baby's skin over the follow-up, it seems quite reasonable to consider this case as a rare self-healing collodion baby. Moreover, at present, it seems more likely that apart from relevant investigations including genetic family counseling, only observation over a period of months will clarify the fate of the skin in this newborn (1).

Conclusion

In this report we present a rare case of collodion baby whose skin retained normal appearance after the collodion membrane was shed.

Abbreviations

CB - collodion baby
NICU - Neonatal Intensive Care Unit
DAN - Douleur Aigue du Nouveau-né
TORCH – Toxoplasmosis, Other infections, Rubella, Cytomegalovirus, and Herpes

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Kolodion beba – prikaz slučaja

Sažetak

Kolodion beba (*Collodion baby*) predstavlja visokospecifičan klinički sindrom u kome se novorođenče rađa zatvoreno u žućkastu translucentnu (prozračnu) opnu koja svojim izgledom podseća na kolodijum. U najvećem broju slučajeva ovo kliničko stanje predstavlja ili uvod u jednu od brojnih oblika ihtioza, najčešće lamelarnu ili nebuloznu ihtioziformnu eritrodermiju, ili u pojedinim slučajevima predstavlja početnu fazu ostalih ihtioza, npr. vulagarne ihtioze. U manje od 10% svih slučajeva, kolodijum opna može spontano nestati ostavljajući za sobom kožu koja se može smatrati manje ili više nepromenjenom, najčešće sa veoma blagim znacima lamelarne ihtioze, tzv. lamelarna ihtioza novorođenčeta.

U ovom radu prikazan je redak slučaj *kolodion bebe*, kod koje je koža poprimila normalan izgled, te su se nakon godinu i po dana posle porođaja, na njoj mogli videti samo veoma blagi znaci vulgarne ihtioze.

Ključne reči

Lamelarna ihtioza; Bolesti novorođenčeta; Kožne bolesti; Ishod terapije; Znaci i simptomi; Dijagnoza

A Report on the 23 rd Congress of the European Academy of Dermatology and Venereology, Amsterdam 2014

The 23rd Congress of the European Academy of Dermatology and Venereology was held in Amsterdam, from 8 - 12 October 2014. The Congress featured: courses, plenary lectures, symposia, workshops, focus sessions, spotlights and controversies, test yourself, masters of dermatology, free communications (short presentations of selected abstracts in thematic sessions) and what's new.

Prof. Miloš Nikolić was the co-chair in the workshop "Dermatomyositis and Overlap Syndromes" and delivered a lecture "Juvenile Dermatomyositis: How to Diagnose and How to Treat". He was also a chair in Free Communications on allergy and adverse drug reactions.

Prof. Marina Jovanović was the co-chair in the symposia "The Changing Spectrum of Photoallergens" and delivered a lecture "Causes of Photocontact Sensitivity: A Two Decade Survey of Research Results of the Allergy Department of the Clinic od Dermatovenereology Diseases in Novi Sad".

Figure 1. Session "The Changing Spectrum of Photoallergens": Gillian Murphy - the Char, with Co-Chairs Marina Jovanović (Novi Sad, Serbia) and Jana Kazandjieva (Sofia, Bulgaria)

Figure 2. Gillian Murphy (Dublin, Ireland), the Chair of the session

Figure 3. Marina Jovanović, giving a lecture: "Causes of Photocontact Sensitivity – a Two Decade Survey of Research Results of the Allergy Department of the Clinic of Dermatovenereology Diseases in Novi Sad."

Figure 4. Jana Kazandjieva, giving a lecture: "Clinical Spectrum of Photoallergy

Prof. Ljiljana Medenica was the co-chair in the symposium "Emergency Dermatology". She delivered a lecture "The Belgrade Moulages: Long Forgotten Historical Treasures of Dermatology and Venereology" in the EADV President's Symposia.

Dr. Dušan Škiljević delivered a lecture "Erythrodermia" in the symposium "Emergency Dermatology". There were 25 E-posters from Serbia.

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Activities of the Dermatovenereology Section of the Serbian Medical Society in 2014

Dermatovenereology Section (DVS) of the Serbian Medical Society (SMS) was very active in 2014. Four meetings and three courses were organized in 2014, and all of them were accredited by the *Health Council of the Republic of Serbia.*

The first course: Psoriasis – How to Improve the Treatment, was organized by the Psoriasis Treatment Group of the DVS at the *Military Medical Academy* on February 28, 2014. Seven lectures were given:

1. Psoriasis – introduction, Prof. Dr. Radoš Zečević
2. Comorbidities in psoriasis, Dr. Miroslav Dinić
3. The proposal for clinical management of patients with psoriasis, Assist. Prof. Dr. Mirjana Milinković
4. Topical therapy of psoriasis, Assist. Prof. Dr. Željko Mijušković
5. Phototherapy in the treatment of psoriasis, Dr. Ljubomir Novaković
6. Classical systemic treatment of psoriasis, Assist. Dr. Ljubinka Matović
7. Biologic therapy of psoriasis, Assoc. Prof. Dr. Lidija Kandolf Sekulović.

The first meeting of the DVS was organized by the *Clinic of Dermatovenereology, Clinical Center of Serbia* on March 7, 2014. The introductory lecture was delivered by Assist. Prof. Dr. Danijela Dobrosavljević Vukojević: Dermatoscopy – new possibilities for dermatologists. Also, 12 case reports were presented at this meeting:

1. Successful treatment with intravenous methylprednisolone pulses and azathioprine in generalized pustular psoriasis in pregnancy – a case report, Assist. Prof. Dr. Danijela Dobrosavljević Vukojević
2. Steatocystoma multiplex – a case report, Assist. Prof. Dr. Jelica Vukićević
3. Nodular pemphigoid – a case report, Dr. Jovan Lalošević
4. Bullous morphea and lichen sclerosus et atrophicus – a case report, Dr. Branislav Lekić
5. Lupus pernio – a case report, Dr. Srđan Tanasilović
6. Pyoderma gangrenosum – a case report, Dr. Iva Maširević
7. Blaschko's lines in different organs (except skin) – a case report, Assist. Prof. Dr. Snežana Minić
8. An unusual presentation of cutaneous mycobacteriosis in a child – a case report, Assist. Dr. Mirjana Gajić Veljić
9. Toxic epidermal necrolysis-like dermatosis induced by pentoxifylline – a case report, Assist. Dr. Jelena Stojković Filipović
10. Pyoderma gangrenosum in a patient with multiple myeloma – a case report, Prof. Dr. Sonja Vesić
11. Toxic epidermal necrolysis (Lyell's syndrome) – a case report, Assist. Prof. Dr. Mirjana Milinković
12. Porphyria cutanea tarda – a case report, Dr. Biljana Arsov.

The second course: Cutaneous melanoma – what's new?, was organized by the *Dermato-oncology group* of the DVS and *Intersectional Committee for Dermato-Oncology* of SMS at the *Military Medical Academy* on March 28, 2014. Nine lectures were given:

1. Prevention and early diagnosis of melanoma, Assist. Dr. Branislava Gajić
2. Classification of melanoma, Prof. Dr. Nada Vučković
3. Surgery of primary melanoma, Dr. Milica Rajović
4. Surgery of metastatic melanoma, Prof. Dr. Dejan Nikolić
5. Multidisciplinary approach in the treatment and chemotherapy of metastatic melanoma, Prof. Dr. Svetislav Vrbić
6. Adjuvant therapy of melanoma, Assoc. Prof. Dr. Lidija Kandolf Sekulović
7. Immunotherapy of metastatic melanoma, Assist. Dr. Borislava Nikolin
8. Target therapy of metastatic melanoma, Dr. Nada Babović
9. Evaluation and primary staging in melanoma patients, Assist. Prof. Dr. Željko Mijušković.

The third course: Diagnosis and treatment of autoimmune bullous diseases?, was organized by the *Group for Diagnosis and Treatment of Autoimmune Bullous Diseases* of the DVS at the *Military Medical*

Academy on April 11, 2014. Seven lectures were given:

1. What is necessary to start the treatment of autoimmune bullous diseases?, Assist. Prof. Dr. Željko Mijušković

2. Correlation between patohistological and clinical findings in patients with autoimmune bullous diseases, Dr. Gorgi Gocev

3. Autoimmune bullous diseases in childhood, Assist. Dr. Mirjana Gajić Veljić

4. Clinical manifestations of patients with autoimmune bullous diseases, Assist. Prof. Dr. Mirjana Milinković

5. Clinical manifestations and treatment of dermatitis herpetiformis, Assist. Prof. Dr. Zorica Gajinov

6. The treatment principles in autoimmune bullous diseases, Prof. Dr. Radoš Zečević

7. New treatment modalities in autoimmune bullous diseases, Assoc. Prof. Dr. Lidija Kandolf Sekulović.

The second meeting of the DVS was organized by the *Clinic of Dermatology and Venereology and the Military Medical Academy* on April 11, 2014. The introductory lecture was presented by Dr. Kristina Kostić: Vasculitis – classification and diagnostic approach. Also, 9 case reports were presented at this meeting:

1. Reactivation of atopic dermatitis and refractory balanoposthitits during adalimumab treatment – a case report, Dr. Dušan Šofranac

2. Acneiform eruptions induced by panitumumab – a case report, Dr. Tatjana Vukanović

3. DRESS syndrome – a case report, Dr. Zorana Kremić

4. Treatment of nonmelanoma skin cancers – a case report, Assist. Prof. Dr. Željko Mijušković

5. Potassium iodide in the treatment of recurrrent erythema nodosum – a case report, Dr. Tanja Tirnanić

6. Intralesional corticosteroids in the treatment of alopecia areata – a report of three cases, Dr. Lidija Cvetković Jordanov

7. Pathomimia – a case report, Dr. Zorana Kremić.

The third meeting of the DVS was organized by the *Clinic of Dermatology and Venereology of the Clinical Center Niš* on May 10, 2014 in Prolom Banja. The introductory lecture was delivered by Prof. Dr. Zoran Pešić: Nonmelanoma skin cancers. Also, 13 case reports were presented at this meeting:

1. Drug-induced subacute cutaneous lupus erythematosus – a case report, Dr. Danijela Popović

2. Disseminated superficial actinic porokeratosis – a case report, Dr. Mirjana Bakić

3. Balloon cell nevus – a case report, Assist. Dr. Danica Tiodorović Živković

4. Juvenile xanthogranuloma – a report of three cases, Assist. Dr. Danica Tiodorović Živković

5. Condylomata acuminata, rare localizations and clinical features – a report of three cases, Dr. Radmila Milenković

6. Syndroma Netherton – a case report, Dr. Vesna Karanikolić

7. CREST syndrome – a case report, Dr. Aneta Aleksandrović

8. Erythroplasia Queyrat – a case report, Dr. Zorana Zlatanović

9. Epidermal verrucous nevus – a case report, Dr. Dragana Ljubisavljević.

The fourth meeting of the DVS was organized by the *Clinic of Dermatovenereology of the Clinical Center of Vojvodina* on October 17, 2014 in the Pavle Beljanski Memorial Collection in Novi Sad. The introductory lectures were given by Dr. Siniša Jolić: Chronic venous insufficiency and comorbidities, and Assist. Prof. Dr. Milan Matić: Risk factors in chronic venous insufficiency in women. Also, 6 more lectures were presented at this meeting:

1. Extramammary Paget's disease – a case report, Dr. Bojana Spasić

2. Stewart-Treves syndrome – a case report, Dr. Tatjana Roš

3. Cutaneous dirofilariasis – a case report, Dr. Biljana Jeremić

4. Nodular vasculitis – a case report, Assist. Dr. Aleksandra Petrović

5. Mastocytosis, Assist. Dr. Ljuba Vujanović

6. Isotretinoin and depression, Assist. Dr. Milica Subotić.

Assist. Prof. Dr. Željko Mijušković
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2014 Annual Report on the Activities of the Dermatovenereology Section of the Society of Physicians of Vojvodina of the Serbian Medical Society

Meetings of the *Dermatovenereology Section* of the *Society of Physicians of Vojvodina*

During 2014, there were three meetings of the *Dermatovenereology Section* of the *Society of Physicians of Vojvodina,* and all of them were accredited by the *Health Council of the Republic of Serbia.*

The first Section meeting was held on April 25, 2014, at the premises of the *Society of Physicians of Vojvodina* (SPV) in Novi Sad and its professional part was carried out by doctors of the *Clinic of Dermatovenereology Diseases* in Novi Sad, *Clinical Center of Vojvodina*. Its main topic was: menagement of cutaneous melanoma. Lectures were given by doctors of the *Clinic of Dermatovenereology of the Clinical Center of Vojvodina:*

1. Guidelines for the menagement of cutaneous melanoma, Prim. Dr. Bojana Spasić
2. Eosinophilic fasciitis – a case report, Mr. sc. med. Dr. Ljubinka Matović
3. Erythema exsudativum multiforme – a case report, Dr. Svetlana Kovačić-Dukić
4. Palmoplantar pustulosis or pustular psoriasis, Full Prof. Dr. Marina Jovanović
5. Successfull treatment of ulcerated phlebo-lymphoedema – a case report, Assist. Prof. Dr. Milan Matić
6. Vivamel honey dressings in the treatment of chronic wounds, Assist. Prof. Dr. Milan Matić.

The second Section meeting was held on October 17, 2014, in Novi Sad in the Pavle Beljanski Memorial Collection. It was a joint meeting of *Dermatovenereology Sections* of the *Society of Physicians of Vojvodina* (SPV) and *The Serbian Medical Society* (SMS). Its professional part was carried out by doctors of the *Clinic of Dermatovenereology Diseases* in Novi Sad, *Clinical Center of Vojvodina,* and Dr. Siniša Jolić from General Hospital Kikinda. The main topic of this meeting was chronic venous insufficiency, with 2 introductory lectures:

1. Chronic venous insufficiency and comorbid diseases: a reflection on clinical picture, Dr. Siniša Jolić, General hospital, Kikinda
2. Risk factors in the development of chronic venous insufficiency in women, Assist. Prof. Dr. Milan Matić

There were six more lectures presented at the meeting:

1. Extramammary Paget disease – a case report, Prim. Dr. Bojana Spasić
2. Stewart-Treves Syndrome – a case report, Dr. Tatjana Roš
3. Cutaneous Dirofilariasis – a case report, Assist. Prof. Dr. Zorica Gajinov
4. Vasculitis nodularis – a case report, Assist. Dr. Aleksandra Petrović
5. Mastocytosis – a case report, Assist. Dr. Ljuba Vujanović
6. Isotretinoin and depression, Assist. Dr. Milica Subotić.

The third Section meeting was held on December 12, 2014, in Novi Sad in the Hotel Garden. Lectures were given by doctors of the *Dermatovenereology Clinic* of the *Clinical Center of Vojvodina:*

1. Contact allergic dermatitis – is it frequent in patients with chronic venous insufficiency? Assist. Dr. Ljuba Vujanović
2. Clinical and dermoscopic presentations of eruptive syringoma – a case report, Assist. Dr. Milana Ivkov-Simić
3. Simultaneous syphilitic and HIV infections and cutaneous manifestations, Assist. Prof. Dr. Zoran Golušin.

Participation of members of the Dermatovenereology Section of the Society of Physicians of Vojvodina of the Serbian Medical Society on other professional meetings in the country and abroad, advancements and awards

As it has been planned, our members were actively involved in education, conferences and meetings in our country and abroad over the past year.

Prof. Dr. Marina Jovanović was our representative on the the 23 rd Congres of the European Academy of Dermatology and Venereology, Amsterdam 2014. She was the co-chair in the symposium: The changing spectrum of photoallergens, and delivered a lecture: Causes of photocontact sensitivity: a two decade survey of research results of the Allergy Department of the Clinic of Dermatovenereology Diseases in Novi Sad.

Assist. Dr. Aleksandra Petrović was awarded a diploma in the field of allergology on April 3, 2014.

Assist. Dr. Ljuba Vujanović received a PhD degree on November 7, 2014.

Dr. Milana IVKOV SIMIĆ
Secretary of the Dermatovenereology Section of the Society of Physicians of Vojvodina of the Serbian Medical Society
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E-mail: milana.ivkovsimic@gmail.com

FORTHCOMING EVENTS

Dermatology and Venereology Events 2015

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
29 - 31 January, 2015	3rd European School of Dermato-oncology, Berlin, Germany	No abstract submission	www.dermato-oncology2015.org
29 January - 1 February, 2015	IMCAS World Congress Paris, France	No deadline information	www.imcas.com
4-7 February, 2015	EUROGIN 2015 Congress Sevilla, Spain	1 October 2014	www.eurogin.com
12-14 February, 2015	COSMEXCHANGE Trieste, Italy	No abstract submission	www.cosmexchange.com
5 - 8 March, 2015	EADV Spring Symposium Valencia, Spain	26 October 2014	www.eadvvalencia2015.org
20 March, 2015	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Serbia, Belgrade, Serbia	No abstract submission	www.sld.org.rs
26-28 March, 2015	13th Aesthetic and Anti-Aging Medicine World Congress, Monte Carlo, Monaco	No deadline information	www.euromedicom.com
7-9 April, 2015	Dubai World Dermatology and Laser Conference, Dubai, UAE	31 December 2014	www.dubaiderma.com
9-11 April, 2015	Psofuture – International Congress of Dermatology dedicated to Psoriasis, Rome, Italy	31 January 2015	www.psofuture.org
24 April, 2015	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Military Medical Academy, Belgrade, Serbia	No abstract submission	www.sld.org.rs
16-18 April, 2015	4th World Congress of Dermoscopy and Skin Imaging, Vienna, Austria	5 December 2014	www.dermoscopy-congress2015.com
9 May, 2015	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Niš, Prolom Banja, Serbia	No abstract submission	www.sld.org.rs
6-10 June, 2015	EAACI Annual Congress Barcelona, Spain	15 January 2015	www.eaaci2015.com
8-13 June, 2015	23rd World Congress of Dermatology Vancouver, Canada	30 September 2014	www.derm2015.org
26-27 June, 2015	Botulinumtoxine – Fostering course Athens, Greece	No abstract submission	www.eadv.org
8-11 July, 2015	4th World Psoriasis and Psoriatic Arthritis Conference, Stockholm, Sweden	5 March, 2015	www.ifpaworldconference.com

Prepared by: Dr. Tatjana Roš, Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia, E-mail: t.rosh@nscable.net

AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

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

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

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

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

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

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

1.4. Cover Letter

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

2. Tables and illustrations

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

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

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

3. References

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

4. Additional information

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

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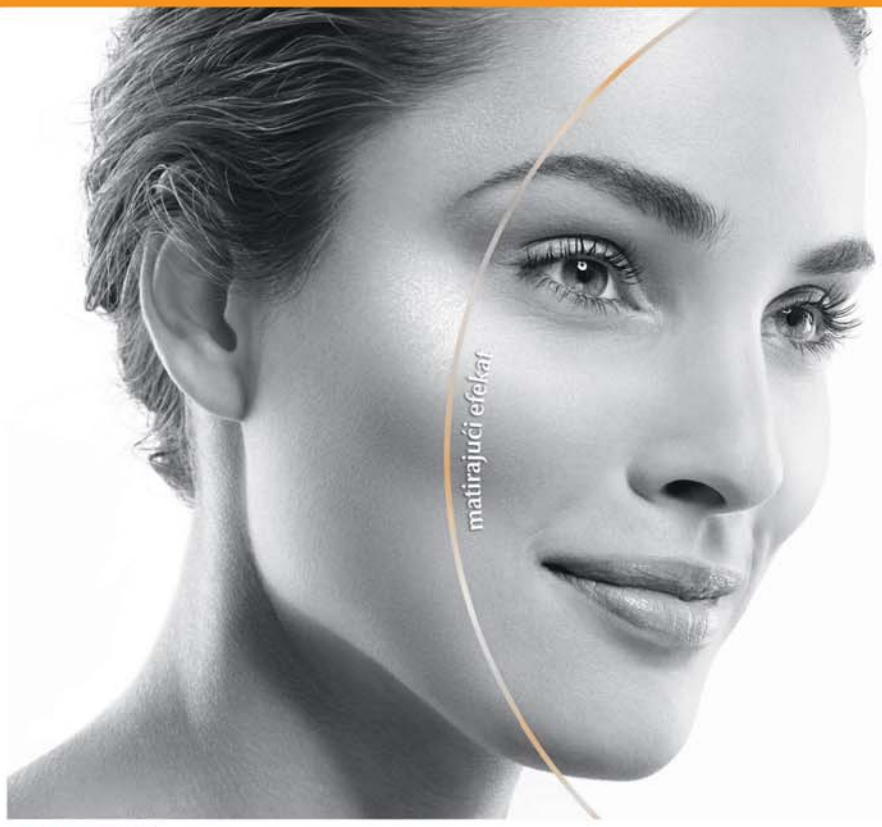

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