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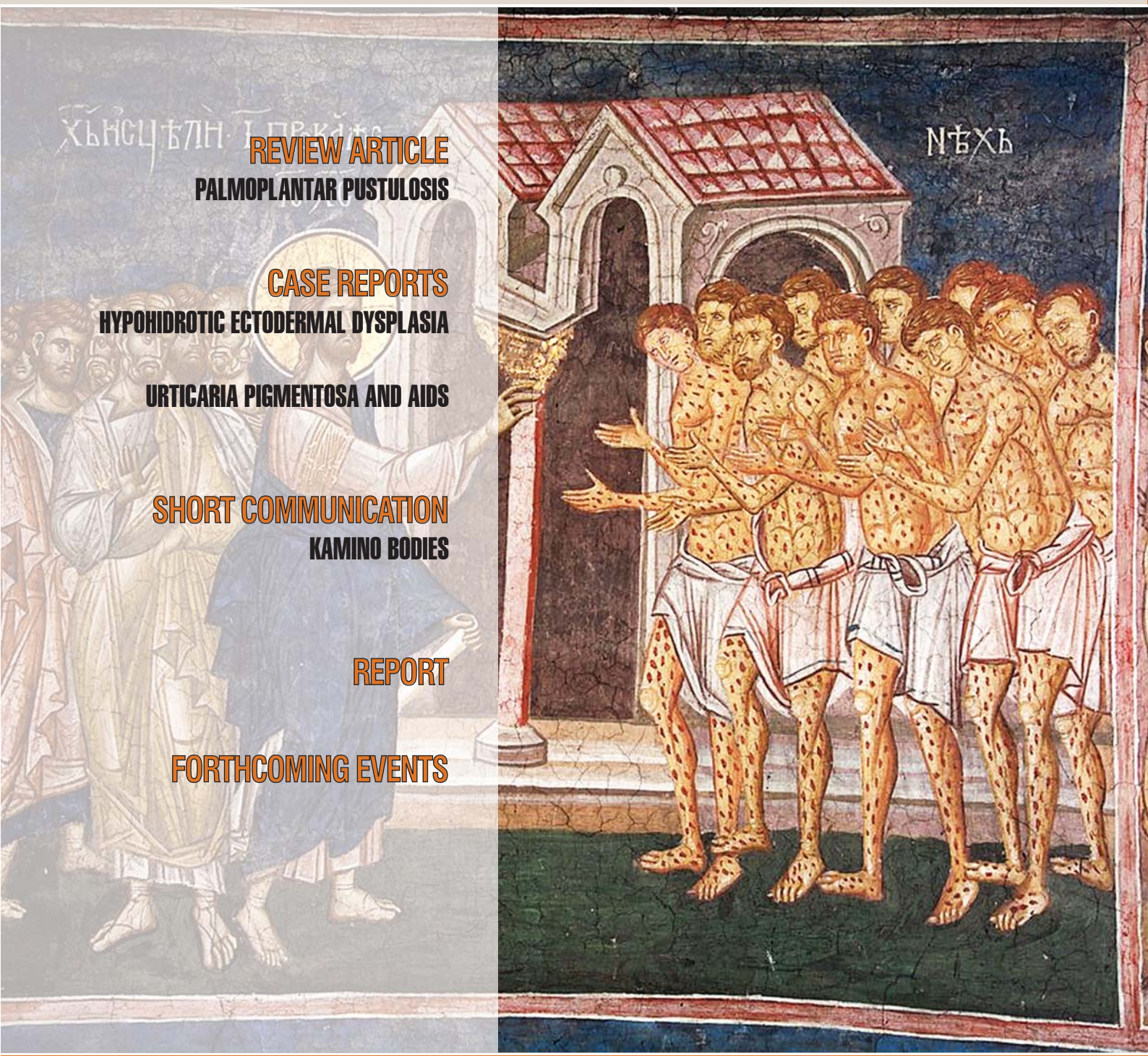

REVIEW ARTICLE

PALMOPLANTAR PUSTULOSIS

CASE REPORTS

HYPOHIDROTIC ECTODERMAL DYSPLASIA

URTICARIA PIGMENTOSA AND AIDS

SHORT COMMUNICATION

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REPORT

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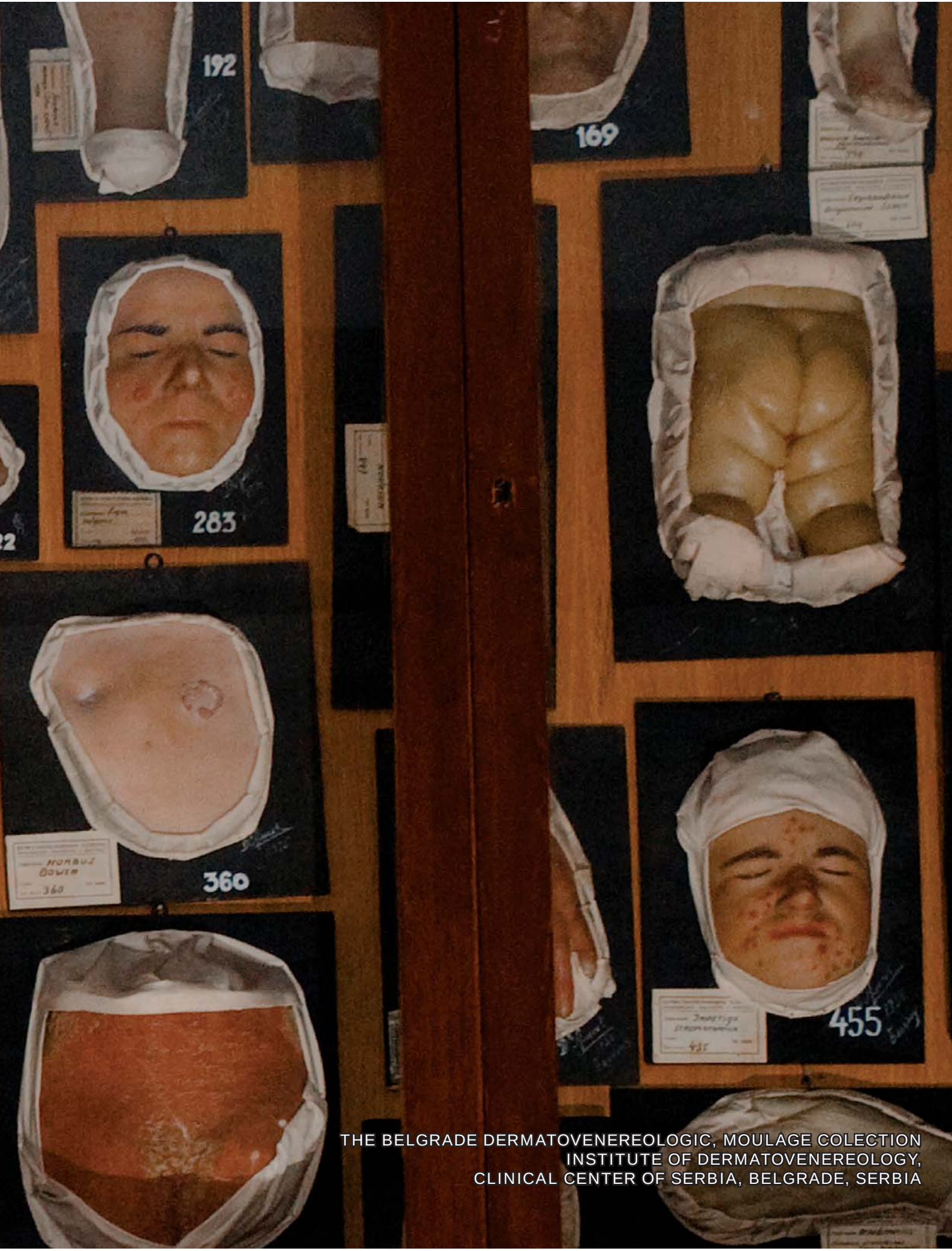

THE BELGRADE DERMATOVENEREOLOGIC, MOULAGE COLECTION
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Palmoplantar pustulosis – is there any progress in the treatment?

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Abstract

Despite, the fact that palmoplantar pustulosis is still widely known by this name, it is currently regarded as a disease distinct from psoriasis. The real cause is still unknown. Septic foci have been blamed, but their removal may not cure eruptions. A case series of *de novo* occurrence of palmoplantar pustulosis induced by tumor necrosis factor–alpha antagonist therapy has been reported. It has been shown that stress may be related to exacerbation of palmoplantar pustulosis. Some authors suggest that palmoplantar pustulosis is an autoimmune disease. In sera of patients with palmoplantar pustulosis circulating autoantibodies against nicotinic acetylcholine receptors were detected. The differences between palmoplantar pustulosis and pustular palmoplantar psoriasis are numerous. Genetic studies have failed to find any link between palmoplantar pustulosis and major genetic susceptibility locus for psoriasis vulgaris. Most patients with palmoplantar pustulosis have no evidence of psoriasis elsewhere. Histologically, it closely resembles psoriasis. However, accumulation of neutrophils just beneath the corneal layer, finding known as Munro's microabscess, and dilation of capillaries in the papillary dermis are lacking. Approximately 90% of patients are women. A significantly higher prevalence of smokers was found in the group with palmoplantar pustulosis than in the normal population and a particularly strong association was confirmed between smoking and pustular lesions in patients with psoriasis, OR=5.3 (2.1-13.0). Nevertheless, according to a recent review from the Cochrane Library, there is no evidence that smoking cessation improves the condition once it has developed.

Topical corticosteroids under occlusion are the first-line therapy. Prolonged therapy is needed on a second or third-day basis, in order to sustain the obtained effects. Oral retinoids in combination with oral PUVA are the best second-line therapy. No difference in the efficacy between etretinate and acitretin was found. The disadvantage of systemic retinoid therapy is its teratogenicity. Oral PUVA is effective and the response is enhanced by combination with retinoids. There is an established increased efficacy of a combination of retinoids with PUVA therapy over each treatment modallity when used alone. Liarozole may be an effective and well-tolerated therapy, but side effects are like in retinoids. The advantage over acitretin is that raised levels of retinoic acid fall to normal within a few days after cessation of therapy. Significant improvement, but no complete clearance, occurs in most patients treated with low dose cyclosporine. Before starting the treatment, it is necessary to consider: patient's individual factors, since many patients have already received some previous treatment; specific treatment factors such as formulation, way of administration, dose, different drug combinations; regimens and periods of treatment; site of involvement, due to differences between hands and feet in the probability of response to treatment.

Key words

Psoriasis + etiology + therapy; PUVA Therapy; Administration, Topical; Retinoids; Teratogens; Drug Therapy + adverse effects

Palmoplantar pustulosis (PPP) is a chronic inflammatory skin condition characterized by crops of sterile pustules (yellow pus spots) on the palms and soles which erupt unpredictably over months or years. Rapidly, lesions are surrounded by an erythematous ring and the affected area becomes red and scaly (Figures 1 and 2). Histology reveales intraepidermal vesicules filled with neutrophils. The treatment is often difficult and frustrating. Full remission is rare.

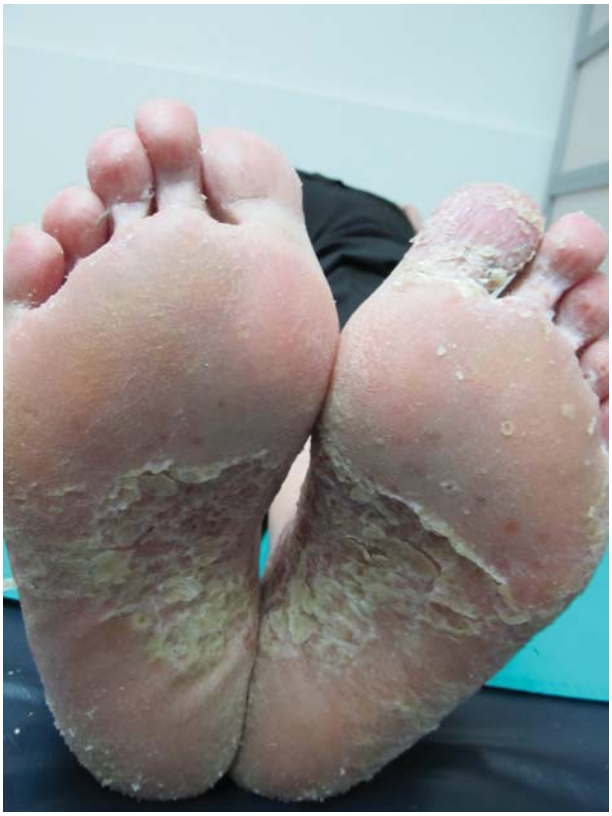

Figure 1. Palmoplantar pustulosis: plantar lesions

Etiology and pathophysiology

Unfortunately, the real cause of PPP is still unknown. Septic foci have been blamed, but their removal may not cure eruptions (1). It has been reported that the disease onsent occurred after several months of lithium treatment (2). A case series of *de novo* occurrence of PPP induced by tumor necrosis factor–alpha (TNF-α) antagonist therapy (biologic therapy for rheumathoid arthritis and psoriasis), has been reported (3). The role of psychological factors in palmoplantar pustulosis has been studied and it has been shown that stress may be related with exacerbation of PPP (4).

Recently, our understanding of psoriasis pathophysiology has greatly progressed, but the pathogenesis of PPP has been poorly investigated. Some authors suggest that PPP is an autoimmune disease. PPP is occasionally associated with thyroid autoimmunity, and the incidence is nearly 16-25% (5,6). Rarely, it is associated with rheumatoid arthritis and Sjogren's syndrome. There are no studies about coexisting vitiligo and alopecia in patients with PPP. I**n sera of patients with palmoplantar pustulosis**, Hagforsen and coauthors detected circulating autoantibodies against nicotinic acetylcholine receptors (7).

Palmoplantar pustulosis and psoriasis

The relationship between PPP and psoriasis vulgaris is unclear. No consensus has been reached regarding the question whether palmoplantar pustulosis represents a variant of palmoplantar pustular psoriasis (PPPP). Despite, the fact that palmoplantar pustulosis is still widely known by this name, the condition is currently regarded as a disease distinct from psoriasis. Social stigma is common. Though the discomfort in PPP is common (itching, burning, fissures, poor mobility), it is also known that patients with palmoplantar psoriasis suffer more physical disability and discomfort than patients with other forms of psoriasis (8).

The differences between PPP and PPPP are numerous. Genetic studies have failed to find any link between PPP and major genetic susceptibility locus for psoriasis vulgaris (9). Most patients with PPP have no evidence of psoriasis elsewhere. Enfors and Molin found that this proportion varies from 2%-24%, depending on the studied groups (10). Some authors found 84% of patients with psoriatic lesions on extra-palmoplantar areas, e.g., forearms, elbows, dorsa of the feet, knees, lower legs, buttocks (11). There is milder tenderness and inflammation of extra–palmoplantar lesions in PPP than in patients with psoriasis (Figure 3). Psoriatic arthritis is only exceptionally associated

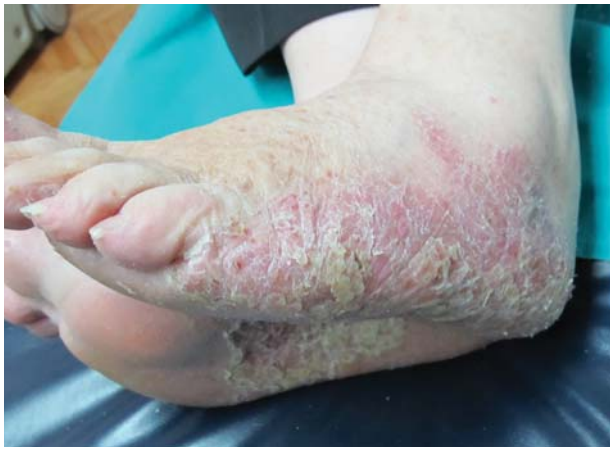

Figure 2. Palmoplantar pustulosis: lesions on the feet

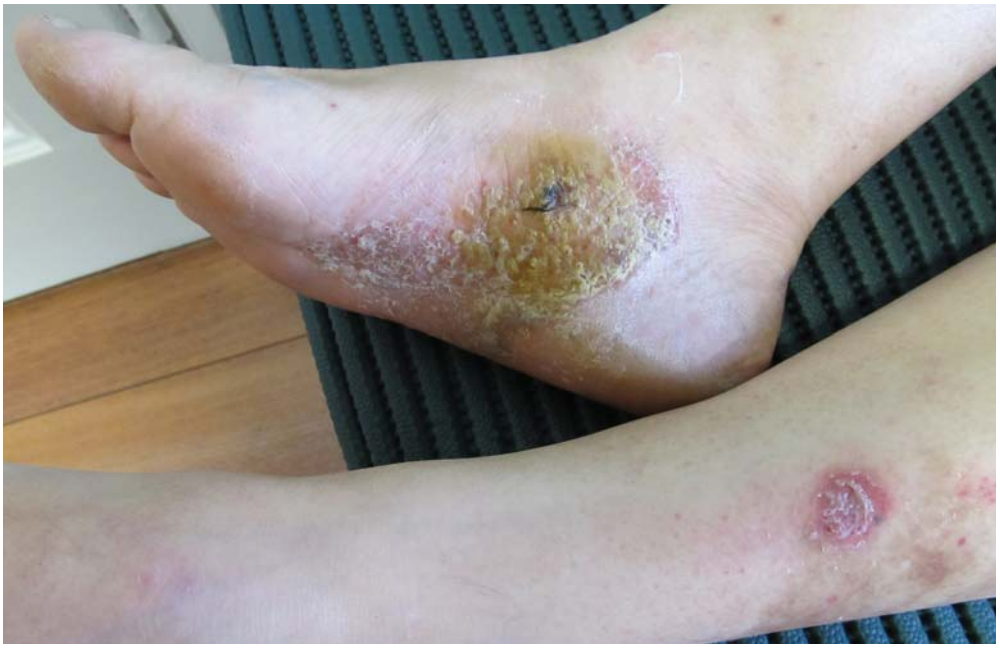

Figure 3. Patient with pustular palmoplantar psoriasis showing extra-palmoplantar lesions

with PPP. Sternocostoclavicular, manubriosternal and sternocostal joints are most frequently affected.

Approximately 90% of PPP patients are women.

Histologically, PPP closely resembles the histology of psoriasis. However, accumulation of neutrophils just beneath the corneal layer, finding known as Munro's microabscess, and dilation of capillaries in the papillary dermis are lacking. There are no specific findings and many features overlap with those seen in eczematous reactions (12,13).

A significantly higher prevalence of smokers was found in the group with palmoplantar pustulosis than in the normal population and a particularly strong association was confirmed between smoking and pustular lesions in patients with psoriasis, OR=5.3 (2.1-13.0). Nevertheless, according to a recent review from the Cochrane Library, there is no evidence that smoking cessation improves the condition once it has developed (14).

Therapy

The therapy for PPP/PPPP is unsatisfactory. There is no specific agent which induces long lasting remission. Many different systemic and topical therapeutic agents have been used. None of them can reliably suppress or cure the condition. Many of them are toxic, and there is little information regarding their relative efficacy. Differences regarding the cost to benefit ratio between various therapeutic modalities are significant.

Chalmers and colleagues (14) have searched the *Cochrane Group Specialized Register* (January 2003), *the Cochrane Central Register of Controlled Trials* (the Cochrane Library issue 1, 2003), the *Medline* (1996 to February 2003), ant the EMBASE (1988 – 2003). They also cross-checked the Salford Database of Psoriasis Trials, the reference list of articles and also contacted authors included in trials, members of *The Cochrane Skin Group* and dermatologists interested in psoriasis. The selection criteria were randomized controlled trials on patients with chronic PPP who received one or more interventions (14). Twenty-three trials including 724 persons were studied.

Systemic retinoides

According to the Cochrane Collaboration Guidelines, out of eight trials that have been conducted, six compared etretinate with placebo, one acitretin with etretinate, and one liarozole versus placebo. The duration of trials was 8-16 weeks. Good or

excellent response was obtained in 39% of patients who received retinoids as compared with 17% who received placebo; 62% of patients who received retinoids maintained chronic remission of three months duration as compared with 21% who received placebo (14). Lassus (15) found no difference in the efficacy between etretinate and acitretin. The main disadvantage of systemic retinoid therapy is its teratogenicity.

Psoralen with ultraviolet A (PUVA) photochemotherapy

Eight trials were conducted to assess the efficacy of psoralen with ultraviolet A (PUVA) photochemotherapy for palmoplantar pustulosis: four studies comparing PUVA with placebo, one topical PUVA with systemic PUVA, and three PUVA with etretinate (Cochrane Collaboration) (14).

Oral PUVA

Oral PUVA therapy for palmoplantar pustulosis produces variable results. In two different studies, oral PUVA produced improvement in 100% and 64% of patients, respectively, and placebo in 59% and 14% of patients, respectively (16,17). When using complete clearance as the outcome measure, in two previously mentioned studies, oral PUVA produced complete clearence in 55% and 21% of invoved areas respectively, while with placebo, there was no complete clearence in any of invoved areas in both studies (16,17).

Topical PUVA

When using clearance of involved areas as the outcome measure, with topical PUVA, Layton (18) found 0% and Matsunami (19) 10% of cleared areas, while both the authors found no complete clearence in any of invoved areas when treated with placebo.

Topical PUVA versus systemic PUVA

Lassus et al. assessed effects of etretinate compared with different regimens of PUVA in the treatment of persistent palmoplantar pustulosis: 8% of patients cleared with topical PUVA, as compared to 0% of patients who were treated with systemic PUVA (20).

PUVA versus retinoids

The obtained results were so different, that the data were not pooled. Thus, no definite benefits of retinoids over PUVA or vice versa were established (14).

Retinoids and PUVA combination (Re-PUVA)

Oral PUVA is effective (16,17) and the response is enhanced by combining it with retinoids (Re–PUVA) (21).

Re-PUVA versus PUVA and RePUVA versus retinoids

Comparing PUVA combined with etretinate and PUVA combined with placebo therapy for palmoplantar pustular psoriasis, Re-PUVA cleared all 100% versus 55.5% of areas treated with PUVA alone (21). However, three studies showed discerepancies in conclusions (17,19,21). Nevertheless, Chalmers and coauthors concluded that there is an established increased efficacy of combination of retinoids with PUVA therapy over each treatment modallity when used alone (14).

Liarozole

An imidazole derivative, liarozole is a member of a new class of drugs that inhibits the methabolism of all-*trans*-retinoic acid by inhibition of retinoic acid 4-hydroxylase. It gives a retinoid-like effect by increasing endogenous levels of naturally occurring all-*trans*retinoic acid and other retinoids upstream of retinoic acid 4-hydroxylase. The advantage of liarozole over acitretin is that the raised levels of retinoic acid fall to normal within a few days after cessation of therapy. A randomized, double-blind, placebo controlled study indicated that 75 mg liarozole, twice daily, may be an effective and well-tolerated therapy for palmoplantar pustulosis (22). Side effects are retinoid-like: teratogenicity, hyperlipidemia and mucocutaneous dryness.

Cyclosporine

Two double-blind placebo–controlled trials of cyclosporine in the treatment of palmoplantar pustulosis were performed in 1998 and 1993, by Erkko and Reitamo, respectively (23,24). Significant improvement, but no complete clearance occurred in most patients with palmoplantar pustulosis treated with low dose cyclosporine of 2.5 mg/kgBW/day.

Methotrexate

Some studies of methotrexate used in the treatment of palmoplantar pustulosis have shown marked improvement, but there are no controlled studies in the literature.

Tetracycline

Only modest improvement was achieved in 38% of patients wih palmoplantar pustulosis treated with tetracycline for one and three months versus 13% treated with placebo (25).

Hydroxycarbamide

Regarding treatment of palmoplantar pustulosis with hydroxyurea, Hattel and Sondergaard found no significant difference in disease severity scores between placebo and intervention periods (26).

Colchicine

Known to inhibit neutrophil function, colchicine has been claimed to be effective in palmoplantar pustulosis. However, this has not been confirmed by randomized controlled trials [27,28]. In 1984 and 1982, two cross–over studies by Thestrup–Pedersen and Mann have been reported, respectively (27,28). In the study by Thestrup–Pedersen, colchicine and placebo produced an improvement in 37% and 11.1% of patients, respectively (27). Failure of colchicine for palmoplantar pustulosis was reported by Mann (28).

Colchicine induces moderate improvement of palmoplantar pustulosis, but it also has a high rate of side effects. Thus, Chalmers et al. concluded that some evidence suggested possible modest benefits from colchicine at the expence of high rate side effects (14). Some authors would, however, still try colchicine as the first line medication in the treatment of palmoplantar pustulosis (29).

Grenz ray therapy

There is some evidence of improvement of palmoplantar pustulosis from Grenz ray therapy (very low voltage X ray therapy) (14). Opposite to this, Lindelof reported that none of the patients achived clearance (30). Since Grenz ray therapy only improves the condition, it may be a useful adjunct in the treatment of palmoplantar pustulosis (14).

Topical corticosteroids and other topical therapy

Potent or superpotent steroids are drugs of choise and may be used under plastic film of hydrocolloid occlusion, particulary at the very beginning of therapy (31).

Superpotent topical corticosteroids may be beneficial for short term treatment. Hydrocolloid gel occlusion can enhance the efficacy of moderate corticosteroid creams, when applied every third day up to a maximum of 4 weeks. In a right-left comparative study, Kragballe found that sides treated with a medium strength corticosteroid cream under hydrocolloid occlusion cleared completely in 12 of 19 patients (63%) compared to sides treated with a highly potent corticosteroid cream, that cleared in 3 of 19 patients (16%) (32). Therefore Mrowietz suggests prolonged topical steroid therapy, on a second-or third-day basis, in order to sustain the obtained effects (31).

Other topical agents, such as vitamin D3 analogues (calcipotriol/calcipotriene), tazarotene or anthralin, may prevent early relapses that occur in some patients. Topical retinoids can be used to avoid adverse effects or to strengthen the effects of steroids.

TNF-α antagonists

In regard to the therapy of palpmoplatar pustulosis with tumor necrosis factor-alpha (TNF-α) antagonists, such as infliximab, no agreement has been reached (14). Though biologic, TNF antagonists are more likely to exacerbate than improve palmoplantar pustulosis. The lack of head-to-head studies makes recommendations concerning their individual use difficult. However, efalizumab, a monoclonal recombinant humanized IgG1 antibody, that binds specifically to the CD11, a subunit of lymphocyte function-associated antigen-1 (LFA-1), specifically developed for psoriasis, has been reported as beneficial for palmoplantar pustulosis. This finding awaits confirmation. Moreover, the drug has recently been withdrawn, due to the development of at least three confirmed cases of progressive, multi-focal leukoencephalopathy in patients on prolonged (>3 years) monotherapy (33).

Further randomized clinical trials are needed to comfirm therapeutic efficacy of biologic agents for palmoplantar pustulosis.

5–aminolevulinic acid photodynamic therapy

A small number of patients have been reported to be treated with photodynamic therapy using 5–aminolevulinic acid (5-ALA) for palmoplantar pustulosis and we have some evidence to suggest a possible modest benefit.

Implications for practice

Many therapeutic modalities have been used to treat palmoplantar pustulosis, but only few high quality studies were identified in the review of Chalmers R, et al. (14). The treatment is often difficult and frustrating.

Topical corticosteroids under occlusion are the first-line therapy. Prolonged therapy is necessary.

Systemic photochemotherapy and systemic retinoids are both of value for palmoplantar pustulosis.

Systemic PUVA can induce clearance in up to 40% of patients with PPP.

Systemic retinoids (0.5 mg/kg/bw/day) may induce improvement in 2/3 of patients with PPP. A good or excellent response may occur in 2/5 of patients with PPP.

Re-PUVA has the best clearance rate in about 2/3 PPP patients and is more favourable in comparison with PUVA or retinoid therapy alone. Oral retinoids in combination with oral PUVA are the best of second-line therapies.

Other therapeutic modalities for PPP have modest effects. Chalmers and coauthors found no eligible studies examining other topical therapies such as tar, anthralin, calcipotriol or tazarotene (14).

Conclusion

Before starting the treatment of patients with PPP, it is necessary to consider the following: patient individual factors - since many patients have already received some previous treatment; specific treatment factors - such as formulation, way of administration (parenteral, oral, topical, physical), dose, concentration, combination of different drugs, different regimens and periods of treatment; site of involvement - due to differences between hands and feet in the probability of response to treatment.

Abbreviations

PPP - Palmoplantar pustulosis
PPPP - Palmoplantar pustular psoriasis
PUVA - Psoralen with ultraviolet A
Re-PUVA - Retinoids and PUVA combination
TNF-α - Tumor necrosis factor–alpha
LFA-1 - Lymphocyte function-associated antigen-1
5-ALA - 5–aminolevulinic acid

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Palmoplantarna pustuloza – ima li pomaka u lečenju?

Sažetak

Definicija: Palmoplantarna pustuloza je hronična upalna bolest koju odlikuju eruptivne pustule na dlanovima i tabanima sa periodima egzacerbacije i parcijalne, retko potpune regresije.

Ne postoji opšta saglasnost da su palmoplantarna pustuloza i lokalizovana, palmoplantarna pustulozna psorijaza ista bolest. Iako je oboljenje poznato pod tim nazivom, palmoplantarna pustuloza se tek trenutno smatra posebnim, od psorijaze odvojenim entitetom.

Etiopatogeneza: Stvarni uzrok nastanka oboljenja nije utvrđen. Fokalne infekcije mogu biti prisutne ali se njihovom sanacijom ne postiže u svim slučajevima izlečenje. Opisani su *de novo* slučajevi u kojima je bolest nastupila u toku terapije antagonistima faktora nekroze tumora alfa. Pojedini slučajevi se mogu povezati sa stresom. Pojedini autori smatraju da je palmoplantarna pustuloza autoimuna bolest. U serumu obolelih otkrivena su antitela usmerena protiv nikotinskih acetilholinskih receptora. Ispitivanja su pokazala da je prevalencija pušača kod pacijenata sa palmoplantarnom pustulozom signifikantno viša od prevalencije u opštoj populaciji i da postoji visoko signitifikantna povezanost između pušenja i pustulozne psorijaze OR=5,3 (2,1–13). Ipak, ne postoje dokazi da prestanak pušenja dovodi do poboljšanja postojećih promena.

Odnos prema psorijazi: Razlike između palmoplantarne pustuloze i plamoplantarne pustulozne psorijaze su brojne. Nedavna genetska ispitivanja nisu utvrdila povezanost između palmoplantarne pustuloze i glavnog lokusa koji se dovodi u vezu sa povišenom genetskom predispozicijom za obolevanje od psorijaze. Većina pacijenata sa palmoplantarnom pustulozom nema psorijazu na drugom delu tela. Prevalencija psorijatičnih promena na udaljenim mestima varira počev od 2% preko 24% do 84%, od studije do studije. Žene obolevaju češće od muškaraca i čine 90% svih obolelih. Palmoplantarna pustuloza pokazuje visok stepen histološke podudarnosti sa psorijazom. Za razliku od psorijaze, kod palmoplantarne pustuloze ne dolazi do vazodilatacije kapilara u paplilarnom dermisu, niti akumulacije neutrofilnih granulocita neposredno ispod kornealnog sloja (*Munro* mikroapscesi).

Terapija: Lečenje palmoplantarne pustuloze

je nezadovoljavajuće Mnogi medikamenti su primenjivani, a nijedan pouzdano ne suprimira bolest niti dovodi do izlečenja (katrani, topijski kortikosteriodi, ditranol, fotohemoterapija, oralni tetraciklini, metotreksat, retinoidi, lokalni ili sistemski, ciklosporin, kolhicin, biološka sredstva).
Lokalna primena kortikosteroida pod okluzijom, jedina je od lokalnih terapijskih procedura, koja se pokazala efikasnom za lečenje palmoplantarne pustuloze. Terapiju održavanja potrebno je sprovesti alternativnim nanošenjem leka svakog drugog/trećeg dana. Potrebne su dalje studije o efikasnosti ostalih preparata za lokalnu primenu.
Najbolji metod za lečenje palmoplantarne pustuloze u drugom terapijskom redu, predstavlja kombinacija sistemskih retinoida i sistemske (oralne) PUVA fotohemoterapije (Re-PUVA). Razlika u efikasnosti između etretinata i acitretina nije utvrđena. Manjkavost sistemske primene retinoida predstavlja opasnost od teratogenog efekta. Sistemskom PUVA terapijom postiže se dobar efekat ali se terapijska efikasnost signifikatno povećava u kombinaciji sa sistemskom primenom retinoida. Ova kombinacija se pokazala suverenom nad monoterapijom, kako u odnosu na PUVA tako i na retinoide.
Liarozole je imidazolski derivat a pripada novoj kategoriji lekova koji blokiraju metabolizam *all-trans* retinoične kiseline putem inhibicije enzima 4-hidroksilaze retinoične kiseline. Pokazao je efikasnost koja s jedne strane obećava ali istovremeno zahteva ozbiljnu proveru. Dobro se podnosi. Neželjena dejstva su kao i kod terapije sistemskim retinoidima, ali je njegova prednost u odnosu na acitretin to što se po prestanku primene lirazola, povišen nivo retinoične kiseline u serumu vraća na fiziološku vrednost u toku samo nekoliko dana.
Ciklosporin primenjen u niskim dozama (2 mg/kgTT dnevno) izaziva signifikantno poboljšanje ali ne i potpuno povlačenje promena.
Zaključak: Terapija treba da bude prilagođena svakom pojedincu, a to znači da je pre započinjanja lečenja potrebno razmotriti činioce kao što su: individualne osobine svakog pojedinog pacijenta, s obzirom da su mnogi pacijenti već prethodno lečeni; faktori specifični za odgovarajući metod lečenja, npr. način primene leka, koncentracija aktivne supstancije, doza, kombinovana primena dva ili više različita leka, različiti režimi u terapijskom pristupu, dužina lečenja; lokalizacija promena, s obzirom na razlike u terapijskom odgovoru između kože dlanova i tabana koje se mogu očekivati.

Ključne reči

Psorijaza + etiologija + terapija; PUVA terapija; Spoljašnja primena; Retinoidi; Teratogeni; Farmakoterapija + neželjena dejstva

Hypohidrotic ectodermal dysplasia - a case report

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Abstract

Ectodermal dysplasias are a large group of disorders characterized by developmental dystrophies of one or more ectodermal structures. Hypohidrotic ectodermal dysplasia is a rare genodermatosis associated with abnormal development of sweat glands, teeth, and hair. Its incidence is 1:100.000 newborns. The full expression of X-recessive forms are only seen in males, while female heterozygotes are moderately or very slightly affected. The disease is characterized by sparse hair, oligodontia, and reduced or absent sweeting, light hair, distinctive facial features, palmoplantar keratoderma.

We report an 11-year-old boy with hypohidrotic ectodermal dysplasia. Despite extensive skin, teeth and hair manifestations, his physical and psychomotor growth and development were normal.

Key words

Ectodermal Dysplasia, Hypohidrotic, Autosomal Recessive; Child; Skin Diseases, Genetic; Signs and Symptoms

Ectodermal dysplasias (ED) are inherited disorders involving the skin, teeth, hair and nails. Hypohidrotic ectodermal dysplasia (HED) or anhidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome) is the most common form of ED. HED was first described by Wedderburn in 1838, and later by Thurnam, in 1848 (1-3).

HED is mainly inherited as an X-linked recessive disorder and the syndrome is fully expressed only in males. Female carriers may show mild features of the syndrome (4,5). The syndrome is characterized by absence of sweating with hyperpyrexia, hypotrichosis and teeth abnormalities (hypodontia or anodontia). The affected individuals have dry skin, sparse and thin scalp hair, while eyebrows may be sparse or totally absent (1-3).

Case report

An 11-year-old boy was admitted to the Pediatric Dermatology Unit, Clinic of Dermatovenereology, Clinical Center of Serbia, with clinical features suggestive of HED. He had dry and sensitive skin since birth. On presentation, his scalp hair and eyelashes were sparse and hypopigmented, the eyebrows were absent and he had marked dark eyelid erythema (Figures 1 and 2). The skin was dry, scaly, lichenified and excoriated. His palms were hyperlinear (Figure 3) with slight nail dystrophy. The nasal bridge was depressed, consistent with a "saddle nose" (Figure 4). Mandibular teeth were absent, while he had maxillar hypodontia with typical conical incisors (Figure 5) and perioral erythema. Further pediatric examination was normal. Routine blood and urine laboratory tests were normal.

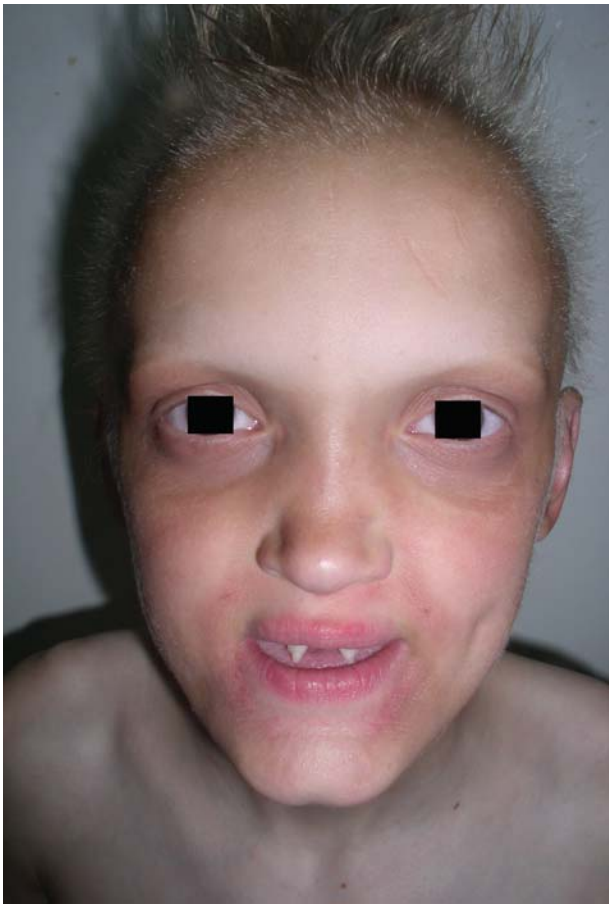

Figure 1. Sparse and hypopigmented hair and eyelashes, absent eyebrows and dark eyelid erythema

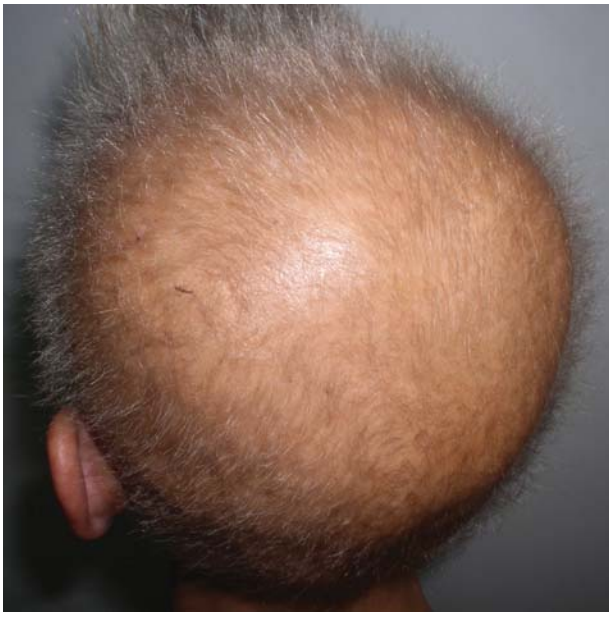

Figure 2. Sparse and hypopigmented hair

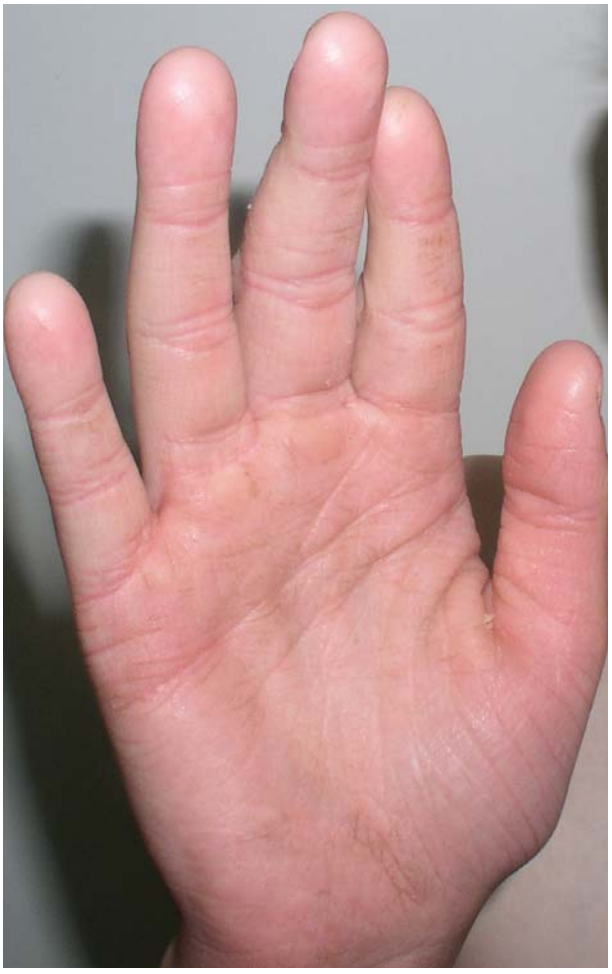

Figure 3. Marked palmar hyperlinearity

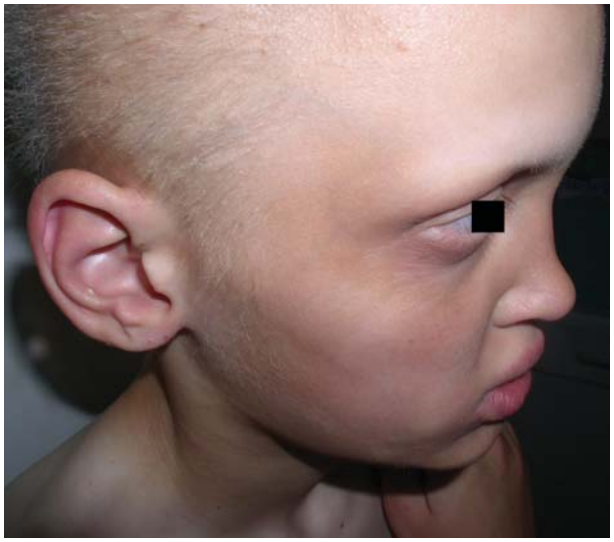

Figure 4. Depressed nasal bridge, thick everted lips, absent eyebrows, dark and wrinkled periorbital skin

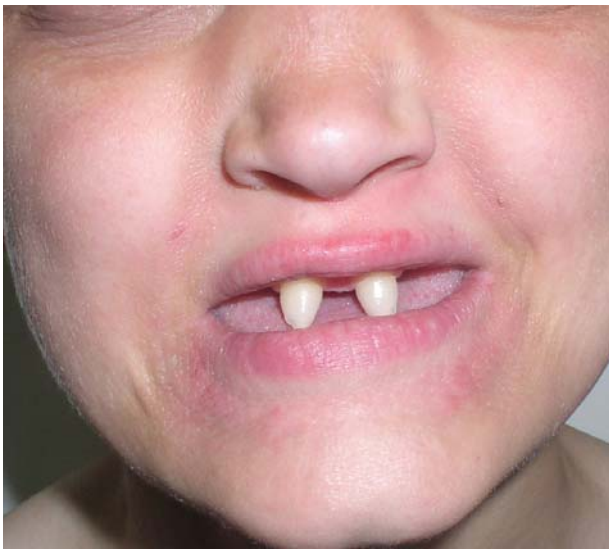

Figure 5. Maxillary hypodontia with typical conical incisors and perioral erythema

The patient's personal history showed one episode of bronchopneumonia during childhood, and congenital hypospadia, for which he underwent surgical correction immediately after birth. The patient also showed physical effort intolerance, reduced sweating and dry and itchy skin. Dentition was delayed, and the first teeth appeared by the end of the first year of life. In family history, the boy's mother suffered from chronic hand eczema.

The treatment included bland emollients and topical glucocorticosteroids for erythematous areas.

Discussion

Hypohidrotic ectodermal dysplasia is a congenital, non-progressive disorder characterized by hypodontia, hypohidrosis and hypotrichosis (1-3). It is inherited in an autosomal dominant, autosomal recessive, or X-linked patterns (4,5). The diagnosis is established by genetic tests or, after infancy, based on physical features. In some patients, the pattern of inheritance is determined by family history, and in others by molecular genetic testing. Also, genetic carrier testing is performed in X-linked and autosomal recessive forms. Ninety-five percent of randomly selected individuals have the X-linked form of HED (4,5).

Three disease-causing genes have been indetified: ectodysplasin A1 (EDA1) gene, accounting for X-linked forms, ectodysplasin A1 receptor (EDAR) gene, and ectodysplasin A1 receptor associated death domain (EDARADD), causing both autosomal dominant and recessive forms (4,5). The EDA1, EDAR, and EDARADD genes provide instructions for making proteins that work together during embryonic development. These proteins form part of the signaling pathway that is critical for the interaction between two cell layers, the ectoderm and the mesoderm. In the early embryo, these cell layers form the basis for many of the body's organs and tissues. Ectoderm-mesoderm interactions are essential for the formation of several structures that arise from the ectoderm, including the skin, hair, nails, teeth, and sweat glands (4,5).

In the neonatal period patients may have dry, scaly skin with periorbital hyperpigmentation. During infancy, the skin may be dry and sensitive, with pronounced heat intolerance (3,6). The diagnosis is often delayed until the teeth fail to erupt at the proper time (6-9 months), or the teeth that erupt are conical in shape. Also, by this age, affected individuals may present with chronic eczema and wrinkled periorbital skin (1,6).

In our patient, skin manifestations were present in the early neonatal period, including scaly and slightly erythematous skin. During infancy, he developed other characteristic manifestations of HED. Dentition was delayed and irregular. His physical and psychomotor development was otherwise normal. Topical bland emollients were recommended, as well as regular dental care and avoiding extreme physical efforts in order to prevent hyperthermia.

Conclusion

Hypohidrotic ectodermal dysplasia is the most common form of ectodermal dysplasias. Patients suffering from hypohidrotic ectodermal dysplasia should be carefully monitored by dermatologists, to provide the best possible skin care agents, and by dentists, in order to prevent caries development and provide interventions if necessary. Patients and parents should be instructed to avoid extreme heat exposure, because of possible problems associated with heat intolerance.

Abbreviations

ED - Ectodermal dysplasias

HED - Hypohidrotic ectodermal dysplasia

EDA1 - Ectodysplasin A1

EDAR - Ectodysplasin A1 receptor
EDARADD – Ectodysplasin A1 receptor associated death domain

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Hipohidrotska ektodermalna displazija – prikaz slučaja

Sažetak

Uvod: Ektodermalne displazije predstavljaju veliku heterogenu grupu naslednih oboljenja kod kojih postoje lezije dva ili više tkiva poreklom iz embrionalnog ektoderma. Nasleđuju se X-vezano recesivno, autozomno dominantno ili autozomno recesivno. Najčešće su zahvaćeni zubi, kosa, ekrine žlezde i nokti. Hipohidrotska ektodermalna displazija – Krist –Simens–Tuarenov sindrom (Christ-Siemens-Touraine) najčešća je forma i čini 80% svih slučajeva ektodermalne displazije.
Prikaz slučaja: Prikazujemo pacijenta, uzrasta 11 godina, koji od rođenja ima suvu kožu i proređenu depigmentovanu dlaku na kapilicijumu. Pri prijemu, koža kapilicijuma, lica, trupa i ekstremiteta bila je u celini suva, sa nejasno ograničenim eritemom i hiperpigmentacijama periokularno, minimalno infiltrovanim bledoeritematoznim lihenihikovanim plakovima na bočnim stranama vrata i fleksurama. Obostrano palmarno i plantarno izražena je hiperkeratoza, hiperlinearnost dlanova, distrofične nokatne ploče. Supercilije u potpunosti nedostaju, cilije proređene, izražena je hipodoncija sa dva klinasto oblikovana zuba na maksili.
Lečenje: Započeta je terapija kortikosteroidnim preparatima za lokalnu primenu i emolijentnim sredstvima. Rutinske laboratorijske analize i pedijatrijski nalaz bili su uredni. Po otpustu, savetovana je upotreba emolijentnih kremova sa preporukom za negu i izbegavanje ekstremnih fizičkih napora. Pacijentu i roditeljima je objašnjen rizik od hiperpireksije.
Zaključak: Hipohidrotsku ektodermalnu displaziju prvi put je opisao Ternam (Thurnam) 1848. godine. Incidencija je 1:100.000 neonatusa. Puna ekspresija X-recesivne forme viđa se samo u muškaraca, dok su ženski heterozigoti umereno ili sasvim slabo aficirani. I pored ekstenzivnih promena na koži, zubima i kožnim adneksima, fizički i psihomotorni rast i razvoj su u fiziološkim granicama za uzrast.

Ključne reči

Hipohidrotska autozomalna recesivna ektodermalna displazija; Dete; Genetske bolesti kože; Znaci i simptomi

Urticaria Pigmentosa in a Patient with Acquired Immunodeficiency Syndrome – a case report

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Abstract

The authors present a case of a man with urticaria pigmentosa and acquired immunodeficiency syndrome - AIDS. The patient was diagnosed as HIV (human immunodeficiency virus) - positive in the year 2000, at the Infectious Diseases Clinic, Clinical Center of Vojvodina in Novi Sad. Urticaria pigmentosa was detected (nine years later) during a dermatological examination at the Dermatovenerology Department of the Outpatient Clinic, Clinical Center of Vojvodina. Urticaria pigmentosa is the most common manifestation of cutaneous mastocytosis. The patient was taking long term antiviral therapy for several years. Approximately 2 years after the onset of urticaria pigmentosa, this patient developed septicemia and ascites along with hepatosplenomegaly, liver damage, chronic cholecystitis, leukopenia, thrombocytopenia and relative eosinophilia. The patient had increased total serum IgE levels and tested positive for 5-hydroxyindoleacetic acid in a 24-hour urine test from the very beginning of urticaria pigmnentosa and during the course of his illness. Immunohistochemical results of dermal biopsy of the affected area confirmed the diagnosis of urticaria pigmentosa. Histology findings confirmed presence of typical dermal mast cell infiltrates with distinct oval and spindle granules that were CD117+ and CD1a-. Systemic mastocytosis was excluded by liver and bone marrow biopsies. To our knowledge, we present the third case of associated mastocytosis and acquired immunodeficiency syndrome published in world literature so far, in order to indicate the possible interaction between HIV infection and mast cells.

Key words

Urticaria Pigmentosa; HIV; Acquired Immunodeficiency Syndrome; Comorbidity

Urticaria pigmentosa is the most common manifestation of cutaneous mastocytosis in children and adults. In children cutaneous mastocytosis can recur, but may also spontaneously involute (1, 2, 3, 4, 5, 6, 7). The clinical picture differs in childhood and adulthood, both regarding the course and prognosis (1,2). Typical clinical manifestations of urticaria pigmentosa are symmetrically distributed yellowish-brown macules or red papular skin changes. The hairy part of the head, hands, feet and face may be spared. Mucosa is rarely affected. Mild irritation (rubbing or scratching) causes release of inflammatory response mediators (histamine, prostaglandins, leukotrienes, cytokines) causing urtica on the irritated site, which is referred to as the Darier's sign (1, 2, 5, 6, 7).

As far as we are concerned, this is a rather peculiar case report, since it represents only the third report of associated acquired immunodeficiency syndrome and mastocytosis in the world literature (8,9); furthermore it arises the question whether this association developes due to possible immunogenetic disorders and immunogenetic rearrangements.

Case report

A male patient 36 years of age, an employed worker, single, with HIV confirmed in the year 2000, was initially diagnosed with idiopathic thrombocytopenia. The patient was taking the same highly active antiretroviral therapy (HAART): ddi (didanosine), 3TC (lamivudine), EFV (efavirenz). His CD4 lymphocyte blood count has been stable ever since (with approximately 300 cells/ml), while HIV Ribonucleic acid (RNA) was undetected in his blood via polymerase chain reaction (PCR). The onset of symptoms occurred approximately 2 years before, when yellowish-brown macules and red papular skin changes appeared mostly on his torso and upper extremities, occasionaly followed by severe itching and reddness when scratched. These symptoms intensified in Fall 2009, when the patient was admitted to the Dermatovenerology Department of the Outpatient Clinic, Clinical Center of Vojvodina. The examination revealed many yellowish-brown maculopapular eflorescences on the torso and upper extremities, associated with severe itching, and a positive Darier's sign (Figures 1 and 2). A punch biopsy was performed by a dermatologist in order to clarify skin changes. Ten days later, the patient was admitted to the Infectious Diseases Clinic due to high fever (up to 39 degrees celsius) and abdominal pain. *Streptococcus agalactiae* was isolated using hemoculture. Inflammatory parameters were lowered by appropriate antibiotic therapy and the patient felt better. However, there was a sudden development of ascites. Control blood CD4 count was decreased (198/ml), while HIV RNA PCR still showed negative results. Symptomatic therapy lead to disappearance of ascites, but splenomegaly persisted.

During 2009, the patient was hospitalized at the Infectious Diseases Clinic, Clinical Center of Vojvodina in Novi Sad four more times, in 2010 six times, and in 2011 on two occasions, when systemic mastocytosis was excluded. The patient had to receive the same highly active antiretroviral HAART therapy, but desloratadine 5mg/day was added as well.

Personal history. Hypersensitivity to various food allergenes. Other problems include irregular bowel movement and diarrhea.

Family history. Negative.

Physical examination. Upon skin examination, yellowish-brown macules and a large number of reddish papules, up to 5mm in size, with a positive Darier's sign were found mainly on the abdomen, chest, back, arms and legs (Figures 1 and 2). No changes were found on patient's mucosa and lips.

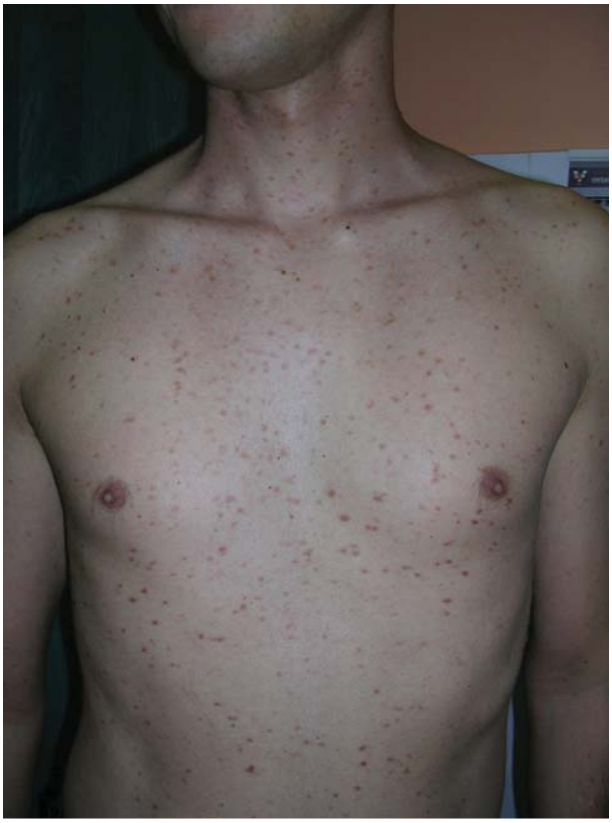

Figure 1. Urticaria pigmentosa in an AIDS patient

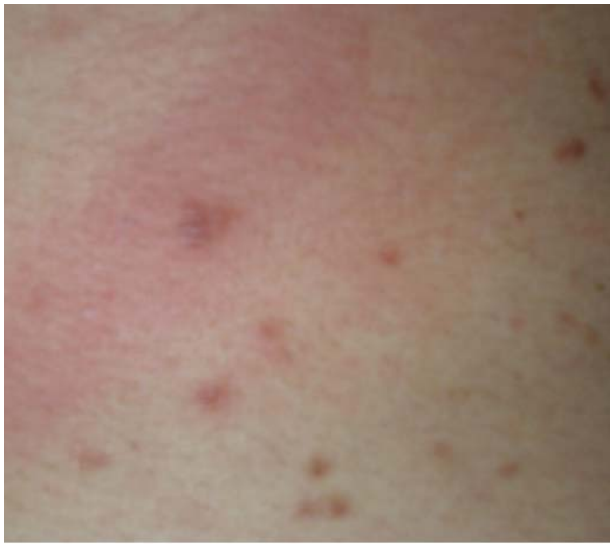

Figure 2. Darier's sign

Laboratory and other test results

Laboratory test revealed the following abnormal results: Leukopenia (low WBC 2.70 x 10^9/L, normally 4-10x10^9/L), thrombocytopenia (78,1 x 10^9/L, normally 140-400 x 10^9/L), relative eosinophilia [0,316 x 10^9/L (normally > 0.470 x 10^9/L); 11.7% of the total white blood count (normally 0-5%)], slightly elevated transaminase activity (ALT 47 UI/mL, AST 56 UI/mL) along with slightly elevated alkaline phosphatase levels 218 U/I (normally < 198 U/I); increased gamma glutamyl transpeptidase levels (223 IU/mL); hemostatic mechanism within reference values (APTT 0.88: PT 1.91; TT 1,10, D-dimer 110); total serum proteins 76 g/l; serum protein electrophoresis indicated hypergammaglobulinemia of 24,9 g/L (normally 7-16 g/L); other basic laboratory test results were normal.

Positive finding of 5-hydroxyindoleacetic acid - 5-HIAA in the 24-hour urine test: 46,9 μmol/dU (reference range 10,4-31.2 μmol/dU).

Total IgE serum levels: significantly increased 1425 IU/ml (reference value 100 IU/ml).

Histopathological result from September 2009: A skin fragment was histologically examined in 12 sections stained with HE, PAS, Gomory and Giemsa methods. The epidermis was uneven and atrophic, with focal irregular elongations and anastomoses with diffuse hyperkeratoses. Slight chronic inflammatory infiltrate with enlarged number of mast cells was found perivascularly in the papilar dermis. Skin adnexa were missing (Figures 3 and 4).

Histological and immunohistochemical test done in September/09 (methods used: HE, Giemsa, immunohistochemical: C-kit): The skin sample revealed a slight ortokeratotic hyperkeratosis, as well as moderate acanthosis with a mild epidermal atrophy and spongiosis. There were dermal edema and moderate perivascular infiltrations of lymphocytes and oval and spindle-shaped cells (CD117+, CD1-). Giemsa staining focally revealed granules within those cells, which undoubtedly indicated mast cells (Figure 4).

Control HIV RNA PCR test: in January/2011 was still negative in the patient's blood**.**

Control blood CD4 counts: were decreased during the 2009-2011 period: in October/09 and January/11 levels were 198/ml and 237/ml, respectively (normally 600-1600/ml).

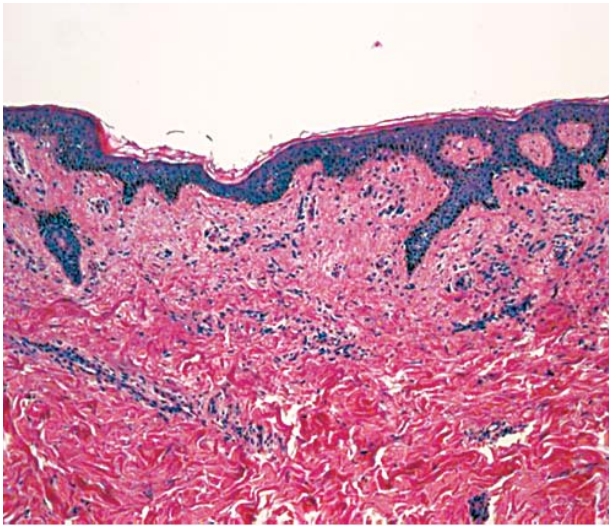

Figure 3. Histological presentation of cutaneous mastocytosis (HE staining x100): scanty perivascular infiltrate in the upper half of dermis.

Control peripheral blood smears: did not point to increased presence of mast cells, but to thrombocytopenia.

Blind liver biopsy showed: signs of a mild form of chronic persisting hepatitis with moderate fibrosis. An increased count of mast cells was not found.

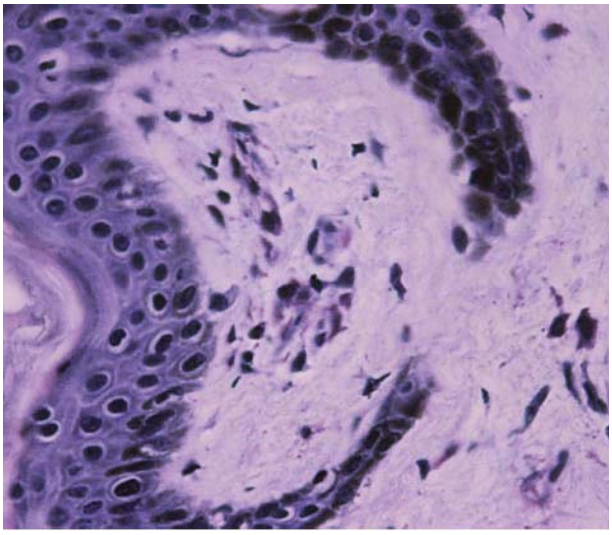

Fig. 4. Histological presentation of mastocytosis (Giemsa staining x400): perivascular infiltrate of mononuclear cells with predominant mastocytes in papillary dermis; the cytoplasms of mast cells are filled with small, faintly visible, eosinophilic or amphiphilic granules which stain metachromatically with the Giemsa stains.

Control bone marrow biopsy: in April/2011 the finding showed no presence of mast cells.

Serum osteocalcin levels were within reference values (21.1 ng/ml; normally 11-46 ng/ml), while **Crosslabs levels** were elevated (857 pg/ml; normally 158-442 pg/ml).

Control immunology tests results were negative: ANA, ANCA, antimitochondrial antibodies, antiparietal cell antibodies, smooth muscle antibodies, and Hep-2 cells ANA test results were negative.

Ultrasound of the upper abdomen: Spleen 167mm. The gallbladder wall was thickened up to 16mm and stratified, without gallstones. A minimal amount of free fluid was registered in the Morison's pouch and around the spleen.

Diagnosis: *Splenomegaly, Ascites, Chronic Cholecystitis.*

Control Doppler US of the portal vein showed: cryptogenic portal vein hypertension; grade IV esophageal varices; thrombosis exclused.

Chest X-ray – normal.

Echocardiography finding normal: without pericardial effusion.

DEXA scan results: within the normal range.

Abdominal computed tomography: Diagnosis: *Splenomegaly, Ascites.*

Abdominal nuclear magnetic resonance: Diagnosis: *Splenomegaly, Ascites.*

Discussion

In our case, the diagnosis of urticaria pigmentosa was established primarily by clinical presentation and the histology of skin biopsy. Taking into consideration the diagnostic criteria which include significantly increased total serum IgE levels and increased levels of 5-hydroxyindoleacetic acid in 24-hour urine, the clinical diagnosis was clearly confirmed. Our patient also had liver damage, chronic cholecystitis, leukopenia, thrombocytopenia and eosinophilia, which at one point suggested a systemic disease.

So far, only two papers have been published on mastocytosis and HIV infection association. The first case was an AIDS patient with systemic mastocytosis and eosinophilia treated with imatinib mesylate therapy (8), and the second was an AIDS patient with cutaneous mastocytosis (9).

According to the The WHO classification of mastocytosis, the following types of mastocytosis and mastocytosis syndromes were differentiated: 1. cutaneous mastocytosis (e.g.urticaria pigmentosa) involving only the skin with excellent prognosis in children, tends to regress spontaneously during adolescence; 2. systemic mastocytosis: mostly affecting more than one organ, without documented cases of spontaneous remission, it exists in several forms: a. indolent systemic mastocytosis, usually occurs with skin changes that are similar to those of urticaria pigmentosa, along with visceral organs involvement with relatively mature mast cells, with absence of hematological abnormalities and signs of progressive damage to internal organs, this form is associated with an almost normal life expectancy; b. aggressive systemic mastocytosis, characterised by progressive infiltration of mast cells which often exhibit cellular atypia into different organs, hematologic abnormalities and splenomegaly are common, while appearance of skin lesions is rare (10%), the prognosis is poor; c. systemic mastocytosis with chronic myelomonocytic leukemia (SM-CMML), characterized by over 10% atypical mast cells in peripheral circulation and diffuse bone marrow infiltration. The disease has a rapid fatal course (3, 4). Due to the suspicion of indolent systemic mastocytosis, the following procedures were repeated in our patient: Doppler portal vein US (which excluded thrombosis); computed tomography and abdominal nuclear magnetic resonance imaging; DEXA-scan – recommended by a hematologist due to elevated alkaline phosphatase levels; bone marrow biopsy. Repeated liver and bone marrow biopsy showed normal count of mast cells, so systemic mastocytosis was excluded as well as the need for interferon therapy.

In differential diagnosis systemic mastocytosis is often mistaken for other lymphoreticular diseases, hairy cell leukemia and histiocytic proliferation due to mast cells granules that may be hard to notice in routine histological sections. The main indication for their identification is the presence of nests of cells that "resemble monocytes" associated with eosinophilia and sclerosis. The systemic mastocytosis diagnosis is than easily confirmed by Giemsa stain method (purple granules), toluidine stain method (metachromatic granules), chloroacetate esterase stain method (bright red granules, with positive granulocytes). Tryptase

immunostaining method is more sensitive than histochemical staining technique for confirming the presence of mast cell differentiation. CD117/c-kit, which shows cell membrane immunoreactivity, also promises to be a sensitive marker (1, 10-13). In our case the diagnosis of urticaria pigmentosa was also confirmed by immunohistochemical findings of numerous spindle-shaped and oval cells (CD117 + and CDla-) present in the dermis. Immunohistochemical finding of mastocytosis is based on the presence of antigen CD117+ on the surface of mast cells (11, 12).

In terms of the aforementioned, systemic mastocytosis is characterised by abnormal mast cell infiltration of the spleen, lymph nodes, bone marrow and liver, with or without skin involvement. There is a predominance of middle-aged male patients, approximately 60 years of age. Patients suffer from skin changes, anaphylaxsis, pain and/or bone fractures (osteoporosis, osteolytic changes, osteosclerosis, or mixed), gastrointestinal symptoms (abdominal pain, diarrhea and peptic ulcer), respiratory difficulties (wheezing, dyspnea), hematological changes (cytopenia, eosinophilia, monocytosis, mast cells in blood circulation) or hepatosplenomegaly. Many of these symptoms are related to the release of histamine from mast cells. Therefore, a third-generation antihistamine was introduced into the therapy of our patient.

Absence of skin changes, presence of cellular atypia, and association with hematological diseases are unfavorable prognostic factors. (1, 10, 11). There are reports on rare association of systemic mastocytosis with mediastinal germ cell tumors (3, 4).

According to several authors, although there are no specific reports on the interaction of human immunodeficiency virus (HIV) and mast cells in AIDS patients, there is an interaction with basophilic granulocytes which are also *FcεRIα* (α subunit of the human high-affinity IgE -receptor) - carriers like mast cells. Firstly, HIV transactivator protein (Tat) acts as a specific chemoattractant for *FcεRIα*-positive cells through its interaction with the CCR3 chemokine receptor (type 3 – protein encoded by CCR3 gene, recently designated as CD193) (13); Secondly, peptides derived from HIV such as HIV-1 envelope gp41 peptides are chemotactic for basophilic granulocytes (14), and finally, basophils show wide HIV receptor surface expression, such as CD4, CCR3, CCR5 (chemokine receptor type 5 – protein encoded by CCR5 gene, recently designated as CD195) and CXCR4 (chemokine receptor type 4 – protein encoded by CXCR4 gene, recently designated CD 184) (15), which, together with HIV Tat protein, can upregulate CCR3 (13). Although there is evidence of HIV infected basophilic granulocytes, the presence of similar analogy between HIV and mast cells remains unclear (9, 13, 16). Nevertheless, recent data provided in *vivo,* showed that in infected persons during HAART, tissue mast cells, raised from infected circulating progenitor mast cells, represent a long-lived reservoir of persistent HIV (17).

Conclusion

We present a case of mastocytosis in an AIDS patient as a third case published in world literature, in order to underline the possibility of development of cutaneous mastocytosis in persons with AIDS, due to immunogenetic damage and possible immunogenetic rearrangements.

Abbreviations

AIDS - Acquired immunodeficiency syndrome
HIV - Human immunodeficiency virus
HAART - Highly active antiretroviral therapy
ddi - Didanosine
3TC - Amivudine
EFV - Efavirenz
RNA - Ribonucleic acid
PCR - Polymerase chain reaction
WBC - White blood count
ALT - Alanine aminotransferase
AST - Aspartate aminotransferase
PT - Prothrombin time
APTT - Activated partial thromboplastin time (
ANA - Antinuclear antibodies
ANCA - Antineutrophil cytoplasmic antibodies
Hep-2 cells.- Ceels derived from a human laryngeal epithelial cell line
US - Ultrasound
DEXA - Dual-energy X-ray absorptiometry
WHO - World Health Organization
SM-CMML - Systemic Mastocytosis with Chronic Myelomonocytic Leukemia
Tat - HIV transactivator protein

FcεRIα - α subunit of the human high-affinity IgE - receptor
CCR3 - chemokine receptor type 3 – protein encoded by CCR3 gene
CCR5 - chemokine receptor type 5 – protein encoded by CCR5 gene
CXCR4 - chemokine receptor type 4 – protein encoded by CXCR4 gene

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Urtikarija pigmentoza kod obolelog od sindroma stečene imunodeficijencije – prikaz slučaja

Sažetak

Uvod: Urtikarija pigmentoza je najčešća manifestacija kutane mastocitoze kod dece i odraslih. Kod dece kutana mastocitoza može da recidivira ali i da spontano involuira. Klinička prezentacija oboljenja kod dece i odraslih razlikuje se, kako po toku tako i po prognozi. Bolest ima tipične kliničke manifestacije u smislu pojave žutosmeđih makuloznih ili crvenih papuloznih promena na koži sa simetričnim rasporedom. Kosmati deo glave, šake, stopala i lice mogu biti pošteđeni. Sluznice su retko zahvaćene. Blaga iritacija (trljanje ili grebanje) izazivaju oslobađanje medijatora inflamatorne reakcije (histamina, prostaglandina, leukotrijena, citokina) koji dovode do pojave urtika na mestu iritacije, što se označava kao Darijeov znak.
Cilj: Prikazujemo slučaj kutane mastocitoze sa urtikarijom pigmentozom kod obolelog od sindroma stečene imunodeficijencije kao treći do sada objavljeni slučaj u nama dostupnoj svetskoj literaturi. Cilj nam je da ukažemo na mogućnost razvoja kutane mastocitoze kod obolelih od AIDS-a zbog imunogenetskih

oštećenja i mogućih imunogenetskih rearanžmana.

Prikaz slučaja: Kod bolesnika (osoba, muškog pola, 36 godine, radnik, zaposlen, neoženjen) je 2000. godine utvrđeno prisustvo infekcije sa virusom humane imunodeficijencije (eng. *Human immunodeficiency virus* – HIV). U Dermatovenerološkom odeljenju Poliklinike Kliničkog centra Vojvodine urtikarija pigmentoza je otkrivena devet godina kasnije pri dermatološkom pregledu. Bolesnik se nalazi na HAART (*Highly Active Anti Retroviral Therapy*) terapiji: (HAART): ddi (didanosine), 3TC (lamivudine), EFV (efavirenz) od 2001. godine. Od tada ima stabilan broj CD4 limfocita oko 300 ćelija/ml i sve vreme nakon uvođenja terapije ima nedetektabilan PCR HIV RNK u krvi. Od pre oko 2 godine dolazi do pojave žućkastosmeđih makula i crvenkastih papula na koži poglavito trupa i gornjih udova, praćenih povremeno jačim svrabom i crvenilom pri trljanju istih. Ove promene se intenziviraju s jeseni 2009. godine. Tada se javlja na pregled u dermatovenerološku službu Poliklinike Kliničkog centra Vojvodine. Na pregledu je utvrđen veći broj žućkastosmeđih makulo-papuloznih eflorescencija na koži trupa i udova, praćenih jačim svrabom. Urađena je „*punch* biopsija" kožnih promena od strane dermatologa, kojom je (Giemsa bojenjem) potvrđena dijagnoza urtikarije pigmentoze. Od pojave urtikarije pigmentoze pa nadalje, bolesnik je imao povišen nivo ukupnih IgE u serumu i pozitivan nalaz 5-hidroksiindol-sirćetne kiseline u 24-časovnom urinu. Imunohistohemijski nalaz, posle uzete biopsije sa mesta kožne promene, potvrdio je dijagnozu pigmentne urtikarije, otkrivanjem tipičnih dermalnih infiltrata mast ćelija sa izraženim granulama, ovalnog i vretenastog oblika koji su bili CD117 + i CD1a- . Bolesnik se javlja na Kliniku za infektivne bolesti zbog visoke temperature do 39˚ C i bolova u stomaku, deset dana kasnije. Iz krvi je iskultivasan *Streptococcus agalactiae.* Bolesnik se dobro osećao posle započinjanja odgovarajuće antibiotske terapije, pokazatelji inflamacije u serumu su bili u padu. Međutim, tada dolazi do naglog razvoja ascitesa. Kontrolni broj CD4 limfocita bio je u daljem padu i iznosio je 198/ml, a PCR HIV RNK u krvi je i dalje bio negativan. Primenjena simptomatska terapija je dovela do iščezavanja ascitesa ali sa održavanjem splenomegalije. U ličnoj anamnezi postojao je podatak o svrabu na mestu promena na koži, neredovnom pražnjenju creva, prolivu, kao i o preosetljivosti na različite nutritivne alergene. Podaci dobijeni u porodičnoj anamnezi nisu imali značaj za sadašnju bolest. U toku 2009. godine pacijent je hospitalizovan na Klinici za infektivne bolesti Kliničkog centra Vojvodine u Novom Sadu još 4 puta, 2010. godine 6 puta, a 2011. godine dvaput, kada je invazivnim dijagnostičkim procedurama (ponovljene kostne srži i biopsije jetre) isključeno postojanje sistemske mastocitoze. Broj CD4+ ćelija je u toku poslednje hospitalizacije iznosio 237/ml, a PCR HIV RNK u krvi je i dalje bio negativan. Pregledom abdomena doplerom, kompjuterizovane tomografije i pomoću nuklearne magnetne rezonancije utvrđena je samo kriptogena portna hipertenzija sa prisustvom variksa jednjaka IV stepena, prisusustvo manje količine ascitesa i hronični holecistitis. Bolesnik je nastavio da po otpustu prima HAART terapiju i desloratadin (5 mg dnevno).

Diskusija: Dijagnoza urtikarije pigmentoze je kod bolesnika postavljena na osnovu anamneze, kliničke slike, relevantnih laboratorijskih nalaza (značajno povišene vrednosti ukupnih IgE u serumu i povišene vrednosti 5-hidroksi-indol sirćetne kiseline u 24-časovnom urinu i histološkim pregledom (specifično bojenje) biopsije kožnih promena i, posebno, imunohistohemijskim nalazom prisustva brojnih vretenastih i ovalnih ćelija u dermisu koje su CD117+ i CD1a-. Kod našeg bolesnika pronađena su i oštećenja jetre, hronični holecistitis, leukopenija, trombocitopenija i eozinofilija (relativna) koji su u jednom momentu pobuđivali ozbiljnu sumnju na sistemsku mastocitozu. Sistemska mastocitoza se karakteriše progresivnom infiltracijom različitih organa mast ćelijama koje često ispoljavaju ćelijsku atipiju. Hematološke abnormalnosti i splenomegalija su uobičajene. Iz ovih razloga rađene su višestruke biopsije jetre i kostne srži, kao i CT i MR pregled jetre i abdomena. Kako ovi pregledi i metode nisu mogle potvrditi prisustvo mast ćelija u većem broju, došlo se do zaključka da u ovom momentu nema elemenata za dijagnozu sistemske bolesti. Biopsija jetre je otkrila samo blag oblik hroničnog persistentnog hepatitisa sa fibrozom.

Prema podacima iz literature, kod obolelih od AIDS-a utvrđena je interakcija između virusa i bazofilnih granulocita: HIV transaktivacioni protein (Tat) predstavlja specifični hemoatraktant za ćelije koje na svojoj površini poseduju receptore visokog afiniteta za vezivanje imunoglobulina klase E (*FcεRI*α pozitivne ćelije), hemotaksija se odvija uz pomoć hemokinskog

receptora tip 3 (CCR3); peptidi u sastavu virusnog glikoproteina gp41 – HIV gp41 predstavljaju hemoatraktante za bazofilne granulocite; na svojoj površini, bazofilni granulociti poseduju HIV receptore (CD4, CCR3, CCR5, CXCR4) koji zajedno sa HIV-Tat proteinom povećavaju ekspresiju CCR3. Ipak, za sada nedostaju publikovani radovi o interakciji između virusa humane imunodeficijencije (HIV) i mast ćelija (koji takođe na svojoj površini nose isti receptor *FcεRI,* kao i bazofili).

Zaključak: Prikazani slučaj ne predstavlja samo treći do sada u svetu publikovan slučaj mastocitoze kod bolesnika sa AIDS-om, nego, ukazuje i na potrebu za daljim ispitivanjem moguće patogenetske uloge imunogenetskih oštećenja i imunogenetskih rearanžmana kod obolelih od AIDS-a.

Ključne reči

Urticaria Pigmentosa; HIV; Sindrom stečene imunodeficijencije; Komorbiditet

Inovacije u savremenoj tehnologiji sečiva i brijača

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UVOD

Vrhunska tehnologija kod brijača

Relativno jednostavan izgled modernih brijača krije njihovu sofisticiranost. Oni su proizvodi godina opsežnih istraživanja.

Dugo nasleđe Gillette-a u dizajnu brijača rezultovalo je dubokim razumevanjem muškaraca, njihove kože i definicijom njihovog idealnog brijanja: Poboljšana blizina sa optimalnim komforom. Iako dodavanje još sečiva na naše brijače sa tri sečiva obezbeđuje poboljšanu blizinu, ispupčenja kože između sečiva mogu da dovedu do povlačenja i nelagodnosti.

Najnovija tehnologija kod brijača optimizuje performanse u obe oblasti i obezbeđuje veliku blizinu u kombinaciji sa velikim komforom i minimalnom iritacijom koze.

CILJ

Optimizovati naše brijače sa tri sečiva za blizinu i udobnost putem napretka inženjeringa, hemije, fizike i biologije.

- Poboljšati blizinu dodavanjem više sečiva
- Optimizovati komfor postavljanjem sečiva bliže jedno drugom
- Postizanje najtanje moguće ivice sečiva zadržavajući snagu i izdržljivost

METODE

Tehnologija koja stoji iza svakog napretka

Ceo proces inovacije počinje i vođen je potrošačem. Laboratorije Gillette tehnološkog centra u Redingu (GTCR), u Velikoj Britaniji (na slici desno) okupljaju naučnike i inženjere sa iskustvom u više disciplina: od razumevanja potrošača, inženjeringa i dizajna do istraživanja muške kože.

Mikroskopske tehnike snimanja, uključujući snimanje velikom brzinom, omogućavaju istraživačima da proučavaju interakciju svakog sečiva sa dlakom i kožom pod uvećanjem. Naučna saznanja i potrebe potrošača su prevedene u ideje i koncepte za novi proizvod. Oni su pretvoreni u radne prototipe preko koncepta modeliranja i mogućnosti inženjeringa.

Ovo je upotpunjeno sa visoko preciznim zasedanjem i inspekcijom brijača za kontinuiranu evaluaciju proizvoda sveopštim testiranjem od strane potrošača. Gillette tehnološka laboratorija za brijanje, GTCR-ova sestra laboratorija u Bostonu, dalje razvija prototipe u komercijalni, proizvodni dizajn, kroz naprednu materijalnu nauku, inženjering i testiranje potrošača.

ZAKLJUČCI

Brijač sa pet sečiva NIBS je glavni tehnološki podvig za naučnike i unapređenje za potrošače u odnosu na našu tehnologiju brijača sa tri sečiva. Naučnici iz Gillette-a su razvili nove načine da optimizuju brijanje:

- Optimizacija raspona između sečiva
- Optimizacija tehnologije ivice sečiva
- Dalja optimizacija tehnologije kertridža i drške brijača (podaci nisu prikazani)

REZULTATI

Pet sečiva sa uskim rasponom međusečiva (NIBS)

Tehnička ispitivanja i istraživanja potrošača ističu prednosti korišćenja pet sečiva raspoređenih blizu jedno drugom u poređenju sa tri sečiva.

Tehnička ispitivanja

Napravljene su replike ispupčenja kože koja se formiraju između sečiva kertridža brijača kada je postavljen na lice sa kontrolisanim punjenjem[1,2].

Analize tih replika pod mikroskopom sa marginalnom projekcijom pokazale su značajno smanjenje veličine ispupčenja kože ispod sečiva kada se koristi brijač sa pet sečiva sa uskim razmakom u odnosu na brijač sa tri sečiva (vidi sliku 1)

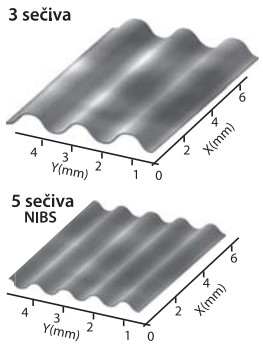
Razmak sečiva koja su na blizini od 0,45 mm dovodi do 40% smanjenja veličine ispupčenja. Ovo smanjenje je povezano sa smanjenjem pritiska na kožu što dovodi do poboljšanja komfora i manje iritacije kože.

Testiranje potrošača

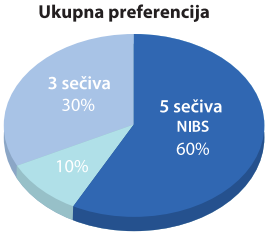
Studija rađena na preko 200 muškaraca koji se briju više od 10 puta procenjuje preferencije muškaraca kada koriste bilo naše standardne brijače sa tri oštrice ili prototip brijača sa pet sečiva raspoređenih blizu jedan drugom. Veliki broj atributa je proučavan, uključujući komfor, blizinu, i ukupno iskustvo brijanja (vidi sliku 2).

Rezultati pokazuju da muškarci znatno ($p<0.05$) osećaju poboljšanje opšteg zadovoljstva brijačem sa pet sečiva.

Štaviše, pri proceni preferencija muškaraca u više od 68 atributa, brijač sa pet oštrica je bio značajno preferiran u svim kategorijama, uključujući blizinu i komfor (podaci nisu prikazani).



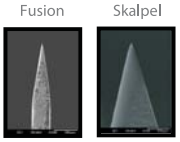
Grafikon 1.3-D Slika replike pokazuje kako brijač sa pet sečiva sa uskim razmakom između uzrokuje manje ispupčenje kože u odnosu na brijač sa tri oštrice.



Grafikon 2. Rezultati istraživanja potrošača pokazuju da muškarci preferiraju brijač sa pet sečiva sa uskim razmakom između u odnosu na nas brijač sa tri oštrice.

Tehnologija ivice sečiva

Što je uža ivica sečiva, lakše može kroz jaku dlaku brade, što dovodi do bližeg, komfornijeg brijanja. Gillette je optimizovao oštrinu svakog sečiva (vidi sliku 3).

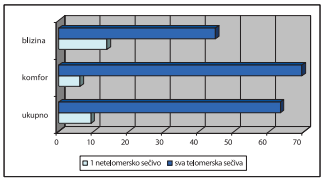


Grafikon 3. Gillette ivice sečiva (levo)su tanje nego hirurški skalpel (desno).

Grafikon 4. Dijagram premaza sečiva

Da bi se zadržalo dovoljno snage u ovoj oštrini, supstrat od nerđajućeg čelika se tretira sa tankim slojem premaza kao sto su Ugljenik nalik dijamantu (DLC) i Platinum-hrom za poboljšanu otpornost na koroziju (vidi sliku 4). Spoljni premaz telomera obezbeđuje površinu sa malim trenjem, koji je povezan sa poboljšanom udobnošću. Ovo je potvrđeno testiranjem potrošača.

Studija sa 65 muškaraca pokazala je značajno ($p<0.001$) manje preferencija u ukupnom zadovoljstvu, komforu i blizini kada se uporede brijač gde telomer nije bio prisutan na prvom sečivu brijača i brijač na kome su sva sečiva obložena telomerom (vidi sliku 5).



Grafikon 5. Rezultati studije potrošača pokazuju efekat telomerom obloženih sečiva prilikom iskustva brijanja muškaraca.

Preporuke:

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Direktor Gradskog zavoda za kožne i venerične bolesti, Beograd

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P&G Lepota i Nega

Hideko Kamino and the eponym linked to her name

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Abstract

In 1979, Kamino and colleagues described pink globules, in the epidermis of Spitz nevi. These globules, later known as Kamino bodies, were PAS-positive, diastase-resistant, and positive on trichrome staining. Their presence does not rule out malignant melanoma completely, but makes it less likely, since similar globules were noted in the epidermis in only 2% of malignant melanomas and 0.9% of ordinary melanocytic nevi. The globules in malignant melanomas and ordinary melanocytic nevi were negative with PAS and trichrome staining. In 2010, Dr. HidekoKamino, received the Walter R. Nickel Award for Excellence in the Teaching of Dermatopathology. This short communication is about Professor Kamino and the dermatopathological condition that bears her name.

Key words

Dermatology; Pathology; Nevus, Epithelioid and Spindle Cell; Awards and Prizes, Non MeSH: Kamino Bodies

Hideko Kamino (Figure 1) is a world-renowned American dermatopathologist who was born to Japanese parents (1). Among her great medical contributions, she is credited for describing eosinophilic globules in cases with Spitz nevus (2), later known as Kamino bodies (3-5). This short communication is about Professor Kamino and the dermatopathological condition that bears her name.

Kamino bodies are pale eosinophilic globules (now known to comprise basement membrane material) that stain positively with periodic acid-Schiff and trichrome and are commonly found in the dermal-epidermal junction of Spitz nevi. The eosinophilic nature of these structures is often obscured by melanin pigmentation.

Kamino bodies are hyaline structures that are seen in skin biopsies of Spitz nevi. Their presence does not rule out malignant melanoma completely, but makes it less likely. Kamino bodies were once believed to have been degenerated basal cells or melanocytes. However, studies have shown that they comprise collagen (type 1V and VII), laminin, and fibronectin, among other substances.

In 1979, Kamino and colleagues described dull pink globules in the epidermis of 65% of junctional, 75% of compound, and 25% of intradermal types of Spitz nevi (the nevi of large spindle and/or epithelioid cells). These globules were PAS-positive, diastase-resistant, and positive on trichrome staining. Similar eosinophilic globules were noted in the epidermis in only 2% of malignant melanomas and 0.9% of ordinary melanocytic nevi. The globules in malignant melanomas and ordinary melanocytic nevi were negative with PAS and trichrome staining.

Kamino and colleagues concluded that PAS- and trichrome-positive eosinophilic globules in the epidermis can aid in the histological differentiation of Spitz nevus from malignant melanoma.

In a latter publication (6), Dr. Kamino studied 9 cases of Spitz nevi of compound type, which had large homogeneous eosinophilic globules at the dermoepidermal junction. All 9 cases were positive

Figure 1. Hideko Kamino, a world-renowned American dermatopathologist who was born to Japanese parents

for fibronectin by indirect immunofluorescence. The study demonstrated that fibronectin, which is present in the extracellular matrix, is expressed in a homogeneous pattern in the eosinophilic globules of Spitz nevi.

Kamino bodies are common in Spitz nevi. However, in 2 recent studies (4,5), Kamino bodies were observed in a minority (11% to 34%) of Spitz nevus cases.

Dr. Hideko Kamino is currently an Associate Professor of Dermatology and Pathology at the New York University School of Medicine (1). Dr. Kamino graduated with honors from the National Autonomous University of Mexico and trained in dermatology at the Institute of Tropical Diseases in Mexico City, sponsored by the National Autonomous University of Mexico (1). She did her anatomic pathology training at the Mount Sinai Hospital in New York City and University of California in Los Angeles. Her dermatopathology fellowship was performed with Dr. A. Bernard Ackerman at New York University.

Dr. Kamino has been a director of dermatopathology and a director of the dermatopathology fellowship training programs at the Duke University and New York University. She has presided over many associations, most notably the American Society of Dermatopathology. Dr. Kamino has published more than 100 papers in peer-reviewed journals and authored several book chapters. During her academic career, her passion has been teaching residents and fellows, for which she has received several awards from the Duke University and New York University (1).

In 2010, Dr. Kamino received the Walter R. Nickel Award for Excellence in the Teaching of Dermatopathology, which is awarded annually to honor an individual who has made great contributions to the education of dermatopathology (1).

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Hideko Kamino i eponim vezan za njeno ime

Sažetak

Uvod: Ovaj rad posvećen je profesorki Kamino i dermatopatološkom fenomenu koji je otkrila i prva opisala, nazvanom njoj u čast, Kamino telašca.

Dr. Hideko Kamino: Doktorka Kamino je vanredni profesor dermatologije i patologije na Medicinskom fakultetu Univerziteta u Nju Jorku. U 2010. godini, Dr Kamino dobila je prestižnu nagradu Walter R Nickel za maestralno održana predavanja iz oblasti dermatopatologije.

Kamino telašca: Dr Kamino je sa saradnicima 1979. godine opisala svetlo ružičaste globule, kasnije nazvane Kamino telašca u epidermisu 65% junkcionih, 75% složenih i 25% intradermalnih tipova Spitz nevusa Ove globule bile su PAS-pozitivne, dijastaza rezistentne i trihom-pozitivne. Prisustvo eozinofilnih globula u epidermisu se može dokazati kod samo 2% malignih melanoma i 0.9% običnih melanocitnih nevusa ali su globule PAS-negativne i trihrom-negativne.

Zaključak: Kamino i saradnici zaključili su da PAS-pozitivne i trihrom-pozitivne eozinofilne globule u epidermisu mogu olakšati histološku diferencijaciju Spitz nevusa od malignog melanoma: njihovo prisustvo smanjuje verovatnoću da se radi o malignom melanomu ali ga u potpunosti ne isključuje.

Ključne reči

Dermatologija; Patologija; Epitelni nevus vretenastih ćelija; Priznanja i nagrade, Ne MeSH: Kamino telašca

Report on the 20th Congress of the European Academy of Dermatology and Venereology, Lisbon 2011

The 20th Congress of the European Academy of Dermatology and Venereology was held in Lisbon, the capital of Portugal, from 20-24 October, 2011. This was the second Congress of the EADV held in Lisbon, the first being held in 1996. There were many exciting new advances in the understanding of the pathogenesis and management of skin and venereal diseases. The leading world authorities on many diseases gave plenary lectures and focus sessions.

There were 1.898 abstracts submitted for the Congress. They were reviewed by 35 international and national reviewers and classified as posters or oral presentations. The Congress Program included the following oral presentations from Serbia: "Autoantibody profiles in connective tissue diseases: diagnostic and prognostic implications" by M. Nikolić (in the session "The Immune System and Autoimmune Diseases"); "The use of fractional Er YAG laser for hair growth in the treatment of androgenetic alopecia" by J. Kozarev; "Q-switched Nd YAG non-ablative and fractional Er YAG ablative procedure for smokers melanocytic pigmentations" by J. Kozarev; "New RF system for dermal tightening: A review of

Figure 1. Assist. Prof. Dr. Lidija Kandolf-Sekulović and Assist. Prof. Dr. Željko Mijušković at the Congress of the EADV in Lisbon, 2011

the technique and results from 1.000 patients" by M. Milojević and I. Jeremić (in the session "Cosmetic Dermatology and Laser"); " Extragenital and intraanal giant condylomata of Buschke-Loewenstein. A new RF system as an effective treatment alternative" by I. Jeremić and M. Milojević (in the session "STD and Miscellaneous"); "The treatment of haemangiomas with propranolol" by B. Trifunović, D. Zamaklar and I. Rakić (in the session "Pitfalls in Clinical Practice/ Systemic Therapy"); "Relationship between GST and IL-10 gene polymorphisms and clinical characteristics of patients with basal cell carcinoma" by Z.P. Mijušković, L. Kandolf-Sekulović, B. Cikota-Aleksić and Z. Magić (in the session "Melanoma and Non-Melanoma Skin Cancers"), regarding polymorphism in genes activated by exposure to UV irradiation, such as glutathione S-transferase (GST).

Ljiljana Medenica was the chair in the session "Acne: related disorders and infectious diseases". There were 39 poster presentations from Serbia.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2012

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
19-21 January, 2012	International Congress in Aesthetic Dermatology (ICAD), Bangkok, Thailand	No deadline information	www.euromedicom.com
26-29 January, 2012	14th International Master Course on Aging Skin (IMCAS) Annual Meeting, Paris, France	No deadline information	www.imcas.com
31 January - 4 February 2012	8th World Congress of the International Academy of Cosmetic Dermatology (IACD), Cancun, Mexico	1 September, 2011	www.wcocd2012.com
12-15 February, 2012	European Academy of Allergy and Clinical Immunology (EAACI) Winter School, Are, Sweden	15 November, 2011	www.eaaci.net/activities/allergy-schools
05-07 March, 2012	2nd World Congress on Clinical and Experimental Dermatology Omaha, United States	No deadline information	www.omicsonline.org/dermatology2012
27-29 March, 2012	Dubai World Dermatology and Laser Conference – Dubai Derma, Dubai, UAE	30 November, 2011	www.dubaiderma.com
29-31 March, 2012	10th Anti-Aging Medicine World Congress and Medispa, Monte Carlo, Monaco	30 November, 2011	www.euromedicom.com
29 March - 01 April, 2012	European Academy of Allergy and Clinical Immunology (EAACI) Allergy School Davos, Switzerland	25 March, 2012	www.eaaci.net/activities/allergy-schools
11-14 April, 2012	European Academy of Allergy and Clinical Immunology (EAACI) focused meeting: Drug Hypersensitivity, Munich, Germany	10 February, 2012	www.eaaci-dhm2012.com
12-15 April, 2012	4th Spring Meeting of the International Society for Dermatologic Surgery (ISDS), New Delhi, India	15 February, 2012	www.isdsworld.com
19-22 April, 2012	9th EADV Spring Symposium Verona, Italy	23 January, 2012	www.verona2012.eadv.org
16-20 June, 2012	European Academy of Allergy and Clinical Immunology Congress 2012 Geneva, Switzerland	18 January, 2012	www.eaaci2012.com
27 June - 01 July, 2012	3rd World Psoriasis and Psoriatic Arthritis Confernce 2012, Stockholm, Sweden	1 March, 2012	www.ifpaworldconference.com
11-14 July, 2012	38th Annual Meeting of the Society for Pediatric Dermatology Monterey, United States	No deadline information	www.pedsderm.net
26-28 August, 2012	6th International Congress on Dermato-Epidemiology, Malmö, Sweden	1 May, 2012	www.idea2012.net
19-22 September, 2012	42nd Annual Meeting of the European Society for Dermatological Research, Venice, Italy	No deadline information	www.esdr2012.org
27-30 September, 2012	21st EADV Congress Prague, Czech Republic	21 March, 2012	www.eadvprague2012.org

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

AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

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

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

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

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

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

All manuscripts should be submitted to the **Editor in Chief: Prof. Dr. Marina Jovanović***, Clinic of Dermatovenereologic Diseases, Clinical Center of Vojvodina, Hajduk Veljkova 1-3, Novi Sad, Serbia, by mail to: serbjdermatol@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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KOMPLEMENTARNA MEDICINSKA NEGA KOJA DELUJE NA SVA 4 UZROKA ZBOG KOJIH NASTAJU AKNE

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

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

Eucerin DermoPURIFYER komplementarna hidratantna krema SPF 30

Osim patentom zaštićenog kompleksa protiv akni ova krema sadrži:

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

Efikasnost i veoma dobra podnošljivost na koži dokazana je kliničkom studijom.
Klinička studija Eucerin DermoPURIFYER Komplementarna hidratantna krema[1]:

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

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

[1] Eksterna klinička in-use studija, 29 pacijenata koji su na nekoj medicinskoj terapiji akni (na primer retinoidi, benzoil peroksid); nakon 8 nedelja korišćenja preparata, vizuelna procena na početku tretmana, nakon 4. i 8. nedelje, fokus na dobroj podnošljivosti

Cover figure: Christ Healing Ten Lepers, Christ's Miracles, XIVth century, The monastery Visoki Dečani, Serbia, Kosovo

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