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

Lisinopril-Induced Pemphigus Foliaceus in a Patient with Diabetes Mellitus and Kaposi-Juliusberg Varicelliform Eruption

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Abstract

Drugs have often been implicated as the cause of pemphigus. Lisinopril is a drug of the angiotensin-converting enzyme inhibitor class primarily used in the treatment of hypertension, congestive heart failure, heart attacks, and also in preventing renal and retinal complications of diabetes mellitus. Various side-effects have been described in the English medical literature related to lisinopril, but only one case with pemphigus foliaceus as an adverse reaction to lisinopril.
To the best of our knowledge, we present the second case of lisinopril-induced pemphigus foliaceus complicated with Kaposi-Juliusberg varicelliform eruption in a patient diabetes mellitus type II.
A 60-year-old man presented with diffuse erythema on the face, trunk and extremities. Disseminated erosions, 2-5 mm in diameter, and umbilicated vesicles were present. Erosions with remnants of the blister roof were partially found on the trunk. Semiannular erosions were present. On the posterior part of the trunk (paravertebral and vertebral) there were inifiltrated, partially grouped, sharply delineated yellowish-reddish plaques, up to 2 cm in diameter. Direct and indirect immunofluorescence test as well as histological analysis revealed a drug-induced pemphigus foliaceus. After treatment of Kaposi-Juliusberg eruption and impetiginization, lisinopril was discontinued. Rapid involution of the skin lesions, was observed. Since, only minor skin lesions still persisted after 6 months of follow-up and treatment, the diagnosis of drug-induced pemphigus foliaceus was established.
It usually takes 1 - 6 months for angiotensin-converting enzyme inhibitors to induce pemphigus. All drugs taken by the patient, including homeopathic agents, over-the-counter drugs, and even medications that were discontinued should be taken into consideration. Medical history taking should be repeated in cases where there is no response to therapy.

Key words

Porokeratosis; Dermoscopy; Cryotherapy; Treatment Outcome

Pemphigus foliaceus (PF) is an acquired autoimmune blistering disease where IgG autoantibodies target the intercellular adhesion glycoprotein desmoglein-1 (dsg-1). Binding of these autoantibodies to dsg-1 is principally expressed in the epidermal granular layer. The consequence is acantholysis and formation of subcorneal blisters within the epidermis (1). Clinical manifestations of the disease are fragile, superficial blisters that easily rupture leaving erosions. The pathogenic effect of IgG4 autoantibodies in PF was demonstrated by positive passive transfer test from human sera to neonatal mice (1). Different factors that may cause pemphigus can be described by the acronym PEMPHIGUS: *PE*sticides, *M*alignancy, *P*harmaceuticals, *H*ormones, *I*nfectious agents and *I*mmunization, *G*astronomy, *U*ltraviolet radiation, and *S*tress (2).

Drugs have often been implicated as the cause of pemphigus. The culprit medication, even over-the-counter (OTC) products should be checked in each new patient with pemhigus (2). Lisinopril ($C_{21}H_{35}N_3O_7$) is a lysine derivative of enalaprilat,

the active metabolite of enalapril, which contains an amide group (3). Lisinopril is a drug of the angiotensin-converting enzyme (ACE) inhibitor class primarily used in the treatment of hypertension, congestive heart failure, heart attacks, and also in preventing renal and retinal complications of diabetes mellitus (4). Various side-effects have been described in the English medical literature, related to lisinopril (3,5,6), but only one case with pemphigus foliaceus as an adverse reaction to lisinopril (3).

We present the second case of lisinopril-induced pemphigus foliaceus complicated with Kaposi-Juliusberg varicelliform eruption in a patient with diabetes mellitus type II.

Case report

This is a case report of a 60-year-old man from the surroundings of Trstenik, Serbia. On admission to our Clinic the patient was subfebrile, with diffuse erythema on his face, trunk and extremities. Also, disseminated erosions, 2-5 mm in diameter, and umbilicated vesicles were present. Erosions with remnants of the blister roof were found partially on the trunk. Semi-annular erosions were also present on the trunk. On the posterior part of the trunk (paravertebral and vertebral) there were inifiltrated, partially grouped, sharply delineated yellowish-reddish plaques, up to 2 cm in diameters. No mucosal lesions were detected.

Personal history revealed a ten-year history of diabetes mellitus and a 2-year history of hypertension. Family history: both parents suffered from arterial hypertension; mother also suffered from diabetes mellitus and asthma. The patient observed the skin condition 1,5 years before admission, and claimed to be allergic to bisoprolol. The first skin lesions appeared in 2007, as erythema, scales and pruritus on the trunk, scalp and upper extremities. The patient was treated for atopic dermatitis with local therapy on occasional dermatological appointments. In September 2011, the patient's skin condition worsened and he presented with high fever. He was admitted to the Dermatology Department and was treated for atopic erythroderma for 8 days with 100 mg of methylprednisolone daily followed by a gradual taper, antihistamine chlorpheniramine maleate tablets 2x25 mg regularly, and chlorpheniramine injections 20 mg/day if necessary. Also, procaine benzylpenicillin 1600 000 i.u. was administered. The patient's standard therapy included metformin tablets 1000 mg/day for diabetes mellitus and lisinopril tablets 10 mg/day for arterial hypertension. Topical corticosteroid and emollient therapy were administered, too. Histology revealed parakeratosis, intact stratum granulosum, and chronic dermal inflammation. This was diagnosed as drug-induced generalized exfoliative dermatitis. The therapy was not changed, as pruritus and skin lesions gradually resolved, and the patient was afebrile. However, 5 days later, disseminated papulo-vesicular eruption appeared. The new lesions mostly involved the face, scalp and trunk and the eruption was accompanied by high fever. On discharge, the patient was recommended to receive metformin tablets 1000 mg/day, Aciclovir tablets 5x200 mg, and B complex vitamins.

Upon admission to our Clinic, the patient presented with erythroderma, umbilicated vesicles and rounded yellowish crusts, erosions with remnants of blister roofs, while some of erosions were semiannular (Figures 1a and 1b). On the proximal parts of the extremities and trunk there were some erythematous patches with scales (Figure 1a).

Laboratory tests revealed the following abnormal results: low erythrocyte count - 3.5 x 10^{12}/L, low hemoglobin levels - 106 g/L, low serum iron level - 4.1 μmmol/L, slightly reduced total iron binding capacity - 44 μmmol/L, blood glucose levels highly elevated up to 27.4 mmol/L, HgbA1c was elevated. Other biochemical results including hepatogram, renogram, proteinogram, lactate dehydrogenase and creatine kinase were within normal ranges.

Immunology tests results: antistreptolysin O (ASO) titre was normal; serum IgE level was elevated - 725 IU/ml (normal range up to 100); antinuclear factor on Hep-2 cells and anti - SS-A (Ro) antibodies, were negative.

Virology tests: anti Herpes simplex virus type-1 immunoglubulin (Ig) G titer of 1: 640 showed four-fold decrease after one month; anti Herpes simplex virus type-2 immunoglubulin G titer was 1: 40 and remained unchanged.

Hormone tests: thyroid-stimulating hormone, free thyroxine and adrenocorticotropic hormone were within normal ranges.

Direct immunofluorescent test revealed IgG in the intercellular substance of epidermis. No IgA,

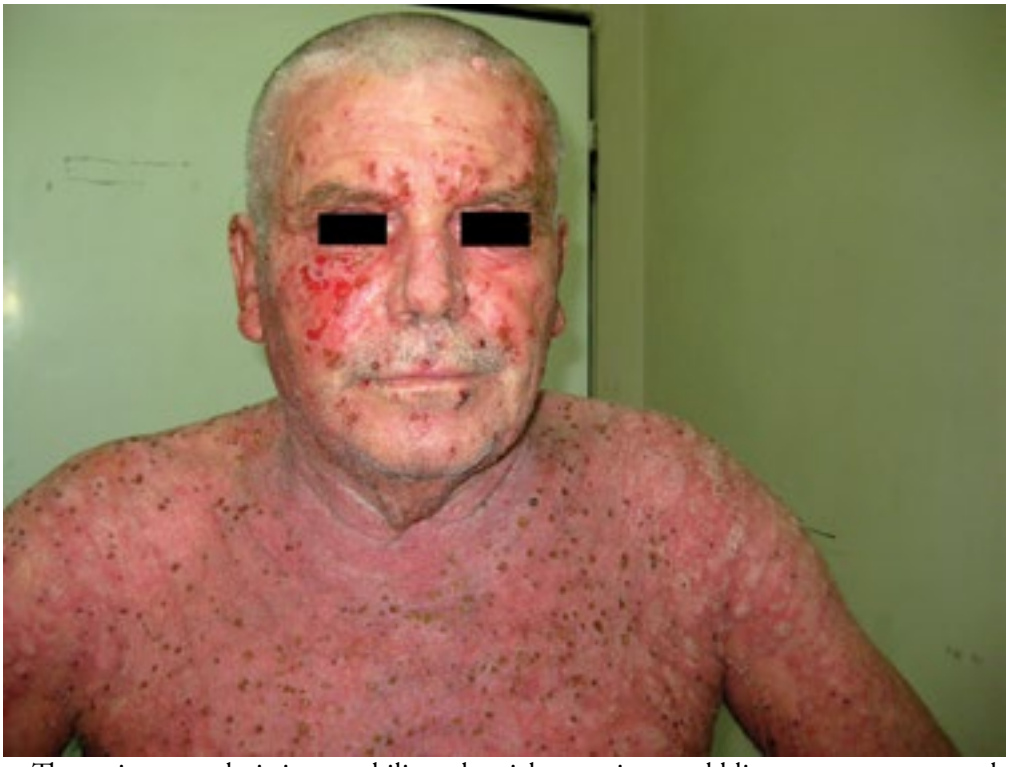

Figure 1a. The patient on admission: umbilicated vesicles, erosions and blister remnants on erythematous infiltrated skin

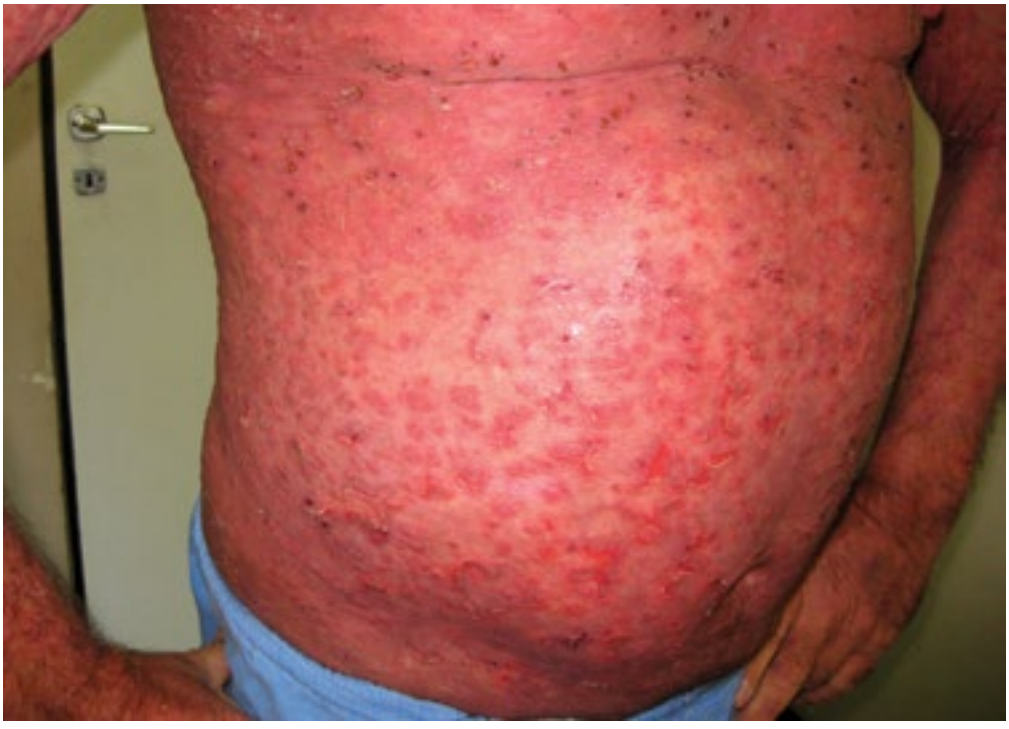

Figure 1b. The patient on admission: erosion with remnants of the blister roof, some semiannular in shape, umbilicated vesicles and erythroderma

IgM and complement component C3 deposits were observed, thus indicating a diagnosis of autoimmune pemhigus. Indirect immunofluorescence test was positive with a titer of 1 : 160. Histological tests revealed epidermal hyperkeratosis and acanthosis, whereas in the corneal layer subcorneal clefts were observed with acantholytic cells. Acantholysis was present focally in the *stratum spinosum*. Dermal blood vessels were surrounded by lymphocytes and eosinophils. Histology was consistent with pemphigus foliaceus (Figure 1c). The first therapy included aciclovir tablets 5x200 mg, antibiotics: (trimethoprim-sulfamethoxazole), metformin tablets 1000mg/day, and insulin (due to unsatisfactory glycemic control). Upon resolution of erosions and umbilicated vesicles, after 10 days, prednisone therapy 40 mg/day and azathioprine 150 mg/day were initiated with gastro- and osteoprotection. Local therapy included: antiseptic lotions and creams containing an antibiotic and a corticosteroid component.

Two weeks after admission, the patient developed new, small blisters on the trunk and erythematous, sharply demarcated plaques on the face, neck and trunk (Figures 2a and 2b). Subsequent histological specimens, taken from the face and trunk, revealed identical findings (Figure 2c). As this finding was consistent with drug-induced pemphigus foliaceus, lisinopril was discontinued. Hydrochlorothiazide 25 mg was introduced if necessary. Lisinopril was discontinued because based on the patient's history, the skin condition dramatically worsened 6 months after lisinopril was introduced. The plaque lesions started resolving rapidly, no new blisters appeared, and after 2 weeks, the patient was dismissed from the hospital. At the 6-month follow-up, the patient presented with small plaques (up to 1 cm in diameter) with minimal infiltration. Indirect immunofluorescence test was positive, with a titer of 1 : 20. Thus, based on all previously mentioned, we established the diagnosis of a drug-induced pemhigus in a patient with diabetes mellitus and Kaposi-Juliusberg varicelliform eruption.

Discussion

Kaposi-Juliusberg varicelliform eruption or *eczema herpeticum* are well known to be associated with several chronic dermatoses including atopic dermatitis,

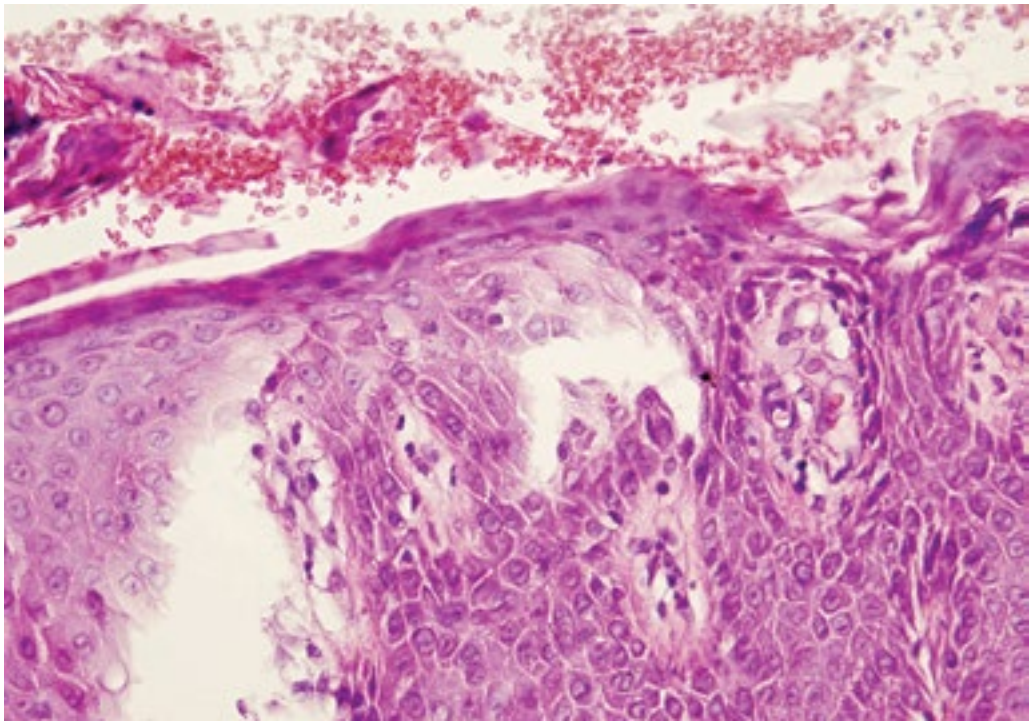

Figure 1c. Histology of trunk lesions: epidermal hyperkeratosis and acanthosis; subcorneal clefts with acantholytic cells; acantholysis in the stratum spinosum; dermal blood vessels surrounded by lymphocytes and eosinophils (HE, x400).

pemphigus foliaceus, seborrheic dermatitis, Darier disease and congenital ichthyosiform erythroderma (7). Some of the cases end up being fatal (7). To the best of our knowledge, this is the second published case of lisinopril-induced pemphigus foliaceus (3), and the first one with the abovementioned association.

According to different authors, there are three groups of chemical structures in drugs that can cause pemphigus: sulfhydryl radicals (thiol drugs or SH drugs) (8), phenol drugs (7), and non-thiol nonphenol drugs (2). Another classification divides drugs causing pemphigus into drugs with sulphydryl group, drugs containing an active amide group and non-thiol, non-amide drugs (9). Examples of sulfhydryl radical drugs include captopril, enalapril, penicillamine, and gold sodium thiomalate. Aspirin, rifampicin, levodopa, and heroin are examples of phenol drugs (8). Nonsterioidal antiinflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, glibenclamide, and dipyrone are examples of non-thiol non-phenol drugs (8). More than 200 cases of drug-induced pemphigus have been reported, with penicillamine accounting for almost 50%. In patients who take penicillamine for longer than 6 months, it is estimated that 7% develop pemphigus (10).

Different mechanisms have been proposed in inducing acantholysis and they differ related to the used drug. Thiol drugs are capable of causing acantholytic changes in skin explants (11). The proposed mechanisms include: inhibition of enzymes that aggregate keratinocytes; activation of enzymes, such as plasminogen activator, which disaggregates keratinocytes; disturbance of cell adhesion by formation of thiol-cysteine bonds instead of cysteine-cysteine bonds, and formation of neoantigen by an immunological reaction. Pemphigus serum and captopril induce heat shock protein 70 and inducible nitric oxide synthase overexpression, thus, triggering apoptosis in human keratinocytes (12). Recently, captopril (ACE inhibitor containing thiol group) was found to modulate acetylcholinesterase in human keratinocytes, *in vitro* (13). Human keratinocytes synthesize and secrete non-neuronal acetylcholine, which acts as a local cell signaling molecule, regulating functions like proliferation, cell adhesion, motility, desmosomal cell contact, and glandular secretion (13). Captopril induces a strong acetylcholinesterase up-regulation leading to acetylcholine degradation and

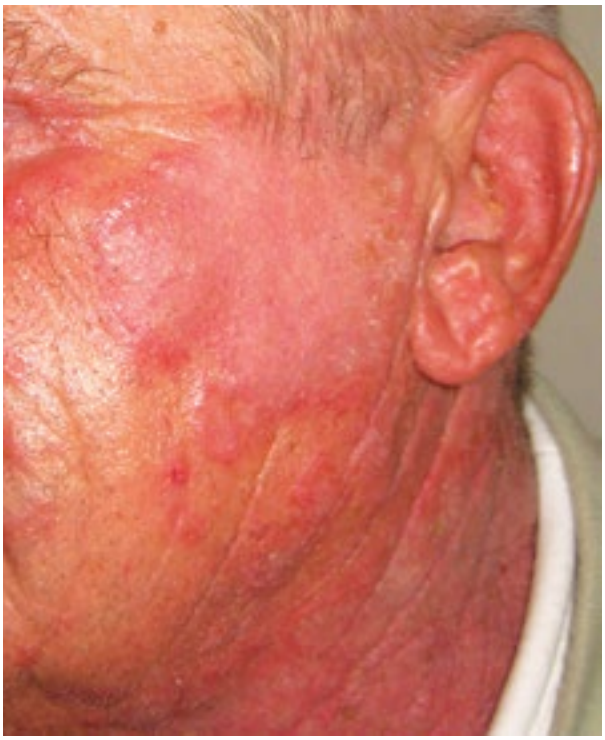

Figure 2a. Sharply demarcated patches of irregular shape (face detail)

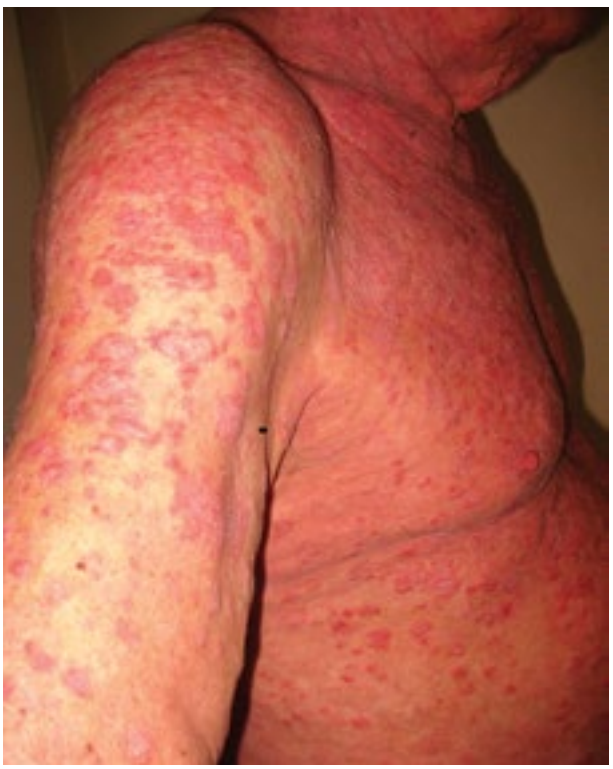

Figure 2b. Erythematous plaques with minimal scaling on the trunk and limbs

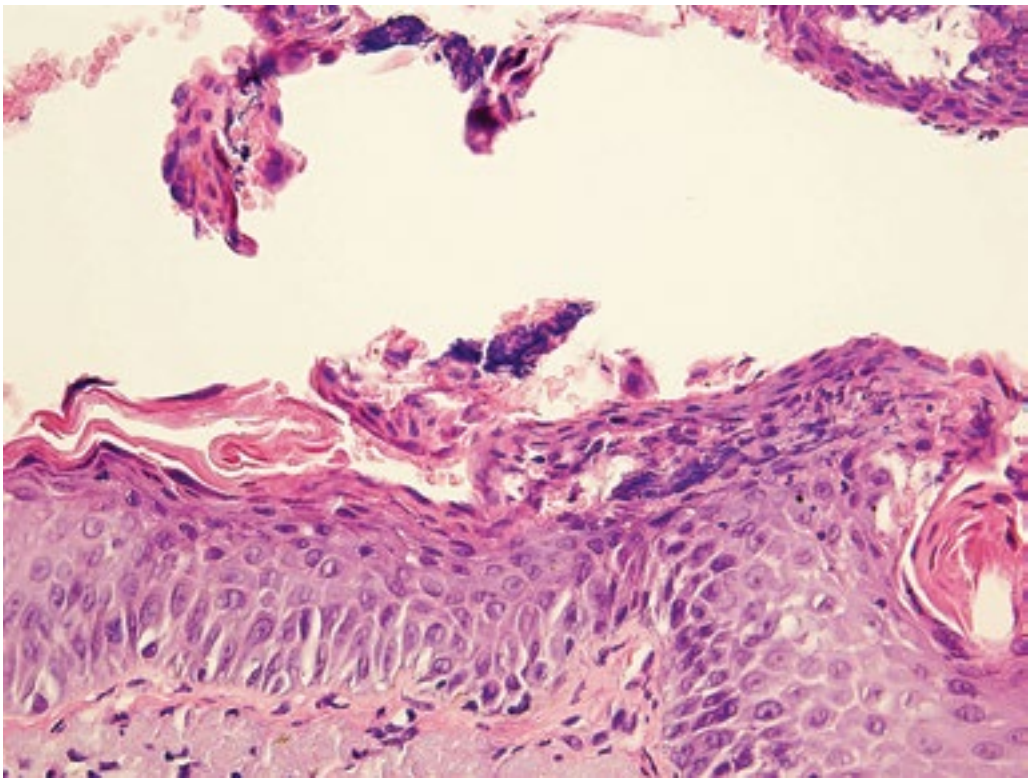

Figure 2c. Histology of facial plaque lesions (see 2a). Subcorneal cleft with acantholytic (HE, x400).

its reduced secretion. This suggests that acantholysis induced by ACE-inhibitors might be linked to altered levels of acetylcholine (13). Phenolic drugs were proposed to release cytokines from keratinocytes, such as tumor necrosis factor (TNF) alpha and interleukin (IL)-1 (14). It is known that they participate in the regulation and synthesis of complement and proteases like plasminogen activator, which take part in acantholysis (15). Calcium channel blockers may cause pemphigus, because calcium is necessary for the activity of enzymes, which play a role in keratogenesis; desmogleins are calcium dependant (11).

Up to now, the following ACE inhibitors were reported to induce pemphigus foliaceus: captopril (16), lisinopril (3), enalapril (17), and fosinopril (18). As a thiol containing ACE inhibitor, captopril was found to induce skin adverse changes (pemphigus, as well), whereas other ACE inhibitors were investigated related to this point in the last two decades. In 1992, enalapril was found to be a powerful *in vitro* acantholytic agent (non-thiol, but amide containing drug) (19). In 1999, *in vivo* enalapril-induced acantholysis was reported (20). In 2001, aggravation of a severe childhood pemphigus vulgaris by enalapril was described (21). Fosinopril has neither a thiol nor an amide component (3) and is unable to block the adhesion molecules *in vivo* like captopril, thus pointing to different mechanism in inducing acantholysis (22).

Historically, lisinopril was the third ACE inhibitor (after captopril and enalapril) and was introduced in the early 1990s. Lisinopril ($C_{21}H_{35}N_3O_7$) contains an amide group. It is a lysine derivative of enalaprilat, the active metabolite of enalapril (3, 23). According to world literature, one case of lisinopril-induced PF was described in a 66-year–old man (3). The diagnosis was established after skin biopsy and direct immunofluorescence. Indirect immunofluorescence was not performed. Unfortunately, the follow-up was limited to 3 weeks because the patient died of bronchopneumonia. Sera from patients with pemphigus foliaceus recognize epitopes of desmoglein-1. Rare cases of pemphigus foliaceus develop antibodies to desmoglein-3 or have both desmoglein-3 and desmoglein-1 antibodies. Patients with pemphigus vulgaris who have lesions limited to the mucous membranes have only desmoglein-3

antibodies, while patients with antibodies to both desmogleins usually develop widespread mucocutaneous lesions (24). Circulating and tissue-bound antibodies to desmoglein 1 and desmoglein 3 found in spontaneous pemphigus foliaceus and pemphigus vulgaris respectively, are also found in drug-induced pemphigus, like in our case, suggesting a similar molecular mechanism (3). Although most patients with drug-induced pemphigus have tissue-bound and/or low-titre circulating autoantibodies with the same antigenic specificity as do patients with idiopathic pemphigus, it has been reported that in the case of penicillamine-induced pemphigus, 10% do not have tissue-bound, and more than 30% do not have circulating autoantibodies (25).

According to international data on side effects of lisinopril (26) a total of 82.414 people reported side effects when taking lisinopril up to September 17th, 2012. Among them, 35 people (0.04%) had pemphigoid, and 11 people (0.01%) had pemphigus. One of the reported cases of pemphigus would be our patient. It took 6 - 12 months for lisinopril to induce pemphigoid (100% patients) and 1 - 6 months to induce pemphigus (100% patients). Female predominance has been observed for pemhigoid cases (67.65%) and male predominance in pemphigus cases (83.33%). Most patients were over 60 years of age: 100% in pemphigoid cases and 91.67% in pemphigus cases (26).

Anatomically, pemphigus lesions are predominant on the trunk. Normal skin explants taken from former pemphigus patients from different areas of their bodies (back and buttocks), when cultured with enalapril presented different thresholds of acantholysis. Lesions on the back showed diffuse acantholysis, while mild to moderate acatholysis was detected on the cultured explants taken from the buttocks. No structural changes were found in control cultures (27. This study demonstrated certain preferential anatomic localizations of pemphigus lesions. Also, in the opinion of the authors of this article, drug-induced pemphigus, shares the same anatomical preference in genetically predisposed persons, especially if induced by ACE inhibitors.

Of special interest is that ACE inhibitors can induce circulating antibodies directed to antigens of the superficial epidermal cells in patients without skin changes, as published recently (28). A group of 68 patients treated with ACE inhibitors and 48 controls were included in the study. Indirect immunofluorescence showed that 33 sera (52.38%) presented autoantibodies directed to an antigen of the cytoplasm of the superficial epidermal keratinocytes. Two of the 33 positive sera had autoantibodies to desmoglein 1 and/or 3 in enzyme-linked immunosorbent assay - ELISA test. Immunoblot analyses were negative. All the 48 control sera were found to have no circulating antibodies using the three assays. This study clearly indicates that ACE inhibitors may induce production of circulating autoantibodies even in patients without clinical manifestations of pemphigus (28). Autoantibody development is not related to the duration of ACE inhibitor administration (28) in these patients. Recently, one case of pemhigus foliaceus induced by an angiotensin II receptor blocker (candesartan) has been published (29). Angiotensin II receptor blockers are widely prescribed as antihypertnesives as a substitute for ACE inhibitors (29).

Vitamin D may be able to prevent ACE inhibitor-induced cell detachment and apoptosis in keratinocytes. The results of an Israeli study *in vitro* confirm that calcitriol protects keratinocytes from captopril-induced cell detachment and apoptosis (30).

It is important to have a detailed history of all drugs taken by the patient, including homeopathic agents, OTC drugs, and even medications that were discontinued. In cases where there is no response to therapy repeated drug history taking should be considered (2). Every case of *de novo* pemphigus should be first estimated as drug-induced. Usually, it takes 1 - 6 months for ACE inhibitors to induce pemphigus (26). If previous dermatosis exists, such as atopic dermatitis, the diagnosis may be delayed. In our patient, solitary, sharply demarcated plaques showed a characteristic histology of pemphigus foliaceus. At the 6-month follow-up, the patient presented with small plaques (up to 1 cm) with minimal infiltration, while indirect immunofluorescence test was positive, with a titer of 1 : 20. It has been estimated that approximately 40 to 50% of patients with thiol-drug-induced pemphigus recover spontaneously when the drug is withdrawn with rapid decline in desmoglein antibody levels (24). Only 15% of cases induced by

non-thiol drugs remit following drug withdrawal. Perhaps drugs act to trigger disease in genetically predisposed individuals (24). Our case also shows that specimen collection should be repeated in doubtful cases, when new lesions on the skin do not correspond to the previous clinical diagnosis.

Abbreviations

ACE - Angiotensin-converting enzyme
OTC - Over-the-counter
PF – Pemphigus foliaceus

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Lizinopril kao uzrok pemphigus foliaceusa kod pacijenta sa dijabetes melitusom i Kaposi-Juliusberg variceliformnom erupcijom

Sažetak

Uvod: Lekovi se sve češće navode kao uzročnici pemfigusa. Lizinopril je inhibitor angiotenzin-konvertujućeg enzima (ACE - eng. angiotensin-converting enzyme) koji se koristi u lečenju hipertenzije, kongestivne srčane bolesti kao i u prevenciji renalnih i retinalnih komplikacija u dijabetesu melitus. Do sada su opisane različite reakcije na lek, ali samo jedan slučaj pemphigusa foliaceus (PF). Prikazujemo drugi slučaj u svetu PF indukovanog lizinoprilom komplikovanog Kaposi-Juliusbergovom variceliformnom erupcijim kod pacijenta sa diabetesom mellitus tip 2.

Patofiziologija: PF je autoimuno bulozno oboljenje gde autoantitela klase IgG pogađaju intercelularni glikoprotein desmoglein-1. Do vezivanja ovih antitela koja pripadaju IgG4 potklasi, dolazi uglavnom u granuloznom sloju epidermisa nakon čega nastupa akantoliza, supkornealno i intraepidermalno formiranje bula. Novonastale bule karakteriše fragilnost; postavljene su superficijalno te lako ruptuiraju pri čemu ostavljaju erozije. Različiti faktori mogu uzrokovati pemfigus, a etiologija bolesti se najbolje opisuje kroz akronim PEMPHIGUS: **PE**sticidi, **M**alignitet, **P** tj. **F**armacija, **H**ormoni, **I**nfekcije i **I**munizacije, **G**astronomija, **U**ltravioletno zračenje i **S**tres.

Lizinopril ($C_{21}H_{35}N_3O_{7)}$ je lizinski derivat enalaprilata, aktivnog metabolita enalaprila. Sadrži amidnu grupu. Različiti neželjeni efekti na lizinopril su do sada opisani, ali samo jedan slučaj PF.

Prikaz slučaja: Muškarac, star 60 godina iz okoline Trstenika primljen je sa supfebrilnim temperaturama. Brojne diseminovane umbilikovane vezikule i eritem bili su prisutni na koži lica, trupa i ekstremiteta, a semi-anularne erozije na koži trupa. Jasno ograničeni žućkasto-crvenkasti plakovi, mestimično grupisani, veličine do 2 cm, bili su lokalizovani na zadnjoj strani trupa (paravertebralno i vertebralno). Osim pojačanih injekcija na obe konjunktive, na ostalim vidljivim sluznicama nisu uočene patološke promene. Iz anamnestičkih podataka saznalo se da boluje od dijabetesa melitus tip 2 ukupno 10 godina, a od hipertenzije 2 godine, i da je od lekova redovno uzimao metformin i lizinopril. U porodičnoj anamnezi naveo je da su oba roditelja imala povišen pritisak, dok je majka bolovala od dijabetesa melitus i astme.

Od 2007. godine kada su se pojavile prve promene na koži, lečen je pod dijagnozom atopijski dermatitis i to uglavnom lokalno. Međutim, pogoršanje kožnog stanja nastupilo je 1,5 mesec pre prijema na našu kliniku, kada je zbog febrilnosti, upućen prvo u regionalnu bolnicu gde je pod dijagnozom eritrodermije lečen pored lokalne terapije i sistemski kortikosteroidima, antihistaminicima i antibioticima. Histologija koja je rađena tom prilikom, upućivala je na eksfolijativni dermatitis kao reakciju na lek. Nakon 5 dana, došlo je do pogoršanja opšteg stanja pacijenta, febrilnosti, sa erupcijom novih kožnih lezija po tipu papulovezikulozne erupcije, te je premešten na Kliniku za dermatovenerologiju KCS u Beogradu. Po prijemu, uočene su semianularne erozije sa ostacima krovova bula kao i pojedinačni žućkasto-crvenkasti plakovi do 2 cm u prečniku na trupu i ekstremitetima, i brojne, diseminovane umbilikovane vezikule.

Laboratorijske analize su ukazale na postojanje blage hiposideremijske anemije, i povišen IgE titar od 725 IU/ml (normalne vrednosti do 100). Imunološke analize su bile uredne, dok je virusološkim analizama zapažen četvorostruki pad titra HSV-1 tokom boravka u bolnici.

Direktna, indirektna imunofluorescencija kao i histologija bile su kompatibilne sa PF.

Lečenje: Nakon primene aciklovir tableta, antibiotika prema antibiogramu i metformina (kojeg je pacijent redovno uzimao) kao i insulina (nezadovoljavajuća glikoregulacija), uključen je prednisolon 40 mg/dan kao i azatioprin 150 mg/dan, antiseptičke boje i kombinovane antibiotsko-kortikosteroidne kreme. Nakon 2 nedelje i rezolucije prvobitnih promena, uočene su nove – superficijelne bule kao i eritematozni, jasno ograničeni plakovi na licu, trupu i ekstremitetima. Histologija sa plakova potvrdila je nalaz PF moguće indukovanog lekovima. Na osnovu

ponovljenih anamnestičkih podataka uočeno je da je do pogoršanja promena na koži došlo 6 meseci pošto je u terapiju uveden lizinopril. Lek je isključen, nakon čega je nastupilo rapidno poboljšanje: nestajanje plakova, epitelizacija erozija i prestanak javljanja novih bula. Nakon 6 meseci praćenja, utvrđeno je da na koži i dalje postoje retke, minimalno infiltrovane promene na trupu i ekstremitetima.

Na osnovu svega iznetog, postavljena je dijagnoza PF pokrenutog lizinoprilom kod pacijenta sa dijabetesom melitus i Kaposi-Juliusbergovom variceliformnom reakcijom.

Diskusija: Sledeći ACE inhibitori mogu indukovati PF (publikovani radovi): kaptopril, enalapril, lizinopril, fosinopril. Zbog tiol grupe (SH) kaptopril često uzrokuje neželjene reakcije na koži. Predloženi su različiti modeli kojim ACE inhibitori mogu oštetiti kožu, kako *in vivo*, tako i *in vitro*. Lizinopril je treći ACE inhibitor koji je devedesetih godina prošlog veka uveden u terapiju, nakon kaptoprila i enalaprila. Poznato je da su ACE inhibitori moćni induktori akantolize *in vivo* i *in vitro*. Do 17.9. 2012. godine ukupno 82 414 pacijenata imalo je neželjene reakcije na pomenuti lek. Među njima 35 (0,04%) je imalo pemfigoid, dok je 11 (0,01%) imalo pemfigus. Jedan od prijavljenih slučajeva pemfigusa je i naš pacijent. Većina navedenih pacijenata bila je starija od 60 godina. Do promena buloznog pemfigoida dolaziloje nakon 6–12 meseci a pemfigusa 1-6 meseci od uvođenja lizinoprila u terapiju.

Cirkulišuća i za epidermis vezana antitela protiv dezmogleina 1 i dezmogleina 3, koja su prisutna kod pacijenata sa spontanim pemfigusom foliaceus odnosno vulgarnim pemfigusom, mogu se dokazati i kod pacijenata sa lekovima izazvanim pemfigusom kao što je to slučaj kod našeg pacijenta. Ipak, treba znati da prema podacima iz literature, kod pacijenata sa pemfigusom izazvanim penicilaminom (najčešće inkriminisani lek), direktni imunofluorescenti test ostaje negativan kod 10% a indirektni kod 30% obolelih.

Posle 6 meseci od ukidanja lizinoprila, naš pacijent je idalje imao retke, minimalno infiltorovane male plakove (dijametra nekoliko mm) na trupu i ekstremitetima. Titar antidezmogleinskih antitela bio je nizak i iznosio je 1 : 20. Poznato je da se samo kod približno 40–50% pacijenata sa pemfigusom izazvanim lekovima koji poseduju tiol (SH) grupu bolest spontano povlači posle ukidanja inkriminisanog leka. Kada su u pitanju ostali lekovi, ovaj procenat nije viši od 15%.

Zaključak: Kod svakog *de novo* slučaja pemfigusa, mora se isključiti uloga leka kao potencijalnog pokretača odnosno uzroka bolesti, s obzirom da svi lekovi koje je pacijent uzimao uključujući i vitamine i homeopatske lekove, pa čak i lekove koje je pacijent prestao da uzima, mogu biti pokretači bolesti. Kod svih pacijenata kod kojih ne dolazi do očekivanog terapijskog odgovora na primenjenu terapiju, treba ponovo insistirati na detaljnim anamnestičkim podacima.

Ključne reči

Lizinopril + neželjena dejstva; Pemphigus + hemijski izazvan; Inhibitori angiotenzin konvertirajućeg enzima; Dermatitis; Kapošijeva variceliformna erupcija

Penile Intraepithelial Neoplasia: Successful Treatment with Topical 5% Imiquimod Cream

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Abstract

The authors present a case of a 36-year-old man with a penile intraepithelial neoplasia who was evaluated at the Outpatient Clinic of the Department of Dermatovenereology Diseases of the Clinical Center of Vojvodina in December of 2010. The patient was referred to this facility by an urologist and had histopathological reports of 4 biopsy specimens taken from different plaques on the glans penis. Biopsy samples were collected from lesions which were clinically diagnosed as leukoplakia. Histopathological findings of all biopsy specimens showed: "dysplasio epithelii planocellularis gradus levioris et partim gradus mediocris diffusa". Given the histopathological diagnosis, the patient was referred to a dermatologist for conservative therapy of these lesions, avoiding radical surgery. On admission, the patient presented with slightly indurated erythematous plaques with some desquamation at the surface, and a tendency for diffuse involvement of the entire glans penis. Topical 5% imiquimod cream was administered on the lesions once a day and was washed off after 8 hours during 10 weeks. Check-ups were scheduled for every other week in order to assess the course and progress of topical treatment. No significant side effects were recorded, except for acute local inflammation accompanied by mild exudation and itching. After 10 weeks of treatment, complete regression of lesions was achieved, and in the following period of 18 months (until present) no recurrence was observed.

Key words

Penile Neoplasms; Aminoquinolines; Administration, Topical; Treatment Outcome

The aim of this report is to present effects of topical 5% imiquimod cream in the treatment of grade II penile intraepithelial neoplasia.

Introduction

Epithelial dysplasia is a term used to describe tissue changes including disturbed epithelial cell polarity and maturity, nuclear atypia, increased mitotic activity and nuclear cytoplasmic ratio. Today, these changes on the glans and prepuce of the penis are known as epithelial dysplasia or penile intraepithelial neoplasia (PIN) (1-4). The term PIN indicates clinical entities which used to be regarded as precancerous lesions. All grades of epithelial dysplasia or PIN are histological pre-stages of *carcinoma in situ* which may gradually lead to penile squamous cell carcinoma (SCS). PIN or penile epithelial dysplasia grading I, II or III, depends on the extent of epithelial involvement by atypical basaloid cells (1, 2). Literature review suggests a strong association between human papilloma virus (HPV) and PIN (1, 2, 3).

Case report

A 36-year-old man was first evaluated by a dermatologist at the Outpatient Clinic of the Clinical Center of Vojvodina in August 2010. He was referred

by a urologist and had histological reports of 4 biopsy specimens collected from different plaques on the glans penis. Histological findings of all specimens showed epidermal dysplasia, that was PIN grade II. Apart from mild mucosal "tightness" on the glans, the patient was symptom-free.

Personal history revealed that the patient was circumcised at the age of 15 and without malignant or systemic diseases. Topical 5% imiquimod cream was not contraindicated.

Family history revealed that none of the patient's immediate or extended family members suffered from mucosal genital or skin diseases. None of his immediate family members suffered from malignant diseases.

Clinical examination showed that on admission, the patient presented with slightly indurated erythematous plaques with some desquamation at the surface and diffuse involvement of the glans penis and *sulcus coronarius* (Fig. 1, 2). Physical examination of organs and organ systems showed no pathological findings and regular vital signs.

Histopathological findings All biopsy specimens from the glans mucosa showed a stratified squamous epithelium with mild parakeratosis, mild to moderate cell dysplasia, disturbed cell maturity, nuclear atypia with hyperchromatosis, perinuclear halo (discrete koilocytosis) on some cells, basal membranes without changes and of the same thickness, abnormal infiltrate distribution of lymphocytes and plasma cells in mildly edematous *lamina propria* around slightly dilated blood vessels, and no dyskeratosis. Based on these findings, the following diagnosis was made: *dysplasio epithelii planocellularis gradus levioris (I) et partim gradus mediocris (II) mucosae* (Fig. 3).

Relevant laboratory tests revealed no abnormal results including serology on syphilis and testing for HIV.

Treatment A thin layer of 5% imiquimod cream (Aldara® cream) was applied once a day and was washed off 8 hours later for 5 days in a week during 10 weeks. Check-ups were scheduled for every other week by a dermatology specialist who established local inflammation accompanied by mild exudation

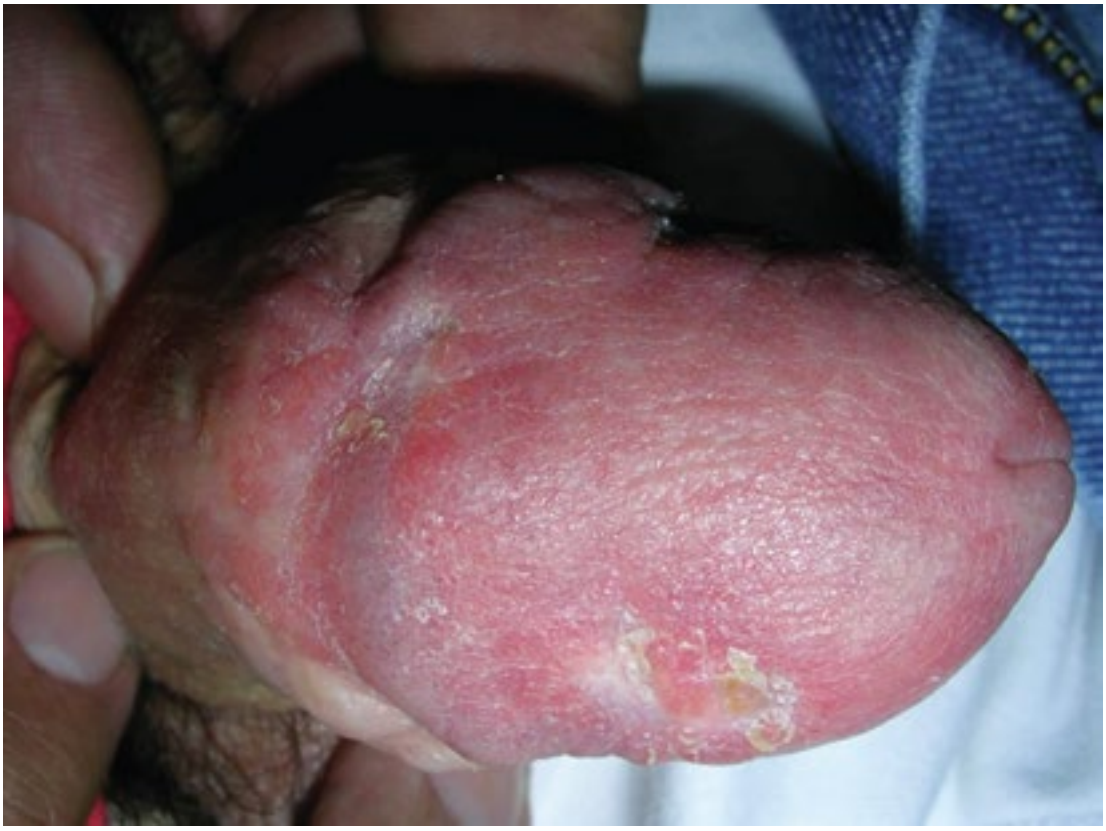

Figure 1. Clinical findings before topical treatment

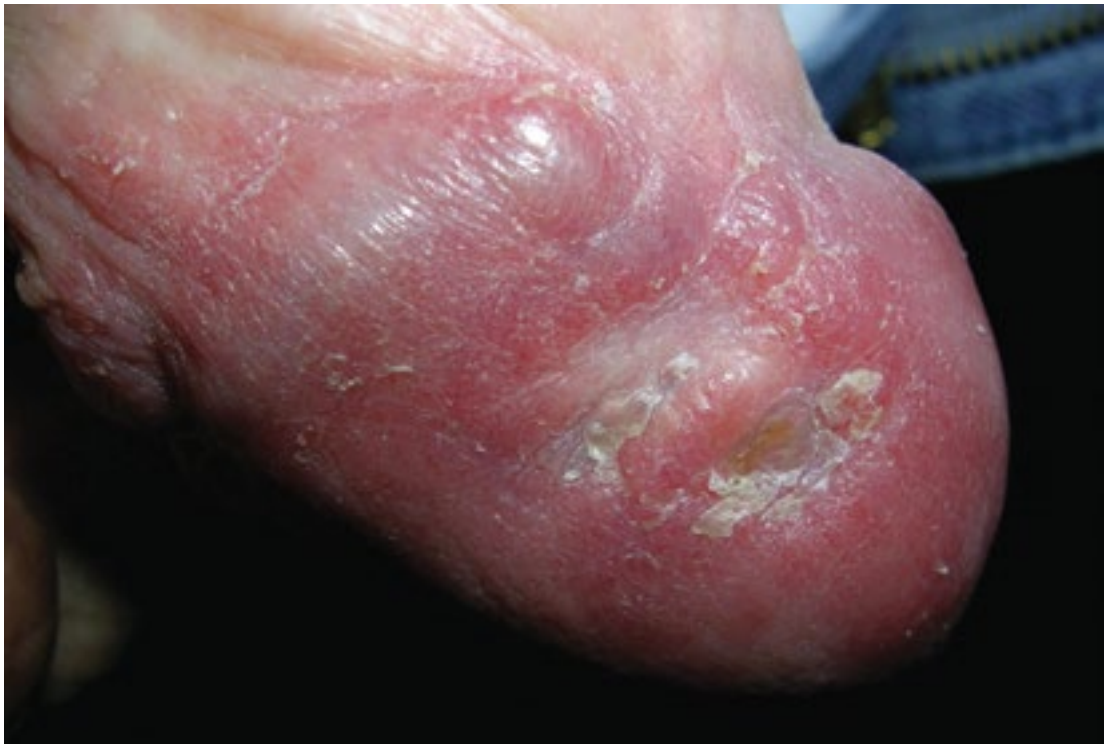

Figure 2. Clinical findings before topical treatment with the visible biopsy site

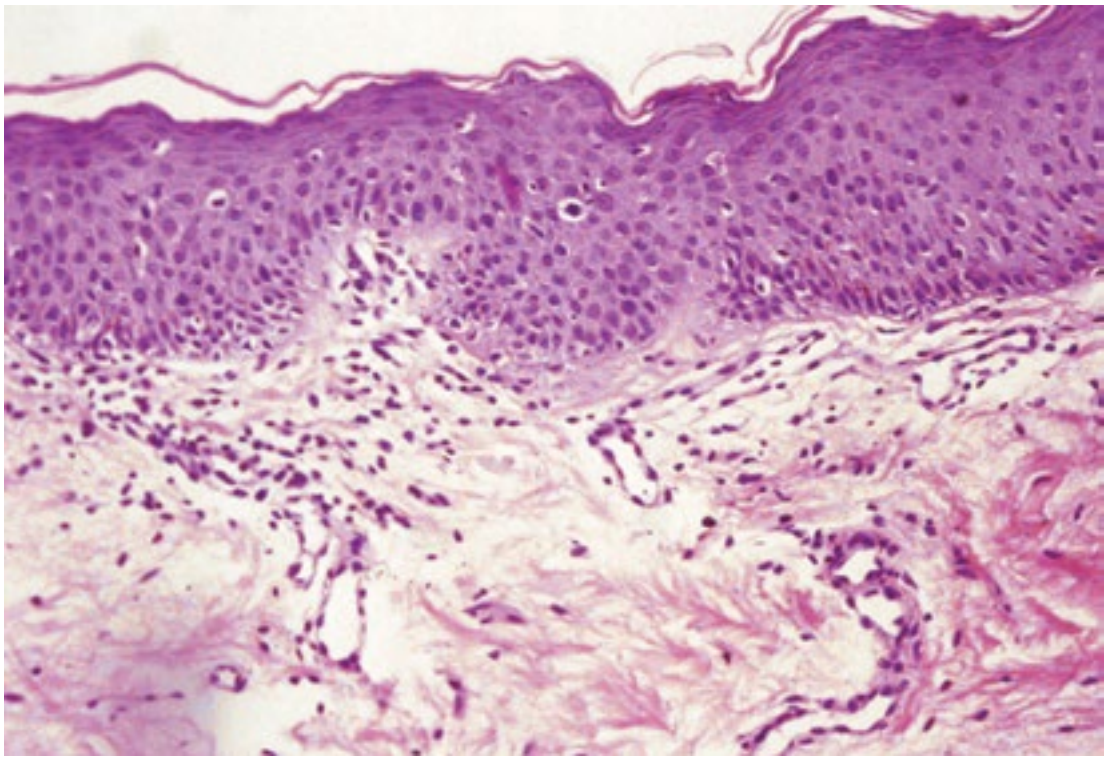

Figure 3. Microphotograph of a biopsy specimen – fragment: mild edema of lamina propria, dilated blood vessels with sparse perivascular infiltrates. Epithelium shows mild to moderate disturbed polarity and cell maturity (HE, x 200)

and suppuration, erythema, mild itching, burning and desquamation. Inflammation, exudation and suppuration with massive desquamation were most severe during the third and fourth week of therapy. After 10 weeks of such treatment, topical fusidic acid and gentamicin creams were used in the following 4 weeks, without other drugs or topical agents. After 14 weeks, complete remission was achieved (Fig. 4a, 4b). In the following period of 18 months no recurrence was observed.

Discussion

Penile intraepithelial neoplasia or epithelial dysplasia of the penis is graded I, II, III, depending on the extent of epithelial involvement by atypical basaloid cells. These cells vary in shape and size, they have hyperchromatic pleomorphic nuclei and loss of polarity. Furthermore, grade I epithelial neoplasia (PIN I) is characterized by atypical cells involving one third of the epithelium, grade II involves two thirds, and grade III involves over two thirds of the epithelium (1, 2). This classification was accepted and recommended by the World Health Organization (WHO) (1, 2, 4).

All grades of PIN are histological pre-stages of *carcinoma in situ* and include clinical entities previously considered to be precancerous lesions: erythroplasia Queyrat (EQ), Bowen's disease of the glans penis (BDP), bowenoid papulosis (BP), Paget disease (PD) which is an intraepithelial form of adenocarcinoma primarily found in the epithelium (4). In the absence of a formal consensus on clinicopathological classification (regarding particularly the 'grade'), in the past PIN corresponding to cervical, vulvar and anal intraepithelial neoplasia, CIN, VIN and AIN, was considered as a convenient umbrella term. In 2000, an alternative expression: "squamous intraepithelial lesion" (SIL) has been proposed and qualified by the descriptor 'high-' or 'low-grade' (5). Although EQ and BDP are synonymous in describing carcinoma *in situ* of the penis, BD is used to refer to squamous cell carcinoma *in situ* at other cutaneous sites. EQ should be used to describe shiny red patches of the 'mucosal' penis (glans and prepuce of the uncircumcised) and BDP refers to scaly patches and plaques of the keratinized penis. BP is analogous to, but clinically different from, EQ and BDP and the term should be used to describe multiple warty lesions, which are often pigmented in keratinized sites, and more numerous

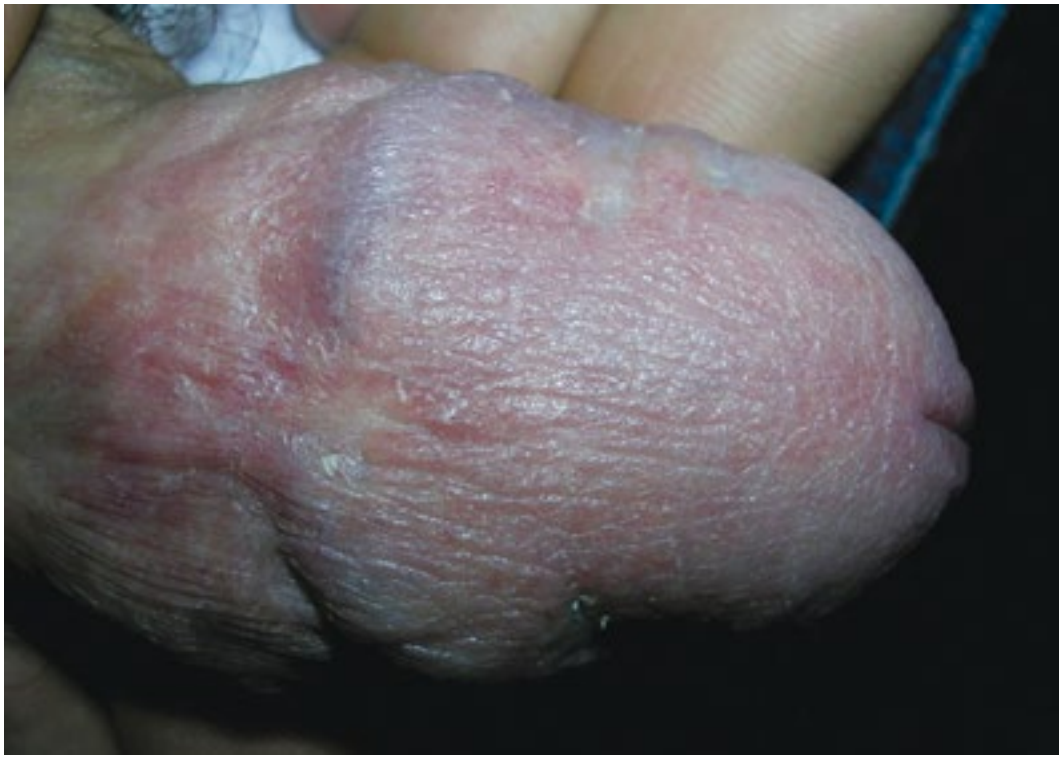

Figure 4a. Appearance 4 weeks after the 5% imiquimod cream therapy

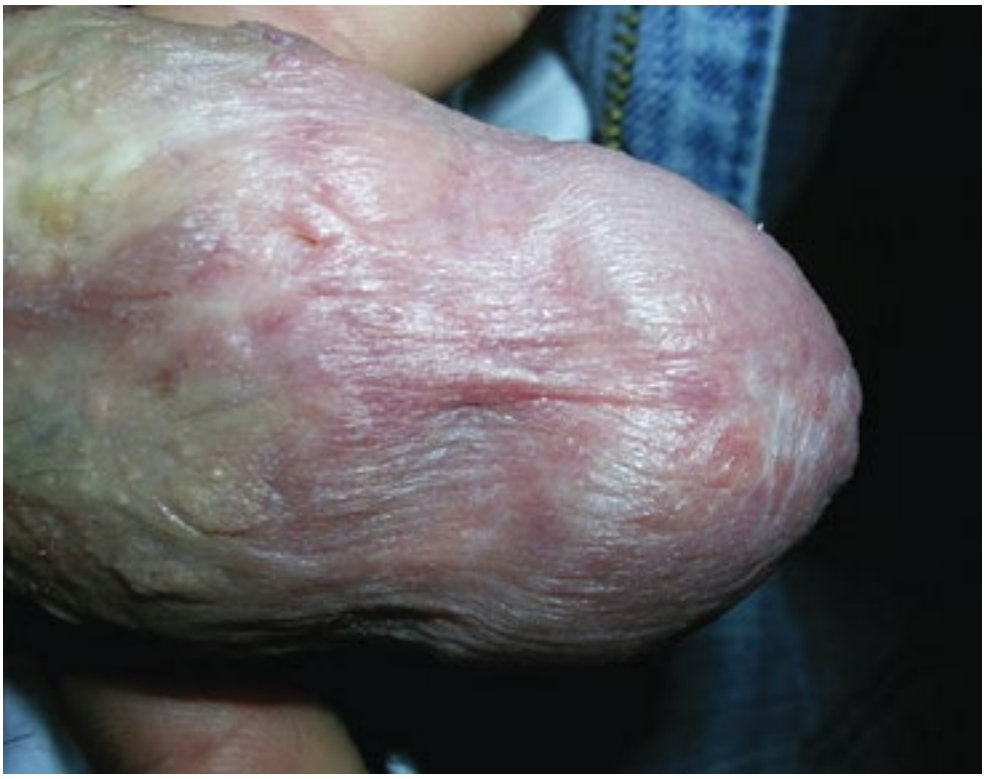

Figure 4b. Appearance 4 weeks after the 5% imiquimod cream therapy

and more inflamed at 'mucosal' sites. In contrast to common genital viral *condylomata acuminata*, BP lesions occur in younger, sexually active men, clinically they are less papillomatous, smoother, more polymorphic and more coalescent (3).

Although the etiology of PIN is not completely understood, the literature indicates that human papilloma virus (HPV) plays a significant role in its etiopathogenesis (1, 2, 3, 4, 6). About 30 different HPV types may be present in PIN lesions. They can be classified into low-oncogenic risk types (6 and 11), and potentially high risk types (16 and 18). Since 2007, literature data point to the importance of microscopic appearance of HPV infected cells in the spinous layer of the penile mucous epithelium, mostly in men under 40 years of age: koilocytosis, dyskeratosis and acanthosis. This histological finding may indicate III grade PIN and provide a timely treatment plan (4).

Imiquimod, 1-(2-methylpropropyl)-1 H-imidazole [4,5-c]quinolin-4-amine, belongs to a group of drugs known as imidazoquinolines that are immune response modifiers with potent antiviral and antitumor activity. Thus, imiquimod represents an imidazoquinoline immunomodulator drug, a toll-like receptor agonist, which induces cytokine production and stimulates the innate and cellular immune responses. Imiquimod is currently used in the management of anogenital warts, actinic keratoses, basal cell carcinoma and other skin lesions, including lentigo maligna (7). The mechanism of its action is likely to be mediated by Toll-like receptor 7 (TLR-7), which represents a cell surface receptor found on monocyte cells. Stimulation of TLR-7 receptor results in a release of large amounts of potent cytokines such as interferon-α, IL-12, and TNF-α. In addition to stimulation of the innate response, these cytokines promote the development of antigen-specific, cell-mediated immune response (8). Imiquimod 5% cream is a topical immunomodulator, but is used as a topical agent against human papilloma viruses as well. It has been shown under in vivo conditions in experimental animals, that imiquimod inhibits cell proliferation in the epidermis of the skin via an opioid receptor mediated mechanism (9). Fortunately, there is no concern for physical dependence since, imiquimod is neither an opioid agonist nor antagonist.

The first clinical application in which imiquimod proved to be useful was for treatment of genital warts, but imiquimod would seem to have a potential in

many additional applications, including treatment of: actinic keratosis, superficial basal cell carcinoma (BCK) less than 2,0 cm in diameter, genital and perianal warts, keratoacanthoma, porokeratosis, as well as *in situ* malignancies (10,11-14). Partial and complete responses have been observed in the treatment of cervical, vaginal and vulvar intraepithelial neoplasia and Bowenoid papulosis, although the results have not been consistent (15-17). Imiquimod is contraindicated in immunosuppressed patients and patients with autoimmune diseases. The frequency and length of imiquimod treatment depend on indications: actinic keratoses have been shown to respond after using imiquimod three times weekly for up to 12 weeks (18); Bowen's disease after daily application for up to 16 weeks (19); actinic cheilitis responded well to imiquimod applied three times weekly for up to 6 weeks (20); in superficial BCC 6 week treatment appeared as effective as the 12 week therapy (21,22). Local skin reactions were common, but these are thought to reflect the immune response to the tumor. The cream should not be used for more than 16 weeks. It is broadly well tolerated; local application-site reactions, including pruritus, erythema, edema and bleeding are common, usually mild, and do not necessitate discontinuation of therapy (2,4,6,10-13,23,24). Inflammatory papules in the surrounding skin have been recorded (14). There is evidence that the more severe the local reaction, the higher the clearance rate (23), without compromising the eventual cosmetic results (24).

According to current literature, topical 5% imiquimod is a treatment option for PIN, while length of follow-up period is of utmost importance in order to detect recurrences (7, 10). In our patient the follow-up lasted 18 months (until present).

Literature data show other treatment options for PIN: 5-fluorouracil cream, cryotherapy, curettage and cautery, CO_2-laser, photodynamic therapy, radiation therapy (which should be avoided), interferon-alpha, excision and Mohs micrographic surgery (particularly in the treatment of recurrences). Special attention should be paid to regular check-ups of sexual partners of HIV-infected patients with PIN, in order to provide early diagnosis and treatment of cervical, vulvar and anal carcinoma (25).

Conclusion

This is a case report of a patient with penile intraepithelial neoplasia successfully treated with 5% imiquimod cream during 10 weeks, and a follow-up period of 18 months. During this period no recurrence was reported. Although topical use of 5% imiquimod cream proved to be successful in the treatment of penile intraepithelial neoplasia grade I and II, final assessment of its therapeutic effects requires a longer period of observation in order to detect any potential recurrence of lesions.

Abbreviations

PIN - Penile intraepithelial neoplasia
SCC - Squamous cell csrcinoma
HPV - Human papilloma virus
HIV - Human immunodeficiency virus
EQ - Erythroplasia of Queyrat - erythroplasia of Queyrat
BDP - Bowen's disease of the penis
BP - Bowenoid papulosis
CIN - Cervical intraepithelial neoplasia
VIN - Vulval intraepithelial neoplasia
AIN - Anal intraepithelial neoplasia
SIL - Squamous intraepithelial lesion
TLR-7 - Toll-like receptor 7
IL-12 - Interleukin-12
TNF- α. - Tumor necrosis factor - α
BCK - Basal cell carcinoma

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Epitelna displazija penisa - lokalno lečenje imikvimodom u obliku 5% krema – prikaz slučaja

Sažetak

Uvod: Pojam epitelne displazije označava prisustvo epitelnih ćelija poremećene polarnosti i sazrevanja, sa atipijom nukleusa, povećanom mitotskom aktivnošću i poremećenim jedarno-citoplazmatskim odnosom. Danas se za navedene promene u predelu glansa i prepucijuma penisa ravnopravno upotrebljavaju pojmovi epitelne displazije penisa i intraepitelne neoplazije penisa (PIN – engl. *penile intraepithelial neoplasia*). PIN obuhvata kliničke entitete ranije smatrane prekancerozama. Svi stepeni epitelne displazije odnosno PIN, predstavljaju histološke predstadijume *carcinoma in situ* i vremenom mogu da dovode do pojave karcinoma skvamoznih (spinoznih) ćelija - SCC (eng. squamous cell carcinoma) penisa. PIN odnosno epitelna displazija penisa I, II i III stepena graduisana je prema stepenu debljine zahvatanja epitela atipičnim bazaloidnim ćelijama. U literaturi se navodi značajna uloga humanih papiloma virusa (HPV) u etiopatogenezi PIN.

Prikaz slučaja: Autori prikazuju muškarca starog 36 godina s epitelnom displazijom na glansu penisa, koji je u decembru 2010. godine pregledan u dermatovenerološkoj službi specijalističke Poliklinike Kliničkog centra Vojvodine. Pacijenta je na pregled uputio regionalni urolog sa histopatološkom analizom biopsije koja je uzeta sa 4 različita mesta sa plakoznih promena na glansu penisa. U 15. godini života je operisan od fimoze (cirkumcizija). Nije imao malignih bolesti niti drugih sistemskih bolesti.

U momentu pregleda, klinički nalaz na glansu je odgovarao neznatno induriranim eritematoznim plakovima sa lakom deskvamacijom na površini, cirkumferentnog rasporeda sa tendencijom difuznog zahvatanja celog glansa penisa.

Histopatološki nalaz: sa sva 4 mesta bioptirane sluznice glansa histopatološki nalaz odgovara sluznici

sa pločasto slojevitim epitelom u kome se uočava: blaga parakeratoza, blago do srednje narušena slojevitost ćelija; poremećeno sazrevanje pojedinih ćelija; uvećanje pojedinih jedara koja su krupnija i sa vidljivim jedarcima; prisustvo perinuklearnog svetlog haloa (diskretna koilocitoza) na pojedinim ćelijama; bazalna membrana očuvane i podjednake debljine; neravnomerno raspoređeni infiltrat limfocita i plazma ćelija u blago edematoznoj lamini propriji, oko blago dilatiranih krvnih sudova; odsustvo diskeratoze. Na osnovu navedene analize zaključeno je da se radi o: *dysplasio epithelii planocellularis gradus levioris (I) et partim gradus mediocris (II) mucosae*.

Lečenje: *Imiquimod* 5% krem nanošen je jedanput dnevno u tankom sloju i ostajao je 8 sati (potom pranje vodom i sapunom do novog nanošenja) svaki dan tokom 5 dana u nedelji, potom 2 dana pauze, u toku ukupno 10 nedelja. Na svake 2 nedelje tokom ovog tretmana činjeni su kontrolni pregledi kod dermatologa. Na kontrolnim pregledima utvrđeno je postojanje lokalne inflamacije sa lakom eksudacijom i supuracijom, eritem, blag svrab, pečenje i deskvamacija. Najjača inflamacija, eksudacija i supuracija sa izraženom deskvamacijom bila je tokom treće i četvrte nedelje lečenja. Posle 10 nedelja lokalnog tretmana ovim kremom, uvedena je lokalna primena masti sa fusidinskom kiselinom i gentamicinom u toku naredne 4 nedelje lokalnog tretmana, bez drugih peroralnih i lokalnih lekova. Nakon 14 nedelja od započinjanja lečenja, došlo je do kompletne sanacije promena. Tokom sledećih 18 meseci praćenja, nije bilo recidiva.

Diskusija: PIN odnosno epitelna displazija penisa I, II i III stepena graduisana je prema stepenu zahvatanja debljine epitela atipičnim bazaloidnim ćelijama. Ove ćelije variraju po svom obliku i veličini, imaju hiperhromatska pleomorfna jedra, sa gubitkom polarnosti. Pri tome, epitelnu neoplaziju stepena I (PIN I) karakteriše zahvatanje atipičnim ćelijama do jedne trećine debljine epitela, stepen II ide do dve trećine debljine epitela, a stepen III karakteriše zahvatanje atipičnim ćelijama više od dve trećine debljine epitela. Navedenu klasifikaciju prihvatila je i preporučuje je Svetska zdravstvena organizacija (engl. *WHO – World health organization*). Svi stepeni epitelne displazije odnosno PIN, predstavljaju histološke predstadijume *carcinoma in situ* i obuhvataju kliničke entitete ranije smatrane prekancerozama: *erythroplasia Queyrat* (engl. *erythroplasia of Queyrat – EQ*), Bowenova bolest penisa (engl. *Bowen's disease of the penis – BDP*), bovenoidna papuloza (engl. *bowenoid papulosis - BP*); Pagetova bolest, koja predstavlja intraepitelnu formu adenokarcinoma primarno nastalog u epitelu.

Iako je etiologija PIN nedovoljno razjašnjena, u literaturi se navodi značajna etiopatogenetska uloga humanih papiloma virusa (HPV). Oko 30 različitih tipova HPV virusa može biti prisutno u lezijama PIN sa podelom na one sa niskim onkogenim potencijalom (tipovi 6 i 11) i visokim onkogenim rizikom (tipovi 16 i 18). U svetskoj literaturi se od 2007. godine ukazuje na značaj mikroskopskog izgleda ćelija inficiranih virusom u spinoznom sloju epitela mukoze penisa, posebno kod muškaraca mlađih od 40 godina: koilocitoza, diskeratoza i akantoliza. Ovaj histološki nalaz može indikovati prisustvo PIN I–III stepena i omogućiti blagovremeni terapijski pristup.

U savremenoj literaturi se 5% imivimod krem navodi kao jedan od metoda lečenja PIN i ističe da je bitna dužina perioda praćenja bolesnika radi rane detekcije pojave recidiva. U našem slučaju period praćenja je za sada 18 meseci.

U literaturi se navode i druge metode lečenja PIN: 5-fluorouracil krem, krioterapija, kiretaža i kauterizacija, CO_2-laser, fotodinamička terapija, radioterapija (koju treba izbegavati), interferon alfa, ekscizija i Mohsova mikrografska hirurgija (naročito u lečenju recidiva). Posebnu pažnju u smislu redovnih kontrolnih pregleda treba pružiti seksualnim partnerima osoba HIV-inficiranih sa PIN, sa ciljem ranog otkrivanja i lečenja cervikalnog, vulvarnog i analnog karcinoma [25].

Zaključak: U radu je prikazan slučaj intraepitelne neoplazije penisa koji je uspešno lečen sa 5% imikvimod kremom tokom 10 nedelja, sa periodom praćenja od 18 meseci. U tom periodu nije bilo recidiva. Iako se metoda lokalne primene 5% imikvimod krema pokazala uspešnom u lečenju intraepitelne neoplazije penisa prvenstveno stepena I i II, za procenu krajnjeg terapijskog efekta potreban je duži period praćenja radi otkrivanja eventualne pojave recidivantnih promena.

Ključne reči

Neoplazme penisa; Aminokvinolini; Topikalna primena; Ishod lečenja

Aldara™ Krem, 5%

Imikvimod

Stimuliše imuni odgovor tamo gde je potrebno

- Spoljašnje genitalne i perianalne bradavice
- Manji površni karcinomi bazalnih ćelija
- Aktinične keratoze

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Hand, Foot and Mouth Disease in an Adult Man – a Case Report

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Abstract

Hand, foot and mouth disease is a systemic infection caused by enteroviruses. It is highly contagious, spreads by direct contact, and is commonly seen in young children. The disease is characterized by ulcerative oral lesions and a vesicular rash on palms, soles and characteristically between the fingers and toes, associated with mild systemic symptoms and signs such as fever and lymphadenopathy.

We present a 35-year-old man referred to a dermatologist with mouth lesions and skin rash. The patient had a fever, followed by a sore throat and malaise, which occurred two days before the rash. Physical examination revealed numerous superficial erosions and small vesicular lesions on the lower lip mucous membrane and on the hard palate, and also, multiple, discrete small vesicular lesions on fingers and toes. The patient was treated symptomatically and all the lesions resolved completely in a week. Adults with hand, foot and mouth disease usually experience milder symptoms than children. In conclusion: the disease should not be overlooked in middle-aged adults with a vesicular rash.

Key words

Hand, Foot and Mouth Disease; Adult; Enterovirus Infections; Signs and Symptoms; Treatment Outcome; Hyaluronic Acid

Although somewhat variable, the syndrome known as hand, foot and mouth disease (HFMD) is characterized by a sudden outbreak of oral vesicles, which rapidly ulcerate and resemble those of herpangina, as well as skin lesions which are inconstant, but when present, particularly in children, may be characteristic and dominate the clinical picture: painful vesicles may appear, usually on the hands and/or feet, especially on the sides or backs of fingers and toes or at the base of the phalanges. Fever is usually mild and of short duration. The disease is caused by a group of enteroviruses, most commonly coxsackievirus A 16, and enterovirus 71 (1).

HFMD primarily affects children, although the infection occasionally occurs in adults. The disease is usually mild. The incubation period varies from three to ten days, and the symptoms usually subside within seven to ten days (2). HFMD is self-limiting and only rarely may be complicated by a systemic disease such as encephalitis. The condition tends to be more severe when it occurs in adults (3).

Case report

A 35-year-old man was referred to a dermatologist with lesions in the mouth and a skin rash. The patient had a fever, followed by a sore throat and malaise, which occurred two days before the rash. Physical examination revealed numerous superficial erosions and small vesicular lesions on the mucous membrane of the lower lip (Figure 1.), on the hard palate, and also, multiple, discrete small vesicular lesions on fingers (Figure 2.) and toes (Figure 3.). The diagnosis was made based on the clinical history, as well as physical examination.

Laboratory findings, including complete blood count and blood chemistry were within normal limits. The patient was treated symptomatically with gingival hialuronic acid 0.2% gel, and his mucosal oral lesions completely resolved in a week.

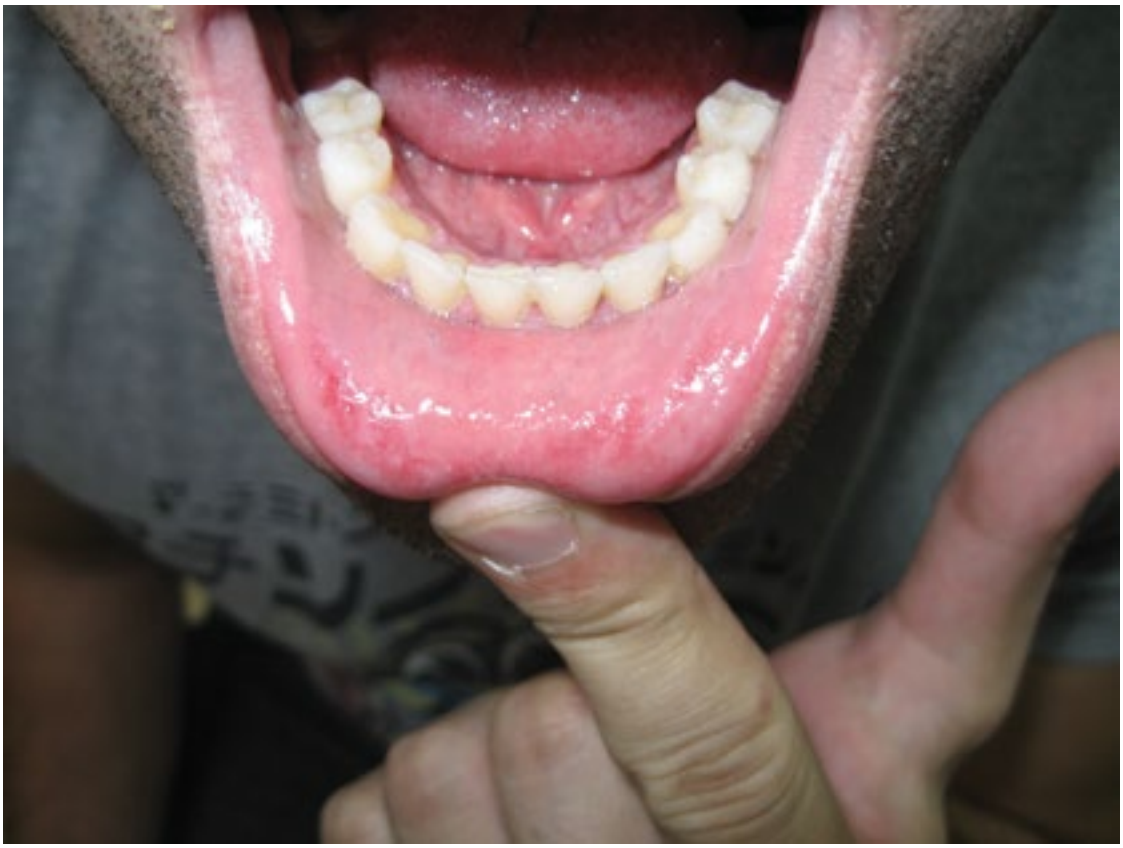

Figure 1. Multiple superficial erosions on the lower lip

Discussion

HFMD is a highly contagious disease, caused by one or several enteroviruses. The disease can be spread from person to person by contact with the saliva, respiratory secretions, vesicular fluid, as well as feces. The disease usually affects infants or young children, and epidemic outbreaks have occurred worldwide in the warmer months (4-8). HFMD has rarely been reported in immunocompetent adults (9).

Many infections are subclinical, but the most characteristic features of the syndrome include: fever, malaise, anorexia; slightly enlarged and tender anterior cervical lymph nodes; linear or oval, usually sparse oral ulcers which may affect any site; painful skin rash, sometimes deep-seated vesicles may appear, usually on the hands and/or feet, particularly on digits or at the base of the phalanges (10).

Following a brief prodrome of fever, sore throat and malaise, a characteristic enanthem and painful stomatitis develop, especially in adults (in children this may be mild). The oral vesicles which rapidly ulcerate resemble those of herpangina, but are rather larger and fewer in number and are irregularly distributed over the gums, buccal mucous membrane, palate, tongue and lips (Figure 1.). A skin rash develops over 1 - 2 days, as seen in our patient. It starts in a form of erythematous macules, evolving rapidly into thin-walled, pearly grey, oval or linear rather than rounded, small (up to 5 mm in diameter) vesicles with a red halo. The lesions are most frequently found on the hands they are usually located on the sides or backs of fingers and toes, especially around the nails, and around the margins of the heels, but may be seen in the finger flexures and on the palms and soles as in our case (Figures 2. and 3.). Lesions on the palms and soles are typically elliptical, with their long axis parallel to the skin lines (Figure 3.). More extensive papular or vesicular exanthem may develop, particularly in infants on the buttocks, but sometimes it is generalized (10).

A sudden outbreak of oral and distal extremity lesions is pathognomonic for HFMD. However, oral

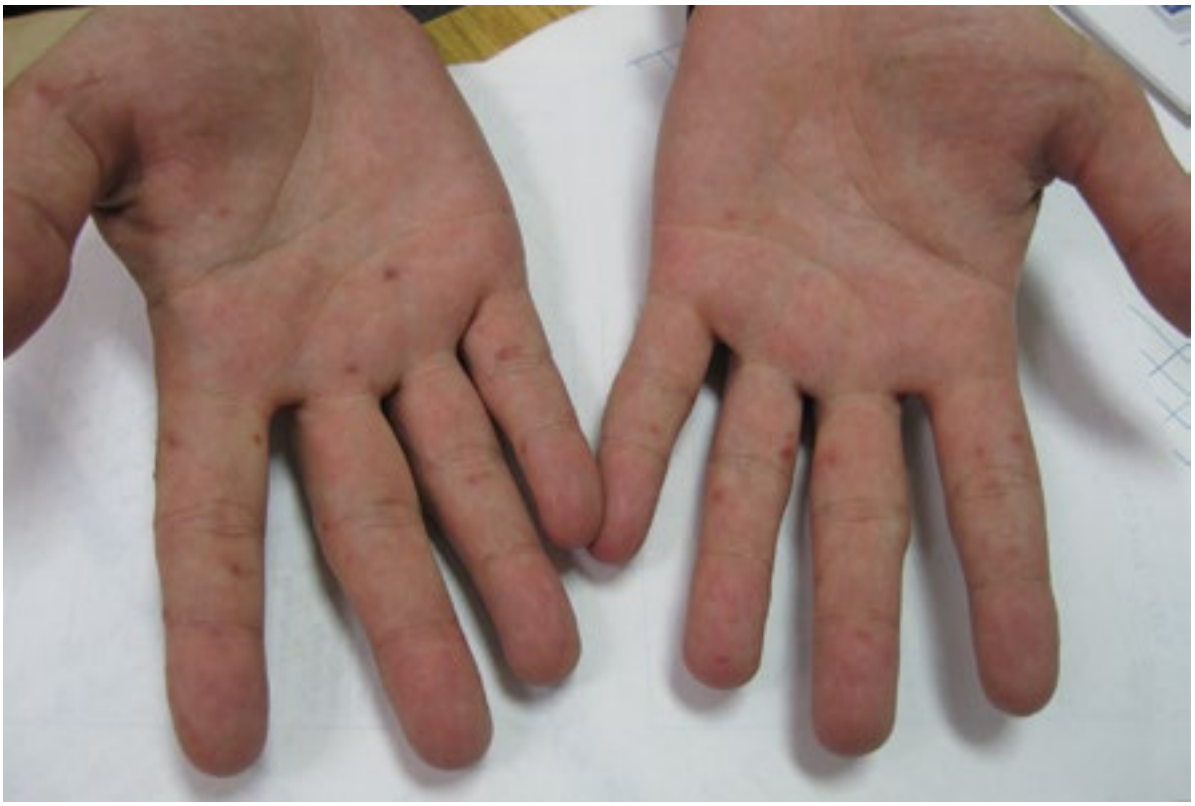

Figure 2. Small multiple erythematous macules on the fingers and palms

lesions may also occur without cutaneous lesions. Skin rashes have been reported in some other coxsackie syndromes, such as Gianotti–Crosti-like syndrome and erythema multiforme. As a rule, an exanthem in these and other coxsackie infections presents with few features to suggest the diagnosis, but the association with oral lesions should arouse suspicion. The differential diagnosis mostly includes herpes simplex stomatitis, chickenpox, vesicular stomatitis and foot and mouth disease (10).

Infection can be confirmed by isolation of the virus from the stool, vesicular fluid or nasopharynx, tissue culture or better in newborn mice, since only a few coxsackie A strains grow in tissue culture. Isolation from fecal samples alone may be misleading in the diagnosis of the disease, owing to the incidence of asymptomatic infections. Serology is of limited value, and slow, just like the culture, and the patient often recovers by the time the diagnosis is confirmed. Conventional histology either from biopsy or the scrappings from the base of blisters can be useful, but there is quite a high rate of false-negative results. Using an electron microscopy technique called negative staining technique, direct detection of virus particles in lesion samples can be achieved within half an hour. This technique has become invaluable in the confirmation of the diagnosis, mostly in lesions such as herpes simplex and zoster, and hand, foot and mouth disease (10). Unfortunately, as in our case, the technique is not widely available. HFMD is caused particularly by coxsackie A viruses, most frequently type 16, less frequently types 4, 5, and 10, but sometimes by coxsackie B viruses or enteroviruses, especially type 71. Coxsackie A strains (types 2, 3, 4, 5, 6, 8 and 10) and group B (type 3) cause herpangina. Herpangina is often found in cases with predominant features of hand, foot and mouth disease. Nevertheless, as with other enteroviruses, the clinical presentation caused by any of the strains is very variable (10).

The illness is usually mild and lasts only a few days, but severe complications such as pneumonia and myocarditis have been reported in adults (11). In our patient, lesions resolved after symptomatic treatment without complications.

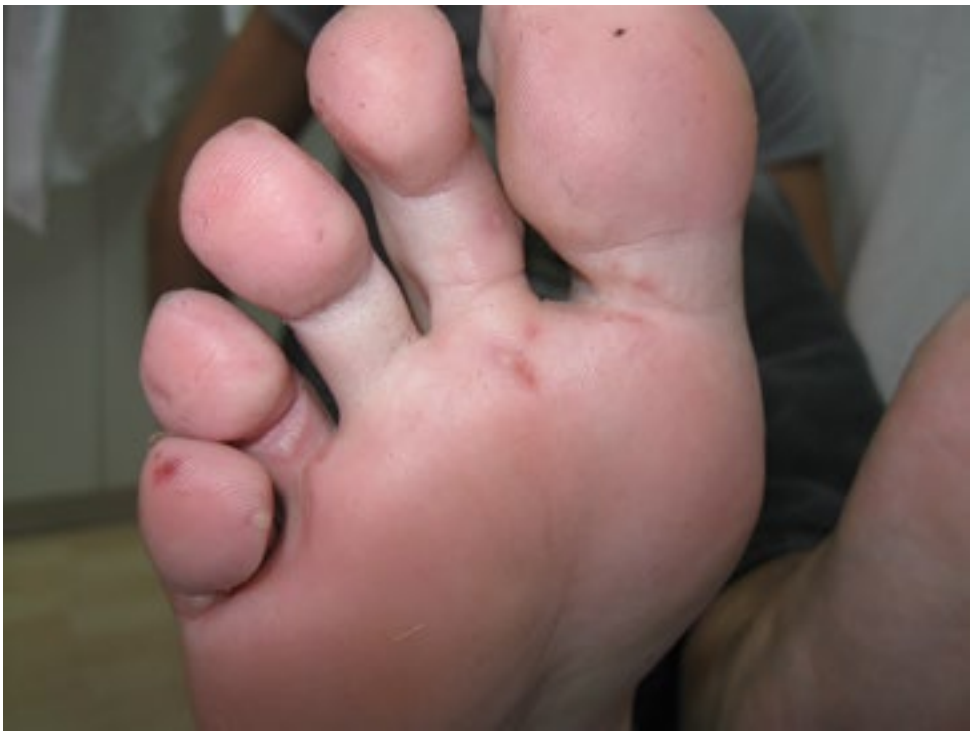

Figure 3. Vesicular lesions on the toes, with a characteristic linear shape

Conclusion

In conclusion, we report this case to remind physicians about the hand, foot and mouth disease, because the disease is rare in immunocompetent adults, and it should not be overlooked in middle-aged adults with vesicular rash. Because it is highly contagious, hygienic precautions are very important.

Acknowledgement

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Abbreviations

HFMD - Hand, Foot and Mouth Disease

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Bolest stopala, šaka i usta kod odraslih – prikaz slučaja

Sažetak

Uvod: Bolest šaka, stopala i usta je veoma kontagiozna sistemska infekcija izazvana enterovirusima koja se najčešće javlja kod dece. Oboljenje najčešće izaziva koksaki virus A16 i enterovirus 71. Karakteriše ga pojava vezikula na orofaringealnoj sluznici koje brzo prskaju ostavljajući bolne erozije i ospa na koži distalnih delova ekstremiteta, najčešće šaka i stopala. Obično se javlja blag poremećaj opšteg stanja.

Prikaz slučaja: Prikazujemo pacijenta starog 35 godina koji je došao kod dermatologa zbog ranica u usnoj duplji i osipa po dlanovima i tabanima. Dva dana pre pojave ovih promena pacijent je imao povišenu temperaturu, malaksalost i gušobolju. Pregledom je utvrđeno prisustvo brojnih erozija na sluznici tvrdog nepca i donje usne, eritematoznih makula na dlanovima i tabanima i vezikula u interdigitalnim prostorima. Promene su se povukle uz simptomatsku terapiju.

Diskusija: Dok promene mogu zahvatiti bilo koji deo oralne sluznice, nepce, jezik ili usne (Slika 1), karakterističan je izgled i lokalizacija osipa po koži. Promene na koži su najčešće lokalizovane na bočnim i dorzalnim stranama prstiju dlanova i tabana, naročito oko nokatnih ploča ali se mogu videti i na prevojima falangealnih zglobova, dlanovima I tabanima (slike 2 i 3). Vezikule su sitne, sivobeličaste boje karakterističnog ovalnog, linearnog, osnosno elipsastog oblika, sa dužom osovinom postavljenom paralelno sa funkcionalnim linijama kože (Slika 3). Kod dece osip može biti generalizovan: makulopapulozan ili papulovezikulozan.

Bolest šaka, stopala i usta se retko javlja kod odraslih osoba očuvanog imunostatusa.

Iznenadan atak oralnih i lezija na distalnim delovima ekstremiteta je patognomoničan, ali se oralne lezije mogu javiti i bez kutanih, što se neretko viđa u tzv. koksaki sindromima, *Gianotti–Crosti-like* sindromu i sindromu multiformnog eritema. Po pravilu, osip koji se javlja u toku ovih sindroma, obično nije dijagnostički punovredan, ukoliko nije zahvaćena orofaringealna sluznica. U diferencijalnoj dijagnozi treba isključiti stomatitis izazvan herpes simpleks virusom, vezikulozni stomatitis, varicelu i bolest stopala i usta.

Infekcija se dokazuje izolacijom virusa iz sadržaja vezikula ili nazofarinksa, u tkivnoj kulturi ili bolje inokulacijom u eksperimentalne životinje s obzirom da samo mali broj koksaki virusa iz grupe A raste u kulturi tkiva. Izolacija virusa isključivo iz fecesa nema dijagnostički značaj s obzirom na visoku učestalost infekcija bez simptoma. Serološka dijagnostika je od ograničenog značaja kao i kultura, naročito ako se uzme u obzir vreme za koje isti pružaju pozitivan nalaz. Konvencionalna histološka analiza bioptiranog uzorka ili skarifikata dna vezikule može imati dijagnostičku vrednost ali pruža veliki procenat lažno-negativnih rezultata. Direktno dokazivanje virusnih partikula u ispitivanom uzorku pomoću elektronskog mikroskopa, tehnikom tzv. negativnog bojenja, omogućuje postavljanje dijagnoze u roku od pola časa. Ova tehnika ima neprocenjiv dijagnostički značaj kod mnogih virusnih oboljenja a naročito kod infekcija izazvanim herpes simpleks i zoster virusima i kod bolesti šaka, stopala i usta. Nažalost, ova metoda nije uvek dostupna što je bio slučaj i kod našeg pacijenta.

U najvećem broju slučajeva bolest izaziva koksaki virus A16, ređe A4, A5, A10, a ponekad tipovi iz grupe B, i enterovirusi – naročito tip 71.

Herpanginu izazivaju koksaki A virusi (tipovi 2, 3, 4, 5, 6, 8 i 10) i koksaki B virus tip 3. Neretko, herpangina prati bolest šaka, stopala i usta. Kao što je slučaj i sa ostalim enterovirusnim infekcijama, klinički sindromi izazvani bilo kojim pojedinim tipom pokazuju veliku kliničku varijabilnost.

Bolest je obično blagog toka i traje nekoliko dana, kao kod našeg pacijenta. Iako retko, moguća je pojava teških komplikacija, pneumonije, miokarditisa i encefalitisa.

Zaključak: Bolest šaka, stopala i usta kod odraslih osoba je obično blažeg toka nego kod dece. Zbog infektivnosti oboljenja ovaj karakteristični osip ne bi trebalo ni kod njih prevideti

Ključne reči

Bolest šaka, stopala i usta; Odrasli; Enterovirusne infekcije; Znaci i simptomi; Ishod lečenja; Hijaluronska kiselina

The First Serbian Dermatovenereologist - Jevrem Žujović

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Abstract

In the early 19th century, after several centuries of slavery, Serbia was liberated and along with the overall organization of the country, health services were formed. The first specialists appeared at the end of the century, among them our first dermatovenereologist, Dr. Jevrem Žujović. He was born in 1860 in Belgrade. He attended high school in Belgrade and in 1885 he graduated from School of Medicine in Paris. Dr. Žujović specialized in dermatovenereology in Paris, with Prof. Fournier as his mentor. He was the first Head of the Department of Skin Diseases and Syphilis at the General Public Hospital since 1889. He organized specialized services all over Serbia. His activity in the work of the Serbian Medical Society was very appreciated. Dr. Žujović studied endemic syphilis and leprosy, and translated A. Fournier's book "Syphilis and Marriage", and Loraine's "Prostitution and Degeneration". Together with M. Jovanović-Batut, he wrote "Instructions on Syphilis".
As an Army Medical Officer, Dr. Žujović participated in the Serbo-Bulgarian war (1885), the First and the Second Balkan War and in the First World War (1912 – 1918). He was the vice-president of the Society of the Red Cross of the Kingdom of Yugoslavia, and the first president of the newly-founded Association of Dermatovenereologists of Yugoslavia. He was a recipient of many awards and decorations.
Jevrem Žujović retired in 1927, and passed away in 1944.

Key words

Biography; Physicians; History of Medicine; Dermatology + history; Venereology + history; Syphilis + history

During the centuries of Ottoman rule in the Balkans, the Renaissance had been flourishing in Europe, while the Serbian medieval state, its culture, nobility and most of the urban population were being destroyed (1). After a long and difficult period and national uprisings, the 19th century was a creative period when Serbia was restored as a vasal state and definitely iberated, becoming the forerunner of the modern state. The country was facing great challenges, and organization of health services was among the most important tasks, but its basic guidelines were already present in the Constitutions of 1835 and 1838 (2). The main argument for this was the spread of infectious diseases, syphilis being one of the most significant. There were no physicians in Serbia of that time. The first physician was Dr. Alexandridi, mentioned in 1818 (2). After that, the number of physicians gradually increased, whereas specialists appeared in the late 19th century, and one of them was Dr. Jevrem Žujović (3), our first dermatovenereologist (Figure 1). He was from a prominent Žujović family, typical in Serbia of the 19th century; many rebels and warriors, politicians, the first educated people and intellectuals who also liberated, developed and protected Serbia, came from such families.

Fleeing from the Turks, the Žujović family moved to Serbia from Sjenica at the beginning of the 19th century and settled in Nemenikuća under the Kosmaj Mountain. Milenko Žujović (1756- 1836), father of the family, participated in the First Serbian Uprising and died of wounds. His brother Jovan (died in 1825), a commander in the Karađorđe's

Figure 1. Dr. Jevrem Žujović, our first dermatovenereologist
(The photograph was taken by the royal photographer V. Danilović in Belgrade)

army, fought all the battles of the First Serbian Uprising (4).

Jevrem Žujović's father, Mladen (1810-1899), was one of our first officers educated in Russia, a member of the St. Andrew Assembly, a Staff Officer of Prince Mihajlo, Mayer of the City of Belgrade, a State Advisor, Head of the Main Military Command in the rank of a Minister, and was involved in the organization of the army (4).

Jovan Žujović (1856 – 1936), Jevrem Žujović's brother, was the founder of the Serbian geology, Professor at the University of Belgrade, Rector of the High School, a member of the *Serbian Learned Society* and of the *Serbian Royal Academy*, its president and secretary, a member of the *Yugoslav Academy of Sciences and Arts* in Zagreb, a member of several international scientific societies, Minister of Foreign Affairs, Minister of Education and Religions, and an important politician, especially during the First World War. He wrote a number of fundamental books and papers in his profession (4, 5). His name is included in the list of "The 100 most prominent Serbs" (6).

Jevrem Žujović was closely related with the Danić family. His maternal grandfather, Rista Danić (the end of the 18th – beginning of the 19th century), originated from Aegean Macedonia, was the president of the Belgrade municipality at the beginning of the 19th century. His grandson, Jovan Danić, our first neuropsychiatrist and the Director of the *Mental Hospital* in Belgrade, was the president of the *Serbian Medical Society* (SMS) (4).

The descendants of Jevrem Žujović were professors at the *School of Medicine* and *School of Law* in Belgrade; one of his sons was a member of the *Serbian Cultural Club*, and an important politician during the Second World War (4).

Jevrem Žujović was born in Belgrade in 1860. His father was Mladen Žujović, and his mother Jelena, born Danić (see above). He graduated from High School in Belgrade in 1878 and in 1885 from *School of Medicine*

in Paris, with graduate thesis "De la Thyroïdite aiguë rhumatismale" with Professor Vulpain as his mentor (4). When he returned to Belgrade, in 1885, he was appointed district physician of the Paraćin District (Ćuprija County) (4). The following year (1886), he was transferred to Belgrade to a post of a secondary physician of the *Mental Hospital* (7). At that time, he decided to specialize in dermatovenereology, and in Europe there was a growing interest in this field of medicine. His dominant interest, however, was venereology, specifically syphilis, which was rapidly spreading. At the beginning of the 20th century, about 20% of European intelligentsia was infected with syphilis (8). Although in Serbia it first appeared at the beginning of the 19th century, after the wars for liberation from the Turks, in the thirties of the 19th century it reached epidemic proportions with numerous and often dense endemic foci (9). As mentioned before, physicians were rare, and there were no specialists whatsoever. In 1887, Jevrem Žujović went to Paris to specialize dermatovenereology in the *St. Louis Hospital* with Professor Fournier, a syphylologist of worldwide reputation. At that moment, medical services in Serbia already gained basic frameworks and guidelines. Some of them were of great importance for dermatovenereology, such as the *Law on the Organization of the Sanitary Profession and Public Health Care*, passed in 1881 (10). Based on this law, the *Belgrade County and City Hospital* had become the major general public hospital in the country (*General Public Hospital – GPH*), with five specialized departments, and *Department for Skin Diseases and Syphilis* among them (11). In 1882, *Prostitution Regulations Rules* were brought (12), as well as the *Law on Sanitary Funding*, in 1879, independent from political interference, putting Serbia ahead of Europe (13). The official announcement about free treatment of syphilis among laborers "workers and peasants" (1887) was also of utmost benefit (2). Jevrem Žujović returned from specialization in 1888 (4), so an educated dermatovenereologist arrived to Serbia at the right moment and his knowledge was well used. He came from one of the leading European dermatovenereological center where modern medicine was being born and where the fight against syphilis was at the highest level. Apart from that, as the rest of our intellectuals of that time, with a high national consciousness and sense of duty, energy and creativity, which had been restricted and accumulated over the centuries, he started the development of a specialized dermatovenereology service. Although a dermatovenereology department was planned by the *Sanitary Law* from 1881, its professional organization began when Jevrem Žujović returned from Paris. With no time to spare, in August of the same year, he sent a request to the Administration of the GPH, describing the situation he found in the venereology service in Belgrade, and we will quote part of it: "The *Women's Ward for Skin Diseases and Syphilis* has 1 room with 13 beds; now there are 30 infected patients, with 2 or even 3 patients per bed. One or two infected women are sent by the police every day, and apart from this, 3-6 prostitutes are referred from brothels every week. Other infected women (so called private), are not admitted, but they are treated as outpatients. None of the venereal diseases can be cured in 7 days, and patients referred by the police cannot be discharged before completely cured. Therefore, it is necessary to raise a building with 2 - 3 rooms with 30 – 40 beds" (14). The Superintendant of the GPH, Dr. Gonsjorovski immediately wrote a request to the Minister of Internal Affairs: " Please urge the competent authorities to build at least one soft material building in the hospital park to accommodate 40 beds for female patients", having in mind patients suffering from venereal diseases (15). The problem was eventually solved, because there were reports about barracks in the yard of the GPH, although there are no documents about their work. The following year, in 1889, as the first and only dermatovenereologist, Jevrem Žujović was elected Head of this Department (4) and organized its work as well as the work of the whole network of dermatovenereological services in Serbia. At the same time, he implemented a modern dermatovenereological doctrine at the above mentioned territory. His collaboration with the dermatovenereology services in all areas of the country was well functioning, and his department became a training center for physicians, where unsolved and critical cases were sent to from all over the country. Prof. Dr. Đ. Đorđević said the following: "Thanks to his quiet, serious and professional work, he managed to keep our profession at a high level in the most critical times for dermatovenereology.... His department was

of such importance that all the others looked up to him, followed his work and thus implemented their knowledge in practice, particularly in relation to syphilis"(16). All the time he kept close ties with European dermatology and in 1909 he revisited the *St. Louis Hospital*, spending 3 months getting familiar with novelties in the profession. Upon his return, he established a modern laboratory at his department and for the first time in Serbia introduced *Wasserman reaction* and microscopic detection of *Treponema pallidum* from syphilis lesions (4, 17).

Although the bibliography of Jevrem Žujović is not complete, reviewing *Serbian Archives for the Whole Medicine*, one can find that he was very active in the SMS, where he reported about rare skin diseases, new therapeutic procedures, translated recent articles and outlines from foreign literature, and presented congress reports from international congresses he attended. As the Prof. Fournier's student, he paid special attention to endemic syphilis. He also studied leprosy, and from 1890 till the Balkan Wars (1912 – 1913), during his holidays, he travelled through Eastern Serbia, Bosnia, Herzegovina and Montenegro, collecting materials about leprosy and syphilis. Unfortunately, documents that he did not get to finish, including medical histories and diary reports, were mostly destroyed during the occupation of Serbia (1914 – 1918) (4). A typewritten text signed by Dr. Jevrem Žujović was saved and it analyzed the incidence of leprosy in Serbia according to annual reports of all hospitals in the country since 1888, and based on papers presented on all meetings of the SMS since its establishment (1872) (18), and reports of several colleagues who worked in areas with leprosy. Zambaco Pasha, a famous Greek leprologist from Istanbul and a naturalized Frenchman, published the material in his book before 1914 in French (19). Another typewritten and signed paper by Dr. Žujović was also saved: " *Rapport de la Société de la Croix rouge des Serbes, Croates et Slovènes à la Conférence régionale de l'Europe orientale sur les maladies veneriennes"* and he presented it in Prague in 1921. This paper has 11 pages and presents a precise and detailed description, always characteristic for his writing, of the development and organization of the fight against syphilis in the whole country. Although everything he wrote about was legally documented, as a member of the *Sanitary Council* he clearly expressed his own opinion about the dermatovenereology service, and summerized his lifelong experience into a series of principles which even today seem incredibly true (20).

Apart from this, in 1892 he translated the book of his mentor, A. Fournier: "Syphilis and Marriage", which was the first book on venereology in Serbian language. He also translated the book "Prostitution and Degeneration" by Loraine, which was published in series in *Serbian Archives for the Whole Medicine.* According to the decision of the SMS, together with M. Jovanović-Batut, he wrote "Instructions on Syphilis" (vrenga) (21).

In 1887, Jevrem Žujović was elected a member of the SMS. Shortly thereafter, in 1888, he became a deputy, and then a regular member of the *Sanitary Council of the Ministry of Internal Affairs* and remained at this important function in the course of thirty years (4, 7). Being our most eminent dermatovenereologist of that time, in 1927 he was elected the first president of the *Association of Dermatovenereologists of Yugoslavia* (16).

In addition to his work in his profession, as a member of the *Sanitary Council* he was engaged in the organization of health services in Serbia. He paid great attention to health education of individuals, the society and especially of the rural population. In one of his papers he wrote about this problem, which points to his personal participation in health education (20).
Apart from the fact that he set his profession into the framework of newly adopted sanitary regulations and opened the route for entering and accepting European scientific dermatovenereology, Jevrem Žujović was very active in wars his country was engaged in. At the very beginning of his medical career, as a regimental doctor, he took part in the Serbo-Bulgarian war that erupted at the end of 1885 (4, 17).

He participated in both Balkan Wars and in the First World War (1912 – 1918) as a Reserve Medical Officer. From October 1912 to August 1913, he was the commander of the *Third Field Hospital* of the Šumadija Devision, located behind the battle lines, and then organized a *Reserve Military Hospital* in Prizren, which had to be transformed into a hospital for patients with typhoid fever. At the end of Balkan Wars, he founded a hospital in Stracin for patients suffering from cholera. During the First World War, in 1914,

he served in the *Belgrade Military Hospital* as a Reserve Sanitary Major. Soon he was transferred to Đevđelija for the commander of the *Reserve Military Hospital*, when he himself got spotted typhus which decimated the Serbian army and the Serbian medical staff, and in mid-1915 he moved to Skoplje and became the Head of the *Military Hospital* and Chief of the *Department for Skin and Venereal Diseases*. After that, as a member of the *Red Cross Committee*, he joined the Serbian army in retreat, and via Peć and Skadar he arrived to St. Jovan Medovski on the Adriatic coast. During this painful exodus, Jevrem Žujović and a prominent retailer from Belgrade Đ. Radojlović, also a member of the *Red Cross Committee,* helped temporary hospitals on their way, and then used the Red Cross funds to organize kitchens and hospitals in Skadar and Lješ for the exhausted and wounded soldiers. At the end of January 1916, they both went to Geneva and with the help of the *International Red Cross Committee* and by virtue of their own authority and diligence, they organized the *Red Cross Information Bureau*, which provided financial assistance to prisoners of war and the population in the occupied Serbia. In recognition of his outstanding work, in 1920, the *League of Red Cross Societies* elected J. Žujović a member of the *Board of Governors of the League*. He was the first vice-president of the *Society of the Red Cross of the Kingdom of Yugoslavia* (4).

For his peacetime and wartime merits, J. Žujović received the following awards: Order of White Eagle, IV class, Memorial Medals for 1885 and 1886, Gold Medals for diligent service, and three Orders of St. Sava (II, IV and V class), as well as the Belgian Red Cross Decoration I class (4).

After the war, J. Žujović continued working at the *Department for Skin Diseases and Syphilis* of the GPH in Belgrade. His department has always been recognized for its innovative ways and commitment to research and it cooperated with renovated and new dermatovenereology institutions in Belgrade and Serbia, while his experience, reputation and authority were the backbone of rapid postwar development of our profession. His help in practical teaching of dermatovenereology at the newly established *School of Medicine* in Belgrade should also be pointed out (22).

J. Žujović retired in 1927. He passed away on the Orthodox New Year, January 14, 1944, at his home in 42 King Milan Street, and was buried at the New Cemetary in Belgrade (4). He did not live to see the liberation of his country, for which he had done so much.

Abbreviations

SMS – Serbian Medical Society
GPH – General Public Hospital

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Prvi srpski dermatovenerolog - Jevrem Žujović

Sažetak

Uvod: Devetnaesti vek je stvaralački period srpske istorije, kada je posle viševekovnog ropstva pod Turcima nastala „obnovljena", a potom i slobodna Srbija. Uporedo sa celokupnom organizacijom zemlje počelo je i formiranje zdravstvene službe; pojavili su se prvi lekari, ali se specijalisti sreću tek krajem XIX veka, među kojima je bio i naš prvi dermatovenerolog – dr Jevrem Žujović. On je poticao iz ugledne porodice Žujović, koja je davala ratnike, političare i naučnike.
Biografski podaci: Jevrem Žujović se rodio u Beogradu 1860. godine. Gimnaziju je završio u Beogradu 1878. godine, a Medicinski fakultet u Parizu; 1885. lekarsku službu je počeo 1885. kao okružni lekar, ali već 1887. otišao je u Pariz da specijalizira dermatovenerologiju.
Stručna aktivnost: Specijalizaciju je obavio kod prof. Furnijea (*Fournier*), vodećeg evropskog sifilologa. U zemlju se vraća 1888. godine, a za šefa Odeljenja za kožne bolesti i sifilis izabran je 1889. U to vreme sanitetska služba u Srbiji već je dobila zakonske okvire i smernice, tako da su kapaciteti J. Žujovića mogli biti iskorišćeni. On organizuje specijalističku službu na svome odeljenju, učestvuje u stvaranju mreže specijalističke službe u celoj Srbiji i sprovodi savremenu dermatovenerološku doktrinu na celom području. Đ. Đorđević kaže da je njegovo odeljenje bilo od takve apsolutne vrednosti, da su se svi po njemu upravljali. Posle ponovnog boravka u pariskoj bolnici, 1909. godine, osniva modernu laboratoriju i u rad uvodi Vasermanovu reakciju i mikroskopsko otkrivanje blede treponeme sa kožnih lezija.
Bio je vrlo aktivan u radu Srpskog lekarskog društva, gde je prikazivao retke dermatoze, nove terapijske postupke, prevode aktuelnih članaka iz strane literature i izveštaje sa inostranih kongresa u inostranstvu. Proučavao je endemski sifilis, a njegov izveštaj o pojavi lepre u Srbiji štampan je u knjizi koju je objavio poznati leprolog toga doba, Zambaco Pasha. Na *Regionalnoj konferenciji istočne Evrope o venеričnim bolestima*, 1921. godine izneo je iscrpan izveštaj u ime *Crvenog krsta Kraljevine Srba, Hrvata i Slovenaca.* Preveo je dve knjige sa francuskog jezika: „*Sifilis i brak",* A. Furnijea i *„Prostitucija i degenerisanje"* Lorana (*Loraine),* a zajedno s M. Jovanovićem – Batutom izradio je „*Pouke o sifilisu*". Pružao je pomoć u praktičnoj nastavi iz dermatovenerologije na novoosnovanom Medicinskom fakultetu u Beogradu.
Učešće u ratovima: Učestvovao je u Srpsko-bugarskom ratu (1885), u oba Balkanska rata i u Prvom svetskom ratu (1912–1918) kao rezervni sanitetski oficir. Prateći srpsku vojsku preko Albanije organizovao je kuhinje, poljske i rezervne vojne bolnice, pri čemu je i sam oboleo od pegavog tifusa. Iz Ženeve, uz

pomoć Međunarodnog komiteta Crvenog krsta, zajedno sa Đ. Radojlovićem organizovao je pomoć ratnim zarobljenicima i stanovništvu u okupiranoj Srbiji.
Druge aktivnosti: Bio je potpredsenik *Društva Crvenog krsta Kraljevine Jugoslavije* i član *Saveta guvernera Lige društava Crvenog krsta*. Kao vodeći dermatovenerolog 1927. godine izabran je za prvog predsednika novoosnovanog Jugoslovenskog dermatovenerološkog društva.
Nosilac je sledećih odlikovanja: Orden belog orla IV stepena, ratne spomenice 1885. i 1886. godine, Zlatne medalje za revnosnu službu, tri Ordena Sv. Save (II, IV i V reda) i Medalje I klase Belgijskog crvenog krsta.
J. Žujović se povlači u penziju 1927. godine. Preminuo je 1944. godine.

Ključne reči

Biografija; Lekari; Istorija medicine; Dermatologija + istorija; Venerologija + istorija; Sifilis + istorija

A Report on the 21st Congress of the European Academy of Dermatology and Venereology, Prague, 2012

The 21st Congress of the European Academy of Dermatology and Venereology (EADV) was held in Prague from 27-30 September, 2012. There were 130 sessions including: 11 courses, 4 separate parts entitled "What's new" in - venereology, pediatrics, clinical dermatology and dermatological therapy, respectively; several workshops, symposia, focus sessions, juniors sessions, and "Test Yourself" session. There were five plenary lectures: "Cancer and Inflammation", "The Changing Face of STDs", "The Reality and Hopes of New Therapeutic Developments in Oncology", "Dermatology, Migration and International Health" and "Skin Barriers". Free communications were divided into 8 different categories.

Professor Ljiljana Medenica was the Co-Chair of the workshop: "Aesthetics Surgery and Dermatology (mini-lifting)". Assistant Professor Mirjana Milinković was the Co-Chair of the workshop "Vasculitis and Red Flags"; and delivered her lecture "Vasculitis as a Red Flag for Sjögren Syndrome and other Autoimmune Diseases". Within the symposium "EADV Juniors Session" Dr. Danica Tiodorović-Živković gave a lecture "Successful Treatment of Two Invasive Squamous Cell Carcinomas with Topical 5% Imiquimod Cream in Elderly Patients". During the Congress, there were 22 E-poster presentations coming from Serbia.

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Figure 1. Danica Tiodorović-Živković at ''EADV junior session" in Praque

Figure 2. Danica Tiodorović-Živković presenting a lecture "Successful treatment of two invasive squamous cell carcinomas with topical 5% imiquimod cream in elderly patients"

FORTHCOMING EVENTS

Dermatology and Venereology Events 2013

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
31 January – 3 February, 2013	15th Annual IMCAS Congress, Paris, France	24 December, 2012	www.imcas.com
6-9 February, 2013	2nd World Congress of Cutaneous Lymphomas /6th International Symposium on the Biology and Immunology of Cutaneous Lymphoma (WCCL 2013), Berlin, Germany	30 November, 2012	www.cutaneouslymphomas2013.com
7-9 February, 2013	Food Allergy and Anaphylaxis Meeting, Nice, France	7 December, 2012	www.eaaci.net
March, 2013	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
12 April, 2013	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, 2013	Dubai World Dermatology & Laser Coference 2013	No deadline information	www.dubaiderma.com
May, 2013	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
8-11 May, 2013	International Investigative Dermatology, Edinburgh, Scotland	3 January, 2013	www.iid2013.org
23-26 May, 2013	10th EADV Spring Symposium, Krakow, Poland	10 November, 2012	www.eadvcracow2013.org
13-15 June, 2013	2nd/19th Congress of Serbian Association of Dermatovenereologists, Belgrade, Serbia	01 March, 2013	www.udvs.org
22-26 June, 2013	EAACI – WAO World Allergy and Asthma Congress, Milan, Italy	21 January, 2013	www.eaaci-wao2013.com
27-30 June, 2013	9th World Congress of Cosmetic Dermatology, Athens, Greece	1 February, 2013	www.erasmus.gr
4-7 July, 2013	4th International Congress of Psoriasis 2013, Paris, France	15 February, 2013	www.pso2013.com
18-20 July, 2013	8th World Congress of Melanoma, Hamburg, Germany	24 March, 2013	www.worldmelanoma2013.com
25-27 September, 2013	12th World Congress of Pediatric Dermatology, Madrid, Spain	No deadline information	www.wcpd2013.com
3-7 October, 2013	22nd EADV Congress, Istanbul, Turkey	10 April, 2013	www.eadv.org
18 October, 2013	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Vojvodina, Novi Sad, Serbia	No abstract submission	www.sld.org.rs
4-7 December, 2013	11th International Congress of Dermatology, Delhi, India	No deadline information	www.icddelhi2013.com

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

AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

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

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

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

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

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.

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3. References

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

4. Additional information

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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Ceramidi	Ojačana lipidna barijera i smanjen gubitak vode
Gliko-glicerol	Stimulacija akvaporin kanala, optimalna hidratacija u dubljim slojevima epidermisa

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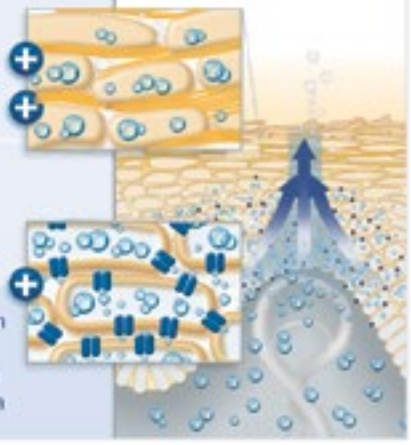

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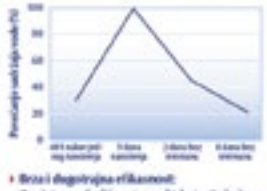
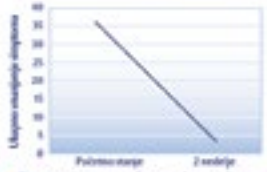


• **Brza i dugotrajna efikasnost:**
Značajno poboljšan stepen hidratacije kože



• **Procena simptoma od strane dermatologa:**
Smanjenje svrbeža, pečenja, osećaja zatezanja i osećaja suvoće kože nakon korišćenja preparata

• **Veoma dobra podnošljivost na koži:**
Dermatološki i klinički dokazano kod pacijenata koji imaju veoma suvu kožu, uključujući i pacijente oboleле od dijabetesa

Cover figure: Christ Healing Ten Lepers, Christ's Miracles, 14th century, The monastery Visoki Dečani, Serbia, Kosovo

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