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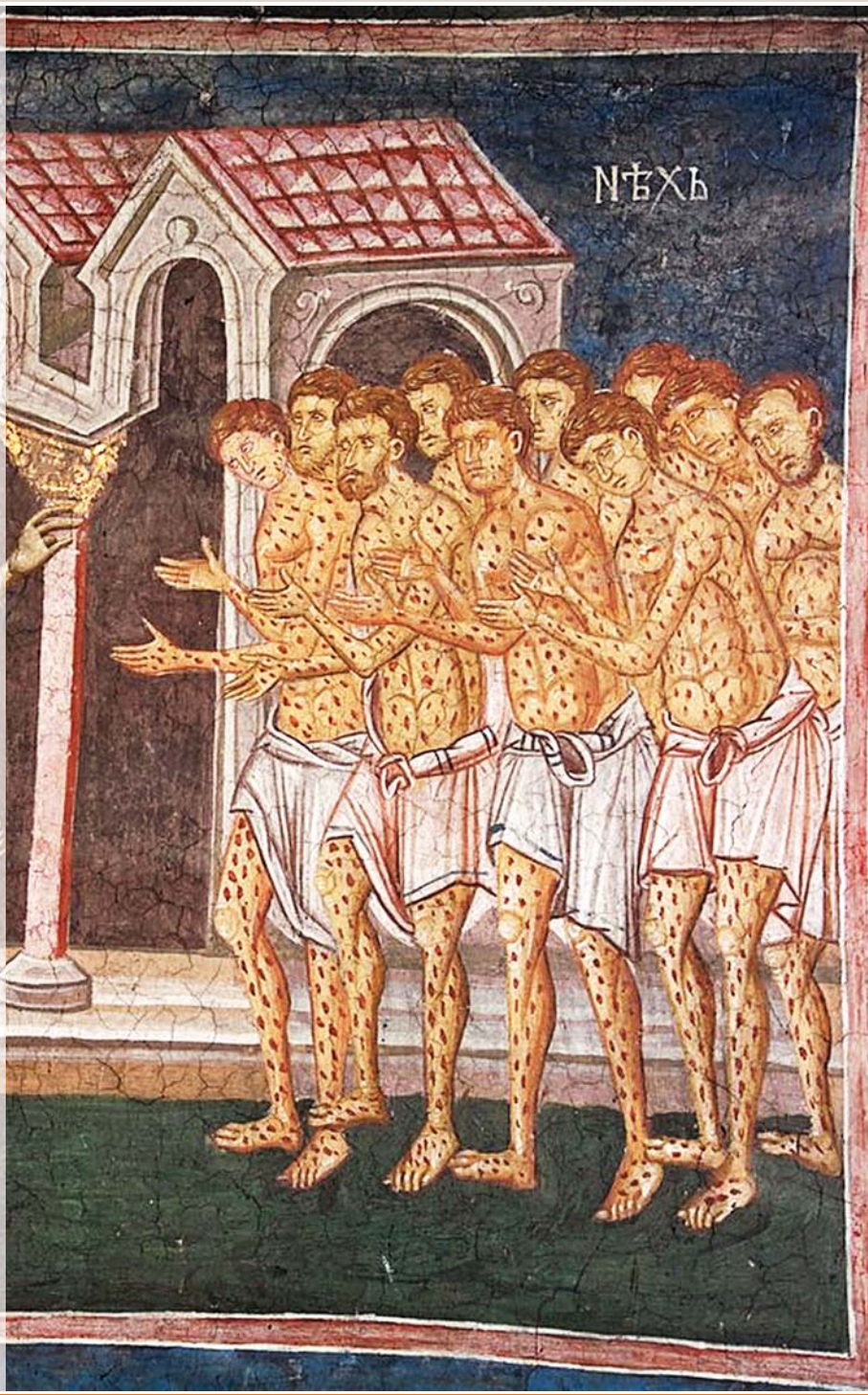

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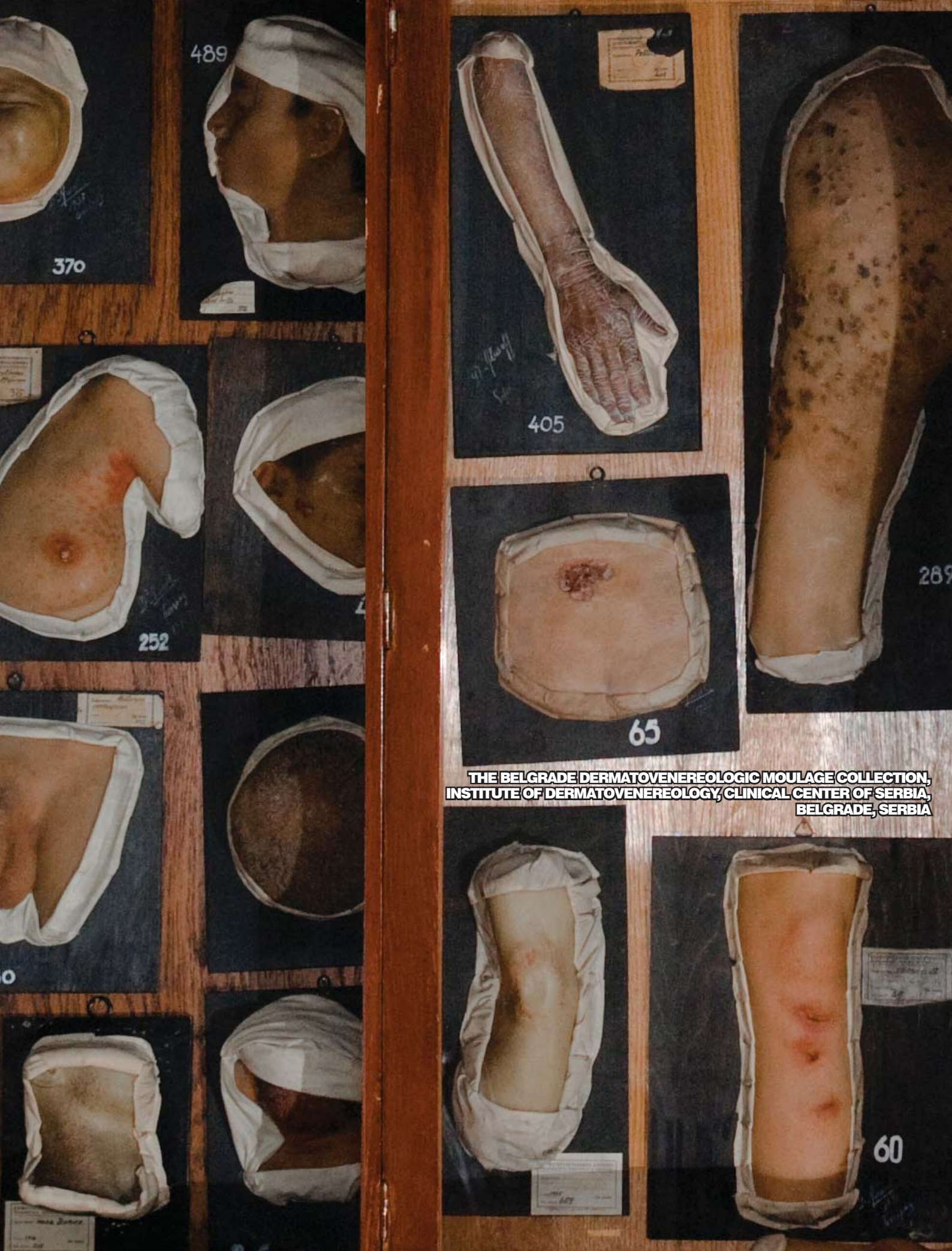

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New Aspects of Melasma

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Abstract

Melasma is a common cosmetic problem and its severity ranges from minor pigmentation during pregnancy that resolves spontaneously, to a chronic, troublesome, disfiguring condition. Today, there are various treatment modalities for melasma, providing a different success rate. The need for an effective treatment for melasma is becoming more and more significant probably due to the current lifestyles with increased UV exposure, broad use of hormones for contraception and hormone replacement therapy, as well as increasing esthetic demands. The mainstay of treatment is regular use of sunscreens along with topical medications suppressing melanogenesis. This review summarizes recent progress in understanding the pathophysiology of melasma and implications for new treatment strategies.

Key words

Melanosis; Dermatologic Agents; Hydroquinones; Sunscreening Agents; Skin Lightening Preparations; Laser Therapy; Diagnosis, Differential

Melasma is a common, acquired, circumscribed hypermelanosis of the face and occasionally of the neck and forearms, which significantly impacts the quality of life. Chloasma comes from the Greek term for "a green spot" and describes melasma during pregnancy or the "mask of pregnancy".

Although it may affect any race, melasma is much more common in darker-skinned individuals (skin types IV to VI) (1). There are few prevalence studies on melasma**,** but there is evidence that the prevalence of this disorder differs among different ethnic groups. Melasma is more common in individuals of Hispanic, Oriental and Asian origin (2). The reported prevalence of melasma ranges from 8% among Latinas in the United States, to 30% in Southeastern Asian populations. Melasma is more prevalent in women, especially during their reproductive years, with the peak age between 20 and 30 years. It is rarely reported before puberty (3). Extra-facial melasma is more prevalent in postmenopausal women (4).

Etiology and pathogenesis

Etiopathogenesis of melasma is multifactorial and remains unclear. Genetic and hormonal factors and exposure to UV radiation are classical influencing factors. There are many other factors that may play a role in the etiology of melasma, such as ingredients in cosmetics, phototoxic and anti-seizure drugs, endocrine disorders (ie, ovarian or thyroid dysfunction), hepatic dysfunction, parasitoses, and nutritional deficiency. It is important to note that most cases of melasma in men and up to one third of cases in women are idiopathic (5).

Ultraviolet exposure is a major triggering and aggravating factor in the development of melasma, since it has a well known ability to stimulate proliferation of melanocytes, their migration, and melanogenesis (1). However, UV-induced hyperpigmentation usually recovers spontaneously, whereas melasma does not. Recently, Kim et al. detected down-regulation of the

H19 gene on microarray analysis of hyperpigmented and normally pigmented skin in patients with melasma (6).

Melasma is commonly reported in women using estrogen-progesterone oral contraceptives, hormone replacement therapy for prevention of osteoporosis, and in men using estrogen derivatives for treatment of prostatic cancer (7). The mechanism of induction of melasma by estrogen may be related to the presence of estrogen receptors on the melanocytes that stimulate cells to produce more melanin (8, 9). One study of melasma in patients who had never been pregnant or used hormone therapy, reported increased serum concentrations of luteinizing hormone (10). Sawney and Anand found a high prevalence of chronic pelvic inflammatory disease in women with melasma (11). These findings may implicate mild ovarian dysfunction as a possible cause of idiopathic melasma.

However, many observations strongly suggest the role of genetic factors. Familial occurrence of melasma has been reported to vary from 20% to 70% in different studies (12).

Characteristic clinical features of melasma are symmetry of hyperpigmentation and distribution related to trigeminal nerves, which suggest that the neural involvement may play a role in the pathogenesis of pigmentation. Bak et al. found higher levels of neural endopeptidase in melasma lesions and suggest that neuroactive molecules, including nerve growth factor, are critical factors for the pathogenesis of melasma (13).

It is still unclear why certain areas of the face are predisposed to develop melasma, while others are not. Besides neural factors and hormone receptors, blood vessels may play a role. Human melanocytes may respond to angiogenic factors because normal human melanocytes express functional receptors for vascular endothelial growth factor (VEGF) (14). In some types of melasma, a pronounced telangiectatic erythema confined to melasma-lesional skin has been observed. Furtermore, increased vascularity is one of the major histologic findings in melasma (15). These findings may explain the effects of localized microinjection of plasmin inhibitor tranexamic acid, and good therapeutic efficacy of vascular lasers in the treatment of melasma (16).

Pathology

Few studies have investigated the histologic alterations in melasma lesions. Compared to uninvolved skin, the areas of hyperpigmentation showed increased deposition of melanin in the epidermis and dermis, as well as enlarged intensely stained melanocytes with prominent dendrites (17).

Clinical presentation

Clinically, melasma presents as a symmetrically distributed macular pigmentation with irregular borders, which can vary in color ranging from a light to dark brown or brown–gray. The number of hyperpigmented lesions may range from one single lesion to multiple patches located on the forehead, cheeks, dorsum of the nose, upper lip, chin, occasionally on the V-neck area and forearms. Pigmentation may be guttate or confetti-like, linear, or confluent; it evolves slowly over weeks or years. The hyperpigmented patches often fade in winter and get worse in the summer.

According to the distribution of lesions, there are three clinical patterns of melasma: centrofacial (65%), malar (20%), and mandibular (15%). The centrofacial pattern involves the forehead, cheeks, upper lip, nose, and chin; the malar pattern involves the cheeks and nose, and mandibular the ramus of the mandible (18) (Figure 1).

Wood's lamp (320–400 nm) is used to determine the depth of melanin in the skin. Wood's light may also serve as a prognostic guide in the treatment of melasma, as the epidermal type of melasma is more likely to respond favorably to topical depigmenting agents. Common reasons for diagnostic failure are topical petrolatum and salicylic acid, lint and soap residues since these may fluoresce under Wood's light (19). Based on Wood's light examination, Sanchez et al. (20) classified melasma into four major clinical types, that show good correlation with the depth of melanin pigments:

1. Epidermal melasma is light brown; its color contrast is enhanced by Wood's light examination.

2. Dermal melasma is brown or bluish-gray by visible light; under Wood's light this

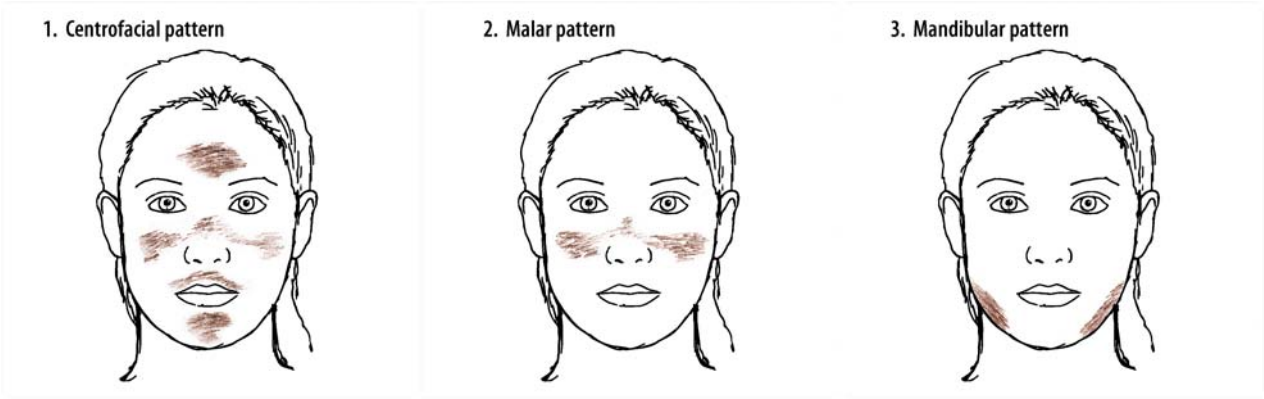

Figure 1. Differnet patterns of melasma

type expresses less distinct borders, with no enhancement of pigmentation.
3. Mixed melasma is dark-brown; enhancement of pigmentation is present under Wood's light in some areas, but not in all.
4. Indeterminate or inapparent melasma is found in individuals with dark-brown skin.

Wood's light does not localize the pigment. Since dermal melanin deposition may be unrecognized under Wood's light, diagnosis and treatment of patients with apparent epidermal melasma is still difficult (21).

Clinical outcome measures

The Melasma Area and Severity Index (MASI) is a common outcome measure, used to assess melasma patients. The severity of melasma in each of the four regions (forehead, right malar region, left malar region and chin) is assessed based on three variables: percentage of the total area involved (A), darkness (D), and homogeneity (H) (22).

Melasma has a significant negative impact on patients' health related quality of life (QoL), and severely affects social life, emotional well-being, and physical health (23). Several instruments have been developed to evaluate QoL in melasma patients. Such instruments need to undergo translation, validation and cultural adaptation (24).

Diagnosis

The diagnosis is clinical and an effort must be made with every patient to detect the individual risk factors and triggers. However, a number of other conditions can mimic melasma (Table 1).

Therapeutical approaches

The aim of melasma treatment is to eliminate already existing pigmentation and to block de novo pigmentation. Numerous treatment options are currently available for melasma. The choice of treatment options of their combination depends mainly on the type of melasma, effectiveness of prior treatments, and expectations of the patient (25). New regimens aim to shorten and simplify the treatment. Difficulties in treatment of melasma arise from the following:

1. Melasma is often recalcitrant to treatment
2. High tendency for recurrence/reappearance
3. Risk of adverse events
4. Successful treatment requires long term patient compliance, because therapeutic effects usually become evident after 1-2 months
5. Treatment costs

The basic principles of melasma treatment include: retardation of proliferation of melanocytes, inhibition of melanosome formation, and enhancement of melanosome degradation.

Protection from sun exposure

Melanocytes in melasma are easily stimulated not only by UVB, but also but UVA and visible radiation. In order to maintain good treatment results and to prevent recurrences, one must make major lifestyle changes. Sunbathing is absolutely contraindicated, as a few minutes of sunbathing can reverse the benefit of

Table 1. Differential diagnosis of melasma

Disease/Condition	Differentiating Signs/Symptoms
Post inflammatory hyperpigmentation	Distribution of the eruption, history of inflammation
Cosmetic dermatitis (Riehl's melanosis)	Reddish-brown pigmentation, reticulate pattern
Poikiloderma of Civatte	Reddish-brown, reticulate pattern, atrophy, telangiectasias
	Distribution (anterior neck, sparing of submental region)
Hori's nevus	Bluish-gray pigmentation, distribution of macules
Drug induced facial pigmentation*	Phenothiazines, tetracyclines, phenytoin, antimalarials
	cytotoxic drugs, amiodarone
Actinic lichen planus:	Papular lesions, histology

*Hyperpigmentation is reversible but may take up to one year for complete resolution after stopping the drug

months of therapy. Sunscreens must be applied daily, during and after the treatment, throughout the sunny months of the year for an indefinite period (18). Sunscreens are crucial for sun protection, so the use of mineral sunscreens containing titanium dioxide or zinc oxide, with a sun protection factor (SPF) of 30 or higher, is mandatory.

Bleaching agents

Skin lightening or skin bleaching is the practice of using chemical substances in order to lighten the skin color or provide an even toned complexion. Bleaching agents act at various levels of melanin production in the skin, many of which act as competitive tyrosinase inhibitors, the key enzyme in melanogenesis. Others inhibit the maturation of this enzyme or the transport of melanosomes from melanocytes to the surrounding keratinocytes (26). The most important medical indications for the use of lightening agents are melasma and postinflammatory hyperpigmentation, but also depigmenting conditions, like vitiligo.

There are three different categories of bleaching agents: phenolic compounds, non-phenolic compounds, and combination formulas (Table 2) (27). Some herbal extracts, flavonoids, coumarins and other derivatives are well known hypopigmenting agents (Table 2). Their classification is difficult, due to a great number of products and various mechanisms of action (28). In clinical practice, reflectance chromameters measure not only the skin color, and ultraviolet (UV)-induced pigmentation, but the bleaching effect of depigmenting agents.

Hydroquinone (HQ)

Hydroquinone ($C_6H_6O_2$) is the most commonly used bleaching agent and the gold standard for

Table 2. Treatment options for melasma

Categoriy	Bleaching agent
Phenolic compounds	Hydroquinone (HQ)
	4-hydroxyanisole (Mequinol)
	N-acetyl-4-Scystaminylphenol (4-S-CAP)
Nonphenolic Compounds	Azelaic acid (AzA)
	Topical Retinoids
	L-ascorbic Acid (vit.C)
	Kojic acid
Chemical peels	Alpha-hydroxy acids (AHAs)
	Beta-hydroxy acid (BHA)
	Jessner's original and modified solutions
	Trichloroacetic acid
Device-Based Therapies	Intense pulsed light
	Lasers
	Microdermabrasion
Plant extracts/active agents	Arbutin, licorice extract, aloesin, oregonin, soy, green tea
	orchid extracts, coumoric acid, ellagic acid, liquirtin, gentisic
	acid, hesperidin, licorice, niacinamide, yeast derivatives
Others	Mercury, indomethacin, ZnSO4, topical corticosteroids

melasma treatment. HQ inhibits the conversion of 3,4-dihydroxyphenylalanine (DOPA) to melanin by tyrosinase inhibition, and it also inhibits RNA and DNA synthesis in melanocytic cells, and degrades melanosomes (27). Since 2001, HQ has been banned in the European Unit (EU) as an ingredient in cosmetics (29) The EU decision was based on its mid-term side effects, mainly exogenous ochronosis and leukoderma-en-confetti (30). During the past decade, concerns over the safety of HQ have increased. Its use has been connected with toxicity and mutagenicity, and an increased incidence of exogenous ochronosis (31). Although animal studies demonstrated its toxicity and/or mutagenic effects, these have not been proven in humans (32). In 2009, the Food and Drug Agency (FDA) renewed its call for additional studies on the safety of HQ. The request for evaluation focuses on uncovering the risks of skin disorders, cancer, and genetic mutations from HQ exposure in humans (33).

However, HQ over 2% can only be prescribed from a doctor's office. The effectiveness of HQ is related to the concentration of the preparation, to the vehicle used and the chemical stability of the product. Concentrations of HQ vary from 2% to as high as 10%. Several formulations are commonly prescribed by dermatologists, in order to reach the desired HQ concentration. HQ is easily oxidized, therefore, antioxidants such as 0.1% sodium bisulphate and 0.1% ascorbic acid should be used (34). The following formula can be prescribed: HQ 3-10% in hydroalcoholic solution (equal parts of propylene glycol and absolute ethanol) or hydrophilic ointment or as a gel containing 10% α-hydroxy acids (AHA) with ascorbic acid 0.1% as preservative. Side-effects of HQ mostly include irritant and rarely allergic contact dermatitis and postinflammatory hyperpigmentation. These side-effects are temporary and they resolve upon discontinuation of HQ. A very rare complication of HQ use is exogenous ochronosis, especially in darker phototypes (34).

Combination formulas

The skin lightening effects of HQ can be enhanced by adding various topical agents such as tretinoin and corticosteroids (Table 3). Tretinoin accelerates cell turnover, and facilitates epidermal penetration of HQ, moreover, it suppresses steroid atrophy, and prevents HQ oxidation. Corticosteroids suppress melanin production, and eliminate the irritation caused by HQ and tretinoin (34).

Azelaic acid

Azelaic acid (AzA) is a naturally occurring byproduct of the metabolism of Pityrosporum ovale and is associated with hypomelanosis seen in tinea versicolor. *In vitro*, azelaic acid reversibly inhibits tyrosinase activity and may also interfere with mitochondrial oxidoreductase activity. Azelaic acid does not appear to affect normal melanocytes, but has an antiproliferative effect on abnormal melanocytes. AzA has antibacterial and anti-keratinizing activities. At 10–20% concentration, twice-daily application may treat melasma with minimal side effects; most patients report a mild but transient irritation of the skin at the beginning of treatment. A recent study suggests that 20% azelaic acid cream applied twice daily may be more effective than hydroquinone 4% in reducing mild melasma (35).

Kojic acid

Kojic acid is a fungal metabolite that inhibits catecholate activity of tyrosinase, used in a 1–4% cream base, alone or in combination with tretinoin, HQ, and/or corticosteroids. Although kojic acid alone is less effective than HQ 2%, (36) in combination with glycolic acid 10% and HQ 2%, it seems to have a synergistic action (37).

L-ascorbic acid (vitamin C)

Several forms of topical vitamin C are used to treat melasma in 5 to 10% concentrations and can be formulated with other depigmenting agents, such as HQ. Other advantages of vitamin C include antioxidant effects and photo protective properties. The weakness of ascorbic acid is its chemical instability and the hydrophilic nature limits its skin penetration. Magnesium ascorbyl phosphate, ascorbyl palmitate and sodium ascorbyl phosphate are stable derivatives of ascorbic acid. Iontophoresis has been used to promote percutaneous absorption of vitamin C into the skin (38).

Topical retinoids

Topical retinoids stimulate the cell turnover and promote rapid loss of melanin via epidermopoiesis. Retinoid-induced changes in the stratum corneum

Table 3. The most commonly used combination formulas

Formula	Comment
Kligman's and Willis formula* (5% HQ, 0.1% tretinoin, 0.1% dexamethasone) in ethanol and propylene glycol 1 : 1 or in hydrophilic ointment	Depigmentation begins within 3 weeks after the twice daily application used for a maximum of 5-7 weeks
Pathak's formula (2% HQ, 0.05–0.1% tretinoin)	By omitting steroids it has been suggested that they should be added only if irritation from HQ or tretinoin is observed
Westerhof's formula** (4.7% N-acetylcystein, 2% HQ, 0.1% triamcinolone acetonide)	The formula leads to significant bleaching within 4 to 8 weeks
Katsambas's formula*** (HQ 4%, tretinoin 0.05%, hydrocortisone acetate 1%) in. ethanol and propylene glycol 1 : 1 or in hydrophilic ointment	The formulation should be dispensed in a 25-ml volume, in a dark-colored bottle with an airtight screw cap and it should be kept in a refrigerator at 2-4°C.

*, Formulation is not preserved by antioxidants, and therefore should never be more that 30 days old; HQ, hydroquinone; **, The mode of action of N-acetylcystein may be attributed to the intercellular increase of glutathione concentration that stimulates pheomelanin instead of eumelanin synthesis;***, By lowering the concentration of tretinoin and the use of a non-fluorinated steroid, the aim is to minimize the irritation caused by tretinoin and eliminate local steroid side-effects

facilitate the penetration of depigmenting agents in the epidermis, leading to increased depigmentation (39).

Tretinoin used at 0.05 – 0.1% concentrations, applied once nightly, can be effective as monotherapy, but requires 20 to 40-week treatment periods. The most common adverse effects include burning, erythema and scaling. Retinoid dermatitis may itself lead to postinflammatory hyperpigmentation, especially in dark-skinned individuals (40).

Adapalene 0.1% was found to be a safe and effective monotherapy in the treatment of epidermal melasma with a lower potential for skin-irritation compared to tretinoin (41).

A study confirms that the efficiency of tretinoin 1% peelings is similar to glycolic acid 70%, with very rare side-effects (42).

Chemical peels

Superficial chemical peeling agents are beneficial in the management of epidermal melasma and may be used in combination with other forms of melasma treatment. The peel solution is selected according to patient's needs, skin type and sensitivities. Because of their superficial action, superficial peels can be used in nearly all skin types (1).

Medium-depth peels may be an alternative treatment in refractory cases of severe melasma. All types of chemical peels, but mainly alpha-hydroxy acids, beta-hydroxy acid, salicylic acid**,** Jessner's original and modified solutions, and trichloroacetic acid are used alone or in combination with other depigmenting agents. It has to be emphasized that the response of melasma to chemical peels is rather unpredictable and there is a tendency for changes in pigmentation after chemical peel, especially in dark skinned individuals. Chemical peeling remains as an alternative modality for patients with melasma (34).

Laser and light therapies

Based on actual evidence, laser and light therapies show the best response in light-skinned patients, and are considered as third-line agents. Post inflammatory hyperpigmentation remains the most important side effect. Recurrences are common and are seen in up to 50% (1).

Melanosomes are the primary target of the laser-induced damage, and melanin is the main chromophore. Therefore it is important to choose wavelengths between 630 nm and 1100 nm which are preferentially absorbed by melanin, and pulse duration between 40 ns and 750 ns (43).

Epidermal melasma can be treated with ablative lasers, such as carbon dioxide (CO2) laser and erbium (Er):YAG laser. Non-ablative 1,550 nm fractional laser therapy has been reported to improve melasma (1).

Q-switched (QS) lasers deliver their energy in nanosecond pulses, hence they selectively target melanosomes. The 1064 nm QS-Nd:YAG is the most widely used laser for melasma. The number of treatments varies from 5 to 10 at 1-week intervals. Encouraging results have been observed in the treatment of the dermal-type melasma by using a novel 694-nm QS ruby fractional laser (44).

Melasma treatment with pulsed dye laser and the newer antiangiogenic lasers (copper bromide laser) is based on the theory that melasma occurs due to the interaction between cutaneous vasculature and melanocytes. These lasers can be used in patients with melasma and pronounced telengiectasia (45).

A combination of lasers can be beneficial for dermal melasma. Ablative lasers remove the epidermis; this can be followed by the use of the Q switched pigment selective laser which reaches deeper layers of the dermis (dermal melanophages) without causing serious side effects.

Intense pulsed light

Intense pulsed light (IPL) is a broadband light source that can target a wide range of cutaneous structures, including deeper pigmentation and vasculature (46).

A study by Figueiredo Souza et al. found that a single session of IPL combined with stable fixed-dose triple combination treatment is a safe and effective treatment for refractory mixed and dermal melasma (47). A new type of intense pulsed light with pulse-in-pulse (PIP) mode (multiple fractionated subpulses in one pulse width), may be a safe and promising treatment for melasma (48).

New and experimental treatments

Because of escalating concerns about HQ therapy (49), multiple novel agents are being investigated in melasma treatment. Aside from plant extracts, they also include mercury, indomethacin, zinc sulphate (ZnSO4) and newer phenolic derivatives. At present,

there are no controlled studies investigating the efficacy and safety of these compounds. Although preliminary data showed beneficial effects of zinc for melasma, a recent study confirmed that topical zinc therapy is not highly effective in reducing the severity of melasma (50).

In recent years, the skin whitening industry has used complex mixtures of ingredients that target different mechanisms like tyrosinase expression, transfer of melanosomes, antioxidant and anti-inflammatory effects. Different commercially available whitening products contain various natural (glutathione; leukocyte extracts), particularly herbal ingredients, although information on some formulations are not always clear (51): Paper mulberry (*Broussonetia kazinoki*); Mitracarpe (*Mitracarpus hirtus*) - the active ingredient is harounoside; Bearberry (*Arctostaphylos uva-ursi*) - the active ingredient is arbutin; Yellow dock (*Rumex crispus*); Licorice root (*Glycyrrhiza glabra*) - the active ingredient is glabridin); Yohimbe (*Pausinystalia Yohimbe*); Cang Zhu (*Atractylodes lancea*), Bai Xian Pi (*Dictamnus albus*); Hu Zhang (*Fallopia japonica*); Gao Ben (*Ligusticum rhizome*); Chuanxiong (*Rhizoma ligustici*); and Fang Feng (Radix sileris also Radix ledebouriella).

Table 4 shows melasma therapies, and level of evidence according to Rendon et al. (52).

Conclusion

At present, there is no universally effective treatment for melasma. The mainstay of treatment is use of

Table 4. Gradation of melasma therapies, due to the level of evidence. according to Rendon et al.

Level*	Therapeutic agent
1	4% HQ + 0.05% RA + 0.01% fluocinolone acetonide
2	4% HQ
3	0.1% tretinoin
4	4% HQ + 10% GA
5	20% Azelaic acid
6	20%-30% GA + 4% HQ
7	70% GA
8	Adapalene
9	2% HQ + 0.05% tretinoin + 0.1% dexamethasone (modified Kligman) + 30%-40% GA peel
10	2% HQ

*, decresing from 1 to 10; HQ, Hydroquinone; RA, retinoic acid; GA, glycolic acid

sunscreens along with topical medications that suppress melanogenesis. Topical hydroquinone alone or in stable fixed-dose triple combination topical therapy is the first line of treatment; chemical peels are considered second-line therapy for refractory cases, and laser and light are considered the third-line treatment. Nowadays, there are no controlled studies investigating the efficacy and safety of multiple novel and experimental agents.

Abbreviations

UV – ultraviolet
VEGF - vascular endothelial growth factor
MASI - Melasma Area and Severity Index
QoL - quality of life
SPF - sun protection factor
HQ - Hydroquinone
DOPA - dihydroxyphenylalanine
EU - European Unit
FDA - Food and Drug Agency
AHA - α-hydroxy acids
AzA - azelaic acid
CO2 - carbon dioxide
Er – erbium
QS - Q-switched
Nd – neodium
IPL - intense pulsed light
PIP - pulse-in-pulse
ZnSO4 - zinc sulphate

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Novi aspekti melazme

Sažetak

Uvod. Melazma je stečena cirkumskriptna hipermelanoza lica, povremeno vrata i podlaktica, koja značajno utiče na kvalitet života. Hloazma je grčki termin za „zelenu mrlju" i opisuje melazmu za vreme trudnoće („znak" trudnoće). Iako može da se javi kod svih rasa, melazma je mnogo češća kod tamnoputih ljudi (tip kože IV–VI). Melazma je češća kod pojedinaca hispanskog, orijentalnog i azijskog porekla. Prevalencija melazme se kreće od 8% kod Latinoamerikanaca u SAD do 30% kod

južnoistočnjačke azijske populacije. Melazma ima veću prevalenciju kod žena, naročito u reproduktivnom periodu, sa pikom između 20 i 30 godina. Retko se pojavljuje pre puberteta. Ekstrafacijalna melazma se mnogo češće sreće kod žena u menopauzi.

Etiopatogeneza. Etiopatogeneza melazme je multifaktorska i nerazjašnjena. Genetska predispozicija, hormonski faktori i izloženost UV zračenju klasični su predisponirajući faktori. Ultravioletno zračenje je najveći uzročnik i otežavajući faktor u razvoju melazme, jer je poznata njegova sposobnost da stimuliše proliferaciju melanocita, njihovu migraciju i melanogenezu. Hiperpigmentacija, UV indukovana, obično se povlači spontano, a melazma ne. Nedavno, Kim i saradnici su otkrili smanjenu ekspresiju H19 gena u hiperpigmentovanoj i normalno pigmentovanoj koži kod pacijenata sa melazmom. Melazma se obično češće javlja kod žena koje koriste oralne kontraceptive sa estrogenom ili progesteronom, hormonsku terapiju za prevenciju osteoporoze i kod muškaraca koji koriste derivate estrogena u tretmanu karcinoma prostate. Melazma indukovana estrogenom može biti povezana sa prisustvom estrogenskih receptora na melanocitima koji stimulišu ćelije da produkuju veću količinu melanina. U jednoj studiji o melazmi, kod pacijentkinja koje nikada nisu bile trudne niti su koristile hormonsku terapiju, uočeno je povećanje koncentracije luteinizirajućeg hormona u serumu. Sovni (Sawney) i Anand utvrdili su visoku prevalenciju hroničnih pelvičnih inflamatornih bolesti kod žena sa melazmom. Ova istraživanja ukazuju na blagu ovarijalnu disfunkciju kao mogući uzrok u idiopatskim slučajevima melazme.

Iako mnoga istraživanja jasno ukazuju na ulogu genetskih faktora, porodična pojava melazme prema različitim studijama kreće se od 20% do 70%.

Karakteristična je klinička distribucija melazme duž trigeminalnih nerava, koja ukazuje na neuralnu ulogu u patogenezi pigmentacije. Bak i saradnici su ustanovili visok nivo nervne endopeptidaze u melanotičnim lezijama i ukazuju da neuroaktivni molekuli, uključujući i neurološki faktor rasta, imaju važnu ulogu u patogenezi melazme.

Još uvek je nerazjašnjeno zašto su određena područja na licu preodređena za nastanak melazme, dok su ostala pošteđena. Pored neuralnih faktora i hormonskih receptora, krvni sudovi mogu da imaju određenu ulogu. Humani melanociti mogu da odgovaraju na vaskularne faktore zato što normalni humani melanociti imaju stimulišuće receptore za vaskularni endotelni faktor rasta (VEGF). U pojedinim tipovima melazme pojavljuje se ograničen telengiektatični eritem na područjima gde se javila melazma.

Povećana prokrvljenost je jedna od glavnih histoloških karakteristika melazme. Ova otkrića mogu da objasne efekat lokalizovane mikroinjekcione aplikacije plazmin-inhibitora traneksaminske kiseline i dobar terapijski odgovor na lasere koji deluju na krvne sudove u tretmanu melazme.

Patohistologija. Nekoliko studija je izučavalo histološke izmene u melanotičnim lezijama. U poređenju sa nezahvaćenom kožom, područja hiperpigmentacije pokazuju prekomerne depozite melanina u epidermisu i dermisu, uvećane intenzivno obojene melanocite sa uvećanim dendritima.

Klinička prezentacija. Klinički, melazma predstavlja simetričnu makularnu pigmentaciju nejasno ograničenu, koja može da varira u boji od svetlosmeđe do tamnosmeđe ili smeđesive. Prema distribuciji lezija, melazma se javlja u jednom od tri oblika: centrofacijalni (65%), malarni (20%), mandibularni (15%).

Vudova lampa (320–400 nm) može da se koristi kako bi se odredila dubina melanina u koži. Klasifikacija melazme na četiri glavna klinička tipa ukazuje na dobru korelaciju sa dubinom pigmenta melanina:

1. epidermalna melazma je vidljiva pri pregledu Vudovom lampom;
2. dermalna melazma pod Vudovim svetlom pokazuje manje jasne granice;
3. mešana melazma se prikazuje samo na nekim područjima pod Vudovim svetlom;
4. neodređena ili neočigledna melazma pod Vudovim svetlom ne lokalizuje pigment.

Dijagnoza. Dijagnoza je klinička i zahteva znatnije angažovanje sa svakim pacijentom kako bi se otkrili individualni rizici i uzroci. Veliki broj drugih faktora može da prikrije melazmu.

Terapija. Bazični principi u tretmanu melazme uključuju: smanjenje proliferacije melanocita, inhibiciju nastanka melanozoma i povećanje degradacije melanozoma.

Zaštita od sunca. Korišćenje mineralnih krema sa zaštitnim faktorima koji sadrže titanijum-dioksid ili

cink-oksid sa faktorom zaštite od sunca (SPF) većim od 30 je obavezno.

Sredstva za izbeljivanje. Sredstva za izbeljivanje deluju na različitim nivoima produkcije melanina u koži, mnogi od njih su inhibitori tirozinaze, ključnog enzima u melanogenezi. Drugi inhibiraju sazrevanje ovog enzima ili transport do melanozoma od melanocita iz okolnih keratinocita. Postoje tri različite kategorije sredstava za izbeljivanje: fenolna jedinjenja, nefenolna jedinjenja i kombinovane formule. Neki biljni produkti, flavonidi, kumarini i drugi derivati dobro su poznati hipopigmentovani agensi.

Hidrohinon ispoljava dejstvo tako što inhibiše konverziju 3,4-dihidro-ksifenilalanina (DOPA) u melanin, inhibicijom tirozinaze; takođe inhibiše RNA i DNA sintezu u melanocitnim ćelijama i degradira melanozome. Od 2001. godine, korišćenje HQ kao sastojka u kozmetici je zabranjeno u EU. Odluku je donela EU i zasnovana je na neželjenim efektima, uglavnom spoljašnjim. Tokom protekle decenije, zabrinutost oko sigurnosti HQ se povećala. Njegova upotreba je bila povezana sa toksičnošću i genskim mutacijama i sa povećanom incidencijom egzogene ohronoze. Iako eksperimenti na životinjama ukazuju na toksičnost i/ili mutagene efekte, oni nisu dokazani kod ljudi. Za sada doktorima je dozvoljeno da propisuju HQ u koncentraciji 2–10%. Nekoliko preskripcija – formulacija poznato je u dermatološkim krugovima. HQ brzo oksidiše i zbog toga se prepisuje u kombinaciji antioksidanasa: 0,1% natrijum-bisulfat i 0,1% askorbinska kiselina. Navedena formula može se propisati: 3–10% HQ u hidroalkoholnoj soluciji (u jednakim delovima propilen-glikola i čistog etanola) ili hidrofilna mast ili kao gel koji sadrži 10% α-hidroksi kiseline (AHA) sa 0,1% askrobinskom kiselinom kao konzervansom.

Posvetljivanje kože HQ može biti poboljšano dodavanjem različitih topikalnih agenasa kao što je tretionin i kortikosteridi. Tretionin ubrzava ćelijski ciklus i olakšava epidermalnu penetraciju HQ, te sprečava steroidnu atrofiju i oksidaciju HQ. Kortikosterodi sprečavaju produkciju melanina i eliminišu iritaciju uzrokovanu HQ i tretioninom.

Azelaična kiselina (AzA) nastaje kao prirodni bioprodukt pri metabolizmu Pityrosporum ovale. Azelaična kiselina nema efekta na normalne melanocite, ali ima antiproliferativni efekat na abnormalne melanocite. Novije studije predlažu da aplikovanje krema sa 20% azelaičnom kiselinom dva puta dnevno može da bude efikasnije nego 4% hidrohininom u blažim oblicima melazme.

Kojic kiselina je gljivični metabolit koji inhibiše kateholinsku aktivnost tirozinaze. Iako je kojic kiselina sama manje efikasna nego 2% HQ u kombinaciji sa 10% glikolnom kiselinom i 2% HQ ima sinergističko delovanje.

Nekoliko oblika topikalnog vitamina C korišćeno je u terapiji melazme u 5–10% koncentracijama i može se koristiti sa drugim depigmentišućim agensima, kao što je HQ. Druge prednosti vitamina C uključuju antioksidativni efekat i fotoprotektivna svojstva. Koristi se jontoforeza radi povećanja penetracije vitamina C u kožu.

Lokalni retionidi stimulišu ćelijski ciklus čime se ubrzava gubitak melanina putem epidermopoeze. Tretionin u koncentraciji 0,05–0,1% aplikovan tokom noći pokazao se kao efikasna monoterapija, ali zahteva 20–40 nedelja lečenja. Adapalen 0,1% predstavlja efikasnu monoterapiju u lečenju epidermalne melazme i pokazuje manju iritaciju u odnosu na tretionin. U jednoj studiji je pokazana ista efikasnost pilinga sa 1% tretioninom u odnosu na 70% glikolnu kiselinu, ali sa manjim neželjenim efektima.

Hemijski pilinzi. Zbog dubine svog delovanja, površinski pilinzi se mogu koristiti na svim tipovima kože.

Pilinzi sa srednjom dubinom delovanja predstavljaju alternativni tretman u refraktornim slučajevima težih oblika melazme.

Svi tipovi hemijskih pilinga, ali uglavnom najčešće korišćeni pilinzi, tj. oni sa α-hidroksi kiselinama, β-hidroksi kiselinama, salicilnom kiselinom, Jesnerovim originalnim i modifikovanim rastvorom, kao i trihlorsirćetnom kiselinom ostaju alternativna terapija kod pacijenata sa melazmom.

Laseri. Lečenje melazme laserom i ostalim vidovima svetlosne terapije daje najbolje efekte kod osoba sa svetlom kožom, a predstavlja treću terapijsku liniju. Postinflamatorne hiperpigmentacije predstavljaju najčešće neželjene efekte. Recidivi se javljaju u oko 50% slučajeva.

Važno je da izbor talasne dužine bude između 630 nm i 1 100 nm, s obzirom da se tada postiže apsorpcija melanina, a da dužina pulsa bude između 40 ns i 750 ns.

Epidermalna melazma se može lečiti ablativnim laserima: karbon-dioksid (CO_2) i Erbium (ER): YAG) laser. Dobar terapijski efekat može se postići i frakcionisanim neablativnim 1 550 nm frakcionim laserom.
Q-switched (QS) laser selektivno deluje na melanozome. Tako se QS-Nd : YAG 1 064 nm najčešće koristi za lečenje melazme. Ohrabrujući rezultati u lečenju dermalnog tipa melazme postignuti su sa novim 694 nm QS rubinskim frakcionim laserom.
Pulsni diodni laser i laseri koji se koriste za lečenje vaskularnih promena novijeg datuma, kao što je bakar-bromid laser mogu se koristiti u lečenju melazme sa izraženim telangiektazijama.
Kombinovana upotreba različitih lasera može biti efikasna u lečenju dermalnog tipa melazme. Ablativni laser uklanja epiderm; potom se Q-switched selektivnim pigmentnim laserom mogu dostići dublje lezije u dermisu čime se utiče na dermalne melanofage i to bez većih neželjenih efekata.
Intenzivna pulsna svetlost. Istovremena primena intenzivne pulsne svetlosti i hidrohinona u stabilnim kombinovanim formulama predstavlja bezbedan i efikasan način lečenja mešovitih i dermalnih melazmi. S obzirom na sve veću obazrivost pri primeni hidrohinona, pribeglo se otkrivanju novih agenasa: biljni ekstrakti, živa, indometacin, cink-sulfat i derivati fenola.
Zaključak. Zasad ne postoji jednako efikasan vid lečenja melazme. Lečenje se bazira na primeni lekova koji suprimiraju melanogenezu uz sredstva za zaštitu od sunca. Prvu terapijsku liniju čini topijski hidrohinon, sam ili u trojnoj kombinovanoj formuli; drugu terapijsku liniju čine hemijski pilinzi; treću terapijsku liniju čine laseri i ostali vidovi svetlosne terapije.

Ključne reči

Melanoza; Dermatološki preparati; Hidrokvinon; Fotozaštitni preparati; Preparati za posvetljivanje kože; Laserska terapija; Diferencijalna dijagnoza

Late Onset of Multiple Basal Cell Carcinomas in a Patient with Gorlin-Goltz Syndrome Previously Treated for Hodgkin's Lymphoma

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Abstract

Development of multiple basal cell carcinomas is commonly associated with immunosuppression or genetic disorders. The latter include congenital diseases such as Gorlin-Goltz syndrome, also known as nevoid basal cell carcinoma syndrome, or basal cell nevus syndrome. It is an autosomal dominant inherited disorder characterized by the development of multiple basal cell carcinomas at an early age and a variable combination of other phenotypic abnormalities that result in multiple organ involvement. The susceptibility gene was mapped to chromosome 9q22.3–3.1. Like other tumor suppressor genes, PTCH1 gene shows frequent deletion and a whole variety of other mutations. A high rate of new mutations and the variable expressivity of the condition make full diagnostic assessment difficult, especially in mildly affected individuals with no family history of the condition. It has been postulated that the presence of two major features or one major feature with two minor features classify a condition as Gorlin-Goltz syndrome.

We present a 42-year-old male patient with a 6-year-long history of multiple smooth and/or rough skin patches and plaques on the back and shoulders. Some of the lesions gradually progressed and increased in number without any sensation. Dot-like, flesh-colored and brownish pits were found on the patient's palms. Further investigations revealed many musculoskeletal and craniofacial congenital abnormalities such as pectus excavatum, frontal and parietal bossing, exotropia, ectopic teeth (impacted tooth), mandibular hyperplasia, broad nose. Histopathological examination by light microscopy of biopsies taken from the nodular and patchy skin lesions showed findings typical for basal cell carcinoma. Family history revealed no members with similar health disorders.

The patient was treated for Hodgkin's lymphoma with chemotherapy and radiation therapy 20 years before, with good therapeutic results, and no additional treatment was administered in the last ten years.

The treatment for multiple basal cell carcinomas included: 5% imiquimod cream, 5 days a week, for 12 weeks. After 12 weeks of treatment, the nodular lesion and all the superficial lesions cleared. One month later the lesions disappeared completely without any residual signs. The patient was advised to use adequate photoprotection and to avoid future uncontrolled sun exposure. On follow-up visits during a three year period, no recurrent or new lesions indicative for BCC were seen.

This is a case with late-onset multiple BCC in a patient with Gorlin-Goltz syndrome and a history of prior Hodgkin's lymphoma. To the best of our knowledge hitherto only two cases of Hodgkin's lymphoma in patients with Gorlin-Goltz syndrome have been reported in the literature. We also present therapeutic results of topical imiquimod for multiple basal cell carcinomas with no recurrent lesions over a three-year follow-up.

Key words

Basal Cell Nevus Syndrome; Carcinoma, Basal Cell; Neoplasms, Multiple Primary; Comorbidity; Hodgkin Disease; Diagnosis; Aminoquinolines; Treatment Outcome

Basal cell carcinoma (BCC) is the most common skin cancer, known for its local malignancy, relatively slow growth, rare metastases and overall good prognosis *quo ad vitam*. In patients with multiple BCC, immunosuppression or genetic disorders need to be considered. The latter include

congenital diseases such as Gorlin-Goltz syndrome, Bazex-Dupré-Christol syndrome, Rombo syndrome, Oley syndrome and xeroderma pigmentosum (1, 2, 3).

Gorlin-Goltz syndrome (GGS), also known as nevoid basal cell carcinoma syndrome (NBCCS), or basal cell nevus syndrome, is an autosomal dominant hereditary cancer syndrome which includes development of multiple basal cell carcinomas (BCCs) at an early age and a variable combination of other phenotypic abnormalities that result in multiple organ involvement. The NBCCS gene was mapped to chromosome 9q22.3–3.1 during the identification of mutations in the patched (PTCH1) gene of patients with NBCCS. Like other tumor suppressor genes, PTCH1 gene shows frequent deletion and a whole variety of other mutations. A considerable part (more than one third) of patients are found to have new mutations (2, 4, 5). A high rate of new mutations and the variable expressivity of the condition makes full diagnostic assessment difficult, especially in mildly affected individuals with no family history of the condition.

The clinical features of this syndrome involve a whole variety of organs and systems including the skin, skeleton, neural, dental and genital structures, eyes, etc. Thus far, distinctive symptoms and signs have been divided into major and minor criteria (2, 4, 6, 7). It has been postulated that the presence of two major features or one major feature with two minor features classify a condition as GGS (2, 8-10).

Major criteria

- More than 2 BCCs or 1 BCC in patients under the age of 20 years
- Odontogenic keratocysts of the jaw (histologically proven)
- Three or more palmar or plantar pits
- Bilamellar calcification of the falx cerebri
- Bifid, fused, or splayed ribs
- First-degree relative with GGS/NBCCS

Minor criteria

- Macrocephaly
- Congenital malformations - cleft lip/palate, frontal/temporoparietal bossing, coarse face, hypertelorism
- Skeletal abnormalities - Sprengel deformity, pectus excavatum/carinatum, syndactyly
- Radiologic abnormalities - bridging sella turcica, vertebral anomalies
- (hemivertebrae, fusion or elongation of the vertebral bodies), defects of the hands and feet, flame-shaped lucencies of the hands and the feet
- Ovarian fibroma/fibrosarcoma or medulloblastoma.

Besides the aforementioned clinical and radiologic categories, many different manifestations and symptoms have been reported in association with GGS:

Cutaneous anomalies: cutaneous dyskeratosis, keratotic papules, other benign dermal cysts and tumors, milia and comedones, palmar and plantar keratosis, dermal calcification.

Musculoskelet anomalies: polydactyly/oligodactyly, scoliosis/kyphosis, brachymetacarpalism, cervical ribs, absent ribs, flat feet, pelvic calcification, spina bifida, arachnodactyly, hallux valgus, cortical defects in long bones.

Craniofacial and orofacial anomalies: brachycephaly, choroid cysts (ventricles), prominent supra orbital ridge, broad nasal root, palatal or maxillary sinus fibroma, high-arched palate, prominent palatine ridges, malocclusion (maxillary hypoplasia, mandibular hyperplasia), fibrosarcoma of the jaws, impacted teeth and/or agenesis, ectopic teeth, ameloblastoma.

Ophthalmic anomalies: wide nasal bridge, strabismus/exotropia, dystopia canthorum, glaucoma, choroidal/optic nerve coloboma, congenital amaurosis/blindness/opaque cornea, ptosis, cataracts, chalazion.

Neurological anomalies: mental retardation, agenesis of corpus callosum, congenital hydrocephalus.

Sexual anomalies: hypogonadism, supernumerary nipple, cryptorchidism, calcified ovarian cysts, female distribution of the pubis hair, sparse growth of beard in men, gynecomastia.

Other anomalies: inguinal hernia, renal anomalies, lymphomesenteric cysts, left ventricular fibroma (neonatal), cardiac fibroma.

The BCC (most frequently on the face and sun-exposed parts of the body) is one of the most important criteria for setting the diagnosis of GGS.

BCCs can vary in number and develop in various stages of the disease, but most often appear between puberty and 35 years of age. The early onset of BCCs defines the disease and often lead to the underlying syndrome diagnosis (4).

There is no unified treatment for skin manifestations of GGS, particularly tumors, papules, plaques or patches. Generally, the treatment is surgical (curettage, electrodesiccation, excision, Mohs micrographic surgery, ablative laser therapy). Many studies have been carried out to assess the applicability and efficacy of alternative, less invasive treatment modalities such as cryotherapy, photodynamic therapy, and topical drugs such as 5-fluorouaracil and imiquimod.

We report a patient with a late onset of multiple BCCs and GGS, presenting with cutaneous, craniofacial, orofacial, ophthalmic and musculoskeletal symptoms. Our case also shows a successful treatment of BCCs in GGS with imiquimod.

Case report

A 42-year-old male patient was ademitted to the Department of Dermatology of the Medical University of Plovdiv, Bulgaria, with multiple smooth and/or rough skin patches and plaques that appeared and spread over his back and shoulders for the last 5-6 years. Some of the lesions gradually progressed and increased in number without any sensation, particularly a small tumor over the largest plaque which slowly developed in the last two years. The patient was treated for Hodgkin's lymphoma with chemotherapy and radiation therapy 20 years before, with good therapeutic results, and no additional treatment was administered in the last ten years. Family history revealed no data about similar health disorders among his relatives.

On examination, the patient presented with multiple smooth, scaly or partly crusty, slightly pigmented or reddish patches and plaques of varying sizes (5 – 35 mm) as well as keratotic papules on the back and shoulders (Figure 1). A nodular tumor (10x12 mm) with crusty and ulcerous center was found in the central part of the largest superficial plaque located in the thoracolumbar area (Figure 2). Pearly papules and comedones were seen in the periphery and on the surface of some lesions. Dot-

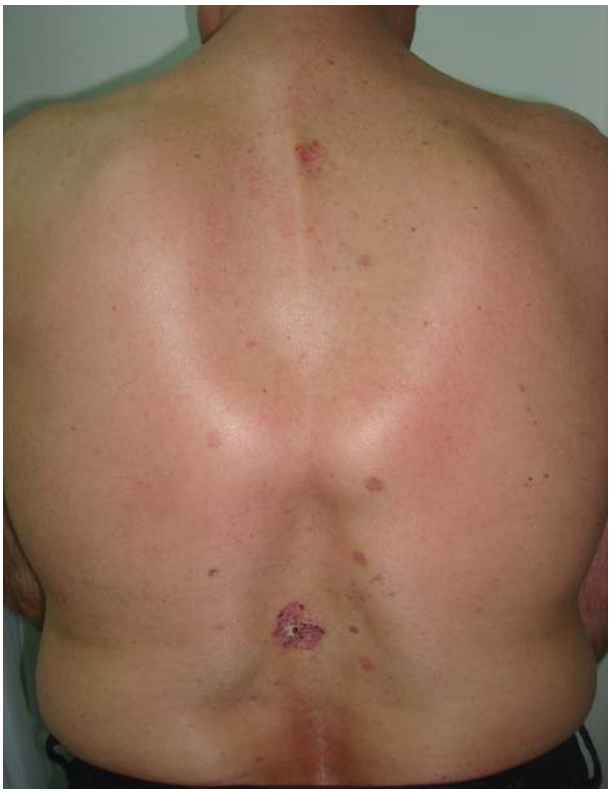

Figure 1. Multiple smooth, scaly or partly crusty, slightly pigmented or reddish patches and plaques over the back and shoulders; prominent paravertebral protuberances on the back

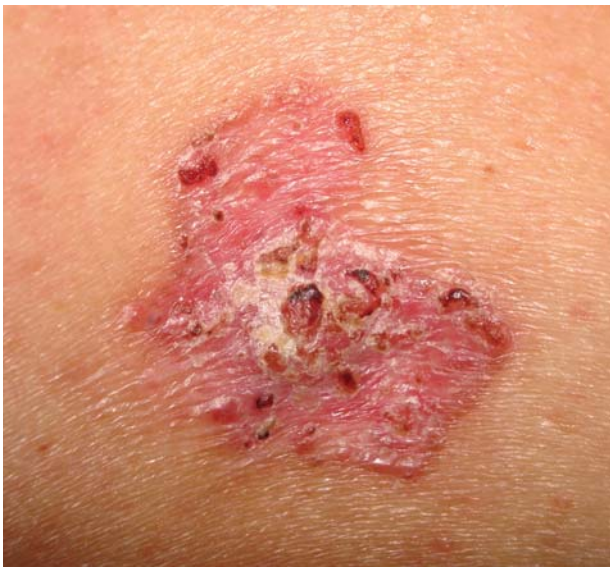

Figure 2. A solitary tumor (10x12 mm) with a crusty and ulcerous center in the central part of the largest superficial plaque in the thoracolumbar area

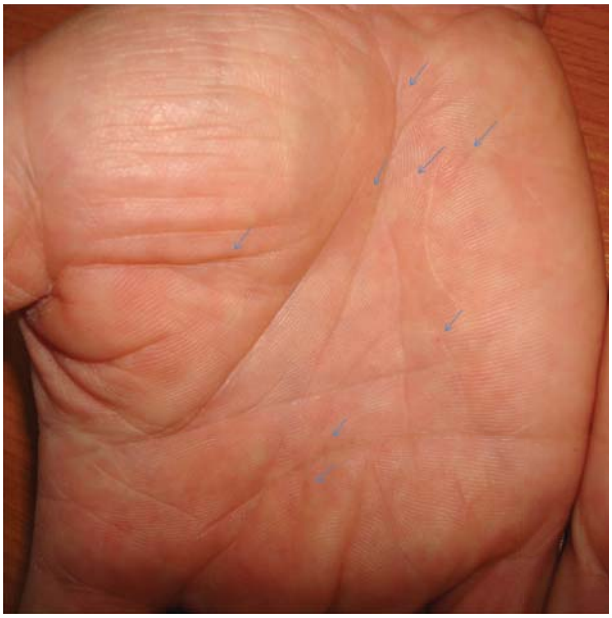

Figure 3. Dot-like, flesh-colored and brownish pits over the palms

like, flesh-colored and brownish pits were discovered on the palms (Figure 3).

Further investigations revealed musculoskeletal abnormalities such as pectus excavatum, back deformity (other than Sprengel's deformity), with prominent paravertebral protuberances (Figure 1) and thoracolumbar kyphosis (Figure 4). Craniofacial and congenital anomalies were also present: frontal and parietal bossing, exotropia, ectopic teeth (impacted tooth), mandibular hyperplasia, broad nose. A cardiologist disclosed aortic stenosis and regurgitation, and severe aortic valve calcification. The findings were consistent with post-radiation pericarditis and aortic valve changes probably induced by therapy on Hodgkin's lymphoma.

Histopathological examination by light microscopy of biopsy specimens, taken from the nodular tumor and patchy lesions, showed findings typical for BCCs. The superficial BCCs were small islets of basaloid tumor cells (Figure 5) limited against normal epithelium, in contact with papillary dermis, but without evident invasion into the deeper dermis. Nodular BCC was characterized by well circumscribed islets of uniform cells with large, hyperchromatic, oval nuclei and little cytoplasm, aligned in a palisade pattern at the periphery of nests and localized in the dermis, where interposed clefts between the cell nests were discovered as retraction artifact (Figure 6).

Figure 4. X-ray showing thoracolumbar kyphosis

Bearing in mind the preceding Hodgkin's lymphoma and the aggressive treatment the patient received, further hematological, biochemical and immunological laboratory tests were performed, but no abnormalities were found. Flow cytometry failed to identify immunosuppression, apart from an activated cell-mediated immunity: lymphocyte blood count 3.969 x 10^9/L (normal range 1 - 2.8 x 10^9/L), T-lymphocytes (CD3+) 2.155 x 10^9/L (normal range

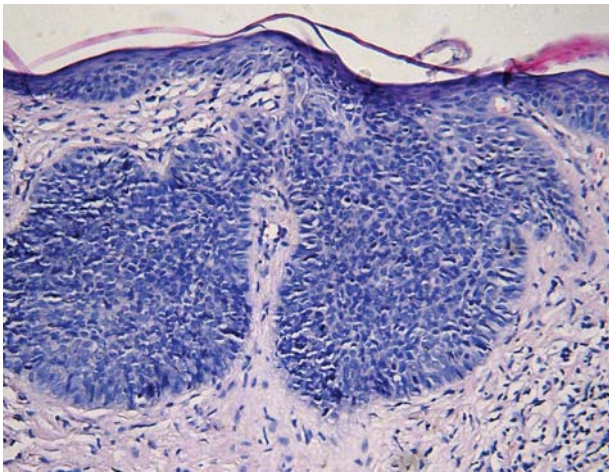

Figure 5. Histopathology examination of the biopsy taken from one of the patchy lesions demonstrated on light microscopy features of the superficial BCCs: small islets of basaloid tumor cells without evident invasion into the deeper dermis (HE x 40)

0.69 - 2.54 x 10^9/L), T- helper/inducer cells (CD3+ CD4+) 1.630 x 10^9/L (normal range 0.41 - 1.59 x 10^9/L), T suppressor/cytotoxic cells (CD3+ CD8+) 0.514 x 10^9/L (normal range 0.19 - 1.14 x 10^9/L), total B-cell count (CD19+) 0.599 x 10^9/L (normal range 0.09 - 0.66 x 10^9/L), NK cells (CD3+ CD56+) 1.143 x 10^9/L (normal range 0.09 - 0.6 x 10^9/L), CD4/CD8 index 3.17 (normal range 0.9 - 3.6).

Multiple BCCs were treated with topical: 5% imiquimod cream, 5 days a week, for 12 weeks. The nodular lesion was preliminarily treated with cautery/electrodesiccation. Our patient's compliance was good; the treatment was well-tolerated, and only a mild erythema was found in the treated areas. After 12 weeks of treatment the nodular lesion and all the superficial lesions cleared. One month later, the lesion disappeared completely without any residual signs. Biopsy from the site of the previous nodular tumor and the specimen from one of the other superficial lesions, taken one month after discontinuing the therapy, showed a histological eradication of the malignant structure and a process of scarring with fibroelastic tissue formation and reduction in cellularity.

The patient was advised to use adequate skin photoprotection and to avoid future uncontrolled sun exposure. On follow-up visits during a three year period, no recurrent or new lesions indicative for BCC were seen.

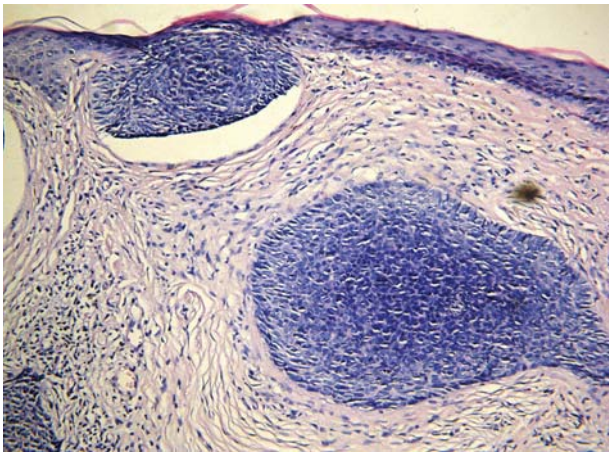

Figure 6. Histopathology examination of biopsy specimens taken from the nodular tumor revealed marked circumscribed nodular islets of uniform cells with large, hyperchromatic, oval nuclei and little cytoplasm, aligned in a palisade pattern at the periphery of the nests and localized in the dermis (HE x 100)

Discussion

The GGS, described by R. Gorlin and R. Goltz in 1960 (11) as an association of basal cell epithelioma, jaw cyst and bifid ribs, was earlier described, partially and independently, by W. Jarisch (12) and J. C. White (13) in 1894, then by G. W. Binkley and H. H. Johnson in 1951 (14).

Later on, many case reports added new characteristics to the primary description of this congenital disorder with a wide variety of basic manifestations (15-19).

Besides NBCCS and basal cell nevus syndrome, there were quite a number of other terms (e.g., nevus epitheliomatodes multiplex; nevoid basal-cell epithelioma, jaw cysts and bifid rib syndrome, etc.) given to GGS, each indicating particular features found in an individual or a group of patients (2, 20).

BCCs represent one of the major clinical problems of this syndrome due to their multitude, wide distribution and early invasion of deep structures, notwithstanding any particular predilection for sun exposed areas. Apparently, clinicians and investigators have been concerned with various features exhibited in this syndrome (4, 8, 21).

In our case, we found two major (multiple BCCs and palmar pitting) and two minor criteria (frontal/

parietal bossing and pectus excavatum) from the basic list found in publications of Evans et al. (8) and Kimonis et al. (7). Furthermore, we disclosed a number of additional abnormalities such as keratotic papules over the back and shoulders, an extraordinary back deformity having markedly prominent paravertebral protuberances, not consistent with the Sprengel's deformity, thoracolumbar kyphosis, exotropia, ectopic teeth (impacted tooth), mandibular hyperplasia, and broad nose.

The variety of clinical features seen in our case, according to a group of authors and R. Gorlin himself, are likely the result of an inborn error in developmental metabolism determines causing multiformity of symptoms (16). Moreover, further reports have only broaden the list of abnormalities found in affected individuals (18, 20, 22-25).

Interesting cardiology findings in our patient included aortic stenosis and regurgitation, whereas severe aortic valve calcification was interpreted as the consequence of a post-radiation pericarditis and aortic valve changes due to radiotherapy applied for Hodgkin's lymphoma. Besides, the BCCs in our patient developed much later. Actually, the association of GGS with lymphoma is very rare and we found only two cases of Hodgkin's lymphoma in patients with GGS in the literature (26, 27). It is postulated that the gene for GGS may act as a tumor suppressor gene perhaps for many types of cell lines and may explain the diversity of tumors (28, 29, 30). Despite the preceding malignant disorder and aggressive radiologic and cytotoxic treatment, our patient was not immunosuppressed. We believe that this pattern of immune reactivity supported the patient's skin own defense mechanisms against the congenital predisposition to cancer development, given the sun exposure abuse reported in his history.

The common therapy for BCCs in GGS includes surgical excision, cryosurgery, electrodesiccation, curettage, and Mohs micrographic surgery (6, 31-35), although these procedures do not ensure tumor eradication in all cases (31, 36, 37, 38). It is known that in patients with multiple or extensive lesions surgical procedures are not always manageable (35), being rather traumatic and painful, time consuming and/or may result in disfigurement. Non-surgical alternatives are recommended for tumors located at sites inappropriate for surgical intervention, due to their lower overall costs and more esthetically acceptable outcomes. Photodynamic therapy (37) is used in patients with wide-ranging skin cancers. Ablative lasers have been successfully used with minimal scarring for particular lesions on the face and other specific locations (39).

Topical drugs such as imiquimod (1, 40-44), 5-fluorouracil (45, 46, 47) and retinoids (46, 48, 49) have been reported with variable results, showing high cure rates in superficial BCC, but much lower efficacy in more extensive lesions. Topical medications appear to be appropriate in patients with superficial BCCs and therefore have been used with some success in GGS, thus becoming the armamentarium of choice among treatment modalities (37, 50, 51, 52).

Topical 5% imiquimod cream monotherapy for superficial BCC and adjuvant therapy following electrodessication of nodular BCC, proved to be a successful treatment modality in our patient, who is tumor-free three years after treatment. Some authors suggest that imiquimod adjuvant imiquimod after surgery shows double activity: it removes residual tumor tissue and provides a better esthetic outcome (32-34, 53, 54, 55). It seems that imiquimod induced inflammation may participate in the clearance of BCC to some extent (33, 50).

Investigations of imiquimod efficacy showed that regression of BCC after imiquimod treatment is related to immune-mediated processes (56). It has been discovered that 5% imiquimod upregulates the release of cytokines such as interferon-alpha and -beta (IFN-α IFN-β), tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1) alpha and beta, IL-6, as well as natural killer cell activity and nitric oxide secretion from macrophages (57). It has also been established that imiquimod upregulates the cell-mediated immune response via indirect stimulation of IFN-gamma (Th-1 cytokine), activates Langerhans cells to promote antigen presentation (58), toll-like receptor 7, which itself activates nuclear factor kappa B to stimulate production of IFN-alpha and cytokines IL-12 and IL-18. Subsequently these cytokines induce IFN-gamma release by naïve T-cells, producing a Th1-type immune response and a stimulation of cytotoxic T lymphocytes, providing a long-term immune memory. Imiquimod has no direct interaction with

tumor cells, but induces pro-inflammatory cytokines production and in this way stimulates both the human innate and cell-mediated immune system response to malignant cells (50).

Nowadays, new diagnostic and treatment protocols are being developed for non-melanoma skin cancer for their future management and prevention (5, 6, 21, 36, 59, 60).

Conclusion

This is a case with late-onset multiple basal cell carcinomas in a patient with Gorlin-Goltz syndrome and a history of prior Hodgkin's lymphoma. To the best of our knowledge hitherto only two cases of Hodgkin's lymphoma in patients with Gorlin-Goltz have been reported in the literature. We also present therapeutic results of topical imiquimod for multiple basal cell carcinomas with no recurrent lesions over a three-year follow-up.

Abbreviations

BCC - basal cell carcinoma
GGS - Gorlin-Goltz syndrome
NBCCS - nevoid basal cell carcinoma syndrome

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Kasna pojava multiplog bazocelularnog karcinoma kod pacijenta sa Gorlin-Golcovim sindromom prethodno lečenog od Hočkinovog limfoma

Sažetak

Uvod. U slučaju pojave multiplih bazocelularnih karcinoma potrebno je kod pacijenta isključiti postojanje imunosupresije i/ili genetske predispozicije. Kada su genetska oboljenja u pitanju, na prvom mestu treba ispitivanje usmeriti na kongenitalni Gorlin-Golcov sindrom, poznat i pod nazivom nevoidnog bazocelularnog sindroma ili nevusnog sindroma bazalnih ćelija, koji predstavlja nasledni autozomno-dominantni karcinomski sindrom, a podrazumeva razvoj multiplih bazocelularnih karcinoma u ranim godinama života i varijabilnu kombinaciju drugih fenotipskih abnormalnosti koje rezultiraju zahvatanjem više organa. Odgovorni gen je mapiran na hromozomu 9q22.3–3.1. Kao i drugi supresorski geni, PTCH1 gen pokazuje učestalu deleciju i čitav niz drugih mutacija. Visok stepen novih mutacija i varijabilna ekspresivnost čine kompletnu dijagnostičku procenu teškom, naročito kod osoba sa blagom kliničkom slikom i bez pozitivne porodične anamneze.

Prisustvo dva glavna kriterijuma ili jedan glavni i dva sporedna kriterijuma definišu pacijente sa Gorlin-Golcovim sindromom. Glavni kriterijumi su: više od dva ili jedan bazocelularni karcinom kod pacijenata mlađih od 20 godina; odontogenetske keratociste vilice – histološki potvrđene; tri ili više palmarnih ili plantarnih udubljenja – rupica; bilamelarna kalcifikacija falksa velikog mozga; bifidna, fuziona ili raširena rebra; rođaci prvog stepena sa sindromom. Sporedni kriterijumi su: makrocefalija; kongenitalne malformacije – rascep usna/nepce, fronto/temporoparijetalna ispupčenja, krupno i grubo lice, hipertelorizam; skeletne malformacije – Sprengel deformiteti, pektus ekskavatum/karinatum, sindaktilija; radiografske abnormalnosti – premošćavanje sele turcika, vertebralne abnormalnosti (hemivertebre, fuzija i elongacija vertebralnih tela), defekti na kostima šaka i stopala, rasvetljenje u obliku plamena na stopalima i šakama; ovarijalni fibromi/fibrosarkomi ili meduloblastomi.

Prikaz slučaja. Prikazujemo 42 godine starog pacijenta, muškog pola, sa šestogodišnjim postojanjem promena u vidu multiplih glatkih i/ili grubih plakova na koži leđa i ramena. Pojedine od ovih promena su vremenom postepeno progredirale i postale brojnije, nisu bile praćene subjektivnim simptomima. Na dlanovima je uočeno prisustvo tačkastih udubljenja crvenkastosmeđe boje. Daljim ispitivanjima otkriveno je prisustvo mnogih mišićno-skeletnih i kraniofacijalnih kongenitalnih abnormalnosti, kao što su pektus ekskavatum, fronto/parijetalna ispupčenja, egzotropija, impaktirani zubi, mandibularna hiperplazija, širok nos. Histopatološkim pregledom bioptiranog materijala uzetog sa nodularne i ostalih pločastih promena na koži utvrđeno je prisustvo dijagnostičkih kriterijuma tipičnih za bazocelularni karcinom. U porodici nije bilo obolelih srodnika.

Pacijent je lečen pod dijagnozom Hočkinovog limfoma sa hemioterapijom i radijacionom terapijom pre 20 godina. Postignuti su dobri terapijski rezultati, tako da se pacijent nalazio u remisiji poslednjih deset godina. Protočnom citometrijom nije utvrđeno stanje imunosupresije u trenutku pregleda.

Lečenje multiplih bazocelularnih karcinoma sprovedeno je 5% imikvimod kremom, pet dana u nedelji, tokom 12 nedelja. Nodularni tumor je prethodno tertiran elektrokoagulacijom. Mesec dana kasnije došlo je do potpunog povlačenja promena bez ikakvih rezidua.

Pacijentu je savetovano da koristi fotoprotekciju i da izbegava nekontrolisanu ekspoziciju sunčevim zracima. Tokom naredne tri godine na kontrolnim pregledima nisu uočeni znaci recidiva.

Diskusija. Prema kriterijumima koje su predložili Evans i saradnici , kao i Kimonis i saradnici, naš pacijent je ispunio dva glavna kriterijuma za postavljanje dijagnoze (multipli bazocelularni karcinomi i tačkasta udubljenja na dlanovima) i dva sporedna kriterijuma (fronto/parijetalna ispupčenja i pektus ekskavatum). Štaviše, mi smo otkrili brojne dodatne nepravilnosti kao što su: keratotične papule

na leđima i ramenima, izuzetan deformitet leđa sa jako izraženim paravertebralnim protuberancijama koji se razlikovao od Sprengelovog deformiteta, torakolumbalna kifoza, egzotropija, dentalna ektopija, mandibularna hiperplazija i širok nos.
Zaključak. U radu je prikazan slučaj kasne pojave multiplih bazocelularnih karcinoma kod osobe muškog pola sa Gorlin-Golcovim sindromom i sa anamnezom o ranije lečenom Hočkinovom limfomu. Prema nama dostupnoj svetskoj literaturi do sada su objavljena dva slučaja Hočkinovog limfoma kod osoba sa Gorlin-Golcovim sindromom. Uspešan terapijski efekat lokalne primene imikvimod krema u lečenju multiplih superficijalnih bazocelularnih karcinoma potvrđen je odsustvom recidiva tokom praćenja pacijenta naredne tri godine.

Ključne reči

Sindrom bazocelularnog nevusa; Bazocelularni karcinom; Multiple primarne neoplazme; Komorbiditet; Hodžkinova bolest; Dijagnoza; Aminokuinolini; Ishod terapije

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Concomitant Psoriasis and Bullous Pemphigoid – a Case Report

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Abstract

Concomitant occurrence of psoriasis and bullous pemphigoid was described in less than 100 cases in the literature. The co-occurrence affects the treatment approach of patients. We present a case of a 58-year-old man with psoriasis presenting with erythematous plaques, tense bullae, erosions and fever up to 39°C. Direct and indirect immunofluorescence and histopathological examination confirmed the diagnosis of bullous pemphigoid. In our case, bullous eruptions were successfully treated with oral methylprednisolone and dapsone, and psoriasis with narrowband ultraviolet B phototherapy and acitretin.

In conclusion, the etiopathogenesis of the coexistence of these two entities remains unknown, but it may be related to relatively high incidence of psoriasis and bullous pemphigoid, respectively. Both conditions are immunologically mediated and combined immunosuppressive regimens, directed at cellular and humoral immune responses, usually result in clinical improvement.

Key words

Psoriasis; Pemphigoid, Bullous; Comorbidity; Fluorescent Antibody Technique; Immunosuppressive Agents; Ultraviolet Therapy

Psoriasis is a complex, chronic, multifactorial, T-cell mediated inflammatory disease with keratinocyte hyperproliferation in the epidermis, and an increase in the epidermal cell turnover rate. Environmental trigger factors (e.g. trauma, medications, infections) in addition to immune and genetic factors, appear to play a role in the pathophysiology of clinical manifestations: sharply demarcated, erythematous plaques with silvery white scales. The most commonly affeted areas are found on the skin, scalp, elbows, knees, lumbosacral region, nails, hands and feet. Joint involvement accounts for up to 30% of all cases (1). Bullous pemphigoid is an autoimmune, subepidermal, blistering disease, which may be associated with significant morbidity, and predomonantly affects the elderly. It is characterized by multiple tense bullae arising on normal or erythematous skin, with a predilection for the groins, axillae and flexural areas. In contrast to psoriasis, bullous pemphigoid represents a distinct autoimmune condition in which the skin is the main target organ, and the role of autoantibodies against basement membrane antigens is well established (230 kD protein bullous pemphigoid antigen 1 and 180 kD protein bullous pemphigoid antigen 2, both of which are localized to the hemidesmosome).

The concomitant occurrence of psoriasis and bullous pemphigoid, as two well-characterized, chronic inflammatory skin diseases was first described in the literature in 1929 by Bloom et al. Since then, less than 100 cases were described worldwide (2). The pathogenic foundations of this phenomenon

are unknown. It may be suggested that psoriasis, as a chronic inflammatory disease, provides a particular predisposition of the immune system that, under certain circumstances leads to autoimmune response. The diagnosis relies on clinicopathologic correlation of direct and indirect immunofluorescence microscopy. Here we present a 58-year-old man with a 30-year history of plaque-type psoriasis presenting with disseminated tense bullae diagnosed as bullous pemphigoid.

Case report

A 58-year-old male with a 30-year-old history of psoriasis was admitted to the Department of Dermatology of the Medical Military Academy in Belgrade with fever (39 °C), extensive eruption of tense bullae and erosions on the trunk and extremities. Blisters and erosions appeared one year before on the trunk, and since then they spread to the extremities. The lesions were intensely pruritic, significantly affecting the patient′s quality of life. Before admission to our Clinic, the patient was treated by a general practitioner and other dermatologists with prednisone 60 mg per day, and after improvement with 20 mg per day. According to the patient's history, limited psoriasis was partially controlled with occasional mid-

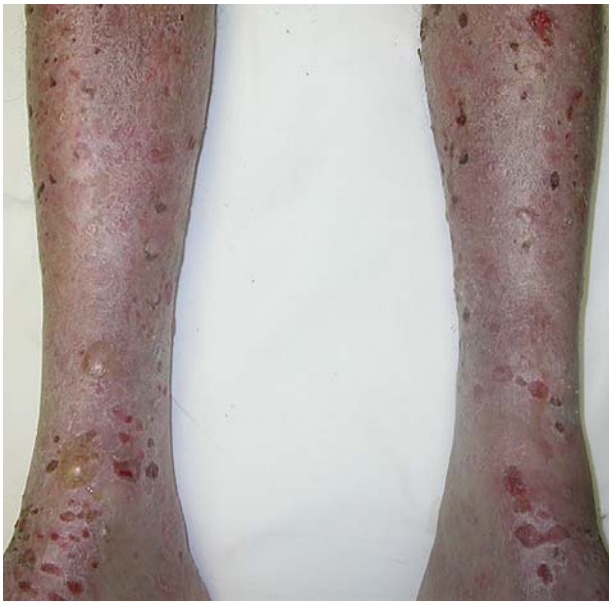

Figure 1. Tense vesicles, bullae and erosions on the lower legs

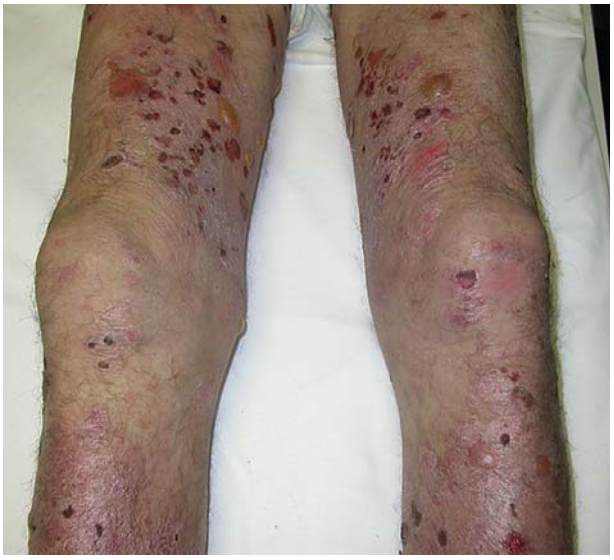

Figure 2. Tense bullae and erosions superimposed on preexisting psoriatic plaques on the thighs and lower legs

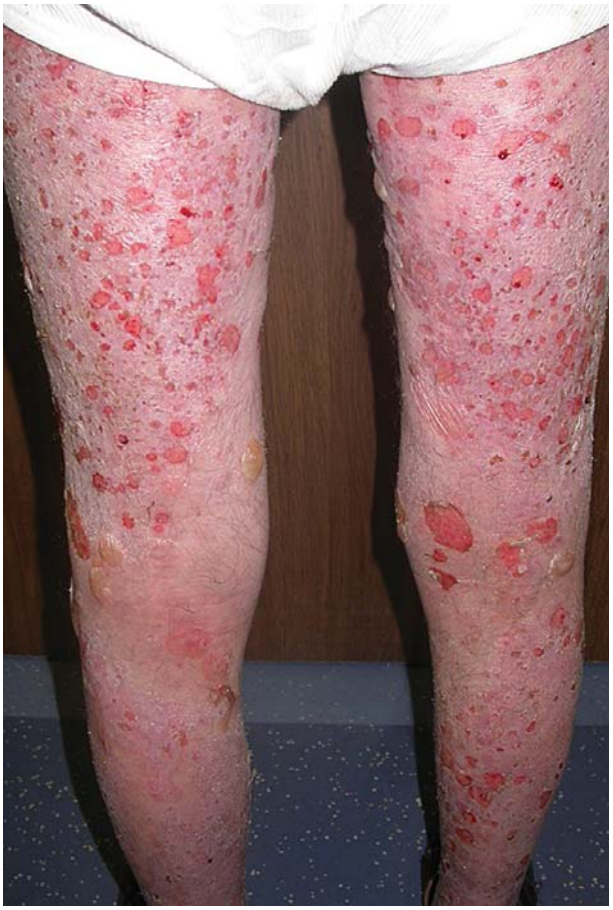

Figure 3. Multiple, extensive erosions and tense bullae on the lower extremities

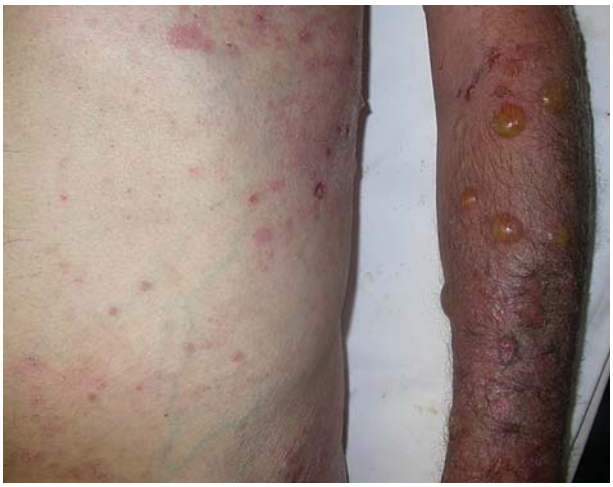

Figure 4. Blisters on the left forearm

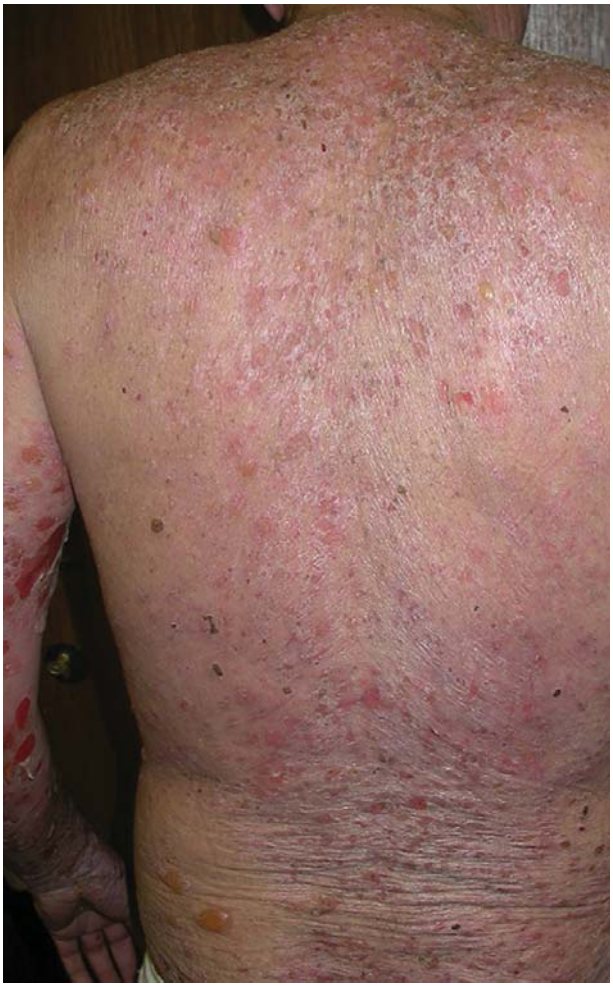

Figure 5. Tense bullae and erosions on the back and right arm, partially superimposed on preexisting psoriatic plaques in the sacral area

to-high-potency topical corticosteroids. The patient was otherwise healthy. There was no family history of psoriasis or autoimmune diseases.

He reported occasional alcohol consumation.

Physical examination revealed tense bullae and erosions on the trunk, lower and upper extremities, (Figures 1-4) partially superimposed on the pre-existing psoriatic erythematous plaques on the forearms and lower legs (Figure 5). The face and mucous membranes were spared. He had a fever up to 39°C.

Laboratory tests revealed increased sedimentation rate, C-reactive protein and fibrinogen, neutrophilia, hyperbilirubinemia, megaloblastic anemia and elevated levels of liver enzymes - alanine aminotransferase and aspartate aminotransferase. Hepatitis B surface antigen (HbsAg), anti-HCV (hepatitis C virus) antibodies, serum creatinine, urea, uric acid, lipids and urine analysis were within physiological limits. The diagnosis of sepsis was established by an infectologist, based on microbiology isolation of staphylococcus aureus in blood cultures and affected lesions.

X-ray of the heart and lungs showed no pathological findings. Ultrasonography of the upper abdomen and pelvis showed hepatomegalia with a bright echostructure.

Pathohistology analysis was performed on skin specimens. Two skin biopsies were taken for histopathology and immunofluorescence examinations. The first biopsy specimen, obtained from a psoriatic lesion, showed psoriasiform hyperplasia with parakeratosis, neutrophils and dilated capillaries in the dermis (Figure 6); the second biopsy specimen obtained from the border of a fresh bulla revealed epidermis separated from the dermal tissue, with serum exudate and a large group of neutrophils and eosinophils (Figures 7 and 8). Direct immunofluorescence from the perilesional skin revealed linear, continuous C3 and IgG deposits along the basement membrane zone. Indirect immunofluorescence assay demonstrated circulated IgG autoantibodies against the dermal-epidermal junction (titer 1 : 320).

Specialist consultations established the following diagnoses: sepsis and alcocholic liver injury (by an infectologist) and megaloblastic anemia (by a hematologist).

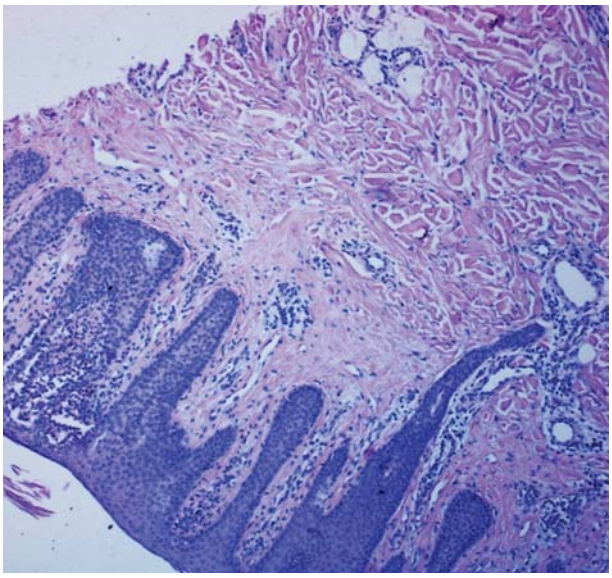

Figure 6. Psoriasiform hyperplasia with parakeratosis and neutrophils and dilated capillaries in the dermis (HE x 5)

A combination of methotrexate and corticosteroids was considered as the first choice treatment, but it was contraindicated due to the history of alcochol consumption, elevated transaminases and enlarged liver, estimated by ultrasonography. The patient was treated with systemic antibiotics: cefprozil 1g/6h i.v. and ciprofloxacin 200 mg/12h during two weeks; cefuroxime tbl. 500 mg were introduced twice a day for one week. At the same time, oral methylprednisolone was initiated at an initial dose of 60 mg/day. The dosage was reduced to 40 mg/day after two weeks, and diaminodiphenyl sulfone (dapsone) 100 mg/day was added. After 12 weeks of treatment, skin lesions resolved almost completely (absence of bullae and PASI <5), so methylprednisolone was slowly tapered to 24 mg daily, and dapsone was reduced to 50 mg daily.

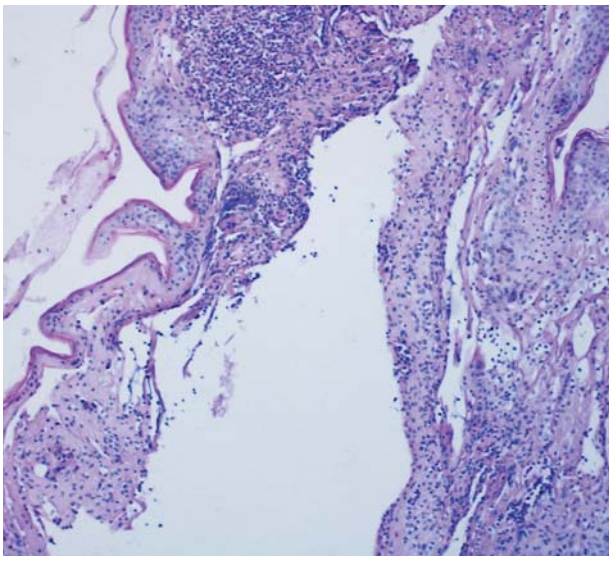

Figure 7. Epidermis separated from the dermal layer (HE x 5)

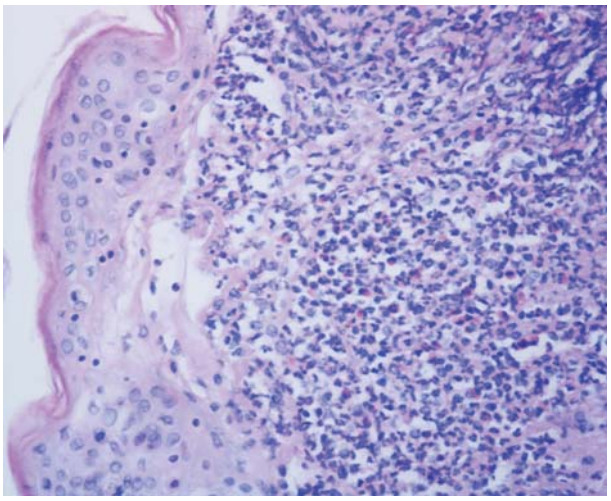

Figure 8. Epidermis separated from the dermal layer: serous exudate of serum with large group of neutrophils and eosinophils (HE x 20)

After 8 months of follow-up, the patient was almost lesion free, but new erythematous plaques were obsered on his forearms and lower legs. Narrowband UVB (NB UVB) phototherapy was given, which proved to be effective for psoriasis treatment, but may aggravate bullous pemphigoid. The patient was irradiated twice weekly for six months, and methylprednisolone and dapsone were continued at the above dose. Complete remission of psoriasis with small single bullae was observed at monthly follow-ups (Figure 9).

Two months after phototherapy was discontinued, the patient had discrete psoriasis eruptions. Since the patient reported alcochol abstinence, reevaluation of alcocholic liver injury revealed that transaminases were at normal levels. Treatment with acitretin (25 mg daily) was initiated with dapsone that was increased to 100 mg daily, and methylprednisolone was reduced to 24 mg per day

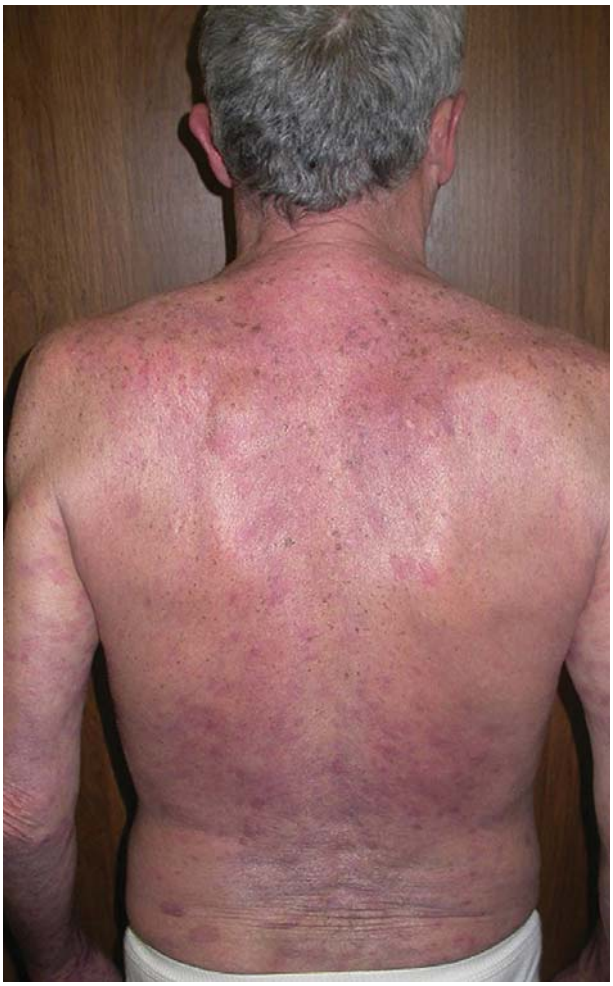

Figure 9. Hyperpigmented macules on the normal back skin

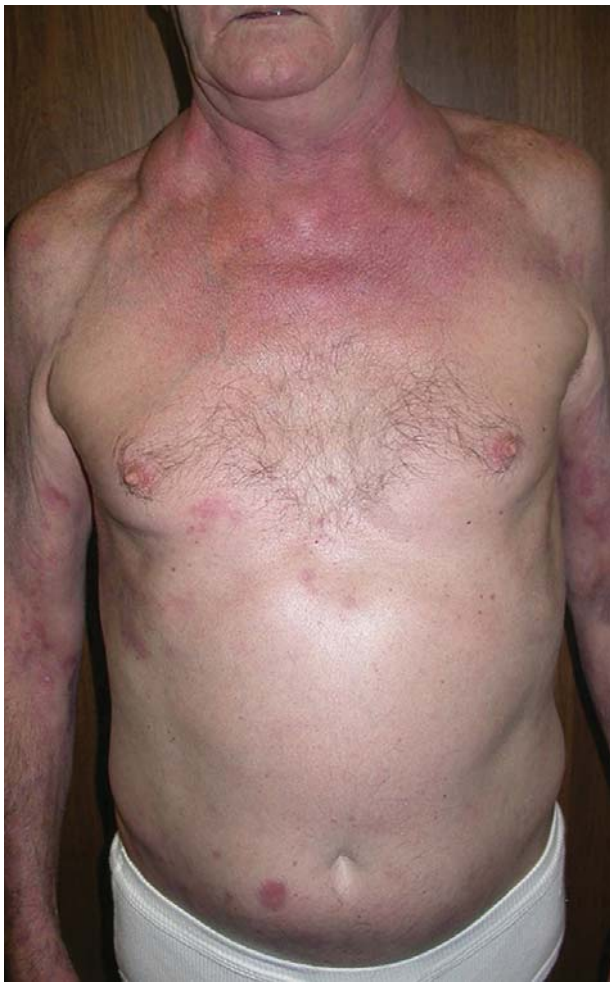

Figure 10. Hyperpigmented macules on the trunk and arms

3 times weekly. At 9 month follow-up, there was no relapse of bullous pemphigoid or psoriasis (Figure 10). The treatment was well-tolerated: a limited elevation in serum lipids (cholesterol 6,4 mmol/l; triglycerides 4,1 mmol/l) was the only side effect, without observed increment of transaminases.

Discussion

In 1929, Bloom et al. were the first to report on the simultaneous occurrence of psoriasis and bullous pemphigoid. Since then, less then 100 cases were described worldwide (2). Psoriasis has consistently been associated with many cutaneous and systemic conditions. Recent epidemiological studies have shown that psoriasis patients are prone to develop cardiovascular and other metabolic syndromes. On the other hand, a variety of cutaneous disorders may be associated with psoriasis (3). Since the initial description of the coexistance of bullous pemphigoid and psoriasis, several autoimmune bullous diseases associated with psoriasis have been reported in the literature. These include pemphigus vulgaris, pemphigus foliaceus, pemphigus herpetiformis, linear bullous dermatoses, cicatricial pemphigoid and, epidermolysis bullosa acquisita (3). Amoung these, bullous pemphigoid is the most frequently reported condition to be associated with psoriasis. It is more common among men than women, with an average age of onset at 63 years. In most cases psoriasis preceded the development of bullous pemphigoid, with an average time interval of 20 years, between the two conditions (4). Our patient, with an interval

of 30 years was well within this range. Also, bullous pemphigoid seems to occur in patients with psoriasis at a younger age than sporadic bullous pemphigoid (2).

The etiologic and trigger factors responsible for co-occurrence of psoriasis and bullous pemphigoid remain unknown. Since the coexistence was seen in patients who received a wide range of treatment for psoriasis, as well as in untreated patients, it is difficult to incriminate a single agent as a potentially causative factor in the development of bullous pemphigoid. A reduced barrier function of the psoriatic epidermis, combined with the irritant effects of therapies administered for psoriasis, such as anthralin, tar and ultraviolet light, psoralen ultraviolet A (PUVA), narrowband UVB irradiation, together with a low grade immunologic basal memmbrane zone (BMZ) insult, may precipitate blister formation (5). Our patient was previously treated only with local corticosteroids. Recently, cases of bullous pemphigoid developing after efalizumab therapy (anti-tumor necrosis factor treatment) of psoriasis have been described (6).

Changes at the BMZ in psoriasis itself may be responsible for precipitating the bullous disease. The presence of chronic inflammation, trafficking of activated lymphocytes and abundance of antigen presenting cells in psoriasis could unmask, expose or alter BMZ antigens, giving rise to autoantibody production (7). Electron microscopy studies have shown a focal discontinuity and reduplication of the basal lamina in psoriasis. The concept of „epitopic spreading“ whereby tissue damage from a primary inflammatory process can cause the release and exposure of a previosly „sequestered“ antigen, leading to a secondary autoimmune response against the newly released antigen, may provide us with a unifying explanation for the development of subepidermal bullous disorders (8). Such changes in structure may result in altered antigenicity of BMZ and keratinocytes, and subsequent generation of antibodies. Kobayashi et al. (4) described blistering that occurred only on psoriatic lesions. They postulated that bullous pemphigoid antigens are unmasked in psoriatic lesions through enzymatic degradation of the BMZ, and thus become accessible to circulating antibodies. Despite this assumption, blistering on both the psoriatic and normal-appearing skin was observed in other patients, including our case.

The autoimmune nature of bullous pemphigoid has been confirmed with the identification of IgG antibodies to bullous pemphigoid antigen 1, a 230-kd protein and bullous pemphigoid antigen 2, a 180-kd molecular weight transmembrane protein, both of which are localized on the hemidesmosome. These antigens account for 90% of patients with bullous pemphigoid (15). Bullous pemphigoid with psoriasis is typically associated with autoantibodies against type XVII collagen – bullous pemphigoid antigen 2, with the main antigenic site occurring within the noncollagenous 16a (NC16a) domain (9). Although specific autoantibodies operate in bullous pemphigoid, the significance of autoimmune mechanism and target autoantigens is only postulated in psoriasis. Circulating autoantibodies against components of the Malpighian layer and stratum corneum have been detected in the serum of psoriatic patients (10). The disregulation ot T-cell activity in psoriasis might result in the induction of specific antibodies to basement membrane antigens (4). Psoriasis has been historically considered as T-helper type-1 (Th1 type) immune mediated disease. However, recent studies have etablished that Th17 is the primary pathogenetic subset; this subset of T-cell also plays a key role in autoimmunity (5). Psoriasis has been associated with other autoimmune diseases such as discoid and systemic lupus erythematosus, miasthenia gravis, Sjögren syndrome, Crohn's disease, ulcerative colitis, vitiligo, Hashimoto thyreoiditis (11). No association with malignant conditions has been noted (11).

It was shown that UVB light can induce autoimmune phenomena characteristic of bullous pemphigoid. Furthermore, the basal cell layer known as the germinative compartment, is critically UV light sensitive (5). PUVA and retinoid therapy have been shown to modulate the glycocalyx and the expression of bullous pemphigoid and pemphigus antigens in nonlesional skin as well as in keratinocyte culture and have been found to decrease the expression of adhesion molecules on circulating and tissue-infiltrating T-lymphocytes. In support of these

observations, bullous pemphigoid has been observed in patients with other PUVA treated diseases, such as mycosis fungoides (5). In our patient, during and after the NB UVB phototherapy, the skin lesions were not aggravated by NB UVB phototherapy, possibly attributable to the concomitant corticosteroid and dapsone therapy.

Infectious agents are also possible triggering factors in the development of bullous pemphigoid. Tomasini et al. (10) speculated on the role of streptococcal infections in the pathogenesis of both psoriasis and bullous pemphigoid. These organisms may increase the production of possibly pre-existing molecules against surface antigens of keratinocytes, which may lead to the development of blisters. Other infections, such as hepatitis C, have been described in linear IgA dermatosis with concomitant psoriasis (12). In addition, infections may trigger immunologic reactions against basement membrane structures which have been altered or disruptured by the inflammatory mechanisms of psoriasis or its treatment. A common genetic predisposition for psoriasis and bullous pemphigoid has not been eluciadated. Although the latter is associated with HLA-B57, Cw6, C7, DR4 and DR7, no distinct association has been found for bullous pemphigoid (13).

Several therapeutic modalities have been described for the treatment of coexisting psoriasis and bullous pemphigoid. Immunosuppressive drugs proved to be effective in both diseases. Roeder C. et al. (14) described the combination of acitretin, which is well established in the treatment of severe psoriasis, and azathioprine, often used as a combination agent to treat bullous pemphigoid. Other therapeutic options include low dose methotrexate, cyclosporine, erythromycin in combination with etretinate (14), or tetracycline in combination with nicotinic acid or dapsone (4).

Oral treatment with fumaric acid showed a good clinical response in both psoriasis and blister formation (4). Two independent cases of psoriasis associated with bullous pemphigoid have been successfully treated with azathioprine and cyclosporine (15). Mycophenolate mofetil monotherapy (2000 mg per day) has proven to be effective (16). Systemic steroids should be avoided to prevent pustular psoriasis upon dose modifications (17). Franceso Cusiano et al. (18) described a patient in whom remission of bullous pemphigoiod was obtained with etanercept used as a single drug therapy. TNF-α antagonists may be used as an effective alternative therapy for coexisting bullous pemphigoid and psoriasis, since corticosteroids may induce a relapse of psoriasis and other well-known side effects and traditional systemic therapies are often associated with organ toxicity. In the literature, two cases of bullous pemphigoid (19, 20) treated with etanercept are described, both coexisting with psoriasis; the first achieved remission using etanercept when the steroid dose was lowered (19), the second patient was given etanercept for psoriasis after being completely cured of bullous pemphigoid with rituximab (20). Methotrexate used in low doses (10 mg weekly) (3) is effective in the treatment of BP-associated psoriasis, but, our patient could not tolerate MTX due to alcocholic liver disease. NB UVB phototherapy was an option, and, surprisingly, without outbreak of bullous pemphigoid; a complete clinical clearing of both diseases was achieved, with addition of dapsone and oral methylprednisolone. Subsequently, after NB UVB was discontinued, the patient continued receiving dapsone and oral methylprednisolone and acitretin was initiated. A limited elevation in serum lipids (cholesterol - 6,4 mmol/l; triglycerides - 4,1 mmol/l) was the only side effect seen. In our case, combination of NB UVB phototherapy with dapsone and oral corticosteroids was highly successful in suppressing lesions of both diseases. Our experience encourages further trials of this combination treatment in patients suffering from psoriasis and bullous pemphigoid.

Conclusion

In conclusion, the etiopathogenesis of the coexistence of psoriasis and bullous pemphigoid, remains unknown and may be related to relatively high incidence of both diseases. Further investigations may shed more light on the pathophysiological mechanism of this phenomenon. The majority of patients with psoriasis and bullous pemphigoid report a serious impairment of their quality of life and they also feel

that current treatment, although often effective, does not provide a satisfactory long-term solution. Due to the fact that both conditions are immune-mediated, combined immunosuppressive regimens, directed at cellular and humoral factors, usually result in clinical improvement. Thus, the challenge is to find appropriate, specific, safe and effective long-term treatment solution.

Abbreviations

PASI - psoriasis area and severity index
NB UVB - Narrowband UVB
PUVA - psoralen ultraviolet A
BMZ - basal membrane zone
Th1 type - T-helper type-1
HLA – human leukocyte antigen

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Udružena pojava psorijaze i buloznog pemfigoida – prikaz slučaja

Sažetak

Uvod. U literaturi je opisano manje od 100 slučajeva udruženosti buloznog pemfigoida i psorijaze. Istovremeno prisustvo ova dva klinička entiteta kod istog pacijenta zahteva kompleksan terapijski pristup.
Prikaz slučaja. Prikazujemo pacijenta starosti 58 godina sa dugogodišnjom evolucijom psorijaze, koji je primljen u Kliniku sa diseminovanim eritematoznim plakovima, bulama, erozijama i znacima sepse. Direktnim i indirektnim imunofluorescentnim testom i histopatološkim pregledom potvrđene su dijagnoze buloznog pemfigoida i psorijaze. U našem slučaju, bulozni pemfigoid je uspešno lečen metilprednizolonom i dapsonom, a psorijaza nb UVB terapijom i acitretinom.

Zaključak. Etiološki faktori i patogenetski mehanizmi koji utiču na udruženost buloznog pemfigoida i psorijaze još uvek su nepoznati. Obe bolesti su imunološki posredovane, tako da kombinovana imunosupresivna terapija, usmerena ka humoralnom i celularnom odgovoru, može da dovede do kliničkog poboljšanja.

Ključne reči

Psorijaza; Bulozni pemfigoid; Komorbiditet; Fluorescentni test na antitela; Imunosupresivni lekovi; Ultravioletna terapija

Biography of Dr. Đorđe-Đurica Đorđević, Founder of the Clinic for Skin and Venereal Diseases in Belgrade

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UDK 616.5:929 Đorđević Đ.

Abstract

orđe orđević, a Serb from Croatia, was born in Grubišno polje (Croatia) on April 22, 1885. He studied medicine in Vienna and graduated in 1909. Till 1912, he advanced his knowledge working at dermatology clinics with Prof. Finger and Prof. Arning, as well as with Prof. Weichselbaum, professor of pathological anatomy and bacteriology.
From 1912 he worked in Zagreb, at the Dermatology Department of the Brothers of Mercy Hospital, and during World War I as a military doctor at the Dermatology Department and the Zagreb Outpatient Department (Second kolodvor). After the war, in 1918, he moved to Belgrade, where he was the Head of the Polyclinic for Skin and Venereal Diseases, and in 1922 he became an Assistant Professor of Dermatology at the School of Medicine in Belgrade. In the same year, he founded the Department of Dermatovenereology at the School of Medicine in Belgrade and the Clinic for Skin and Venereal Diseases, of which he was also the Head. In 1923, he became an Associate Professor, and in 1934 a Full Professor. He is given credit for passing legislation on prostitution and banning brothels.
The professional work of Prof. orđe orđević encompasses all areas of dermatology, including his special interest in experimental studies in the field of venereology.
He organized medical-research trips to study people's health status, and his teams visited the South Serbia (today Macedonia), Sandžak and Montenegro.
In 1927, he founded the Dermatovenereology Section of the Serbian Medical Society (19) and the Association of Dermatovenereologists of Yugoslavia. He was the chairman of the I, II and III Yugoslav Congress of Dermatology in Belgrade, and of the II Congress of the Pan-Slavic Association of Dermatovenereologists with international participation. He was an honorary member of the Bulgarian, Czechoslovakian, Polish and Danish Dermatological Societies, as well as a regular member of the Association of French Speaking Dermatologists, and of French, German and Biology Society. He was the Vice dean of the School of Medicine.
He died suddenly on April 27, 1935, shortly after his 50th birthday, and was mourned by colleagues, friends and students.
On the first anniversary of his death, his family, friends and colleagues established a "Foundation of Dr. orđe-urica orđević" meant for "doctors and health workers". Unfortunately, the foundation was disestablished in the early eighties of the 20th century.

Key words

Biography; Physicians; Dermatology; Venereology; History of Medicine; Serbia; Skin Diseases; Syphilis

Biographies are one of the ways of writing the history of classical (traditional) medical history (1). They give us a way to tie together the parallel currents of history at the level where the events and ideas occur (2), including past and present, history and medicine, and close study of an individual also provides an insight into the creative process itself (3). However, in the mid-twentieth century, medical biographies have become much rarer, under the influence of academic historians, whose main idea was to study the impact of medicine on the health and development of people (social context: social history of medicine) (4). In this

framework, biographies were not relevant to the new historical science, because the history of medicine is infinitely more than history of great doctors and their books (5). This has decreased the stimulating effects of medical-historical facts, observation, critical and scientific reasoning, thus limiting the development of medical thought.

In the last three decades, these disagreements and mutual antagonism were followed by a return of biography, which became a respected scientific genre once again (1).

The biography of Đ. Đorđević (Figure 1), which covers geographical, existential, professional and socio-cultural aspects, confirms the value of this historiography genre, including the social context, because his life and work are relevant for the development of dermatovenereology in Serbia, but are also features of the era in which he lived.

Đorđe Đorđević, a Serb from Croatia, was born in Grubišno polje (Croatia) on April 22, 1885. It was a territory of the Military Frontier (border), which was a strong anti-Ottoman defense line preventing Ottoman expansion in Europe. He attended elementary school in Vukovar, the first four years of high school in Novi Sad, and the higher grades and graduation in Zagreb (6). He studied medicine in Vienna and graduated in 1909. Very early on he showed interest in scientific research and he worked diligently and systematically. During his studies in Vienna, he was an assistant to A. Weichselbaum, professor of pathological anatomy (and histology) and bacteriology (6, 7). In the same period he worked at the *University Clinic for Skin and Venereal Diseases* with Prof. Finger (8), who belonged to Hebra's school (9) and was known for his works on gonorrhea and syphilis (10). After he graduated, till August 1911, Đ. Đorđević was the first assistant to professor Merck in Innsbruck, and later, till 1912, he worked with E. Arning, professor of dermatology at the University of Hamburg. Then he moved to Zagreb where he had a private practice, but also worked at the *Department of Skin Diseases* of the *Brothers of Mercy Hospital* (6, 8). The head of the department was Dr. J. Thierry (6), the founder of venereology in Croatia, who worked on prevention of sexually transmitted diseases and health education of common people (11). When the First World War started in 1914, Đ. Đorđević was mobilized as a military doctor and worked at the *Dermatology Department* and the *Zagreb Outpatient Department (Second kolodvor)* till the end of the war (6, 12). So, until his arrival to Belgrade, he spent almost all his life in areas under the Austro-Hungarian monarchy, whereas he was a Serb by his national origin and identity.

Although Serbia was on the winning side after the end of the World War I, the country was devastated by long occupation and outbreaks of infectious disease. At the beginning of war, 30.000 grenades were thrown at Belgrade, so the city was in ruins. Health facilities were severely damaged or destroyed, and the entire hospital inventory, medical supplies, medicines and instruments were taken away, as well as medical records and books from the library. The University building (Captain Miša's Mansion), an architectural beauty of Belgrade, was turned into stables and munitions depot (13). One third of the population was lost during the war, as well as half of the army (14), and 35% of doctors (15), among which there were three dermatologists: Milorad Savićević, Pop-Milutin Jovanović, Milutin Perišić (16), being an irreparable loss to the profession. The development of dermatovenereology service in Serbia, initiated in the nineteenth century by general physicians and surgeons, with special efforts of the first educated dermatovenereologist, Dr. J. Žujović, who was introducing European scientific dermatology, was destroyed.

Đ. Đorđević was among the Serbs who lived scattered in the Habsburg Monarchy, never letting go of the dream to return to their country and help its restoration. Thus, immediately after the war, he fulfilled the ideal of his youth: in 1918 he moved to Belgrade (6), where he lived to the end of his life. His arrival was followed by trains bringing clothing, food, medicines, sanitary materials, beds and bedding for the country which was to be rebuilt from ruins (6, 12).

From the very beginning, he had a clear goal and a plan to achieve it; being a systematic person, in the course of a few years, first he founded institutions necessary for health care, development and education in the field of modern dermatovenereology.

During his short but fruitful life, events were taking place in a continuous and dynamic manner: in 1919 he became the Head of the newly established *Outpatient Service for Skin and Venereal Diseases* (OSSVDs) (17, 18), while the School of Medicine in

Figure 1.Professor Đurica Đorđević

Belgrade was established in 1920 (13). As of 1922, Đ. Đorđević was elected as Assistant Professor and the first teacher of dermatology in Serbia, after which he founded the *Department of Dermatovenereology* at the School of Medicine in Belgrade (13), and the *Clinic for Skin and Venereal Diseases* (CSVDs), remaining its managing director till his premature death (18). He was elected as Associate Professor in 1923, when he began teaching at the university, and in 1934 he became a Full Professor (8). He founded the Clinical Library, with valuable books and periodicals from the nineteenth and the first decades of the twentieth century, and initiated the creation of the Belgrade Dermatovenereology Moulage Collection. After World War II, we learned from our senior colleagues about the newly established Department for Experimental Work with Experimental Animals. In 1927, major institutions were founded under his leadership: the *Dermatovenereology Section* (DVS) of the *Serbian Medical Society* (SMS) (19) and the *Association of Dermatovenereologists of Yugoslavia* (ADVY), which included all Dermatovenereology Sections of the Kingdom of Serbs, Croats and Slovenes (later Yugoslavia) of that time (20). He was one of the initiators of the idea of uniting and grouping Slavic dermatologists, while foundation of the ADVY provided inclusion of all dermatovenereology sections of the Kingdom of Serbs, Croats and Slovenes into the *Pan-Slavic Association of Dermatovenereologists* (PSADVs). In Belgrade, he organized the First (1927), Second (1928) and Third (1929) Yugoslav Dermatovenereology Congresses (18). In 1931, in the second term of PSADV, he was elected as the president of the association, and in the same year, the II PSADV Congress was organized in Belgrade, under his leadership, with international participation and a rich program (21). His young associates were also included in these activities, like the irreplaceable M. Kićevac, later professor and his successor as the Head of the Clinic

(18). With his exceptional gift for communication, he gathered and encouraged them with his creative spirit, inexhaustible ideas and enthusiasm: his ideas were recognized in their work. In the academic year 1933/34 (13), he was elected as the Vice Dean of the School of Medicine in Belgrade, and he held this position till death.

Đ. Đorđević also had a very active professional and teaching career, and his former work with experienced specialists in dermatology centers was of great benefit.

Although the newly established *Outpatient Service for Skin and Venereal Diseases* (OSSVDs) (1919), was situated in an inadequate building with poor conditions, he succeeded in organizing a free of charge modern laboratory service, held classes for medical students and young doctors specializing in dermatovenereology (17, 18).

The professional work of Đ. Đorđević included dermatology in general, but his main interest was venereology. The research that he conducted and encouraged, from the point of view of medicine of that time, demonstrated his professional and scientific competence. He investigated the biological characteristics of Treponema pallidum (TP) in rabbits, insisted on the importance of its early detection and serological reactions, studying their relationships. Treatment of syphilis was surely his favorite subject of research. He studied effects of modern treatment, paying special attention to the whole body, as opposed to partial approach. In addition, he believed that the outcome of treatment was not directly influenced by the drug, but by the reaction of the organism, which he stimulated by vaccines and blood transfusions, but he was also a supporter of pyretotherapy in all forms of early and latent syphilis. In gonorrhea, he bacteriologically studied gonococci and "banal diplococci", seeking causes of their variable virulence, trying to explain the relationship with "banal" urethritis, being a major problem for venereologists of that time and long after that (7, 17, 21). Accepted or not by modern medicine, his ideas were progressive for that time; M. Kićevac emphasized the intuition of his mentor, and his ability to get deeply into the essence of the problem (7).

Owing to the obituary written by M. Kićevac (7), we have the bibliography of Đ. Đorđević: he published 49 papers, of which 31 were in the field of venereology, and 17 were published in German and French journals. This number does not include many case reports presented at meetings of SMS and DVS.

Teaching was among his most important duties. He used to spend a lot of time with his students at lectures and outside the class, and not only with medical students, but with students of the entire University of Belgrade. He was interested in the conditions of their life, financial problems and their other activities (7, 12); he founded the canteen for medical students and was the honorary president of the Association of Medical Students (12). Due to all the above, he was "the favorite teacher" (6).

Social medical work was among the most important areas of his work and he worked on its implementation on a broad scale. He was highly respected as a person spreading social medical measures in fighting venereal diseases and as a founder of free of charge outpatient dermatovenereology service (17, 22). From the beginning of his work in Belgrade, he started fighting against prostitution, which spread throughout Europe after the war. In early 1919, "Temporary rules for fighting against venereal diseases in Belgrade" were brought, and thus control of prostitution was transferred from the police to the Polyclinic where he was the Head, and prostitutes were treated free of charge. He is given credit for passing legislation on prostitution and banning brothels. Following the example of this Polyclinic, on his initiative, the Ministry of Public Health organized a number of similar clinics in other cities in the country (17).

His medical research trips were truly invaluable. In the first years after arriving in Belgrade, Đ. Đorđević began organizing medical research trips with a team of doctors, clinicians of all specialties, with complete laboratory; among them were some professors from the School of Medicine. Destinations were mostly poor and inaccessible areas, distant from health centers, where medical help was most needed, and their objective was to study the general health of the nation, as well as diseases with highest incidence in each area. Thus, the trip to Sandžak was dealing with endemic syphilis, tuberculosis, and liver diseases. Đ. Đorđević believed that this type of work was useful both for physicians on the team, as well as for local

doctors, since various pathology was rarely found in areas closer to health centers. Thanks to his authority, some state institutions supported this work financially (travel expenses, accommodation and organization of team work), and all examinations were free of charge. Team participants were volunteers, working without compensation (23).

In 1924, he organized a small expedition to investigate the incidence of syphilis in the area of Požarevac. The interest of the population was huge (22), so in 1925 he organized another medical trip to South Serbia (today Macedonia), where 10.000 people were examined in the course of one month (22, 23). The next expedition was to Sandžak in 1929 (23). His last expedition was in 1933, and in addition to many professors, it was attended by the rector, V. Petković, and the vice rector, M. Ilić. According to incomplete data, its destination was Montenegro (22).

Unfortunately, data on these events are missing. After World War II, Prof. S. Ilić, director of the CSVDs, claimed that some of the gathered materials were processed, but he could not obtain any reports, so in his monograph on the treatment of endemic syphilis, he provided only oral statements of participants, general and sporadic, on one of the expeditions (24). However, it is known that during World War II, the CSVDs was occupied by the enemy (13, 25) and that in that period the complete Clinic Archive disappeared (25), probably together with these reports.

Prof. Đ. Đorđević was a man of great humanity. During World War I, as a military doctor in Zagreb, he organized the rescue of a large number of nationally oriented Serbs and Croats, who were considered to be politically incorrect, and as recruits of the Austrian army, they were systematically sent to the most dangerous parts of the Austrian front, where they would certainly end up dead (6). Among them, there were further editors of the "Literary South" (literary magazine of Yugoslav nationally oriented writers, which was published in Zagreb in 1918 and 1919) (26): Niko Bartulović, a writer; Ivo Andrić, later a Nobel Prize winner in literature and Vladimir Ćorović, one of the most significant Serbian historians (12).

After the war, he also provided financial support to people who came from internment or prison, as well as numerous children from Bosnia and Herzegovina who have lost their parents (6). He put some of them through school (12).

Đ. Đorđević was an ethical and highly professional person, fully dedicated to the Hippocratic Oath. Those who worked with him knew how passionate he was about his job, also conscientious, consistent and accurate in carrying out his duties, a great organizer. On the other hand, socially, he was a bright and witty man, fond of people, arts and artists, a bohemian. J. Nedeljković, an internist-pulmonologist, later a professor at the School of Medicine in Belgrade, one of the participants of his health expeditions, wrote about his youthful memories in the obituary: "He made people feel cheerful and good, and he spread serenity and goodness ..... which came from perfect inner harmony ..... in his most intimate being he was an exceptional and truly generous man"; he boosted his associates with self-confidence and wish to work independently, so they could develop their skills. He loved people and they felt it, so he made lasting friendships, both with the common people from areas he visited on his expeditions (22), and with learned scholars. With his wife Krista, born Šumanović, he was a patron of modern art, and his home in Belgrade was one of the most popular meeting places for the intellectual and artistic elite. Among his friends were sculptors Sreten Stojanović and Toma Rosandić, painters Milo Milunović and Ignjat Job, composers Petar Konjović, Kosta Manojlović, Miloje Milojević, writers Miloš Crnjanski, Tin Ujević (12), Branislav Nušić (22) and others. He was their moral support, and to some he provided financial assistance. Thus, he supported specializations abroad for the sculptor Sreten Stojanović, and Radivoje Pavlović, later a distinguished professor of pharmacology (12).

He was an honorary member of the Bulgarian, Czechoslovakian, Polish and Danish dermatological societies, as well as a regular member of the Association of French-Speaking Dermatologists, and of the French, German and Biological Society (8). The Clinic of Dermatology and Venereology of the School of Medicine in Belgrade was named after him.

Prof. Đ. Đorđević died shortly after his 50th birthday. He worked till the last day of his life. Although he already had symptoms of the disease that would result in death, as the vice dean, he hosted Professor Debré from France: he gave a welcome speech, the next day he attended his lecture, and held a reception

for more than 100 people at his home. During the following days, shortly before his death, he visited the playwright Branislav Nušić and gave him advice on taking his medications; for the next day he scheduled a game of cards at home, where B. Nušić read his new play "Uježˮ. A few days later, he went to Aranđelovac, full of optimism and good spirits. That evening he played his last piquet card game with his friends. Prof. J. Nedeljković wrote: "He lay down in good earnest and fell asleep forever" (22). He died at dawn of April 27, 1935. It was during the Easter holidays, and it was announced over radio and newspapers; people expressed grief in many parts of our country (6). He was buried at the New Cemetery in Belgrade; his grave has a white marble headstone with a symbolic relief full of emotions: a kneeling girl with arms outstretched towards the leaving ship; candelabra with caryatids, described by the art historian J. Sekulić, and the work of his protégé and friend, sculptor Sreten Stojanović (27) is unfortunately missing.

After his death, his family, professors, assistant professors, teaching assistants of the School of Medicine, and staff of the CSVDs, OSSVDs, as well as doctors of other institutions established the "Foundation of Professor Đorđe-Đurica Đorđević" meant for rewards "of doctors and medics" on his death anniversary. The director of CSVDs was the Head of the Foundation and the President of the jury; it was to be a permanent foundation. Unfortunately, due to poor management, the Foundation was disestablished in the early eighties (28).

This paper will end with the words taken from the obituary written by Prof. Kićevac "After his sudden death, his associates, assistants and staff are filled with deep sorrow at the early loss of their superior, but also with great affection for the kind and cordial man Prof. Đorđe Đorđević was. "

His early death was a great loss for Serbian dermatovenereology, as well as for the society. But, like every man with a vision, he left behind a group of exceptional Serbian dermatologists who followed his path: Prof. Milan Kićevac, Assist. Prof. Sava Bugarski, Assoc. Prof. Nemanja Barjaktarević, and Prof. Sima Ilić.

Abbreviations

OSSVDs - Outpatient Service for Skin and Venereal Diseases
CSVDs - Clinic for Skin and Venereal Diseases
DVS - Dermatovenereology Section
SMS - Serbian Medical Society
ADVY - Association of Dermatovenereologists of Yugoslavia
PSADVs - Pan-Slavic Association of Dermatovenereologists
TP - Treponema pallidum

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Biografija dr Đorđa - Đurice Đorđevića, osnivača Klinike za dermatovenerologiju i venerologiju u Beogradu

Sažetak

Uvod. Biografija profesora dr Đorđa Đorđevića ukazuje na važnost ovog istoriografskog roda, jer su njegov život i rad značajni za razvoj dermatovenerologije u Srbiji, ali i kao obeležje epohe u kojoj je živeo.
Biografski podaci. Đorđe Đorđević, Srbin iz Hrvatske, rodio se u Grubišnom Polju (Hrvatska) 22. aprila 1885. godine. Osnovnu školu pohađao je u Vukovaru, a gimnaziju u Novom Sadu i Zagrebu. Medicinu je studirao u Beču i diplomirao je 1909. godine. Do 1912. godine usavršavao se na dermatološkim klinikama kod prof. Fingera i prof. Arninga, kao i kod Vajhzelbauma, profesora patološke anatomije i bakteriologije, gde je stekao široko dermatovenerološko obrazovanje.
Stručna aktivnost. Od 1912. godine radio je u Zagrebu, at the Department of Skin Diseases of the "Hospital of Brothers of Mercy", a u toku I svetskog rata kao vojni lekar na Kožnom odeljenju i Ambulanti Drugog zagrebačkog kolodvora. Posle završetka rata, 1918. godine prešao je u Beograd sa ciljem da pomogne u obnovi svoje zemlje razorene ratom. Odmah je postavljen za rukovodioca Poliklinike za kožne i venerične bolesti u Beogradu. Godine 1922.

izabran je za docenta za Dermatovenerologiju na Medicinskom fakultetu u Beogradu. Iste godine bio je jedan od glavnih osnivača Klinike za dermatologiju i venerologiju i Katedre za dermatovenerologiju. Za vanrednog profesora izabran je 1923. godine, kada je počeo sa nastavom, a redovni profesor postao je 1934. godine. I pored nepovoljnih smeštajnih uslova, na Klinici je organizovao stručni i naučno-istraživački rad, kao i nastavu za studente i lekare na specijalizaciji. Njegova je zasluga donošenje zakonskih odredbi o regulisanju prostitucije, na osnovu kojih je kontrola prostitucije prešla iz policije u Polikliniku za kožne i venerične bolesti, gde je lečenje bilo besplatno i ukinuo je javne kuće. Svojim stručnim radom obuhvatao je kompletnu dermatovenerologiju, s posebnim interesovanjem i eksperimentalnim studijama u oblasti venerologije. Objavio je 49 radova – 31 rad je iz venerologije; 17 radova je publikovano u nemačkim i francuskim časopisima. Podsticao je stručni i naučni rad svojih saradnika.

Kao nastavnik bio je vrlo cenjen. Pored predavanja, učestvovao je i u drugim studentskim aktivnostima i problemima; osnovao je menzu za studente medicine, bio je počasni predsednik Udruženja studenata medicine i jedan od najomiljenijih nastavnika.

Značajan je bio njegov socijalno-medicinski rad. Organizovao je zdravstveno-naučne ekskurzije radi proučavanja zdravstvenog stanja naroda i sa svojim ekipama obišao je Južnu Srbiju (danas Makedonija), Sandžak i Crnu Goru.

Već 1927. godine bio je jedan od glavnih osnivača Dermatovenerološke sekcije Srpskog lekaraskog društva i Jugoslovenskog dermatovenerološkog društva koje je objedinilo sve dermatovenerološke sekcije u tadašnjoj Kraljevini Srba, Hrvata i Slovenaca. Jedan je od pokretača ideje zbližavanja slovenskih dermatovenerologa; njegovom inicijativom Jugoslovensko dermatovenerološko društvo uključeno je u Sveslovenski dermatološki savez. U drugom mandatu izabran je za predsednika ovog saveza. Pod njegovim rukovodstvom održan je u Beogradu I, II i III jugoslovenski dermatovenerološki kongres i II kongres Sveslovenskog dermatološkog saveza sa internacionalnim učešćem.

Bio je počasni član Bugarskog, Čehoslovačkog, Poljskog i Danskog dermatološkog društva, kao i redovni član Društva dermatologa francuskog jezika, Francuskog, Nemačkog i Biološkog društva. Bio je prodekan Medicinskog fakulteta.

Društvena aktivnost. Humanost Đ. Đorđevića bila je neiscrpna. U toku I svetskog rata, kao lekar u Zagrebu pomagao je nacionalno orijentisanim Srbima i Hrvatima da izbegnu mobilizaciju kao austrijski vojni obveznici i mnogima je tako spasao život. Materijalno je pomagao naše ljude koji su se posle završetka rata vraćali iz internacije i zatvora, kao i mnogobrojnu decu koja su u ratu ostala bez roditelja. Neke od njih je i školovao.

Kao čovek je predstavljao izuzetnu ličnost: odan svome pozivu, na poslu je bio neumoran i strog, dobar učitelj i odličan organizator. S druge strane bio je širokogrudi, veseo i duhovit čovek, voleo je društvo, umetnost i umetnike. Bio je zaštitnik moderne umetnosti i njegov dom je bio sastajalište intelektualne i umetničke elite u Beogradu.

Preminuo je iznenada, 27. aprila 1935. godine, neposredno posle svog 50. rođendana, ožaljen od kolega, prijatelja i studenata.

Njegova porodica, kolege i prijatelji osnovali su „Fond dr Đorđa-Đurice Đorđevića“ za nagrađivanje „lekara i medicinara“ o godišnjici njegove smrti. Lošim rukovanjem, fond je ugašen početkom osamdesetih godina XX veka.

Ključne reči

Biografija; Lekari; Dermatologija; Venerologija; Istorija medicine; Srbija; Kožne bolesti; Sifilis

Activities of the Dermatovenereology Section of the Serbian Medical Society in 2013

Five meetings of the *Dermatovenereology Section* (DVS) of the *Serbian Medical Society* were organized in 2013, and all were accredited by the *Health Council of the Republic of Serbia.*

The first meeting of the DVS was organized by the *Clinic of Dermatovenereology, Clinical Center of Serbia* on March 8, 2013. The introductory lecture was delivered by Assist. Dr. Jelena Stojković Filipović: Cutaneous lymphomas – what`s new in classification, diagnosis and therapy. Also, 12 case reports were presented:

1. Angiosarcoma of the scalp, Prof. Dr. Ljiljana Medenica
2. Non-Hodgkin lymphoma, Assist. Prof. Dr. Mirjana Milinković
3. Cutis marmorata talangiectatica congenita, Assist. Dr. Mirjana Gajić Veljić
4. Laugier-Hunziker syndroma, Assist. Dr. Dušan Škiljević
5. Eruptive xanthomas, Dr. Biljana Marenović
6. Bullous lichen sclerosus et atrophicus, Assist. Prof. Dr. Jelica Vukićević
7. Tinea incognito, Dr. Danijela Milčić
8. Pyoderma gangrenosum in a patient with multiple myeloma, Dr. Jelena Perić
9. Klinefelter syndrome and venous ulceration of the lower legs – significance of association, Assist. Prof. Dr. Danijela Dobrosavljević Vukojević
10. Collodion baby, _____?
11. Glucagonoma syndrome, Dr. Jovan Lalošević
12. Hydroa vacciniforme, Dr. Iva Maširević

The second meeting of the DVS was organized by the *Department of Dermatology and Venereology, Military Medical Academy* on April 19, 2013. The introductory lecture was presented by Assist. Prof. Željko Mijušković: Treatment of advanced basal cell carcinoma. Also, 8 case reports were presented:

1.Adverse cutaneous reactions to erlotinib – a report of two patients, Assist. Prof. Željko Mijušković
2.Panitumumab-induced acneiform eruptions, Assoc. Prof. Dr. Lidija Kandolf Sekulović
3.Nodular amyloidosis, Dr. Kristina Kostić
4.Scleromyxedema, Dr. Miroslav Dinić
5.Acne fulminans, Assist. Prof. Željko Mijušković
6.Reiter's disease, Dr. Miroslav Dinić
7.Tinea capitis and systemic lupus erythematosus, Prof. Dr Radoš Zečević.

The third meeting of the DVS was organized by the *Clinic of Dermatology and Venereology, Clinical Center Niš* on May 11, 2013 in Prolom Banja. The introductory lecture was delivered by Prof. Dr. Dragan Mihailović: Mesenchymal tumors – immunohistochemisty aspect. Also, 9 case reports were presented:

1. Clinical and dermoscopic characteristics of patients with lichen planus, lichen sclerosus and morphea, Assist. Dr. Danica Tiodorović Živković
2. Transient acantholytic dermatosis (Grover's disease), Dr. Danijela Popović
3. Pyoderma gangrenosum, Dr. Vesna Karanikolić
4. Scrotal angiokeratomas, Dr. Milica Petrović
5. Scleredema adultorum Buschke, Dr. Slađana Cekić
6. Sweet syndrome, Dr. Radmila Milenković
7. Bullous pemhigoid in pregnancy, Dr. Zorana Zlatanović
8. Adjuvant therapy with 5% imiquimod cream in a melanoma patient in resected stage IIIb, Assist. Dr. Danica Tiodorović Živković
9. Erythroplasia of Queyrat – treatment with imiquimod cream, Dr. Mirjana Milosavljević.

The fourth meeting of the DVS was organized by the *Clinic of Dermatovenereology, Clinical Center of Vojvodina* on October 18, 2013 in Novi Sad. The introductory lecture was delivered by Dr. Siniša Tasić: New approaches in the treatment of dermatomycosis. Also, 8 more lectures were presented at this meeting:

1.Scabies – what is new?, Assist. Prof. Zoran Golušin
2. Ivermectin in human use, Assoc. Prof. dr. Slobodan Stojanović
3. Systemic sclerosis, Assist. Prof. Zorica Gajinov
4. Mastocytosis, Assist. Dr. Aleksandra Petrović
5. Dress syndrome, Assist. Dr. Ljuba Vujanović
6. Imiquimod 5% cream in the treatment of squamous dysplasia in a patient with polycythemia and rosacea, Dr. Tatjana Roš
7. Porokeratosis of Mibelli – treatment with 5% imiquimod cream, Dr. Branislava Gajić
8. Treatment of atopic dermatitis, Assist. Dr. Aleksandra Petrović.

The fifth meeting of the DVS was organized by the *Department of Dermatovenereology, Clinical Center of Kragujevac* on November 8, 2013 in Kragujevac. The introductory lecture was delivered by Assist. Prof. Ana Ravić Nikolić: The effect of PUVA treatment on cytokine expression in psoriatic plaques. Also, 7 more lectures were presented at this meeting:

1.Infliximab in the treatment of psoriasis, Assist. Dr. Vesna Miličić
2.Generalized eruptive xanthoma? Assist. Prof. Ana Ravić Nikolić
3.Neurofibromatosis von Recklinghausen associated with liposarcoma, Prof. Dr. Nebojša Krstić
4.Electrical burns, Dr. Gordana Ristić
5.Acute febrile neutrophilic dermatosis (Sweet syndrome) – a case report, Assist. Dr. Vesna Miličić
6.Lichen amyloidosus, Assist. Dr. Vesna Miličić
7.Dermatitis factitia (Pathomimia), Dr. Bojana Jovović Dagović.

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2013 Annual Report on the Activities of the Dermatovenereology Section of the Society of Physicians of Vojvodina of the Serbian Medical Society

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

During 2013, there were three meetings of the *Dermatovenereology Section* of the *Society of Physicians of Vojvodina.*

The first Section meeting was held on April 5, 2013, in Novi Sad at the premises of *Dermatovenereology Section* of the *Society of Physicians of Vojvodina* and its main topic was: Dermatology in elderly persons. Lectures were given by doctors of the *Dermatovenereology Clinic* of the *Clinical Center of Vojvodina.*

1. Dermatology in elderly persons, Assist. Prof. Zorica Gajinov
2. Skin therapy in elderly persons, Assist. Dr. Milica Subotić
3. Multiple cutaneous reticulohistiocytomas, Dr. Branislava Gajić
4. Malignant hemopathies and skin carcionomas – a case series, Dr. Tatjana Roš
5. Erythema annulare with hypereosinophilia – a diagnostic problem, Dr. Ljubinka Matović.

The second Section meeting was held on October 8, 2013, in Novi Sad at the Serbian Academy of Science and Arts (Novi Sad). It was a joint meeting of *Dermatovenereology Sections* of the *Society of Physicians of Vojvodina* (SPV) and *The Serbian Medical Society* (SMS). Its professional part was carried out by doctors of the *Clinic of Dermatovenereology Diseases* in Novi Sad, *Clinical Center of Vojvodina*. The main topic of this meeting was: New approaches to the treatment of dermatomycoses.

1. New approaches to the treatment of dermatomycoses, Prim. Dr. Siniša Tasić
2. Scabies - what is new?, Assist. Prof. Zoran Golušin
3. Ivermectin in human medicine, Assoc. Prof. Dr. Slobodan Stojanović
4. Systemic sclerosis – a case report, Assist. Prof. Zorica Gajinov
5. Mastocytosis – a case report, Assist. Dr. Aleksandra Petrović
6. DRESS syndrome – a case report, Assist. Dr. Ljuba Vujanović
7. Therapy with imiquimod 5% cream of squamous dysplasia in a patient with rosacea and polycythaemia rubra vera – a case report, Dr. Tatjana Roš
8. Porokeratosis of Mibelli successfully treated with imiquimod 5% cream, Dr. Branislava Gajić
9. Atopic dermatitis treatment – a commercial lecture, Assist. Dr. Aleksandra Petrović.

The third Section meeting was held on December 13, 2012, in Novi Sad at the premisses of *Dermatovenereology Section* of the *Society of Physicians of Vojvodina. The m*ain topic was: Quality of life in patients with psoriasis. Lectures were given by doctors of the *Dermatovenereology Clinic* of the *Clinical Center of Vojvodina.*

1. Quality of life in patients with psoriasis, Assist. Dr. Milana Ivkov-Simić
2. Lichen sclerosus et atrophicus – a case report, Prim. Dr. Bojana Spasić
3. Oedema Quincke – a case report and differential diagnosis, Dr. Svetlana Kovačić-Dukić
4. Aquarium granuloma – a case report, Dr. Jasmina Jovanović-Ljubičić
5. Treatment of actinic keratoses with imiquimod cream 5%, Assist. Dr. Milana Ivkov-Simić.

Participation of the members of the Section in other professional and scientific meetings

As it has been planned, over the past year our members actively participated in different education courses, conferences and meetings in our country and abroad. Thus, the 2nd/19th Congress of the Serbian Association of Dermatovenereologists that was held from 12-15 June 2013 in Sava Center, Belgrade, was attended by the following members of our Section:

a) Lectures by invitation:

Causes and symptoms of contact sensitivity

– a two decade research review of the Allergy Department of the Clinic of Dermatovenereology Diseases in Novi Sad, Prof. Marina Jovanović.
Treatment of genital warts – current concepts, Assist. Prof. Zoran Golušin.
b) Free communications:
Eccentric hyperpigmentation seen with dermoscope in thin melanomas and dysplastic naevi – a case series report, Assist. Dr. Milana Ivkov-Simić et al.
Unususal clinical and/or dermoscopic presentation of basal cell carcinoma, Dr. Tatjana Roš et al.
Risk factors for chronic venous insufficiency in women, Assist. Prof. Milan Matić et al.
Systemic lupus erythematosus and Erythema multiforme – a case report, Assist. Dr. Aleksandra Petrović et al.
Incidence of contact sensitivity in patients with chronic venous insufficiency, Assist. Dr. Ljuba Vujanović et al.
Surgical excision of skin cancers in dermatology settings in Serbia, Dr. Branislava Gajić et al.
Incontinentia pigmenti – a case report, Prim. Dr. Bojana Spasić et al.
Eosinophilic fasciitis, Assist. Prof. Zorica Gajinov et al.
Multiple seborrheic keratosis – Leser-Trelat sign, Dr. Svetlana Kovačević Dučić
c) Poster presentations
Segmental vitiligo associated with atopic dermatitis. Assist. Dr. Ljuba Vujanović et al.

Promotions and awards of Section members

Prof. Dr. Marina Jovanović was elected a full member of the Academy of Medical Sciences in Belgrade in May 2013.

Assist. Dr. Zoran Golušin was elected Assistant Professor at the Faculty of Medicine of the University of Novi Sad.

Assist. Dr. Ljuba Vujanović received an award for the best poster presentation - Segmental vitiligo associated with atopic dermatitis, from the Scientific Committee of the 2nd/19th Congress of the Serbian Association of Dermatovenereologists.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2014

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
8-10 April, 2014	Dubai World Dermatology & Laser Conference 2014, Dubai, United Arab Emirates	31 December, 2013	www.dubaiderma.com
11 April, 2014	Symposium on Autoimmune Bullous Diseases, Military Medical Academy, Belgrade, Serbia	No abstract submission	www.sld.org.rs
11 April, 2014	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Military Medical Academy, Belgrade, Serbia	No abstract submission	www.sld.org.rs
23-26 April, 2014	9th European Lupus Meeting, Athens, Greece	15 January, 2014	www.lupus2014.org
24-26 April, 2014	European Workshop on Skin Immune Mediated Inflammatory Diseases, Verona, Italy	16 February, 2014	www.simid2014.org
7-10 May, 2014	10th EADO Congress, Vilnius, Lithuania	1 February, 2014	www.eado2014.com
10 May, 2014	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Niš, ProlomBanja, Serbia	No abstract submission	www.sld.org.rs
22-25 May, 2014	11th EADV Spring Symposium, Belgrade, Serbia	17 January, 2014	www.eadvbelgrade2014.org
4-7 June, 2014	6th Summer Academy Practical and Aesthetic Medicine, Sofia, Bulgaria	No abstract submission	www.summerdermatology.com
9-12 June, 2014	2014 STD Prevention Conference In Collaboration with the 15th IUSTI World Congress and the 2nd Latin American IUSTI-ALACITS Congress, Atlanta, Georgia, USA	15 April, 2014	www.cdc.gov
5-7 June, 2014	23rd COSMODERM – Congress of the European Society of Cosmetic and Aesthetic Dermatology, Venice, Italy	No abstract submission	www.escad.org
12-14 June, 2014	12th European Congress of the Society for Pediatric Dermatology, Kiel, Germany	20 January, 2014	www.espd2014.com
14 June, 2014	12th Congress of European Society for Contact Dermatitis, Barcelona, Spain	20 January, 2014	www.escd2014.com
19-22 June, 2014	1st Regional Congress of Reconstructive Dermatology in 21st Century, Budva, Montenegro	1 February, 2014	www.antiage2014.net

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AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

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

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

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

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

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

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

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

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

1. Manuscript Preparation Guidelines

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

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

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

- A running title (limited to 30 characters);

- Authors' names and institutional affiliations;

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

1.2. Abstracts

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

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

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

1.3. A list of abbreviations

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

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.

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

- 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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