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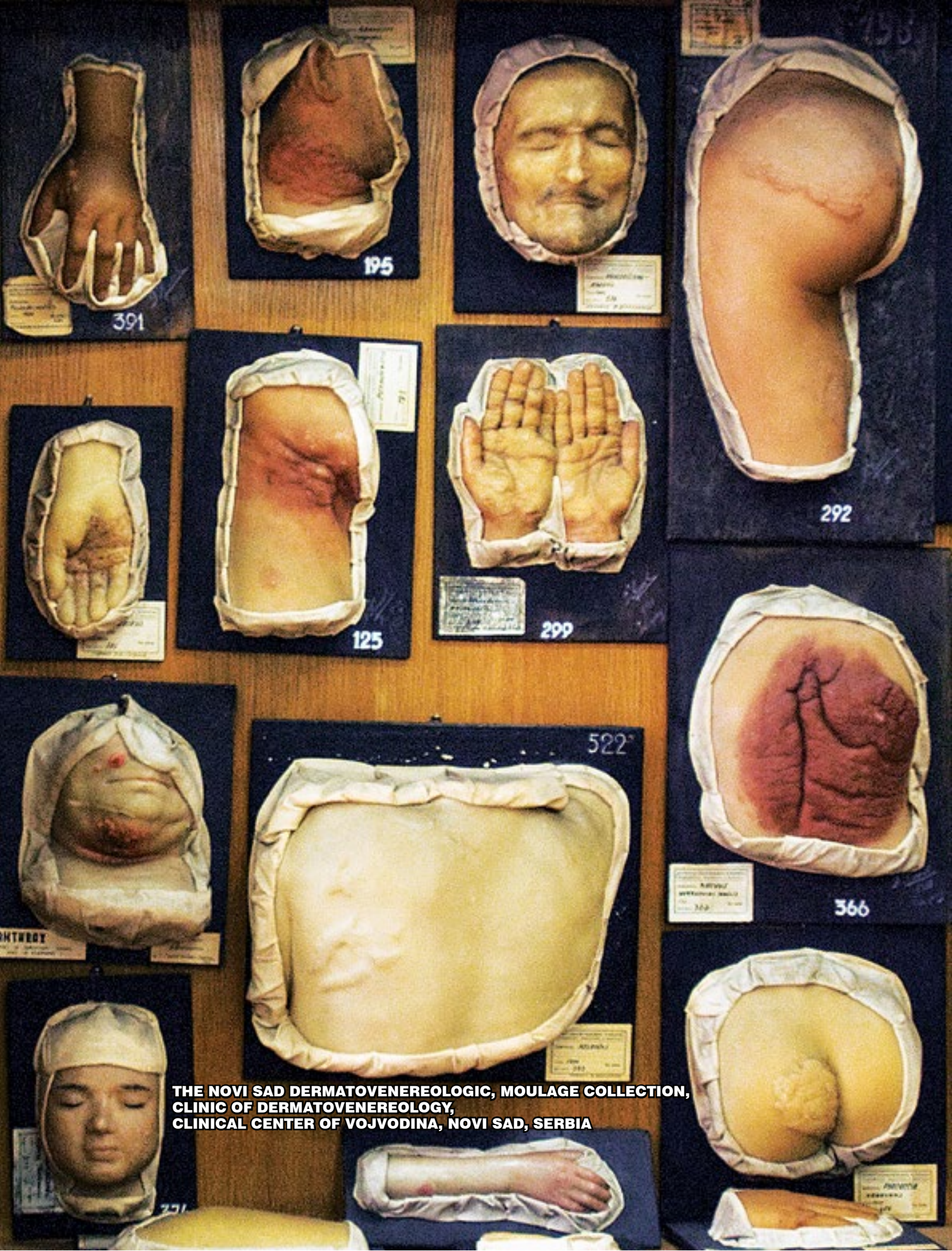

THE NOVI SAD DERMATOVENEREOLOGIC, MOULAGE COLLECTION,
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Widening competency gaps in the state of the art dermatology

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Dermatology is really unique among medical and surgical specialties today; it encompases a huge number of disorders originating either in the skin and subcutaneous tissue, or affecting the skin of other organs. Dermatologists are probably dealing with more diagnoses and disease entities than any other specialists in modern medical practice. Apart from deepening their knowledge about mechanisms of many skin diseases, including their genetic background, and of sophisticated novel medical treatment modalities, new exciting approaches to the management of many skin disorders found their way into the clinical practice of dermatology over the last decades. Some like to dub it procedural dermatology, others simply dermatologic surgery.

As a natural extension of these developments, a further step in the growth of dermatology has been marked by birth of cosmetic dermatology and dermatosurgery. The probable reasons for such changes in dermatology are manifold, but irrespective of the motives, now they must be respected. Though many colleagues, even fellow specialists, feel reluctant to think that a dermatologist should be using a scalpel or a liposuction cannula - it comes with the territory and the bell cannot be unrung. It is indisputable that dermatologists are best suited to treat skin disorders: inflammatory, cancerous or esthetic. Unfortunately, specialty training programs in Serbia and some neighboring countries are obviously short of courses improving knowledge and skills. Ever more competitive environment in the field of medicine forces us to move on.

In a way this is an appeal to all those who are in a position to have an impact on the creation of the specialty training curricula for dermatology, but mostly to those chairing university departments responsible for education. We should not let things slip through our fingers. At the prospects of restricted hospital resources for dermatology, we are threatened from two sides: lack of general medical knowledge and skills (so far considered to be internistics), and failure to master surgical skills pertinent to skin and subcutaneous tissue including phlebology. There are many countries, including Austria, Germany, Spain and UK, which may serve as a good example of how the things should be managed. However, strong opposition may be expected from many colleagues, especially surgeons and internists, but it should not be a reason to give up. The crucial first step for our Dermatological Society, along with chairwomen and chairmen of the University Departments is to include basic specialty training programs in dermatology. These programs should include a minimum of surgical skills (not only skin biopsy or simple excisions), while specialized dermatology centers should offer advanced training in surgical dermatology, phlebology, and some other areas (we actually used to, like allergology). Only a collective effort may make headway. International societies and many colleagues, experts in the field of dermatology, could give best assistance to this purpose. If we fail to react immediately, we simply risk losing a large part of our specialty taken over by others, from doctors to beauticians. It has alredy been happening over the last years. In the near future, we may witness specialists of physical medicine, plastic or general surgery, specialists of "anti-aging medicine", oncologists, pediatricians, rheumatologists and many others, to set standards of care and regulate our practice. It will, of course, be only our fault.

Though dermatosurgery seems to be the weakest point, many other areas, even those well established by our predecessors more than a century ago, may be lost for dermatology: just like allergology and phlebology. The former has already been officially transferred to internists as a subspecialty, and as such it may be lost for future generations of dermatologists.

In some countries of the former Yugoslavia, internists-allergologists have already found themselves best suited to diagnose and treat atopic and contact dermatitis! As a result of our passiveness, phlebology has been limited to conservative care of venous ulcers and a bit of diagnostics but crucial therapeutic aspects of chronic venous insufficiency like ambulatory phlebectomies, foam sclerotherapy or endovenous vein ablation techniques, are being done by vascular surgeons. Nevertheless, the first two procedures have been devised and practiced by dermatologists for decades, and the last modern techniques were mastered and promoted also by our colleagues (S. Schuller-Petrović, T. M. Proebstle, M. P. Goldman, M. Stücker...).

In efforts to reach the goal we may ask and get expert guidelines and advice from many of our foreign colleagues, especially those already having strong connections to our country. They will surely be willing to help.

I do hope that this appeal will find its way to all responsible for remedying our profession, by enabling young colleagues to be actually involved in areas of dermatology so far underrepresented, forgotten and even unregistered within our specialty and subspecialty curricula. With every year lost, we risk to allow others to confine us to "second-class" doctors, prescribing creams and lotions for ill-defined skin changes nobody wants to deal with. In other words, as a specialty, we are signing our own death warrant. The ball is now in the court of the *Serbian Association of Dermatovenereologists* and Heads of University Dermatology Departments. Let's hope they will succeed!

Optical properties of the human skin

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Abstract

Visual perception of human skin is determined by the light that reflects off the skin surface to retina and interpretation of these information by visual centers in the brain cortex. Skin has a partly translucent and turbid structure and visual perceptions depend on interactions between the light and structures of the skin surface and below it, through absorption, reflection and scattering. Light absorption by the skin depends on the composition, absorption spectra and amount (volume fraction) of chromophores. Subsurface scattering occurs within the skin layers: Rayleigh scattering (subcellular structures sized up to 1/10 of incident wavelength) and Mie scattering (collagen, melanosomes). Due to fluctuations of the refractive index within tissue components and intense scattering, the spatial distribution of light within the skin is diffuse. Skin images are created by the light that reflects off the skin after being color-modified by absorption and being scattered on the skin surface and internal skin structures.

Key words

Skin; Skin Absorption; Light; Optical Processes; Sunlight

Our perception of human skin is determined by the visible light that reflects off the skin surface to retina and interpretation of these information by visual centers in the brain cortex. Skin is partly a translucent medium, similar to various natural (ice, marble, wax, plant leaves) and artificial materials (plastics), and important visual information depend on interactions between the light and structures below the skin surface. That complexity of human skin makes painting realistic portraits a demanding artistic task. Optical properties which determine the skin appearance may be summarized through the process interaction between the light and the skin tissues - absorption, reflection and scattering.

Interaction between the skin and visible light

Visible light energy interacts with the skin by: absorption (chromophores absorb photon energy and transform it into heat), elastic scattering (light changes its path due to differences in refraction index within the skin), fluorescence (incident photons induce electron conversion into molecule, followed by emission of a photon of lower energy and longer wavelength) and inelastic scattering (photons lose energy to vibrational states followed by emission of lower energy photons of longer wavelength). Absorption and elastic scattering are the most prevalent interactions. Fluorescence occurs frequently, but with 10-100 times lower intensities.

High-power light sources of visible wavelengths (lasers with femtosecond pulses) may induce nonlinear processes (two-photon conversion, second harmonic generation) but these are not visible to the human eye, and require complex instruments to be analyzed.

Skin images humans see (by naked eye, photography ...), called diffuse reflectance images, are created by the light that reflects off the skin after being color-modified by absorption and being scattered on the skin surface and internal skin structures (1-3).

Absorption

Light absorption in the skin depends on the composition and amount of chromophores. Corneal layer is thin, corneal absorption within it is minimal, and transmission of light to deeper epidermal layers is uniform. In viable epidermis, a melanin is a natural light-absorbing chromophore, with broad absorption spectra (being the most intensive in the ultraviolet spectrum and shorter wavelengths). The intensity of absorption (mathematical term of epidermal absorption coefficient) directly depends on the volume fraction of epidermis that is occupied by melanosomes (1.3 - 43%). Jacques et al. reported that the volume fraction of melanin in the epidermis is 1 to 3% for light-skinned Caucasians, 11 to 16% for Mediterranean types, and 18 – 43% for darkly pigmented Africans (4, 5).

The dermis consists of two layers network of connective tissue fibers, and blood vessels. Hemoglobin is the main dermal chromophore. Absorption of both oxyhemoglobin and deoxy-hemoglobin have absorption peaks in blue (400-420 μm), and green-yellow range (540-577 μm), and decrease gradually for longer wavelengths. Deoxy-hemoglobin has its highest absorption peak at 420 μm, and a second peak at 580 μm. Oxy-hemoglobin shows its highest absorption peak at 410 μm, and two secondary peaks at 550 - 600 μm range. The intensity of absoprtion directly depends on the volume fraction of tissue occupied by hemoglobin (0.2-7%). The blood volume fraction in the cutaneous blood content (in the superficial plexus about 100 – 200 μm from the surface) is about 2-5%, while in other parts of the dermis the volume fraction is much lower (2, 6).

Other blood derived pigments, bilirubin and carotenoids, are responsible for yellowish and olive hue in basic skin tan. Beta-carotene and lycopene have absorption peaks at 488 and 515 μm, and bilirubin at 460 μm (7).

Absorption of visible light in subcutis is neglible; considering the white color of adipose tissue, most of the light that reaches the subcutis is reemitted into the dermis (6).

Light absorption by other skin structures is not contributing to visual appearance, due to absorption maxima being out of the visual spectrum. Epidermal nucleic acids (peak at 260 μm), urocanic acid (peak at 277 μm), keratin (peak approximately at 280 μm) absorb UV radiation. Water is absorbed in the infrared spectrum (peak approximately at 980 μm) and the thermal effect is mediated by water content of tissues. Dermal proteins are absorbed near UV, collagen in the visible and near the infra-red spectra.

Coefficient of absorption

Absorption coefficient of the human skin (determined in vivo) is wavelength dependent, and in agreement with in-vitro determined values for various chromophores. Maximal absorption coefficient is at around 500 μm, with a twofold decrease if wavelengths increase from 500 to 600 μm, and it corresponds to melanin and hemoglobin absorption maxima in this region. With further wavelength increase, from 600 to 800 μm, the absorption coefficient decreases smoothly. The absorption spectra of darker skin types (Fitzpatrick's V-VI types) have a greater slope in the visual wavelength region, compared to lighter skin types (I-II and III-IV), being the consequence of differences in melanin concentrations in various skin types, assuming other chromophore concentrations are similar. At wavelengths longer than 900nm (infrared spectra), the absorption coefficients of three skin type groups have almost the same magnitude and a characteristic prominent absorption peak induced by water absorption at 980 μm (8). In conclusion, at wavelengths shorter than 600 μm, absorption by melanin and hemoglobin is dominant, while at 600-800 μm, the reflectance spectral features are mainly affected by scattering.

Reflection

Reflection of light on the skin surface occurs on the account of differences in refraction indices between the air (1,0) and the corneal layer (1,45). Fresnel's equation illustrates proportions of light that is reflected and refracted (transmitted towards deeper layers) on air-skin interface, as functions of incident angle of light and refraction indices of medium from which the light beam approaches the skin (air usually) and medium that further transmits the light (incident and transmissive medium). When the incident angle is close to normal (< 40°) about 5% of light is directly reflected from the corneal layer surface, and the rest 95% enters the epidermis. The reflected light is not

interacted with the interior of the skin and is not color-modified by skin chromophores. The increase of the incident angle of light increases the amount of light reflected from the skin surface. Presence of sebum smoothes the roughness of the skin surface, and due to the fact that a higher refractive index (1.5) increases the amount of light reflected off the air-sebum interface, it accentuates the appearance of shine (9).

Scattering

Scattering is a dominant type of interaction of visible and near infra-red light spectra with tissues, being 100-1000 times stronger than absorption (10). Scattering is a deflection of light beams from a straight trajectory caused by microscopic non-uniformities in the medium through which the light passes (scattering particles), and fluctuations of refractive index. Type and intensity of scattering depends on the size of the scattering particles in relation to the wavelength of the incoming light.

Elastic scattering

Elastic scattering refers to processes where photons of incident and scattered light have the same energy (wavelength), whereas Rayleigh and Mie models of elastic scattering are applied for light scattering in tissues.

Rayleigh scattering occurs on particles much smaller than incident wavelength (up to 1/10 of incident wavelength size). Oscillating electromagnetic field of incident radiation induces the electron distribution of a molecule (scattering particle) to oscillate, inducing point dipole in the molecule, while light is scattered uniformly in all directions. According to Rayleigh theory, scattering probability is inversely proportional to the fourth power of the wavelength of the scattered light, therefore shorter wavelengths are scattered more efficiently than longer wavelengths.

Mie scattering occurs when the scattering particles are of similar size as the wavelength of light. These large particles do not act as dipoles, and intra-particle interference causes an angular dependent scattering pattern. It depends on particle size and shape (spherical particles); the intensity of forward scattering (in the same direction as the incident light) is in correlation with these parameters.

Illustrative didactic examples for Mie and Rayleigh scattering are optical phenomena in atmosphere: Rayleigh scattering is responsible for blue sky (shorter blue wavelengths are scattered more efficiently by small particles in the air than longer wavelengths), and Mie scattering for white color of clouds (due to water droplets) (11, 12).

Surface and subsurface scattering of light in the skin

In human skin, scattering has two mayor components: surface and subsurface scattering. Surface scattering is influenced by irregularities in the corneal layer (wrinkles, skin dehydration), and it is similar to reflection.

Subsurface scattering within the skin occurs in cell membranes and corpuscles, keratohyaline granules, melanosomes, cellular organelle, mitochondria, nuclei, extracellular lipid droplets, protein aggregates, and collagen fibers. Corneal layer and epidermis are characterized as forward scattering media, due to the orientation of keratin fibrils and Mie scattering in cellular structures of similar size and wavelength (organelle, melanosomes) (13). Large cylindrical collagen fibers in the reticular dermis are responsible for Mie scattering that is directed forward, while Rayleigh scattering occurs on smaller collagen fibrils in papillary dermis and other microstructures. Light is scattered many times within the dermis, until finally being absorbed or transmitted to the next layer, which means that spatial distribution of light scattered within the dermis soon becomes diffuse, and tissues with intense scattering seem turbid (14, 15).

Light scatterers in the skin

Parameters that affect the scattering properties of tissues are tissue morphology (size of organelles and cells in relation to the wavelength of incident light, which affect the angular distribution of the scattered light), and biochemistry (refraction index is determined by biochemical characteristics of tissues). Great differences in the refractive index of a cell component and its surrounding will result in increased scattering (binary fluctuation of refractive index).

The matter surrounding the scatterers (intercellular liquid and cytoplasm, ground substance) is composed mainly of water with salts and organic components, and the refractive index is 1.35–1.37.

The scattering particles (organelles, protein fibrils, membranes, protein globules) have a higher density of proteins and lipids in comparison with the ground substance and thus a greater index of refraction (1.39–1.47).

Collagen fibers are the main scatterers in the stroma; due to their fibrilar structure, high refractive index (axial 1.32-1,45, radial 1.40-1.61), scattering in the stroma is much more abundant than in the epithelial layers (3, 17).

Melanin has a high index of refraction (1.7) compared with the surrounding cell components; the size of melanosomes is 100 μm – 1000 μm. Large increase in melanin scattering has been observed in vitro (18), but in vivo, no significant differences have been detected between scattering properties of melanocytic nevus and healthy skin. This suggests that the primary optical function of melanin is absorption, and that Rayleigh scattering in melanin is negligible in comparison with melanin absorption and scattering in other microstructures of the skin (19).

Penetration of human skin by visible light

Visible light (400-760 μm) goes through intense absorption and scattering within the skin, and that attenuation of incident light is limiting the depth to which visible radiation may penetrate. At wavelengths shorter than 600 nm, light absorption by hemoglobin and melanin is dominant, while skin scattering is attributed to small Rayleigh scatterers, such as melanin dust and structural cell components, much smaller (<300 μm) than the wavelength. At visible wavelengths, longer than 600 μm, absorption decreases; Mie scattering occurs on large collagen and elastin bundles, sized several μm, being intensely directed forward (following the direction of incident light towards deeper skin layers) (20, 8). With longer wavelengths (700 to 1300 μm) scattering in the skin decreases; due to low scattering these wavelengths have the greatest penetration depth into the skin, and are referred to as the optical window. Light of longer wavelength is absorbed by water and does not penetrate deeply into skin.

The penetration depth of light into the skin is defined as the depth at which the incident intensity is attenuated to a certain level outside the skin; it is an indication of the rate at which the intensity of the incident light is attenuated in the tissue (1, 21).

Polarized light scattering in the skin

Scattered light carries important information about the morphology of tissues. Upon scattering, distribution and direction of light changes, and methods using polarized light can more precisely determine scattering characteristics of the medium. Optical activity of molecules determines the speed and level of polarized light randomization. Dermal collagen has a property of birefringence (double refraction of polarized light), dependent on orientation of fibers in relation to vectors of polarization of incident light, and both birefringent and the scattering effects can change the polarization state of light. Information about the structure of a tissue and the birefringence of its components can be extracted from the registered depolarization degree of initially polarized light. Polarization properties of light reflected from tissues can be used as a selector of photons coming from different depths in the tissue. Such polarization gating can provide novel contrast mechanisms for tissue imaging and spectroscopy (22-24). Human eye is not sensitive to the polarization characteristics of light, therefore complex instruments are necessary for such precise measurements.

Light passing through the skin

Pathway of light through the skin is presented in Figure 1. On the surface of the corneal layer 4-7% of light is being reflected; the remaining light enters and traverses the corneal layer, being scattered only by degraded melanosomes (melanin dust) in flattened corneal cells. The light then enters the viable epidermis where it is absorbed and scattered by the epidermal melanin pigment. The direction of travel of the light is changed whenever a change in the index of refraction occurs in its path of travel. Cell membranes and organelles have slightly different indices of refraction than the bulk index of the epidermis, and therefore cause slight changes in the direction of travel through the corneal layer; due to scattering in the epidermal layers, it is directed forward into dermis. A proportion of light is absorbed by melanin, in correlation with the volume fraction of tissue occupied by melanosomes. Upon entering the dermis, light is scattered due to Rayleigh scattering in small collagen fibrils in the

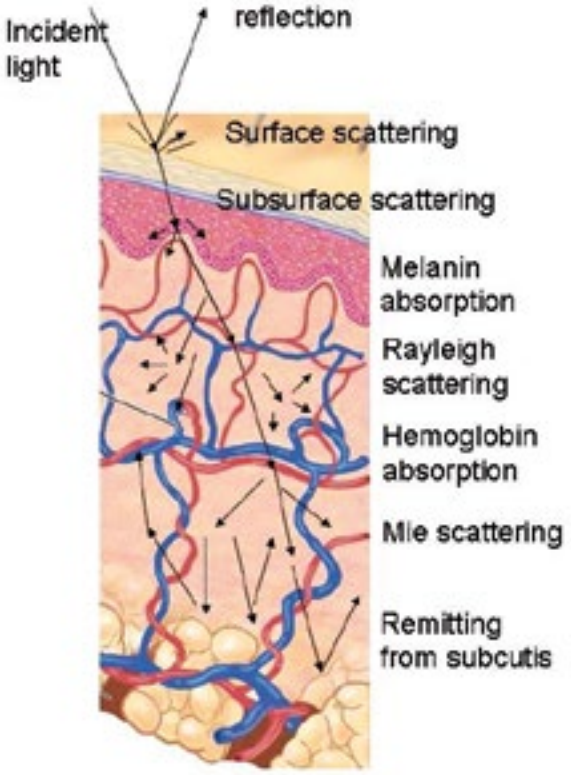

Figure 1. Optical pathway of visible light through the skin

papillary dermis, while light scattered backward enters epidermis again, scatters preferentially towards the surface of the skin and out of it. Upon entering reticular dermis the light scatters in larger collagen fibers (Mie scattering) directing forward to deeper layers, subcutis. Therefore, light reemitted from the reticular layer is thus considered negligible due to the highly forward-directed Mie scattering. A proportion of light in dermis is absorbed by hemoglobin, proportionally to its volume fraction in the tissue.

Upon Mie scattering, light in reticular dermis reaches subcutis and is largely reemitted back and then traverses the hemoglobin and melanin filter and after that it is again reflected and scattered by the air interface out of the skin. The light we detect (photograph) has traveled twice through the melanin and the hemoglobin filters.

Conclusion

When describing the state of skin we need to characterize the surface features (contours, scars, fine texture, surface appearance) as well as the subsurface features (erythema, pigmentation and dermal collagen scattering) that contribute to the appearance of the skin (25). Understanding and modeling optical properties of the skin is a dynamic field of investigation, driven by various medical and industrial needs (diagnostic or photo-therapeutic use in medicine, cosmetic science, entertainment industry, computer graphics, computer vision etc.). Skin has irregular morphology, with follicles and glands, layered structures, and exhibits anisotropic behavior. Therefore all models of light interaction with the skin are simplified, only representing some important features. More comprehensive models of skin optics are still necessary.

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Optičke osobine ljudske kože

Sažetak

Vizuelni utisak o ljudskoj koži potiče od vidljivog svetla, koje sa površine kože dolazi do mrežnjače oka, i interpretacije tih informacija u moždanim centrima za vid. Koža je delimično translucentna mutna sredina; vizuelna informacija potiče od interakcija svetla i struktura površine i ispod nje, putem procesa apsorpcije, refleksije i rasipanja svetlosti. Apsorpciju svetlosti u koži određuju sastav, apsorpcioni spektar i količina (volumen tkivne frakcije) hromofora. Rasipanje unutar tkiva ima dve glavne komponente koje rasipaju svetlost po *Rayleigh* modelu (sitnije čestice) i *Mie* modelu (krupnije strukture kolagena, elastina, melanozomi). Usled velikih fluktuacija u indeksu prelamanja unutar tkiva, i intenzivnog rasipanja, prostorna distribucija svetla u koži je difuzna. Slika kože koju ljudi registruju posledica je svetlosti koja izlazi iz kože, nakon modifikacije boje (apsorpcija) i rasipanja na površini kože i strukturama unutar nje.

Ključne reči

Koža; Apsorpcija kože; Svetlo; Optički Procesi; Sunčeva svetlost

Chronic bullous disease of childhood – A case report

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Abstract

Linear IgA bullous dermatosis is a chronic, acquired, autoimmune subepidermal vesiculobullous disease. Both children and adults are affected. It is characterized by direct immunofluorescence findings of linear immunoglobulins class A (IgA) deposits along the dermal-epidermal junction (basement membrane zone). In children, the disease is commonly referred to as chronic bullous disease of childhood and it mostly affects children between 2 and 5 years.

The onset of the disease is acute; the first episode is the most severe, while recurrences tend to wax and wane in severity and last till puberty or even longer. Diaminodiphenylsulfone is the treatment of choice, although systemic corticosteroids are reported to be very effective as well.

We report a 3-year-old boy with a vesiculobullous eruption which developed one week following administration of cephalexin for upper respiratory infection. He was referred to our Clinic from other health institutions as treatment failure for suspected *strophulus* or *impetigo bullosus*. On admission, the patient had fever and numerous vesiculobullous and erosive lesions distributed on the face and trunk. After immunohistological verification, the treatment with prednisone 25 mg/d was introduced, due to rapid progression of the disease and the fact that diaminodiphenylsulfone was not available. Improvement occurred after 2 weeks, so the dose was carefully tapered, taking into account the possibility of adrenal suppression. The medication was completely excluded within the next three months. No serious side effects were observed, except transitory hirsutism. The patient has had no relapses over the last 20 months of clinical follow-up.

Key words

Child, Preschool; Skin Diseases, Vesiculobullous; Cephalexin; Autoimmune Diseases; Chronic Disease; Disease Progression

Linear IgA bullous dermatosis (LABD) is an acquired, autoimmune subepidermal vesiculobullous disease affecting both children and adults. Historically, it has often been referred to as chronic bullous dermatosis of childhood (CBDC) (1). The disease is rare, with an estimated annual incidence of 1 per 500,000 children in the United Kingdom (2). The onset is usually between 2 and 5 years of age. Typically, it is characterized by large, often pruritic blisters arranged in a rosette fashion. In children, lesions commonly involve the perioral region, upper inner thighs, lower abdomen and the anogenital area with frequent involvement of the perineum. The disease is often misdiagnosed with bullous impetigo. Oral lesions are common, presenting in 50% of patients. Clinical course of the disease is usually benign and often self-limiting (3).

Case report

In January 2009, othertwise healthy 3-year-old boy, was admitted to the University Clinic of Dermatology in Skopje (Republic of Macedonia), with a two-week-history of widespread itchy blistering eruptions confined to the skin. The first lesions developed one week following oral intake of cephalexin for infection of the upper respiratory tract. Skin lesions had originally been thought to be due to *bullous impetigo* or *strophulus*. Systemic and topical antibiotic therapy, as well as antihistamines, did not produce any effect and the disease progressed.

The boy was systemically well, normally developed for his age. Skin examination revealed multiple vesicles and tense blisters arising from erythematous skin on his face (Figure 1), forearms and lower legs (Figure 2). The vesicles and blisters were seen at the edge of annular or polycyclic lesions, the appearance of which has been described as the "string of beads" sign (Figure 3). Some of them were grouped in a herpetiform pattern, described as the "cluster of jewels" sign. Within one week new blisters developed on the lower trunk, buttocks, thighs, groins and perineal surfaces. Large confluent lesions and extensive denuded surfaces were present on the back. (Figure 4). Ophthalmologic examination revealed conjunctivitis. Each flare of new lesions was associated with fever and leukocytosis. The oral mucosa was not involved.

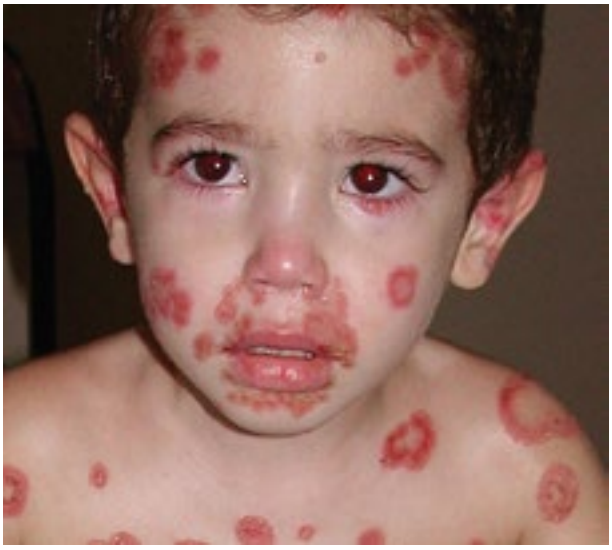

Figure 1. Facial lesions resembling bullous impetigo

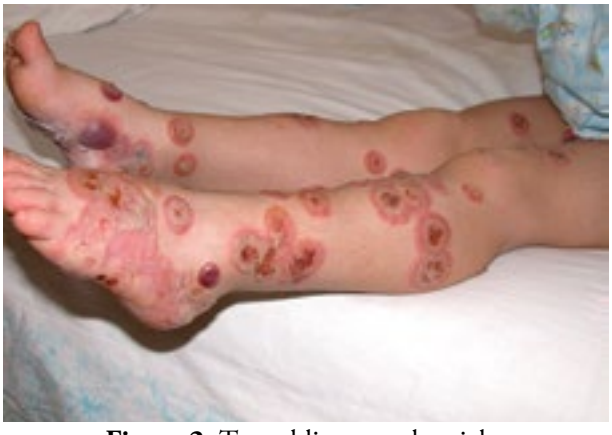

Figure 2. Tense blisters and vesicles

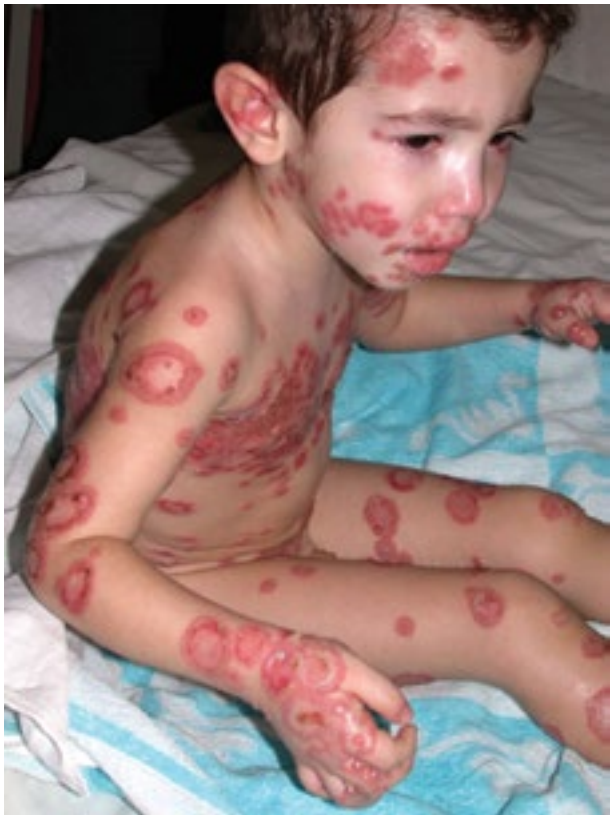

Figure 3. New blisters around old lesions

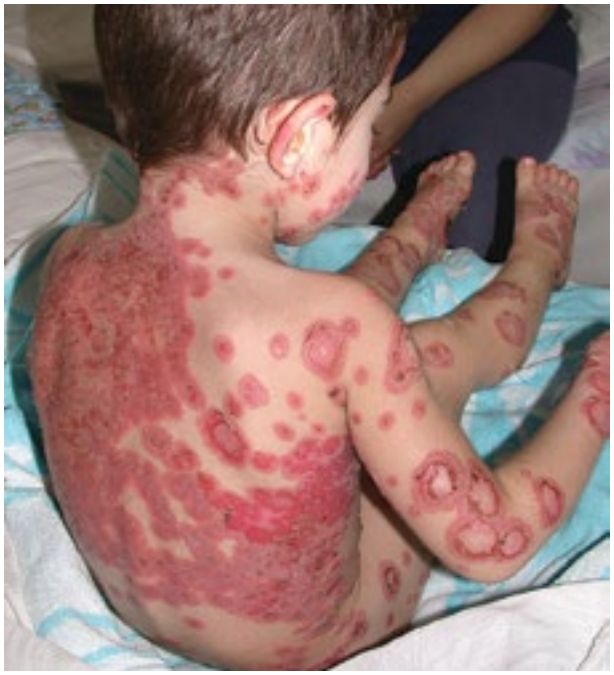

Figure 4. Extensive denuded surfaces on the back caused by peripheral extension and confluence of lesions

Laboratory investigations revealed the following abnormalities: white blood cell count was elevated to 22 x 10^9/L followed by increase up to 40 x 10^9/L, with neutrophylia and thrombocytosis. The skin swab was positive for *Staphylococcus aureus*, while hemoculture was negative.

Histopathology revealed subepidermal blistering (Figure 5) and immunohistochemical examinations demonstrated linear deposition of IgA along the basement membrane zone of the epidermis (Figure 6). The diagnosis of chronic bullous dermatosis of childhood (CBDC) was confirmed on the basis of clinical, histological, and immunofluorescence findings.

The patient was initially treated with prednisolone 25 mg/daily, and concomitant antibiotic treatment for *Staphylococcus aureus* infection. Treatment with steroids was indicated due to the widespread disease, and current deficiency of diaminodiphenylsulfone at the Clinic. After 2 weeks, the initial dose of prednisolone was reduced to 15mg/day. Skin lesions improved (Figure 7), although during the first two months, occurrence of new vesicles and itchy erythematous patches was observed (Figure 8). After 4 months, the maintenance therapy was discontinued, and the patient has had no relapses over the last year. No side effects were observed.

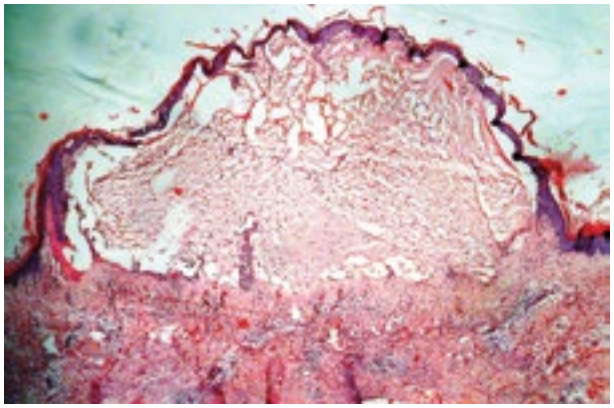

Figure 5. H&E-stained section showing subepidermal bulla (hematoxylin and eosin, x100)

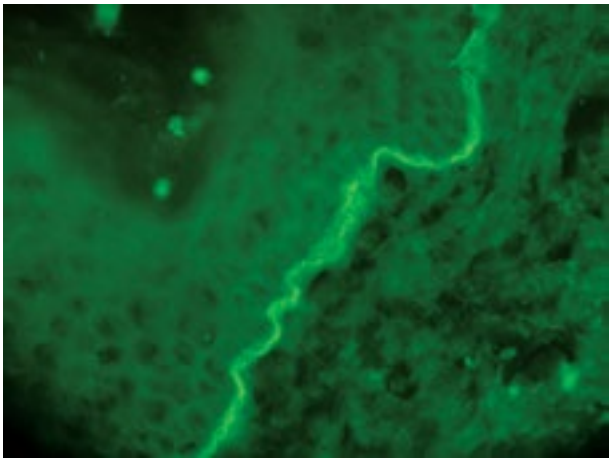

Figure 6. Direct immunofluorescence showing linear IgA deposits along dermal-epidermal junction

Discussion

In 1975, based on immunopathological findings, Chorzelski & Jablonska first suggested that linear IgA bullous dermatosis (LABD) represents a separate entity (4). On a molecular basis, some authors consider CBDC and LABD the same disease, only occurring in different age groups (2). The autoantibodies found in the diseased are IgA, directed against the certain number of different target antigens within the adhesion complex. They include two that may be

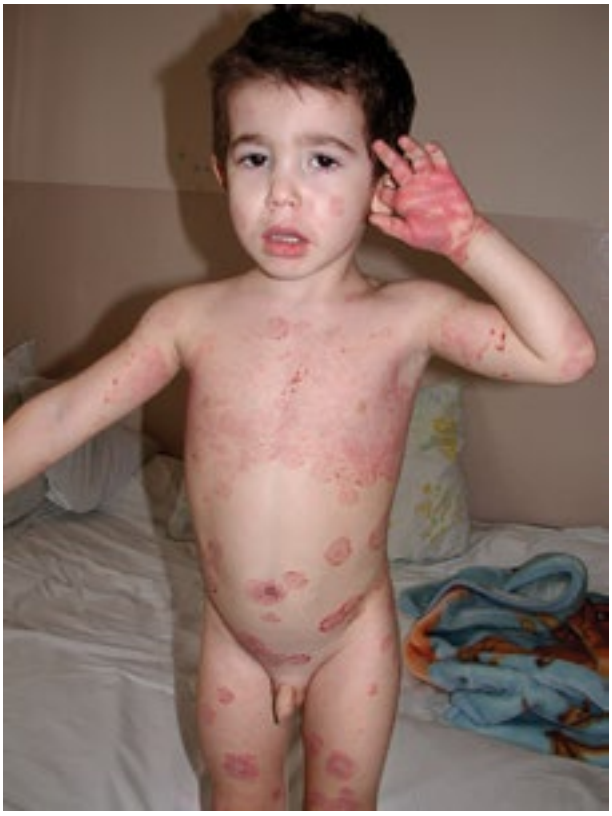

Figure 7. Improvement after 2 weeks

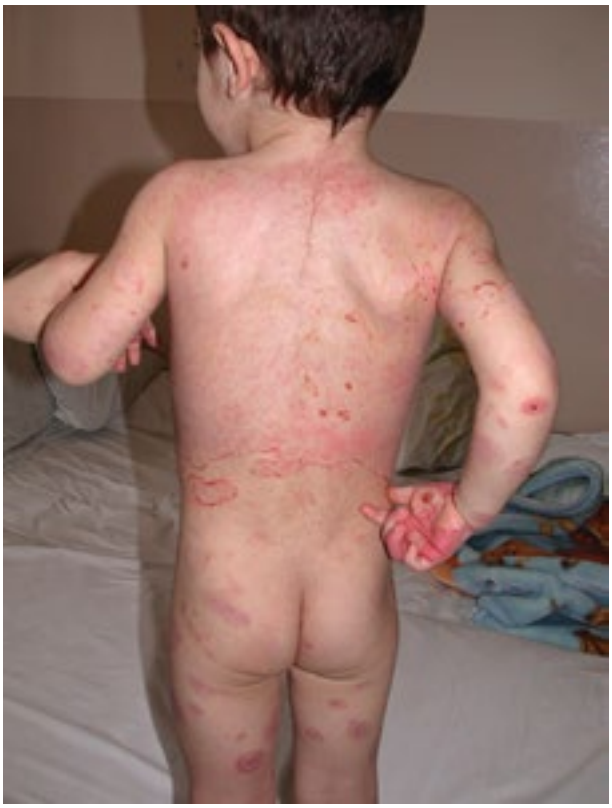

Figure 8. Improvement after 2 weeks

unique to linear IgA disease with molecular weights of 285 kD and 97/120 kD, bullous pemphigoid antigens BP 230 and BP 180 antigens, collagen VII, the anchoring fibril component, as well as some antigens uncharacterized yet (5-7).

Three distinct clinical lesions characterize this disease: large tense blisters as seen in bullous pemphigoid, grouped vesicles as seen in dermatitis herpetiformis, and lesions similar to those seen in erythema multiforme. One lesion type may predominate, or a combination of the tree may be found. Bullae arise on normal or inflamed skin; they are often arranged in a rosette manner; as new blisters cluster around the older lesions, they form a "cluster of jewels" sign. Healing is rapid, with hyperpigmentation, but without scarring (1).

Our patient developed polymorphic itchy lesions, single or grouped vesicles and bullae, showing "string of beads" patterns. He did not have mucosal involvement. The clinical features included: abrupt onset of the disease, presence of great number of vesicles and blisters, extensive denuded surfaces associated with fever and elevated number of leukocytes in the peripheral blood. Immunofluorescence findings confirmed the diagnosis and provided its differentiation from multiple causes of blistering in children. The treatment of CBDC was directed towards reducing the frequency and severity of outbreaks.

The disease is very responsive to sulfapyridine (35 mg/kg PO bid; not over 100 mg/kg/d) or diaminodiphenylsulfone (1-2 mg/kg PO qd initial; not over 3-4 mg/kg/d).

CBDC is also well corticosteroid-responsive. Remissions are usually induced within 6 - 12 months (2). Patients may still develop occasional bullae, but relapses are uncommon (1). Our patient responded well to systemic corticosteroid therapy with prednisolon and improvement was observed in 2 weeks.

The prognosis of CBDC is generally favorable. While recent reports have described a subset of patients with episodic recurrences that persisted until adulthood, in most patients eruptions usually resolve between 3 and 5 years (8).

Mild single vesicles and blisters or erythematous infiltrates were observed in the first 2 months after initiating the treatment. After 20 month-follow-up, we did not observe any recurrences. Our patient developed initial skin eruptions one week after receiving cefalexin for upper respiratory infection.

Cases of linear IgA dermatosis associated with gastrointestinal diseases, autoimmune diseases, malignancy and infections have been reported (9). The significance of these associations has yet to be determined, but they may play a role in the initial stimulation of the IgA mucosal immune system. On the other side, reports have shown that as many as two-thirds of all occurrences may be drug-induced. The most frequently implicated drugs were antibiotics, especially vancomycin, penicillin, amoxicillin-clavulanate, cephalosporin, sulfonamides, sulfamethoxazole/trimethoprim, non-steroidal anti-inflammatory drugs such as diclofenac, naproxen, piroxicam, antihypertensive drugs such as captopril, angiotensin converting enzyme inhibitor (ACE), and diuretics (10).

However, in contrast to adult patients, the role of possible precipitating factors in childhood cases of LABD, has been less commonly discussed in the

literature and only isolated reports on associations with underlying conditions exist. A 2-year-old boy developed LABD during amoxicillin-clavulonic acid therapy (11). Polat et al., published a case of a 5-year-old boy with acute lymphoblastic leukemia in remission, in whom CBDC developed after treatment with trimethoprim/sulfamethoxazole (12).

Conclusion

In conclusion, we present a 3-year-old boy in whom diagnosis of chronic bullous dermatosis of childhood was established according to clinical, histopathological and direct immunofluorescence findings. The patient developed initial skin eruptions one week after receiving cephalexin for upper respiratory infection. The clinical follow-up confirmed a benign nature of the disease. A follow-up of 20 months after discontinuation of treatment showed neither recurrence of the disease nor side effects of corticosteroid treatment.

As far as the world literature is concerned, this is the 3rd report on chronic bullous dermatosis of childhood associated with drug intake.

Abbreviations

ACE – Angiotensin-converting enzyme
BP - Bullous pemphigoid
IgA - Immunoglobulin class A
LABD - Linear IgA bullous dermatosis
CBDC - Chronic bullous dermatosis of childhood

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Hronična bulozna bolest kod dece – prikaz slučaja

Sažetak

Uvod: Linearna IgA bulozna dermatoza (LABD) je hronična, autoimuna, subepidermalna bulozna dermatoza, koja se javlja kod odraslih i kod dece. Za djagnozu odlučujući je nalaz linearnih depozita IgA u zoni bazalne membrane dokazanih direktnim imunofluorescentnim pregledom (DIF) perilezionekože ili sluznice. Bolest je u dečjem uzrastu poznata i pod nazivom hronične bulozne bolesti dece (HBBD). Javlja se najčešće između druge i pete godine života. Bolest je retka, sa godišnjom incidencijom u Velikoj Britaniji od 1/500 000 dece. Tipična klinička slika je pojava napetih bula na neizmenjenoj ili eritematoznoj koži. Pojava novih mehurova na periferiji starih, daje izgled poznat kao „gomile dragulja". Predilekcione regije su perioralno područje, perineum i donji deo trbuha. Kod 50% bolesnika lezije su oralno smeštene. Početak bolesti je akutan, prva epizoda je najteža a recidivi su uobičajeno sa lakšom kliničkom slikom. Bolest kod dece najčešće spontano prolazi posle 3 do 5 godina, iako su opisani slučajevi perzistencije bolesti i nakon puberteta.
Prikaz slučaja: Prikazujemo trogodišnjeg dečaka sa

vezikulobuloznom erupcijom, koja se javila nedelju dana po prekidu terapije infekcije gornjih respiratornih puteva cefaleksinom. Na našoj Klinici je hospitalizovan januara 2009. godine, posle dvonedeljnog neuspešnog lečenja u drugim zdravstvenim ustanovama, kao bulozni strofulus i impetigo sa sistemskim i lokalnim antibioticima i antihistaminicima.

Objektivni status na koži i vidljivim sluznicama: Pregled je pokazao brojne vezikule i bule u predelu lica, perineuma, podlaktica i potkolenica. Prvih dana hospitalizacije, nove lezije su se javile u području ekstremiteta i tela. Promene su bile polimorfnog karaktera: veliki mehurovi, vezikule herpetiformnog i anularnog rasporeda, lezije sa izgledom „gomile dragulja". U predelu leđa, perifernim širenjem i konfluiranjem lezija, nastupila je denudacija velike površine. Sluznice nisu bile zahvaćene. Erupcija novih promena je bila praćena pruritusom i povišenom temperaturom.

Laboratorijske analize: Laboratorijska ispitivanja krvi su otkrila leukocitozu, neutrofiliju, eozinofiliju i trombocitozu. U brisu kože je identifikovan *Staphylococcus aureus*. Hemokultura je bila negativna.

Patohistološke analize: Svetlosnom mikroskopskopijom bioptičkog uzorka obolele kože, rutinski bojenim H&E, otkriven je subepidermalni rascep. Imunofluorescentnom mikroskopijom je pomoću direktne imunofluorescencije utvrđeno postojanje linearnih depozita imunoglobulina klase A – IgA, u zoni bazalne membrane. Na osnovu ovih nalaza, postavljena je dijagnoza HBBD.

Terapija: Zbog nedostupnosti diamunodifenilsullfona, lečenje je započeto prednizolonom, u dozi od 25 mg/dnevno. Posle dve nedelje nastupila je morbostaza, pa je doza smanjena na 15 mg/dnevno. Dalja redukcija doze bila je pažljiva, sa ukupnim trajanjem terapije od 4 meseca. U tom periodu bilo je nekoliko erupcija solitarnih vezikula i pruritičnih eritema, koji su spontano prolazili za 2-3 dana. Ove epizode nisu bile pridružene temperaturom i leukocitozom. 20 meseci posle prekda terapije nije registrovan recidiv. Nije bilo neželjenih efekata terapije, osim tranzitornog hirzutizma.

Diskusija: Uprkos izvesnim razlikama u kliničkoj slici i toku bolesti, većina autora smatra da su LABD i CBBD jedan isti entitet. U dijagnozi ovog oboljenja presudan je nalaz direktne imunofluorescencije koji omogućava razlikovanje HBBD od drugih buloznih dermatoza dečjeg uzrasta. Tri tipa lezija su karakteristična za ovu bolest: velike tenzione bule kao kod pemfigoida; grupisane vezikule kao kod herpetiformnog dermatitisa; lezije slične multiformnom eritemu. Kod našeg bolesnika lezije su bile polimorfne, pruritične, bez zahvatanja mukoze. Lek izbora za HBBD je diamunodifenilsullfon (1-2 mg/kg/d). U našem slučaju, zbog nedostupnosti ovog leka, bili smo primorani da terapiju započnemo prednizolonom. Morbostaza je nastupila za dve nedelje, a ukupna terapija je trajala 4 meseca. Jedan interesantan momenat našeg slučaja je moguća povezanost infekcije (akutni rinofaringit) i leka (cefaleksin) sa pojavom bolesti. Podaci iz literature prikazuju da LABD-odraslih može biti povezana sa bolestima gastrointestinalnog trakta, autoimunim bolestima, malignitetima i infekcija. Pretpostavlja se da ova stanja mogu da stimulišu IgA mukozalni imuni sistem. Postoje mnogobrojni izvestaji o povezanosti bolesti sa lekovima (vankomicin, penicilini, cefalosporini, kaptopril, naproksen, diklofenak, fenitoin). Za razliku od odraslih, kod dece, lek kao mogući okidač je opisan u dva slučajeva.

Zaključak: Prikazujemo slučaj hronične bulozne bolesti kod deteta koji, prema nama dostupnim podacima iz literature, predstavlja treći do sada u svetu objavljen slučaj u kome je lek imao ulogu mogućeg okidača.

Ključne reči

Predškolsko dete; Vezikulobulozne bolesti kože; Cefaleksin; Autoimune bolesti; Hronična bolest; Tok bolesti

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Risk of a second cutaneous primary melanoma and basal cell carcinoma in patients with a previous primary diagnosis of melanoma: true impact of dermoscopy follow-up in the identification of high-risk persons

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Abstract

In clinical practice, positive personal history is considered to be as an indication of increased melanoma risk. The thickness of melanoma (Breslow Index) is the most important independent predicting factor of survival for stage I patients. We present a case of a second primary melanoma and basal cell carcinoma in a 48-year-old female patient with personal history of a superficial spreading melanoma located at the dorsal trunk with Breslow's thickness of 0,5 mm and Clark's II (stage IA) excised a year before, and a family background of melanoma. We would like to emphasize the benefits of digital dermatoscopy as well as teledermoscopy, and new teledermatology web services, in the follow-up of high-risk patients.

Key words

Melanoma; Neoplasms, Second Primary; Dermoscopy; Lymph Nodes; Carcinoma, Basal Cell; Telemedicine; Follow-up Studies

Telemedicine, or distance medicine, represents a rapidly growing sector in clinical medicine. It is the process of using audio and video communications to convey or exchange medical for information the purpose of consulting and sometimes for remote medical procedures or examinations. Telemedicine is practiced on the basis of two concepts: real time (videoconferences) and store-and-forward, that is synchronous and asynchronous telemedicine (1). In teledermatology the second concept is mainly used because it is less time-consuming and has lower costs (2).

Dermoscopy (also known as epiluminescence microscopy, dermatoscopy, and amplified surface microscopy) is an *in-vivo* diagnostic procedure used for visualization of skin structures that cannot be seen by the naked eye and for classification of lesions as melanocytic or non-melanocytic (3). The main role of dermoscopy is early detection of melanoma, vital for its proper treatment (4,5).

Case report

We present a 48-year-old female patient with personal history of superficial spreading melanoma located at the dorsal trunk with Breslow thickness of 0,5 mm and Clark level II (stage IA) excised a year before, and a family background of melanoma. The patient was admitted due to a new pigmented lesion on the left thigh detected six months before. The patient noticed a progressive increase in size and changes in color.

Clinical examination revealed skin type I, without increase in the number of moles (< 25), but some solar lentigo in exposed areas, especially on the upper back. The scar of the previous surgery of the primary melanoma and lymph node areas were normal.

The tumor was 10.5x12 mm in maximal diameter and more palpable in the center. The lesion exhibited light brown, dark brown to black, and gray colors (Figure 1).

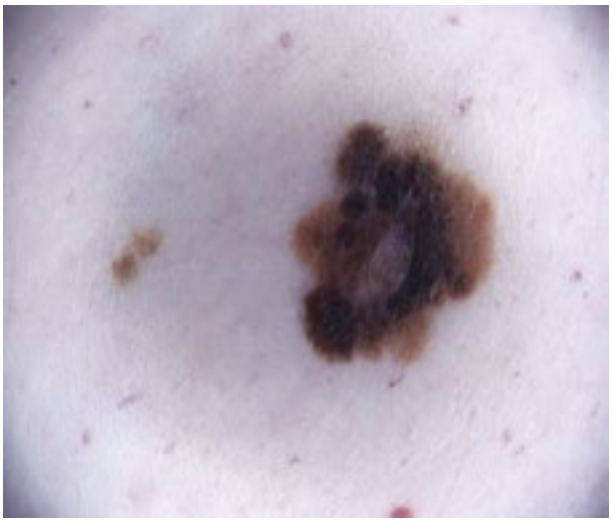

Figure 1. Superficial spreading melanoma on the left thigh

Dermoscopy of the lesion showed a melanocytic lesion with the following features: atypical pigmented network, irregular streaks, globules/dots, and blotches, and a homogeneous hypopigmented center (Figure 2).

The second tumor was 1.5x0.9 mm in maximal diameter, and it was located on the right scapular region (Figure 3). A solitary flat lesion was slightly palpable, light-brown to reddish in color.

Figure 2. Dermoscopy of superficial spreading melanoma on the left thigh

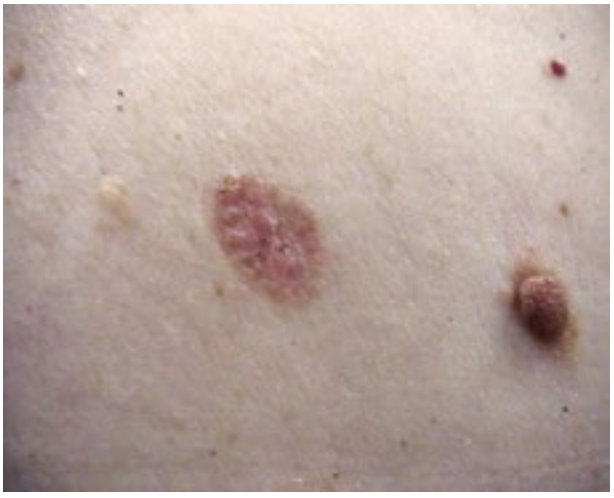

Figure 3. Basal cell carcinoma in the right scapular region

Dermoscopy revealed a negative pigment network with thin arborizing vessels in the center of the lesion, and a few small ulcers covered by light brown crusts (Figure 4).

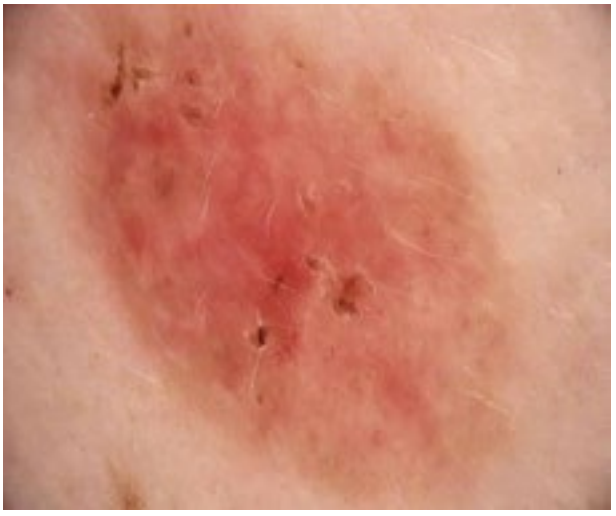

Figure 4. Dermoscopy of basal cell carcinoma in the right scapular region

Management

A full surgical removal of the tumor, with 2 mm margins, under local anesthesia was performed to evaluate the tumor histologically. A superficial spreading melanoma (SSM), Breslow 1 mm, Clark level III, without ulcerations and abundant lymphocytic inflammatory infiltrate with five mitoses/10 High

Power Fields (HPF) was reported. Reexcision was done with 10 mm margins (6), and sentinel lymph node biopsy revealed a negative sentinel node on the left thigh without micro-metastases. The patient was staged IA, based on the American Joint Committee on Cancer (AJCC) staging system (7). A follow-up with clinical examination (skin and lymph nodes), including digital dermoscopy, was recommended with 3 to 6 months between each visit.

A surgical excision under local anesthesia was also performed for the second lesion to evaluate the tumor histologically. A basal cell carcinoma - pT1 (Stage I, primary tumor) 2cm or less in diameter, according to the TNM Classification of Malignant Tumors (available at www.uicc.org/index.php?id=508.) located at the scapular region was reported.

Discussion

Melanoma is a malignant tumor of melanocytes, and it affects all age groups. It is most common in Australia, but the mortality rate for melanoma is quite low compared to other countries (8). Early detection of melanoma followed by appropriate treatment, has led to a significant reduction in melanoma mortality (9). However, patients with a prior melanoma are at an increased risk for developing a second primary melanoma (10).

Since the patient in our report had a history of a previous superficial spreading melanoma located at the dorsal trunk, the case was posted to the International Dermoscopy Society (IDS) discussion forum, for other experts to give their opinions whether it was a second primary skin melanoma, or a potential skin metastasis (http://www.dermoscopy-ids.org). Most participants in the discussion thought that most likely it was a second, or a secondary skin melanoma (11). Since histopathology analysis revealed a SSM, this finding actually confirmed that the tumor was a primary skin melanoma.

Melanoma risk is highest in lower latitude areas, where levels of ultra-violet light are high. However, apart from genetics, environment and lifestyle may also contribute to one's chances of developing melanoma. In our case, the patient had a few severe sunburns from childhood and teenage years, skin type I, as well as family and personal history of melanoma.

Unfortunately, in our country there are no precise data on the morbidity and mortality rates. Nevertheless, from day to day, our practitioners see more and more melanomas. Since we use digital dermoscopy, micro-invasive melanomas are more often reported (12).

Nowadays there are many e-dermatology sites, including those focused on teleconsultations: telederm.org, dermoscopy-ids.org, eMedicine; DermIS.net; dermatlas.org etc. Their help and support is invaluable whenever a physician needs a second opinion i.e. expert opinion.

On the other hand, basal cell carcinoma is the most common type of non-melanoma skin cancer, seen mostly in elderly people. Sun exposure is responsible for over 90% of skin cancers (13,14).

In conclusion, the emphasis should be upon early and proper assessment of all high-risk patients. Total body skin examination (TBSE) is strongly recommended at the time of the first consultation. It should include clinical examination, palpation and self-examination. Patients with family or/and personal history of melanoma, or with one or more other risk factors (phototypes I and II, five moles larger than 6 millimeters in diameter vs. dysplastic nevi, or more than 25 common nevi, changes in the existing moles etc.), should be included in the follow-up program by digital dermoscopy. Early treatment of melanoma is crucial.

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Značaj dermoskopskog praćenja u identifikaciji osoba s visokim rizikom od pojave drugog primarnog kutanog melanoma – prikaz slučaja

Sažetak

Uvod: Telemedicina koristi savremene informatičke i komunikacione tehnologije za prenos medicinskih podataka sa jednog na drugo mesto, čime se stiču uslovi za pružanje zdravstvenih medicinskih usluga po principima kliničke medicine, bez obzira na to gde se geografski nalaze davalac zdravstvenih usluga, pacijent, medicinska informacija ili oprema. Telemedicinske aplikacije obuhvataju: teledijagnostiku, telekonsultacije, telemonitoring, telenegu, telekonzilijume i daljinski pristup informacijama koje se nalaze u jednoj ili više baza podataka.

Telemedicina funkcioniše u dva konceptualno različita vremenska okvira: u realnom, tj. sinhronom (videokonferencija) i odloženom, tj, asinhronom. U teledermatologiji se najčešće koristi ovaj drugi pristup. Dermoskopija (epiluminiscentna mikroskopija; dermatoskopija) predstavlja *in vivo* dijagnostičku proceduru koja služi za bolju vizualizaciju kože, njene strukture i promena nastalih u njoj. Novonastale promene, ukoliko su nedovoljno vidljive golim okom, postaju zahvaljujući dermoskopskom pregledu bolje vidljive i mogu se klasifikovati kao melanocitne ili nemelanocitne. Glavni zadak dermatoskopije je rano otkrivanje i pravilno lečenje melanoma.

Prikaz slučaja: Prikazujemo četrdesetosmogodišnju pacijentkinju koja je u svojoj ličnoj anamnezi navela podatak da joj je godinu dana ranije odstranjen melanom sa kože leđa. Takođe je navela podatak o srodniku obolelom od melanoma. Javila se na pregled zbog nove pigmentovane promene lokalizovane na levom bedru, koja se pojavila šest meseci ranije i na kojoj je zapazila porast i promenu boje lezije.

Iz priložene medicinske dokumentacije, tumor koji je odstranjen godinu dana ranije, predstavljao je melanom debljine 0,5 mm po Breslowu i Clark II (stadijum IA).

Kliničkim pregledom, kod pacijentkinje je utvrđen tip kože I (po Fitzpatrickovoj skali), bez povećanog broja mladeža (< 25), i sa nekoliko promena tipa solarnog lentiga na fotoeksponiranim regijama, posebno na gornjoj polovini leđa. Postoperativni ožiljak na mestu prethodno postojećeg melanoma nije pokazivao znake aktivnosti, a regionalne limfne žlezde nisu bile palpabine.

Pacijentkinja se javila na pregled zbog nove pigmentne promene lokalizovane na levom bedru, koja se pojavila šest meseci ranije, vremenom se povećavala i promenila boju.

Kliničkim pregledom je na koži levog bedra uočena tumorska promena s maksimalnim dijametrima 10,5 x 12 mm, palpabilna, naročito u svom centralnom delu. Na površini lezije uočavala se različita obojenost, od svetlosmeđe, tamnosmeđe do crne i sive.

Na dermoskopskom pregledu uočen je melanocitni karakter promene sa sledećim strukturnim elementima: atipična mreža, iregularne crte, iregularne globule/tačke, iregularne mrlje, centralna homogena hipopigmentovana zona.

U predelu desne lopatice, nalazila se lako indurovana promena tumorskog izgleda, svetlosmeđe do crvenkaste boje, ovalnog izgleda, zaravljene površine, sa maksimalnim dijametrima 1,5 x 0,9 mm.

Dermoskopskim pregledom lezije utvrđene su sledeće strukture: nedostak pigmente mreže, gracilni arborizovani krvni sudovi u centralnom delu, nekoliko

malih ulceracija prekrivenih svetlosmeđom krustom.
Radi sprovođenja patohistološke analize, izvršena je uz pomoć lokalne anestezije kompletna hirurška ekscizija pigmentne lezije, uključujući okolno, klinički nepromenjeno tkivo, u širini od 2 mm. Analiza je pokazala da se radilo o površinski širećem melanomu: Breslow 1 mm, Clark III stadijum, bez ulceracija, gust limfocitni inaflamatorni infiltrat (5 mitoza/10 vidnih polja HPF – eng. *high power fields*). Usledila je reekscizija sa zahvatanjem klinički neizmenjene kože u širini od 10 mm. Pregledom stražarskog limfnog čvora u predelu levog bedra, dobijen je negativan nalaz, u stražarskom čvoru nisu utvrđene mikrometastaze. Radilo se o Ia stadijumu po kriterijumima Američkog združenog komiteta za kancer – AJCC. Indikovno je praćenje pacijentkinje kako kliničko tako i dermoskopsko, s kontrolnim pregledima u intervalima 3-6 meseci.
Radi patohistološke analize, u lokalnoj anesteziji izvršena je totalna ekscizija tumora i postavljena je dijagnoza bazocelularnog karcinoma u pT1 stadijumu.
Diskusija: Melanom se može javiti u bilo kom životnom dobu. Najveća incidencija melanoma je u Australiji, ali zahvaljujući ranom otkrivanju i adekvatnoj terapiji stopa mortaliteta u odnosu na druge zemlje je niska. Osobe sa primarnim melanomom su pod povišenim rizikom od nastajanja drugog primarnog kutanog melanoma. S obzirom da je pacijentkinja već ranije imala površinski šireći primarni melanom na koži, ceo slučaj je bio poslat na telekonsultaciju u Internacionalno dermoskopsko društvo na ekspertizu da li je tumor bio primarni ili metastatski. Zaključak je bio da se nije mogla isključiti ni jedna ni druga mogućnost. Dilemu je rešila patohistološka analiza (početak u epidermisu).
Najviši rizik od dobijanja melanoma je u područjima sa malom geografskom širinom, gde je količina UV zračenja najveća. Pored klimatskih faktora, genetska predispozicija i način življenja takođe utiču na primečivost za dobijanje melanoma. Kod naše pacijentkinje, pored anamnestičkih podataka o nekoliko epizoda opekotina od sunca u detinjstvu, fototip I kože i pozitivna lična i porodična anmneza u vezi sa melanom, povećali su rizik od obolevanja.
Nažalost, u našoj zemlji ne raspolažemo preciznim epidemiološkim podacima o morbiditetu i mortalitetu od malignog melanoma, ali ono što je evidentno, nakon uvođenja digitalne dermoskopije u rutinski rad dermatologa, svakodnevno se dijagnostikuje sve veći broj melanoma, prvenstveno mikroinvazivnih.
Radi što boljeg dijagnostičkog, a samim tim i terapijskog postupka, veliku pomoć pružaju telemedicinske platforme, naročito one koje su usmerene na telekonsultacije, kao što su: telederm.org; dermoscopy-ids.org; eMedicine; DermIS.net; dermatlas.org.
Istovremeno postojanje bazocelularnog karcinoma kod naše pacijentkinje, ukazuje na prisustvo najučestalijeg nemelanomskog karcinom kože, za čiji nastanak izlaganje UV zracima predstavlja najvažniji faktor rizika. Za razliku od skvamocelularnog, za nastanak bazocelularnog karcinoma, veći značaj se danas pridaje intermitentnoj a ne kumulativnoj dozi UV zračenja.
Zaključak: Najznačajnije je rano otkrivanje svih faktora rizika i adekvatna evaluacija pacijenata koji spadaju u rizičnu grupu. Potrebno je sprovoditi preglede i kontrolne preglede čitave kože, koji pored inspekcije treba da obuhvate i palpaciju, ali i da se dopunjuju samopregledima za koje treba obučiti pacijente. Najveći zadatak dermoskopije je upravo edukacija pacijenata sa ciljem sprovođenja redovne i adekvatne samoinspekcije. Pozitivna lična i porodična anamneza za melanom, ili prisustvo jednog ili većeg broja ostalih faktora rizika (fototip kože I ili II, najmanje pet mladeža dijametra većeg od 6 mm, displastični nevusi, više od 25 običnih nevusa; novonastale promene na postojećim nevusima), svrstavaju određenog pacijenta u grupu rizičnih i zahtevaju njegovo stalno dermoskopsko praćenje. Prevencija i profilaktička terapija su od neprocenjivog značaja.

Ključne reči

Melanom; Druga primarna neoplazma; Dermoskopija; Limfne žlezde; Bazocelularni karcinom; Telemedicina; Praćenje bolesnika

A Case of Granulomatous Rosacea: Successful treatment with Topical Azelaic acid 20% cream

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Abstract

Granulomatous rosacea is considered to be the only true variant of rosacea. Diascopy of larger lesions often reveals apple-jelly nodules, indicating their granulomatous histology. Other signs and symptoms of rosacea are not required to make a diagnosis of granulomatous rosacea. The response to treatment may be slow, which must be the most important consideration for both the clinician and the patient. We present an otherwise healthy 62–year-old non-atopic woman with a 15-year history of episodic facial flushing, often accompanied by a burning sensation without sweating. Exclusively affecting the face, lesions had a high tendency to spread each year. The patient was a lifelong non-smoker. A seller on the local market, she spent most of her time outdoors. She had no positive family history of rosacea. At the time of presentation, she was not taking any medications, except for topical neutral creams. Multiple reddish-brown papules without comedones, associated with telangiectasia were scattered over the erythematous background on the chin, forehead, cheeks, nose, glabella and eyelids, while small pustules clustered over the eyelids. The nasolabial folds, neck and ears were not affected. There was neither lymphadenopathy, nor ocular involvement. Based on the history, physical, laboratory and other relevant investigations including histopathology, the diagnosis of granulomatous rosacea was established. The therapy was conducted with topical azelaic acid 20% cream, twice daily for six months. Clinical evaluation was done every 14 days during the first month, and once monthly during the next five months. Affter two weeks, there was a significant decrease in the mean inflammatory lesion count. At the end of the therapy, telangiectasia and facial erythema almost disappeared. There were no side effects. Apart from several short episodes of erythema, during the five-year-long follow-up, there were no other signs of the disease. In conclusion, azelaic acid 20% cream may be an effective and safe treatment option for some patients with granulomatous rosacea.

Key words

Words: Rosacea; Granulomatous Disease, Chronic; Administration, Topical; Dicarboxylic Acids

Rosacea represents a common inflammatory condition that is more frequent after the age of thirty, and is diagnosed almost three times more often in women than in men (1). More than 1% of all patients seen i dermatology units suffer from rosacea, but its exact prevalence in the general population is lacking (2).

Rosacea is a highly heterogeneous entity with uncertain etiology (3). It is characterized by presence of one or more of the following signs with a central face distribution: flushing, persistent erythema, papules and pustules without comedones, and telangiectasia (4).

Granulomatous rosacea is a rare variant and a dinstinct form of rosacea. Actually, granulomatous rosacea is considered to be the only true variant of rosacea (4, 5). It presents with multiple, hard, less inflammatory, monomorphic reddish-brown papules or nodules, located on the cheeks and periorificial facial skin. In acne agminata, also considered a variant of rosacea, moreover, a self-limiting variant of the granulomatous form of rosacea, the lesions may cluster around the mouth or on the eyelids or eyebrows, so that the term 'agminata' is appropriate (3). However,

the term 'acne rosacea' is used synonymously with rosacea, but should better be avoided, since the epidemiology, etiology and pathology of rosacea are quite distinct from those in acne vulgaris. It only denotes the occurrence, in both diseases, of papules and pustules on the face (3).

Some lesions contain granulomas which can be epithelioid, elastolytic or pallisaded around altered collagen accumulations. Foreign-body type giant cells may also be observed. Such findings can accurately be predicted by clinical examination. Diascopy of larger lesions often reveals apple-jelly nodules indicating their granulomatous histology and central caseation. The background facial skin is otherwise normal (5). Other signs and symptoms of rosacea are not required to make a diagnosis of granulomatous rosacea (5). However, the response to treatment may be slow, which is the most important consideration for both the clinician and the patient (3).

Azelaic acid (1,7-heptanedicarboxylic acid) is a naturally occurring saturated dicarboxylic acid. It is a relatively safe, though mildly irritant agent (the local irritant reactions are often mild or transient) with several effects important for dermatology. Besides its depigmenting effects and antikeratinizing properties, azelaic acid 20% cream is effective in the treatment of acneiform lesions. This is likely due to a combination of anti-microbial and anti-inflammatory properties. It can inhibit growth of *Propionibacterium acnes* and *Staphylococcus epidermidis*, and inhibits production of free radicals by polymorphs. The latter property may also explain why it is effective in rosacea. It may also prove to have a role as an antimycotic, inhibiting growth of dermatophytes, and as a topical antimicrobial agent with activity against antibiotic resistant *Staphylococcus aureus* (3). Azelaic acid 15% gel was approved by the US Food and Drug Administration (FDA) in 2002, for the topical treatment of inflammatory papules and pustules of mild to moderate rosacea (6).

We present a 62–year-old woman with granulomatous rosacea, who was succesfully treated by topical azelaic acid cream.

Case report

History

An otherwise healthy 62–year-old non-atopic woman had a 15-year history of episodic facial flushing. From the very beginning, the flushing was often accompanied by a burning sensation without sweating. Exclusively affecting the face, lesions had a high tendency to spread each year. Erythema, which gradually became more persistent and easily triggered by minor irritants, was meanwhile accompanied by erythematous papules and pustules with increasingly prominent telangiectasia. At that time, she was treated by a general practioner, by topical corticosteroids. She was a lifelong non-smoker. As a seller on the local market, she spent most of her life outdoors and had no positive family history of rosacea. At the time of presentation, she was not taking any medications, except for topical neutral creams.

Physical examination

When first seen by us, the patient was in a good general health condition. The pertinent findings were confined to the facial skin. The lesions affected the central convex areas of the face. There were multiple reddish-brown papules, 3-5 mm in diameter, without comedones, and small pustules scattered over the erythematous background on the chin, forehead, cheeks, nose, glabella and eyelids. Erythema was

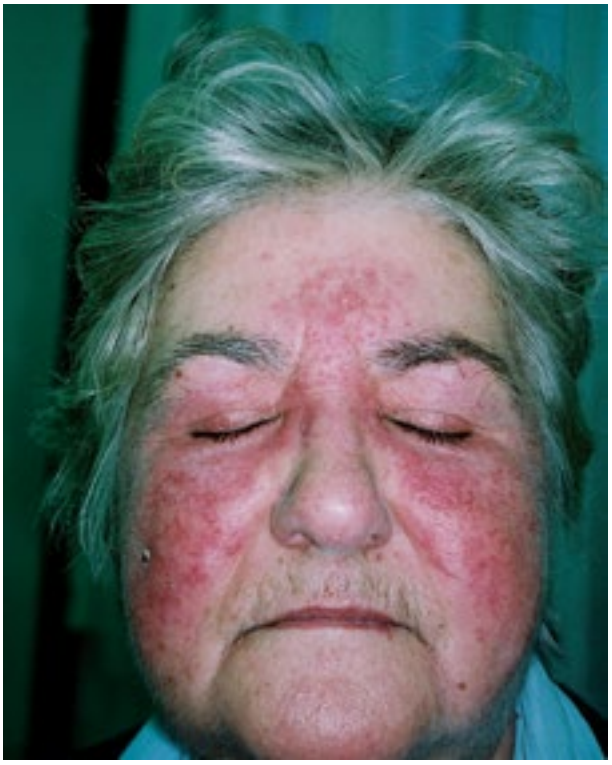

Figure 1. Before treatment: nasolabial folds, neck and ears were not affected

associated with increasingly prominent telangiectasia. Small pustular lesions clustered over the eyelids (Figures 1, 2, 3). The nasolabial folds, neck and ears were not affected. A marked edema of the skin was located over glabella. There was no lymphadenopathy, or ocular involvement.

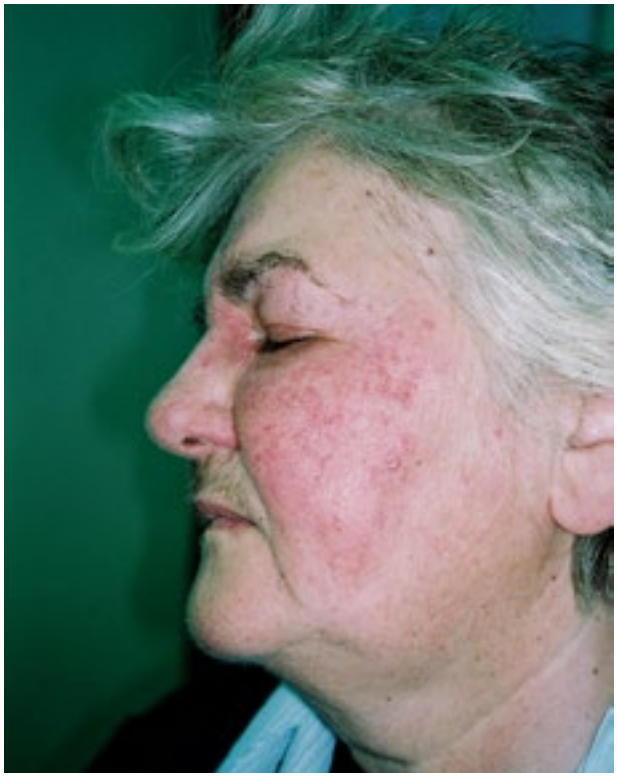

Figure 2. Before treatment: erythema associated with increasingly prominent telangiectasia

Laboratory and other relevant investigations

A complete blood count with differential counts, erythrocyte sedimentation rate, rutine serum biochemical analysis, urinalysis, serum protein electrophoresis, serum autoimmune antibodies, serum complement components, thyroid function, viral serologies, vaginal smear, Pap test, abdominal ultrasound, chesr x-ray, were all within normal limits. The purified protein derivative skin test (PPD) was negative.

Histopathology

Skin biopsy was performed, and a skin sample of the papule taken from the cheek was sent for histopathological analysis. It revealed moderate

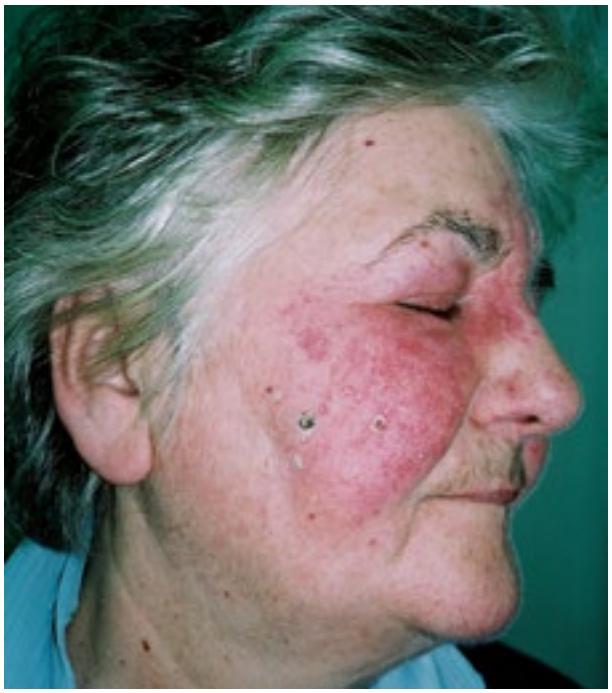

Figure 3. Before treatment: small pustular lesions clustered over the eyelids

hyperkeratosis of the epidermis with mild follicular plugging, dilated upper dermal capillaries, a non specific lymphohistiocytic perivascular infiltrate and dilated hair follicles. No *Demodex folliculorum*

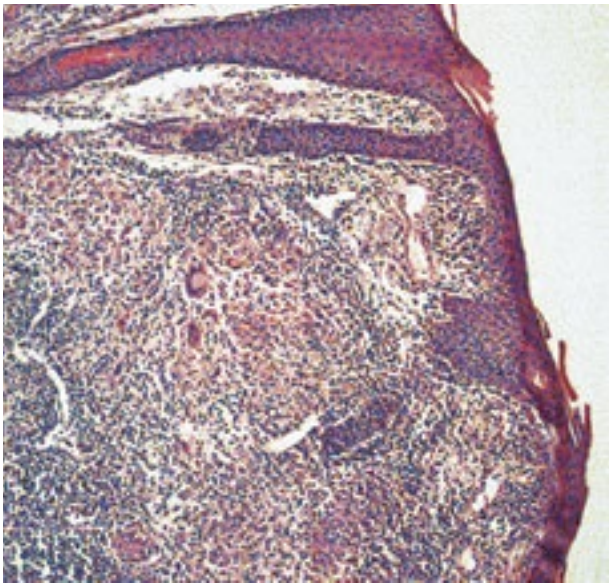

Figure 4. Skin biopsy with moderate epidermal hyperkeratosis and granuloma in the upper dermal part (HE x 50)

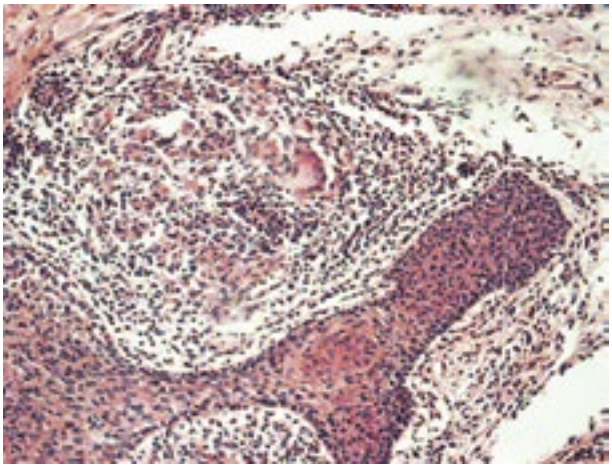

Figure 5. Skin biopsy with granuloma in the upper dermis. Granuloma with multiple giant cells of foreign body type and Langerhans cells type, without necrosis (HE x 200)

mites were found. The upper and middle dermis contained noncaseating tuberculoid granulomas with lymphocytes, epithelioid histiocytes, plasma cells, multinucleated foreign-body type, giant cells, and occasional Langhans' cells. The finding was consistent with granulomatous dermatitis, preferentially granulomatous rosacea (Figures 4, 5).

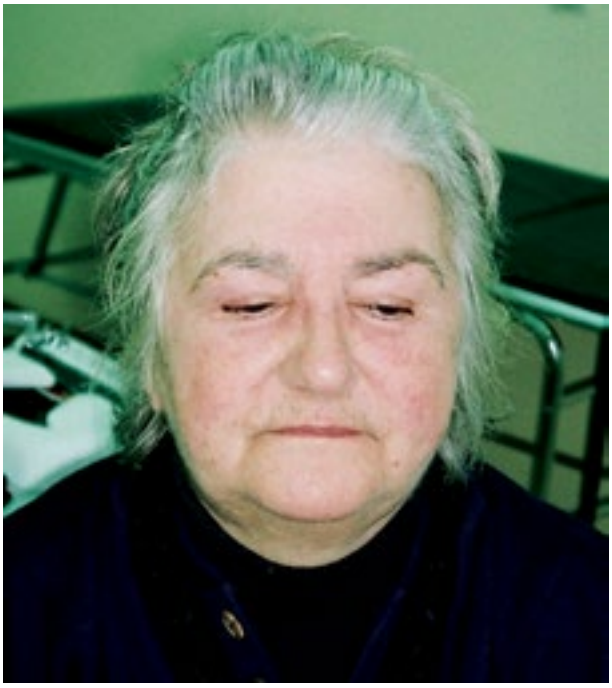

Figure 6. At the end of the treatment: a significant improvement

Figure 7. At the end of the treatment: facial erythema almost completely disappeared

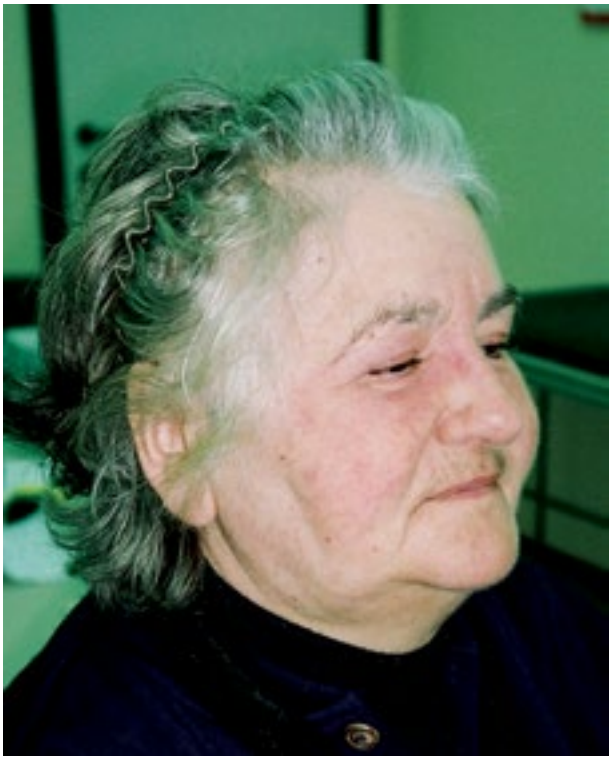

Figure 8. At the end of the treatment: dilatation of the small blood vessells almost completely disappeared

Therapy

Our patient was initially treated with oral 100 mg doxycycline once daily, and oral metronidazole 400 mg twice a day over 10 days. The therapy was discontinued after ten days, when gastrointestinal symptoms with nausea, vomiting, malaise, and stomach pain occurred. Local therapy was continued with topical azelaic acid 20% cream twice a day. The patient was advised to apply the cream gently in a circular manner, for at least six months. Follow-up evaluation was done every 14 days during the first month, and once monthly during the next five months of treatment. On the first control, there was a significant decrease in the mean inflammatory lesion (papulas and pustules) count. At the end of therapy, dilatation of small blood vessells and facial erythema almost disappeared (Figures 6, 7, 8). There were no side effects observed, and/or reported by the patient. After cessation of topical azelaic acid therapy, the patient was advised to use neutral creams and UV protecting creams with a sun protection factor-SPF > 15.

Apart from several short episodes of erythema, during the five-year follow-up, there were no other signs or symptoms of the disease.

Discussion

Based on the history, physical examination, laboratory and other relevant investigations, including histopathological analysis, the diagnosis of granulomatous rosacea was established in our patient (4). The age of onset, history of flushing and burning without sweating, absence of comedones and clear nasolabial folds, differentiated our case from a late-onset of acne vulgaris, postmenopausal flushing, corticosteroid-induced rosacea, seborrhoeic dermatitis, acne agminata, and granulomatous perioral dermatitis in children (3). Unlike in rosacea, telangiectasia and flushing are not common in perioral dermatitis. Perioral dermatitis, like seborrhoeic dermatitis, affects the nasolabial area. Scaling (present in our patient) is not a feature of rosacea, but is common not only in seborrheic, but also in contact dermatitis. However, rosacea and contact dermatitis often seem to occur concurrently (7). Acne agminata is seen mainly in young adults and adolescents. It is a synonym for *'lupus miliaris disseminatus'* which originates from a historical classification. It now seems most unlikely to be tuberculous in etiology, since several studies failed to demonstrate *Mycobacterium tuberculosis* or other mycobacterial agents by culture (3). Whilst the clinical appearance, distribution and histology of lesions are similar with granulomatous rosacea, acne agminata may represent a self-limiting variant of the granulomatous form of this disease. Some authors believe that the natural history and the tendency to affect younger males and females approximately equally, means that they are not a form of rosacea. However, it may be difficult to distinguish it from micropapular sarcoidosis. Similar to our study, a chest X-ray, tuberculin skin test and antistreptolysin 0 titre (ASOT) may be obtained in such instances to exclude causes such as sarcoidosis, tuberculosis or streptococcal infection (8).

Granulomatous infiltrates are reported to occur in about 10% of all cases of rosacea, while caseation necrosis, which was not a feature in our patient, has only been identified in about 10% of these patients (9).

For prevention and better treatment of rosacea, it is important to establish its etiopathogenesis. Rosacea represents a common disease, but its etiology is still a mistery (10). Several endocrinological, pharmacological, immunological, infectious, alimentary, climatic and thermal factors are implicated as triggers for rosacea (3, 5). However, no true relations have been established between most of these factors and rosacea. Thus, in a recent study done by Abram et al, there is no relation between rosacea and *Helicobacter pylori* infection, caffeine intake or alcohol consumption (11). Significant risk factors associated with rosacea included: age, photosensitive skin types (by Fitzpatrick), positive family history, outdoor working conditions and ex-smoking status (10). These findings suggest that rosacea is related to photoaging. Moreover, it has been proposed that damage to dermal connective tissue, often caused by solar irradiation, may be the initiating factor. This may result in a dysfunction of the unsupported facial blood vessels and consequent endothelial damage, leakage, edema and inflammation. It has been suggested that abnormal vascular reactivity plays a central role (3). It is the heat, not the caffeine content of hot drinks, that causes flushing (3,10).

Smoking seems to prevent several granulomatous diseases, which could be a result of a decreased inflammatory response in smokers. Thus, rosacea

was previously considered predominantly a disease of non-smokers. However, in a recent study done by Abram et al, the risk of getting rosacea was higher among ex-smokers (previous smoking period with at least 1 cigarette per day, but not any more), than among current smokers (at least 1 cigarette per day), or lifelong non-smokers (never smoked). The authors argue that the withdrawal of the immunosuppressive effect of smoking acts as a trigger for the disease onset (10).

Our patient had several risk factors: outdoor working conditions, advanced age, sun reactive skin type II, and lifelong non smoker category (never smoked).

The first step in therapy of rosacea should begin with education of patients to use sunscreens and mild cleaners, as well as avoid risk factors including common irritants. Curently, there is no cure for rosacea. It seems that standard medical therapies have focused mainly to minimizing inflammation (1, 11-14). Thus, the main goal of the treatment is disease control. Reduction of the inflammatory component of rosacea by broad-spectrum antibiotics may slow down its progression (3). Similar to our case, troublesome side effects and compliance have been their major limitations. Combinations of topical and systemic treatment are often used in patients with severe forms of the disease, and may be more effective than either used alone. Effective oral agents include tetracyclines and azithromycin (3, 14).

Topical antibiotics like clindamycin, erythromycin, and tetracycline are the first choice therapy for inflammatory lesions, in addition to metronidazole and azelaic acid (3, 6). Metronidazole 1% gel once a day, and azelaic acid 15% gel twice a day alone, or in combination, are the best evaluated topical agents (6). Metronidazole can be used with or without oral antibiotics. Moreover, metronidazole 400 mg daily over a 4-month period, followed by metronidazole 200 mg daily, markedly reduces facial swelling (3). Topical pimecrolimus 1% and tacrolimus 0.3 - 0.1%, have recently been proposed, but only as alternative (unapproved) agents for rosacea (12, 14).

In a recent study done by Mostafa et al, it was found that in comparison with metronidazole 0.75% gel and permethrin 5% cream, azelaic acid 20% cream was significantly more effective reducing the mean inflammatory lesion count, but not erythema. However, patients who used azelaic acid 20% cream were significantly more satisfied with azelaic acid cream with regard to cosmetic results (13).

It is important to explain to patients (with papulopustular lesions), that none of the above measures will significantly suppress the troublesome flushing or the burning discomfort which often accompanies this condition. Treatment of flushing and burning is the most difficult in rosacea.

In our case, once the therapy with oral doxycycline and metronidazole was discontinued, azelaic acid 20% cream was introduced, regarding all the above mentioned reports on azelaic acid effects, obtained in the treatment of patients with papulopustular rosacea (3, 6, 13).

In conclusion, azelaic acid 20% cream may be an effective and safe treatment option for some patients with granulomatous rosacea.

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Granulomatozna rozacea – lokalno lečenje azelaičnom kiselinom u obliku 20% krema – prikaz slučaja

Sažetak

Uvod: Rozacea predstavlja čestu inflamatornu dermatozu, koja se značajno češće javlja posle tridesete godine života i skoro je tri puta češća kod žena nego kod muškaraca. Rozacea predstavlja heterogeni entitet nepoznate etiologije, karakterističnih, jednog ili više, sledećih znakova: iznenadni naleti rumenila (eng. *flushing*), perzistentni eritem, papule i pustule bez komedona, teleangiektazije.

Granulomatozna rozacea, koja predstavlja kliničku varijantnu oboljenja, manifestuje se multiplim, tvrdim, manje inflamiranim, monomorfnim crvenkastosmeđim papulama i/ili nodusima lokalizovanim na obrazima i periorificijalnoj koži lica. Akne agminata predstavljaju varijantu granulomatozne rozacee, a lezije se često grupišu oko usta, očnih kapaka ili obrva, što opravdava naziv *agminata*. Suprotno tome, naziv akne, odnosno *acne rosacea,* koji se često koristi kada je rozacea u pitanju, trebalo bi izbegavati s obzirom da se etiologija, epidemiologija i patologija rozacee potpuno razlikuje od vulgarnih akni. U ovom slučaju termin *acne* označava za oba oboljenja pojavu papula i pustula lokalizovanih na licu.

Neke lezije granulomatozne rozacee sadrže granulome, koji mogu biti epiteloidni, elipsoidni, elastoidni ili biti palisadno raspoređeni oko izmenjenih kolagenih vlakana u koži. Granulomi mogu biti formirani i od džinovskih višejedarnih ćelija tipa „oko stranog tela“ i/ili Langhans višejedarnih džinovskih ćelija. Dijaskopskim pregledom većih lezija dobija se karakteristična „boja želea od jabuka“, koja ne samo da ukazuje na granulomatozni patohistološki supstrat nego i na centralnu nekrozu granuloma. Okolna koža može biti klinički nepromenjena u granulomatoznoj rozacei, a ostali simptomi i znaci koji predstavljaju kriterijume za dijagnozu klasične rozacee (ranije navedeni), ne moraju biti prisutni. Povoljan terapijski odgovor pacijenata sa ovim oblikom rozacee može biti značajno usporen, što ima veliki značaj i za lekara i za pacijenta.

Dikarboksilna kiselina, po svom hemijskom sastavu azelaična kiselina, ispoljava nekoliko efekata koji su značajni za dermatologiju: inhibicija keratinizacije, depigmentacija, antizapaljensko delovanje, antimikrobno delovanje (inhibiše rast *Propoinibacterium acnes* i *Staphylococcus epidermidis*), antimikotično delovanje (inhibicija rasta dermatofita), inhibicija produkcije slobodnih radikala iz polimorfonuklearnih granulocita.

Ova poslednja osobina objašnjava povoljan terapijski efekat azelaične kiseline u lečenju pacijenata sa rozaceom. Azelaična kiselina u obliku pripravka za lokalnu primenu, na osnovu svojih antimikrobnih efekata, može da se koristi za sprečavanje antibiotske rezistentnosti na *Staphylococcus aureus.* Lečenje rozacee lokalnom primenom azelaične kiseline u vidu 15% gela je FDA (eng. *Food and Drug Administration*) zvanično odobrila 2002. godine.

Cilj rada: Prikazujemo slučaj pacijentkinje obolele od granulomatozne rozacee, koja je uspešno lečena lokalnom primenom azelaične kiseline.

Prikaz slučaja: Pacijentkinja stara 62 godine, neatopičar, dobrog opšteg stanja, u momentu pregleda dala je podatak da unazad 15 godina ima povremene nalete iznenadnog rumenila lica. Na samom početku bolesti ove epizode su bile praćene

pečenjem, ali ne i pojačanim znojenjem. Vremenom tegobe su se pojačavale, crvenilo lica je postajalo trajno prisutno, pojačavalo se prilikom izlaganja različitim iritansima (npr. začinjena hrana, alkohol, toplota), a na koži su počele da se pojavljuju bubuljice i čvorići, kao i prošireni kapilari. Lečenje se zasnivalo na kortikosteroidnim kremama, po savetu lekara opšte prakse. U momentu kada se javila dermatologu koristila je samo neutralne kreme.

U momentu dermatološkog pregleda, promene su bile ograničene na kožu lica, u vidu multiplih, crvenkastosmeđih papula, 3-5 mm u dijametru, bez komedona i malih pustula, koje su bile diseminirane na eritematoznoj koži obraza, čela, nosa, glabele i očnih kapaka.

Teleangiektazije su bile jasno izražene, a male pustulozne lezije grupisane na očnim kapcima. Koža je bila pošteđena promena u predelu nazolabijalnih brazda, ušnih školjki i nosa. Otok na licu je bio najizraženiji u predelu glabele. Bolest nije zahvatala regionalne limfne žlezde.

Sve relevantne laboratorijske, imunološke, ultrazvučne i RTG analize (pluća), kao i kožni testovi (PPD), bili su u granicama fizioloških vrednosti.

Histopatološka analiza: Isečak kože uzet sa papule podvrgnut je histopatološkoj analizi: epidermis je lako hiperkeratotičan, sa umereno izraženim folikularnim keratinskim čepovima; prošireni kapilari u gornjem dermisu obloženi su nespecifičnim histiocitnim infiltratom, uočava se proširenje folikula dlaka i odsustvo *Demodex folliculorum*; gornji i srednji dermis sadrže tuberkuloidne granulome bez kazeozne nekroze, sastavljene od limfocita, epiteloidnih histiocita i plazma ćelija, a uočavaju se i višejedarne džinovske ćelije tipa oko stranog tela i pojedinačne Langahansove ćelije. Nalaz ukazuje na granulomatozni dermatitis, u prvom redu na granulomatoznu rozaceu.

Lečenje: Lečenje je započeto peroralnim davanjem doksiciklina u dozi od 100 mg dnevno i metronidazolom u dozi od 800 mg dnevno (podeljeno u dve pojedinačne doze) u toku deset dana. S obzirom da se kod pacijentkinje javio osećaj mučnine, povraćanje i bolovi u stomaku, sistemska terapija je obustavljena. Lečenje je nastavljeno isključivo lokalnom terapijom i to sa azelaičnom kiselinom u obliku 20% krema, koji je nanošen dva puta dnevno na obolelu kožu tokom šest meseci. U toku prvog meseca lečenja pacijentkinja je kontrolisana svakih 14 dana, a potom jednom mesečno tokom narednih pet meseci.Već na prvoj kontroli uočavalo se značajno smanjenje broja inflamiranih lezija, papula i pustula. Posle šest meseci lečenja crvenilo i prošireni kapilari su se gotovo potpuno (> 85%) izgubili. Lečenje nije bilo praćeno neželjenim efektima. Pacijentkinji je savetovano da koristi neutralne kreme i kreme za zaštitu od UV zračenja (zaštitni faktor > 15). Tokom sledećih pet godina pacijentkinja je imala nekoliko kratkotrajnih epizoda crvenila lica bez drugih simptoma i znakova oboljenja.

Diskusija: Postavili smo dijagnozu granulomatozne rozacee na osnovu anamneze, fizičkog pregleda i relevantnih analiza, uključujući i patohistološku. Životno doba na početku bolesti, napadi rumenila i osećaj pečenja bez znojenja, odsustvo komedona i promena na nazolabijalnim brazdama, jesu karakteristike koje razlikuju rozaceu od akni vulgaris u starijem dobu, valunga u postmenopauzi, kortikosteroidima izazvane rozacee, seboroičnog dermatitisa, akne agminata i granulomatoznog perioralnog dermatitisa kod dece (juvenilna rozacea). Teleangiektazije i naleti rumenila kod naše pacijentkinje isključuju perioralni dermatitis. Nazolabijalne brazde su zahvaćene kod perioralnog dermatitisa i seboroičnog dermatitisa. Deskvamacija (viđena kod naše pacijentkinje) nije karakteristična za rozaceu; po pravilu se javlja kod seboriočnog, ali i kod kontaktnog dermatitisa. Štaviše, rozacea i kontaktni dermatitis se javljaju udruženo mnogo češće nego što se na to pomišlja.

Akne agminata se javljaju u mlađem životnom dobu i kod adolescenata. Sinonim *Lupus miliaris disseminatus* potiče iz stare klasifikacije. Sa današnje tačke gledišta isključena je tuberkulozna etiologija (izostanak kultivacije tipičnih i atipičnih mikobakterija). Izgled, distribucija i histološka građa lezija kod granulomatozne rozacee i akne agminata se praktično ne mogu razlikovati, stoga neki autori smatraju akne agminata kliničkom varijantom granulomatozne rozacee.

Promene kod akne agminata se javljaju ranije, podjednako često kod osoba muškog, odnosnog ženskog pola, što po nekim autorima izdvaja akne agminata kao poseban entitet. Relevantne

analize, uključujući RTG pluća, tuberkulinski test, antistreptolizinski titar (ASTO), koje smo sproveli kod naše pacijentkinje, mogu isključiti sarkoidozu, tuberkulozu ili streptokoknu infekciju.

Granulomatozni ćelijski infiltrat se može javiti kod oko 10% svih pacijenata sa rozaceom, dok se kazeozna nekroza (nije je bilo kod naše pacijentkinje) može dokazati kod samo 10% ovih pacijenata.

Radi bolje prevencije i lečenja oboljenja potrebno je dobro poznavanje njegovog etiopatogenetskog mehanizma. Iako se rozacea smatra čestim oboljenjem (dijagnostikuje se kod 1% svih dermatoloških pacijenata), njena etiologija ostaje misterija.

Endokrinološki, farmakološki, imunološki, infektivni, alimentarni, klimatski i termalni faktori se smatraju okidačima za pojavu rozacee. Međutim, značaj većine ovih činilaca nije statistički dokazan. Ispitivanja novijeg datuma nisu potvrdila značajnu ulogu infekcije *Helicobacter pylori*, konzumacije kafe ili alkohola.

Značajni faktori rizika od nastanka rozacee bili su starost, fotosenzitivni tipovi kože (po Fitzpatricku I,II), pozitivna porodična anamneza (najznačajnija), obavljanje posla na otvorenom prostoru i prestanak pušenja.

Iz svega navedenog se može zaključiti da je rozacea izraz „fotostarenja" (eng. p*hotoaging*). Pretpostavlja se da oštećenje vezivnog tkiva u dermisu, koje se često viđa nakon solarne iradijacije, može biti inicijalni događaj i rezultovati disfunkcijom krvnih sudova sa konsekutivnim oštećenjem endotela, transudacijom, edemom i inflamacijom.Takođe se ističe centralna uloga abnormalne vaskularne reaktivnosti. Toplota, a ne kofein u toploj kafi izaziva napad rumenila (*flushing*).

Veći broj do sada sprovedenih ispitivanja ukazao je na preventivnu ulogu pušenja u nastanku granulomatoznih oboljenja, a kao moguće objašnjenje navodi se smanjen inflamatorni odgovor kod pušača. Zato je rozacea smatrana bolešću nepuša. U već ranije navedenoj studiji o faktorima rizika od nastanka rozacee ističe se statistički značaj statusa „bivšeg pušača" (najmanje jedna cigareta dnevno ranije, a nijedna sada), koji se pokazao značajnijim okidačem od statusa nepušača (nijedna cigareta tokom celog života). Nagli prekid imunosupresivnog delovanja koje ima pušenje može da deluje kao okidač.

Edukacija predstavlja prvi korak u lečenju rozacee, a ona podrazumeva ne samo izbegavanje faktora rizika, nego i upotrebu krema za zaštitu od sunca. Za sada ne postoji nijedan lek koji bi doveo do potpunog izlečenja rozacee. Standardne terapijske metode dovode do smanjenja inflamacije. Zato je glavni cilj lečenja rozace kontrola njenog toka.

Upotrebom antibiotika širokog spektra (antiinflamatorni efekat tetraciklina npr. doksiciklina i/ili makrolida, npr. azitromicina), može se usporiti progresija oboljenja. Kao i u našem slučaju, pojava neželjenih efekata primene sistemskih antibiotika često ograničava njihov trajni terapijski efekat.

U težim oblicima oboljenja uvek treba kombinovati sistemsku i lokalnu terapiju, jer se ona pokazala efikasnijom od upotrebe isključivo sistemske ili isključivo lokalne terapije. Lokalna primena antibiotika (klindamicin, eritromicin i tetraciklini) u kombinaciji sa metronidazolom i azelaičnom kiselinom predstavljaju prvu liniju izbora za lokalno lečenje rozacee.

Najveći broj studija o lokalnom lečenju rozacee odnosi se na pojedinačnu ili istovremenu primenu metronidazol 1% gela koji se nanosi jednom dnevno i azelaične kiseline 15% gela, koji se nanosi dva puta dnevno. Lečenje metronidazolom (sistemski i/ili lokalno) može se kombinovati sa sistemskom primenom antibiotika. Metronidazol u dnevnoj dozi od 400 mg tokom četiri meseca, a potom u dnevnoj dozi od 200 mg može u značajnoj meri da smanji otok kože na licu.

Lokalna primena pimekrolimusa 1% i takrolimusa 0,3-0,1% u lečenju rozacee još nije zvanično odobrena.

Najnovije studije su istakle superiornost antiinflamatornog efekta (smanjenje broja papula i pustula, ali ne i eritema) i kozmetičke prihvatljivosti azelaične kiseline u obliku 20% krema u odnosu na metronidazol 0,75% gel i permetrin 5% krem. Zato je značajno objasniti pacijentu sa rozaceom da nijedna od gore navedenih metoda lečenja, neće značajno uticati na iznenadne napade rumenila, crvenilo i osećaj pečenja.

Imajući sve ovo u vidu, nakon prekida desetodnevne terapije započete sistemskom primenom doksiciklina i metronidazola, kod naše pacijentkinje je nastavljena lokalna terapija sa azelaičnom kiselinom u obliku

20% krema, koja je uspešno sprovedena bez ikakvih neželjenih efekata.
Zaključak: Lokalna primena azelaične kiseline u obliku 20% krema može biti efikasna i bezbedna terapijska opcija kod nekih pacijenata sa granulomatoznom rozaceom.

Ključne reči

Rozacea; Hronična granulomatozna bolest; Lokalna primena; Dikarboksilne kiseline

Euromelanoma Campaign 2010 in Serbia

Euromelanoma Campaign 2010 in Serbia, was organized by Serbian Association of Dermatovenereologists and Euromelanoma Europe, under the auspices of the Ministry of Health of the Republic of Serbia, and supported by Beiersdorf Eucerin Company. This year Euromelanoma Monday was set for May 10th, 2010. The motto for all European countries included in the campaign was: "Cool in the Sun".

The aim of the Campaign was to identify as many people as possible at risk for skin cancer at an early stage, provide information about risk factors and symptoms of melanoma in early stages and alert the public about the potential dangers of sun exposure.

A mass media campaign was undertaken a month prior to the screening day including: radio and TV announcements, a facebook campaign (application and fun page), informative posters in public places, newspaper advertisements and PR articles on melanoma and Euromelanoma Day, an open line center for information on participating dermatologists, addresses and so forth. Websites: www.udvs.org and www.euromelanoma.org/serbia provide basic information about the prevention, screening, diagnosis and treatment of melanoma and other skin cancers.

In order to take part in the Campaign, people could get information on participating dermatologists (their addresses and phone numbers) and make appointments throught free of charge phone calls (from April 29th, to May 7th, 2010, call center: 0800 222 888 from 08:00-20:00).

A unique Euromelanoma questionnaire was translated into Serbian and sent to the participating dermatologists after the list of appointments was closed.

Dermatologists from all over Serbia participated in the Euromelanoma Campaign. There were 119 dermatologists (~ 50 % of all dermatologists from the Serbian Association of Dermatovenereologists) performing skin screening of patients on their list; there were 107 dermatologists from public hospitals and 12 dermatologists having private practice. Free-of-charge screening was performed in 1602 subjects at the Dermatology Clinics of Medical Centers, Outpatient Clinics or at Private Offices.

Statistical analysis

Most patients who underwent screening were females. There were 1093/1602 (68.6%) females and 500/1602 (31.4%) males. There was a wide spectrum of ages. Over 65.9% of individuals had sensitive phototypes II or III. A significant percentage reported working outdoors. More impressively, 24.5% of individuals reported getting sunburnt before adolescence, and this may correlate with the fact that most individuals belonged to the sensitive photo types. Also, 13% used solarium tanning, which would be worth comparing with other European countries, given its implication in skin cancer risk.

The results of clinical examination of screens revealed that 24.1% of screens had dysplastic nevi, 20.9% had actinic keratoses (AKs), 4.9% basal cell carcinomas (BCCs), 0.7% squamous cell carcinomas (SCC), while 13.4% were diagnosed as having melanoma. We have performed a statistical analysis for the group of patients with melanoma, BCC and SCC suspected lesions.

Based on the univariate logistic regression analysis significant predictors of melanoma included: number of moles >25, presence of lentigenes and atypical moles. However, the most significant predictors of melanoma were: number of moles >25 and presence of lentigenes.

Univariate logistic regression analysis showed that significant predictors of BCC were: male sex, age >50 years, outdoor occupation (especially for more than 10 years), low education (elementary schooll), skin type I, never using sunscreens when exposed to the sun longer than 1 hour and at vacation, living a year or more in a country with high sun exposure, personal history of skin cancer (BCC, SCC), presence of lentigenes and actinic keratoses.

Multivariate logistic regression analysis showed that significant predictors for BCC were: age >50 years, skin type I, and personal history of skin cancer (BCC, SCC).

Based on significant predictors of BCC found by logistic regression analysis, the prediction score for suspicious lesions was made. Cut-off point was 4. It means that if a participant had four or more predictors (male sex, age >50 years, outdoor occupation, outdoor

occupation >10 years. etc) there was a great possibility (sensitivity=90.6%, specificity =68.4%) for suspicious lesions.

Univariate logistic regression analysis revealed that significant predictors for SCC were: age >70 years, skin type I, personal history of skin cancer (BCC, SCC), presence of lentigenes and actinic keratoses.

Multivariate logistic regression analysis showed that significant predictors for SCC were: skin type I and presence of lentigenes.

Euromelanoma Day Campaign team from Serbia was presented by Prof. Lj. Medenica, Prof. M. Nikolić, Ass. Prof. D. Škiljević, Mrs. N. Miletić-Nevajda (Beiersdorf - Eucerin).

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Figure 1. Poster for the Euromelanoma Campaign 2010 in Serbia

A report on the Dr. David Gruby's 200 year birth anniversary

David Gruby was born on August 20, 1810 in Kis-Kér (now Bačko Dobro Polje, Serbia) a small village near Novi Sad. At taht time, his birthplace was in a fertile area in the Southern Hungary. The area was known for constant migration of people and military personnel and many infectious diseases. The fact that Dr. Gruby came from this region might have contributed to his becoming a pioneer in the fields of microbiology and medical mycology. After a poor and difficult childhood, he graduated from highschool in Budapest. After 5 years of studies, he went to Vienna to study medicine, and granduated

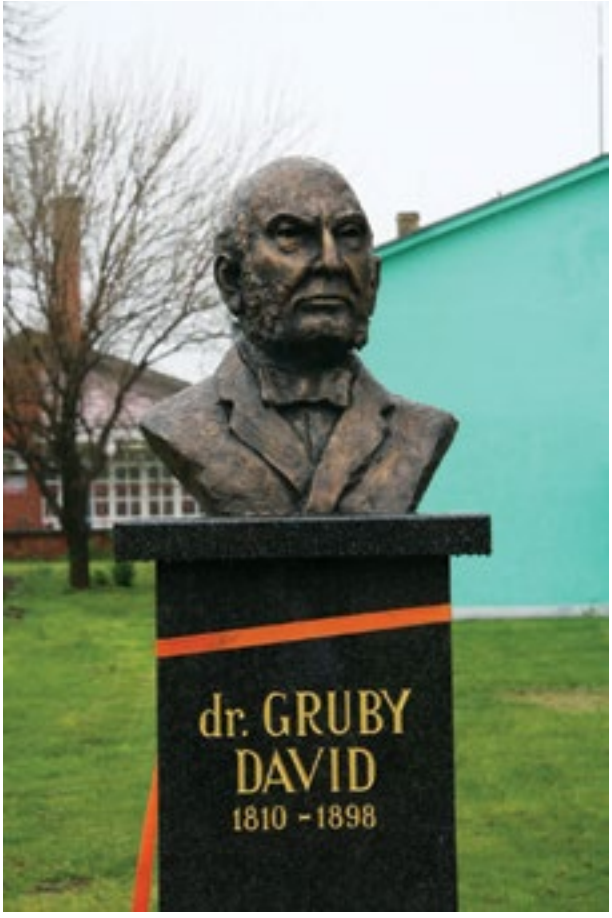

Figure 1. Dr. David Gruby's portrait bust in Bačko Dobro Polje

Figure 2. Prof. Dr. Karl Holubar, Dr. Željko Vidović, Academician of Medical Sciences Prof. Dr. Teodor Kovač, Academician of Medical Sciences Dr. Vladimir Jokanović

in 1839. In 1841, he described the fungus that causes favus. This discovery was independent of Johann Lukas Schonlein's findings. In 1842, he described *Trichophyton ectothrix*, a microscopic cryptogram, which causes a dermatological disease known as *sycosis barbae*. The following year Gruby described another fungus which he called *Microsporum audouini,* in honor of Jean Victor Audouin and this disease is sometimes referred to as ''Gruby's disease". Gruby also discovered an animal parasite in the blood of frogs he called *Trypanosoma sanguinis*. He was one of the most popular practicians in Paris, were he died in 1898.

Dr. Gruby's portrait bust, work of the Academician of Medical Sciences Dr. Vladimir Jokanović, was unveiled in his birth place, in front of the Health Care Center. After the ceremony, a Scientific Meeting was held in the Vrbas City Hall,

organized by the *Scientific Society for History of Health Culture of Vojvodina*, *Dermatovenereology Section* of the *Society of Physicians of Vojvodina of the Serbian Medical Society*, *Section for History of Medicine* of the *Serbian Medical Society* and the *Medical Academy of the Serbian Medical Society*. The event was opened by the President of the Vrbas municipality, Dr. Željko Vidović. Prof. Dr. Karl Holubar from Vienna spoke about Dr. David Gruby and his place in the early development of mycology and bacteriology.

There were four more lectures: Life and work of Dr. David Gruby, by the Academician of Medical Sciences Dr. Vladimir Jokanović; History of dermatovenereology in Vojvodina, by Asst. Dr. Zoran Golušin; Medical mycology since the epoch of Dr. David Gruby to the present, by Prim. Dr. Siniša Tasić, and Medical Discoveries at the time of David Gruby, by Asst. Dr. Vladimir Sakač.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2011

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
25-27 March, 2011	MedicReS International Congress on "Good Medical Research", Istanbul, Turkey	3 December, 2010	www.ic2011.medicres.com
7-8 April, 2011	International Congress on Tracing New Occupational Diseases, Amsterdam, Netherlands	15 December, 2010	www.icohscom2011.nl
14-17 April, 2011	8th EADV Spring Symposium Carlsbad, Czech Republic	31 October, 2010	www.eadv.org
24-29 May, 2011	22nd World Congress of Dermatology, Seoul, Korea	31 October, 2010	www.wcd2011.org
11-15 June, 2011	30th Congress of the European Academy of Allergy and Clinical Immunology (EAACI), Istanbul, Turkey	1 April, 2011	www.eaaci.2011.com
20-23 June, 2011	7th Congress of the European Association of Dermato-Oncology (EADO), Nantes, France	11 March, 2011	www.eado2011.com
31 August – 3 September, 2011	32nd Symposium of the International Society of Dermatopathology, Geneva, Switzerland	No abstract submission	www.isdpssdv2011.com
7-10 September, 2011	41st Annual ESDR Meeeting (European Society for Dermatological Research) , Barcelona, Spain	20 May, 2011	www.esdr2011.org
8-10 September, 2011	26th IUSTI Europe Congress Riga, Latvia	1 June, 2011	www.iusti-europe2011.org
15-17 September, 2011	2nd 5-Continent-Congress for Lasers and Aesthetic Medicine, Cannes, France	31 March, 2011	www.5-cc.com
22-24 September, 2011	32nd Annual Meeting of the International Society for Dermatologic Surgery, Heidelberg, Germany	In construction	www.isdsworld.com
20-24 October, 2011	20th Congress of the European Academy of Dermatology and Venereology, Lisbon, Portugal	20 March, 2011	www.eadv.org
2-5 November, 2011	12th IUSTI World Congress New Delhi, India	15 June, 2011	www.iusti2011.org
1-3 December, 2011	6th International Congress of Psoriasis, London, UK	1 August, 2011	www.psoriasisg2c.com
31 January - 4 February 2012	8th World Congress of the International Academy of Cosmetic Dermatology (IACD), Cancun, Mexico	1 September, 2011	www.wcocd2012.com

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

AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

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

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

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

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

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

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

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

1. Manuscript Preparation Guidelines

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

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

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

- A running title (limited to 30 characters);

- Authors' names and institutional affiliations;

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

1.2. Abstracts

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

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

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

1.3. A list of abbreviations

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

1.4. Cover Letter

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

2. Tables and illustrations

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

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

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

3. References

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

4. Additional information

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

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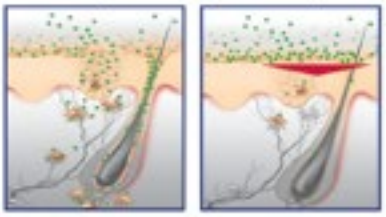

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Cover figure: Christ Healing Ten Lepers, Christ's Miracles, XIVth century, The monastery Visoki Dečani, Serbia, Kosovo

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