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Dermoscopy of difficult-to-diagnose Melanomas

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Abstract

Dermoscopy is a non-invasive procedure that allows the evaluation of cutaneous lesions, and is considered to be a useful tool that improves the diagnostic accuracy of melanoma. Many dermoscopic criteria of melanoma have been established and several algorithms have been created for melanoma detection. However, the recognition of some melanomas remains challenging. Melanomas on specific body sites, melanomas in patients with multiple atypical moles, and nodular melanomas represent the most difficult-to-recognize melanoma subtypes, since they typically lack the "classic" melanoma-specific criteria. This paper provides an update on dermoscopy of difficult-to-diagnose melanomas by summarizing the newest data. Lastly, we highlight the importance of digital dermoscopy in the follow-up of melanocytic lesions for the detection of incipient melanomas while maintaining a low excision rate.

Key words

Dermoscopy; Melanoma; Diagnosis; Skin Neoplasms

Dermoscopy is a non-invasive diagnostic procedure that allows the visualization of structures located in the epidermis, dermoepidermal junction and papillary dermis, that normally cannot be seen with the naked eye (1). Dermoscopy was first introduced for diagnosis and evaluation of skin tumors and melanomas, and gradually has become a commonly used skin cancer screening tool. (2). Nowadays, digital dermoscopy follow-up has gained ground for the monitoring of patients especially those with multiple and atypical moles.

The traditional dermoscopic criteria of melanoma have been investigated and established in the context of superficial spreading melanoma (SSM). SSM is the most common and the easiest to recognize type of melanoma. However, it might be difficult to detect in early stages.

Dermoscopic features of SSM include atypical pigment network, irregular dots or globules, irregular streaks and regression structures (Figure 1) (3, 4). Asymmetric pigmentation pattern, asymmetric shape, irregular blotches, blue-white veil and a multicomponent global pattern can also be observed (4 - 6). An atypical vascular pattern of linear irregular vessels, dotted vessels, or milky-red areas are also a common finding (4 - 6).

Sadayasu et al. suggested the presence of a sudden change of the intralesional color, from a blue-gray structureless area in the center to a peripheral light-brown pigment network, as a diagnostic indicator of melanomas (3).

The aforementioned melanoma criteria have been tested in several studies and showed valid for melanoma diagnosis. Based on these criteria, several dermoscopic algorithms have been created (ABCD rule, 7-point checklist, Menzies method). However, melanomas on specific body sites, melanomas in patients with multiple atypical moles, and nodular melanomas often lack the "traditional" melanoma criteria, rendering their recognition particularly troublesome.

This paper aims to summarize recent advances on the dermoscopic patterns of difficult-to-diagnose melanomas.

Acral melanoma

Acral melanoma (AM) is considered to have poorer prognosis compared to other melanoma types. Therefore, its early detection is of utmost importance.

Dermoscopy allows clinicians to detect morphological characteristics of melanomas that precede the appearance of clinical symptoms (7).

AM is dermoscopically characterized by a multicomponent pattern, a parallel ridge pattern, irregular diffuse pigmentation (also called blotches), milky-red areas, peripheral dots and globules, and an abrupt peripheral margin (Figure 2) (8). It has to be noted that, besides the dermoscopic patterns, clinicians should always take into account the maximum diameter of the acral lesions. Saida et al. and Braun et al. observed that lesions with a diameter >7 mm and >1 cm, respectively, are more likely to be melanomas, regardless of dermoscopic characteristics (9-11, 8).

As for the subungual melanoma, dermoscopic criteria include light to dark brown coloration of the background, the lines are barely visible, brown to black longitudinal lines, the color, spacing and the width are irregular, parallelism and Hutchinson's sign (periungual pigmentation) (Figure 3) (12, 13).

Lallas et al. developed the BRAAFF scoring system for the detection of AM without nail-apparatus melanoma. The dermoscopic variables include four positive predictors (irregular blotches, parallel ridge pattern, asymmetry of structures, asymmetry of colors) and two negative predictors (parallel furrow pattern, fibrillary pattern). The authors highlighted that these variables should always be counted in the overall clinical context of the patient and recommend histopathological examination in equivocal cases (14).

Mucosal melanoma

Although dermoscopy is widely used in the diagnosis of pigmented and nonpigmented lesions of the skin, its role in the evaluation of pigmented mucosal lesions is not well established. The two largest studies referring to dermoscopy of pigmented mucosal lesions were conducted by Lin et al. (15) and the *International Dermoscopy Society* (IDS) (16), and included 40 and 140 pigmented mucosal cases, respectively, from lips, penis, vulva and other anogenital areas.

According to the results of the first study, asymmetry of structure, multiple colors, blue-white veil and irregular dots/globules are the commonest features in mucosal melanoma compared with the findings of benign lesions. In the second study, a combination of at least 1 of 3 colors (blue, gray or white) with structureless zones was shown to have a relatively high diagnostic accuracy when differentiating between benign and malignant lesions. Moreover, authors noted that multiple colors outmatch the multiple patterns. Finally, the presence of structureless parts and gray color may be indicative of early stages of mucosal melanomas (MM). On the contrary, multiple patterns and additional colors, especially blue or white, seem to be more indicative of late MM stages.

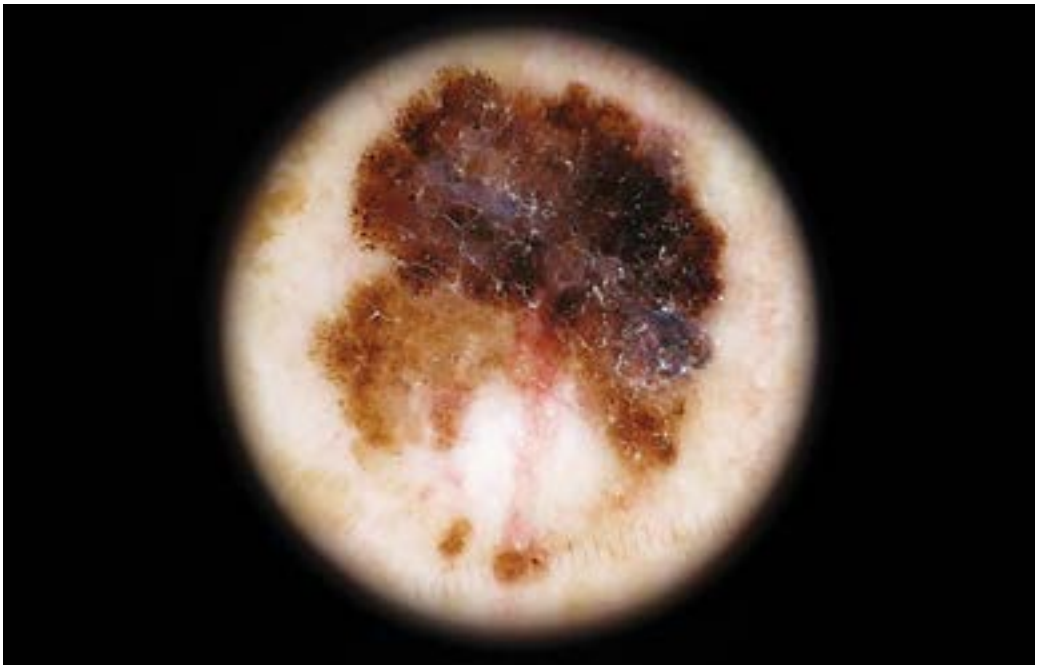

Figure 1. A typical superficial spreading melanoma dermoscopically displaying a multicomponent pattern consisting of irregular blotches, irregular dots or globules, irregular streaks and regression structures

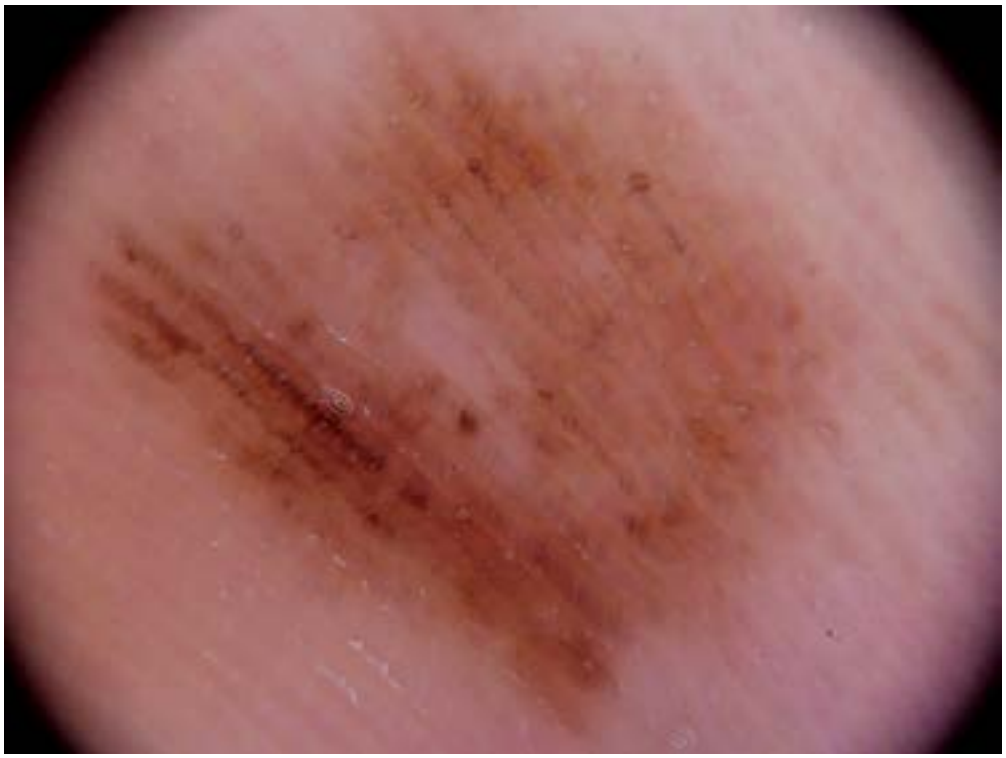

Figure 2. An acral melanoma dermoscopically typified by a parallel ridge pattern and asymmetry of colors and structures

Lentigo maligna melanoma

Differentiating lentigo maligna melanoma (LMM) from solar lentigo or seborrheic keratosis (SL/SK), pigmented actinic keratosis (PAK) and lichen planus-like *keratosis* (LPLK) is highly challenging, even with the use of dermoscopy.

Schiffner et al. (17, 18) were the first to propose a progression model for LMM that includes four dermoscopic criteria: asymmetrical pigmented follicular openings, dark rhomboidal structures, slate-gray dots forming an annular-granular pattern, and slate–gray globules (Figure 4). The combination of these features showed a sensitivity of 89% and a specificity of 96% in the diagnosis of LMM. Furthermore, light brown fingerprint areas and horny pseudocysts were indicated as features representing benign growths.

Later, Pralong et al. (19) studied 125 cases and noted that at least one of the four 4 Schiffner-Stolz criteria were present in 87% of lesions, and further described four additional criteria: mainly vascular – increased density of the vascular network, red rhomboidal structures, target-like patterns and darkening at dermoscopic examination (when compared with naked-eye examination).

Tschandl et al. (20) analyzed dermatoscopy images of 240 flat pigmented facial skin lesions and claimed that a pattern of circles is highly suggestive for LMM, while the presence of gray color strengthens the diagnosis.

Finally, Lallas et al. (21), attempted to differentiate facial LMM from PAK, and conducted a study of 144 lesions with LMM, PAK and SL/SK and created a scoring scheme for LMM diagnosis; a total score of ≥ 1 has a sensitivity of 92.9% and a specificity of 55.4% for the diagnosis of LMM. Furthermore, the absence of evident follicles (the follicular openings within the pigmented lesion are not clearly visible and obvious and are obscured by pigmentation of any color) in combination with gray rhomboidal lines are suggestive of LMM and biopsy is required.

Nodular melanoma

Nodular melanoma (NM) is a rapidly progressing neoplasm with a high risk for metastasis, even in its early stages (22, 23). NM lacks an initial radial growth phase, presenting with a vertical growth (22). Furthermore, it lacks the commonly used ABCD criteria (asymmetry, border irregularity, color variegation, diameter ≥ 6mm), while, dermoscopically, NM displays no "traditional" melanoma-specific criteria. For these reasons, the EFG

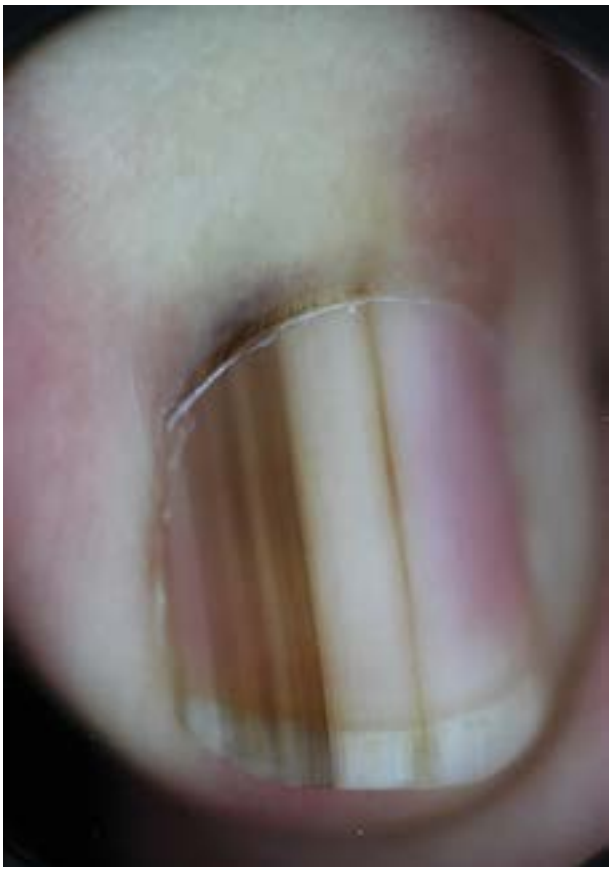

Figure 3. Dermoscopy of a subungual melanoma revealing brown to black longitudinal lines, characterized by irregularity in terms of color, spacing and width. Hutchinson's sign is also evident

rule (Elevation, Firmness on palpation, continuous Growth over one month) has been introduced in clinical practice in the diagnosis of NM.

Several studies attempted to examine and propose dermoscopic features for NM recognition. Argenziano et al, (24) proposed the blue-black rule, that is blue (usually structureless) and black (dots, globules, blotches) areas involving at least 10% of the lesion surface, as a significant indicator of NM. The blue color corresponds to pigmented melanocytes in the deep dermis, while black arises from intraepidermal melanin or from dense dermal proliferation of pigmented melanocytes under a thinned epidermis, usually due to ulceration (25). The combination of the blue-black feature and one or more of the standard melanoma criteria has a 84.6 % sensitivity and 80.5 % specificity.

In 2015, Pizzichetta et al. (5) studied 457 pigmented skin lesions in order to describe dermoscopic characteristics of pigmented NM, compared with SSM and pigmented nodular non melanocytic and benign melanocytic lesions. A multivariate analysis showed that asymmetric pigmentation, blue-black pigmented areas, homogeneous disorganized pattern, a combination of polymorphous vessels and milky red globules/areas or red homogeneous areas, significantly increased the risk of NM (Figure 5). On the other hand, homogeneous pattern was found to be a positive factor for non-melanocytic and benign melanocytic lesions. Finally, ulcerations, homogeneous disorganized patterns, and homogeneous blue pigmented structureless areas, are features favoring a NM diagnosis, in contrast with peripheral light brown structureless areas which advocate in favor of SSM.

Melanomas in patients with multiple nevi

It has been demonstrated that dermoscopy is more accurate than naked eye examination for melanoma detection (26, 27). However, in patients with multiple atypical nevi, dermoscopy might be inadequate to uncover a melanoma among a plethora of clinically and dermoscopically atypical moles (28).

A high number of melanocytic nevi is considered to be a major risk factor for melanoma (29, 30). Given that melanoma can sometimes be misdiagnosed as a nevus, the diagnosis of the malignancy among patients with more than 50 common nevi in total, or multiple clinically 'atypical' or 'dysplastic' moles (referring to diagnostic uncertainty of being a melanoma) is very challenging. Subsequently, early melanoma detection and reduction of unnecessary excisions is of utmost importance. The most effective strategy to manage these patients includes clinical and dermoscopic examination of all lesions, in order to identify the 'signature nevus pattern' of each patient (comparative approach). The comparative approach is based on the observation that the majority of an individual's nevi display similar dermoscopic characteristics, while melanoma deviates this "signature pattern" (31- 33). Another suggested strategy for the management of these patients includes the use of digital dermoscopy monitoring of melanocytic lesions, based on the fact that benign lesions stay stable while melanomas change over time (34).

Meta-analytic data of digital dermoscopy follow-up (DDF) of melanocytic skin lesions (35), suggested that DDF is a reliable method for the detection of early melanomas, while maintaining a reasonably low rate of excisions of benign moles. Specifically, more than half of excised melanomas in patients under DDF were in situ and, among invasive tumors, none was thicker than 1 mm. It was also noted that longer follow-up period was related with the diagnosis of more melanomas. Therefore, one can assume that close surveillance,

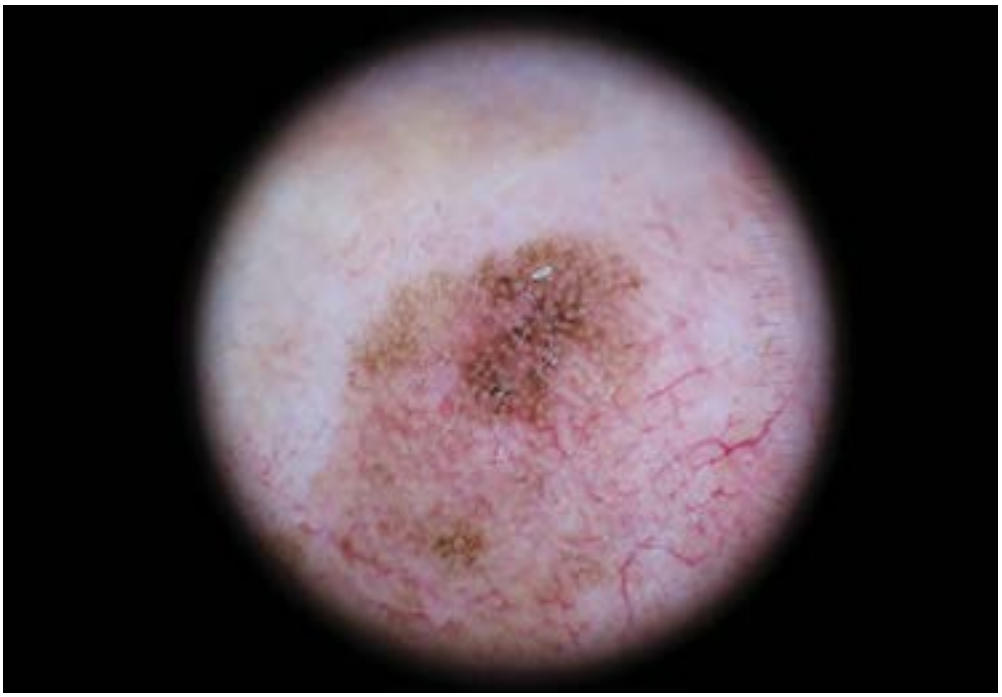

Figure 4. Dermoscopy of an early lentigo maligna characterized by asymmetrically pigmented follicular openings and slate-gray dots and globules

especially of high-risk patients, is mandatory for early diagnosis of the malignancy. Moscarella et al. (36) noted that not only long- but also short-term dermoscopy monitoring is highly effective for melanoma detection in patients with multiple atypical nevi.

The *International Dermoscopy Society* (37), suggested two different strategies of follow-up based on the number of lesions. When clinicians face a suspicious lesion in a patient with a single or a few lesions, an excision or a 2 to 4 month monitoring period should follow. If the lesion is benign, no further examination is needed. The second strategy is suggested for patients with multiple lesions, where a comparative approach should be first applied (with a possible excision of the most atypical lesion). Consequently, a follow-up (of flat reticular lesions only) should be first scheduled after a 3-month interval following the baseline visit, and then after a 6 -12 month interval. Elevated equivocal lesions with significant regression should not be monitored but excised because of the possibility of being invasive melanomas. Finally, it has to be stated that patients' compliance was found to be optimized by short- rather than long-term intervals between the visits (38).

Conclusion

Dermoscopy is considered to be an integral part of clinical examination for the evaluation and detection of melanoma. Recent advances in the morphological evaluation of melanomas, changing the "traditional" criteria, enhance recognition of melanomas that might otherwise escape detection. As more studies are performed and new data are gathered, clinicians should always update their knowledge in order to minimize the risk of missing a melanoma.

Abbreviations

SSM - Superficial spreading melanoma
AM - Acral melanoma
IDS - International Dermoscopy Society
MM - Mucosal melanomas
LMM - Lentigo maligna melanoma
PAK - Pigmented actinic keratosis
LPLK - Lichen planus-like keratosis
NM - Nodular melanoma
ABCD - Asymmetry, border irregularity, color variegation, diameter ≥ 6mm
EFG -Elevation, Firmness, Growth
DDF - Digital dermoscopy follow-up

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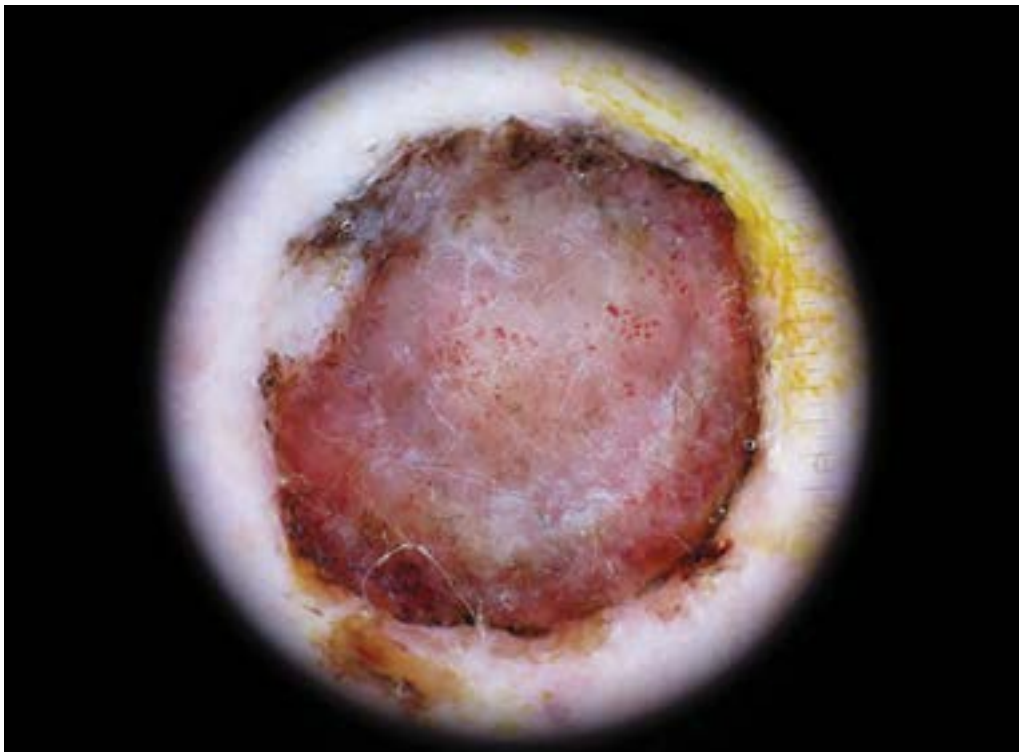

Figure 5. Dermoscopy of an amelanotic nodular melanoma revealing linear, irregular, and tortuous vessels over a milky-red background. Hemorrhages are also evident

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Dermoskopija melanoma s otežanom dijagnostikom

Sažetak

Dermoskopija je neinvazivna procedura koja omogućava procenu kožnih lezija i predstavlja korisnu metodu koja značajno unapređuje *tačnost* u dijagnostici melanoma. Postoje brojni dermoskopski kriterijumi za melanome, kao i nekoliko algoritama kreiranih za detekciju melanoma. Međutim, prepoznavanje nekih melanoma i dalje je izazov. Melanomi koji nastaju na specifičnim delovima tela, melanomi kod pacijenata sa brojnim netipičnim mladežima i nodularni melanomi, spadaju u podvrste melanoma, jer obično nemaju „klasične" specifične kriterijume melanoma. Ovaj rad se bavi novijim informacijama o dermoskopiji melanoma teških za dijagnozu sumirajući najnovije podatke. Na kraju, izdvajamo značaj digitalne dermoskopije u praćenju melanocitnih lezija za otkrivanje početnih melanoma uz održavanje niske stope ekcizija.

Ključne reči

Dermoskopija; Melanom; Dijagnoza; Kožne neoplazme

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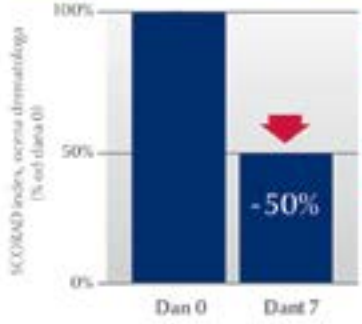

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National Guidelines for the Treatment of Atopic Dermatitis

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Epidemiology of atopic dermatitis

Atopic dermatitis (AD) is a disease that usually presents in the early childhood (1). AD is one of the most common skin diseases and it affects approximately 20% of children and 1 - 3% of adults (2). In 60% of patients the first manifestations appear within the first year of life, and in 90% of patients before the age of five. In most patients manifestations of AD disappear before the adulthood, while in 25% of patients AD persists throughout life (2). Rarely, the first AD manifestations appear in adulthood (2). Approximately 25% of AD patients may develop some form of hand eczema during the life (3).

Clinical presentations of AD

The clinical presentations of AD vary depending on the age and course of the disease; the major manifestations include erythema, edema, xerosis, erosions/excoriation, oozing and crusting, and lichenification (1, 4, 5, 6, 7). Intense itching is common in AD resulting in excoriation, pruritic papules, lichenification and eczematous skin lesions (2, 3, 4). The itch is particularly pronounced at night causing sleep impairment, thus having significant negative impact on the quality of life of both patients and their families (2, 3, 5, 6). The disease may take an acute, subacute or chronic course. Acute lesions are characterized by intense pruritus, presence of papules and vesicles on erythematous skin, and are associated with excoriation, erosion and serous exudates. Subacute lesions manifest as erythematous, excoriated scaly papules, while typical skin thickening with pronounced skin markings (lichenification) and pruritic papules are distinctive for the chronic course of the disease. In infants and young children, AD commonly starts as an acute or subacute condition, whereas chronic forms are characteristic for older children and adults (5, 6, 7). These three distinct phases are often observed in the same patient (6, 7).

Clinical presentations in children

During the first month of life, the first signs of atopic dermatitis may present as pronounced yellowish scales on the scalp, commonly known as „cradle cap“ or infantile seborrheic dermatitis (1). In infants, 3 - 6 months old, the predilection sites for eczematous changes on the face are cheeks, forehead and chin, whereas the central part of the face (nose, perioral region) and diaper area are often spared. Skin changes are acute or subacute, with unclear margins, and present with erythema, edema, papulovesicles, excoriations, often associated with oozing and crusting, while chronic changes are rare and manifest as erythematous papules and plaques with desquamation. In infants 8 - 10 months old, AD progresses to extensor surfaces of the extremities, and after the first year it may affect the upper trunk, where the changes manifest as nummular dermatitis (1, 5, 6, 7). After the age of 2 years, the clinical presentations change, that is, the disease takes a chronic course, or AD develops de novo. The symptoms include poorly marginated lichenified plaques with excoriations

localized to cubital and popliteal fossae, on the neck and in the region of wrist and ankle joints. Dry skin affects the entire body. Lichenification occurs as a consequence of scraping and scratching due to intense (predominantly nocturnal) itching. At intervals, acute eczematous eruptions, manifesting as papules and papulovesicles, may develop on the lesions (1, 3, 4, 5). Adolescents often present with persistent lichenified plaques in large joint flexures, associated with chronic changes on the face (periorbital dermatitis), neck, hands, feet and back (5, 7).

Clinical presentations in adults

Adult patients with AD commonly present with lichenified plaques localized mainly in the flexural areas of the extremities and anogenital region. Facial edema associated with lichenification on the neck and eyelids, as well as chronic eczema on the hands and/or feet is a common finding. Pruritic type of AD is characterized by excoriated pruritic nodules. The disease may have a chronic recurrent course. Exacerbations often start with pronounced itching, without visible skin lesions, followed by erythema, papules and infiltrations (1, 5, 6, 7).

Patients with AD have increased susceptibility to skin infections, mostly those of bacterial etiology, but viral and fungalas well (5, 6, 7, 9). **Bacterial infections** are commonly associated with *Staphylococcus aureus* and somewhat more rarely with *Streptococcus pyogenes* (6, 7). **Viral infections** are more frequent in patients with AD, showing tendency of dissemination and spread of lesions (1, 8, 10). Depending on the causative viral agent, eczema herpeticum, eczema molluscatum, eczema coxsackium or eczema vaccinatum may develop (1, 9, 10, 11). **Fungal infections** associated with *Malassezia sympodialis (Pityrosporum ovale*) lead to head and neck dermatitis (12).

The extent and severity of AD are estimated by SCORing atopic dermatitis (SCORAD) (usually used in Europe) and eczema area and severity index (EASI) (usually used in USA) indices (8).

Etiopathogenesis of atopic dermatitis

The etiopathogenesis of AD is multifactorial, including disturbances in skin barrier function, immune reaction with key role of T-cells, dendritic cells, lymphocytes, mast cells, eosinophils, as well as environmental factors. Skin barrier dysfunction in AD is a consequence to three main causes: reduced filaggrin gene expression, decreased level of ceramides in the skin, and increased activity of epidermal proteases. Almost 50% of patients with AD have a reduced expression for filaggrin gene synthesis, protein with a key role in maintaining the structural skin barrier function, while its absence, disturbing this structure, facilitates penetration of haptens and proteins (13, 14).

Ceramides are natural lipids essential for the retention of water in the corneal layer of epidermis. Patients with AD exhibit a significant decrease of ceramides, both in lesional and non-lesional skin. The amount of ceramides in the skin is in a reverse relation with transepidermal water loss, which is a characteristic of AD skin. The fact that in children, decreased amount of ceramides is sometimes found only in lesional skin, is explained as a postinflammatory reaction, not as a genetic factor (13, 14).

In regard to immunological aspects, the etiopathogenesis of AD is very complex, since it includes genes that encode factors of the adaptive and innate immune system. Skin resident cells, as keratinocytes, dendritic cells, mastocytes, macrophages and innate lymphocytes, have a role in the inflammatory reaction in patients with AD. Besides, T-lymphocytes, plasmacytoid dendritic cells, monocytes and granulocytes from circulation also have a role in the etiology of eczematous reaction (13, 14).

In the pathogenesis of AD, T helper (Th) lymphocytes have a central role. In AD patients, activity of specific ThLy clones is unbalanced, with predominance of Th2 cell response to allergens, which differs in healthy individuals, where Th1 response is dominant. Pathological activation of Th2 cells induces amplified production of IL4, IL5 and IL13, resulting in accumulation of other types of immune cells and development of acute lesions in AD patients. Contrary to acute AD lesions, Th1 cell activity is dominant in chronic AD lesions (13, 14).

Different incidence of AD in different geographical areas points to the significant role of environmental factors in its etiopathogenesis, such as climate factors, dietary factors, obesity, tobacco smoke exposure and microbiological exposure.

Novel studies highlighted the role and effects of skin microbiome both on its homeostasis as well as on the onset of different pathological conditions, including

AD. In episodes of AD exacerbation, increased amount of *S. aureus*, but also *S. epidermidis* is evident. Exacerbation of cutaneous inflammation is mediated by superantigens such as staphylococcus enterotoxins A and B, as well as toxic shock syndrome toxin 1 which result in T cells polyclonal activation (13, 14).

Increases in Streptococcus, Propionibacterium and Corynebacterium species on the skin are observed following therapy, also with differences to the skin microbiota of healthy individuals (13). Differences of gut and intestinal microbiota between AD patients and healthy individuals are also shown (13).

Table 1. Diagnostic criteria for atopic dermatitis by Hanifin and Rajka

Major (3 of 4)	**Minor (at least 3)**
- Pruritus	- Positive prick allergy tests
	- Increased total IgE concentration
- Typical morphology and distribution of skin lesions: flexural dermatitis in children older than 2 years and adults; facial dermatitis in infants	- Early onset of disease
	- Dry skin
	- Facial pallor and/or redness
	- Pityriasis alba
- Chronic or chronic relapsing course	- Ichthyosis
	- Orbital darkening
- Personal and/or family history of atopy	- Dennie-Morgan infraorbital folds
	- Palmar hyperlinearity
	- Keratosis pilaris
	- Cheilitis
	- Hand and foot eczema
	- Areolar eczema
	- Pruritus upon sweating
	- Wool intolerance
	- White dermographism
	- Perifollicular accentuation
	- Anterior neck folds
	- Subcapsular cataract and keratoconus
	- Susceptibility to bacterial and viral infections (S. aureus, HSV)
	- Decreased cell-mediated immunity
	- Worsening of skin condition under emotional, environmental stressors and irritants
	- Food intolerance, especially in children younger than 2 years

In regard to the climate factors, UV exposition and worm climate show protective effects on the onset of eczema, contrary to decreased UV exposition and high humidity.

Acidic pH of the skin, which contributes to the repair of the barrier function, has antibacterial effect and role in desquamation. In AD patients, pH of the entire skin is increased, resulting in exacerbation of the disease. The most common factors that disturb the pH of the skin are detergents and soaps. They change the amount of the lipids on the skin surface, enhance proteases and make the corneal layer thinner (13, 14).

The interaction of above-mentioned genetic factors, immune factors and environmental factors is very complex in the etiopathogenesis of AD. With a great amount of new discoveries in this field, this is for sure a great challenge for further investigations in this area.

Diagnostic criteria for atopic dermatitis

The European Task Force on Atopic Dermatitis defined atopy as a genetic susceptibility to Th2 immune response to usual environmental allergens with clinical signs and symptoms of asthma, allergic and/or atopic dermatitis. In the majority of patients, the diagnosis of atopic dermatitis is based on personal history and typical clinical manifestations. Various diagnostic criteria have been developed in recent decades, but they are most important for epidemiological and clinical studies to define inclusion criteria (1, 15, 16).

Diagnostic criteria for atopic dermatitis include combinations of clinical signs and symptoms, allergy tests and laboratory test results that confirm the presence of atopy. The most popular diagnostic criteria were developed by Hanifin and Rajka in 1980 (Table 1) (15). According to these criteria, 3 major and 3 minor criteria are needed for the diagnosis of atopic dermatitis. These criteria were validated in 2 studies, showing a diagnostic sensitivity of 87.9% and 96% and specificity of 77.6% and 93%, respectively (16).

The second, less frequently employed criteria are those of UK Working Party's Criteria. Based on these criteria, atopic dermatitis is diagnosed in persons with typical skin lesions in the last 12 months, and at least 3 of 4 following criteria: early onset under the age of 2 (not used in children under the age of 4), personal history or current presence of flexural dermatitis, dry skin and personal history of atopy (or family history in children younger than 4 years) (17). These criteria were validated in numerous studies, with specificity of 10 - 100% and sensitivity of 89 - 99%.

Furthermore, the American Academy of Dermatology recommended criteria which were divided into: essential, important, and associated features, based on their frequency and importance (18). Several other criteria were also recommended, but without wider acceptance in everyday clinical practice (19, 20).

In recent analysis and systematic literature review of all the studies that examined validity of different diagnostic criteria, the authors concluded that methodology of validation should be more uniform in order to draw the final conclusion of their utility (16)

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Emollient therapy and skin care in AD

The management of AD requires efficient control of flares by treatment of acute inflammatory symptoms, along with restoration of the skin barrier homeostasis, and avoidance of trigger and exacerbating factors. Certain moisturizers may improve the skin barrier function and reduce skin susceptibility to irritants (21, 22).

Cleansing and bathing

In general, dryness is worse during cold months, when it is aggravated by heat in the house and low humidity. Daily baths are considered an excellent means of hydrating the skin. The skin must be cleansed thoroughly, but gently and carefully. A daily bath or shower removes scales, crusts, irritants, and allergens and provides an opportunity to moisturize the skin. The water should be lukewarm, and 20 min immersion is adequate. Short baths (only 5 minutes) and the use of bath oils (in the last 2 minutes of bathing) are aimed at avoiding epidermal dehydration (8, 23). Soaps, shampoos, and shower gels and foams should be avoided; they can irritate and dry the skin. Prepubertal children produce little sebum and require minimal shampoo. Bath oils may have a moisturizing effect, but evidence for efficacy is limited. Neutral or low pH non-soap cleansers that are hypoallergenic and fragrance free are available, but any moisturizer cream or lotion can be used as a soap substitute. It is easiest to apply the moisturizer before getting into

the bath or shower, and then massage it into the skin once in the water (19, 24). Topical emollients are preferentially applied immediately after taking a bath or a shower following gentle drying when the skin is still slightly humid. The key to maintaining hydration after bathing in patients with atopic dermatitis is application of a thick emollient within 3 minutes after exiting the bath, before evaporative loss occurs (8, 22, 23).

Emollient therapy

Proper use of an emollient for hydration is a keystone of AD treatment and emollients are the mainstay of maintenance therapy. Emollients are available in various formulations. Lotions are thin with high water content and are useful for hairy areas and weeping eczema, but ineffective for severe xerosis. Gels are similar to lotions, with high water content. Creams (emulsions of water and oil) are most popular: easily rubbed in and do not leave a shine, but greasier than lotions and gels. Some oils solidify in cold climates, but soften at body temperature. Ointments are thick and greasy and are suitable for very dry eczema. However, they are less cosmetically acceptable, can cause heat trapping and folliculitis, and can stain clothing and bedding. Additives can cause irritation or allergy, and added fragrance should be avoided (24).

Patients should be encouraged to try different emollients, as well as advised about the best type for their skin condition, climatic conditions, and lifestyle. Hydration of the skin is usually maintained by application of moisturizers at least twice daily. Patients might use a gel- or cream-based emollient during the day and in hot weather, and an ointment at night and in cold weather. The amount needed is often underestimated. Approximately 600 g/week is required for adults and 250 g/week for children with generalized eczema. Emollients should be applied as liberally and frequently as possible (up to 4 hourly), ideally when the skin is moist from a bath. They should be used all over and not just to the affected skin and smoothed onto the skin in the direction of the hair follicles to avoid folliculitis (19, 24).

The use of emollients is widely recommended for the management of AD, especially between flares. The direct use of emollients on inflamed skin is poorly tolerated and it is better to treat the acute flare first (8). A regular use of emollient has a short and long term steroid sparing effect in mild to moderate AD. An induction of remission with topical corticosteroids is required first (short-term therapy). Maintenance of stable disease (long-term maintenance therapy) can be obtained with emollients used twice weekly or more frequently in a subset of patients, after an induction of remission with topical corticosteroids. The 1-week stand-alone application of an emollient, may offer benefits for the improvement of mild to moderately severe localized flares of AD (25).

An imbalance of skin microflora is suspected of playing a key role in exacerbations of AD. A twice-daily application of a new emollient balm, containing an extract of a non-pathogenic gram-negative bacteria, in children with mild AD, protects the skin from S. aureus proliferation and preserves biodiversity of the microflora (26, 27).

Topical anti-inflammatory therapy

Effective topical therapy depends on three fundamental principles: sufficient strength, sufficient dosage and correct application. Topical treatment should always be applied on hydrated skin, especially when using ointments. Topical corticosteroids (TCS) and immunomodulators are first-line treatment of flares, whereas long-term management is based on the use of emollients that aim to improve skin hydration, maintain the barrier integrity, relieve pruritus and prevent new flares (28).. Patients with acute, oozing and erosive lesions, children in particular, sometimes do not tolerate standard topical application, and may first be treated with "wet wraps" until the oozing stops. They are highly effective in acute eczema and improve tolerance (29). Even without wet wraps, topical therapy is time consuming: patients should plan 30 min for one session. One well-conducted treatment per day is usually sufficient; oozing eczema may require a few days with higher treatment frequency (8).

By tradition, anti-inflammatory topical therapy has been administered to lesional skin only and has been stopped or tapered down once visible lesions were cleared. This traditional, reactive approach has in the last years been challenged by a proactive treatment concept, which is defined as a combination of predefined, long-term, low dose, anti-inflammatory treatment applied to previously affected areas of skin

in combination with liberal use of emollients on the entire body and a predefined appointment schedule for clinical control examinations (30). The proactive, usually twice a week treatment regimen is initiated after all lesions have successfully been treated by an intensive, usually twice daily treatment approach in addition to ongoing emollient therapy for previously unaffected skin (8).

Topical corticosteroids

Topical corticosteroids (TCS) are important anti-inflammatory drugs used in AD, especially in the acute phase. TCS are recommended for AD-affected individuals who have failed to respond to good skin care and regular emollient use. Patient age, areas of the body affected, degree of xerosis, patient preference, and costs of medicines should be considered. TCS are a first-line anti-inflammatory treatment, applied on inflamed skin as needed (pruritus, sleeplessness, new flares) (8, 18, 22). Twice-daily application of TCS is recommended, although once daily may be sufficient (25). There is no evidence for higher efficacy with application more than twice a day. Absorption is better with moisturized skin; after taking a bath is ideal, 20 min before applying the emollient. Itch is the key symptom for evaluation of response to treatment, and tapering should not be initiated before the itch has disappeared. Dose tapering should be gradual to avoid withdrawal rebound; tapering strategies consist of using a less potent corticosteroid on a daily base, or keeping a more potent one while reducing the frequency of application (intermittent regimen) (8). Proactive, intermittent use of TCS is recommended on areas that commonly flare (18, 22). Potential side effects should be considered. Monitoring for cutaneous side effects during long-term, potent TCS use is recommended. With mild activity, a small amount of topical corticosteroids twice to three times a week (monthly amounts in the mean range of 15 g in infants, 30 g in children, and up to 60 – 90 g in adolescents and adults), with a liberal use of emollients, generally allows a good maintenance keeping SCORAD values below 15 – 20. Such monthly amounts of even potent topical steroids usually do not have adverse systemic or local effects (8). The combination of topical corticosteroids with topical calcineurin inhibitors does not seem to be useful (31). The application amount of topical anti-inflammatory therapy should follow the "finger-tip unit" (FTU) rule. A FTU is the amount of ointment expressed from a tube with a 5-mm diameter nozzle and measured from the distal interphalangeal joint to the tip of the index finger. One FTU is equivalent to approximately 0.5 g and should cover an area equal to both palms (8, 24).

Topical calcineurin inhibitors

Topical calcineurin inhibitors (TCI) are immuno-suppressive agents which inhibit calcineurin in the skin, blocking early T-cell activation, and cytokine release. They are effective in reducing the skin inflammation in AD patients. In the UK, tacrolimus 0.03% ointment and pimecrolimus 1% cream are approved for children aged 2 – 15 years; tacrolimus 0.1% can be used >16 years (28, 32). Both topical calcineurin inhibitors are approved in the EU in patients above 2 years of age (8). In Serbia, pimecrolimus 1% cream is approved for children older than 2 years.

TCI are recommended for short-term, long-term, and maintenance treatment of AD in adults and children. TCI are preferable in situations that include recalcitrance to steroids, sensitive areas, steroid-induced atrophy, and long-term uninterrupted topical steroid use. They are particularly useful for areas where the skin is already thin, such as the face and flexures. TCI are recommended as steroid-sparing agents. For patients <2 years of age with mild-to-severe disease, off-label use of TCI can be recommended. Proactive intermittent use with TCI is recommended on areas that commonly flare (18, 22). Proactive tacrolimus ointment therapy, used twice a week, has shown to be safe and effective for up to 1 year in reducing the number of flares and improving the quality of life in adult patients and children (33).

Side effects, including skin burning and pruritus, should be considered and patients should be informed. The most common side-effect is a transient feeling of warmth or burning at the application site during the first days (34, 35). It starts about 5 min after each application and may last up to 1 h, but intensity and duration typically decrease within 1 week to zero (36).

Clinicians should be aware of the black-box warning on the use of TCI (18, 22). Although effective sun protection is recommended in patients treated

with TCI, there is no significant systemic absorption and TCI have been used in children for more than 15 years with no evidence of increased malignancy (24).

Topical antipruritic therapy

There is little specific and effective antipruritic treatment for eczema itch (37). There is evidence that TCS can be used in the initial phase of AD exacerbation to control pruritus. Also, TCI significantly relieve pruritus in AD. Itch is completely relieved after the first days of treatment in adults and children.

Specific antipruritic therapies

Topical anesthetics (benzocaine, lidocaine, polidocanol, mixture of prilocaine and lidocaine) when used as short-term therapy may reduce itch in AD (8). **Cannabinoid receptor agonists** (N-palmitoylethanolamine, applied twice a day) have been described to exhibit antipruritic and analgesic properties (38). **Capsaicin** is a naturally occurring alkaloid which exerts its functions via binding to a capsaicin-specific receptor which is located on free nerve endings. There is preliminary evidence that capsaicin is useful in the treatment of AD itch (39). **Topical doxepin (5% cream)** exhibited antipruritic effects in controlled studies of AD (40). However, topical doxepin therapy is not licensed or used in any European country due to an increased risk of contact allergy. **Topical mast cell stabilizer** sodium cromoglycate showed improvement in SCORAD (41). Other new topical agents include thiol derivative **N-acetylcysteine,** but without convincing evidence of its efficacy in AD (42). At the moment, there is not enough evidence by randomised controlled trials (RCT) to support the use of these substances in the treatment of AD itch. However, none of these substances is licensed for AD in Europe, and routine clinical use is not recommended as an adjuvant antipruritic therapy in AD (8).

Other anti-inflammatory agents

The development of a more specific anti-inflammatory treatment which is easy to use and targets pruritus could provide clinically meaningful improvements for patients with AD. The majority of emerging therapies for AD are focused on inhibiting phosphodiesterase 4 (PDE4), an enzyme which is increased in inflammatory disorders such as AD (43).

Topical **crisaborole** 2% ointment, (formerly known as AN2728) is a benzoxaborole, nonsteroidal, topical, anti-inflammatory phosphodiesterase 4 (PDE4) inhibitor. By inhibiting PDE4 and thus increasing levels of cyclic adenosine monophosphate (cAMP), crisaborole controls inflammation. Once crisaborole reaches systemic circulation after topical application, it is metabolized to inactive metabolites. This limits systemic exposure to crisaborole and systemic PDE4 inhibition. Crisaborole 2% ointment was generally well tolerated and improved AD disease severity scores, pruritus, and all other AD signs and symptoms. Two large, randomized, controlled, phase 3, clinical trials assessing the efficacy and safety of topical crisaborole 2% ointment, in children, adolescents, and adults with mild to moderate AD, were recently completed with positive results (44, 45, 46, 47).

Tofacitinib is a small-molecule Janus kinase (JAK) inhibitor that affects the interleukin (IL)–4, IL-5, and IL-31 signaling pathways, interfering with the immune response that leads to inflammation. Tofacitinib 2% ointment, applied twice daily for 4 weeks, showed significant efficacy and safety/local tolerability with early onset of AD. JAK inhibition through topical delivery is potentially a promising therapeutic target for AD (48).

Systemic treatment of AD

The use of systemic corticosteroid therapy is not recommended in AD because of short-term, transient positive, and potential side effects.

During flares, oral H1-antihistamines, cephalosporins and macrolides are indicated. In severe, generalized and resistant forms of AD, oral cyclosporine and methotrexate may be used. Methotrexate is not allowed before the age of two.

Antihistamines. Oral antihistamines (H1) are safe for long-term treatment. Although there are opinions that non-sedating antihistamines do not relieve pruritus in AD patients as sedating antihistamines, modern treatment protocols and our experience indicate that systemic therapy with non-sedating antihistamines reduces pruritus, has a positive impact on clinical presentations, and the quality of life in AD patients.

H1 antihistamines act via H1 receptor by inhibiting the response of mediators released by mast

cells and basophils. Suppression of the inflammatory response is achieved by reducing chemotaxis and antigen presentation, reduced expression of cell adhesion molecules and reducing the levels of pro-inflammatory cytokines (49). Oral antihistamines alleviate pruritus in AD. Antihistamines are used once or several times a day, as recommended by the manufacturer.

Chloropyramine is an antihistamine that reduces pruritus and exhibits local anesthetic, local vasoconstrictor effect and central sedative effect. It is contraindicated during pregnancy and lactation, in newborns and premature infants. In children, it is recommended only in case of severe allergic reactions. We do not recommend it in the treatment of AD in pediatric patients. In adult patients caution is advised if there is an increased sensitivity to the sedative effects of antihistamines and comorbidities such as epilepsy, hyperthyroidism and others. It is used 1 - 3 times during 24 hours by deep intramuscular or slow intravenous injection.

The newer, oral non-sedating antihistamines (loratadine, desloratadine, cetirizine, levocetirizine, etc.) are more comfortable and safe for long-term use. According to the manufacturer, they are used in a single dose (1x1 tablet/day). However, in dermatology we use it in up to four times higher doses. Desloratadine is an oral solution that can be used from the sixth month of life, while levocetirizine is recommended after the age of two. In addition to effects on H1 receptors, oral antihistamines also have anti-inflammatory effects improving the signs and symptoms of AD.

Antibiotics. Antibiotics (cephalosporins, and macrolides) are crucial during flares. An impaired epidermal barrier function enhances the development of infection. Furthermore, pruritus leads to scratching and dissemination of *Staphylococcus aureus* on inflamed and non-inflamed skin areas. Superantigen stimulation by *S. aureus* contributes to the development and maintenance of inflammation in AD (50, 51). During flares, cephalexin is considered to be the drug of choice, while azithromycin may be used in patients allergic to penicillins and cephalosporins.

Antifungals. Fungal infections can also be associated with the development and maintenance of inflammation in AD. Head and neck variant of AD is often associated with increased *Malassezia sympodialis* (52). Oral ketoconazole or itraconazole and topical ciclopiroxilamine or imidazole (miconazole, clotrimazole), during 7 - 14 days, reduce inflammation in patients with head and neck variant of the disease (53). Another imidazole preparation, fluconazole is also successfully used in this variant of AD.

Viral infections, particularly *Molluscum contagiosum* virus and herpes simplex, easily spread due disrupted skin barrier function in AD. *Eczema herpeticum* occurs almost exclusively in AD patients and may be a life-threatening infection, particularly in pediatric patients. The treatment of choice for *Molluscum contagiosum* is liquid nitrogen and curettage. Acyclovir is a drug of choice for eczema herpeticum (10).

Phototherapy. During summer and sunny months, AD tends to improve in most patients. Artificial, UVA and UVB phototherapy, have an important role in the treatment of AD in our country, especially during the late fall and winter. It was found that UV rays have a beneficial effect on the sensory innervations of the skin (54), induce apoptosis of inflammatory cells and reduce production of cytokines (55). UV radiation also recovers the skin/epidermal barrier function (56).

Currently, there are several available UV protocols:

Broadband UV (UVA + UVB = 290 - 400 nm)
Broadband Ultraviolet B (UVB-HB = 280 - 315 nm)
Narrow-band UVB (nbUVB = top: 311 - 313 nm)
UVA1 (340 - 400 nm)

Phototherapy is good as a maintenance therapy and as a support treatment. It is rarely used as a monotherapy in stages of disease exacerbation. PUVA therapy is not recommended in patients under the age of 12. In general, depending on the physical characteristics of UV chamber and patients' age, the initiation of UVB phototherapy in younger patients is individually estimated. Rarely the use of this type of therapy is possible before the age of five. During sunny months, controlled sun exposure is recommended.

Cyclosporine. Cyclosporine inhibits production of IL-2. The results of meta-analyses (57) confirm the efficacy of cyclosporine in the treatment of AD. Rapid recurrence is possible after discontinuation of cyclosporine treatment. Before cyclosporine is initiated, control of blood pressure, serum creatinine,

and basic biochemical analysis of blood and urine should be performed. The initial dose of cyclosporine is 2.5 - 5 mg/kg in two divided daily doses (every 12 h). At the beginning, lower doses of cyclosporine are recommended. Later, if the renal function, the serum concentration of cyclosporine and blood pressure are normal, the dose may be increased up to 5 mg/kg/day. Doses higher than 5 mg/kg/day may be associated with nephrotoxic effects.

Methotrexate. Methotrexate (MTX) is also successfully used in the treatment of severe forms of AD. It is not recommended before the age of two. Before the introduction of MTX, complete blood count test (CBC), serum creatinine, AST, ALT as well as urine analysis, HBsAg and anti-HCV tests should be performed. The MTX test-dose is administered 5 - 7 days before the first therapeutic dose. In pediatric patients (under the age of 5) 1.25 mg (1/2 tablets) of MTX may be considered as a test dose, while in older and adult patients the test dose is 2.5 mg (1x1 tablet). After 5 - 7 days, CBC, hepatic function and urine analysis should be performed and if they are within normal limits therapeutic doses of MTX may be introduced. The initial therapeutic dosage for pediatric patients is 0.2 - 0.4 mg/kg weekly and 0.2 mg/kg weekly in adult patients. MTX is administered in a single dose orally or subcutaneously. Laboratory tests (CBC, creatinine, hepatic function and urine) are performed once a week during the first month, then every two weeks in the second month, then monthly during treatment. After withdrawal of skin lesions or during remission we recommend slow tapering of MTX. In remission phase we recommend low doses of MTX (5 - 10 mg) for several months. In adult patients, contraception is necessary during the treatment and for six months after discontinuation of MTX. Folic acid, 5 mg a week should be administered 48 hours after MTX.

Azathioprine. Azathioprine is used in the UK and USA in the treatment of adult forms of AD. Therapeutic dose is 2.5 mg/kg/day, in patients over 17 years of age (58). Before the introduction of azathioprine and during the treatment, CBC, blood and urine tests are recommended. Contraception is necessary during the treatment with azathioprine.

Biologics. Numerous biologics (ustekinumab, fezakinumab, apremilast, dupilumab, OC000459) are used in the treatment of AD, with promising results. However, so far, these preparations are not routinely used in the treatment of AD (59, 60). Larger studies and longer follow-up periods will point to efficacy and safety of biologics in the treatment of AD.

General measures in AD patients

Hygiene

The skin should be cleaned thoroughly, but gently and carefully, in order to remove crusts in case of bacterial superinfection. Bathing should last approximately 5 - 10 minutes, water temperature between 27 and 30°C. In order to avoid dehydration of the epidermis, patients are recommended to use a bath oil, during the final 2 minutes of bathing. Adding sodium hypochlorite to the bath water may be useful, considering its antibacterial effect (8). Taking a bath in salt water can be beneficial for patients with impetiginized lesions or ichthyosis. It has been shown that water hardness is linked with an increased AD prevalence, which means that hard water can increase the risk of atopic dermatitis in children (61).

Emollients are primarily applied immediately after a shower or bath, while the skin is still slightly damp. Newer studies have suggested that by limiting the amount of products used to clean the skin and by applying emollients at least once a day, the risk of atopic dermatitis can be reduced (62).

Clothing

Wearing smooth, cotton clothes and avoiding irritating fabrics (primarily wool) is crucial for avoiding skin irritation. In addition, overly occlusive clothing which increases the temperature of the skin should be avoided; in winter months, children should not be dressed too warmly. Low humidity and indoor heating make the skin drier, so the use of air humidifiers is recommended. There is a consensus that patients with atopic dermatitis should avoid occupations which involve a risk of serious skin damage or contact with irritating substances (8).

Lifestyle

Numerous factors and substances in our surroundings can irritate the sensitive skin of patients with AD and cause the development of eczema. The irritants may be mechanical (for example, wool), chemical (acids, solvents, water) or biological (microorganisms). Informing patients and their family members about

the importance of non-specific irritants and their role in the development of eczema is an extremely important precondition for successful treatment of patients with AD.

Many patients are aware of the fact that contact with animals can make their skin symptoms worse. The exposure to cat fur in childhood can increase the risk of AD, especially in children with a filaggrin gene mutations (8, 63). There is no evidence that contacts with dogs increase the risk of AD (8).

Cigarette smoking in facilities or rooms where children with AD spend time should be avoided, since it can make the irritation and itching worse and increase the tendency towards the development of asthma later in life.

Many patients have problems with perspiration and sweat retention during the summer, which can intensify the itching. However, children with AD should be encouraged to actively play sports. Swimming is an excellent activity for children with AD, if they can tolerate exposure to chlorinated water.

Spending time in air-conditioned rooms during the summer months can significantly decrease the itching.

Diet

Among the food allergens, cow's milk, eggs, wheat, soy, walnuts, and peanuts are usually responsible for the development or exacerbation of eczema in early childhood. Double-blind, placebo-controlled food challenges are considered to be the gold standard for food allergy diagnosis (64). In a systematic review of eight randomized, controlled trials (57) which examined the effect of elimination diets in patients with AD, no conclusive evidence has been found to support the claim that an elimination diet (for example, eggs and milk) is beneficial for AD patients. However, another study has shown that egg-free diet has led to the improvement of AD in patients who have shown clinical symptoms since the last egg consumption (65).

Restrictive diets are not recommended for patients with AD who have not been diagnosed with a food allergy (66). Patients suffering from a mild or severe AD should follow elimination diets which exclude foods that cause a sore or delayed skin reaction which appears after the controlled oral provocation test has been conducted (8).

There is sound evidence that probiotics are safe and efficient in the prevention of AD and that they decrease the risk by about 20% (67). However, it is still unclear how probiotics should be taken (should mothers take them during pregnancy, should they be given to children when they are born, or both) and which strain should be taken. In contrast to their positive effect with regard to prevention, the efficacy of probiotics in patients suffering from AD has not been established (68).

Alternative treatments

There is insufficient evidence to determine whether phytotherapy, aromatherapy, acupuncture, homeopathy, traditional Chinese medicine, or bioresonance therapy are effective forms of treatment for AD (8).

Abbreviations

AD – Atopic dermatitis
EASI - Eczema area and severity index
FTU -"finger-tip unit"
JAK - Janus kinase
MTX- Methotrexate
nbUVB - Narrow-band UVB
PDE4 - phosphodiesterase 4
SCORAD - Scoring atopic dermatitis
Th - T helper
TCS - Topical corticosteroids
TCI - Topical calcineurin inhibitors
UVA - Ultraviolet A rays
UVB - Ultraviolet B rays

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Nacionalni vodič za terapiju atopijskog dermatitisa

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Epidemiološke karakteristike atopijskog dermatitisa

Atopijski dermatitis (AD) je oboljenje koje obično počinje u ranom detinjstvu (1). AD je jedno od najčešćih oboljenja kože i javlja se kod približno 20% dece i 1–3% odraslih (2). Kod 60% pacijenata prve manifestacije se javljaju u prvoj godini života, a kod 90% obolelih do navršene pete godine. Kod većine pacijenata bolest se povlači do odraslog doba; kod 25% perzistira tokom života, dok se kod manjeg broja obolelih prve manifestacije AD pojavljuju u adultnom periodu (2). Približno četvrtina obolelih od AD razviće i neku formu ekcema na šakama tokom adultnog perioda (3).

Klinička slika atopijskog dermatitisa

Klinička slika se razlikuje u zavisnosti od životnog doba i toka bolesti, a glavni znaci su eritem, edem, erozije i ekskorijacije, vlaženje, kruste, suva koža i lihenifikacija (1, 4–7). Intenzivan svrab je karakterističan za AD i dovodi do nastanka ekskorijacija, prurigo papula, lihenifikacije i ekcematoznih kožnih lezija (2–4). Posebno je izražen noću, što onemogućava spavanje i značajno utiče na kvalitet života i pacijenta i porodice (4, 5, 7, 8). Promene na koži mogu biti akutnog, subakutnog i hroničnog tipa. Za akutne lezije su karakteristični: intenzivan svrab, eritem, pojedinačne i slivene papule (nekad i vezikule); prate ih ekskorijacije, erozije i serozni eksudat. Subakutne lezije se manifestuju kao eritematozne, ekskorisane papule sa skvamom, dok su za hronični tip promena tipična zadebljanja kože s naglašenim kožnim crtežom (lihenifikacija) i prurigo papule. Kod odojčadi i mlađe dece, AD je pretežno akutnog i subakutnog toka, dok kod starije dece i odraslih poprima hronični oblik (5–7). Kod jednog pacijenta često su prisutne sve tri faze promena (6, 7).

Klinička slika kod dece

U prvom mesecu života, žućkaste, izražene skvame u kapilicijumu, poznate kao *temenjača* ili tzv. *seboroični dermatitis* odojčadi, mogu biti prvi znak atopijskog dermatitisa (1). U uzrastu odojčeta, od trećeg do šestog meseca života, predilekciono mesto za nastanak ekcemskih promena je lice (obrazi, čelo i brada), dok su centralni deo lica (nos, perioralna regija) i regija koju pokriva pelena (tzv. pelenska regija) najčešće pošteđeni. Promene na koži su akutnog i subakutnog toka, nejasno ograničene, u vidu eritema, edema, papulovezikula, ekskorijacija, često sa vlaženjem i krustama, ređe hronične u vidu eritematoznih papula i plakova sa skvamom. Od osmog do desetog meseca života, AD se širi na ekstenzorne strane ekstremiteta, a nakon prve godine života na gornji deo trupa, gde promene mogu imati numularan izgled (1, 5–7). Nakon druge godine života, klinička slika se menja prelaskom prethodne forme u hronični oblik, ili AD može nastati de novo. Javljaju se nejasno ograničeni lihenifikovani plakovi sa ekskorijacijama, lokalizovani u kubitalnim i poplitealnim pregibima, na vratu i u okolini ručnih i skočnih zglobova. Koža celog tela je suva. Lihenifikacija je posledica češanja, zbog izraženog, pretežno noćnog, svraba. Povremeno se na ovim lezijama razvijaju akutni ekcemski naleti u vidu papula i papulovezikula (1, 5–7). U adolescenciji perzistiraju lihenifikovani plakovi u pregibima velikih zglobova, uz nastajanje hroničnih

promena na licu – periorbitalni dermatitis, zatim na vratu, šakama, stopalima i leđima (5, 7).

Klinička slika kod odraslih

Kod odraslih osoba, u kliničkoj slici dominiraju lihenifikovani plakovi, koji se obično nalaze u pregibima ekstremiteta i u anogenitalnoj regiji. Često je prisutan edem lica sa lihenifikacijom na vratu i očnim kapcima i hronični ekcem šaka i/ili stopala. Prurigo tip AD karakterišu ekskorisani pruriginozni čvorovi. Bolest ima hronično recidivirajući tok. Egzacerbacije bolesti često počinju sa izraženim svrabom bez vidljivih lezija, a kasnije se pojavljuje eritem, papule i infiltracija (1, 5–7).

Pacijenti sa AD pokazuju povećanu sklonost ka infekcijama kože, uglavnom bakterijskim ali i virusnim i *gljivičnim (5, 6, 7, 9). Bakterijske infekcije najčešće izaziva Staphylococcus aureus, ređe Streptococcus pyogenes* (6, 7). Virusne infekcije su češće kod obolelih od AD, sa sklonošću ka diseminaciji i širenju promena (1, 8, 10). U zavisnosti od virusa koji ih izaziva, može nastati *eczema herpeticum*, *eczema molluscatum*, *eczema coxsackium* ili *eczema vaccinatum* (1, 9–11). Gljivična infekcija izazvana specijesom *Malassezia sympodialis* (*Pityrosporum ovale*) dovodi do nastanka takozvanog *head and neck* dermatitisa (12).

Za procenu težine kliničke slike AD kod dece i odraslih koriste se indeksi SCORAD (više u Evropi) i EASI (više u Severnoj Americi) (8).

Etiopatogeneza atopijskog dermatitisa

Etiopatogeneza AD je multifaktorska. Obuhvata defekt kožne barijere, imunsku reakciju sa ključnom ulogom T-ćelija, dendritičnih ćelija, limfoidnih ćelija, mastocita i eozinofila, kao i faktora sredine.

Disfunkcija barijere kože kod AD posledica je tri bitna faktora: defekta ekspresije gena za filagrin, smanjene količine ceramida u koži i povećane aktivacije epidermalnih proteaza. Skoro 50% pacijenata sa AD ima defekt ekspresije gena za sintezu filagrina, proteina koji ima ključnu ulogu u održavanju strukturne barijere kože, dok njegov nedostatak remećenjem ove strukture olakšava penetraciju haptena i proteina (13, 14). Ceramid je lipid važan za zadržavanje vode u kornealnom sloju epiderma.

Kod pacijenata sa AD, u odnosu na zdrave osobe, identifikovano je značajno smanjenje količine ceramida u lezijama, ali i u neizmenjenoj koži. Dokazano je da je količina ceramida u epidermu u obrnutoj srazmeri sa transepidermalnim gubitkom vode, bitnom karakteristikom kože atopičara. Kod dece se međutim smanjena količina ceramida prema nekim autorima nalazi samo u lezionoj, a ne i u neizmenjenoj koži, što se objašnjava postinflamatornom reakcijom, a ne genetskom uslovljenošću (13, 14). U odnosu na imunske aspekte, patogeneza AD je veoma složena jer obuhvata sadejstvo urođenog i stečenog imuniteta. Ćelije prisutne u koži, poput keratinocita, dendritičnih ćelija, mastocita, makrofaga i nezrelih limfocita, učestvuju u zapaljenskoj reakciji. Pored njih, u nastanku ekcemske reakcije takođe učestvuju T-limfociti, plazmocitoidne dendritične ćelije, monociti i granulociti iz cirkulacije (13, 14). U patogenezi AD, T-helper (pomoćnički) limfociti imaju centralnu ulogu. Kod bolesnika sa AD postoji neuravnoteženost aktivnosti specifičnih klonova pomoćničkih T-ćelija, sa predominacijom TH2 tipa ćelijskog odgovora na alergene, za razliku od normalnih osoba gde dominira TH1 tip. Patološka aktivacija TH2 ćelija vodi pojačanoj produkciji IL-4, IL-5 i IL-13, što ima za posledicu nakupljanje drugih tipova imunskih ćelija i razvoj akutnih lezija kod AD. Za razliku od akutnih, u hroničnim lezijama AD dominira TH1 ćelijska aktivnost (13, 14).

Razlika u incidenciji i prevalenciji AD u različitim geografskim oblastima ukazuje i na značajnu ulogu faktora sredine u etiopatogenezi, poput klimatskih faktora, faktora ishrane, gojaznosti, izloženosti duvanskom dimu i drugim zagađivačima okoline, kao i mikrobiološkoj izloženosti. Novija istraživanja naglašavaju ulogu i uticaj mikrobioma kože, kako na njenu homeostazu tako i na pojavu različitih patoloških stanja, uključujući i AD. U epizodama pogoršanja kliničke slike kod AD evidentno je povećanje količine *S. aureus*, ali i *S. epidermidis*. Egzacerbacija kutane inflamacije posredovana je superantigenima poput stafilokoknih enterotoksina A i B, kao i dejstvom toksičnog šok-simptom toksina 1 koji dovodi do poliklonske aktivacije T-ćelija (13, 14). Ustanovljeno je da povećana ekspozicija UV zracima i toploti deluju protektivno na pojavu ekcema, nasuprot smanjenoj ekspoziciji UV zracima i povećanoj vlažnosti vazduha (13, 14). Kiseli pH kože doprinosi barijernoj funkciji, jer ima antibakterijsko dejstvo i ulogu u deskvamaciji. Pokazano je da je kod pacijenata sa AD pH čitave kože povećan, što dovodi do egzacerbacije bolesti, a najčešći faktori koji dovode do remećenja pH

kože su deterdženti i sapuni. Time se remeti sadržaj lipida na površini kože, pojačava dejstvo proteaza i istanjuje kornealni sloj epiderma (13, 14). Veoma je složena interakcija ranije navedenih genetskih faktora, imunskih faktora i faktora sredine u etiopatogenezi AD i, uz brojna aktuelna saznanja, predstavlja veliki izazov za buduća istraživanja koja bi ponudila nove i preciznije odgovore na mnoga, još uvek nedovoljno razjašnjena pitanja.

Dijagnostički kriterijumi za atopijski dermatitis

Evropska radna grupa za atopijski dermatitis (engl. *Europan Task Force on Atopic Dermatitis*) definisala

Tabela 1. Dijagnostički kriterijumi za atopijski dermatitis (15)

Major (tri od četiri)	**Minor (najmanje tri)**
- Pruritus	- Pozitivni prik kutani testovi (I tip preosetljivosti)
- Dermatitis koji zahvata fleksorne površine kod dece starije od dve godine i odraslih ili lice u prvoj godini	- Povećana ukupna koncentracija IgE u serumu
	- Pojava bolesti u najranijem detinjstvu (kod 90% pre pete godine)
	- Suvoća kože
	- Bledilo i/ili eritem lica
- Hronični ili hronično-recidivirajući tok bolesti	- *Pityriasis alba*
	- Ihtioza
	- Tamni podočnjaci
- Lična i porodična anamneza o atopiji	- Deni-Morganovi (*Dennie-Morgan*) infraorbitalni nabori
	- Hiperlinearnost dlanova
	- *Keratosis pilaris*
	- Heilitis
	- Ekcem šaka i stopala
	- Ekcem areola dojki
	- Svrab prilikom znojenja
	- Nepodnošenje vune
	- Beli dermografizam
	- Perifolikularna akcentuacija
	- Nabori prednje strane vrata
	- Supkapsularna katarakta i keratokonus
	- Sklonost bakterijskim i virusnim infekcijama kože (*S. aureus*, HSV)
	- Smanjen ćelijski posredovan imunski odgovor
	- Pogoršanje promena na koži pod uticajem emocionalnih faktora, faktora sredine i iritanasa
	- Preosetljivost na hranu, naročito kod dece mlađe od dve godine

je atopiju kao „porodičnu sklonost ka razvoju Th2 imunskog odgovora na uobičajene antigene okoline“ sa razvojem tipičnih bolesti – atopijskog dermatitisa, astme, i/ili alergijskog rinitisa. Dijagnoza, atopijskog dermatitisa postavlja se pre svega na osnovu anamnestičkih podataka i karakteristične kliničke slike, a proteklih decenija razvijani su različiti dijagnostički kriterijumi čija je pouzdanost različita. Dijagnostički kriterijumi su neophodni, pre svega, u epidemiološkim i kliničkim studijama koje moraju imati precizno definisane kriterijume za uključenje pacijenata (1, 15, 16).

Dijagnostički kriterijumi za atopijski dermatitis većinom uključuju kliničke znake i delom rezultate alergoloških i laboratorijskih testiranja kojima se dokazuje atopija. Istorijski najpoznatiji i najviše korišćeni u svakodnevnoj kliničkoj praksi su kriterijumi Hanifina i Rajke – Tabela 1 (15). Prema ovim kriterijumima, za dijagnozu je potrebno tri od četiri major kriterijuma i tri minor kriterijuma. Ovi dijagnostički kriterijumi validirani su u dve studije u kojima je njihova dijagnostička senzitivnost bila 87,9% i 96%, a specifičnost 77,6% i 93% (16).

Drugi, manje korišćeni kriterijumi su britanske radne grupe (engl. *UK Working Party*) kriterijumi koji podrazumevaju da se atopijski dermatitis dijagnostikuje na osnovu prisustva promena na koži u poslednjih 12 meseci i još najmanje 3 od sledećih kriterijuma: pojava promena na koži pre druge godine života (ne primenjuje se kod dece mlađe od 4 godine), anamneza o zahvatanju fleksornih površina ili prisustvo ovakvih promena na pregledu, suvoća kože i lična anamneza o drugim atopijskim bolestima (ili porodična anamneza za decu mlađu od 4 godine) (17). Ovi kriterijumi su validirani u najvećem broju studija, a specifičnost je varirala 10–100%, a senzitivnost 89–99%.

Takođe, Američka akademija za dermatologiju predložila je svoje kriterijume koji su podeljeni u obavezne, značajne i udružene kriterijume u odnosu na njihovu učestalost i dijagnostičku važnost (18). Nekoliko drugih dijagnostičkih kriterijuma takođe je objavljeno, ali nisu našli primenu u svakodnevnoj praksi (19, 20).

Nedavnom analizom i sistematskim pregledom studija koje su validirale različite dijagnostike kriterijume utvrđeno je da je metodologija ovih validacija veoma različita što onemogućava konačne zaključke (16).

Lokalna terapija i nega kože

Emolijentna terapija i nega kože

Lečenje AD zahteva efikasnu kontrolu akutnih simptoma i znakova bolesti, obnavljanje funkcije barijere kože i izbegavanje faktora sredine koji pokreću i pogoršavaju bolest. Pojedina sredstva za hidriranje kože poboljšavaju barijernu funkciju kože i smanjuju osetljivost kože na iritanse (21, 22).

Pranje i kupanje

Suvoća kože je više izražena tokom hladnih meseci zbog suvog toplog vazduha i niske vlažnosti u stanovima. Kupanje svakog dana se smatra jednim od najboljih načina hidriranja kože. Koža se mora prati temeljno, ali nežno i pažljivo, kako bi se uklonili skvama i kruste sa površine, iritansi i alregeni i obezbedila mogućnost za hidriranje kože. Voda treba da bude topla, a optimalna dužina boravka u vodi je do 20 minuta. Kratkotrajnim kupanjem (samo 5 min), uz upotrebu uljane kupke (poslednja 2 minuta tuširanja), može se izbeći dehidracija epiderma (8, 23). Sapuni, šamponi i gelovi za tuširanje koji stvaraju penu treba da se izbegavaju jer iritiraju i isušuju kožu. Kod dece u prepubertetskom sebumu se ne produkuje, tako da je potrebna minimalna količina šampona. Uljane kupke mogu imati efekat hidriranja, ali su dokazi o njihovoj efikasnosti nedovoljni. Na tržištu su dostupna neutralna ili sredstva za pranje sa fiziološkim pH koja su hipoalergogena i bez mirisa, ali se kao zamena za sapun mogu primenjivati i kremovi i losioni koji hidriraju tako što će se naneti na kožu pre kupanja ili tuširanja i umasirati u kožu tokom kupanja (19, 24). Poželjno je nanošenje emolijenasa odmah nakon kupanja i brisanja kože, dok je koža još uvek vlažna. Najbolji način za održavanje vlažnosti kože kod pacijenata sa AD je nanošenje debljeg sloja emolijensa tokom prva 3 minuta posle kupanja, pre nego što dođe do isušivanja kože (8, 22, 23).

Emolijentna terapija

Pravilna upotreba emolijenasa za hidriranje je ključna u lečenju pacijenata sa AD. Emolijensi predstavljaju osnovu terapije održavanja. Dostupni su u različitim oblicima. Losioni su retke konzistencije sa visokim sadržajem vode, korisni su za regije obrasle dlakom i za ekcem sa vlaženjem, ali su neefikasni kod izražene kseroze. Kremovi (emulzije vode i ulja) najčešće se

primenjuju jer se lako nanose, ne ostavljaju sjajan trag, ali su masniji od losiona. Pojedina ulja se zgušnjavaju u hladnijim klimatskim uslovima, ali postaju ređa na temperaturi tela. Masti su guste, mogu se naneti u debelom sloju i pogodne su za veoma suv ekcem. Međutim, manje su kozmetički prihvatljive, mogu da izazovu pretopljavanje i folikulitis i mogu da ostavljaju mrlje na odeći i posteljini. Aditivi mogu da izazovu iritaciju ili alergijske reakcije, a najbolje je da emolijensi koji se koriste za atopičare budu bez parfema (24).

Pacijente treba podsticati da probaju različite emolijense, ali i preporučiti odgovarajuće u zavisnosti od njihovog tipa kože, načina života i klimatskih uslova u kojima žive. Hidriranje kože se obično postiže nanošenjem preparata za hidriranje najmanje dva puta dnevno. Pacijenti mogu primenjivati emolijense na bazi krema tokom dana i toplog vremena, a masti tokom noći i hladnog vremena. Često se ne upotrebljava dovoljna i potrebna količina emolijentnog preparata. Kod odraslih pacijenata sa generalizovanim ekcemom potrebno je približno 600 g emolijensa nedeljno, a kod dece 250 g nedeljno. U toku hladnijih meseci u godini, emolijense je potrebno primenjivati više puta dnevno, a najvažnija je primena na vlažnu kožu, posle kupanja. Treba da se nanose na celu kožu, ne samo na zahvaćene zone, i da se utrljaju u kožu u smeru rasta dlake kako bi se izbegao nastanak folikulitisa (19, 24).

Upotreba emolijenasa je široko preporučena za lečenje AD, posebno između recidiva. Potrebno je prvo primeniti diferentno terapijsko sredstvo na lezije, a tek kasnije, na celu površinu kože, emolijentni krem (8). Ako se emolijensi nanose posle primene lokalnih kortikosteroida, savetuje se da prođe 15–20 minuta od aplikacije leka, a ukoliko se primenjuju posle topikalnih kalcineurinskih inhibitora, savetuje se da prođe 30-ak minuta od primene leka. Redovna upotreba emolijenasa ima kratkoročne i dugoročne *steroid sparing* (ušteda kortikosteroida) efekte kod pacijenata sa blagim do umereno teškim AD. Da bi se postigla remisija, prvo je potrebna primena lokalnih kortikosteroida (kratkotrajna terapija). Održavanje stabilne remisije (dugoročna terapija održavanja) može se kod jednog broja pacijenata postići primenom emolijenasa dva puta nedeljno ili češće, nakon postizanja remisije topikalnim kortikopreparatima. Čak nanošenje emolijensa jedan put nedeljno može biti korisno za poboljšanje blagih do umereno teških lokalizovanih recidiva AD (25).

Poremećaj ravnoteže epidermalne mikroflore verovatno igra jednu od ključnih uloga u egzacerbaciji AD. Nanošenje novih tipova emolijenasa koji sadrže ekstrakt nepatogenih gram-negativnih bakterija dva puta dnevno štiti kožu od proliferacije patogenog stafilokoka i omogućava očuvanje raznolikosti mikroflore (26, 27).

Lokalna antiinflamatorna terapija

Efikasna lokalna terapija se oslanja na tri osnovna principa: dovoljna jačina, odgovarajuće doziranje i pravilna primena. Topikalnu terapiju uvek treba aplikovati na hidriranu kožu, posebno kada se primenjuju antiinflamatorni preparati u obliku masti. Topikalni kortikosteroidi (TKS) i imunomodulatori predstavljaju terapiju prvog reda za recidiv bolesti, dok se dugoročna terapija bazira na primeni emolijenasa koji poboljšavaju vlažnost kože, održavaju integritet epidermalne barijere, smanjuju intenzitet pruritusa i sprečavaju novi recidiv (28). Pacijenti sa akutnim ekcemom sa vlaženjem i erodovanim lezijama, posebno deca, ponekad ne tolerišu standardnu lokalnu terapiju, tako da se mogu prvo tretirati vlažnim oblogama (engl. *wet wraps*) dok se vlaženje ne zaustavi. Vlažne obloge su veoma efikasne kod akutnog ekcema i poboljšavaju toleranciju (29). I bez vlažnih obloga, topikalna terapija zahteva dosta vremena: pacijenti treba da planiraju 30 minuta za jednu aplikaciju lokalne terapije. Kako bi se postigao pozitivan efekat, jedan dobro sproveden tretman dnevno je obično dovoljan, osim kod akutnog ekcema sa vlaženjem koji zahteva nekoliko dana sa češćim nanošenjem lokalne terapije (8).

Uobičajeno se antiinflamatorna lokalna terapija nanosi samo na kožu sa promenama, a kada se vidljive promene izgube, aplikovanje se postepeno proređuje. Ovaj tradicionalni, reaktivni pristup se poslednjih godina zamenjuje proaktivnim konceptom lečenja, koji se definiše kao kombinacija unapred definisane, dugotrajne antiinflamatorne terapije malim dozama na prethodno zahvaćenim područjima kože u kombinaciji sa slobodnom upotrebom emolijenasa na celo telo i unapred određenim rasporedom kontrolnih kliničkih pregleda (30). Proaktivni postupak lečenja, koji se sprovodi obično dva puta nedeljno, počinje nakon uspešnog tretiranja svih lezija intenzivnom terapijom, obično aplikovanom dva puta dnevno, pored redovne emolijentne terapije prethodno neizmenjene kože (8).

Topikalni kortikosteroidi

Topikalni kortikosteroidi (TKS) najvažniji su antiinflamatorni lekovi koji se koriste u terapiji AD, posebno u akutnoj fazi. Preporučuju se pacijentima sa AD kod kojih pravilna nega i upotreba emolijenasa nije dovela do pozitivnog odgovora. Pri izboru TKS preparata u obzir treba uzeti godine pacijenta, zahvaćenu regiju, stepen kseroze kože, želje pacijenta i cenu preparata. Topikalni kortikosteroidi predstavljaju terapiju prvog reda koja se primenjuje na inflamiranu kožu u zavisnosti od potrebe (pruritus, poremećaj sna, nove promene) (8, 18, 22). Preporučuje se aplikacija TKS dva puta dnevno, mada i jednodnevna primena može biti dovoljna (25). Nije dokazana veća efikasnost ukoliko se aplikuju češće od dva puta dnevno. Apsorpcija je bolja ukoliko je koža hidrirana. Najbolji trenutak aplikovanja TKS je posle kupanja, 15–20 minuta pre nanošenja emolijensa.

Svrab je glavni simptom koji služi za procenu odgovora na terapiju. Snižavanje doziranja TKS ne bi trebalo započeti pre nestanka pruritusa i treba da bude postepeno kako bi se izbegao *rebound* fenomen. Strategija snižavanja doze sastoji se od svakodnevne upotrebe slabije potentnih kortikosteroida ili nastavka primene potentnijih TKS, uz smanjivanje učestalosti primene (intermitentni režim) (8). Proaktivna, intermitentna upotreba TKS se preporučuje na područjima gde su recidivi česti (18, 22). Treba razmotriti mogućnost razvoja neželjenih efekata. Potrebno je praćenje u smislu nastanka neželjenih efekata tokom dugotrajne primene potentnih TKS. Kod pacijenata sa AD blage aktivnosti, mala količina TKS primenjena dva do tri puta nedeljno (mesečno 15 g kod beba, 30 g kod dece, 60–90 g kod adolescenata i odraslih), uz odgovarajuću primenu emolijenasa, obično omogućava dobro održavanje remisije sa SCORAD indeksom ispod 15–20. Ove mesečne količine, čak i potentnih TKS, obično nemaju negativne sistemske ili lokalne efekte (8). Kombinacija TKS istovremeno sa topikalnim kalcineurinskim inhibitorima najverovatnije nema koristan efekat u lečenju AD (31). Količina topikalnog antiinflamatornog preparata koja se nanosi treba da bude određena pravilom koje koristi „vrh-prsta jedinicu“ (engl. *finger-tip unit*, FTU). FTU je količina masti koja se istisne iz tube pomoću mlaznice prečnika 5 mm i meri se od distalnog interfalangealnog zgloba do vrha kažiprsta. Jedna FTU odgovara približno 0,5g i trebalo bi da bude dovoljna za pokrivanje površine koja odgovara površini oba dlana (8, 24).

Topikalni kalcineurinski inhibitori

Topikalni kalcineurinski infibitori (TKI) su imunosupresivni agensi koji inhibiraju kalcineurin u koži, blokirajući ranu T-ćelijsku aktivaciju i oslobađanje citokina. Oni su efikasni u redukovanju inflamacije kod AD. U Velikoj Britaniji, takrolimus 0,03% mast i pimekrolimus 1% krem su odobreni za upotrebu kod dece od dve do 15 godina, a takrolimus 0,1% mast kod dece starije od 16 godina (28, 32). U Evropskoj uniji oba TKI su odobrena od druge godine života (8). U Srbiji, takrolimus 0,03% mast i pimekrolimus 1% krem su odobreni za decu stariju od dve godine. TKI se preporučuju za kratkotrajnu, dugoročnu i terapiju održavanja AD kod odraslih i dece. Oni su poželjni u situacijama kada su kortikosteroidi kontraindikovani, na osetljivim regijama, zonama sa atrofijom usled primene steroida i ukoliko bi bila potrebna dugotrajna kontinuirana upotreba TKS. Posebno su korisni za regije gde je koža već tanka kao što su lice i pregibi. TKI se preporučuju kao *steroid-sparing* agensi. Kod pacijenata mlađih od dve godine sa blagim do teškim oblicima AD, može se preporučiti tzv. *off-label* (zvanično neodobrena za ovaj uzrast) primena TKI. Proaktivna, intermitentna upotreba TKI takođe se preporučuje na područjima gde su recidivi najčešći (18, 22). Proaktivna terapija pomoću takrolimus masti aplikovane dva puta nedeljno sigurna je i efikasna do godinu dana trajanja, za redukciju broja relapsa i poboljšanje kvaliteta života odraslih pacijenata i dece sa AD (33).

Potrebno je uzeti u obzir mogućnost nastanka neželjenih efekata, uključujući osećaj peckanja i svraba, i o njima informisati pacijenta. Najčešće uočen sporedni efekat je prolazna toplotna senzacija na mestu aplikacije tokom prvih dana primene (34, 35). Počinje obično pet minuta nakon aplikacije, može trajati do jedan sat, ali se intenzitet i dužina trajanja obično smanjuju do potpunog nestanka tokom jedne nedelje (36). Pacijentima koji primenjuju TKI se preporučuje efikasna zaštita od sunca. Nema značajne sistemske apsorpcije TKI. TKI se primenjuju kod dece duže od 15 godina i nema dokaza o povećanom broju maligniteta (24).

Topikalna antipruriginozna terapija

Postoji mali broj specifičnih i efikasnih antipruriginoznih sredstava za svrab kod ekcema (37). TKS se zbog svog antipruriginoznog dejstva mogu primenjivati u inicijalnoj fazi egzacerbacije AD. Takođe, TKI značajno smanjuju pruritus kod AD već posle prvih nekoliko dana terapije i kod odraslih i kod dece.

Specifična topikalna antipruriginozna terapija

Topikalni anestetici (benzokain, lidokain, polidokanol, kombinacija prilokaina i lidokaina) kratkotrajno mogu smanjiti osećaj pruritusa kod AD (8). Agonisti kanabinoidnih receptora (N-palmitoiletanolamin, aplikovan dva puta dnevno) mogu uticati na smanjenje pruritusa i bola (38). Kapsaicin je prirodni alkaloid koji svoje funkcije ostvaruje preko kapsaicin-specifičnih receptora, lokalizovanih na slobodnim nervnim završecima. Postoje preliminarni dokazi o pozitivnom učinku kapsaicina kod pruritusa kod AD (39). Topikalni doksepin (5% krem) ispoljava korisne efekte u smanjenju pruritusa kod AD (40). Međutim, ovaj preparat nije registrovan i nije u upotrebi u evropskim zemljama zbog povećanog rizika od kontaktne preosetljivosti. Topikalni stabilizator mastocita natrijum-kromoglikat i inhibitori degranulacije mastocita smanjuju SCORAD indeks (41). Drugi novi lokalni preparati uključuju i tiolski derivat N-acetilcistein, ali do sada ne postoje ubedljivi dokazi o efikasnosti kod AD (42). U sadašnjem momentu nema dovoljno dokaza randomiziranih kliničkih studija koji bi podržali upotrebu ovih preparata u terapiji pruritusa kod AD. Nijedan od ovih preparata nije registrovan u Evropi i ne preporučuje se njihova rutinska klinička upotreba kao pomoćna antipruriginozna terapija kod AD (8).

Drugi antiinflamatorni agensi

Razvoj specifične antiinflamatorne terapije koja je jednostavna za upotrebu i deluje na pruritus može obezbediti klinički značajan napredak u lečenju pacijenata sa AD. Većina novih terapijskih preparata se bazira na inhibiciji fosfodiesteraze 4 (PDE4), enzima čiji je nivo povišen kod inflamatornih poremećaja kao što je AD (43).

Krisaborol 2% mast (ranije poznat kao AN2728) je benzoksaborol, nesteroidni topikalni antiinflamatorni inhibitor PDE4. Inhibicijom PDE4 i povećanjem nivoa cAMP, krisaborol kontroliše inflamaciju. Kada dospe u sistemsku cirkulaciju posle topikalne aplikacije, metaboliše se u inaktivne metabolite. Ovo ograničava sistemsko prisustvo krisaborola i sistemsku PDE4 inhibiciju. Krisaborol 2% mast se uglavnom dobro toleriše i popravlja indeks težine AD, pruritus i sve druge znake i simptome AD. Dve velike randomizirane kontrolisane kliničke studije (faza 3) koje su procenjivale efikasnost i bezbednost krisaborol 2% masti kod dece, adolescenata i odraslih sa blagim i umerenim AD su nedavno završene pozitivnim ishodom (44–47).

Tofacitinib je inhibitor malog molekula Janus kinaze (JAK) koji utiče na interleukin (IL)-4, IL-5 i IL-31 signalne puteve, menjajući imunski odgovor koji dovodi do inflamacije. Tofacitinib 2% mast, aplikovana dva puta dnevno tokom četiri nedelje, pokazuje značajnu efikasnost i bezbednost/lokalnu podnošljivost u ranoj fazi AD. JAK inhibicija, ostvarena preko topikalnog dejstva, predstavlja potencijalno obećavajući terapijski princip za AD (48).

Opšta terapija atopijskog dermatitisa

S obzirom da se radi o hroničnom inflamatornom oboljenju, primena opšte kortikosteroidne terapije nije opravdana zbog kratkotrajnih i tranzijentnih pozitivnih efekata i potencijalnih neželjenih efekata.

U fazama pogoršanja opravdana je upotreba peroralnih H1 antihistaminika (zbog svraba), kao i cefalosporina ili makrolida per os (u slučaju bakterijske infekcije). Kod teških, generalizovanih i rezistentnih formi AD, savetuje se i terapija ciklosporinom per os, a posle druge godine života u terapiju je moguće uvesti i metotreksat.

Antihistaminici. H-1 antihistaminici za sistemsku primenu su bezbedni lekovi i tokom duže primene. Iako postoje mišljenja da nesedirajući antihistaminici nemaju adekvatan uticaj na smanjenje pruritusa kod obolelih od AD, savremeni terapijski protokoli i naša iskustva ukazuju da sistemska terapija antihistaminicima kod znatnog broja pacijenata umanjuje pruritus, poboljšava lokalni status na koži i pozitivno utiče na kvalitet života obolelih od AD.

H1 antihistaminici, blokadom H1 receptora dovode do blokade odgovora posredovanog aktivacijom H1 receptora i na taj način inhibiraju

oslobađanje medijatora iz mast-ćelija i bazofila. Supresija inflamatornog odgovora postiže se smanjenjem prezentacije antigena i hemotakse, smanjenom ekspresijom ćelijskih adhezivnih molekula i smanjenjem nivoa proinflamatornih citokina (49). Oralni antihistaminici ublažavaju pruritus u AD. Sedativni antihistaminici pored navedenog olakšavaju spavanje tokom noći koje je značajno poremećeno zbog pruritusa (49). Antihistaminici se koriste jednom ili više puta dnevno, prema preporuci proizvođača.

Hloropiramin, pored antipruriginoznog, ispoljava i lokalno anestetičko i vazokonstriktorno dejstvo kao i centralno sedativno dejstvo. Kontraindikovana je primena kod trudnica, novorođenčadi i nedonoščadi kao i kod žena u periodu laktacije s obzirom da se izlučuje i putem mleka. Kod dece se primena ovog leka savetuje samo u slučaju teških alergijskih reakcija. Ne savetujemo ga u terapiji AD u pedijatrijskom uzrastu. Kod odraslih pacijenata treba biti posebno oprezan ukoliko postoji povećana osetljivost na sedativne efekte antihistaminika i komorbiditeti kako što su epilepsija, hipertiroidizam i dr. Primenjuju se 1–3 ampule tokom 24 h kao duboka intramuskularna ili spora intravenska injekcija.

Noviji nesedativni antihistaminici (loratadin, desloratadin, cetirizin, levocetirizin i dr.) nalaze se u formi tableta i oralnih rastvora, komforni su i bezbedni za dugotrajnu primenu. Prema preporuci proizvođača, koriste se u jednoj dozi (1 x 1 tbl/dn), međutim, u dermatologiji su opravdane i primene do četiri puta veće doze. Desloratadin oralni rastvor može da se primenjuje od šestog meseca života dok se upotreba levocetirizina savetuje od druge godine života. Pored dejstva na H1 receptore, oralni antihistaminici ispoljavaju i antiinflamatorna dejstava tako da višestruko utiču na poboljšanje znakova i simptoma AD.

Antibiotici. Antibiotici (cefalosporini i makrolidi) imaju značajno mesto u opštoj terapiji AD, u fazama pogoršanja. Pored toga što narušena funkcija barijere epiderma kod pacijenata sa AD olakšava nastanak i razvoj infekcije, pruritus i češanje doprinose diseminaciji bakterije *Staphylococcus aureus* na inflamirane ali i na i neinflamirane delove kože. Sam *S. aureus* superantigenskom stimulacijom doprinosti razvoju i održavanju inflamacije kod pacijenata sa AD (50, 51). U fazama pogoršanja, cefaleksin smatramo lekom izbora, dok azitromicin može da se ordinira pacijentima preosetljivim na peniciline i cefalosporine.

Antimikotici. Pored značajne uloge bakterijskih infekcija u pokretanju inflamatorne kaskade i pogoršanja AD, gljivične infekcije takođe mogu da budu udružene sa razvojem i održavanjem inflamacije kod obolelih od AD. Antimikotici se savetuju kod tzv. *head and neck* varijante AD koja je često udružena sa superinfekcijom gljivicom *Malassezia sympodialis* (52). Opšta terapija ketokonazolom ili itrakonazolom i lokalna terapija ciklopiroksolaminom ili imidazolskim topikalnim antimikoticima (mikonazol, klotrimazol), tokom 7–14 dana, poboljšava nalaz, odnosno umanjuje inflamaciju kod pacijenata kod kojih su pretežno zahvaćeni glava i vrat (53). Drugi sistemski imidazolski preparati (flukonazol) takođe se sa uspehom koriste kod ove varijante AD. Po supresiji (super)infekcije gljivicama iz roda *Malassezia*, potrebno je nastaviti sa lokalnom (eventualno i sistemskom) antiinflamatornom terapijom, u skladu sa kliničkim nalazom.

Antivirusni lekovi. Virusne infekcije, pre svega *molluscum contagiosum* i infekcija *Herpes simpex* virusom lakše se diseminuju kod obolelih od AD. *Eczema herpeticum* se praktično javlja samo kod obolelih od AD i može da bude životno ugrožavajuća infekcija, posebno kod pacijenata u pedijatrijskom uzrastu. Terapija izbora kod *molluscum contagioszum* je primena tečnog azota i kiretiranje promena, dok je sistemski dat aciklovir lek izbora za *eczema herpeticum* (10).

Fototerapija. Tokom sunčanih meseci, AD se poboljšava kod većine pacijenata. Arteficijalni UV zraci (UVA i UVB fototerapija) imaju značajnu ulogu u lečenju obolelih od AD, u našim krajevima posebno tokom perioda kasne jeseni i zime. Ustanovljeno je da UV zraci povoljno utiču na senzornu inervaciju kože (54), indukuju apoptozu u ćelijama inflamatornog infiltrata i smanjuju produkciju citokina koji doprinose fazama pogoršanja (55), poboljšavaju – regenerišu barijernu funkciju kože (56) i drugo.

Trenutno su dostupni sledeći vidovi lampi:
Broadband UV (UVA + UVB = 290–400 nm),
Broadband ultraviolet B (BB-UVB = 280-315 nm),
Narrow-band UVB (nbUVB = peak: 311–313 nm),
UVA1 (340–400 nm).

Fototerapija se najčešće uvodi ukoliko se ne

postižu zadovoljavajući efekti primenom optimalne lokalne terapije i odlična je kao terapija održavanja. Retko se koristi kao monoterapija u fazama pogoršanja. PUVA terapija se ne savetuje kod pacijenata mlađih od 12 godina. Generalno, zavisno od izgleda kabine u kojoj se nalaze UV lampe i saradnje samog pacijenta, individualno se procenjuje mogućnost započinjanja UVB fototerapije kod mlađih pacijenata. Retko je primena ovog vida terapije, uz asistenciju medicinskih radnika ili roditelja (ukoliko u kabini za UVB fototerapiju ima prostora za dete i odraslu osobu), moguća pre pete-šeste godine života. Tokom sunčanih meseci, savetuje se kontrolisana fotoekspozicija.

Ciklosporin. Ciklosporin ostvaruje dejstvo sprečavanjem produkcije IL-2. Rezultati metaanalize (57) potvrdili su efikasnost ciklosporina u terapiji AD. Ciklosporin dovodi do kliničkog poboljšanja, poboljšanja sna i umanjuje potrebu za lokalnom kortikosteroidnom terapijom. Po isključivanju ciklosporina mogući su brzi recidivi. Pre uvođenja ciklosporina u terapiju neophodna je kontrola arterijske tenzije, nivoa kreatinina u serumu kao i osnovne biohemijske analize krvi i urina. Ciklosporin se primenjuje 2,5–5 mg/kg telesne mase dnevno, podeljeno u dve doze (na 12 h). Savetuje se započinjanje terapije nižim dozama ciklosporina, a zatim, uz kontrolu bubrežne funkcije, nivoa ciklosporina u serumu i kontrolu arterijske tenzije, podizanje doze do 5 mg/kg. Nije opravdano ordinirati više od 5 mg/kg zbog povišenog rizika od razvoja nefrotoksičnih efekata.

Metotreksat. Metotreksat (MTX) takođe se sa uspehom koristi u lečenju težih formi AD. Primena metotreksata se ne preporučuje pre druge godine života. Pre uvođenja MTX u terapiju kontroliše se KKS, kreatinin, AST, ALT, kao i nalaz urina. Inicijalno je značajno uraditi virusološke analize (HBsAg i anti-HCV ukupni). Probna doza MTX ordinira se 5–7 dana pre ordiniranja prve, pune terapijske doze leka. Kod pedijatrijskih pacijenata, do 4-5. godine života probna doza može da iznosi 1,25 mg (1/2 tbl) dok kod starijih i odraslih pacijenata probna doza iznosi 2,5 mg (1 x 1 tbl). Posle 5–7 dana kontrolišu se KKS, hepatogram i sediment urina i, ukoliko su nalazi uredni, smatra se da se može započeti sa terapijskim dozama MTX. Inicijalna doza kod pedijatrijskih pacijenata iznosi 0,2–0,4 mg/kg telesne mase jedanput nedeljno, dok kod odraslih pacijenata iznosi 0,2 mg/kg telesne mase/jedanput nedeljno. MTX se ordinira u jednoj dozi, per os ili supkutano. Laboratorijske analize (KKS, kreatinin, hepatogram, pregled urina) rade se jednom nedeljno tokom prvog meseca, zatim na svake dve nedelje u drugom mesecu, a kasnije jednom mesečno ili na dva meseca. Savetuje se postupno snižavanje doze MTX po postizanju stabilnog značajnog poboljšanja kliničke slike ili remisije. Po postizanju remisije, savetuje se primena nižih doza MTX (5–10 mg) tokom nekoliko meseci. Kod odraslih pacijenata, neophodna je kontracepcija pre započinjanja terapije, tokom terapije i šest meseci po obustavljanju terapije. Folna kiselina, 5 mg, primenjuje u jednoj dozi, 48 h nakon ordiniranog MTX.

Azatioprin. Azatioprin se koristi u Velikoj Britaniji i SAD u lečenju adultnih formi AD. Savetuje se doza od 2,5 mg/kg telesne mase/dnevno, posle sedamnaeste godine života (58). Rutinski se pre uvođenja azatioprina kontrolišu KKS, biohemijski parametri krvi i pregled urina. Kontrola ovih parametara neophodna je i tokom terapije. Neophodna je kontracepcija tokom terapije azatioprinom.

Biološki lekovi. Veći broj bioloških lekova (ustekinumab, fezakinumab, apremilast, dupilumab, OC000459) primenjivan je u lečenju AD, sa rezultatima koji obećavaju, međutim, za sada se nigde u svetu ovi preparati još uvek ne koriste u rutinskoj terapiji AD (59, 60). Potreban je veći broj studija i duže praćenje pacijenata da bi se pouzdano procenili efikasnost i bezbednost primene ovih preparata u lečenju AD.

Opšte mere

Održavanje higijene

Kožu treba temeljno očistiti, ali nežno i pažljivo, kako bi se uklonile kruste u slučaju bakterijske superinfekcije. Kupanje treba da traje oko 5–10 minuta, pri temperaturi vode od 27 do 30° C. Savetuje se nanošenje uljanih kupki poslednja 2 minuta kupanja, kako bi se izbegla dehidracija epiderma. Dodavanje natrijum-hipohlorita u kadu s vodom može biti koristno, s obzirom na njegovo antibakterijsko dejstvo (8).

Kupanje u slanoj vodi može pogodovati pacijentima sa impetiginizovanim lezijama ili prisutnom ihtiozom. Pokazano je da je tvrdoća vode u vezi

s povećanom prevalencijom AD, tj. da tvrda voda povećava rizik za razvoj atopijskog dermatitisa kod dece (61).

Emolijensi se prvenstveno nanose odmah posle kupanja ili tuširanja, dok je koža još uvek vlažna. Noviji radovi ukazuju da ograničavanje korišćenja sapuna i primena emolijenata najmanje jednom dnevno može smanjiti rizik od nastanka atopijskog dermatitisa (62).

Odevanje

Nošenje mekane pamučne odeće i izbegavanje iritirajućih tkanina u kontaktu s kožom (pre svega vune, ali i svile) od suštinskog je značaja za izbegavanje iritacije kože. Takođe, treba izbegavati okluzivnu odeću koja povećava toplotu kože, a tokom zimskih meseci treba izbegavati pretopljavanje dece. Niska vlažnost tokom zime i grejanje u stanovima povećava suvoću kože, tako da se može savetovati upotreba ovlaživača vazduha. Postoji konsenzus da osobe sa atopijskim dermatitisom treba da izbegavaju zanimanja kod kojih postoji mogućnost oštećenja kože ili postoji kontakt s iritantnim supstancijama (8).

Uslovi življenja

Brojni faktori i supstancije iz okoline mogu da iritiraju osetljivu kožu pacijenata sa atopijskim dermatitisom i mogu da dovedu do nastanka ili pogoršanja ekcema. Oni mogu biti fizički, kao što su mehanički iritansi (npr. vuna), hemijski (kiseline, rastvarači, voda) ili biološki (mikroorganizmi). Informisanje pacijenata i članova njihovih porodica o značaju i ulozi nespecifičnih iritanasa za nastanak ekcema je veoma važan preduslov za uspešno lečenje pacijenata s atopijskim dermatitisom.

Mnogi pacijenti su već svesni činjenice da kontakt sa životinjama može da dovede do pogoršanja simptoma na koži. Izloženost mačjoj dlaci tokom detinstva može povećati rizik od nastanka atopijskog dermatitisa, naročito kod dece koja imaju mutaciju gena za filagrin (8, 63). Nema dokaza da kontakt sa psima povećava rizik za nastanak atopijskog dermatitisa (8).

Pušenje cigareta treba izbegavati u prostorijama gde borave deca s atopijskim dermatitisom, jer to može dovesti do povećanja iritacije i svraba i može da poveća sklonost ka kasnijem razvoju astme.

Mnogi pacijenti imaju problem s lučenjem i retencijom znoja tokom letnjih meseci, što dovodi do povećanja svraba. Ipak, decu s atopijskim dermatitisom treba ohrabriti da se aktivno bave sportom. Plivanje može biti odličan sport za decu sa atopijskim dermatitisom, ukoliko se dobro toleriše izlaganje hlorisanoj vodi. Pre plivanja se savetuje aplikacija emolijenata na celu površinu kože i odmah posle plivanja kupanje uljanom kupkom uz dodatnu aplikaciju emolijenata. Boravak u klimatizovanim prostorijama tokom letnjih meseci značajno može smanjiti osećaj svraba.

Ishrana

Među alergenima hrane, kravlje mleko, jaja, pšenica, soja, orasi i kikiriki su najčešće odgovorni za nastanak ili pogoršanje ekcema u ranom detinjstvu. Dvostruko slepo, placebo-kontrolisano izlaganje hrani smatra se zlatnim standardom za dijagnozu alergije na hranu (64). U sistematskom pregledu osam randomizovanih, kontrolisanih studija (57) koje su proučavale efekat eliminacione dijete kod pacijenata sa atopijskim dermatitisom pokazano je da ne postoje ubedljivi dokazi da je eliminaciona dijeta (npr. jaja i mleko) korisno za pacijente sa atopijskim dermatitisom. Međutim, u drugoj studiji pokazano je da je izostavljanje jaja u ishrani dovelo do poboljšanja atopijskog dermatitisa kod pacijenata koji su imali kliničke simptome posle prethodnog konzumiranja jaja (65).

Ne savetuje se da pacijenti sa atopijskim dermatitisom, kod kojih nije dokazana alergija na hranu, sprovode restrikcione dijete (66). Pacijenti s umerenim i teškim atopijskim dermatitisom treba da se pridržavaju eliminacione dijete one vrste hrane koja provocira ranu ili kasnu reakciju na koži koja je pokazana posle sprovedenog kontrolisanog oralnog provokacionog testa (8).

Postoje određeni podaci da probiotici mogu biti korisni i bezbedni u prevenciji atopijskog dermatitisa, sa smanjenjem rizika za oko 20% (67). Međutim, i dalje postoji nejasnoća kada i kome treba dati probiotike (majkama pre rođenja deteta pod rizikom za razvoj AD, deci posle rođenja, ili oboje) i koji specijes i soj bakterija treba dati. Za razliku od verovatno pozitivnog preventivnog dejstva, nije pokazana efikasnost probiotika kod pacijenata s već razvijenim atopijskim dermatitisom (68).

Alternativni vidovi lečenja

Ne postoje odgovarajući dokazi da fitoterapija, aromaterapija, akupunktura, homeopatija, kineska tradicionalna medicina ili biorezonanca imaju pozitivan efekat u lečenju atopijskog dermatitisa (8).

Skraćenice

AD – atopijski dermatitis
EASI – indeks procene težine i površine ekcema (engl. *Eczema area and severity index*)
FTU – jedinica vrha prista (engl. *finger-tip unit*)
JAK – Janus kinaza
MTX – metotreksat
nbUVB – UVB zraci uskog spectra (engl. *Narrow-band UVB*)
PDE4 – fosfodiesteraza 4
SCORAD – indeks procene težine atopijskog dermatitisa (engl. *Scoring atopic dermatitis*)
Th – T-pomoćničke
TKS – topikalni kortikosteroidi
TKI – topikalni inhibitori kalcineurina
UVA – ultravioletni zraci spektra A
UVB – ultravioletni zraci spektra B

Izjava

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Verrucous Carcinoma of the Foot - Report of Two Cases

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Abstract

Verrucous carcinoma (VC) is a rare variant of a well-differentiated squamous cell carcinoma (SCC) with a low grade of malignancy. Epithelioma cuniculatum (EC) is a subtype of VC, usually found on the sole of the foot.
Two patients, a 55-year-old female, and a 77-year-old male, with VC were treated at the Clinic of Dermatology and Venereology, Clinical Center of Serbia, from 2002 to 2011. Both patients presented with a tumor on the foot. Incisional biopsies showed a well differentiated squamous cell carcinoma. Foot x-rays showed bone involvement in one case. One patient underwent surgical amputation of the lower extremity, while the other had a partial amputation of the affected foot.
In the initial stage of the disease, it is difficult to distinguish pseudoepitheliomatous hyperplasia from verrucous carcinoma. The superficial biopsy of EC lesion may mislead to a histopathological diagnosis of warts or condylomas. Multiple deep biopsies are necessary for accurate and timely diagnosis of verrucous carcinoma.

Key words

Carcinoma, Verrucous; Foot Diseases; Diagnosis; Skin Neoplasms; Biopsy; Amputation

Verrucous carcinoma (VC) is a rare variant of a well-differentiated squamous cell carcinoma (SCC) with a low grade of malignancy (1). It is usually found in the oral cavity (Ackerman, 1948) (2), lower legs (Gottron, 1932) (3), perianal or genital area (Buschke and Lowenstein, 1925) (4) and soles. Epithelioma cuniculatum (EC), first described by Ian Aird in 1954, is a subtype of verrucous carcinoma usually found on the sole of the foot (5). EC has a local invasive growth with destruction of all substructures including the bone tissue (6).

Case reports

Patient 1

A 55-year-old female patient was admitted to the Clinic of Dermatology and Venereology, Clinical Center of Serbia in March 2002 due to a widespread polymorphous skin eruption, with erythematous exudative patches, tense blisters, and with a warty-like formation located on the left plantar and dorsal side of the 4th and 5th metatarsals (Figure 1). The Tzanck test showed a large number of eosinophils, and histopathological and direct immunofluorescence examinations confirmed the diagnosis of bullous pemphigoid. A deep biopsy was taken from the foot lesion, and the histopathological examination confirmed VC (Figure 2). Foot x-ray findings showed no bone involvement. A partial amputation of the patient's left foot was performed. No signs of recurrence were noted at 10-year-follow-up.

Patient 2

A 74-year-old male patient, with a ten-year history of a lesion on the left sole, was admitted to the Clinic of Dermatology and Venereology in December 2011. He presented with an irregularly shaped enlarging ulceration, 6 x 4 cm in diameter, covered by fibrin and granulation tissue and centrally localized

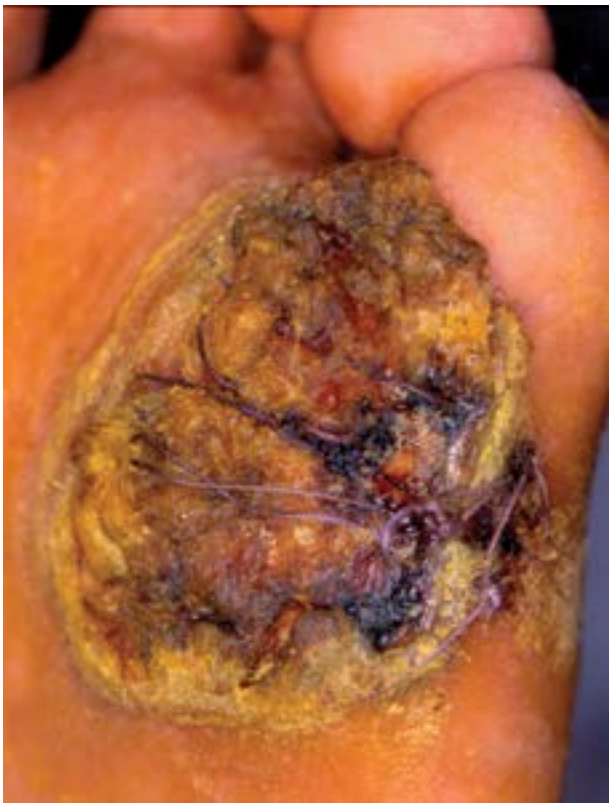

Figure 1. Hyperkeratotic tumefaction on the left sole

verrucous formations (Figure 3). The patient's history showed a prior total surgical excision of a lesion in 2007. At that time, the histopathological findings correlated with pseudoepitheliomatous hyperplasia. Due to the recurrence, a second surgical intervention was performed in 2009. The histopathological examination revealed VC, a tumor tissue on the lower line of the resection (Figure 4). A repeated foot x-ray showed progression of osteolytic changes (Figure 5). Amputation of the patient's left lower leg was performed in February 2012. Eleven months later, the patient's general condition was good and his rehabilitation has been going well.

Discussion

VC is a rare tumor with uncertain incidence, although it is known that it is more common in men, and in the sixth decade of life (79 - 89% of patients) (7, 8). VC is usually found on the soles, but it may occur on palms, as well as in other regions (esophagus, oral cavity, larynx, nail, penis) (9, 10, 11, 12, 13, 14). It is well known that chronic irritation and inflammation have an important role in the pathogenesis of VC, while the role of human papilloma virus (HPV) infection

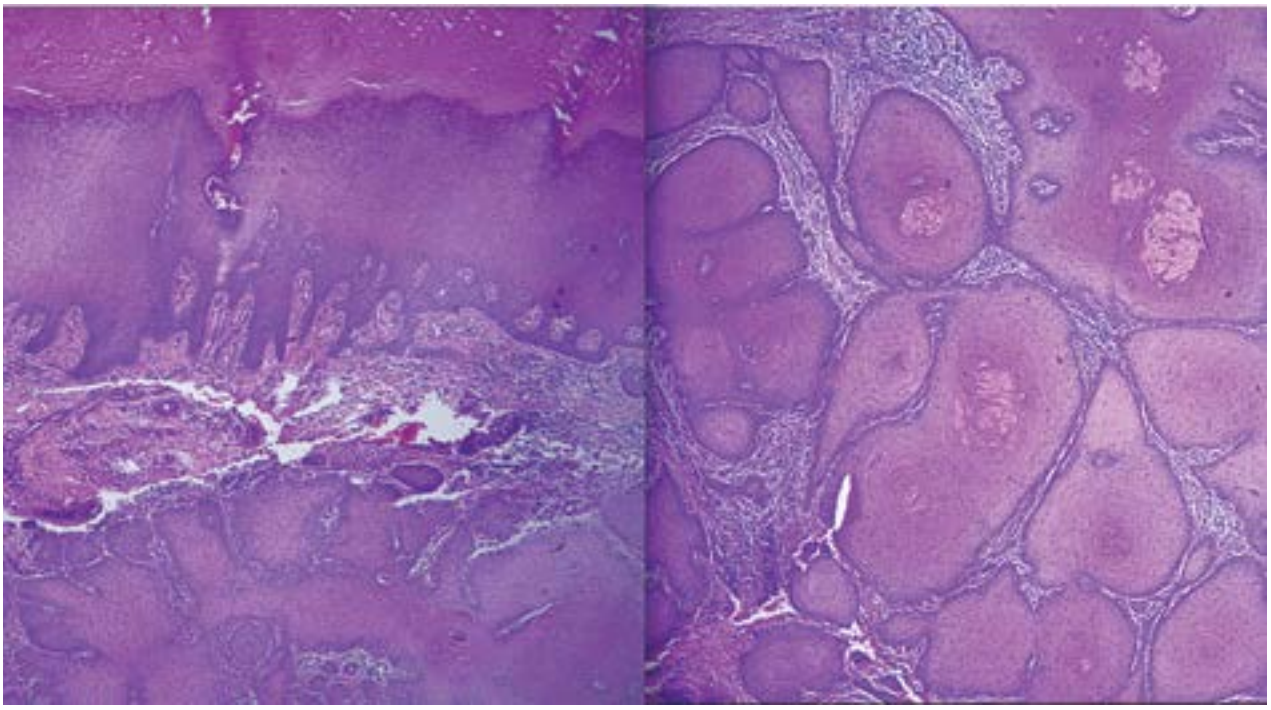

Figure 2. Verrucous carcinoma: exophytic component – hyperkeratosis; endophytic component –a well differentiated squamous epithelium growing downward into the underlying tissue (Hematoxylin-eosin, 40x)

is still controversial (15, 16). HPV types 1, 4, 6, 11, 16, 18 have been cited as possible etiologic factors involved in the pathogenesis of EC (17, 18). EC usually appears on the metatarsal region of the foot or area that is most exposed to mechanical trauma during movement (8). Typical lesions have exophytic and endophytic growth patterns and papillomatous surface with keratin filled sinuses. EC has a progressive dorsal growth leading to the destruction of local tissue, first the plantar fascia, then the metatarsal bone (19). Penetrating and profound tumor growth creates deep sinuses and clefts, resembling rabbit holes in the original description, hence the term *cuniculatum*, Latin for "rabbit hole". The diagnosis of EC in the initial stage is extremely difficult because of its similarity to plantar warts. The differential diagnosis also includes reactive epidermal hyperplasia, adnexal tumors, giant seborrheic keratosis, giant keratoacanthoma, verruciform xanthoma and verrucous melanoma (20, 21). The course of our male patient's disease supports the fact that a long-term callus or recurrent epidermal hyperplasia, usually on a site of chronic irritation or infection, may precede the appearance of EC (21). Regardless of its localization, typical clinical and histopathological presentation of EC shows an exophytic and endophytic component. The exophytic component consists of massive hyperkeratosis, often parakeratosis, acanthosis and papillomatosis. The

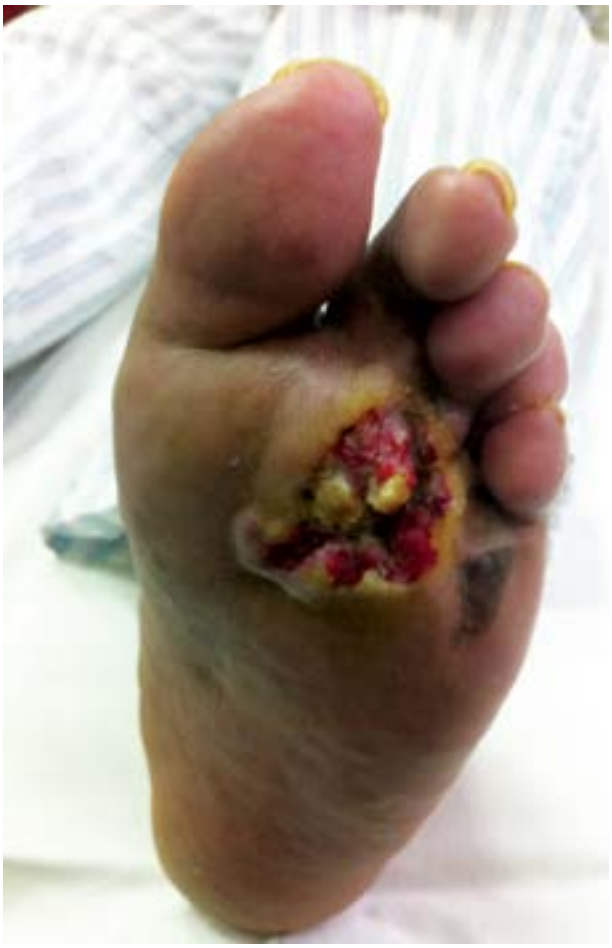

Figure 3. Ulcer with verrucous formation on the left sole

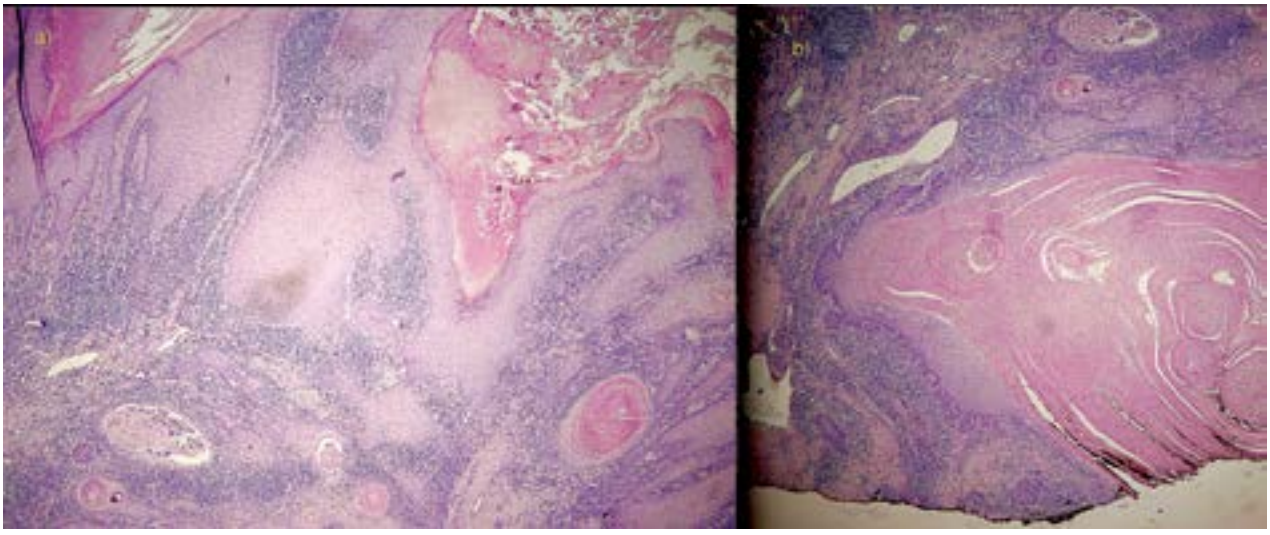

Figure 4. Histopathological presentation of verrucous carcinoma: (a) massive hyperkeratosis, often parakeratosis, acanthosis and papillomatosis, well differentiated squamous epithelium showing a characteristic pushing margin (Hematoxylin-eosin, 40x) (b) tumor tissue on the lower line of resection (Hematoxylin-eosin, 40x)

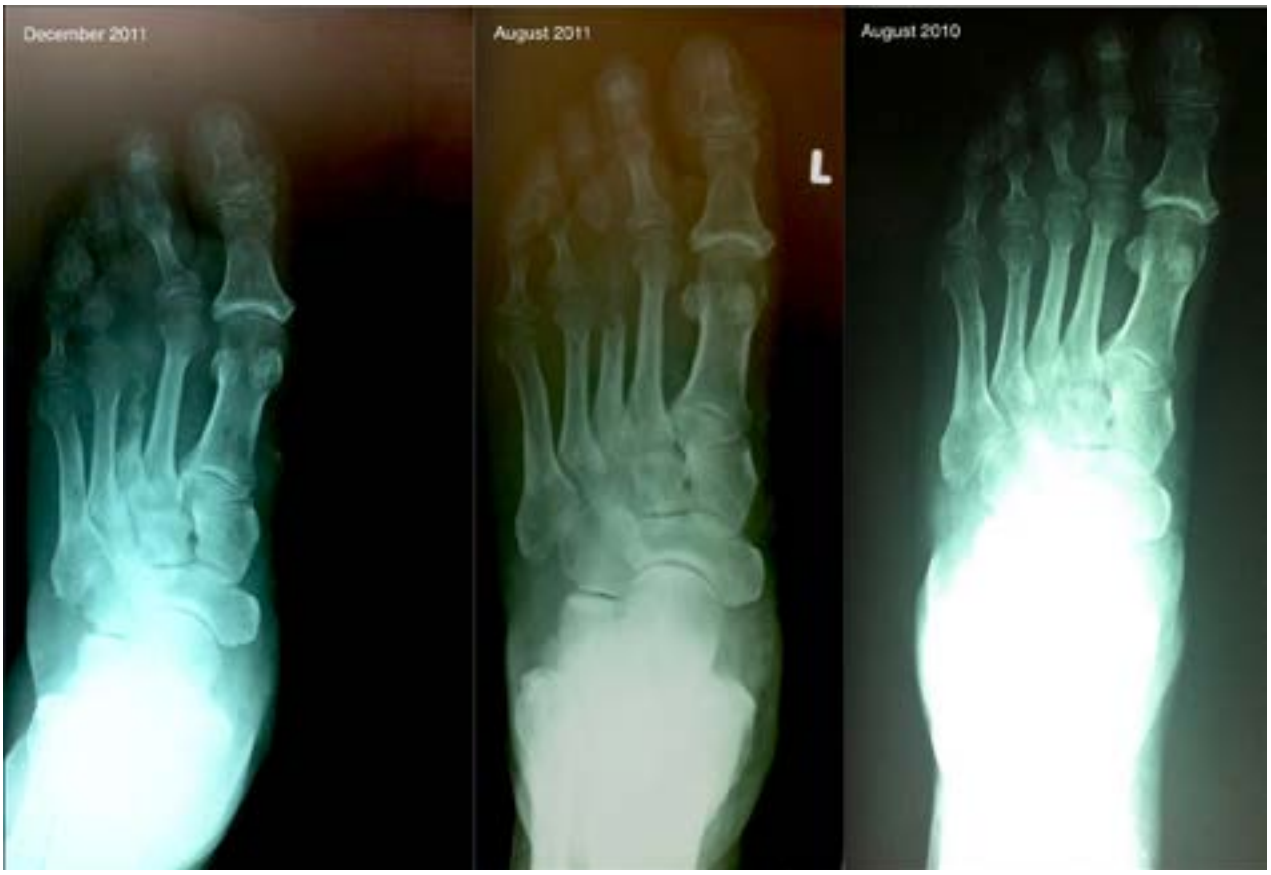

Figure 5. Repeated x-ray of the left foot. Primarily, osteolysis of the proximal phalanx of the 3rd toe, a year later extended on the 4th metatarsal head. On the last x-ray in December 2011, osteolysis of the 3rd metatarsal bone was verified, as well as the involvement of the 3rd proximal and middle phalanx, 2nd and 4th metatarsal bones

endophytic component consists of well-differentiated squamous epithelium growing downward into the underlying tissues, showing characteristic pushing margin. In most cases, squamous cell carcinoma, in contrast to EC, has an infiltrative border. The well-differentiated proliferation refers to tumor cells with minimal atypia, very low mitotic activity and extensive keratinization (1). Superficial biopsy of EC lesion may mislead to a histopathological diagnosis of warts or condylomas (22). In the initial stage of the disease it is difficult to distinguish the clinical presentation of pseudoepitheliomatous hyperplasia from verrucous carcinoma (21, 22). Therefore, small and superficial biopsies may give a false result leading to the wrong diagnosis (22). Multiple deep biopsies are necessary for accurate and timely diagnosis of verrucous carcinoma (6, 7, 8, 22). Searching the MEDLINE database we did not find any association between EC and bullous pemphigoid. Needless to say, our second patient is the first reported case of coexistence between EC and bullous pemphigoid.

Treatment of EC includes surgical excision of the tumor when the localization is adequate for the procedure. A histopathological verification on the line of resection should be mandatory (23). In inoperable cases, radiotherapy, retinoids, interferon-γ and photodynamic therapy can be efficient, but the number of such reports is limited, therefore they are not widely accepted (24, 25, 26). In severe cases when the bone tissue is affected, amputation is the main therapeutic modality (7, 8, 19).

In conclusion, in the early development, EC can easily be mistaken for a various number of hyperkeratotic disorders. A proper incisional biopsy and histopathological examination may be considered crucial in the differential diagnosis. The timely

diagnosis and treatment can prevent significant surgical disfigurement of these patients.

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Verukozni karcinom stopala – prikaz dva slučaja

Sažetak

Uvod. Verukozni karcinom predstavlja dobro diferentovani oblik skvamocelularnog karcinoma sa niskim stepenom maligniteta. *Epithelioma cuniculatum* je podtip verukoznog carcinoma, najčešće lokalizovan na tabanima.

Prikaz slučajeva. Dva pacijenta, uzrasta 55 i 77 godina, kod kojih je dijagnostikovan verukozni karcinom lečeni su na našoj klinici u period od 2002. do 2011. godine. Oba pacijenta su imali prisutnu tumefakciju na stopalu. Incizionim biopsijama potvrđen je dobro diferentovan skvamocelularni karcinom. Zahvaćenost kostiju bila je prisutna kod jednog pacijenta.

Kompletna amputacija donjeg ekstremiteta urađena je kod jednog od pacijenata, dok je kod drugog urađena parcijalna amputacija zahvaćenog stopala.
Zaključak. U inicijalnom stadijumu bolesti teško je klinički razlikovati pseudoepiteliomatoznu hiperplaziju od verukoznog karcinoma. Površne biopsije *Epithelioma cuniculatum* mogu lažno navesti na dijagnozu kondiloma ili bradavica. Ponavljane duboke biopsije neophodne su za tačnu i pravovremenu dijagnozu verukoznog karcinoma.

Ključne reči

Verukozni karcinom; Bolesti stopala; Dijagnoza; Kožne bolesti; Biopsija; Amputacija

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Cutaneous Sarcoidosis in a patient with left Hilar calcification of the lungs - A Case Report

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Abstract

Sarcoidosis is an acquired idiopathic granulomatous disease, which is characterized by noncaseating epithelioid granulomas in organs and tissues. Most frequently it affects the lungs, liver, lymph nodes, skin, eyes and other organs. The cutaneous lesions appear in 20 - 30% of patients with systemic manifestations, and in 25% of them they appear without systemic manifestations. Based on the histopathological characteristics, cutaneous lesions are divided into specific, characterized by cutaneous granuloma, and non-specific, which are not granulomatous. Moreover, they can be classified as typical and atypical. We are presenting a female patient with unilateral hilar calcification of the lungs, who exhibited plaque skin lesions typical for sarcoidosis, with a specific granulomatous histology and a favorable response to corticosteroid and antimalarial therapy.

Key words

Sarcoidosis; Skin Diseases; Lung Diseases; Case Reports; Prednisone; Antimalarials; Treatment Outcome

Sarcoidosis is an acquired idiopathic granulomatous disease, which is characterized by noncaseating epithelioid granulomas in the organs and tissues (1). Most frequently it affects the lungs, liver and heart (1, 2). Sometimes, granulomas are large and numerous, damaging the function of the affected organs.

The first description of sarcoidosis was published by Hutchinson in 1877 (3). Lupus pernio was described in 1889 by Besnier (4), and Tenneson in 1892 (5). Hutchinson described the Mortimer's disease in 1898, which was probably sarcoidosis, and the term sarcoidosis was first used by Boek in 1899 (6). The Boeck's assumption that the disease affected the skin, but also internal organs, was confirmed by Schaumann (7).

The disease affects all races and all ages (8), but also both sexes, although it is more frequent in women. The highest incidence is seen in persons under the age of 40 years (peak age, 20 - 29). The other peak occurs in women over 50 (9). The highest prevalence of sarcoidosis is in Europe, in Sweden and Ireland (60 in 100.000) (10). In African Americans, the incidence is 35.5 - 64 in 100.000, in women even up to 107 in 100.000, and in Caucasians in America 10 -15 in 100.000. It is 3 to 4 times more frequent, acute and serious in Afro-Americans than in Caucasians, and it is more commonly asymptomatic in Caucasians.

Cutaneous lesions appear in 20 - 30% of patients with systemic manifestations, and in 25% of them they appear without systemic manifestations.

When accompanied by systemic manifestations, lungs and intrathoracic lymph nodes are most frequently affected. Therefore, cutaneous lesions can appear as the only, the first manifestation, usually in the first stages of the disease (11), or with systemic manifestations, simultaneously or later. Cutaneous lesions are divided, based on the histopathological characteristics, into specific, and non-specific (1, 12). Moreover, they can be classified as typical and atypical. One patient can have different lesions simultaneously. Cutaneous sarcoidosis is known as a great imitator in dermatology, or a "clinical chameleon" (13, 14, 15, 16), because the lesions can have a wide range of clinical presentations.

We are presenting a female patient with unilateral hilar calcification of the lung, plaque skin lesion typical for sarcoidosis that exhibited specific granulomatous histology and favorable response to corticosteroid and antimalarial therapy.

Case report

Medical History

A 68-year-old female was referred to our Department with a 15-year-long history of skin lesions that first appeared on her back. Although she claimed that skin

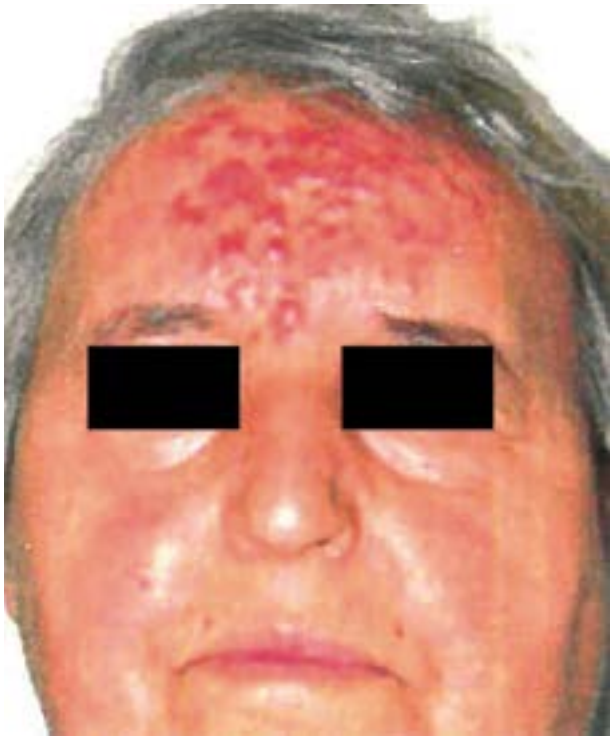


Figure 1. Multiple infiltrated plaques with distinct edges on the forehead and the apex, yellowish-orange to amber in color, in some places covered with crusts

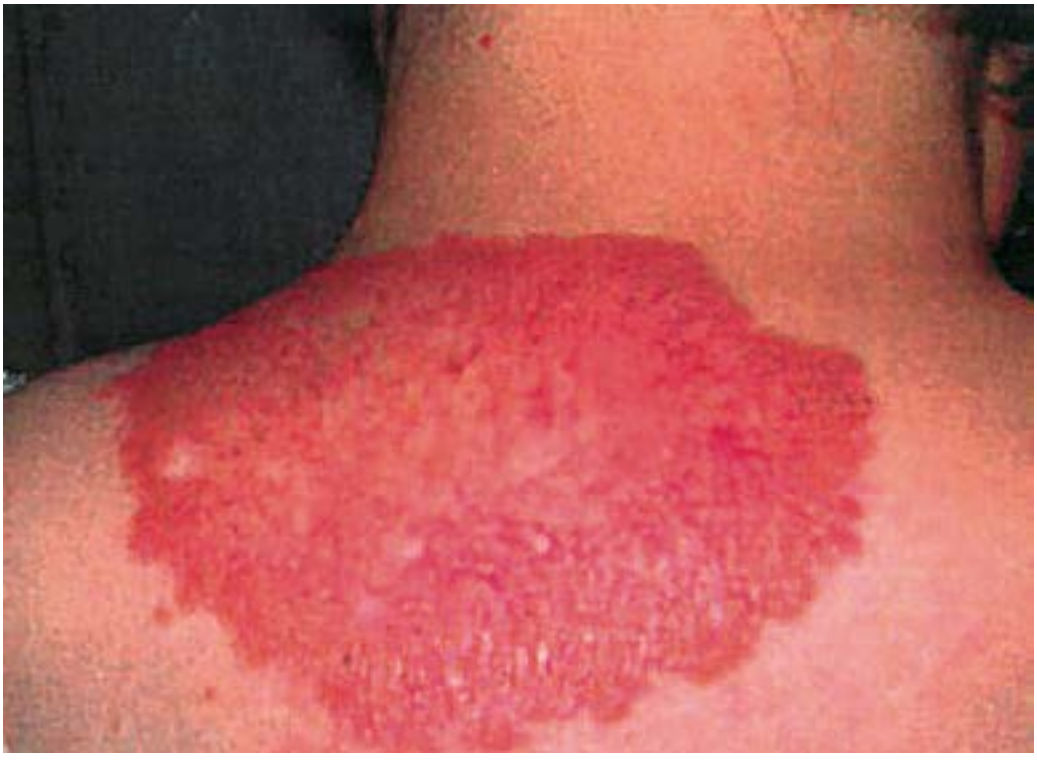


Figure 2. A lesion with a prominent edge, 12 x 10 cm on the back

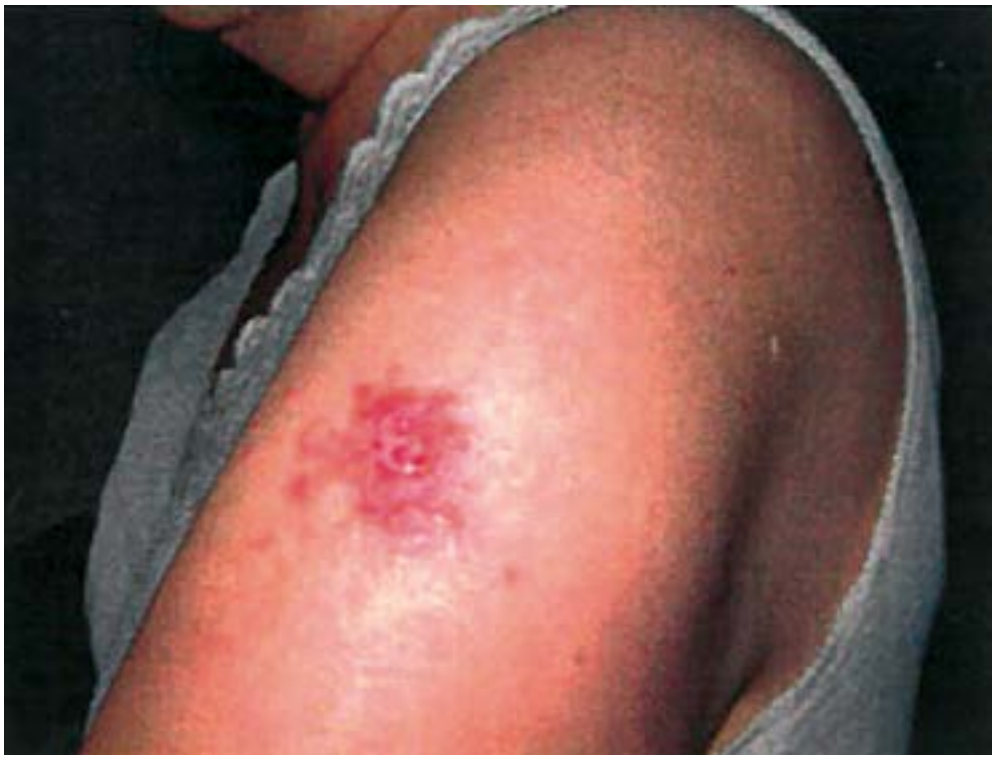
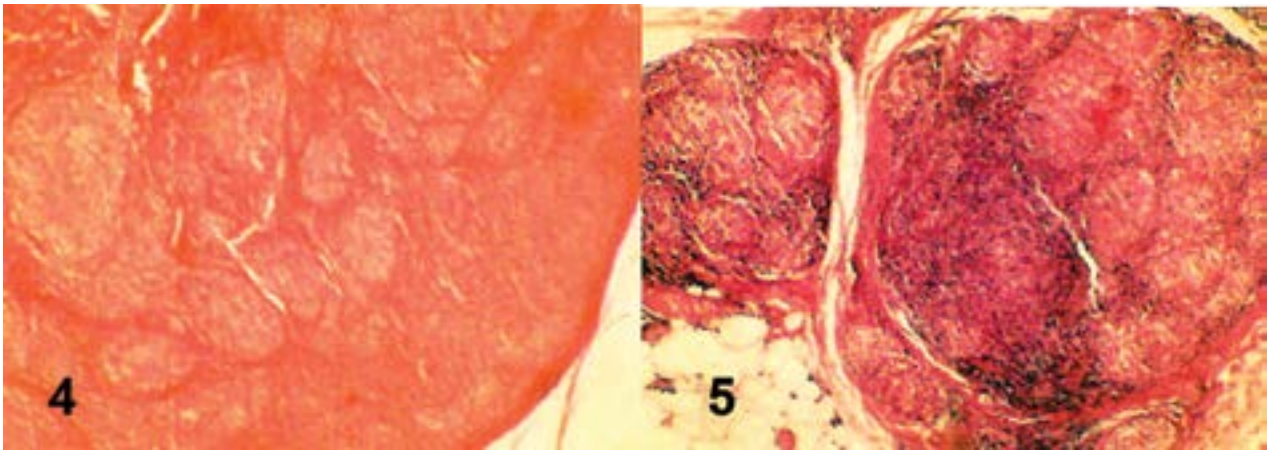


Figure 3. Nodular lesions, 2 cm in diameter, on both upper arms, similar in color, translucent

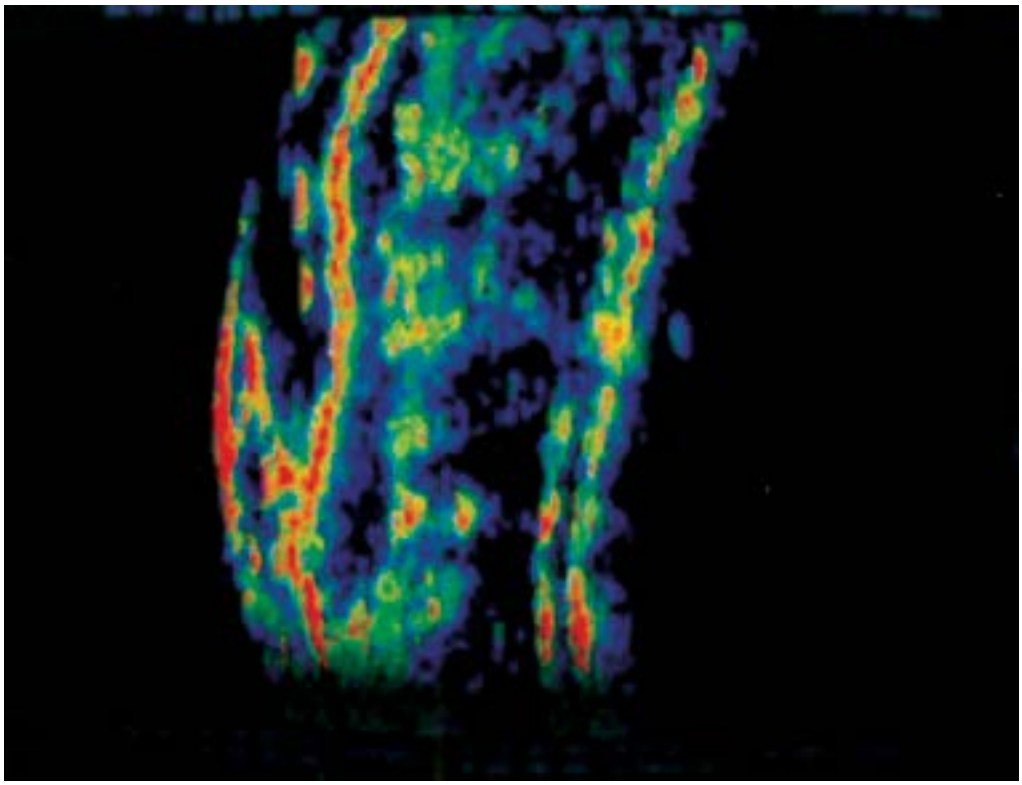
biopsy was taken 15 years before, unfortunately she did not have any medical reports. Three years ago, a new lesion appeared on her head and upper arms. There were no symptoms in other organs. She used various ointments, without any visible effect. Otherwise, she was in a good health and denied having any affected relatives.

Clinical examination

A clinical examination showed a lot of well defined plaques on the forehead and apex of the nose, yellowish-orange to amber color, some lesions covered with scabs (Figure 1). A lesion with prominent edge 12 x 10 cm (Figure 2) was visible on the back. Nodular lesions, 2 cm in diameter,



Figures 4. and 5. A strong granulomatous inflammatory reaction with numerous epithelioid and multinuclear Langerhans cells beneath the atrophic epidermis



Figures 6. Ultrasound of skin lesions on the forehead, above the root of the nose (at the beginning of treatment): A clearly limited lesion, different in thickness, resembling a string of beads. The thickest part of the skin lesion is 2.43 mm

were present on both upper arms, similarly colored, translucent (Figure 3).

Laboratory test results

All routine biochemical test results were within normal limits. Tuberculin testing was done by the Mantoux test with a 110 mm diameter of infiltration.

Histopathology

A strong inflammatory reaction of the granulomatous type with numerous epithelioid and multinucleated Langhans and/or foreign body cells were present beneath the atrophic epidermis (Figures 4 and 5).

X-ray and ultrasound imaging

Left hilar calcification was detected by chest X-ray. The ultrasound of the skin changes on the forehead, above the root of the nose, performed at the beginning of treatment revealed a well defined lesion without internal echo, different in thickness, looking like a string of beads. The thickest part of the skin lesion was 2.43 mm (Figure 6).

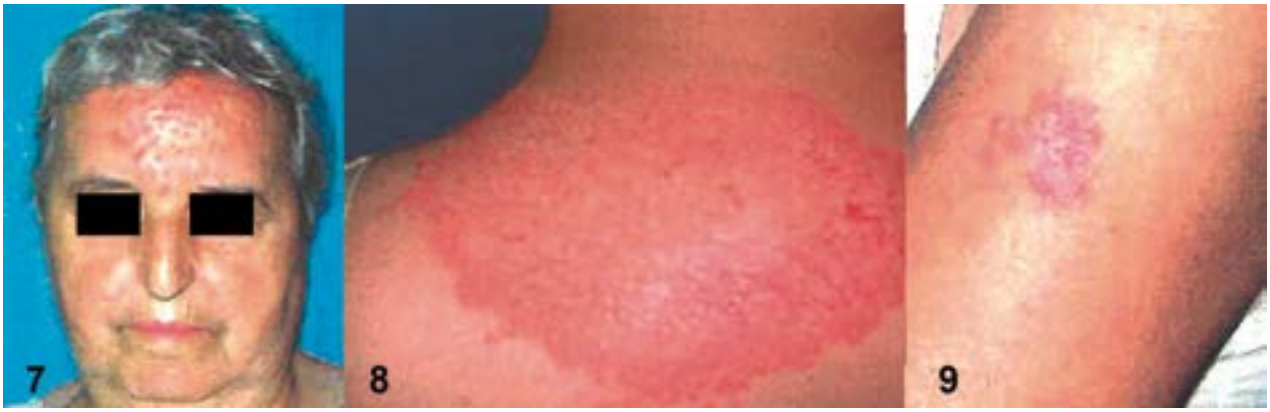
Therapy

Pronisone therapy, at a daily dose of 60 mg, slowly reduced to 20 mg per day, was initiated along with chloroquine phosphate (Delagyl) tablets, 250 mg twice a day. Betamethasone dipropionate ointment was applied topically twice a day, and cryotherapy with liquid nitrogen was commenced.

A significant improvement of the skin lesions was reported after three months of therapy: infiltration was paler, with less prominent (Figures 7, 8, 9) and reduced thickness (to 0,84 mm) identified by ultrasound (Figure 10).

Discussion

Sarcoidosis is an immune-mediated, complex inflammatory disease which represents abnormal immune response to various environmental factors in persons with genetic predisposition to granulomas (17, 18, 19, 20). It is characterized by activation of macrophages and CD4+ cells, and by accumulation of mononuclear phagocytes forming non-caseating epithelial cellular granuloma (21, 22).



Figures 7, 8 and 9. A significant improvement of skin lesions after three months: the lesions are paler, the infiltration is less prominent

Although the exact etiology of sarcoidosis has not been established, various agents which may act as antigens are believed to be responsible. These include viruses (Herpes virus, Epstein-Barr virus, Coxsackie B virus, Cytomegalo virus) and bacteria (Mycobacterium tuberculosis and other mycobacteria, Propionibacterium acnes (23), Borrelia burgdorferi, mycoplasma, Chlamydia (24), numerous nonorganic substances (aluminum, insecticides, lampblack, mold, titanium, silicon, iron, building materials, industrial dust) and organic substances (pine pollen, loam) (8, 24).

Genetics contributes a wide variety of clinical presentations and phenotypes noticed in sarcoidosis (18, 21).This has been confirmed by two findings - certain ethnicity was identified as an important risk factor, as well as the family history (19).

Antigen-presenting cells – macrophages and dendritic cells, interact with the antigen, which

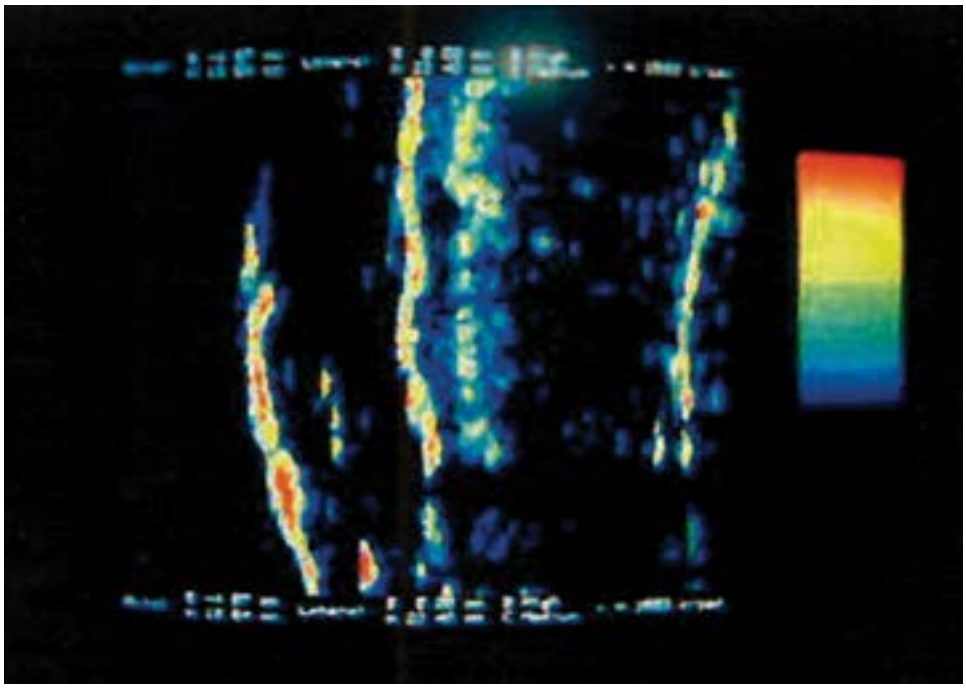


Figure 10. The ultrasound showed a reduced thickness - 0,84 mm

leads to activation and multiplication of CD4+ lymphocytes, initiating the immune process with Th1 cytokine profile. The produced cytokines: INF gamma (interferon gamma), TNF alfa (tumor necrosis factor alfa), IL-2 (interleukin-2), IL-12 (interleukin-12). IL-18 (interleukin-18), MIP 3 (macrophage proinflammatory human), GM-CSP (granulocyte-macrophage colony-stimulating factor) maintain the activation status and stimulate further mediator releasing and inflammation appearance, which are the characteristics of the disease. This occurs in various organs where the antigen is located, so due to the inability to remove the antigen, a typical epitheloid granuloma is created (25). In contrast to immune response at the site of inflammation in certain organs, state of energy is present on the periphery, which is characterized by decreased response when testing for delayed hypersensitivity and lower lymphocyte count in the peripheral blood in sarcoidosis patients, with unknown pathomechanisms (24).

Patients with sarcoidosis are at increased risk of malignant diseases, especially lymphoproliferative (26). There are a few mechanisms that can explain this phenomenon (27) – chronic inflammation, immune dysfunction, common etiological agents and genetic predisposition to autoimmune diseases and carcinoma (28, 29). Malignancies can develop after sarcoidosis, they can precede it, or, rarely, they develop simultaneously (30). Sarcoidosis can appear as a paraneoplastic syndrome. The antineoplastic treatment of either hematologic malignancies or solid tumors has also been observed to induce the initial onset or flare of sarcoidosis (31). The association between cutaneous sarcoidosis and malignancies is higher than with other types of sarcoidosis (29). Administration of immunosuppressants in sarcoidosis treatment increases the risk of infections, both fungal and bacterial. Association of sarcoidosis and HIV infection, which is rarely seen, is attributed to damaged immune system where CD4+ lymphocytes play the main role, causing granuloma formation in patients infected with HIV.

The cinical presentation of sarcoidosis may be quite peculiar, and it has been postulated that there is no disease with more varied manifestations (32). Cutaneous sarcoidosis without systemic involvement may occur in about one-quarter of all patients, and the same proportion of patients who develop a systemic disease may develop cutaneous sarcoidosis (32). When associated with systemic manifestations, lungs and intrathoracic lymph nodes are most frequently affected. Cutaneous lesions of sarcoidosis are generally classified as specific, if they are granulomatous infiltrates, and typical, if they appear as usual presentations of the disease.

Specific lesions include: papules or small nodules, plaques, nodules, subcutaneous and scarring forms, lupus pernio, angiolupoid and more rarely - scarring, but also non-scarring alopecia, erythroderma, ulcers, pustules, psoriasiform, ungual, and mucosal lesions (32, 33, 34).

Non-specific lesions include erythema nodosum, erythema multiforme, calcinosis cutis, ichthyosiform, as well miscelaneous, such as pruriginous varietas (35, 36).

Typical forms are most common and they are characterized by erythema nodusum, lupus pernio, nodular, papular, plaque forms, as well as subcutaneous and scarring forms (37, 38).

Atypical forms include erythrodermic, ichthyosiform, atrophic, ulcerous, verrucous, lichenoid, pruriginous, ungual, mocosal lesions, hyperpigmentations, and alopecia. Our patient had plaques on the forehead, on the capillitium and on the back (10 x 12 cm in diameter) and nodular lesions on the upper arms, up to 2 cm in diameter. The lesions were typical, both in localization and appearance.

Nodular lesions, including small nodular/papular lesions are most frequent (32). The lesions are localized on the face, extensor surfaces of the extremities, less commonly on the torso, gluteus, eyelids, and mucous membranes. The patients may have from several to hundreds of pale red, yellowish, and sometimes purple papules, 2 – 6 mm in diameter, with smooth surface, and sometimes with desquamation, up to larger, usually single or relatively few lesions, which remain circumscribed most often affecting proximal parts of the limbs, as in our patient.

Plaques manifest as red-brown, usually symmetrical circular or oval lesions, with elevated indurated edges, smooth, thin and paler skin in the center. Dilated blood vessels near the surface of the skin can be seen (angiolupoid), and annular forms are possible, most commonly on the face, forehead and neck. Plaques are, generally, most frequently

localized on the skin above the bones, on the forehead, shoulders, gluteus, thighs and ulnar aspect of forearms. Our patient had plaques on the forehead, on the capillitium and on the back (10 x 12 cm in diameter) and nodular changes on the upper arms, up to 2 cm in diameter. The lesions were typical, both in localization and appearance. The diagnosis of sarcoidosis was established based on the medical history, clinical presentation and typical histology with granuloma showing no caseation. Typical tuberculosis is usually distinguishable by histological features. On the other side, all attempts were made to delineate the full extent of the disease.

Any organ of the body may be affected by sarcoidosis, and the extent of cutaneous lesion does not correlate with the extent of the systemic disease.

The lungs are the most commonly affected organ (8) and more than 90% of patients with sarcoidosis present with lung symptoms. Based on chest radiography, lung sarcoidosis is divided into stages (32): stage 0 – normal chest x-ray (5 - 10%); stage I – bilateral hilar lymphadenopathy (only) (60 - 90%); stage II – bilateral hilar adenopathy with parenchymal changes (50 - 60%); stage III – diffuse pulmonary infiltration (less than 30%); stage IV – pulmonary fibrosis.

In our patient, the chest x-ray revealed a calcification of the left hilum, without other organ involvement. In sarcoidosis, atypical pattern of involvement of lymphadenopathy is not rare, which makes differentiation of sarcoidosis from other mediastinal diseases such as tuberculosis and especially Hodgkin's lymphoma, more difficult. Unilateral hilar lymphadenopathy is seen in less than 8% of sarcoidosis cases, but it is not uncommon in Hodgkin's lymphoma, where it accounts for 37.8% of cases. In sarcoidosis, unilateral hilar lymphadenopathy (if present) is approximately twice as common on the right side compared to the left side, and presence of lymph node calcification is more consistent with sarcoidosis. Contrast-enhanced CT scans may be helpful in differentiating intrathoracic sarcoidosis from Hodgkin's lymphoma based on the anatomical distribution of enlarged lymph nodes (39). Unfortunately, CT scan was not performed in our patient, and there was no other visible lymphadenopathy on the chest x-ray.

Treatment modalities for sarcoidosis are rather numerous, depending on the symptoms and the degree of systemic involvement (40), as well as on the possibility of spontaneous remission. In patients with isolated cutaneous forms, topical corticosteroids should be initiated, or even more effective intralesional corticosteroids (triamcinolone acetonide, 2 – 10 mg/ml in intervals of 2, 3 or 4 weeks). Application of topical tacrolimus has also showed satisfactory results. If this therapy fails to yield expected results, especially in chronic forms, like in plaque form, systemic therapy is applied (41).

Corticosteroids are usually prescribed in case of lung involvement, most frequently at initial dose of 20 – 40 mg/day of prednisone or equivalent doses, with gradual reduction during a couple of months.

Antimalarials – hydroxychloroquine, 200 – 400 mg/day, is the therapy of choice for mild isolated cutaneous forms over a longer period of time. Methotrexate can also be applied for pulmonary and extra-pulmonary manifestations (41) at doses of 10 – 25 mg per week, through an extended period, combined with low doses of corticosteroids.

Azathioprine has similar efficacy as methotrexate, and it can also be combined with corticosteroids.

Cyclophosphamide can be used orally and intravenously (50 – 150 mg/day - orally, or 500 – 2000 mg/week - intravenously), while chlorambucil in combination with low doses of prednisone.

Mycophenolate mofetil (45 mg/kg daily) combined with corticosteroids, showed significant improvements with no side effects in patients with pulmonary and extensively mucocutaneous sarcoidosis.

Thalidomide (42), tetracyclines (minocycline 200 mg/day, average period of administration 12 months, and doxycycline for relapse) (41), tumor necrosis factor–alfa (TNF–alfa) inhibitors (infliximab, etanercept) are also applied.

Ultraviolet therapy (UVA 1 and PUVA), showed good results with cutaneous forms of sarcoidosis. A favorable response to corticosteroid and antimalarial systemic therapy was achieved in our patient after three months.

The prognosis of sarcoidosis is generally better in females, in those with less severe pulmonary disease at the onset, and in patients with a positive tuberculin test (32).

Spontaneous remission occurs in 2/3 patients, while 1 - 3% of patients have a chronic course. Papular and nodular lesions resolve over the course of months or years, while the plaques are more resistant. The overall level of mortality from sarcoidosis varies from 1 - 5%, and with chronic liver disease the percentage increases to 12%.

Conclusion

This is a case of a female patient with unilateral hilar calcification of the lung, who exhibited plaque skin lesions typical for sarcoidosis, with specific granulomatous histology and a favorable response to corticosteroid and antimalarial therapy, confirmed by ultrasound skin imaging.

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Sarcoidosis cutis kod pacijenta sa kalcifikacijom u levom hilusu pluća - prikaz slučaja

Sažetak

Sarkoidoza je stečena idiopatska granulomatozna bolest za koju je karakteristično prisustvo nekazeifikujućih epiteloidnih granuloma u organima i tkivima. Bolest se javlja kod osoba svih rasa i u svim uzrastima, takođe kod oba pola, nešto češće kod žena. Na osnovu histopatoloških karakteristika, kutane manifestacije se dele na specifične, koje karakteriše sarkoidni granulom i nespecifične, koje nisu granulomatozne. Takođe se mogu klasifikovati kao tipične i atipične. Kada su u kombinaciji sa sistemskim zahvatanjem, najčešće se radi o plućima i intratorakalnim limfnim žlezdama. Kutana sarkoidoza je poznata kao jedan od velikih „imitatora" u dermatologiji ili kao „klinički kameleon", jer lezije mogu imati širok spektar poremećaja.

Prikaz bolesnice. Kod bolesnice od 68 godina prve promene su se javile na koži leđa pre 15 godina, a pre tri godine i na glavi i nadlakticama. Nema simptome od drugih organa. Klinički, na čelu i temenu prisutno više jasno ograničenih infiltrovanih plaža narandžastožućkaste do mrke boje, mestimično pokrivenih krustama. Na leđima plaža 12 x 10 cm, sa naglašenim rubom. Na obema nadlakticama nodularne promene do 2 cm u prečniku, slično prebojene, translucidne. Laboratorijske analize u granicama normale. Testiranjem na tuberkulin *Mantoux* metodom registrovana induracija od 10 mm. Patohistološki nalaz: ispod atrofičnog epiderma jaka inflamatorna reakcija granulomatoznog tipa sa brojnim epiteloidnim i multijedarnim ćelijama *Langhansovog* tipa. X-zracima registrovana kalcifikacija u levom plućnom hilusu. EHO promene na čelu iznad korena nosa (na početku lečenja): najveća debljina same promene 2,43 mm. Primenjena terapija: pronizon tablete u dnevnoj dozi od 60 mg do smanjenja na 20 mg dnevno, *chloroquin phosphat* (*Delagyl*) tablete a 250 mg 2 x 1 dnevno, betametazon propionat mast dvaput dnevno, krioterapija tečnim azotom. Posle tri meseca registrovano znatno poboljšanje promena na koži: promene bleđe, manje izražena infiltracija i EHO pregledom registrovano smanjenje debljine na 0,84 mm.

Diskusija. Sarkoidoza je imunoposredovana inflamatorna kompleksna bolest koja predstavlja abnormalni imunoodgovor na raznolike faktore iz okruženja (virusi, bakterije, razne organske i neorganske materije) kod osoba genetski predisponiranih da razvijaju granulome. Kod naše bolesnice promene su bile tipične po lokalizaciji i izgledu. Rtg pluća pokazao kalcifikaciju levog hilusa. Dijagnoza sarkoidoze zahteva određene postupke: iscrpnu anamnezu, kliničku prezentaciju i tipičnu histologiju granuloma bez kazeifikacije. Na osnovu ovih procedura, postavljena je dijagnoza kod naše bolesnice . Dodatno je urađen i EHO kožne promene

na početku i posle tri meseca primene terapije. Pored lokalne terapije kortikosteroidima, bilo je neohodno primeniti i sistemsku terapiju (kortikosteroidima i antimalaricima), što je dovelo do poboljšanja.
Zaključak. Prikazana je bolesnica sa unilateralnom hilarnom kalcifikacijom pluća, sa plak tipom kožnih lezija tipičnih za sarkoidozu, sa specifičnim histološkim nalazom i povoljnim odgovorom na terapiju kortikosteroidima i antimalaricima, što je potvrđeno ultrazvučnim pregledom kože.

Ključne reči

Sarkoidoza; Kožne bolesti; Plućne bolesti; Prikazi slučajeva; Prednizon; Antimalarici; Ishod terapije

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A Rare Comorbidity: Dermatitis Herpetiformis and Sarcoidosis - A Case Report

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Abstract

Sarcoidosis is an enigmatic, multisystem granulomatous disease of unknown etiology and wide range of clinical presentations. Case report: A 54-year-old female presented with facial rash: polymorphic, round, infiltrated erythematous plaques, 1 - 3 cm in size, disseminated on several areas of the face. The medical history was consistent with dermatitis herpetiformis and persistent intrahepatic cholestasis. The laboratory test results suggested celiac disease (strong positivity of IgA anti-tissue transglutaminase antibodies) but upper endoscopy was not performed to confirm it. The skin biopsy revealed noncaseating epithelioid-cell granulomas, and negative direct immunofluorescence showed IgA deposits in the dermis. Sarcoidosis with cutaneous and hepatic involvement was established based on compatible clinical findings and supportive histology. The period between manifestations of Duhring disease and skin manifestations of sarcoidosis was 20 years. Conclusion: Our clinical case supports the hypothesis for common immune pathogenic factors in gluten-sensitive diseases and sarcoidosis. The simultaneous occurrence of celiac disease and sarcoidosis is rare, but should not be under recognized.

Key words

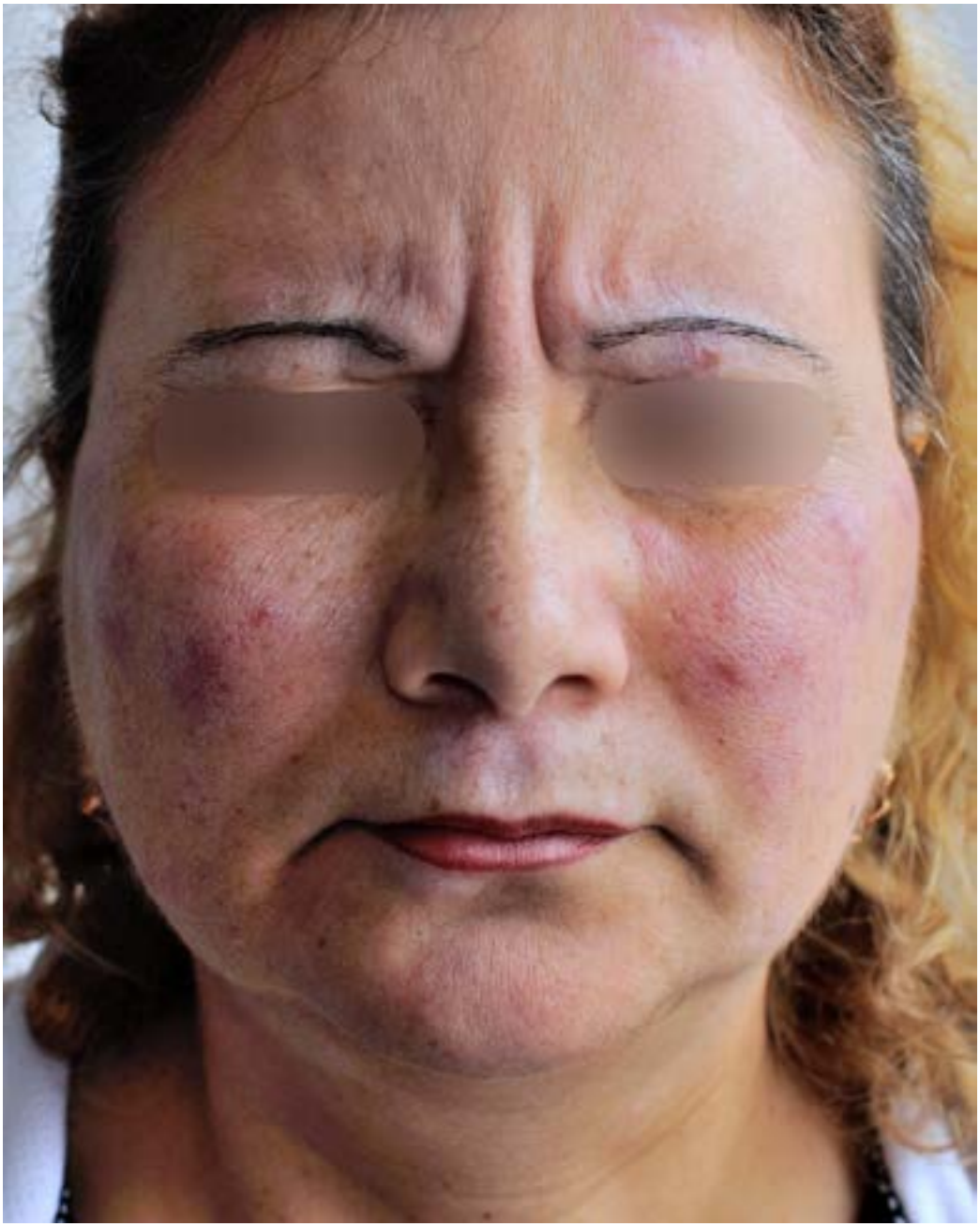
Sarcoidosis; Dermatitis Herpetiformis; Comorbidity; Wheat Hypersensitivity; Diet, Gluten-Free; Epithelioid Cells; Granuloma; Case Reports

Sarcoidosis is a systemic granulomatous disease that primarily affects the lungs and lymphoid tissues of the body, and is due to altered immune response to unidentified antigens. During the course of sarcoidosis, approximately 25% of patients develop skin involvement with diverse manifestations, thus cutaneous sarcoidosis is known as a "great imitator". The reported skin lesions, associated with specific noncaseating granulomas, are infiltrated plaques, maculopapular eruptions, subcutaneous nodules and scars, lupus pernio and rare entities like alopecia, ulcers, hypopigmented patches and ichthyosis. Hepatic involvement occurs in 5 - 15% of patients with sarcoidosis, including asymptomatic abnormal liver enzyme levels, hepatosplenomegaly, chronic intrahepatic cholestasis, hilar adenopathy, and Budd-Chiari syndrome. The diagnosis of sarcoidosis is based on compatible clinical features, accompanied by evidence of imaging studies and tissue biopsy, with all other causes of granulomas ruled out (1). Sarcoidosis has been associated with different autoimmune disorders, such as celiac disease (CD), primary biliary cirrhosis, Crohn's disease, and Sjogren's syndrome. Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Dermatitis herpetiformis, or Duhring disease (DD) is a rare chronic, blistering skin disorder with pathognomonic immunoglobulin A (IgA) deposits in the papillary dermis. It is considered the specific cutaneous expression of a gluten-sensitive

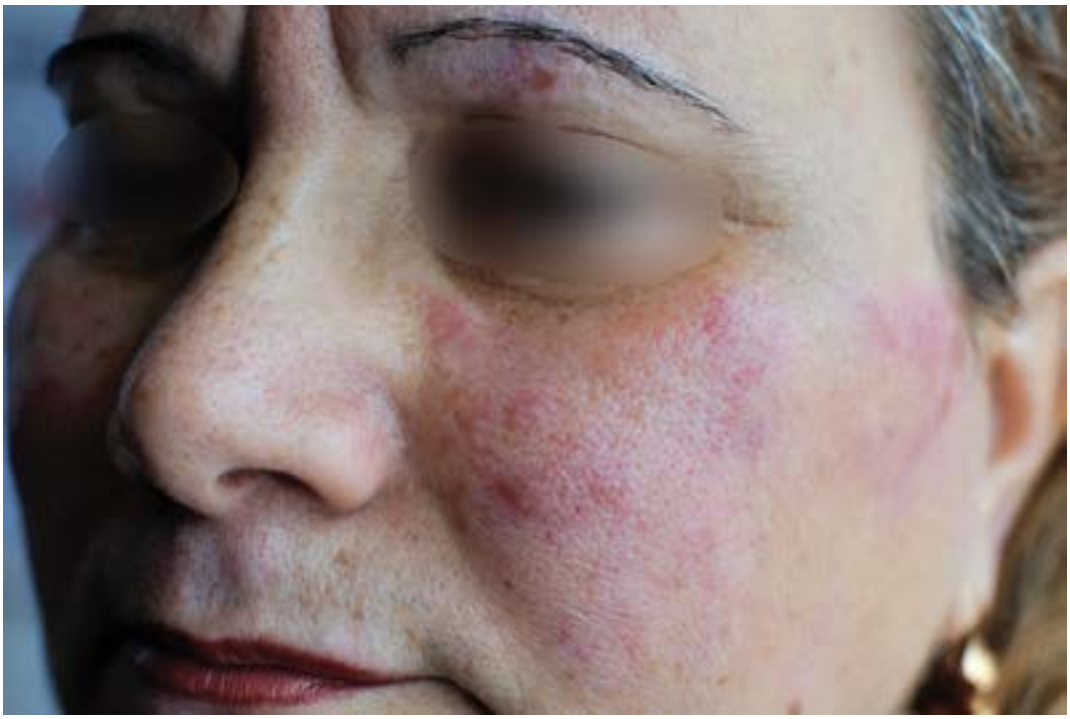
enteropathy indistinguishable from CD, that is responding to gluten withdrawal (2). More than 90% of the patients with DD exhibit characteristics of CD intestinal histology. However, the reported prevalence of classical, symptomatic CD is low, up to 12.6%, based on the Mayo Clinic experience (3).

Case report

A 54-year-old woman was admitted to the Dermatology Clinic for evaluation of facial rash presenting with polymorphic, disseminated, round, infiltrated erythematous plaques,_1 - 3 cm in size, bilaterally affecting the zygomatic and suborbital



Figures 1a. The appearance of the affected skin



Figures 1b. The appearance of the affected skin

areas, the left pre-auricular area, and the forehead. Several telangiectasia were also found on affected regions (Figure 1). No systemic signs and symptoms of chronic inflammation or gastrointestinal complaints were observed.

In 1995, at the age of 34, the patient suffered from papulovesicular eruptions, affecting the elbows, knees and the groin area, and Duhring disease was confirmed by skin biopsy and direct immunofluorescence. A gluten-free diet was prescribed, but the patient showed a poor dietary compliance. Nevertheless, resolution of the rash was achieved. In 2009, fourteen years after DD was established, she had a mild fatigue and the laboratory tests showed elevated transaminases (alanine transaminase (ALT) up to 2 times the upper limit of normal (ULN)), cholestasis (alkaline phosphatase *(AP)* up to 3 times the ULN), normal blood count, erythrocyte sedimentation rate (ESR), *C-reactive protein* (CRP), serum albumin and immunoglobulin G (IgG) level, negative markers for chronic viral hepatitis, negative anti-mitochondrial autoantibodies, but positive anti-nuclear antibodies (+++), antibodies to tissue transglutaminase – tTG IgA (++) and antibodies to gliadin (+). With a suspicion of autoimmune hepatitis, overlap syndrome with primary biliary cirrhosis, a percutaneous liver biopsy was done. Histology revealed portal fibrosis, one broad fibrotic P-P septa, scarce portal lymphoid infiltrates, balloon degeneration of hepatocytes, numerous granulomas in the lobules containing lymphoid, epithelioid and fibroblast cells, few giant multinuclear cells and eosinophils (Figure 2).

The past medical history of our patient showed dermatitis herpetiformis (Duhring disease) and chronic granulomatous hepatitis; celiac disease is a presumptive diagnosis, but the patient refused upper endoscopy and endoscopic and histological proof of celiakia was not obtained. Treatment with low-dose oral methylprednisolone (4 mg per day), azathioprine (50 mg per day) and ursodeoxycholic acid (750 -1000 mg per day) was introduced in 2009, but with frequent interruptions, and the patient again failed to follow a strict gluten-free diet. Remission of DD was achieved, however cholestatic liver enzymes remained slightly elevated.

In 2015, on current admission, a biopsy of the affected facial skin was done and the histology report supported skin involvement of sarcoidosis (epithelioid

granulomas without caseous necrosis, few giant/ Langerhans cells, surrounding tissue with lymphoid infiltrates and very mild perivascular mononuclear infiltrations and negative immunofluorescence findings for IgG, IgA, IgM and C3) (Figures 3a and 3b).

Retrospectively, sarcoidosis can be established to correlate with chronic, relatively benign course of disease with a period of 6 years between diagnosis of hepatic and cutaneous involvement.

The patient provided a written informed consent for planned examinations and use of the results for scientific purposes.

Discussion

Sarcoidosis is a chronic idiopathic granulomatous disease. Extra-thoracic involvement is not rare, and it can initiate the course of sarcoidosis. Systemic work-up is necessary in patients with histological findings of sarcoid-like granulomas to rule out tuberculosis and other (fungal, parasitic) infections, as well as a first signs of lymphoma or a systemic autoimmune disease. The association of sarcoidosis, as a chronic idiopathic granulomatous disease, and CD has previously been described (4 - 10). Reports linking sarcoidosis and DD are less numerous. Large cohort studies of patients with DD found occurrence of concomitant sarcoidosis in 1.3% to 1.5% of patients, and the mean interval between diagnoses was 1 year (3, 11). Strong association with class II haplotype HLA-DR3, DQ2

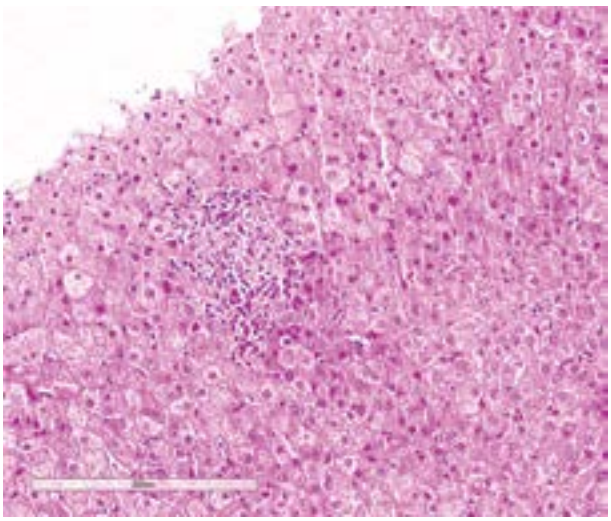


Figure 2. Histology of a blind liver biopsy suggesting chronic granulomatous hepatitis

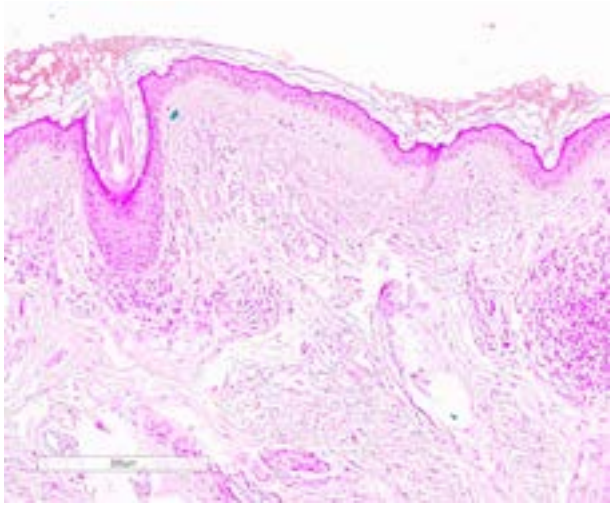


Figure 3a. Histology of skin biopsy, consistent with cutaneous sarcoidosis (hematoxylin and eosin staining)

and HLA-B8 have been demonstrated in sarcoidosis, CD and DD, and these disorders probably share immunological disturbances (2, 4). Enhancing the expression of class II HLA molecules, diseases may predispose to each other (9). The manifestations of sarcoidosis seem to improve during a gluten free diet and relapse after reintroduction of gluten into the diet (10). Because sarcoidosis and CD have variable, atypical presentations, the physicians should be aware and search for their association. Also, a routine screening for CD should be considered in patients with sarcoidosis, due to a potential benefit from a gluten free diet.

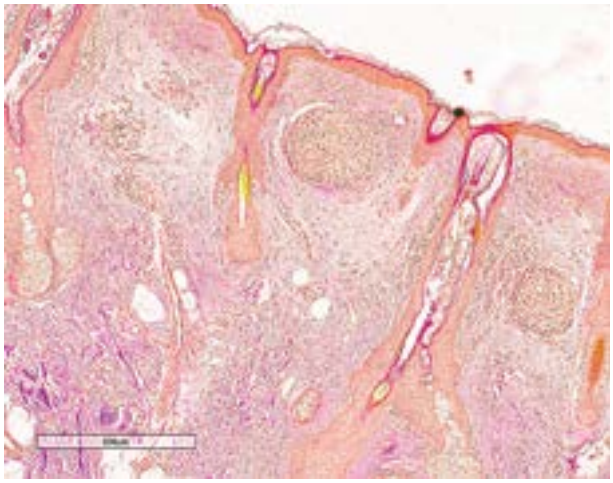


Figure 3b. Histology of skin biopsy, consistent with cutaneous sarcoidosis (Van Gieson's stain)

On the other hand, the pathogenesis of DD is not well understood (2). In our case we observed a clinical remission of DD at the time when manifestations of hepatic granulomatosis appeared, and negative direct immunofluorescence test for DD during investigations of skin sarcoidosis. Interestingly, DD patients show high rate of positivity (16 of 17 of cases) of in vitro Kmif test for cellular immunity, characteristic for disorders with epithelioid granulomas (12). Another study suggests the common role of human macrophage metalloelastase (MMP-12) for elastin degradation occurring in granulomatous skin diseases and for macrophage migration through the epidermal and vascular basement membranes in skin inflammatory disorders, such as DD (13). Therefore, our case report may be a small contribution to the concept of a common genetic predisposition and pathogenesis of DD and sarcoidosis.

Abbreviations

CD - celiac disease
DD - Duhring disease
IgA - immunoglobulin A
ALT - alanine transaminase
ULN - upper limit of normal
AP - alkaline phosphatase
IgG - immunoglobulin G
tTG - tissue transglutaminase
MME-12 - macrophage metalloelastase-12

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Dermatitis herpetiformis i sarkoidoza − redak komorbiditet - prikaz slučaja

Sažetak

Uvod. Sarkoidoza je zagonetna, multisistemska granulomatozna bolest nepoznate etiologije sa širokim spektrom kliničkih simptoma. Prikaz slučaja. Pacijentkinja stara 54 godine primljena je na *Kliniku za dermatologiju* sa osipom na licu: polimorfni, okrugli, infiltrirani eritematozni plakovi, veličine 1−3 cm, bili su rasuti po delovima lica. Istorija bolesti je ukazivala na dermatitis herpetiformis i perzistentnu intrahepatičku holestazu. Rezultati laboratorijskih testova ukazivali su na celijakiju (visoka pozitivnost *IgA* anti-transglutaminska antitela), ali gornja endoskopija nije urađena da to potvrdi. Biopsija kože otkrila je nenekrotizirajuće epitelioidne ćelije granuloma, a negativna direktna imunofluorescencija pokazala je IgA depozite u dermisu. Sarkoidoza kože i jetre ustanovljena je na osnovu kompatibilnosti kliničkog i histopatoloških nalaza. Između manifestacija Duringove bolesti i kožnih manifestacija sarkoidoze prošlo je 20 godina. Zaključak. Naš klinički slučaj podržava hipotezu

da su patogeni imunofaktori zajednički kod bolesti osetljivih na gluten i sarkoidozu. Istovremena pojava celijakije i sarkoidoze je retka, ali ne bi trebalo da bude neprepoznata.

Ključne reči

Sarkoidoza; Dermatitis herpetiformis; Komorbiditet; Hipersenzitivnost na pšenicu; Bezglutenska ishrana; Epiteloidne ćelije; Granulom; Prikazi slučajeva

A Report on the 25th Congress of the European Academy of Dermatology and Venereology, Vienna 2016

The 25th Congress of the European Academy of Dermatology and Venereology was held in Vienna (Austria), September 28 - October 2, 2016. All major fields of dermatology, including the fast moving field of onco-dermatology, psoriasis, inflammatory and allergic diseases, clinico-pathological correlations for clinicians and *Aesthetic Sunday* for excellence and training in aesthetics, were presented by the most prominent experts in these fields. The intensive 4-day program included 180 stimulating sessions. Contributors from more than 30 different countries worldwide and more than 700 speakers presented their lectures.

Prof. Miloš Nikolić was a session chair for the: "Vasculitis, vasculopathies and treatment" and delivered a lecture "Vasculitis and vasculopathies: what makes the difference?".

Prof. Ljiljana Medenica was a session chair for the: "Autoimmune bullous diseases". She delivered a lecture "The pemphigus group: clinical manifestations and different diagnosis".

Prof. Lidija Kandolf-Sekulović was a session chair for the "Non-melanoma skin cancer" and delivered a lecture "Clinical and pathological spectrum: basal cell carcinoma".

Dr. Mirjana Milinković was a session chair for the: "Chronic inflammatory disease" and delivered a lecture "The million faces of sarcoidosis".

Dr. Svetlana Popadić delivered a lecture: "Splenectomy in a patient with unrecognized Sweet syndrome: was it necessary?" in the session "Dermatology from around Europe".

There were 23 e-Posters from Serbia.

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Figure 1. Svetlana Popadić, giving a lecture: "Splenectomy in a patient with unrecognized Sweet syndrome: was it necessary?"

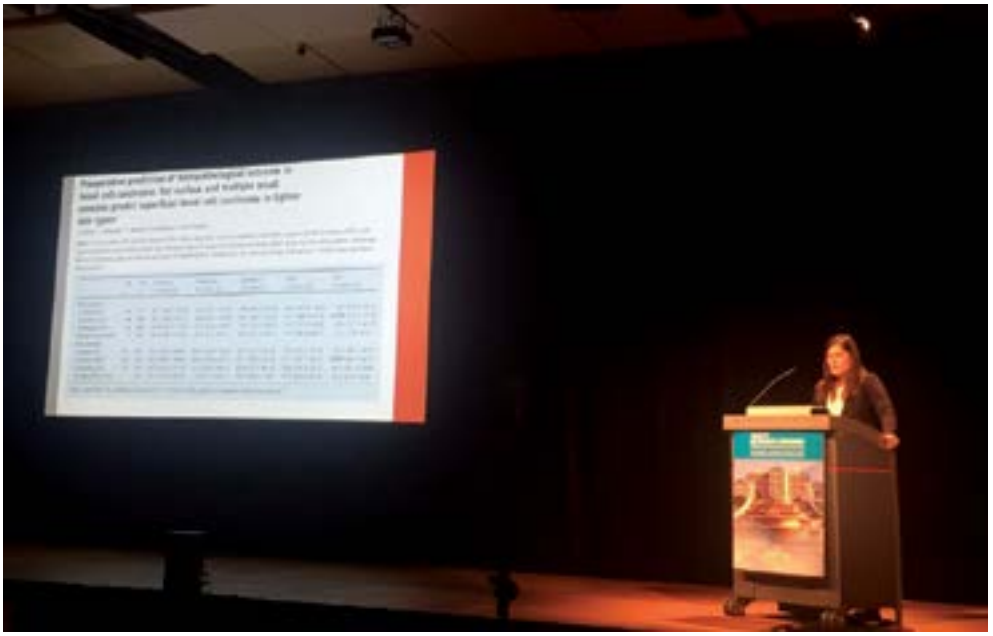

Figure 2. Lidija Kandolf Sekulović, giving a lecture: "Clinico-pathological spectrum of basal cell carcinoma"

Figure 3. EADV Congress President's Dinner: Lidija Kandolf Sekulović, Ana-Maria Forsea, Veronique del Marmol and Željko Mijušković

A Report on the 16th World Congress on Cancers of the Skin, Vienna 2016

The 16th Congress on Cancers of the Skin, and the 12th Congress of the European Association of Dermato-Oncology was held in Vienna (Austria), from August 31 to September 3, 2016. This prestigious meeting, a major interdisciplinary conference for clinicians, as well as for basic scientists working in the fields of skin cancers, took place in the beautiful historic *Hofburg Conference Center*, in the heart of Vienna. The program was conceived to cover the entire spectrum of cutaneous malignances. All the world-renowned experts in melanoma and non-melanoma skin cancers presented their remarkable and up-to-date lectures. Many of the world's leading investigators in the field of skin malignances were active participants, which was very interesting and useful for the numerous audience. Clinicians and researchers focused on the state of the art in prevention, recognition and treatment of cutaneous neoplasms covering not only melanoma and non-melanoma skin cancers, but also lymphomas

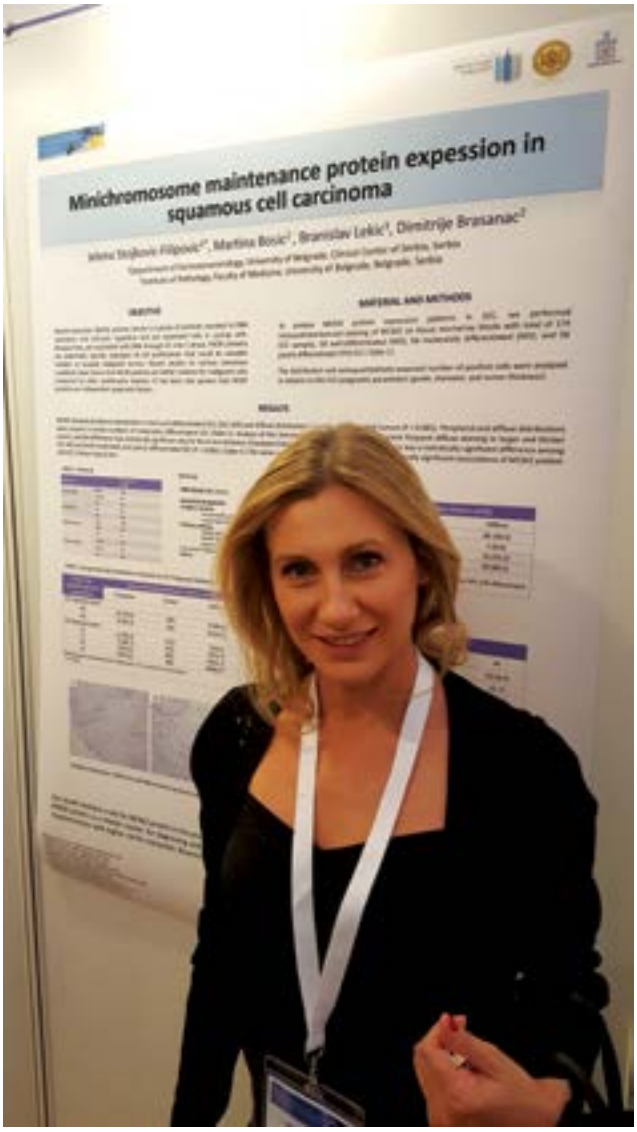

Figure 1. Dr. Jelena Stojković-Filipović in Hofburg Conference Center in Vienna

and rare skin tumors. Before the opening ceremony, two great plenary lectures were delivered, the first about "Immunotherapy of melanoma", by Jeffrey Weber, and the second about "Target therapy of basal cell carcinoma" presented by US-based dermatologist Alexandar Sekulic. After that, Hubert Pehamberger, Claus Garbe, Perry Robins, and Markus Muller welcomed the participants with proper speeches. The scientific program included numerous sessions on the Epidemiology of Skin Cancer, Public Education and Primary Prevention, Biology of the Skin Cancer Development, Dermoscopy, Genetic Testing in Skin Cancers, Cutaneous Immunology, Immunotherapy, Melanoma Therapy Drugs and Trials, Melanoma Surgery, Lymph Nodes to Distant, Locoregional Therapy of Melanoma Metastases, Preventive Biomarkers in Melanoma, BCC and SCC/AK Epidemiology, Biology, Genetics, Clinical Data and Treatment, Surgery of Skin Cancer, Dermatopathology of Cutaneous Tumors, Sentinel Lymph Node Surgery, Vaccines in Cutaneous Tumors, Chemotherapy, Cutaneous Side Effects of Oncological Drugs, Skin Cancers in Special Patient Subgroup, UV-protection, Vitamin D and Photoaging, Phychodermatooncology, Side Effects of Systemic Skin Cancer Therapies, Current Standards of Imaging Methods for Skin Cancer Patients, New Methods in Early Detection of Skin Cancer and Future Targets and Combinations in Dermatooncology. The intensive 4-day program included 58 stimulating sessions. Contributors from different countries worldwide with more than 80 speakers presented their lectures covering all the embankments of skin malignancies. Additional interesting cases and researches were presented in 219 poster presentations. Prof. Lidija Kandolf-Sekulović was a session chair in the session "Locoregional Therapy of Melanoma Metastases" and delivered a lecture "Access to Innovative Medicines for Metastatic Melanoma in Europe" in the session "Skin Cancer Centers – What is the Worldwide Standard". There were three poster presentations from Serbia. It was a pleasure and privilege to participate in this EADV meeting and spend days in scientific communications and exchanges regarding skin cancers.

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A Report on the 4th European School of Dermato-Oncology, Berlin 2016

The 4th European School of Dermato-Oncology (ESDO) was held from January 28 - 30, 2016 at the Novotel Berlin am Tiergarten, Germany. The ESDO is an annual event, gathering experts in the field of dermato-oncology to give research update through lectures and inspirational debates on a wide spectrum of topics: from skin cancer prevention and diagnostic options to novel therapies of skin cancers.

Due to the results accomplished during *Euromelanoma Campaign* in Serbia, Associate Prof. Dušan Škiljević and myself had been awarded attendance grants for the ESDO 2016.

During a two and a half day program, about 100 participants from various European countries were able to attend a total of 15 plenary lectures and 8

Figure 1. Tatjana Roš and Dušan Škiljević during one of the session breaks

comprehensive courses.

One of the plenary lectures on prognostic factors of melanoma was given by Prof. Lidija Kandolf Sekulović, while other lectures referred to epidemiologic trends of skin cancers, sun protection key messages, significance and imaging techniques for skin cancer early detection, signaling pathways, adjuvant and neoadjuvant therapies for melanoma, cutaneous side effects of innovative antineoplastic agents, treatment of actinic keratosis, skin cancer chemo-prevention, photodynamic therapy, electro-chemotherapy, and radiation therapy of skin cancers.

In order to improve interaction during comprehensive courses, attendees were divided into four educational groups, and followed a precise time-table switched the classrooms to learn about dermoscopy of skin cancers, topical, systemic and surgical treatment of non-melanoma skin cancers, staging and follow up of skin cancers, sentinel node biopsy and treatment of metastatic melanoma.

With many compliments to the organizers and lecturers, I find the ESDO very useful and highly valuable source of knowledge to all the dermatologists with a special interest in oncology.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2016/2017

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
08-11 September, 2016	3rd Regional Congress, Mostar, Bosnia and Herzegovina	01 August, 2016	www.derma-regional2016.org
15-17 September, 2016	IUSTI Europe 2016, Budapest, Hungary	15 May, 2016	www.iusti2016.com
28 September – 02 October, 2016	25th EADV Congress, Vienna, Austria	18 April, 2016	www.eadvvienna2016.org
14 October, 2016	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Vojvodina, Novi Sad, Serbia	No abstract submission	www.sld.org.rs
20-22 October, 2016	2nd International Conference of Dermatology, Kathmandu, Nepal	15 June, 2016	www.icderm2016.com
26-28 October, 2016	3rd World Congress of Cutaneous Lymphomas, New York City, USA	01 July, 2016	www.cutaneouslymphoma.org
03-05 November, 2016	19th Belgrade Dermatology Days, Belgrade, Serbia	15 September 2016	www.udvs.org
09-10 December, 2016	Congress of the Association of Serbian Cosmetic and Aesthetic Dermatology, Belgrade, Serbia	No abstract submission	www.asked.rs
26-29 January, 2017	IMCAS World Congress 2017, Paris, France	19 December, 2016	www.imcas.com
26-28 January, 2017	5th European School of Dermato-Oncology, Berlin, Germany	No abstract submission	www.dermato-oncology2017.org
02-05 February, 2017	Many Faces of Dermatology – Clinical, Surgical and Aesthetical Dubrovnik, Croatia	28 October 2016	www.isdregional2017.org
16-18 February, 2017	Cosmexchange, Trieste, Italy	No abstract submission	www.cosmexchange.com
17 March, 2017	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Serbia, Belgrade, Serbia	No abstract submission	www.sld.org.rs
27-29 March, 2017	Dubai Derma 2017, Dubai, UAE	No abstract submission	www.dubaiderma2017.org
07 April, 2017	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Military Medical Academy, Belgrade, Serbia	No abstract submission	www.sld.org.rs
18-22 April, 2017	12th International Congress of Dermatology – International Society of Dermatology, Buenos Aires, Argentina	9 December, 2016	www.icd2017.com.ar

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AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

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

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

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

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

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

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

All manuscripts should be submitted to the **Editor in Chief: Prof. Dr. Lidija Kandolf Sekulović***, Clinic of Dermatovenereology, School of Medicine, Military Medical Academy, Crnotravska 17, Belgrade, Republic of Serbia, by mail to: serbjdermatol@mts.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/.

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

2. Tables and illustrations

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

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

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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.

- Open access: Every article published in the **Serbian Journal of Dermatology and Venereology** will immediately be accessible on **www.udvs.org** to everyone at no charge.

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

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