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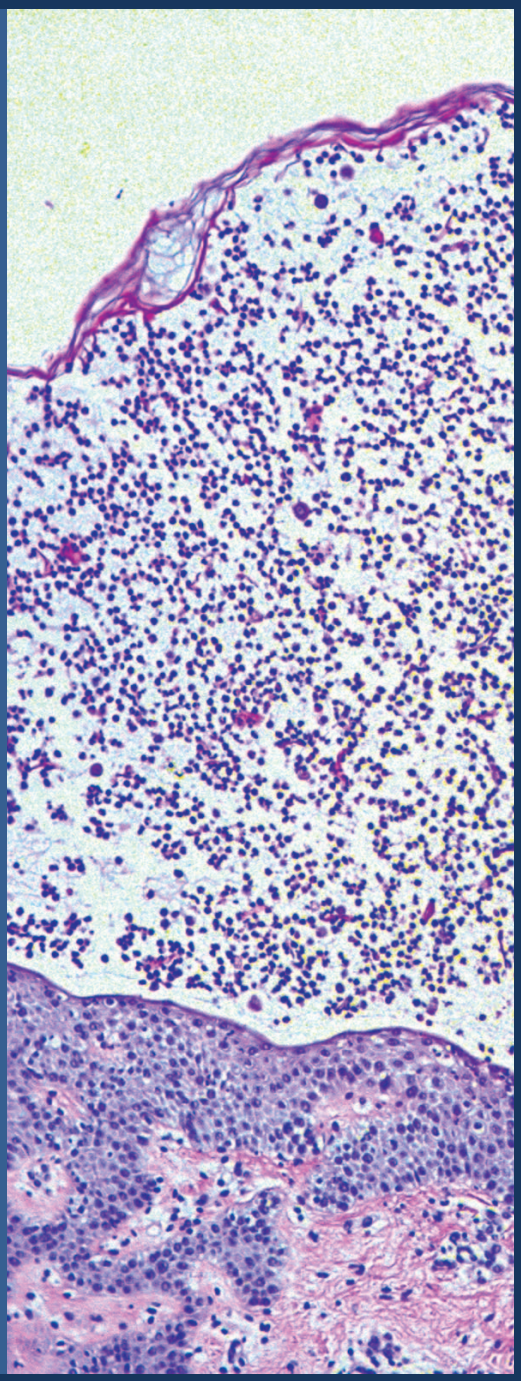

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Sunbed Use Among Belgrade High School Students

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Abstract

Introduction: The incidence of melanoma has been increasing worldwide. Ultraviolet (UV) radiation from the sun and sunbeds are the major risk factors for the development of melanoma and non-melanoma skin cancers. Excessive UV exposure during childhood and adolescence increases the probablity of skin cancer in adulthood. The objective of this study was to analyze the exposure to artificial UV radiation using sunbeds among Belgrade high scool students. Material and Methods: The study was conducted using a questionnaire among 549 3rd and 4th grade students in 4 Belgrade high schools. The questionnaire included 10 questions on the sunbed use, attitudes, and general knowledge about effects of UV radiation from sunbeds. Statistical analysis assessed the frequency rate and relative frequency as methods of descriptive statistics. Results: A total of 39% of participants had used a sunbed at least once, and 38% plan on using it in the future. When asked at what age they first used a sunbed, 45.66% of high school students stated that it was at the age of 13 or 14. Most adolescents have used a sunbed less than 5 times (38%), whereas 8% of them used it over 30 times. Conclusion: The awareness of the risks associated with UV exposure in sunbeds is not at a satisfying level among Belgrade high school students. Educational and legislative measures are necessary to protect this highly sensitive population and prevent malignant consequences.

Key words: Skin Neoplasms; Sunbathing; Ultraviolet Rays; Neoplasms, Radiation-Induced; Melanoma; Adolescent

The incidence of melanoma is steadily increasing worldwide, making it a global health problem. The number of newly diagnosed patients is increasing at a faster rate than for any other neoplasm, with the exception of lung cancer in women. The incidence increase varies, but on average it is estimated to be 3 - 7% per year among white population (1). This increase can partially be explained by earlier detection and better diagnosis of the disease, but it is believed that higher exposure to risk factors can also be of great influence (2).

Ultraviolet (UV) radiation plays an important role in the pathogenesis of both melanoma and non-melanocytic skin cancer (3). International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) considers exposure to natural and artificial sources of UV radiation an important risk factor, as level 1 – "carcinogenic to humans" (4). It is well established that excessive exposure to sun in the childhood and adolescence increases the risk of skin cancer in adulthood. As much as 50 - 80% of the total amount of UV radiation is accumulated in this period of life, although the exact mechanism of this phenomenon is not yet elucidated (5).

Acute skin reactions to the UV radiation in sunbeds include erythema, phototoxic skin reactions, pseudoporphyria, while potential chronic effects of sunbed use are premature skin aging and skin cancer (6). A recent study revealed that the risk of melanoma was 41% higher in participants who had used a sunbed compared with those who had never used a sunbed, and also that the risk of melanoma was greater with earlier age at first use of sunbeds and for earlier disease onset. The participants who reported more than 10 lifetime sessions appeared some six times more likely to be diagnosed with melanoma before 30 years of age compared with never-users (7).

The objective of this study was to analyze the exposure to artificial UV radiation among Belgrade high school students, as well as their knowledge and attitudes towards its harmful effects on health.

Material and Methods

The study was conducted among students of four high schools in Belgrade, two general high schools, and two high schools of special profiles. Since all schools are in the city territory, our sample represented mainly urban population.

Using a questionnaire, we interviewed 549 students of the 3rd and 4th grade (17- and 18-year-olds) of the selected schools, 406 females and 143 males. The study took place over the course of 2 weeks (January 16 – February 01, 2012). The timing of the researcher's school visits was based on each school's program schedule.

The questionnaire about the sunbed use was anonymous and included 10 questions (Table 1). The questionnaire was pilot tested among fifty 5th year students of the School of Medicine, University of Belgrade, who evaluated it and gave their suggestions.

The researcher was present while students completed their questionnaires and was available to any student who needed clarification regarding the questions.

Statistical analysis assessed the frequency rate and relative frequency as methods of descriptive statistics.

Results

The results are shown in the Table 1. The first question was "Have you ever used a sunbed?" A total of 39% of interviewees (n=219) answered positively: the majority were females (almost half of all females – 206/406) compared to only 9% (13/143) of males who have used a sunbed at least once in their lives.

The next five questions were answered only by those students who reported using sunbeds (n=219). When asked at what age they first used a sunbed, most students (45.66%) answered that it was at the age of 15 or 16, while almost a negligible percent of students (1.37%) reported using a sunbed before the age of 12. The next question was about the use of sunbeds in the past year, that is, in 2011, and most adolescents used sunbeds less than 5 times (38%), whereas 8% of them used it over 30 times. The students used sunbeds predominantly during the spring season (39%), followed by summer and winter season (about one quarter of them). The students were able to circle more than one answer to this question; therefore the percentages were calculated based on all the answers (282 answers in total). The next question was about the average time spent in sunbeds. The vast majority (69.41%) of interviewees answered 5 - 10 minutes, but 16.44% of adolescents spent 11 - 16 minutes sun tanning in sunbeds during each visit. Furthermore, around 56.62% of students were given instructions by sunbed employees about the proper use and potential harmful effects. However, the answers differed significantly between genders – only 4/13 males (31%) compared to almost twice as much percentage of females (120/206, 58%) reported receiving the information.

As for the use of sunbeds in the future, 37.7% of all interviewees are planning to continue using sunbeds, while 62.3% do not. All students were instructed to answer this question, that is, both those who have and those who have not used sunbeds before. The next question was about the financial aspects of sunbed use, i. e., whether the examinees would use it more often if they could afford it. As it turned out, money was not the main issue, because 84.34% of students said they would not. The following question was about the adolescents' attitude towards sunbeds. The majority of students considered their use to be very harmful (43.53%), but on the other hand, a high proportion of students (38.44%) believed that harmful effects depend on the number of visits and the total time spent on a sunbed. Merely 1.09% of interviewees thought that using sunbeds is not harmful, whatsoever.

Moreover, the largest proportion of students considered that tanned skin, obtained either using sunbeds or in the sun, was a sign of skin damage, but at the same time, one third considered that it gives them slimmer and more beautiful appearance. Almost every eight adolescent thinks that tanning helps treat acne (12.01%), and every tenth feels that it makes him or her look 'cool' (10.43%). In the survey, choosing more than one answer was possible (total number of answers was 633).

Discussion

Sunbed use is a well-known risk factor for skin cancer; it has been included in differ-

Table 1. Questionnaire about the sunbed use among Belgrade high school students

Questions	Answers				
Have you ever used a sunbed? (n=549)	Yes	No	–	–	–
Number (%) of females (n=406)	206 (50.74%)	200 (49.26%)	–	–	–
Number (%) of males (n=143)	13 (9.09%)	130 (90.91%)	–	–	–
At what age have you used a sunbed for the first time? (n=219)	<11	11 - 12	13 - 14	15 - 16	17 - 18
Number (%)	3 (1.37%)	3 (1.37%)	61 (27.85%)	100 (45.66%)	52 (23.75%)
How many times have you used a sunbed during the past year? (n=219)	<5 times	5 - 10 times	11 - 15 times	16 - 30 times	> 30 times
Number (%)	82 (37.44%)	71 (32.42%)	18 (8.22%)	31 (14.16%)	17 (7.76%)
At what season do you use a sunbed most frequently? (n=282)	Spring	Summer	Autumn	Winter	–
Number (%)	111 (39.36%)	68 (24.11%)	37 (13.12%)	66 (23.41%)	–
How much time do you spend in sunbed on average? (n=219)	<5 minutes	5 - 10 minutes	11 - 15 minutes	16 - 20 minutes	–
Number (%)	21 (9.59%)	152 (69.41%)	36 (16.44%)	10 (4.57%)	–
Did you get any information about the possible consequences of sunbed use from the employees? (n=219)	Yes	No	–	–	–
Number (%)	124 (56.62%)	95 (43.38%)	–	–	–
Do you plan on using the sunbed in the future? (n=549)	Yes	No	–	–	–
Number (%)	207 (37.7%)	342 (62.3%)	–	–	–
Would you use the sunbed more often if you could afford it? (wn=549)	Yes	No	–	–	–
Number (%)	86 (15.66%)	463 (84.34%)	–	–	–
I think that sunbed UV radiation is: (n=549)	Very harmful	Moderately harmful	Not harmful at all	Health hazard depends on the frequency and length of exposure	–
Number (%)	239 (43.53%)	93 (16.94%)	6 (1.09%)	211(38.44%)	–
I think that suntan from sunbeds: (n=633)	Reflects general health	Means that I am in trend	Helps treating acne	Gives more beautiful and slimmer look	Represents a type of skin damage
Number (%)	30 (4.74%)	66 (10.43%)	76 (12.01%)	212 (33.49%)	249 (39.33%)

ent risk prediction models not only for melanoma (8, 9), but also for other forms of skin cancer, such as squamous cell carcinoma (10). The questions in our questionnaire were primarily targeted at different aspects of sunbed use among the high school population. It has been proved that sunbed use before the age of 35 increases the risk of melanoma development by 75% (11). A large number of Belgrade high school students have used a sunbed at least once in their lives (almost 40%), which is significantly more than their peers in England (11.2%) (2), United States (15.6%) (12) and Hungary (15.1%) (13), but similar to Danish population (38%) (14). On the other hand, most of our adolescents used it at the age of 15 or 16 years for the first time, which is nearly two years later compared to English high school students (2).

About 70% of our examinees, who reported using sunbeds, have used them less than 10 times during the previous year, whereas, for example, American students answered similarly only in 51% of cases (12). The majority of students use sunbeds for 5 - 10 minutes per visit; 16% of our students use them for >11 minutes (the same as in England) (2). On the other hand, a higher proportion of English students were properly informed about the potential hazards of tanning – only 20% of them were not given proper information, compared to 40% of our students.

Tanning is thought to be very dangerous by 44% of Belgrade adolescents, and every other Turkish student agrees with this (15). Nevertheless, one third of our students and as much as two thirds of Greek peers feel that dark skin tone from tanning improves their appearance (5). As for another example, 32% of young Americans and 45% of young Maltese even consider it to be a reflection of good health (5); only 5% of Belgrade students agree with this.

Conclusion

In conclusion, awareness about risk factors associated with sunbed UV exposure is not at a satisfying level among the Belgrade high school population. A high number of our adolescents show poor behavior patterns: alarmingly large number use sunbeds regularly (and plan to continue doing so) and appreciate dark skin tone from tanning. Taking into consideration the extent of damage that UV exposure in sunbeds may have at this age, it seems reasonable to ban the use of sunbeds for minors (under the age of 18) in our country, as it has been done in numerous countries in the world.

Abbreviations

UV - Ultraviolet
WHO - World Health Organization
IARC - International Agency for Research on Cancer

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Upotreba solarijuma kod beogradskih srednjoškolaca

Sažetak

Uvod. Incidencija melanoma je u stalnom porastu širom sveta. Ultravioletna radijacija, koja potiče od sunca i veštačkih izvora – solarijuma, predstavlja jedan od glavnih faktora rizika za razvoj melanoma i nemelanomskih kancera kože. Produženo izlaganje suncu u detinjstvu i adolescenciji povećava rizik za nastanak raka kože u odraslom dobu. Cilj ovog rada jeste analiza ponašanja beogradske srednjoškolske populacije po pitanju izlaganja veštačkim izvorima ultravioletnih zraka. Materijal i metode. Studija je izvedena anketiranjem 549 učenika trećeg i četvrtog razreda u četiri beogradske srednje škole. Anketa se sastojala od 10 pitanja u vezi sa upotrebom solarijuma i informisanosti o efektima ultravioletnog zračenja koje potiče iz solarijuma. Od statističkih metoda korišćeni su procena učestalosti i relativni brojevi, kao metode deskriptivne statistike. Rezultati. Čak 39% ispitanika koristilo je solarijum bar jednom u životu, 38% planira da ga koristi i u budućnosti. Na pitanje kada su prvi put koristili solarijum, 45,66% srednjoškolaca je odgovorilo da je to bilo sa 13 ili 14 godina. Većina adolescenata (38%) koristila je solarijum manje od pet puta, dok je njih 8% koristilo solarijum više od 30 puta. Zaključak. Svest o rizicima koje nosi izlaganje ultraviolentnim zracima u solarijumu nije na zadovoljavajućem nivou među beogradskom srednjoškolskom populacijom. Stoga je od ključne važnosti sprovođenje edukativnih i zakonskih mera da bi se ova osetljiva populacija zaštitila od malignih posledica.

Ključne reči: Neoplazme kože; Sunčanje; Ultravioletni zraci; Zračenjem indukovane neoplazme; Melanom; Adolescenti

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A Pediatric Case of Disseminated Lichen Sclerosus – a Case Report

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Abstract

Lichen sclerosus (LS) is an uncommon chronic inflammatory skin disorder with a predilection for the anogenital area, characterized by porcelain white papules, plaques and atrophic patches. We report a prepubertal, 12-year-old girl who presented with chronic, disseminated pearly, flat-topped papules, plaques and atrophic patches located on the trunk, limbs and in the anogenital area, consistent with LS based on clinical and histologic findings. Potent and ultrapotent topical corticosteroids should be considered as first-line treatment. The ultraviolet A1 (UVA1) and calcipotriol for extragenital lesions, as well as calcineurin inhibitors for anogenital lesions, are other treatment options for pediatric LS.

Key words: Lichen Sclerosus et Atrophicus; Vulvar Lichen Sclerosus; Child; Diagnosis; Clobetasol; Skin Diseases; Treatment Outcome; Signs and Symptoms

Lichen sclerosus is an uncommon chronic inflammatory skin disorder with a predilection for the anogenital area, characterized by porcelain white papules, plaques or atrophic patches. It was first described in 1887, by Hallopeau. Since then, many synonyms have been in use, notably 'guttate scleroderma,' 'white spot disease,' 'dermatitis lichenoides chronica atrophicans" or Csillag's disease,' 'kraurosis vulvae,' 'vulvar dystrophy, 'balanitis xerotica obliterans', 'lichen albus or Von Zumbusch Disease', or 'lichen sclerosus et atrophicus'. Since not all cases of LS et atrophicus exhibit atrophic tissue, 'et atrophicus' was dropped and replaced by 'lichen sclerosus,' which is now used for genital and extragenital lesions (1). LS is mostly seen in females with two peak ages of presentation: prepubertal girls and postmenopausal women. The prevalence rate of vulvar LS ranges between 1:70 to 1:1000 in women and 1:900 in children (2, 3).

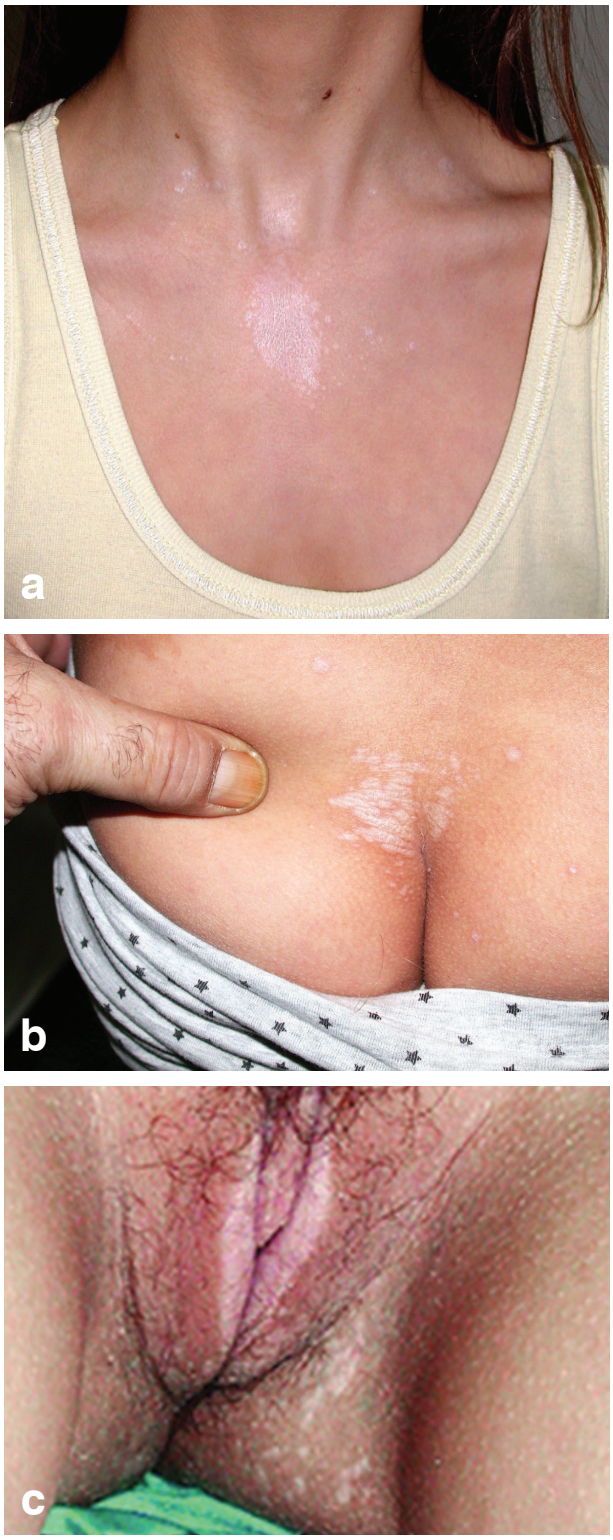
The patogenesis of LS has not yet been completly elucidatet; however, genetic factors and autoimmunity have been implicated. The most common autoimmune diseases associated with LS were autoimmune thyroiditis (12 %), alopecia areata (9%), vitiligo (6%), and pernicious anemia (2%) (4, 5). Hormonal, environmental, and infectious factors have also been implicated as possible causes of this disease.

Initially, the lesions are pearly, flat-topped papules that coalesce into plaques, over time becoming atrophic patches. Telangiectasias, follicular plugging and bullous lesions may also be seen. The most common location is the anogenital area, although extragenital lesions can be present, mostly affecting buttocks, breasts, submammary area, neck, back, chest, axillae and wrists. Oral mucosal involvement has also been reported. Extragenital lesions are rare, especially in children.

We report a prepubertal female child with LS with genital and disseminated extragenital lesions.

Case Report

A 12-year-old prepubertal girl with a 12-month history of numerous mildly pruritic hypochromic lesions distributed on the trunk, limbs, and genital area was referred to the University Clinic of Dermatology, Skopje, Macedonia. She had visited several physicians due to these complaints which were misdiagnosed as vitiligo, tinea, psoriasis and verrucae planae. She used various ointments such as



Figures 1a, 1b, 1c. White, shiny atrophic plaques located on the chest and sacral region. Hypochromic plaques seen on the labia majora

ketoconazole, betamethasone, salicylic acid and crytherapy with liquid nitrogen. However, the lesions did not disappear. Her past medical history was unremarkable. Dermatological examination revealed numerous pearly-white papules distributed on the trunk and predominantly on the extensor surfaces of the extremities (Figures 2a and 2b). Some of the papules had depressed centers, while the others presented with whitish thickened surface. In some areas, they formed larger plaques (Figures 1a and 1b) and linear lesions, showing the Koebner phenomenon (Figure 2c). In the genital area, papules coalesced into hypochromic plaques seen on the labia majora, clitoris and intergluteal cleft (Figure 1c). Although the clinical picture was highly diagnostic, a biopsy of the non-treated older lesion was obtained (6). Histopathological examination showed hyperkeratosis, follicular plugging, basal layer rectification, epidermal atrophy, edema in the papillary dermis, perivascular lymphocytic infiltrate in the reticular dermis and loss of elastic fibers, feature that is typical for LS and not found in scleroderma. (Figures 3a and 3b). Routine laboratory tests results, screening for associated autoimmune diseases with an autoantibody screening, and the thyroid status, were negative. According to the clinical and histological findings, a diagnose of disseminated LS was made. Topical clobetasol propionate 0.05% cream was applied twice daily for a month. She was adviced to use silk underwear to reduce physical trauma by clothing. On the first follow-up, the lesions were improved and the itching reduced. The application frequency of clobetasol propionate was reduced to once daily in the following two months, but the patient missed her next follow up visit, and since then she was not seen in our office.

Discussion

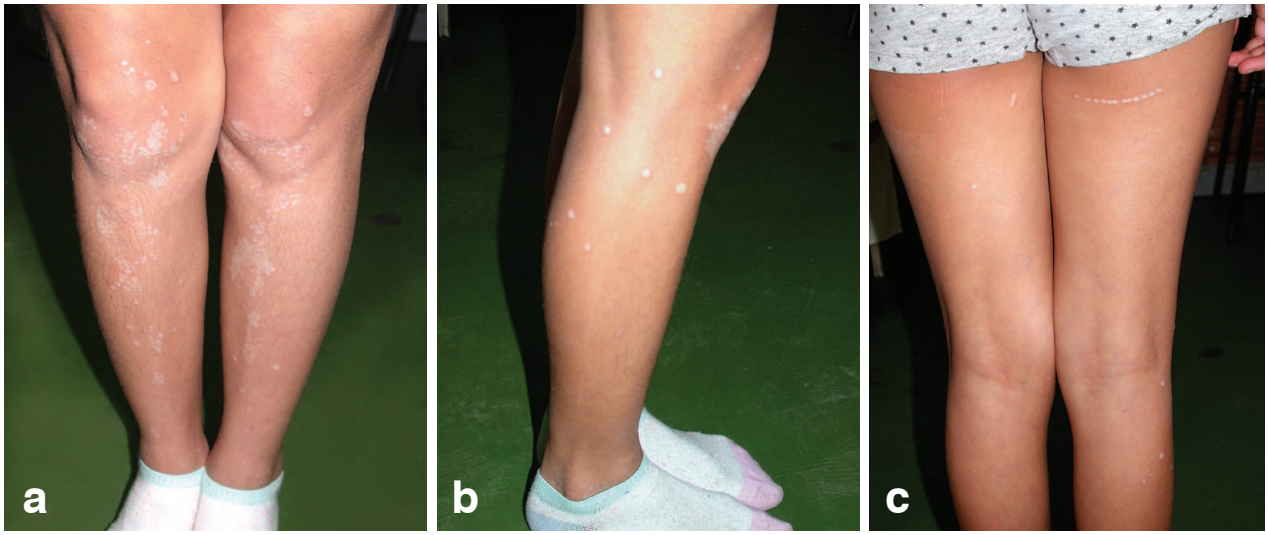
The exact prevalence of LS is unknown. However, the suspected prevalence in children is estimated to be 0.1%. The disseminated, extragenital form of LS is poorly described in literature and accounts for 15 to 20% of cases. Only 6% of affected children have pure extragenital LS (7). The diagnosis of LS in children is often delayed, with avarage duration until diagnosis of 1 to 1.6 years (8). The patient in this report belongs to the small group of pediatric patients with extra-

genital lesions with a 12–month delay until the correct diagnosis. It was misdiagnosed as vitiligo, psoriasis, tinea and verrucae planae. The main differential diagnosis of the genital lesions are vitiligo and sexual abuse if ecchymosis and petechial foci are present in the genital region.

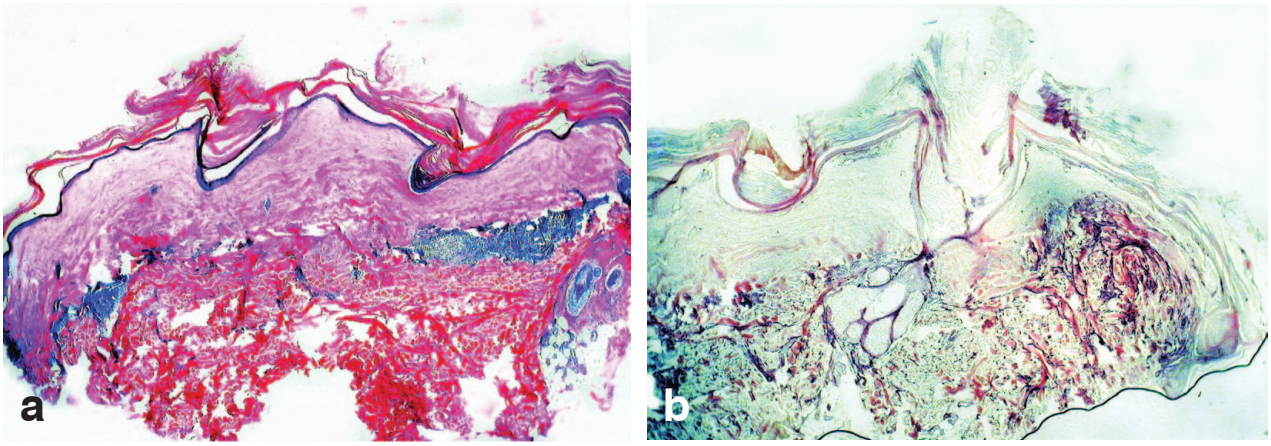
Our patient presented with clinical symptoms typical for extragenital LS, including polygonal, ivory white, slightly elevated papules and plaques formed by a coalescence of papules, some of them with surface atrophy. The lesions were prone to koebnerization and appeared in the areas of physical trauma or continuous pressure. Some lesions showed prominent follicular plugging. A biopsy was obtained from a fully formed, non-treated lesion from the forearm and a specific histological pattern of LS was found: hyperkeratosis, epidermal atrophy with flattening of the rete ridges, vacuolar interface changes, loss of elastic fibers, and marked dermal edema with perivascular lymphocytic infiltrate. Thus, the final diagnosis of LS was made due to this positive clinicopathologic correlation.

The cause of LS remains unknown. According to the literature, 6.6% of prepubertal girls with anogenital LS present with an associated autoimmune disease (vitiligo and alopecia areata), and 56% of their parents or grandparents also suffer from LS (9). Immunogenetic studies have demonstrated a significant association with the HLA class II antigen DQ7 in 66% of female children (9). In our case, there was no association between LS and autoimmune diseases or any family cases.

Topical corticosteroids are highly effective, and remain the first-line treatment for LS. Topical clobetasol propionate is the gold standard in the treatment of vulval LS in women and girls (10). Long-term use of either very potent or moderate topical corticosteroids appears to be effective and safe (11). Our patient was treated with topical clobetasol propionate cream for three months. After the relief of symptoms and partial improvement of skin lesions, tapering of clobetasol propionate was recommended. Phototherapy is effective in patients with extragenital, disseminated LS. Among different UV regimens, UVA1 phototherapy is a potential first-line treatment option for extragenital LS (12). Other topical treatment modalities, such as tacrolimus and pimecrolimus for anogenital, and calcipotriol for extragenital LS, are found to be both effective and safe for long-term use (13). They are recommended for long-term application and for maintenance of the remission after initial treatment with clobetasol propionate (10). The clinical course of LS is variable. It is usually chronic, especially in women and girls, although the incidence of spontaneous remission in girls in puberty is estimated at 25% (14). However, one should not forget the intrinsic potential of the disease for development of squamous cell carcinoma (SCC) as a



Figures 2a, 2b, 2c. Characteristic pearly-white, polygonal, slightly elevated papules coalescing into plaques on the lower extremities. Linear lesion showing the Koebner phenomenon on the right thigh



Figures 3a, 3b. Hyperkeratosis in the epidermis, follicular plugging, flattening of the rete ridges, vacuolar disruption in the basal layer, epidermal atrophy, extensive edema in the papillary dermis and erivascular lymphocytic infiltrate in the reticular dermis (H&E staining x 40); Loss of elastic fibers in the upper dermis (Orcein staining X 40)

result of chronic inflammation. The development of indurated plaques or nodes and ulcers that do not heal indicate a malignant transformation.

Conclusion

Our case report of a female child with disseminated extra-genital lesions and discrete genital lesions illustrates a rare clinical presentation of LS. Taking into account that the disease in women may be associated with development of vulvar SCC, long-term follow-up should be recommended to all prepubertal girls with vulvar LS.

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Diseminovani *Lichen Sclerosus* u dečjem uzrastu – prikaz slučaja

Sažetak

Lichen sclerosus (LS) predstavlja retku, hroničnu inflamatornu dermatozu, lokalizovanu uglavnom u anogenitalnoj regiji, za koju je karakteristična pojava porcelanskobeličastih papula, plakova ili atrofičnih makula. U radu je prikazana devojčica u prepubertetskom uzrastu – 12 godina, sa kliničkim nalazom hroničnih, diseminovanih, ravnih papula, plakova i atrofičnim makulama, distribuiranih po telu, ekstremitetima i anogenitalnoj regiji. Klinički i histopatološki nalaz su karakteristični za LS. Potentne i ultrapotentne topijske kortikosteroide treba razmotriti kao lekove prve linije za lečenje LS. Ostale terapijske opcije, koje se mogu upotrebiti u pedijatrijskom uzrastu, uključuju UVA1 i kalcipotriol za ekstragenitalne lezije i inhibitore kalcineurina za anogenitalne promene.

Ključne reči: Lichen sclerosus et atrophicus; Vulvarni lichen sclerosus; Dete; Dijagnoza; Clobetasol; Kožne bolesti; Ishod terapije; Znaci i simptomi

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IgA Pemphigus in a Child – a Case Report

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Abstract

IgA pemphigus (IGAP) is a rare autoimmune bullous disease characterized by IgA deposits on keratinocyte cell surfaces. The IGAP is classified into: 1) subcorneal pustular dermatosis (SPD) type, and 2) intraepidermal neutrophilic (IEN) IgA dermatosis type. So far, only 9 children with IGAP have been described in the literature, of whom only 3 with SPD type. We report a 3-year-old boy with SPD type of IGAP. Clinically, he presented with pruritic vesicles, pustules and erosions on the face, trunk, groin area, and extremities. Histopathology showed subcorneal pustules containing a few acantholytic cells. Direct immunofluorescence (DIF) test of Tzanck smear showed intercellular IgA deposits on the surface of the groups of epidermal cells. Oral dapsone and prednisone induced remission after two weeks; the treatment was discontinued 11 months later, and complete remission was achieved during 19 months without any treatment. Direct immunofluorescence of Tzanck smear is a simple, sensitive, rapid and non-aggressive test, very suitable for the diagnosis of IGAP in children.

Key words: Immunoglobulin A; Pemphigus; Child, Preschool; Signs and Symptoms; Diagnosis; Cytodiagnosis; Skin Tests; Dapsone; Prednisone; Treatment Outcome

IgA pemphigus (IGAP) is a rare variant of pemphigus presenting with vesiculopustular skin lesions; histopathologically, IGAP is characterized by neutrophil infiltration and acantholysis in the epidermis (1). Binding of IgA antibodies to keratinocyte cell surface antigens leads to accumulation of neutrophils in the epidermis, resulting in intraepidermal blistering (2). Depending on blister location, two variants of the disease have been recognized: 1) subcorneal pustular dermatosis (SPD) and 2) intraepidermal neutrophilic (IEN) IgA dermatosis (3). The incidence and prevalence of IGAP is not known, but it is certainly very low (3, 4). The disease is extremely rare in pediatric age group; up to now, only 9 children have been described in the literature, of whom only 3 with SPD type (5).

Case report

We present a 3-year-old Caucasian boy, with a 2-month history of pruritic vesicles, pustules and erosions on the face, trunk and extremities. The lesions were first treated as impetigo with systemic and topical antibiotics, with no improvement. The patient's medical history was unremarkable. On admission, the boy had pustules and erosions covered with crusts, predominantly on the face and trunk (Figure 1). During the following days, numerous vesicles and pustules appeared on erythematous base, mainly over the trunk (Figure 2) and groin area (Figure 3). Nikolsky's sign was negative. The oral mucosa was uninvolved.

Routine laboratory test results were normal. Bacterial cultures from pustules were all negative. Serum IgA autoantibodies to tissue transglutaminase and to endomysium were negative. The cytological (Tzanck) test showed rare acantholytic cells, numerous neutrophils and neutrophils surrounding acantholytic cells ("Sertoli rosette" phenomenon).

Histological examination revealed subcorneal pustules with neutrophils and a few acantholytic cells (Figures 4 and 5).

Direct immunofluorescence (DIF) of perilesional skin and indirect immunofluorescence (IIF) - IgG and IgA - with monkey esophagus tissue were negative. DIF test per-

formed on Tzanck smear showed intercellular IgA deposition on the surface of segregated groups of epidermal cells (Figure 6). No deposition of other immunoglobulins or complement components was detected.

The boy was treated with oral prednisone at 1 mg/kg/day with gradual dose tapering over 9 months, in combination with dapsone at 1.6 mg/kg/day with gradual dose tapering over 11 months, and, before complete epithelization of erosions, with topical antibiotics and corticosteroids. The two-week therapy resulted in a complete resolution of skin lesions, leaving only residual but transitory pigmented macules. There were no signs of recurrence 19 months after the therapy cessation.

Discussion

IgA pemphigus is a rare, neutrophilic, acantholytic skin disorder that usually occurs in middle-aged and elderly persons (approximately 70 cases have been reported in the literature); the average age of onset is 48 years (6). IGAP is an extremely rare condition in children – detailed PubMed search revealed only 9 cases, of whom 3 were classified as SPD type (two girls and one boy), 2 were IEN type (one girl and one boy), one was classified as pemphigus vegetans variant IGAP (one boy) and the other 3 cases were unclassified (three girls) (5, 6, 7, 8, 9, 10, 11, 12, 13). The youngest reported patient was a 1-month-old girl (9).

Patients with both types of IGAP clinically present with flaccid vesicles or pustules, or both, on erythematous or normal skin (14). Patients with the SPD type sometimes show irregular erythematous skin lesions with vesiculopustules, erosions and desquamation resembling the features of subcorneal pusular dermatosis (Sneddon-Wilkinson disease) (15). The IEN type demonstrates a characteristic clinical feature, the so-called "sunflower-like" configuration (16). A herpetiform appearance has also been reported (17). A pemphigus vegetans variant of the IGAP occurring during immunosuppressive drug therapy was described in a 7-year-old boy (10). The sites of predilection are groin, axillae, trunk, proximal extremities and lower part of the abdomen, scalp and postauricular areas (3, 5). Mucous membranes are rarely involved (3). Teraki et al. reported a 7-year-old girl with lesions involving not only the skin, but also the oral mucosa (13). Pruritus is also a significant symptom that may interfere with the patient's daily activities (18). In children, the main clinical differential diagnosis includes impetigo contagiosa, linear IgA dermatosis, subcorneal pustular dermatosis, and pemphigus foliaceus (7).

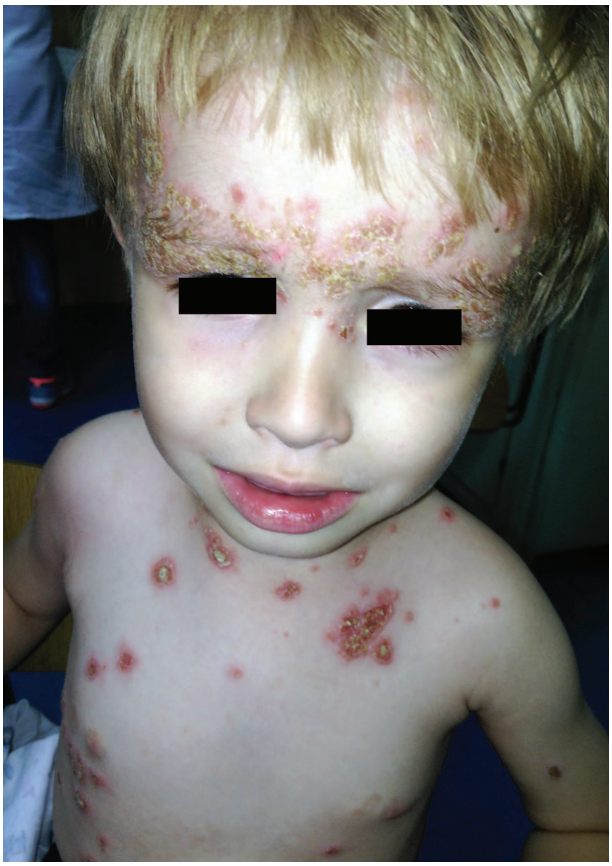

Figure 1. Pustules, superficial erosions, yellow crusts and erythematous plaques on the face and trunk

In both variants, the blisters contain acantholytic keratinocytes and a variable number of neutrophils (19). Acantholysis in IgA pemphigus is much milder than in classic pemphigus. Characteristically, the clefts and pustules localize in the subcorneal region in SPD type IGAP, whereas they are present in the entire or mid epidermis in IEN type IGAP (3, 16). In the upper dermis, a superficial perivascular and interstitial infiltrates of lymphocytes, neutrophils and sometimes eosinophils are present (19).

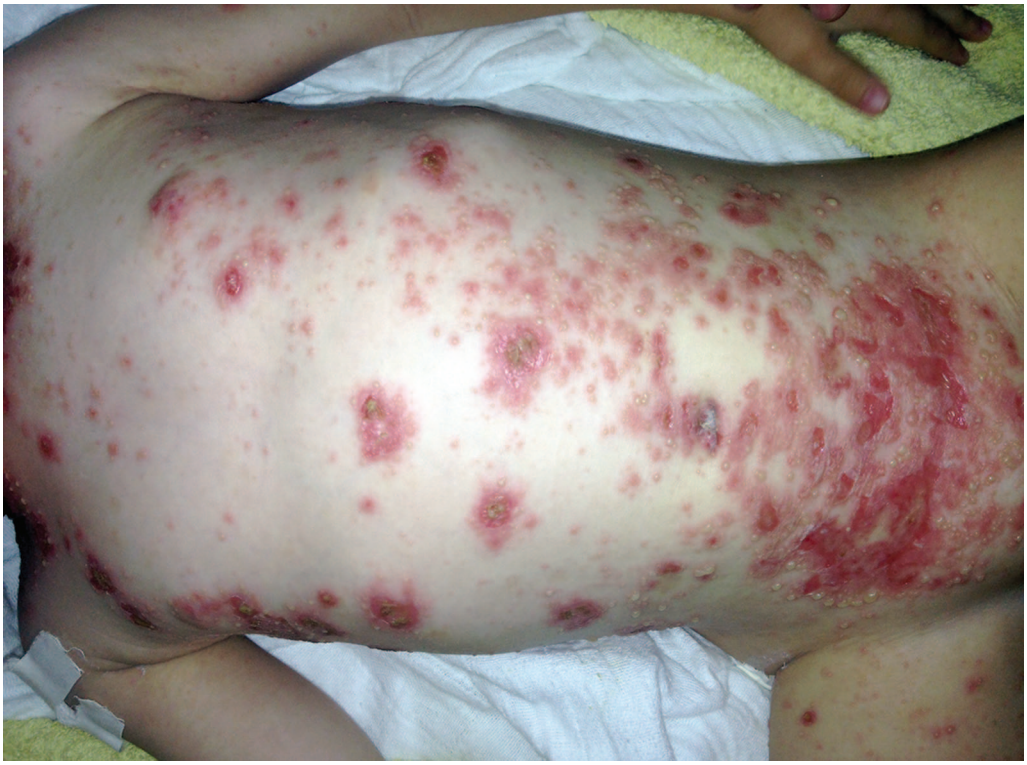

Figure 2. Pustules, superficial erosions and erythematous plaques on the trunk

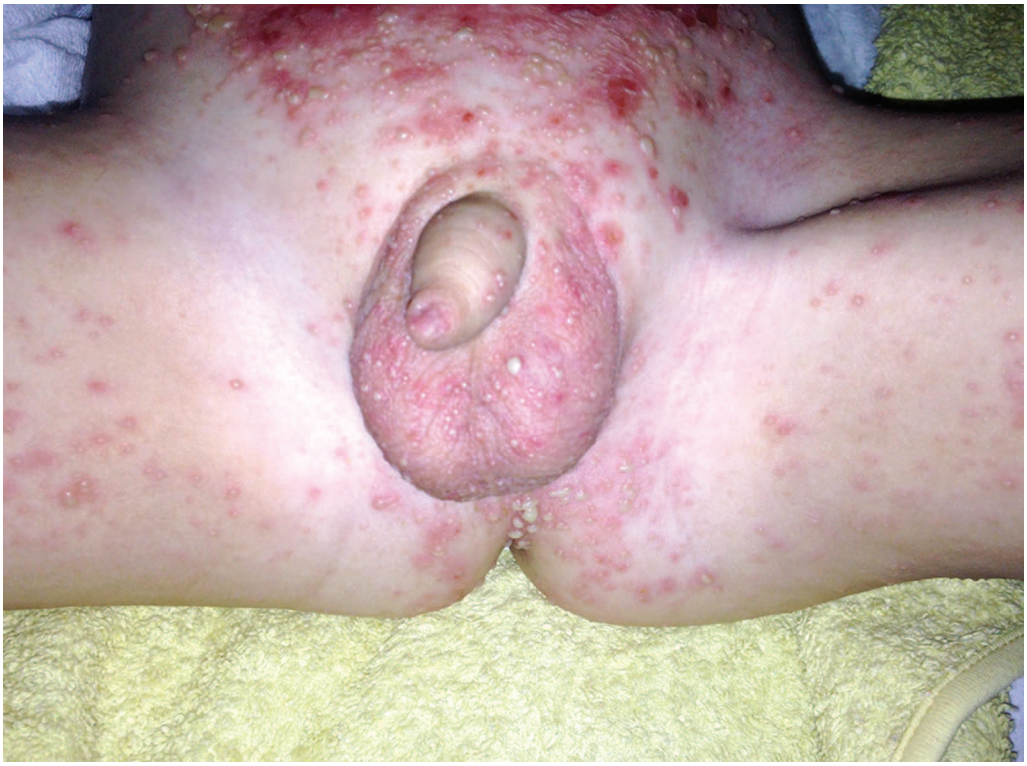

Figure 3. Vesicles, pustules and erythema in the groin area

Desmocollin 1 (Dsc1) has recently been identified as the target antigen of the SPD type (15). In the IEN type, no reactivity of autoantibodies with Dsc 1, 2, and 3 has been found, whereas desmoglein 1 and 3 were suggested as putative target antigens of IEN type in single case reports (20, 21). Although the autoantigen for IEN type has not been identified, immunoelectron microscopic studies suggest that it is an unknown nondesmosomal protein (22). There is no clear explanation for the mechanism by which IgA autoantibodies produce characteristic skin lesions in IGAP. IgA autoantibodies might bind to the Fc receptor CD89 on monocytes and granulocytes, resulting in accumulation of neutrophils and subsequent proteolytic cleavage of the keratinocyte cell–cell junction (3).

The diagnosis can only be confirmed by immunofluorescence examinations. DIF tests using perilesional skin from affected patients were positive in all reported cases and showed deposits of IgA on the surface of keratinocytes. In SPD type, IgA deposition is seen predominantly in the upper epidermal layers, whereas in IEN type, it is seen throughout the epidermis or restricted to the lower epidermis. IgG or complement component C3 is also sometimes deposited, but is weaker than IgA (3, 5, 16, 23).

In addition to routine cytological tests, Tzanck smears were studied by DIF staining to detect antibodies present on the cell surfaces, as acantholytic cells of pemphigus also bear antigens. The deposition occurs on the cell surface without staining the nucleus (24). The role of DIF techniques on Tzanck smear samples has also been evaluated for the diagnosis of pemphigus vulgaris, and the results were found to be comparable with respective skin biopsies in the same set of patients. Thus, Tzanck smear can be used as a substitute to biopsy (25). In our case, IgA deposits were present on the individual cells and in the intercellular substances where the cells were present in clusters.

IIF tests of the patient's serum on normal human skin, and monkey and guinea-pig esophagus tissue, show binding of IgA autoantibodies with an intercellular pattern. The titers for autoantibodies are much lower than in classic pemphigus (3, 23). IIF using monkey esophagus tissue did not detect autoantibodies in our patient, and it may not be suitable for detection of anti-Dsc1 antibodies, because esophagus expresses undetectable levels of Dsc (26). Since IIF microscopy has a sensitivity of about only 50% in IGAP, a more sensitive IF molecular assay has been developed using Dsc-transfected COS-7 cells (4). The vectors coding for Dsc1-Dsc3 are individually transfected to COS-7 cells. Then, patient sera are reacted with these transfected cells. Dotted fluorescent signals are obtained at the cell surfaces if patient sera react with such target antigens (3).

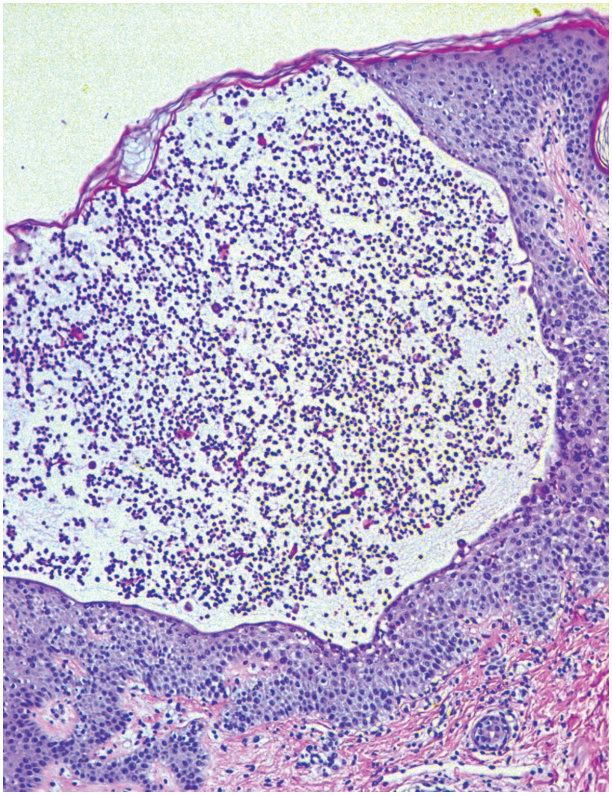

Figure 4. Histopathology of the skin lesion: subcorneal neutrophilic pustules, mild epidermal spongiosis and perivascular and interstitial lymphocytic infiltrate with neutrophils in the upper dermis (HE x 100)

Enzyme-linked immunosorbent assay (ELISA) is used for the diagnosis of IGAP and for detection of autoantibodies in individual patients (16, 27). The specificity and sensitivity of Dsc and ELISA is not very high compared with immunofluorescence study using Dsc-transfected COS-7 cells (4, 28). Immunoblotting using a desmosome-enriched frac-

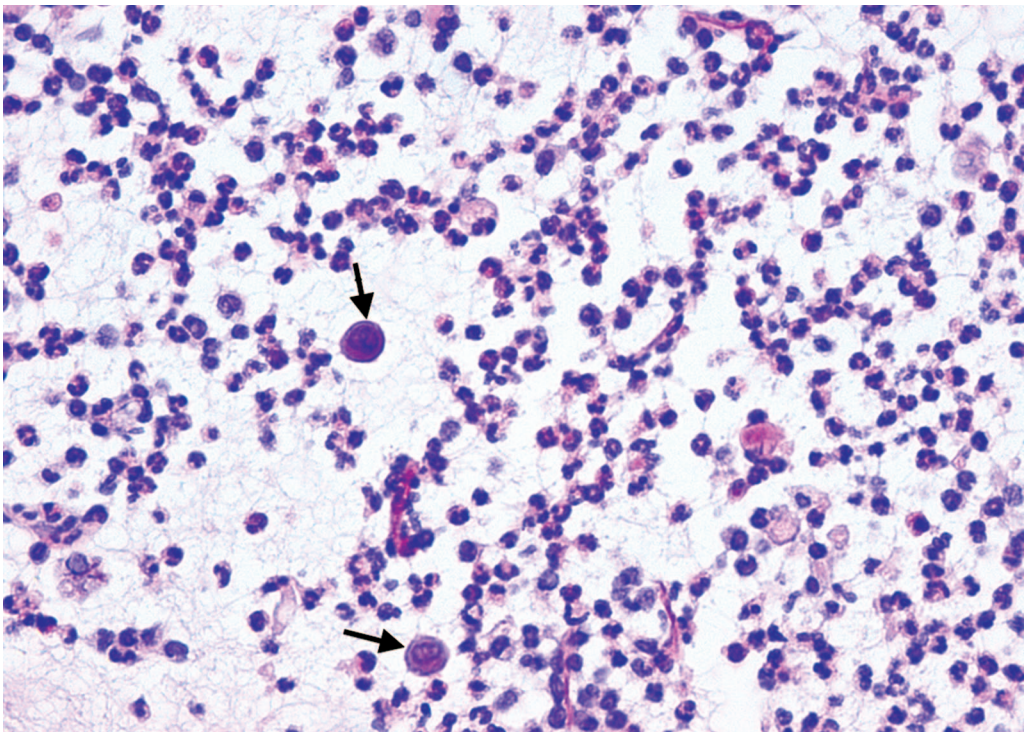

Figure 5. Histopathology of the skin lesion: a few acantholytic cells (black arrows) and numerous neutrophils (HE x 400)

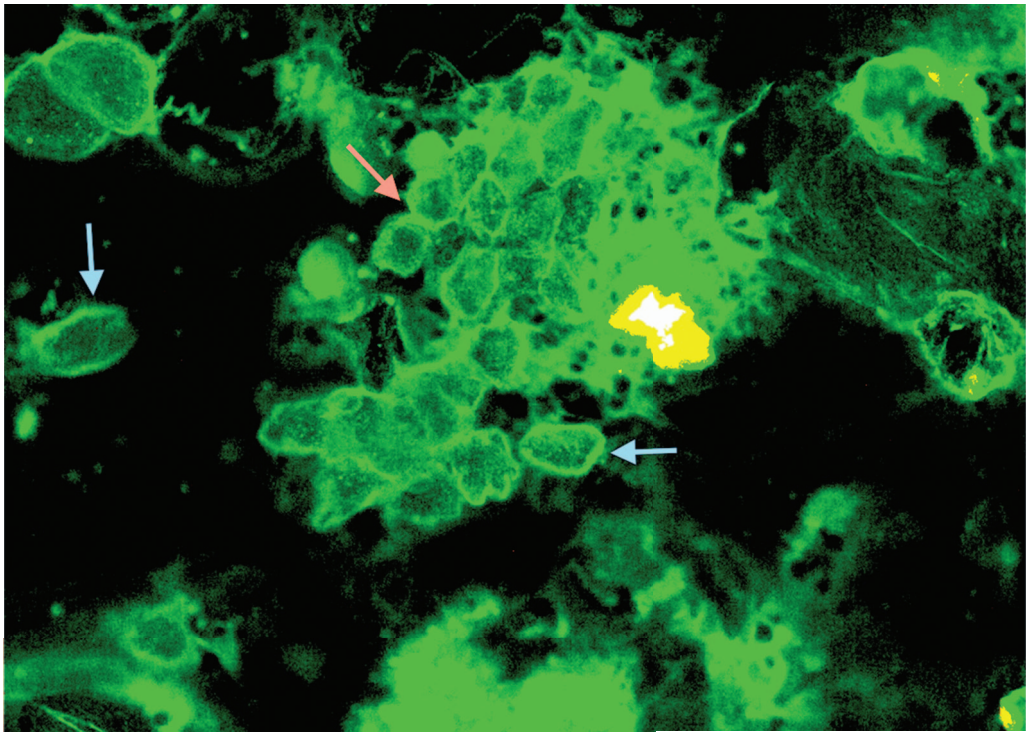

Figure 6. DIF of Tzanck smears (IgA) showing classical distinct regular pericellular membranous ring-shaped deposits on individual acantholytic cells (blue arrows) and those in groups (red arrow)

tion of a bovine snout epidermal extract can be helpful to detect IgA autoantibodies against Dsc, although the sensitivity is similarly low (4).

Monoclonal IgA gammopathy (benign or malignant) was present in 20% of cases with SPD type. In cases associated with malignant IgA gammopathy, the prognosis depends on the malignancy. In the IEN type, no association with monoclonal IgA gammopathy has been reported (15). Gastrointestinal disease may also be associated with IGAP. One case of Crohn's disease and one with gluten-sensitive enteropathy have been reported in the literature (29).

The treatment of choice for both types of IGAP is dapsone (18). If dapsone is not well tolerated, sulphapyridine in combination with prednisone or photochemotherapy with psoralen-ultraviolet A, alone or in combination with etretinate are usual alternatives (14, 29). Other reported therapeutic agents include colchicine (30), isotretinoin (31), acitretin (32), azathioprine (33), azithromycin (34), mycophenolate mofetil, adalimumab (35), plasmapheresis and cyclophosphamide (17) and various combinations of these treatments. The overall prognosis in children with IGAP seems to be good and the disease can be easily controlled by a combination of low dose steroids and dapsone (5, 7).

Conclusion

Autoimmune blistering diseases are rare in the pediatric patients. Our patient represents a very rare pediatric case with SPD type IGAP. The presence of acantholytic cells in cytology and IgA deposition on acantholytic cells found using DIF would make the Tzanck test more specific and very useful in the diagnosis of IGAP. The DIF of Tzanck smear is a simple, sensitive, rapid and non-aggressive test, very suitable for the diagnosis of IGAP in children.

Abbreviations

IGAP - immunoglobulin A pemphigus
SPD - subcorneal pustular dermatosis
IEN - intraepidermal neutrophilic
DIF - direct immunofluorescence
IIF - indirect immunofluorescence
Dsc1 - desmocollin 1
ELISA - enzyme-linked immunosorbent assay

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IgA pemphigus kod deteta – prikaz slučaja

Sažetak

IgA pemfigus (IGAP) je retka autoimunska bulozna dermatoza koju karakterišu IgA depoziti u međućelijskim prostorima epiderma. IGAP se klasifikuje na dva tipa: 1) supkornealnu pustuloznu dermatozu (SPD) i 2) intraepidermalnu neutrofilnu IgA dermatozu. Do sada je u literaturi opisano samo devetoro dece sa IGAP, od toga tri slučaja sa SPD tipom. Prikazujemo slučaj trogodišnjeg dečaka sa SPD tipom IGAP. Na licu, trupu, preponama i ekstremitetima bile su prisutne pruriginozne vezikule, pustule i erozije. Histopatološki nalaz je pokazao supkornealnu pustulu sa nekoliko akantolitičkih ćelija. DIF test Cankovog (*Tzanck*) razmaza pokazao je međućelijske

depozite IgA u grupi segregovanih epidermalnih ćelija. Nakon dve nedelje opšte terapije dapsonom i prednizonom pacijent je uveden u remisiju, a nakon 11 meseci terapija je obustavljena. Pacijent je 19 meseci u kompletnoj remisiji bez terapije.

DIF test Cankovog razmaza je jednostavan, senzitivan, brz i neagresivan test, veoma pogodan za dijagnostiku IGAP kod dece.

Ključne reči: Imunoglobulin A; Pemfigus; Predškolsko dete; Znaci i simptomi; Dijagnoza; Citodijagnoza; Kožni testovi; Dapson; Prednizon; Ishod terapije

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Pyoderma Vegetans – a Case Report

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Abstract

Pyoderma vegetans (PV) or blastomycosis-like pyoderma (BLP) is a chronic inflammatory disease, by some authors considered a rare variety of pyoderma gangrenosum (PG), and others describe it as a distinct entity. It commonly presents with verrucous plaques with multiple pustules. The etiology of this disease is unknown, but it has been connected with staphylococcal and streptococcal infections, inflammatory bowel disease, hematological diseases, primary immunodeficiency, alcoholism, and nutritional deficit. Here we present a 66-year-old, otherwise healthy female, with a 2-year-long history of well-defined, vegetative livid plaques with multiple pustules on the dorsal side of both hands. Histopathological analysis of the skin biopsy of the hand showed chronic inflammation and micro-abscesses, ruptured follicular cysts and follicular pseudoepitheliomatous hyperplasia. Treatment with anti-tuberculosis drugs and antibiotics showed to be ineffective, as well as the treatment with systemic corticosteroids, dapsone and cyclosporine. Itraconazole was given for its immunomodulatory effects and findings of Penicillium species in one of the swabs, which led to partial regression of lesions. Since the treatment did not lead to complete resolution, acitretin was indicated 3 months later, but the patient was lost to follow-up.

Key words: Pyoderma; Blastomycosis; Hand Dermatoses; Cyclosporine; Dapsone; Itraconazole; Treatment Outcome; Case Reports

Pyoderma vegetans (PV) or blastomycosis-like pyoderma (BLP) was first described by Hallopeau in 1898, under the name of "pyodermite végétante", and five years later, in 1903, by Azua and Pons as "pseudo-epitheliomatous cutane". Commonly used synonyms for this disease include pyodermitis chronica vegetans of Azua, pseudoepithelioma of Azua, mycosis-like pyoderma, coral reef granuloma (in Australia), and hyperinflammatory proliferative pyoderma (1, 2, 3).

It is characterized by exudative, verrucous plaques with well-defined elevated borders and multiple pustules (4). Although its etiology is unknown, this disease has been connected to bacterial infections (staphylococcal and streptococcal). Fungal infections have also been implicated in the context of immunosuppression, as demonstrated by a case of treatment-resistant Trichophyton mentagrophytes-induced infection of the hands, resulting in a chronic pyoderma vegetans (5). Other diseases that might be associated with this condition include inflammatory bowel disease, cutaneous T-cell lymphoma, primary immunodeficiency, chronic myeloid leukemia, alcoholism, HIV infection and nutritional deficit. However, it has also been reported in healthy persons (4, 6). Major histopathological features of PV are pseudoepitheliomatous hyperplasia and intraepidermal and subepidermal neutrophilic or eosinophilic micro-abscesses (1). In most cases this disease has a chronic course and it is often refractory to antibiotic therapy (1, 7). No standard treatment guidelines are available for PV, maybe because of its rarity.

Here, we present a case of PV in an otherwise healthy adult female, and a short review of literature on the treatment challenges of this rare disorder.

Case report

A 66-year old female was referred to our clinic with a 2-year history of well-defined erythematous livid plaques, with mild desquamation and pustules on erythematous base, lo-

cated on the dorsum of the right hand, measuring 5 x 5 cm. Also, similar plaque characteristics, measuring 3 x 3 cm, were found on the IV and V fingers on the dorsal side of the left hand. There was a non-healing lesion, 1 cm in diameter, covered with a crust, on the skin of the left knee (Figure 1).

The patient was previously treated as an out-patient with topical and systemic corticosteroids and systemic antibiotic therapy based on culture, but without favourable results. In April 2015, Mantoux test was performed and it was positive, with erythema and induration 30 mm in diameter, the patient received therapy with isoniazid, rifampicin, ethambutol and pyrazinamide during two months, but without effects. Tissue cultures for typical and atypical mycobacteria were negative and therapy was discontinued. She was otherwise healthy, except for the hypertension treated for several years with combination antihypertensive therapy (enalapril maleate, bisoprolol, acetylsalicylic acid and amlodipine).

Laboratory test results revealed elevated erythrocyte sedimentation rate of 44 mm/h; fibrinogen 5.6 g/L (< 4) and C-reactive protein 9.86 mg/l (<4); immunoglobulin E 171 IU/ml (< 100); free triiodothyronine (FT3) 12.62 pmol/l (< 6.5). All other findings were within normal limits including the following: complete blood count, kidney, liver function tests and serum electrolyte levels, rheumatoid factor, lipid status, immunoglobulins (A, G, M), complement factor C3 and C4, angiotensin converting enzyme, free thyroxin, thyroid stimulating hormone (TSH), anti-thyroid peroxidase antibodies, thyroglobulin antibodies, TSH receptor antibodies, serum protein electrophoresis and complete urinalysis. VDRL/TPHA, Anti-HIV antibodies, HBsAg, and anti-HCV were negative. Bacteriological cultivation was repeatedly positive for Staphylococcus aureus. Skin biopsy tissue mycological cultivation was negative as well as cultivations for typical and atypical mycobacteria. Further diagnostic work-up did not reveal hematologic malignancy (peripheral blood smear), inflammatory bowel disease (with colonoscopy), connective tissue diseases (ANA, ENAA, ANCA, circulating immune complexes, RF) and paraneoplastic process was also excluded. Also, patch testing to standard allergens of the European series was negative.

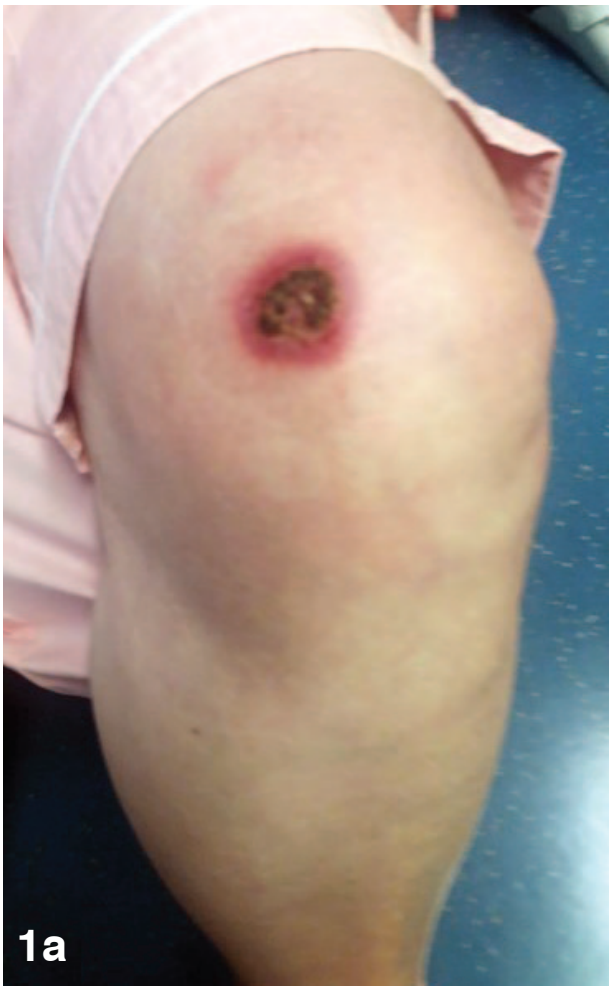


Figure 1 a. A non-healing lesion, 1 cm in diameter, covered with crust, on the left knee

Histopathological analysis of skin biopsy specimens showed chronic inflammation and cutaneous micro-abscesses, ruptured follicular cysts and follicular pseudoepitheliomatous hyperplasia (Figure 2). Periodic acid Schiff (PAS) and the Ziehl-Neelsen staining did not show presence of microorganisms in biopsy specimens. Repeated biopsies revealed pseudo-epitheliomatous hyperplasia and formation of micro-abscesses. Direct immunofluorescence microscopy did not show deposits of immunoreactants in the basement membrane zone.

Based on clinical and histopathological findings, the patient was diagnosed with vegetans form of pyoderma gangrenosum and treatment was initiated with methylprednisolone 40 mg/day and dapsone 100 mg/day (due

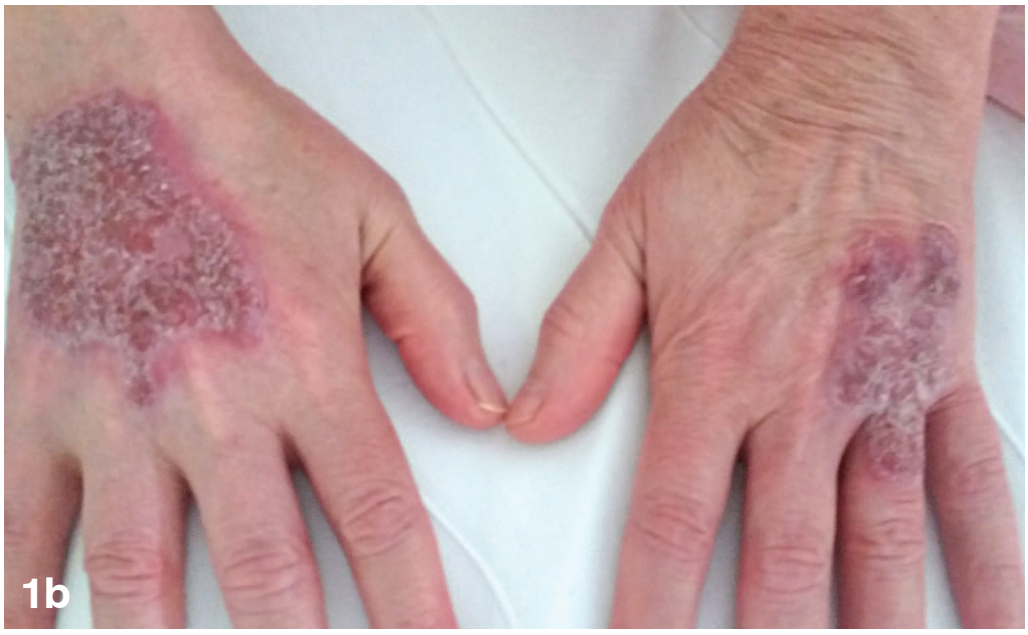


Figure 1 b. Erythematous livid plaques on the dorsal side of the hands

to methemohlobinemia, the dose was reduced to 50 mg/day after 2 weeks). Topical betamethasone dipropionate 0.5 mg/g ointment was used twice a day during two months, then pimecrolimus 1% cream for one month. Also, on two occasions, 6 weeks apart, intralesional triamcinolone-acetonide was applied. Three months after the initial treatment, skin lesions deteriorated, with spreading of erythematous-violaceous plaques on the skin of both dorsal aspects of hands and the left knee. Since the initial treatment proved ineffective, it was discontinued and cyclosporine was used (5 mg/kg), but it was also ineffective and discontinued after one month. After that, the patient was treated with amoxicillin and clavulanic acid tablets for 10 days (625 mg 3 x 1), based on findings of Staphylococcus aureus, but again without improvement.

Saprophytic Penicillium species were found in one of the repeated fungal cultures. Having in mind the possible role of saprophytic mould in chronic inflammation, immunomodulatory properties of itraconazole and one case report of effective treatment of pyoderma vegetans using this drug, treatment with itraconazole was initiated at a dose of 400 mg/day for 7 days followed by a 3-week break for 2 months, with initial regression, after which the treatment was continued with itraconazole 100 mg/day for another month. During treatment, liver function tests were within the physiological range. Topical miconazole 2% cream was applied twice a day for one month. Skin lesions showed significant regression in terms of their size, infiltration and erythema (Figures 3a and 3b). However, since the treatment did not lead to complete resolution of the lesions, acitretin was indicated 3 months later, but the patient was lost to follow-up.

Discussion

Pyoderma vegetans, also named blastomycosis-like pyoderma, is a very rare disease. There is no actual data about the incidence of this disease. The largest case series was reported by Scuderi et al. in 2016. They described 39 patients collected over a 35-year period to demonstrate its clinical features and histological findings. Of the 39 cases, 29 (74%) were men. The average age was 71; the youngest patient was 44 and the oldest 91 years old. In all 39 cases, the most common site was the forearm in 25 (64%) cases. Three patients had multiple lesions at clinical presentation (8). Our patient also belongs to elderly population with more than one lesion.

Pyoderma vegetans is believed to represent a vegetating inflammatory tissue reaction

to a bacterial infection, generally occurring in patients with reduced immunological resistance or in immunosuppressed patients. It has been reported in association with HIV infection/AIDS, hematologic and solid malignancies, malnutrition, alcoholism, diabetes mellitus, obesity, inflammatory bowel diseases, psoriatic arthritis, pulmonary granuloma, immunosuppressive therapies, X-radiation, and other conditions (2, 3, 5 - 11). However, several cases of PV were described in immunocompetent patients without any underlying factors (1, 2, 7). Minor trauma may be the trigger factor for the beginning of lesions, probably creating a localized area of impaired resistance (2, 8). In Australia, a variant of PV has been reported under the term of coral reef granuloma, which typically occurs on sun-damaged skin of elderly patients (2, 12). In our patient, no underlying disease was diagnosed after a thorough follow-up, but it did develop on sun-damaged areas.

The diagnosis of BLP is based on clinical, pathological, and laboratory findings. Su et al. proposed five diagnostic criteria for this disease in 1979: 1) large verrucous plaques with multiple pustules and elevated border, 2) pseudoepitheliomatous hyperplasia with abscesses in tissue biopsy, 3) growth of at least one pathogenic bacterium, 4) negative culture for deep fungi, atypical mycobacteria or mycobacterium tuberculosis, and 5) normal bromide levels (1). In 2005, Nguyen at al. adopted these criteria and added another one - negative fungal serological tests (2). Our patient fulfilled four of the six criteria, but fungal serology tests were not performed and halogen blood levels were not measured due to negative history of using medications containing halogens.

The differential diagnosis of PV should include pemphigus vegetans, deep fungal infections, verrucous cutaneous tuberculosis, skin infections caused by mycobacterium marinum, squamous cell carcinoma, pyoderma gangrenosum, keratoacanthoma, cutaneous botryomycosis, halogenoderma and insect bites (2, 12). We excluded these conditions in our patient by evaluation of skin lesions, negative mycobacterium tuberculosis culture and by negative direct immunofluorescence test. Also, the 2-month course of anti-tuberculosis therapy was ineffective, as it proved to be effective in vegetative pyoderma gangrenosum.

Various modalities have been used in the management of PV. Currently there is no guide to treatment, but systemic corticosteroids are usually the first choice. Doses of 1 mg/kg/day were reported to be successful to control the inflammation and relieve pain in some cases. This dose should be continued until the lesions show evidence of healing and then, gradually decreased. A steroid-sparing agent, such as minocycline, dapsone, rifampicin, vancomycin or clofazimine may be added (6, 7). However, these treatment modalities were found to be completely ineffective in our patient. Systemic antibiotics have been used, including minocycline, penicillin

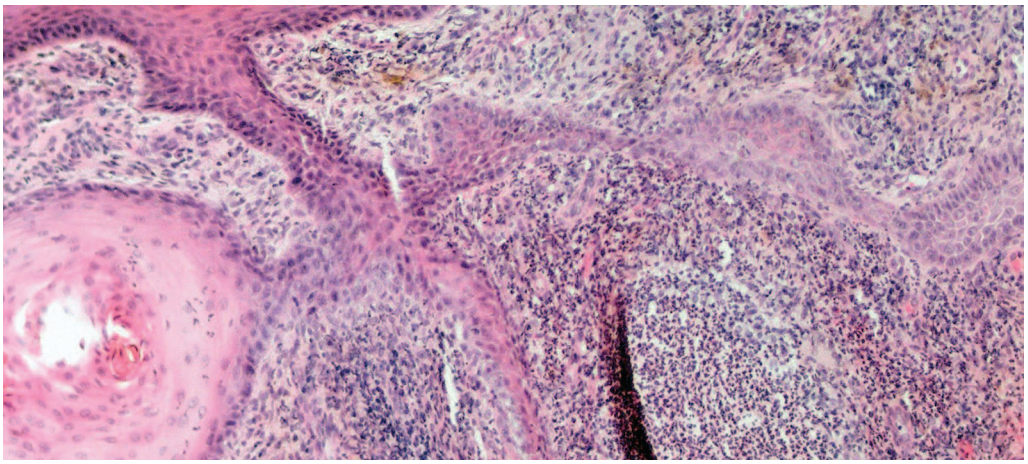
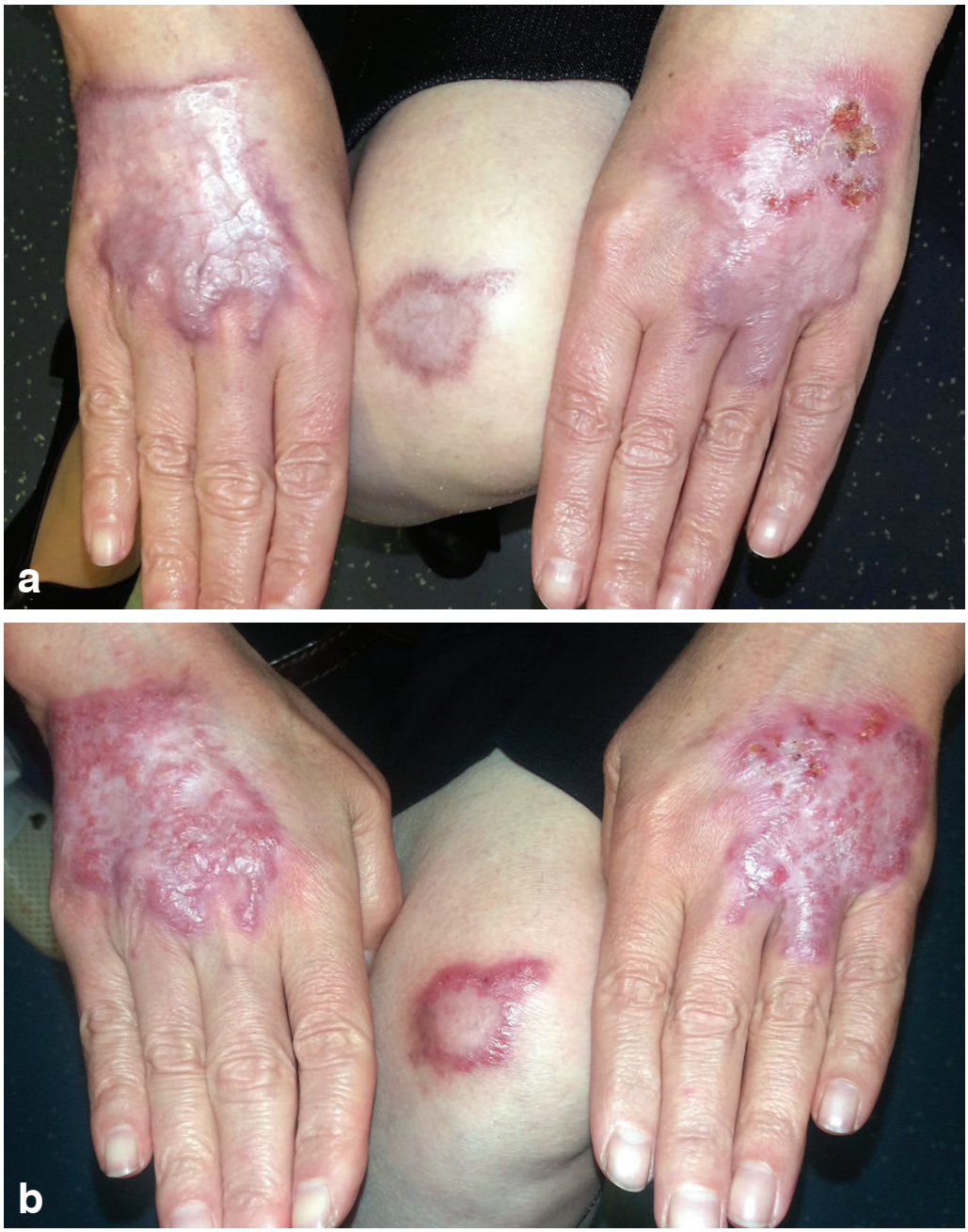


Figure 2. Microscopic features of skin biopsy specimen, with cutaneous microabscesses, ruptured follicular cysts, and follicular pseudo-epitheliomatous hyperplasia (Hematoxylin and eosin, 40x)



Figures 3a. October 2016. Plaques on the dorsal side of the hands and left knee three weeks after thepary with itraconazole; **3b**. March 2017. Plaques on the dorsal side of the hands and left knee 6 months after initiation of itraconazole

and ciprofloxacin (8). Physical therapies, such as curettage and a carbon dioxide laser, have also been successfully employed in one case report (13). Recently, a few authors described good response with the use of acitretin. Case reports demonstrate a response to doses ranging from 10 to 37.5 mg/per/day of acitretin for a variable duration, the longest being 8 months (2, 8, 12, 14). Coulombe J. et al. also successfully treated one patient with PV in association with Candida albicans using itraconazole (3). An analogy between chronic

vegetating pyoderma and recalcitrant tinea is yet to be discussed (9). Carrera et al. reported a patient with pyoderma associated with psoriasis that was successfully treated with tumor necrosis factor inhibitor etanercept (5).

In our patient, itraconazole led to partial regression of lesions, possibly due to its immunomodulatory properties. In a review of the immunomodulatory activity of antifungal drugs, Yamaguchi et al. suggested that azoles, in general, not just itraconazole, tend to act as immunosuppressants (15). Naranjo et al. investigated itraconazole activity on lung levels of certain cytokines both anti-inflammatory (IL-13, TGF-β) and pro-inflammatory (IL-1β, TNF-α, IFN-γ) and PGE2, in healthy and Paracoccidioides brasiliensis infected mice and showed that levels of IL-1β and IL-1α were decreased significantly in the lungs of treated mice; these cytokines are considered important molecules in antifungal host defences and key to induction of the Th1 protective response and showed that pulmonary levels of IL-4, IL-10, and IL-13, considered anti-inflammatory molecules, were higher during and even 4 weeks after the end of ITC treatment in mice (16). However, in our patient complete regression was not achieved and the treatment with acitretin was considered, but the patient refused this treatment option and was lost to follow-up.

Further studies regarding the treatment duration and efficacy are necessary to determine which modalities are the most successful and timely.

Conclusion

There are no clinically controlled trials examining the efficacy of different treatment regimens for pyoderma vegetans, or blastomycosis-like pyoderma. Previous reports and small case series showed that response to therapy is variable or poor, whereas the course of the disease is often long and frustrating for both patients and physicians. Our patient showed significant improvement after administration of itraconazole, with significant regression. Based on individual case reports, the treatment with acitretin should also be considered in this treatment resistant disease.

Abbreviations

PG - Pyoderma gangrenosum
PV - Pyoderma vegetans
BLP - Blastomycosis like pyoderma
HIV - Human Immunodeficiency Virus
VDRL/TPHA - Venereal disease research laboratory/Treponema pallidum hemagglutination assay
TSH - Thyroid stimulating hormone
HBsAg - Hepatitis B surface antigen
anti-HCVAt - Antibodies for hepatitis C virus
ANA - Antinuclear antibody
ENAA - Extractable Nuclear Antigen Antibodies
ANCA - Anti-neutrophil cytoplasmic antibodies
RF - Rheumatoid factor
IL-13 - Interleukin-13
TGF-β - Transforming Growth Factor-Beta
IL-1β – Interleukin-1 Beta
TNF-α - Tumor necrosis factor-alpha
IFN-γ - Interferon gamma
PGE2 - Prostaglandin E2
IL-1α – Interleukin-1 alpha
IL-4 - Interleukin-4
IL-10 - Interleukin-10

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Pyoderma vegetans – prikaz slučaja

Sažetak

Pioderma vegetans (*Pyoderma vegetans* – PV) ili blastomukoza nalik piodermi (Blastomycosis-like pyoderma – BLP) hronično je inflamatorno oboljenje koje pojedini autori smatraju retkim oblikom pioderme gangrenozum (*Pyoderma gangrenosum* – PG) dok je drugi opisuju kao poseban entitet. Za ovo oboljenje najčešće je karakteristično prisustvo verukoznih plakova sa multitplim pustulama. Etiologija ovog oboljenja je nepoznata, mada je povezivana sa infekcijom stafilokokom i streptokokom, inflamatornim bolestima creva, hematološkim malignitetima, primarnim imunodeficijencijama, alkoholizmom i malnutricijom. Ovde opisujemo slučaj PV kod 66-godišnje ženske osobe, bez udruženih bolesti, kod koje su jasno ograničeni vegetativni lividni plakovi sa pustulama na dorzalnim stranama obe šake bili prisutni unazad dve godine. Histopatološka analiza bioptata kože šaka ukazala je na hroničnu inflamaciju i mikroapscese, rupturirane folikularne ciste i folikularnu pseudoepiteliomatoznu hiperplaziju. Lečenje antituberkuloticima i antibioticima u drugoj ustanovi bilo je bez efekta, a u našoj ustanovi je sprovođena sistemskim kortikosteroidima, dapsonom i ciklosporinom takođe bez odgovora. Itrakonazol je dat zbog svoje imunomodulatorne aktivnosti i nalaza gljivice iz roda Penicillium što je rezultiralo parcijalnom regresijom lezija, ali ne i potpunom regresijom, te je predložena i terapija acitretinom, ali je kontakt sa pacijentkinjom izgubljen.

Ključne reči: Pioderma; Blastomikoza; Dermatoze šaka; Ciklosporin; Dapson; Itrakonazol; Ishod terapije; Prikazi slučajeva

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A Red Nodule on the Cheek - a Case Report

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Abstract

Introduction: Merkel cell carcinoma (MCC) is a rare, very aggressive neuroectodermal tumor of the skin typically located on sun-exposed areas and frequently found in Caucasian men between 70 and 80 years of age. Case Report: We present a case of a 86-year-old woman who was referred to our Skin Cancer Unit with a red and well defined nodule located on her left commissure of the mouth, that grew during a couple of months and was completely asymptomatic. Dermoscopic examination revealed a reddish background with linear and arborizing irregular vessels, some out of focus vessels and whitish areas. The lesion was excised, histological examination showed that the tumor was hypercellular and composed of round epithelial elements with large nuclei and scant cytoplasm suggestive of MCC. Immunohistochemical stains confirmed a diffuse positivity with cytokeratin (CK) 2 chromogranin, and synaptophysin; CK7 and thyroid transcription factor-1 (TTF-1) were negative. Sentinel lymph node biopsy was done, resulting negative for neoplastic cells, and computed tomography (CT) of the chest, abdomen and pelvis showed no distant metastasis. Adjuvant radiotherapy on the tumor site and on homolateral neck lymph nodes was also done. Conclusion: Merkel cell carcinoma presents as an asymptomatic, rapidly growing nonpigmented nodule without specific characteristics. Dermoscopic features may help to distinguish MCC from other similar tumors: linear irregular vessels, milky pink areas, architectural disorders and structureless areas, even if not specific, when present are strongly suggestive of MCC. Wide excision with 2 cm margins with adjuvant radiotherapy is the treatment of choice in high-risk primary tumors, while sentinel lymph node biopsy and computed tomography scans are necessary for early diagnosis of metastatic disease.

Key words: Carcinoma, Merkel Cell; Diagnosis; Skin Neoplasms; Cheek; Facial Neoplasms; Aged, 80 and over; Diagnosis, Differential

Merkel cell carcinoma (MCC) is a rare, very aggressive neuroectodermal tumor of the skin (1) associated with increasing incidence and mortality (2). It is typically located on sun-exposed areas and frequently found in Caucasian men between 70 and 80 years of age. It presents with a high local recurrence rate and regional lymph node metastasis. Dermoscopy is a useful tool for skin cancer diagnosis and it was used to diagnose a solitary red nodule that could clinically be mimicking several tumor entities. Specific dermoscopic diagnostic features are described for Merkel cell carcinoma (3, 4) and a definitive diagnosis is made by histopathologic examination and immunohistochemical staining.

Case Report

An 86-year-old woman was referred to our Skin Cancer Unit presenting with a red and well defined nodule, with a diameter of 2.8 cm, located on her left commissure of the mouth (Figure 1). The lesion grew during a couple of months and it was completely asymptomatic. Dermoscopic examination revealed a reddish background with linear and arborizing irregular vessels, some out of focus vessels and whitish areas (Figure 2). The clinical and dermoscopic differential diagnosis included amelanotic melanoma, squamous cell carcinoma, basal cell carcinoma, cutaneous lymphoma, atypical fibroxanthoma, porocarcinoma, angiosarcoma, hemangioma,

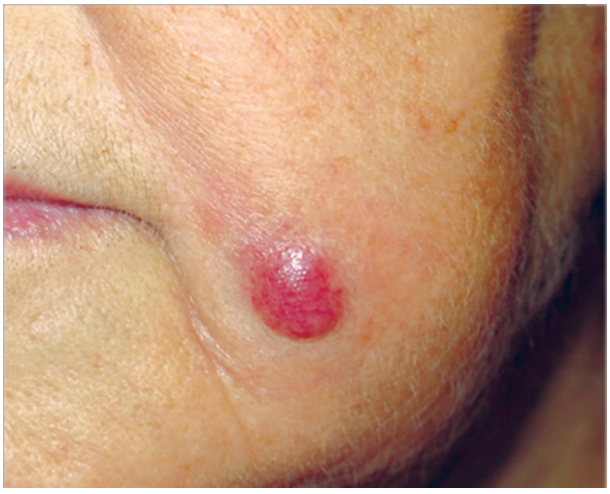

Figure 1. A reddish well defined nodule on left commissure of the mouth

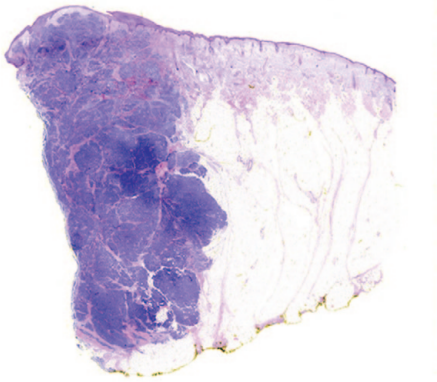

Figure 3. Low histological examination showed a tumor deeply invading the hypodermis with irregular, solid nodules. The epidermis is thinned but apparently uninvolved

Merkel cell carcinoma, and skin metastasis from internal malignancy. The lesion was excised, and gross examination revealed a well-defined grayish nodule. Low histological examination showed a tumor deeply invading the hypodermis with irregular, solid nodules (Figure 3). The epidermis was thinned, but apparently uninvolved. A high power view showed that the tumor was hypercellular and composed of round epithelial elements with large nuclei and scant cytoplasm (Figure 4), suggestive of MCC. Vascular invasion was evident throughout the tumor (Figure 5). Immunohistochemical stains confirmed a diffuse positivity with cytokeratin (CK) 20 and chromogranin (Figure 6) and synaptophysin; CK7 and thyroid transcription factor-*1* (TTF-1) were negative. The tumor infiltrated the dermis, subcutaneous tissue and muscular plane and focally reached the deep margin. Given the aggressiveness of the tumor, a sentinel lymph node biopsy was done, resulting negative for neoplastic cells.

Computed tomography (CT) of the chest, abdomen and pelvis showed no distant metastasis.

The patient was referred to our radiation therapy department. A decision was made to

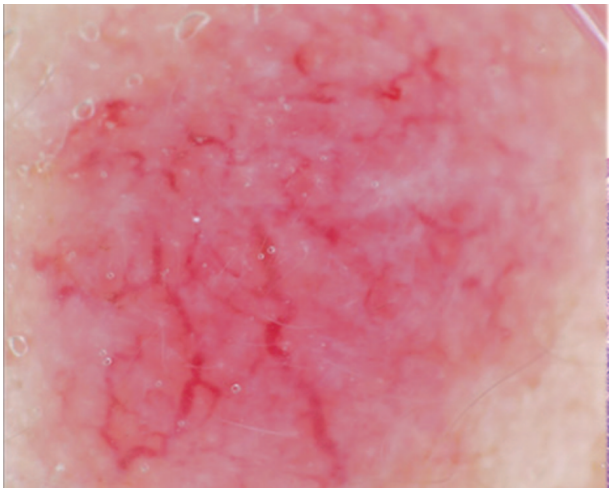

Figure 2. A reddish background with linear and arborizing irregular vessels, some out of focus vessels and whitish areas

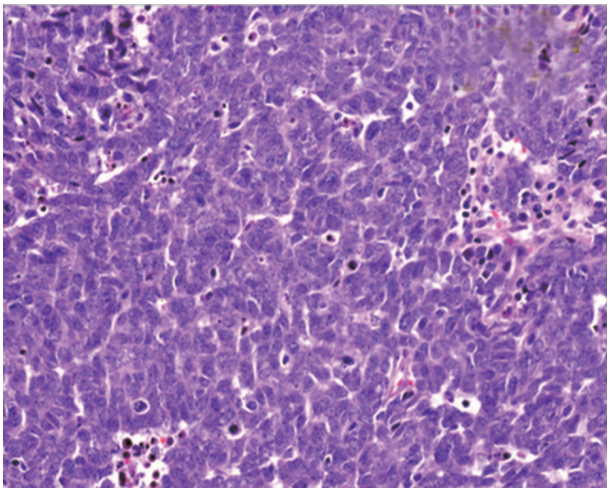

Figure 4. At high power view, the tumor is hypercellular and composed of epithelial elements with large nuclei and scant cytoplasm

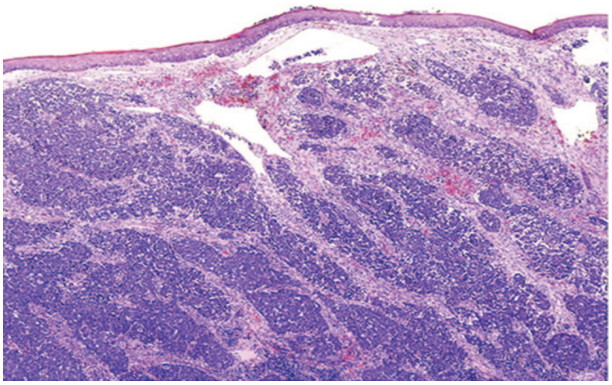

Figure 5. Multiple foci of neoplastic vascular invasion are evident throughout the tumor

Figure 6. Diffusely positive immunohistochemical staining with chromogranin (left) and keratin 20 (right)

perform radiation therapy on the tumor site and on homolateral neck lymph nodes.

Discussion

Merkel cell carcinoma is an uncommon skin cancer with epithelial and endocrine features and a high mortality rate. Well documented risk factors for the development of MCC include ultraviolet exposure, immunosuppression, male sex and older age (5, 6). Recently, a newly discovered Merkel cell polyomavirus has been implicated in the development of MCC (7).

The tumor typically presents as an asymptomatic, rapidly growing nonpigmented nodule without specific characteristics. The predominant sites are the head and neck region and extremities, whereas the trunk, oral, and genital mucosa are involved in less than 10% (8). The MCC is a rarely suspected diagnosis based on clinical examination alone at first clinical visit. Due to its red, pink or purple nodular presentation, the differential diagnosis includes cutaneous lymphoma, atypical fibroxanthoma, porocarcinoma, amelanotic melanoma, angiosarcoma, hemangioma, squamous cell carcinoma, or skin metastasis from internal malignancy.

Dermoscopic features may help to distinguish MCC from other similar tumors (3, 4, 9): linear irregular vessels, milky pink areas, architectural disorders and structureless areas, even if not specific, when present are strongly suggestive of MCC. However, the diagnosis is made by histopathology, while immunohistochemical staining contributes to clarification of the diagnosis. A correct work up comprises ultrasound of the locoregional lymph nodes and total body scanning examinations. The primary tumor should be excised with 2 cm margins. In patients without clinical evidence of regional lymph node involvement, sentinel lymph node biopsy is recommended. If it is positive, a radical lymphadenectomy is recommended. Adjuvant radiotherapy should be considered in patients with multiple affected lymph nodes of extracapsular extension.

Abbreviations

MCC - Merkel cell carcinoma
CK - cytokeratin
TTF-1 - thyroid transcription factor-1
CT - computed tomography

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Crveni nodus na obrazu – prikaz slučaja

Sažetak

Uvod. Karcinom Merkelovih ćelija je redak, veoma agresivan neuroektodermalni tumor kože, koji se najčešće javlja na suncu izloženim regijama, kod osoba bele rase između 70. i 80. godine života. Prikaz slučaja. Žena, starosti 86 godina, upućena je u našu ustanovu zbog eritematoznog nodusa na levoj komisuri usana, koji se pojavio pre nekoliko meseci, bez simptoma. Dermoskopskim pregledom, na eritematoznoj osnovi bili su viđeni linearni i arborizujući iregularni krvni sudovi, neki krvni sudovi van fokusa i beličasta područja. Lezija je ekscidirana, a histopatološkim pregledom viđen je tumor sastavljen od ovalnih epitelnih ćelija sa velikim nukleusima i oskudnom citoplazmom koje su ukazivale na karcinom Merkelovih ćelija. Imunohistohemijskim bojenjem, dokazana je pozitivna reakcija na citokeratin-2, hromogranin i sinaptofizin, dok nije pokazana ekspresija citokeratina-7 i tiroidnog transkripcionog faktora-1. Učinjena je biopsija limfnog čvora stražara, koja je potvrdila odsustvo metastatske bolesti u limfnom čvoru, dok su pregledi kompjuterizovanom tomografijom isključili postojanje udaljenih metastaza. Terapijski, učinjena je široka ekscizija mesta primarnog tumora, a potom i adjuvantna radioterapija kako mesta primarnog tumora, tako i homolateralnog limfnog basena, zbog visokorizičnog tumora radi sprečavanja lokalnog recidiva. Zaključak. Karcinom Merkelovih ćelija najčešće se manifestuje kao asimptomatski, brzorastući nodus bez pigmenta i bez drugih specifičnih karakteristika. Dermoskopija može da doprinese preoperativnoj dijagnostici, a najčešće dermoskopske karakteristike koje su značajno povezane sa dijagnozom karcinoma Merkelovih ćelija su: linerani iregularni krvni sudovi, mlečnoroze područja, narušena arhitektonika i područja bez strukture. Široka ekscizija sa marginama od 2 cm i adjuvantna radioterapija su terapija izbora, a biopsija limfnog čvora stražara i radiološka dijagnostika kompjuterizovanom tomografijom neophodna je za ispitivanje postojanja udaljenih metastaza.

Ključne reči: Karcinom Merkelovih ćelija; Dijagnoza; Kožne neoplazme; Obraz; Facijalne neoplazme; Stari preko 80 godina; Diferencijalna dijagnoza

A Report on the 5th EADO School of Dermato-Oncology, Berlin, Germany, 2017

The 5th European Association of Dermato-Oncology (EADO): Update on Cutaneous Oncology, was held in Berlin, Germany, from 26th to 28th January, 2017. Berlin is the capital city of Germany, and the host of this event every year, the first being held in 2013. The meeting venue of the 5th EADO School was the Novotel Hotel.

The EADO was founded in 1999, to promote, coordinate and improve the clinical and laboratory research activities in the field of skin cancer including primary and secondary prevention, early detection, clinical diagnosis and clinical and experimental research.

The 5th course was dedicated to fundamentals in skin cancer targeted to specialists and residents in the final phase of their residency program.

This year, there were many exciting new advances in understanding and management of all types and stages of skin cancer, from diagnosis, primary treatment and adjuvant treatment, to the management of locoregional disease and distant metastatic disease.

The leading world authorities, such as Claus Garbe, Axel Hauschild, Josep Malvehy, Iris Zalaudek, and others, gave plenary sessions and interactive outbreak sessions. The main part of the course consisted of 8 interactive sessions, each with up to 30 attendants, and every participant took part in each session, which mainly comprised case-based discussions.

The participants have acquired knowledge in: 1. Strategies for diagnosis of melanoma, Merkel cell and non-melanoma skin cancer, including dermoscopy and confocal laser microscopy; 2. The indications, risks, benefits and strategies for mole screening; 3. The indications and methods for genetic diagnosis and genetic counseling of skin cancer pa-

Figure 1. Lidija Kandolf Sekulović, Danica Tiodorović, Miroslav Dinić, Jelena Stojković Filipović, Tatjana Radević and Zorana Kremić

tients; 4. The present American Joint Committee on Cancer staging systems and how to stage melanoma, Merkel cell and cutaneous squamous cell carcinoma, and other non-melanoma skin cancers; 5. The value of imaging and biomarkers for the detection of metastases and disease staging; 6. Adjuvant treatment of skin cancer: radiotherapy, immunotherapy, chemotherapy; 7. New systemic treatments for stage IV melanoma: targeted agents and immunotherapeutics; 8. New treatment options for advanced basal cell carcinoma; 9. New systemic treatments for advanced Merkel cell and squamous cell carcinoma; 10. The characteristics and treatment options for mucosal and uveal melanomas; 11. Topical treatment for epithelial skin cancers; 12. The current classification of cutaneous lymphomas, staging and treatment options for different subtypes of lymphomas; 13. Clinical trials in skin cancer: an update; 14. The indications and strategies for supportive treatments including best supportive care.

Prof. Dr. Lidija Kandolf Sekulovic, from Serbia, participated in the Clinical skin cancer case discussion, and she presented several interesting cases.

The 6th European School of Dermato-Oncology will be held from 18th - 20th January, 2018, in Berlin.

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International Society of Dermatology – Regional Meeting Many Faces of Dermatology - Clinical, Surgical and Aesthetical, Dubrovnik, 2017

The International Society of Dermatology (ISD) organized a Regional Meeting from February 2 - 5, 2017 at the Hotel Kompas in Dubrovnik, Croatia with the theme: Many Faces of Dermatology – Clinical, Surgical, and Aesthetical. Prof. Branka Marinović was president of the Meeting, and Prof. Zrinka Bukvić-Mokos was secretary general. During the 3-day program, lecturers from Europe, Asia, and the USA shared their expertise on a variety of topics. Also, during the conference, on February 3rd, the Meeting participants had an opportunity to watch the Saint Blaise Festival - Dubrovnik's Day. The topics covered during this conference were challenges in clinical dermatology, dermatosurgery and procedural dermatology, esthetic dermatology, hair and nails: what's new, and clinical aspects of sexually transmitted diseases. Prof. Željko Mijušković presented a lecture "Treatment of advanced basal cell carcinoma".

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Figure 1. Krešimir Kostović, Nevena Skroza, Sonja Radaković, Zrinka Bukvić-Mokos, Branka Marinović, Asja Prohić, Evangeline Handog, Mirna Šitum and Željko Mijušković

FORTHCOMING EVENTS

Dermatology and Venereology Events 2017/2018

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
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
03-06 May, 2017	13th European Association of Dermato-Oncology Congress 2017, Athens, Greece	20 March, 2017	www.eado2017.org
05-06 May, 2017	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Niš, Prolom Banja, Serbia	No abstract submission	www.sld.org.rs
18-20 May, 2017	20th Congress of the Serbian Association of Dermatovenereologists Belgrade, Serbia	1 April, 2017	www.udvs.org
25-28 May, 2017	14th EADV Spring Symposium Brussels, Belgium	30 December, 2016	www. eadvbrussels2017.org
01-04 June, 2017	2nd Antiage Congress of the Montenegrin Association of Dermatovenerology Bečići-Budva, Montenegro	1 May, 2017	www.udvcg.me
12–16 June, 2017	5th International Conference on Radiation and applications in various fields of research Budva, Montenegro	31 December, 2016	www.rad2017. rad-conference.org
07-08 June, 2017	16th European Dermatology Congress, Milan, Italy	No deadline information	www.dermatology.conferenceseries.com/europe
25-29 July, 2017	5th International Summer Academy of Practical Dermatology Munich, Germany	No abstract submission	www.isa2017.com
13-17 September, 2017	26th EADV Congress Geneva, Switzerland	16 March, 2017	www. eadvgeneva2017.org
27-30 September, 2017	6th Congress of Dermatovenereologists of Macedonia with international participation Ohrid, Macedonia	20 June, 2017	www.unet.com. mk/dermatology
13 October, 2017	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
15-17 October 2017	9th World Congress on Itch Wroclaw, Poland	31 May, 2017	www.itch2017.syskonf.pl

Tatjana Roš, MD, PhD, Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, and Dragana Ilinčić, MD, Department of Dermatovenereology, Health Care Centre of Novi Sad, Novi Sad
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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 ofliterature 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 are to 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@gmail.com

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 ofthe article, which shouldbe 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 nonstandard 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:// w*ww. bipm.fr/en/si/.

1.4. Cover Letter

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

2. Tables and illustrations

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

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

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3. References

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

4. Additional information

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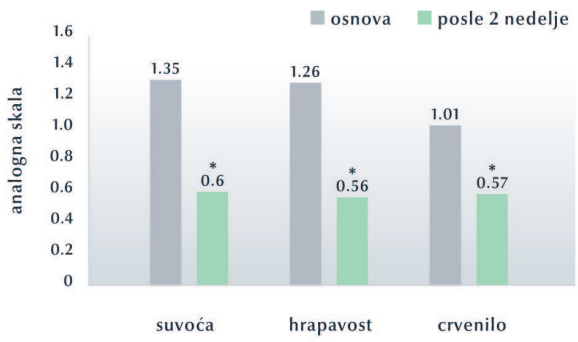

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