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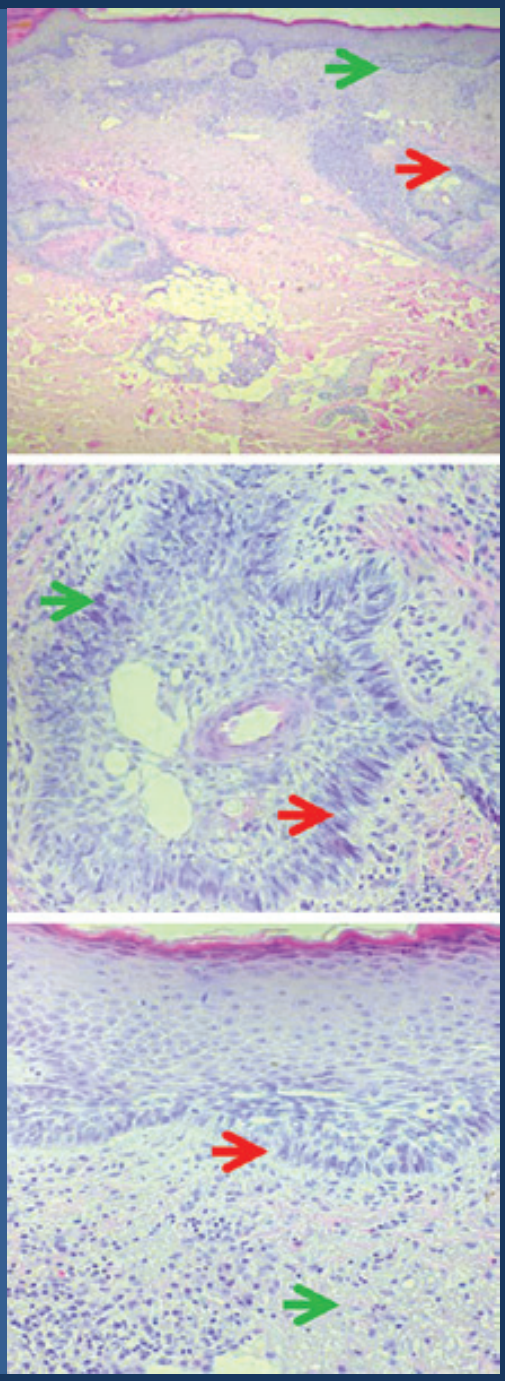

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Radiodermatitis - review of treatment options

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Abstract

Radiation dermatitis is one of the commonest side effects of ionizing radiation which is applied in radiotherapy of carcinoma of all localizations, most frequently of tumors of breast, head and neck region, lungs and soft tissue sarcomas. It usually occurs as a complication of breast radiotherapy and thus it is more often recorded in female patients on the skin in the region of breast subjected to radiation. Clinical manifestations of radiation dermatitis can be divided into four phases: acute phase (erythema, dry desquamation, moist desquamation, ulceration and necrosis with resulting re-epithelialization, residual post-inflammatory hyperpigmentation, reduction and suppression of sebaceous and sweat glands and epilation); subacute phase (hyperpigmentation and hypopigmentation, telangiectasia, skin atrophy, even ulceration); chronic phase (skin atrophy, dermal fibrosis and permanent skin epilation) and late phase (increased risk of skin cancer). In order to prevent radiation dermatitis, skin care products should be applied throughout radiotherapy that will decrease the frequency of skin reactions or block them and thus improve life quality. Although the therapy includes not only topical corticosteroids but numerous other products with active ingredients such as aloe vera, calendula, hyaluronic acid, sucralfat, sorbolene, mineral and olive oil, honey, vitamin C, zinc, antimicrobials and silver, common therapeutic consensus has not been reached on their application in radiation dermatitis. Therefore, the treatment should be conducted according to the basic guidelines but tailor-made for each individual patient.

Key words: Radiodermatitis; Signs and Symptoms; Radiation Injuries; Radiation Protection; Skin Care; Deodorants; Skin Cream; Anti-Infective Agents

Introduction

Radiotherapy is a mode of treating tumor by using ionizing radiation, i.e. high energy radiation of affected tissue. Any radiation that is in interaction with a substance through which it penetrates either directly or indirectly and performs ionization of its atoms and molecule is ionizing radiation. Ionizing radiation has both direct and indirect effects on a living matter. It is implemented by high energy x and gamma photons, electrons, heavy ions (carbon ion), Pi mesons, protons and neutrons. A standard-fractionated radiotherapy is implemented in doses of 40 to 50 Gy, 5 days a week for 5 to 6 weeks. Radiotherapy should be started 6 to 8 weeks after the completion of the previous mode of treatment. About 95% of patients undergoing radiotherapy experience some of its complications, which are a major therapeutic problem and interfere with life quality of patients (1, 2). Radiotherapy side effects can be divided into early or acute complications, which occur during the first six months from the beginning of radiation and they are usually reversible, and late complications, which occur from 6 months to several years and they are often irreversible. Complications are directly proportional to the applied dose, type of radiation and regimen of exposure, but they also depend on other factors as well (3, 4).

Radiation dermatitis is one of the commonest side effects of ionizing radiation which is applied in radiotherapy of carcinoma of all localizations, most frequently of tumors of breast, head and neck region, lungs and soft

tissue sarcomas (1, 5, 6). The incidence and severity of RD depend on several factors, characteristics of patients, mode and duration of treatment. The incidence of severe RD can be significantly decreased by applying megavoltage radiation and conformal radiotherapy.

Radiation dermatitis results from a high dosage of ionizing radiation of the skin during radiotherapy treatment of the above-mentioned tumors.

Radiation dermatitis most frequently occurs as a complication of breast radiotherapy and it is therefore most commonly found in female patients on the skin of breast subjected to radiation (2).

Factors Effecting Skin Damage Degree

The degree of skin damage depends on two main groups of factors: physical properties of the applied radiation on one side and the characteristics of the patients undergoing radiotherapy on the other.

Type and dose of ionizing radiation: megavoltage high energy linear accelerators enable the delivery of the maximum radiation dose under the skin surface, thus the skin can be protected better when such types of radiation are applied. Orthovoltage and kilovoltage linear accelerators produce ionizing radiation of lower penetrability, thus the doses on the skin are higher and therefore more severe damage can be expected with the increased dose of ionizing radiation and due to longer exposure to ionizing radiation (higher number of fractions) or higher individual dose in one fraction (7).

Size of radiation field and site of irradiation: the larger the field of exposure to ionizing radiation the higher is the possibility of damaging the skin, particularly in the regions of irregular surface (folds, joints, point of contact of two surfaces), where it is impossible to achieve a homogenous distribution of the dose but “hot spots” occur (7).

Fractionation regimen: radiation therapy can be implemented by the standard fractionation (daily dose on every working day at a dose of 1.8-2 Gy) or as hypofractionated radiotherapy (daily doses over 2Gy) or in several daily fractions (hyperfractionated radiotherapy). Hypofractionated regimens are particularly recommended when toxic effects of ionizing radiation are expected because a dose less than 1.8Gy per a fraction is then given and healthy cells can repair themselves in the period between two fractions (7–9).

Skin integrity damaged before the beginning of radiation: due to previous radiotherapy of the same region, connective tissue disease, eczema, psoriasis, colagenoses, postoperative scar (10).

Skin type: Individuals having Fitzpatrick skin type I and II are more prone to radiation damage (11). They have fair complexion, fair hair and blue or green eyes. Fitzpatrick scale

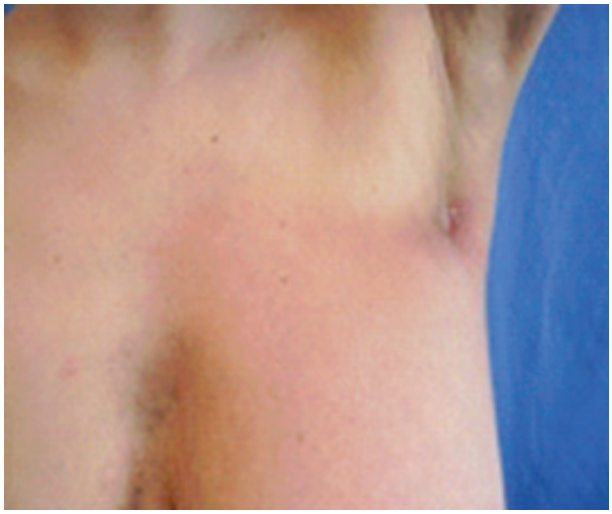

Figure 1. Female patient: Skin erythema, visible at 10th fraction of planned RT (2Gy per fraction).

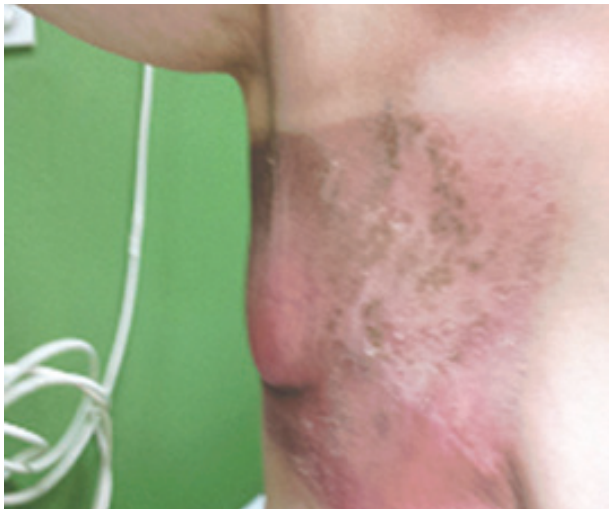

Figure 2. Female patient: Dry desquamation at 20th fraction of planned RT

includes six types of skin and it determines the skin reaction to UV radiation. The scale is constantly developed to predict the skin reaction to trauma and some dermatological procedures – lasers and dermato-surgery, i.e. its ability to tan.

Smoking: due to the damaged tissue oxygenation and increased level of carboxyhemoglobin (2, 12, 13).

Nutritional status: due to the damaged mechanism of skin reparation (2)

Age: children are more sensitive

Comorbidities: (chronic renal insufficiency, diabetes, obesity, hormone disorders): due to disturbed metabolism and accumulation of toxic substances (urea, creatinine, uric acid, glucose) as well as disturbed distribution of water in the organism.

Clinical Picture

Radiation dermatitis has its phases in changes successively taking place in the skin. Thus, the clinical picture of RD can be divided into four phase (3):

Acute phase happening at the beginning of radiation up to 6 months after the exposure to radiation. The following side effects are the most frequent consequences of skin irradiation: erythema, dry desquamation, moist desquamation, ulceration and necrosis with the consequent re-epithelialization, residual post-inflammatory hyperpigmentation, reduction and suppression of sebaceous and sweat glands and epilation.

Erythema is the earliest change happening during even the first week of radiation at the dose of 2Gy. Real erythema develops within 3-4 weeks as a consequence of obliteration of arterioles. Clinically, the skin is erythematous, edematous, and warm and the subjective feeling is that the skin is tight and painful.

Dry desquamation most frequently develops as a result of reduction in the germinative layer of epidermis in the second week of radiation therapy. Destroyed cells are replaced by division of survived cells in the epidermis within 2-4 weeks. One of the clinical manifestations is skin desquamation and itching.

Moist desquamation results from further increase in doses or in case of excessive doses with the already present complications from the early phase such as erythema and dry desquamation. Moist desquamation develops as a consequence of the damaged basal layer, damaged vascular elements resulting in the denuded dermis so that the fluid is diffused from the dermal capillaries onto the surface.

Ulceration and necrosis rarely develop, and if they do, they result from re-irradiation usually 6 weeks or 2 months after radiation if vascular elements and connective tissue are damaged or if an infection has developed.

Re-epithelialization develops within 6 to 8 weeks by merging of healthy cell islets. The tissue recovery is a result of stimulation of homeostatic mechanisms and it starts with the cell migration from the edges of radiation field and cell differentiation from the basal layer.

Skin pigmentation occurs most frequently 2 to 3 weeks after the beginning of radiation at doses of 12-20Gy, with the resulting production of melanin in melanocytes.

Reduction and suppression of sebaceous and eccrine glands are one of early complications of radiotherapy and result in skin dryness, fissures on the skin and increased possibility of developing infection and skin necrosis.

Epilation caused by radiation is a result of high sensitivity of anagen follicles to radiation. Loss of dystrophic hairs (anagen effluvium) caused by acute damage of active separation of matrix cell of anagen follicle is followed by telogenic withdrawal due to early transition of follicles into late anagen (14). 3Gy produces complete, reversible anagen alopecia; permanent alopecia begins at 5Gy (14). Complete regeneration of hair mostly begins 2 to 4 months after radiation in the reversible type of alopecia induced by radiation.

Evaluation of early skin reactions to radiotherapy can be done by a validated tool, and the most frequently used validated scale is the one created by the Radiotherapy Oncology Group (RTOG) (15) (Table 1):

Before radiotherapy is started, it is necessary to estimate the current condition of patients' skin and continue to follow up skin changes in the patients during radiotherapy at least once a week in order to prevent and reduce unwanted reactions of radiotherapy on the skin (16, 17).

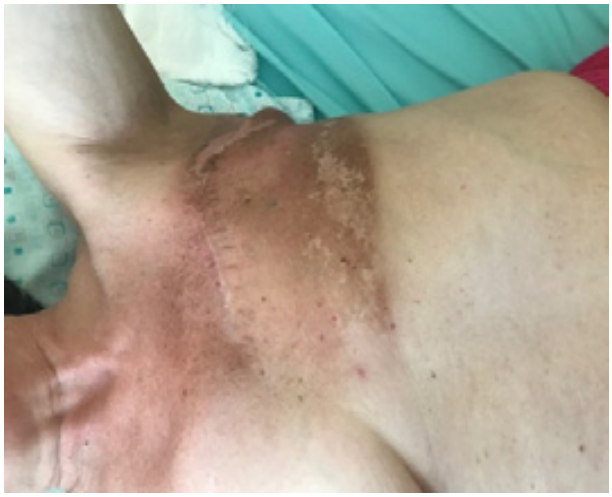

Figure 3. Female patient: Moist desquamation and hyperpigmetation of the skin after completed postoperative RT with TD 50Gy in 25 fraction

Subacute phase commences in the period from 6 months to a year after the completion of radiotherapy when hyperpigmentation and hypopigmentation, telangiectasia, skin atrophy occur and even ulcerations are possible on the spots of skin re-epithelialization.

Chronic phase commences in the period from a year to 5 years after the completion of radiotherapy. The most common manifestations are skin atrophy, dermal fibrosis (damaged fibroblast , increased production of collagen in dermis), telangiectasias (damaged blood vessels, ischemia and necrosis of small blood vessels) and permanent skin epilation.

Late phase begins 5 years after radiation. The radiated skin regions are at higher risk of developing skin cancer (3, 18).

Various pathogenetic mechanisms of development of secondary carcinoma after radiotherapy have been described (4). Ionizing radiation leads to disruption of one of DNA chains, which can be converted into disruption of both DNA chains. Disruption of both DNA chains leads to mutation in genes, which results in malignant transformation of irradiated cell. Proteins synthesized during incorrect DNA reparation can also lead to the predisposition of development of malignant neoplasm. Cancerogenic potential of ionizing radiation is particularly increased when doses of and exceeding 45G are applied. Bystander effect implies development of secondary malignancies in a region away from the primary

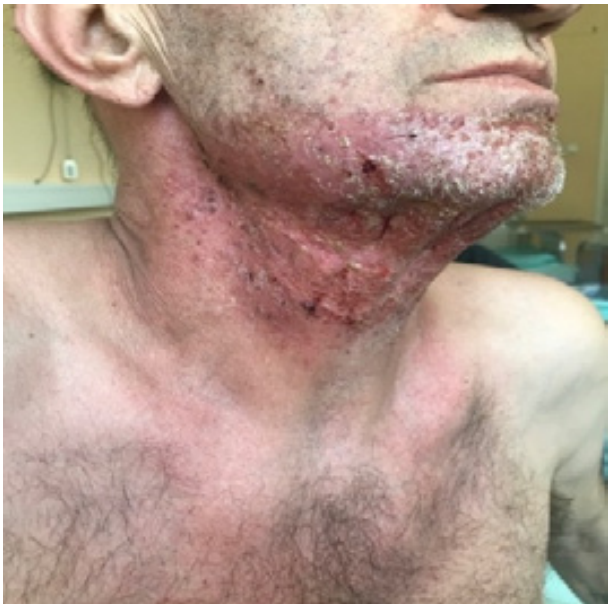

Figure 4. Male patient: Ulceration, moist desquamation and acneiform reaction as a complication of combined radiotherapy treatment (RT accompanied with Cetuximab)

tumor as a result of systemic effect of cytokines which are released during radiotherapy (19). After the initial dose of X-radiation, a certain percentage of DNA chain basal cells is damaged, and other cells receive a signal for mitosis in order to compensate for damage, they mature faster, which leads to a disorder in the balance between epidermopoiesis of basal cells and necrosis of cells with damaged DNA. When radiation treatment is continued, apoptosis of basal cells continues; inflammatory response with secretion of histamine and serotonin is stimulated as well as vascular response with capillary dilation and extracapillary damage of monocytes.

Prevention of Radiation Dermatitis

Before radiotherapy is started, the effect of various factors influencing the development of skin reactions during radiotherapy should be considered. These factors can be internal – age, diabetes, hormone status, obesity, smoking habit (patients should be advised about diet and to stop smoking) and external, which are associated only with radiation, adjuvant chemotherapy and target therapy (13, 20, 21). An important aspect during radiother-

Table 1. Evaluation of the intensity of early skin reactions induced by ionizing radiation, RTOG

grade 0	grade 1	grade 2	grade 3	grade 4
	painless erythema	intense, sensitive, painful erythema	desquamation	ulcerations
no changes	epilation	desquamation	moist desquamation	hemorrhage
	desquamation	moist desquamation	expressed edema	necrosis
	dry skin	moderately expressed erythema		

apy is the application of skin care products, which should reduce or prevent the frequency of skin reactions and improve life quality of patients undergoing radiotherapy (22, 23).

Recommendations regarding skin care in patients undergoing radiotherapy are different because of the insufficient number of clinical studies whose results would corroborate or reject the application of any topical preparation. Gosselini et al. believe that skin care should be directed to alleviation of symptoms (pain in the first place) and achievement of the feeling of comfort, i.e. maintenance of life quality of patients. It is important to include a psychologist in treatment of oncologic patient because it is known that patients prefer to undertake "an action" than do nothing (24). Recommendations given in more recent studies are contrary to traditional ones stating that the skin should not be washed and deodorants should not be used, which would affect life quality of patients in a way that they would worry about their body odor (25-29).

Nowadays it is recommended to wash the irradiated field with tepid water and mild Ph neutral or non-alkaline soap as a routine skin care procedure of patients during radiotherapy. It has been concluded that limitations in body washing and hair shampooing may affect social health of the patients (30-32).

According to the evaluations of skin condition done by RTOG assessors during and after radiotherapy, the patients who used water and soap to wash themselves were found to have reduced itching, erythema and desquamation at the end of treatment (33, 34). Aqueous cream can also be used instead of soap (British National Forum). After washing, the skin must be dried gently, a rough towel must not be used to avoid skin irritation (35-37). The skin must not be warmed or cooled, exposed to wind. Rubbing should be avoided; razors should not be used for shaving nor should wax be used for hair removal (24, 38). Hair is to be washed with usual shampoo, but it should not be dried with a hair-dryer be-

Table 2. Therapy of Radiation Dermatitis

Therapeutic options of radiation dermatitis
– water and mild Ph neutral or non-alkaline soap
– aqueous cream
– deodorants
– non steroid topical therapy: lotions, creams, ointments, dressings, barrier films with active ingredients including aloe vera, calendula, hyaluronic acid, sucralfate, sorbolene, mineral and olive oil, honey, vitamin C, zinc,
– topical steroid therapy
– antimicrobials agents, including silver sulfadiazine
– hydrophilic dressings
– semipermeable dressings or hydrogels
– surgery
– sunscreens

cause of irritation and drying of the skin if the head region is being irradiated (35, 39).

The patients are not allowed to use deodorants unless the skin is intact (25-28, 37). They are advised to wear comfortable clothes made from natural fibers, such as cotton T-shirts (24). They should apply sunscreens on the photoexposed skin (the skin must not be exposed to direct solar radiation) and wear wide brim hats (40).

In 2014 Chan et al. made a systematic review of literature including 47 randomized controlled trials within a meta-analysis aimed at determining the effect of systemic and local therapy (skin washing, use of deodorants, steroids, non-steroid local therapy and dressing) in treatment of RD in the period from 1962 to 2012. Six of these trials examined oral systemic therapy; 2 trials compared the condition of skin washed and not washed during radiation therapy; 4 trials dealt with the use of deodorants; 5 and 23 trials examined the application of topical steroid therapy and non-steroid topical therapy, respectively and 6 trials examined dressings. Out of 47 RCT, 36 trials were assessed as having a high level of risk of bias, 10 trials had an undefined risk and one had a low risk of bias.

The absence of consensus regarding the issue of standard skin care of patients undergoing radiotherapy results from non-standardized methodology of choice, follow-up and evaluation of examined parameters (41). However, common consensus on guidelines may be reached in two fields: 1) aqueous cream as a substitution of soap, but it should not be used as an additional moisturizer, i.e. it cannot replace moisturizing creams (emollient creams); 2) deodorants – there is no proof based on the evaluation of toxicity, life quality and symptoms done by RTGO which would corroborate the practice of avoiding the application of deodorant 1 to 4 hours before radiotherapy (42). They are now commonly believed not to have a negative effect as it used to be thought before (27). Although the results of studies performed so far suggest that there was no difference between metallic and non-metallic deodorants and that skin reactions occur as a consequence of irritating chemical ingredients of the product but not as a consequence of radiation, increased surface of radiation or bolus effect, the application of deodorants with aluminum must be further researched (28).

Topical therapeutics

In addition to corticosteroids a lot of products such as lotions, creams, ointments, dressings, barrier films with active ingredients including aloe vera, calendula, hyaluronic acid, sucralfate, sorbolene, mineral and olive oil, honey, vitamin C, zinc, antimicrobials and silver have been recommended; however, there is no common consensus on their use (Table 2).

Although the results of numerous studies suggest that aqueous cream applied to prevent development of erythema does not have any effects (24), the Society and College of Radiographers (SCoR) have published data which state that in 65% of departments performing radiotherapy aqueous cream is recommended and used to alleviate erythema, reduce the feeling of skin dryness, increase moisturizing of the skin and achieve higher satisfaction of patients (43). Aloe vera is also recommended to be used to alleviate erythema in 11% of departments performing radiotherapy but there is no consensus on its application either (17, 44, 45). However, when higher cumulative doses of radiation therapy, exceeding 27Gy are given, administration of aloe vera gel has yielded some protective effects from unwanted reactions, which is due to its anti-inflammatory and anti-bacterial effect (46). *Calendula officinalis* cream has been categorized as a “probably efficient” cream by Oncology Nursing Society (ONS) according to the putting evidence into practice analysis (47, 48).

Hyaluronic acid is a polymer that stimulates fibroblasts and simultaneously neutralizes free oxygen radicals; in the form of 0.2% hyaluronic acid cream, it can accelerate the phase of granulation in radiation ulceration healing (49, 50). The results of studies done by Leonardi et al. and Primavera et al. have shown that there is a considerably reduced intensity and duration of unwanted reactions, erythema on the skin and subjective feeling in the patients who used hyaluronic acid as compared with the placebo group (51, 52).

Enhanced migration of keratinocytes into the wound region, faster replication of these cells and faster epithelialization were deter-

mined by examining the influence of low molecular fraction of hemodialysate on wound healing after radiation therapy (53, 54).

According to SCoR data, hydrocortisone is used locally in 10% of departments performing radiotherapy to treat dry desquamation, that being in accordance with guidelines published by the College of Radiographer, 2000 and those of the Multinational Association for Skin Care of Patients treated with radiotherapy (27). Corticosteroids are often prescribed to prevent and treat RD due to their anti-inflammatory effects. However, the results of studies which compared the effects of prophylactic application of 0.2% hydrocortisone cream and placebo in management of post-irradiation reactions of skin are contradictory (55-61). The results of double blind randomized study on the prophylactic use of mometasone fuorate (MMF) or emollient cream in prevention of acute complications of radiotherapy on the skin of women with breast cancer have shown that the degree of erythema and pigmentation in the patients who had used emollient cream was considerably higher compared with the patients who had used MMF (58, 62).

Prophylactic use of sucralfate, which is a stimulator of cell growth in the form of cream, has not resulted in the expected reduction of intensity of erythemic radiation reactions in the skin, contrary to the anti-inflammatory effect exerted by sucralfate on experimental animals (63).

Barrier films are skin protectors that physically prevent the loss of skin moisture and reduce skin trauma and thus decrease skin damage caused by radiation. They have been proved efficient in treatment of moist desquamation of radiodermatitis (44, 64).

Antimicrobial agents, including silver sulfadiazine, should not be used for prophylaxis but only to treat infections, taking advantage of sulfadiazine ability to reach a high concentration locally on the skin with minimal systemic absorption (65).

Hydrophilic dressings

Hydrophilic dressings are dressings which could be partially permeable in the form of hydrocolloid or gel. Dressings mske wound re-epithelialization faster by promoting migration of epithelial cells. The most frequently cited study estimated the effect of moisture vapor permeable (MVP) dressing, i.e. dressings which permit evaporation and retain moisture in the treatment of RD in the phase of moist and dry desquamation. The comparison of effects of MVP dressings and hydrophilic lanolin dressings has shown that MVP dressings are superior (66).

It is well known that silver dressings have good effects in treatment of venous ulcers, burns, chronic wounds with secondary bacterial infection. fVong et al. compared silver sulfadiazine cream with silver leaf nylon dressings. Their study has underlined the benefit of anti-bacterial dressings, which have been proved to have good therapeutic effects in the patients with neoplasm of the anal and genital region whose perineum skin has also been affected by radiotherapy. The dressings have considerably reduced development of grade 3 skin reactions whereas grade 4 skin reactions did not develop (67).

Therapeutic Guidelines

The patients are advised to use moisturizing, emollient creams, free of sodium lauryl sulphate to reduce skin irritation during radiotherapy (68, 69). These recommendations are also given for therapeutic and preventive reasons to the patients having RD grade 1 and 2 (according to RTOG scale), i.e. erythema, edema, and dry desquamation.

Administration of calendula cream and certain formulations of creams with hyaluronic acid is recommended to reduce the incidence of moist desquamation in grade 3 and barrier films are recommended for treatment.

If a bigger skin area is denuded in grade 3, toilet of skin changes is necessary with hydrophilic, hydrocolloid, semipermeable dressings or hydrogels, which should be changed several times a day. Topical corticosteroids are also useful as well as silver dressings in prevention of bacterial infections.

In case of increased risk or justified suspicion of development of secondary bacterial infection, sulfadiazine cream can be applied until biogram and antibiogram are made. Topical antibiotics should be avoided unless the wound smear has been taken and bacterial infection proved (70, 71).

If skin changes aggravate, ulcers are formed and bleeding and/or intense pains occur in grade 4, a surgeon must be consulted.

Conclusion

Skin reactions to radiation therapy can be severe, grave, disturbing and unpleasant; therefore, treatment and prevention of skin reactions must be approached seriously, and the pre-condition is to make the timely and accurate diagnosis. Treatment must be conducted according to the basic guidelines but tailor-made for each individual because of multifactor causes of development of radiation dermatitis (72).

Abbreviatioins

RD – radiation dermatitis
RTOG – Radio Therapy Oncology Group
SCoR – Society and College of Radiographers
ONS – Oncology Nursing Society
MMF – mometasone fuorate

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Radiodermatitis - pregled mogućnosti lečenja

Sažetak

Radijacioni dermatitis predstavlja jedan od najčešćih neželjenih efekata jonizujućeg zračenja koje se primenjuje u radioterapiji karcinoma svih lokalizacija, a najčešće kod tumora dojke, regije glave i vrata, pluća i sarkoma mekih tkiva. Najčešće se javlja kao komplikacija radioterapije dojke, te se stoga češće i registruje kod pacijenata ženskog pola na koži u regiji dojke koja se zrači. Klinička slika radijacionog dermatitisa se može podeliti na 4 faze: akutna (eritem, suva deskvamacija, vlažna deskvamacija, ulceracija i nekroza sa posledičnom reepitelizacijom, rezidualna postinflamatorna hiperpigmentacija, redukcija i supresija sebacealnih i znojnih žlezda i epilacija); subakutna (hiperpigmentacije i hipopigmentacije, telangiektazije, atrofija kože, a moguće su i ulce-

racije), hronična (atrofija kože, dermalne fibroze i trajna epilacija kože) i kasna faza (povečan rizik za pojavu kancera kože). Radi prevencije radijacionog dermatitisa važno je da se tokom radioterapije upotrebljavaju proizvoda za negu kože koji će smanjiti ili zaustaviti učestalost kožnih reakcija i poboljšati kvalitet života. Iako se u terapiji osim topijskih kortikosteroida preporučuju brojni proizvodi sa aktivnim sastojcima kao što su npr. aloja vera, kalendula, hijaluronska kiselina, sukralfat, sorbolen, mineralna i maslinova ulja, med, vitamin C, cink, antimikrobna sredstva i srebro, nije postignut zajednički terapijski konsenzus o njihovoj upotrebi kod radijacionog dermatitisa. Iz tog razloga tretman treba da bude vođen osnovnim smernicama, a prilagođen individualnim potrebama svakog pojedinog pacijenta.

Ključne reči: Radiodermatitis; Znaci i simptomi; Radijacione povrede; Zaštita od radijacije; Nega kože; Dezodoransi; Kreme za kožu; Antimikrobna sredstva

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Giant Basal Cell Carcinoma – a Case Report

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Abstract

Basal cell carcinoma is the most common form of cutaneous cancer. In majority of cases it is locally invasive with slow growth, ranging in size from a couple of milimeters to a couple of centimeters and located primarily on sun-exposed regions. Giant basal cell carcinoma, defined as a tumor that is larger than 5 cm in diameter, is a very rare type of cutaneous malignancy accounting for 0.5-1% of all basal cell carcinomas. We present a case of a 74-year-old man with a 17 x 14 cm giant basal cell carcinoma in the right supraclavicular region. Detailed history revealed that the lesion had started as a papule 15 years before presentation. Despite its growth, the lesion was neglected until admission. Histological examination of skin lesion confirmed superficial and focally infiltrative types of basal cell carcinoma. Electron radiotherapy was administered with 54 Gy total dose delivered in 20 daily fractions which resulted in healing of lesions and adequate response. Thus, definitive radiotherapy can be just as effective as excision when the criteria are met.

Key words: Carcinoma, Basal Cell; Diagnosis; Neoplasm Metastasis; Skin; Radiotherapy; Biopsy; Treatment Outcome; Case Reports

Introduction

Basal cell carcinoma (BCC) is the most common form of cutaneous cancer. Most cases are locally invasive, indolent, characterized by slow growth, rare metastasis, located predominantly on ultraviolet (UV) exposed areas such as the head and neck (in 80-85% of cases) and on the trunk (roughly only 10%) (1). Caucasians over the age of 40 are the most affected group (2). The majority of BCCs range from a couple of millimeters to a couple of centimeters (mean size of 11.7mm ± 5.9 mm), with surgical excision being the preferred method of treatment leading to a 5-year cure rate of 95% (3). In rare instances, basal cell carcinomas can be larger in size leading to a potentially more aggressive clinical course and difficulties in opting for the appropriate therapeutic modality. According to the American Joint Committee on Cancer, tumors with a diameter larger than 5 cm are defined as Giant Basal Cell Carcinoma (GBCC) (4). The incidence of this rare variant has been reported to be 0.5% - 1% (5). Some authors think that a diameter greater than 10 cm should be the cutoff value for GBCC (6). When the maximum diameter is more than 20 cm, the term Super Giant Basal Cell Carcinoma can be used and, to the best of our knowledge, there are only 10 reported cases in the literature (7, 8).

Case Report

We report a case of a 74-year-old male with an extensive histopathologically verified basal cell carcinoma that slowly progressed over the course of 15 years on the right supraclavicular region of the shoulder. The lesion started in 2003 as an erythematous papule that was neglected for many years. The patient was examined for the first time in 2008 when he was diagnosed to have a suspicious basal cell carcinoma and/or discoid erythematous lupus and he was treated with local corticosteroids, antibiotics and 5% fluorouracil cream with no improvement. The lesion was afterwards biopsied and histopathologic examination confirmed superficial type of basal cell carcinoma; however, further

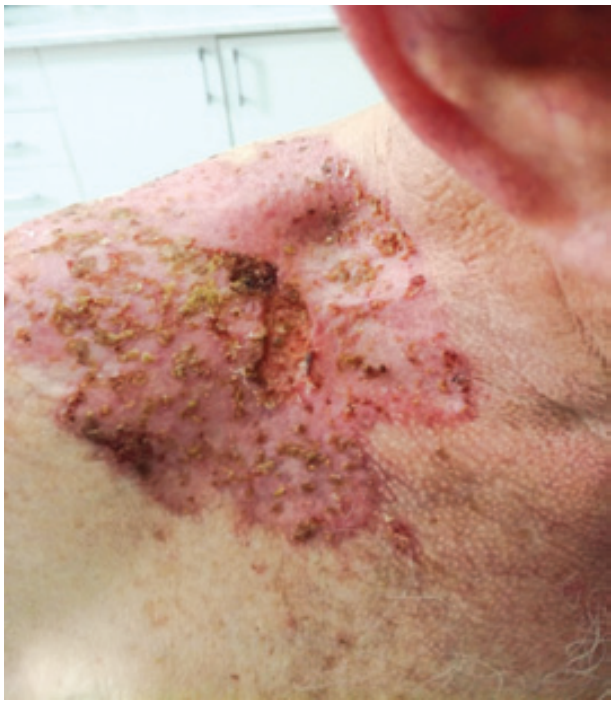

Figure 1. Infiltrative erythematous plaque 17 cm x 14 cm. Multiple irregular ulcerations and erosions covered by purulent and hemorrhagic crusts, and without regional lymphadenopathy.

treatment and medical control was ignored by the patient until 2018. On admission, the patient presented with an extensive, well demarcated, oval erythematous, infiltrative plaque 17 cm x 14 cm in diameter on the right supraclavicular region, with multiple irregular ulcerations and erosions covered by purulent and hemorrhagic crusts, and without regional lymphadenopathy (Figure 1). Anamnestic exploration revealed neither personal nor family history of previous BCC, other skin diseases, radiation or arsenic exposure, sunbathing or previous sunburns. Co-morbidities at presentation included chronic obstructive pulmonary disease, diabetes mellitus type II, hypertension and cardiac arrhythmia.

Routine laboratory analysis, including complete blood count (CBC) revealed elevated sedimentation rate (94 mm/h), increased C reactive protein level (62.8 mg/L), leukocytosis (16.9 $x10^9$/L), the decreased number of erythrocytes (3.68 $x10^{12}$/L) and decreased level of hemoglobin (110 g/L). Biochemistry, urinalysis and tumor markers were within normal limits. Bacterial cultures taken from lesion ulcerations were positive for Staphylococcus aureus. Abdominal ultrasound showed no pathological findings. Since lung x-ray showed a 4.5 cm x 2 cm oval soft tissue shadow with diffuse bilateral bronchial shadows, a pulmonologist was consulted who required a thoracic multiple detector computed tomography (MDCT) to exclude metastasis and tuberculosis evaluation. Thus, three consecutive sputum samples for Koch bacillus (BK) and Lowenstein cultures were taken and were

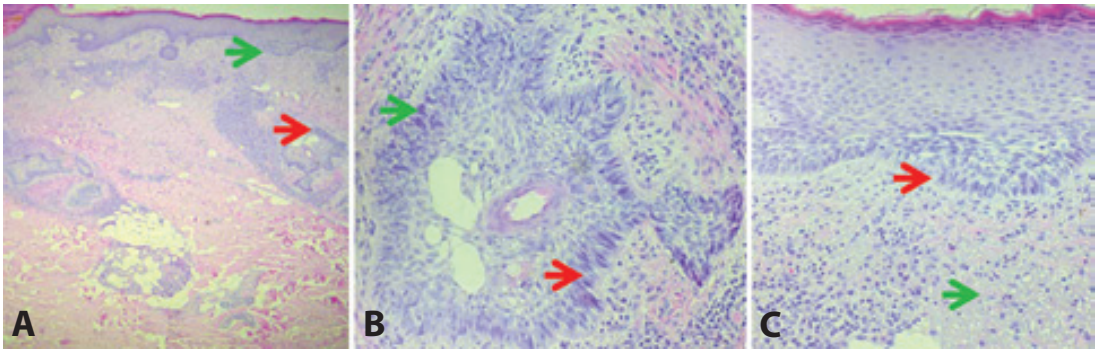

Figure 2.
A) Superficial type of BCC limited to the epidermis with budding pattern (→). Focal infiltrative type of BCC (→).
B) Infiltrative type of BCC, deeper involvement with irregular tumor nests, palisading arrangement of atypical cells (→) showing high nuclear cytoplasm ratio, hyperchromatic nuclei and pleomorphism (→).
C) Superficial type of BCC, budding superficial nests of atypical basaloid epithelium confined to the papillary dermis (→). Underlying elastosis in dermis (→).

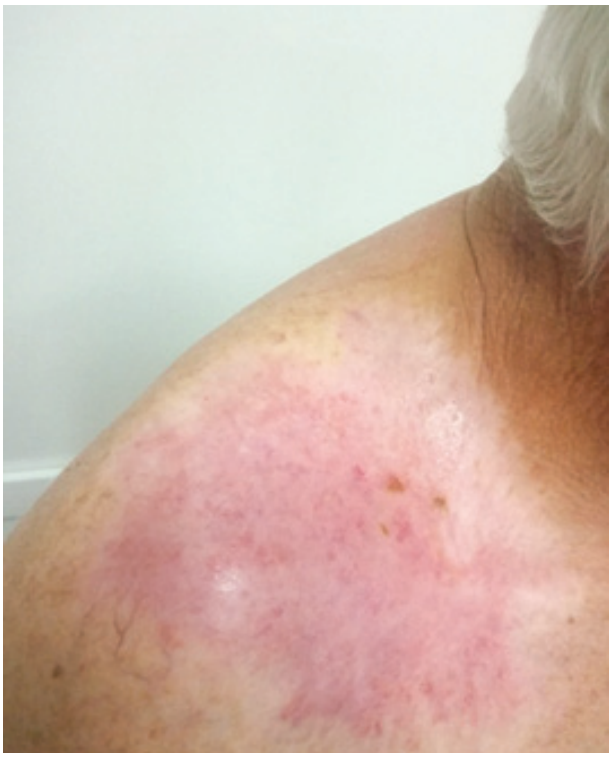

Figure 3. Photo taken 6 months after irradiation. Resolution of ulcerations and lesion spreading. Contraction of the residual paler erythematous plaque with individual telangiectasias along the surrounding white halo like borders.

negative. Thoracic MDCT revealed multiple annular changes in the right upper lobe with active peripheral pyogenic membranes and central, fluid filled cavities with a maximum diameter of 33 mm. Reactive lymph nodes were present in 4R group of the mediastinum and right hilus. Final diagnosis was abscess pneumonia. Intravenous antibiotics including i.v. Ceftriaxone amp. 1g b.i.d, i.v. Levofloxacin amp. 5mg/ml b.i.d and i.v. Metronidazole flacc. 500mg/100ml t.i.d. were administered and resulted in clinical improvement of infection and inflammation. Regression on follow up chest X-ray and MDCT was achieved.

Histological examination of skin lesion confirmed superficial and focally infiltrative types of basal cell carcinoma (Figure 2).

When the patient was presented to the Oncology and Radiology skin and soft tissue specialist committee, his lesion was found to be inoperable and radiotherapy was indicated. The patient was treated with electron radiotherapy consisting of a total dose (TD) of 54 Gy delivered in 20 daily fractions (2.5 Gy/fraction), with appropriate margins over the course of 20 days. The radiotherapy resulted in resolution of ulcerations and lesion spreading, leading to contraction of the residual paler erythematous plaque, post-irradiation telangiectasias and the surrounding white halo-like borders (Figure 3).

After 6 months post-radiotherapy follow up, two biopsies were taken and histopathology revealed post radiation fibrosis with no elements of BCC.

Discussion

Giant basal cell carcinoma is a rare variant of non-melanoma skin cancer with an epidemiological profile being Caucasian, male gender, and a peak occurrence in the seventh decade. The reported sites of predilection, by a slim margin, were the back (27.5%) and face (23.5%) with the upper extremities amounting to 13.7%. Rarer cases have been reported on the abdominal wall, genital region, anterior trunk, and lower extremity. One clinicopathological study and

Table 1. BCC and SCC: Recommended fractionation dose schedules (29)

Fractionation dose	Indication	Biological effective dose
Single dose 12-20 Gy fraction-	Elderly, frail (palliative)	
7 fractions of 5 Gy (TD 35 Gy)	Elderly, + medical comorbidity	44 Gy
10 fractions of 4 Gy (TD 40 Gy)	Older and healthy	47 Gy
15 fractions of 3 Gy (45 Gy)	Older and healthy	49 Gy
20 fractions of 2.5 Gy (50 Gy)	Younger and/or <2-3 cm lesion	52 Gy
30 fractions of 2 Gy (60 Gy)	Younger and/or large lesion	60 Gy

Table 2. Recommended criteria for radiotherapy (29)

Patient factors	Patients older than 70 years
	Patient autonomy: preference to avoid surgery
	Anti coagulation and platelet functioning medication
	Discernible co-morbidities
Pathological characteristics of tumor	Site: ala nasi, nasal tip and bridge, lower eyelid, medial canthus, ear
	Extensive and superficial size and/or depth
	Complex surgery required for locally advanced stage

review of literature concluded the mean size to be 14.77 cm, ranging from 5 to 40 cm. The reported total duration of the tumor presence was 14.57 years on average (9).

Clinically, GBCC has been reported as the following subtypes: nodular-ulcerative (10), vegetant/exophytic (11), extensively ulcerative (12), morpheaform (13), and polypoid (14). Naturally, they are more likely to invade the extradermal structures due to their size and years of growth, thus potentially causing cosmetic deformations. Invasion of the underlying cartilage, soft tissue, and bone was not seen in our patient during the workup.

In terms of histology, there are differences between conventional sized BCCs and GBCCs. Purnell et al. published a review of 57 cases comparing the histological differences contributing to excessive growth. Besides size, GBCCs were thicker, with higher incidence of ulcerations, and possessed a more infiltrative growth than conventional BCC, but the authors concluded that histological features alone were unlikely to be the reason for the large clinical size (15). Up to 27 histological subtypes of basal cell carcinoma have been reported (16). The histological subtype is an important factor that leads to the progression and formation of GBCCs, and they can be broadly categorized as non-aggressive and aggressive. Non-aggressive one includes superficial and nodular, while aggressive GBCC includes metatypical, micronodular and morpheaform subtypes. Archontaki et al. reported that 54% of GBCCs reviewed were histologically nodular, 19% infiltrating, 9.5% were metatypical or morpheaform, and only 4.76% were accounted as superficial spreading (9). On the other hand, in a study of 50 patients with GBCC by Randle et al., 72% were classified as infiltrative or micronodular. Finally, the World Health Organization (WHO) classification, currently in use, only recognizes the following subtypes: nodular, superficial, micronodular, infiltrating, sclerosing/morphoeic, basosquamous, pigmented, BCC with sarcomatoid differentiation, BCC with adnexal differentiation, and fibroepithelial, which leads to improved clarity and reproducibility (17).

Metastasis is a rare complication of conventional, mostly indolent, BCC as it spreads more horizontally rather than vertically. According to the literature, there have been roughly 300 cases reported (18), with an estimated incidence rate of 0.0028% to 0.5% (19, 20). Mean time interval from tumor onset to metastasis is roughly 9 years and only half of the patients survive 8 months after the beginning of metastatic symptoms (21). In a published review, Randle et al., concluded that BCCs larger than 2 cm in diameter, located on the ear or mid face, with aggressive histopathological type, previous treatment and, history of neglect or radiation have a higher propensity for potential metastasis (22). A positive correlation of the tumor size and metastatic potential has been established. Tumors larger than 3 cm, 5cm and 10 cm in diameter increase the incidence of metastasis to 2%, 25%, 50% respectively (23). All of these factors apply to GBCC making it essential to rule out metastasis in patients. In fact, most cases of metastatic BCCs are in fact GBCC. Archontaki et al. reported that metastasis was present in 17.6% of GBCC patients during the primary examination (9). Contrary to the general belief, multiple studies have confirmed that there is no correlation between specific histopathological subtype of BCC with a high-

er incidence of metastasis (24). The most common sites of metastasis are lymph nodes, lung and bone, but there are individual documented cases of hematogenous spread to other organs. Despite a detailed work-up, we did not find any signs of metastasis in our patient.

There are no specific guidelines for treating GBCC or metastatic disease. Wide surgical excision with free margins remains the preferred treatment of choice for GBCC, as well as for BCC. In general, BCCs less than 1 cm implement margins 2-4 mm achieving a 5-year cure rate of 95% (3). Larger lesions require clinical margins of 3-5 mm due to subclinical extension. Other potential treatment options include immunomodulators (25), topical chemotherapeutic agents (25), photodynamic therapy (26), biological therapy (Vismodegib, a sonic hedgehog pathway inhibitor, FDA approved in advanced cases and metastasis, 150 mg once daily) (8), Mohs micrographic surgery, and radiotherapy, whether definitive or adjuvant. In general, surgery and radiotherapy are the most effective treatment options (27). The risk of tumor residue in GBCC post excision has been reported to be 68% (13). When the tumor is inoperable or surgery is contraindicated in an elderly patient, as it was in our patient, radiotherapy is an appropriate alternative. In general, radiotherapy can be administered by using linear accelerators for high-energy X-rays, or by electron radiotherapy (regularly preferred due to the accurate prescription of used energy for depth of penetration) for many clinical applications including GBCC. There is a high degree of variation in fractionation regimes in non-melanoma skin cancers. According to one survey done in the United Kingdom (UK), the four most common regimes used were (18–20 Gy in 1 fraction, 35 Gy in 5 fractions, 45 Gy in 10 fractions and 55 Gy in 20 fractions) (28). Other dosing fractions suggested in literature are included in Table 1. Guidelines for BCC state 0.5 cm deep margins and lateral margins to be 0.5 cm (morphoeic, large, infiltrative or poorly defined require 0.7cm-1cm) with an additional 0.5 to 1cm for electron therapy to account for penumbra of electrons (30). Factors and tumor specificities indicating radiotherapy as the treatment option are presented in Table 2. There is a correlation between greater tumor size and depth, with a decrease in local cure rates. Regular follow-up is required since currently there are no guidelines suggesting when to take a control biopsy to rule out post radiotherapy BCC recurrence. Early detection and adequate, timely treatment remain imperative in preventing recurrence and metastasis.

Conclusion

Giant basal cell carcinoma is a rare subtype of BCC that requires a thorough work up and can lead to difficulties in choosing the appropriate treatment. Patient awareness needs to be increased as timely medical consultation is essential for the treatment success. When the criteria are met, definitive radiotherapy can be just as effective and therefore it is an adequate alternative to surgical excision. Since there is a lack of guidelines for GBCC treatment criteria, follow up and radiotherapy dose fractionation schedules, they should be provided as soon as possible.

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Abbreviations

Amp. – Ampule
BCC – Basal Cell Carcinoma
CBC – Complete Blood Count
FDA – Food and Drug Administration
GBCC – Giant Basal Cell Carcinoma
Gy – Gray
MDCT – Multidetector computed tomography
TB – Tuberculosis
TD – Total dose
UK – United Kingdom
WHO – World Health Organization

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Bazocelularni karcinom – prikaz slučaja

Sažetak

Bazocelularni karcinom je najčešći oblik karcinoma kože. U većini slučajeva je lokalno invazivan sa sporim rastom koji može da varira od nekoliko milimetara do nekoliko centimetara sa predominantnom lokalizacijom na fotoeksponiranim regijama. U retkim slučajevima, 0,5 – 1%, dimenzije bazocelularnog karcinoma mogu prevazići i 5 cm i tada se klasifikuje kao gigantski bazocelularni karcinom. Lezije ovakve veličine mogu dovesti do teškoća u izboru odgovarajućeg tretmana. Predstavljamo slučaj 74-godišnjeg muškarca sa gigantskim bazocelularnim karcinomom u predelu desnog ramena, dimenzija 14 cm x 17 cm koji se pojavio 2003. godine. Iako se lezija konstantno uvećavala, pacijent se do 2018. godine nije javio na pregled. Histopatološkim nalazom dijagnostikovan je bazocelularni karcinom – superficijalni, fokalno infiltrativni tip. Nakon toga je uvedena zračna terapija elektronima, sa 54 *Gyu* 20 dnevnih seansi što je dovelo do adekvatnog odgovora. Ovim prikazom želimo da naglasimo da kada su ispunjeni kriterijumi, radioterapija može biti efikasna terapija koliko i hirurgija kod gigantskog bazocelularnog karcinoma.

Ključne reči: Bazocelularni karcinom; Dijagnoza; Metastaze; Koža; Radioterapija; Biopsija; Ishod Terapije; Prikazi Slučajeva

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The Evolving Pattern Of Primary Skin Cancers in Ile-Ife, Nigeria

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Abstract

Background. The increasing solar intensity and HIV epidemic have progressively eroded the protective effects of melanin among black race. This study was aimed at evaluating the pattern of primary skin cancers in Ile-Ife, Nigeria. **Methods.** This retrospective study, which was conducted at the Obafemi Awolowo University Teaching Hospital, Ile-Ife, included the patients diagnosed with primary skin cancers between January 2008 and December 2017. The data were analyzed using SPSS version20. **Results.** The frequency of primary skin cancers was 1.0%. Females (58.3%) outnumbered the males (41.7%), the ratio being 1.4:1. The spectrum of primary skin cancers documented by this study are squamous cell carcinoma (33.3%), malignant melanoma (25%), Kaposi sarcoma (15.3%), basal cell carcinoma (9.7%), and cutaneous lymphoma (6.9%). **Conclusion.** Melanin remains a major protective factor for skin cancers among negroids. Albinism and high burden of HIV were identified risk groups for skin cancers. The eradication of HIV and enhanced sun protection will reduce the prevalence of skin cancers.

Key words: Skin Neoplasms; Nigeria; Carcinoma, Squamous Cell; Melanoma; Sarcoma, Kaposi; Carcinoma, Basal Cell, African Continental Ancestry Group; Prevalence

Introduction

Primary neoplastic changes affecting the cells of the epidermis and the dermis are common occurrences encountered in dermatologic practice. The sun is a major inducer of skin cancers such as squamous cell carcinoma, basal cell carcinomas and melanomas. Melanin provides protection from the damaging effect of solar radiation by absorbing these radiations and thus prevents the vulnerable cells of the epidermis from associated damage.

The black skin with larger quantities of melanin is much better protected from the harmful effect of solar radiation and has a reduced incidence of primary skin cancers as compared to the skin of Caucasians (1). This very important factor in the prevention of skin cancer is being progressively undermined by the increasing incidence of immunosuppression, higher burden of sexually transmitted disease (STD), and detrimental climate change (2-5) with attendant depletion of ozone layer.

The prevalence of skin cancers have previously been reported in some centres in Nigeria. A prevalence of 5.5% was reported in Osogbo, whereas a prevalence of 27% was reported in Benin (6, 7). While the incidence of skin cancers may still be higher in the Caucasians, an alteration in the ratio of the incidence as well as in the prevalence may require verification. The frequency of some specific types (subtypes) of skin cancer may also be influenced by some of these evolving mutagenic factors. It is important to document our local experience with the occurrence of primary skin cancer because it will provide reference data to compare with other regions and also direct planning by providing data for policy formulation, and hence the need to evaluate the pattern of primary skin cancers among the patients of African origin in Ile-Ife, South-Western Nigeria.

Material and Methods

The study was conducted among the patients of dermatology and the plastic surgery units of the Obafemi Awolowo University

Table 1. Demographic characteristics of patients with primary skin cancers

Skin cancers	Gender				Mean age	Standard deviation	Median age	Frequency N= 72		Skin type	
	M		F								
	Frequency	%	Frequency	%				Frequency	%	I	IV
Squamous cell carcinomas	7	29.2	17	70.8	39.3	15.7	36.5	24	33.3	8	16
Melanoma	7	38.9	11	61.1	63.6	15.7	67.5	18	25	–	18
Kaposi sarcoma	7	63.6	4	33.4	32.6	9.2	35	11	15.3	–	11
Basal cell carcinomas	2	28.6	5	71.4	55.1	18.9	52	7	9.7	4	3
Mycosis fungoides	4	80	1	20	59	10.2	53	5	6.9	–	5
Dermatofibroasarcoma	1	50	1	50	58	33.9	58	2	2.8	–	2
Neurofibrosarcoma	–	–	2	100	58	31.1	58	2	2.8	–	2
Mucoepitheliosarcoma	1	50	1	50	44.5	14.9	44.5	2	2.8	–	2
Trichoepitheliosarcoma	1	100	–		30	–	30	1	1.4	–	1

Teaching Hospitals Complex, Ile-Ife, South Western Nigeria.

The study sample patients were largely negroid with Fitzpatrick skin type VI and high level of skin melanin. However, a few patients with reduced/absent melanin (albinism), hence Fitzpatrick skin type I, were also seen. Ile-Ife is located on the longitude 7° 28' 0.001" N and the latitude 4° 34' 0.001" E and it receives a relatively high solar intensity throughout the year.

Design

The records of patients referred to the dermatology and venereology outpatient clinic and the out-patient clinic of the plastic surgery unit of the hospital were examined be-

Table 2. The pattern of skin cancers and associated risk groups in Ile-Ife

Skin cancers	RISK FACTORS						
	HIV N=72 (%)	Genital Wart N=72 (%)	Albinism N=72 (%)	Xeroderma Pigmentosum N= 72 (%)	Other N= 72 (%)	Chronic ulcer N=72 (%)	Total
Kaposi sarcoma	11 (15.3)	–	–	–	–	–	11 (15.3)
Mycosis fungoides	–	–	–	–	5 (6.9)	–	5 (6.9)
Melanoma	–	–	–	–	18 (25.0)	–	18 (25.0)
Basal cell carcinomas	–	–	4 (5.6)	–	3 (4.2)	–	7 (9.7)
Squamous cell carcinomas	1 (1.4)	4 (5.6)	8 (11.1)	1 (1.4)	7 (9.7)	3 (4.2)	24 (33.3)
Dermatofibrosarcoma	–	–	–	–	2 (2.8)	–	2 (2.8)
Neurofibrosarcoma	–	–	–	–	2 (2.8)	–	2 (2.8)
Mucoepitheliosarcoma	1 (1.4)	–	–	–	1 (1.4)	–	2 (2.8)
Trichoepitheliosarcoma	–	–	–	–	1 (1.4)	–	1 (1.4)
Total	13 (18.1)	4 (5.6)	12 (16.7)	1 (1.4)	39 (54.2)	3 (4.2)	72 (100)

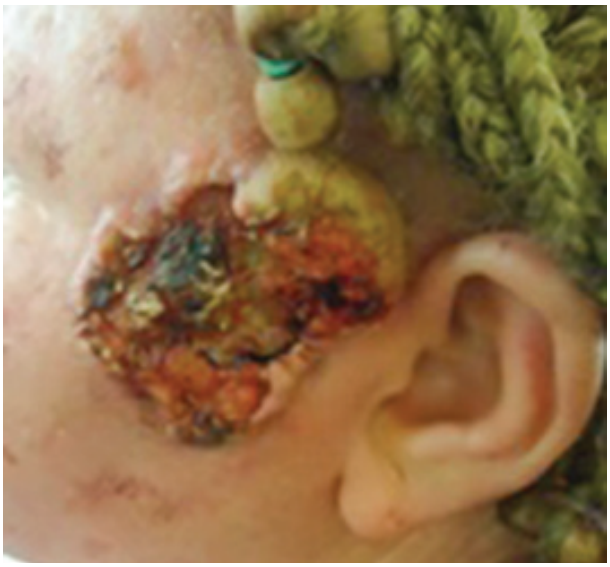

Figure 1. Basal cell carcinoma in an Albino

tween January 2008 and December 2017. All patients presenting with dermatological disorders over the period were noted and those diagnosed with primary skin cancers were recruited. Data such as age, sex, skin type, predisposing factor, occupation and family history of the disease, and laboratory and histological reports of cancers were assessed.

Exclusion: The patients diagnosed with secondary skin cancers or metastases were not considered as primary skin cancer. Data were analyzed using IBM/SPSS version 20, and the test of association and the level of significance were assessed using chi-square. Data were collectively processed with confidentiality strictly ensured.

Results

A total of 7,325 new patients with dermatological disorders were referred to the dermatology and plastic surgery clinic during the study period of 10 years spanning from January 2008 to December 2017. Among these, 72 cases of primary skin cancers were diagnosed, the frequency being 1% (72/7325%). The male/female ratio was 1:1.4 (Table 1). The mean age of patients presenting with primary skin cancers in this study was 48.32+/-19.16 years, while the median age was 44 years.

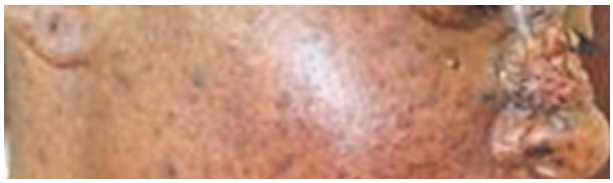

Figure 2. Xeroderma pigmentosum with squamous cell carcinoma

The distribution of different types of cancers observed in descending order of occurrence is shown in Table 2. Specific factors such as Albinism, HIV, Genital wart, Xeroderma pigmentosum, were found to have a significant correlation with primary skin cancers. (p-value=0.001) (Table 2). Kaposi sarcoma was exclusively associated with HIV while albinism was predominantly affected by Basal cell carcinoma and squamous cell carcinomas (Table 2).

Discussion

The Caucasians are at greater risk of getting skin cancer than the negroids. This reduces the index of suspicion and cause late presentation when cancer occurs in the black. In this study, skin cancer occurs at an average prevalence of 7.2/year and affects 1% of patients presenting with skin diseases. A study conducted among population with similar distribution of skin type in Benin and Osogbo reveals 27% and 5.5% of skin cancer, respectively. This higher prevalence may be due to the inclusion of biopsied cases only and therefore suggests the prevalence of skin cancer among skin biopsy specimen while excluding a large population of cases whose lesions were not biopsied. The most frequently observed primary skin cancer was squamous cell carcinoma, and it occurs at a frequency of 33.3% and at a mean age of 39.3 years This is however in contrast with the review of biopsy specimen at other Centre where melanoma was found to be most frequent (6, 7).

The direct effects of exposure to ultraviolent light, and ionizing radiation as well as exposure to other carcinogens may contribute to the enhanced propensity to develop skin cancers.

The near equatorial location of Ile-Ife and other communities served by the hospital gives a unique advantage of an angle of incidence of solar radiation with enhanced solar intensity. While this may be considered as an advantage for solar energy generation and in the production of renewable energy, it is det-

rimental to the health of the skin by inducing solar elastosis and ultimately skin cancers. Johnson et al have observed a doubling in the incidence of squamous cell carcinomas following every 10 degree reduction in the latitude thereby suggesting increased incidence of squamous cell carcinomas in the regions around the equator (8). Solar radiation (UVA & UVB) damage the DNA of the cell, and cancer develops when the inherent ability to clear the damaged cell by p53 enhanced apoptosis is overwhelmed (9, 10). The sun also has some immunosuppressive effect on the immunological functions of the skin.

This study has shown that primary skin cancers develop at increasingly younger age. The patients with squamous cell carcinoma present at a mean age of 39.3 years and median age of 36.5 years. This observation is consistent with previous reports that suggest that squamous cell carcinoma is becoming more prevalent after the 40 years age of among the Caucasian (11, 12).

The presence of basal cell carcinoma and squamous cell carcinomas among the albino population in the study suggests that the melanin still plays a significant role in protecting from skin cancer despite several other environment and genetic interplay in the black population. This observation aligns with low prevalence of skin cancers reported in the past among people with black skin (13, 14).

Basal cell carcinoma account for 9.7% of the observed skin cancers (Figure 1). The mean age of patients who got them was 55.1 years. Although the frequency was higher in the Caucasians, the mean age of patients when cancers developed in this study was consistent with that reported among the Caucasians in whom basal cell carcinoma have also been documented to be most prevalent between the age of 55 and 70 years (11, 12). This further reinforces the importance of high solar intensity and its effects among the albino population who are mostly affected by basal cell carcinoma, as shown by our study. Although malignant melanoma was reported as the commonest skin cancers in previous studies in our environment, it ranked second in this study where it accounted for 25% of the observed skin cancers. It occurs at a mean age of 63.6 years, and occurs more often in the lower limbs, which is similar to other studies.

Human activities and practices which cause increased out-door exposure to the sun, as well as environment alterations such as deforestation have progressively led to the increased solar intensity in the zone. The depletion of ozone layer also contributes to the increased intensity and exposure of the skin to ultraviolet C (UVC) radiations thereby increasing the prevalence of observed skin cancers.

The prevalence of Kaposi sarcoma increased with the onset of HIV epidemic, and was the third commonest skin cancer observed in the study. Its occurrence in the patients whose mean age is 32.6 years reflects its association with HIV which is common among young and middle aged adults. The characteristic association of some of these cancers with genital wart suggests the possible role of the oncogenic sexually transmitted infections such as human papilloma virus (HPV). HPV can independently cause cancers even in immunocompetent host; however, their propensity to cause cancers in the presence of diminished immunity is greatly enhanced.

Xeroderma pigmentosum (XP) is a disorder arising from heritable defects in the ability of the cells to repair damaged DNA. It is a rare disorder and occurs at a prevalence of 1/250,000. While XP increases the risk of skin cancers by a factor of 2000 in individuals below twenty years of age, and overall lifetime prevalence of 57%, it did not significantly impact the prevalence of skin cancers observed in this study due to the rarity of XP (15). The only case of xeroderma pigmentosum (1.4%) observed in our study was associated with squamous cell carcinoma (Figure 2).

The population under review includes the patients with albinism who are deprived of the protection that is characteristically conferred on the negroid skin by melanin. Albinos have reduced or absent melanin due to a genetic defect with the associated impairment in the synthesis and transport of melanin (16). These patients are at an increased risk of acquiring skin cancers, which is similar to their Caucasian counterparts with similar Fitzpatrick skin type. As shown in this study, 16.7% of the observed primary skin cancers were among patients with albinisms.

Conclusion and Recommendation

The large melanin content found in the black skin offers prominent protection from primary skin cancers. This study affirms the importance of melanin in preventing primary skin cancers despite the increasing intensity of ultraviolet radiations in the region. The high prevalence of HIV and albinism were factors identified with increased incidence of primary skin cancers among the black skin population. While sun avoidance and use of sun screens remain the major preventive approach to skin cancers, the prevention of HIV transmission and coordinated effort aimed at reducing the prevalence of HIV as well as availability of HAART may be an additional effort efficient in reducing the prevalence of primary skin cancers.

Limitations

Although the determination of risk factors has not been included in the objective of this study, a cohort or case control study will be required to determine risk factors of primary skin cancers.

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Primarni kanceri kože u Ile-Ilfeu, Nigerija

Sažetak

Uvod. Povećani intenzitet sunčevog zračenja i epidemija HIV-a neprestano uništavaju zaštitne efekte melanina kod ljudi crne rase. Cilj ove studije bio je da proceni obrazac primarnih kancera kože u Ile-Ilfeu, Nigerija. **Metode.** Ova retrospektivna studija, koja je izvedena u *Obafemi Awolowo* univerzitetskoj bolnici, u Ile-Ilfeu, obuhvatila je pacijente sa dijagnozom primarnih kancera kože između januara 2008. i decembra 2017. godine. Za analizu podataka korišćena je SPSS verzija 20. **Rezultati.** Učestalost primarnih kancera kože bila je 1%. Bilo je više ženskih (58,3%) nego muških pacijenata (41,7%), a odnos je bio 1,4 : 1. Spektar primarnih kancera kože dokazanih ovom studijom su skvamocelularni karcinom (33,3%), maligni melanom (25%),

Kapošijev sarkom (15,3), bazocelularni karcinom (9,7%) i kutani limfom (6,9). **Zaključak.** Melanin je i dalje osnovni zaštitni faktor od kancera kože kod ljudi crne rase. Albinizam i HIV identifikovani su kao nosioci rizika za kancere kože. Iskorenjivanje HIV-a i povećana zaštita protiv sunca smanjiće prevalenciju kancera kože.

Ključne reči: Kožne neoplazme; Nigerija; Karcinom skvamoznih ćelija; Melanom; Kapoši sarkom; Bazocelularni karcinom; Narodi Negroidne grupe afričkog porekla; Prevalencija

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Genotyping of Mycobacterium leprae in a Son-and-Father Pair of Patients Indicated the Possible Mode of Leprosy Transmission: a Case Report

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Abstract

One of the success indicators of the World Health Organization (WHO) leprosy eradication program is the decreasing number of new cases of pediatric leprosy with a grade 2 disability. A case of borderline lepromatous (BL) leprosy with partial claw hand in a 13-year-old boy was reported. On physical examination, we found claw fingers on the fourth and fifth fingers of the left hand accompanied by hypoesthetic erythematous plaques on both cheeks. The patient also presented with the enlargement of bilateral great auricular, ulnar, and peroneal nerves. The bacteriological examination showed the bacterial index 3+ and morphological index 35%. The results of histopathological and serological anti-phenolic glycolipid-I examinations supported the diagnosis of BL type of leprosy. Genotyping of *Mycobacterium leprae* by variable number tandem repeat of the patient showed 24 copies thymine-thymine-cytosine that were similar to his father, who had been diagnosed with leprosy 12 years before, without adequate therapy. The result indicated the possibility of leprosy transmission from the father to a son. This case report revealed the presence of leprosy in children with a multibacillary infection who have been living with leprosy family members. Genotyping seems to be feasible for epidemiological analysis of leprosy transmission.

Key words: Leprosy + transmission; Mycobacterium leprae; Leprosy, Borderline; Genotyping Techniques; Case Reports

Introduction

Leprosy is one of the health problems in developing countries (1) including Indonesia (2). The incidence rate of leprosy in children can be an indicator of the prevalence of leprosy in the general population (3), and related to the presence of an active source of transmission (4). Leprosy in children is still common, especially in greater endemic countries (5). The risk of leprosy transmission is increased from five to ten times if one family member has leprosy, particularly if it is lepromatous leprosy (LL) type (6). The proportion of leprosy incidence in children varies in every country, ranging from 0.6% in Argentina (6), 10.3% in Sri Lanka (7), 11% in the Philippines (5), to 32% in Africa (6). Based on the data from the Ministry of Health of Indonesia in 2014, out of 16,131 new cases of leprosy in Indonesia, 1,755 cases (10.88%) were diagnosed in children aged 0-14 years and 1,525 cases (9.45%) were with disability grade 2 (8).

Genotyping of *Mycobacterium leprae* (*M. leprae*) can be used to recognize whether the patients have been infected with the same strain, therefore being suggestive of belonging to the same transmission mode (9). This case report was aimed at providing an example of leprosy case in children with a grade 2 disability whose father was suspected as the source of transmission, through genotyping of *M. leprae* by variable number tandem repeat (VNTR).

Case Report

A 13 year-old-boy presented with weakness on the fourth and fifth fingers of the left hand, accompanied by skin lesions on the

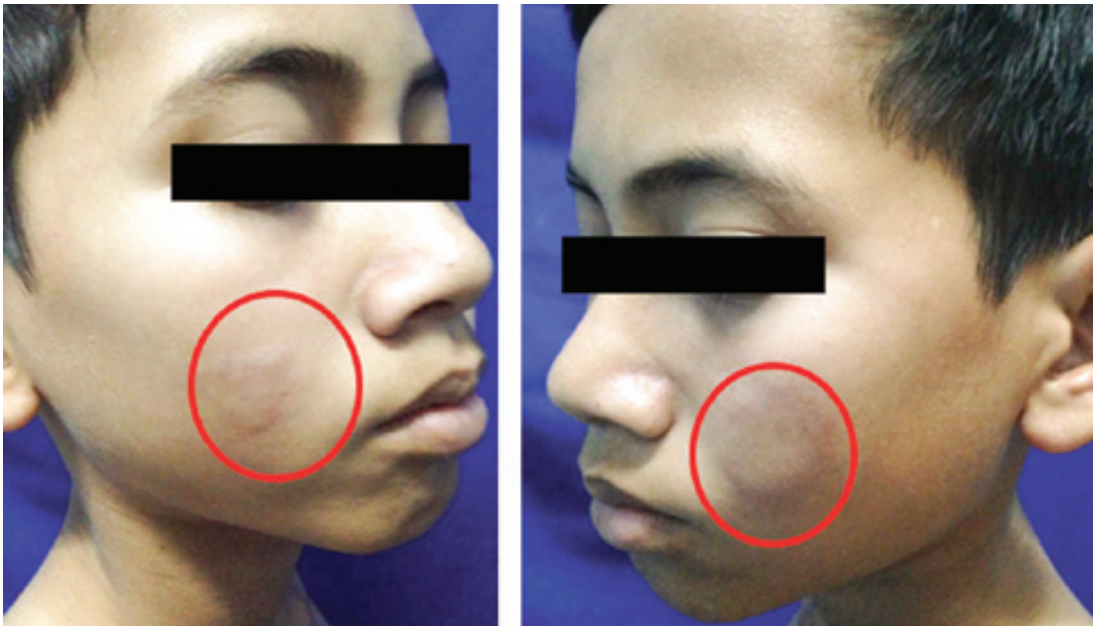

Figure 1. Hypoesthetic erythematous plaques

cheek. Four years prior to consultation, he often felt tingling in his left hand. Six months afterwards, the fourth and fifth fingers of the patient's left hand became weak. One year later, redness on both cheeks developed in nummular-size. He had never received any treatment before. Physical examination showed clawing on the fourth and fifth fingers of the left hand, accompanied by hypoesthetic erythematous plaques on the cheek and thickening of both ulnar, great auricular, and common peroneal nerves. Bacteriological examination revealed bacterial index (BI) 3+ and morphological index (MI) 35%. Histopathological examination of the erythematous plaque showed granuloma consisting of lymphocytes, epithelioid cells, and foamy macrophages. Serological examination revealed 1.017 u/mL anti-phenolic glycolipid-I (anti-PGL-I) immunoglobulin (Ig) M and 1.052 u/mL anti-PGL-I IgG. Genotyping of *M. leprae* by VNTR of the patient showed 24 copies thymine-thymine-cytosine (TTC) that were similar to his father, who had been diagnosed to have leprosy 12 years before. Initially, the patient's father developed anesthetic hypopigmented macules on his chest, back, and both upper arms, associated with hypoesthetic soles. He also noted the thickening of both pinna, hence he consulted our hospital

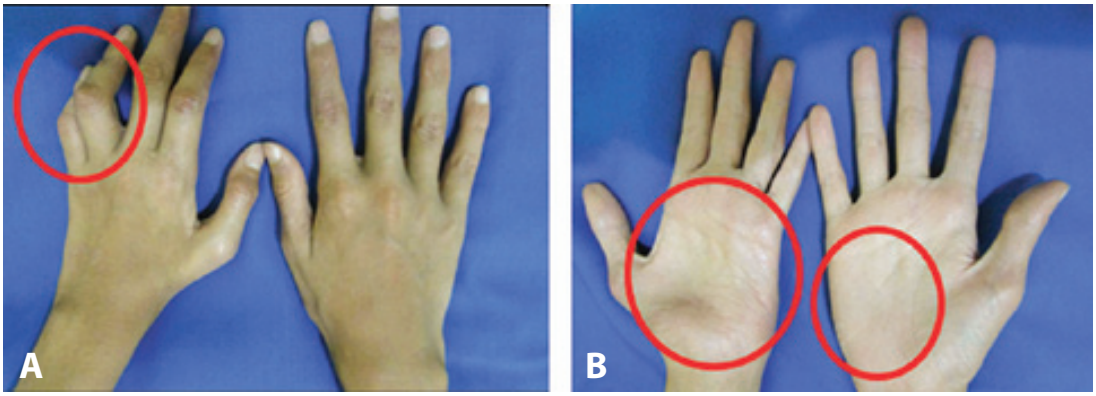

Figure 2. (A) Clawing of 4th and 5th fingers on the left hand Thenar and hypothenar atrophy on the left hand (**B)** Hypothenar atrophy on the right hand

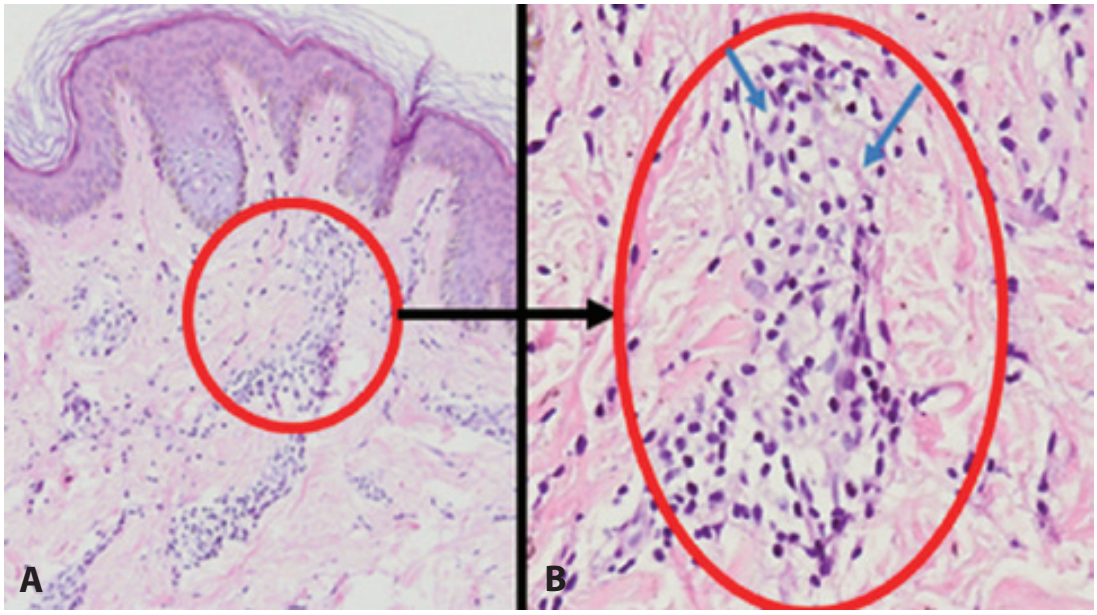

Figure 3. The pathologic features are **(A)** epidermal, dermal, massive infiltration of neutrophils and **(B)** foamy macrophages (hematoxylin-eosin(HE), original magnification 200x)

and was diagnosed to have leprosy. The patient's father received multidrug therapy (MDT) but he consumed the drug for only three months of therapy and did not collect the treatment regularly, then he became a defaulter leprosy patient. The recent serological examination of the patient's father was 101,000 u/mL for anti-PGL-I IgM and 448 u/mL for anti-PGL-I IgG. Histopathological examination from clinically normal appearing skin on his right knee showed granuloma consisting of foam cells and some lymphocyte that supported the diagnosis of LL type.

The patient was diagnosed as borderline lepromatous (BL) leprosy with grade 2 disability, then received MDT for multibacillary (MB) WHO therapy and home physiotherapy program for range of movement of four extremities and fingers exercise to prevent further deformities.

Discussion

Leprosy is an infectious disease caused by *M. leprae* with a long incubation period (7), therefore this disease usually occurs in adults. However, children are also susceptible to leprosy (3). The leprosy rate in children is an important epidemiological indicator in determining the transmission rate of leprosy in one area (3, 4). The mean age of children with leprosy is generally between 10-14 years. Based on several studies, the incidence ratio of boy and girl with leprosy is 2:1 (3). One of the indicators of success of eradication program of leprosy according to the WHO is the decreasing number of new leprosy cases in children with disability (2). One study performed by Liangbin, *et al*.(10) in China (2011) showed that 80% of 165 leprosy patients in children aged between 7 and 11 years have family members suffering from leprosy and 13.3% of these patients develop grade 2 disability. Imbiriba et al. (11) included 474 leprosy patients aged 0-14 years in their study in Manaus, North Brazil.

Leprosy spreads through airborne transmission (6, 12) and direct skin contact (2). The risk of leprosy transmission increases five to ten times if one family member has leprosy (6). Clinical features of leprosy in children are not as clear as in adults (3). Sensory function tests are also difficult to assess and bacteriological examination is generally negative. Histopathological examination may help the diagnosis of leprosy in children (3). Various studies have shown that leprosy in children occurs more often in tuberculoid type than in lepromatous type (3, 6).

In this case, leprosy with grade 2 disability was found in a 13-year-old boy, whose father had been diagnosed to have leprosy 12

years before. In this patient, there were only two skin lesions of hypoesthetic erythematous plaques in both cheeks, accompanied by symmetrical nerves enlargement. Bacteriological, serological, and histopathological examinations supported the diagnosis of BL leprosy.

The genotyping examination of *M. leprae* was performed to identify strains and sources of transmission of *M. leprae* (13). In this patient, genotyping of *M. leprae* showed VNTR counts of 24 copies TTC. The source of the patient's leprosy is thought to have originated from his father who had been diagnosed to have leprosy 12 years before with no adequate therapy. This can be seen from the results of the genotyping of *M. leprae* in the patient's father which showed the VNTR number of 24 copies TTC that were similar to the patient.

Genome sequence from an isolate of *M. leprae* is now available for strain typing to identify the transmission chains using leprosy multiple-locus VNRT analysis (14). VNRT pattern was related to those found in some multicase families which were detected in patients in the same regions, indicating the utility of VNRT strain typing to identify and detect transmission (15). One study of *M. leprae* genotyping using VNRT analysis by Weng et al (15). in China showed that out of eleven families, six families had the similar *M. leprae* VNRT profiles. The other study performed by Masuoka et al. (13) in North Sulawesi revealed that out of five families whose members had leprosy, three families showed identical TTC genotypes, while the other two families had different TTC genotype between a father, his son, and among brothers. The inconsistency of the genotypes *M. leprae* isolated in the family members living in the same household indicates that leprosy patients are not always a source of infection for other family members (13). In this case, the result of *M. leprae* VNRT genotyping revealed a similar result from the patient and his father, therefore indicating that leprosy was transmitted to him from his father.

Conclusion

The new cases of leprosy in children with grade 2 disability are still detected and it is suspected that a family member may be the source of transmission. Genotyping of *M. leprae* seems to be feasible for epidemiological analysis of leprosy transmission.

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Genotipizacija *Mycobacterium leprae* kod sina i oca ukazuju na mogući način prenošenja lepre: prikaz slučaja

Sažetak

Jedan od pokazatelja uspešnosti programa Svetske zdravstvene organizacije za iskorenjivanje lepre je smanjeni broj novih slučajeva lepre kod dece sa drugim stepenom invaliditeta. Prikazan je slučaj granične lepromatozne lepre sa delimično kandžastom šakom (*claw hand*) kod trinaestogodišnjeg dečaka. Pregledom smo ustanovili kandžaste prste na četvrtom i petom prstu leve šake zajedno sa hipoestetskim eritematoznim plakom na oba obraza. Pacijent je takođe imao i uvećane bilateralne velike aurikularne, ulnarne i peronealne nerve. Bakteriološki pregled je pokazao da je bakterijski indeks 3+ a morfološki indeks 35%. Rezultati histopatološkog i serološkog antifenolnog glikolipidnog-I pregleda podržali su dijagnozu granične lepromatozne vrste lepre. Genotipizacija *Mycobacterium leprae* različitog broja tandemskih ponavljanja kod pacijenta pokazala je 24 primerka timin-timin-citozin kao kod njegovog oca, kod kog je lepra dijagnostikovana pre 12 godina ali je bio bez adekvatne terapije. Rezultat ukazuje na mogućnost prenošenja lepre sa oca na sina. Ovaj prikaz slučaja otkriva prisustvo lepre kod dece sa multibakterijskom infekcijom koja žive sa leproznim članovima porodice. Čini se da je genotipizacija izvodljiva za epidemiološke analize prenošenja lepre.

Ključne reči: Lepra + prenošenje; Mycobacterium leprae; Granična lepra; Genotipske metode; Prikazi slučajeva

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DERMOSCOPY OF THE MONTH
Azithromycin-Induced Longitudinal Melanonychia in a Child-a Case Report

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Abstract

Melanonychia refers to a brown or black coloration of the nail plate caused by numerous factors. Regarding the arrangement of pigmentation, we can differentiate between total melanonychia, when pigmentation involves the whole nail plate, or transverse or longitudinal melanonychia, when pigmentation involves the nail in a form of transverse or longitudinal band of pigmentation, respectively. Since longitudinal melanonychia can be a sign of numerous benign and malignant lesions, it often poses a diagnostic challenge for a dermatologist. Herein, we report a case of a 13-year-old girl who developed longitudinal melanonychia on multiple nails after receiving a therapy with azithromycin.

Key words: Azithromycin; Nail Diseases; Melanoma; Dermoscopy; Hyperpigmentation; Pigmentation Disorders; Adolescent

Introduction

Melanonychia refers to a brown or black coloration of the nail plate caused by numerous factors as a result of activation or proliferation of nail melanocytes as well as of direct production of melanin by pathogens (1-3). Regarding the arrangement of pigmentation, we can differentiate between total melanonychia, when pigmentation involves the whole nail plate, or transverse or longitudinal melanonychia, when pigmentation involves the nail in a form of transverse or longitudinal band of pigmentation, respectively (1, 2). The vast majority of melanonychia belongs to longitudinal melanonychia, while other two forms are reported occasionally (1-3).

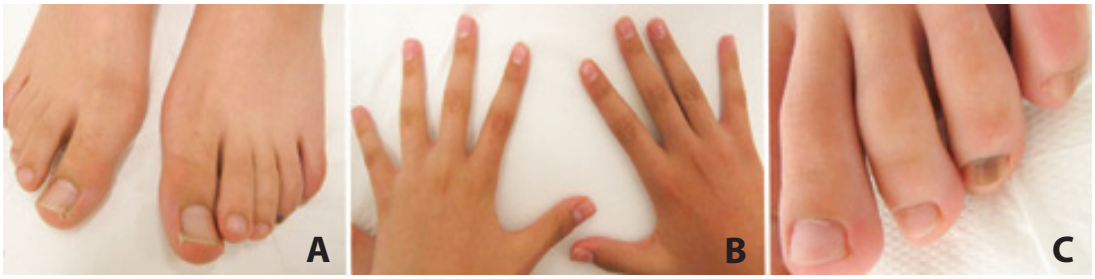

Figure 1. Pigmentation on the fourth right toenail and the fourth and the fifth left toenail without affecting the fingernails (A, B, C)

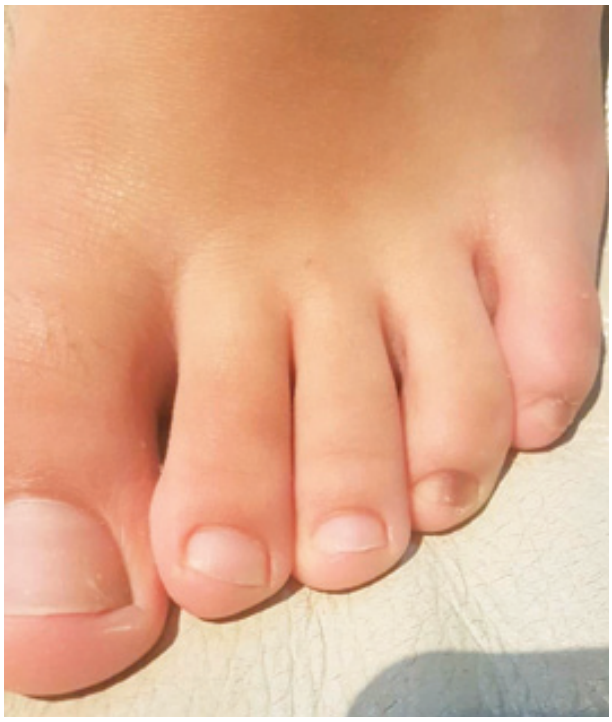

Figure 3. Partial regression of pigmentation after one-year follow-up

Longitudinal melanonychia, also known as melanonychia striata, is clinically manifested as a longitudinal streak of tan, brown or black pigmentation extending from the ma matrix along to the tip of the nail plate (1, 2). Depending on the number of nails involved, it can be presented in a form of single or multiple longitudinal melanonychia (1, 2).

The reported prevalence in white population is 1.4%, whereas it is reported more often in darkly pigmented population, with the prevalence ranging from 77% in African Americans in their twenties to approximately 100% in individuals older than 50 (4).

Longitudinal melanonychia can be a sign of numerous benign lesions including nail matrix melanocytic nevus, lentigo, drug-induced pigmentation, ethnic related pigmentation, trauma induced pigmentation, as well as subungual hemorrhages (1, 3). However, the possibility of subungual melanoma, although rare, should be considered.

Regarding the long list of differential diagnoses, the presence of longitudinal melanonychia in patients often poses a diagnostic challenge for a dermatologist. In addition, the fact that longitudinal melanonychia can be an early sign of subungual melanoma which carries a poor prognosis, the diagnostic evaluation in the patients with those lesions should be crucial.

Herein, we report a pediatric patient who developed longitudinal melanonychia after receiving a therapy with azithromycin.

Case Report

A 13-year-old girl was referred to our Department for an evaluation of the nail pigmentation. Her personal history was uneventful. Also, there were no reported malignancies in personal or family history. Four weeks prior to the onset of the nail pigmentation, the patient was on therapy with azithromycin due to otitis media. Apart from azithromycin, she did not report use of any other medication in the recent past.

Clinical examination revealed some brown colored streaks along the nail plate on the fourth right toenail and the fourth and fifth left toenail (Figure 1 A, B, C). Hyperpigmentation was not observed on other nails, skin, mucous membranes, or sclerae. Dermoscopic examination showed a repetitive pattern of tan to brown regular longitudinal lines on the brown background extending from the proximal fold to the tip of the nails on fingers, which was visible through the cuticle (Figure 2 A,B). A routine hematological and biochemical examination was done along with the hormonal status (ACTH, T3, T4, TSH, and Cortisol), which did not reveal any abnormalities. The diagnosis of longitudinal melanonychia triggered by azithromycin was favored based on the history, clinical and dermoscopic findings.

We decided to do a regular follow-up every 6 months. After the one-year follow-up, the nail pigmentation partially disappeared (Figure 3).

Discussion

In pediatrics, the occurrence of longitudinal melanonychia is less commonly observed when compared to the elderly population. Furthermore, the underlying causes of this pigmentation significantly differ from the causes frequently reported in elderly patients (5, 6). Benign melanocytic nevi, lentigines, and melanocyte activation due to various causes are most commonly reported in etiol-

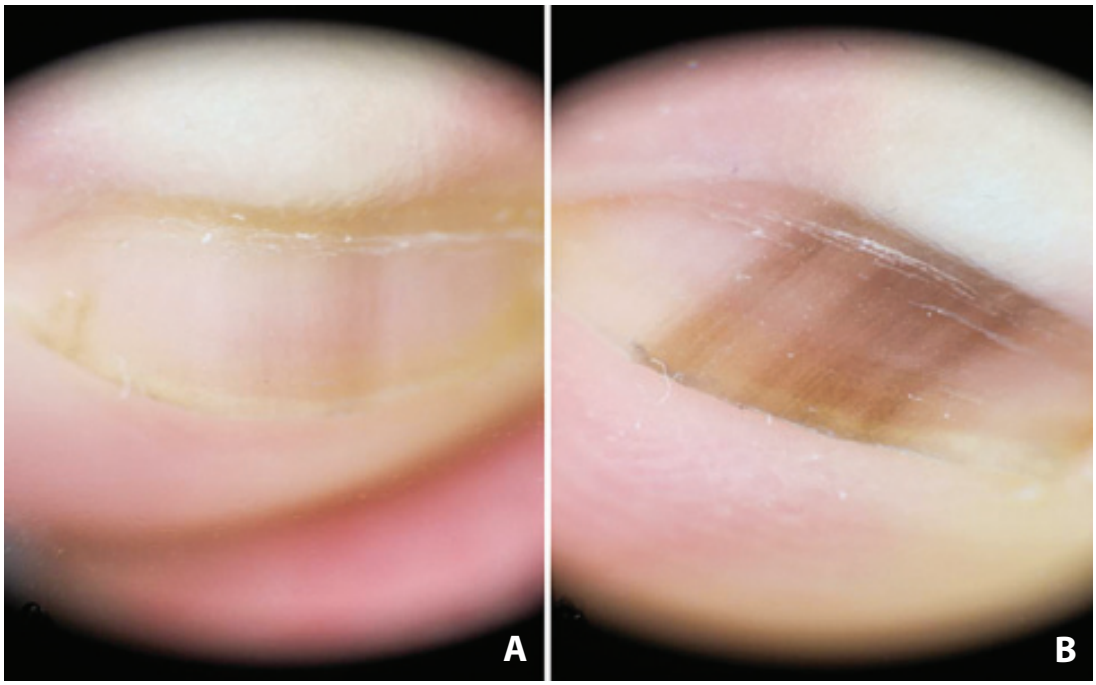

Figure 2. Regular tan to brown longitudinal lines on brown background observed by dermoscopy (A, B)

ogy of longitudinal melanonychia in childhood, whereas the presence of invasive subungual melanoma has not been reported in literature as far as we know, except for few cases of subungual melanoma in situ (5-7). However, approximately 6% of lesions presented as longitudinal melanonychia are melanomas in adult population (8). This implicates different clinical approach in the assessment of pigmented nail lesions between these two populations.

In most cases, the diagnostic assessment of nail pigmentation includes detailed personal history, clinical and dermoscopic examination (3). On the clinical ground, the onset during adulthood, monodactylic presentation, nail plate dystrophy, as well as rapidly evolving pigmentation with exclusion of other causes, should raise a clinical suspicion of subungual melanoma (1-3).

Proximal or lateral periungual skin involvement, also known as Hutchinson's sign, is highly related to subungual melanoma (3,9). However, it is not pathognomonic since it can be also found in nail melanocytic nevi (10). Moreover, hyperpigmentation that extends beneath the cuticle, without involving either cuticle or proximal nail fold, can simulate Hutchinson's sign. This is explained as a reflection of pigmentation due to the transparency of the cuticle and it is known as pseudo-Hutchinson's sign (1, 10, 11).

Dermoscopy has proven its efficiency in the diagnosis of melanocytic and non-melanocytic lesions. Dermoscopy also plays an important role in the evaluation of nail apparatus pigmentation since very subtle pigmentations not even visible to the naked eye can be observed. The term "micro" Hutchinson's sign is used for the pigmentation of cuticle only observed through dermoscopy and not clinically, and it is highly suggestive of subungual melanoma (11). In addition, irregularity of lines in color, thickness, and spacing should raise a suspicion of subungual melanoma. In this case, the longitudinal lines were regularly spaced out in parallel patterns in all involved nails (9, 11).

Drug-induced melanonychia most often occurs on several nail units, usually with multiple brown to black transverse or longitudinal streaks (1-3, 12). Interestingly, in the category of transverse melanonychia, drug-induced melanonychia accounts for the majority of the cases (3). Most commonly, chemotherapeutic drugs have been incriminated as the principal

cause, but other drugs including antiretrovirals, antimalarials and antibiotics are also known to have been the cause. Among the antibiotics, tetracyclines and sulfonamide are most often observed as drugs that cause this condition. After the cessation of therapy, the pigmentation disappears partially or completely in most cases (1-3). However, the process may take longer, as it was observed in this case.

Since other causes were excluded by performing the detailed clinical examination, insignificance in past medical and drug histories, the underlying cause of longitudinal melanonychia in this case was in favor of azithromycin therapy. To our knowledge, this is the first drug-induced longitudinal melanonychia related to azithromycin. In conclusion, clinical and dermoscopic examination of all nails, along with the detailed medial and drug history of the patient, provides sufficient information for the clinician when dealing with longitudinal melanonychia.

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Longitudinalna melanonihija izazvana azitromicinom kod deteta – prikaz slučaja

Sažetak

Melanonihija predstavlja braon ili crnu prebojenost nokatnih ploča uzrokovanu brojnim faktorima. U odnosu na raspored pigmentacije, možemo razlikovati totalnu melanonihiju, kada pigmentacija zahvata čitavu nokatnu ploču, ili longitudinalnu i transferzalnu melanonihiju, kada je pigmentacija prisutna u vidu uzdužne ili poprečne pigmentne trake. Zato što uzdužna melanonihija može biti znak brojnih benignih i malignih promena, ona često predstavlja dijagnostički izazov dermatolozima. Prikazujemo trinaestogodišnju pacijenkinju kojoj se pojavila uzdužna melanonihija na više nokatnih ploča, a nakon terapije azitromicinom.

Ključne reči: Azitromicin; Bolesti noktiju; Melanom; Dermoskopija; Hiperpigmentacija; Poremećaji pigmentacije; Adolescenti

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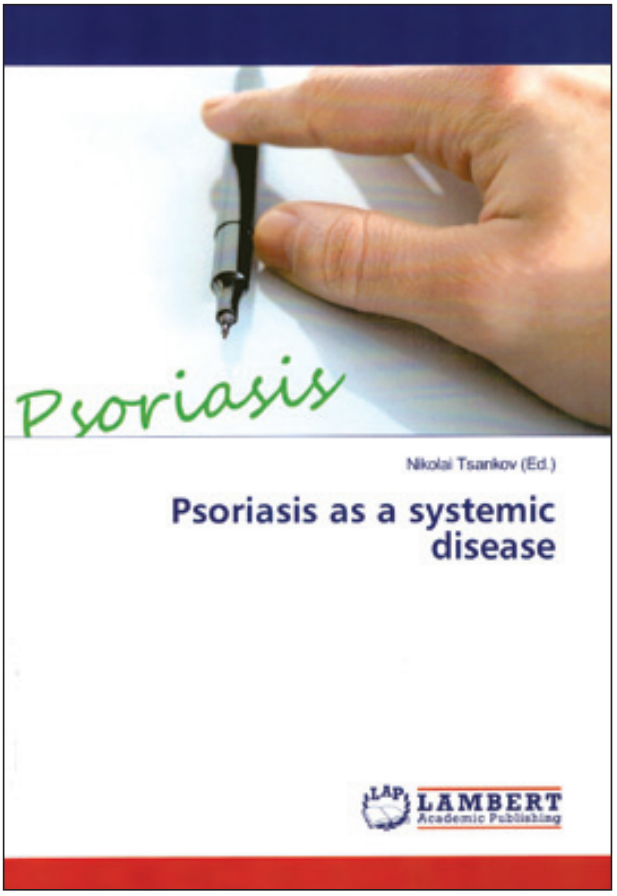
Psoriasis as a Systemic Disease by Professor Nikolai Tsankov, Editor



Professor Nikolai Tsankov is a well-known dermatologist from Bulgaria and he is also an honorary member of the Serbian Association of Dermatovenereologists. We were very happy and honored when Professor Tsankov asked us for the review of his book to be published in the Serbian Journal of Dermatology and Venereology.

The book has 192 pages, without the Introduction, Content, and Epilogue and it is divided into 3 main chapters: Psoriasis – General information, Psoriasis – Systemic disease and Treatment of psoriasis. References are listed at the end of each chapter. The book contains 9 tables and 3 schemes.

In the first chapter, Psoriasis – General information, the author describes the current knowledge about the epidemiology and heredity of psoriasis, pathogenesis of psoriasis, triggers for psoriasis, and its histology and clinical forms as well as psoriasis in childhood and pregnancy.

The second chapter, Psoriasis – Systemic disease, reviews special clinical situations and individual groups of patients requiring specific and/or modified treatment options. This chapter also describes psoriatic arthritis, quality of life in patients with psoriasis, psoriasis in dialysis patients and patients with renal transplantation, and relationship of psoriasis with obesity, atherosclerosis, metabolic syndrome, Crohn's disease, neoplastic diseases, stress and depression.

The third chapter, Treatment of psoriasis, reviews modalities for biologic therapy of psoriasis and it also dedicates space to the role of rifampicin and climatotherapy in the treatment of psoriasis.

In summary, this book gives an overview of psoriasis, its comorbidities and therapeutic options. It can be very useful to all dermatologists, especially those who are interested in the treatment of psoriasis.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2018

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
12-16 September, 2018	27th EADV Congress, Paris France	13 March, 2018	www.eadvparis2018.org
05-06 October, 2018	Pediatric Dermatology, Specialist Course, Lausanne, Switzerland	13 March, 2018	www.eadv.org
4-6 October, 2018	ESTRO School, Multidisciplinary management of non- melanoma skin cancer, Brussels, Belgium		www.estro.org
11-13 October, 2018	22ndBDD, Belgrade, Serbia	1 June, 2018	www.udvs. org
29-30 October, 2018	6th International Conference on HIV/AIDS, STDs and STIs, San Francisco, USA		www.hiv-aids-std.conferenceseries.com
6-9 November, 2018	14th Congress of the EADO, Barcelona, Spain	10 September, 2018	www.congresseado-melanomacenters2018.com
9-11 November, 2018	EADV Course- Skin Cancer, Trieste, Italy		www.eadv.org
14-17 November, 2018	CILAD 2018, Sao Paulo, Brazil	10 September, 2018	www.cilad2018.com
5-6 December, 2018	GA2LEN Global Urticaria Forum (GUF 2018), Berlin, Germany	10 September, 2018	www.globalurticariaforum.org

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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.

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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

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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:

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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;

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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 sho uld avoid using abbreviations.

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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/.

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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.

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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.

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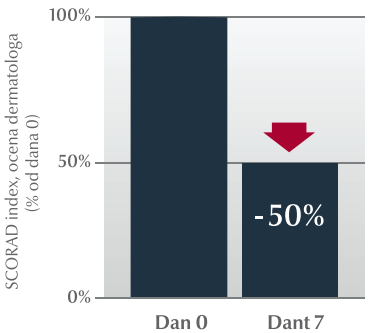

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