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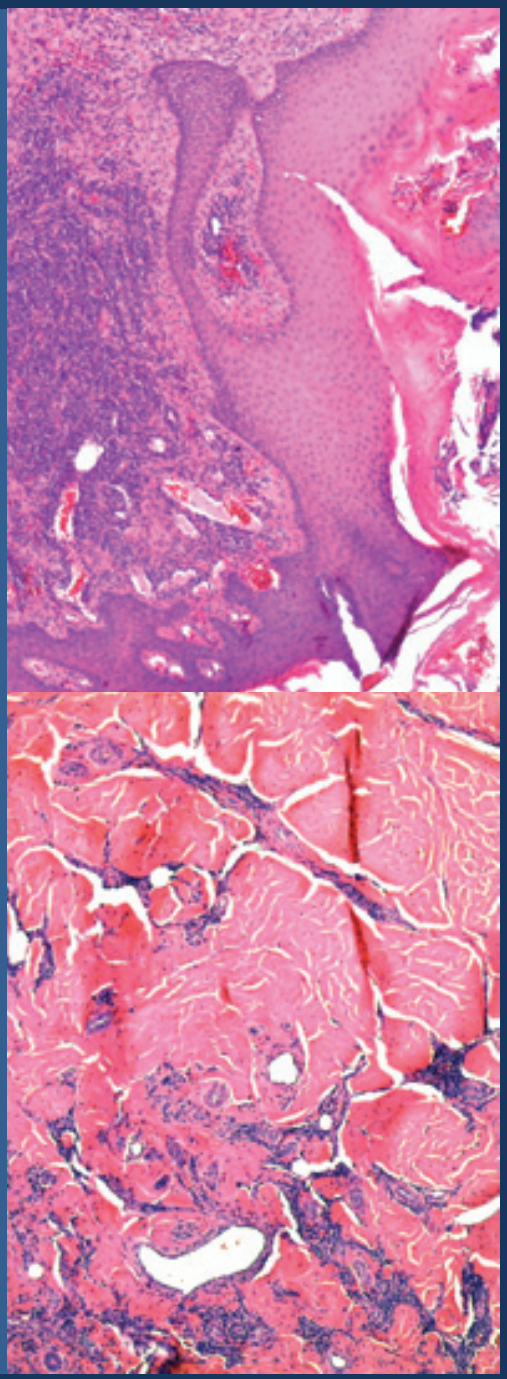

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Glucocorticoids in Leprosy Reversal reaction

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Abstract

Leprosy is a disease that is caused by *Mycobacterium leprae* which results in lots of disabilities in the patients. Leprosy is treated by multi-drug therapy regimen; however, this therapy might cause leprosy reactions in the patients. There are several types of lepromatous reaction: type 1 reaction, type 2 reaction and neuritis. Type 1 reaction mainly occurs in BB, BL and BT forms of leprosy and is characterized by exacerbation of preexisting lesions. The therapy of this reaction according to the WHO guideline is corticosteroid therapy. This article will explain several key points related to the corticosteroid therapy in leprosy reversal reactions, including the side effects and alternative therapies available.

Key words: Leprosy; Gene Expression Profiling; Glucocorticoids; Comorbidity; Diagnosis; Prednisolone; Indonesia

Introduction

Leprosy is a disease that has already existed for a long time and remains a significant health burden in a lot of nations worldwide up to this day. Leprosy, which is caused by *Mycobacterium leprae,* can affect peripheral nerve systems and cause disability. The initial symptoms of leprosy are hypopigmented patches with hypoesthesia or anesthesia. However, these symptoms are often ignored by the patients, hence patients often present with more severe symptoms of leprosy, mainly nerve damage symptoms (numbness and weakness of the limbs). According to the WHO, the diagnosis of leprosy can be made if one of the following cardinal signs are met: (i) the presence of hypopigmented macules or erythematous macules with loss of sensorium sensation in the affected area, (ii) thickening or enlargement of peripheral nerves, (iii) discovery of acid-resistant bacteria on the *slit-skin smear* preparation (1).

Immunological reactions in leprosy are often found during treatment or after the completion of *multi-drug therapy* (MDT). There are two major types of lepromatous reactions: Type 1 (reversal) reaction, and Type 2 (ENL) reaction (2). Type 1 reaction mainly occurs in non-polar forms of leprosy (BB, BT, and BL forms); however, it could sometimes happen in a subset of LL patients that received MDT regimen (3). Forms of leprosy reactions that could possibly happen in each type of leprosy are described in **Table 1**. Type 1 reactions, also known as reversal reactions, are delayed-type (type IV) immunological reactions which have become the major cause of persistent disability. Type I reactions are more prevalent than Type II reactions in the patients receiving multi-drug therapy regimen (4).

Most of the cases of reversal reaction are diagnosed at the same time with leprosy itself or during the first two years of receiving MDT therapy; however, the highest incidence of

Table 1. Leprosy reactions that could possibly happen in each of the leprosy clinical forms (Adopted from Nery J, et al)[3]

Pausibacillary Patients	Multibacillary Patients			
TT	BT	BB	BL	LL
(–)	Type 1 (RR)	Type 1 (RR)	Type 2 (ENL) Type 1 (RR)	Type 2 (ENL)

reversal reactions themselves happens during the 6th month up to the 12th month after MDT therapy is started, and then gradually declines (2, 5). Patients having "borderline tuberculoid" form of leprosy have shorter interval from the introduction of therapy to the development of reversal reactions, usually as short as 3-9 months. "Borderline lepromatous" patients have longer intervals (15 months), and the interval is even longer in "lepromatoid lepromatous" patients (up to two years). Reversal reactions usually recur less than ENL reactions (3). Recurrences of reversal reactions happen in about 31.8% of patients (6).

Some of the conditions that might increase the risk of reversal reactions are vaccination, chemotherapy, and puerperium. These conditions might increase the risk of reversal reactions due to the underlying changes such as improvement in cell immunity after pregnancy, intercurrent infections, stress, trauma, and oral contraceptive administration (3). Another study in Nepal found that seropositivity to anti-phenolic glycolipid-I, positive bacterial index, and a disease in more than two body areas were also identified as risk factors for type 1 reaction (7). The development of cutaneous type 1 reaction has a significant correlation with facial patches, and the development of neural type 1 reaction has a significant correlation with enlarged ulnar nerves. The presence of IgM anti-PGL-1 antibodies is one of the independent risk factors in the development of type 1 reactions. PGL-1 itself is a product of viable *Mycobacterium leprae* (7). Coinfections with viruses and bacteria might also increase the risk of type 1 reactions in lepromatous patients; and leprosy patients could also have immunological characteristics that would impair the clearance of certain type of viruses, most notably hepatitis B virus (HBV) and hepatitis C virus (HCV) (8).

Type 1 reactions result from the activation of cellular immunity against antigens of *Mycobacterium leprae* (3). Clinically, the expression of this reaction is exacerbation of skin and nerve trunk inflammation, which results in motor and sensory alterations. This reaction is different from Type 2 reactions, where there

Table 2. Differences in type 1 and type 2 reactions in leprosy

	Reversal reaction (Type 1)	ENL (Type 2)
Leprosy category	Borderline (borderline tuberculoid, borderline borderline, borderline lepromatous)	Lepromatous leprosy, borderline lepromatous
Skin lesion	Transformation of the existing lesion into an edematous and reddish lesion Distribution: similar to the existing lesion site	Newly formed erythematous dermal or subcutaneous modules Painful Distribution: upper and lower extremities, face, back, abdomen
Signs and symptoms	Edema on upper and lower extremities Neuritis: painful sensation on nerves, newly occurring anesthesia Sudden loss of motoric function: *claw hand, foot drop, facial palsy*	Fever, anorexia, malaise Arthralgia, myalgia Neuritis Epididymitis, orchitis Lymphadenitis Hepatosplenomegaly Glomerulonephritis Iridocyclitis Lobular panniculitis Dermal and subdermal edema
Histopathological findings	Edema in existing granulomas Lymphocyte increase Central fibrinoid necrosis in some of the tuberculoid granulomas Fusion of tuberculoid granulomas in the dermis	

are acute inflammatory reactions with systemic involvement which activates a plethora of pro-inflammatory cytokines such as IL-1, IL-6, IL-8 and TNF (3). The distinctive features of Type 2 reactions are the formation of new lesions instead of the transformation of the pre-existing lesions, with more significant inflammation-related symptoms in the patient, as shown in **Table 2**. There is also another kind of lepromatous reactions called reactional neuritis, which affects the peripheral nerves. This reaction is characterized by sudden pain of palpation of peripheral nerve, whether spontaneous or promoted by compression of a nerve trunk, which can be accompanied with the thickening of nerve trunks (9). Neuritis may occur in patients without other signs of reaction. Type 1 reaction is diagnosed when there are hypopigmented macular skin lesions which have become reddish and edematous, with or without edema in the hands and feet. Damage to the sensory nerves can be characterized by spontaneous nerve pain and paresthesia. In worst cases, the patient can experience loss of pain sensation, therefore increasing his/her susceptibility to injury. Motor nerve damage generally occurs in the ulnar nerve, median nerve, communical nerve, facial nerve, and posterior tibialis peroneus which results in foot drop, wrist drop and facial palsy. Facial nerve involvement may cause lagophthalmos and keratitis, which might result in blindness (10, 11).

Diagnosis of Reversal Reactions

Reversal reactions are characterized clinically by increased inflammation of preexisting lesions, which are confirmed by clinical diagnosis (3). The hypopigmented macules that have already regressed since the introduction of treatment would turn red and edematous. In some rare cases, the lesion might become ulcerated. This might be accompanied with the presence of new lesions with similar characteristic to the reversal reaction lesions described above. In "borderline lepromatoid" patients, face or extremities edema might present, appearing by itself or together with another lesions. Sometimes, edema in the hands and/or feet could possibly be a key symptom of reversal reactions (3).

There are several clinical variants of the reversal reaction. In melanodermic patients, nodules/pseudonodules might be present, mostly on the face but could possibly arise in other areas, that resemble (and may be misdiagnosed as) erythema nodosum. Some of the lesions might appear similar to erysipelas, and the ulceration that happened might result in scars after resolution. Macular reverse reactions with hypochromic or erythematous maculae are common in patients with the borderline form after completing the specific treatment. This hypochromic or erythematous nodule is sometimes accompanied with local hypersensitivity. MB patients could experience cutaneous lesions that are similar to papulae and small disseminated plaques (9).

Reversal reactions might also involve nerves. Nerves could become thick and painful, eventually causing worsening of a previous peripheral neuropathy (in terms of motoric, sensory or autonomic functions). Upon physical examination, we can find nerve enlargement and pain when palpating the nerve. This might cause patients to complain that they felt burning sensation in skin lesion, pain in the extremities or on the face, accompanied with decreased muscular sensitivity and muscular strength. Monofilament test can be used as a screening test for sensory function abnormalities. This is done by doing bristle test using standard nylon monofilaments (12). *Voluntary motor testing,* using a numerical system, can be applied for examining the motor function. This test, when done regularly and carefully, could possibly assist in the early detection of a reaction. Deterioration of VMT may precede more obvious clinical signs (12). More sophisticated methods such as EMG, sensory and motor nerve conduction velocity testing, evoked response testing, and autonomic reflexes measurement do not significantly add diagnostic value to detect reversal reaction (12). A biopsy is not routinely done for reversal reactions; however, some of the hallmarks of reversal reactions are the formation of granulomas and dermal edema. Other signs that can be found are macrophage epithelial differentiation, increase in lymphocyte numbers, epidermal thickening, and destruction of nerves by granuloma infiltrates (2).

In a previous study, there was an increase of IFN-α, IL-10, and IL-17 levels and a decrease of IL-10 found in serological tests of patients diagnosed with reversal reactions.

The ratio of proinflammatory cytokines with IL-10 can be used as an early diagnostic marker for reversal reactions and to evaluate the treatment (13). Another research concerning immune responses and gene expressions in the patients diagnosed with lepromatous reversal reaction found an elevation of IFN-γ, IP-10, CXCL9, IL-17A, and VEGF in the patients after the diagnosis of reversal reactions compared to the levels before they were diagnosed with reversal reaction. The elevation of these cytokine levels was also accompanied by diminished levels of $CD39^{+}CCL4^{+}$ and $CD25^{high}$ (14). Another study conducted by Andersson, et al. has found that blood TNF-α profiles do not have any diagnostic values for reversal reactions because they do not have a significant difference compared to healthy controls. The increase in TNF-α and its decrease after receiving prednisolone therapy are only found on the skin (15).

Therapy of Reversal Reactions

The therapy for reversal reactions aims to suppress the cellular immune response. Polychemotherapy should be continued throughout the episode of lepromatous reaction; whether it is reversal reaction or ENL. Corticosteroids are one of the most efficient drugs used in the therapy of reversal reactions, and are still mainly used in the therapy of reversal reactions. Corticosteroids reduce vascular permeability and vasodilation by inhibiting the mediators such as prostaglandins from arachidonic acids, and inhibiting the release of platelet-activating factors (PAF), vasoactive amines, neuropeptides, IL-1, TNF and nitric oxide. Glucocorticoids can inhibit the activation of neutrophil and eosinophil, reducing the adherence of neutrophil and eosinophil through the endothelial cells, and preventing the polymorphonuclear cells to migrate to the area with tissue inflammation. Glucocorticoids also inhibit the phagocytic capacity and production of oxygen free radicals, reducing the number of eosinophils circulating in peripheral bloods (causing rough granulation in polymorphonuclear neutrophils); they also inhibit the migration of monocytes and lymphocytes to the tissue with an increase in the endothelial adhesion of lymphocytes, as well as the vascular permeability; including cellular migration and activation (3).

Corticosteroids have several effects on the disease course of reversal reactions. Corticosteroids reduce intraneural and cutaneous edema, therefore it results in the quick improvement of symptoms and reduces post inflammatory scarring (16). The main effect of corticosteroids is suppressing the inflammatory immune response to the antigens of *Mycobacterium leprae* in the skin and nerves, by interfering with the activation of immune cellular response (3).

According to the WHO, the standard therapy for type 1 leprosy reaction is prednisolone at a dose of 1 mg/kgBW/day for 12 weeks for paucibacillary cases, and for 24 weeks for multibacillary cases (17). The same therapeutic dose is also applicable in pediatric patients (18). Initial dose of 40 mg prednisolone is sufficient to control most type 1 reactions (19). Patients with neural involvement need higher doses of prednisolone, sometimes up to 2 mg/kgBW/day (16). Prednisone dose should only be reduced following clinical improvement and upon reaching the dose of 20mg/day. General improvement of the symptoms begins to happen within three to six months (3). Prednisone should be continually given until clinical regression and neural functions are fully recovered (3). Sevalsekar *et al.* found complete remission after oral corticosteroid use (20). However, several studies have indicated that some of the nerve function impairment would eventually resolve without steroid therapy. This improvement might be spontaneous or might be attributable to the MDT therapy (21). However, in Hyderabad (India), only 50% of patients with leprosy reactions ex perienced an improvement in nerve function after treatment with steroids (6).

Pulse therapy using endovenous methylprednisolone is applied as an alternative to the oral corticosteroids to control reactional states. This method is used to reduce the side effects and period of morbidity. Indications for pulsotherapy are serious reversal reactions or reactions that are difficult to control using normal regimens, erythema nodosum, widespread and difficult to control erythema multiforme, and acute or chronic cases of neuritis where the patient has already undergone prolonged oral therapy with corticosteroids (3, 9). The dosage of this pulsotherapy

is 1 gram endovenous methylprednisiolone as a single daily dose during three days in the first week, followed by a 1 gram single weekly dose for four consecutive weeks, and followed again with 1 gram single monthly dose for four consecutive months. Between the pulse therapy dose, the patients are given 0.5 mg/kgBW/day prednisone (9).

The steroid may also have physicochemical and genomic effects. The physicochemical effects are mediated by receptors or might work through other non-specific physicochemical activities. This effect might cause symptom improvement in a brief period of time, such as in terms of edema reduction. The genomic effects of steroids begin with the penetration of cell membranes by glucocorticoids, attachment of glucocorticoids to receptors, and steroid binding to DNA which influences the process of transcription, translation, the stability of mRNA and protein products. Glucocorticoids are known to inhibit NF-$_k$B activity, which is a transcription factor that regulates TNF-α, IL-1β, IL-2 and *inducible nitric oxide synthase* (iNOS) (15, 21).

Another research done by Lockwood *et al* showed a significant decrease in interferon gamma (IFN-γ), interleukin-2 (IL-2), and mainly TNF-α after 28 days of treatment with steroids (11). Similar results were also found in the study of Raju, et al. who studied 7 serological markers related to the pathogenesis of reversal reactions, namely TNF-α, antibodies to phenolic glycolipid-1 (PGL-1 IgM and IgG), lipoarabinomannan (IgG1 dan IgG3 LAM), C2-ceramide, and S100B. They found a decrease in the levels of TNF-α, C2-ceramide, S100B, PGL-1, dan LAM after one-month prednisolone therapy (22). On the other hand, Anderrson et al. found that prednisolone was thought to have no effect on cytokines in the blood, and the effect was only localized to skin lesions. Furthermore, the effects obtained from prednisolone therapy might be caused by inhibition of the formation of prostaglandins and leukotrienes produced by mast cells and macrophages by the glucocorticoids, which ultimately functions as vasodilators and bronchoconstrictors. In addition, the effect of glucocorticoids can also be caused by non-specific non-genomic processes that result in changes in intracellular activity such as calcium and sodium transport. This activity is known to be important for immune cell activation (15).

Lately, the concern has been put on the antioxidant profile in leprosy patients and leprosy patients that experienced an immunological reaction. A prospective study found a decrease in oxidative stress during clinical remission after reversal reaction treatment with prednisolone. However, residual oxidative stress still existed, rendering the increase of oxidative stress afterward. This study shows the importance of evaluating the addition of antioxidants as an adjuvant therapy for leprosy reversal reaction (23). Another study showed a decrease in uric acid levels after reversal reaction maximum dose (40-80 mg/day) prednisone therapy. This can be caused by increased uric acid excretion from the kidneys due to the effects elicited by the glucocorticoid. Uric acid is one of the antioxidant agents found in the body. Uric acid levels that are too high or too low are associated with mortality from cardiovascular disease and decreased kidney function (24).

There might be several side effects related to the prednisolone therapy, depending on the therapeutic dose and duration of treatment. Major side effects that possibly happen are peptic ulcer, diabetes, tuberculosis, hypertension, psychosis, glaucoma, cataracts, corneal ulcers, and parasitic infections. The minor side effects that possibly happen are heartburn, moon face, acne, local fungus infection, and weight gain, as found in the study of Wagenaar et al. (25).

A variety of alternative therapies are being developed as replacement therapy as well as adjuvant therapy. A study conducted by Lambert et al in patients who did not respond to prednisolone or in patients with severe side effects has shown cyclosporine to be an effective replacement therapy (26). Other studies have found that fusidic acid, which acts by affecting proinflammatory cytokines, is an effective and safe adjuvant therapy for leprosy reactions (27). Immunosuppressants, such as azathioprine and cyclosporine A can be used alone for reversal reactions, or can be used in association with corticosteroids as a corticosteroid sparing agent (28). Cyclosporin A inhibits the transcription of IL-12 mRNA, therefore the proliferation of T cells will be blocked. Azatiophrine inhibits synthe-

sis of nucleic acids and works in a much slower manner. With the invention of these adjuvant therapies, prednisolone dose can be reduced, therefore the adverse effect that occurred because of prednisone supplementation can be subsequently reduced.

Various studies have been developed to prevent nerve damage in leprosy. Nerve damage can occur without an immunological reaction. A study by Sahay, et al. recommends 8 months of prednisolone therapy for all multibacillary cases as a prophylaxis to prevent nerve damage, after comparing the control group that only underwent MDT therapy with the treatment group that received MDT plus prednisone 20 mg/day, followed by tapering off at a 5 mg/2 weeks dose in the seventh and eighth week. This was done to prevent deformities that would possibly happen in patients with leprosy (29). One study has found that the prophylaxis effect of prednisolone will continue to exist whilst patients are still taking the medicine, but the effect was found to be lost in the 12 months follow up (30). On the other hand, Wagenaar, et al do not recommend prednisolone to be given as prophylaxis medication after reviewing the effectivity of prednisolone use after 20 weeks and effectivity of prednisolone to treat neuropathies in cases with subclinical neuropathy (23).

Conclusion

Reversal reactions are immunological reactions that occur in leprosy patients and they are the biggest cause of disability in these patients. Glucocorticoids, especially prednisolone, have been established as standard therapy for reversal reactions. Many studies have shown that glucocorticoids, especially prednisolone, have genomic effects that affect cytokine regulation, but other studies have also shown the possibility that glucocorticoids actually work through non-specific non-genomic processes. However, there are a variety of side effects in prednisolone that may manifest clinically, as well as side effects on the antioxidant profile. Therefore, several studies have developed replacement therapy and adjuvant therapy for reversal reactions.

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Glukokortikoidi u reverziblinim reakcijama kod lepre

Sažetak

Lepra je oboljenje izazvano *Mycobacterium leprae* i ona dovodi do deformacija i unakaženja bolesnika. Za lečenje lepre primenjuje se nekoliko lekova, međutim, ta terapija može izazvati leprozne reakcije kod pacijenta. Ima nekoliko tipova leprozne reakcije: reakcija tipa 1, reakcija tipe 2 i neuritis. Reakcija tipa 1 se uglavnom pojavljuje u BB, Bl i BT oblicima lepre i ispoljava se pogoršanjem postojećih lezija. Terapija za ovu reakciju prema smernicama SZO je kortikosteroidna terapija. U ovom radu ćemo objasniti nekoliko ključnih momenata u vezi sa kortikosteroidnom terapijom kod reverzibilnih reakcija lepre, uključujući i neželjene efekte i raspoložive alternativne terapije.

Ključne reči: Lepra; Profil ekspresije gena; Glukokortikoidi; Komorbiditet; Dijagnoza; Prednizolon; Indonezija

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Acne Keloidalis Nuchae – Case Report

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Abstract

Acne keloidalis nuchae (AKN) / folliculitis keloidalis nuchae (FKN) is a chronic inflammatory condition which involves hair follicles localized predominantly in occipital scalp and posterior neck area leading to hypertrophic scarring alopecia. We present a 59-year-old factory worker, Caucasian male with a whitish alopecic oval plaque about 10 cm in diameter in the occipital region. The peripheral part of plaque was mildly inflammated, with groups of tufted terminal hairs, while the central part showed cicatricial alopecia and discrete non-adherent dry scales. Skin changes firstly occurred 6 years earlier, as itchy papules and pustules that sometimes healed with scarring. The applied relevant diagnostic and therapeutical measures are discussed in this report.

Key words: Acne Keloid; Folliculitis; Diagnosis; Alopecia; Cicatrix; Case Reports; Therapeutics

Introduction

Acne keloidalis nuchae (AKN) /folliculitis keloidalis nuchae (FKN) is a chronic inflammatory condition which involves hair follicles predominantly localized in occipital scalp and posterior neck area leading to hypertrophic scarring alopecia. The disorder was first described in 1869 by Kaposi, who called it “dermatitis papillaris capillitii“ (1). The term “acne keloidalis nuchae“ was coined by Bazini in 1872 (2). AKN is the most prevalent in Afican American population, but it is also frequently observed among Hispanic and Asian men. However, it is rarely observed among Caucasian men (3, 4). AKN usually occurs in people aged 14-25 years and mostly affects males, with male-female ratio of approximately 20:1 (5, 6).

Case report

We present a 59-year-old, factory worker, Caucasian male with a whitish alopetic oval plaque about 10 cm in diameter in the occipital region. The peripheral part of plaque was mildly inflammated, with groups of tufted terminal hairs, while the central part showed cicatricial alopecia and discrete non-adherent dry scales **(Figure 1)**. Skin changes started

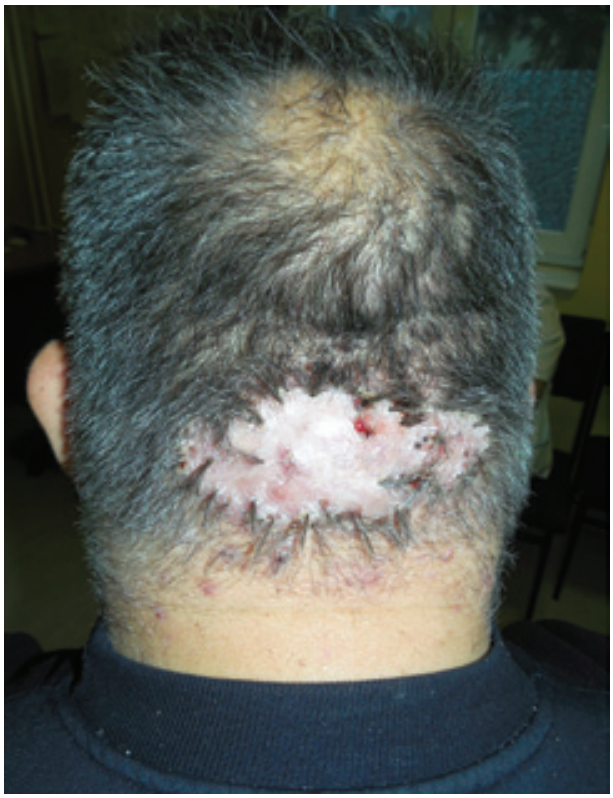

Figure 1. Clinical presentation of alopecic oval plaque in occipitial region

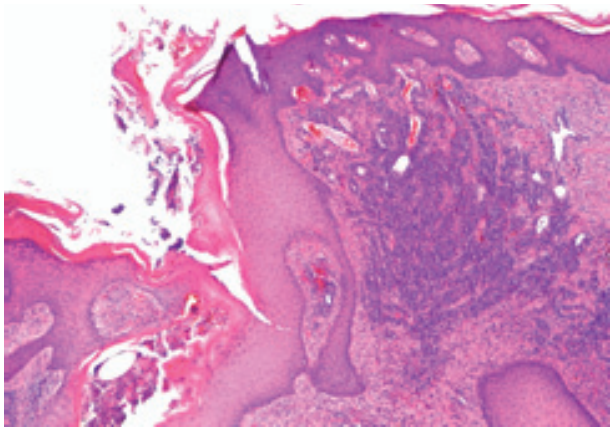

Figure 2. Inflammatory infiltration with plasma cell, neutrophilic granulocytes and giant multinucleated cells (hematoxylin and eosin, x 20)

6 years earlier, as itchy papules and pustules that sometimes healed with scarring. For many years he had a short haircut. Short courses of oral antibiotics combined with topical antiseptic were administered on several occasions over the years. All relevant clinical and laboratory findings were within normal limits, except for slightly elevated bilirubin, higher sedimentation rate and BMI > 30. Biopsy was performed to exclude other causes of cicatricial alopecia (eg discoid lupus erythematosus, cicatricial lichen), confirming chronic inflammatory plasmocytic infiltrate with scarring, sparing the distal third of the follicle. Since the inflammation was under control with topical antiseptics and the process was contained, the patient was referred to a plastic surgeon.

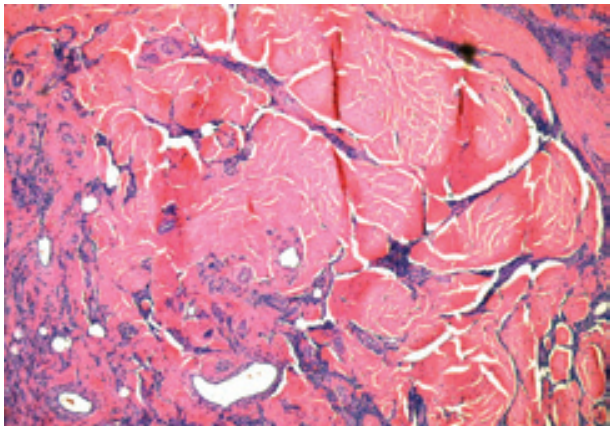

Figure 3. Dermal fibrosis (hematoxylin and eosin, x 50)

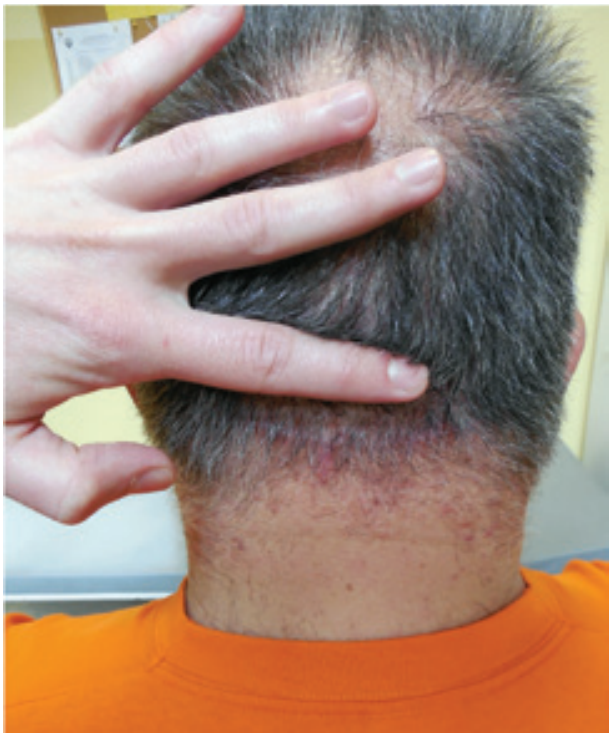

Figure 4. Clinical presentation seven months after surgical excision

Pathohistological analysis of the excised plaque showed hyperkeratotic epidermis with focal parakeratosis, perivascular chronic inflammatory infiltration with plasma cells, neutrophilic granulocytes and giant granulomatous cells, **(Figure 2)** without infiltrating the distal one-third of hair follicles. The significant fibrosis of dermis was also present **(Figure 3)**.

Seven months after surgical procedure was performed, the patient was in remission with satisfactory cosmetic outcome **(Figure 4)**.

Discussion

The cause of acne keloidalis is still unknown, but the suggested etiologies include different predisposing factors such as close shaving of the neck, constant irritation from collars or athletic gear, chronic low-grade bacterial infections, an autoimmune process, use of antiepileptic drugs or cyclosporine or an increased number of mast cells in the occipital region like those descibed in skin of African American population (7). Acne keloidalis nuchae occurs predominantly in males, suggesting that androgens may be a factor which contributes directly or indirectly. This

disease rarely begins before puberty and it also seldom develops after the age of 55 (8).

Acne keloidalis usually starts with pruritus or mild irritation a few hours or days after a haircut or after wearing headwear sports gear. The disease is characterized by development of follicular papules or pustules on the nape of the neck below the hair line, and rarely extends upwards into the scalp. Pruritus, pain, and contact bleeding are common in active lesions. Pruritus sets up a cycle of itch, scratch, irritation and inflammation. Secondary bacterial infection, usually caused by Staphylococcus aureus, is frequent and can lead to pustules, sinuses and abscesses. Recurrence of this form of folliculitis leads to patchy scars, which can enlarge and form keloids. The scars are without hairs, however, multiple hair shafts emerged from a single follicular opening can form a look of tufted hairs. Inflammation begins in the upper one-third of the hair follicles. Crusting and excoriation may be evident (9). In advanced or severe cases, disfiguring tumor-like masses, abcesses and pus-exuding sinus tracks may be present (10, 11).

The histological examination depends on the duration and activity of the lesion. Initially, inflammatory infiltration is composed of neutrophils and lymphocytes, to predominantly plasma cells (12). In more chronic lesions, follicles and sebaceous glands are destroyed with fragments of naked hair shafts surrounded by granulomatous inflammation and dermal fibrosis. Collagen fibers are like those in hypertrophic scarring rather than those in real keloids. Also, histopathological examination can reveal different stages of inflammation in one lesion (13).

Diagnosis is usually clinical and biopsy is performed to exclude other conditions and dermatoses, such as tinea capitis, lichen planopilaris, hidradentitis supurativa, follicular cutaneous t-cell lymphoma, etc. (9). Dermoscopy can also be a useful aid to the clinical diagnosis, especially in detecting the early signs of perifollicular fibrosis (14, 15).

The first step in management is education and prevention, avoiding short haircuts and wearing helmets or hats, and avoiding picking, rubbing, scratching the affected area. Mild to moderate cases can be treated with potent or ultrapotent topical corticosteroids, alone or in combination with topical/oral antiobiotics or topical/oral retinoids (10). Recently it has been shown that targeted ultraviolet B phototherapy can be usefull to improve the clinical appearance of the lesions (16). Intralesional corticosteroids should be considered for a resistant cases and for the treatment of keloidal scarring (10). Laser therapy should be considered for the hair removal and/or softening of the keloidal plaques (17, 18). Several authors have reported that laser hair removal is an option to prevent relapsing folliculitis (13). If pustules and draining sinuses are present and bacterial culture is positive, oral antibiotics should be administered in addition to topical antibiotics (19). Surgical excision is the cornerstone of the management for extensive plaques and tumor-like masses (9, 11). An alternative surgical approach includes electrosurgery and cryosurgery. Electrosurgery allows for excision of the lesion with simultaneous coagulation of small vessels, however, cryosurgery provides varied responses to lesions, though it may be best suited for more vascular lesions (20, 21).

Radiotherapy should be reserved for the most severe and refractory cases, considering the side effects of such treatment (20).

Abbreviations

AKN – Acne keloidalis nuchae
FKN – Folliculitis keloidalis nuchae

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Acne keloidalis nuchae: prikaz slučaja

Sažetak

Acne keloidalis nuchae (AKN)/*Folliculitis keloidalis nuchae* (FKN) predstavlja hronično zapaljensko stanje koje zahvata folikule dlake dominantno lokalizovane u okcilipitalnoj regiji i zadnjoj strani vrata, dovodeći do nastanka hipertrofične ožiljne alopecije. Predstavljamo slučaj 59 godina stare osobe muškog pola, radnika u fabrici, bele rase, sa beličastim alopecičnim ovalnim plakom, dijametra oko 10 cm, lokalizovanog u okcipitalnoj regiji. Periferni deo plaka je bio blago inflamiran, sa grupicama „čuperaka" terminalne dlake, dok je centralni deo odgovarao ožiljnoj alopeciji sa diskretnom neadherentnom skvamom. Promene su počele da se javljaju šest godina ranije, u vidu papula i pustula praćenih svrabom, koje su u nekim slučajevima zarastale ožiljavanjem. Relevantne sprovedene dijagnostičke i terapijske mere, biće opisane u prikazu ovog slučaja.

Ključne reči: Keloidne akne; Folikulitis; Dijagnoza; Alopecija; Ožiljak; Prikazi slučajeva; Terapija

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Alternative Leprosy Treatment Using Rifampicin Ofloxacin Minocycline (ROM) Regimen – Two Case Reports

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Abstract

Introduction. Leprosy is a disease that predominantly affects the skin and peripheral nerves, resulting in neuropathy and associated long-term consequences, including deformities and disabilities. According to the WHO classification, there are two categories of leprosy, paucibacillary (PB) and multibacillary (MB). The standard treatment for leprosy employs the use of WHO MDT (Multi Drug Treatment) regimen, despite its multiple downsides such as clofazimine-induced pigmentation, dapsone-induced haematological adverse effects, poor compliance due to long therapy duration, drug resistance, and relapse. Multiple studies and case reports using ROM regimen have reported satisfactory results. Nevertheless, there are still insufficient data to elucidate the optimum dosage and duration of ROM regimen as an alternative treatment for leprosy. Previous experience from our institution revealed that ROM regimen given three times weekly resulted in a satisfactory outcome. **Case Reports.** We report two cases of leprosy treated with ROM regimen from our institution. The first case was PB leprosy in a 64-year-old male who presented with a single scaly plaque with erythematous edge on the right popliteal fossa. Sensibility examination showed hypoesthesia with no peripheral nerve enlargement. Histopathological examination confirmed Borderline Tuberculoid leprosy. ROM regimen was started three times weekly for 6 weeks and the patient showed significant clinical improvement at the end of the treatment with no reaction or relapse until after 6 months after treatment. The second case was MB leprosy in a 24-year-old male patient with clawed hand on the 3rd-5th phalanges of the right hand and a hypoesthetic erythematous plaque on the forehead. Histopathology examination confirmed Borderline leprosy. The patients received ROM therapy 3 times a week with significant clinical improvement after 12 weeks. **Conclusion**. ROM regimen given three times weekly for 6 weeks in PB leprosy and 12 weeks in MB leprosy resulted in a significant clinical improvement. Thus, ROM regimen could be a more effective, safer, faster alternative treatment for leprosy.

Key words: Cranial Nerve Diseases; Herpes Zoster Oticus; Neuritis; Signs and Symptoms; Diagnosis; Antiviral Agents; Rare Diseases

Introduction

Leprosy, also known as Hansen's disease, is a chronic disease caused by *Mycobacterium leprae (M. leprae)* that primarily affects the skin and peripheral nervous system which may result in neuropathy. The most frightening part of this disease is that it can cause deformity and disability. It can occur to all ages, from an infant to a very old person. Even though the WHO (World Health Organization) attempted to eliminate leprosy in 2000, new cases continued to occur and more than 200,000 new cases of leprosy were reported in 2016 (1). The transmission of this disease is still poorly understood. It is thought to be transmitted through inhalation of droplets containing *M. leprae* as well as through direct skin contact (1).

In most cases, diagnosis of leprosy can be made by finding one of the three cardinal signs of leprosy: loss of sensation in a hypopigmented or erythematous skin lession; thickening or enlargement of the peripheral nerve accompanied by loss of sensation and/or muscle weakness in the affected nerve; or positive slit skin smear (1, 2).

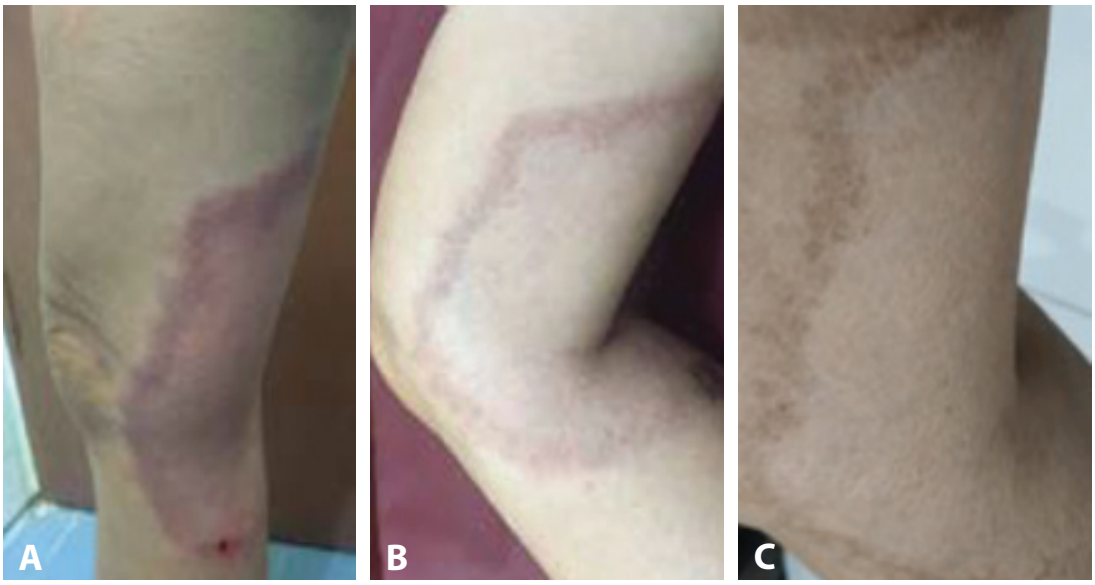

Figure 1. (A) Erythematus lession with hypoesthesia on the right popliteal fossa on day-0, (B) After 6 weeks (day-42) of treatment the erythematous plaque started to fade. (C) Six months after treatment (day-168) the lesion became hyperpigmented with no leprosy reaction or relapse.

Leprosy is classified as paucibacillary (PB) or multibacillary (MB), and the standard treatment for leprosy is MDT (Multi Drug Treatment) regimen recommended by the WHO involving the use of rifampicin and dapsone for 6 months for PB leprosy and rifampicin, clofazimine and dapsone for 12 months for MB leprosy. However, MDT has been linked to multiple downsides such as clofazimine-induced pigmentation, dapsone-induced haematological adverse effects, poor compliance due to long therapy duration, drug resistance, and relapse (1, 3). Thus, an effective alternative regimen with shorter duration and fewer side effects is needed.

In this report, we show a case of PB and MB leprosy, respectively which were successfully treated using ROM regimen three times a week that showed significant clinical improvement with no side effects until after six months of follow-up.

Case Reports

Case Report 1

A 64 year-old man presented with a chief complaint of a single painless and non-itchy erythematous plaque on the right popliteal fossa which had appeared three months before admission. Physical examination revealed erythematous lesion with hypoesthesia without peripheral nerve enlargement. There were no other lesions on his body. Slit skin smear showed no acid fast bacilli. Histopathology examination showed epidermal atrophy with clear subepidermal zone and abundant granuloma that infiltrated the adnexa and consisting of epitheloid histiocytes with a lot of lymphocytes and datia langhans cell, consistent with borderline tuberculoid (BT) leprosy. Based on clinical examinations, slit skin smear, and histopathological features, BT leprosy was diagnosed. Since the patient refused the MDT regimen, he was prescribed with ROM regimen (Rifampicin 600 mg, Ofloxacin 400 mg, and Minocycline 100 mg) three times weekly for six weeks.

After four weeks of treatment, the erythematous plaque started to fade along with improvement of the hyphoestesia **(Figure 1a)**. At the end of treatment (week 6), the erythematous plaque became flat and faded **(Figure 1b).** The patient himself also reported a subjective, significant improvement of the sensibility that was proven objectively by sensoric examination. There was no leprosy reaction or relapse until after six months after treatment.

Case Report 2

A 24-year-old male patient presented with clawed hand on the 3rd–5th phalanges of the right hand and single hypoesthetic erythematous plaque on the forehead which had ap-

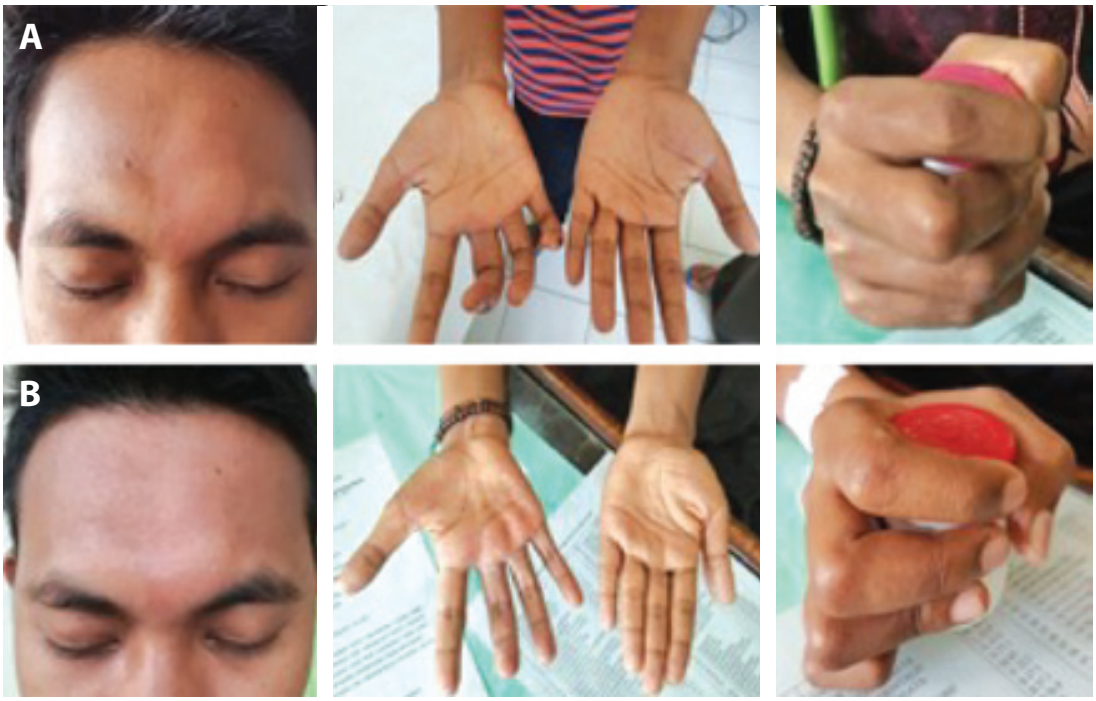

Figure 2. (A) single hypoesthetic erythematous plaque on the forehead with clawed hand on the right hand (day-0). (B) In the 12th week (day-84), the lesion on his forehead disappeared and the patient was able to straighten his finger.

peared 5 months before. There was no pain or pruritus at the lesion. Physical examination revealed hypoesthesia at the lesion and also at the third, fourth, and fifth finger of the right hand with peripheral right ulnar nerve enlargement. Hypotrophy of the tenar and hypotenar muscle was evident and there were no other lesions on his body. Motor tests using voluntary muscle and hand grip tests showed the same strength in both hands.

Slit skin smear showed positive-1 acid fast bacilli. Histopathology examination showed epidermal atrophy with a clear subepidermal zone. Epithelioid granulomas surrounded by lymphocytes near adnexa and nerve with no datia langhans cell were found at the dermis. These features were consistent with borderline (BB) leprosy. Based on clinical examinations, slit skin smear, and histopathological features, BT leprosy was diagnosed. Due to the risk of skin pigmentation, the patient refused MDT regimen and was prescribed ROM regimen (Rifampicin 600 mg, Ofloxacin 400 mg, and Minocycline 100 mg) three times weekly for 12 weeks.

After 4 weeks of treatment the erythematous plaque on the forehead started to fade and an improvement in the sensory and motor test was found. In the 12th week, the lesion on his forehead disappeared and the patient reported significant improvement in sensibility. In addition, the patient was able to straighten his finger. Slit skin smear showed negative acid fast bacilli **(Figure 2)**.

Discussion

Until today, the current standard treatment for leprosy remains the MDT regimen that has been recommended by the WHO. This regimen requires not only supervised monthly rifampicin and clofazimine doses but also daily self-administration of dapsone and clofazimine that is related with poor compliance and drug resistance. However, drug resistance, and relapses have been reported (4). The three drugs that comprise MDT have recognized adverse effects. Dapsone, especially in those with glucose-6-phosphate dehydrogenase deficiency, is associated with infrequent but serious toxicities. Clofazimine is associated with generalized skin pigmentation which is the leading cause for MDT refusal. Besides that, long treatment duration leads to low compli-

ance and high drop-out rate (5, 6). Thus, there is still a need to find new alternative regimens that will be more effective and of shorter duration to improve both the compliance and effectiveness of the treatment (6).

Alternative regimen recommended by the WHO is a single dose of rifampicin (600 mg), ofloxacin (400 mg), and minocycline (100 mg) (ROM) for PB leprosy patients with single lesion (2). Ofloxacin and minocycline are significantly more potent than dapsone and clofazimine against *M. leprae* and when combined with rifampicin provide a potent bactericidal activity that could kill 98% *M. leprae* in the first administration (7). Publication from the Philippines showed that 24 supervised monthly doses of ROM were proven to be safe, tolerable, provided similar clinical, bacteriologic, and histologic improvements to the MDT regimen. Furthermore, no skin pigmentation, increased rates of reactions, nor relapses after five years of follow-up were found (6).

Pathogenesis for nerve impairment in leprosy is still unclear, it is suspected due to *M. leprae* ability to modulate and induce cytokine production that cause Schwann cell apoptosis and ultimately cause nerve impairment in leprosy (8). In our case there was sensoric and motoric improvement in our patient. This improvement is due to minocyline effect that could repair acute nerve impairment. Minocycline is known to have antiapoptotic and imunomodulator effect, as well as the capacity to inhibit proteolisis, angiogenesis and collagen degradation which makes it the right choice for axonal degeneration management. In addition, Minocycline also has a higher bioavailability in the nerve tissue and skin due to its lipophilic nature (9, 10). There was a study that showed minocycline as an alternative option to prevent permanent disability in acute nerve impairment (<6 months) and in a patient who was unresponsive to corticosteroid. Around 80% of subjects showed complete or partial recovery in acute nerve impairment caused by leprosy (10).

This new alternative regimen is especially useful for patients who are concerned about clofazimine-induced skin pigmentation, compliance issues, sensitivity to an MDT component and it could potentially provide faster improvement. The downside of this regimen is that ROM treatment is expensive, thus preventing its mass administration and MDT is free, i.e. provided by the government (6). One of the reasons one of our patients refused to have MDT regimen was pigmentation caused by clofazimine, whereas the patient with PB refused MDT regimen because he wanted to search for an alternative regimen that was faster, and simpler.

Unfortunately, a meta-analysis comparing monthly doses of ROM to MDT in MB leprosy patients did not provide sufficient data to conclude the efficacy of ROM therapy in MB patients. Thus, an additional study is required to evaluate effectiveness of this regimen in MB leprosy (3). Nonetheless, from our experience, the patients treated with ROM regimen 3 times weekly displayed satisfactory outcome due to the absence of skin pigmentation, similar effectiveness, and potentially shorter treatment durations. To that end we administer ROM given 3 times weekly to the patients who refuse MDT regimen recommended by the WHO and, as in the case above, it yields significant clinical improvement. Not only do the lesions disappear but this regimen could also improve the patient's sensory and motor problem subjectively.

Conclusion

ROM regimen given 3 times weekly for 6 weeks for PB leprosy and 12 weeks for MB leprosy showed significant clinical improvement in our leprosy patients. Thus, ROM regimen could be a more effective, safer, faster alternative treatment than MDT regimen recommended by the WHO for leprosy. However, there are still insufficient data to come to a valid conclusion on this regimen. Thus, long-term randomized controlled trials using ROM therapy in leprosy are needed.

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Alternativni tretman lepre kombinacijom *Rifampicin Ofloxacin Minocycline* (ROM) – Prikaz dva slučaja

Sažetak

Uvod. Lepra je oboljenje koje uglavnom zahvata kožu i periferne nerve, a rezultat je neuropatija i združene dugoročne posledice, uključujući deformitete i invalidnost. Prema klasifikaciji SZO, postoje dve kategorije lepre; paucibacilarna (PB) i multibacilarna (MB). Standardni tretman za lepru primenjuje MDT režim Svetske zdravstvene organizacije, uprkos njegovim brojnim nedostacima poput pigmentacije izazvane klofaziminom, hematološkim nuspojavama izazvanih dasonom, loše komplijanse zbog dugog trajanja lečenja, rezistencije na lekove i pogoršanje. Zadovoljavajući rezultati su prijavljeni u mnogobrojnim studijama i prikazima slučajeva u kojima je korišćen ROM. Pa ipak, još nema dovoljno podataka da se odredi optimalna doza i dužina trajanja režima ROM kao alternativnog tretmana za lepru. Prethodno iskustvo iz naše institucije govori da ROM režim primenjen tri puta nedeljno daje zadovoljavajući ishod. **Prikaz slučajeva.** Prikazujemo dva slučaja lepre lečene ROM režimom u našoj instituciji. Prvi je slučaj PB lepre kod muškarca starog 64 godine koji je došao sa jednim ljuspičastim plakom na desnoj poplitealnoj flosi. Ispitivanje senzibiliteta pokazalo je hipoesteziju bez uvećanja perifernog nerva. ROM režim je uveden tri puta nedeljno u trajanju od šest nedelja i kod pacijenta je došlo do značajnog kliničkog poboljšanja na kraju tretmana bez reakcije ili pogoršanja sve do posle šest meseci posle tretmana. Drugi slučaj je bio MB lepra kod muškarca starog 24 godine sa kandžastom šakom na trećoj i petoj falangi desne ruke i hipoestetskim eritematoznim plakom na čelu. Histopatološki pregled je potvrdio graničnu lepru. Pacijenti su primili terapiju tri puta nedeljno sa značajnim kliničkim poboljšanjem posle 12 nedelja. **Zaključak.** ROM režim primenjen tri puta nedeljno u trajanju od šest nedelja kod PB lepre i 12 nedelja kod MB lepre dao je značajno kliničko poboljšanje. Stoga, ROM režim bi mogao da bude efikasniji, bezbedniji i brži alternativni tretman za lepru.

Ključne reči: Bolesti kranijalnih nerava; Ušni herpes zoster; Neuritis; Znaci i simptomi; Dijagnoza; Antivirusni lekovi; Retke bolesti

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Acne Necrotica (Varioliformis) – Case Report

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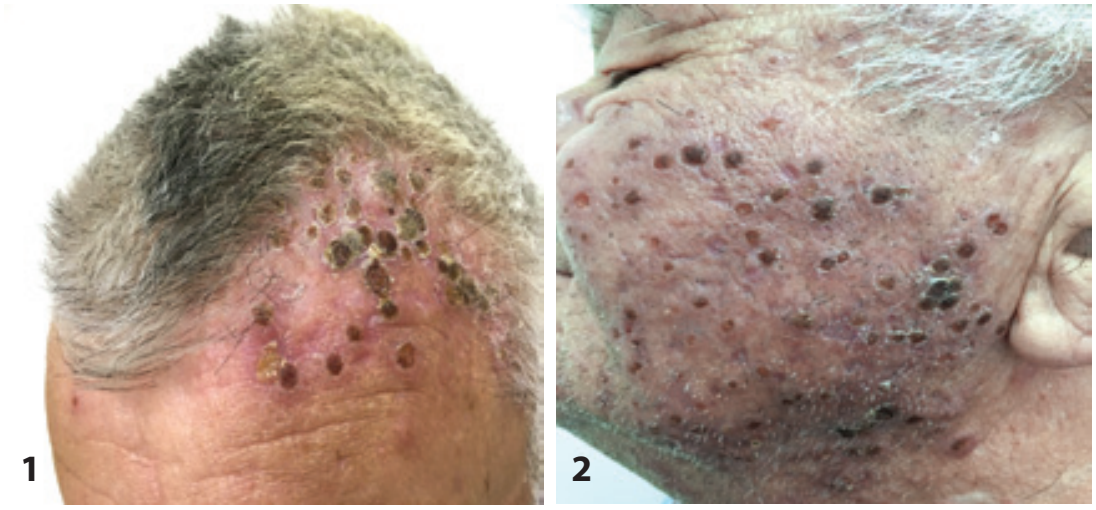
Abstract

Acne necrotica is a rare disease, characterized by repeated cropping of inflammatory papules and papulo-pustules, which rapidly necrotize and leave varying degrees of varioliform scars that may lead to cicatricial alopecia when terminal hair-bearing sites are involved. In early lesions, pathology shows necrotizing lymphocytic folliculitis. We report a 63-year-old male patient with chronic, relapsing, umbilicated and centrally necrotic erythematous papules and papulo-pustules involving the frontal hairline area, face, and neck. Histopathology showed epidermal spongiosis and lymphocytic exocytosis, extensive necrosis and destruction of the follicular epithelium, a dense diffuse lymphohistiocytic infiltrate and necrosis of the perifolicular dermis. The diagnosis of acne necrotica was made based on the correlation of clinical and histopathological findings. A complete clinical remission was achieved with topical erythromycin and benzoyl peroxide.

Key words: Acne Vulgaris; Cicatrix; Necrosis; Alopecia; Folliculitis; Erythromycin; Benzoyl Peroxide; Treatment Outcome

Introduction

Acne necrotica is a puzzling disease, rarely described in the literature. Bazin first proposed the term acne necrotica in 1851 (1). Hebra named this condition as *acne necrotica varioliformis* based on the round depressed scars resulting from active disease. Sabouraud and Lane (in 1928 and a few years later, respectively) described a non-scarring superficial folliculitis, characterized by intensely pruritic, pinpoint pustules on the scalp, and called it *acne necrotica miliaris* (1). This form of acne necrotica surely should be differentiated from scarring varioliform variant, but it is still uncertain whether this condition represents a minor variant of the same disease



Figures 1 and 2. Multiple, grouped reddish-brown papules and papulo-pustules, partly umbilicated and centrally necrotic covered with round adherent hemorrhagic crusts

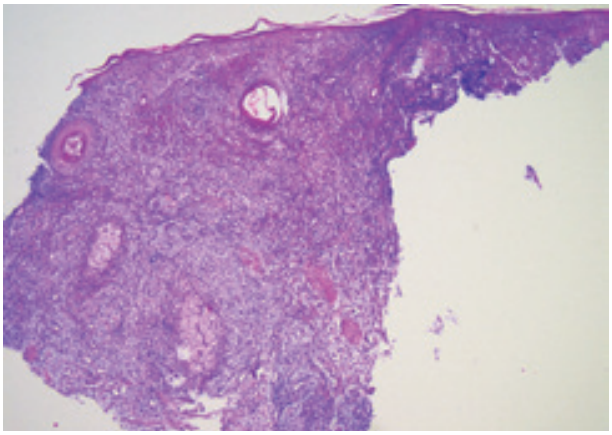
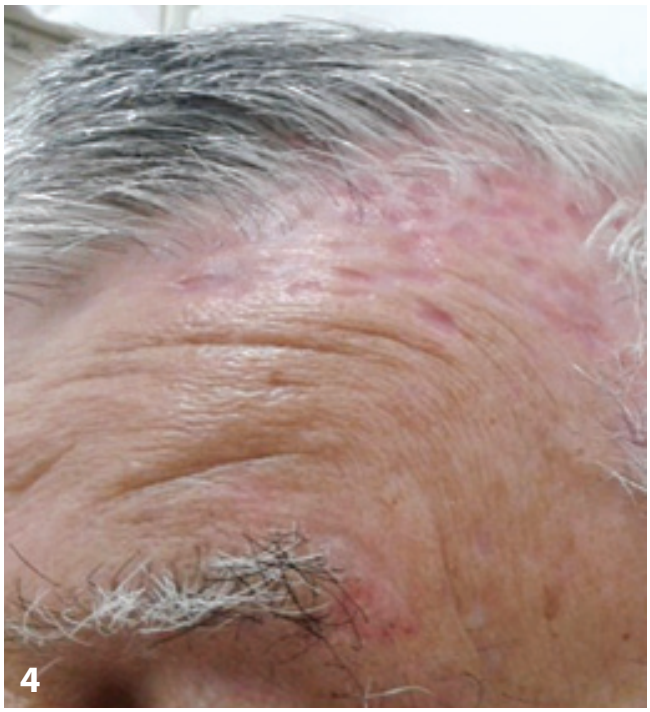


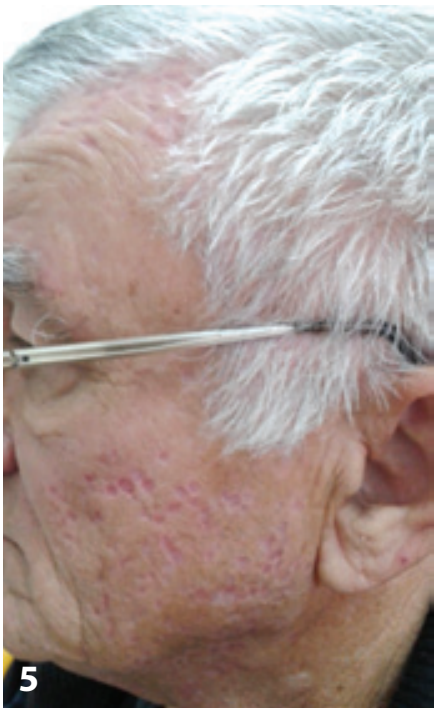
Figure 3. Histopathology showed epidermal spongiosis and lymphocytic exocytosis, extensive necrosis and destruction of the follicular epithelium, a dense diffuse lymphohistiocytic infiltrate and necrosis of the perifolicular dermis. (HE x40)

process or different entity (2). Other synonyms for *acne necrotica* are *acne frontalis, acne atrophica*, necrotizing lymphocyte folliculitis or pustular perifolliculitis (2, 3). Based on limited data, the disease affects more females than males and usually starts in the fourth and fifth decade of life (3, 4). The lesions generally present as grouped, erythematous papules and papulo-pustules, 2–5 mm in diameter that are umbilicated and within few days develop central necrosis, followed by an adherent hemorrhagic crust, which sheds after 3 or 4 weeks and result in varioliform scars (2, 5). In some patients, the appearance of the skin changes is accompanied by a burning sensation or pruritus (5). The most frequently affected areas are the frontal scalp and upper forehead, but the disease may also affect the nape, the nose, the cheeks, rarely extra facial regions like the chest and back (3, 5).

Case Report

A 63-year-old male patient with a 6-month history of multiple, relapsing papules and pustules in scalp and face was admitted to our Clinic. The patient complained about itching and burning sensations that followed the appearance of new lesions. His medical history was positive only for arterial hypertension, well-controlled with ramipril. He denied usage of any new medications. A year before presentation the patient had Herpes zoster infection affecting ophthalmic branch of the left trigeminal nerve. Physical examination revealed multiple, grouped reddish-brown





Figures 4 and 5. Residual varioliform scars and scarring alopecia

papules and papulo-pustules, mostly umbilicated or centrally necrotic covered with round adherent hemorrhagic crusts, and depressed varioliform scars, distributed in frontal hairline, face, and neck **(Figures 1 and 2)**. Skin biopsy was performed and histopathology showed epidermal spongiosis and lymphocytic exocytosis, extensive necrosis and destruction of the follicular epithelium, a dense diffuse lymphohistiocytic infiltrate and necrosis of the perifolicular dermis **(Figure 3).** Complete and differential blood cell count, sedimentation rate, routine biochemistry, C-reactive protein, and protein serum electrophoresis were within the normal ranges. Hepatitis B, C, and HIV antibodies were negative. Bacterial swabs showed physiological flora and Demodex folliculorum was not found. Based on clinical and histopathological findings the diagnosis of acne necrotica was made. Treatment was started with topical erythromycin 2% cream and benzoyl peroxide 4% wash suspension. After two weeks of treatment, all lesions regressed with residual varioliform scars and scarring alopecia **(Figures 4 and 5)**. There was no evidence of new lesions during the 6-month follow-up.

Discussion

Acne necrotica is a rare but clinically distinctive form of cicatricial alopecia with obscure pathogenesis. Most patients have an abnormal inflammatory reaction to the pathogenic microorganisms such as Propinibacterium acnes, Malassesia spp., Demodex folliculorum and, in more severe cases, Staphylococus aureus (7). Mechanical manipulations of pre-existing lesions such as rubbing and scratching may only exacerbate the disease but are not a cause (3, 6). Association of acne necrotica with phenylbutazone treatment has been reported in only one patient (1, 7). In rare cases of acne necrotica herpes simplex virus was identified in the lesions (6). The differential diagnosis is extensive and includes bacterial folliculitis, tinea capitis, eczema herpeticum, folliculitis decalvans, eosinophilic pustular folliculitis, pyoderma gangrenosum, cicatricial pemphigoid, blastomycosis-like pyoderma, erosive candidiasis of the scalp and pustular erosive dermatosis of the scalp, among other possibilities (1–3, 5, 6). Systemic and topical antibiotics, oral isotretinoin, systemic and intralesional corticosteroids, topical benzoyl peroxide and topical 0.005% calcipotriol cream have been recommended for the treatment of acne necrotica (1–3, 6, 8). Doxepin has been suggested in patients manipulating skin lesions (5, 8). The clinical course is variable, with some cases showing spontaneous resolution and others resistant to therapy, where treatment can last for months with frequent recurrence of lesions (1).

Conclusion

Acne necrotica (varioliformis) represents a distinctive form of lymphocytic folliculitis with specific cutaneous involvement. Initially, only superficial parts of the follicles are involved (2, 9), therefore early and adequate intervention can enable recovery of the follicles and help new hair regrowth.

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Acne necrotica (varioliformis): prikaz slučaja

Sažetak

Acne necrotica su retka, misteriozna bolest, za koju su karakteristični rekurentni naleti pustula i papulopustula koje podležu centralnoj nekrozi i ostavljaju varioliformne ožiljke i cikatricijalnu alopeciju različitog stepena. U ranim lezijama histopapatološki nalaz karakteriše prisustvo nekrotizujućeg limfocitnog folikulitisa. Prikazujemo pacijenta starosti 63 godine, sa ponavljnim naletima papula i papulopustula na kapilicijumu, licu i vratu. Histopatološki nalaz je odlikovalo prisustvo epidermalne spongioze i egzocitoza limfocita, ekstenzivna nekroza i destrukcija folikularnog epitela i gust, difuzan limfohistiocitni infiltrat i nekroza perifolikularnog derma. Dijagnoza je postavljena na osnovu kliničke slike i histopatološkog nalaza. Kompletna klinička remisija postignuta je lokalnom primenom eritromicina i benzoil-peroksida.

Ključne reči: Acne vulgaris; Ožiljak; Alopecija; Folikulitis; Eritromicin; Benzoil peroksid; Ishod Terapije

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DERMOSCOPY OF THE MONTH
Balloon Cell Nevus – Report of Three Cases

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Abstract

The balloon cell nevus is a rare and unusual benign melanocytic lesion characterized histologically by complete or predominant presence of balloon-cell transformed melanocytes. They represent approximately 1.7% of all melanocytic nevi. Three female patients, aged 30, 14 and 7 years, with lesions located on the back and head are included in the presented report. The dermoscopic examination revealed the repetitive dermoscopic features in all three patients: white and yellowish aggregated globules. In conclusion, balloon cell nevi are clinically indistinguishable from the common nevi. Dermoscopy can be useful in their recognition since balloon cell nevi exhibit some distinct dermoscopic features in a form of aggregated white and/or yellow globules.

Key words: Nevus, Pigmented; Dermoscopy; Skin Neoplasms; Melanoma; Case Reports

Introduction

The balloon cell nevus (BCN) is a benign melanocytic lesion characterized histologically by complete or predominant presence of large transformed melanocytes known as ″balloon cells″ (1–4). This histological entity was first reported by Judalaewitsch a century ago, in 1901. Then in 1932 Miescher gave a comprehensive case description of BCN in a nine-year-old boy; however, in this article he erroneously considered balloon cells to be nevus cells that underwent a sebaceous transformation (2). Nowadays, it is known that balloon cells are formed by progressive vacuolisation of melanosomes in nevi cells (2, 3).

BCNs are commonly reported in patients younger than 30 years, with no gender predominance, most commonly occurring on the head or in the neck area, but also on the trunk and extremities (1, 2). They represent approximately 1.7% of all melanocytic nevi (3). Clinically, BCNs are indistinguishable from the common nevi. Those asymptomatic melanocytic lesions usually appear as a macule or papule, but also may have a polypoid appearance (1, 2). Herein, we report three female patients with dermoscopic features of BCN.

Case Reports

Case 1

A 30-year old female patient was referred to our Department for a regular mole examination. The patient had the history of a previously excised dysplastic nevus and positive family history of melanoma. The clinical examination revealed numerous melanocytic nevi without dermoscopical atypia. However, the pigmented lesion on the right central part of the back **(Figure 1 A)** showed dermoscopically multiple aggregated whitish globular structures over the pigment network **(Figure 1 B)**, patognomonic for the diagnosis of the balloon cell nevus. The patient was reassured about this benign feature and advised for a regular follow-up.

Case 2

A 14-year-old girl was admitted to our Department for the evaluation of a solitary, oval and brown pigmented lesion on the central part of the upper back **(Figure 2 A)**. Her personal and family history was unremarkable. The dermoscopic examination revealed numerous whitish globules on the brown structureless background with discrete brown

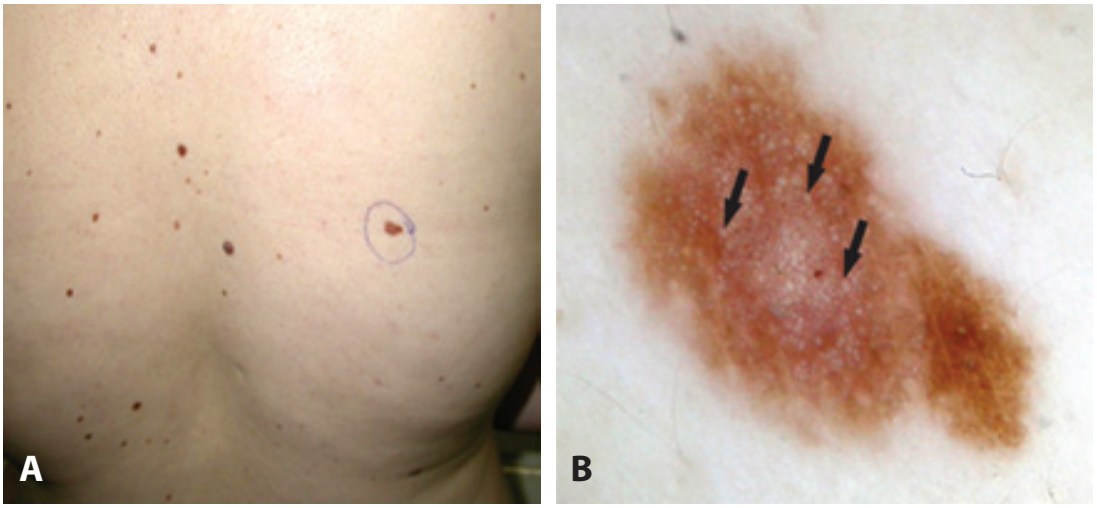

Figure 1. A. Clinical image of asymetric brown nevus on right part of the back. **B.** Dermoscopy showed multiple and clustered white globules (arrows) over brown pigment network.

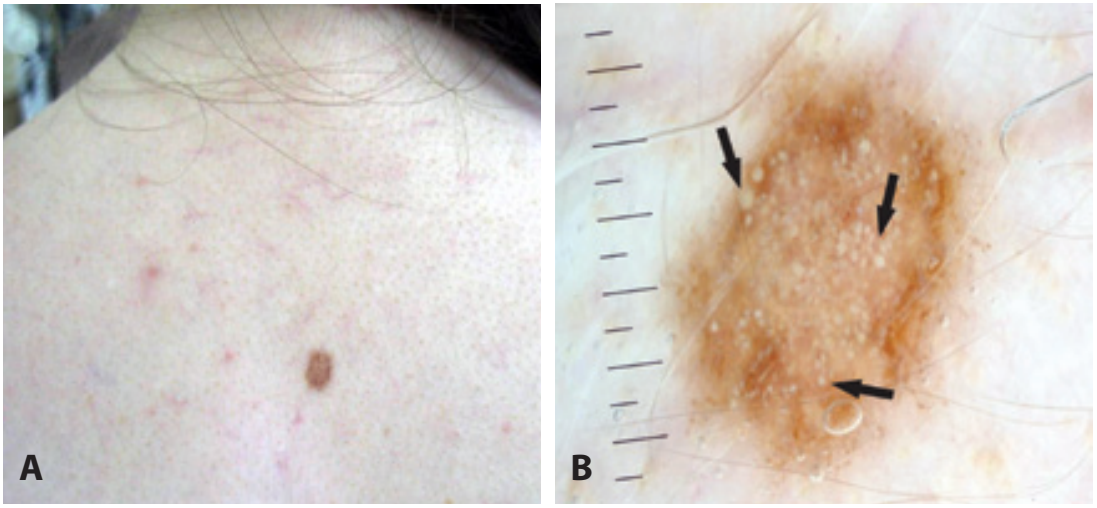

Figure 2. A. Soliatry brown nevus on the central part of the upper back. **B.** Brown structurless pigmentation, peripheral brown dots and globules and multiple whitish globules (arrows) were observed by dermoscopy.

dots/globules on the periphery, corresponding to the balloon cell nevus **(Figure 2 B)**. A regular follow-up was scheduled.

Case 3

The third, the youngest patient, was a 7-year-old girl, who was sent by a pediatrician for the examination of a recently noticed lesion on the scalp. The clinical examination showed a brown pigmented lesion, measuring approximately 10x12 mm on the skin of the central parietal scalp **(Figure 3 A)**, while the dermoscopic examination displayed a brownish coloration with multiple, grouped whitish and some yellowish globules, typical for the balloon cell nevus **(Figure 3 B)**.

Discussion

The BCN is a histopathological term used for intradermal or compound melanocytic lesions that contain a preponderance of balloon-transformed cells. Based on a percentage of involved cells, the balloon cell transformation can be subdivided into a primary and secondary phenomenon. If more than 50% of cells are affected by the change, the balloon cell transformation is considered to be a primary phenomenon, which classifies those lesions as a

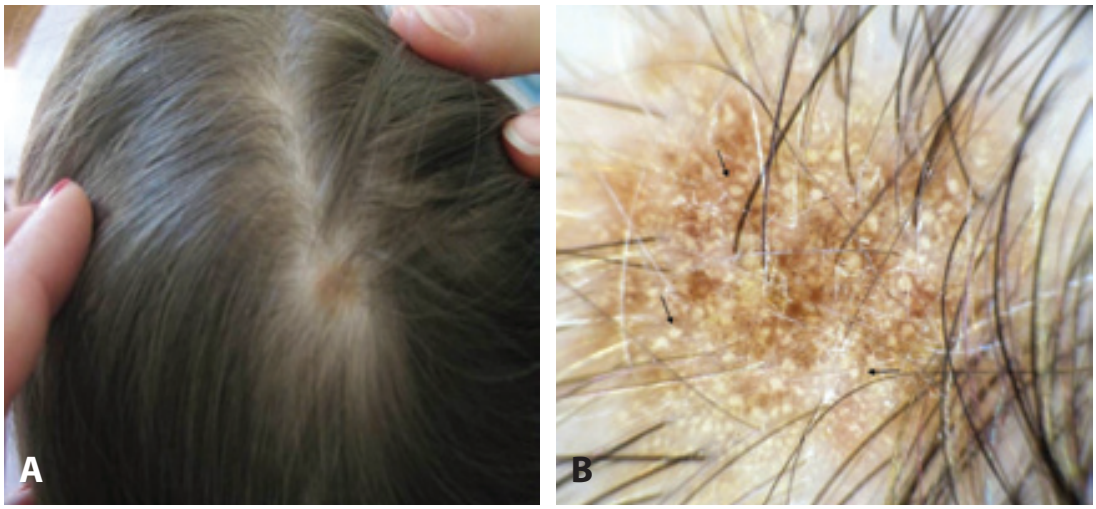

Figure 3. A. Clinical appearance of brown pigmented nevus on the scalp. **B.** Multiple whitish and some yellowish globules (arrows) over brown colored background were noticed by dermoscopy.

balloon cell nevus or balloon cell melanoma. In 2% of melanocityc nevi, small foci of balloon-transformed cells can be observed, which is considered to be a secondary phenomenon (3).

The balloon cell transformation has been described in both benign and malignant melanocytic lesions. Furthermore, ballon cell changes have also been reported in other non-melanocytic lesions including dermatofibroma and adnexal tumors (5, 6). The vacuolated appearance of the cells in BCN is attributed to the altered melanogenesis that results in accumulation of melanin precursors in premelanosomes (2–4).

Dermoscopy of BCN consists of multiple aggregated whitish or yellowish globular structures that histopathologically correspond to balloon cell transformed nests (1, 7–10). The coloration of globules (white or yellow) depends on the degree of the melanosome degeneration (8). Considering that balloon cells nests are admixed with normally pigmented melanocytes on histopathology, it is not surprising that pigment network, globules/dots or brown structureless pigmentation can be observed dermoscopically (7–10). All three cases in this report displayed multiple aggregated whitish and yellowish globules which undoubtedly confirmed the diagnosis of BCN.

The yellowish globules should be differentiated from those seen in sebaceous lesions, including sebaceous hyperplasia, naevus sebaceous or sebaceous adenoma, as well as in juvenile xanthogranuloma (8). In contrast, white globules should be differentiated from milia-like cysts, which are most commonly seen in seborrheic keratosis (9, 10). However, the differentiation between BCN and seborrheic keratosis should not be a challenge if there are other dermoscopic clues for seborrheic keratosis (sharp demarcation, comedo-like openings, mouth-eaten border or fingerprint-like areas).In addition milia-like cysts are not equally well observed by the employment of nonpolarized and polarized dermoscopy. Namely, by applying the polarized dermoscopy, milia-like cysts are less conspicuous. In contrast, globules seen in balloon cell nevi are similar regardless of which of the two types of dermoscopy is applied (9, 10).

Balloon cell melanoma (BCM) is a rare type of melanoma with a high mortality rate. Clinically, BCM cannot be distinguished from other types of melanoma. Owing to the rarity of this form of melanoma, dermoscopic features have not been well characterized. In a review of the relevant literature, typical white and yellow globules seen in BCN have not been reported in the dermoscopic description of BCM. Apparently, histopathologic diagnosis of BCM is more challenging considering morphologic similarity of cells in both BCM and BCN. The presence of cytological atypia, greater nuclear pleomorphism, higher Ki 67 mitotic index, and a lack of maturation of melanocyte towards the base of the lesion should help in differentiating those lesions from BCN (2, 11).

Conclusion

The balloon cell nevus is a rare and unusual benign melanocytic lesion. Despite the fact that the presence of the balloon cell transformation has no intrinsic clinical significance, dermatologists should be aware of this occurrence. In addition, both benign and malignant lesions can display the balloon cell transformation, which increases the possibility of a misdiagnosis. Dermoscopy can be useful in the recognition of this transformation since balloon cell nevi exhibit some distinct dermoscopic features in the form of aggregated white or yellow globules.

Abbreviations

BCN – balloon cell nevus
BCM – balloon cell melanoma

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Balloon cell nevus – prikaz tri pacijenta

Sažetak

Nevus sa balonskim ćelijama je retka i atipična benigna lezija koju histološki karakteriše potpuno ili predominantno prisustvo melanocita koji su transformisani u balonske ćelije. One čine približno 1,7% svih melanocitičnih nevusa. U ovom radu prikazujemo tri pacijentkinje, 30, 14 i 7 godina starosti, sa lezijama na koži leđa i kapilicijuma. Dermosopska evaluacija pokazala je kod sve tri pacijentkinje repetitivni obrazac: bele i žućkaste grupisane globule. U zaključku, Nevus sa balonskim ćelijama se ne može klinički razlikovati od običnog nevusa. Dermoskopija može pomoći u dijagnozi ovih nevusa prepoznavanjem specificnih dermoskopskih krakteristika u vidu grupisanih belih i/ili žutih globula.

Ključne reči: Pigmentni nevus; Dermoskopija; Kožne neoplazme; Melanom; Prikazi slučajeva

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A Report on the 9th Post-Chicago Meeting on Melanoma/Skin Cancer

The 9thPost-Chicago Meeting on Melanoma/Skin Cancer was held from June 20-21, 2019 in the Hotel Hilton Tucherpark in Munich. Prof. Axel Hauschild and Prof. Claus Garbe were the Congress presidents. The Post-Chicago Meeting 2019 attracted more than 700 participants from 34 countries working in the field of dermatology, medical oncology, immunology, radiooncology and other specialties. The interactive congress offers a comprehensive overview on all new developments in melanoma diagnostics and therapy and a direct communication with the world´s leading experts in these fields.During the 2-day program, a wide spectrum of topics in dermato-oncology were covered. International key opinion leaders on melanoma were invited to give an overview through specified presentations to present the latest clinical trial results, and to discuss on exciting new drugs with the audience. The aim of this meeting is to grant deep overall insight into the development of new drugs for melanoma and other cutaneous malignancies.

Our delegation had two participants. Prof. Lidija Kandolf Sekulović was a chairperson with Prof. Carola Berking in the session "Systemic treatment of non-melanoma skin cancer and non-cutaneous melanoma". Prof. Željko Mijušković was a chairperson with Prof. Petr Arenberger in the "EADO Forum session" and he presented two interesting melanoma cases in the same session.

The next Post-Chicago Meeting will take place in the Hotel Hilton Tucherpark in Munich from July 9-10, 2020.

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Figure 1. Faculty Dinner of the Post-Chicago Meeting 2019 (from left to right): Prof. Petr Arenberger, Prof. Lidija Kandolf Sekulović, Prof. Axel Hauschild (Congress president) and Prof. Željko Mijušković

FORTHCOMING EVENTS

Dermatology and Venereology Events 2019

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
17-19 January, 2019	7th EADO School of Dermato-Oncology, Berlin, Germany		www.eado.org
27-30 March, 2019	4th Dermatology and Cosmetology Congress with International Participants (NDERCOS 2019), Istanbul, Turkey	27 January, 2019	www.indercos.org
24-27 April, 2019	15th EADO Congress of Dermato-Oncology, Paris, France		www.esdoparis2019.com
10-15 June, 2019	24th World Congress of Dermatology, Milan, Italy	15 September, 2018	www.wcd2019milan.org
9-13 October, 2019	28th EADV Congress, Madrid, Spain		www.eadv.org
28 November - 1 December, 2019	3th National Medical Aesthetics Congress, Antalya, Turkey	25 September, 2019	www.mastder2019.org

Prepared by: Dr. Zorana Kremić, MD, Department of Dermatoveneorology Diseases, Military Medical Academy, Belgrade, Serbia

AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

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

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

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

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

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

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

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

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

1. Manuscript Preparation Guidelines

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

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

– The title ofthe article, which shouldbe informative, without abbreviations and as short as possible;

– A running title (limited to 30 characters);

– Authors’ names and institutional affiliations;

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

1.2. Abstracts

A structured abstract in English (limited to 150 words) should follow the title page. The abstract should provide the context or background for the study, as well as the purpose, basic procedures, main findings and principal conclusions. Authors sho uld avoid using abbreviations.

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

1.3. A list of abbreviations

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

1.4. Cover Letter

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

2. Tables and illustrations

Tables should capture information concisely

and precisely. Including data in tables, rather than in the text, reduces the length of the article itself.

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

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3. References

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

4. Author's Statements

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To ensure fair and objective decision-making, authors must declare any associations that pose a conflict of interest (financial, personal or professional) in connection with evaluated manuscripts. If there are no conflicts of interest, the following statement should be included *before the References* (or at the end of the *Acknowledgments sectio*n):

Conflict of interest: Authors state no conflict of interest.

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The protection of privacy is a legal right that must not be breached without individual informed consent. In cases where the identification of personal information is necessary for scientific reasons, authors should obtain full documentation of informed consent, including written permission from the patient prior to inclusion in the study.

The following (or similar) statement should be included *in the Methods section*:

Informed consent: Informed consent has been obtained from all individuals included in this study.

– Authorization for the use of human subjects

Manuscripts containing information related to human use should clearly state that the research has complied with all relevant national regulations and institutional policies and has been approved by the authors' institutional review board or equivalent committee. Copies of the guidelines and policy statements must be available for review by the Managing Editor if necessary. The editors reserve the right to seek additional information or guidance from reviewers on any cases in which concerns arise. All investigation with human subjects must have been conducted by following the tenets of the Helsinki Declaration, what is more authors must identify the committee or review board approving the experiments, and provide a statement indicating approval of the research. The following (or similar) statement should be included *in the Methods section*:

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If the manuscript does not contain any study that requires human or animal ethical approval, the following statement should be included in the *Methods section*:

Ethical approval: The conducted research is not related to either human or animals use.

5. Additional Information

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

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NEGA KOŽE SA ATOPIJSKIM DERMATITISOM PRILAGOĐENA FAZAMA BOLESTI

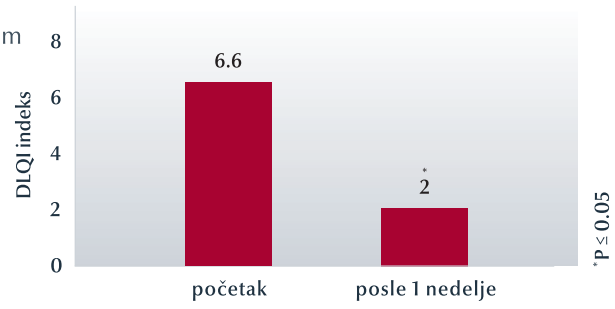
Značajno poboljšanje kvaliteta života i sna

- Manje egzacerbacija i svraba
- Akutna i redovna nega kože sa atopijskim dermatitisom
- Pogodno za bebe

- 91% značajno poboljšanje kvaliteta sna [2]
- 97% poboljšanja stanja kože [2]

Source: PIU May 2017 Italy. N = 142 adults (men and women) 30+ years old. Combined use of AtopiControl Lotion and Acute Care cream. (1) Validated DLQI questionnaire. (2) PIU questionnaire. Data on file BDF.

69.7% poboljšanje kvaliteta života [1]



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