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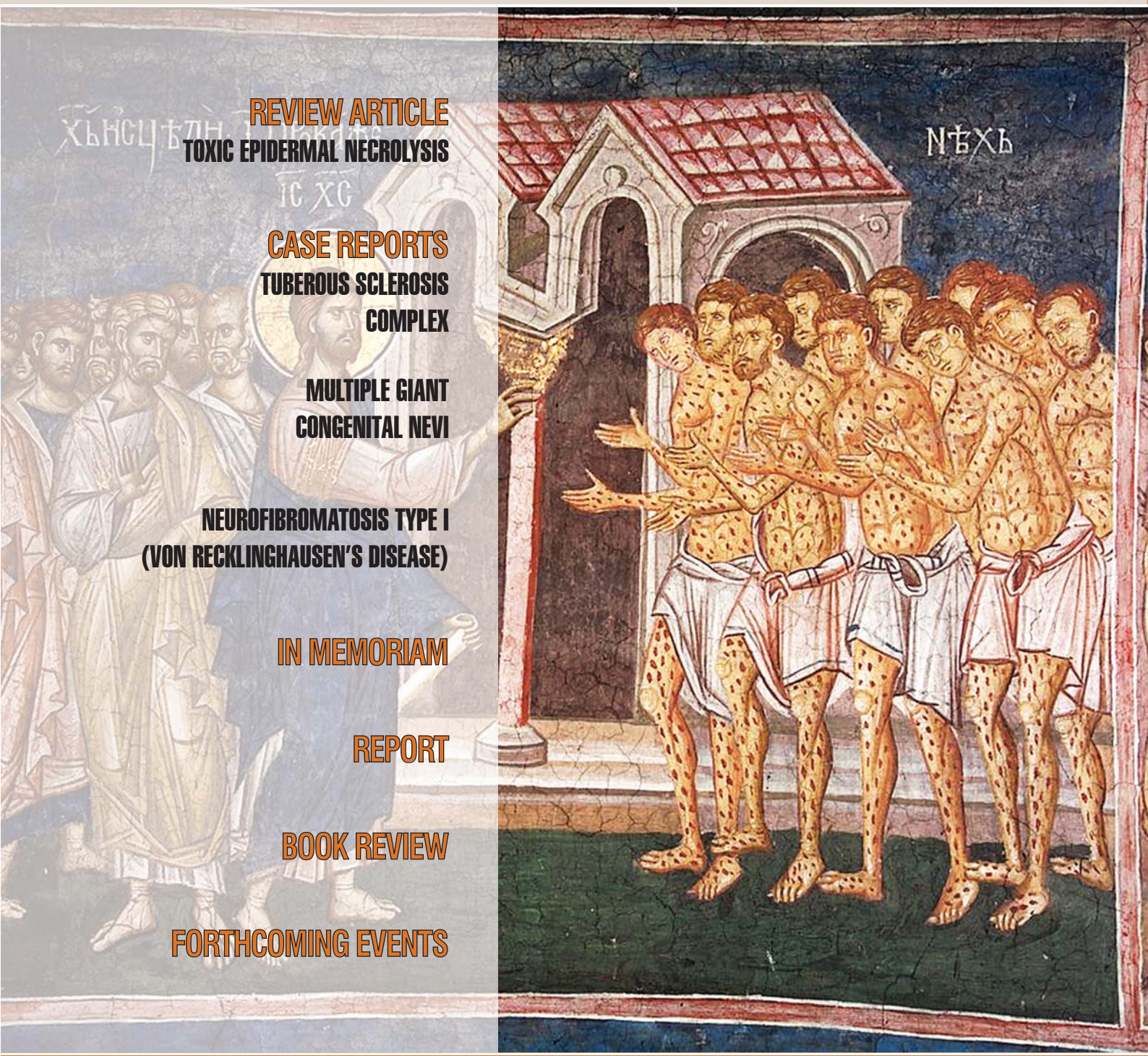

REVIEW ARTICLE

TOXIC EPIDERMAL NECROLYSIS

CASE REPORTS

TUBEROUS SCLEROSIS COMPLEX

MULTIPLE GIANT CONGENITAL NEVI

NEUROFIBROMATOSIS TYPE I (VON RECKLINGHAUSEN'S DISEASE)

IN MEMORIAM

REPORT

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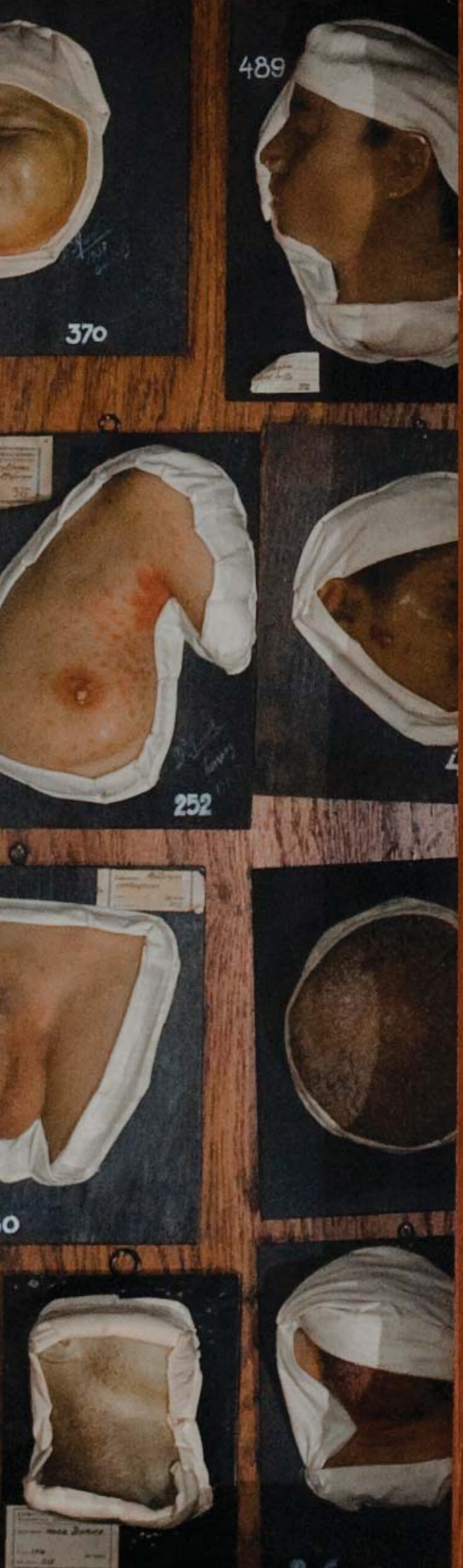

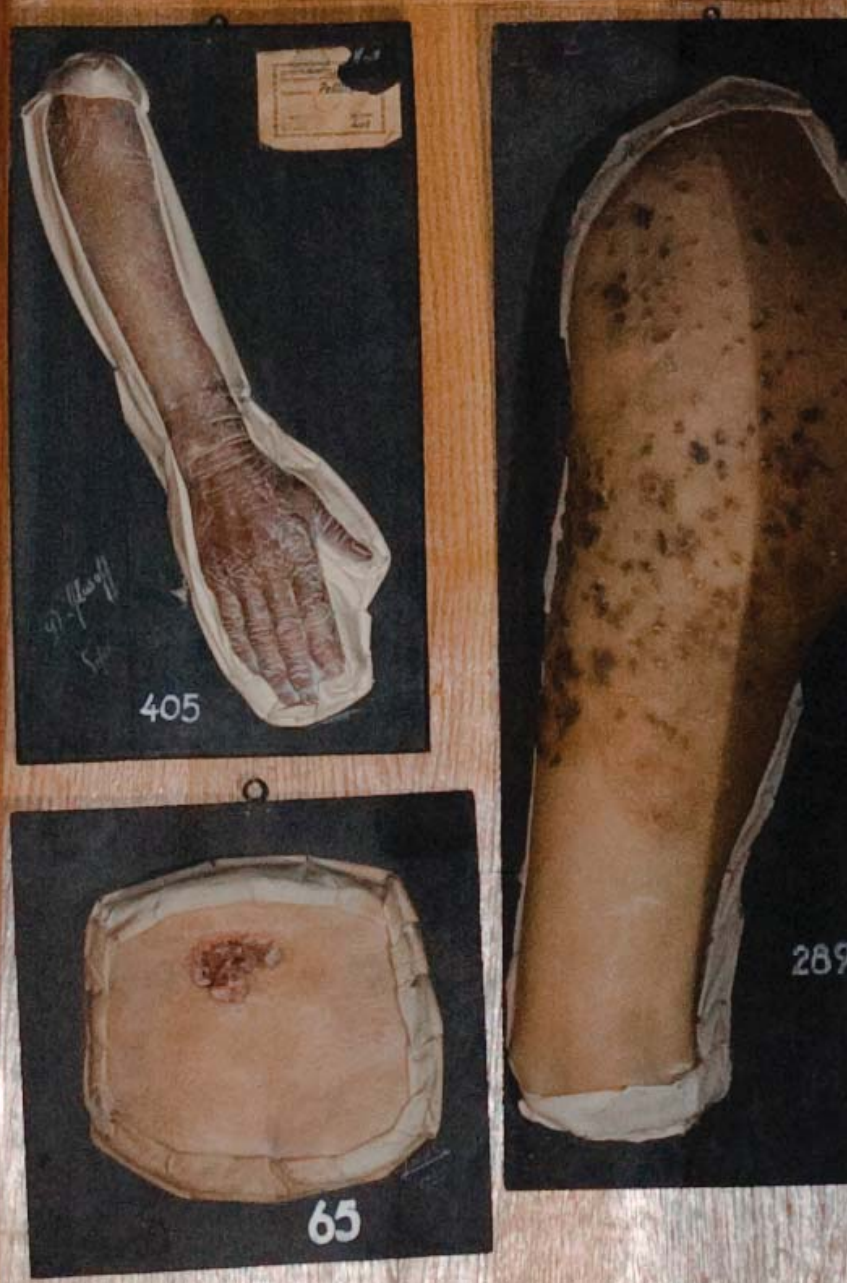

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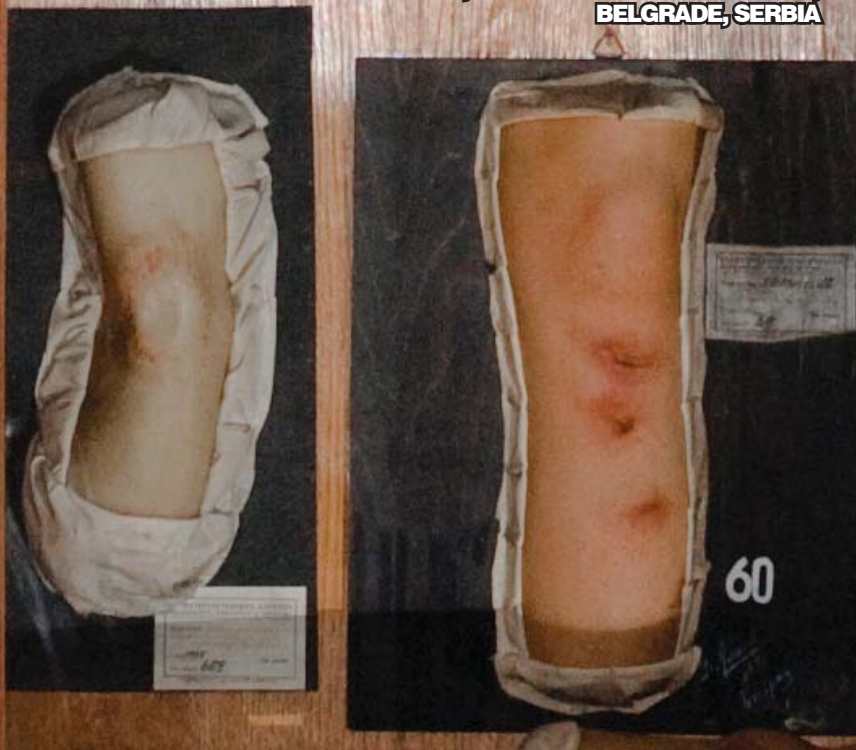

An update on diagnosis and treatment of toxic epidermal necrolysis

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Abstract

Toxic epidermal necrolysis is an idiosyncratic drug reaction which manifests with extensive epidermal detachment due to the massive keratinocyte apoptosis, mucous membrane involvement, and potentially lethal outcome. It is caused by adverse reactions to drugs, mostly idiosyncratic, unpredictable and independent of the applied dose, which develops 7-21 days after initiation of the drug, and is most commonly caused by the following drugs: sulfonamides, allopurinol, carbamazepine, phenobarbitone, phenytoin and oxycam group of nonsteroidal anti-inflammatory drugs. The treatment outcome depends on several factors, while older age, multiple drug use, late exclusion of the drug inducing toxic epidermal necrolysis, raised serum levels of urea, creatinine and cytopenia are poor prognostic indicators which are rated in SCORTEN scoring which proved to be of great help in the assessment of disease outcome. The basic approach to the treatment is early diagnosis, immediate suspension of the probable inducing drug, and emergency transport to the closest burn center, since treatment in burn units is associated with a lower risk of infection and mortality of these patients. Exclusion of the drug that induced toxic epidermal necrolysis, and supportive therapy, is the first and only therapy for which there is a consensus in different centers. Various forms of adjuvant therapy are also applied: in France, supportive therapy is a standard of care, in Germany it is short-term use of high-dose corticosteroids, while in USA, in the last decade high-dose intravenous immunoglobulins are the most widely accepted treatment modalities. Case reports and small patients' series described therapeutic effects of plasmapheresis, cyclosporine and other immunosuppressants. In conclusion, elimination of the possible causal agent, rapid transport to the burn unit, and multidisciplinary approach to treatment are of utmost importance for favorable outcome of the disease with 20-30% mortality rate. An update on diagnosis and the treatment of toxic epidermal necrolysis is provided in this review.

Key words

Epidermal Necrolysis, Toxic + diagnosis + therapy + etiology + epidemiology; Drug Toxicity; Signs and Symptoms; Disease Progression; Mortality; Prognosis

Toxic epidermal necrolysis (TEN) is an idiosyncratic drug reaction which manifests with extensive epidermal detachment due to the massive keratinocyte apoptosis, mucous membrane involvement, and potentially lethal outcome (1, 2). TEN belongs to the clinical spectrum of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and it is the most severe form of the disease, whereas distinction of these two entities relies on certain criteria – primarily on severity and percentage of body surface and mucous membrane involvement (Table 1).

Historically, toxic epidermal necrolysis and Stevens-Johnson syndrome were described within the clinical spectrum of erythema multiforme, where Stevens-Johnson syndrome was a member of a spectrum of *erythema multiforme major*. Although final consensus has not been reached, nowadays most authors consider these two entities to be separate (1-5).

Ruskin first described a condition similar to toxic epidermal necrolysis in 1948, whereas a Scottish dermatologist Alan Lyell first described 4 cases of acute exanthema with mucous membrane

Table 1. Clinical spectrum of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

	SJS	Overlap SJS/TEN	TEN
Primary lesion	Purple erythematous livid atypical target lesions	Purple erythematous, livid atypical target lesions	Poorly delineated erythematous plaques, spontaneous or friction-induced epidermal detachment
Distribution	Single, isolated lesions with confluence on the face	Single, isolated lesions, with confluence on the face and trunk	Single, isolated lesions, with confluence on the face, trunk and extremities
Mucous membrane involvement	Yes	Yes	Yes
Systemic symptoms	Sometimes present	Always present	Always present
Percentage of BSA involvement with epidermal necrolysis	< 10	10- 30	>30

Modified according to French LE (5); BSA, Body surface area; SJS, Stevens-Johnson Syndrome; TEN

involvement in 1956, so the disease was named after him – Lyell's disease (4). Lyell combined the main clinical feature – epidermolysis and necrosis – the main histopathological features. Out of 4 described, 2 patients in fact had staphylococcal scalded skin syndrome (SSSS), so the author believed that the disease was caused and mediated by bacterial toxins, so he named it – toxic (4). Nowadays, even though the diagnosis of TEN is mostly clinical, skin biopsy with histopathological analysis has an important role in differential diagnosis of these two diseases, especially in pediatric population.

Epidemiology, etiology and pathogenesis

Toxic epidermal necrolysis is caused by adverse reactions to drugs, mostly idiosyncratic, unpre-dictable and independent of the applied dose. The estimated annual incidence of SJS is 1.6-6/10^6, and of TEN it is 0.4-0.6/10^6. It is more common in women (female to male ratio of 1.5: 1), whereas the risk increases with age. TEN usually begins 7-21 days after initiation of the drug, although, very rarely, it may occur before the 7th day, but also after 28 days from taking the medication. In most cases, it is only possible to set the suspicion that a certain drug induced adverse reactions, because exposure testing is contraindicated in this group of patients. Furthermore, a common problem is the use of several medications simultaneously before the onset of reaction. For particular drugs, such as lamotrigine and carbamazepine, in vitro lymphocyte transformation assay has proven useful in identifying the drug which causes the reaction (6). Sassolas and associates constructed an algorithm (ALDEN) for assessment of Drug Causality in Epidermal Necrolysis, but this algorithm needs confirmation in larger studies (7). Except for drugs, cases of TEN after vaccination, exposure to industrial chemicals and fumigants have rarely been described, as well as extremely rare association with *Mycoplasma pneumoniae* infection (1-5).

More than 200 different drugs have been reported to cause TEN (Table 2), whereas in a large international study, conducted in 6 European cities (EuroSCAR), the following drugs showed significant association with the development of

Table 2. Drugs inducing toxic epidermal necrolysis

Group	Primarily involved drugs
Sulfonamides	(primarily trimethroprim/sulfamethoxazole)
Antibiotics	Aminopenicillins
	Cephalosporins
	Macrolides
	Quinolones
	Tetracyclines
Anticonvulsants	Carbamazepine
	Phenobarbitone
	Phenytoin
Nonsteroidal anti-inflammatory drugs	Oxycams
Other	Nevirapine
	Abacavir
	Alopurinol

*Modified according to Tartarone A. and Lerose R.

TEN: sulfonamides, allopurinol, carbamazepine, phenobarbitone, phenytoin and oxycam group of nonsteroidal anti-inflammatory drugs, as well as new drugs nevirapine and lamotrigine (8).

Bearing in mind that TEN is an idiosyncratic reaction to drugs, it can affect anyone, but it is likely that certain individuals may have a genetic predisposition, as is the case with a higher incidence of HLAB12 in patients with TEN, HLA*B5801 in patients with SJS/TEN reaction to allopurinol, and HLA*B1502 in patients with drug reactions to carbamazepine in different populations (9-11). An increased risk of developing TEN was reported in persons with reduced acetylating capacity (slow acetylators), in immunocompromised (HIV infection and lymphoma), and in individuals with brain tumors, undergoing radiotherapy and receiving anticonvulsants (5, 12).

The period of 1-3 weeks after initiation of drug therapy, which represents a refractory period before the development of TEN, shows that a specific immune response is responsible for the development of the disease. In subjects who previously had SJS/TEN reaction, this period is significantly shorter. The pathogenic substrate of toxic epidermal necrolysis is a massive, drug-induced apoptosis of keratinocytes, activated by drug-specific CD8+ cytotoxic lymphocytes (not by its metabolites, as previously assumed). The existence of drug-specific cytotoxic CD8+ lymphocytes was reported in two studies (13, 14). Presence of CD8+ T-lymphocytes expressing cutaneous lymphocyte antigen (CLA), responsible for skin homing, is already evident in the early stages of TEN (13, 14). It has been demonstrated that cytotoxicity of T-cells in TEN is mediated by

the granzyme, which causes programmed cell death by activating procaspase-8 and perforin, leading to formation of pores in the cells being in contact with T-lymphocytes (13-15). An increased expression of IL-6, TNF-α, IL-18, interferon-γ and FasL was reported in TEN lesions, originating from T-lymphocytes, monocytes/macrophages and keratinocytes (5, 16). Presence of these cytokines is responsible for general symptoms associated with the disease, while increased FasL expression on the surface of keratinocytes, probably induced by interferon-γ is responsible for massive apoptosis of keratinocytes by interaction with Fas molecule, which is constitutively expressed on the surface of keratinocytes (5, 17, 18). Except for the FasL expression on keratinocytes, presence of soluble FasL in the serum of patients with TEN was reported, showing its ability to induce apoptosis of normal keratinocytes (19). Increased concentration of IL-10 was also established, which probably has a role in the termination of an immune response.

Clinical manifestations

Toxic epidermal necrolysis begins with general symptoms: fever, shivering, sore throat, fatigue, cough, sometimes diarrhea and vomiting. This prodromal phase mimics acute respiratory infection and lasts 48-72 hours (rarely up to 7 days), after which generalized macular exanthema develops, with dark erythematous livid maculae of irregular borders, target-shaped with darker centers or bright red maculae with central bullae, which generally become confluent as they spread into great areas of erythema with epidermal detachment and positive Nikolsky sign (Figures 1 and 2). The detached epidermis on the surface of the skin resembles wet cigarette paper which peels away easily, so it is necessary to reduce the patient's movement to a minimum. First symptoms occur at the same time on the trunk, proximal extremities and face, later spreading to the neck, hands and soles, while in most patients, lower extremities are less involved. In less than 24 hours, extensive detachment of the epidermis may involve large skin areas.

Simultaneously, or sometimes a few days after the skin involvement, symptoms affect the mucous membranes of the eyes, nose, mouth, urethra, genitalia, gastrointestinal and mucous membranes of the lower respiratory tract (Figure 2 and 3). Mucous membranes of the eyes, nose, mouth, and genitalia are involved

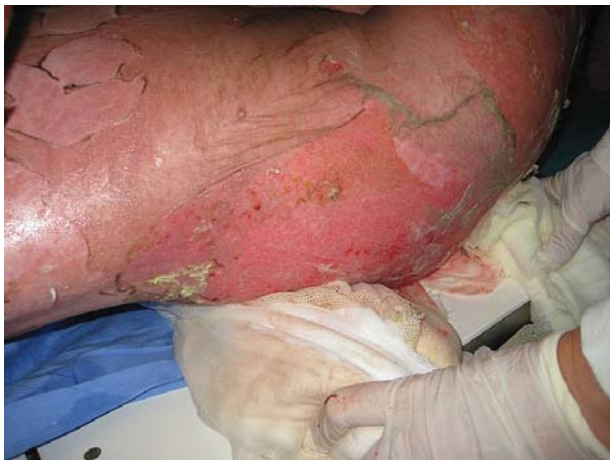

Figure 1. Widespread epidermal detachment resembling wet cigarette paper on the buttocks

in >90% of cases. Ocular manifestations may include purulent and pseudomembranous conjunctivitis, sometimes with erosions or corneal ulcerations, whereas oral lesions mostly occur along the lip vermilion. Involvement of respiratory mucous membranes is registered in 30% of cases, causing bronchial epithelial detachment and development of hypoxemia. In some cases, esophagitis, rectal hemorrhage, vomiting and diarrhea are the consequence of gastrointestinal tract mucous membrane involvement. Common systemic manifestations of the disease include hepatitis, leukopenia, thrombocytopenia and anemia, as well as elevated serum amylase (1-5, 20).

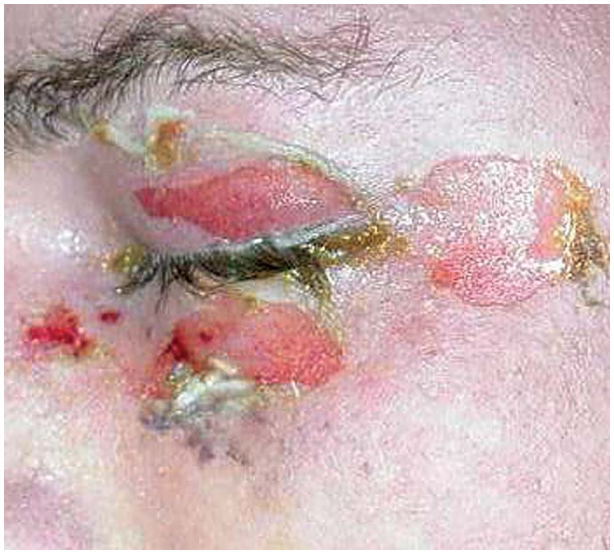

Figure 2. Erosions around the eyes with conjunctival eroisons and secretion

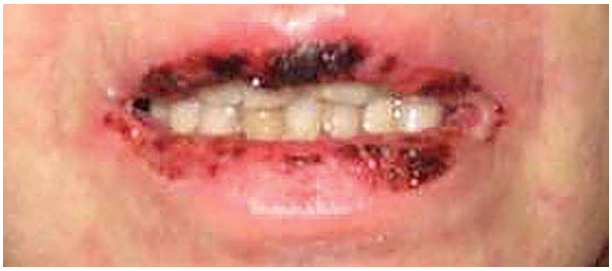

Figure 3. Healing erosions covered with hemorrhagic crusts on the lips

Massive transepidermal fluid loss leads to electrolyte imbalance with prognosis of hypoalbuminemia, insulin resistance, hypercatabolic state, with increased risk for disseminated intravascular coagulation. A compromised skin barrier function increases the risk of sepsis, mostly caused by *Staphylococcus aureus* or *Pseudomonas aeruginosa*, which are the most common causes of lethal outcome in patients with TEN (21).

Diagnosis, differential diagnosis and disease severity assessment

The diagnosis of toxic epidermal necrolysis is primarily based on the typical clinical symptoms, but skin biopsy is necessary for histological analysis and direct immunofluorescence test.

Histopathological analysis shows subepidermal cleavage with confluent keratinocyte necrosis of the whole epidermis and slightly pronounced perivascular lymphocytic infiltrate in the dermis (Figure 4). Rapid histopathological diagnosis is based on the analysis of cryostatic skin sections. Immunohistochemically, lymphocytes present in the epidermis are $CD8^+$, whereas those in the papillary dermis belong to $CD4^+$ subpopulation. Direct immunofluorescence analysis is important for differential diagnosis of TEN and autoimmune bullous dermatoses, some also drug-induced, as well as of lupus erythematosus (Table 3.). Based on clinical findings and massive necrosis of

Table 3. Differential diagnosis of toxic epidermal necrolysis

Disease
Staphylococcal scalded skin syndrome
Other severe adverse drug reactions:
Acute generalized exanthematous pustulosis
DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms)
Drug-induced linear IgA dermatosis
Erythema multiforme
Lupus erythematosus with symptoms similar to TEN
Acute graft versus host disease (GVHD)
Paraneoplastic pemphigus
Kawasaki disease (in children)
Thermal and chemical burns

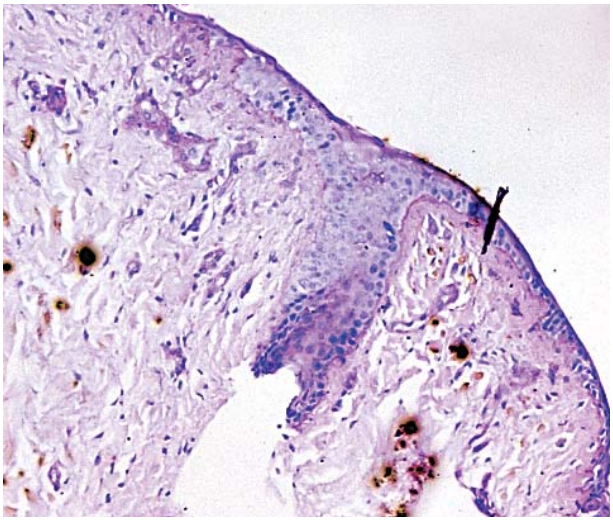

Figure 4. Subepidermal cleavage with confluent keratinocyte necrosis of the whole epidermis and sparse perivascular lymphocytic infiltrate in the dermis (H&E x100)

keratinocytes in the histopathological biopsy finding, it is possible to confirm the clinical diagnosis and make a differential diagnosis in relation to other diseases with symptoms of epidermal detachment (Table 3.).

Course and prognosis

Re-epithelialization starts 2-3 days after the onset of TEN, even concomitantly with emergence of new lesions, and it ends after 2-3 weeks. Long-term follow-up data on patients with TEN are scarse. The most common long-term morbidity involves the eyes, which means that consultation with ophthalmologist is mandatory in these patients, as well as intensive topical ophthalmologic therapy. During acute phase of the disease, ocular sequelae include development of entropion, symblepharon and synechiae, as well as dry eye, even in patients without significant eye mucous membrane involvement (1-5, 22). Sequelae also include nail dyschromia, whereas cutaneous scarring rarely leads to disturbances in affected persons. Management of oral mucous membrane and tongue lesions has been reported, as well as of genital (vaginal) mucous membranes, which may cause synechiae. That is why local intensive care of both oral and genital mucous membranes is of great importance.

The treatment outcome depends on several factors, while older age, multiple drug use, late exclusion of the drug inducing TEN, raised serum levels of urea, creatinine and cytopenia are poor prognostic indicators (22). Bastuji-Garin and associates created a scoring system called SCORTEN, which proved to be of great help in the assessment of disease outcome, although based on SCORTEN, some authors found an overestimated risk for lethal outcome in their patients (23-25) (Table 4.).

Treatment approaches

The basic approach to the treatment of toxic epidermal necrolysis is recognition of the disease, immediate

Table 4. SCORTEN – a TEN-specific severity of illness and mortality score

Clinical-biological parameters	Individual score	SCORTEN	Expected mortality (%)
Age > 40 years	Yes – 1, No - 0		
Malignant disease	Yes – 1, No - 0	0 - 1	3.2
Tachycardia > 120/min	Yes – 1, No - 0	2	12.1
Initial epidermal involvement >10%	Yes – 1, No - 0	3	35.3
Serum urea >10mmol/L	Yes – 1, No - 0	4	58.3
Serum glucose > 14mmol/L	Yes – 1, No - 0	>5	90
Bicarbonates < 20mmol/L	Yes – 1, No - 0		

suspension of the probable inducing drug, and emergency transport to the closest burn center. It was found that the treatment in burn units is associated with a lower risk of infection and mortality of these patients, as well as shorter hospital stay (26 – 28).

General measures

General measures are fundamental for the outcome of the disease, including metabolic balance control and skin care, which is essential for prevention of skin infections and sepsis.

Anamnestic data should provide information on a new drug introduced during the past month, and even earlier appearance of skin reactions associated with certain medications. It is necessary to exclude from therapy all unnecessary medications and any medication that is suspected to cause TEN (1-5, 26, 28). Initial lab tests should include sedimentation rate (ESR), C-reactive protein (CRP), complete blood count (CBC) with leukocyte formula, biochemical tests including urea, creatinine, albumins, total proteins, total bilirubin, electrolytes, liver enzymes, biochemical analysis and analysis of urinary sediment, procalcitonin if DRESS syndrome is suspected, and IgA if intravenous immunoglobulin therapy is intended. Also, chest x-ray is recommended. In case of fever it is necessary to obtain blood, urine and sputum cultures, as well as eye and skin swabs on admission, and later every three days. Skin biopsy is necessary for histopathological analysis and direct immunofluorescence, best obtained on the borderline of the affected and nonaffected skin (1-5, 26, 28).

In order to prevent hypothermia, the room temperature should be maintained at 30º C. Based on laboratory findings, fluid and electrolyte replacement is initiated, preferably using peripheral venous access, which is better than using a central venous catheter (28). Fluid replacement requirement is lower than in patients with burns, so monitoring and maintenance of diuresis is mandatory at 60-80 ml/h, in order to avoid hypervolemia. Broad spectrum antibiotics are not recommended if there are no signs of sepsis or infection, but if they are present, the therapy should be modified according to the antibiogram results based on microbiological analyses. If there is doubt, serological test for *Mycoplasma pneumoniae* should be performed, which is recommended as routine analysis in TEN patients, in some centers (1-5, 28).

If food intake is not possible, it is best to start with total parenteral nutrition (TPN), because it is associated with better disease outcome (29). Except for oral cavity erosions, gastrointestinal mucous membrane involvement significantly reduces absorption of nutrients, so in this case TPN is more effective (1-5). Just as in patients with burns, nutritional requirements are calculated according to the percentage of the affected area (29). On the other hand, some centers use nasogastric tubes for nutrition, while other authors point out that due to involvement of the gastrointestinal tract, it should be avoided, and the decision should be made individually for each patient (1-5, 29). As in intensive care patients, prevention of deep vein thrombosis is necessary using low molecular heparin, as well as prevention of stress ulcerations using proton pump inhibitors. In case of significant leukopenia development (1000/ml), use of G-CSF (filgrastim) growth factor is indicated (1-5, 28). Consultations with ophthalmologists, otolaryngologists, gastro-enterologists and pulmologists are necessary for evaluation of certain mucous membrane involvement, as well as for choosing adequate therapy. That is why a multidisciplinary approach to treatment is of great importance for a favorable outcome.

Local therapy and skin care

Today, conservative wound treatment is essential. Bullae should be punctured, and roof should be left on the skin, since it can speed re-epithelialization. Debridement is done only in areas with pronounced necrosis and if signs of infection are present. A non-adhesive vaseline-impregnated dressing is a good choice at places where the epidermis is present, whereas according to different studies, open erosions should be treated by special silver-impregnated dressings, artificial skin substitutes, or biological materials which are not easy to obtain (1-5, 28). According to the protocols, published by the University of Miami in 1991 and 2007, including guidelines for TEN therapy, non-adhesive dressings with 0.5% silver-nitrate changed every three days are sufficient for infection control, which can significantly facilitates patient care (28). A group of authors, however, believe that preparations containing silver sulfadiazine may be used in patients without hypersensitivity to medications with sulfa group, whereas Guidelines of the University of Miami

do not recommend silver-sulfadiazine in patients with TEN, especially not on large body surfaces, due to risk of systemic sesnsibilization and leukopenia (28).

Management of mucous membranes and early inclusion of ophthalmologists in the treatment is necessary to prevent complications, especially development of synechiae. Vaseline impregnated gauze is used for the lips, oral antiseptics are used for mouth wash (hydrogen peroxide, chlorhexidine and so on) and anesthetics in oral gel for reduction of oral pain. Ophthalmologic treatment includes administration of eye drops every 2-3 hours, and combination of antibiotics and corticosteroid creams preparations every 6 hours. Vaseline dressing in the genital area is recommended few times a day, and are also very important for prevention of synechiae (1-5, 28).

Pharmacological therapy

Exclusion of the drug inducing TEN, and supportive therapy, is the first and only therapy for which there is a consensus in different centers. Various forms of adjuvant therapy are applied in various countries. In France, supportive therapy is a standard of care, in Germany it is short-term use of high-dose corticosteroids, while in USA, in the last decade high-dose intravenous immunoglobulins are the most widely accepted treatment modality (1-5, 26, 28). A retrospective multicetner European study (EuroSCAR), published in January of 2008, including 75 patients, showed that there is no certain evidence that treatment with intravenous immunoglobulins and short-term corticosteroid pulse therapy have any effects on TEN outcomes. Similar studies examined effects of plasmapheresis, cyclosporine and other immunosuppressants (30).

In some studies, use of corticosteroids showed positive effects on disease outcome, while in other increased mortality was reported. That is why majority of experts today believe that long-term use of corticosteroids is contraindicated in patients with TEN, due to prolonged re-epithelialization and increased risk of sepsis. Also, in the presence of TNF-α, corticosteroids decrease NF-KB expression and proapoptotic effects, possibly explaining poor disease outcome with use of corticosteroids (26, 31). In some centers, primarily in Germany, the use of corticosteroids continued in the form of pulse therapy of 250 mg during 2-5 days (30, 32). However, the multicenter study from 2008, EuroSCAR, showed that the average 5-day 60 mg corticosteroid therapy (in France) and 250 mg a day (in Germany) did not affect disease outcome, but authors suggest that their effects could probably be shown in a larger study. Until then, use of high-dose corticosteroid therapy may be justified only in the early phase of the disease, while long-term therapy is contraindicated (1-5, 26, 31).

High-dose intravenous immunoglobulin therapy has been accepted by some experts in USA as the first line therapy in the last decade based on findings that intravenous immunoglobulins can inhibit Fas-FasL interaction. Most studies investigating intravenous immunoglobulin therapy – 3-4 g/kg/BW (1g/kg/BW a day, during 3 days) in the first 48-72 hours from the onset of the disease, showed relief of symptoms and fast re-epithelialization, as well as significantly lower mortality in comparison to historic controls in one study, and in comparison to supportive measures in another (33, 34). In several studies, however, intravenous immunoglobulins showed no significant difference in disease outcome, although in many of them the dosage of immunoglobulins was lower, or the therapy was initiated after 48-72 hours from the onset (30, 35). EuroSCAR study from 2008, conducted in several European countries, reported no significant effects of intravenous immunoglobulin therapy, but the average dose used in patients was only 1.9g/kg/BW (35).

Plasmapheresis has proven successful in treating various antibody and immune complex mediated diseases. Several studies have shown favorable effects of plasmapheresis on the course of TEN, whereas in some studies it was combined with primary intravenous immunoglobulins with accelerated effects (36, 37, 38). It is not known whether the effect of plasmapheresis is associated with removing the drug inducing the disease from the blood, or removing the inflammatory mediators. However, in two case reports, patients treated with plasmapheresis showed decreased concentrations of Il-6, IL-8, and TNF-alpha in 1 patient, which may explain the mechanism of action of this treatment modality (39).

A total of 18 patients with TEN, reported so far, was treated with cyclosporine, due to the role of T-lymphocytes in the pathogenesis of the disease, with favorable effects on promoting re-epithelialization, but it was a small sample and an uncontroled study

(38-40). Nonetheless, Arevalo and associates treated 11 patients with cyclosporine (3mg/kg/BW) and reported reduced mortality in regard to the control group of patients with the same anamnesis who were not treated with cyclosporine (40). Prospective studies are necessary for the final verdict on this modality of treatment. Furthermore, due to the importance of TNF-alpha in the pathogenesis of the disease, biological therapy with infliximab and etanercept was used in individual cases with TEN, with fairly good response to therapy (41, 42).

Cyclophosphamide was also used in individual cases, but given its significant side effects and lack of evidence of its effectiveness, this medication is not recommended in the current treatment of TEN (2). Wolkenstein and associates started a placebo-controlled study of thalidomide with immunosuppressive and anti-angiogenic effects, mediated by reduced release of TNF-alpha from monocytes. However, the study was ended because higher mortality was recorded in the group of patients receiving thalidomide (43).

Conclusion

In conclusion, toxic epidermal necrolysis is one of the most serious emergency conditions in dermatology. Elimination of the possible causal agent, rapid transport to the burn unit, and multidisciplinary approach to treatment are of utmost importance for favorable outcome of the disease with mortality rate reduced to 20-30%.

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Novine u dijagnostici i lečenju toksične epidermalne nekrolize

Sažetak

Definicija: Toksična epidermalna nekroliza (TEN) je idiosinkratička reakcija na lek, koju je, usled masivne nekroze keratinocita, karakteristična po ekstenzivnom odvajanju epiderma i zahvatanjem sluzokoža sa potencijalnim smrtnim ishodom zbog mogućih komplikacija.
Istorijski podaci: Oboljenje slično toksičkoj nekrolizi epiderma prvi put je opisao Ruskin 1948. godine, dok je škotski dermatolog Alan Lajel (Alan Lyell) 1956. objavio četiri slučaja akutnog egzantema sa zahvatanjem sluzokoža, po kome je ovo oboljenje dobilo svoj drugi naziv – Lajelova bolest. Lajel je u nazivu bolesti kombinovao epidermolizu kao glavnu kliničku i nekrozu kao glavnu histopatološku odliku bolesti. Dva pacijenta, od opisanih četiri, zapravo su bili oboleli od stafilokoknog sindroma oparene kože (engl. *staphylococcal scalded skin syndrome*, SSSS), te je autor smatrao je oboljenje izazvano i posredovano bakterijskim toksinima, nazivajući je *toksičkom*. I danas, uprkos tome što je dijagnoza TEN najčešće klinička, biopsija kože sa histopatološkom analizom ima značajnu ulogu u diferencijalnoj dijagnozi ova dva oboljenja, posebno u pedijatrijskoj populaciji.
Etiopatogeneza: Imajući u vidu da je idiosinkratička, može se javiti potpuno nepredvidivo i nezavisno od

primenjene doze leka, od 7. do 21. dana od započinjanja terapije, i to najčešće izazvana sledećim lekovima: sulfonamidi, alopurinol, karbamazepin, fenobarbiton, fenitoin i oksikamski nesteroidni antiinflamatorni lekovi. Imajući u vidu da je u pitanju idiosinkratička reakcija na lek, ona može da se javi kod bilo koga, ali je verovatno da postoji genetska predispozicija, kao što je slučaj sa većom učestalošću HLA B12 kod pacijenata sa TEN, HLA*B5801 kod pacijenata sa SJS/TEN reakcijom na alopurinol i HLA*B1502 kod pacijenata koji su imali reakciju na karbamazepin u različitim populacijama. Povećan rizik od nastanka TEN zabeležen je kod osoba sporih acetilatora, kod imunokompromitovanih (HIV infekcija i limfomi) i kod osoba sa tumorima mozga koji su na radioterapiji i uzimaju antikonvulzive.

Period od jedne do 3 nedelje, koji prođe od početka uzimanja leka do razvoja reakcije TEN, ukazuje na to da je specifičan imunoodgovor odgovoran za nastanak oboljenja. Kod osoba koji su već imale manifestacije SJS/TEN, ovaj period je znatno kraći. Patogenetski supstrat toksičke epidermalne nekroliza je masivna apoptoza keratinocita izazvana lekom, aktivicijom indukovane apoptoze posredovane $CD8^+$ citotoksičnim limfocitima specifičnim za lek (a ne za njegove metabolite, kako se ranije pretpostavljalo). Postojanje citotoksičnih CD8+ limfocita specifičnih za lek je pokazano u dve studije. Prisustvo CD8+ T-limfocita koji eksprimiraju i kutani limfocitni antigen (engl. *cutaneous lymphocyte antigen-CLA*), koji je odgovoran za usmeravanje T-limfocita u kožu, evidentno je već u ranim fazama TEN. Dokazano je da je citotoksičnost T-ćelija u TEN posredovanoj grenzimom koji izaziva programiranu ćelijsku smrt aktivacijom prokaspaze-8 i perforinom koji dovodi do stvaranja pora na ćeliji koja je u kontaktu sa T-limfocitom. U lezijama TEN zabeležena je povećana ekspresija IL-6, TNF-α, IL-18, interferona-γ i FasL, poreklom od T-limfocita, monocita/makrofaga i keratinocita. Prisustvo navedenih citokina odgovorno je za opšte simptome koji prate oboljenje, dok je povećana ekspresija FasL na površini keratinocita, najverovatnije indukovana interferonom γ odgovorna za masovnu apoptozu keratinocita interakcijom sa Fas molekulom, koji se konstitutivno eksprimira na površini keratinocita. Osim ekspresije FasL na keratinocitima, zabeleženo je prisustvo solubilnog FasL u serumu pacijenata sa TEN i pokazana njegova sposobnost da indukuju apoptozu normalnih keratinocita. Povećana koncentracija IL-10 koja je takođe utvrđena, verovanto ima ulogu u terminaciji imunoreakcije.

Dijagnoza, diferencijalna dijagnoza oboljenja i procena težine bolesti: Dijagnoza bolesti postavlja se pre svega na osnovu tipične kliničke slike, ali je neophodno učiniti biopsiju kože radi histopatološke analize i direktnog imunofluorescentnog pregleda.

Histopatološka analiza ukazuje na prisustvo subepidermalnog rascepa sa konfluentnom nekrozom keratinocita celog epiderma i blago izraženim perivaskularnim limfocitnim infiltratom u dermu. Brza histopatološka dijagnoza moguća je i na osnovu pregleda kriostatskih preseka kože. Imunohistohemijski, limfociti koji su prisutni u epidermu su $CD8^+$, dok su oni u papilarnom dermu pripadaju $CD4^+$ subpopulaciji. Direktni imunofluorescentni pregled je važan za diferencijalnu dijagnozu TEN i autoimunih buloznih dermatoza od kojih su neke takođe pokrenute lekom, kao i eritemskog lupusa. Na osnovu kliničke slike i nalaza masovne nekroze keratinocita u histopatološkom nalazu bioptata kože, moguće je potvrditi kliničku dijagnozu i napraviti diferencijalnu dijagnozu u odnosu na druga oboljenja koja se manifestuju odvajanjem epiderma.

Lečenje: Osnovni pristup lečenju je što ranija obustava leka uzročnika i svih nepotrebnih lekova u terapiji, te hitan transport u jedinicu za opekotine, jer je lečenje u njoj povezano sa nižim rizikom od infekcije i smanjenjem smrtnosti ovih bolesnika. Postignut je konsenzus u različitim centrima u svetu da terapiju izbora predstavljaju prekid terapije inkriminisanim lekom i simptomatska potporna terapija: nadoknada tečnosti i elektrolita, regulacija temperature, parenteralna ishrana, lokalna terapija i nega kože i sluzokoža. Različiti oblici adjuvantne terapija primjenjuju se u različitim zemljama: u Francuskoj, suportivna terapija je standard lečenja, u Nemačkoj to je kratkotrajna primena visokih doza korstikosteroida (2-5 dana), dok je u SAD-u, u poslednjih deset godina terapija visokim dozama intravenskih imunoglobulina široko prihvaćen način lečenja. Prikazi slučajeva i prikazi serija ispitivanja koji su sprovedeni na malom broju pacijenata opisuju i povoljan terapijski učinak plazmafereze, ciklosporina i drugih imunosuppresiva.

Lokalna terapija i nega kože: Danas preovlađuje stav o konzervativnoj obradi rana: bule je potrebno probušiti i epiderm ostaviti kao prirodnu oblogu koja će ubrzati epitelizaciju, dok je debridman potreban samo na pojedinim mestima sa izraženom nekrozom i znacima

infekcije. Sloj neadhezivnih zavoja impregniranih vazelinom na mestima gde je epiderm prisutan je dobar izbor, dok na mestima gde postoje otvorene erozije, u različitim studijama su opisani ili posebne obloge impregnirane najčešće srebrom, veštački supstituenti kože, ili biološki materijali koji su teško dostupni. Prema protokolima sa Univerziteta u Majamiju koji su u 1991. i 2007. godine objavili svoje vodiče za lečenje TEN, neadhezivni oblozi sa 0,5% srebro-nitratom su dovoljni za kontrolu infekcije, a menjaju se na svaka tri dana, što značajno olakšava negu. Prema jednim autorima, preparati sa srebrosulfadijazinom mogu da se primenjuju kod pacijenata koji nisu preoseltjivi na lekove sa sulfa grupom, dok je prema vodiču sa Univerzieta u Majamiju srebrosulfadijazin ne treba primenjivati kod pacijenata sa TEN, posebno ne na velike površine tela, zbog rizika od sistemske senzibilizacije i leukopenije.

Nega sluzokoža i rano uključivanje oftalmologa u lečenje je neophodno za sprečavanje komplikacija tokom ožiljavanja, pre svega stvaranja sinehija. Gaze impregnirane vazelinom za usne, ispiranje usne duplje oralnim antiseptikom (vodonik-peroksid, hlorheksidin, i sl.), primena lokalnog anestetika u vidu gela za usnu duplju sa ciljem smanjenja bolova u usnoj duplji osnova su simptomatske terapije oralne sluzokože. Oftalmološka terapija podrazumeva primenu veštačkih suza na svaka 2-3 sata, kombinaciju antibiotika i kortikosteroida u vidu oftalmološke masti svakih 6 sati. Primena vazelina za regiju genitalne sluzokože više puta dnevno je takođe važna za sprečavanje stvaranja sinehija.

Farmakološka terapija: Isključivanje leka uzročnika TEN iz terapije i suportivna terapija su prva i jedina terapija za koju postoji konsenzus među različitim centrima. Stav većine autora danas jeste da je dugotrajna primena kortikosteroida kod pacijenata sa TEN kontraindikovana, zbog mogućeg produženja vremena reepitelizacije, i povećanja rizika od sepse. U nekim centrima, pre svega u Nemačkoj, primena kortikosteroida je nastavljena u vidu kratkotrajnih pulseva od 250 mg tokom tokom 2-5 dana. Primena kortikosteroida je možda opravdana samo u ranoj fazi bolesti u visokim dozama, dok je dugotrajna terapija kontraindikovana.

Terapija visokim dozama intravenskih imunoglobulina prihvaćena je u poslednjoj deceniji na osnovu nalaza moguće blokade Fas-FasL interakcije primenom ove terapije. U većini studija sa primenom IvIg u dozama od 3-4 g/kg TT (1g/kg TT dnevno, tri dana) i to u prvih 48-72 h od početka bolesti, pokazano je zaustavljanje širenja promena i brza epitelizacija. U nekoliko studija, međutim, nije pokazan značajan efekat intravenskih imunoglobulina, mada je u mnogima od njih doza primenjenih imunoglobulina bila manja ili je početak terapije bio posle 48-72 h. Plazmafereza se pokazala uspešnom u lečenju različitih oboljenja posredovanih antitelima i imunokompleksima. U TEN, u nekoliko studija je pokazan povoljan efekat plazmafereze na tok bolesti, a u nekima je plazmafereza bila kombinovana sa primenom intravenskih imunoglobulina sa brzim efektom. Nije poznato da li je efekat plazmafereze povezan sa uklanjanjem leka – uzročnika iz krvi ili uklanjanjem inflamatornih medijatora, mada je u prikazu slučaja dva pacijenta lečena plazmaferezom zabeleženo smanjenje koncentracije IL-6, IL-8 i TNF-α kod jednog pacijenta, što može da objasni mehanizam dejstva ovog modaliteta terapije.

Biološka terapija infliksimabom i etanerceptom korišćena je u pojedinačnim slučajevima TEN sa dobrim odgovorom na terapiju.

Ciklofosfamid nema mesto u savremenoj terapiji. Wolkenstein i saradnici su započeli placebom kontrolisanu studiju primene talidomida, koji ima imunosupresivne i antiangiogene efekte, posredovane između ostalog smanjenjem oslobađanja TNF-α iz monocita. Ipak, studija je prekinuta jer je zabeležen veći mortalitet u grupi kod koje je primenjen talidomid.

Tok i prognoza: Loši prognostički faktori kao što je starije životno doba, primena multiplih lekova, kasno isključenje leka – uzročnika, pojava uremije, povišenih vrednosti kreatinina i citopenije, zbirno se boduju u SCORTEN sistemu, koji se pokazao korisnim u proceni ishoda bolesti čija je smrtnost 20-30%.

Zaključak: Prekid terapije lekom verovatnim uzročnikom, hitan transport u jedinicu za opekotine i multidisciplinarni pristup lečenju su najvažniji za povoljan ishod bolesti.

Ključne reči

Toksična epidermalna nekroliza + dijagnoza + terapija + etiologija + epidemiologija; Toksičnost lekova; Znaci i simptomi; Tok bolesti; Mortalitet; Prognoza

Tuberous Sclerosis Complex - A case report

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Abstract

Tuberous sclerosis complex is a multisystem, autosomal dominant disorder affecting children and adults, which results from mutations in either of two genes, TSC1 (encoding hamartin) or TSC2 (encoding tuberin). Tuberous sclerosis complex often causes disabling neurologic disorders, including epilepsy, mental retardation, and autism. Major features of the disease include dermatologic manifestations, such as facial angiofibromas, renal angiomyolipomas, and pulmonary lymphangiomyomatosis.

We report a 20-year-old woman with epilepsy and subnormal intelligence, who was admitted for evaluation of multiple facial papules that have gradually increased in number over the past 15 years. She had been previously diagnosed with tuberous sclerosis complex based on findings of cardiac ventricular rhabdomyomas, tuberosclerotic nodules of glial proliferation in the cerebral cortex, and renal angiomyolipoma. The facial papules were angiofibromas, confirming the clinical presentation of tuberous sclerosis complex. Detailed examination of the skin and mucosa revealed Shagreen patches, nontraumatic subungual and gingival fibroma, all features of tuberous sclerosis complex.

A multidisciplinary team approach was used for diagnosis and medical care of tuberous sclerosis complex in order to treat many organ systems affected by tuberous sclerosis in our patient. The patient received antiepileptic medications, while rapamycin was recommended.

Key words

Tuberous Sclerosis; Comorbidity; Diagnosis; Anticonvulsants; Sirolimus; Adult

Tuberous sclerosis complex (TSC) is a multisystem, autosomal dominant disorder affecting children and adults which results from mutations in either of two genes, *TSC1* (encoding hamartin) or *TSC2* (encoding tuberin). TSC often causes disabling neurologic disorders, including epilepsy, mental retardation, and autism. Major features of the disease include dermatologic manifestations, such as facial angiofibromas, renal angiomyolipomas, and pulmonary lymphangiomyomatosis.

Though genetic testing for *TSC1* and *TSC2* mutations is commercially available, current diagnostic criteria are still based on clinical manifestations.

We describe the clinical and laboratory findings of a 21-year-old female patient with TSC.

Case presentation

A 21-year-old woman with epilepsy and subnormal intelligence, previously diagnosed with TSC, was admitted to University Clinic of Dermatology in Skopje for evaluation of multiple facial papules that have gradually increased in number over the past 15 years. Her facial papules were previously misdiagnosed as acne vulgaris and mollusca contagiosa. A diagnosis of facial angiofibromas (Fig. 1.), a major feature of TSC, was made. Detailed examination of the skin and mucosa revealed Shagreen patches in the lumbosacral region (Fig. 2.), nontraumatic subungual fibroma (Koenen tumor) (Fig. 3.) and gingival fibroma (Fig. 4.), all features of TSC.

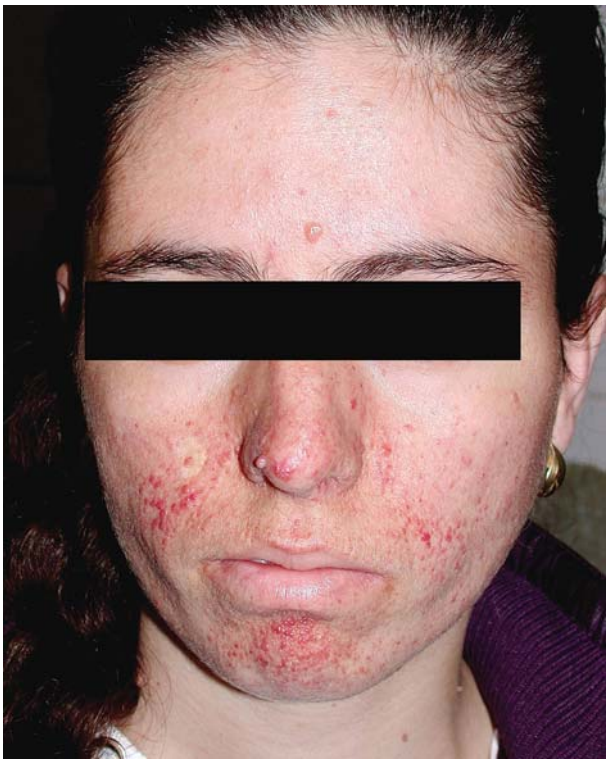

Figure 1. Multiple facial angiofibromas a major feature of TSC

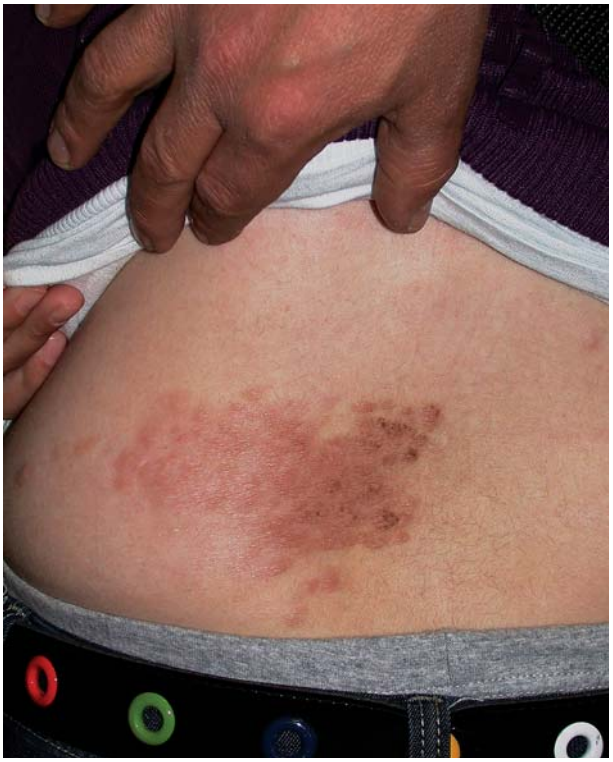

Figure 2. A chagreen patsh in lumbosacral region

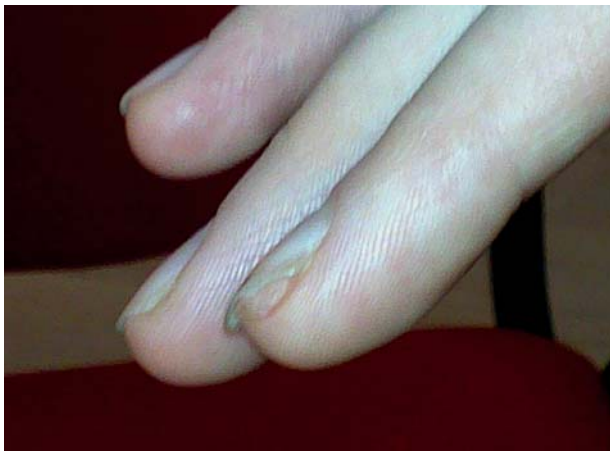

Figure 3. Nontraumatic subungual fibroma-Koenen tumor

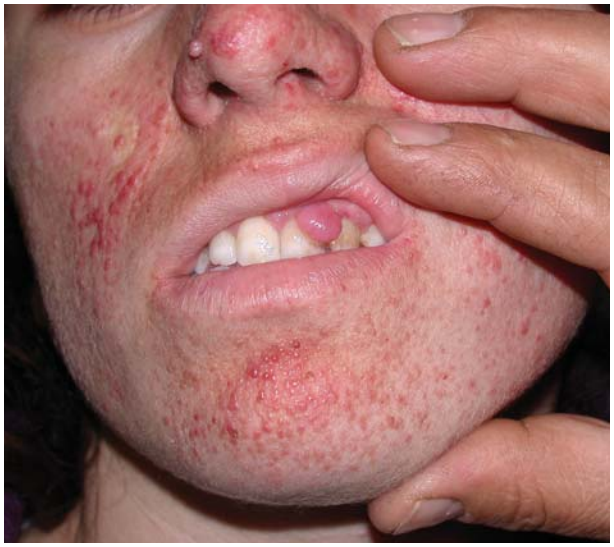

Figure 4. Gingival fibroma

A skin biopsy was obtained from facial papule for histopathologic analysis. It revealed dermal fibrosis, associated with vascular proliferation and dilatation. Also, compression of hair follicles was noted, which was due to growth of dermal fibrous tissue (Fig. 5.).

The diagnosis of TSC was previously made based on the presence of tuberosclerotic nodules of glial proliferation in the cerebral cortex - parietal, frontal and occipital lobes, cardiac ventricular rhabdomyomas and angiomyolipoma in the left kidney.

The patient was without significant family medical history; specifically, no family members suffered from mental retardation, seizures, skin lesions, or renal diseases.

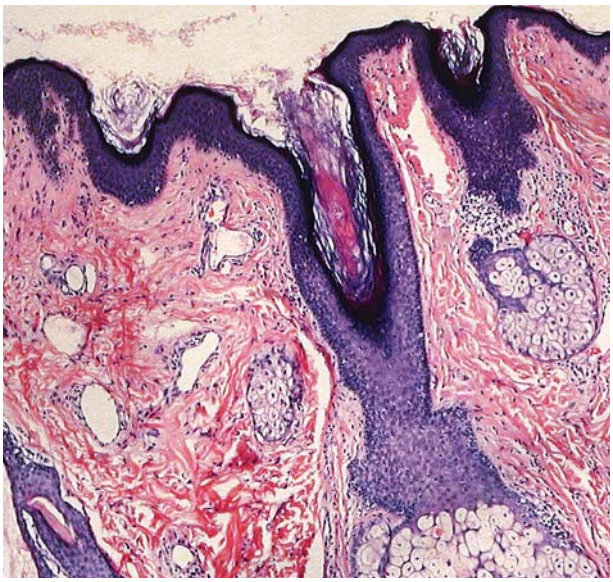

Figure 5. Histopathology pattern of skin biopsy showed abundant sebaceous glands, subepidermal fibroblast proliferation and associated vascular proliferation and dilatation.(H&E x 100)

Disscusion

Tuberous sclerosis complex is an autosomal dominant disorder characterized by the formation of hamartomatous lesions in multiple organ systems. It has a prevalence of about 1 in 6,000 newborns and affects approximately 1.5 million people worldwide, occurring in all races and both genders equally (1).

TSC is an autosomal-dominant disorder with high penetrance and variance (2). The mutation rate in TS is high, and 60-70% of cases seem to present with new mutations (3).

The diagnostic criteria for TSC consist of a set of major and minor diagnostic features (4). Cases meeting these criteria fulfill a clinical diagnosis of TSC; the results of molecular genetic testing of the *TSC1* or *TSC2* loci are currently viewed as corroborative (5).

Almost all patients with TSC have numerous cutaneous stigmata, some of which can be subtle (5, 6).

Hypopigmented macules, also known as ash-leaf spots, are generally detected in infancy or early childhood, whereas the so-called shagreen patches are identified with increasing frequency after the age of 5. Subungual fibromas typically appear after puberty, but may develop in adulthood. Facial angiofibromas, formerly called adenoma sebaceum, may be detected at any age, but they are generally more common in late childhood or adolescence (5). We found all cutaneous stigmata in our patient, including facial angiofibromas, shagreen patches and subungual fibroma with exception of hypopigmented macules.

Seizures are the most common symptoms of tuberous sclerosis. Epilepsy due to tuberous sclerosis usually starts in infancy or childhood, in 80-90% of cases (7). This applies to our patient as well. She has had epilepsy since her early childhood.

Neurologic manifestations of TSC, which include epilepsy, cognitive disability, and neurobehavioral abnormalities, such as autism, appear to be closely related to cerebral cortical tubers, that are present in over 80% of patients. Tubers are developmental abnormalities of the cerebral cortex histologically characterized by a loss of the normal six-layered structure of the cortex, and by dysmorphic neurons, large astrocytes, and a unique type of cells known as giant cells (8, 9).

Approximately half of the individuals diagnosed with tuberous sclerosis complex present with global intellectual impairment and developmental psychopathologies (10). In our patient it was subnormal intelligence.

Renal lesions commonly associated with tuberous sclerosis are angiomyolipomas (11). Angiomyolipomas, despite frightening histopathologic appearance, are benign (12). In our patient computerized tomography revealed an angiomyolipoma of the left kidney.

Up to two-thirds of newborns with TSC have rhabdomyomas, and they are often multiple (13). Cardiac rhabdomyomas are intracavitary or intramural tumors that are present in nearly 50 to 70% of infants with TSC. However, they cause important clinical problems in only a very small fraction of these patients (5). There are reports of complete regression of rhabdomyomas in patients with TSC (14). Using ultrasonography, cardiac ventricular rhabdomyomas were detected in our patient.

Conclusion

We report a case of tuberous sclerosis complex with 6 major features of tuberous sclerosis: facial angiofibromas, Shagreen patch, nontraumatic subungual fibroma, tuberosclerotic nodules of glial proliferation in the cerebral cortex, cardiac ventricular rhabdomyomas, renal angiomyolipoma, and 1 minor feature: gingival fibroma. The patient was treated with antiepileptic medications, while rapamycin was recommended.

A multidisciplinary team approach is needed for diagnosis and medical care of tuberous sclerosis complex in order to treat many organ systems that are affected. For diagnostic evaluation, full dermatological examination of the skin is necessary.

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Kompleks tuberozne skleroze – prikaz slučaja

Sažetak

Uvod: Kompleks tuberozna skleroza (*eng. tuberous sclerosis complex* – TSC), multisistemsko, autozomno dominantno oboljenje, kod dece i odraslih, rezultat je mutacija u jednom od dva gena, TSC1 (koji kodira hamartin) ili TSC2 (koji kodira tuberin). TSC često izaziva neurološke poremećaje koji dovode do invalidnosti, uključujući i epilepsiju, mentalnu retardaciju, i autizam. Dodatne glavne karakteristike bolesti su manifestacije na koži, npr. angiofibromi lica, angiomiolipomi bubrega i plućna limfangiomiomatoza.
Prikaz bolesnice: Prikazujemo 20-godišnju bolesnicu sa epilepsijom i potprosečnom inteligencijom, koja se javila na Kliniku za dermatologiju zbog većeg broja papula na licu, čiji se broj postepeno povećavao u poslednjih 15 godina. Kod nje je ranije bila postavljena dijagnoza TSC na osnovu nalaza rabdomioma srčanih komora, tuberosklerotskih nodula nastalih usled glijalne proliferacije u moždanoj kori i angiomiolipoma u levom bubregu. Papule na licu bile su dijagnostikovane kao angiofibromi, upotpunjavajući kliničku prezentaciju TSC-a. Detaljnim ispitivanjem kože i sluzokoža otkriveni su: šagrinska mrlja, netraumatski subungvalni fibrom i fibrom gingive, koji predstavljalju karakteristike kompleksa tuberozne skleroze.
Lečenje i nega: Kod prikazane bolesnice korišćen je multidisciplinarni timski pristup radi postavljanja korektne dijagnoze, lečenja i nege mnogih organskih sistema koji su bili pogođeni tuberoznom sklerozom. Bolesnica je lečena antiepilepticima sa preporukom da se u dalje lečenje uključi i imunomodulator rapamicin (poznat i pod nazivom sirolimus; po hemijskoj građi makrolidni antibiotik sa snažnim imunosupresivnim i antoproliferativnim dejstvom).

Ključne reči

Tuberozna skleroza; Komorbiditet; Dijagnoza; Antikonvulzivi; Sirolimus; Odrasli

Multiple Giant Congenital Nevi – A case report

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Abstract

Giant congenital melanocytic nevi are benign nevomelanocytic proliferations of 20 cm or more in diameter, present at birth. They are primarily found on the posterior trunk, but they may arise on any other part of the body, covering more than 2% of the body surface. Giant congenital nevi are major risk factors for the development of melanoma, and the risk has been estimated to be as high as 5–7%. Persons with giant congenital melanocytic nevi on the head, neck and along the midline of the back are at increased risk for leptomeningeal melanocytic lesions. Most patients with neurocutaneous melanosis present with neurologic manifestations of the disease in the first 2 years of life. Melanoma occurs in 62–80% of cases, but even without neoplasms, symptomatic neurocutaneous melanosis has a poor prognosis. This is a report of a 23-year-old female patient who presented with multiple congenital pigmented and pilous nevi covering over 2% of her total body surface, without malignant alterations or association with other abnormalities. At birth, a nevus covered her neck, shoulders and the upper left arm, whereas several nevi over 5cm in diameter were present in the gluteal region, on the abdomen and legs. During the first 2 years of life, the existing nevi increased in size and progressed into darker brown. New, smaller pigmented changes appeared on the whole body and the face, while at the age of 17 they reached their current size and layout. At puberty, nevi over 10cm in size grew dark hairs. There were neither melanoma nor skin tumor cases in the family. Nuclear magnetic resonance imaging was not performed in the childhood or later in life, but other parameters – neurologic and ophthalmologic findings were in normal range all the time, as was growth and development. A complete photo-documentation was made, including macroscopic and dermoscopic images and regular follow-ups continue.
Giant congenital melanocytic nevi may cause considerable esthetic and psychosocial problems. Due to their high malignant potential, association with other abnormalities, no consensus on the treatment, and monitoring problems, giant congenital melanocytic nevi represent a therapeutic problem as well.

Key words

Nevus, Pigmented + congenital; Skin Neoplasms + congenital; Neurocutaneous Syndromes + congenital; Melanoma + etiology; Skin Abnormalities; Abnormalities, Multiple

Giant congenital melanocytic nevi (GCMN) are benign nevomelanocytic proliferations of 20 cm or more in diameter, present at birth (1). They are primarily found on the posterior trunk, but they may arise on any other part of the body, covering over 2% of the total body surface (2). The appearance of GCMN may change over time: the color may get darker, with dark thick pigmented hairs, whereas the surface may be smooth, wrinkled, verrucous or cerebriform. Satellite nevi of different sizes surround the GCMN. Several developmental abnormalities have been reported to be associated with GCMN: scoliosis, spina bifida, clubfoot, elephantiasis, cranial bone hypertrophy, and neorocutaneous melanosis (3).

Congenital nevi are major risk factors for melanoma (2, 3, 4). Fortunately, melanoma remains an uncommon malignancy in children aged 0-9 years, with an annual incidence of 0.7 cases per 1 million children. For GCMN, the risk has been estimated to be as high as 5–7%. However, in cases with GCMN during the first 15 years of life, this risk increases up to 8.52%. GCMN may cause considerable esthetic and psychic problems.

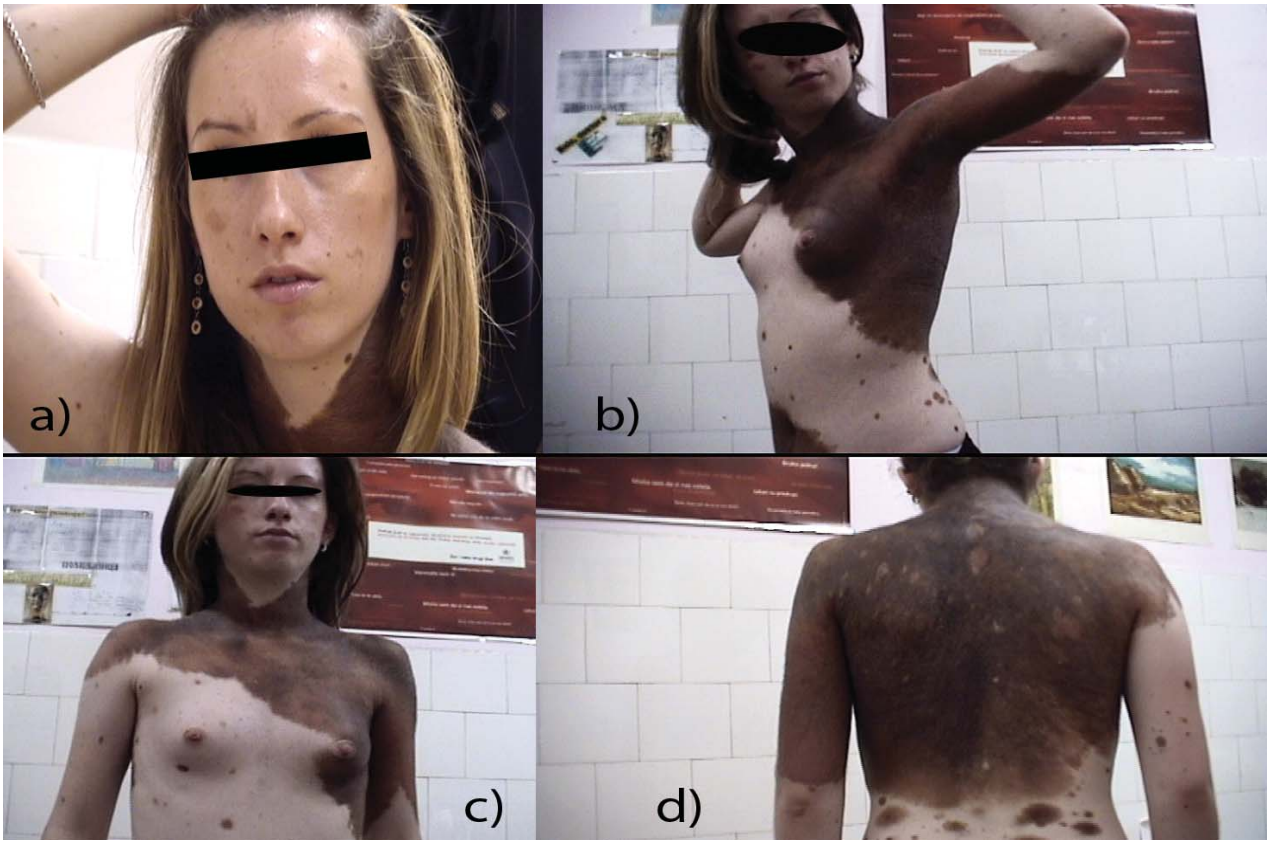

Figure 1. A dark brown nevus covering a) the entire neck; b) both shoulders, left upper arm, left breast; c) anterior thorax from the right shoulder to the left rib cage; d) the entire back up to the waist

This is a report of a female patient with nevi affecting over 2% of the total body surface, which makes a problem in controlling the patient properly.

Case report

This is a report of a 23-year-old female patient who presented with multiple congenital pigmented and pilous nevi, covering over 2% of her total body surface. At birth, a giant nevus covered her neck, shoulders and the upper left arm, whereas several nevi over 5cm in diameter were present in the gluteal region, on the abdomen and legs. During the first 2 years of life, the existing nevi increased in size and progressed into darker brown. New, smaller pigmented changes appeared on the whole body and the face, while at the age of 17 they reached their current size and layout. At puberty, nevi over 10cm in size grew dark hairs. There were neither melanoma nor skin tumor cases in the family.

During the first years of life, the patient was controlled by a pediatrician, a neurologist and an ophthalmologist. Although the patient was diagnosed with a giant congenital nevi, magnetic resonance imaging (MRI) of the head was not performed in the first two years of life. Fortunately, she had no signs and symptoms of increased intracranial pressure and spinal cord compression. Growth and development was in normal range, so annual monitoring by a neurologist and an ophthalmologist was continued.

On the first examination in 2007, more nevi were observed: a dark brown nevus of unclear edges, partially with thick dark hairs, covered the entire neck circumference (except for a v-shaped part on the lower jaw), both shoulders, the left upper arm, left breast, anterior thorax – from the right shoulder to the left rib cage, and the entire back up to the waist (Figures 1a, 1b, 1c, 1d).

The skin of the gluteus and extremities (Figures 2a, 2b, 2c 2d), as well as of the right sole and the left foot (Figures 3a, 3b), was covered by a total of over 100 nevi, mostly oval in shape, of uniform light

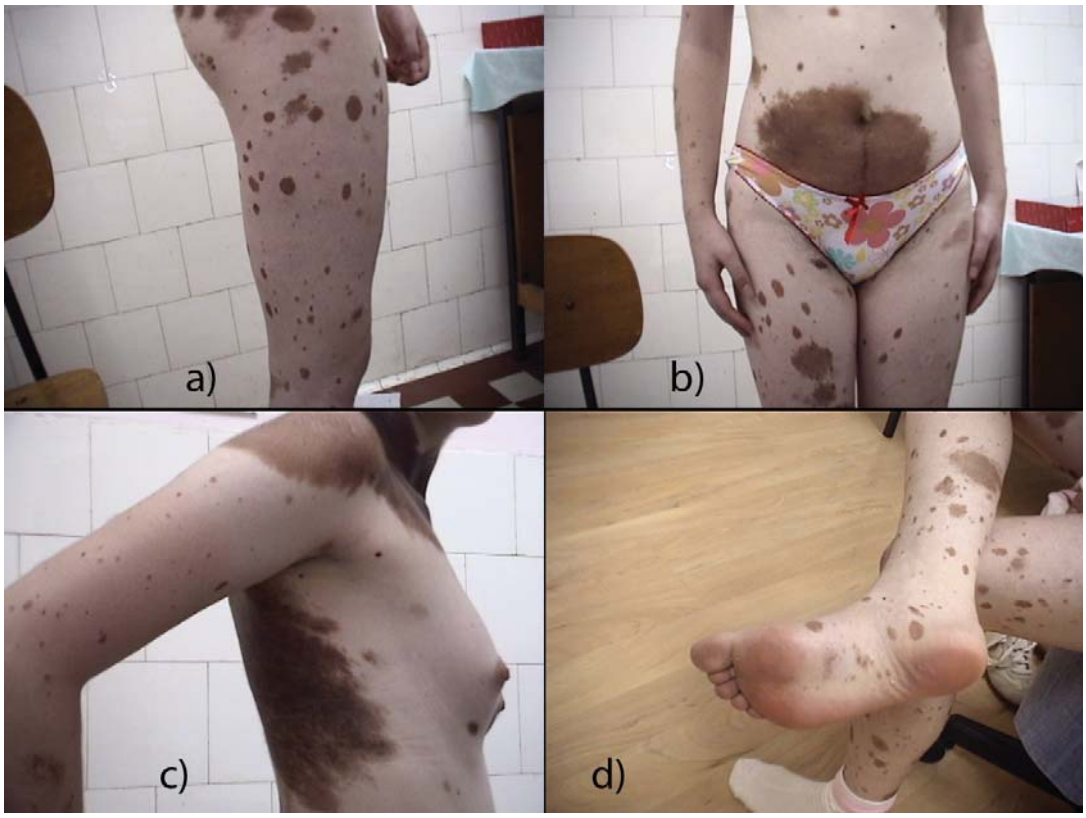

Figure 2. A total of over 100 nevi, mostly oval in shape, of uniform light to dark brown color from 0,5 to 26cm in size covering the skin of the: a) right buttock; b) lower abdomen and both upper legs; c) right arm; d) righ sole and lower leg

to dark brown color, some growing hair, from 0.5 to 26cm in size (Figures 4a, 4b)**.**

Dermoscopy revealed a homogenous brown pigmented network with oval shaped skin-colored macules, with regular distribution corresponding to follicular ostia. The pigmentation of the edge of ostia was marked and symmetrical, indicating benign pigment changes (Figure 5). Apart from a homogenous, a globular pigment network was found in some parts of the nevus, resembling paving stone,

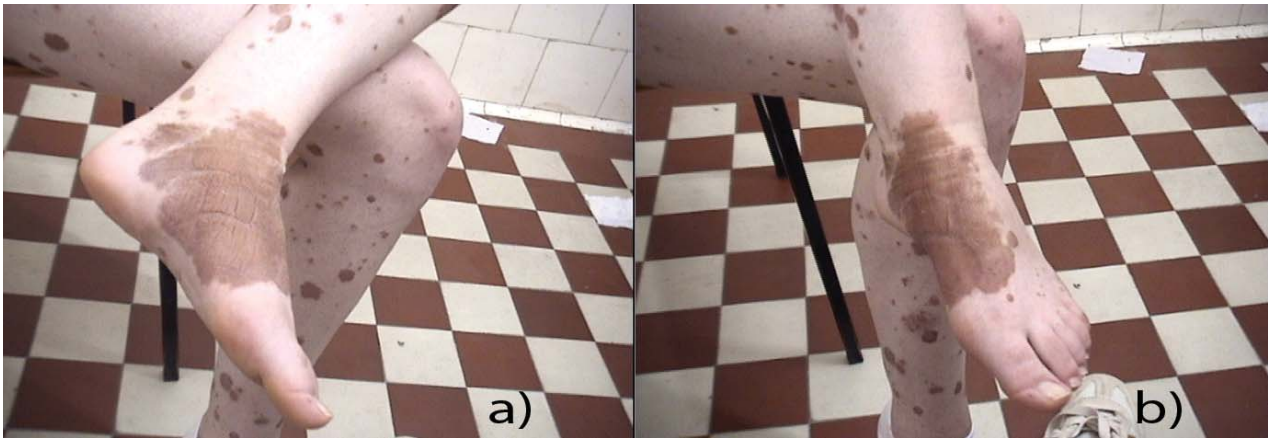

Figure 3. A light brown nevus covering the skin of the left foot: a) from the entire dorsum; b) to the inner sole.

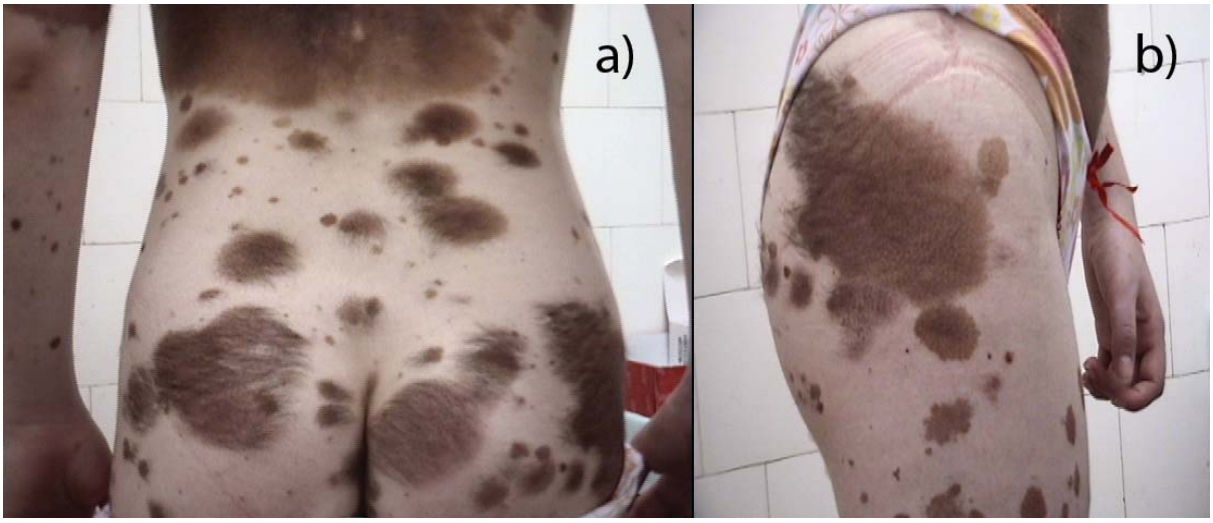

Figure 4. Dark brown nevi growing hair covering the skin on the: a) gluteal region; b) right buttock

which is a typical finding in congenital nevi (Figure 6). Individual, small to medium sized nevi presented with a globular brown network. Some of them had globules of the same size and shape, distributed on the edges, pointing to the growth of changes. Palmar and plantar nevi were monochrome, with parallel and lattice-like patterns, and of benign type (Figures 7a, 7b).

A photo-documentation was made, including macroscopic whole-body images, and dermoscopic images of some nevi and parts of nevi.

Discussion

In the evaluation of patients with GCMN, it is necessary to exclude association with other abnormalities and syndromes, as well as differential diagnosis of other pigment changes, such as:

Neurocutaneous melanosis (NCM) is a rare congenital syndrome characterized by the presence of large and multiple congenital melanocytic cutaneous nevi and benign or malignant melanotic neoplasms. Persons with large GCMN on the head, neck and along the midline of the back are at increased risk of leptomeningeal melanosis. The syndrome is probably an error in the morphogenesis of embryonal neuroectoderm. Most patients with neurocutaneous melanosis show neurologic manifestations of the disease in the first two years of life. Melanomas occur in 62–80% of cases, but even without neoplasms, symptomatic neurocutaneous

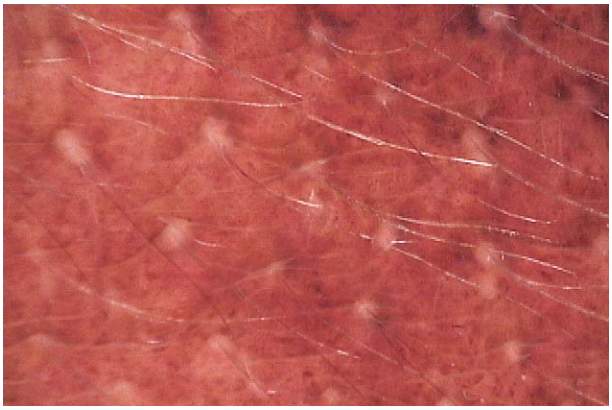

Figure 5. Dermoscopy of the dark brown nevus on the back revealing a homogenous brown pigmented network with oval shaped skin-colored macules with regular distribution corresponding to follicular ostia; the pigmentation of the edge of ostia is marked and symmetrical

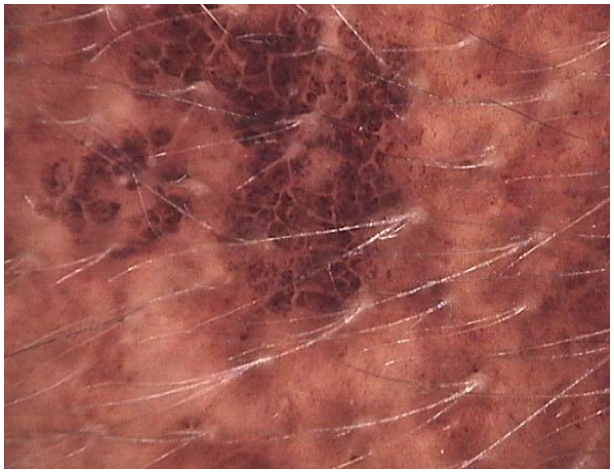

Figure 6. Dermoscopy of the dark brown nevus on the back revealing a globular pigment network in some parts of the nevus, typically resembling paving stone

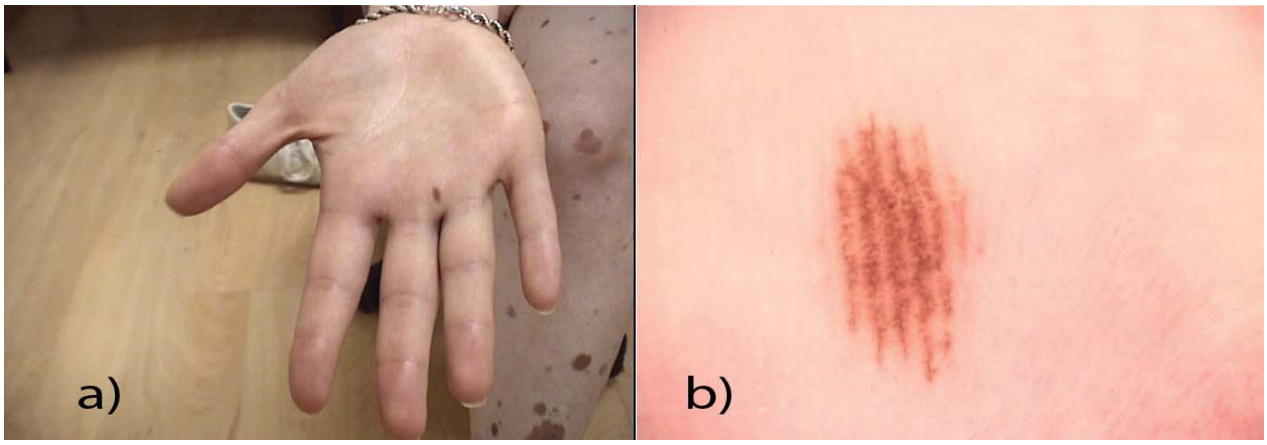

Figure 7. a) Light brown nevus on the left palm; b) dermoscopy showing parallel and "lattice-like patterns"

melanosis has a poor prognosis. MRI of the head and neck is recommended until the second year of life, in order to establish leptomeningeal melanosis, whereas after that a follow up of neurological signs and symptoms pointing to increased intracranial pressure should be done. (4,5,6).

Nevus of Ito is a dermal melanocytic nevus affecting the shoulder area. It is often associated with nevus of Ota, which commonly involves the ocular area – innervated by the trigeminal and maxillary nerves. Both nevi are rare in Caucasians, but common in Asian populations, 0.2-0.6%. Nevus of Ito is an esthetic problem. To date, only one case of melanoma has been described as nevus of Ito, in a 78-year-old male Caucasian (7).

Becker's nevus is a pigmented hairy epidermal nevus. It is more common in male population. It initially presents with an asymptomatic macula, irregular in shape, tan-to-brown in color, most commonly located on the shoulder, upper back and the thorax, in the first 15 years of life, but not at birth. With time, the pigmentation keeps spreading, and hairs start growing (8).

Giant congenital melanocytic nevi may lead to esthetic and psychological problems. Due to their high malignant potential, association with other abnormalities, no consensus on the treatment, and monitoring problems, GCMN is a therapeutic problem as well

Whether treatment should be initiated (2, 3), and what type of treatment it should be depends on many factors: size of the nevus, localization, cosmetic effects, age, and risk of general anesthesia (9). Although the risk of malignant alterations of small and medium congenital nevi has not been established, most dermatologists believe that the risk is not so great as to perform a prophylactic removal of these nevi. Literature data show that there are more and more physicians speaking in favor of prophylactic excision of nevi until puberty, because it is the time when the risk of developing melanoma is greatest. Assessing the risk of melanoma, of general anesthesia, and psychological factors, the best time for excision is between the 6th and the 9th months, and between the 8th and 12th years of life.

Therapeutic modalities include all means which may reduce the melanocyte count that theoretically reduces the risk of cutaneous melanoma: removal of the full depth of nevus, partial excision of nevus, curettage, dermabrasion, laser therapy, and chemical peeling (4). However, apart from complete excision of nevus, other therapeutic modalities do not affect the risk of melanoma in the deep layers of the nevus. For example, superficial nevus destruction by laser results with minimal scarring, and that is why it is most acceptable for patients, but due to insufficient tissue removal, it causes nevus recurrence (4,10). Effects of sublethal laser energy treatment on melanocytes, in regard to malignant alterations, are unfamiliar, but after laser therapy, no malignant alterations have been reported. Furthermore, if melanoma appears on the site of nevus treated by laser, it will be deep in the tissue, which limits the clinical diagnosis, until it reaches an advanced stage. Nevertheless, even total excision of GCMN will not entirely remove the risk of extracutaneous melanoma.

In places that are visible and excision is difficult, application of corrective cosmetics is possible, to

achieve a satisfactory esthetic appearance. Otherwise, a combination of dermabrasion/peeling and corrective cosmetics is recommended.

If focal growth, with changes in color or texture, as well as local sensitivity or ulcerations, potential signs of melanoma, is noticed, biopsy and histopathology analysis are necessary. Also, recommendations for rigorous sun protection and self-examination once a month are crucial.

Proper follow-up of patients with GCMN includes the following procedures:

1. Newborn infants with giant congenital nevi (4) should undergo MRI of the head, in order to detect NCM in the first 4 months of life, before myelinization is complete, because it has been observed that myelin may obscure deposits of melanocytes in the leptomeninges. MRI should be repeated in the first 2 years of life, regardless of the presence or absence of neurological symptoms, because the peak incidence of extracutaneous melanomas and of other tumors is by the second year of life. The necessity of MRI later in life has not been proven, especially in people with regular neurological status and normal development (4).
2. In patients with GCMN and regular neurological status, without atypical findings, periodical follow-up of nevi is recommended, with photo-documentation including macroscopic and dermoscopic images, whereas neurological examinations and sun protection are necessary.
3. In patients with GCMN, regular neurological status and presence of atypical findings, biopsy and histopathological analysis are recommended. If alterations correspond to melanoma, total excision should be considered, or excision with appropriate margins for tumor thickness, as well as regular follow-ups according to the protocols for monitoring melanoma patients.
4. In patients with GCMN and regular neurological status, but with MRI findings pointing to NCM (asymptomatic NCM), frequent MRI is recommended, as well as further therapeutic measures, depending on the disease progression.
5. In patients with symptomatic NCM, neurosurgery may be elected: ventriculo-peritoneal shunt placement may significantly improve the condition in some patients, but also enable migration of melanocytes from leptomeninges to the peritoneal cavity. Patients with symptomatic NCM, whose symptoms have improved, should undergo regular MRI and neurological examinations.

Despite the fact that most patients with GCMN will never develop melanoma, the relative risk is rather high and it should be taken into consideration when evaluating these patients. The decision on the choice of treatment should be left to the patient, after good assessment of risks and benefits of each therapeutic procedure.

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Abbreviations

GCMN - Giant congenital melanocytic nevi
NCM - Neurocutaneous melanosis
MRI - Magnetic resonance imaging

Multipli gigantski kongenitalni nevusi – prikaz slučaja

Sažetak

Uvod: Gigantski kongenitalni melanocitni nevusi (GKMN) su benigne nevomelanocitne proliferacije veličine od 20 cm i više u dijametru, prisutne na rođenju.1 Najčešće su lokalizovani na zadnjem delu trupa ali mogu biti prisutni na bilo kom delu tela zahvatajući od 2% od ukupne površine tela i više. GKMN se smatraju jednim od faktora rizika za nastanak melanoma (M), i to 8,52% u toku prvih 15 godina života. Procenjen životni rizik za razvoj melanoma kod GKMN iznosi 5-7%.

Nekoliko razvojnih anomalija je udruženo sa GKMN: skolioza, spina bifida, kriva stopala, elefantijaza, hipertrofija kranijalnih kostiju i neurokutana melanoza3 (NKM).Neurokutana melanoza je redak kongenitalni sindrom koga karakteriše prisustvo velikih ili multiplih kongenitalnih melanocitnih nevusa i benignih ili malignih melanotičnih neoplazmi leptomeninga. Osobe sa velikim GKMN na glavi, vratu i duž srednje leđne linije imaju povišen rizik zahvaćenosti leptomeninga. Većina pacijenata sa neurokutanom melanozom već u prve 2 godine života dobije neurološke pritiska. manifestacije bolesti. Melanom se javlja u 62% - 80% slučajeva, ali i bez prisutne neoplazme simptomatska neurokutana melanoza ima lošu životnu prognozu. Preporuka je da se uradi MR glave i vrata do 2. godne života radi dokazivanja postojanja leptomeningealne melanoze, a kasnije nastavi sa praćenjem pojave neuroloških simptoma i znakova povišenog intrakranijalnog pritiska.

Prikaz slučaja: Prikazujemo osobu ženskog pola, 23 godine, sa mnogobrojnim kongenitalnim nevusima koji zahhvataju više od 2% površine tela kod koje nije primeća maligna alteracija i udruženost sa drugim anomalijama. Magnetna rezonanca nije radjena u detinjstvu, ali su ostali parametri – neurološki i oftalmološki nalazi bili u granicama normale, kao i rast i razvoj. Napravljena je kompetna foto dokumentacija uključujući makro snimke nevusa i dermoskopske snimke, i kontrole se obavljaju perodično.

Diskusija: Gigantski kongenitalni melanocitni nevusi predstavljaju kozmetski i psihosocijalni problem pacijentima. S obzirom na visok maligni potencijal i udruženost sa drugim abnormalnostima, nepostojanja konsezusa po pitanju terapijskog pristupa, teškoćama pri monitoringu pacijenata, GKMN predstavlja terapijski problem i lekarima.

Da li će se preduzeti terapija2,3, i kakva će ona biti zavisi od mnogo faktora: veličine nevusa, lokalizacije, kozmetskog efekta, godišta pacijenta i rizika od opšte anestezije.9 Mada rizik maligne alteracije kod malih i srednjih kongenitalnih nevusa nije utvrđen, većina dermatologa smatra da rizik nije tako veliki da bi se pristupilo profilaktičkom uklanjanju ovih kongenitalnih nevusa. Za GKMN se sve više u literaturi pojavljuju stavovi koji govore u prilog profilaktičke ekscizije nevusa, i to do puberteta jer je najveći rizik za razvoj melanoma upravo do tada. Procenjujući rizik za razvoj melanoma, rizik od opšte anestezije i psihosocijalne faktore, smatra se da je najbolji period za eksciziju GKMN izmedju 6. i 9. meseca života i izmedju 8. i 12. godine.

Terapijski modaliteti4 uključuju sve načine kojima je moguće smanjiti broj melanocita što teoretski treba da smanji rizik nastanka kutanog melanoma: ekscizija kompletne debljine nevusa, delimična ekscizija nevusa, kiretaža, dermabrazija, laserska terapija i hemijski piling. Medjutim, osim kompletne ekscizije nevusa, ostali načini terapije ne utiču adekvatno na rizik od nastanka melanoma u dubljim slojevima nevusa, ali čak i totalnom ekscizijom GKMN ne anulira se mogućnost nastanka ekstrakutanog M.

Na mestima koja su vidljiva, a ekscizija je teško izvodljiva, moguća je upotreba korektivnih kozmetičkih preparata radi postizanja zadovoljavajućeg estetskog izgleda ili kombinacija dermabrazije/pilinga i korektivne kozmetike.

Tok i kontrole: Uzimanje biopsije uz sledstvenu histopatološku analizu predstavlja postulat ukoliko se primeti fokalni rast sa promenom boje i teksture, pojava lokalne osetljivosti ili nastanka ulceracije, što predstavlja znake mogućeg razvoja melanoma. Takođe, neophodan je savet za rigoroznu zaštitu od sunca i samopregledi 1 x mesečno.

Adekvatna kontrola pacijenata sa GKMN obuhvata sledeće postupke:

1. novorođenčad sa gigantskim kongentialnim nevusima 4 treba uputiti na magnentnu rezinancu (MR) glave radi otkrivanja asimptomatske NCM u toku prva 4 meseca života, pre završetka mijelinizacije jer je primećeno da mijelin može da prikrije postojanje depozita melanocita na leptomeningama. MR treba ponoviti u toku prve dve godine života bez obzira na prisustvo ili odsustvo neuroloških simptoma jer je pik incidence ekstrakutaanog melanoma i drugih tumora upravo do druge godine života. Neophodnost ispitivanja MR u kasnijem životnom dobu nije dokazana, naročito kod osoba sa urednim neurološkim statusom i normalnim razvojem4;
2. Kod pacijenata sa GKMN i urednim neurološkim statusom, bez prisustva ,,atipičnih" polja preporučuje se periodična kontrola nevusa uz foto dokumentaciiju;

3. periodične kontrole koje podrazumevaju makroskopske i dermoskopske slike, neurološki pregled i preporuke o zaštiti od sunca;
4. kod pacijenata sa GKMN i urednim neurološkim statusom, i prisustnim ,,atipičnim" poljem preporučuje se biopsija i histopatološka analiza. Ukoliko promena odgovara melanoma, potrebno potrebno je razmotriti totalnu eksciziju nevusa ili eksciuiju sa odgovarajućim amrginama za debljinu tumora i redovne kontrole prema protokolu praćenja za melanome;
5. Kod pacijenata sa GKMN i urednim neurološkim statusom, a MR sugestivnim na NKM (asimptomatska NKM) preporučuju se učestale kontrole MR i zavisno od napredovanja bolesti dalje terapijske mere;
6. Kod pacijenata sa simptomatskom NKM moguća je neurohiriška terapija kao što je postavljanje ventrikuloperitonealnog šanta koji može značajno da popravi stanje kod nekih pacijenata, ali i omogući migraciju melanocita sa leptomeninga u peritonealnu duplju;
7. pacijente sa simptomatskom NKM čiji se simptomi popravljaju treba dalje kontrolisati uz ponavljane MR i neurološke preglede.
Zaključak: Relativni rizik za razvoj melanoma je veliki i ne treba ga podceniti uprkos činjenici da većina pacijenata sa GKMN neće nikada dobiti melanom, relativan rizik za razvoj melanoma je veliki i treba ga imati u vidu u evaluaciji ovih pacijenata. Odluku o terapijskom izboru treba prepustiti pacijentu posle dobrog upoznavanja sa rizikom/benefitom svake terapijske procedure ponaosob.

Ključne reči

Pigmentni nevus + kongenitalni; Neoplazme kože + kongenitalne; Neurokutani sindromi + kongenitalni; Melanom + etiologija; Abnormalnosti kože; Multiple abnormalnosti

Neurofibromatosis type I (von Recklinghausen's disease): A report of three cases

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Abstract

Neurofibromatosis type I (NF1) is an autosomal dominant, multisystemic disease that usually affects the skin, nervous system and bones. Diagnosis is made by matching at least two of the following 7 diagnostic criteria: six or more café-au-lait macules over 15 mm in diameter, two or more neurofibromas, axillary and/or inguinal freckles, optic glioma, two or more Lisch's nodules (iris hamartoma), changes in the bones in the form of sphenoid dysplasia, thinning of the cortex of long bones and existence of neurofibromatosis in the first degree relatives. We report three patients, two men and a woman aged 18 to 33 years, in whom the first changes occurred at puberty, and there was no positive family history in any of them. All three patients had café-au-lait spots over 15 mm in diameter and numerous localized neurofibromas on the skin of the trunk and extremities that were histologically verified. In two patients, ophthalmic examinations recorded Lisch's nodules in the iris. In one of the patients, MRI of the head, revealed presence of oval lesions with diameters of 10-15 mm, which may correspond to neurofibromas, and in the other patient fibrous dysplasia of the femur and tibia were observed. Psychological testing in one patient revealed IQ at the lower limits of average (IQ 68). After the diagnosis of neurofibromatosis type I, the patients were given advice about the disease and a plan for the monitoring and control of possible symptoms, and also the possibility of genetic testing during pregnancy. A multidisciplinary approach is required for diagnosing and monitoring of patients with neurofibromatosis type 1.

Key words

Neurofibromatosis 1 + diagnosis + epidemiology + etiology + therapy; Genes, Neurofibromatosis 1; Signs and Symptoms;Disease Progression; Café-au-lait spots

Neurofibromatosis type I (NF1), von Recklinghausen's disease, is an autosomal dominant neurological and multisystem disease that usually affects the skin, nervous system and bones. The incidence of NF1 is 1 in 3000 live births. NF-1 is caused by changes (mutations) of a, relatively large gene on the long arm (q) of chromosome 17 (17q11.2). The gene regulates production of a protein known as neurofibromin, which is thought to function as a tumor suppressor. In about 50 percent of individuals with NF-1, the disorder results from spontaneous, sporadic mutations of the gene. In the other half, NF-1 is inherited as an autosomal dominant trait. First manifestations of disease usually appear in the early childhood.

Clinical diagnosis requires the presence of at least 2 of the following 7 diagnostic criteria:

1. Six or more café-au-lait spots or hyperpigmented macules larger than 5 mm in diameter in children under 10 years of age and to 15 mm in adults;
2. Two or more typical neurofibromas or one plexiform neurofibroma;
3. Axillary or inguinal freckles;
4. Optic nerve glioma;
5. Two or more Lisch nodules (iris hamartomas);
6. Sphenoid dysplasia or typical long-bone abnormalities;
7. A first-degree relative with NF1.

The earliest clinical findings are multiple *café-au-lait* spots. These may be present at birth, or may appear over time, frequently increasing in size and number throughout the lifetime. In adults, *café-au-lait* spots tend to fade and may be less obvious on clinical examination. Axillary or inguinal freckles are rarely present at birth, but appear during childhood through adolescence. Subcutaneous or cutaneous neurofibromas are rarely seen in young children, but appear over time in older children and adolescents. Deep-seated lesions can be detected only by palpation, whereas cutaneous lesions may appear initially as small papules on the trunk, extremities, scalp or face. Plexiform neurofibromas have more diffuse growth that can be locally invasive with bone erosion and pain. Lisch nodules occasionally can be seen with a direct or indirect ophthalmoscope, especially in individuals with light-colored iris.

Some of the more severe complications include visual loss secondary to optic nerve gliomas, spinal cord tumors, scoliosis, vascular lesions, and long bone abnormalities. Optic gliomas and both malignant and benign peripheral nerve sheet tumors are the most common malignancies arising in NF-1 patients (1). The treatment is symptomatic, such as surgical removal of neurofibromas if painful, or if they compromise a function due to the pressure.

Case reports (Table 1)

We report three patients, two males and one female, aged 18 to 33 years, who were after a commission of examination at our Department, diagnosed with neurofibromatosis type I.

In all three cases, the first change in the form of light brown spots and small soft nodules on the skin, occurred during puberty. There were no family members suffering from neurofibromatosis or other genodermatoses. The patients were in good general condition and without health problems.

All three patients had *café-au-lait* macules over 15 mm in diameter (Figures 1, 2) and a number of neurofibromas present on the trunk and extremities (Figures 3, 4), while in the female patient nodular changes were localized also on the scalp (Figure 5).

All three patients underwent the following diagnostic procedures: basic laboratory tests (SE, blood tests, liver enzymes, immunoglobulins, urinalysis),

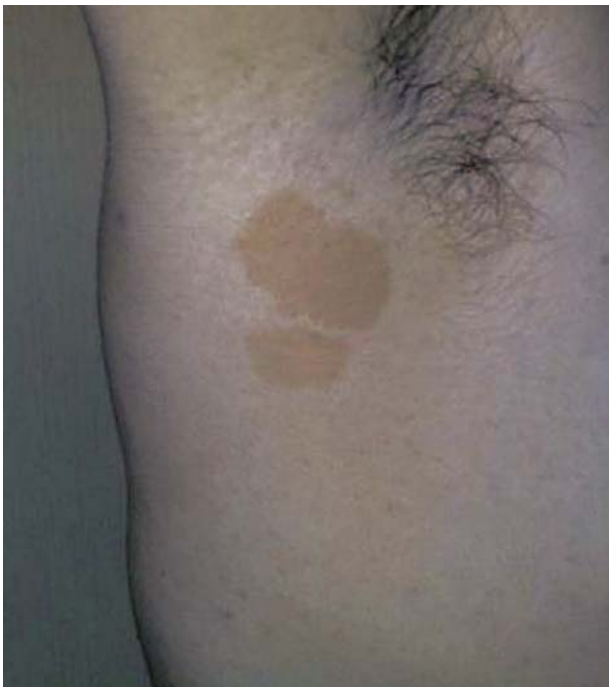

Figure 1. Patient No. 1. Two large *café-au-lait* macules on the trunk

biopsy of skin nodules with histopathological analysis, chest and long bones radiography, abdominal ultrasound, magnetic resonance imaging (MRI) of the head. Ophthalmological, neurological and orthopedic examinations were performed as well as psychological with testing IQ.

In all patients, neurofibromas were confirmed by histopathological examination (Figure 6). In two

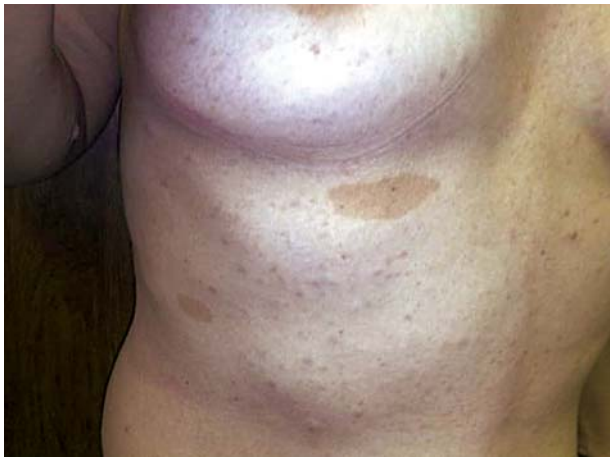

Figure 2. Patient No. 2. One large *café-au-lait* macula under the breasts, and a lot of small, brown neurofibromas

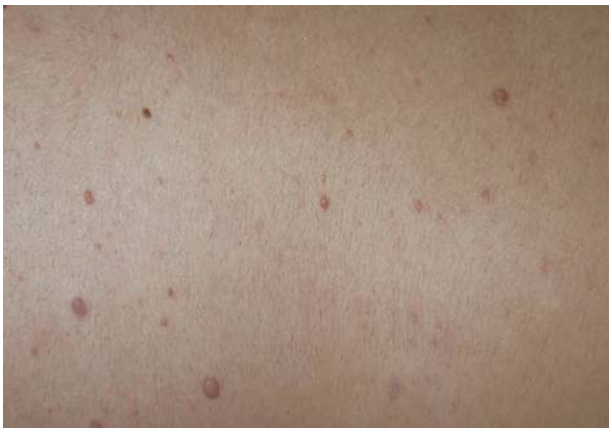

Figure 3. Patient No. 3. A lot of small neurofibromas on the trunk

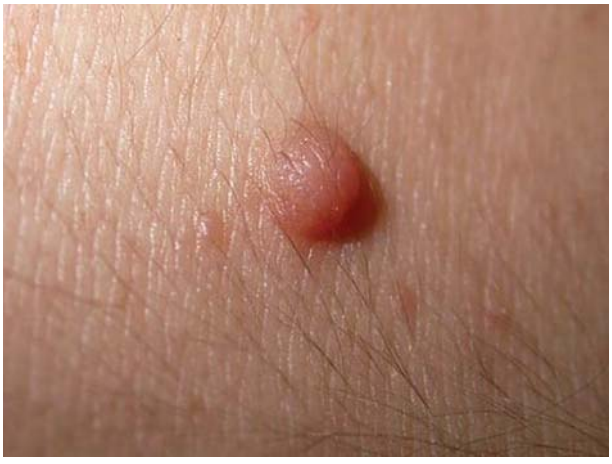

Figure 3a. Detail of fig. 3. One pink, soft neurofibroma on the back

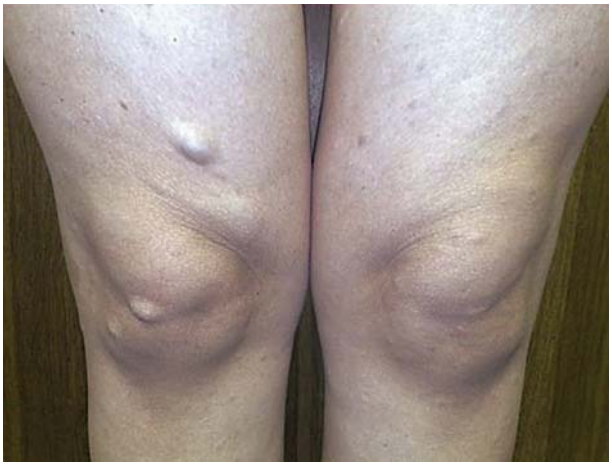

Figure 4. Patient No. 2. Deep neurofibromas on the legs

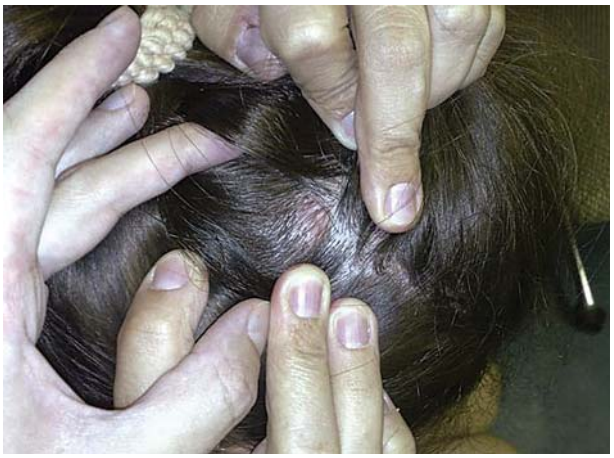

Figure 5. One big (> 2 cm in diameter) neurofibroma on the scalp of our female patient

patients, ophthalmologic examination revealed Lisch's nodules on the iris (Figure 7), while in one patient ophthalmological examination was normal. In one patient, brain MRI revealed intracranial presence of oval lesions 10-15 mm in diameter, which may correspond to neurofibromas. In other two patients brain MRI findings were normal.

In two patients there were no changes on the bones; in one patient in both the femur and the tibia fibrous dysplasia were observed. In two patients IQ (intelligence quotient) was average, 93 (IQ 80 -115) and in one under average, 68.

After examination the diagnosis of neurofibromatosis type I (Table 1), was made based

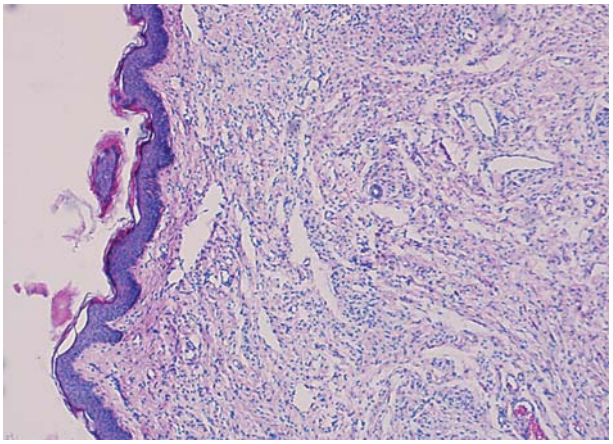

Figure 6. Histopathological analysis confirmed neurofibromas: well–differentiated tumors that contain elongated spindle-shaped cells as well as pleomorphic fibroblast-like cells (H&E x 100)

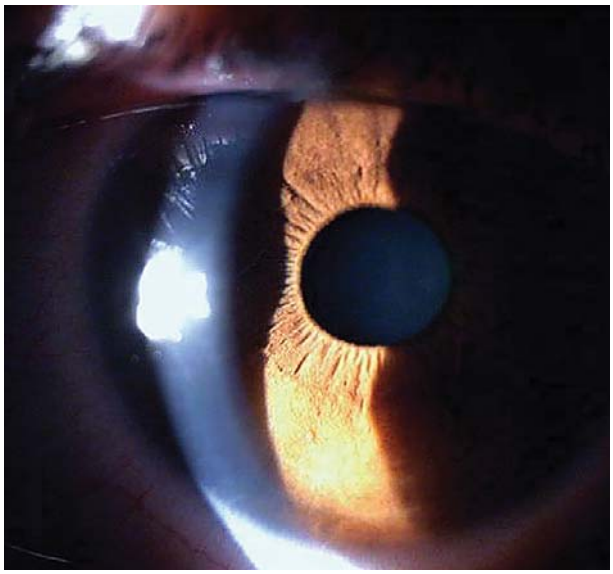

Figure 7. Lisch nodules of the iris

on diagnostic criteria. It was concluded that, for the time being, there were no indications for surgery. Patients were given advice about the disease and a plan for monitoring and control of possible symptoms.

Discussion

The estimated incidence of NF1 is 1 in 3000, and both sexes are affected equally with this autosomal dominant desease. The actual incidence of the disease may be higher, due to possible underdiagnosis of patients without family history of the disease, that represents cases with a new genetic event, i.e. mutation (2). None of our patients had positive family history of neurofibromatosis. The first manifestations of the disease usually occur in early childhood, but clinical manifestations may appear slowly over many years (3). In our patients first manifestations of the disease appeared during puberty, and the first manifestations of the disease were *café-au-lait* spots. Most ofen, the first manifestations of the disease appear before 10 years of age, but in about 30% of patients disease appears later.

Learning disabilities, with or without so called attention deficit hyperactivity disorder (ADHD), are found in approximately 40% of NF1 affected individuals (4). A much smaller percentage experiences more significant cognitive difficulties, such as mild or moderate mental retardation (4). One

Table 1. Diagnostic examination of three patients affected with NF1

	Patient 1	Patient 2	Patient 3
Age	23 years	33	18
Gender	male	female	male
Basic laboratory tests	Normal	Normal	Normal
Lisch nodules	+	-	+
Radiography of long bones	-	-	Femoral and tibial fibrous dysplasia
Brain MRI	3 intracranial neurofibromas	-	-
Psychology test	IQ 113	IQ 68	IQ 93

MRI, magnetic resonance imaging; IQ, intelligence quotient

of our patients with IQ near the lower average limits, also presented with speech disabilities. The occurrence of Lisch nodules appears to be age dependent; more than 95% of NF1–affected individuals older than 10 years have this iris finding (5). Two of our patients were diagnosed with Lisch nodules of the iris.

Histopathological analysis confirmed neurofibromas in all three of our patients. Neurofibromas were described as well–differentiated tumors that contained elongated spindle-shaped cells as well as pleomorphic fibroblast-like cells (Figure 7).

Clinical diagnosis requires presence of at least 2 of 7 criteria to confirm the presence of NF1. Two of our patients had 4 criteria (*café-au-lait* spots over 15 mm in diametar, neurofibromas, axillary freckles, Lisch nodules) and one patient had 5 criteria (*café-au-lait* spots over 15 mm in diametar, neurofibromas, axillary freckles, Lisch nodules and fibrosis of long bones). In one of our patients radiography of the long bones showed fibrosis of both femur and tibia bones, without any clinical symptoms.

Lifetime risks for ocurrence of benign and malignant tumors are increased in NF-1 affected individuals (6). Optic gliomas and both malignant and benign peripheral nerve sheet tumors are the most common malignancies arising in NF-1 patients (1).

No known medical therapies are beneficial to patients with NF1. Several clinical trials have been initiated, looking for medications that slow or stop growth of neurofibromas (farnesyl-transferases in combination with lovastatin, sorafenil, rapamycin complex 1 inhibitor, hyaluronan oligomers). So far, none of these medications has demonstrated significant benefit (4).

Treatment is symptomatic and most often it is surgical removal of neurofibromas for cosmetic reasons or if they cause complications. Some of the more severe complications are visual loss secondary to optic nerve gliomas, spinal cord tumors, scoliosis, vascular lesions, and long bone abnormalities.

It is necessary to inform patients with NF1 in reproductive period, that this genetic disease can be diagnosed during the prenatal period with specialized cytogenic tests (6). Only two clear correlations have been observed between particular mutant *NF1* alleles and consistent clinical phenotypes. The first is a whole *NF1* gene deletion associated with large numbers and early appearance of cutaneous neurofibromas, more frequent and more severe than average cognitive abnormalities, and sometimes somatic overgrowth, large hands and feet, and dysmorphic facial features. The second is a 3-bp in-frame deletion of Exon 17 (c.2970–2972 delAAT) associated with typical pigmentary features of NF1, but no cutaneous or surface plexiform neurofibromas (7).

Genetic testing is necessary to provide prenatal diagnosis and may be used as an adjunct to clinical diagnosis in cases with atypical presentation or in which the child is too young to have developed most characteristic features. A multi-step mutation detection protocol that identifies 95% of pathogenic *NF1* mutations in individuals fulfilling the NIH diagnostic criteria is available (8). This protocol, which involves analysis of both mRNA and genomic DNA, includes real-time polymerase chain reaction, direct sequencing, microsatellite marker analysis, multiplex ligation-dependent probe amplification, and interphase fluorescence in situ hybridization. Because of the frequency of splicing mutations and the variety and rarity of individual mutations found in people with NF1, methods based solely on analysis of genomic DNA have lower detection rates. Testing by fluorescence in situ hybridization, multiplex ligation dependent probe amplification, or analysis of multiple single nucleotide polymorphisms (SNPs) or other polymorphic genetic markers in the *NF1* genomic region is sometimes performed to look just for whole *NF1* gene deletions when the "large deletion phenotype" is clinically suspected. Whole *NF1* gene deletions occur in 4% to 5% of individuals with NF1 (9).

Conclusion

In conclusion, neurofibromatosis 1 is a relatively rare autosomal dominant disease. For individuals diagnosed with NF1 routine examinations should focus on the potential complications. Annual examinations permit early detection of complications, decreasing morbidity and improving quality of life. Annual eye examinations are important in early detection of optic nerve lesions. Removal of neurofibromas for medical or cosmetic reasons is one of the most common procedures in individuals with NF1. In most cases, symptoms of NF1 are mild, and patients live normal and productive lives.

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Neurofibromatoza tip I (von Recklinghausenova bolest): prikaz tri slučaja

Sažetak

Uvod: Neurofibromatoza tip I (NF1) je autozomno dominantno, nasledno neurogeno, multisistemsko oboljenje koje najčešće zahvata kožu, nervni sistem i kosti. Dijagnoza ovog oboljenja se postavlja ukoliko su ispunjena najmanje dva od sledećih 7 dijagnostičkih kriterijuma: šest ili više *café au lait* makula promera preko 15 mm, dva ili više neurofibroma, aksilarne i/ili ingvinalne makule, optički gliom, dva ili više Lisch-ovih nodula (hamartromi dužice), promene na kostima u vidu sfenoidne displazije, istanjenje korteksa dugih kostiju sa ili bez pseudoartroze i postojanje neurofibromatoze kod rođaka prvog stepena.
Prikaz bolesnika: Prikazujemo tri bolesnika, dva muškarca i ženu starosti od 18 do 33 godine kod kojih je, nakon učinjenog kliničkog ispitivanja postavljena dijagnoza neurofibromatoze tipa I. Kod sva tri bolesnika prve promene u vidu svetlosmeđih mrlja i sitnih mekih čvorića na koži javili su se u dobu puberteta. Sva tri pacijenta imala su *café-au-lait* makule promera preko 15 mm i brojne neurofibrome lokalizovane na koži trupa i ekstremiteta koji su patohistološki verifikovani. Kod dva pacijenta oftalmološkim pregledom evidentirani su Lischovi noduli na dužici, dok je kod jednog pacijenta pregled pomoću nuklearne magnetne rezonancije glave ukazao na endokranijalno prisustvo ovalnih lezija dijametara od 10-15 mm koji mogu odgovarati neurofibromima, a rendrengrafijom na oba femura i obe tibije uočena fibrozna displazija.
Lečenje: Terapija neurofibromatoze tipa I je simptomatska i predominantno hirurška uz adekvatno praćenje i multidisciplinarni pristup bolesniku i odgovarajuće genetsko savetovanje.

Ključne reči

Neurofibromatoza tip 1 + dijagnoza + epidemiologija + etiologija + terapija; Geni neurofibromatoze tipa 1; Znaci i simptomi; Tok bolesti; Pigmentne fleke boje bele kafe

Doc. Dr. Aleksandar Janković
1969 – 2011

The sad news of the sudden death of Doc. Dr. Aleksandar Janković, in September 2011, was deeply distressing. It is hard to imagine that we will no longer be able to enjoy the company of a young expert who was always full of energy and willingness to move boldly into new challenges.

Doc. Dr. Aleksandar Janković was born in Niš, in January 1969. Since 2000, he worked at the Clinic of Dermatology and Venereology in Niš. He passed his specialization exam in 2003, recieved his Master's degree in 2004, and in 2007 he defended his doctoral thesis in teledermatology, the first in this field in Serbia. In the same year he became a Docent at the School of Cosmetology and Esthetic Medicine in Banja Luka. He was one of the founders and vice president of the Serbian Association of Cosmetic and Esthetic Dermatology. He was the author and coauthor of 3 books and monographs, and of a great number of scientific papers in the field of his interests.

He was a man with a beautiful mind, full of love for his friends, family, colleagues, patients, always with right words for each of them. Thanks to his inexhaustable energy and endless ideas, that he managed to realize no matter what, in a relatively short time in dermatology, he left behind a trail that will be remembered and has taken his place in the history of Serbian dermatology.

Prof. Dr. Ivana BINIĆ
Clinic of Dermatology and Venereology Niš
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A report on the 22nd World Congress of Dermatology, Seoul, Korea 2011

The 22nd World Congress of Dermatology was reportedly the largest international scholarly society meeting in Korea's medical history, bringing together an international audience of 12,000 attendees from 110 different countries of the world. In Seoul, between 24-29 May, 2011, world-renowned scholars conducted 320 programs under the motto "Connecting the World Through Innovative Dermatology".

Since its launch in Paris in 1889, the Woirld Congress of Dermatology has been striving to promote and improve skin health for people from all parts of the world. By previous attendees it was described as "an invaluable educational opportunity for all dermatologists".

Prestigious scientists delivered lectures covering some of the most recent discoveries in medical science. Other programs included advanced lectures, which provided an in-depth and updated analysis of novel approaches that have become available in medical, surgical and investigative dermatology. As Korea represents the forefront of modern information technology, a new electronic-poster system has been introduced by this year's World Congress of Dermatology.

Plenary lectures were delivered on the following topics: The Emergence of Infections as Important Human Carcinogens, Antimicrobial Peptides: More than Epidermal Antibiotics, Aging Skin, Inhibitory and Stimulatory: Topical Immunomodulation, Patch Testing: 100 Years after Bloch and Jadassohn, Spectrum of Drug Hypersensitivity Syndromes, Whole Genome Sequencing: Impact on Dermatology, Skinomics: Molecular Profiling as a Diagnostic Tool, Melanoma: Do We Need a New Classification?, Non-Invasive Dermatopathology, Molecular Approach in Mycology, Adult Skin Cells: A Source of Stem Cells,

Figure 1. Sanja Djordjević gave a lecture "Assessment of Quality of Life in Adolescents with Acne"

Figure 2. Scholarship recipients: Dušan Škiljević and Ivana Dunić

Stem Cells in Skin Cancer, Regeneration and Repair, Stem Cell Transplantation in Dermatological Diseases, Within the Black Box: Blocking Central Disease Pathways, Cosmetic Dermatology – Nanotechnology, The Role of Inflammation in Metabolic Syndrome, Psoriasis: More than One Disease?, Acne and Acneiform Diseases (Inducers of Follicular Inflammation), Dermatology Life Quality Index (DLQI): Measuring Disease Related Quality of Life, UV and Vitamin D, Phereses and Aphereses, Innate Immunity and the Skin, Sexually Transmitted Infections and Global Migration, Role of Protease and Protease-activated Receptor-2 (Par-2) in Inflammatory Skin Diseases, Neurophysiology of Itch - More than Scratching the Surafce, Fractional Laser Treatment of Medical and Cosmetic Conditions.

Sanja Djordjević was the only dermatologist from Serbia with oral presentation. In the session Free Communications "Acne and Related Disorders" she gave a lecture "Assessment of Quality of Life in Adolescents with Acne". There were 14 poster presentations from Serbia.

Zoran GOLUŠIN
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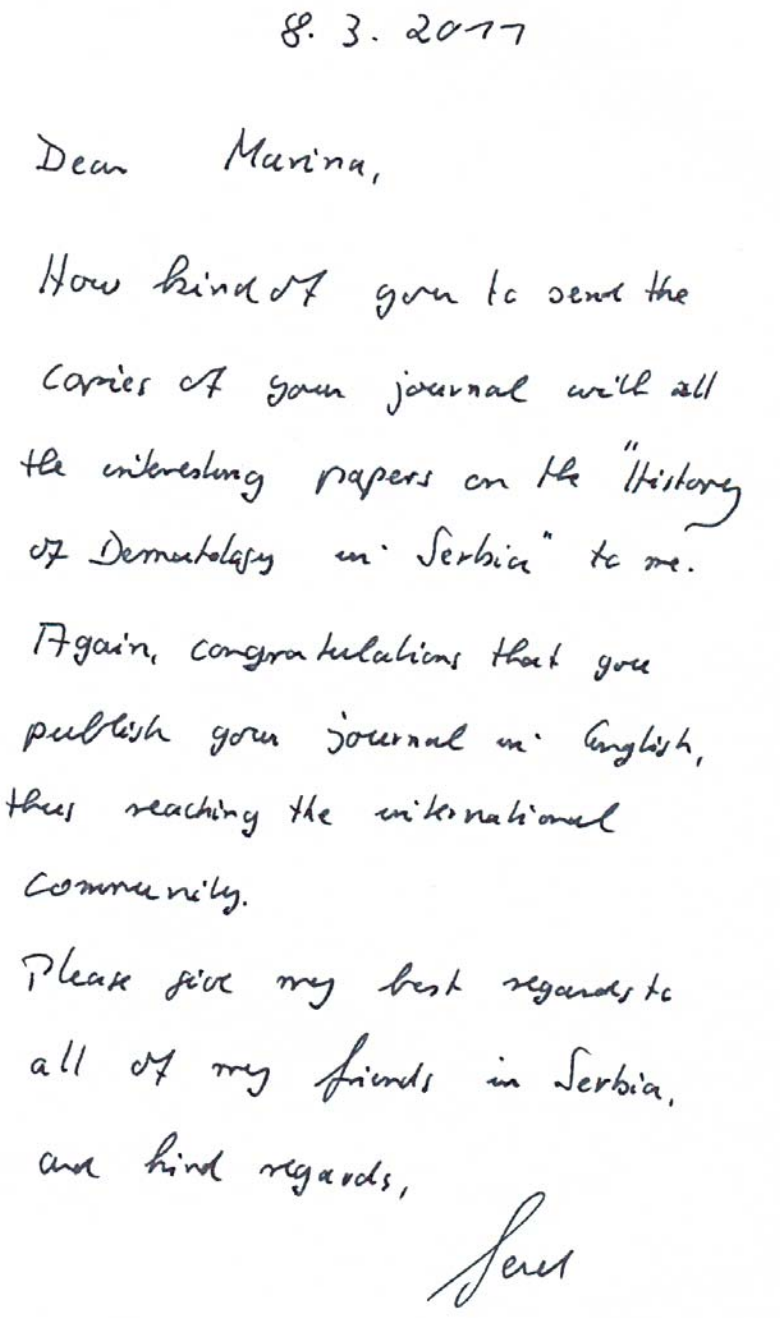
Clinical Center of Vojvodina, Novi Sad, Serbia
E- mail: zgolusin@eunet.rs



8. 3. 2011

Dear Marina,

How kind of you to send the copies of your journal with all the interesting papers on the "History of Dermatology in Serbia" to me.

Again, congratulations that you publish your journal in English, thus reaching the international community.

Please give my best regards to all of my friends in Serbia,

and kind regards,

Jens

Professor Plewig's letter to Professor Marina Jovanovic,
Editor in Chief of the Serbian Journal of Dermatology and Venereology

Braun-Falco' s Dermatology 3rd

Burgdorf W.H.C., Plewig G., Wolff H.H., Landthaler M. (Eds.).

Edition. Springer Berlin Heidelberg, 2009

Dermatology in Serbia has long relied on the French, Anglo-Saxon and German schools of dermatology. One of the editors of the *Braun-Falco's Dermatology, 3rd Revised Edition*, Gerd Plewig, was a guest lecturer on the Belgrade Dermatology Days, in November 2010. Prof. Dr. Marina Jovanović, Editor in chief of the *Serbian Journal of Dermatology and Venereology* (SJDV), posted by mail to Prof. Plewig all the editions of the SJDV. We would like to express our sincere appreciation to Prof. Plewig for copies of the newest *Braun-Falco's Dermatology* he gave us. We are also honored that Prof. Plewig has expressed his desire for the review of *Braun-Falco's Dermatology* to be published in the *Serbian Journal of Dermatology and Venereology.*

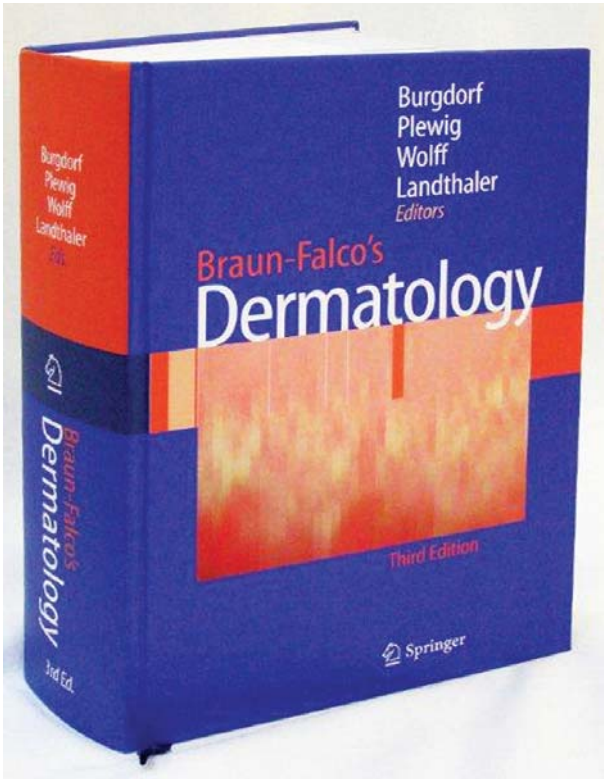


Figure 1. The cover of the Braun-Falco's Dermatology - 3rd Edition

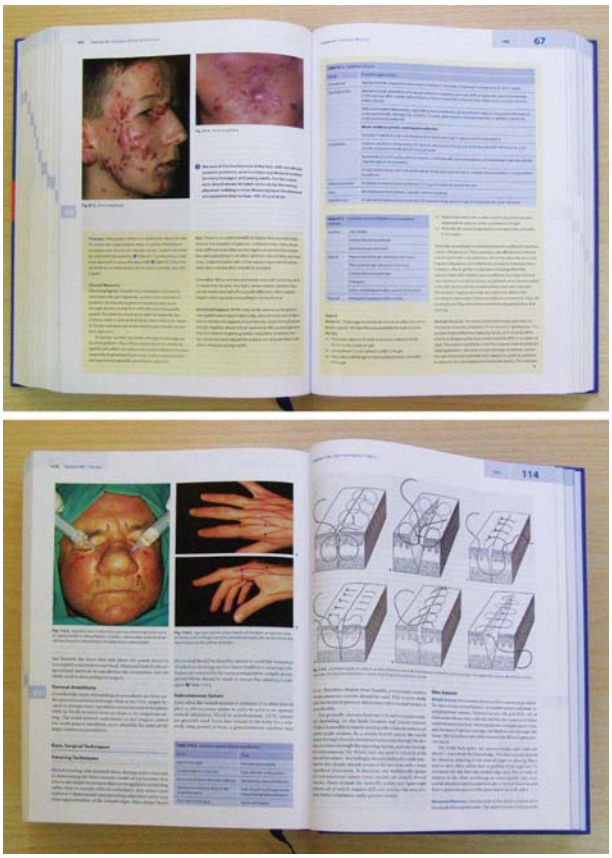


Figure 2. The inside of the Braun-Falco's Dermatology - 3rd Edition

Ever since its first publication in 1961, Braun-Falco's Dermatology became an excellent reference for dermatologists. In the following 30 years, there have been limitations considering readers' knowledge of German language, but in 1991 the first English edition contributed to the popularity and widespread usage of the book. The latest, 3rd English edition of this educational classic was issued in 2009, updated and refreshed.

The book contains all fields of dermatology and venereology, classified into 116 chapters, with 1.712 pages and 1.200 carefully selected color illustrations and photographs, of great importance in dermatology practice. Editors, all respected names, continued writing in a simple and practical style, making it very easy to follow the contents of the book. Comprehensive review of dermatology is given, from the basic principles and diagnostic tools,

Figure 3. Boat tour on the Lake of Starnberg during ISA 2011: Prof. Plewig with his wife and the author of this books review

to therapy, including infectious diseases, intolerance reactions, inflammatory diseases, environmental diseases, blistering diseases, connective tissue diseases, hereditary diseases, vascular diseases, pigmentary diseases, diseases of adnexal structures, metabolic diseases and tumors. "Regional and Special Disorders" section covers distinct pathology with respect to the anatomy, sexual, racial, age-related and professional differences.

Besides overall noticeable high quality summarized knowledge and experience that Braun-Falco's Dermatology brings, I need to commend the editors efforts to publish the name of the first researcher who described each mentioned entity in dermatology (the term in German is Erstbeschreiber). Also, fundamental and important tips are separated and framed, in order not to be missed. Dermoscopy, a very easy-to-perform diagnostic tool, is recognized as a necessity in everyday practice, therefore deserving a full chapter. Within the "Sports Dermatology" chapter, the focus is on skin changes related to frequent practicing specific sport activities, so one can find a diversity of amusing terms, such as "biker's nodule", "Nike nodules", "joggers nipples", paintball purpura etc.

On the whole, the latest Braun-Falco's Dermatology is highly recommended to medical students, interns, dermatologists, but also other clinicians and general practitioners. Once you start reading this text book, it is hard to put it down.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2011

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
7-10 September, 2011	41st Annual ESDR Meeting (European Society for Dermatological Research), Barcelona, Spain	20 May, 2011	www.esdr2011.org
8-10 September, 2011	26th IUSTI Europe Congress, Riga, Latvia	1 June, 2011	www.iusti-europe2011.org
15-17 September, 2011	2nd 5-Continent-Congress for Lasers and Aesthetic Medicine, Cannes, France	31 March, 2011	www.5-cc.com
22-24 September, 2011	32nd Annual Meeting of the International Society for Dermatologic Surgery, Heidelberg, Germany	No abstract submission	www.isdsworld.com
30 September – 1 October, 2011	7th European Masters in Aesthetic and Anti-Aging Medicine, Paris, France	30 May, 2011	www.euromedicom.com
13-15 October, 2011	European Academy of Allergy and Clinical Immunology (EAACI) Focused Meeting, Barcelona, Spain	14 September, 2011	www.eaaci-paam2011.com
20-24 October, 2011	20th Congress of the European Academy of Dermatology and Venereology, Lisbon, Portugal	20 March, 2011	www.eadvlisbon2011.org
2-5 November, 2011	12th IUSTI World Congress, New Delhi, India	15 June, 2011	www.iusti2011.org
11-12 November, 2011	16th Belgrade Dermatology Days, Belgrade, Serbia	30 June, 2011	www.udvs.org
1-3 December, 2011	6th International Congress of Psoriasis, London, UK	1 August, 2011	www.psoriasisg2c.com
4-8 December, 2011	World Allergy Congress, Cancun, Mexico	15 September, 2011	www.worldallergy.org
8-10 December, 2011	19th Annual World Congress on Anti-Aging edicine and Biomedical Technologies, Las Vegas, USA	No abstract submission	www.worldhealth.net
19-21 January, 2012	International Congress in Aesthetic Dermatology (ICAD), Bangkok, Thailand	No deadline information	www.euromedicom.com
26-29 January, 2012	14th International Master Course on Aging Skin (IMCAS) Annual Meeting, Paris, France	No deadline information	www.imcas.com
31 January - 4 February 2012	8th World Congress of the International Academy of Cosmetic Dermatology (IACD), Cancun, Mexico	1 September, 2011	www.wcocd2012.com

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

AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

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

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

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

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

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

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

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

1. Manuscript Preparation Guidelines

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

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

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

- A running title (limited to 30 characters);

- Authors' names and institutional affiliations;

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

1.2. Abstracts

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

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

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

1.3. A list of abbreviations

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

1.4. Cover Letter

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

2. Tables and illustrations

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

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

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

3. References

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

4. Additional information

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

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

For further information please contact the Editorial Office (Tel: +381 21/484 35 62) or visit our web site: **www.udvs.org**.

Erratum

Published in Volume 2 Number 2, pp. 66-72.
The paper by Lalević-Vasić contains the following error:
• Page 68 the third line of the figure 2 legend – Erratum: „Prof. Dr. Milan Kićevac is standing in the last row (indicated by an arrow)“. Corrigendum: „Prof. Dr. Sima Ilić is standing in the last row (indicated by an arrow)“.

CIP – Каталогизација у публикацији
Народна библиотека Србије, Београд

616.5(497.11)

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ISSN 1821-0902 = Serbian Journal of Dermatology and Venerology
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Cover figure: Christ Healing Ten Lepers, Christ's Miracles, XIVth century, The monastery Visoki Dečani, Serbia, Kosovo

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