CASE REPORTS

MALIGNANT ACANTHOSIS NIGRICANS ASSOCIATED WITH GASTRIC ADENOCARCINOMA

TREATMENT OF VERRUCOUS EPIDERMAL NEVUS BY RADIOFREQUENCY ABLATION

LAMOTRIGINE ASSOCIATED DRESS SYNDROME

MAJOCCHI’S GRANULOMA IN A HEALTHY ADULT MAN

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INSTITUTE OF DERMATOVENERELOGY, CLINICAL CENTER OF SERBIA, BELGRADE, SERBIA
Malignant Acanthosis Nigricans, Florid Cutaneous Papillomatosis and Tripe Palms Syndrome Associated with Gastric Adenocarcinoma - a Case Report

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Abstract

Malignant acanthosis nigricans is a rare obligate paraneoplastic dermatosis which accounts for 20% of all acanthosis nigricans cases. The clinical features of the disease are the same as in the benign forms: symmetrical, hyperpigmented, velvety papillomatous lesions mostly involving the axillae, neck, groins, periumbilical cubital and popliteal areas, mammary areolae and less often mucous membranes. However, unlike other forms, it is characterized by sudden onset and rapid spread, commonly (80%) after the age of 40, which may be a marker of malignancy and a key to early diagnosis, indicating the need for a detailed examination. It is a disorder that has no gender differences. Most cases are detected at the moment of cancer diagnosis (61.3%), in fewer cases (about 20%) prior to cancer diagnosis, and in 21% at a later stage of malignant disease. Acanthosis nigricans is usually associated with one of the three or all three forms of paraneoplastic lesions: florid cutaneous papillomatosis, acanthosis palmaris (tripe palms, pachydermatoglyphia) involving the palms and soles, as well as multiple seborrhoeic keratosis (sign of Leser-Trélat).

We report on a female patient with clinically established three paraneoplastic syndromes: malignant acanthosis nigricans, florid cutaneous papillomatosis, and acanthosis palmaris, which appeared before the diagnosis of advanced gastric adenocarcinoma, leading to fatal outcome.

Key words

Acanthosis Nigricans; Paraneoplastic Syndromes; Comorbidity; Adenocarcinoma; Stomach Neoplasms; Case Reports

Acanthosis nigricans (AN) is a symmetric cutaneous eruption characterized by the presence of a hyperpigmented, velvety skin thickening, that can develop on any part of the body, but mostly affects the axillae, back of the head region, sides of the neck, groins, cubital, popliteal and umbilical areas (1 - 6); less often it affects eyelids, palms, soles, nipples and phalanges (1, 7, 8). Histological analysis of skin biopsy specimens shows predominantly papillomatosis and hyperkeratosis (5). Acanthosis nigricans rarely affects the oral, laryngeal, conjunctival and anal mucosa (3).

The term acanthosis nigricans was introduced by Unna from the Greek “acanthus” meaning “thorn” and “nigricans” from the Latin, meaning “becoming black”. The first cases of patients with AN were described by Politzer (9) and Janowski (10) in 1890.

The simplest classification of AN was given by Brown (11): malignant AN is associated with malignant internal neoplasms, and benign AN, which may be idiopathic, hereditary, drug-induced, and associated with endocrine abnormalities.

Curth (12) classified AN into malignant, benign, and syndromic or pseudo-acanthosis nigricans (identical to the benign form, but associated with diabetes).

AN (coexistence of two types of AN). The benign type can be acquired or inherited (1, 13), but there are discussions about autoimmune AN (14, 15).

Diseases and drugs that may be associated with benign type AN (1) include: 1. endocrine diseases (acromegaly, Addison’s disease, Cushing’s syndrome, type 2 diabetes, insulin resistance syndrome type A, B, C, obesity, polycystic ovary syndrome); 2. congenital syndromes (ataxia telangiectasia, Bloom syndrome, Prader-Willi syndrome, total lipodystrophy); 3. drugs (estrogens, glucocorticoids, fusidic acid, nicotinic acid). There are many other drugs that may induce AN: insulin injections (16), oral contraceptives, preparations containing melanocyte-stimulating hormone, triazine, methyltestosterone (17).

Diseases associated with malignant AN: squamous cell carcinoma (lungs, cervix, subglottis); 2. adenocarcinoma (stomach, intestines, hepatic ducts, pancreas, ovaries, urinary bladder, lungs, testicles, mammary gland); lymphomas (Hodgkin’s and non-Hodgkin’s disease; other (mycosis fungoides, osteosarcoma). AN may be present at birth or appear during puberty and adolescence, although it can also be registered at a later age. Malignant AN develops in adult life usually in late middle age or old age, but it was also reported in young patients associated with gastric cancer (12).

In obese and diabetic patients the prevalence varies from 7% to 75%, according to age, race, frequency of type, degree of obesity and concomitant endocrinopathy (5). Malignant AN is less common, although the exact incidence has never been established (18). It has been reported that 2 of 12,000 patients with cancer had signs of AN (19, 20), and 1 out of 35 patients with intra-abdominal or intrathoracic malignancy (21).

Here we present a female patient with paraneoplastic skin lesions.

Case Report
A female patient, 54 years of age, a laboratory technician by profession, sought consultation due to changes in skin color and skin thickening in folds of large joints, and simultaneous appearance of warty and papillomatous lesions. Personal history showed that after the previous summer she noticed somewhat darker skin patches, which she attributed to extensive sun exposure. Since December of the same year, wart-like lesions started appearing in the thickened skin folds of her hands and feet, with numerous small tumorous lesions. She had an impression that it all started suddenly, after one night with severe itching all over the body. Since then she noticed hair and eyebrow loss. Occasionally she experienced itching or burning of the skin, especially in the armpits after excessive sweating. In general, she felt healthy, went to work regularly, and her appetite was normal. In recent months she lost a few kilos, in her opinion due to family problems. She felt weak when going up the stairs and had difficulty breathing. She denied epigastric pain and digestive problems.

Patient history. The patient history showed that she underwent ovarian cyst surgery 25 years ago, and stomach ulcer surgery 3 years ago (detected and treated for 2 - 3 years before); she entered menopause 8 years ago. She was smoking 40 cigarettes a day and did not consume alcohol.

Family history. The patient denied serious diseases or surgeries within the family, as well as skin diseases, especially skin lesions similar to her own.

Physical examination. The initial examination showed a patient of medium height in a good general condition. Skin examination revealed general hyperpigmentation which was especially pronounced on the back of the head and both sides of the neck, with velvety skin thickening and pronounced dermatoglyphics. The thickening of the skin was much more pronounced in the axilla (Figure 1), groins, the inner thighs, perigenital area and the corners of the mouth, where the skin was very rough, thick, wrinkled, particularly in the central parts of the axillae and groins, resembling the fissured bark of *Quercus cerris*, dark brown or black in color. A great number of papillomatous skin tags were found in these areas, some without hyperpigmentation. These papillomatous lesions also involved the lower right eyelid.

Also, multiple verrucous pea to hazelnut sized lesions were found on the dorsal aspects of hands (Figure 2), forearms, lower legs and some on the face. The skin on the palms and to a lesser degree on the soles was hyperkeratotic; hyperkeratosis was also present on the sides of the fingers and the lateral part of the fifth toe on both feet. Pronounced, thickened, velvety pachydermatoglyphia was affecting the palms.
The nails were unaffected.

The lips and the mucous membranes of the soft and hard palate presented with a clearly limited thickening, with uneven surfaces, yellowish pink in color. Two transverse erosions appeared on the tongue, that did not previously exist.

**Laboratory and other test results**

All tests were performed to detect the presence of any visceral organs neoplasms.

**Laboratory test revealed the following abnormal results:** fibrinogen 5.2 g/L (normal range 2.0 - 4.0), total protein serum level 92.9 g/l (normal range 63 - 80.0), T4: 179 nmol/l (normal range 55.0 – 165.0), IgE 144 IU/ml (normal range – less than 100), IgA 2.99 g/l (normal range 0.74 - 4.0), IgM 1.52 (normal range 0.30 – 2.93), IgG 23.0 g/l ((normal range 8.8 – 18.0), soluble immune complexes 206 IU/ml (normal range 24 - 116).

- **Chest X-ray** – normal.
- **Skull x-ray**: normal.
- **Eye fundus examination**: Fundus arterioscleroticus.

**Figure 1.** Pigmentation and velvety thickening of the skin, mainly in the axillae

**Figure 2.** Multiple verrucous papules on dorsal sides of hands
Stomach X-ray, gastroscopy, histopathological examination of the stomach biopsy sample: gastric adenocarcinoma.

Treatment, further course: Since gastric adenocarcinoma was diagnosed at an advanced stage, the course of the disease was progressive, with rapid fatal outcome.

Discussion
Malignant acanthosis nigricans (MAN) is a rare obligate paraneoplastic dermatosis (22) which accounts for 20% of all acanthosis nigricans cases (18, 23). The term MAN is recognized and accepted, but as such it is not malignant, it only co-occurs with cancer (1, 24). A more accurate term would be paraneoplastic AN.

The clinical features of the disease are the same as in the benign AN: symmetrical, hyperpigmented, velvety papillomatous lesions mostly involving the axillae, neck, groins, periumbilical cubital and popliteal areas, mammary areolae and less often the mucous membranes, although according to some data 30 to 50% of patients with MAN have oral lesions, mostly on the tongue and lips (25 – 28). However, unlike other forms, MAN is characterized by sudden onset and rapid spread, commonly (80%) after the age of 40 (21), which may be a marker of malignancy and a key to early diagnosis (29), indicating the need for a detailed examination (4). It is a disorder that has no gender differences. Most cases are detected at the moment of cancer diagnosis (61.3%), in fewer cases (about 20%) prior to cancer diagnosis, and in 21% at an advanced stage of malignant disease (30).

In our patient, changes typical of AN appeared at the age of 53, without symptoms of malignant disease, which was diagnosed a few months later, but at an advanced stage, which does not exclude the possibility that the malignancy preceded it, or appeared simultaneously with the skin changes.

The most common malignancy associated with malignant acanthosis nigricans is abdominal adenocarcinoma, especially of the stomach. In an early study (12) of 191 patients with MAN, 177 (92%) had an underlying abdominal cancer, of which 69% were gastric. The remaining 31% had carcinoma of the uterus, liver, intestine, colon, rectum or ovaries, and only 14 had extra-abdominal malignancies (breast, lung and mediastinum). In another study (31), of 94 cases with MAN, 58 (61%) persons were diagnosed with gastric cancer. According to other authors (11, 18, 32), the most common malignancies are adenocarcinomas of the digestive tract and uterus, while carcinomas of the lung, breast, prostate, and ovary are less frequent. Recently, more papers have been published on the association between MAN and gastric adenocarcinoma (18, 29, 30, 33, 34),
ovarian cancer (35), hepatocellular carcinoma (36), adenocarcinoma of the bladder (4) and metastatic laryngopharyngeal carcinoma (37). Our patient with AN was also diagnosed with gastric adenocarcinoma. The malignancy was diagnosed several months after the onset of skin lesions, but unfortunately at an advanced stage without prospect of cure.

MAN was first described by Clarke (38); it may be associated with other cutaneous markers of internal malignancies: AN commonly occurs with some of the three or all three forms of paraneoplastic lesions, florid cutaneous papillomatosis (FCP), lesions on the palms and soles (tripe palms; pachydermatoglyphia), and multiple seborrheic keratoses (sign of Leser-Trélat). These paraneoplastic syndromes are considered abortive forms of MAN (19), especially as they have similar epidemiological, morphological and histological characteristics (38). However, these are special type of paraneoplastic dermatoses (39) which can occur individually (13, 40, 41).

Florid cutaneous papillomatosis (Schwartz-Burgess syndrome) is characterized by numerous warty papules on the trunk, extremities and face that are similar to viral warts, but show different clinical and histological features (18). This condition was described and named by Schwartz and Burges in 1978 (42). It is commonly associated with gastric adenocarcinoma and MAN. The lesions regress after cancer surgery or chemotherapy, but reappear with tumor recurrence and metastasis (43, 44).

Tripe palms (acanthosis palmaris, pachydermatoglyphia) is an acquired palmoplantar keratoderma (19, 45 - 48) which clinically manifests with thick and pronounced velvety-white folds in the lines of the hands (so the skin resembles boiled tripe); in 90% of cases it is associated with malignancy of the internal organs (46, 49, 50); histologically it is characterized by hyperkeratosis, papillomatosis and acanthosis (50); MAN was first described by Clarke (51); it may be the only paraneoplasia in 30-40% of cases, or it is associated with AN or Leser-Trélat (52). It mainly occurs in male patients with lung cancer. In most cases, tripe palms is associated with lung and stomach cancer (53), but also with urogenital tract carcinoma. Nail changes are common in lung cancer, whereas gastric cancer is associated with AN. The condition resolves once the underlying cancer is treated (52).

Leser-Trélat sign is characterized by the abrupt appearance of multiple seborrheic keratoses, with or without itching. It may be a cutaneous indicator of internal malignancy, most commonly digestive tract adenocarcinoma (13) when it is associated with MAN, breast or lung cancer (54); it is rarely reported in malignant hemangiopericytoma, malignant melanoma or kidney carcinoma. In lymphoproliferative diseases it occurs more often than MAN, and this comorbidity is found in about 20% of cases (52). It may occur in HIV (Human Immunodeficiency Virus) infection, acromegaly, and resolution phase of exfoliative dermatitis (49). Multiple seborrheic keratoses are common in elderly people, pruritic or eruptive, but if there is a sudden appearance of seborrheic warts with severe itching, measures should be taken in order to prove or exclude malignancy. Comorbidity between seborrheic warts and benign AN has not been reported so far.

Our patient presented with three paraneoplastic dermatoses: malignant acanthosis nigricans, florid cutaneous papillomatosis and tripe palms as a manifestation of gastric adenocarcinoma.

The pathogenesis of AN has not been fully elucidated (13, 55). In the case of insulin resistance, which is extremely rare or remains undiagnosed (56), insulin acts through a classical insulin receptor or other insulin-like receptors: high levels of insulin may activate the insulin-like growth factor 1 receptor (IGF-1R) and mediate cell proliferation (2, 57). Perspiration and/or friction may be necessary cofactors (5).

The pathogenic mechanism involved in the development of MAN is still obscure (55). A current hypothetical mechanism is the secretion of large amounts of transforming growth factor alpha (TGF-a) by the tumor into the circulation that is thought to stimulate keratinocyte growth via an endocrine route (58). There is a positive correlation between the stages of tumor progression and expression of this factor. TGF- alpha is a primary mediator of benign and malignant keratinocyte hyperproliferation in vivo (58). Some authors speculate that activation of fibroblast growth factor receptor 3 (FGFR3) might have some relevance to the formation of MAN (59). Simultaneous activation of epidermal growth factor receptor 3 (EGFR3), insulin-like growth factor-α -1 (IGF-1) and melanocyte stimulating hormone α (MSH-α) stimulates the development of MAN (55,
59); a systemic immunologic response to the primary tumor as a cause cannot be discarded (13).

There is no specific therapy for AN. Phenytoin and metformin are used in insulin resistance (56); in benign and malignant forms topical therapy is used with varying success: retinoids, ammonium lactate, trichloroacetic acid, salicylic acid, podophyllin, urea, calcipotriol, dermabrasion, laser therapy; systemic therapy includes retinoids and PUVA, and cyproheptadine in MAN (5, 60-62). It is well known that paraneoplastic syndromes regress after cancer surgery, chemotherapy or radiotherapy, but may reappear with tumor recurrence or metastasis.

Conclusion

We report on a female patient with clinically established three paraneoplastic syndromes: malignant acanthosis nigricans, florid cutaneous papillomatosis, and acanthosis palmaris, which appeared before the diagnosis of advanced gastric adenocarcinoma was made, leading to fatal outcome.

Abbreviations

AN - acanthosis nigricans  
T4 - thyroxine  
Ig - immunoglobulin  
MAN - malignant acanthosis nigricans  
FCP - florid cutaneous papillomatosis  
HIV - human immunodeficiency virus  
IGF-1R - insulin-like growth factor-1 receptor  
TGF-α - transforming growth factor-alpha  
FGFR3 - fibroblast growth factor receptor 3  
EGFR3 - epidermal growth factor receptor 3  
IGF-1 - insulin-like growth factor-1  
αMSH - alpha melanocyte stimulating hormone  
PUVA - psoralen plus ultraviolet A

References


Maligna acanthosis nigricans, floridna kutana papilomatoza i acanthosis palmaris udruženi sa adenokarcinomom želuca – prikaz slučaja

Sažetak

Uvod. Maligna acanthosis nigricans obligantna je paraneoplazijska dermatoza, koja se retko javlja i čini 20% od svih slučajeva acanthosis nigricans. Kliničke osobine bolesti su iste kao kod benigne forme bolesti, međutim, za razliku od drugih formi, karakteriše je iznemanog naglo i brzo širenje, najčešće (u 80%) pojavom posle 40. godine života, što kao marker maligniteta ili ključ za ranu dijagnostiku može da ukaže na potrebu za detaljnim ispitivanjem u tom smislu. Najveći broj slučajeva se detektuje u momentu dijagnostike maligniteta (61,3%), manje pre dijagnostike (oko 20%) i 21% u kasnom stadijumu maligne bolesti. Obično se uz acanthosis nigricans javlja i jedan od tri ili sva tri oblika paraneoplazija: floridna kutana papilomatoza, acanthosis palmaris (tripe palms, pachydermatoglyphy) sa promenama na dlanovima i tabanima i multiple seboroične keratoze (Leser T relatov znak). Bolesti udružene sa malignom. Bolesti udružene sa malignom acanthosis nigricans: skvamocelularni karcinom (pluća, cervix. subglotis); adenokarcinom (ezofagus, želudac, interstium, hepatički duktusi, pankreas, ovarijumi, mokraćna beška, pluća, testisi, mlečne žlezde); limfomi (Hočkinova i nehočkinska bolest; 4 ostalo (mycosis fungoides, osteosarcoma).

Cilj rada. U radu je prikazana bolesnica kod koje je klinički registrovana kombinacija tri paraneoplazijske sindroma: maligna acanthosis nigricans; floridna kutana papilomatoza i acanthosis palmaris, koje su se pojavile pre dijagnostikovanja adenokarcinoma želuca koji je otkriven u odmakloj fazi, što je rezultovalo smrtnim ishod.

Prikaz slučaja. Bolesnica stara, 54 godine, javila se na pregled zbog promene boje kože i zadebljanja na pregibima velikih zglobova i istovremene pojave bradavićastih i papilomatoznih tvorevina. Iz anamneznih podataka se saznalo da je od prethodnog leta primetila zaostatak nešto tamnije boje kože, što je ona pripisivala dugom sunčanju. Od decembra meseca iste godine, počele su da joj se javljaju bradavice po rukama i nogama, a u pregibima zadebljanje kože sa mnoštvom sitnih tumoroznih promena. Njen utisak je bio da je sve počelo odjednom, posle jedne noći kada je imala intenzivan svrab po čitavoj koži. Od tada je počela da joj opada kosa i proređuju obrve. Povremeno se javljao svrab ili pečenje kože, naročito u pazuhima i to posle jačeg znojenja. U celini se sve vreme osećala zdravom, redovno je odlazila na posao, nije gubila apetit. Poslednjih meseci je izgubila neoliko kilograma u telesnoj težini, što je objašnjavala porodičnim problemima. Jedino je primetila da se zamara kada ide uz stepenice, i tada ima otežano disanje. Boleve u epigastrijumu i smetnje pri varenju nije imala. U ličnoj anamnezi je dala podatke da je pre 25 godina imala operaciju ciste na jajniku, a pre 3 godine čira na želucu, koji je pre operacije otkriven i lečen tokom 2-3 godine; menopauza je nastupila pre 8 godina. Sve vreme, bez prestanka, pušila je po 40 cigareta dnevno; nije konzumirala alkohol. U ličnoj anamnezi je dala podatke da je pre 25 godina imala operaciju ciste na jajniku, a pre 3 godine čira na želucu, koji je pre operacije otkriven i lečen tokom 2-3 godine; menopauza je nastupila pre 8 godina. Sve vreme, bez prestanka, pušila je po 40 cigareta dnevno; nije konzumirala alkohol. U porodičnoj anamnezi izjavila je da kod ostalih članova porodice nije bilo težih oboljenja niti operacija i da niko nije imao oboljenja kože, naročito ne promene na koži slične njenim. Prilikom prvog pregleda, bolesnica srednjeg rasta, nalazila se u dobrom opštem stanju. Prilikom pregleda kože i vidljivih...
sluznica, uočena je jača pigmentacija kože u celi; hiperpigmentacija je naročito bila izražena u potiljačnoj regiji i na bočnim stranama vrata, sa zadebljalom kožom somotaste površine i naglašenim kožnim crtežom. Mnogo izrazitije zadebljane kože bilo je u aksilama (Slika 1), preponama, na unutrašnjim stranama butina i perigenitalno i na uglavnom usana, gde je koža bila izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito gruba, deblja, naborana, naročito u centralnim delovima aksila i prepona, sa izgledom crive kore, mrko izrazito.

Kod naše bolesnice registrovan je trijas paraneoplazijskih dermatoza: maligna acanthosis nigricans, floridna kutana papilomatoza i tripe palms kao manifestacija adenokarcinoma želuca.

Patogeneza acanthosis nigricans još uvek nije potpuno razjašnjena. Kada se radi o insulinskoj rezistenciji, koja je ekstremno retka ili ostaje nedijagnostikovana, insulin deluje preko klasičnog receptora i drugih receptora nalik na insulinski: visoke koncentracije insulina mogu da aktiviraju receptor za insulin – sličan faktoru rasta 1 (eng. insulin growth factor-1 receptor, IGF-1R) i budu medijatori ćelijske proliferacije. Znojenje i/ ili trenje može biti neophodan kofaktor. Patogenetski mehanizam koji dovodi do maligna acanthosis nigricans nije potpuno jasan. Važeći hipotetički mehanizam podrazumeva sekreciju iz tumora u cirkulaciju velike količine TGF-alfa (eng. transforming growth factor-alpha), za koji se smatra da stimulše rast keratinocita preko endokrinog puta. Utvrđena je pozitivna korelacija između faze progresije tumora i ekspresije ovog faktora; TGF-alfa predstavlja primarni medijator kako benigne tako i maligne hiperproliferacije keratinocita in vivo. Neki autori sugerišu da aktivacija receptora 3 za fibroblastni faktor rasta (eng. fibroblast growth factor receptor 3 - FGFR3) ima uticaja u formiranju maligne acanthosis nigricans. Istovremena aktivacija EGFR3 (eng. epidermal growth factor receptor 3), IGF-1 i MSH-α (melanocitni stimulišući hormon alfa), stimuliše razvoj maligne acanthosis nigricans; sistemski imunski odgovor usmeren na primarni tumor kao uzrok poremećaja, ne može se odbaciti. Nema specifičnog tretmana acanthosis nigricans. Kod insulinske rezistencije koriste se fenitoin i metformin; kod benignih i maligne forme sa različitim uspehom primenjuje se lokalna terapija: retinoidi, amonijum-laktat, trihlorsirćetna kiselina, salicilna kiselina, podofilin, urea, kalcipotriol, dermoabrazija, laser, a u sistemskoj terapiji, retinoidi PUVA i kod maligne acanthosis nigricans cyproheptadin.

Zaključak. U radu je prikazan slučaj osobe ženskog pola kod koje je klinički registrovana kombinacija tri paraneoplazijska sindroma: maligna acanthosis nigricans, floridna kutana papilomatoza i acanthosis palmaris, koje su se pojavile pre dijagnostike adenokarcinoma želuca, koji je otkriven u odmakloj fazi, te je bolest rezultovala smrtnim ishodom.

Ključne reči

Acanthosis nigricans; Paraneoplazijski sindromi; Komorbiditet; Adenokarcinom; Neoplazme Żeluca; Prikazi slučajeva

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Treatment of Verrucous Epidermal Nevus by Radiofrequency Ablation: a Case Report

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Abstract

Verrucous epidermal nevi are noninflammatory, congenital, cutaneous hamartomas composed of keratinocytes, abnormal clone(s) of cells that reflect genetic mosaicism arising from different somatic mutations. Some of these mutations are well recognized, but some are still unidentified. Molecular techniques are used for identification and classification of molecular causes of certain epidermal nevi, whereas all verrucous epidermal nevi are divided into epidermolytic and non-epidermolytic types. They are typically present at birth, but may appear during childhood, even later. Their prevalence in adults ranges from 0.1 to 0.5%, equally affecting both sexes, and about 1 in 1000 newborns.

Warty, brown papules without inflammation distinguish verrucous nevi from other epidermal nevi, while presence at birth and persistence distinguish verrucous epidermal nevi from linear viral warts. Epidermolytic and non-epidermolytic verrucous epidermal nevi are almost always hard to distinguish, except by histology. As a rule, verrucous epidermal nevi are asymptomatic, they have a benign course, except occasionally, and therapy is mostly used for cosmetic reasons. Simple excision is usually the treatment of choice. Topical agents are rarely curative, as well as surgery which is associated with relapses, unless both epidermis and the underlying dermis are removed or destroyed at the same time.

We present a case of an otherwise healthy 21-year-old female patient, who presented with a solitary congenital verrucous cauliflower-like lesion in the right zygomatic region of the face. The lesion was present from birth. Due to its gradual growth during years, the lesion became a great esthetic and functional problem for this young patient. There was no family history of similar or any other tumorous skin lesions in the family. On examination, the patient had a solitar unilateral, well defined yellowish cauliflower-like verrucous lesion confined to the right malar side of the face. The lesion was distributed along the lines of Blaschko extending horizontally, from its wider 1.5 cm cauliflower-like part on the right zygomatic region, towards its tail-like 0.5 cm thick end on the preauricular region, in approximately 3 cm long tail-like manner without crossing the midline.

Since the patient refused biopsy, no exact differentiation between epidermolytic and non-epidermolytic nevi was possible. The diagnosis of verrucous epidermal nevus was based on history and clinical presentation, as a diagnosis of exclusion. Due to the fact that patients with epidermolytic verrucous epidermal nevi are at risk of parenting a child with bullous ichthyosiform erythroderma, the patient was counseled on this risk, and on the possibility of first-trimester antenatal diagnosis. The lesion was successfully treated by radio-wave surgery.

Key words

Nevus, Sebaceous of Jadassohn; Prevalence; Diagnosis; Ablation Techniques; Case Reports; Catheter Ablation

According to a rather historical, but still existing classification, all nevi are generally classified and further subdivided based upon the origin of their component cells, tissues or organs and according to the macroscopic or histological features, respectively. Thus, epidermal nevi are composed of keratinocytes (1, 2, 3) and categorized as follows: keratinocyte nevi, sebaceous nevi, follicular nevi, apocrine nevi, eccrine nevi, inflammatory epidermal nevi, other nevoid epidermal disorders (linear lichen planus, nevoid psoriasis, linear porokeratosis, Hailey–Hailey-like epidermal nevus, Darier-like epidermal
nevus, atrophoderma of Moulin, ‘blaschkitis’), and epidermal nevus syndrome (3). Since more research has been recently conducted in order to clarify the molecular basis of certain epidermal nevi, it has been suggested that probably all epidermal nevi comprise an abnormal clone of cells, as a consequence of genetic mosaicism arising from a somatic mutation (3, 4). By using molecular techniques for the identification and classification of molecular causes of certain epidermal nevi, all verrucous epidermal nevi are divided into epidermolytic and non-epidermolytic types. Epidermolytic and non-epidermolytic verrucous epidermal nevi are almost always hard to distinguish except by histology (due to presence/absence of epidermolytic hyperkeratosis), which is important because contrary to non-epidermolytic nevi, a parent with an epidermolytic verrucous epidermal nevus is at risk to have gonadal mosaicism as well as cutaneous mosaicism and to produce offspring with generalized autosomal dominant bullous ichthyosiform erythroderma (BIE). Though the risk has not been exactly quantified, counseling may be of benefit for affected individuals and their families (3).

Warty, brown papules without inflammation distinguish verrucous nevi from other epidermal nevi, while presence at birth and persistence distinguish verrucous epidermal nevi (VEN) from linear viral warts (3, 5).

VEN are the most common type among all other epidermal nevi. They are usually present at birth, but may appear during childhood, even later. Thus, their prevalence in adults ranges from 0.1 to 0.5%, equally affecting both sexes, and about 1 in 1000 newborns (3, 6, 7, 8).

They are expected to be blistered at birth, and only later to become verrucous. At birth, in the majority of cases, VEN have a macerated, whitish appearance, but within a few days they become pink or slightly pigmented velvety streaks or plaques. In young children they appear as slightly pigmented velvety or warty streaks or plaques. Their extent and distribution may considerably vary (3, 5).

As a rule, verrucous epidermal nevi are asymptomatic, they generally have a benign course, except on rare occasions, thus, the therapy is mostly used for cosmetic reasons (9).

Various therapeutic modalities have been attempted (10 - 13). Topical agents are rarely curative, as well as surgery. Simple excision is usually the treatment of choice, but relapses may occur (3). World literature reports show that a great majority of treatment outcomes of verrucous epidermal nevi using various therapeutic modalities, do not differentiate epidermolytic and non-epidermolytic nevi (3).

Case Report
We present a case of an otherwise healthy 21-year-old female patient with a solitary congenital verrucous cauliflower-like lesion in the right zygomatic region of the face. The lesion was present from birth in a form of a small, verrucous papule which gradually became more verrucous.

Due to its gradual growth during years, the lesion became a great esthetic and functional problem for this young patient. There was no family history of similar or any other tumorous skin lesion in the family.

On examination, the patient had a solitary unilateral, well defined yellowish cauliflower-like verrucous lesion confined to the right malar side of the face. The lesion was distributed along the lines of Blaschko, extending horizontally, from its wider 1.5 cm cauliflower-like part on the right zygomatic region, towards its tail-like 0.5 cm thick end on the preauricular region, in approximately 3 cm long tail-like manner without crossing the midline (Figure 1).

Since the patient refused biopsy, no exact differentiation between epidermolytic and non-epidermolytic nevi was possible. The diagnosis of verrucous epidermal nevus was based on history and clinical presentation, as a diagnosis of exclusion. Due to the fact that patients with epidermolytic verrucous epidermal nevi are at risk of parenting a child with bullous ichthyosiform erythroderma (BIE), the patient was counseled on this risk and on the possibility of first-trimester antenatal diagnosis.

The lesion was successfully treated by radiowave radiosurgery (radiofrequency knife: Proxima VF, Proxima D.O.O, 18250 Niš, Srbija) under local anesthetic cream (EMLA®). An electrode tip in the shape of a fine needle cutting with coagulation selected position of waveform output power of 6/7 was used in the first session (range between 0 and 9). A second session was performed 7 days later, the edges were melted by spherical electrode tip, using the same position and intensity (Figure 2).
Further therapy included local use of antibiotic ointments and anti-scar gel (Figure 3). On 4 week follow-up, VEN was totally removed, with no scars, with only mild erythema on previously affected skin (Figure 4). Due to the fact that VEN can recur, partially or completely, the patient was advised to do regular follow-ups, as well as maximum sun protection during summer months.

**Discussion**

Verrucous epidermal nevi (VEN) account for more than 60% of all epidermal nevi (14). They can occur at birth, early childhood, or at later age (7, 8). The size and number of nevi varies. Most frequently they are localized on the limbs or trunk, and less commonly on the face or neck (15, 16). Oral mucosal has rarely been reported due to extension of nevi on the adjacent mucosal surface (17). These lesions virtually never cross the midline. Both, the shape and distribution of almost all epidermal nevi including verrucous, follow the pattern of Blaschko's lines that are features of mosaic conditions of the epidermis and probably the paths of ectodermal cell migration from the neural crest (3). Rarely, lesions may occur on both sides (18). As a rule, VEN are asymptomatic. The lack of inflammation, presence at birth, warty, brown appearance and persistence distinguish them from most other types of epidermal nevi (19). In the past, verrucous epidermal nevi have been confused with a certain number of other epidermal nevi distinct from VEN, that have been recognized more recently (3, 20).

As it has been previously mentioned, after identifying the molecular causes of certain epidermal nevi, all VEN are divided into epidermolytic and non-epidermolytic types that are almost always hard to distinguish except by histology. In our patient, who refused biopsy, the diagnosis of verrucous epidermal nevus was made based on history and clinical presentation, as a diagnosis of exclusion. Due to mosaicism, both epidermolytic and non-epidermolytic VEN are sporadic and cannot be passed on from parent to child and recur in the same family. However, in light of the new molecular data, epidermolytic and non-epidermolytic verrucous epidermal nevi should be distinguished histologically. VEN represent a noninflammatory congenital cutaneous hamartomas composed of keratinocytes that are abnormal clone/
clones of cells that reflect genetic mosaicism which arises from different somatic mutations (3, 21, 22). Some of these mutations are well recognized, but some are still unidentified (3). It has been confirmed that epidermolytic VEN represent clones of cells expressing a mutation in one of the bullous ichthyosiform erythroderma (BIE) gene: KRT10 (21, 23) or KRT1 (24). Such VEN cannot be passed on from parent to child, but contrary to non-epidermolytic VEN, that present mosaicism for different, and as yet unidentified, mutations, a parent with an epidermolytic VEN may have gonadal mosaicism as well as skin mosaicism, and can therefore produce offspring with generalized BIE (21, 24-27). Though the risk has not been exactly calculated yet, efforts should be made to counsel affected individuals (3).

In contrast to epidermolytic VEN, where mutations affect keratin genes that are expressed only in epithelia, non-epidermolytic VEN, which represent mosaic expression of still unidentified mutations, may (in approximately 10%) be associated with extracutaneous abnormalities particularly of the central nervous system, eye and skeleton (e.g. epidermal nevus syndrome) (3, 28). Several other changes have been reported in verrucous epidermal nevi, such as Bowen’s disease, verrucous and adnexal carcinomas (3, 29), basal cell (30) and squamous cell carcinomas (31, 32) within epidermal nevi. However, it has not yet been clarified whether these represent age and/or site-dependent differences in the same condition or different nevi (3). In our patient there were no such associations. The management of the associated anomalies requires careful clinical and noninvasive relevant investigations, including ophthalmological examination and cranial ultrasound (3).

Therapeutic modalities are numerous and they are used depending on the localization and size of the lesion with different level of success (9). Topical or intraläsional corticosteroids were used, as well as calcipotriol, 5-fluorouracil, podophyllin, retinoid, chemical peeling (33, 34), cryotherapy, dermabrasion, electro-surgery (1, 2), photodynamic therapy (11), different types of lasers, such as argon (35) ruby (36), erbium: yttrium aluminium garnet (Er : YAG) (37), carbon dioxide laser (2, 9, 10, 35, 38-40).

**Figure 3.** Treated area 7 days after the therapy

**Figure 4.** Treated area 4 weeks after the therapy
In the recent years, radiofrequency ablation (radiosurgery, high frequency electrocautery) has become a very important and effective tool in dermatosurgical everyday practice (41, 42). Therefore, we conducted a radio wave technique for surgical management of VEN in our patient. The radio wave probe Proxima VF is a modern high-frequency radio surgical instrument which converts electrical current into radio wave frequency on the principle of increasing the frequency and voltage and simultaneously decreasing the amperage of alternating current. By further modification, different wave forms are produced, with three main tissue effects: electrosection (cutting), electrocoagulation (deep tissue destruction) and electrodessication/electrosurgery (superficial tissue destruction).

The selection of wave form as well as the shape of probes (fine needle, wire loop, ellipse or triangle, diamond), depend on the primary aim, e.g. cutting or coagulation (41, 42). Radiofrequency ablation has become popular because of several advantages in comparison to other surgical procedures, particularly electric cautery, surgical excision and laser treatment. It is a simple, time-consuming, less painful, rather safe and simultaneously decreasing the amperage of alternating current. By further modification, different wave forms are produced, with three main tissue effects: electrosection (cutting), electrocoagulation (deep tissue destruction) and electrodessication/electrosurgery (superficial tissue destruction).

The selection of wave form as well as the shape of probes (fine needle, wire loop, ellipse or triangle, diamond), depend on the primary aim, e.g. cutting or coagulation (41, 42). Radiofrequency ablation has become popular because of several advantages in comparison to other surgical procedures, particularly electric cautery, surgical excision and laser treatment. It is a simple, time-consuming, less painful, rather safe technique, causing less lateral heat spread and tissue damage, with fewer side effects and complications (41 - 45). Nevertheless, regardless of the therapy used, a high relapse rate has been reported, thus follow up is therefore advised (3)

Conclusion
This is a report of a localized congenital verrucous epidermal nevus in an otherwise healthy young woman, who was successfully treated by radiofrequency ablation.

References

**Ablacija verukoznog epidermalnog nevusa pomoću radiotalasa – prikaz slučaja**

**Sažetak**

Uvod. Epidermalni nevusi su sastavljeni od keratinocita, a kategorisani su na sledeći način: keratinocitni nevusi, sebacealni nevusi, follicularni nevusi, apokrini nevusi, ekrini nevusi, inflamatorni epidermalni nevusi, ostali nevoidni epidermalni poremećaji (linearni lihen planus, nevoidna psorijaza, linearna parakeratoza, Hailey–Hailey-like epidermalni nevus, Darier-like epidermalni nevus, atrofoderma Moulin, Blaschkitis) i sindrom epidermalnog nevusa. Na osnovu rezultata molekularnih istraživanja, pretpostavlja se da svi epidermalni nevusi predstavljaju abnormalni ćelijski klon u okviru genetskog mozaicizma nastalog iz somatske mutacije.

Epidermolitični i non-epidermolitični verukozni nevusi mogu se međusobno diferencirati skoro isključivo na osnovu pathohistološke analize (prisustvo, odnosno odsustvo epidermolitične hiperkeratoze). Ova diferencijacija nema samo akademska, nego i praktičan značaj, s obzirom na to da za razliku od osobe koja ima non-epidermolitični nevus, osoba sa epidermolitičnim nevusom poseduje povišen rizik za nastanak gonadnog i kutanog mozaicizma, što za posledicu može imati radanje deteta sa autozomno dominantnom buloznom ihtioziformnom eritrodermijom. Iako stepen rizika nije precizno utvrđen, neophodno je pravovremeno informisati i instruisati obolelu osobu.
Bradavićast, smeđ izgled i odsustvo infl amacije, izdvaja verukozni nevus od ostalih epidermalnih nevusa, a prisustvo na rođenju i perzistiranje, omogućuju diferenciranje verukoznog epidermalnog nevusa od linearnih virusnih Bradavicica.

Na samom rođenju, epidermalni verukozni nevus se može manifestovati prisustvom vezikulica, da bi tek u kasnijem periodu poprimio bradavićast izgled. U većini slučajeva, verukozni epidermalni nevus na rođenju poprima macerirani, beličasti izgled, koji se već nakon nekoliko dana menjaju u ružičaste ili lako hiperpigmentovane linearne somotaste formacije ili plakove. U detinjstvu dobijaju bradavićast izgled.

Veličina i distribucija verukoznog epidermalnog nevusa može veoma varirati. Po pravilu verukozni epidermalni nevusi su asimptomatski. U principu imaju u najvećem broju slučajeva benigni tok, tako se njihova terapija sprovodi uglavnom zbog estetskih razloga. Postoji veliki broj terapijskih modaliteta za otklanjanje verukoznog epidermalnog nevusa, ali su i lokalna konzervativna i klasična hirurška terapija udružene sa visokom stopom recidiva. U objavljenim radovima koji se odnose na ishod terapije, uglavnom se ne navodi da li se radi o epidermolitičnom ili o non-epidermolitičnom verukoznom nevusu.

Prikaz slučaja. U radu je prikazan slučaj inače zdrave dvadesetjednogodišnje osobe ženskog pola iz čije se anamneze saznalo da je promenu zbog koje se javila na pregled imala još na rođenju i da se tokom života ona povećavala tako da je u datom trenutku postala i estetski i funkcionalni problem. U porodici nije bilo oboljela srodnika niti je iko od srodnika imao tumore kože. Prilikom prvog pregleda, na desnoj zigomatičnoj regiji lica uočena je solitarna unilateralna verukozna žućkasto prebojena karfi olasta jasno ograničena tumorska lezija, koja se prostirala horizontalno u dužini od oko 3 cm prateći Blaschko liniju od svog šireg karfi olastog kraja dijametra oko 1,5 cm smeštenog u desnoj zigomatičnoj regiji do užeg, nalik na rep, debljine 0,5 cm, na desnoj preaurikularnoj regiji, ne prelazeći pritom središnju liniju lica.

Dijagnoza verukoznog epidermalnog nevusa postavljena je na osnovu anamneze, kliničkog izgleda metodom isključivanja. S obzirom da je pacijentkinja odbila uzimanje biopsije, nije bilo moguće izdiferencirati da li se radi o epidermolitičnom ili non-epidermolitičnom verukoznom nevusu. verzifikacija o mogućem riziku za dobijanje potomstva sa buloznom ihtioziformnom eritrodermijom i mogućnosti, tj. neophodnosti sprovođenja antenatalne dijagnostike.


Na kontrolnom pregledu sprovedenom četiri nedelje kasnije, verukozna promena bila je u celini odstranjena, bez ožiljaka a na tretiranom mestu zaostao je samo blag eritem. S obzirom da verukozni epidermoidni nevus ima sklonost ka recidiviranju, delimičnom i kompletnom, pacijentkinji je savetovano da dolazi redovno na kontrole i da se maksimalno štiti od sunčevog zračenja tokom letnjih meseci.

Diskusija. S obzirom da se u osnovi i epidermolitičnog i non-epidermolitičnog verukoznog nevusa nalazi mozaicizam, oni se ne mogu preneti sa roditelja na decu niti se pojavljuju u istoj porodici. Verukozni epidermoidni nevus predstavlja klon ćelija koje poseduju mutacije gena za buloznu ihtioziformnu eritrodermiju. KRT10 i KRT1. Kao takav, verukozni epidermoidni nevus se ne može preneti sa roditelja na dete a na razliku od non-epidermolitičnog verukoznog nevusa koji je posledica mozaicizma za različite, još uvek nedovoljno identifikovane mutacije. Roditelj koji ima epidermolitični verukozni nevus može imati povišeni rizik od nastanka gonadog i kutanog mozaicizma,
te tako može imati potomstvo sa generalizovanom buloznom ihtioziformnom eritrodermijom. Iako navedeni rizik nije još uvek egzaktno kvantifikovan, neophodno je pacijentu dati savet i dalje instrukcije. Za razliku od epidermolitičnog verukoznog nevusa, predstavlja posledicu mozaicizma nastalog iz različitih još uvek nedovoljno identifikovanih mutacija i može (u oko 10% slučajeva) biti udružen sa ekstrakutanim poremećajima, najčešće centralnog nervnog sistema, oka i skeleta (npr. epidermalni nevus sindrom). U verukoznom epidermalnom nevusu mogu se, iako retko, razviti: Bovenova bolest, verukozni i adneksalni karcinomi, bazocelularni karcinom, spinocelularni karcinom; još uvek nije razjašnjeno da li ove promene predstavljaju rezultat specifičnih razlika vezanih za lokalizaciju promena i starost osobe u samom nevusu ili se radi o različitim nevusima. Kod našeg pacijenta ovakve promene nisu nađene.

Terapijski modaliteti su brojni a mogu se koristiti u zavisnosti od lokalizacije i veličine lezije sa različitim uspehom. Lokalnu konzervativnu ali i klasičnu hiruršku terapiju prate recidivi, ukoliko se istovremeno pored epidermisa ne odstrani i susedni dermis. U terapiji se mogu koristiti topikalni ili intralezionali kortikosteroidi, kalcipotriol, 5-fluorouracil, podofilin, retinoid, hemijski piling, krioterapija, dermoabrazija, elektrokoagulacija, fotodinamička terapija, različiti tipovi laser (argon ruby, erbium: yttrium aluminium garnet - Er: YAG, carbon dioxide).

Poslednjih godina radiofrekventna ablacija (sinonimi − radiohirurgija, visoko-frekventna elektrohirurgija) postala je značajna kao efikasan terapijski modalitet u svakodnevnoj dermatohirurškoj praksi. Zato smo ablaciju verukozno epidermalnog nevusa kod naše pacijentkinje izveli pomoću radiotalasnog noža Proxima VF. Ovaj nož predstavlja moderan visokofrekventni radiohirurški instrument sposoban da pretvara električnu struju u radiotalasnu frekvenciju na principu povećanja frekvencije i voltaže i istovremenog smanjenja jačine − amperaže naizmenične struje. Daljom modifikacijom i postizanjem različitih talasnih formi, postižu se tri glavna efekta na tretiranom tkivu: elektrosekcija (isecanje), elektrokoagulacija (destrukcija dubokog tkiva) i elektrodesikacija/ elektrofulguracija (destrukcija površnog tkiva). Odabir talasne forme kao i oblika vrha elektrode (fina igla, žičana omča, elipsa ili trougao, dijamant), zavisi od primarnog cilja, npr. isecanje ili koagulacija. Radiofrekventna ablacija je postala popularna zbog nekoliko prednosti u odnosu na ostale hirurške procedure, naročito u odnosu na elektrokoagulaciju, klasičnu i lasersku hirurgiju: predstavlja jednostavnu metodu, lako izvodljivu, brzu, manje bolnu, bezbednu tehniku, sa manjim zagrevanjem i destrukcijom okolnog tkiva, sa značajno manje komplikacija i neželjenih efekata. Bez obzira na sve i ovde je indikovano praćenje s obzirom na mogućnost čestih recidiva.

Zaključak. U ovom radu prikazujemo slučaj lokalizovane forme kongenitalnog verukoznog epidermalnog nevusa kod inače zdrave mlade osobe ženskog pola koji je uspešno tretiran radiofrekventnom ablacijom.

**Ključne reči:** Sebaceozni Jadassohnov nevus; Prevalenca; Dijagnoza; Ablativne tehnike; Prikazi slučajeva; Ablacija kateterom
Lamotrigine Associated DRESS Syndrome – a Case Report

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Abstract

Drug-induced delayed multiorgan hypersensitivity syndrome, also known as drug rash (reaction) with eosinophilia and systemic symptoms (DRESS) syndrome, represents a drug-induced cluster of skin, hematologic and systemic symptoms. More than forty drugs have been associated with this syndrome. We present a case of DRESS syndrome suspecting that lamotrigine was directly responsible for the patient’s rash and other symptoms. A female patient presented with extensive skin rash, fever, hematologic abnormalities, organ involvement such as hepatitis, pancreatitis and respiratory symptoms. The symptoms developed four weeks after the initiation of the offending drug, and disappeared eight weeks after its discontinuation.

Key words

Drug Hypersensitivity Syndrome; Anticonvulsants; Drug-Related Side Effects and Adverse Reactions; Antipsychotic Agents; Case Reports

Drug-induced delayed multiorgan hypersensitivity syndrome (DIDMOHS) (1), also known as drug rash (reaction) with eosinophilia and systemic symptoms (DRESS) syndrome, is a severe, unexpected drug reaction which affects several organ systems at the same time (2, 3, 4). Most commonly it causes a combination of high fever, morbiliform skin rash and inflammation of one or more internal organs including the liver, kidneys, lungs and/or heart. It generally starts two to eight weeks after taking the offending medicine. The drugs most often reported with DRESS include anticonvulsants (particularly those with aromatic structures), sulfa derivatives, antidepressants, non-steroidal anti-inflammatory drugs, and antimicrobials (5, 6, 7).

Case report

We present a 44-year-old unemployed nurse with psychiatric history since her teens. She was first admitted to the Emergency Department seven days before admission to our Clinic, because of persistent symptoms of high fever (body temperature above 38°C), severe nonproductive cough, nasal secretion, facial swelling, especially around the nose, and erythema on the hands. A differential white blood cell count and urinalysis were performed, and except mild eosinophilia of 6% (normal range 0 - 5%) all other findings were within normal limits. She was advised to stop taking all drugs. The patient was using three drugs (olanzapine: an antipsychotic serotonin blocker; lamotrigine: an antiepileptic and mood stabilizer; and losartan: an antihypertensive and angiotensin II receptor blocker), since she was discharged from the Clinic of Psychiatric Diseases a month before, where she was hospitalized under the diagnosis of paranoid personality disorder. Due to persistent high temperature and worsening of respiratory symptoms, the patient was examined by the specialist for infectious diseases, who set the diagnosis of acute bronchiolitis, and introduced azithromycin 500 mg once daily

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during three days; the chest X-ray was normal and the patient was advised to visit a dermatologist. At the first dermatological examination, the patient had diffuse facial flushing with mild edema, and morbidiform skin rash mainly on the extremities. In addition to azithromycin, an antihistamine levocetirizine was introduced. In spite of the therapy, the skin rash was spreading, therefore hospitalization was recommended. On admission, the dermatology examination revealed diffuse erythematous and slightly edematous face, generalized maculopapular livid erythematous rash partly confluent on the trunk and extremities involving more than 50% of the body surface (Figures 1, 2). No peripheral lymphadenomegaly was detected.

**Laboratory and other relevant findings**

Laboratory findings on admission were as follows: erythrocyte sedimentation rate (ESR) - 13 mm/h, C-reactive protein (CRP) - 4.7 mg/L (normal range: 0 - 5 mg/L), white blood cell count (WBC) - 17.3x10⁹/L (normal range: 3.4 - 9.3 x10⁹/L), red blood cell count (RBC) - 4.1x10¹²/L (normal range: 3.9 - 5.4 x10¹²/L), platelets (PLT) - 246x10⁹/L (normal range: 140 - 400x10⁹/L), differential white blood cell count: neutrophils - 6.46x x10⁹/L or 38.2% (normal range: 2 - 7.5x10⁹/L or 50 - 75%), lymphocytes - 5.67x10⁹/L or 32.8% (normal range: 0.8 - 4x10⁹/L or 20 - 40%), monocytes - 0.9 x10⁹/L or 5.4% (normal range: 0.08 - 1x10⁹/L or 2 - 10%), eosinophils - 2.38x10⁹/L or 13.8% (normal range: 0 - 0.5x10⁹/L or 0 - 5%), basophils - 0.33x10⁹/L or 1.9% (normal range: 0 - 0.1x10⁹/L or 0 - 1%), total bilirubin - 8.2 μmol/L (normal range: 3 - 21 μmol/L), direct bilirubin - 2.0, μmol/L (normal range: 0.1 - 5.2 μmol/L), aspartate aminotransferase (AST) - 52 IU/L (normal range: 0 - 35 IU/L), alanine aminotransferase (ALT) - 136 U/L (normal range: (0 - 35 U/L), gamma glutamyl transferase - 24.4 U/L (normal range: 1 - 38 U/L), creatine kinase - 65 U/L (normal range: 24 - 170 U/L), urea - 5.2 μmol/L (normal range: 2.5 - 7.5 μmol/L), creatinine - 72 μmol/L (normal range: 44 - 98 μmol/L), serum amylase - 79 U/L (normal range: 20 - 118 U/L), urine amylase - 601 U/L (normal range: 20 - 118 U/L), lipase - 48U/L (normal range: 0 - 160 U/L), urinalysis was normal, ELISA herpes simplex virus typus 1 (HSV-1) IgM and IgG negative, HSV-2 IgM and IgG negative, anti Epstein–Barr virus (EBV) IgM negative, anti-EBV IgG 1.54 (positive > 1.1), anti cytomegalovirus (CMV) IgM and IgG negative. Peripheral blood smear: eosinophils - 15% (normal range: 0 - 5%), atypical lymphocytes - 8% (normally < 5%), immature myelocytes (1%). The upper abdomen ultrasound was normal. On the third day of hospitalization, the abnormal laboratory findings improved: WBC 10.5x10⁹/L, eosinophils 8.8%, AST 15 IU/L, ALT 50 IU/L.

The diagnosis of DRESS syndrome was established based on the diagnostic criteria for DRESS syndrome, including skin rash, blood count and laboratory abnormalities that were as follows: leukocytosis (>11x10⁹/L), eosinophilia (>1.5x10⁹/L), atypical lymphocytes (>5%) and liver abnormalities (ALT>100 IU/L) (6, 8).
During the seven-day hospital stay, the patient received 40 mg methylprednisolone daily, a systemic steroid, and oral ranitidine, loratadine; an antihistaminic, butamirate citrate - an antitussic, and losartan - an antihypertensive. After being discharged, the patient continued oral corticosteroid therapy with 40 mg prednisolone daily, with dose reduction by 10 mg after every seven days. She continued taking ranitidine and losartan. On discharge, she still presented with erythematous macular rash. Three weeks later, laboratory findings (WBC with differential count, RBC, AST, ALT, urinanalysis and serum amylase) normalized, but the pale residual pinkish macular skin rash was still persistent (Figures 3 - 6). On last visit, six weeks after hospitalization and 8 weeks after lamotrigine and olanzapine were discontinued, the skin lesions completely resolved. Due to the psychiatrist’s recommendation, olanzapine was reintroduced into the therapy, and since then the patient has been taking it without any problems.

**Discussion**

Before 1996, when Bouquet and associates described the DRESS syndrome, several different terms have been used such as: anticonvulsant hypersensitivity syndrome, first described in 1936 during the treatment with anticonvulsant drugs; drug hypersensitivity syndrome; drug-induced hypersensitivity syndrome (9, 10, 11). The “R” was previously used to indicate “rash” (9), now it indicates “reaction” (3).
Though DRESS syndrome was recognized as a serious form of skin drug adverse reaction from the very beginning, it is currently viewed as a drug-related syndrome with life-threatening organ dysfunctions. A long interval from first drug exposure to symptom onset and a prolonged course after discontinuation of the offending drug even with flares, represent the two highly typical features of the syndrome (12). The syndrome is also characterized by an extensive rash, fever, lymphadenopathy, hematologic abnormalities, hepatitis, and involvement of the kidneys, lungs, heart, or pancreas. Although skin lesions may rapidly aggravate from erythematous to purpuric, pustular or turn to exfoliative dermatitis, they can be overshadowed by the severity of organ involvement, hence “reaction” instead of “rash” in the acronym DRESS (13). The onset of symptoms is often delayed, occurring 2 – 8 weeks after drug initiation (14). In our patient symptoms occurred one month after initiation of three drugs, two of which being psychoactive (olanzapine - antipsychotic serotonin blocker; lamotrigine - antiepileptic and mood stabilizers; and losartan - antihypertensive and angiotensin II receptor blockers).

The incidence of DRESS has been estimated to be between 1 in 1,000 and 1 in 10,000 drug exposures. It carries a mortality rate of 10 – 20%, with most fatalities due to liver failure (15).

The exact pathogenesis of DRESS syndrome is not yet well understood. Although it is considered an idiosyncratic reaction, three potential causative factors have been identified among multiple cases: 1) a defect in drug metabolism resulting in the failure to eliminate toxic reactive intermediates (e.g. slow acetylation and defects in enzymes responsible for drug metabolism such as arene oxidase for anticonvulsants); 2) reactivation of human herpes virus-6 (HHV-6), human herpes virus-7 (HHV-7), Epstein-Barr virus (EBV), or cytomegalovirus (CMV), which may act as a trigger for the immune reaction; 3) or genetic predisposition that alters immune response (4, 16, 17).

Two groups have developed specific criteria for making the diagnosis of DRESS syndrome: The European Registry of Severe Cutaneous Adverse Reactions Group (The RegiSCAR group) and Japanese Consensus Group (SCAR-J). The RegiSCAR study group developed a set of inclusion criteria (Table 1) and established a scoring system (total score ranges from 4 to 9), for classifying DRESS cases as definitive with final score >5, probable with final score 4 - 5, possible with final score 2 - 3, and no case with final score <2 (8).

According to RegiSCAR group criteria, our patient met all criteria except lymphadenopathy and reduced platelets. According to the RegiSCAR group scoring system, eosinophilia (>1.5x10⁹/L), atypical lymphocytes (>5%), skin involvement (>50%), suggestive skin rash, and liver abnormalities (ALT>100 IU/L) were scored as 2+1, +1, +1, and +1, respectively (8). Since the final score was +6, the diagnosis of DRESS syndrome was definite in our patient.

According to the Japanese Consensus Group criteria for DRESS syndrome, our patient fulfilled the first five, thus being classified as having atypical DRESS syndrome (Table 2) (6). In comparison to criteria developed by the RegiSCAR group, the major difference was inclusion of HHV-6 reactivation (6). However, the use of HHV-6 reactivation as a criterion is controversial, because no definite evidence of the causative role of herpes viruses in DRESS syndrome has been reported (18). In the in vitro studies, it was found that drugs associated with DRESS syndrome do not only potentiate HHV-6 and EBV replication by inhibition of epigenetic control mechanisms (the two main are methylation and histone acetylation), but also induce an antiviral T-cell immune response in individuals with genetic susceptibility factors, by interacting with the major histocompatibility complex receptor (12). Since anticonvulsant drugs can induce hypogammaglobulinemia, it has been hypothesized that use of drugs associated with DRESS syndrome may promote viral reactivation by inducing immunosuppression. However, the mechanism underlying the direct drug-virus interaction remains unknown. Only a minority of transplant recipients with marked viral reactivation develop systemic manifestations. The systemic manifestations are suggested to be related to a strong immune response against the reactivated virus. Thus, DRESS syndrome, develops only in patients with both marked viral reactivation and an ability to produce a strong antiviral immune response (e.g. genetic polymorphisms for cytokines, receptors, or antagonists (as demonstrated for the TNF-receptor) (12). Meanwhile, Japanese criteria are less practical in routine clinical practice,
as viral serologic tests are unhelpful (18). Quantitative PCR of the whole blood must be used in order to detect viral reactivations (12).

The liver is the most commonly involved organ in DRESS syndrome, and hepatitis, present also in our patient, occurs in about 80% of all cases (19, 20, 21). The degree of hepatitis is related to the interval between the onset of the syndrome and the discontinuation of the offending drug. Apart from the liver, another, most frequently affected organs are the kidneys in 40% and lungs in 33% of cases. Cardiovascular symptoms develop in 15% of cases, and pancreas is involved in about 5% of cases (22). The most common hematologic disorders that occur in DRESS syndrome are as follows: atypical lymphocytes (63%), eosinophilia (52%), lymphocytopenia (45%), and thrombocytopenia (25%) (23, 24). Our patient had leukocytosis (>11x10⁹/L), eosinophilia (>1.5 x 10⁹) and atypical lymphocytosis (>5%).

The outcome is usually favorable after discontinuation of the casual drug, although full symptom resolution requires at least two weeks and flares may occur. Moreover, after prompt withdrawal of the offending agent, complete resolution of skin lesions and visceral injury can be achieved in up to several weeks, which happened after 8 weeks in our patient. Although in less severe cases resolution can be achieved by using only supportive measures, in cases with internal organ impairment, moderate to high doses of corticosteroids should be commenced, but not before infection has been carefully ruled out! Corticosteroids should be gradually tapered over a period of 6 - 8 weeks as in our patient, in order to prevent relapse which may occur especially with rapid discontinuation. Time to onset is shorter after re-challenge with the same drug.

There are more than 40 drugs, including lamotrigine and olanzapine, that have been reported to be associated with DRESS syndrome (18). Aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine) and sulphonamides are the most common causative drugs, but a variety

Table 1. RegiSCAR criteria for diagnosis of DRESS syndrome (published by RegiSCAR)

<table>
<thead>
<tr>
<th>All criteria fulfilled</th>
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</thead>
<tbody>
<tr>
<td>1. Hospitalization</td>
</tr>
<tr>
<td>2. Reaction suspected to be drug-related</td>
</tr>
<tr>
<td>3. Acute rash</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Three of the following four criteria</th>
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<tbody>
<tr>
<td>4. Fever &gt;38°C</td>
</tr>
<tr>
<td>5. Enlarged lymph nodes at least at 2 sites</td>
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<tr>
<td>6. Involvement of at least 1 internal organ</td>
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<tr>
<td>7. Blood count abnormalities - defined either by:</td>
</tr>
<tr>
<td>- Lymphocytes above or below normal limits ; or</td>
</tr>
<tr>
<td>- Eosinophils above the laboratory limits ; or</td>
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<tr>
<td>- Platelets below the laboratory limits</td>
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of other drugs have been reported such as: dapsone (DDS, 4,4-diaminodiphenylsulphone), allopurinol, captopril, calcium-channel blockers, ranitidine, thalidomide, minocycline, sulfasalazine, non-steroidal antiinflammatory agents, antituberculotic drugs, α-methyldopa and antiretroviral drugs (abacavir, zalcitabine, nevirapine) (18, 20-27). Lamotrigine \[6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine\] is an antiepileptic drug, used in the management of a broad range of seizures in adults and children which is not an aromatic antiepileptic, thus being structurally and pharmacologically unrelated to other antiepileptic medications e.g. carbamazepine (28, 29). Lamotrigine has been reported in association with severe skin rash, multiorgan failure, DRESS syndrome, acute hepatic failure, and disseminated intravascular coagulation. Severe rashes due to lamotrigine occur almost regularly within the first 6 - 8 weeks of exposure, rarely after 12 weeks and almost exclusively later (30). Several reports of lamotrigine-induced DRESS syndrome have been reported in the literature (12, 27, 28, 29, 31-34). The second psychoactive drug our patient was taking in combination with lamotrigine was an antipsychotic - olanzapine, an oxazepine that is prescribed to patients with schizophrenia or recurrent bipolar disorder. Regarding cutaneous adverse drug reactions due to olanzapine, the literature contains few reports of DRESS syndrome, contrary to lamotrigine that has commonly been reported as a causative agent in DRESS syndrome. Actually, in a frequently cited review on DRESS syndrome published in 2011 by Cacoub et al, only one case involved olanzapine (35). Since then, according to available literature, there are four new published cases of DRESS syndrome associated with olanzapine (12, 36-38). Although drug-drug interactions have been reported between antiepileptic and antipsychotic drugs, there was only one report of cross-sensitization between carbamazepine (aromatic antiepileptic drug) and olanzapine (aromatic antipsychotic drug) (38).

The diagnosis of DRESS syndrome in our case was definite. However, regarding causality, due to the scoring system established by Naranjo et al, it was a probable adverse drug reaction caused by lamotrigine (final score 7); we did not confirm the adverse event by at least one objective evidence e.g. by skin testing (39). Skin tests can assist in the causality assessment, but performed at a time distance from the DRESS

### Table 2. Japanese group’s criteria for diagnosis* ** of DRESS syndrome

1. Maculopapular rash developing >3 weeks after initiation of the suspected drug
2. Prolonged clinical symptoms: 2 weeks after discontinuation of the suspected drug
3. Fever >38°C
4. Liver abnormalities (alanine aminotransferase >100U/L)
5. Blood count abnormalities - defined either by:
   - Lymphocytes above or below normal limits ; or
   - Eosinophils above the laboratory limits ; or
   - Platelets below the laboratory limits
6. Lymphadenopathy
7. Human herpes virus-6 reactivation

*The diagnosis of typical syndrome is confirmed by the presence of all 7 criteria
**The diagnosis of atypical syndrome is confirmed by the presence of the first 5 criteria
syndrome episode (12). Given the fact that lamotrigine, opposed to olanzapine, is known as a common cause of DRESS syndrome, that there is no cross reactivity between them, and there was a necessity of its use in the given moment, the psychiatrist considered that olanzapine should be reintroduced into the therapy. If the psychiatrist had not reintroduced olanzapine into the therapy, patch testing would be performed in 6 months, and olanzapine would gradually be reintroduced under hospital supervision. Therefore, now we can only hypothesize that lamotrigine was directly responsible for our patient’s rash, and all other symptoms and signs.

**Conclusion**

We present a case of a female patient who was treated with an antipsychotic - olanzapine in combination with an anticonvulsant – lamotrigine. Since both drugs were discontinued due to the development of DRESS syndrome, and with regard to the chronology of events, lamotrigine was considered the main suspected drug.

**Abbreviations**

- DRESS - drug rash (reaction) with eosinophilia and systemic symptoms
- DIDMOHS - drug-induced delayed multiorgan hypersensitivity syndrome
- ESR - erythrocyte sedimentation rate
- CRP - C-reactive protein
- WBC - white blood cell count
- RBC - red blood cell count
- PLT - platelets
- AST - aspartate aminotransferase
- ALT - alanine aminotransferase
- ELISA - enzyme-linked immunosorbent assay
- HSV - herpes simplex virus
- Ig – immunoglobulins
- EBV - Epstein–Barr virus
- CMV - cytomegalovirus
- RegiSCAR - Registry of Severe Cutaneous Adverse Reactions
- HHV - human herpesvirus
- TNF - tumor necrosis factor
- PCR - polymerase chain reaction

**References:**

Pacijentkinji je savetovano da odmah obustavi uzimanje svih lekova, s obzirom da je mesec dana ranije lečena i otpuštena sa psihijatrije klinike, gde je zbog paranoidnog personalnog poremećaja započeto lečenje sledećim lekovima: olanzapin (antipsihotik i blokator serotoninina), lamotrigin (antiepileptik) i losartan (antihipertenziv, blokator angiotenzin II receptor). Zbog perzistirajuće febrilnosti i pogošanja respiratornih simptoma i znakova, infektolog je postavio dijagnozu akutnog bronhiolitisa i u terapiju uveo azitromicin u dnevnoj dozi od 500 mg tokom tri dana; rendgenski snimak pluća bio je u granicama refernalnog nalaza, pa je pacijent upućen na pregled dermatologu. Prilikom prvog dermatološkog pregleda, utvrđeno je prisustvo difuznog jako izrženog eritema i umerenog edema na licu i morbiliformnog eritema na koži ekstremiteta. I pored antihistaminika koji je uključen u terapiju, osip na koži se i dalje pojačavao i širio na ostale delove tela, tako da je na prijemu u bolnici, pored difuznog eritema i edema lica, bio prisutan generalizovani lividni makulozni osip koji je zahvatio više od 50% površine tela sa tendencijom konfluenca, bez periferne limfadenomegalije (slike 1−6). Kožne promene su potpuno nestale na kontrolnom pregledu šest nedelja posle obustave uzimanja olanzapina (antipsihotika) i lamotrigina, i dalje bez ikakvih tegoba.

Diskusija. DRESS sindrom klinički tipično karakterišu dug period 2−8 nedelja od prvog uzimanja leka do pojave prvih simptoma, kao i prolongirani vremenski period od trenutka obustavljanja uzimanja leka, do potpunog povlačenja svih znakova uključujući i promene na koži. Pored visoke febrilnosti, limfadenomegalije i promena kožnih znakova, sindrom karakterišu i odstupanja u hematološkim i biohemijskim parametrima koja ukazuju na zahvaćenost unutrašnjih organskih organa, najčešće jetre, bubrega, pluća, srca ili pankreasa. Iako promene na koži mogu progredirati od purpuričnih i pustuloznih, pa sve do eksofolijativnog dermatitisa, one mogu ostati u senci u odnosu na jako izražene simptome i znake zahvaćenih unutrašnjih organskih organa, te zato „reakcija” umesto „raš” označava „R” u akronimu DRESS. Kod naše pacijentkinje, prvi simptomi su se javili mesec dana posle uzimanja dva bila psihoaktivna (olanzapin, antipsihotik i blokator serotoninina i lamotrigin) i treći lek je bio antiepileptik (blokator angiotenzin II receptor). Iako tačan patogenetski mehanizam odgovora za nastanak DRESS sindroma nije u potpunosti razjašnjen, radi se najverovatnije o idiosinkrastijskoj reakciji zasnovanoj na jednom ili više od navedenih
uzroka: 1) defekt u metabolisanju leka koji rezultira neadekvatnom eliminacijom toksičnih reaktivnih intermedijarnih produkata (npr. usporena acetilacija ili poremećana aktivnost arena oksidaze, enzima odgovornog za metabolisanje antikonvulzivnih lekova; 2) reaktivacija humanog herpes virusa-6 (HHV-6), humanog herpes virusa-7 (HHV-7), Epštajn-Barovog virusa (EBV), ili citomegalovirusa (CMV), koja može da pokrene reakciju imunskog sistema; 3) genetska predispozicija za poremećan imunski odgovor.

Evropska, RegiSCAR grupa istraživača (engl. The European Registry of Severe Cutaneous Adverse Reactions Group) i Japanska konsenzus grupa (engl. The Japanese Consensus Group), utvrdile su dijagnostičke kriterijume za DRESS sindrom: Inkluzioni kriterijumi koje je uspostavila RegiSCAR grupa izneti su u Tabeli 1 i oni služe za postavljanje dijagnoze DRESS sindroma, dok se na osnovu skoringa sistema (ukupni skor se kreće od -4 do +9), vrši klasifikacija dijagnoze DRESS sindroma na definitivnu (ukupni skor > 5), verovatnu (ukupni skor 4-5), moguću (ukupni skor 2-3), ili se dijagnoza isključuje (ukupni skor < 2).

Prema RegiSCAR kriterijumima, kod naše pacijentkinje su osim trombocitopenije i limfadenopatije bili prisutni svi ostali kriterijumi, koji su skorovani: eozinofilia (> 1,5 x 10^9/L) sa +2, atipični limfociti (> 5%) sa +1, procentualna zahvaćenost kože (> 50%) sa +1, osip koji ne isključuje dijagnozu DRESS sindroma sa +1, poremećaj funkcije jetre (ALT > 100 IU/L) sa +1. S obzirom da je ukupni skor koda naše pacijentkinje iznosio +6, dijagnoza DRESS sindroma kod naše pacijentkinje je bila definitivna.

Prema kriterijumima Japanske konsenzus grupe za postavljanje dijagnoze DRESS sindroma, naša pacijentkinja je imala pet prvih od ukupno sedam kriterijuma, što je potrebno isključiti sistem, kod kojeg je dijagnoza DRESS sindroma ponovno utvrđena. Ukoliko se u terapiju ponovo uvede inkriminisani lek, simptomi se javljaju posle kraćeg vremenskog perioda od uključivanja leka.

Preko 40 različitih lekova među kojima su i lamotrigin i olazapin su u literaturi povezani sa razvojem DRESS sindroma, najčešće su to aromatski antikonvulzivi (fenitoin, fenobarbital, karbamazepin) i sulfonamidi, a potom slede i ostali kao što su dapson (DDS, 4,4-diaminodifenilsulfon), alopurinol, kaptopril, minociklin, nesteroidni antiinfl amatorni lekovi, antituberkulotici, α-metildopa i antiretrovirusni lekovi (abakavir, zalcitabin, nevirapin). Lamotrigin (6-(2,3-diklorofenil)-1,2,4-triazine-3,5-diamine) neznačajno se razlikuje od drugih lekova, što je pokazano u studijama.

Jeta je najčešće zahvaćen organ, a hepatitis, prisutan i kod naše pacijentkinje, može se javiti u preko 80% slučajeva, potom sledi zahvaćenost bubrega u 40%, pluća u 33%, kardiovaskularnog sistema u 15% i pankreas kao kod naše pacijentkinje u 5% slučajeva. Najčešće opisani hematološki poremećaji u DRESS sindromu su: povećan broj atipičnih limfocita (63%), eozinofilia (52%), limfocitopenija (45%), trombocitopenija (25%). Kod naše pacijentkinje bila je proučena: leukocitocita (> 11 x 10^9/L), eozinofilia (> 1,5 x 10^9) i povišen broj atipičnih limfocita (> 5%). Prognoza je dobra ukoliko se na vreme isključi inkriminisani lek, iako je za postizanje kompletne remisije potrebno nekoliko nedelja, kao kod naše pacijentkinje, gde je do kompletne rezolucije bilo potrebno 8 nedelja.

Ukoliko je prosjek neznačajno, potrebno je u terapiju uključiti sistemske kortikosteroide u srednjim i visokim dozama, ali je potrebno prethodno isključiti postojanje infekcije. Ukoliko se pažljivo, tokom 6−8 nedelja smanjuje doza kortikosteroida, smanjuje se rizik od recidiva, što smo i mi sproveli kod naše pacijentkinje. Kada se u terapiju ponovo uvede inkriminisani lek, simptomi se javljaju posle kraćeg vremenskog perioda od uključivanja leka.
strukturne niti farmakološke povezanosti sa ostalim antiepilepticima kao što je to npr. karbamazepin. Lamotrigin može izazvati različite simptome i znake: osipe po koži uključujući i urtikariju, multiplu insuficijenciju unutrašnjih organsa, DRESS sindrom, akutnu insuficijenciju jetre, kao i diseminovanu intravaskularnu koagulaciju. Egzantemi udruženi sa teškim opštim simptomima koji su izazvani lamotriginom, javljaju se najščešće unutar 6–8 nedelja od započinjanja lečenja, rede nakon 12 nedelja, a po pravilu – nikad kasnije. U literaturi je do sada opisano nekoliko slučajeva DRESS sindroma izazvanog lamotriginom; drugi psihoaktivni lek koji je uzimala naša pacijentkinja je bio antipsihotik olanzapin. Za razliku od lamotrigina, u literaturi postoji veoma mali broj (oko pet), do sada objavljenih radova u kojima se pojava DRESS sindroma povezuje sa upotrebom olanzapina. 

Dijagnoza DRESS sindroma kod naše pacijentkinje klasifikovana je kao definitivna; neposredni uzrok sindroma definitisan je na osnovu skoring sistema koji je uspostavio Naranjo sa saradnicima, kao verovatna neželjena reakcija izazvana lamotriginom (finalni skor 7); mi nismo objektivno dokazali da je neželjena reakcija bila izazvana lekom, što se moglo učiniti da smo npr. sproveli kožne testove, koji su indikovani nakon određene vremenske distance od jednog do nekoliko meseci (zavisno od dužine terapije potrebne za kompletnu sanaciju svih simptoma i znakova DRESS sindroma). S obzirom da je lamotrigin poznat kao čest uzrok DRESS sindroma, za razliku od olanzapina, da među njima nema unakrsnog reagovanja, a imajući u vidu neophodnost njegove primene u datom trenutku, psihijatar je smatrao da u terapiju ponovo treba uvesti olanzapin. Mi bi za 6 meseci sproveli epikutano testiranje i postepeno ponovo uveli olazapin, kontrolisano, postepeno, u bolničkim uslovima. Iz tog razloga, možemo samo pretpostaviti da je lamotrigin direktno odgovoran za nastanak DRESS sindroma kod naše pacijentkinje, ali je za nju uzimanje ovog leka strogo kontraindikovano. Zaklučak. Prikazujemo slučaj ženske osobe sa DRESS sindromom koji se povukao nakon prestanka uzimanja antikonvulzantnog leka lamotrigina i antipsihotika olanzapina, ali se na osnovu daljeg toka moglo pretpostaviti da je lamotrigin bio uzrok oboljenja.

Ključne reči
Sindrom preosetljivosti na lekove; Antikonvulzivi; Neželjena dejstva i reakcije na lekove; Antipsihotici; Prikazi slučajeva
Abstract

Majocchi’s granuloma was first described by Domenico Majocchi in 1883, as a deep chronic dermatophyte infection of hair follicles, in which dermatophytes penetrate the dermis through hair canals, forming granulomatous changes in the dermis and/or hypodermis. Majocchi’s granuloma has two different clinical variants: the first is a small perifollicular papular type, seen in otherwise healthy individuals, that occurs secondary to trauma (e.g. in women with chronic tinea pedis that extends to the legs and who shave their legs); the second is a type with deep plaques or nodular lesions in immunocompromised hosts. The diagnosis is primarily made using direct microscopy of unstained specimens and fungal cultures, while additional diagnostics (histology, PCR) are generally not necessary. It is most commonly caused by Trichophyton rubrum.

We present a 26-year-old otherwise healthy man exhibiting blue erythematous patches over the skin of his abdomen on clinical examination, which agglomerated to form slightly raised plaques with irregular ovoid contours, spreading from umbilicus to the pubic region; they were covered with multiple red-blue, erythematous partly coalescing scales, eroded, firm papules and nodules. On pressure, some nodules excreted viscid and turbid sero-purulent content. The lesions were slightly itchy. The patient was previously unsuccessfully treated during at least 4 weeks with a topical steroid cream prescribed by his physician. Direct microscopy for fungi of skin scrapings and pus mounted in potassium hydroxide was negative. Cultures of the contents and scrapings were performed on Sabouraud’s glucose agar and Trichophyton rubrum was isolated. The diagnosis of Majocchi’s granuloma was made, and the patient was treated with itraconazole (200 mg daily) for eight weeks, when all lesions resolved and fungal culture was negative.

Misapplication of topical corticosteroids over a long period, as in our case, can produce Majocchi’s granuloma. When assessing skin lesions of unusual appearance, especially if aggravated by corticosteroids, dermatologists and general practitioners should consider tinea incognito, which may appear in its invasive form of Majocchi’s granuloma. The available world literature shows that Majocchi’s granuloma presenting as tinea incognito caused by topical corticosteroids has been reported extremely rarely.

Key words
Granuloma; Skin Diseases; Trichophyton; Tinea; Anti-inflammatory Agents + adverse effects; Treatment Outcome; Itraconazole; Case Reports

Dermatophytes are fungal pathogens that commonly infect the outer keratinized layer of the epidermis, therefore causing mainly superficial infections of the skin, hair and nails, termed dermatophytoses. Subcutaneous infections due to dermatophytes are usually limited to immunosuppressed hosts (1, 2, 3). However, in immunocompetent individuals, deep or inflammatory forms of dermatophytoses are usually acute suppurative forms such as kerion, or e.g. much less often chronic granulomatous infiltrates surrounding the hair follicles. The latter was first described in 1954, by Wilson et al. as “nodular granulomatous perifolliculitis of the legs caused by Trichophyton rubrum”, where nodular lesions are within the plaques of scaly erythematous trichophytosis (4). Much earlier, in 1883, Domenico Majocchi described granuloma trichophiticum, a deep chronic granulomatous infection in the dermis caused by Trichophyton spp. now known as Majocchi’s granuloma. He believed that both clinically and
pathologically, this condition should be distinguished from common tinea profunda, an acute suppurative condition which usually occurs as kerion celsi, sycosis parasitaria, and folliculitis aguminata parasitaria (5). Though the pathogenesis and classification of trichophytic granuloma have not yet been satisfactorily explained, it has widely been suggested that Wilson’s nodular granulomatous perifolliculitis should be categorized as Majocchi trichophytic granuloma (6).

Majocchi’s granuloma has two different clinical variants (1): the first are small perifollicular papular lesions seen in healthy individuals, and the second are deep plaques or nodular lesions in immunocompromised hosts. It is most commonly caused by Trichophyton rubrum (1).

Topical agents are usually ineffective, because of the deep location of infection, and thus oral antifungal agents are generally required.

Herein we present a case of an otherwise healthy, immunocompetent male, who developed Majocchi’s granuloma on the abdominal wall after a prolonged application of a potent topical corticosteroid.

**Case report**

A 26-year-old man with a 1.5 month history of expanding abdominal lesions was referred to the City Institute for Skin and Venereal Diseases in Belgrade by his physician who had unsuccessfully treated the lesions as eczematous with a topical steroid cream (betamethasone dipropionate) during the least 4 weeks. On physical examination he exhibited blue erythematous patches over the skin of his abdomen, which agglomerated to form slightly raised plaques with irregular ovoid contours, spreading from the umbilicus to the pubic region, covered with multiple red-blue, erythematous partly coalescing scaled, eroded, firm papules and nodules. On pressure, some nodules excreted viscid and turbid sero-purulent content (Figure 1). The plaques were erythematous and sharply demarcated. However, some satellite papules and pustules were noticed on his trunk and in the inguinal area. The patient complained of mild pruritus. He was otherwise healthy, not receiving any medications and had an unremarkable medical history.

**Figure 1.** Multiple livid and red bluish papules and firm nodules coalescing into sharply demarcated plaques. On pressure, some nodules excreted viscid and turbid serous or purulent content. There are also some satellite papules and pustules on the trunk and in the inguinal area.
Full blood count and routine biochemistry, including bacteriological examination of smears from swabs taken from the lesions, were normal. The patient denied any history of trauma, like shaving the abdomen or previous cutaneous fungal infections, such as athlete’s foot, onychomycosis or fungal infections on other regions. Direct microscopy for fungi of skin scrapings and pus mounted in potassium hydroxide was negative. Cultures of the content and scrapings were performed on Sabouraud’s glucose agar and *Trichophyton rubrum* was isolated. The diagnosis of Majocchi’s granuloma was made and the patient was treated with itraconazole, 200 mg daily, for eight weeks. After four weeks of therapy, a marked improvement of lesions with significant reduction in erythema, lack of pustules and flattening of the papules and nodules was recorded (Figure 2). Over the next four weeks, the papules and nodules disappeared, leaving postinflammatory hyperpigmented macules. The potassium hydroxide examination and fungal cultures were negative. No relapse was observed in the 9-month follow up.

**Figure 2.** After four weeks of therapy, there is a marked improvement of lesions with reduced erythema, lack of pustules and flattening of the inflamed papules and nodules

**Discussion**

Majocchi’s granuloma was first described by Domenico Majocchi in 1883, as a deep dermatophyte infection of hair follicles, in which dermatophytes penetrate the dermis through hair canals, forming granulomatous changes in the dermis and/or hypodermis (5). Undoubtedly, this granuloma occurs in the background of superficial trichophytosis, and may develop from an infected hair follicle. *Trichophyton rubrum* is the most common cause and it is most frequently associated with the potential for tissue invasion (2). Other dermatophytes associated with Majocchi’s granuloma are as follows: *Trichophyton mentagrophytes, Trichophyton epilans, Trichophyton violaceum, Microsporum audouinii, Microsporum gypseum, Microsporum ferrugineum*, and *Microsporum Canis* (7).

There are two types of Majocchi’s granuloma: the first represents a small perifollicular papular form in otherwise healthy individuals that occurs secondary to trauma (e.g. in women with chronic tinea pedis that extends to the legs, and in those who shave their
In differential diagnosis, other eruptions that are more traditionally associated with deep cutaneous and/or systemic infections than dermatophytes, e.g. mycobacteria or nondermatophyte fungi, must be ruled out. In contrast to fungal suppurative folliculitis or Majocchi granuloma, these deep dermatophyte infections are typically found in immunosuppressed hosts, they are more sudden in onset, may be more aggressive, larger, or more deep-seated in location, and should not necessarily be associated with hair follicles (2). Regarding tinea profunda, a common inflammatory (deep) dermatophytosis, as previously mentioned, even Majocchi believed that both clinically and pathologically (absence of keratin or hair elements, the scarcity of foreign-body giant cells), these conditions, (e.g., kerion celsi), should be distinguished from Majocchi’s granuloma, as more acute, suppurative and painful conditions which usually occur as sycosis parasitaria and folliculitis aguminata parasitaria (5). Nevertheless, though the pathogenesis and classification of trichophytic granuloma have not yet been satisfactorily explained, whether or not deep or locally invasive dermatophyte infections are sufficiently unique to support their classification as a distinct entity, remains to be determined. It is possible that both types of infection represent a single pathologic process, with a broad spectrum of clinical presentations different in severity, from mild localized to severe widespread disease, where Majocchi granuloma may represent the most indolent form of dermatophytosis involving the dermis (2). In our patient, lesions were only slightly itchy.

The treatment of Majocchi’s granuloma with topical antifungals is usually ineffective (20). Systemic antifungal treatment is preferred in both patients who are immunocompetent and in those who are immunocompromised, and should last at least 4 - 6 weeks. There is no standard regimen for the treatment. According to the literature data, griseofulvin, ketoconazole, terbinafine and itraconazole have been used (20, 21, 22). Although griseofulvin and ketoconazole have each been used successfully, terbinafine and itraconazole and fluconazole (the newer azoles) have been used in recent cases with good results (2). Several studies have shown that oral terbinafine, 250 mg daily for six weeks, was effective in the treatment of this condition (21, 23). Our
patient was successfully treated with itraconazole, 200 mg daily, for eight weeks. However, Gupta et al. (20) have shown that itraconazole pulse therapy (three pulses – 200 mg twice daily for one week, followed by two weeks off, between pulses) is also effective in the treatment of Majocchi’s granuloma. However, due to possible interactions between antifungals and immunosuppressants, since terbinafine involves fewer risks of drug interactions, it is preferable to azole antifungals in Majocchi granuloma (Majocchi 1) (22).

Conclusion
We present a case of an otherwise healthy, immunocompetent male, who developed Majocchi granuloma on the skin of his abdominal wall after prolonged application of a potent topical corticosteroid. When assessing skin lesions of unusual appearance, especially if aggravated by corticosteroids, dermatologists and general practitioners should consider tinea incognito, which may appear in its invasive form as Majocchi’s granuloma. The available world literature shows that Majocchi’s granuloma presenting as tinea incognito caused by application of topical corticosteroids has been reported extremely rarely.

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References
Majocchis granulom kod zdravog odraslog muškarca – prikaz slučaja

Sažetak

Uvod. Majocchis granuloma je prvi opisao 1883 Domenico Majocchi, kao dermatofitima izazvanu duboku hroničnu infekciju dllačnog folikula u kojoj dermatofiti invadiraju dermis putem penetracije dllačnog kanala i izazivaju granulomatozne promene u dermisu i/ili hipodermisu. Oboljenje se retko javlja, a može se klinički ispoljiti u dva morfološki raličita oblika, površni i duboki: prvi se pretežno manifestuje sekundarno kao posledica trauma kod inače zdravih, imunokompetentnih osoba u vidu malih perifolikularnih papula (najčešće kod žena koje imaju hroničnu tinu) na stopalima kada posle brijanja dllačica na donjim ekstremitetima dolazi s jedne strane do do širenja infekcije na podkolenice,a s druge strane do utiskivanja delova keratina iz epidermisa neophodnog za rast dermatofita u dermisu; duboki oblik se manifestuje plakovima i nodusima kod imunosuprimiranih osoba, koji dobijaju imunosupresivnu terapiju, npr posle transplantacije organa. Dijagnoza se postavlja na osnovu anamneze, kliničke slike i izolacije uzročnika, a potvrđuje identifikacijom uzročnika iz kulture s obzirom da mikroskopski pregled nativnog preparata može biti negativan; u protivnom potrebno je uraditi dodatne analize dokazivanja uzročnika kao što je patohistološka analiza PAS-bojenog preparata ili PCR.

Najčešći ali ne i jedini dermatofit uzročnik Majocchi granuloma je Trichophyton rubrum.

Prikaz slučaja. U ovom radu prikazujemo slučaj dvadesetšestogodišnje osobe muškog pola, inače dobrog opšteg zdravlja, koja je upućena od strane izabranog lekara na pregled dermatologa u Gradskom Zavodu za kožne i venerične bolesti u Beogradu. Iz anamneze se saznalo da su se promene zbog kojih se javio na pregled počele javljati pre više od mesec i po dana. Potom se pacijent javio na pregled kod svog izabranog lekara na pregled dermatologa u Gradski Zavod za kožne i venerične bolesti u Beogradu. Iz anamneze se saznalo da su se promene zbog kojih se javio na pregled počele javljati pre više od mesec i po dana. Potom se pacijent javio na pregled kod svog izabranog lekara koji je preporučio lokalnu aplikaciju potenčnog kortikosteroida u obliku masti, jer je sumnjao da je priroda promena ekcemska. Tokom više od četiri nedelje pacijent je svakodnevno redovno aplikovao mast na obolelo područje kože. Promene su bile lokalizovane na koži prednjeg trbušnog zida ispod pupka, da bi se tokom lečenja pošele povećavati, slivati u veće čvorove, širiti do stidnog predela. U mom entu pregleda, na koži prednjeg trbušnog zida, celom širini i dužinom od umbilikusa do publične regije, uočavale su se brojne numularne indurirane površine lividne i tamno eritematozne boje, koje su većim delom međusobno konfl uirale čineći jasno demarkirani ovoidni plak tamno eritematozne boje sa čije su površine izdizane brojne promene tipa papula i nodusa razne veličine, od zrna graška do manjeg oraha zagasito lividno eritematozne boje. Promene su bile črvrste konzistencije dok se iz drugih na pritisak mogao izdizati židak, viskozan serozan sadržaj, od centralnog plaka, nalazilo se nekoliko satelitskih promena u vidu pojedinačnih papula, nodusa i plakova numularnog oblika i veličine, Iz anamneznih podataka se saznalo da niti je sam pacijent niti je bilo ko iz njegove porodice imao oboljenja kože, kose i noktiju. Svi laboratorijski nalazi su bili u granicama normale; iz brisa uzetog sa površine promena i na pritisak istisnutog sadržaja izolovana je normalna bakteriološka flora. U nativnom mikroskopskom pregledanom preparatu nisu nađeni gljivični elementi, ali je uzet materijal zasejan na Sabouraud-ov glukozni agar a iz kulture je izolovan Trichophyton rubrum.

Dijagnoza i diferencijalna dijagnoza. Na osnovu kliničke slike i mikološke analize, postavljena je dijagnoza Majocchi granuloma. U diferencijalnoj dijagnozi bitno je isključiti druge uzročnike na koje se u praksi češće pomišlja kada su duboke infl amatorne nodularne lokalne i/ili sistemski invazivne dermatoze u pitanju, kao što su atipične mikobakterije i nedermatofitne gljive. Za razliku od mikotičnog hroničnog supurativnog Majocchi granuloma, ove duboke infekcije ukoliko su izazvane dermatofitima, imaju mnogo akutnijih početak, agresivniji tok, dostižu veće dimenzije, smeštene su dublje, ne moraju obavezno zahvatati dllačne folikule i skoro po pravilu javljaju se kod osoba sa visokim stepenom imunosupresije. Kada je tinea profunda u pitanju, ona predstavlja primer infl amatornih (dubokih)
dermatofitoza koje se relativno često dijagnostikuju u dermatološkim ordinacijama: još i sam Majocchi je verovao da njih treba razlikovati od njegovog granuloma, kako klinički (značajno akutniji nastanak, jača supuracija, bolnost, npr. *sycosis parasitaria* i *folliculitis aguminata parasitaria*), tako i histološki (odsustvo keratina, delova dlake, mali broj džinovskih ćelija tipa oko stranog tela, zavatanje dubljih slojeva). Imajući sve navedeno, možemo zaključiti da patogeneza i klasifikacija trihofitičnog granuloma i dalje ostaje predmet novih istraživanja, koja treba da odgovore na pitanje: da li se lokalno invazivne dermatofitoze dovoljno jasno međusobno razlikuju da bi se klasifikovale kao posebni entiteti. Vrlo je moguće da se u osnovi sve tri gore navedene grupe dermatofitoza nalazi isti patogenetski mehanizam sa širokim spektrom kliničkih manifestacija, od blagih lokalizovanih do agresivnijih diseminovanih, u kome Majocchi granulom predstavlja najmanje bolnu dermatofitiiju koja zahvata dermis/hipodermis i ima hroničan ili hronično-recidivirajući tok.

**Terapija.** Lećenje je započelo peroralno sa itrakonazolom u dozi 200 mg dnevno: nakon četiri nedelje lećenja, došlo je do značajnog, kliničkog poboljšanja, a nakon 8 nedelja do potpuno kliničkog i mikološkog izlečenja. Diskusija. Direkstan uzrok Majocchi granuloma može biti neopravdana lokalna aplikacija kortikosteroidnih preparata tokom dužeg vremenskog perioda, kao što je to bio slučaj kod našeg pacijenta, U svakom slučaju u kome su promene zadobile neobičajen izgled i agravaciju nakon primene kortikosteroidnih preparata za lokalnu primenu, svaki lekar, ne samo dermatolog koji leći takvog pacijenta, treba da u diferencijalnoj dijagnozi isključi *tinea incognito* koja može zadobiti invazivni tok, u formi Majocchi granuloma.

*Zaključak*: U radu prikazujemo sučaj inače zdrave muške osobe kod koje je *Trichophiton rubrum* izazvao Majocchi granulom u formi *tinea incognito*. U nama dostupnoj literaturi ovakvi slučajevi su u izuzeno retko objavljeni.

**Ključne reči**

Granulom; Kožne bolesti; Trihofton; Tinea; Anti-inflamatorni lekovi + neželjena dejstva; Ishod lećenja; Itrakonazol; Prikazi slučajeva

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A Handbook of Dermatopathology
by
Jagoda Balaban
Radoslav Gajanin

A Handbook of Dermatopathology, edited by Jagoda Balaban and Radoslav Gajanin, and published by School of Medicine of the University of Banja Luka, Bosnia and Herzegovina, is a unique book which deals with fifty different clinical and morphological entities. The book has 125 pages, including the text part and 101 images of clinical and histopathological conditions, divided into 8 chapters: tumors and nevi, bullous diseases, infectious dermatoses, erythematous-squamous diseases, T-cell lymphoma, infiltrative diseases, granulomatous diseases, inflammatory, hereditary, and other diseases.

The first chapter deals with the pathogenesis, diagnosis and treatment of the most common skin tumors: benign epidermal and pigmented tumors; benign adnexal epithelial neoplasms - hamartomas; the most common precancerous skin conditions; in situ skin carcinomas on mucocutaneous areas; basal and squamous cell skin cancers, malignant pigmented tumors of the skin and mucous membranes. The second chapter discusses the etiopathogenesis of common and less common acquired and hereditary autoimmune dermatoses, their clinical features, diagnosis and treatment. The third chapter presents the most common viral infections causing epithelial hyperplasia. The fourth chapter focuses on the description, diagnosis and treatment of erythematous-squamous dermatoses: chronic benign lesions, series of more or less clearly defined reactive conditions, and lymphoid proliferations. The fifth chapter presents the so-called infiltrative dermatoses: pseudotumor reactions resulting from the process of endocytosis following lipoprotein extravasation, deposition of acid mucopolysaccharides in dermopathy, in endocrine and internal organ malignant diseases, and proliferative conditions associated with tumor growth, for example of mast cells. Chapter six refers to granulomatous diseases including the most common dermatoses: panniculitis with characteristic patterns of collagen fibers and blood vessels. Chapter seven deals with inflammatory dermatoses where cytotoxic immune phenomena play a major role directed either to immune complexes and their deposition/degradation, or to cytotoxic cell activation, which clinically manifest as various forms of panniculitis. The last, eighth chapter describes conditions that result from hereditary or acquired disorders of natural adaptive mechanisms of different skin cells caused by provoking environmental factors (mechanical, chemical, biological). As a result, particular pathological processes occur in different skin cells, such as keratinocytic dyskeratosis, immune lymphocyte dysfunction, and histiocytic proliferation.

All entities are presented in a uniform and comprehensive manner, accompanied by original clinical and histological images of skin changes, to help students, residents, physicians and other health care professionals involved in education or research in the field of dermatology and pathology.

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<td>3 April, 2015</td>
<td>Course on Melanoma Update, Military Medical Academy, Belgrade, Serbia</td>
<td>No abstract submission</td>
<td><a href="http://www.sld.org.rs/intersekcijski-odbor-za-melanom/">http://www.sld.org.rs/intersekcijski-odbor-za-melanom/</a></td>
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<td>7-9 April, 2015</td>
<td>Dubai World Dermatology and Laser Conference, Dubai, UAE</td>
<td>31 December, 2014</td>
<td><a href="http://www.dubaiderma.com">www.dubaiderma.com</a></td>
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<td>24 April, 2015</td>
<td>Meeting of the Serbian Medical Society’s Section of Dermatology and Venereology, Military Medical Academy, Belgrade, Serbia</td>
<td>No abstract submission</td>
<td><a href="http://www.sld.org.rs">www.sld.org.rs</a></td>
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<td>16-18 April, 2015</td>
<td>4th World Congress of Dermoscopy and Skin Imaging, Vienna, Austria</td>
<td>5 December, 2014</td>
<td><a href="http://www.dermoscopy-congress2015.com">www.dermoscopy-congress2015.com</a></td>
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<td>9 May, 2015</td>
<td>Meeting of the Serbian Medical Society’s Section of Dermatology and Venereology, Clinical Center of Niš, Prolom Banja, Serbia</td>
<td>No abstract submission</td>
<td><a href="http://www.sld.org.rs">www.sld.org.rs</a></td>
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<td>25-29 May, 2015</td>
<td>2nd Congress of the MNEADV, Prcno, Montenegro</td>
<td>1 April, 2015</td>
<td><a href="http://www.udvcg.me">www.udvcg.me</a></td>
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<td>8-13 June, 2015</td>
<td>23rd World Congress of Dermatology, Vancouver, Canada</td>
<td>30 September 2014</td>
<td><a href="http://www.derm2015.org">www.derm2015.org</a></td>
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<td>26-27 June, 2015</td>
<td>Botulinum Toxin – Fostering Course, Athens, Greece</td>
<td>No abstract submission</td>
<td><a href="http://www.eadv.org">www.eadv.org</a></td>
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<td>28 July -1 August, 2015</td>
<td>4th International Summer Academy of Practical Dermatology, Munich, Germany</td>
<td>No deadline information</td>
<td><a href="http://www.isa2015.com">www.isa2015.com</a></td>
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<td>5-9 September, 2015</td>
<td>27th European Congress of Pathology, Belgrade, Serbia</td>
<td>8 April, 2015</td>
<td><a href="http://www.esp-congress.org">www.esp-congress.org</a></td>
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Prepared by: Dr. Tatjana Roš, Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia, E-mail: t.rosh@nscable.net
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.

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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.

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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.

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- 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;
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- An abstract in Serbian language, (limited
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