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GUIDELINES

GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF PSORIASIS

PROFESSIONAL ARTICLE

SEROLOGICAL TESTS FOR ACQUIRED SYPHILIS IN IMMUNOCOMPETENT PATIENTS

CASE REPORTS

GRANULOMA ANNULARE-LIKE WELLS SYNDROME IN A CHILD

DRESS SYNDROME

BERARDINELLI-SEIP SYNDROME

REPORTS

FORTHCOMING EVENTS

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CONTENTS

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Serbian Association of Dermatovenereologists' Guidelines for the Diagnosis and Treatment of Psoriasis

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Psoriasis is a chronic, recurrent, inflammatory, systemic skin disease, which is believed to be genetically and immunologically conditioned and has a major negative impact on patients' quality of life. If we were to concur with the estimation that about 2% of the Serbian population is affected, like in Europe and North America, it means that up to 140.000 people in Serbia suffer from psoriasis. Around 30% of people with psoriasis, about 42.000 patients, have a moderate to severe form of the disease, either accompanied by psoriatic arthritis or not.

There is a clear link between psoriasis and metabolic disorders and cardiovascular disease (1, 2). If this link was previously considered accidental, or if it was interpreted as a consequence of lifestyle (smoking, alcohol consumption, and other habits affecting patient's psychological condition), today it is clear that these diseases may have various genetic and immunological mechanisms in common.

Clinical types of psoriasis

The most common type is chronic plaque psoriasis (*psoriasis vulgaris in placibus),* and it affects 80 to 90% of people with psoriasis. Most patients show clinical signs of psoriasis before the age of 35, while in around 10% of patients the condition appears in childhood. The course of psoriasis is particularly chronic, with occasional exacerbations.

Besides the most general type, *psoriasis vulgaris*, there are also:

- guttate psoriasis,
- inverse (flexural) psoriasis,
- erythrodermic psoriasis,
- pustular psoriasis,
- palm and/or sole psoriasis.

Diagnosis of psoriasis

Clinical signs and symptoms of psoriasis are usually clearly visible, but sometimes it is necessary to perform a skin biopsy, generally in cases when the clinical picture is not entirely typical.

Approach to the patient

Patients should undergo a thorough skin examination, provide information about joint problems, and describe how psoriasis affects their quality of life, especially if it runs in the family, including information about previous treatment modalities.

Prior to the initiation of treatment, severity assessment is performed in order to make a qualified decision about the method of treatment. The simplest way is by using BSA (Body Surface Area) of involvement, which uses the patient's open hand (from wrist to tips of fingers) that equals about 1% of BSA. Psoriasis is generally considered as mild if it affects less than 3% of BSA, moderate between 3% and 10%, while patients with a BSA over 10% suffer from a severe form of the disease (3).

The Psoriasis Area Severity Index (PASI) is the most widely used tool for the measurement of severity of psoriasis. Apart from the affected body surface area, it also assesses infiltration, desquamation and erythema. The highest possible score is 72 (3).

In addition to BSA and the PASI score, the localization of the disease also plays a significant role in assessing the severity of psoriasis. For example, palm and sole psoriasis is classified as severe, regardless of the fact that it affects no more than 4% of the body surface.

When determining the impact of psoriasis on the physical, social and psychological day-to-day life, the following questionnaires are used: Koo-Menter Psoriasis Instrument, Health Related Quality of Life Index, Psoriasis Quality of Life Questionnaire-12, Dermatological Quality of Life Index, etc. In accordance with the European consensus, mild psoriasis is defined as BSA≤10, PASI≤10 and DLQI≤10, while moderate and severe forms are characterized by BSA>10, PASI>10, and DLQI>10.

If treatment fails to yield minimum required results (PASI 50, DLQI<5), it needs to be modified, either by increasing the dose or by taking the medication more frequently, introducing another medication or transitioning to another medication. Additionally, if the condition improves between 50% and 75%, compared to the PASI score at initiation, treatment continuation or discontinuation is recommended, depending on the DLQI assessment (Figure 1) (4). As part of disease monitoring, it is necessary to evaluate the effectiveness of treatment regimen every 8 weeks.

Psoriasis treatment

Figure 2 shows a treatment algorithm for chronic plaque psoriasis, depending on the severity of lesions (5).

Topical therapy

Approximately 80% of persons affected with psoriasis have a mild to moderate forms of the disease. Most of these patients are treated with topical therapy alone, which is usually effective and safe. Topicals are also used as additional treatment for patients receiving photo- or systemic therapy. However, using topical monotherapy is not recommended in patients with recalcitrant psoriasis or spread psoriasis. At the moment, there is no scoring system that clearly defines the border between the use of topical and systemic therapy for patients with psoriasis vulgaris. Yet, topical monotherapy is typically recommended to patients with BSA £10%.

Emollients. Regular application of emollients, especially during the winter months, significantly

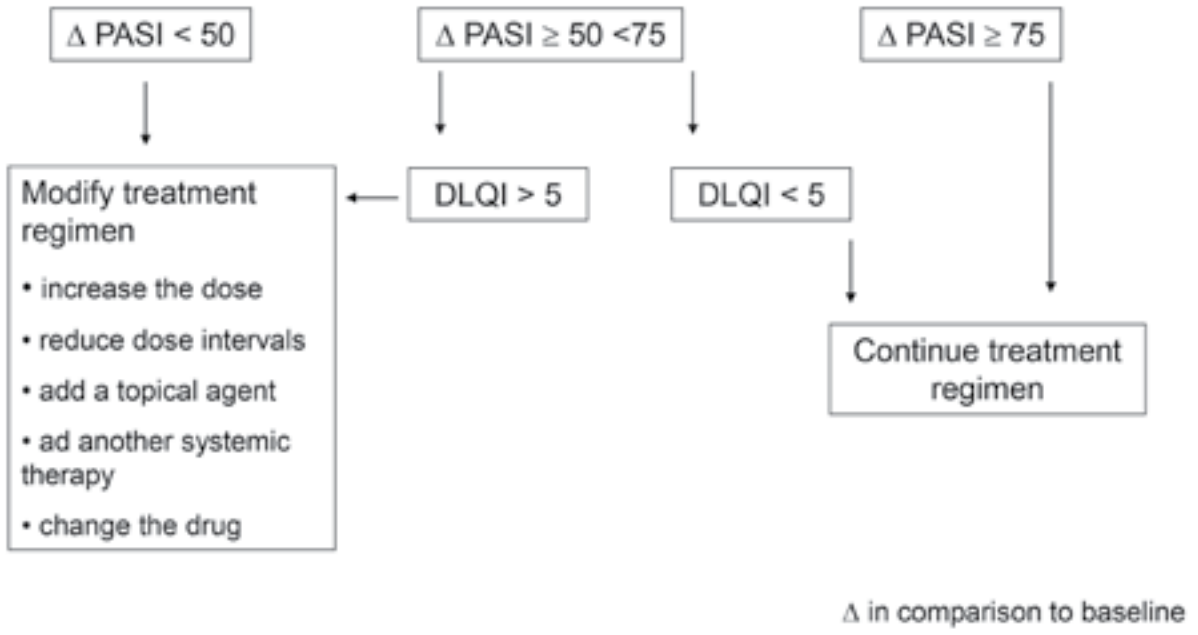

Figure 1. Condition improves between 50% and 75%, compared to the PASI score at initiation, treatment continuation or discontinuation is recommended, depending on the DLQI assessment

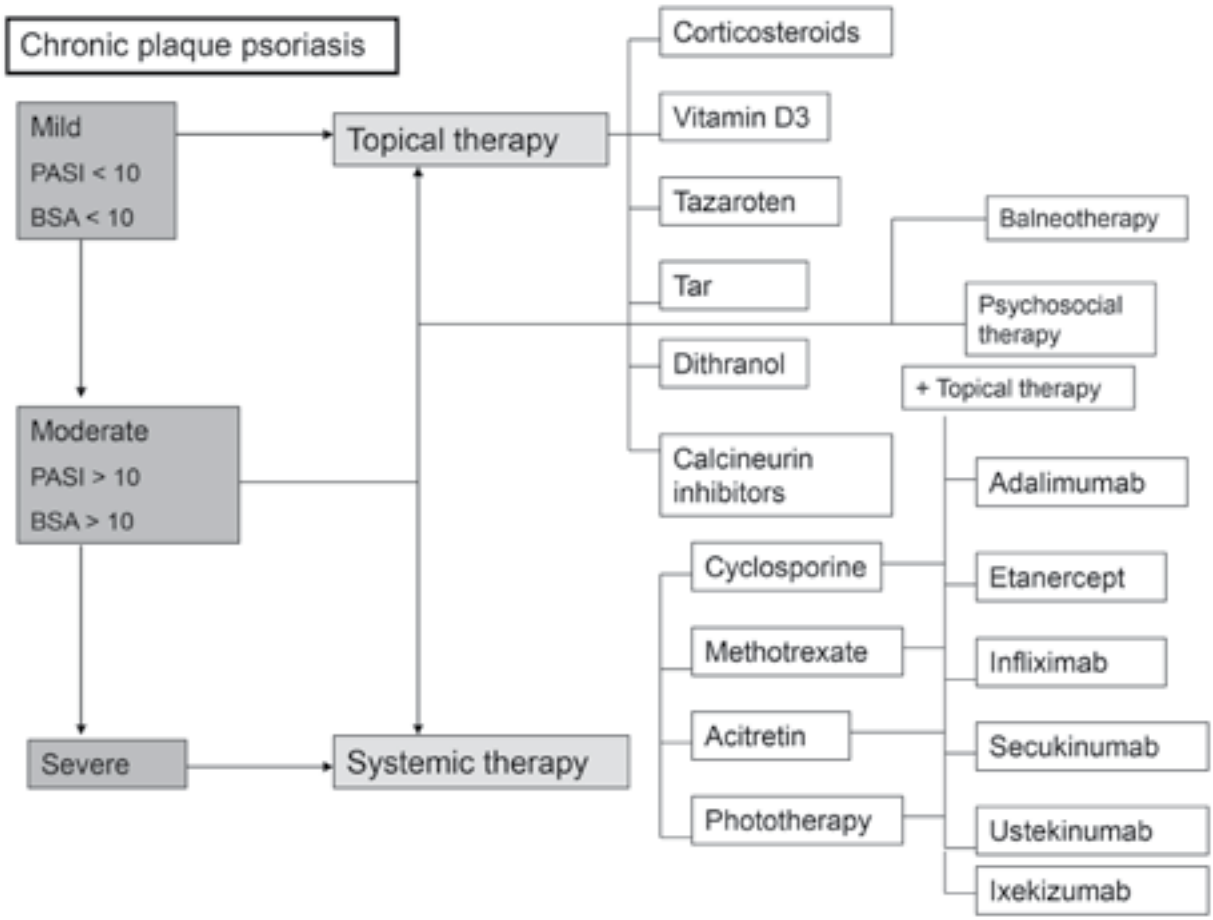

Figure 2. Treatment algorithm for chronic plaque psoriasis, depending on the severity of lesions

reduces itching and desquamation, and enhances the penetration of specific anti-psoriasis drugs. Therefore, it is necessary to explain to the patients the importance of daily application of emollients in the process of psoriasis treatment. There are no contraindications to the use of emollients, and they are safe to use during pregnancy and lactation, as well as by children (6).

Keratolytics. Salicylic acid and urea, in different concentrations, are added to various topical anti-psoriasis formulations in order to reduce hyperkeratosis and desquamation, as well as to enhance the penetration of preparations. Systemic absorption of topical salicylic acid, although rare, may occur when applied to more than 20% of the body surface, or in patients with impaired hepatic and renal function. They are also safe to use during pregnancy and lactation.

Corticosteroids. Topical corticosteroids are the cornerstone of psoriasis treatment for most patients, especially those with a limited form of the disease. There are no absolute contraindications with respect to psoriasis treatment with topical corticosteroids. Low-potency corticosteroids are most often used for a limited period of time to treat skin lesions on the face, on intertriginous areas and areas with thinner skin, as well as in the treatment of psoriasis in children. Moderate to high-potency corticosteroids are recommended as initial therapy for psoriasis in other areas, and in adults. In patients with very thick plaques, high-potency and super-potent preparations are recommended. Numerous studies have shown that Class 1 preparations are not recommended for over two to four weeks, because of increased risk of systemic adverse effects and absorption of the medication. However, duration of low-potency corticosteroids is not clearly defined. Long-term and continuous use of topical corticosteroids, especially super-potent and

high-potency corticosteroids, may lead to a decrease in the response to the therapy (tachyphylaxis) and increase the risk of adverse effects. Discontinuation of this kind of therapy may lead to a rapid relapse, or even to pustular psoriasis or erythroderma. In general, when topical corticosteroids are used to treat psoriasis, it is recommended to gradually reduce the frequency of application, depending on the therapeutic response. The use of polythene occlusion dressings may increase the absorption of the medication and its effectiveness. It is recommended to use corticosteroids in combination with other kinds of topical medications, e.g. calcipotriol or tazarotene (7, 8).

Vitamin D analogues. Calcipotriol, tacalcitol and calcitriol are particularly effective when it comes to chronic plaque psoriasis, after 4 to 6 weeks of therapy. The efficacy of all vitamin D analogues is equivalent to that of moderate to high-potency corticosteroid preparations, but it takes longer to induce the same effects as corticosteroid therapy (9, 10).

In case of local irritation, combining vitamin D analogues with topical corticosteroids may be a good choice. Furthermore, combination of vitamin D analogues and phototherapy is also possible. Since calcipotriol is rendered inactive under the influence of UVA radiation, it must be applied after and by no means prior to UVA therapy. There are no contraindications to calcipotriol and UVB phototherapy.

When it comes to the use of vitamin D analogues during pregnancy, they are all classified as risk category C of the U S Food and Drug Administration (FDA) risk category classification.

Tazarotene. It is recommended for the treatment of mild to moderate psoriasis which covers less than 20% of the body. The effects of tazarotene become visible soon after the first application, and results last for up to 12 weeks after cessation of therapy (11). A combination therapy with tazarotene and topical corticosteroids yields results quickly and it is overall effective, in addition to significantly reducing the adverse effects of tazarotene. According to the FDA, tazarotene belongs to risk category X and it is not recommended during pregnancy and lactation.

Tacrolimus and pimecrolimus. They are calcineurin inhibitors used on sensitive and thin-skinned areas, such as the face and body folds (12). The first effects of calcineurin inhibitors are expected after two weeks of therapy. No cases of skin atrophy have been reported following their application. Adverse effects of tacrolimus and pimecrolimus are rare and quite mild. According to the FDA, they belong to risk category C.

Dithranol (anthralin). It is highly efficient in the treatment of plaque psoriasis and it is available in concentrations, from 0.1% to 6%, and is usually used in the form of short-term (up to 2 hours) or long-term (up to 24 hours) exposure to 1% dithranol, which can be gradually increased over time, depending on the tolerance level and the therapeutic response (13). It can be used in combination with UVB phototherapy (the Ingram method). The most common adverse effects of dithranol are irritation and discoloration of lesions and perilesional skin, nails, clothing, and everything else that may come in contact with the medication. According to the FDA, dithranol is classified as risk category C.

Coal tar derivatives. There are several concentrations and forms of coal tar derivatives. Recent studies have shown that psoriasis treatment using coal tar derivatives does not increase the risk of skin cancer, or any other type of cancer (14). The application of coal tar derivatives under occlusion in combination with UVB phototherapy (Goeckerman method) is rather common in the treatment of psoriasis.

Systemic therapy

Phototherapy involves controlled exposure of the affected skin to artificial ultra violet (UV) (UVA and UVB) radiation.

There are two types of UVB phototherapy: broadband UVB phototherapy, which uses the whole UVB range, and narrowband UVB phototherapy, which emits radiation at wavelengths of 311nm. Clinical studies have shown that narrowband UVB phototherapy is far more effective in the treatment of psoriasis than broadband UVB phototherapy. Before starting UVB phototherapy, it is necessary to determine the individual's hypersensitivity to UV radiation, i.e. the minimal erythema dose (MED), and then start the therapy at 50 to 70% MED, depending on the protocol (15 – 17). Chronic plaque psoriasis that has not responded adequately to topical therapy, or has a BSA of >10%, as well as persistent guttate psoriasis, indicates that UVB phototherapy should be used (15–17).

It is possible to use systemic or topical psoralen in PUVA therapy. Topical application includes liquid psoralen (shower or bath) or ointment. 8-Methoxypsoralen (8-MOP) or 5-Methoxypsoralen (5-MOP) is usually used in the systemic PUVA therapy. As with UVB phototherapy, it is necessary to determine the individual minimal phototoxic dose (MPD) in accordance with the Recommendations of the European Society for Photodermatology. As an alternative, the Photomedicine Society suggests starting PUVA therapy based on the patient's skin phototype. PUVA therapy is recommended for patients who are resistant to topical treatment modalities or suffer from moderate or severe psoriasis with a BSA of >10% (15–17).

Acitretin. Acitretin is used in the treatment of generalized and other types of pustular psoriasis, moderate chronic plaque psoriasis and psoriasis affecting hands, feet, or scalp, in cases where topical therapy showed ineffective, and in patients who are not candidates for phototherapy (18). In such cases, acitretin should be combined with topical therapy in order to achieve full benefit, usually after three to six months. Additionally, acitretin may be part of rotational therapy, after achieving remission with, for example, cyclosporine, or after several months of methotrexate therapy, in order to reduce its cumulative toxicity after remission has been achieved. Patients in whom phototherapy (narrowband UVB, PUVA) has failed to produce the desired effect, a combination of phototherapy and acitretin is far more efficient than acitretin monotherapy or phototherapy alone. The daily dose of acitretin is lower and easier to tolerate, whereas the adverse effects of both treatment modalities, as well as the total amount of UV radiation are reduced (17). In conjunction with PUVA therapy, acitretin reduces the risk of squamous cell carcinoma and development of actinic keratosis (19). Taking into account the fact that acitretin is not an immunosuppressant; it is the first choice for HIV positive patients with a severe form of psoriasis. On the other hand, there are no proven benefits of using acitretin to treat psoriatic arthritis, and thus it is not a therapeutic option for these patients. Acitretin is taken orally, one dose of 10 to 50 mg a day, with food or milk. The initial dose is usually 0.3 to 0.5 mg/kg body weight (BW) and it is taken for 3 to 4 weeks. After that, based on the effects and tolerance level, the dose is increased to 0.5 to 0.8 mg/kg BW, with the maximum dose being 1mg/kg. The full effects of therapy are seen after three to six months. Relatively common and expected adverse effects of acitretin include dry skin and mucous membranes. Acitretin is contraindicated in: women of childbearing age, pregnancy (absolute contraindication), severe liver and kidney damage, chronically elevated blood lipid levels (18).

Methotrexate is a folic acid antagonist. It is recommended in the treatment of generalized psoriasis; palm and sole psoriasis if phototherapy is not efficient or cannot be conducted; in patients with a significant lipid metabolism disorder, and if acitretin is contraindicated (18). Prior to the initiation of methotrexate therapy, a detailed medical history, physical examination and laboratory tests (complete blood count, urea, creatinine, albumin, total bilirubin, AST, ALT, γ-GT, HBsAg, anti-HCV antibodies, anti-HIV antibodies, a Quantiferon Gold test or a PPD test with chest x-ray) are conducted (5). The therapy should start with a test dose of 2.5 to 7.5 mg, and after 5 to 7 days, the occurrence of potential significant myelosuppression should be checked in predisposed patients by case-control analysis. The weekly dose can be gradually increased by 2.5mg and with laboratory controls every seven days, the dose can be increased up to 15 to 25mg per week, five days after methotrexate application, depending on the effect, in case the patient is treated with the minimal effective dose. The maximum methotrexate dose in psoriasis patients should not exceed 30 mg per week. According to most experts, 24 to 48 hours after methotrexate treatment, folate supplementation (1 to 5 mg) is recommended to reduce gastrointestinal, hepatic and hematological toxicity. The most common adverse effects of methotrexate include gastrointestinal toxicity (nausea, loss of appetite and exhaustion), myelosuppression, hepatotoxicity, pulmonary fibrosis and the related risk of infections. Absolute contraindications are: pregnancy and breastfeeding, alcoholism, chronic and alcoholic liver diseases, immunodeficiency syndromes, bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anemia, methotrexate hypersensitivity, attenuated vaccination (BCG, polio, yellow fever, mumps, etc.).

Cyclosporine should always be considered in the treatment of erythrodermic and generalized pustular psoriasis, as well as in cases of acute exacerbation of chronic plaque psoriasis, and psoriasis that has not responded to other types of systemic therapy and phototherapy (18, 20). It can also be included in rotational therapy for 3 to 4 months, in order to reduce the overall adverse effects of systemic therapy. In cases where topical therapy is not efficient and biologic, photo- and photochemotherapy are not possible, it is the best option for women of childbearing age with erythrodermic and generalized pustular psoriasis (*impetigo herpetiformis*) during pregnancy, where other types of systemic therapy are contraindicated. Prior to starting the therapy, the occurrence of tuberculosis, hepatitis B and C, and a personal and family medical history of kidney disease and hypertension must be determined (18, 20). The starting daily dose is 2.5 to 3 mg/kg of body weight, always divided into two doses. In obese patients (Body Mass Index >30), cyclosporine doses are determined based on the ideal, instead of the actual weight of the patient. After four weeks, the dose can be further increased by 0.5 mg/kg BW until complete control of the disease is achieved, with the maximum dose being 5 mg/kg BW. After achieving clinical remission, the medication dose is gradually reduced by 0.5 mg/kg BW every 2 to 4 weeks in the maintenance period, down to 1 to 1.5 mg/kg BW, when discontinuation is considered, provided that no exacerbations occur. Upon therapy discontinuation, psoriasis relapse usually occurs rapidly, so it is necessary to continue therapy using another medication, or phototherapy. The most significant adverse effect, limiting its long-term use, is nephrotoxicity. Contraindications of cyclosporine are: simultaneous PUVA or UVB phototherapy, simultaneous use of methotrexate and other immunosuppressives, a medical history of radiation therapy or more than 200 PUVA treatments, uncontrolled hypertension, renal insufficiency, malignant disease (except non-melanoma skin cancer), cyclosporine hypersensitivity, attenuated vaccination, uncontrolled and chronic infections.

Biological therapy

Over the last two decades, the treatment of psoriasis has evolved towards biological therapy. It modifies the immune response and inflammatory cascade, and consequently the therapeutic effect, by using cytokine inhibitors and molecules inhibiting certain signaling pathways.

Biological medications used in psoriasis treatment are classified into two groups: T-cell activated inhibitors, and cytokine inhibitors, or more precisely, tumor necrosis factor a (TNFa), and interleukin-12. They were named based on the technology which was used in their production: monoclonal antibodies have the suffix – *"mab"*, while fusion proteins have the suffix – *"cept"*.

Prior to initiation of biological therapy, a detailed medical history must be obtained, and physical examination, laboratory analysis (complete blood count, biochemical test, hepatogram, urinalysis, screening for hepatitis B, hepatitis C and HIV), as well as screening for tuberculosis (chest x-ray, Quantiferon TB test) must be conducted (5, 21, 22).

In Europe, biologics are usually second-line therapy in patients without satisfactory response to phototherapy and classic systemic therapy. However, they are also applied as first-line therapy if phototherapy is unavailable, and if there are contraindications to classic systemic therapy, or if it has led to adverse effects. Certain biologics are especially suitable for patients who are young, planning to start a family, have many responsibilities and whose lifestyle makes phototherapy impossible. In such cases, classic systemic therapy is contraindicated, because they are planning to start a family or because of comorbidity, and the therapy is usually carried out by patients themselves.

Contraindications of biologic therapy include: active severe infections (sepsis, active tuberculosis, hepatitis B and C), class III and IV cardiomyopathy, demyelinating diseases of the central nervous system (patients suffering from multiple sclerosis or first cousins of patients suffering from multiple sclerosis), malignancy (data about earlier or currently diagnosed and treated malignancies, except basal cell carcinoma), severe hepatic insufficiency, recent attenuated vaccination (5, 21, 22).

Etanercept is a recombinant TNF-a receptor fusion protein that acts as an inhibitor of TNF-a by binding to and inactivating TNF-a, thus preventing its interactions with cell surface receptors. It is most

commonly used as monotherapy in the treatment of psoriasis, subcutaneously, 50 mg twice a week, over a period of 12 weeks, and then 50 mg once a week, continually. After 12 weeks, it induces a PASI =75 response in 49% of patients, and continuous treatment with the same dose leads to PASI =75 in 59% of patients after 24 weeks of therapy (23). In some patients, its efficacy decreases with dose reduction to 50 mg once a week. In few patients, the efficiency is reduced over a period of several months, probably due to the formation of etanercept antibodies. Etanercept has been used in a group of children aged 4 to 17, and after 12 weeks of therapy, the PASI =75 response was recorded in 57% of patients. No rebound phenomenon was reported after the discontinuation of etanercept therapy. The only common adverse effect is a mild reaction followed by itching at the subcutaneous application point, usually in the first two to three weeks of therapy. The injections, applied by patients themselves, contain latex and are thus contraindicated in patients who are allergic to latex. Contraindications to etanercept are sepsis and other active infections, in which cases the therapy should be delayed until after full improvement.

Infliximab is a chimerical anti-TNF-alpha monoclonal antibody composed of human IgG1-a constant region and mouse variable region, which binds with both the soluble and the membrane TNF-a. In the treatment of psoriasis, it is applied intravenously at a dose of 5 mg/kg BW over a period of 2 to 3 hours, with a previous antihistamine and systemic corticosteroid premedication (24). Infusions are repeated two and six weeks after the first infusion, and then every 6 to 8 weeks continuously. At this dose, infliximab leads to a PASI =75 response in 80% of patients after three infusions, in the tenth week of therapy, which places it amongst biological medications with the quickest effect. Continuous use of infliximab every 6 to 8 weeks is a better option compared to repeated treatment cycles in exacerbation periods, because of a reduced incidence of infliximab antibodies and decrease of efficiency, which, according to one study, leads to 60% of patients keeping the PASI =75 response in the sixtieth week of therapy (24, 25). Some experts combine infliximab with small doses of methotrexate to prevent antibody formation.

Adalimumab is a human anti-TNF-a monoclonal antibody which binds to both the membrane and the soluble TNF-a. In psoriasis, it is administered subcutaneously at a dose of 80 mg during the first week, 40 mg a week later, and then 40 mg every two weeks, leading to a PASI =75 response in 71% of patients after 16 weeks of therapy. According to another study, a PASI =75 response was achieved in 79%, and PASI= 90 in 51.9% of patients (21). In the latter study, the efficiency was compared to methotrexate in increasing doses (7.5 to 25 mg), which achieved PASI =75 in 35.5%, and PASI =90 in 13.6% of patients after 16 weeks of therapy (26). After therapy discontinuation, a rebound phenomenon was not reported, but continuous use is more efficient, taking into account the efficiency decrease after discontinuation and the reintroduction of adalimumab into therapy.

Golimumab is an anti-TNF agent approved in the USA in 2009 as a treatment for psoriatic arthritis, but it has not been approved in Europe so far. It is a human IgG1 monoclonal antibody with a high affinity for TNF-a. Its efficiency was estimated in phase III of some studies, and it was applied subcutaneously at doses of 50 and 100 mg once a month, over a period of 20 weeks. The recorded PASI= 75 response after 14 weeks was 40% (for 50 mg) and 58% (for 100 mg), and the adverse effects were similar to other TNF antagonists (21).

Ustekinumab is a recombinant human IgG1k antibody which binds to p40 subunit of the IL-12/IL-23 molecule. The binding of this antibody prevents the IL-12 from binding with its receptor on the NK cells and T-cells, thus preventing activation and proliferation of T-cells towards a Th1 and Th17 subpopulation of regulatory T-lymphocytes, which are crucial in psoriasis pathogenesis. Since 2009, ustekinumab has been approved in Europe for treating moderate and severe psoriasis unresponsive to classic systemic therapy (phototherapy, methotrexate, retinoids, cyclosporine), or if there are contraindications or adverse effects due to which it cannot be applied. At a dose of 45 mg (or 90 mg for patients who weigh more than 100 kg) once a month for two months, and then every 12 weeks, ustekinumab leads to a PASI =75 response in 67% of patients; the higher dose of 90 mg was not significantly more efficient in patients

weighing less than 100 kg, but it was more efficient in patients weighing more than 100 kg (27, 28).

Secukinumab is a recombinant, highly affinitive, completely human monoclonal IgG1κ antibody which binds selectively and neutralizes IL-17A. It is used at ın a dose of 300 mg once a week during the first 4 weeks, and then the treatment continues at 300 mg once a month. After 12 weeks, the recorded PASI =75 response in clinical studies was 81.6% and 77.1% (for 300 mg) and 71.6% and 67% (for 150 mg) (29). Anti-secukinumab antibodies were detected in a very small percentage (0.3 to 0.4%) causing no reduction in therapy efficiency or occurrence of adverse effects. The most common adverse effects are nasopharyngitis, headaches and upper respiratory tract infections. In a study which compared the efficacy of secukinumab and ustekinumab, after 52 weeks, 76% of patients who were given secukinumab and 61% of the patients who were given ustekinumab had PASI =90, while 46% of patients who were given secukinumab and 36% of patients who were given ustekinumab achieved PASI =100 (30).

Ixekizumab is an anti IL-17A monoclonal IgG4 antibody with a high binding affinity to IL-17A, one of the main cytokines in psoriasis pathogenesis. It is administered subcutaneously, with a starting dose of 160 mg; from the 2nd to the 12th week it is used at a dose of 80 mg every other week, and then 80 mg every fourth week. Literature data show that, 81.8% i.e. 98.7% of patients suffering from chronic plaque psoriasis had a PASI =75 response after 12 weeks of therapy (31, 32). The most common adverse effects include nasopharyngitis, candidiasis and reactions at the application point.

Apremilast is an oral phosphodiesterase-4 (PDE4) inhibitor which has been approved for the treatment of psoriasis and psoriatic arthritis. In the European Union, apremilast has been recommended for the elderly patients with moderate and severe plaque psoriasis, who did not respond to other types of systemic therapy, did not tolerate it, or it was contraindicated. Clinical studies have shown that 33.1% of patients had a PASI =75 response after 16 weeks (33). In the treatment of psoriatic arthritis, it can be used as monotherapy or combined with other systemic medications.

A diverse clinical picture, numerous clinical studies and extensive psoriasis pathogenesis research have shown that psoriasis is not a single disease, but a group of diseases with several subtypes, different phenotypes and genotypes, as well as different responses to certain therapeutic options. The future of psoriasis therapy, and generally, the future of dermatology, lies in the personalized approach to the patient, which includes identification of psoriasis subtypes, patient genotype, comorbidity, psychological and social environmental factors, and an integrative approach to treatment, which takes into account all of these factors to provide a highly efficient, safe treatment – perhaps even a full recovery in the future. This guide will contribute to a better and more systematic treatment of patients suffering from psoriasis in Serbia, in accordance with the applicable recommendations of the European and American associations of dermatologists.

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Vodič Udruženja dermatovenerologa Srbije za dijagnostiku i lečenje psorijaze

Psorijaza je hronična, rekurentna, zapaljenska, sistemska bolest koja je uslovljena genetskim i imunološkim karakteristikama osobe i ima izrazito negativan efekat na kvalitet života. Ako prihvatimo procenu da, kao i u Evropi i Severnoj Americi, i u Srbiji ima oko 2% ljudi sa psorijazom, to bi značilo da populaciju obolelih čini do 140.000 ljudi. Oko 30% obolelih od psorijaze ima umerenu do tešku formu psorijaze, sa psorijaznim artritisom ili bez njega, što predstavlja oko 42.000 bolesnika.

Jasno je uočena udruženost psorijaze i metaboličkih i kardiovaskularnih bolesti (1, 2). Ako se ta udruženost ranije mogla smatrati akcidentalnom ili se pokušavala tumačiti životnim navikama (pušenje, alkohol i drugo, što bi moglo biti posledica psihičkog stanja bolesnika), danas se zna da ove bolesti imaju mnoge zajedničke genetske i imunološke mehanizme.

Klinički oblici psorijaze

Najčešći klinički oblik jeste hronična plak-psorijaza (psorijaza u pločama ili *psoriasis vulgaris in placibus*). Viđa se kod 80–90% bolesnika sa psorijazom. Kod najvećeg broja obolelih klinički znaci psorijaze javljaju se pre 35. godine, a kod oko 10% pacijenata bolest se javlja već u detinjstvu. Bolest je izrazito hroničnog toka, sa povremenim pogoršanjima.

Pored obične ili *psoriasis vulgaris*, razlikuje se i:

- gutatna forma,
- psorijaza pregiba (inverzna),
- eritrodermijska psorijaza,
- pustulozna psorijaza,
- psorijaza dlanova i/ili tabana.

Dijagnoza psorijaze

I pored najčešće jasne kliničke prezentacije, ponekad je neophodno uraditi biopsiju kože, najčešće kada klinička slika nije u potpunosti jasna.

Pristup pacijentu

Neophodno je uraditi kompletan pregled kože, tražiti podatke u vezi sa tegobama sa zglobovima, podatke o uticaju psorijaze na kvalitet života pacijenta, da li je bolest prisutna u porodici i podatke o ranijim terapijskim modalitetima.

Pre započinjanja lečenja potrebno je uraditi procenu težine bolesti, kako bi se kvalifikovano donela odluka o načinu lečenja. Najjednostavnija je primena BSA (engl. *Body Surface Area*), gde je jedinica mere površina pacijentovog dlana približno 1%. Ako je raširenost promena na koži do 3%, govori se o blagoj formi, od 3 do 10% je umerena psorijaza, a bolesnici sa BSA preko 10% imaju tešku formu psorijaze (3).

Neophodan instrument za procenu težine kliničke slike je PASI skor *(engl. Psoriasis Area Severity Index*), koji pored raširenosti, procenjuje infiltraciju, deskvamaciju i eritem psorijaznih promena. Maksimalan skor iznosi 72 (3).

Za procenu težine bolesti, pored BSA i PASI skora, veliku ulogu ima i lokalizacija bolesti. Na primer, psorijaza dlanova i tabana može se smatrati teškom formom, bez obzira što može da zahvati najviše 4% površine.

Prilikom određivanja uticaja psorijaze na svakodnevni fizički, socijalni i psihički život bolesnika koriste se sledećei upitnici: *Koo-Menter Psoriasis Instrument, Validated Health Related Quality of Life Index, Psoriasis Quality of Life-12, Dermatological Quality of Life Index,* itd. Prema evropskom konsenzusu blaga psorijaza definiše se sa BSA ≤ 10, PASI ≤ 10 i DLQI ≤ 10, dok na srednje tešku i tešku psorijazu ukazuje BSA > 10 ili PASI > 10 ili DLQI > 10.

Ako lečenjem nije postignut minimalni cilj (PASI 50, DLQI < 5), potrebno je promeniti terapiju, povećanjem doze ili smanjenjem vremenskog intervala doziranja leka, uvođenjem drugog leka ili prelaskom na drugi lek. Zatim, ako je postignuto poboljšanje bolesti između 50% i 75% od početne vrednosti PASI skora, preporučuje se nastavak ili prekid dotadašnjeg lečenja u zavisnosti od procene DLQI (Slika 1) (4). U praćenju bolesnika potrebno je svakih osam nedelja procenjivati efekat lečenja.

Lečenje psorijaze

Na Slici 2 shematski je prikazan algoritam lečenja hronične plak-psorijaze u zavisnosti od težine bolesti (5).

Topijska terapija

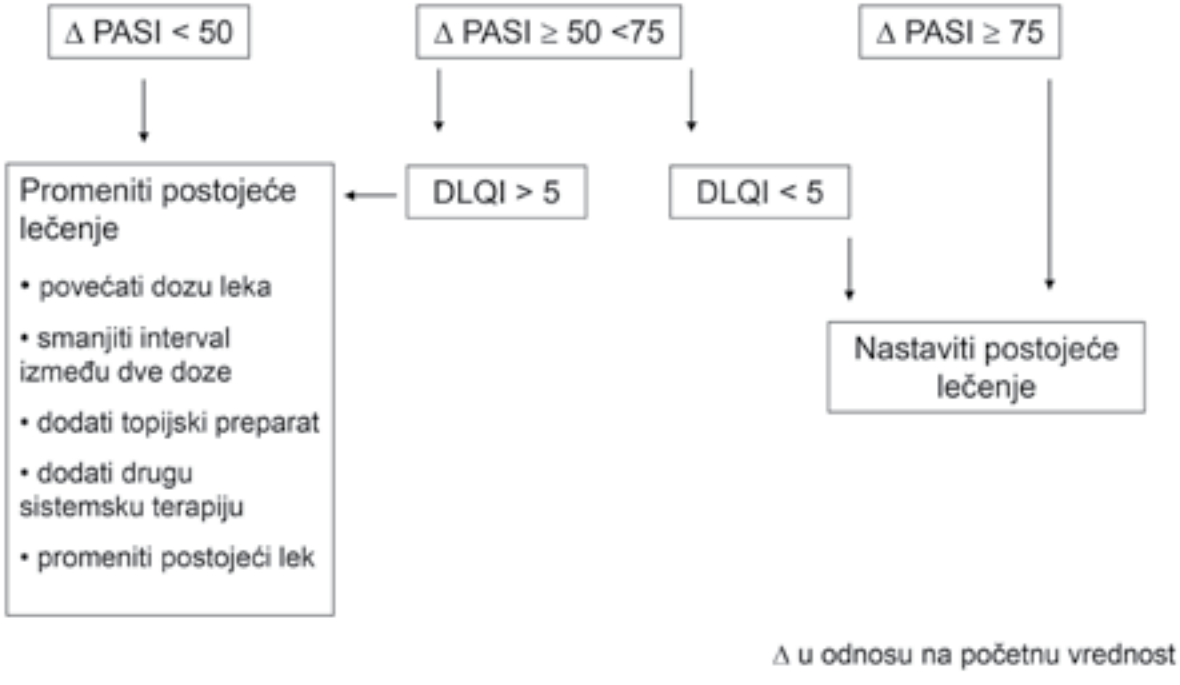
Oko 80% obolelih od psorijaze ima blago do umereno oboljenje. Većinu ovih pacijenata moguće je lečiti samo topijskom terapijom, koja je najčešće efikasna i bezbedna. Topijski preparati koriste se i kao dodatna terapija kod pacijenata na fototerapiji ili kod obolelih koji uzimaju sistemsku terapiju. Međutim, ne preporučuje se korišćenje topijskih preparata kao monoterapija kod pacijenata s proširenom ili rekalcitrantnom psorijazom. Trenutno ne postoji skoriranje koje jasno definiše granicu između primene topijske i sistemske terapije kod pacijenata koji boluju od vulgarne psorijaze. Ipak, najčešće se preporučuje da topijska terapija, kao monoterapija, bude primenjena kod pacijenata koji imaju BSA £ 10%.

Emolijenti. Redovno nanošenje emolijenata, naročito tokom zimskih meseci, može značajno smanjiti svrab, redukovati deskvamaciju i pojačati penetraciju specifične antipsorijazne terapije. Zbog toga je neophodno pacijentima objasniti značaj svakodnevnog nanošenja emolijenata u lečenju psorijaze. Ne postoje kontraindikacije za primenu emolijenata, a njihova primena bezbedna je tokom trudnoće, laktacije, kao i u dečjem uzrastu (6).

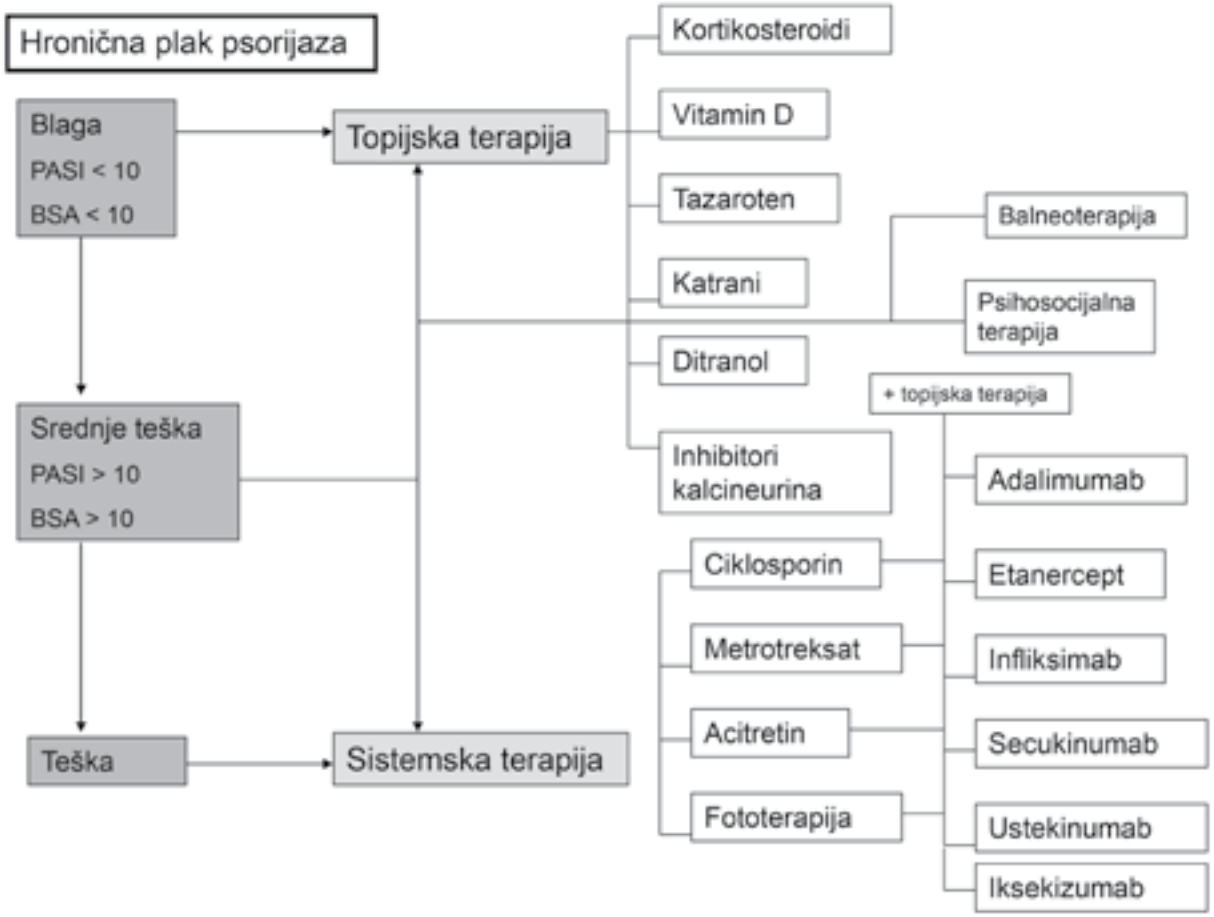
Keratolitici. Salicilna kiselina i urea se u različitim koncentracijama dodaju različitim formulacijama topijske antipsorijazne terapije kako bi redukovali hiperkeratozu, smanjili deskvamaciju i pojačali penetraciju preparata. Sistemska apsorpcija topijske salicine kiseline, iako retka, može se manifestovati kod nanošenja na više od 20% površine kože i kod pacijenata sa oslabljenom funkcijom jetre i bubrega. Primena u trudnoći i tokom laktacije je bezbedna.

Kortikosteroidi. Topijski kortikosteroidni preparati predstavljaju osnovu lečenja kod većine pacijenata obolelih od psorijaze, posebno kod onih s ograničenom formom bolesti. Ne postoje apsolutne kontraindikacije za primenu topijskih kortikosteroida.

Slabo potentni kortikosteroidi najčešće se koriste u ograničenom periodu za promene na koži lica, intertriginoznih regija, kod regija s istanjenom kožom, kao i kod dece. Za ostale regije, kao i kod



Slika 1. Poboljšanje bolesti između 50% i 75% od početne vrednosti PASI skora, preporučuje se nastavak ili prekid dotadašnjeg lečenja u zavisnosti od procene DLQI



Slika 2. Algoritam lečenja hro-nične plak-psorijaze u zavisnosti od težine bolesti

odraslih osoba, umereno i veoma potentni preparati preporučuju se kao inicijalna terapija. Kod pacijenata s veoma zadebljalim plakovima neophodna je primena veoma potentnih i superpotentnih preparata. Brojne studije pokazale su da se ne savetuje primena preparata klase 1 duže od dve do četiri nedelje zbog povećanog rizika od nastanka neželjenih efekata i sistemske apsorpcije leka. Kod kortikosteroida slabije potentnosti nije jasno definisana dužina primene. Dugotrajna i kontinuirana primena topijskih kortikosteroida, naročito superpotentnih i veoma potentnih, može dovesti do izostanka efikasnosti terapije (tahifilaksija) i povećanog rizika od nastanka neželjenih efekata. Prekidom ovakvog načina lečenja može doći do brzog relapsa bolesti ili čak i manifestacije pustulozne psorijaze ili eritrodermije. Generalno, kada se topijski kortikosteroidi koriste u lečenju psorijaze, preporučuje se postepeno smanjivanje učestalosti njihovog nanošenja, u zavisnosti od terapijskog odgovora. Primena polietilenske okluzije može poboljšati apsorpciju leka i njegovu efikasnost. Preporučuje se kombinovanje kortikosteroida sa ostalim topijskim vrstama lečenja, npr. kalcipotriol ili tazaroten (7, 8).

Analozi vitamina D. Kalcipotriol, takalcitol i kalcitriol pokazuju značajnu efikasnost u lečenju hronične plak-psorijaze posle terapije 4–6 nedelja. Svi analozi vitamina D imaju efikasnost koja odgovara umereno do veoma potentnim kortikosteroidnim preparatima, ali je vreme do postizanja efekta duže nego kod kortikosteroida (9, 10).

Kombinacija s topijskim kortikosteroidima može biti dobar izbor ukoliko je izražena lokalna iritacija. Moguća je kombinacija analoga vitamina D i fototerapije. S obzirom na to da se kalcipotriol inaktivira pod dejstvom UVA zračenja, neophodno je kalcipotriol aplikovati posle, a nikako pre UVA fototerapije. Ne

postoje kontraindikacije u primeni kalcipotriola i UVB fototerapije.

Kada se radi o primeni u trudnoći, svi analozi vitamina D pripadaju grupi C lekova Agencije za lekove i hranu SAD.

Tazaroten. Preporučuje se za lečenje blage do umereno izražene psorijaze, koja zahvata manje od 20% površine tela. Efekat tazarotena ispoljava se veoma brzo po započinjanju nanošenja, a efekat lečenja prisutan je i do 12 nedelja posle završetka terapije (11). Kombinovanjem tazarotena i topijskih kortikosteroida postiže se brz efekat terapije i ukupna efikasnost, a značajno se redukuju neželjeni efekti tazarotena. Tazaroten, prema Agenciji za lekove i hranu SAD, pripada X grupi lekova i ne sme se koristiti za vreme trudnoće i laktacije.

Takrolimus i pimekrolimus. Koriste za delove kože gde je koža tanja, kao što su lice i pregibne površine (12). Prvi efekti primene kalcineurinskih inhibitora očekuju se posle dve nedelje. Posle nanošenja kalcineurinskih inhibitora nisu zabeleženi slučajevi atrofije kože. Neželjeni efekti takrolimusa i pimekrolimusa su retki i veoma blagi. Pripadaju C grupi lekova prema Agenciji za lekove i hranu SAD.

Ditranol (antralin). Veoma je efikasan u lečenju plak-psorijaze. Dostupan je u više koncentracija, 0,1−6%, a najčešće se primenjuje u vidu kratkotrajnog (do 2 sata) ili dugotrajnog izlaganja leku (do 24 sata) u koncentraciji od 1%, koja se vremenom može postepeno povećavati u zavisnosti od podnošljivosti i terapijskog odgovora (13). Može se kombinovati s UVB fototerapijom (Ingramov metod).

Najčešći neželjeni efekti ditranola su iritacija i prebojavanje lezione i perilezione kože, noktiju, odeće i svega što može doći u kontakt s lekom. Ditranol pripada C grupi lekova prema Agenciji za lekove i hranu SAD.

Derivati katrana. Postoji više koncentracija i više oblika derivata katrana. Novije studije pokazale su da lečenje psorijaze derivatima katrana ne povećava rizik od nastanka karcinoma kože, kao ni karcinoma drugih organa (14). Relativno često primenjuje se aplikovanje pod okluzijom derivata katrana i UVB fototerapije (Gekermanov metod).

Sistemska terapija

Fototerapija predstavlja kontrolisano izlaganje kože veštačkim izvorima UV (UVA i UVB) zračenja.

Postoje dve vrste UVB fototerapije: širokospektralna UVB fototerapija, čiji spektar emisije obuhvata ceo UVB opseg i uskospektralna UVB fototerapija, koja emituje zračenje talasne dužine 311 nm. Kliničke studije pokazale su značajno bolji efekat uskospektralne nego širokospektralne UVB fototerapije u lečenju psorijaze. Pre započinjanja UVB fototerapije neophodno je odrediti individualnu preosetljivost na UVB zračenje, tj. minimalnu eritemsku dozu – MED, te potom započeti terapiju sa 50–70% od MED, u zavisnosti od protokola (15−17). Indikacije za primenu UVB fototerapije su hronična plak-psorijaza koja nije adekvatno odgovorila na topijsku terapiju ili kod koje je BSA > 10% i perzistentna gutatna psorijaza (15−17).

Prilikom sprovođenja PUVA terapije moguće je primeniti sistemski ili topijski način aplikacije psoralena. Topijska aplikacija moguća je u obliku delimičnog ili kompletnog nanošenja psoralena u vidu tečnosti (kupke, kada ili tuš), ili krema. Za sistemski oblik PUVA terapije najčešće se koristi 8-metoksipsoralen (8-MOP) ili 5-metoksipsoralena (5-MOP). Kao i kod UVB fototerapije, neophodno je odrediti individualnu minimalnu fototoksičnu dozu (engl. skr. MPD) prema preporukama Evropske grupe za fototerapiju. Kao alternativu, Američka grupa za fototerapiju predlaže započinjanje PUVA terapije na osnovu fototipa kože. PUVA terapija je indikovana kod pacijenata koji su rezistentni na topijske modalitete lečenja ili koji imaju srednje tešku ili tešku formu psorijaze, čiji je BSA > 10% (15−17).

Acitretin. Pacijenti sa generalizovanom pustuloznom psorijazom i drugim oblicima pustulozne psorijaze, pacijenti sa srednje teškom hroničnom plak-psorijazom i psorijazom dlanova i tabana ili poglavine kod kojih lokalna terapija nije dovoljno efikasna, a nisu kandidati za fototerapiju, mogu da budu lečeni acitretinom (18). U ovim slučajevima acitretin je uvek neophodno kombinovati sa lokalnom terapijom do punog efekta leka, koji se javlja 3−6 meseca terapije. Takođe, acitretin se može davati u rotacionom režimu, posle postizanja remisije npr. ciklosporinom, ili nakon višemesečne primene metotreksata radi smanjenja njegove kumulativne doze kada se postigne remisija. Kod pacijenata kod kojih fototerapija (uskospektralna UVB, PUVA) nije dovela do željenog efekta, kombinacija sa acitretinom

značajno je efikasnija od monoterapije acitretinom ili same fototerapije, a neželjeni efekti oba modaliteta lečenja se smanjuju, dnevna doza acitretina koja se koristi je manja i lako se podnosi, a smanjuje se i ukupna doza UV zračenja (17). U kombinaciji sa PUVA terapijom acitretin smanjuje rizik od pojave planocelularnog karcinoma i aktiničnih keratoza (19). Imajući u vidu da nije imunosupresiv, acitretin je lek prvog izbora kod pacijenata sa infekcijom HIV-om i teškim oblikom psorijaze. S druge strane, acitretin nema dokazan efekat kod psorijaznog artritisa, te kod ovih pacijenata nije terapijska opcija. Acitretin se primenjuje *per os* u jednoj dozi 10–50 mg/dan, uz jelo ili sa mlekom. Najčešće se primenjuje u početnoj dozi 0,3−0,5 mg/kg TT tokom 3–4 nedelje, a zatim se, na osnovu efekta i podnošljivosti doza povećava 0,5–0,8 mg/kg TT, dok je maksimalna doza 1 mg/kg. Pun efekat terapije postiže se posle 3−6 meseci lečenja. Veoma česti i očekivani neželjeni efekti acitretina vezani su za suvoću kože i sluzokoža. Kontraindikacije za primenu acitretina su: žene u reproduktivnom periodu, trudnoća (apsolutna kontraindikacija), teška oštećenja jetre i bubrega, hronično povišene vrednosti lipida u krvi (18).

Metotreksat je antagonist folne kiseline. Indikovan je u lečenju generalizovane psorijaze ili psorijaze dlanova i tabana kod koje fototerapija nije efikasna ili ne može da se sprovodi; postoji i značajan poremećaj metabolizma lipida, a i kontraindikacija za primenu acitretina (18). Pre započinjanja terapije metotreksatom neophodno je uzeti detaljnu anamnezu, uraditi klinički pregled i laboratorijske analize (kompletna krvna slika, urea, kreatinin, albumin, ukupni bilirubin, AST, ALT, γGT, HBsAg, anti HCV antitela, anti HIV antitela, *Quantiferon Gold test* ili PPD test sa radiografijom pluća i srca) (5). Terapiju treba započeti test-dozom 2,5−7,5 mg, a potom kontrolnim analizama za 5–7 dana kod pacijenata koji imaju predispoziciju proveriti postojanje eventualne značajne mijelosupresije. Daljim postepenim povećanjem doze za 2,5 mg i kontrolom laboratorijskih analiza svakih sedam dana, pet dana posle uzimanja metotreksata, doza se može povećati 15–25 mg nedeljno, u zavisnosti od efekta, vodeći računa da pacijent bude lečen minimalnom efikasnom dozom. Maksimalna doza metotreksata u lečenju psorijaze, ne sme biti veća od 30 mg nedeljno. Suplementacija folatom (1–5 mg), 24−48 časova, posle uzimanja metotreksata, prema većini eksperata, neophodna je radi smanjenja gastrointestinalne, hepatične i hematološke toksičnosti. Najčešći neželjeni efekti lečenja metotreksatom su gastrointestinalna toksičnost (mučnina, gubitak apetita i malaksalost), mijelosupresija, hepatotoksičnost, fibroza pluća, povezan rizik za nastanak infekcija. Apsolutne kontraindikacije za primenu metotreksata su: trudnoća i dojenje, alkoholizam, hronična bolest jetre i alkoholna lezija jetre, sindromi imunodeficijencije, hipoplazija koštane srži, leukopenija, trombocitopenija ili značajna anemija, preosetljivost na metotreksat, vakcinacija živim vakcinama (BCG, polio, žuta groznica, mumps, itd.)

Ciklosporin uvek treba razmotriti u lečenju eritrodermijske i generalizovane pustulozne psorijaze, ali i kod akutnih pogoršanja hronične plak-psorijaze i psorijaze koja nije reagovala na druge oblike sistemske terapije i fototerapije (18, 20). Takođe, u sklopu rotacione terapije može se uključiti tokom 3-4 meseca radi smanjenja neželjenih efekata ukupno primenjene sistemske terapije. Takođe, kod neefikasnosti lokalne terapije i u odsustvu opcije biološke, foto i fotohemoterapije, ciklosporin je najbolja opcija kod žena u reproduktivnom periodu i u eritrodermijskoj i generalizovanoj pustuloznoj psorijazi (*impetigo herpetiformis*) u trudnoći, gde su drugi oblici sistemske terapije kontraindikovani. Pre započinjanja terapije neophodno je ispitati postojanje tuberkuloze, hepatitisa B i C i ličnu i porodičnu anamnezu o bolestima bubrega ili hipertenzije (18, 20). Terapija se može započeti sa 2,5-3 mg/kg telesne težine, uvek podeljeno u dve doze. Kod gojaznih pacijenata (indeks telesne mase >30) ciklosporin se dozira na osnovu idealne, a ne stvarne težine pacijenta. Doza se može dalje povećati posle četiri nedelje za 0,5 mg/kg/TT do potpune kontrole bolesti, sa maksimalnom dozom od 5 mg/kg TT. Posle postizanja kliničke remisije, doza leka se može smanjivati u periodu održavanja, postepeno na 2–4 nedelje za 0,5 mg/kg TT, do doze od 1-1,5 mg/kg TT kada se, ukoliko ne dođe do pogoršanja, može razmišljati o prekidu terapije. Posle prekida terapije najčešće se javlja brzi relaps psorijaze, te je neophodno terapiju nastaviti drugim lekom ili fototerapijom. Najvažniji neželjeni efekat, koji limitira njegovu dugotrajnu

upotrebu, jeste nefrotoksičnost. Kontraindikacije za primenu ciklosporina su: istovremena primena PUVA ili UVB fototerapije, istovremena primena metotreksata i drugih imunosupresiva, anamneza o terapiji zračenjem ili više od 200 PUVA tretmana, nekontrolisana hipertenzija, bubrežna insuficijencija, maligna bolest (osim nemelanomskog karcinoma kože), preosetljivost na ciklosporin, vakcinacija živim vakcinama, nekontrolisane i hronične infekcije.

Biološka terapija

U protekle dve decenije lečenje psorijaze razvilo se u pravcu biološke terapije, u kojoj se primenom inhibitora citokina i molekula koji blokiraju pojedine signalne puteve postiže modifikacija imunoodgovora i kaskade inflamacije, a time i terapijski efekat.

Biološki lekovi u psorijazi mogu se podeliti u dve grupe: molekule koji se vezuju za aktivacione molekule T-limfocita i inhibitore citokina, i to faktora nekroze tumora-a (engl. TNF-a) i interleukina-12. Njihovi nazivi formiraju se na osnovu tehnologije kojom su proizvedeni: monoklonska antitela imaju nastavak *-mab*, a fuzioni proteini nastavak – *cept*.

Pre uvođenja biološke terapije neophodno je uzeti detaljnu anamnezu i uraditi klinički pregled, laboratorijske analize (kompletna krvna slika, biohemija, hepatogram, analiza urina, skrining za hepatitis B, hepatitic C i HIV), skrining za tuberkulozu (radiografija pluća i srca, *Quantiferon TB test*) (5, 21, 22).

U Evropi se najčešće primenjuju kao druga linija terapije kod pacijenata kod kojih fototerapija i klasična sistemska terapija nisu bile efikasne, ali se primenjuju i kao prva linija terapije ukoliko je fototerapija nedostupna a postoje kontraindikacije za primenu klasične sistemske terapije ili je ona ispoljila neželjene efekte. Pojedini lekovi prilagođeni su za primenu od samih pacijenata, pa su pogodni i kod pacijenta koji su mladi, planiraju porodicu, imaju veliki broj obaveza i kod kojih fototerapija nije izvodljiva zbog načina života, a klasična sistemska terapija je kontraindikovana zbog planiranja porodice i komorbiditeta.

Kontraindikacije za primenu biološke terapije su: aktivne teške infekcije (sepsa, aktivna tuberkuloza, hepatitis B i C), kardiomiopatija klase III ili IV, demijelinizirajuće bolesti CNS-a (pacijenti sa multiplom sklerozom ili rođaci prvog stepena pacijenata sa multiplom sklerozom), malignitet (podatak o ranijem ili trenutno dijagnostikovanom i lečenom malignitetu, osim bazocelularnog karcinoma), teška insuficijencija jetre, skorašnja vakcinacija živom vakcinom (5, 21, 22).

Etanercept je rekombinantni receptor za TNF-a, fuzionisan Fc delom IgG1 molekula koji se vezuje za solubilni i membranski TNF-a. U psorijazi se najčešće primenjuje kao monoterapija u dozi od 50 mg supkutano dvaput nedeljno tokom 12 nedelja i nakon toga 50 mg jedanput nedeljno, kontinuirano. Primenom ovih doza posle 12 nedelja postiže se PASI-75 odgovor kod 49% pacijenata, a sa nastavkom lečenja u istoj dozi PASI-75 postiže se kod 59% pacijenata u 24. nedelji terapije (23). Kod nekih pacijenata efikasnost se gubi sa smanjenjem doze na 50 mg jedanput nedeljno. Kod malog broja pacijenata efikasnost se smanjuje tokom višemesečne primene, najverovatnije zbog stvaranja antitela na etanercept. Etanercept je primenjivan i kod grupe dece od 4 do 17 godina, a posle 12 nedelja terapije zabeležen je PASI-75 odgovor kod 57% pacijenata. *Rebound* fenomen nije zabeležen posle prekida terapije etanerceptom. Jedini česti neželjeni efekat je blaga reakcija praćena svrabom na mestu supkutane primene, najčešće u prve dve do tri nedelje terapije. Injekcije koje treba da primenjuju sami pacijenti sadrže lateks, te su kontraindikovane kod osoba sa alergijom na lateks. Kontraindikacija za primenu etanercepta je sepsa i druge aktivne infekcije, gde je potrebno odložiti terapiju do njihovog saniranja.

Infliksimab je himerno antitelo prema TNF-a molekulu sastavljeno od humanog konstantnog regiona IgG1-a i mišjeg varijabilnog regiona, koje se vezuje i za solubilni i za membranski TNF-a. U lečenju psorijaze primenjuje se intravenski u dozi od 5 mg/kg TT tokom 2-3 sata, uz prethodnu premedikaciju antihistaminikom i sistemskim kortikosteroidom (24). Infuzije se ponavljaju posle dve i šest nedelja od prve infuzije, a zatim svakih 6–8 nedelja kontinuirano. U ovoj dozi infliksimab dovodi do PASI-75 odgovora kod 80% pacijenata posle tri infuzije leka, u desetoj nedelji terapije, čime se svrstava u biološke lekove sa najbržim efektom. Kontinuirana primena infliksimaba svakih 6–8 nedelja bolja je opcija u odnosu na ponavljane cikluse lečenja u periodima pogoršanja, zbog smanjene incidencije stvaranja

antitela na infliksimab i gubitka efikasnosti, te je prema jednoj studiji u šezdesetoj nedelji terapije 60% pacijenata zadržalo PASI-75 odgovor (24, 25). Neki eksperti kombinuju infliksimab sa niskim dozama metotreksata radi sprečavanja nastanka antitela.

Adalimumab je humano monoklonsko antitelo na TNF-a, koje se takođe vezuje i za membranski i za solubilni TNF-a. U psorijazi se primenjuje u dozi od 80 mg supkutano prve nedelje, potom 40 mg nedelju dana kasnije, a potom 40 mg svake dve nedelje, uz postizanje PASI-75 odgovora kod 71% pacijenata posle 16 nedelja terapije, dok je u drugoj studiji PASI-75 postignut kod 79%, a PASI-90 kod 51,9% pacijenata (21). U ovoj poslednjoj studiji efikasnost je poređena sa metotreksatom u rastućim dozama (7,5–25 mg), koji je posle 16 nedelja terapije postigao PASI-75 kod 35,5%, a PASI-90 kod 13,6% pacijenata (26). Posle prestanka terapije nije zabeležen *rebound* fenomen, ali je kontinuirana primena delotvornija, imajući u vidu gubitak efikasnosti posle prekida i ponovnog uvođenja adalimumaba u terapiju.

Golimumab je TNF-inhibitor, registrovan u SAD 2009. godine za lečenje psorijaznog artritisa, ali do sada nije registrovan u Evropi. On predstavlja humano IgG1 monoklonsko antitelo sa visokim afinitetom za TNF-a. Njegova efikasnost procenjivana je u fazi III studija, gde je primenjivan u dozama od 50 mg i 100 mg supkutano jednom mesečno, tokom 20 nedelja. Zabeleženi PASI-75 odgovor posle 14 nedelja bio je 40% (sa 50 mg) i 58% (sa 100 mg), a profil neželjenih efekata sličan je drugim TNF antagonistima (21).

Ustekinumab je rekombinantno humano IgG1k antitelo koje se vezuje za p40 subjedinicu IL-12/IL-23 molekula. Vezivanjem ovog antitela sprečava se vezivanje IL-12 za njegov receptor na NK-ćelijama i T-ćelijama, a time i aktivacija i proliferacija T-ćelija u pravcu Th1 i Th17 subpopulacije regulatornih T-limfocita, koje su ključne u patogenezi psorijaze. Ustekinumab je od 2009. godine registrovan u Evropi za primenu u srednje teškoj i teškoj psorijazi koja nije reagovala na klasičnu sistemsku terapiju (fototerapija, metotreksat, retinoidi, ciklosporin), ili postoje kontraindikacije ili neželjeni efekti zbog kojih se ona ne može primeniti. U dozi od 45 mg (ili 90 mg kod pacijenata težih od 100 kg) jednom mesečno dva meseca, potom svakih 12 nedelja, ustekinumab dovodi do PASI 75 odgovora kod 67% pacijenata, a veća doza od 90 mg nije bila značajno efikasnija kod pacijenata sa težinom manjom od 100 kg, ali je bila efikasnija u većoj dozi kod onih sa težinom većom od 100 kg (27, 28).

Secukinumab je rekombinantno, visoko afinitetno, potpuno humano monoklonsko IgG1κ antitelo koje se selektivno vezuje i neutrališe IL-17A. Primenjuje se u dozi od 300 mg jednom nedeljno tokom prve 4 nedelje, a potom se lečenje nastavlja sa 300 mg jednom mesečno. Zabeleženi PASI-75 odgovor u kliničkim studijama posle 12 nedelja bio je 81,6% i 77,1% (sa 300 mg) i 71,6% i 67% (sa 150 mg) (29). Anti-secukinumab antitela detektovana su u veoma malom procentu (0,3-0,4%) i nisu uticala na smanjenje efikasnosti terapije ili nastanak neželjenih efekata. Najčešći neželjeni efekti bili su nazofaringitis, glavobolja i infekcije gornjeg respiratornog trakta. U studiji u kojoj je poređena efikasnost secukinumaba i ustekinumaba, posle 52. nedelje PASI-90 imalo je 76% pacijenata koji su primali secukinumab i 61% ustekinumab, dok je PASI-100 postiglo 46% pacijenata sa sekukinumabom i 36% sa ustekinumabom (30).

Iksekizumab je anti IL-17A monoklonsko IgG4 antitelo sa visokim afinitetom vezivanja za IL-17A, jednim od glavnih citokina u patogenezi psorijaze. Primenjuje se supkutano, u početnoj dozi od 160 mg, zatim 2−12. nedelje 80 mg svake druge nedelje i potom 80 mg svake četvrte nedelje. U do sada publikovanim studijama, PASI-75 odgovor posle 12. nedelje terapije imalo je 81,8% odnosno 98,7% pacijenata sa hroničnom plak- psorijazom (31, 32). Nejčešći neželjeni efekti bili su nazofaringitis, infekcija kandidom i rekacija na mestu aplikacije leka.

Apremilast je oralni, inhibitor fosfodiesteraze-4 (PDE4) koji je odobren za lečenje psorijaze i psorijaznog artritisa. U Evropskoj uniji, apremilast je indikovan za lečenje starijih pacijenata sa srednje teškom i teškom plak-psorijazom, koji nisu odgovorili na druge vidove sistemske terapije, ili je nisu dobro tolerisali ili je bila kontraindikovana. Kliničke studije pokazale su da je PASI-75 odgovor imalo 33,1% pacijenata posle 16. nedelje (33). U lečenju psorijaznog artritisa, može se primeniti kao monoterapija ili u kombinaciji sa drugim sistemskim lekovima.

Raznolika klinička slika, brojne kliničke studije i veliki broj istraživanja patogeneze psorijaze

otkrivaju da psorijaza nije jedna bolest, već da predstavlja grupu bolesti u okviru koje postoji više podtipova sa različitim fenotipom i genotipom, te različitim odgovorom na određene terapijske opcije. Budućnost terapije psorijaze, i u širem smislu budućnost dermatologije, pripada personalizovanom pristupu pacijentu, koji uključuje određivanje podtipa psorijaze, genotipa pacijenta, prisutne komorbiditete, psihološke i socijalne faktore okoline i integrativni prisutup lečenju koji uzima u obzir sve ove faktore u cilju visokoefikasnog, a bezbednog lečenja – možda i trajnog izlečenja bolesti u budućnosti. Ovaj vodič doprineće boljem i sistematičnijem lečenju pacijenata obolelih od psorijaze u Srbiji, a u skladu sa važećim preporukama Evropskog i Američkog udruženja dermatologa.

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Serological Tests for Acquired Syphilis in Immuno-competent Patients

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Abstract

Serological tests represent a valuable tool for the diagnosis and monitoring the syphilis treatment. Non-treponemal antibodies are nonspecific to detect the infection, but antibody titers are used to monitor the effects of syphilis treatment. A definitive diagnosis of syphilis is made using treponemal tests, because they detect specific antibodies to the treponemal strains or treponemal fragments, which cause syphilis. These tests may remain reactive for years, sometimes for life, regardless of the therapy outcome. Even after successful treatment, approximately 85% of patients remain positive for treponemal antibodies for the rest of their lives. However, treponemal tests cannot differentiate past infections from a current infection. Therefore, we use a combination of specific and non-specific tests, the two most frequently used diagnostic algorithms. The traditional algorithm begins with a non-treponemal assay, and if it is positive, the treponemal test is done. A positive treponemal test indicates syphilis. The reverse serology algorithm detects early, primary, and treated syphilis that may be missed with traditional screening. However, non-treponemal test is necessary to detect patients with active syphilis.

Key words

Syphilis; Syphilis Serodiagnosis; Serologic Tests; Treponema pallidum; Algorithms; Immunocompetence; Review

In the absence of microbiological diagnosis, serological antibody tests are the mainstay of laboratory diagnosis for all stages of syphilis other than primary. The diagnosis of syphilis is not simple due to the fact that there is no single serological test to diagnose syphilis or monitor the effects of treatment. Treponema pathogenic for humans has the same antigens and a high degree of concordance of DNA, complicating the interpretation of serological tests in geographic areas with endemic treponematoses. The clinical presentation of acquired syphilis is so varied, that definitive diagnosis is made only by serological testing. Serological tests are divided into two groups: non-treponemal and treponemal tests.

Non-treponemal tests

Non-specific serological tests detect IgM and IgG antibodies (anticardiolipin antibodies) which react with cardiolipin, lecithin and cholesterol from treponema, but also with the same lipid material from damaged host cells. Therefore, these antibodies are not specific to confirm Treponema pallidum infection, but they indicate a tissue damage caused by the infection. Today, the most commonly used non-treponemal tests are the following:

VDRL (*Venereal Disease Research Laboratory*) – flocculation test. Inactivated serum or cerebrospinal fluid, without a complement, given the blurring ("floc") if it is added an antigen (cardiolipin). Examine under a microscope.

RPR (*Rapid Plasma Reagin*) – a variant of VDRL test with colored substances for macroscopic reading. It is used when quick view of a large number of sera is necessary. Both of these tests use cardiolipin, a phospholipid, combined with lecithin and cholesterol, as the active antigen for the detection of antibodies suggestive of syphilis (1).

These tests are done manually. They are not automated, so the interpretation of results is subjective. Non-specific antibodies appear about 6 weeks after the infection (2, 3). During the primary stage, these antibodies have low titers (≤1: 4) and they are present in 40% of infected subjects, while in the secondary stage low antibody titers are present in only 11% of patients (4). The highest antibody titer is seen in the secondary stages of syphilis, from 1:16 to 1: 256, and declines thereafter, typically falling to 1:4 or lower in untreated late-latent infection. The advantage of these tests is that they are quick and cheap. The antibody titers mostly correlate with the disease activity. The results should be reported quantitatively, and as such they are used to monitor disease activity and efficacy of treatment. Therefore it is necessary to determine the antibody titer (quantitative VDRL/RPR) on the day of treatment initiation. After healing, the antibody titers are reduced or completely absent. Quantitative non-treponemal testing can also be used to determine if a patient, who appears to have failed treatment, has been re-infected or is "serofast". Serofast patients fail to fully resolve serologically and perpetually exhibit low non-treponemal titers, whereas re-infected patients have persistently higher antibody titers (5). The VDRL and RPR are equally valid assays, but quantitative results from the two tests cannot be compared directly because RPR titers are commonly slightly higher than VDRL titers.

The limitation of these tests is frequent occurrence of false positive or false negative reactions. False positive reactions may be acute (lasting for 6 months) and chronic (lasting longer than 6 months) and account for 20% of tests. Acute false positive reactions may be seen in the post-immunization period, after recent myocardial infarction and in many febrile infectious diseases (e.g. malaria, hepatitis, chicken pox, measles, etc.), and possibly during pregnancy. Chronic false positive reactions may be seen in injecting drug users, autoimmune diseases, HIV infection, chronic infections such as leprosy, malignancies, chronic liver disease and older age. Also, false positive reactions are due to connective tissue disorders, and Lyme disease. False negative results are obtained in too early or too late stage of infection, when the antibody titers are low, or in the secondary stage of syphilis, with high antibody titers and there is no agglutination – the so-called prozone phenomenon, which occurs in 1 - 2% of patients, usually in pregnant women and HIV infected patients (2, 6, 7, 8).

Generally, up to 90% of false-positive reactions have a titer of less than 1:8, and reactive non-treponemal tests with titers less than 1:8 and subsequent nonreactive treponemal tests are considered to be biological false-positive reactions (2).

Treponemal tests

The treponemal tests are used for definitive diagnosis of syphilis because they detect specific antibodies (antiterponemal antibodies) utilizing either whole cells or antigens derived from cells of *T. pallidum* causinge syphilis. Specific tests become reactive before nonspecific, but unlike them, they remain reactive for years, sometimes for life, regardless of therapy outcome. Even after successful therapy, approximately 85% of patients remain positive for treponemal antibodies – for life (9). However, 15 - 25% of patients treated during the primary stage revert to being serologically nonreactive after 2 - 3 years (10). Therefore, treponemal tests are not used to monitor disease activity, as well as to distinguish active from treated syphilis. The most commonly used specific tests are:

TPHA (*Treponema pallidum Hemagglutination Assay*) is a hemagglutination test often used in laboratories. It detects the presence of specific antibodies in the serum of patients with sensitized sheep erythrocyte agglutination. The test is easy to perform, quick and cost-effective, but it is automatic and subject to individual variations in interpretation.

TPPA (*Treponema pallidum Particle Agglutination Assay*) is an agglutination test which utilizes gel particles that are sensitized with *T. pallidum* antigens. If an antigen/antibody reaction occurs, a smooth mat of agglutinated gel particles is well seen in a microtiter tray; if antibody is not present there is no agglutination. The TPPA test is less expensive and

less complicated than the FTA-ABS tests. The results are read with the unaided eye. It is one of the most commonly used treponemal tests.

FTA-ABS test (*Fluorescent Treponemal Antibody Absorption Test*) is a fluorescence test used to detect specific antibodies in serum by indirect immunofluorescence.

FTA-ABS test includes an absorption step to increase specificity by removing antibodies directed to nonpathogenic treponema that occur as part of the normal bacterial flora. The resulting antigen/antibody reaction is visualized. The results are graded based on the intensity of the fluorescence. The test has a high sensitivity. It is manual, expensive, and fluorescence interpretation is complex, requires good training, and it is rarely used routinely. A modification of this test is used for the detection only of IgM antibodies (19S IgM FTA-ABS) in the diagnosis of congenital syphilis, because these antibodies do not cross from the mother to the fetus.

EIA (*Enzyme Immunoassay*) is an enzyme immunoassay and a representative of a new generation of reliable and rapid tests for the detection of specific IgG and IgM antibodies.

It is efficient in testing a large number od specimens. Now, it is widely available and increasingly used for screening. The test is automated, but expensive. EIA tests are very sensitive in the detection of primary and secondary syphilis with the IgM EIA being the first test positive in some instances (11). In suspected primary syphilis a IgM should be requested, since these antibodies can be detected at the end of the second week after infection, while IgG antibodies are detected 4 - 5 weeks after infection.

EIA tests have been shown to be equal to or better than FTA-ABS and TPPA tests in overall sensitivity and specificity and are more useful in HIV coinfected individuals (12). There are several versions of immunoassays, depending on the method of detection, such as chemiluminescent immunoassays (CIA), and microbead immunoassays (MIA). These immunoassays may detect IgG, IgM or both IgG and IgM antibodies, are produced against *Treponema pallidum* (13).

IgM immunoblot is another sensitive metod to detect congenital syphilis.

TPI test (*Treponema pallidum Immobilization Test*) is the most reliable test, but it is difficult to perform and today, in the era of fluorescence, this test is rarely applied. To perform this test, live strain of treponema is required. It is based on the fact that serum or cerebrospinal fluid of affected individuals contains immobilizsed specific antibodies. In contact with the immobilizer, live treponema is immobilized. We should not forget that the specific cause of syphilis is associated with movement, and not just a single appearance.

Treponemal assays detect primary infection at a slightly earlier stage than non-treponemal assays (14). Approximately 4 weeks after infection, TPHA and FTA-ABS tests become reactive, and TPI is the last to become positive, even months later.

Before the appearance of chancre and in the first 5 to 15 days, all tests (treponemal and non-treponemal) are negative. Specific tests are rarely false positive, and the reasons may be: HIV infection, bacterial infections, autoimmune disorders, hypergammaglobulinemia and pregnancy (2, 15). In more and more countries, point-of-care (POC) rapid diagnostic tests are available for the detection of antitreponemal antibodies (16). They are used for testing certain populations with high prevalence, where immediate diagnosis and treatment is the overriding concern due to a likely lack of follow-up care. Their advantage and significance may be in the strategy for global elimination of congenital syphilis and mother-to-child-transmission of both syphilis and HIV, because they permit screening and treatment at the same visit, at field level or peripheral clinics remote from laboratories (8).

Serological diagnostic criteria for syphilis

In screening, if only treponemal serological tests are used, they identify persons with previous successful treatment of syphilis, as well as persons with untreated syphilis. Treponemal tests cannot differentiate earlier infection from current infection. Therefore, a combination of specific and non-specific tests is recommended. If the screening starts with a specific serological test (e.g. EIA), then it is necessary to do a new specific test to confirm (e.g. TPHA) the diagnosis of syphilis. If both tests are positive, then a quantitative non-specific test is necessary (VDRL or RPR) (6).

If the confirmatory treponemal test is positive and non-treponemal test is negative, in patients with

suspicion of early syphilis, an EIA-IgM test may be used (8). However, the development of IgM and its persistence after the early latent stage of syphilis is not well understood. Further research is needed before IgM assays can be recommended for routine use in adult testing (17).

If the screening starts with an unspecific serological test, then its positive quantitative findings need to be confirmed by a specific test. If the primary screening consists of both nonspecific and specific tests, it is necessary to quantify the titer of the non-specific test, especially if the ‑specific test is positive (14). A finding of a non-specific test (VDRL or RPR) with a titer greater than 1:16, and/or IgM positive test, generally indicates active syphilis and it has to be treated, although serology must be interpreted in the light of the treatment history and clinical findings. The VDRL/RPR and EIA-IgM are often negative in late syphilis, but this does not exclude the need for treatment (15).

Traditional diagnostic algorithm

The traditional diagnostic algorithm begins with a non-specific test (VDRL or RPR). If it is positive, a specific test is also necessary (Figure 1). In the past, and in many countries today, the most frequently used specific tests are TPHA or TPPA. Thus, all the tests in this algorithm are manual tests, which is justified for economic reasons. This algorithm is cost-effective for small diagnostic laboratories and hospitals. The results of VDRL or RPR screening may correlate more with the disease activity than the results of the reverse algorithm (18).

However, the traditional algorithm has significant limitations, including the use of a screening assay that lacks specificity, requires manual operation, and is subjective (19).

This algorithm does not reveal all subjects with syphilis, which is seen in a study conducted in four laboratories in New York in 2005 and 2006. A total of 116.822 results were reviewed, of which 6.587 (6%) were reactive to a treponemal screening test (EIA). Among the 6.587 EIA-reactive samples, 3.664 (56.7%) were found to be nonreactive by RPR. Of the 3.664 discordant sera, a subset (2.512) were tested by TPPA or FTA, of which 433 (17.2%) were nonreactive, suggesting false-positive EIA screening results (20). The conclusion of this study was that

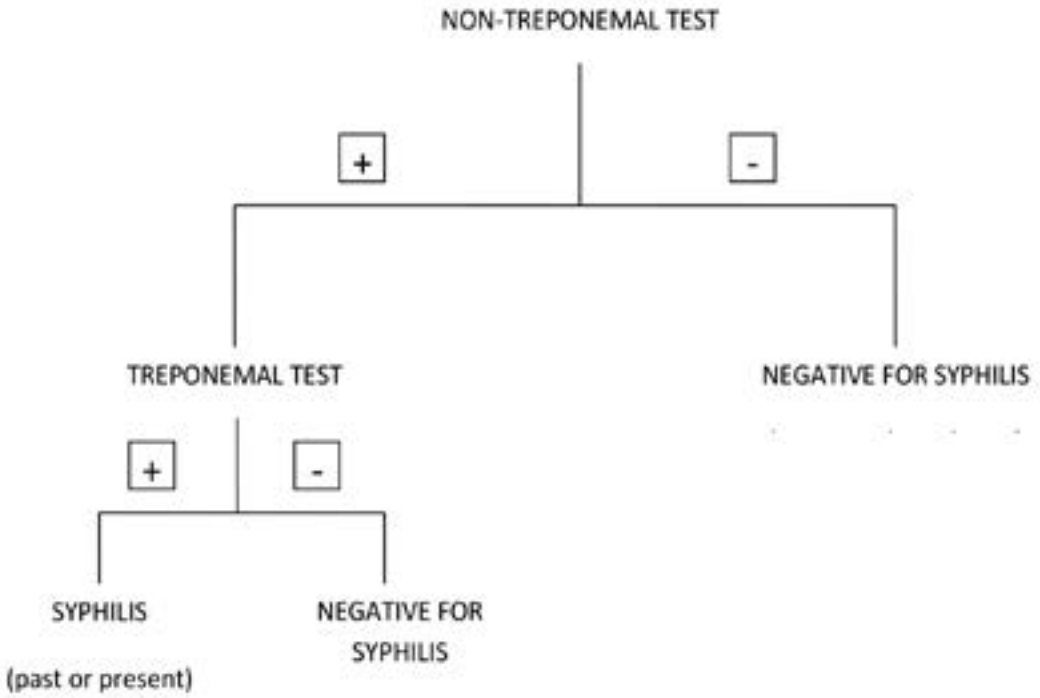

Figure 1. Traditional syphilis serology testing algorithm

3.664 patients identified by screening, would not have been detected by the traditional algorithm.

In another study, among 24.124 tested samples, there were 2.756 reactive to TPPA. The results of non-treponemal tests in these patients showed that 667 of 2.756 (24.2 %) samples were RPR nonreactive (21).

For subjects at a certain stage of the disease the traditional algorithm does not provide diagnostic reliability.

The traditional algorithm, approach could be missing some untreated cases, especially patients at the late latent stage of the disease where seroreactivity to non-treponemal tests declines (1).

Across different studies and demographic populations (including HIV patients), up to 40% of untreated late latent cases were found to be nonreactive to non-treponemal assays. The potential for false-negative results in early primary syphilis or in late latent syphilis may be greater when using a non-treponemal assay for initial screening (7).

Using the clinical diagnostic results as the gold standard, the sensitivity of the traditional algorithm was only 75.81%. The negative likelihood ratio was 0.24 (>0.1), indicating a high probability of false-negative results (21).

Reverse diagnostic algorithm

The increasing availability of commercial and automated treponemal tests, as well as the shortcomings observed in the traditional algorithm, imposed the need for creating a new diagnostic algorithm.

The reverse diagnostic algorithm starts with modern treponemal tests, and then it is followed by a non-treponemal test (Figure 2). In reverse diagnostic algorithm, sera are examined with automated methods (e.g. EIA) that can be linked to the information system in the laboratory, which reduces the possibility of errors when manually entering results. The new algorithm increases the number of people detected in the primary stage and in late syphilis, because in these stages of the disease treponemal tests have greater sensitivity and specificity than non-treponemal tests. The disadvantages of the new diagnostic algorithm are: EIA cannot differentiate an active disease from a case with cured syphilis (which in practice leads to unnecessary re-treatment), the results show more false-positives results than the traditional algorithm, the traditional algorithm tests (VDRL/RPR) are easier to perform, cheaper, do not require expensive laboratory equipment and a large number of samples (rapid screening) can be examined in a short time (19).

In order to avoid discrepancies, it is recommended that sera testing reactive by EIA, but nonreactive by RPR, should be tested by another treponemal test (TPPA), which serves as confirmatory treponemal assay, which is particularly important in a population with a low prevalence in order to avoid false positive diagnosis of syphilis (22).

Treponemal evaluation tests, used in reverse algorithm, are automated immunoassays and the microplate enzyme immunoassays are suitable for first screening, whilst the TPPA particle agglutination is more adaptive to be used as a second, confirmatory treponemal assay (23).

The reverse algorithm still has a high diagnostic significance in early syphilis, as well as in late syphilis in high-prevalence population (with a syphilis rate of 11.40%) (21).

To improve the diagnosis of the primary stage syphilis, we should expect more frequent use of real-time PCR for the detection of *T. pallidum*.

The PCR assay demonstrated a sensitivity and specificity of 87.0% and 93.1%, respectively, compared to dark-field microscopy in patients with suspected primary syphilis. However, the PCR assay showed only 43.0% sensitivity in patients with suspected secondary syphilis, so its application after the primary stage of syphilis would not have advantages over the standard serological methods (24). The next step in improving the diagnosis of syphilis will be introduction of POC tests, that can accurately identify and differentiate patients with treated versus untreated syphilis. A promising POC device described by Castro et al. uses immunofiltration to detect and differentiate treponemal and nontreponemal antibodies in the same test. Results are available in 2 – 10 min, with reported sensitivities and specificities of at least 96.0 and 97.0%, respectively (25).

Monitoring the effects of treatment

The monitoring of the effects of syphilis treatment includes identification of the titer by a non-specific test on the first day of treatment, to provide a baseline for measuring a decrease in antibody titers. Sera

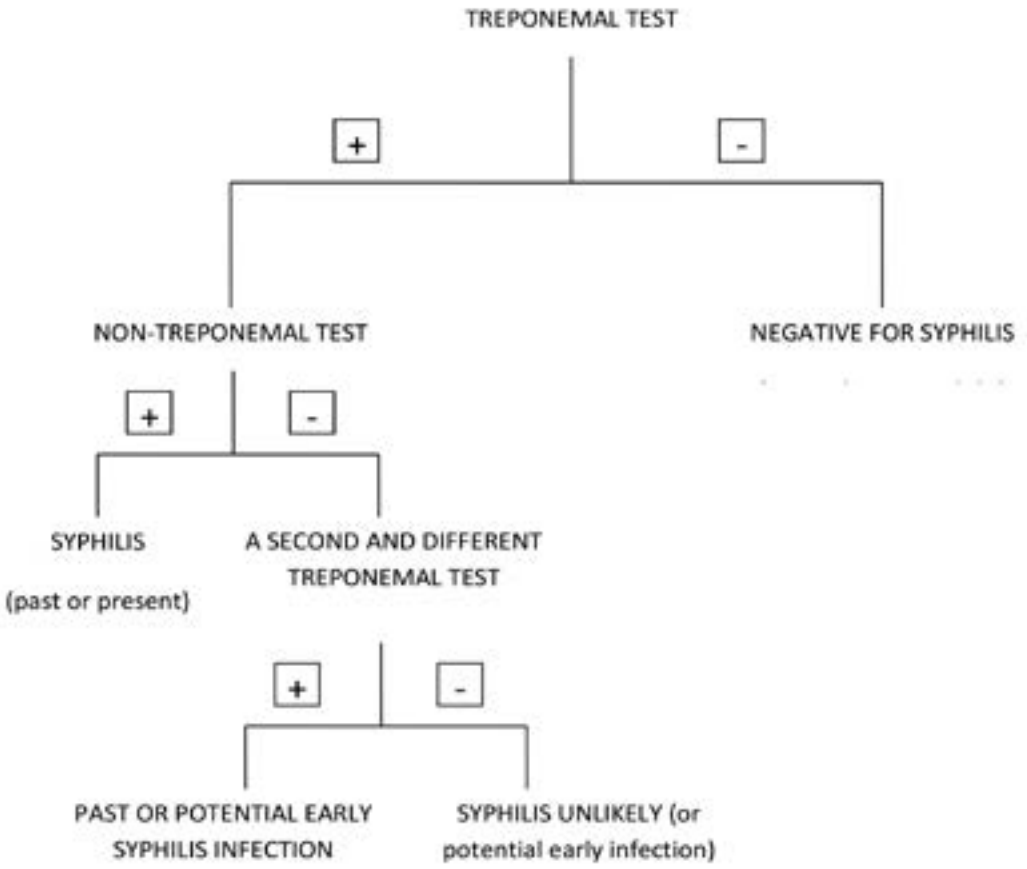

Figure 2. Reverse syphilis serology testing algorithm

should be obtained at 1 month, 3 months and every 6 months subsequently, ideally the identical non-treponema test should be used and all samples tested in the same laboratory. This should be continued until the non-treponemal test becomes negative, attains a low plateau (≤1:4, sustained for 1 year and in the absence of ongoing risk) (8).

Adequate treatment is demonstrated by a 4-fold drop in titer by non-treponemal assay within 3 to 6 months. However, the serologic response following successful treatment of syphilis infection remains unclear. Some individuals may have increasing titers or be serofast, where appropriate treatment causes little or no change in titer (18).

Typically, the non-treponemal antibody titer declines by a 4-fold after three months (eg, from 1:32 to 1:8) and by 8-fold after six months (eg, from 1:32 to 1:4) with standard therapy. The time for decline in antibody titer may be longer with the RPR test than with the VDRL test (26). However, there is evidence that 15% of treated patients with early syphilis will not show a 4-fold decline in titer at one year post-treatment (27).

After successful treatment, the RPR and VDRL tests usually become nonreactive after one year in patients with primary syphilis, after two years in patients with secondary syphilis, and after five years in latent syphilis (28).

Some experts define treatment failure as a 4-fold or greater increase in the non-treponemal test titer or a recurrence of signs or symptoms (29).

Some authors also consider the persistence of RPR/VDRL titers at or over 1:64 as a serologic treatment failure (30).

Interpretation of serological tests in cerebrospinal fluid for neurosyphilis

Neurosyphilis cannot be diagnosed serologically, and diagnosis must be based on the clinical judgment. Cerebrospinal fluid (CSF) assessment is not indicated in early syphilis (HIV positive or negative), unless there are neurological, ocular or auricular symptoms. Indications for cerebrospinal fluid testing are: clinical evidence of neurological, ocular and auricular involvement, regardless of the stage of the disease, and in tertiary syphilis (cardiovascular, gummatous). Although robust data are lacking, CSF control may be indicated also in asymptomatic patients in the following situations for exclusion of asymptomatic neurosyphilis: in HIV positive patients with late syphilis and CD4+ cells ≤350/mm^3 and/or a serum VDRL/RPR titer ≥1:32; in case of serological failure; in case of use of alternative treatment (tetracyclines) during late syphilis (8).

Accurate interpretation of serological findings means that the CSF must not be macroscopically contaminated with blood. In the majority of patients with symptomatic neurosyphilis more than 5 leukocytes/mm^3 are found. The level of proteins may not be elevated in neurosyphilis. It is always necessary to quantitatively determine the positivity of serological tests in CSF.

The sensitivity of VDRL/RPR test in the CSF ranges from 10% in asymptomatic patients, and 90% in symptomatic patients, which means that a negative VDRL/RPR test does not rule out neurosyphilis (31). A negative treponemal test (TPPA/TPHA) on CSF excludes neurosyphilis, and a positive test is highly sensitive for neurosyphilis but lacks specificity, because the reactivity may be caused by transudation of immunoglobulins from the serum into the CSF or by leakage through a damaged blood brain barrier resulting from conditions other than syphilis. Because of that, positive CSF TPHA/TPPA does not confirm the diagnosis of neurosyphilis.

Neurosyphilis is unlikely when the CSF TPHA titer is < 320 or the TPPA titer <640 (15).

Establishing the so-called TPHA index (CSF TPHA/albumin quotient [CSF albumin x109/serum albumin]) can help establishing the final diagnosis. A TPHA index >70 and a CSF TPHA titer >320 are the most reliable in supporting the diagnosis of neurosyphilis, but unfortunately determination of the TPHA index is not widely available (32). In case of an abnormal CSF examination (high protein level and/or hypercytosis), repeat CSF examination must be performed after treatment (6 weeks to 6 months) (8).

Diagnosis of cardiovascular syphilis

Every patient with aortic insufficiency or thoracic aortic aneurysm should be screened for syphilis (8). Positive serologic tests combined with typical clinical changes found in cardiovascular syphilis are indispensable diagnostic indicators of cardiovascular syphilis. Patients with suspected cardiovascular syphilis need to be assessed by a cardiologist.

Conclusion

Given that each algorithm for serological diagnosis of syphilis has some minor or major deficiencies, rapid tests based on PCR technology should be developed. They should aid in differentiation of untreated from treated syphilis, and improve diagnosis to distinguish specific and non-specific antibodies in a single assay.

Abbreviations

VDRL - Venereal Disease Research Laboratory
RPR - Rapid Plasma Reagin
HIV - Human Immunodeficiency Virus
TPHA - Treponema pallidum Hemagglutination Assay
TPPA - Treponema pallidum Particle Agglutination Assay
FTA-ABS test - Fluorescent Treponemal Antibody Absorption Test
EIA - Enzyme Immunoassay
TPI - Treponema pallidum Immobilization
POC - Point-of-Care
PCR - Polymerase Chain Reaction
CSF – Cerebrospinal fluid

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Pregled seroloških testova na stečeni sifilis kod imunokompetentnih osoba

Sažetak

U nedostatku rutinske mikrobiološke dijagnoze, serološki testovi predstavljaju osnovu laboratorijske dijagnostike sifilisa. Nespecifični (netreponemski) testovi se rade manuelno, odnosno nisu automatizovani, pa je interpertacija rezultata subjektivna. Nespecifična antitela javljaju se tokom primarnog stadijuma sifilisa u niskom titru (≤ 1 : 4) kod 40% obolelih, dok je u sekundarnom stadijumu kod samo 11% obolelih prisutan nizak titar nespecifičnih antitela. Specifični (treponemski) testovi postaju reaktivni pre nespecifičnih, ali za razliku od njih ostaju reaktivni godinama, nekad i doživotno, bez obzira na adekvatnu terapiju.

Ukoliko bismo u skriningu koristili samo specifične testove, ne bismo mogli da razlikujemo osobe sa nelečenim sifilisom od osoba sa uspešno lečenim sifilisom. Takođe, specifični testovi ne mogu da razlikuju nekadašnju infekciju od aktuelne infekcije. Zbog toga koristimo kombinaciju specifičnih i nespecifičnih testova.

Tradicionalni dijagnostički algoritam započinjemo nespecifičnim testom (VDRL ili RPR). Ukoliko je on pozitivan, radimo specifičan test (najčešće TPHA ili TPPA). Svi testovi u ovom algoritmu su manuelni testovi što ima opravdanja iz ekonomskih razloga. Međutim zbog određenih manjakovosti ovog algoritma, predložen je reverzni algoritam u kojem se serumi prvo pregledaju automatizovanim metodama (na primer EIA). Preporuka je da se serumi koji su EIA reaktivni, a RPR nereaktivni, testiraju pomoću još jednog treponemskog testa (na primer TPPA) koji služi kao potvrdni, što je naročito bitno u populaciji sa niskom prevalencijom sifilisa kako bi se izbegla lažno pozitivna dijagnoza.

Da bismo pratili efekte lečenja sifilisa, moramo imati titar nespecifičnog testa određen prvog dana lečenja, pre započinjanja terapije. Uspešno sprovedenom terapijom smatra se četvorostruki pad titra nespecifičnih antitela, tri do šest meseci po završetku terapije.

S obzirom na to da svaki algoritam za serološku dijagnostiku sifilisa ima određene manje ili veće nedostatke, treba očekivati razvoj brzih testova baziranih na PCR tehnologiji koji bi mogli da razlikuju lečeni od nelečenog sifilisa, kao i unapređenje dijagnostike koja bi razlikovala specifična od nespecifičnih antitela u jednom testu.

Ključne reči: Sifilis; Serološka dijagnoza sifilisa; Serološki testovi; Treponema pallidum; Algoritmi; Imunokompetencija; Pregled

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Granuloma Annulare-like Wells Syndrome in a Child - A Case Report

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Abstract

Wells syndrome (WS) is a rare inflammatory skin disease of unknown etiology. Possible triggers for WS include insect bites/stings, infections, medications, malignancies, and vaccination. Most cases have been reported in adults, but WS may also occur in children.

We report a case of idiopathic WS in a 12-year-old boy, who presented with pruritic papulonodular and granuloma annulare-like lesions on his legs. The patient had an excellent response to topical and systemic corticosteroids.

WS may present as plaque, granuloma annulare-like, urticaria-like, papulovesicular, bullous, papulonodular, or fixed drug eruption-like lesions. Erythematous annular lesions are most common in adults, while plaques are mostly found in children. The histopathologic features are dynamic, starting with dermal edema and infiltration of eosinophils, then flame figures develop, and finishing with the appearance of histiocytes and giant cells.

Our patient represents a rare pediatric case with granuloma annulare-like WS syndrome.

Key words

Skin Diseases; Cellulitis; Granuloma Annulare; Signs and Symptoms; Child; Eosinophilia; Diagnosis; Treatment Outcome

Wells syndrome (WS) is a rare inflammatory dermatosis, of unknown etiopathogenesis, first described by George Wells as a "recurrent granulomatous dermatitis with eosinophilia" in 1972. (1). In 1979, Wells and Smith reported eight additional cases and renamed the disease into "eosinophilic cellulitis" (2). Classically, patients present with pruritic cellulitis-like eruptions, and occasionally with papular and nodular lesions (3). The histologic findings include marked eosinophil infiltration and degranulation leading to the formation of flame figures. The flame figures are distinctive, but not pathognomonic for WS (4). The etiology is unknown, but some hypothesize that this syndrome may represent a hypersensitivity reaction to a circulating antigen. Other possible precipitating factors include infections, arthropod bites, hematological disorders, malignancies, drug reactions and recent immunization (5). Most cases have been reported in adults, but it may occur in children as well.

Case report

We present a 12-year-old Caucasian boy, with a 6-month history of erythematous pruritic papules on the legs. He was unsuccessfully treated with oral antihistamines, systemic and topical antibiotics. He did not have any systemic disease or known triggering factors, including insect bites, bacterial, viral, parasitic or fungal infections. Drugs were excluded as the possible cause of the condition. His personal and family history of atopic diseases was negative.

On admission, the boy presented with infiltrated papulonodular lesions and plaques, many of them of annular shape (resembling granuloma

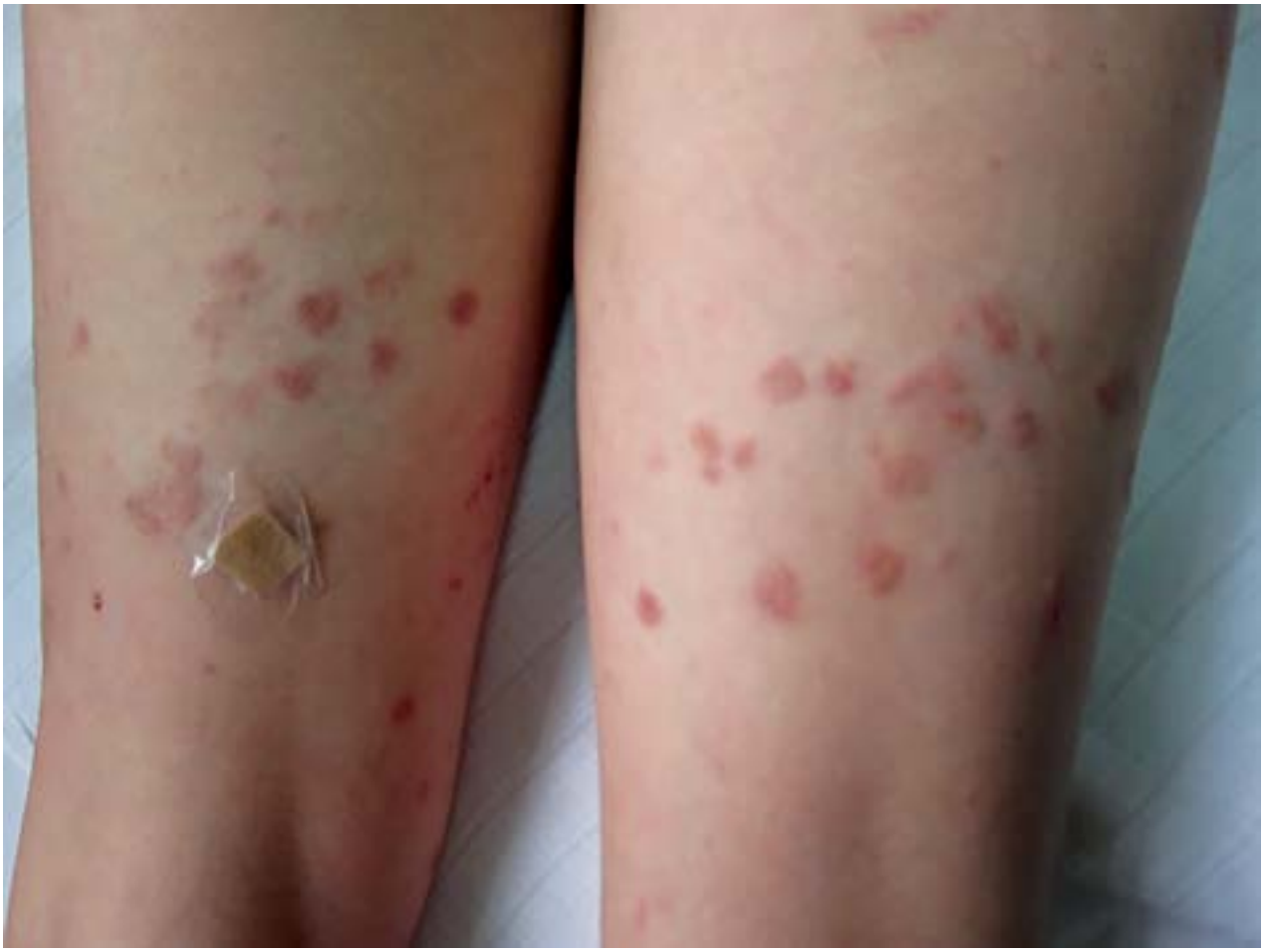

Figure 1. Papulonodular and granuloma annulare-like lesions on the thighs

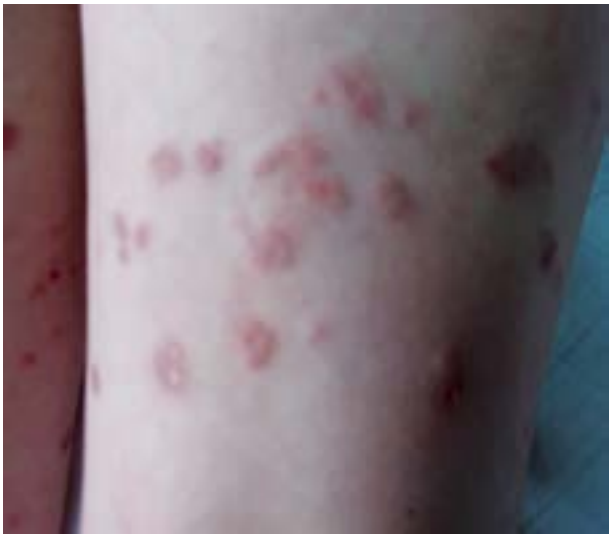

Figure 2. Granuloma annulare-like lesions on the flexor surface of the right thigh

annulare), localized mainly on the flexor surface of his thighs (Figures 1 and 2). The lymph nodes were not enlarged. The eosinophil count was $0.73x10^9$/L (normal 0 - $0.4x10^9$/L). Other laboratory test results (erythrocyte sedimentation rate - ESR, hepatic and renal functions tests, C-reactive protein, anti-streptolysin O, IgE, antinuclear antibodies, urinalysis, and parasitological stool examination) were normal or negative. Ultrasonography of the abdomen and the neck soft tissues, as well as the chest X-ray were normal.

The histopathology of a papulonodular lesions showed an interstitial infiltrate of eosinophils in the superficial dermis (Figure 3) and flame figures, consisting of amorphous eosinophilic deposits of collagen surrounded by a palisade of histiocytes and giant cells in the deep dermis (Figure 4).

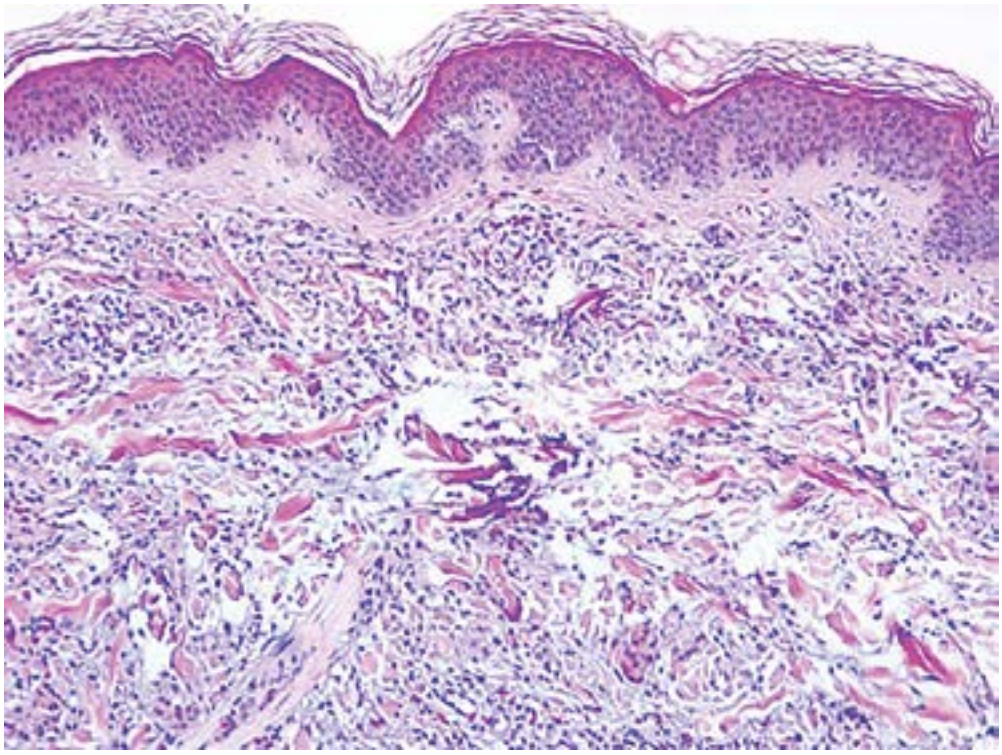

Figure 3. Superficial and deep perivascular and interstitial inflammation composed of eosinophils and lymphocytes, with flame figures throughout the dermis (HE x100).

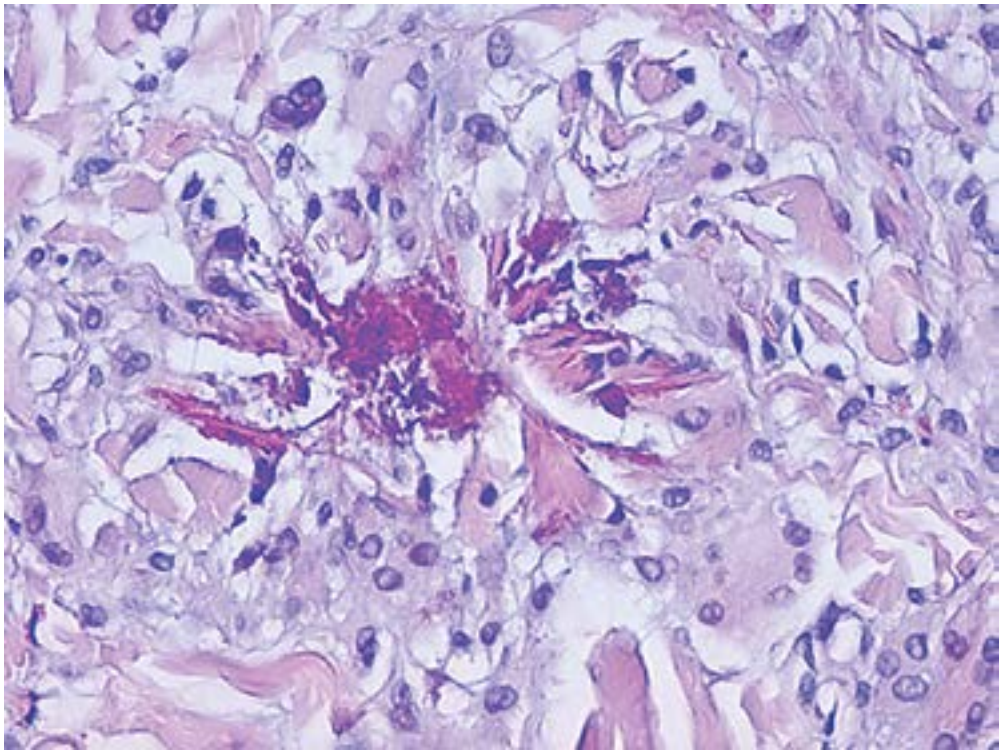

Figure 4. The regression phase of WS: flame figure, numerous histiocytes and multinucleated giant cells (HE x400)

The patient was treated with oral prednisone at 0.5 mg/kg/day with gradual dose tapering over 3 months, in combination with topical corticosteroids for three weeks and then with topical tacrolimus ointment. The therapy resulted in a complete resolution of skin lesions. The peripheral eosinophilia disappeared. There were no signs of recurrence nine months after therapy cessation.

Discussion

The pathogenesis of WS is still unknown. The first hypothesis, proposed by Wells, was that the lesions begin as an urticarial type of reaction that persists when there is an abnormal reaction to eosinophils (1). The second hypothesis was that allergic hypersensitivity may be involved in the pathogenesis: frequently associated urticaria, peripheral eosinophilia, and presence of drug/insect/parasitic triggers pointed to a possible allergic phenomenon (6). Reported precipitanting factors comprise arthropod bites/stings (bees, spiders) (7), cutaneous viral infections (mumps, molluscum contagiosum (8), varicella (9), herpes simplex virus (10)), bacterial, parasitic, and fungal infections (5). Numerous medications have been implicated as WS triggers (antibiotics, anticholinergic agents, anesthetics, non-steroidal anti-inflammatory agents, thiazide diuretics, anti=thyroid drugs, chemotherapeutic agents, thimerosal-containing vaccines and anti-TNF agents) (11, 12, 13). Among adults, several cases of WS have been associated with hematologic disorders, lymphoproliferative malignancies, and carcinomas (5). One case of WS was reported in a 17-year-old girl with nasopharyngeal carcinoma, and this is the only pediatric case of WS associated with malignancy (14). No precipitating factor was found in approximately half of the reported pediatric cases (5, 8).

Wells syndrome is diagnosed by a combination of clinical and histopathological findings (15). WS usually affects adults, but it occurs in children as well. There is no racial or gender predilection (16). Two cases of congenital WS have been described (4). The disease is often sporadic, but some familial cases have been reported (17). WS typically presents as a mildly pruritic or tender cellulitis-like eruption (5). Skin lesions may be single or multiple. WS presenting as a solitary lesion is more common in children than in adults (11). Various forms of WS have been described in the literature: plaque(s), granuloma annulare-like lesions, urticaria-like, papulovesicular, bullous, papulonodular, and fixed-drug eruption-like lesions (11, 18). In a case series of Caputo at al. (18), the classic plaque-type variant proved to be the most common clinical presentation in children but not in adults. In adults, erythematous annular lesions resembling granuloma annulare were most frequently found.

Blood eosinophilia was reported in approximately 50% of cases during the active phase of the disease. ESR was elevated in some patients. Increased IgE was described in several reports (5, 11). Systemic symptoms, such as asthma, arthralgia, fever and lymphadenopathy have been described, and these findings may be indicators of a more severe or progressive course (5).

The histopathological features are dynamic: 1) the acute phase exhibits dermal edema and diffuse dermal infiltration of eosinophils, without signs of vasculitis; 2) the subacute phase is characterized by infiltrate of phagocytic histiocytes together with flame figures where amorphous or granular eosinophilic material adheres to collagen and 3) the regression phase shows gradual disappearance of eosinophils with persistence of histiocytes and appearance of giant cells around collagen deposits, forming microgranulomas (4, 11, 18). Flame figures are characteristic but not pathognomonic for WS. These figures represent a histological cutaneous reaction pattern and may be detected in other inflammatory dermatoses associated with cutaneous eosinophilia such as bullous pemphigoid, herpes gestationis, eczema, prurigo, arthropod bites/stings, scabies and drug eruptions (15, 19). Approximately 50% of patients with WS showed evidence of flame figures (18). In most cases direct immunofluorescence was negative (4).

The differential diagnosis of WS includes bacterial cellulitis, erythema chronicum migrans, erythema annulare centrifugum, arthropod bites/

Table 1. Proposed diagnostic criteria for WS *

Major (2 of 4 required)	Minor (at least 1 required)
1. Diverse clinical picture to include any of the previously reported variants: - Plaque type - Granuloma annulare-like - Urticaria-like - Papulovesicular - Bullous - Papulonodular - Fixed-drug eruption-like	1. Flame figures
2. Relapsing, remitting course	2. Histology: Granulomatous changes
3. No evidence of systemic disease	3. Peripheral eosinophilia not persistent and not greater than >1500/μL
4. Histology: eosinophilic infiltrate, no vasculitis	4. Triggering factor (eg. drug)

* Heelan K et al. J Dermatol Case Rep 2013;7:113-20. [11]

stings, chronic idiopathic urticaria, urticarial vasculitis, Churg-Strauss syndrome, hypereosinophilic syndrome and eosinophilic fasciitis (5, 11, 19).

Heelan et al. (11) proposed diagnostic criteria for WS: four major (two of which need to be present) and four minor criteria (at least one of which needs to be present) (Table 1).

Conclusion

Many WS cases resolve spontaneously, and treatment for WS is sometimes unnecessary. The standard first-line treatment includes systemic corticosteroids, both for adults and children, and most cases seem to respond to oral prednisone. Treatment with topical corticosteroids has been reported, both as monotherapy, and in combination

with systemic corticosteroid therapy (5, 20). Successful treatment outcomes were reported with cyclosporine A, minocycline, colchicine, antimalarials, azathioprine, interferon-α, antihistamines, psoralen with ultraviolet A (19, 20).

In our patient, no precipitating factor was found, and eruptions cleared with systemic and topical corticosteroid therapy. The regressing papules and macules were additionally treated with topical tacrolimus ointment. Our patient's presentation with papulonodular and granuloma annulare-like lesions is a rare clinical variant of WS in children.

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Wells-ov sindrom nalik na granuloma annulare kod deteta – prikaz slučaja

Sažetak

Velsov (*Wells*) sindrom je retka inflamatorna dermatoza nepoznate etiologije. Trigeri mogu biti ujedi/ubodi artropoda, infekcije, lekovi, maligniteti i vakcinacija. U većini slučajeva se dijagnostikuje kod odraslih, ali se može javiti i kod dece.

Prikazujemo slučaj idiopatskog Velsovog sindroma kod dvanaestogodišnjeg dečaka, sa pruriginoznim papulonodularnim i lezijama nalik na *granuloma annulare* lokalizovanim na nogama. Promene su se brzo povlačile na lokalnu i sistemsku kortikosteroidnu

terapiju, bez znakova recidiva.

U literaturi su opisane različite forme Velsovog sindroma u vidu plaka, nalik na *granuloma annulare*, urtikarijalne, papulovezukularne, bulozne, papulonodularne i lezije nalik na *erythema fixum*. Kod odraslih, najčešća klinička prezentacija su eritematozne anularne lezije, a kod dece plak-lezije. Histopatološke karakteristike su dinamične, počinju kao edem i infiltracija derma eozinofilima, potom dolazi do stvaranja „plamenih figura" i završavaju se pojavom histiocita i multinuklearnih džinovskih ćelija.

Kod našeg pacijenta Velsov sindrom se prezentovao u vidu lezija nalik na *granuloma annulare* koja se retko dijagnostikuje u dečjem uzrastu.

Ključne reči

Kožne bolesti; Celulitis; Granuloma Annulare; Znaci i simptomi; Dete; Eozinofilija; Dijagnoza; Ishod terapije

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Dress Syndrome - A Case Report

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Abstract

The drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is an adverse drug-induced reaction that occurs most commonly after exposure to drugs, most frequently anticonvulsants, sulfa derivates, antidepressants, nonsteroidal anti- inflammatory drugs, and antimicrobials. We present a 61-year-old male, with a generalized maculopapular exanthema on the trunk, face, extremities, palms, soles, palate, and fever (38°C). His medical history was notable for generalized epilepsy, treated with carbamazepine during 1 month. The diagnosis of DRESS syndrome was confirmed by specific RegiSCAR criteria. In our case, skin eruptions were successfully treated with oral methylprednisolone, cephalexin, and topical corticosteroid ointment.

In conclusion, although the mechanisms of this syndrome are not completely understood, numerous cases were reported in children and adults. This syndrome should be considered in every patient with skin eruption, fever, eosinophilia, liver and hematological abnormalities. Prompt recognition, supportive therapy and initiation of corticosteroids may prevent systemic manifestations.

Key words

Drug Hypersensitivity Syndrome; Signs and Symptoms; Case Reports; Diagnosis; Treatment Outcome

The drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe adverse drug-induced reaction, that occurs most commonly after exposure to drugs, such as anticonvulsants, sulfa derivates, antidepressants, nonsteroidal anti-inflammatory drugs, and antimicrobials (1, 2). The drugs most frequently reported with DRESS syndrome are anticonvulsants. DRESS syndrome shares many characteristics with anticonvulsant hypersensitivity syndrome (AHS), also referred to as drug-induced hypersensitivity syndrome (DIHS), but it appears to be a variation, rather than a distinctly different syndrome (3).

DRESS syndrome has been found to represent the major cause of hospitalization for dermatologic complications in patients treated with anticonvulsants (4, 5).

The syndrome is characterized by severe skin eruption, fever, lymphadenopathy, hematologic abnormalities (eosinophilia, atypical lymphocytes), and internal organ involvement (liver, kidneys, lungs, heart, or pancreas) (6).

The incidence of DRESS syndrome is between 1 in 1,000 and 1 in 10,000 drug exposures, and it has a mortality rate of 10 - 20% (7). There may be a familial component associated with this condition.

The pathogenesis of DRESS syndrome is not well understood. Different mechanisms have been implicated in its development, and it is hypothesized to consist of a complex interaction between two or more of the following: 1) a genetic deficiency of detoxifying enzymes leading to accumulation of drug metabolites that bind to cell macromolecules causing cell death or inducing secondary immunological

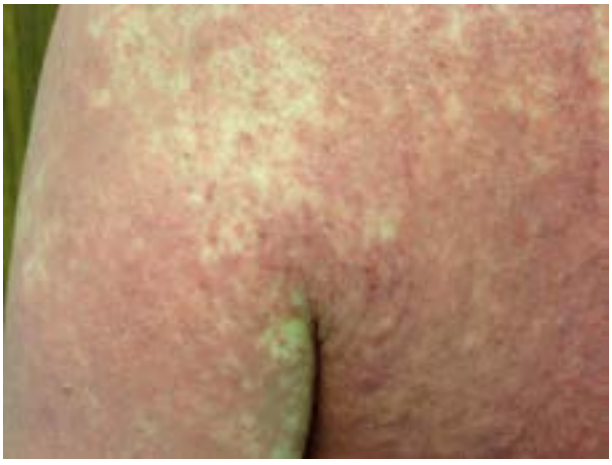

Figure 1. Generalized maculopapular eruption over the back and shoulders

response. Eosinophilic activation as well as activation of the inflammatory cascade may be induced by T-cell releasing IL-5 (9); 2) reactivation of human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7), Epstein-Barr virus (EBV), or cytomegalovirus (CMV) which may trigger a reaction (10), and

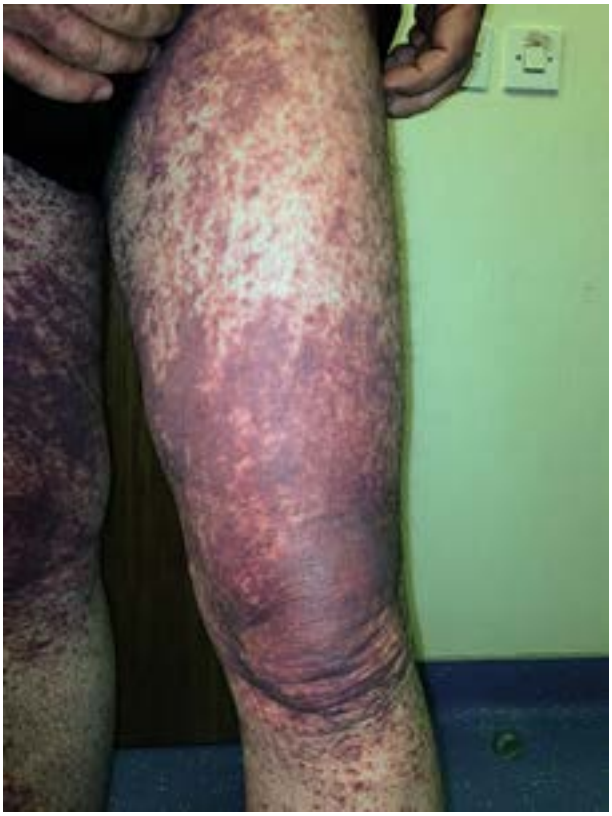

Figure 2. Maculopapular darkly livid erythema on the lower extremities

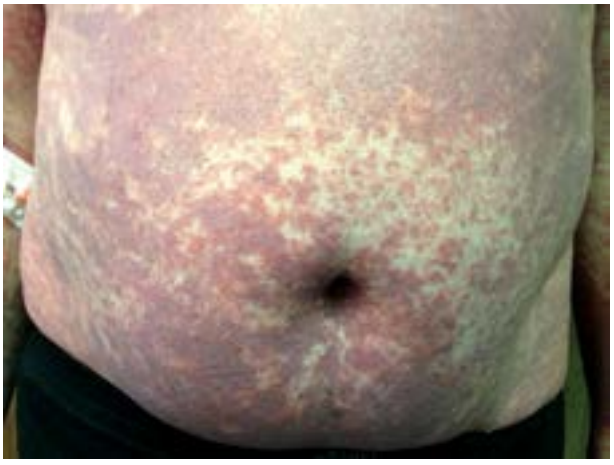

Figure 3. Generalized exanthema on the trunk

3) genetic associations between human leukocyte antigen (HLA) associations and drug hypersensitivity may occur. The genetic association of carbamazepine-induced drug hypersensitivity reactions is probably phenotype-specific (9, 11).

The symptoms are often delayed, anywhere between 2 - 8 weeks after initiating the offending drug.

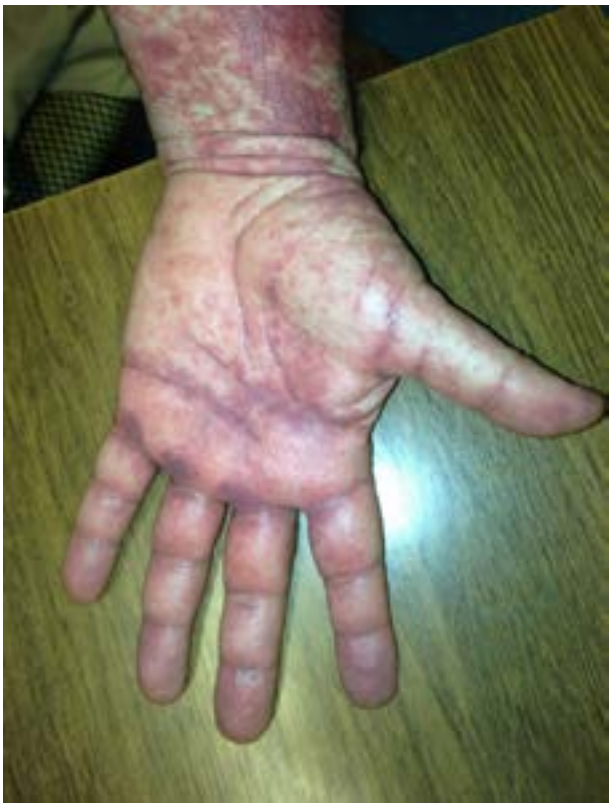

Figure 4. Maculopapular eruptions of the palms

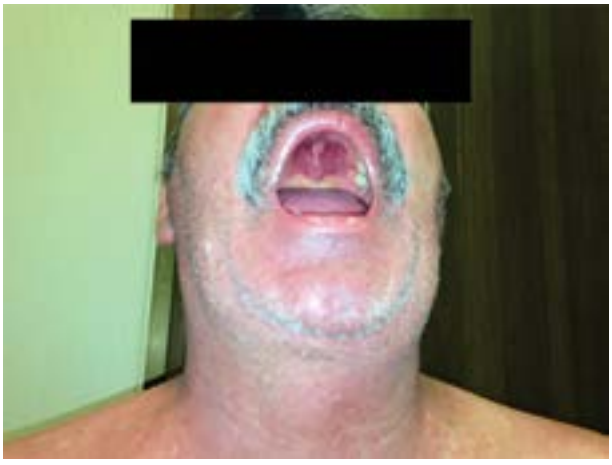

Figure 5. Palate exanthema

The most common clinical presentation includes skin eruption, fever, lymphadenopathy, abnormal liver function tests; etc.. Fever is the most common feature, seen in 90 - 100% of cases, and it may precede the cutaneous eruption (10). Eruption is present in 90% of cases. It is usually a macular erythema that becomes confluent and may generalize into erythroderma. Periorbital and facial edema may be severe and occurs in 25% of cases. Blistering can also be seen (4). Local or generalized and benign lymphoid hyperplasias are usually detected. Hematologic abnormalities are found in 50% of cases, and may include hemolytic anemia, thrombocytopenia, eosinophilia, leukocytosis, and atypical lymphocytes. Internal organ involvement includes transitory increase in liver enzymes, liver necrosis, and hepatitis, potentially life-threatening conditions (12). Other fatal complications include pericarditis, pneumonitis, nephritis, pancreatitis, colitis, myositis, and meningitis.

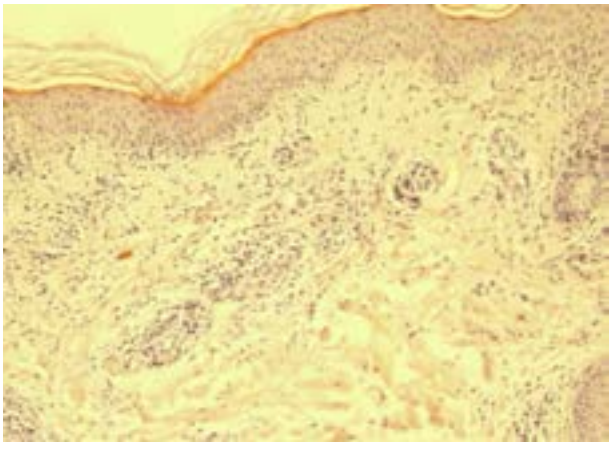

Figure 6. Vacuolar interface dermatitis

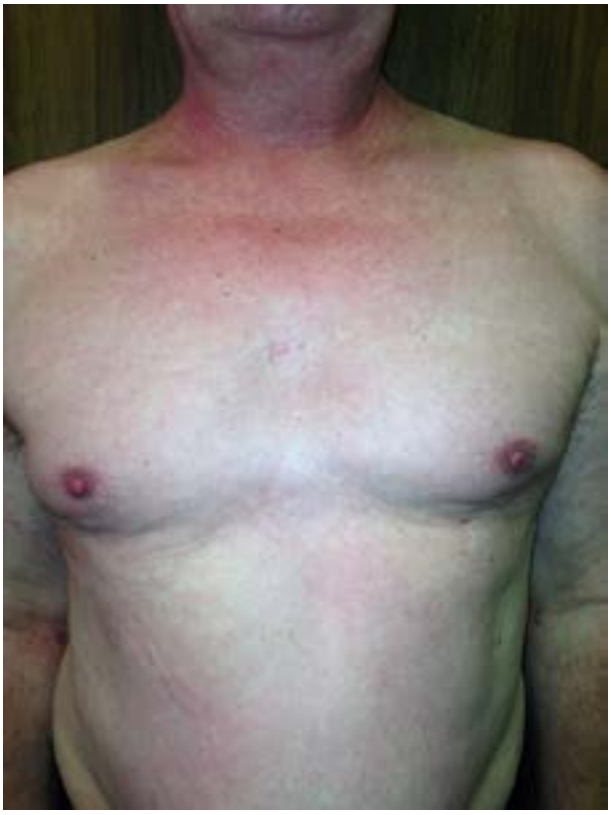

Figure 7. Residual hyperpigmented macules on the trunk

To make the diagnosis of DRESS syndrome, patients must have three of the four main RegiSCAR criteria: fever above 38°C, lyphadenopathy at two sites, involvement of at least one internal organ, and abnormalities in lymphocyte and eosinophil counts.

The DRESS syndrome must be recognized promptly and the causative drug withdrawn. Patients with anticonvulsants-induced DRESS syndrome should not be treated with carbamazepine phenytoin and phenobarbital, because of the risk of cross-reactivity amongst aromatic anticonvulsants. The treatment consists of supportive therapy, topical or oral corticosteroids, and antihistamines, maintenance of fluid and electrolyte balance.

Case report

We present a 61-year-old male, who was admitted to the *Clinic of Dermatology and Venereology*, *Faculty of Medicine*, *Military Medical Academy* in Belgrade with a skin eruption and fever (38°C) lasting for 3 days. His medical history was notable for generalized epilepsy,

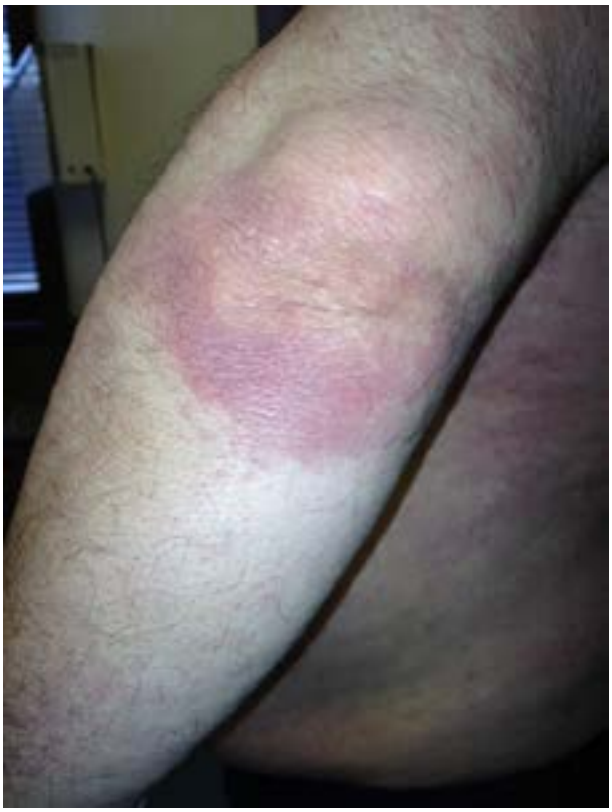

Figure 8. Erythematous macules on the arms

treated with carbamazepine during 1 month. On physical examination he presented with a temperature of 38°C and headache. He also had a generalized maculopapular exanthema on the trunk, face, extremities, palms, soles, and palate. The blood report showed a white blood cell count of 18.95 x 10^9/l, lymphocytes 7.61x10^9/l, neutrophils 8.6x10^9/l. A peripheral blood smear showed eosinophils 2%. Liver enzymes were increased: aspartate aminotransferase (AST) 91 U/L, alanine aminotransferase (ALT) 243 U/l, lactate dehydrogenase (LDH) 888 U/L, g-glutamyl transpeptidase (GGT) 674 U/l. The diagnosis of sepsis was established, based on microbiologic isolation of Staphylococcus aureus in blood culture and affected lesions. Antinuclear antibodies were negative. Proteins in 24-h urine were 0.464 g/24-h.

Radiography of the heart and lungs and ultrasonography of the abdomen and pelvis showed no pathological findings.

Histopathological findings showed vacuolar interface dermatitis. The direct immunofluorescence test was negative. After consultation with a neurologist, carbamazepine was discontinued.

Methylprednisolone (80 mg/day) and cephalexin 2 g/day were immediately introduced, with topical corticosteroid ointment. The dose of methylprednisolone was gradually tapered.

After one month there was a complete remission of skin changes.

Discussion

The first documented cases of DRESS syndrome can be traced to hydantoin drugs as early as the 1930s, although a formal name for the syndrome was not coined until 1980s. The term DRESS syndrome was first presented in 1996s by Bocquet and colleagues (6).

The DRESS syndrome is most frequently caused by aromatic anticonvulsants (carbamazepine, phenytoin, and phenobarbital). The incidence of the DRESS syndrome due to aromatic anticonvulsants is approximately 1/5000 exposures (12 - 4).

Carbamazepine is an iminostilbene derivative chemically related to the tricyclic antidepressants. Carbamazepine induced adverse reactions have been reported in as many as 30 - 50% patients treated with this drug. Reactions to carbamazepine include: cutaneous, renal, hematologic and hepatic disorders. The most common cutaneous reaction is maculopapular eruption, occurring in up to 10% of patients (10, 15).

The onset of the disease has been reported to be 2.86 days (mean 35 days) after starting the offending drug (14).

Our case of DRESS syndrome has been reported with clinical features 4 weeks after the administration of carbamazepine. He had 4 of 5 diagnostic RegiSCAR criteria for DRESS syndrome. The clinical manifestations included acute maculopapular eruption, fever, liver and renal dysfunction, as well as blood abnormalities.

Using the Naranjo adverse drug reaction probability scale there was a presumable relationship (score of 5) between the development of the DRESS syndrome and treatment with carbamazepine (2 - 8).

In the management of this syndrome it is of great importance to recognize the signs of stigmata and immediately discontinue the drug.

After meeting the RegiSCAR criteria for DRESS syndrome, our therapeutic approach was withdrawal of carbamazepine and administration of

systemic corticosteroids and systemic antibiotics. The symptoms resolved within 4 weeks.

There were no recurrences, although relapse of the syndrome is often seen (17).

Conclusions

Although the mechanisms of DRESS syndrome are not completely understood, numerous cases have been reported in children and adults. The DRESS syndrome should be considered in any patient with skin eruption, fever, eosinophilia, or liver and hematological abnormalities, because this syndrome is a life-threatening multisystem adverse drug reaction. Prompt recognition, with supportive therapy and initiation of corticosteroids may prevent systemic manifestations.

All cases of DRESS syndrome should be reported to local pharmacovigilance centers.

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DRESS sindrom - prikaz slučaja

Sažetak

Uvod. DRESS sindrom, predstavlja reakciju na lek, koja se javlja u vidu generalizovane kožne erupcije, udružene sa eozinofilijom i sistemskim simptomima. Najčešće je izazvana antikonvulzivima, a takođe može biti izazvana i sulfa derivatima, antidepresivima, nesteroidnim antiinflamatornim lekovima, kao i antimikrobnim lekovima.

Prikaz slučaja. Prikazujemo pacijenta starosti 61 godinu, sa generalizovanim makulopapularnim egzantemom, na licu, trupu, ekstremitetima, dlanovima, tabanima, nepcu, kao i febrilnošću do 38° C. Iz lične anamneze, dobijen je podatak da je pacijent, zbog generalizovane epilepsije, lečen karbamazepinom, tokom jednog meseca. Prateći zvanične kriterijume, postavljena je dijagnoza DRESS sindroma. U ovom slučaju, pacijent je uspešno lečen metilprednizolonom, cefaleksinom i topijskim kortikosteroidima.

Zaključak. Iako etiopatogeneza DRESS sindroma nije u potpunosti jasna, opisani su mnogobrojni slučajevi. Dijagnozu ovog sindroma treba uzeti u obzir kod pacijenta sa generalizovanim kožnim promenama, povišenom telesnom temperaturom, eozinofilijom, kao i lezijama jetre i hematološkim poremećajima. Brzo ordiniranje odgovarajuće terapije može da prevenira sistemske manifestacije ove bolesti

Ključne reči

Sindrom preosetljivosti na lekove; Znaci i simptomi; Prikazi slučajeva; Dijagnoza; Ishod terapije

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Berardinelli-Seip Syndrome - A Case Report

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Abstract

Congenital generalized lipodystrophy (CGL), also known as Berardinelli-Seip syndrome (BSS), is a rare autosomal recessive disease characterized by near total absence of adipose tissue and muscular hypertrophy. Additional common clinical signs are acanthosis nigricans, acromegaloid features, hepatomegaly, hyperandrogenism, altered glucose intolerance, cardiomyopathy and hypertriglyceridemia. An 11-year-old girl was admitted to our Clinic presenting with hyperandrogenic features, generalized lack of adipose tissue, generalized muscular hypertrophy and brownish colored skin on the neck, axillas and inguinal folds associated with impaired glucose tolerance and hypertension. A clinical diagnosis of congenital generalized lipodystrophy was made.

Key words

Lipodystrophy, Congenital Generalized; Acanthosis Nigricans; Masculinity; Hypertrichosis; Signs and Symptoms; Case Reports

An 11-year-old girl was admitted to our Clinic for the first time for hypertrichosis mainly affecting the face and linea alba. In 2004, she was diagnosed with generalized lipodystrophy. Her symptoms included abdominal bloating, recurrent vomiting, reduced subcutaneous fat and prominent muscles. The girl was a normal full-term baby with no family history of genetic diseases or consanguinity.

Objectively, she was found to have dysmorphic features: male habitus, massive bone structure (Figures 1 and 2), strong and well-shaped muscles, big hands and feet, triangle face with rough features, rough voice, brownish thick skin on the neck, axillas and inguinal folds and hypertrihosis on the face and linea alba (Figures 3 and 4).

At the age of 11 her weight was 70 kg, height - 169 cm, and BMI - 24.36 kg/m^2.

Laboratory reports showed high levels of triglycerides - 2.06 mmol/l (normal range < 1.7 mmol/l), cholesterol - 5.3 mmol/l (normal range < 5.2 mmol/l), LDL - 4.66 mmol/l (normal range < 4.0 mmol/l), VDRL - 1.14 mmol/l (up to 0.85 mmol/l). The results of glucose tolerance tests were abnormal. Random blood sugar estimations at frequent intervals varied from 129 to 300 μIU/ml. Complete blood count, urinalysis, liver function tests, electrolytes and hormonal status including TSH, follicle-stimulating hormone, luteinizing hormone, cortisol, growth hormone, estradiol, androstendione, dihydroepiandrostendione, C-peptide were within normal limits.

Cytogenetic analysis showed 46 XX – a normal female karyotype without numerical or structural aberrations. According to the medical history, the genetic analysis performed in 2004, showed that the patient had Berardinelli-Seip syndrome (BSS), subgroup 1.

The X-ray of the right wrist revealed a bone age corresponding with the age of 14,5 years, and a "closed" sella turcica. The ultrasound findings were normal, except for a fatty liver.

Figure 1. 11- year-old girl with male habitus, massive bone structure, strong and well-shaped muscles

Cardiac examination showed a normal status of the lungs, but also left ventricular hypertrophy, hypertension (142/89 mm Hg), and heart rate between 97 and 131 bpm. Gynecological examination revealed moderate hypertrophy of the clitoris and hypoplastic uterus. No neurological abnormalities, hepatosplenomegaly or renal disorders were found. The patient was examined by a psychologist who established

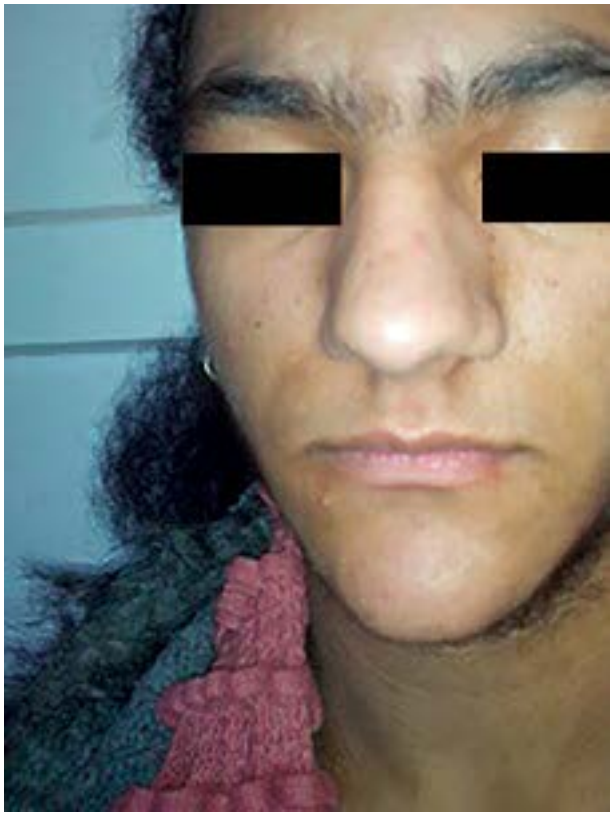

Figure 2. Typical features in Berardinelli-Seip Syndrome -triangle face, rough features and hypertrihosis on the face

a mental deficiency (IQ 88), inhibited behavior, low self-esteem, and poor social maturity.

The initial treatment, including 0.9% NaCl 500 mg infusions and glucose 75 g, lasted for a week. Thereafter, metformin hydrochloride, a subclinical dose of 500 mg/day was administered. Later on, the therapy was increased gradually, up to 2550 mg/day (850 mg three times a day). A fat-restricted diet (20%-30% fat intake) was initiated. Laser removal of the excess hair on the face was recommended.

Discussion

Lipodystrophies are a group of metabolic disorders characterized by varying degrees of adipose tissue loss (1). They are characterized by absence of adipocytes thus relating to accumulation of lipids in the muscles, liver and other areas of the body (2). Lipodystrophies are often associated with metabolic complications such as diabetes mellitus, hypertriglyceridemia and hepatic steatosis (3, 4). They can be classified into 3 groups –

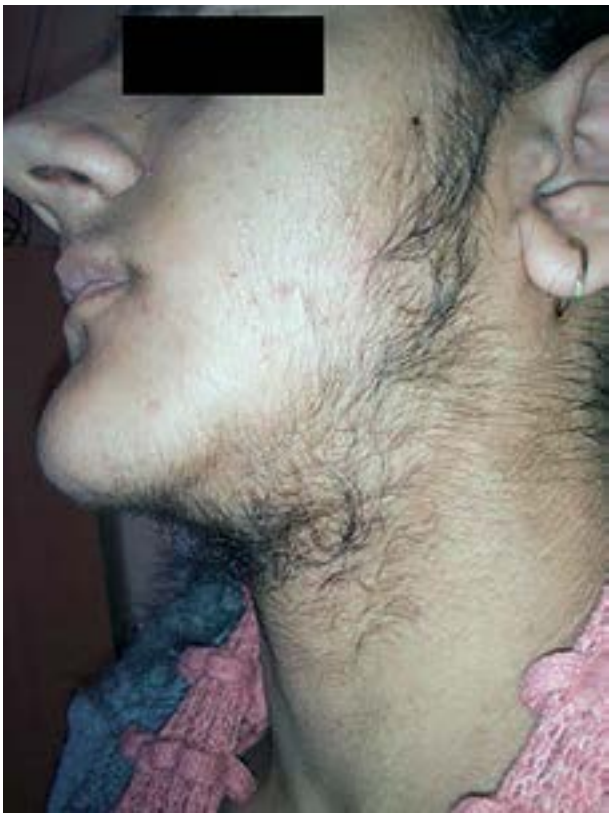

Figure 3. Hypertrihosis on the face in 11-year-old girl (left side)

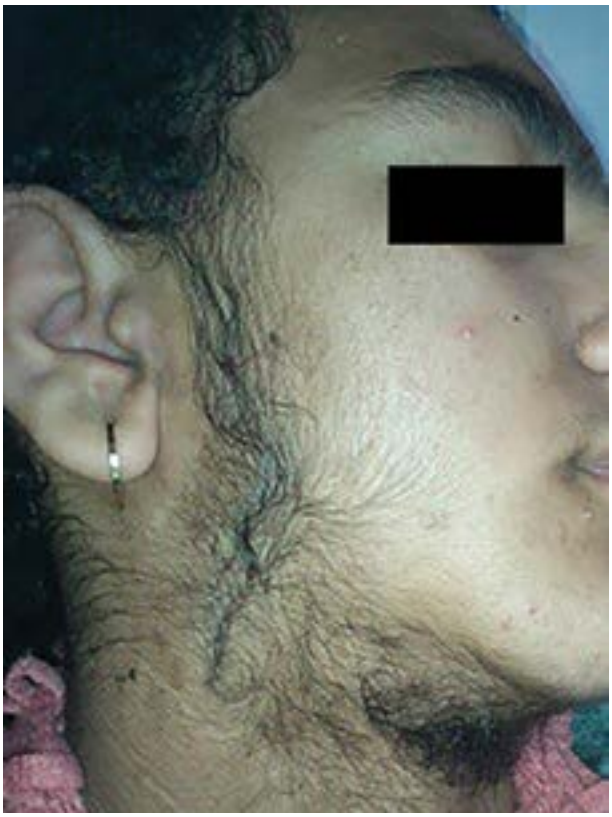

Figure 4. Hypertrihosis on the face in 11-year-old girl (right side)

generalized, partial and local, depending on the degree and localization of fat loss. The first two groups are divided into 2 types - inherited and acquired.

Berardinelli-Seip syndrome is an autosomal recessive disease of a generalized type lipodystrophy with a worldwide prevalence of 0.2:100.000 (5). BSS is mainly found in Lebanon, Portugal, Norway and USA, as well as in a few Asian, African and Brazilian families (6, 7, 8). The disease was first described by Berardinelli in 1954 (9) and by Seip in 1959 (10). CGL is linked mainly to AGPAT2 (BSS type 1) and BSCL2 (BSS type 2) genes and rarely to CAV1 and PTRF genes. It is believed that type 1 is less severe than type 2. The sex ratio is 1:1. Van Maldergern et al. (11) reported an excess of females with AGPAT2 mutations and an excess of males with seipin mutations. According to the same author, females have a more severe disease course.

Manifestations and major findings are generalized lack of adipose tissue, insulin-resistant diabetes without ketoacidosis, hypertrygliceridemia, and hepatosplenomegaly. Other features include generalized muscular hypertrophy, prominent ears, acanthosis nigricans, hypertrichosis, thick curly scalp hair, hypertension, sometimes – corneal opacities, elevated metabolic rate, cutaneous xanthomas (12) and mental retardation in 50% of cases (13).

To date there are approximately 300 reported cases in which patients are virtually completely without body fat (7, 8, 14).

CGL is difficult to treat, but insulin therapy, lipid-lowering drugs and moderate calorie restrictions (20% - 30%) are recommended. A new, therapeutically effective, long-term option for severe forms of lipodystrophy, is leptin – adipocyte hormone which may improve the insulin resistance, dyslipidemia and hepatic steatosis, characteristic for patients with BSS (15, 16).

Conclusion

We present a rare case of BSS type 1 with characteristic features of "masculine look" with generalized lack of subcutaneous tissue, muscular hypertrophy, acanthosis nigricans and hypertrichosis associated with

impaired glucose tolerance, hypertrygliceridemia and hypertension.

Abbreviations:

CGL - Congenital generalized lipodystrophy
BSS - Berardinelli-Seip syndrome

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Berardineli-Sip sindrom - prikaz slučaja

Sažetak

Kongenitalna generalizovana lipodistrofija, poznata i kao Berardineli-Sip sindrom, je retka autozomna recesivna bolest koju karakteriše potpuno odsustvo masnog tkiva i mišićna hipertrofija. Osim ovih, prisutni su i drugi klinički znaci kao što su: akantoza, akromegalija, hepatomegalija, hiperandrogenizam, poremećaj tolerancije na glukozu, kardiomiopatija i hipertrigliceridemija. Jedanaestogodišnja devojčica primljena je na Kliniku sa hiperandrogenim karakteristikama, generalizovanim nedostatkom masnog tkiva, generalizovanom mišićnom hipertrofijom, braonkastom bojom kože na vratu, ispod pazuha i predelu prepona, poremećajem tolerancije na glukoze i hipertenzijom. Postavljena je dijagnoza kongenitalne generalizovane lipodistrofije.

Ključne reči

Kongenitalna generalizovana lipodistrofija; Akantoza nigrikans; Muški habitus; Hipertrihoza; Znaci i simptomi; Prikazi slučajeva

A Report on the 13th EADV Spring Symposium, Athens 2016

The 13th Spring Symposium of the European Academy of Dermatology and Venereology was held in Athens, May 19 - 22, 2016. The programme was characterized by a variety of interesting topics: highlights on skin, sun, sea, and Mediterranean dermatology, as well as numerous sessions on dermoscopy, and hair and nail diseases. The Symposium's theme "Moving Boundaries" has been selected to reflect upon the daily challenges that physicians are confronted with in their endeavor to expand their specialty towards new and fascinating territories in keeping up with the ever-changing world of skin diseases.

Prof. Lidija Kandolf-Sekulović was the chair in the Free Communications "Non-melanoma Skin Cancer/Dermoscopy". Assist. Prof. Dušan Škiljević delivered the lecture "Serum DNase I Activity in Lupus Erythematosus: Pathogenetic and Therapeutic Implications" in the session "Autoimmune Diseases".

There were 15 E-posters from Serbia.

Countries candidates for the host of the 15th Spring Symposium of EADV were presented in Athens. Montenegro won the majority of votes and in May 2018, the symposium will be held in Budva. The other candidates were Porto (Portugal) and Reykjavik

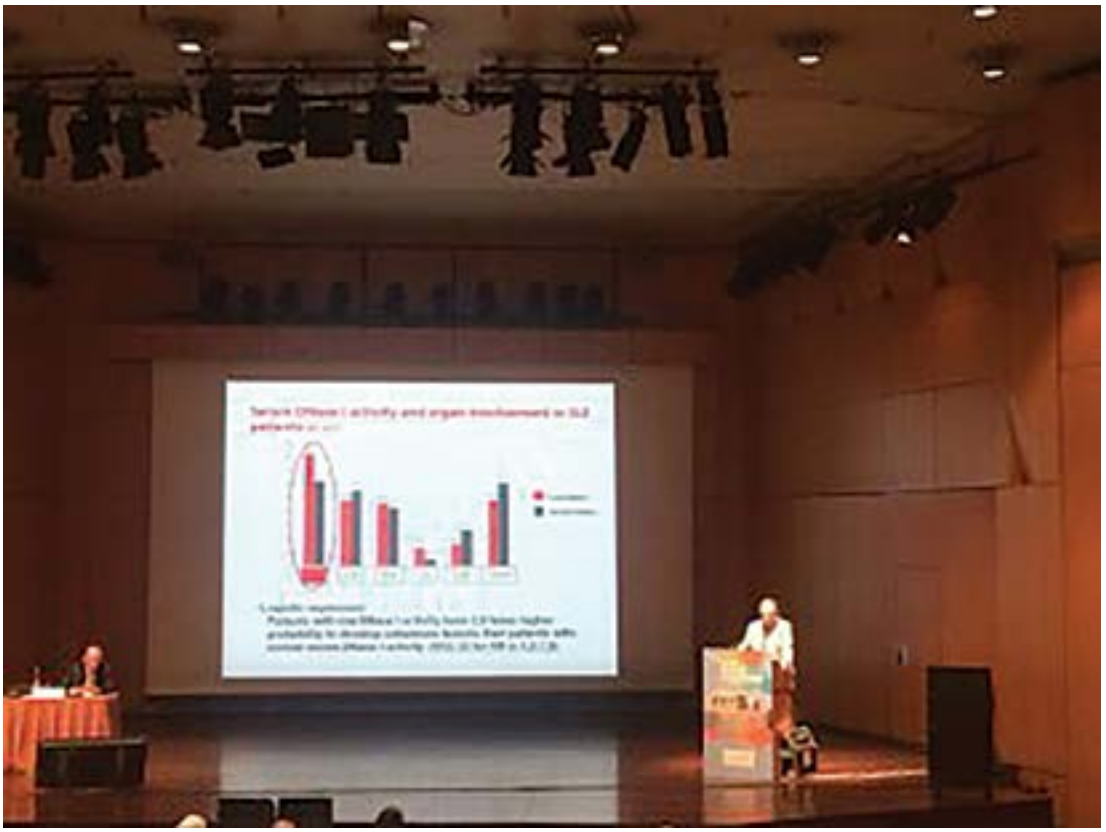

Figure 1. Dušan Škiljević presenting a lecture in Athens

Figure 2. Our participants: Lidija Kandolf-Sekulović with colleagues from Lithuania and Georgia

Figure 3. Ljiljana Medenica, Predrag Štilet and Branka Marinović

(Island). This is a great success for a small country with only twenty dermatovenereologists. A great merit for winning the candidacy for the organization of this symposium belongs to Dr. Predrag Štilet, who is a member of EADV Board of Directors.

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A Report on the 6th Post-Chicago Meeting on Melanoma/ Skin Cancer, Munich 2016

The 6th Post-Chicago Meeting on Melanoma/ Skin Cancer was held from June 30 - July 1, 2016 in *Leonardo Royal Hotel* in Munich. Prof. Axel Hauschild and Prof. Claus Garbe, were presidents of the Congress. It was the largest Post-Chicago Meeting so far, with more than 600 participants from 35 countries. Since the first Post-Chicago Meeting on Melanoma/Skin Cancer, which took place in 2011, it has attracted 450 - 500 participants each year from all over the world. The interactive congress offers a comprehensive overview on all new developments in melanoma diagnosis and therapy, and direct communication with the world´s leading experts in these fields. Since 2011, there is a rapid change of therapeutic approaches for metastatic melanoma. New drugs, like BRAF- and MEK-inhibitors, and CTLA4 and PD1-antibodies, have been established in melanoma treatment. It remains an open question how to combine them and how they should be sequentially applied.

The 2-days program covered a wide spectrum of topics in dermato-oncology. International key opinion leaders on melanoma gave an overview and

Figure 1. Prof. Lidija Kandolf-Sekulović and Prof. Željko Mijušković

presented the latest clinical trial results in melanoma treatment. In addition to the scientific value of this meeting, every participant had an opportunity to interact with experts in a familiar setting. This year we had two invited speakers. Professors, Lidija Kandolf-Sekulović and Željko Mijušković, presented interesting melanoma cases in the EADO Forum session.

The next Post-Chicago Meeting will take place in the *Leonardo Royal Hotel* in Munich from June 29 - 30, 2017.

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In Lucija KOSI et. al., Localized Bullous Pemphigoid on the Site of Knee Arthroplasty: a Case Report, SJDV 2016; 8 (1): 39-44, DOI: 10.1515/sjdv-2016-0004, incorrect version of Figure 2, appeared on page 41. The corrected figure follows below.

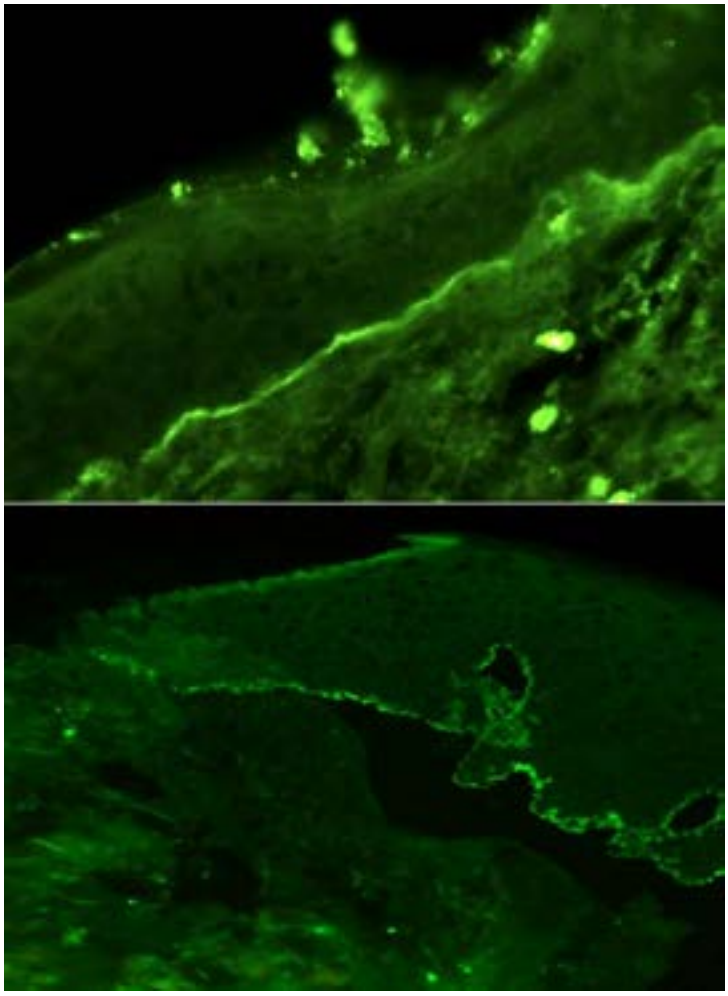

Figure 2. Direct immunofluorescence microscopy of perilesional skin showing IgG and C3c deposits at the epidermal-dermal junction; (b) Direct immunofluorescence on salt-split skin shows IgG and C3c deposits confined to the epidermal side of the split skin

FORTHCOMING EVENTS

Dermatology and Venereology Events 2015/2016

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
11-15 June, 2016	Congress of the European Academy of Allergology and Clinical Immunology, Vienna, Austria	10 January, 2016	www.eaaci2016.org
13-15 June, 2016	7th European Dermatology Congress, Alicante, Spain	No submission deadline	www.dermatology.conferenceseries.com/europe
07-09 July, 2016	5th Congress of the Psoriasis International Network – Psoriasis 2016, Paris, France	12 February, 2016	www.pso2016.com
11-14 August, 2016	1st International Conference on Tropical Dermatology, Colombo, Sri Lanka	1 April, 2016	www.ictd2016.org
31 August - 03 September, 2016	16th World Congress on Cancers of the Skin, Vienna, Austria	31 July, 2016	www.wccs2016.com
08-11 September, 2016	3rd Regional Congress, Mostar, Bosnia and Herzegovina	1 August, 2016	www.derma-regional2016.org
15-17 September, 2016	IUSTI Europe 2016, Budapest, Hungary	15 May, 2016	www.iusti2016.com
28 September – 02 October, 2016	25th EADV Congress, Vienna, Austria	18 April, 2016	www.eadvvienna2016.org
14 October, 2016	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Vojvodina, Novi Sad, Serbia	No abstract submission	www.sld.org.rs
20-22 October, 2016	2nd International Conference ~~in~~ of Dermatology, Kathmandu, Nepal	15 June, 2016	www.icderm2016.com
26-28 October, 2016	3rd World Congress of Cutaneous Lymphomas, New York City, USA	1 July, 2016	www.cutaneouslymphoma.org
03-05 November, 2016	19th Belgrade Dermatology Days, Belgrade, Serbia	15 September, 2016	www.udvs.org
09-10 December, 2016	Congress of the Association of Serbian Cosmetic and Aesthetic Dermatology, Belgrade, Serbia	No abstract submission	www.asked.rs
26-29 January, 2017	IMCAS World Congress 2017, Paris, France	19 December, 2016	www.imcas.com
26-28 January, 2017	5th European School of Dermato-Oncology, Berlin, Germany	No abstract submission	www.dermato-oncology2017.org
02-05 February, 2017	Many Faces of Dermatology – Clinical, Surgical and Aesthetical, Dubrovnik, Croatia	28 October, 2016	www.isdregional2017.org

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AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

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

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

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

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

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

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

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

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

1. Manuscript Preparation Guidelines

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

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

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

- A running title (limited to 30 characters);

- Authors' names and institutional affiliations;

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

1.2. Abstracts

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

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

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

1.3. A list of abbreviations

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

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

2. Tables and illustrations

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

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

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

4. Additional information

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

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