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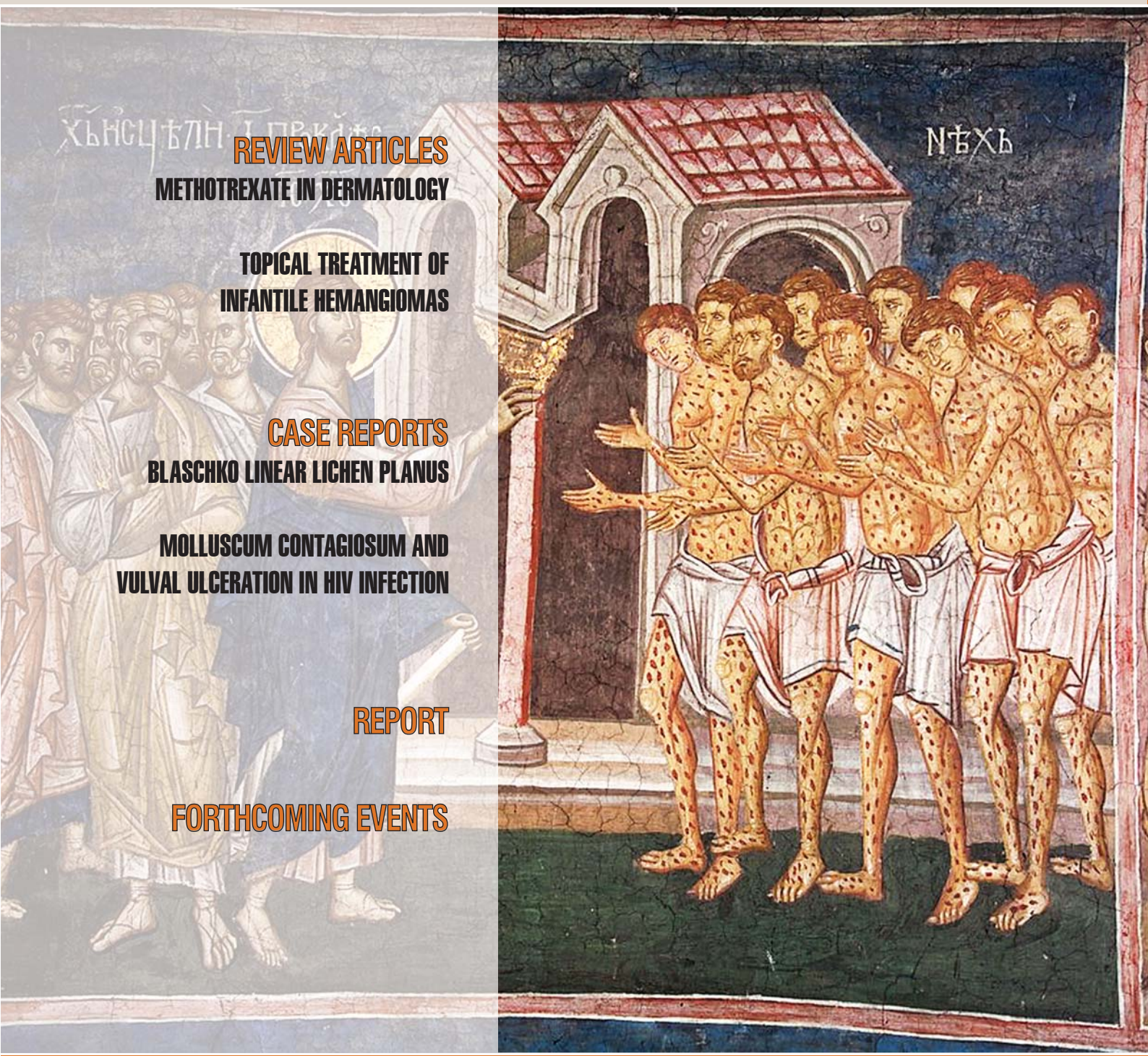

REVIEW ARTICLES

METHOTREXATE IN DERMATOLOGY

TOPICAL TREATMENT OF INFANTILE HEMANGIOMAS

CASE REPORTS

BLASCHKO LINEAR LICHEN PLANUS

MOLLUSCUM CONTAGIOSUM AND VULVAL ULCERATION IN HIV INFECTION

REPORT

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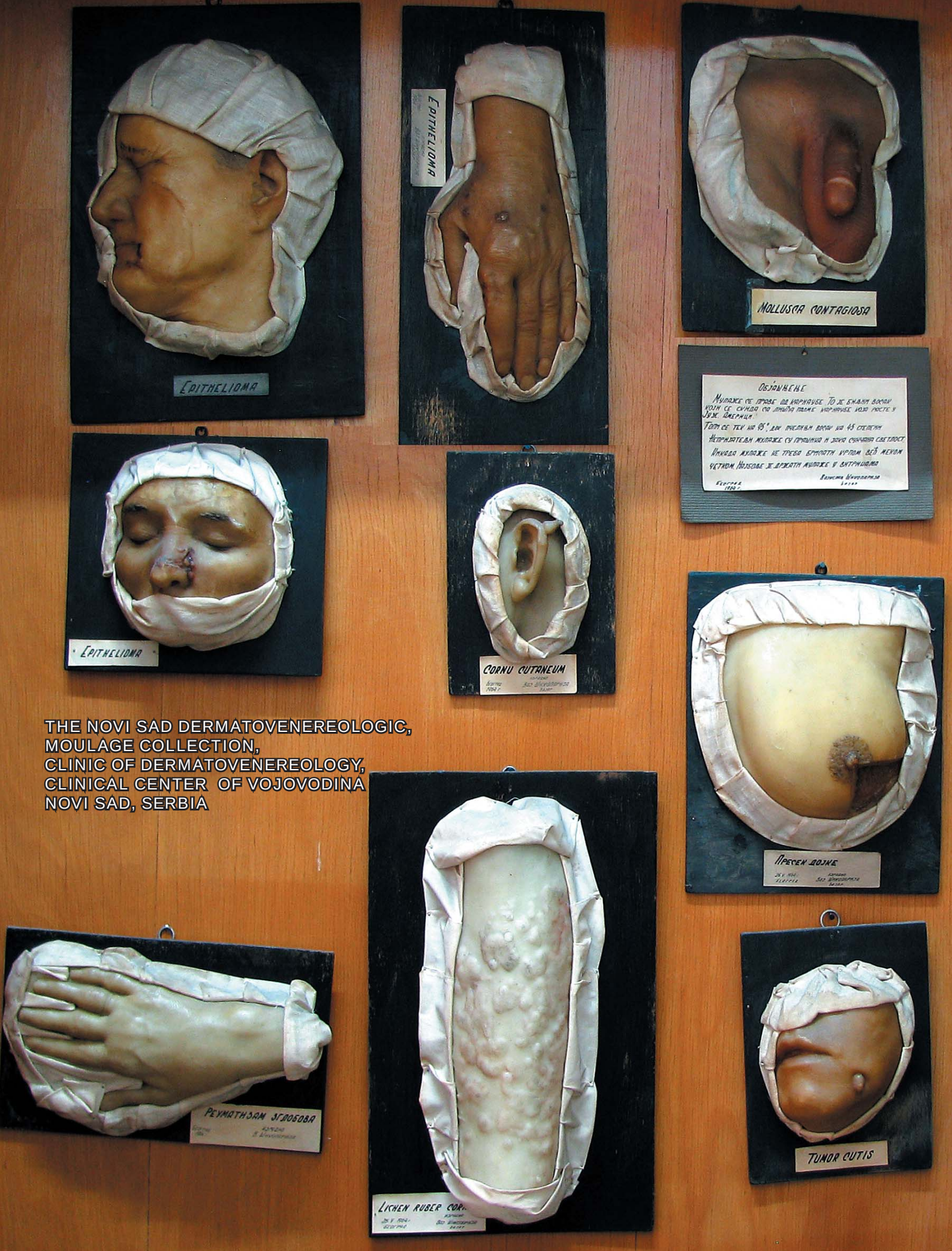

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The use of methotrexate in dermatology

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Abstract

Methotrexate is a cytotoxic antimetabolite agent and a folic acid antagonist. Except for its use in oncology and rheumatology, it is widely used in dermatology. The most important indications include severe forms of psoriasis, but also a wide range of autoimmune diseases and dermatoses with different etiology and pathophysiology such as: bullous pemphigoid, dermatomyositis, pityriasis rubra pilaris, sarcoidosis, T-cell lymphomas, Behcet's disease, adult atopic eczema, scleroderma, Reiter's syndrome and many others. For dermatological indications methotrexate is usually taken in low oral doses, 5-25 mg once a week. In certain diseases it can be applied to the lesion itself, or in the form of local preparations. Considering the fact that numerous drugs affect various metabolic phases of methotrexate and may increase its toxicity, it is of utmost importance to consider other prescribed drugs, especially certain antibiotics, nonsteroidal antiinflammatory drugs, antiepileptic drugs, retinoids, proton pump inhibitors and so on. If the selection of patients is correct, if drugs are taken regularly and laboratory monitoring is included, methotrexate is a truly efficient and safe drug that can be taken for months or years if necessary.

Key words

Methotrexate + administration and dosage + adverse effects + pharmacokinetics + therapeutic use + toxicity; Skin Diseases + drug therapy; Dermatology; Dermatologic Agents

Methotrexate (MTX) is a cytostatic drug from the group of antimebolites, analogous to folic acid. It is not only used to treat severe cases of psoriasis, but also a wide range of autoimmune diseases. Analogous to folic acid, MTX inhibits enzyme dihydrofolate-reductase, thus decreasing the levels of synthesis of purine basis, nucleic acids and some amino acids. Low oral doses of up to 25 mg, once per week, are often used in dermatology. After oral intake of these doses of MTX, maximal blood concentration is achieved in 45 minutes to 2 hours time. It is accumulated in erythrocytes by reverse protein binging and hepatocytes. It is mostly excreted through kidneys by glomerular filtration (up to 70%), and less by tubular secretion via bile and feces. Pharmacokinetics of the drug is also associated with the age of the patient, increasing the distribution and elimination of the drug as the age decreases (1-2).

Interactions with other drugs

Various drugs affect and modify the metabolic phase of MTX. Some antibiotics (neomycin) and retinoids (etretinate) modify the resorption and increase the hepatotoxicity of the drug. Certain drugs: phenytoin, barbiturates, tetracyclines, phenylbutazone, salicylates, trimethoprim-sulfamethoxazole suppress MTX binding to plasma proteins and increase the amount of free, biologically active drug in the blood, thus increasing the risk of hematologic toxicity. Other drugs, like nesteroidal antiinflammatory drugs, salicylates, and sulphonamides increase the half-life of biologically active MTX. Cyclosporine reduces the renal clearans of MTX. Dipyridamole leads to prolonged activity of MTX due to intracellular accumulation. Drugs that affect the metabolism of folic acid, like phenytoin can increase the toxicity of MTX as well (4,5).

Administration of methotrexate

In dermatological indications, MTX can be taken either in one dose or in multiple doses at 12 hour intervals. Usually, patients begin with a test dose 2.5-5 mg; after the initial phase, patients are given 10-15 mg per week, with an increase of the dose from 2.5 mg to 5 mg per week over the next few weeks, when full therapeutic effect is expected. After achieving the therapeutic effect, the dose is lowered by 2.5-5 mg per week, till the lowest effective dose. MTX treatment takes a long time and oral therapy is conducted in hospitals. It is crucial for patients to be well acquainted with the characteristics of the drug, and it is necessary to inform their dermatologist or family doctors about possible changes healthwise. That includes the potential toxic effects of the drug (6).

Choice of patients and intake monitoring

In regard to anamnestic data and laboratory diagnostics, it is necessary to exclude patients who should not take the drug. Anemia, thrombocytopenia and leukopenia are contra-indicatios for the therapy, as well as infections, peptic ulcers, ulcerative colitis, alcoholism, immunodeficiency, pregnancy, lactation. Before the initiation of the therapy, all patients need to obtain: erythrocyte sedimentation rate (ESR), complete blood count, transaminases (AST, ALT, gamma GT, AP), urea, creatinine, urine. Patients with liver diseases need to examine anti-HIV antibodies, hepatitis-B antigens and HCV RNA. During first three months of therapy erythrocytes, leukocytes and thrombocytes need to be controlled once per week, a day before taking the next dose of drug. Later on, if there are no side effects, laboratory tests are done less often. During the first three months of therapy, biochemical tests are regularly done once per month, and later on, every three months. Biochemical tests are done more often in cases with significant pathological transaminase levels, or if other hepatotoxic drugs are taken simultaneously (2,7).

Due to interactions of MTX with other drugs and the necessity for their intake, as well as because of necessary dose calculations, patients are advised to fill the evidence chart for MTX which is used by Clinical Center Banjaluka since 2001 (Figure 1). Patients note the taken weekly dose, so it is easy to calculate the total monthly and annual intake. The chart consists of a list of drugs whose intake may be potentially dangerous when taken at the same time as MTX, as well as the intake manner, and laboratory monitoring data.

Side effects

Side effects of MTX include gastrointestinal toxicity, hepatotoxicity, and hematological toxity. Nausea is the main symptom of digestive tract disease which is observed in approximately one quarter of patients. It is managed by lowering the dose or by changing the manner of drug intake. Diarrhea and anorexia are observed less often. Hepatotoxicity can be either acute or chronic. Acute hepatotoxicity is mostly transitory, while chronic can be observed when high doses are taken. About 10-20% of patients exhibit fibrosis and 6-10% exhibit liver cirrhosis. The above-mentioned complications call for immediate termination of MTX therapy. Recent literature data suggest that MTX hepatoxicity is less than it was previously thought however diabetes and obesity are significant factors for liver damage **(8).** Most often observed hematological complications include megaloblastic anemia, rarely leukopenia and thrombocytopenia. If the leukocyte count is less than 3000/mm^3, or thrombocyte count is less than 100 000 mm^3, the therapy should be terminated for a period of time. If the levels are stabilized during the next week, therapy continues, usually with lower intake. About 2-19% of patients exhibit coutaneous or mucosal erosions which calls for immediate termination of MTX therapy. Less often, patients exhibit urticaria, acral erythema, anagen alopecia. Rarely, side effects affect the respiratory system as pneumonia and fibrosis. Lung fibrosis is another indication for MTX therapy termination (7-9).

Liver biopsy and cumulative dose of methotrexate

There are still controversies regarding liver biopsy during long term MTX therapy. Today, it is generally accepted that if a patient does not exhibit risk factors for liver diseases and if laboratory analysis shows that the liver function is within acceptable limits, biopsy should be done after cumulative dose of 4 g. Previosly, the limit was thought to be much lower, 1.5 g. Patients who exhibit liver disease risk factors should undergo biopsy after two to four months of therapy, and the second one after cumulative dose of 1.5 g. (10).

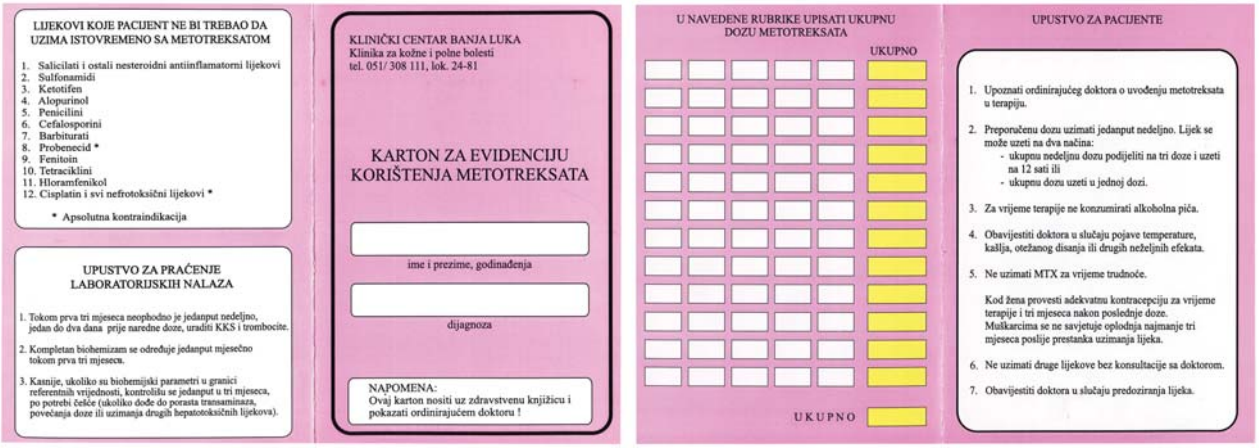

Figure 1. Evidence chart for methotrexate

Methotrexate and folic acid

It is generally thought that hepatotoxic effects of MTX (oral dose of 5-30 mg) can be prevented by intake of folic acid for almost all indications. Previosly, the usual oral dose of folic acid was 5-10 mg per day, at least two days after MTX intake; however, some authors think that it should be taken every day, except for the days when methotrexate is taken. Today, 5 mg of folic acid is usually given a day after taking MTX. If acute side effects of methotrexate occur, it is advised to take active folic acid (11-14).

Indications for methotrexate

Psoriasis

In dermatology, MTX is usually used to treat psoriasis. Most often psoriasis is exhibited in sever cases of: erythrodermia, psoriatic arthropathy, pustular psoriasis and some forms of plaque psoriasis. Psoriatic erythoderma is a severe, generalized form of psoriasis where 90% of skin is covered with erythema, infiltrations and scaling. Considering the fact that inflammation of a high percentage of skin can significantly influence thermoregulation, hemodynamics, metabolism of water and proteins, intestinal absorption, these patients have not only skin changes, especially in acute forms of the disease, but also significant disorders of general wellbeing and febrility. Psoriatic arthropathy is a simultaneous occurrence of psoriasis vulgaris and of polyarthritic joint changes, particulary on the distal joints (fingers and toes). Joint changes manifest as distal psoriatic arthritis, mutilating psoriatic arthritis, psoriatic polyarthritis, ankylosing spondylitis. Severe forms may lead to joint deformations, as well as invalidity. *P*ustular psoriasis is a form of psoriasis that is clinically manifested by eruptions of erythema and sterile pustules. Changes can be both local and general. The general form is a severe form of the disease accompanied by fever and changes in well-being. Methotrexate is also used in the treatment of chronic, resistant plaque forms of *psoriasis vulgaris* which cover more than 50% of the skin. It is also efficient in treating nail psoriasis *(psoriasis unguium*). Regular doses of MTX in psoriatic patients are from 7.5 to 20 mg per week (5-19).

In around 80% of psoriatic patients effects of methotrexate are satisfactory, and full remission is noticed in around 60% of patients. Usually, noticeable improvement is achieved within two to three weeks of therapy, and full effect is achieved in eight weeks. The obtained treatment effects are maintained by lowest dosage of the drug that can be taken for months, sometimes even years. If the treatment is terminated, there is no rebound phenomenon. That means that the overall psoriatic condition is worsened (2). MTX today also has a place in the treatment of psoriasis in children (20,21). Local methotrexate is used efficiently in treating certain forms of psoriasis, in the form of 0.25% and 1% hydrophilic gel (22).

Bullous dermatoses

MTX is used to treat autoimmune bullous dermatoses, usually bullous pemphigoid. Clinically, it manifests with erythema, large or small blisters and

itching. Around 25% of patients have mouth mucosal erosions. The disease mainly occurs in the elderly. Adequate therapeutic effects can be achieved by using low doses of MTX, 5-10 mg per week. Methotrexate is less often used in treating pemphigus. It is used for generalized, persistent forms of benign familial pemphigus (Hailey-Hailey disease) (23, 24).

Dermatomyositis

Dermatomyositis is an autoimmune, systemic disease of connective tissues, manifesting with idiopathic, inflammatory myopathy (symmetric weakness and pain in shoulder muscles, neck, hands, esophagus). The skin exhibits noticeable pathognomonic papules (Gottron), livid periorbital edema and erythema, telangiectasas around the nail, and severe maculopapullar rash. Systemic manifestations include: general weakness, gastrointestinal symptoms, as well as joints, heart and lungs complications. MTX in doses from 25-50 mg per week is used to treat dermatomyositis resistant to corticosteroid therapy (25).

Discoid lupus erythematosus

It is a chronic skin disease that usually manifests in photo exposed regions of the skin. The main symptoms of the disease are: hyper- and hypopigmentation, telangiectasias and atrophy. Its manifestations include a number of clinical variations. MTX is used as adjuvant therapy, mostly when the disease is resistant to standard therapy (26).

Pityriasis rubra pilaris

It is a hereditary or acquired chronic disease manifested by more or less circumscribed keratotic papules, palmoplantar yellowish keratoderma, rearly with erythroderma. It may appear as a classical or atypical form in adults as well as in children. Most patients achieve remission by using low doses of MTX, 5-10 mg per week, for a few months (27).

Sarcoidosis

Sarcoidosis is a granulomatous multisystemic disease of unknown etiology. Cutaneus sarcoidosisis is usually manifested by skin changes: erythema nodosum, papular, plaque or nodular type, as well as by a wide range of atypical forms. For treating chronic forms MTX is used 15-20 mg per week for six to eight weeks (28).

Keratoacanthoma

Keratoacanthoma is a rapidly growing epidermal skin tumor composed of keratinizing squamous cells originating from pilosebaceous follicles and resolving spontaneously untreated. A typical keratoacanthoma shows raised margins and a central keratin-filled crater. Apart from the typical form, there are also a number of atypical forms: giant, centrifugum marginatum, eruptive. Some forms of keratoacanthoma, like centrifugum marginatum, can be treated successfully by intralesional application of MTX (29).

Reiter's syndrome

Reiter's syndrome is a multisystemic disease which is preceded by enteric or genitourinary, infection, continued by arthritis, eye lesions and various skin changes, mostly hyperkeratotic plantar plaques and penile lesions. Sever chronic diseases, resistant to nonsteroidal antiinflammatory agents and conventional therapy are treated with MTX in doses from 7.5-15 mg per week (30).

T-cell lymphomas

Epidermal T-cell lymphomas (*mycosis fungoides,* Sezary syndrome, pagetoid reticulosis*)* are a group of rare, highly malignant T-cell lymphomas, in which the skin is the primary selection of malignant T-cell clone. In regular practice, *mycosis fungoides* is mostly encountered. MTX administration regimen is used in stage III lymphomas (TNM staging T-cellular lymphoma) as mono-therapy or in combination with other therapy modalities (31,32).

Behçet's disease

Behçet's disease is a multi-systemic inflammation of small blood vessels, mostly veins. It is manifested by recurrent oral and genital ulcerations, skin changes shuch as erythema nodosum, pseudofolliculitis, pustules and eye lesions. Considering the fact that any blood vessel can be affected by inflammation, patients can have different systemic manifestations, mostly in joints, gastrointestinal tract or in the central nervous system. MTX is an adjuvant therapy given in doses from 7.5-15 mg per week (33).

Atopic eczema

Atopic eczema (dermatitis) is a chronic, inflammatory, itchy skin disease that is mostly found in children, but

can persist or manifest for the first time in adulthood as well. Apart from allergic rhinitis and asthma, it is one of the four most common atopic diseases. Lately, more and more researches have shown positive effects of low doses of MTX in treating average to severe, refractory variations of atopic eczema in adults (34, 35).

Localized scleroderma (Morphea)

Localized scleroderma is a connective tissue desorder of unknown etiology characterized by skin fibrosis. The condition has various clinical forms: circumscript plaques *(„en plaque"),* linear (*„en bande"),* frontoparietal lesions („*en coup de sabre*") or generalized *morphea*. MTX is used in the treatment of all forms of localized scleroderma in adults and in children, usually in combination with systemic corticosteroids. It is given in doses 15-20 mg per week (36,37).

Other indications

In the last few years, there has been an increasing amount of research supporting successful use of methotrexate in treating various skin diseases: universal and total alopecia areata, erosive vulvovaginal lichen planus, parthenium dermatitis (a form of allergic contact dermatitis found mainly in India and Australia on the plants of the Compositae family), reticulohistiocytosis, resistant acute varioliform lichenoid pityriasis (38-41).

Abbreviations

MTX – Methotrexate
ESR - Erythrocyte sedimentation rate
AST - Aspartate aminotransferase
AP – alkaline phosphatase
HIV - Human immunodeficiency virus
HCV – Hepatitis C virus
RNA - Ribonucleic acid
ALT - Alanine aminotransferase
gamma GT - gamma glutamyl transpeptidase

References

1. Bangert CA, Costner MI. Methotrexate in dermatology. Dermatol Ther 2007;20(4): 216-28.
2. Milojević M. Citotoksična sredstva. U: Karadaglić Đ. Dermatologija. Beograd: Vojnoizdavački zavod; 2000. str. 2251-6.
3. Barker J, Horn EJ, Lebwohl M, Warren RB,Nast A, Rosenberg W, et al. Assessment and management of methotrexate hepatotoxicity in psoriasis patients: report from a consensus conference to evaluate current practice and identify key questions toward optimizing methotrexate use in the clinic. J Eur Acad Dermatol Venereol 2011;25(7):758-64.
4. Katchamart W, Trudeau J, Phumethum V, Bombardier C. Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and meta-analysis. Ann Rheum Dis 2009;68(7):1105-12.
5. Hider SL, Bruce IN, Thomson W. The pharmacogenetics of methotrexate. Rheumatology 2007;46(10):1520-4.
6. Suzuki K, Doki K, Homma M, Tamaki H, Hori S, Ohtani H, et al. Co-administration of proton pump inhibitors delays elimination of plasma methotrexate in high-dose methotrexate therapy. Br J Clin Pharmacol 2009;67(1):44-9.
7. Lindsay K, Fraser AD, Layton A, Goodfield M, Gruss H, Gough A. Liver fibrosis in patients with psoriasis and psoriatic arthritis on long-term, high cumulative dose methotrexate therapy. Rheumatology 2009;48(5):569-72.
8. Berends MA, Snoek J, de Jong EM, van de Kerkhof PC, van Oijen MG, van Krieken JH, et al. Liver injury in long-term methotrexate treatment in psoriasis is relatively infrequent. Aliment Pharmacol Ther 2006;24(5):805-11.
9. Carneiro SC, Cássia FF, Lamy F, Chagas VL, Ramos-e-Silva M. Methotrexate and liver function: a study of 13 psoriasis cases treated with different cumulative dosages. J Eur Acad Dermatol Venereol 2008;22(1):25-9.
10. Thomas JA, Aithal GP. Monitoring liver function during methotrexate therapy for psoriasis: are routine biopsies really necessary? Am J Clin Dermatol 2005;6(6):357-63.
11. Prey S, Paul C. Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. Br J Dermatol 2009;160(3):622-8.
12. Strober BE, Menon K. Folate supplementation during methotrexate therapy for patients with psoriasis. J Am Acad Dermatol 2006;55(2):366-7.
13. Kozub P, Simaljakova M. Systemic therapy of psoriasis: methotrexate. Bratisl Lek Listy 2011;112(7):390-4.
14. Morgan SL, Baggott JE. Folate supplementation during methotrexate therapy for rheumatoid arthritis. Clin Exp Rheumatol 2010;28(61):102-9.
15. Haustein UF, Rytter M. Methotrexate in psoriasis: 26 years' experience with low-dose long-term treatment. J Eur Acad Dermatol Venereol 2000;14(5):382-8.
16. Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol 2009;60(5):824-37.
17. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4: Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol 2009;61(3):451-85.
18. Chládek J, Simková M, Vanecková J, Hroch M, Chládkova

J, Martínková J, et al. The effect of folic acid supplementation on the pharmacokinetics and pharmacodynamics of oral methotrexate during the remission-induction period of treatment for moderate-to-severe plaque psoriasis. Eur J Clin Pharmacol 2008;64(4):347-55.
19. Asawanonda P, Nateetongrungsak Y. Methotrexate plus narrowband UVB phototherapy versus narrowband UVB phototherapy alone in the treatment of plaque-type psoriasis: a randomized, placebo-controlled study. J Am Acad Dermatol 2006;54(6):1013-8.
20. Jager ME, Jong EM, Kerkhof PC, Seyger MM. Efficacy and safety of treatments for childhood psoriasis: a systematic literature review. J Am Acad Dermatol 2010;62(6):1013-30.
21. Collin B, Vani A, Ogboli M, Moss C. Methotrexate treatment in 13 children with severe plaque psoriasis. Clin Exp Dermatol 2009;34(3):295-8.
22. Syed TA, Hadi SM, Qureshi ZA, Nordstrom CG, Ali SM. Management of psoriasis vulgaris with methotrexate 0.25% in a hydrophilic gel: a placebo-controlled, double-blind study. J Cutan Med Surg 2001;5(4):299-302.
23. Patton T, Korman N. Role of methotrexate in the treatment of bullous pemphigoid in the elderly. Drugs Aging 2008;25(8):623-9.
24. Mutasim DF. Autoimmune bullous dermatoses in the elderly: an update on pathophysiology, diagnosis and management. Drugs Aging 2010;27(1):1-19.
25. Marie I. Therapy of polymyositis and dermatomyositis. Presse Med 2011;40(4):257-70.
26. Walling HW, Sontheimer RD. Cutaneous lupus erythematosus: issues in diagnosis and treatment. Am J Clin Dermatol 2009;10(6):365-81.
27. Klein A, Landthaler M, Karrer S. Pityriasis rubra pilaris: a review of diagnosis and treatment. Am J Clin Dermatol 2010;11(3):157-70.
28. Doherty CB, Rosen T. Evidence-based therapy for cutaneous sarcoidosis. Drugs 2008;68(10):1361-83.
29. Krunić A. Keratoakantom. U: Karadaglić Đ. Dermatologija. Beograd: Vojnoizdavački zavod; 2000. str. 834-41.
30. Graham RM. Reiter's disease. In: Rook A, Wilkinson DS, Ebling FJG, Champion RH, Burton JL, editors. Textbook of dermatology. 5th ed. Oxford: Blackwell Scientific Publications; 1992. p. 2455-67.
31. Mestel DS, Beyer M, Steinhoff M, Sterry W,Assaf C.The treatment of mycosis fungoides. Ital Dermatol Venereol 2008;143(6):395-408.
32. Whittaker SJ, Foss FM. Efficacy and tolerability of currently available therapies for the mycosis fungoides and Sezary syndrome variants of cutaneous T-cell lymphoma. Cancer Treat Rev 2007;33(2):146-60.
33. Yazici H, Fresko I, Yurdakul S. Behçet's syndrome: disease manifestations, management, and advances in treatment. Nat Clin Pract Rheumatol 2007;3(3):148-55.
34. Zoller L, Ramon M, Bergman R. Low dose methotrexate therapy is effective in late-onset atopic dermatitis and idiopathic eczema. Isr Med Assoc J 2008;10(6):413-4.
35. Weatherhead SC, Wahie S, Reynolds NJ, Meggitt SJ. An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. Br J Dermatol 2007;156(2):346-51.
36. Beltramelli M, Vercellesi P, Frasin A, Gelmetti C, Corona F. Localized severe scleroderma: a retrospective study of 26 pediatric patients. Pediatr Dermatol 2010;27(5):476-80.
37. Kroft EB, Creemers MC, van den Hoogen FH, Boezeman JB, de Jong EM. Effectiveness, side-effects and period of remission after treatment with methotrexate in localized scleroderma and related sclerotic skin diseases: an inception cohort study. Br J Dermatol 2009;160(5):1075-82.
38. Jang N, Fischer G. Treatment of erosive vulvovaginal lichen planus with methotrexate. Australas J Dermatol 2008;49(4):216-9.
39. Sharma VK, Bhat R, Sethuraman G, Manchanda Y. Treatment of parthenium dermatitis with methotrexate. Contact Dermatitis 2007;57(2):118-9.
40. Kaçar N, Tasli L, Argenziano G, Demirkan N. Reticulohistiocytosis: different dermatoscopic faces and a good response to methotrexate treatment. Clin Exp Dermatol 2010;35(4):120-2.
41. Lazaridou E, Fotiadou C, Tsorova C, Trachana M, Trigoni A, Patsatsi A, et al. Resistant pityriasis lichenoides et varioliformis acuta in a 3-year-old boy: successful treatment with methotrexate. Int J Dermatol 2010;49(2):215-7.

Upotreba metotreksata u dermatologiji

Sažetak

Uvod: Metotreksat (MTX) je citoksični lek iz grupe antimetabolita, antagonist folne kiseline. Osim u onkologiji i reumatologiji, široko se upotrebljava i u dermatologiji.

Najznačajnije indijacije su teži oblici psorijaze, ali se s uspehom koristi kod niza drugih, etiološki i patogenetski različitih dermatoza: buloznog pemfigoida, dermatomiozitisa, pitirijaze rubre pilaris, sarkoidoze, T-ćelijskih limfoma, Behčetove bolesti, adultnog atopijskog ekcema, sklerodermije, Rajterovog sindroma i mnogih drugih.

Kod dermatoloških indikacija metotreksat se obično uzima u niskim, oralnim dozama, 5-25 mg jedanput sedmično. Nakon oralne primene ovih doza MTX maksimalna koncentracija u krvi se postiže od 45 minuta do dva sat. Farmakokinetika leka je vezana i za starost pacijenta, tako da je kod mlađih osoba veća distribucija i eliminacija leka nego kod starijih. Kod

nekih oboljenja se može primeniti intraleziono ili u vidu lokalnog pripravka.

Neželjena dejstva: Najčešće neželjene reakcije MTX su od strane digestivnog trakta, hepatotoksičnost i hematološki poremećaji. Dijabetes i gojaznost su signifikantni rizični faktori za oštećenje jetre. Od hematoloških poremećaja najčešće se javlja megaloblastna anemija, ređe leukopenija i trombocitopenija. Ukoliko broj leukocita padne ispod 3000/mm³ ili broj trombocita ispod 100 000/mm³ lečenje se privremeno prekida. Ukoliko se vrednosti normalizuju tokom naredne nedelje, lečenje se može nastaviti, najčešće nižom dozom. U oko 2-19% lečenih mogu se javiti erozije na koži ili sluzokoži, što zahteva prekid terapije MTX. Ređe se mogu javiti: urtikarija, akralni eritem, alopecija. Neželjene reakcije se rijetko javljaju i od strane respiratornog sistema u vidu pneumopatija i fibroze. Fibroza pluća je takođe indikacija za prekid terapije MTX.

Kumulativna doza MTX i punkciona biopsija jetre : Sve više je pristalica koji smatraju da ukoliko bolesnik nema faktore rizika za oboljenja jetre i ukoliko ima laboratorijske analize u granici referentnih vrednosti, biopsiju treba uraditi nakon kumulativne doze od 4 g.

MTX i folna kiselina: Danas se obično daje 5 mg folne kiseline, dan nakon uzimanja MTX. Ukoliko se jave akutni neželjeni efekti metotreksata savjetuje se primjena ampuliranog oblika fiziološki aktivne forme folne kiseline.

Interakcije: S obzirom da određeni lekovi utiču na različite metaboličke faze metotreksata i mogu povećati njegovo toksično dejstvo, neophodno je voditi računa o istovremenom propisivanju drugih lekova. To se pre svega odnosi na neke antibiotike, lekove iz grupe nesteroidnih antiinlamatornih lekova, antiepileptike, retinoide, inhibitore protonske pumpe. Lekovi kao što su: fenitoin, barbiturati, tetraciklini, fenilbutazon, salicilati, sulfametoksazol-trimetoprim, potiskuju MTX vezan za proteine plazme i povećavaju količinu slobodnog, biološki aktivnog leka u krvi, a samim tim povećavaju rizik hematološke toksičnosti. Drugi lekovi kao npr. nesteroidni antiinflamatorni lekovi (ketoprofen, fenilbutazon, salicilati), sulfonamidi smanjuju tubularnu sekreciju i renalni klirens, produžavajući poluživot biološki aktivnog MTX. Ciklosporin snižava renalni klirens MTX. Dipiridamol dovodi do produženog djelovanja MTX zbog intracelularne akumulacije. Lekovi koji utiču na metabolizam folne kiseline, kao npr. fenitoin, sulfonamidi, trimetoprim takođe mogu povećati toksičnost MTX.

Dermatološke indikacije: Najznačajnije indikacije su teži oblici psorijaze, ali se s uspehom koristi kod niza drugih, etiološki i patogenetski različitih dermatoza: buloznog pemfigoida, dermatomiozitisa, pitirijaze rubre pilaris, sarkoidoze, T-ćelijskih limfoma, Behčetove bolesti, adultnog atopijskog dermatitisa, sklerodermije, Rajterovog sindroma i mnogih drugih.

Psorijaza: Najčešća dermatološka indikacija za upotrebu MTX je psorijaza. Uglavnom se radi o težim oblicima bolesti: eritrodermija, atropatska psorijaza, pustulozni oblici, izvjesne forme plak psorijaze (kod kojih je zahvaćeno više od 50% kože). Efikasan je i u lečenju nokatne psorijaze (*psoriasis unguium*). Uobičajene doze MTX u lečenju psorijatičnih bolesnika su 7,5-20 mg sedmično. Do vidnog poboljšanja dolazi obično nakon dve do tri nedelje lečenja, a potpuna remisija nakon osam nedjelja. Postignuti terapijski efekat se održava najmanjom efikasnom dozom lijeka koja se može uzimati mesecima, nekada godinama. U slučaju prestanka uzimanja leka (iz bilo kog razloga), ne dolazi do tzv. *rebound* fenomena, odnosno pogoršanja kliničke slike psorijaze. MTX danas ima aktuelno mesto i u lečenju psorijaze u dječjem uzrastu. Postoji i lokalni pripravak metotreksata koji se s efikasno koristi u lečenju određenih oblika psorijaze u vidu 0,25% i 1% hidrofilnog gela.

Bulozna oboljenja: Od autoimunih buloznih dermatoza MTX se najčešće koristi u lečenju buloznog pemfigoida. Zadovoljavajući terapijski efekat kod ovih bolesnika može se postići malim dozama MTX 5-10 mg sedmično. Kod grupe pemfigusa metotreksat se ređe koristi, uglavnom kao ađuvantna terapija. Primjenjuje se u generalizovanim, upornim oblicima benignog familijarnog pemfigusa (*Hailey-Haileyjeva* bolest).

Dermatomiozitis: Kod slabog odgovora na prednizon MTX i azatioprin su prva linija imunosupresiva u lečenju ove bolesti.

Diskoidni eritemski lupus: MTX je kod ovog oboljenja ađuvantni lek i upotrebljava se uglavnom kod oblika rezistentnih na standardnu terapiju.

Pitirijaza rubra pilaris: Kod većine pacijenata zadovoljavajuća remisija se može postići malim

dozama MTX (5-10 mg sedmično) u periodu od nekoliko meseci.
Sarkoidoza: U hroničnim oblicima MTX se upotrebljava u dozi 15-20 mg sedmično, 6-8 nedjelja.
Keratoakantom: Kod nekih oblika keratoakantoma, kao što je *centrifugum marginatum* oblik, s uspehom se koristi intraleziona aplikacija MTX.
Rajterov sindrom: Kod težih, hroničnih oblika oboljenja, rezistentnih na nesteroidnu anti-inflamatornu terapiju i konvencionalnu terapiju, lek izbora je MTX u dozi 7,5-15 mg nedeljno.
T - ćelijski limfomi: U ovu grupu spadaju: *mycosis fungoides*, *Sy. Sezary, reticulosis pagetoides*, granulomatozni kutani i grupa retkih, visoko malignih T ćeliskih limfoma. U dermatološkoj praksi češće od ostalih sreće se *mycosis fungoides*. Terapija MTX se kod ovih bolesnika najčešće sprovodi u III stadijumu (po TNM *staging*-u T ćelijskih kutanih limfoma) kao monoterapija ili u kombinaciji sa ostalim terapijskim modalitetima
Behčetova bolest: Kod ove bolesti MTX je ađuvantni lek i može se u izvesnim slučajevima dati 7,5-15 mg sedmično. Atopijski dermatitits: U posljednje vreme sve više je radova koji navode povoljan efekat niskih doza MTX u lečenju umerenih do teških, refrakternih oblika atopijskog dermatitisa kod odraslih osoba .
Morfea: MTX se koristi u lečenju svih oblika cirkumskriptne sklerodermije kod odraslih, ali i kod dece, obično u kombinaciji sa sistemskim kortikosteroidima.
Ostale indikacije: U poslednjih nekoliko godina se u literaturi mogu naći podaci o uspešnom korišćenju metotreksata u lečenju niza drugih dermatoza kao što su: univerzalna i totalna alopecija, erozivni vulvovaginalni lihen planus, *Parthenium* dermatitis, retikulohistiocitoza, rezistentni oblik *pityriasis lichenoides et varioliformis acuta* (36-39).
Zaključak: Ukoliko se napravi pravilan odabir bolesnika, lek uzima pravilno i poštuje preporučeni laboratorijski monitoring, radi se o efikasnom i sigurnom leku koji je može uzimati mesecima i godinama.

Ključne reči

Metotreksat + primena i doziranje + neželjena dejstva + farmakokinetika + terapijska primena + toksičnost; Kožne bolesti + farmakoterapija; Dermatologija; Dermatološki agensi

Topical treatment of infantile hemangiomas – where are we now?

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Abstract

Infantile hemangiomas are the most common, benign vascular tumors of infancy. Their main feature is spontaneous involution over months to years after an initial phase of rapid proliferation. Small, superficial lesions usually resolve without sequel, but scarring and disfigurement are still possible, while the cosmetic outcome is unpredictable. Thus, inflantile hemangiomas benefit from non-aggressive topical treatment, because it is safe and with an overall outcome comparable to spontaneous involution. The available topical agents reported in the literature to satisfy these requirements are topical beta-blockers, imiquimod and topical corticosteroids. However, none of these have been assessed in randomized controlled trials, and standardized treatment recommendations about precise dosing and patient selection are not available yet.

Key words

Hemangioma + diagnosis + therapy; Skin Neoplasms; Administration, Topical; Aminoquinolines; Neoplasm Regression, Spontaneous; Treatment Outcome

Infantile hemangiomas (IHs) are the most common, benign vascular tumors of infancy affecting up to 10% of all children. They are characterized by a natural course of three phases – fast initial proliferation, stabilization and prolonged spontaneous involution. According to the depth of involvement, IHs are classified into superficial, mixed and deep. Regarding their distribution, IHs are localized and segmental.

The current concept in the management of IHs is to prevent or improve scarring and disfigurement, as well as functional and life-threatening complications. Small lesions (< 5 cm) are usually managed with active non-intervention, i.e. active monitoring without active treatment. Nevertheless, even small superficial hemangiomas may leave residual lesions or be associated with complications, ulceration, crusting and bleeding. Besides from expected spontaneous involution, factors that lead to complications have not yet been identified, and the cosmetic outcome remains unpredictable. Additionally, IHs are often distressing for both the parents and the growing child, especially when on the face and neck, and parents are anxious to achieve early improvement rather than wait and see.

Even though treatment is not warranted for small and superficial IHs, since the overall outcome may be compared with spontaneous involution in the long term, early non-aggressive therapeutic intervention with a safe and effective topical modality has several advantages over "active non-intervention". Such advantages include prophylaxis for better cosmetic outcome, by preventing fibro-fatty tissue deposition and parents' and patient's psychological distress.

Several topical agents have been used in recent years to treat IHs with variable success. These include topical beta-blockers, imiquimod and topical corticosteroids. Unfortunately, data from large, prospective, randomized, controlled trials are not available for any of these agents, so recommendations about their use and monitoring are based on case reports/series and small studies. Currently, a protocol

for a standardized management of small, superficial IHs does not exist. Treatment associated morbidity prevents the use of systemic therapies, thus creating a niche for a therapeutic agent with a more favorable risks/benefits ratio is necessary. The ideal topical treatment for these cases should be both efficient and minimally irritant at the site of application. At the same time, it should provide very little absorption to prevent systemic effects.

Topical beta-blockers

Propranolol is a well-known non-selective β-adrenergic antagonist, which competitively inhibits the β_1 and β_2-adrenoreceptors expressed on endothelial cells. It has been used to treat heart problems in children for over 40 years. Its anti-proliferative effect in IHs has been serendipitously found in 2008 by Léauté-Labrèze et all., during the treatment of secondary hypertrophic obstructive cardiomyopathy induced by systemic corticosteroid treatment administrated for nasal capillary hemangioma (1). The first report of the index case was followed by numerous reports, case series and randomized clinical trials showing its remarkable efficacy and good safety. Propranolol has since become the first choice therapy for complicated and/or large IHs.

The knowledge about the action of beta-blockers in IHs is incomplete. Three pharmacodynamic mechanisms are believed to contribute to their effectiveness. These are early vasoconstriction, angiogenesis inhibition and apoptosis induction, clinically translated into change of surface color within the first 24-72h, growth arrest and regression, respectively (2).

Two topical beta-blockers are reported to be highly effective and safe in the treatment of IHs: timolol maleate and propranolol hydrochloride.

Timolol maleate

Timolol is a topical non-selective beta-adrenergic antagonist, licensed and used for the treatment of open-angle glaucoma and increased intraocular pressure for over 30 years. The drug is available as a 0.1% or 0.5% solution or gel formulation. Several case reports/series give evidence about its efficacy for small, superficial IHs (3-6).

The pharmacokinetics of topically applied timolol has not been thoroughly studied. Following ophthalmic administration, up to 80% of the drug is systemically absorbed (7) with about 50% bioavailability in healthy volunteers (8). However, ophthalmic data should not be directly extrapolated for cutaneous application given the differences in structure, permeability and vascular supply between the skin and the ophthalmic tissues. Studies on the pharmacokinetics and beta-blocking effects of transdermal timolol patches (5% timolol, 0.2 mg/cm^2) showed plasma concentration levels below the detection limit after application for 48 hours (9). The only side effect observed after patch application is skin irritation with 20% timolol. When used to treat IHs, 0.1% and 0.5% timolol maleate has so far not given any systemic adverse reactions (3-5). Nevertheless, the available safety data are still insufficient, and specialists involved in the treatment with timolol should be alert about the side effects of beta-blocker and monitor infants accordingly.

The first report on the topical treatment of IHs with timolol was published in 2010, when Guo and Ni observed complete regression of a superficial capillary peri-orbital hemangioma in a 4-month old baby treated with topical timolol solution 2 times daily for several months (10). They further reported 7 children with superficial peri-ocular IHs treated by the same protocol with reduction of the size and volume of lesions that varied from 55% to 95% (4). Regression of hemangiomas was associated with fast resolution of the visual impairment and function recovery.

Chakkittakandiyil et al. performed a retrospective, multicenter, cohort study, including 73 children with IHs. Sixty two were treated with 0.5% and the other 11 with 0.1% timolol gel solution twice daily without occlusion (6). The mean treatment duration was 3.4 ± 2.7 months with a mean visual analogue scale - VAS improvement at the last follow-up visit of 45 ± 29.5%. Only one patient did not respond to the treatment, and only one experienced systemic side effects (sleep disturbance). The authors identified predictors of better response: superficial type of hemangioma, duration of treatment for more than 3 months and higher drug concentration.

The results from available studies and our experience from a prospective study (in press) show that topical timolol is highly effective and a relatively safe treatment option for superficial IHs. It can be recommended primarily for small, localized lesions on the face for achieving a predictable cosmetic

outcome. Timolol is also suitable for small, superficial hemangiomas on the trunk and extremities or for larger superficial lesions, when parents prefer treatment to active non-intervention.

For maximum effectiveness the treatment should continue for at least 4-6 months or until complete resolution, and should be started early - in the proliferative phase. The drug is also effective for involuting lesions in consistency with the reported effectiveness of oral propranolol (11). Therefore, topical timolol may also be used in patients who have not sought or have not benefited from early therapy. In contrast with recent literature reports (12), our experience and literature data show that IHs requiring systemic intervention are highly unlikely to benefit from topical treatment as both the amount of active substance applied and the rate of absorption are relatively low.

Propranolol

Topical formulations of 1% propranolol have also shown beneficial effects on small IHs without safety concerns (13). Kunzi-Rapp reported 45 children with 65 hemangiomas treated with 1% propranolol in a hydrophilic ointment. The drug was applied twice daily and treatment duration varied from 1 to 10.5 months. Seven infants included in the study were pre-term and low-weight. Regression or stabilization of growth was observed in 85% of hemangiomas with early intervention in the proliferative phase. No side effects, including changes in blood pressure or heart rate in pre-term infants, were noticed or reported by parents.

Similar to timolol, propranolol pharmacokinetics after topical cutaneous application has not been studied in details. *In vitro* studies of transdermal delivery systems for topical propranolol showed 10.4% to 36.6% skin accumulation of the drug (14). Absorption resulting in systemic bioavailability was 4.1% to 16.1%. Skin irritations have been reported with high concentrations and dosage, but in recent studies of percutaneous permeation of propranolol no signs of irritation were observed on both human and rat skin (15).

Imiquimod

Imiquimod is a topical immunomodulator that stimulates activation of immune response at the site of application. It activates dendritic cells toll-like receptor (TLR) 7 and triggers production of proinflammatory cytokines - IFN-α, IFN-γ, TNF-α, IL-1, IL-5, IL-8, IL-10, IL-12, and the antiangiogenic factor such as tissue inhibitor of matrix metalloproteinases (16). Imiquimod has antiproliferative and antiangiogenic effects in a murine model of vascular tumor (17). Its primary function as an immune response trigger translates clinically into expected inflammation with erythema, edema and scales or crusts. Some children may not achieve satisfactory regression due to suppressed reactivity to TLR-antagonists in newborns, or due to the lack of effectively functioning TLR-7 in this age group (18).

Martinez et al. were the first to apply 5% imiquimod to treat IHs in 2002 (19). They reported regression in two children, aged 4 and 7 months, with mixed hemangiomas. The drug was applied 3 times a week for the first 4 weeks, followed by 5 times a week until achievement of desired results. This pioneering report was followed by several other case/series reports and trials (20-23).

Therapy with imiquimod 5% cream is effective only for superficial IHs or for the superficial part of mixed IHs, as observed in retrospective studies (20) and in an open prospective study designed to assess the efficacy and safety of this treatment modality (21).

To properly compare the efficacy versus spontaneous involution, Jiang et al. conducted a prospective self-controlled study of imiquimod 5% cream in uncomplicated, proliferative, superficial or mixed hemangiomas in 44 patients aged 1 to 12 months (24). Each treated lesion was divided into two sections: one half was treated with the active drug once every other night for 16 weeks, and the other half was left as an untreated self-control site. Marked improvement was observed in the treated half, compared to the non-treated one. Local skin reactions occurred in 61%. The most common were crusting (55%) and erythema or edema (16%). Scarring developed in 5% of all patients. The incidence of side effects was not statistically different between the sides with active treatment and control sides.

Currently, there are no established recommendations for dose and duration of treatment with imiquimod and the therapy should be individualized for each child's clinical response and rate of irritation. Most patients benefit from applying

imiquimod 3 times per week. In case of unsatisfactory response after 4 weeks, the frequency of application may be increased to 5-7 times a week (20-23). The average duration of treatment is 16 weeks, but this period may be prolonged or shortened if necessary. In case of serious skin irritation with crusting and/or erosion, drug application should be discontinued until fading of local symptoms to prevent or minimize the risk of scarring.

Imiquimod 5% cream has a good safety profile in children. Side effects are similar to those observed in adults and include local irritation at the site of application with erythema, crusts and development of contact dermatitis (21).

Pharmacokinetic studies in infants and children show that systemic absorption following local application is very low and, as a rule, systemic effects, including functional impairment of internal organs, are highly unlikely (21, 25). The most commonly reported systemic adverse reactions are flu-like symptoms, particularly fever (23).

Besides its proven efficacy and relative safety, imiquimod 5% cream is not widely used. Its main limitation is the risk of severe irritation resulting in scarring. Additionally, imiquimod should be used with caution for peri-orbital hemangiomas, since the expected but unpredictable extent of inflammation may lead to peri-orbital and intra-orbital edema and visual impairment (26).

Topical corticosteroids

Although systemic corticosteroids have been the mainstay of treatment for IHs for many years, the use of topical corticosteroids is not a common practice and only a limited number of case series in the literature support their efficacy (27-30). The main concern related to the use of topical steroids in children is atrophy and related skin side effects associated with prolonged application and suppression of the adrenal axis resulting from possible systemic absorption after extensive application. These effects, however, can be prevented by strict criteria for lesion size and controlled duration of treatment.

Corticosteroids inhibit the expression of vascular endothelial growth factor–A (VEGF-A), monocyte chemoattractant protein-1 (MCP-1), urokinase plasminogen activator receptor (uPAR), and interleukin-6 (IL-6) by targeting the NF-κB in hemangioma stem cells (HemSCs), but not in hemangioma endothelial cells (HemECs) in a murine model and *in vitro* (31,32) Downregulation of VEGF-A in these cells translates into vasculogenesis inhibition *in vivo*. This most probably accounts for the higher rates of effectiveness in the early proliferative phase when the ratio of immature stem cells to mature endothelial cells is higher.

Elsas and Lewis reported five children (27) and Cruz et al. reported three children (28) with vision-threatening peri-ocular capillary hemangiomas treated with topical clobetasol propionate cream. All patients experienced improvement with a reduction in the size of hemangioma and clearing of the visual axis, but the duration of treatment was not specified. The rate of improvement was slower compared to intralesional corticosteroids, but the overall effect was comparable. Local side effects were not observed in any of the 8 children, and the adrenal function was not impaired in patients reported by Cruz et al.

In a retrospective study, Garzon et al. (29) reviewed 34 infants aged 2.5 weeks to 8 months, 24 with superficial and 10 with mixed and deep hemangiomas. Patients were treated with topical clobetasol propionate, applied once or twice daily for a period of 2 to 21.5 weeks. Thirty-five percent had a good response, 38% had partial response, and 27% did not respond to the treatment. Cessation of growth occurred earlier than expected for spontaneous involution. No significant difference in the age among the 3 response groups or duration of treatment was observed. Due to the retrospective nature of the study, side effects were not evaluated.

A mid-potency topical corticosteroid was also assessed in one study as an alternative to intralesional application. Mometasone furoate, applied twice daily as a thin film, was used to treat 52 children with small (< 5 cm), superficial hemangiomas. Excellent response with cessation of growth, lightening of color and flattening of the surface was achieved in 50%, good response in 36.5% and poor in 13.4%. The overall response rate was 86.5%, comparable to the response rate of intralesional steroids. Complications observed were mild itching and irritation (19.2%) and hypopigmentation (7.6%).

Treatment of ulcerations

Becaplermin

Becaplermin is a platelet derived growth factor used in the treatment of diabetic ulcers. It was first used for pediatric patients in 2002, to treat an ulcerated hemangioma associated with PHACES (the association of large perineal haemangiomas – P, with the following congenital abnormalities: external genitalia malformations – E; lipomyelomeningocoele – L; vesicornenal abnormalities – V; imperforate anus – I; and skin tags - S) syndrome leading to complete reepitelization (33). Metz et al. used 0.01% becaplermin gel in 8 children with perineal ulcerations and achieved 100% resolution during a period of 3 to 21 days (34). No adverse events were reported. Despite its high cost, the short course of treatment and the limited number of medical visits reduce the overall cost of treatment to make it the least expensive alternative compared with all other ulceration management modalities.

Nevertheless, becaplermin is currently recommended as a second line treatment for ulcerated IHs resistant to standard care. The main reason is a warning issued by FDA about increased mortality, but not morbidity, from malignancies in adult patients regular users of the drug. Even though such tendency has not been reported in infants, until further data are available, becaplermin is recommended only for ulcerated hemangiomas that fail to respond to first line management (35).

Conclusion

The majority of IHs are superficial, and the decision to treat or not should be individualized for each case. Although spontaneous involution with time is a rule, residual fibro-fatty depositions and scarring are not unusual and a potential for cosmetic disfigurement could be considered as a treatment rationale, given that there are therapeutic options that are comparable to active non-intervention, regarding efficacy and safety.

Compared to other available treatment modalities, considered in mild, uncomplicated IHs, topical beta-blockers have so far shown the same efficacy paired with a better safety profile. This highly favourable efficacy/safety ratio justifies their use as a first-line treatment for this subset of IHs.

However, further studies are required to identify precise dosing regimens of all available therapies in order to minimize side effects and enhance the efficacy.

Abbreviations

His - Infantile hemangiomas
VAS – visual analog scale
TLR toll-like receptor
IFN-α – Interferon gamma
IFN-γ – Interferon gamma
TNF-α – Tumor necrosis factor-alpha
IL-1 – Interleukin – 1
VEGF-A- vascular endothelial growth factor–A
MCP-1 - Monocyte chemoattractant protein-1
uPAR - Urokinase plasminogen activator receptor
NF-κB – Nuclear factor kB
HemSCs - hemangioma stem cells
HemECs - hemangioma endothelial cells
PHACES - perineal haemangiomas (P) with the following congenital abnormalities: external genitalia malformations (E), lipomyelomeningocoele (L), vesicorenal abnormalities (V), imperforate anus (I) and skin tags
FDA - Food and Drug Administration

References

1. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo, JB, Taïeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008;358:2649-51.
2. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. Br J Dermatol 2010;163:269-74.
3. Pope E, Chakkittakandiyil A. Topical timolol gel for infantile hemangiomas: a pilot study. Arch Dermatol 2010;146:564-5.
4. Ni N, Langer P, Wagner R, Guo S. Topical timolol for periocular hemangioma: report of further study. Arch Ophthalmol 2011;129:377-9.
5. Blatt J, Morrell DS, Buck S, Zdanski C, Gold S, Stavas J, et al. {beta}-Blockers for Infantile Hemangiomas: A Single-Institution Experience. Clin Pediatr (Phila) 2011;50:757-63.
6. Chakkittakandiyil A, Phillips R, Frieden IJ, Siegfried E, Lara-Corrales I, Lam J, et al. Timolol Maleate 0.5% or 0.1% Gel-Forming Solution for Infantile Hemangiomas: A Retrospective, Multicenter, Cohort Study. Pediatr Dermatol. 2011; [Epub ahead of print].
7. Volotinen M, Hakkola J, Pelkonen O, Vapaatalo H, Mäenpää J. Metabolism of ophthalmic timolol: new aspects of an old

drug. Basic Clin Pharmacol Toxicol 2011;108:297-303.
8. Zimmerman TJ, Kooner KS, Morgan KS. Safety and efficacy of timolol in pediatric glaucoma. Surv Ophthalmol 1983;28:262-4.
9. Kubota K, Yamada T, Kikuchi K, Koyama E, Ishizaki T. Pharmacokinetics and beta-blocking effects of transdermal timolol. Eur J Clin Pharmacol 1993;44:493-5.
10. Guo S, Ni N. Topical treatment for capillary hemangioma of the eyelid using beta-blocker solution. Arch Ophthalmol 2010;128:255-6.
11. O'Loughlin A, O'Donnell B, Watson R. Mature infantile haemangiomas role for propranolol. J Eur Acad Dermatol Venereol 2010;25:1363-4.
12. Khunger N, Pahwa M. Dramatic response to topical timolol lotion of a large hemifacial infantile haemangioma associated with PHACE syndrome. Br J Dermatol 2011;164:886-8.
13. K, Kunzi-Rapp. Topical Propranolol Therapy for Infantile Hemangiomas. Pediatr Dermatol 2011; [Epub ahead of print].
14. Ademola JI, Chow CA, Wester RC, Maibach HI. Metabolism of propranolol during percutaneous absorption in human skin. J Pharm Sci 1993;82:767-70.
15. Ahad A, Aqil M, Kohli K, Sultana Y, Mujeeb M, Ali A. Interactions between novel terpenes and main components of rat and human skin: mechanistic view for transdermal delivery of propranolol hydrochloride. Curr Drug Deliv 2011;8:213-24.
16. Hurwitz DJ, Pincus L, Kupper TS. Imiquimod: a topically applied link between innate and acquired immunity. Arch Dermatol 2003;139:1347-50.
17. Sidbury R, Neuschler N, Neuschler E, Sun P, Wang XQ, Miller R, et al. Topically applied imiquimod inhibits vascular tumor growth in vivo. J Invest Dermatol 2003;121:1205–9.
18. Levy O, Zarember KA, Roy RM, Cywes C, Godowski PJ, Wessels MR. Selective impairment of TLR-mediated innate immunity in human newborns: neonatal blood plasma reduces monocyte TNF-alpha induction by bacterial lipopeptides, lipopolysaccharide, and imiquimod, but preserves the response to R-848. J Immunol 2004;173:4627–4.
19. Martinez MI, Sanchez-Carpintero I, North Pe, Mihm MC. Infantile haemangioma: clinical resolution with 5% imiquimod cream. Arch Dermatol 2002;138:881-4.
20. Ho NTC, Lansang P, Pope E. Topical imiquimod in the treatment of infantile haemangiomas: A retrospective study. J Am Acad Dermatol 2007;56:63-8.
21. McCuaig CC, Dubois J, Powell J, Belleville C, David M, Rousseau E, et al. A Phase II, Open-Label Study of the Efficacy and Safety of Imiquimod in the Treatment of Superficial and Mixed Infantile Hemangioma. Pediatr Dermatol 2009;26:203-12.
22. Welsh O, Olazaran Z, Gomez M, Salas J, Berman B. Treatment of infantile haemangiomas with short-term application of imiquimod 5% cream. J Am Acad Dermatol 2004;51:639–42.
23. Barry RBM, Hughes BR, Cook LJ. Involution of infantile haemangiomas after imiquimod 5% cream. Clin Exp Dermatol 2008;33:446–9.
24. Jiang C, Hu X, Ma G, Chen D, Jin Y, Chen H, et al. A prospective self-controlled phase II study of imiquimod 5% cream in the treatment of infantile hemangioma. Pediatr Dermatol. 2011;28:259-66.
25. Myhre PE, Levy ML, Eichenfield LF, et al. Pharmacokinetics and safety of imiquimod 5% cream in the treatment of molluscum contagiosum in children. Pediatr Dermatol 2008;25:88–95.
26. Hussain W, Judge MR. The role of imiquimod in treating infantile haemangiomas: cause for concern? Clin Exp Dermatol 2009;34:e257.
27. Elsas FJ, Lewis AR. Topical treatment of periocular capillary hemangioma. J Pediatr Ophthalmol Strabismus. 1994;31:153-6.
28. Cruz OA, Zarnegar SR, Myers SE. Treatment of periocular capillary hemangioma with topical clobetasol propionate. Ophthalmology 1995;102:2012-5.
29. Garzon MC, Lucky AW, Hawrot A, Frieden IJ. Ultrapotent topical corticosteroid treatment of hemangiomas of infancy. J Am Acad Dermatol 2005;52:281-6.
30. Pandey A, Gangopadhyay AN, Sharma SP, Kumar V, Gupta DK, Gopal SC. Evaluation of topical steroids in the treatment of superficial hemangioma. Skinmed 2010;8:9-11.
31. Greenberger S, Adini I, Boscolo E, Mulliken JB, Bischoff J. Targeting NF-κB in infantile hemangioma-derived stem cells reduces VEGF-A expression. Angiogenesis 2010;13:327-35.
32. Greenberger S, Boscolo E, Adini I, Mulliken JB, Bischoff J. Corticosteroid suppression of VEGF-A in infantile hemangioma-derived stem cells. N Engl J Med 2010;362:1005-13.
33. Sugarman JL, Mauro TM, Frieden IJ. Treatment of an ulcerated hemangioma with recombinant platelet-derived growth factor. Arch Dermatol 2002;138:314-6.
34. Metz BJ, Rubenstein MC, Levy ML, Metry DW. Response of ulcerated perineal hemangiomas of infancy to becaplermin gel, a recombinant human platelet-derived growth factor. Arch Dermatol 2004;140:867-70.
35. Frieden IJ. Addendum: Commentary on becaplermin gel (Regranex) for hemangiomas. Pediatr Dermatol 2008;25:590.

Topikalni tretman infantilnih hemangioma – gde smo danas?

Sažetak

Uvod: Infantilni hemangiomi (IH) predstavljaju najčešće benigne vaskularne tumore u infantilnoj dobi; mogu biti prisutni kod 10% dece. Karakteriše ih prirodni tok koji protiče kroz tri faze: inicjalna s brzom proliferacijom; stabilizacija; prolongirana spontana involucija koja može trajati meseci i godinama. Male (< 5 cm), površinske lezije obično izčezavaju bez sekvela, ali ožiljavanje i kozmetski defekti mogu biti nepredvidivi.

Terapija: Savremeni koncept u lečenju IH se zasniva na prevenciji i ublažavanju ožiljavanja, kao I funkcionalnih pa i po život opasnih komplikacija.

Lokalna terapija: Trenutno ne postoji standardizovani protokol zbrinjavanja malih, površinskih IH. Morbiditet koji prati sistemsku terapiju, uslovljava da se lokalna terapija, kao lečenje prvog izbora u ovim slučajevima ogleda kroz efikasnost, minimalnu iritativnost na mestu aplikacije i nizak stepen apsorbcije a sve u cilju prevencije sistemskih efekata.

Preparati za lokalu primenu koji na osnovu literaturnih podataka ispunjavaju ove kriterijume su beta-blokatori, imikvimod i kortikosteroidi. Ipak, za sve tri grupe lekova, nedostaju rezultati randomiziranih kontrolisanih ispitivanja pa samim tim i standardizovane terapijske preporuke koje se odnose na izbor pacijenata i preciznost doziranja.

Beta-blokatori za lokalnu upotrebu: Pretpostavlja se da tri farmakodinamska mehanizma doprinose terapijskoj efikasnoti ovih preparata, rana vazokonstrikcija, inhibicija angiogeneze i indukcija apoptoze, što se klinički ogleda u promeni boje unutar prvih 24-72h, zaustavljanju daljeg porasta i sledstvenoj regresiji.

Lokalni pripravci dva beta-blokatora su u dosadašnjim ispitivanjima pokazala visok stepen efikasnosti i bezbednosti u lečenju IH: timolol maleat i propranolol hidrohlorid.

Timolol maleat: Ovo je lokalni neselektivni beta adrenergijski antagogonist. Dostupan je u obliku rastvora/gela u koncentraciji od 0.1% i 0.5% i treba ga aplikovati 2 puta dnevno u toku nekoliko meseci. Podaci o bezbednosti lečenja s timolom su nedovoljni i lekari treba da budu na oprezu kada su neželjena dejstva beta-blokatora u pitanju. Mi smo na osnovu rezultata sopstvenih istraživanja utvrdili faktore prediktore boljeg terapijskog ogovora: površinski tip hemangioma, trajanje lečenja duže od tri meseca, veća koncentracija leka. Timolol se preporučuje za lečenje prvenstveno malih, na licu lokalizovanih lezija, ali se može primeniti i kod onih lokalizovanih na leđima i ekstremitetima, kao i kod površinskih IH većih dimenzija, ukoliko roditelji to žele. Na osnovu svog iskustva, pojedini autori porede efikasnost u lečenju sa efikasnošću oralne primene propranolola.

Propranolol: Hidrofilna mast sa 1% propranololom aplikovana dva puta dnevno u trajanju od 1 do 10.5 meseci pokazala se efikasnom za lečenje malih IH. Na osnovu ispitivanja *in vitro* posle lokalne primene, akumulacija propranola u koži dostiže 10.4% do 36.6%. Posle absorpcije, sistemska bioraspoloživost je 4.1% do 16.1%. Do iritacije je dolazilo samo u slučajevima gde je primenjena visoka koncentracija leka.

Imikvimod: Imikvimod je imunomodulator a koristi se za lokalno lečenje, pri čemu je njegov antiproliferativni i antiangiogenezni efekat na vaskularne tumore ispitivan i dokazan kod eksperimentalnih životinja. Pokazao se efikastan bezbedan u obliku 5% krema za lečenje površinskih IH i za lećenje površinskih delova mešanih IH. U odsustvu zvaničnih preporuka, a u cilju postizanja maksimalne terapijske efikasnosti ali i izbegavanja iritacije, dozu leka i dužinu lečenja treba prilagoditi svakom pojedinom pacijentu. I pored dokazane efikasnosti i relativne bezbednosti, imikimod se nekoristi rutinski, uglavnom zbog povišenog rizika od pojave iritacije i ožiljavanja. Ukoliko se primeni za lečenje periorbitalnih HI, potreban je veliki oprez, s obzirom na nepredvidivu mogućnost pojave inflamacije, peri- i intra-orbitalnog edema, sa oštećenjem vida.

Kortikosteroidi: I pored toga što se lečenje IH godinama zasnivalo na sistemskoj primeni kortikosteroida, lokalna primena kortikosteroida ne predstavlja svakodnevnu praksu. Najveći oprez kod lokalne primene kortikosteroida kod dece usmeren je na prevenciju razvoja neželjenih efekata koji se javljaju nakon njihove dugotrajne i ekstenzivne aplikacije, kada usled atrofije kože može doći do njihove sistemske resorpcije te i supresije adrenalne povratne sprege.

Prevencija ovih neželjenih efekata sastoji se u poštovanju kriterijuma prilikom određivanja veličine površine na koju će se aplikovati kortikosteroidi i vremenskog trajanja njihove primene. Komparativne studije, koje su imale za cilj poređenje terapijskog efekta lokalne aplikacije i intralezionog ubrizgavanja kortikosteroida, nisu utvrdile značajnost razlika u stepenu postignutog poboljšanja nego u brzini njegovog nastanka.
Lečenje ulceracija: Bekaplermin predstavlja faktor rasta izolovan iz trombocita. Bekaplermin 0,01% gel preporučuje se samo za lečenje ulcerisanih hemangioma koji nisu reagovali povoljno na primenu prve terapijske linije.
Zaključak: Najveći broj infantilnih hemangioma pripada grupi površinskih hemangioma. Odluku o započinjanju lečenja treba uvek doneti individualno za svakog pacijenta. Iako do spontane regresije dolazi vremenom, gotovo po pravilu, nije neuobičajen razvoj lokalnog fibrolipomatoznog zadebljanja i ožiljnog tkiva na mestu postojeće lezije. Ukoliko govorimo o odnosu između poželjnog terapijskog benefita i bezbednosti njegovog postizanja, onda lokalna primena beta blokatora predstavlja prvu terapijsku liniju u lečenju infantilnih hemangioma.

Ključne reči

Hemangiom + dijagnoza + terapija; Neoplazme kože; Topikalna primena lekova; Aminokvinolini; Spontana regresija neoplazmi; Ishod lečenja

Lichen planus in the lines of Blaschko – a case report

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Abstract

Lichen planus is an acquired inflammatory disease of the skin, mucous membranes and nails. It is characterized by pruritic polygonal livid papules. The disease was first described by Erasmus Wilson in 1869. It is primarily a disease of adults, and it usually occurs between the ages of 30 and 60, without gender predominance. The exact incidence and prevalence of this disease are unknown, but it is thought to affect less than 1% of the general population (0.14 to 0.80%) (1).

A 63-year old male patient was admitted to our Department with itchy erythematous papules and plaques which appeared a month before admission. On admission, numerous erythematous and livid papules and plaques of polygonal shape up to 5 mm in diameter were present in the lines of Blaschko, along the left lower extremity, left side of the trunk and the left upper arm (Figures 1-3), while mucous membranes, nails and scalp were spared.

Blaschko-linear distribution of skin lesions was first described by a German dermatologist Alfred Blaschko in 1901 in his work "The distribution of nerves in the skin and their relationship to diseases of the skin". In 1978, Happle first published that genetic mosaicism was the cause of these peculiar skin changes (1,4,6). Although knowledge of mosaicism in the skin was further elucidated in articles of several authors (Taieb in 1994, Bolognia in 1994, Heide 1996), the exact mechanism and molecular basis for the development of Blashcko linear distribution has not been fully clarified yet (5). Blaschko lines may be related to X-linked, congenital and inflammatory dermatoses, and they may be found in several skin conditions like segmental forms of atopic dermatitis, erythema multiforme, pemphigus vulgaris, vitiligo, and granuloma annulare. This is a case report of a patient with a rare form of lichen planus, with typical clinical manifestations and with Blaschko-linear distribution. Lichen planus in the lines of Blaschko was also described in several other dermatoses: lichen striatus, lichen sclerosus, morphea, porokeratosis of Mibelli, mucinosis follicularis and psoriasis vulgaris. The treatment included topical corticosteroids under occlusion, due to comorbidities, with satisfactory response. Other options include, topical calcineurin inhibitors, intralesional and systemic corticosteroids, retinoids, phototherapy and in resistant cases that severely affect the quality of life methotrexate, cyclosporine and thalidomide.

Key words

Lichen Planus; Signs and Symptoms; Administration, Topical; Adrenal Cortex Hormones; Retinoids; Phototherapy

Lichen planus is an acquired inflammatory condition of the skin, mucous membranes and nails. It is characterized by eruption of pruritic polygonal livid papules. It was first described by Erasmus Wilson in 1869. It primarily affects adults, usually between 30 and 60 years of age, without gender predominance. The exact incidence and prevalence of this disease is unknown, but it is thought to affect less than 1% of the general population (0.14 to 0.80%) (1).

Lichen planus is a polygenic disorder, but sometimes it may show a segmental distribution, as a result of postzygotic mutation at an additional predisposing gene locus. The loss of heterozygosity may occur from a mutation, deletion or DNA recombination, leading to the formation of a keratinocyte clone that is more susceptible to development of the disease. Linear lichen planus is a rare manifestation of this disease and occurs in less than 0.2% of all patients (1).

Case report

A 63-year-old man was admitted to our Department due to itchy erythematous papules and plaques which appeared a month before admission. On admission, the patient presented with numerous erythematous and livid papules and plaques of polygonal shape, up to 5 mm in diameter, in the lines of Blaschko, along the left lower extremity, on the left side of the trunk and on the left upper arm (Figures 1-3), while mucous membranes, nails and scalp were spared. In the past 15 years the patient was treated for diabetes mellitus with complications: microangiopathy, polyneuropathy, and hyperlipidemia. Diabetes was treated with insulin and metformin, hyperlipidemia with simvastatin, polyneuropathy with alpha-lipoic acid, and hypertension with fosinopril and furosemide. The regular therapy was not changed before the onset of the disease. Complications led to amputation of the fifth toe on both feet and malum perforans pedis on

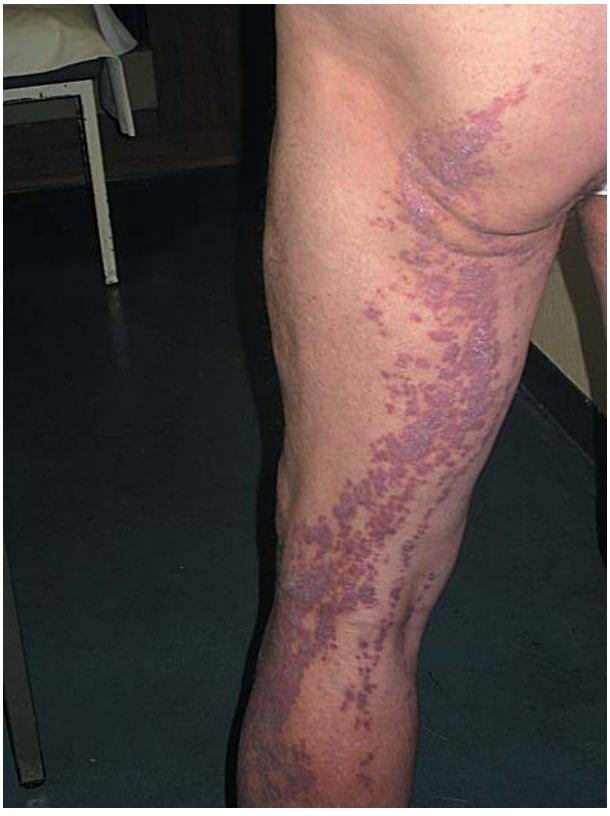

Figure 1. On admission, numerous erythematous and livid papules and plaques of polygonal shape up to 5 mm in diameter were present in the linear Blaschko distribution, along the left lower extremity

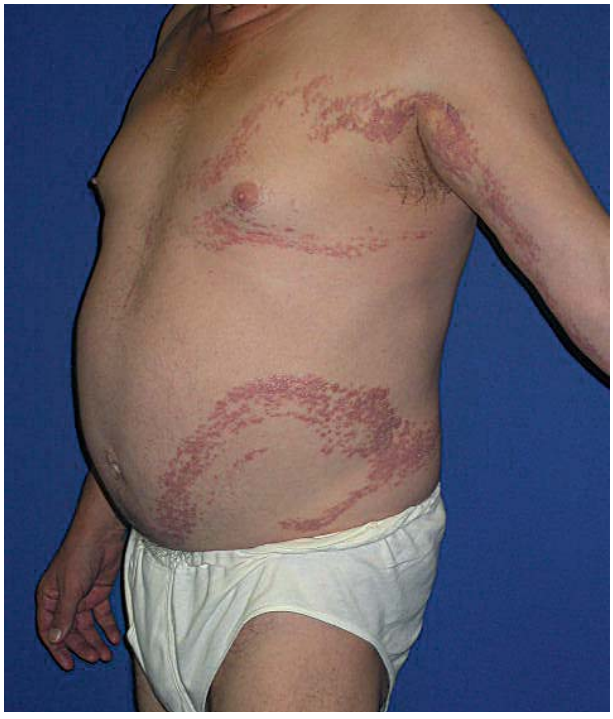

Figure 2. On admission, numerous erythematous and livid papules in the linear Blaschko distribution, along the left side of the trunk

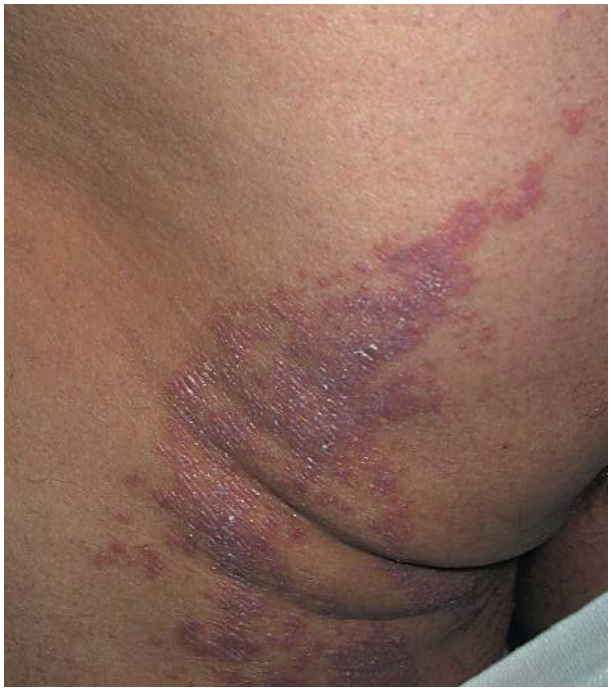

Figure 3. On admission, numerous erythematous and livid papules in the linear Blaschko distribution, along the left thigh

the left foot, with osteolysis of the phalanges up to the middle third of the fifth metatarsal bone.

Laboratory examination revealed increased sedimentation rate (51 and 33 mm/h), elevated CRP concentration (34,1 i 4,32 g/l), slight anemia with normal hemoglobin levels (RBC $3,95x10^{12}$/L), fasting blood sugar of 9.9 mmol/l, repeated 11.8 mmol/l, HbA1c 8,2%, while other parameters (CBC and DBC, AST, ALT, urea, creatinine, cholesterol, triglycerides, total bilirubin, albumin) were within normal range. Doppler ultrasonography of the lower extremities revealed diffuse metabolic changes on the large arterial vessel, but without stenoses or other hemodynamic changes, with arterial flow that could be traced to the distal parts with satisfactory perfusion. There were also no signs of venous insufficiency.

Biopsy of erythematous-livid papules was performed and histopathological analysis was consitent with lichenoid interface dermatitis, while direct immunofluorescence did not reveal deposits of immunoreactancts (immunoglobulins, complement or colloid boides) (Figure 4).

The long-term diabetes and its complications were relative contraindications for treatment with systemic corticosteroids, so therapy with potent topical steroids under occlusion (betamethasone dipropionate 0.05% ointment) was used leading to significant partial regression of lesions, with disappearance of itching after two weeks. Since the response to therapy was satisfactory at that point, the initially planned acitretin therapy was not introduced.

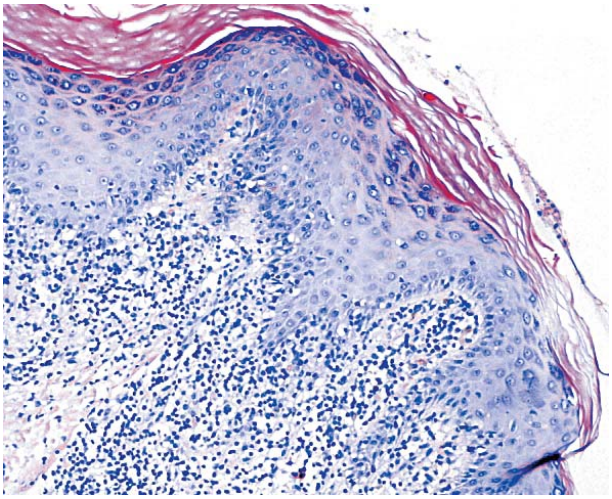

Figure. 4. Skin biopsy with hyperkeratosis, uneven hypergranulosis, moderate acanthosis and irregularly elongated epidermal ridges and signs of interface dermatitis (hematoxylin and eosin x 100)

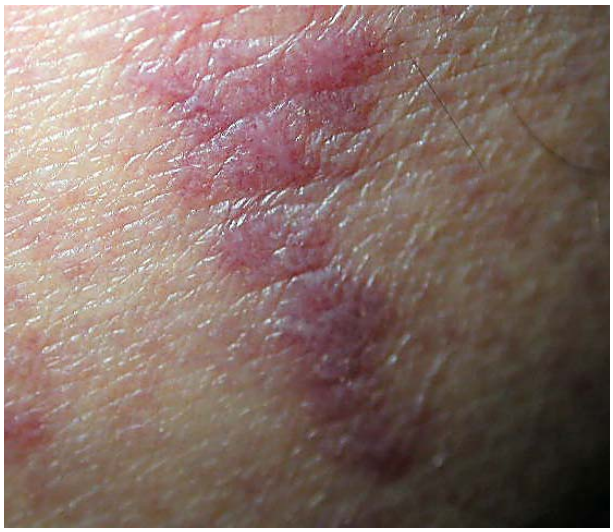

Figure 5. Numerous erythematous and livid papules of polygonal shape up to 5 mm in diameter in the linear Blaschko distribution

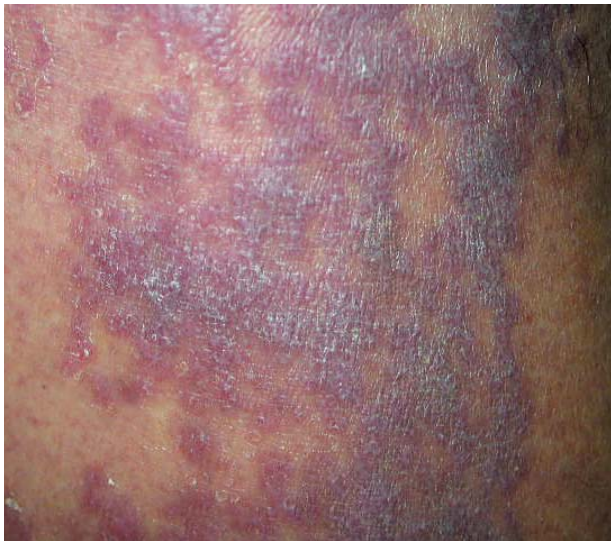

Figure 6. Numerous erythematous and livid papules of polygonal shape agglomerate to form a plaque

Discussion

Blaschko distribution of skin lesions was first described by the German dermatologist Alfred Blaschko in 1901 in his work "The distribution of nerves in the skin and their relationship to diseases of the skin". In 1978, Happle first reported that genetic mosaicism was the cause of these peculiar skin changes (1,4,6).

Although the knowledge of mosaicism in the skin was further elucidated in articles of several authors (Taieb in 1994, Bolognia in 1994, Heide 1996), the exact mechanism and molecular basis for the development of Blashcko distribution has not been fully clarified yet (5). Blaschko lines do not correspond to any known nervous, vascular or lymphatic structures, and they differ from other morphological lines like: Voight, Langer, embryonic cleavage and pigmentation demarcation lines. They are V-shaped on the upper back, inverted U-shaped on the upper chest, S-shaped on the abdomen, perpendicular on the extremities and never cross the center, but go along the central line of the trunk (2, 8). It is assumed that they represent the distribution of autonomous motor-visceral afferent nerve fibers, or are the result of stretching of the skin during embryogenesis. Blaschko lines may be related to X-linked, congenital and inflammatory dermatoses, and they are described in several skin conditions like segmental forms of atopic dermatitis, erythema multiforme, pemphigus vulgaris, vitiligo, and granuloma annulare (Table 1) (3).

Blaschko lichen planus was described in 0.2% of patients, resulting probably from postzygotic mutations, deletions or DNA recombination, in one of the genes that carry a predisposition to the development of the disease. Therefore, contrary to the generalized eruption to the yet unknown antigen, the reaction to the antigen manifests in a clone of keratinocytes susceptible to this disease.

In differential diagnosis, lichen striatus has similar clinical manifestations and distribution of skin lesions, but lichen striatus can be distinguished by its rapid development, generally after the fi rst year of life, thus being more common in children, the condition is often asymptomatic and usually self-limiting. Moreover, histopathological analysis in our patient was consistent with lichen planus. However, direct immunofluorescence was negative (which is not uncommon), probably due to the relatively short duration of the disease in our patient.

Table 1. Blaschko linear dermatoses and mosaicism*

X-linked mosaicism	Autosomal dominant mosaicism of non-lethal genes	Autosomal dominant mosaicism of lethal genes	Mosaicism of chromosomal abnormalities	Chimerism
Incontinentia pigmenti	Epidermolytic hyperkeratosis	Epidermal nevus	Hypomelanosis of Ito	Segmental hyperpigmentation
Goltz syndrome	Darier's disease	McCune-Albright syndrome		
Happle syndrome	Neurofibromatosis type I	CHILD syndrome		
Hypohydrotic ectodermal dysplasia	Gorlin syndrome	ILVEN		
	Comedo nevus	Proteus syndrome		
Menkes syndrome	Porokeratosis			
	Psoriasis			
	Lichen planus			
	Eczema (lichen striatus)			
	Vitiligo			

CHILD, congenital hemidyplasia with ichthhyosiform erythroderma and limb defects; ILVEN, inflammatory linear verrucous nevus.

The coexistence of lichen planus and diabetes mellitus has been described in the literature, and in one study around 50% of patients with lichen planus had glucose metabolism disorders and 25% had diabetes mellitus (9). In patients with lichen planus, levels of HbA1C, fasting glucose levels and insulin resistance were statistically higher than in the control group, and authors concluded that further studies are needed to examine this correlation, which can be explained by autoimmune etiopathogenesis of both diseases (9).

Conclusion

In conclusion, a patient with a rare form of lichen planus is described, with typical clinical manifestations of lichen planus but in the lines of Blaschko, which distribution is also described in several other dermatoses: lichen striatus, lichen sclerosus, morphoea, porokeratosis Mibelli, mucinosis follicularis and psoriasis vulgaris. The treatment included topical corticosteroids under occlusion, due to comorbidities, with a satisfactory response. Other options include topical calcineurin inhibitors, intralesional and systemic corticosteroids, retinoids, phototherapy and in resistant cases, that severely affect the quality of life, methotrexate, cyclosporine and thalidomide.

References

1. Kabassh C, Laude T, Weinberg J, Silverberg N. Lichen planus in the lines of Blaschko. Pediatr Dermatol 2002;19(6):541-5.
2. Pinheiro A, Mathew MC, Thomas M, Jacob M, Srivastava VM, Cherian R, et al. The clinical profile of children in India with pigmentary anomalies along the lines of Blaschko and central nervous system manifestations. Pediatr Dermatol 2007;24(1):11–7.
3. Moss C. cytogenetic and molecular evidence for cutaneous mosaicism: the ectodermal origin of Blaschko lines. Am J Med Genet 1999;85:330–3.
4. Rott HD. Extracutaneous analogies of Blaschko lines. Am J Med Genet 1999;85:338–41.
5. Grosshans EM. Acquired blaschkolinear dermatoses. Am J Med Genet 1999;85:334–7.
6. Traupe H. Functional x-chromosomal mosaicism of the skin: Rudolf Happle and the lines of Alfred Blaschko. Am J Med Genet 1999;85:324–9.
7. Stojanović S, Jovanović M, Vučković N. Lichen planus–like dermatosis with Blaschko line distribution: a case report. Acta Dermatovenerol Alp Panonica Adriat 2008;17(3):137-8.
8. Ber Rahman S, Ul Bari A, Mumtaz N. Unilateral Blaschkoid lichen planus involving the entire half of the body, a unique presentation. Dermatol Online J 2007;13(3):36.
9. Seyhan M, Ozcan H, Sahin I, Bayram N, Karincaoğlu Y. High prevalence of glucose metabolism disturbance in patients with lichen planus. Diabetes Res Clin Pract 2007; 77(2):198-202.

Blaschko linearni lichen planus – prikaz slučaja

Sažetak

Uvod: Lihen planus (lat. *lichen planus*) predstavlja stečenu inflamatornu papuloznu pruritičnu dermatozu koja zahvata kožu, vidljive sluznice i nokte. Tačna incidencija i prevalencija ovog oboljenja i dalje je nepoznata, ali se može reći da bolest zahvata manje od 1% pripadnika opšte populacije.
Patofiziologija: U osnovi oboljenje se javlja kao posledica poligenskog poremećaja. U retkim slučajevima kliničkom slikom dominira segmentalni raspored promena za koji se pretpostavlja da predstavlja posledicu postzigotske mutacije na genskom lokusu koji je u klasičnim slučajevima odgovoran za povišenu prijemčivost za nastajanje oboljenja. Gubitak heterozigotnosti može nastati kao posledica mutacije, delecije ili DNA rekombinacije, a posledica je stvaranje klona keratinocita koji poseduje povišenu prijemčivost za lihenske promene. Linearni raspored lezija koji tom prilikom dominira kliničkim nalazom viđa se kod samo 0,2% svih pacijenata sa lihenom planus.
Prikaz slučaja: Prilikom prvog pregleda, odrastao muškarac, star 69 godina, u anamnestičkim podacima istakao je pojavu crvenih čvorića i ploča koji su se počeli pojavljivati u toku poslednjih mesec dana. Promene prati intenzivan svrab, a one zahvataju isključivo kožu. Od ranijih bolesti navodi šećernu bolest i povišene količine masnoća u krvi. Kliničkim nalazom prillikom prvog dermatološkog pregleda koji je urađen na prijemu u bolnicu, dominiralo je prisustvo mnogobrojnih eritematoznih i lividnih papula poligonalnog oblika oko 5 mm u prečniku koje su bile pojedinačne ili aglomerirane u manje plakove. Navedene promene su imale karakterističnu distribuciju po tzv. *Blaschko* linijama: duž levog donjeg ekstremiteta, na levoj strani trupa i duž leve nadlaktice; poglavina, nokti i sluznice bili su pošteđeni. Iz priložene dokumentacije zaključilo se da se bolesnik leči od dijabetesa melitus tokom poslednjih 15 godina i da su nastupile komplikacije: mikroangiopatija, polineuropatija i hiperlipidemija. Dijabetes je lečen insulinom i metforminom, hiperlipidemija simvastatinom, polineuropatija alfa lipoičnom kiselinom, a hipertenzija fosinoprilom i furosemidom. Navedena terapija nije menjana u periodu neposredno pre i za vreme pojave

promena na koži. Usled nastalih komplikacija izvršena je u prethodnom periodu amputacija malog prsta na oba stopala, razvio se malum perforans na levom stopalu, osteoliza falangi koja je zahvatila kost sve do srednje trećine pete metatarzalne kosti.

Relevantne analize: Laboratorijski nalazi, koji su odstupali od fizioloških, uključivali su povišenu sedimentaciju, povišenu koncentraciju C-reaktivnog proteina u serumu, blagu anemiju, povišenu vrednost glikemije od 9,9 mmol/l do 11,8 mmol/l. Vrednost hemoglobina A1c (HbA1c) iznosila je 8,2%. Prilikom ultrazvučnog dopler pregleda krvnih sudova donjih ekstremiteta, na arterijama nisu uočene stenoze, u arterijskom protoku nisu registrovani hemodinamički poremećaji, dok na venama nije bilo znakova insuficijencije.

Histopatotološka analiza: U isečku uzetom sa papulama zahvaćene kože, histološkom analizom dobijen je nalaz lihenoidnog *interface* dermatitisa, dok je direktna imunofluorescencija pokazala odsustvo depozita imunoglobulina, komplementa ili koloidnih telašaca.

Lečenje: Postojanje dijabetesa i razvoj njegovih komplikacija predstavljali su kontraindikaciju za lečenje sistemskim kortikosteroidima, tako da je terapija bila zasnovana na aplikaciji potentnih kortikosteroida za lokalnu primenu pod okluzijom (*bethamethasone dipropionate* 0,05% mast) što je izazvalo delimičnu ali značajnu regresiju promena i prestanak svraba nakon dve nedelje. S obzirom da je terapijski odgovor bio zadovoljavajući, odustalo se od ranije planirane sistemske primene acitretina.

Diskusija: *Blaschko* distribuciju kožnih promena prvi put je opisao nemački dermatolog Alfred Blaschko 1901. godine. Happle je 1978. godine prvi povezao postojanje genetskog mozaicizma sa karakterističnom distribucijom promena na koži. I pored brojnih ispitivanja, tačan mehanizam kojim nastaje *Blaschko* distribucija, ni do danas nije dovoljno razjašnjen na molekularnom nivou. Pružanje *Blaschko* linija ne prati raspored nervnih, vaskularnih niti limfatičnih struktura, a razlikuje se od svih ostalih poznatih morfoloških linija kao što su: *Voight*, *Langer*, embrionske pukotine i pigmentovane demarkacione linije. One su u obliku slova „V“, duž gornjih delova leđa, na gornjim delovima grudnog koša poprimaju oblik obrnutog „U“ slova, na abdomenu velikog slova „S“. Na ekstremitetima su perpendikularnog rasporeda, pri čemu nikada ne prelaze središnju liniju, za razliku od trupa na kome se mogu rasprostirati duž centralne linije. Pretpostavlja se da svojim oblikom prate distribuciju autonomnih motorno-visceralnih aferentnih nervnih vlakana, ili predstavljaju rezultat rastezanja kože za vreme embriogeneze. *Blaschko* linije se mogu javiti kod X-zavisnih naslednih poremećaja, kongenitalnih ili inflamatornih dermatoza, a opisuju se i kod segmentalnih formi atopijskog dermatitisa, multiformnog eritema, vitiliga, vulgarnog pemfigusa i anularnog granuloma. *Blaschko* linearni lihen planus je opisan kod svega 0,2% obolelih, i može se verovatno smatrati posledicom postzigotskih mutacija, delecija ili DNA rekombinacija u jednom od gena odgovornih za sticanje predispozicije za razvoj oboljenja. Za razliku od generalizovane erupcije, reakcija na nepoznati antigen se u tim slučajevima odvija samo u klonu keratinocita prijemčivih za nastanak lihena.

U diferencijalnoj dijagnozi značajno je isključiti postojanje strijatnog lihena koji nije praćen svrabom i koji, iako može imati identičnu kliničku sliku i distribuciju lezija, ima karakterističan tok: pojava u prvim godinama života, brza spontana regresija unutar nekoliko meseci do dve godine. Kod našeg bolesnika starog 69 godina, promene su bile praćene svrabom a patohistološka analiza je odgovarala lihenu planus. Direktnom imunofluorescencijom nisu uočeni imunodepoziti što nije neuobičajen nalaz kod lihena planus, a u našem slučaju on se može objasniti relativno kratkim trajanjem bolesti. Udruženost sa dijabetesom melitus dobro je poznata i ukazuje na moguću autoimunu etiologiju.

Zaključak: U radu je opisan slučaj lihena planus u kome su karakteristične lihenske papule i plakovi poprimili karakterističnu i retko, samo kod 0,2% oblelih, prisutnu *Blaschko* distribuciju. Navedenu distribuciju mogu poprimiti promene i u drugim, sa lihenom planus patogenetski nesrodnim dermatozama: lihen striatus, lihen sklerozus morfea, porokeratoza *Mibelli*, folikularna mucinoza i vulgarna psorijaza. Potentni kortikosteroidi primenjeni lokalno i pod okluzijom, dali su za kratak vremenski period zadovoljavajući efekat, te se iz tog razloga kao i zbog postojećeg komorbiditeta – insulin-zavisnog dijabetesa melitus, u terapiju nisu uključili sistemski retinoidi. Ostali terapijski modaliteti podrazumevaju lokalne pripravke inhibitora kalcineurina, intralezionu i sistemsku primenu kortikosteroida, retinoide, fototerapiju i u terapijski najrezistentnijim slučajevima, u kojima kvalitet života može biti teško narušen, metotreksat, ciklosporin i talidomid.

Ključne reči

Lichen planus; Simptomi i znaci; Topikalna primena lekova; Kortikosteroidi; Retinoidi; Fototerapija

Head & Shoulders - 50 godina nauke i inovacija za drevni problem

Perut i seboreični dermatitis su među najčešćim stanjima, sa preko 50% globalne populacije koja pati od njih bar jednom u svom životu. Za perut, putovanje otkrivanja je počelo sa francuskim mikrobiologom Louis Charles Malassezom (1842 - 1909) koji je prvi video ono što je nazvao "supstanca nalik kvascu" na glavama pacijenata sa seboreičnim dermatitisom. To je bila prva sugestija da su gljivice uzrok ovog opšteg stanja kože glave. U to vreme Malassez je bio na čelu za mikologiju i – od tada – niz vrhunskih naučnika koji dele interes u otkrivanju pravih uzroka peruti, imaju naprednije dalje razumevanje ovog stanja.

Naučnici iz P&G Lepote & Nege su istraživali perut i njene uzroke preko 50 godina. U skorije vreme, pravac boljeg razumevanja ovog stanja je bio podstaknut od strane nove ere životnih nauka. Alati kao što su "Omics" discipline (npr. Genomika, Proteomika, Metabolomija, Transkriptomija, itd.) su promenili naše razumevanje kompleksnih odnosa između molekula i procesa u koži glave. Ovo je postavilo temelje značajno poboljšanje znanja o molekularnim uzrocima peruti i seboreičnog dermatitis, kao i razvoj delotvornih tretmana za ova stanja.

Prvi korak u stvaranju znanja o ovim stanjima kože glave je bila identifikacija tačne vrste gljivica odgovorne za perut i seboreični dermatitis. Prvobitno identifikovana kao Pityrosporum ovale, klasifikacija gljivičnih uzroka peruti kasnije je rafinirana u jedanaest vrsta Malassezia genus (nazvane u čast Malasseza zbog njegovog otktića gljivičnih uzroka peruti). U ovo vreme (1996), se verovalo da je vrsta Malassezia furfur odgovorna za izazivanje ovih stanja kože glave. Međutim, genomske metodologije omogućile su naučnicima u P&G Lepota & Nega da dokažu da su sestrinske vrste istog roda pravi uzročnici peruti, i to kvasac Malassezia globosa.

Rad (Malassezia globosa)

Sekvenciranje genoma Malassezia globosa je postignuto primenom tehnika molekularne biologije i biohemije:

- Izolacija genomske DNK
- Generisanje 76,900 klonova plazmida
- Integracija 153,600 nasumičnih sekvencioniranja reakcija
- Završetak ukupnog niza od 1,500 završnih sekvencija
- Anotacija kompletnog genoma
- Identifikacija preko 500 lučenih proteina putem Proteomike

Rezultati (Malassezia globosa)

Malassezia globosa je prva Malessezia vrsta koja je sekvencionirana:

- 4285 proteinskih kodiranih gena
- Među najmanjim genomima među eukariotskim ćelijama koje slobodno žive
- 300x manji od ljudskog genoma
- Adaptacija Malassezia-e okruženju kože i patogenosti je posledica jedinstvenih metaboličkih ograničenja i mogućnosti otkrivenih ovom studijom
- Najbliži srodnik *Malassezia globosa-e* je *Ustilago maydis* – uobičajeni biljni patogen (kukuruzna gljivica).
- Prisustvo gena za parenje – verovatno sposobnih za seksualnu interakciju (dalji dokaz za visoko uspešnu adaptaciju).

Otkriće anti-gljivičnog načina delovanja ZPT

P&G naučnici su vodili 50 godina razvoja evolucije nakon prvog uvođenja aktivnog ZPT, čineći ga sada, najuspešnijim i opšte poznatim aktivom protiv peruti. Međutim njegov anti-gljivični mehanizam delovanja je bio slabo razumljiv sve do nedavno. Da bi otkrili efekat koji ZPT ima na Malassezia globosa, gljivični uzročnik peruti i seboreičnog dermatitisa, naučnici P&G Lepote & Nege su koristili niz molekularnih tehnika analize (između ostalih) biblioteke brisanja gena, metabolizam gljivica, merenje aktivnog otpora, itd. Ove studije, bazirane na inhibiciji mitohondrijske metalo-sinteze proteina u ćelijama gljivica, dovele su do otkrića delovanja ZPT. Rad sa S. cerevisiae bibliotekom brisanja gena pokazao je da porast nivoa bakra unutar ćelija igra ključnu ulogu u aktivnosti ZPT (efekti faktora CUP2 i CTR1). Dalja istraživanja su pokazala da povećanje nivoa bakra izazvano ZPT-om ima efekat na skup osnovnih proteina sumpora gvožđa u mitohondrijama ćelija gljivica u koje spadaju protein od centralne važnosti kao što je acotinase (faktor u suštinskom Krebsovom ciklusu). Ovo je prvi mehanizam svoje vrste otkriven kao anti-gljivični aktiv, i u skladu sa ranijim istraživanjima na nekim antibakterijskim aktivom koji može da funkcioniše putem povećavanja nivoa bakra u ciljnim ćelijama. Ovo istraživanje ima cilj da otvori novi put za razvoj novih anti-gljivičnih aktiva, a takođe može dovesti do dalje optimizacije aktivnog ZPT trenutno korišćenog u proizvodima P&G Lepota & Nega.

Selen Sulfid

Selen sulfid je alternativni aktiv protiv peruti koji se koristi u tretiranju peruti i seboreičnog dermatitisa dugi niz godina. Šamponi koji sadrže selen sulfid su dokazali efikasnost koja je zasnovana na visokoj aktivnosti protiv gljivica Selen sulfid aktiva. Kao ZPT, selen sulfid je čestica, a njegova efikasnost zavisi od veličine čestica za optimizaciju pokrivenosti, što znači da formulacija efikasnosti može biti optimizovana krojenjem veličine čestica i drugih karakteristika šampona. Zbog visoke moći protiv gljivica, i drugih tehnoloških razloga, P&G Lepota & Nega formulacije sa selen sulfidom su specijalno dizajnirane kao intezivni tretmani za akutne slučajeve peruti i seboreičnog dermatitis.

Kombinacija nege kose i nege kože glave koristi nagonu saglasnosti

Moderni proizvodi za negu kože glave ne tretiraju samo kožu glave, nego i zadovoljavaju potrebe nege kose za čišćenjem i kondicioniranjem. Značaj kombinacije koristi nege kože glave i nege kose u istom proizvodu bez ustupaka u estetici je od suštinskog značaja za efektivni tretman, jer mogu biti uključeni u rutinski režim nege kose i voditi do visoke saglasnosti korisnika. Visoka saglasnost je ključ za uspešno tretiranje jer obilje parazita Malassezia kvasca može dovesti do recidiva stanja kože glave ubrzo nakon što je tretman zaustavljen. Najuspešniji pristup povećanju saglasnosti korisnika je da se kreira niz različitih prilagođenih proizvodnih tehnologija za negu kose i kože glave koji se pružaju prema potrebama kože glave i kose širokog spektra korisnika. Stoga, P&G Lepota & Nega je razvio paletu proizvoda koji kombinuju efikasni ZPT aktiv sa različitim nivoima i mešavinama regenerativnih sastojaka, i drugih čulnih atributa kao što je miris. Van koristi za kožu glave, tehnologije šampona omogućavaju efikasno čišćenje, najosnovnija korist šampona, i jačanje kose kako bi se omogućio optimizovan izgled kose i osećaj i uspešnu zaštitu vlasi. Zajedno sa tehnologijama šampona, prilagođeni balzami dopunjuju režim nege kože glave i kose jer pružaju dodatne pogodnosti nege kose i poboljšavaju koristi nege kože glave koje već pruža šampon. Razvoj šampona i balzama koji su prilagođeni da rade zajedno donosi koristi nege kože glave i kose korisnicima koji podržavaju saglasnost za maksimalni uspeh tretmana.

Pripremio: Ass. dr. Zoran Golušin

Molluscum contagiosum and chronic vulval ulceration as the first manifestations of HIV infection – a case report

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Abstract

Molluscum contagiosum is a very common, benign, often self-limiting skin disease caused by Molluscum contagiosum virus, member of the poxvirus family. Genital ulcers in HIV positive women are usually acute or subacute, mostly idiopathic or aphtous. Sixty percent of cases are caused by herpes simplex virus syphilis or chancroid. We present a 31-year-old woman with a 2.5 month history of vulval ulceration and a several month history of molluscum contagiosum in the pubic region, neck and face. After she was admitted to our department, the patient underwent physical examination using enzyme-linked immunosorbent assay, and an immunoblot test for HIV 1/2. Both tests were positive. Thereafter, the patient was referred to an infectologist who recommended application of 5% imiquimod cream 3 times per week for molluscum contagiosum and acyclovir 3x400 mg/day. Considering that there are more accepted indications for HIV testing, we agree with other authors that all adults with molluscum contagiosum or chronic genital ulceration should be tested for HIV serology.

Key words

Molluscum Contagiosum; Molluscum Contagiosum Virus; Vulvitis; HIV Infections; Comorbidity; Diagnosis

Molluscum contagiosum (MC) is a very common, benign, often self-limiting skin disease caused by *Molluscum contagiosum* virus (MCV), member of the pox virus family. The first peak incidence is in pre-school children, and the second occurs in young adults, where the condition is generally considered a sexually transmitted infection. MC is extremely rare in immunosuppressed non-human immunodeficiency virus (HIV)-infected patients. However, in HIV infection, MC is not self-limited, it may be widespread, recurrent, giant, atypical, resistant to therapy, and an important cutaneous marker of disease progression.

Genital ulcers are frequently found in HIV positive persons. In a study performed in Nigeria, 19.6% of HIV positive commercial sex workers had genital ulcerations (1). HIV was detected in lesions of almost 50% of HIV-positive men with genital ulcer disease (2). In HIV positive women genital ulcers are usually acute or subacute, mostly idiopathic or aphtous (60%) caused by herpes simplex virus (HSV), syphilis or chancroid (3).

Case Report

A 31-year-old woman with a 2.5 month history of vulval ulceration and a several month history of MC in the pubic region, neck and face was admitted to our department. In her personal history, she denied intravenous drug abuse or blood transfusions during lifetime. Previously, MCs were unsuccessfully treated by cryosurgery. Three months before, she had aphtous lesions in the mouth, while three years before, she had undergone surgery for microinvasive cervical carcinoma and pilonidal sinus.

The physical examination revealed an oval, shallow ulceration, with irregular edges on the right labia majora (Figure 1) and several MC on the pubis, neck and face (Figure 2). She was feeling well and the rest of the physical examination was normal.

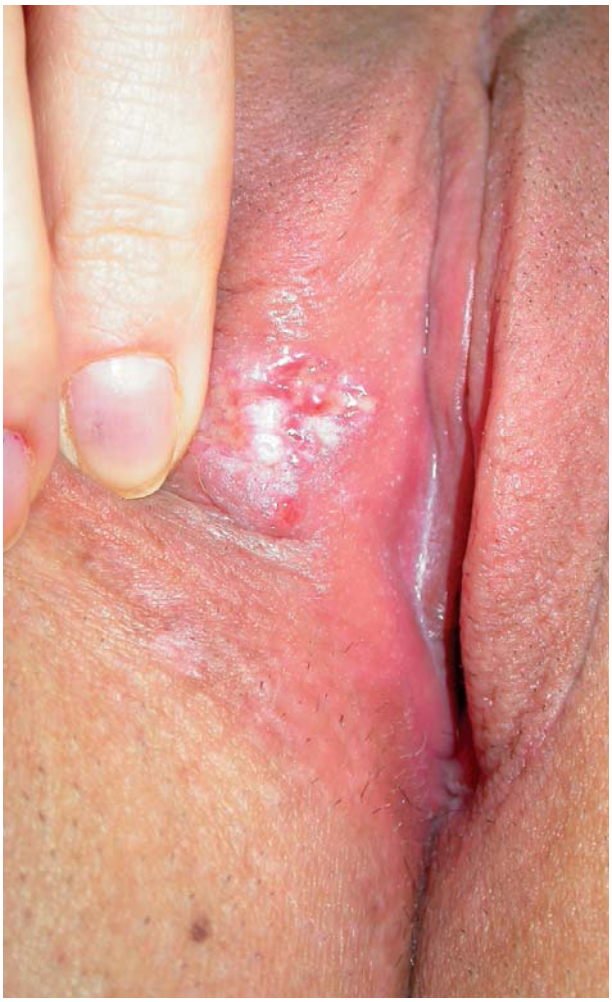

Figure 1. Shallow ulceration with irregular borders on the right labia majora

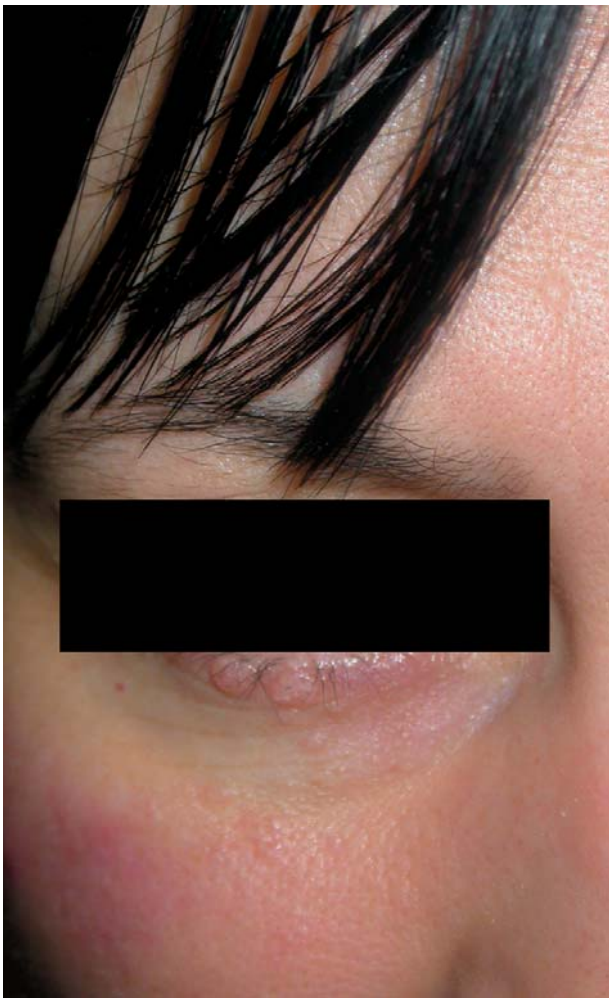

Figure 2. Molluscum contagiosum on the lower eyelid

However, laboratory tests showed the following abnormal values: ESR 95 mm/h, white blood cell count of 3.64 and 3.97x10^9/l (n.v. 4.8-10.8x10^9/l), hemoglobin 96 and 97 g/l (n.v. 120-180), hematocrit 0,29 l/l (n.v. 0.37-0.52), platelets 100 and 104x10^9/l (n.v. 130-400), aspartate-aminotrasferase 48 u/l (n.v. 0-38). Total serum IgG concentration was 24.9 g/l (n.v. 7-16), IgA 14.2 g/l (n.v. 0.7-4), IgM 2.67 g/l (n.v. 0.4-2.3). Lactate-dehydrogenase, gamma-glutamyl transferase, alanine aminotransferase, bilirubin, glucose, urea, creatinine, complement components C3 and C4, and antinuclear antibodies were within normal range or negative. *Escherichia coli* 60000/ml was identified by urine culture test. Swab culture taken from the vulval ulcer base *Staphylococcus aureus.* Since Molluscum contagiosum in adulthood is considered to be a sexually transmitted disease, STD panel was performed. Enzyme-linked immunosorbent assay (ELISA) tests for HSV-1, HSV-2, HBsAg and HCV were negative. Syphilis serology, VDRL and TPHA tests were also negative. ELISA and immunoblot tests were performed, and both tests were positive for HIV 1/2.

Thereafter, the patient was referred to an infectologist, who recommended application of 5% imiquimod cream 3 times per week for MC and acyclovir 3x400 mg/day (3).

Discussion

MC has a worldwide incidence as high as 8% (4). Up to 18% of patients with HIV infection have symptomatic MC, and the incidence increases to 33%

in patients with CD4+ cell counts less than 100/μl (4). The diagnosis is based on the clinical presentation and only a small number of cases are confirmed by biopsy. Contrary to this, in patients with advanced HIV disease, MC can present as an opportunistic infection and cause disseminated, giant lesions that are particularly resistant to therapy.

Koopman et al. revealed that MC tends to affect more advanced stage HIV-positive patients and with low CD4+ levels (5). This study was further supported by Schwartz and Myskowski, who found that HIV-positive patients with low CD4+ had significantly more MC lesions (6). Disseminated giant MC was also described in a patient with idiopathic CD4+ lymphocytopenia (7).

Most studies did not find any significant differences in the appearance or location of lesions in immunosuppressed versus healthy patients (8). Furthermore, most of the studies found that clinical presentation of aggressive, disseminated and atypical MC lesions (giant or verrucous) are more common in HIV-positive patients. Laxmisha et al. demonstrated that HIV-positive patients had more extensive disease, with multifocal involvement, and multiple and giant lesions (9). However, in this study, only patients who had suspicious findings other than MC were tested for HIV status. A study performed in Australia found that facial and neck MC lesions were more common than genital lesions (10).

A Pubmed search showed that only one study answered the question whether presence of MC in a patient is associated with severe immunodeficiency. Mahe´ et al. (11) tested 305 patients in Mali for HIV, and reported that MC yields a positive predictive value of 47% for HIV seropositivity.

However, this study has limitations: it included only one center, the study sample may not represent general population with dermatoses in Mali, and the authors did not report if HIV status was related to any atypical features of MC.

Many different options have been described in the treatment of MC: destructive, cytotoxic, antiviral and immune-modifying modalities (4, 7, 12, 13). However, there is no standard treatment for MC. Imiquimod has potent antiviral and antiproliferative effects inducing production of a large number of proinflammatory and antiviral cytokines, IFN-α, IL-12, TNF-α and IFN-γ, and chemokines (7). Also, it seems that imiquimod directly induces apoptosis regardless of death-receptors and increases activation and migration of Langerhans cells to the draining lymph nodes (7). Several studies showed good clinical response of MC lesions to treatment with imiquimod, although mainly in immunocompetent patients (14-16).

Chronic vulval ulcerations in HIV-positive patients are rare, while the pathogenesis remains unknown (17). Immunosuppression, altered host response, and direct infection by HIV are proposed etiologies. Gbery et al. analyzed 29 patients with chronic genital ulceration in Ivory Coast and found that herpes was the cause in 19 (65.5%) patients (18). All patients with herpes were HIV-positive and 18 of these patients had stage C3 of HIV infection (18). We think that possible causes of vulval ulceration in our patient include aphtous ulceration or HSV infection.

She previously had apthous lesions in the mouth, and it is possible that she had similar lesions on the genital region. In our patient, HSV infection was not excluded by performing assays that directly detect HSV in genital specimens such as virus isolation in cell culture or HSV DNA detection, thus antviral therapy was commenced on clinical suspicion alone (19).

Also, heterosexual mode of HIV transmission was most probable in our patient, since there were no data of intravenous drug abuse or blood transfusions.

In conclusion, considering that there are more accepted indications for HIV testing, we agree with other authors that all adults with MC or chronic genital ulceration should be tested for HIV serology. On the other hand, HIV testing cannot be recommended in pediatric patients, unless other suspicious features are present (8).

Abbreviations

MC - Molluscum contagiosum
MCV Molluscum contagiosum virus
HIV - Human immunodeficiency virus
HSV - Herpes simplex virus
ESR - Erythrocyte sedimentation rate
n.v. - Normal values
Ig - Immunoglobulines
STD - Sexually transmitted disease

ELISA - Enzyme-linked immunosorbent assay
HBsAg - Hepatitis B virus s antigen
HCV - Hepatitis C virus
VDRL - Venereal Disease Research Laboratory
TPHA - *Treponema pallidum* haemagglutination assay
IFN - Interferon
IL - Interleukin
TNF - Tumor necrosis factor

References

1. Fayemiwo SA, Odaibo GN, Oni AA, Ajayi AA, Bakare RA, Olaleye DO. Genital ulcer diseases among HIV-infected female commercial sex workers in Ibadan, Nigeria. Afr J Med Med Sci 2011;40:39-46.
2. Paz-Bailey G, Sternberg M, Puren AJ, Steele L, Lewis DA. Determinants of HIV type 1 shedding from genital ulcers among men in South Africa. Clin Infect Dis 2010;50:1060-7.
3. Clark R, Anderson J. Idiopathic genital ulcer disease in an HIV-infected woman. AIDS Patient Care STDS 1998;12:819-23.
4. Sisneros SC. Recalcitrant giant molluscum contagiosum in a patient with advanced HIV disease: eradication of disease with paclitaxel. Top HIV Med 2010;18:169-72.
5. Koopman RJJ, van Merriënboer FC, Vreden SGS, Dolmans WMV. Molluscum contagiosum: a marker for advanced HIV infection. Br J Dermatol 1992;126:528-9.
6. Schwartz JJ, Myskowski PL. Molluscum contagiosum in patients with human immunodeficiency virus infection. J Am Acad Dermatol 1992;27:583-8.
7. Böhm M, Luger TA, Bonsmann G. Disseminated giant molluscum contagiosum in a patient with idiopathic CD4+ lymphocytopenia: successful eradication with systemic interferon. Dermatology 2008;217:196-8.
8. Gur I. The epidemiology of molluscum contagiosum in HIV-seropositive patients: a unique entity or insignificant finding? Int J STD AIDS 2008;19:503-6.
9. Laxmisha C, Thappa DM, Jaisankar TJ. Clinical profile of molluscum contagiosum in children versus adults. Dermatol Online J 2003;9:1.
10. Thompson CH, de Zwart-Steffe RT, Donovan B. Clinical and molecular aspects of molluscum contagiosum infection in HIV-1 positive patients. Int J STD AIDS 1992;3:101-6.
11. Mahe´ A, Simon F, Coulibaly S, Tounkara A, Bobin P. Predictive value of seborrheic dermatitis and other common dermatoses for HIV infection in Bamako, Mali. J Am Acad Dermatol 1996;34:1084-6.
12. Chularojanamontri L, Tuchinda P, Kulthanan K, Manuskiatti W. Generalized molluscum contagiosum in an HIV patient treated with diphencyprone. J Dermatol Case Rep 2010;4:60-2.
13. Baxter KF, Highet AS. Topical cidofovir and cryotherapy: combination treatment for recalcitrant molluscum contagiosum in a patient with HIV infection. J Eur Acad Dermatol Venereol 2004;18:230-1.
14. Theiler M, Kempf W, Kerl K, French LE, Hofbauer GF. Disseminated molluscum contagiosum in a HIV-positive child: improvement after therapy with 5% imiquimod. J Dermatol Case Rep 2011;5:19-23.
15. Brown CW Jr, O'Donoghue M, Moore J, Tharp M. Recalcitrant molluscum contagiosum in an HIV-afflicted male treated successfully with topical imiquimod. Cutis 2000;65:363-6.
16. Strauss RM, Doyle EL, Mohsen AH, Green ST. Successful treatment of molluscum contagiosum with topical imiquimod in a severely immunocompromised HIV-positive patient. Int J STD AIDS 2001;12:264-6.
17. Reddy V, Luzzi GA. Chronic vulval ulceration: another immune reconstitution inflammatory syndrome? Int J STD AIDS 2005;16:454-5.
18. Gbery IP, Djeha D, Kacou DE, Aka BR, Yoboue P, Vagamon B, et al. Chronic genital ulcerations and HIV infection: 29 cases. Med Trop (Mars) 1999;59:279-82.
19. Jovanović M. Genital herpes. Serb J Dermatol Venereol 2011;3(1):7-22.

Molluscum contagiosum i hronične vulvalne ulceracije kao prve manifestacije HIV infekcije – prikaz slučaja

Sažetak

Uvod: *Molluscum contagiosum* je veoma često, benigno, često samolimitirajuće oboljenje kože koje je izazvano virusom *Molluscum contagiosum*, članom poxvirus porodice. Genitalni ulkusi kod HIV (eng. human immunodeficiency virus) pozitivnih žena najčešće su akutni ili subakutni, uglavnom idiopatski ili uzrokovani aftama (60%). Česti uzroci su i herpes simpleks virus (HSV), sifilis i šankroid.

Prikaz slučaja: Prikazujemo pacijentkinju staru 31. godinu koja 2,5 meseca pre prijema u našu Kliniku primećuje ulceraciju na vulvi, a nekoliko meseci pre toga prisustvo *molluscum contagiosum* na koži pubisa, vrata i lica. Neposredno posle fizikalnog pregleda urađeni su ELISA i imunoblot testovi na HIV 1/2 i oba testa su bila pozitivna. Posle dobijanja nalaza, pacijentkinja je upućena infektologu s preporukom da nanosi 5% imikvimod krem 3x nedeljno na *molluscum contagiosum* promene i da uzima aciklovir tablete 3x400

mg dnevno.
Zaključak: Imajući u vidu da se indikacije za testiranje na HIV šire, slažemo se sa drugim autorima da je neophodno testirati na HIV sve odrasle pacijente sa *molluscum contagiosum* ili hroničnom genitalnom ulceracijom.

Ključne reči

Molluscum contagiosum; Molluscum contagiosum virus; Vulvitis; HIV infekcije; Komorbiditet; Dijagnoza

A report on the 12th World Congress of Sexually Transmitted Infections and AIDS, New Delhi 2011

Sexually Transmitted Infections represent a major health problem in both developed and developing countries. "Promoting Sexual Health: Basic Science to Best Practices" was the theme of the 12th World Congress of Sexually Transmitted Infections and AIDS, November 2-5, 2011 held in New Delhi, India. The main goal of the Congress was implementation of the latest scientific discoveries and best practices regarding prevention, diagnosis and treatment of sexually transmitted infections and HIV, through integrated program approaches to achieve sexual health.

"Today, there are at least 35 sexually transmitted pathogens, which cause at least 35 different syndromes affecting at least 10 organ systems. The scope of diagnostic, therapautic and prevention interventions and strategies is growing equally. Control of these infections and achieving sexual health now requires a coordinated, interdisciplinary approach", said Dr. King K. Holmes, the President of International Union against Sexually Transmitted Infections (IUSTI). There were 2 keynote lectures ("Antiretrovirals for

Figure 1. Zoran Nedić, Scholarship recipient (Serbia), Somesh Gupta, IUSTI Membership Secretary and Co-Chair of the 12th IUSTI Congress (India), Angelika Stary, IUSTI Immediate Past President (Austria), King Holmes, IUSTI President (USA), Charlotte Gaydos, IUSTI Regional Director North America and Co-Chair of the International Scientific Committee (USA), and Zoran Golušin, Scholarship recipient (Serbia)

prevention of HIV: Bridging the efficacy-effectiveness gap" and "Progress, reversals and future priorities in STI/HIV Control"), 9 plenary lectures, 19 course lectures, 84 lectures in various symposia, 41 lectures in the Oral Session and 180 posters. A special contribution for a well-organized Congress belongs to Dr. Somesh Gupta and Dr. Vinod K. Sharma.

There were 2 poster presentations from Serbia: "Epidemiological changes of syphilis in the northern part of Serbia" by Z. Golušin, S. Stojanović, P. Djurić, S. Ilić, S. Rajčević, Z. Nedić, and "Azithromycin in the treatment of gonococcal and non-gonococcal urethritis" by Z. Nedić, Z. Golušin and D. Mojašević.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2012

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
05-07 March, 2012	2nd World Congress on Clinical and Experimental Dermatology, Omaha, United States	No deadline information	www.omicsonline.org/dermatology2012
27-29 March, 2012	Dubai World Dermatology and Laser Conference – Dubai Derma, Dubai, UAE	30 November, 2011	www.dubaiderma.com
29-31 March, 2012	10th Anti-Aging Medicine World Congress and Medispa, Monte Carlo, Monaco	30 November, 2011	www.euromedicom.com
29 March - 01 April, 2012	European Academy of Allergy and Clinical Immunology (EAACI) Allergy School, Davos, Switzerland	25 March, 2012	www.eaaci.net/activities/allergy-schools
11-14 April, 2012	European Academy of Allergy and Clinical Immunology (EAACI) Focused Meeting: Drug Hypersensitivity, Munich, Germany	10 February, 2012	www.eaaci-dhm2012.com
12-15 April, 2012	4th Spring Meeting of the International Society for Dermatologic Surgery (ISDS), New Dehli, India	15 February, 2012	www.isdsworld.com
19-22 April, 2012	9th EADV Spring Symposium, Verona, Italy	23 January, 2012	www.verona2012.eadv.org
16-19 May, 2012	11th Congress of the European Society for Pediatric Dermatology, Istanbul, Turkey	20 January, 2012	www.espd2012.org
17-19 May, 2012	3rd World Congress of Dermoscopy, Brisbane, Australia	12 December, 2012	www.dermoscopycongress2012.org
16-20 June, 2012	European Academy of Allergy and Clinical Immunology Congress 2012, Geneva, Switzerland	18 January, 2012	www.eaaci2012.com
27 June- 01 July, 2012	3rd World Psoriasis and Psoriatic Arthritis Confernce 2012, Stockholm, Sweden	1 March, 2012	www.ifpaworldconference.com
11-14 July, 2012	38th Annual Meeting of the Society for Pediatric Dermatology, Monterey, United States	No deadline information	www.pedsderm.net
26-28 August, 2012	6th International Congress on Dermato-Epidemiology, Malmö, Sweden	1 May, 2012	www.idea2012.net
19-22 September, 2012	42nd Annual Meeting of the European Society for Dermatological Research, Venice, Italy	No deadline information	www.esdr2012.org
27-30 September, 2012	21st EADV Congress, Prague, Czech Republic	21 March, 2012	www.eadvprague2012.org
5-7 October, 2012	European Academy of Allergy and Clinical Immunology (EAACI) Focused Meeting: International Symposium on Molecular Allergology, Rome, Italy	No deadline information	www.eaaci-isma2012.com

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

AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

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

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

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

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

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

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

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

1. Manuscript Preparation Guidelines

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

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

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

- A running title (limited to 30 characters);

- Authors' names and institutional affiliations;

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

1.2. Abstracts

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

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

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

1.3. A list of abbreviations

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

1.4. Cover Letter

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

2. Tables and illustrations

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

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

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3. References

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

4. Additional information

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