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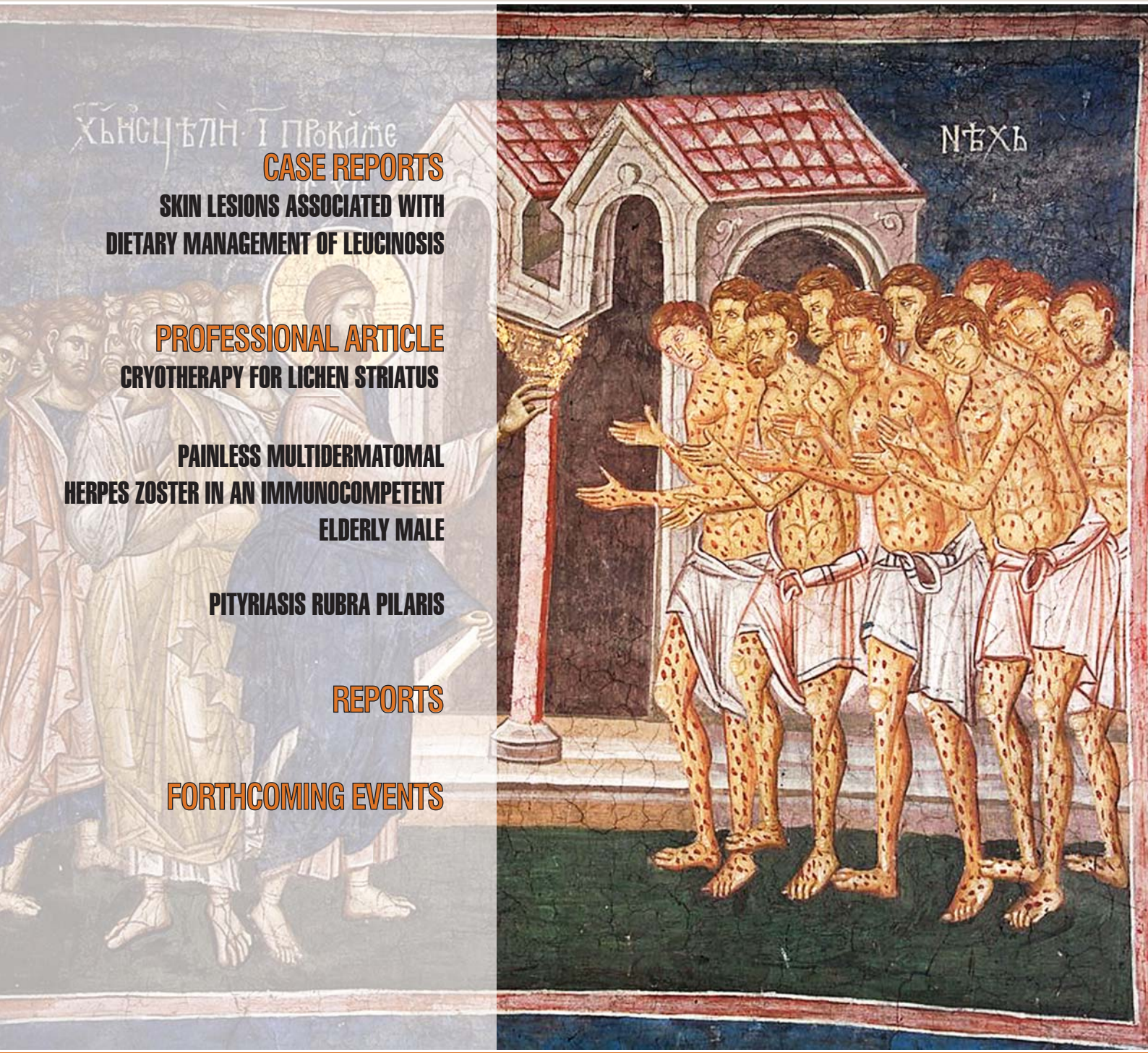

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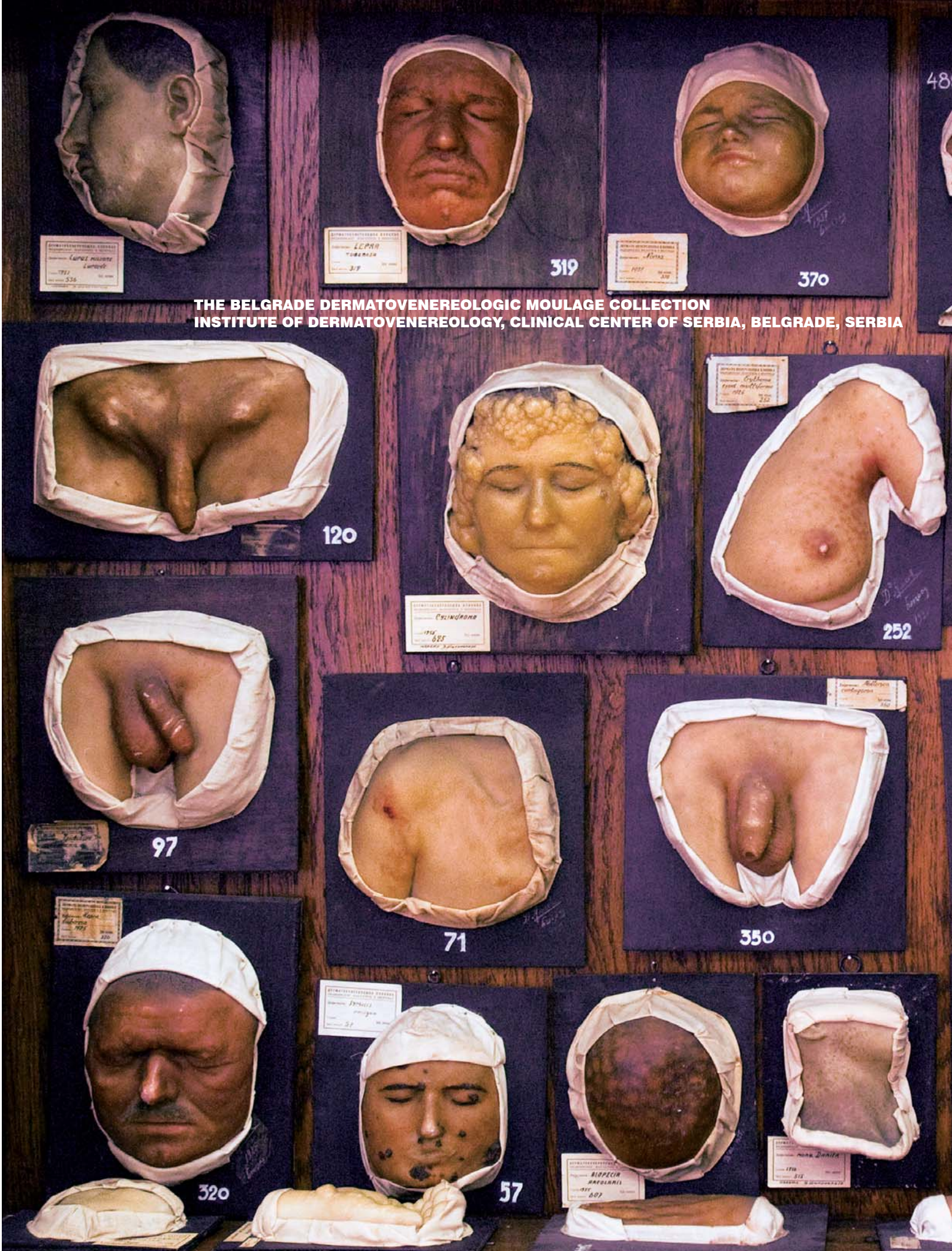

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Skin Lesions Associated with Dietary Management of Maple Syrup Urine Disease: a Case Report

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Abstract

Leucinosis (maple syrup urine disease - MSUD) is an inherited aminoacidopathy and organic aciduria caused by severe enzyme defect in the metabolic pathway of amino acids: leucine, isoleucine, and valine. The classical variant of the disease is characterized by accumulation of both amino and □-keto acids, particulary the most toxic rapid elevation of circulating leucine and its ketoacid, □-ketoisocaproate, which cause encephalopathy and life-threatening brain swelling. However, patients with the most severe form, classical maple syrup urine disease, may appear normal at birth, but develop acute metabolic decompensation within the first weeks of life with typical symptoms: poor feeding, vomiting, poor weight gain, somnolence and burnt sugar-smelling urine, reminiscent of maple syrup. Early diagnosis and dietary intervention improve the patient's condition, prevent severe complications, and may allow normal intellectual development.

We present a 4-month old infant with leucinosis dignosed 3 months earlier, due to elevated levels of amino acids: leucine, isoleucine and valine. The patient was full-term neonate with an uncomplecated delivery, without any family history of metabolic disorder or consanguinity. The infant was referred to a dermatologist, because of maculopapular exanthema on the scalp, trunk, upper and lower extremities, and exfoliative dermatitis of the perioral, particularly anogenital regions, associated with diarrhea. Skin involvement was associated with poor general condition of the infant exhibiting severe hypotension, anemic syndrome, dyspepsia and neurological symptoms. Exanthema developed a few days after the initiation of nutritional therapy for MSUD: isoleucine-, leucine-, and valine-free powdered medical food (MSUD-2) supplemented with iron. Zink levels were within normal ranges. Rapid skin improvement occurred after adequate branched-chain amino acids supplementation was commenced under regular laboratory control (normal zinc serum level with deficiencies of leucine and valine), skin hygiene with antiseptics, emollients and low potent topical corticosteroids.

Treatment of acute metabolic decompensation and dietary restriction of branched-chain amino acids are the main aspects in the management of maple syrup urine disease. Common findings in patients with MSUD include: plasma amino acid imbalance, particularly of essential amino acids, failure to thrive attributed to restriction of particular precursor amino acids and natural proteins, micronutrient deficiencies or higher energy requirement due to chronic illness or inflammation. Due to low intake of branched-chain amino acids, some patients develop skin lesions known as acrodermatitis enteropathica-like syndrome.

Here we report a case of an infant who developed acrodermatitis enteropathica-like skin eruptions due to branched-chain amino acid deficiency during treatment of maple syrup urine disease. According to available world literature, this is the first report of acrodermatitis enteropathica-like syndrome in an infant with maple syrup urine disease (leucinosis) in the Republic of Bulgaria.

Key words

Maple Syrup Urine Disease; Diet Therapy; Infant; Acrodermatitis; Isoleucine + deficiency; Signs and Symptoms; Treatment Outcome; Case Reports; Bulgaria

Leucinosis (maple syrup urine disease - MSUD) is an inherited aminoacidopathy caused by severe enzyme defect in the metabolic pathway of amino acids (AA): leucine, isoleucine, valine and their α-ketoacid derivatives. The classical variant of the disease is characterized by accumulation of both amino and α-keto acids, particulary the most toxic rapid elevation of circulating leucine and its ketoacid

derivate, α-ketoisocaproate (α-KIC), which causes encephalopathy and life-threatening brain swelling. However, patients with the most severe form, classical MSUD, may appear normal at birth, but develop acute metabolic decompensation within the first weeks of life (1). The disease is characterized by poor general condition, ketoacidosis, poor feeding, poor weight gain, somnolence, ataxia and burnt sugar-smelling urine, which is reminiscent of maple syrup. Severe complications such as encephalopathy, progressive neurodegeneration and coma are observed in untreated patients (1, 2). Treatment of acute metabolic decompensation and dietary restriction of branched-chain amino acids are the main therapeutic aspects, but they are commonly associated with muscular hypotonia, nausea, metabolic decompensation, infections, retardation and swallowing difficulties. Common findings in treated patients include: imbalances in the plasma essential AA and failure to thrive due to restriction of micronutrients or because of a higher energy need due to chronic illness or inflammation (3). Due to low intake of branched-chain amino acids (BCAA), some patients develop skin lesions known as acrodermatitis enteropathica (AE)-like syndrome.

Case report

A 4-month-old female infant was referred to the Department of Pediatrics due to poor general condition, poor weight gain and maple syrup urine odor. The patient was full-term neonate with an uncomplecated delivery, without any family history of metabolic disorder or consanguinity. The disease started 3 months earlier, when an adapted milk formula was introduced. The infant was previously treated in another hospital and received blood and plasma transfusion twice, because of severe anemic syndrome, but without any improvement.

On phisical examination, the measured infant 3000 g and 50 cm length; it was somnolent and hypotonic exhibiting: dysmorphic facies with retrognathia; tense fontanelle, increased chest diameter and tachycardia. Neurological examination revealed that the baby was unable to hold head up without support, lethargy, inability of sitting without support, as well as overactive knees and exaggerated Achilles tendon reflexes.

Biochemical examination showed high levels of lactatae dehydrogenase (LDH), creatine phosphokinase (CPK), uric acid, and ammonia (>145 μmol/l, reference values 11 - 31 μmol/l) along with metabolic acidosis, serum leucine level (> 8000 μmol/l, reference values 2.07 - 4.57 μmol/l), serum valine level (>100 μmol/l, reference values 2.0 - 4.8 μmol/l), and severe anemic syndrome.

Cervical edema was established by transfontanelle ultrasound; electroencephalography (EEG) showed uniform low-amplitude complex of electrical potential and almost no differentiation of cortical areas.

The diagnosis of MSUD was made based on clinical, biochemical and imaging data.

The treatment included fluid and electrolyte imbalance management, dietary restriction of BCAA by using an isoleucine-, leucine-, and valine-free powdered medical food MSUD 2, and adjunct treatment of neurological complications. A few days after starting the dietary restriction of (AA): leucin, isoleucine and valine, a disseminated maculopapular exanthema appeared on the skin of the scalp, face, trunk and extremities, as well as exfoliative dermatitis of the perioral and particularly anogenital region, together with diarrhea. Erosions, yellowish crusts and lamellar exfoliation were observed in the periorificial region and extremities (Figures 1 - 4). Skin involvement was associated with poor general condition of the infant exhibiting lethargy, severe hypotension, anemic syndrome, dyspeptic syndrome and neurological symptoms. Zink levels were within normal ranges. (AE)-like syndrome, secondary to leucine and valine deficiency, was suspected.

Rapid skin improvement, observed after BCAA supplementation under laboratory control (normal zinc serum level with deficiencies of leucine and valine) confirmed our suspicions. In addition, skin hygiene control with antiseptics, emollients and low potent topical corticosteroids was administrated. Mycological and mycrobiologicyl examination was performed and gave negative results.

Discussion

Leucinosis or MSUD is an aminoacidopathy secondary to defective activity of the human mitochondrial branched-chain alpha-keto acid dehydrogenase (BCKD) multienzyme complex,

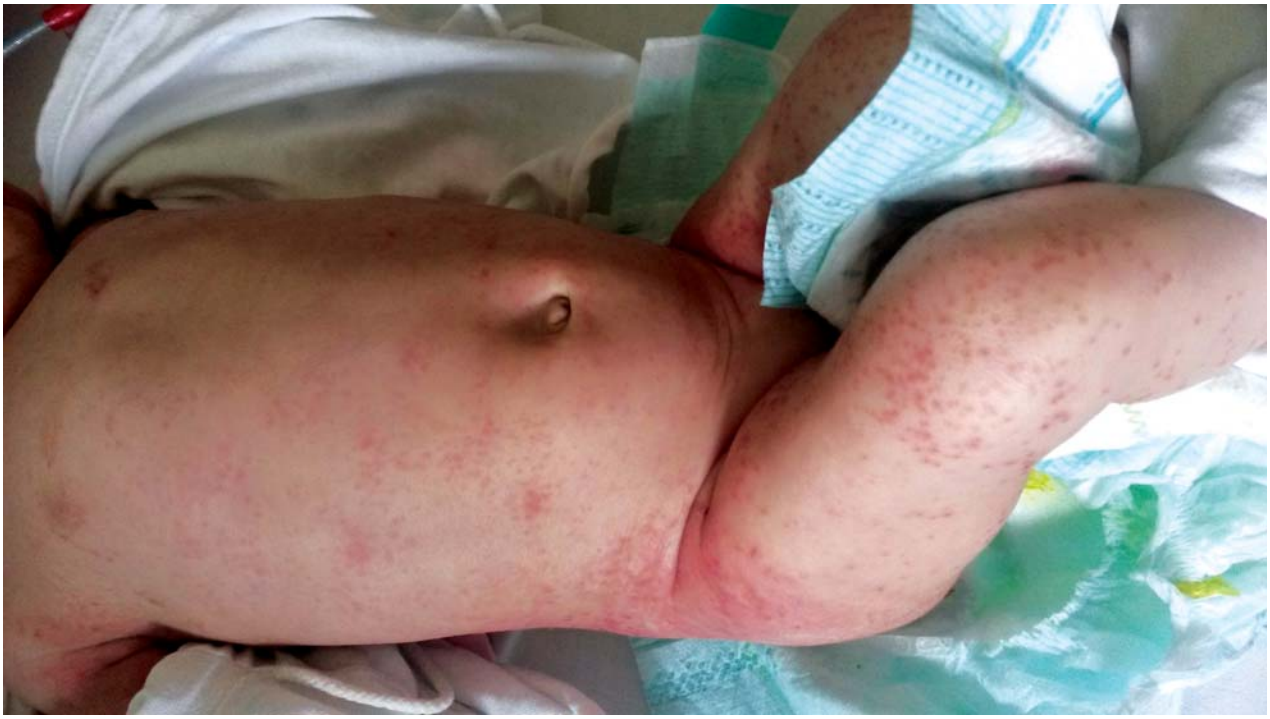

Figure 1. Disseminated maculopapular exanthema

which catalyzes decarboxylation of BCAA (leucine, isoleucine, and valine) to their corresponding metabolites-α-keto acids (1). Catabolic pathways of BCAA consist of multiple steps including reversible transamination, irreversible oxidative decarboxylation and dehydrogenation. Congenital errors of these pathways are inherited in an autosomal recessive fashion. As a consequence, degradation of 3 BCAA: leucine, isoleucine, and valine, is blocked in MSUD after the first catabolic step (transamination), resulting in accumulation of BCAA and their corresponding branched-chain α-keto acids (BCKA) in biological fluids. Because of the combined toxic effects of AA, particularly leucine, and organic acid intermediates, such as the keto- and hydroxyacid metabolites of BCAA, MSUD can be considered both an amino acidopathy and organic aciduria (3). Accumulation of leucine causes neurological symptoms, whereas high level of isoleucine in plasma is associated with a sweet-smelling odor of the urine. Leucine is rapidly transported across the blood-brain membrane and is neurotoxic at high concentrations (4). By inhibiting the transport of essential AA across the blood-brain barrier e.g, tyrosine, tryptophan, hyperleucinemia limits cerebral catecholamine, serotonin, and protein synthesis. Transaminases in brain tissue normally convert leucine to α-ketoglutarate. Accumulation of α-KIC - ketoacid derivative of leucine, depletes the brain of glutamate since it favors synthesis of leucine by consuming glutamate in the bidirectional transaminase reaction. Glutamate is an important metabolic currency that is used as a neurotransmitter as well as a source of energy. Proposed mechanisms of neurotoxicity in MSUD include unbalanced cerebral essential AA uptake, neurotransmitter deficiencies, energy deprivation, osmotic dysregulation, inhibition of mitochondrial enzymes and respiratory chain (2, 5). Moreover, MSUD patients present with deficiency of l-carnitine (l-car), a compound with antioxidant properties whose supplementation has recently been shown to decrease DNA damage in treated MSUD patients (6).

The BCKD complex, which catalyzes an irreversible second step within the inner mitochondrial membrane, represents a multi-enzyme macromolecule consisting of three different catalytic components E_1 ($E_{1\alpha}$, $E_{1\beta}$), E_2, E_3 which require cofactors thiamin flavin and two regulatory enzymes, a-kinase and

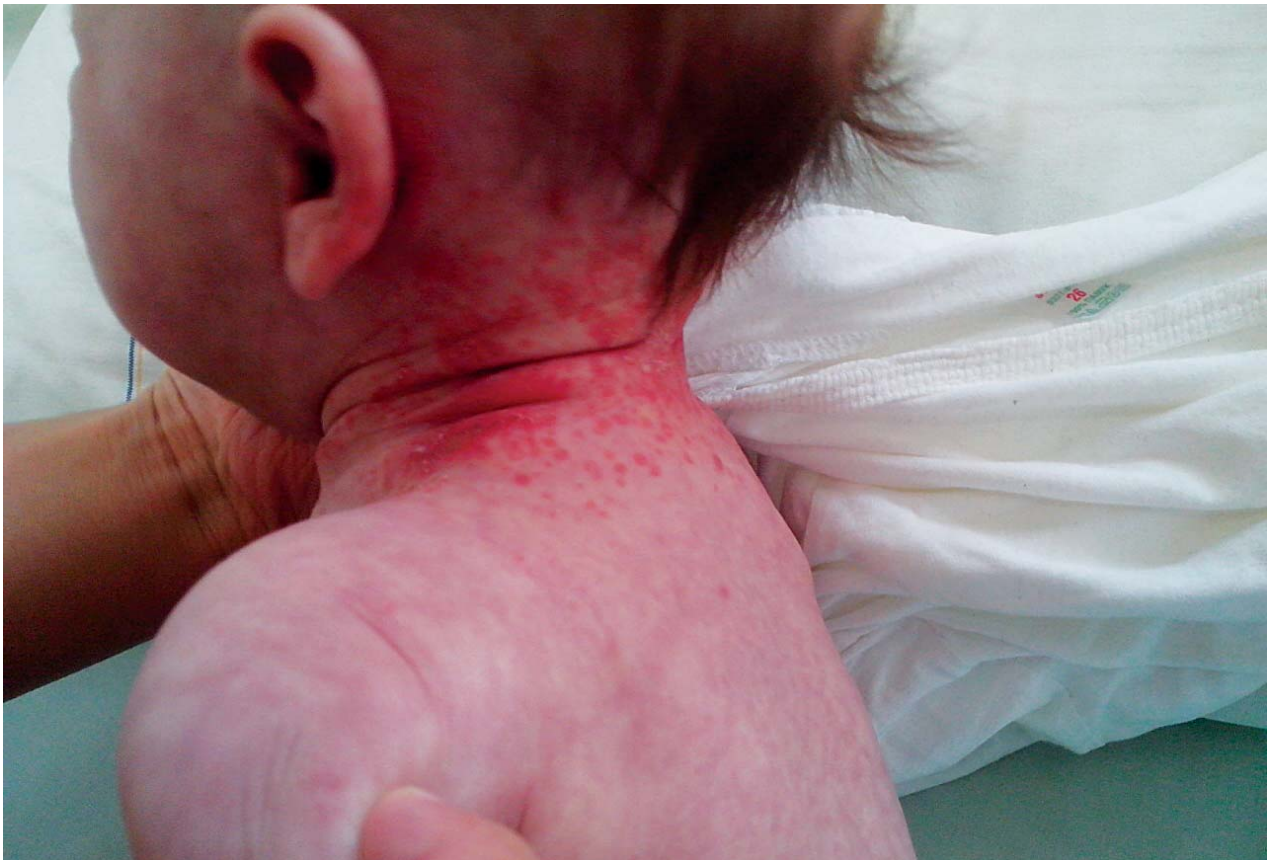

Figure 2. Sharply demarcated erosions and macular exanthema on the scalp, face, trunk and extremities

a-phosphatase. The genes encoding the various BCKD complex catalytic subunits/components E1α, E1β, E2, E3, kinase and phosphatase have been mapped to chromosome loci: 19q13.1–13.2; 6q14; 1p31; 7q31–32, 16p11.2 and 4q22.1, respectively. MSUD is predominantly caused by mutations in the BCKDHA, BCKDHB, and DBT genes, which encode for the E1a, E1b, and E2 subunits of the human mitochondrial BCKD complex (1).

In 1954, Menkes et al. reported that four siblings from a single family from Massachusetts died within the first 3 months of their lives because of neurodegenerative complications. The urine of these infants had an odor resembling maple syrup (burnt sugar) (7). Later, Dancis et al. identified the pathogenic compounds in the pathway of branched-chain amino acids (BCAA) BCAA (8). Maple syrup urine disease (MSUD) is a rare inherited central nervous system (CNS) disorder described in all ethnic groups and occurs in about 1/185.000 and 1/101.624 newborns in the USA and Taiwan, respectively (1, 9). Five different clinical phenotypes are distinguished based on the age of onset, severity of clinical symptoms and response to the therapy – classical, intermediate, intermittent, thiamine-responsive and E_3-deficient. All forms are characterized by poor feeding, vomiting, poor weigh gain, somnolence, maple syrup odor of the urine. Encephalopathy and progressive neurodegeneration resulting in accumulation of BCAA and their corresponding BCKA may occur in untreated infants. Asymptomatic newborns with MSUD have better outcome compared to infants diagnosed after they have become symptomatic (2). Because early detection and dietary restriction can prevent complications and may allow normal intellectual development, MSUD has been added to metabolic screening program of newborns (9). However, the screening becomes uncertain in non-classical forms of the disease, e.g. the intermittent form where symptoms usually appear between the ages of 5 months and 2 years (10).

As the basis of treatment includes a specific dietary therapy, it must comprise careful adjustment of caloric and protein intake along with micronutrient and vitamin supplementation in selected instances (e.g., rare cases of thiamine-responsive MSUD), carnitine administration and adjunct treatment (e.g., neurotropic and psychotropic drugs when neurological symptoms form a component of the phenotype) as was required in our patient. The mainstay in the treatment of MSUD encompasses acute-phase treatment of acute episodes, which gradually shifts to long-term management, depending on the patient's condition (11). Prospective studies are needed to optimize current therapeutic strategies including life-time risk in affected individuals by testing the effectiveness of adjunct therapies such as antioxidants or-alpha-ketoglutarate in addition to specialized precursor/protein restriction diets and substitution (3). Liver transplantation may be performed in very severe cases as an effective way to eliminate acute decompensation risks, but currently available evidence suggests it may not improve the intelligence quotient (IQ) or reverse psychiatric disease (12).

Along with infant's aminoacidopathy, particularly in children with BCAA disorders, cutaneous lesions, with special predilection to diaper periorificial regions and neck folds, resembling acrodermatitis enteropathica (AE) may develop, (13 - 19). Acrodermatitis AE is a rare autosomal recessive disease characterized by zinc deficiency attributed to the inability to absorb zinc from the gastrointestinal system. Clinical presentation is based on the triad: dermatitis, diarrhea and alopecia. Skin eruptions resembling acrodermatitis enteropathica can be caused by deficiencies of other nutrients such as biotin, essential fatty acids and AA. Apart from "AE-like skin lesions", the term "acrodermatitis acidemica" and recently "acrodermatitis dysmetabolica" have been proposed. Since acrodermatitis acidemica is rarer than AE, children are first treated with zinc supplements, instead of higher amounts of natural proteins rich in essential AA. The exact pathogenesis of skin lesions has not been established yet, but it is believed that BCAA are essential for normal growth and differentiation of keratinocytes. In our patient the diagnosis of AE-like iatrogenic acrodermatitis enteropathica-like syndrome in MSUD was made based on the following: clinical picture of exfoliative dermatitis, failure to trive, diarrhea, lethargy and encephalopathy; diet free of

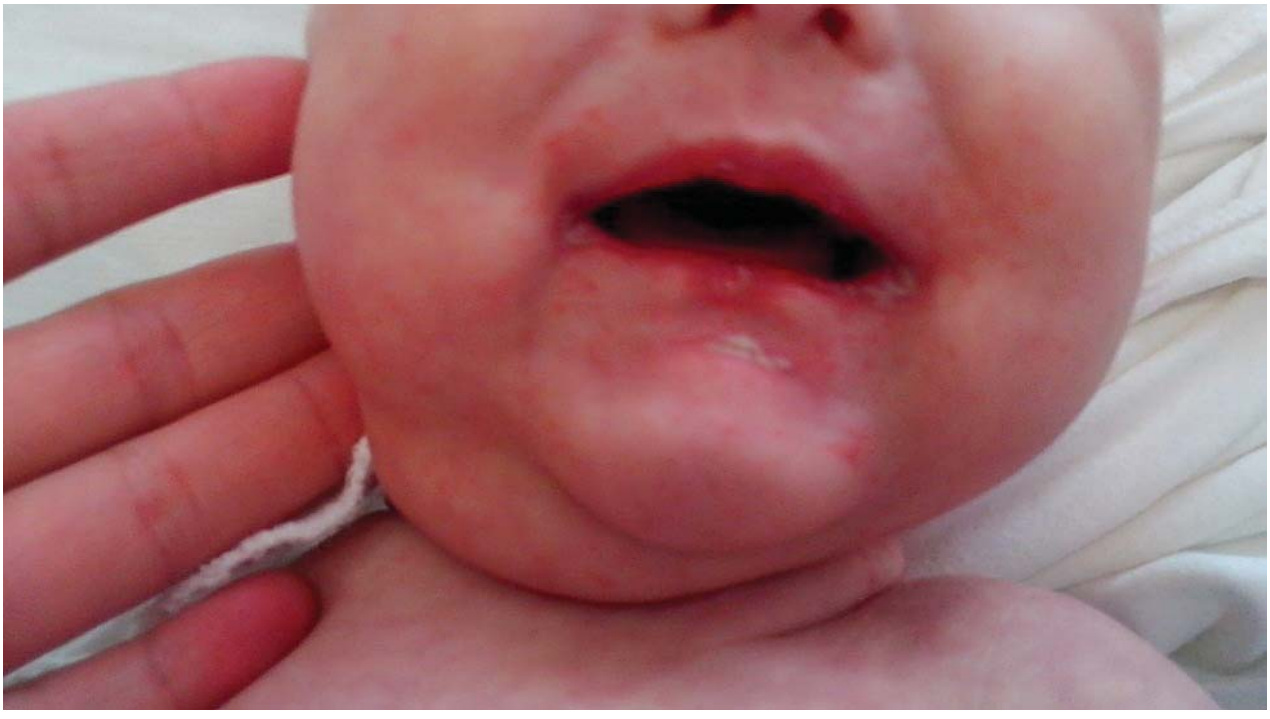

Figure 3. Perioral exfoliation, erythematous patches and erosions

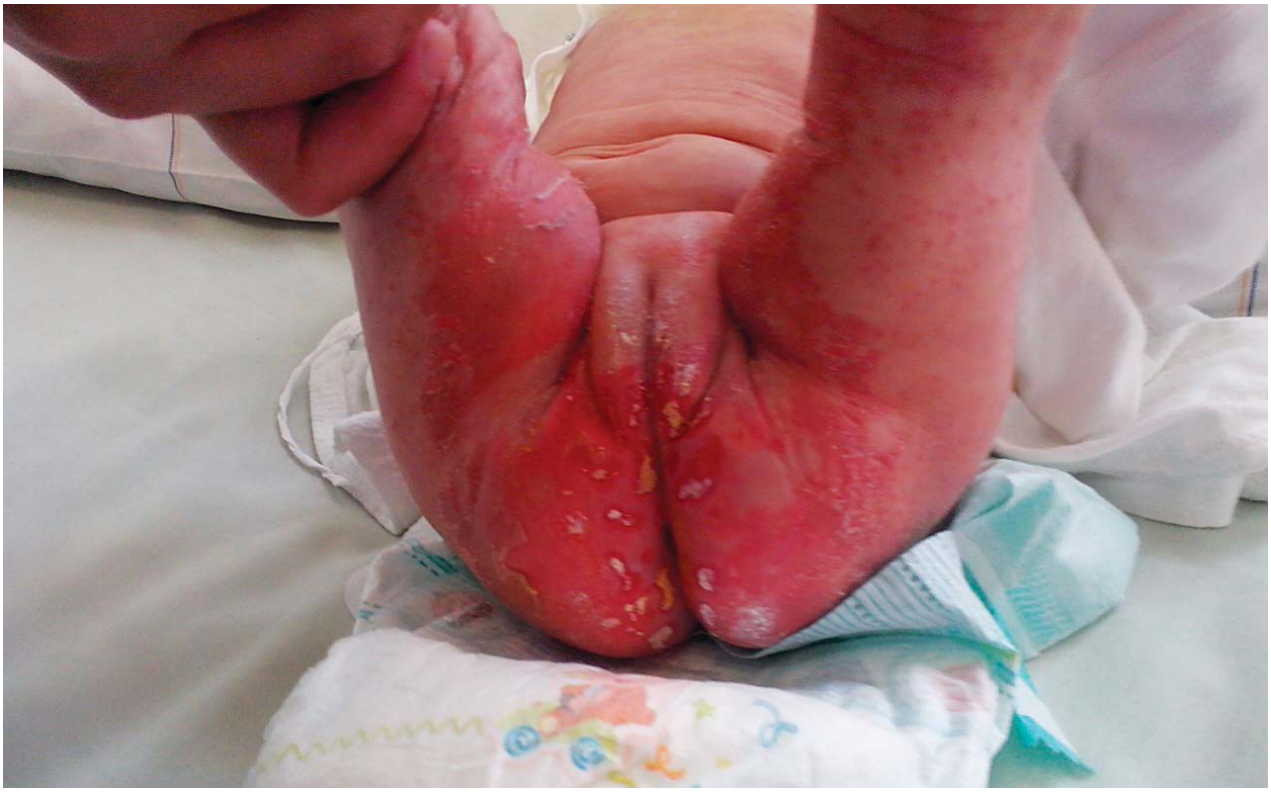

Figure 4. Diaper exfoliative dermatitis

isoleucine, leucine and valine, as well as valine and isoleucine supplementation resulted in prompt resolution. In differential diagnosis we ruled out other conditions such as acrodermatitis entheropathica, candidosis, atopic dermatitis, staphylococcal scalded skin syndrome and toxic epidermal necrolysis.

Recently, formulas enriched with AA that compete with BCAA for transport (e.g., tryptophan, tyrosine, phenylalanine, methionine, threonine etc.) and also help maintaining physiological AA plasma levels and transport into the brain, have been designed for patients with MSUD. They improve growth and adequate nutritional status by providing energy and protein required by patients with growth disorders (5). Moreover, in order to develop nutrition management guidelines for inherited metabolic disorders, Genetic Metabolic Dietitians International (GMDI) and Southeast Regional Newborn Screening and Genetics Collaborative (SERC) used a model that gathers both evidence- and consensus-based guidelines for MSUD, which turned to be the first one to be completed (20).

Still, there is an uknown risk for skin eruptions when the so-called "branched-chain amino acid-free formula" is used. We believe that the list with causes of acrodermatitis enteropathica-like syndrome should include diet restriction of branched-chain amino acids for maple syrup urine disease. Although being more prevalent in populations with high incidence of consanguinity, (incidence rate: 1:200 births), most clinics see very few individuals with MSUD. With such a small patient populations, only multicenter collaboration may provide new data and allow creation of new strategy achievements (20).

Conclusion

The acrodermatitis enteropathica–like syndrome in our patient was due to a iatrogenic amino acid nutritional imbalance. According to available world literature, this is the first report of acrodermatitis enteropathica-like syndrome in a child with maple syrup urine disease (leucinosis) in the Republic of Bulgaria.

Abbreviations

MSUD – maple syrup urine disease
MSUD-2 - nutritional formula for MSUD with iron
AA - amino acid
α KIC - α-ketoisocaproate
BCAA – branched-chain amino acids
AE - acrodermatitis enteropathica
LDH - lactatae dehydrogenase
CPK - creatine phosphokinase
EEG – electroencephalography
BCKD – branched-chain alpha-keto acid dehydrogenase
BCKA - branched-chain α-keto acid
l-car - l-carnitine
GMDI - Genetic Metabolic Dietitians International
SERC - Southeast Regional Newborn Screening and Genetics Collaborative

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Promene na koži u toku nutricione terapije leucinoze – prikaz slučaja

Sažetak

Uvod. Leucinoza ili bolest sa mirisom urina koji podseća na sirup javora (sinonim engl. *maple syrup urine disease* – MSUD) nasledna je aminoacidopatija koju izaziva defekt u metabolizmu amino-kiselina (AA): leucina, izoleucina i valina, kao i njihovih α-ketoacidnih derivata. Kod obolelog sa klasičnom formom MSDU, nastaje encefalopatija i otok moždanog tkiva, kao posledica akumulacije navedenih AA i njima odgovarajućih derivata, α-keto kiselina, naročito leucina i njegovog ketoacidnog derivata, α-ketoizokaproata (α KIC) u serumu. S obzirom da se u najtežoj, klasičnoj formi MSUD bolest ispoljava tokom prvih nedelja života, na rođenju novorođenče odaje utisak zdravog deteta. Bolest karakteriše pojava ketoacidoze, otežana ishrana i napredovanje, somnolencija, ataksija i karakteristični miris mokraće koji zbog sličnosti sa šećerom koji gori, podseća na sirup od javora (engl. *maple syrup*). U nelečenim slučajevima, dete umire sa znacima encefalopatije, progresivne neurodegeneracije i kome. Lečenje akutne metabolijske dekompenzacije kroz restriktivni unos navedenih AA koje pripadaju grupi amino- kiselina sa razgranatim lancem (engl. *branched-chain amino acids* – BCAA), predstavlja stub terapije, ali ishranu otežava mišićna hipotonija, mučnina, infekcija, metabolijske komplikacije, retardacija i otežano gutanje. Kod lečene dece, glavne komplikacije nastaju zbog disbalanasa u esencijalnim AA, otežanog razvoja usled restriktivnog unosa mikroelemenata u uslovima njihove povećane potrebe ili usled povećanih energetskih potreba koje izaziva hronično oboljenje, odnosno inflamacija. Usled smanjenog i nedovoljnog unosa BCAA, kod obolelog novorođenčeta/dojenčeta nastaju promene na koži koje po svojim osobinama odgovaraju promenama enteropatskog akrodermatitisa.

Prikaz slučaja. Četvoromesečna devojčica je hospitalizovana na dečjem odeljenju zbog opšteg lošeg stanja, slabe uhranjenosti i karakterističnog mirisa mokraće. Prvi znaci bolesti su se kod deteta javili tri meseca ranije, u vreme kada je počela ishrana deteta adaptiranim mlekom. Prethodno je devojčica bila lečena u drugoj bolnici gde je zbog teškog stepena anemije primala transfuzije krvi i plazme, ali bez željenog efekta. Na pregledu, telesna težina je iznosila 3 kg a dužina 50 cm, dete je bilo somnolentno, hipotono, lice dizmorfno sa retrognacijom, fontanele su bile napete, dijametar grudnog koša bio je povećan a sračani rad ubrzan. Neurološkim statusom su dominirali: nesposobnost da samostalno drži glavu, nemogućnost viđenja detalja (otežana konvergencija očnih jabučica), nemogućnost samostalnog sedenja, hiperpokretljivost kolenih zglobova i povišeni Ahilovi refleksi.

Rezultati biohemijskih analiza ukazali su na povišene vrednosti serumske laktatne dehidrogenaze (LDH), kreatin fosfokinaze (CPK) i amonijaka (> 145 μmol/l, referalne vrednosti 1–31 μmol/l), metabolijsku acidozu, visok serumski nivo leucina (> 8 000 μmol/l, referalni raspon 2,07–4,57 μmol/l) i valina (> 100 μmol/l, referalni raspon 2–4,8 μmol/l) i tešku anemiju. Ultrazvučni pregled je ukazao na postojanje otoka mozga; elektroencefalografski (EEG) utvrđen je uniformno nizak električni potencijal čija se amplituda nije skoro uopšte razlikovala od kortikalne.

Dijagnoza MSUD je postavljena na osnovu kliničkog, biohemijskog i radijacijskog nalaza.

Lečenje je podrazumevalo korekciju hidro-elektrolitskog disbalansa, restrikciju unosa BCCA upotrebom medicinske hrane sa MSUD-2 formulacijom i simptomatsko lečenje neuroloških komplikacija.

Nekoliko dana posle započinjanja ovog dijeteskog režima MSUD-2 formulacijom koja se zasniva na restrikciji unosa leucina, izoleucina i valina, na koži nastaje makulopapulozni egzantem sa zahvatanjem kože kapilicijuma, lica, trupa i ekstremiteta i eksfolijativni dermatitis perioralne i angenitalne regije, praćeni dijarerom. Dermatološkim pregledom su dominirale erozije, žućkasto prebojene krustozne naslage i lamelozna periorificijelna eksfolijacija koja se širila i na susedne delova ekstremiteta (slike 1–4). Opšte stanje je bilo ozbiljno narušeno, sa znacima letargije, hipotenzije, anemije, dispepsije i neorološkim simptomima. Na osnovu svega navedenog, kod

devojčice je postavljena dijagnoza sekundarnog sindroma nalik na enteropatski akrodermatitis nastao kao posledica nedostatka amino-kiselina leucina i valina. Posle supstitucije BCAA pod laboratorijskom kontrolom (nivo cinka unutar referalnih vrednosti, snižen nivo leucina i valina ispod referalnih vrednosti), nastupilo je promptno povlačenje svih simptoma uključujući i promene na koži, što je potvrdilo našu radnu dijagnozu; za negu kože korišćeni su lokalni antiseptici, emolijensi i lokalni niskopotentni kortikosteroidi. Diskusija. Leucinoza (sinonim *maple syrup urine disease* – MSUD) predstavlja sekundarnu amino-acidopatiju nastalu usled defektne aktivnosti multienzimskog kompleksa mitohondrijske BCAA α-keto kisele dehidrogenaze (BCKD), koja katalizuje dekarboksilaciju BCAA (leucin, izoleucin i valin) do njima odgovarajućih metabolita, α-keto kiselina. Katabolijski put BCAA odvija se u nekoliko etapa: reverzibilna transaminacija, ireverzibilna oksidativna dekarboksilacija i dehidrogenacija. Do kongenitalnih poremećaja može doći, a oni se nasleđuju autozomno recesivnim putem. U MSUD degradacija tri BCCA, leucina, izoleucina i valina biva zaustavljena posle prve etape, transaminacije), te dolazi do nakupljanja BCAA i njihovih α-keto kiselina (BCKA) u biološkim tečnostima. MSUD spada u grupu aminoacidopatija i u grupu organskih acidurija istovremeno, s obzirom na toksične efekte nakupljanja amino-kiselina (AA), naročito leucina i organskih kiselih intermedijernih – keto i hidroksikiselih BCCA metabolita. Akumulacija leucina izaziva neurološke simptome, a izoleucina karakterističan miris urina, po kome je bolest dobila naziv. Pri visokim koncentracijama leucin brzo prolazi hemato-encefalijsku barijeru i u moždanom tkivu izaziva neurotoksične efekte: inhibicija transporta esencijalnih AA preko hemato-encefalijske barijere, npr. tirozina i triptofana zbog čega u mozgu dolazi do smanjenjene sinteze kateholamina, serotonina i proteina. U fiziološkim uslovima, transaminaze vrše konverziju leucina u α-ketoglutarat; ukoliko nastupi nakupljanje ketoacidnog derivata leucina, α-ketoizokaproata (α KIC), nastupa smanjenje glutamata u moždanom tkivu, s obzirom da α KIC povratnim mehanizmom (tzv. dvosmerna transaminazna reakcija) stimuliše sintezu leucina i tom prilikom koristi glutamat. Glutamat ima dve značajne uloge: u stvaranju energije i procesima neurotransmisije. Pretpostavlja se da mehanizmi odgovorni za nastanak neurotoksičnosti u MSUD uključuju sledeće: poremećaj preuzimanja esencijalnih AA u mozgu, nedostatak neurotrasmitera, smanjenje energetskog nivoa, osmotska disregulacija, inhibicija mitohondrijskih enzima i respiratornog lanca. Oboleli od MSUD imaju deficit l-karnitina, supstancije sa antioksidativnim osobinama, čijom se suplementacijom smanjuje oštećenje DNA kod obolelih sa MSUD.

Multienzimski BCKD kompleks katalizuje ireverzibilnu sekundarnu metabolijsku etapu kao multienzimski makromolekul unutar unutrašnje mitohondrijske membrane, sastavljen od tri različite katalizatorske komponente E_1 ($E_{1\alpha}$, $E_{1\beta}$), E_2, E_3, za čije funkcionisanje su potrebni kofaktori tiamin, flavin i dva regulatorna enzima, kinaza i fosfataza. Geni koji kodiraju sintezu subjedinica/komponenti BSKD kompleksa, E1α, E1β, E2, E3, kinaze i fosfataze smešteni su na odgovarajućim hromozomskim lokusima: 19q13.1–13.2; 6q14; 1p31; 7q31–32, 16p11.2 i 4q22.1. MSUD u najvećem broju slučajeva izazvan je mutacijama gena BCKDHA, BCKDHB, i DBT koji kodiraju sintezu E1a, E1b, i E2 subjedinice humanog mitohondrijskog BCKD kompleksa.

MSUD predstavlja redak nasledni poremećaj CNS, koji se javlja u svim etničkim grupama sa incidencijom koja iznosi npr. 1/1/185 000 novoređene dece u Sjedinjenim Američkim Državama ili 1/101 624 novorođenčadi na Tajvanu. Opisano je pet različitih fenotipova koji se međusobno razlikuju po vremenu nastanka, kliničkoj slici i terapijskom odgovoru: klasični, intermedijerni, intermitentni, zavisan od tiamina i sa deficitom E3 subjedinice. Sve navedene fenotipske forme oboljenja karakteriše: poremećena ishrana, povraćanje, slabo, usporeno dobijanje na težini, somnolencija i karakteristični miris urina. Kod nelečene dojenčadi, encefalopatija i pregresivna neurodegeneracija nastaju kao posledice nakupljanja BCAA i njihovih odgovarajućih metabolita BCKA; slučajevi MSUD kod kojih je bolest otkrivena u asimptomatskom stadijumu imaju bolju prognozu od slučajeva koji su imali simptome u trenutku postavljanja dijagnoze. S obzirom da rana detekcija i sprovođenje dijetetskog režima sprečavaju nastajanje komplikacija i omogućuju nesmetan intelektualni razvoj, MSUD je uključena u metabolijski skrining

program za novorođenčad; ipak, ovaj program nije efikasan ukoliko je u pitanju neklasična, npr. intermitentna forma oboljenja, s obzirom da se simptomi tada javljaju između pet meseci i dve godine starosti.
Lečenje se temelji na primeni specifičnog dijetetsko restriktivnog reežima u akutnoj fazi, da bi se kako vreme odmiče, postepeno terapija usmeravala u određenom pravcu u zavisnosti od individualnog stanja pacijenta. Potrebne su prospektivne studije kako bi se optimizirala terapijska strategija zasnovana na životnom riziku svakog pojedinca, putem testiranja efikasnosti adjuvantne terapije antioksidansima ili alfa-ketoglutaratom uz specijalizovani prekurzor/protein restriktivni unos ili supstituciju. Transplantacija jetre se može primeniti u veoma teškim slučajeviam MSUD sa ciljem kupiranja i smanjivanja razika od akutne dekompenzacije, ali rezultati novijih istraživanja ukazuju da transplantacija ne poboljšava koeficijent inteligencije niti smanjuje psihijatrijsku simptomatologiiju.
Paralelno sa simptomima i znacima aminoacidopatije, naročito kod dece sa poremećenim metabolizma BCAA, mogu se razviti promene na koži koje predilekciono zahvataju periorificijsku pelensku regiju i vratne nabore, a po svom izgledu odgovaraju onima koje nastaju u enteropatskom akrodermatitisu. Kliničku trijadu čine dermatitis, dijareja i alopecija; promene na koži smatraju se direktnom posledicom deficita biotina, esencijalnih masnih kiselina i AA. Pored sindroma sličnog enteropatskom akrodermatitisu, u novije vreme predlažu se nazivi *acrodermatitis acidemica* ili *acrodermatitis dysmetabolica.* Tačan mehanizam nastanka lezija na koži nije dovoljno rasvetljen ali se smatra da su BCAA od esencijalnog značaja za normalan rast i diferencijaciju keratinocita. Dijagnoza sindroma sličnog enteropatskom akrodermatitisu sekundarno nastalog u okviru MSUD je u slučaju opisanom u ovom radu postavljena na osnovu sledećeg: klinička slika eksfolijativnog dermatitisa, otežan rast, dijareja, letargija, encefalopatija, dijagnostikovan MSUD, lečena dijetom bez leucina, izoleucina i valina, da bi supsticija izoleucinom rezultirala promptnom rezolucijom svih promena.
U novije vreme, proizvedene su dijetetske formulacije za pacijente sa MSUD obogaćene AA (npr. triptofan, tirozin, fenilalanin, metionin, treonin) koje stupaju u kompeticiju sa BCAA za transport i pospešuju održavanje fiziološkog nivoa AA u plazmi i transport u mozak, čime se obezbeđuje dovoljan unos proteina i dovoljna količina nergije.
I dalje je nepoznat rizik za nastajanje promena na koži kada se u ishrani koriste formule bez BCAA. Predlažemo da se na listu mogućih uzroka sindroma sličnog enteropatskom dermatitisu, upiše i restrikciona dijeta sa BCAA radi lečenja MSUD.
Zaključak. Sindrom sa promenama na koži sličnim enteropatskom akrodermatitisu se kod prikazanog deteta razvio kao posledica jatrogenog nutricionog disbalansa u unosu aminokiselina. Prema nama dostupnoj svetskoj literaturi, ovo bi bio prvi objavljen slučaj koji se javio kod deteta sa leucinozom u Republici Bugarskoj.

Ključne reči

Bolest urina s mirisom javorovog sirupa; Dijetetska terapija; Odojče; Akrodermatitis; Isoleucin + deficijencija; Znaci i simptomi; Ishod terapije; Prikazi slučajeva; Bugarska

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Cryotherapy for Lichen Striatus in an Adult – a Case Report

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Abstract

Lichen striatus (linear lichenoid dermatosis) is an uncommon, self-limited, inflammatory, linear skin condition of unknown origin. The causes of linear distribution are unknown, though the pattern of lichen striatus (LS) mostly follows the lines of Blaschko (BL). The condition most commonly occurs in children between 5 and 15 years of age, usually after the first year of life.

We report a 27-year-old, otherwise healthy flight attendant with LS whose diagnosis was based on: the history of sudden appearance and rapid linear spread of lesions; clinical presentation of small pink, coalescing scaly papules without umbilication or Wickham's striae, linear distribution following one BL down a lower limb to the ankle, with a band broadening into plaque on the left buttock; histology showed some hyperkeratosis, lichenoid dermatitis similar to lichen planus, but with the presence of inflammatory infiltrate in the papillary dermis and also deeper in the perifollicular region. The inflammatory infiltrate consisted mainly of limphocytes, with some melanophages and histiocytes.

There is no standard treatment for LS, and it is given for cosmetic or psychological reasons only, as we have done in our patient due to slight pruritus and occupational reasons. With regard to her occupational demands, in order to achieve satisfying results, she was successfully treated with cryotherapy, which she tolerated well, without any side effects. Cryotherapy was performed twice, with a two-week interval. Full resolution was achieved twelve weeks after cryotherapy.

In conclusion, we present an adult female who developed lichen striatus suddenly three months after delivery and was successfully treated with cryotherapy.

Key words

Lichen Sclerosus et Atrophicus; Lichenoid Eruptions; Adult; Cryotherapy; Treatment Outcome; Case Reports

Lichen striatus (linear lichenoid dermatosis) is an uncommon self-limited, inflammatory, linear dermatitis of unknown origin. The factors causing linear distribution are unknown, though the pattern of lichen striatus (LS) follows the lines of Blaschko (1, 2, 3). The condition most commonly affects children between 5 and 15 years of age, usually after the first year of life. A female to male predominance of 2:1 has been reported (1, 2, 4). Occasionally, LS is seen in adults as a linearly distributed array of closely adjacent small flesh-colored, erythematous to pinkish papules without umbilication or Wickham's striae, with little or no scales (1, 4). LS is characterized by rapid development: discrete at first, small papules rapidly coalesce, soon forming a dull-red, slightly scaly, often irregular linear band, usually 2 mm to 2 cm in width. Sometimes they broaden into plaques, especially on the buttocks. The lesion may be only a few centimetres in length, but may extend the entire length of the limb. Almost any skin site may be affected, including the face (3). However, a common presentation is a progressively lengthening collection of erythematous

papules starting on the proximal portion of the upper or lower extremity, progressing over several months to acral skin, commonly a digit, even extending down a limb to the nails. The abdomen, buttocks and thighs may be involved by unilateral extensive lesions. Generally, multiple lesions are rare, bilateral involvement is exceptional, but parallel linear bands or zosteriform patterns have been reported (1). No associated systemic abnormalities have been identified (1). While some of the skin lesions are asymptomatic, others may be quite pruritic (5).

Histological presentation of lichenoid dermatitis with patchy or band like lymphocytic interface dermatitis similar to lichen planus may occur, but presence of psoriasiform epidermal hyperplasia, inflammatory infiltrate of lymphocytes, melanophages and histiocytes in the papillary dermis, especially in the deeper perifollicular layer is believed to be a relatively characteristic finding (2, 4).

Just as rapidly as LS starts, it resolves, leaving variable dyspigmentation (4). In most cases spontaneous resolution can be expected within 3–6 months, but some lesions may persist for over a year. There is no standard treatment for LS, apart from observation, and it should be given for cosmetic or psychological reasons only (1).

Here we present a case of lichen striatus in an adult female with Blaschko linear acquired inflammatory skin eruption successfully treated with cryotherapy.

Case Report

History

A 27-year-old, otherwise healthy flight attendant was referred to our Outpatient Department with an erythematous, linear, slightly itchy eruption on the left leg. The lesion developed suddenly, three months after delivery, rapidly progressing over the first week involving the entire length of the limb, and subsequently became stable. The eruption was not preceded by a sore throat, recent infection, sick contacts or constitutional symptoms. There was no history of drug use or any topical application. The patient's medical history was unremarkable, but her family history was positive, as her mother suffered from allergic rhinitis.

Dermatologic examination

The physical examination of the flexor aspect of the lower left limb showed small pink, coalescing scaly papules without umbilication or Wickham's striae, with a linear distribution following one BL down to the ankle, with a band broadening into plaque on the left buttock; the surface of the lesion was rough, slightly hyperkeratotic and scaly (Figures 1, 2). Apart from generalized xerosis, there was no other sign of atopic dermatitis.

Laboratory tests

Laboratory tests results were within normal limits, except the total IgE serum levels: significantly increased 700 IU/ml (reference value ≤ 100 IU/ml).

Histopathological findings

Histological analysis of skin lesion revealed: slightly hyperkeratotic epidermis, with rather deep invagination filled with keratin and vacuolar alteration of the basal layer showing very few necrotic keratinocytes; papillary dermis with a band-like infiltrate of lymphocytes admixed with some histiocytes and melanophages; the infiltrate extended into the basal layer of the epidermis, and perifollicularly into the deeper dermal region (Figures 3 and 4).

Based on patient's history, clinical examination and pathohistological analysis, the diagnosis of LS was made.

Therapy

First, a topical corticosteroid cream (mometasone furoate 0.1%) was applied twice daily for 2 weeks, primarily for esthetical reasons. Besides relieving the itching, the therapy showed to be ineffective in reducing the linear lesions. For this reason, sequential cryotherapy was performed in two freezing cycles, using a Cry-Ac® device (Brymill Cryogenic Systems, Brimill company, Ellington, USA). Liquid nitrogen was applied to the linear lesions for 30 seconds, and a 2-mm white halo formed. Cryotherapy was performed twice, with a 2 week interval, whereas the treated surface was treated with an antibiotic cream (Gentamicin) (Figure 5). Apart from common post-therapeutic reactions including mild burning sensation, erythema and development of small blisters 48 hours after cryotherapy, there were no other complications.

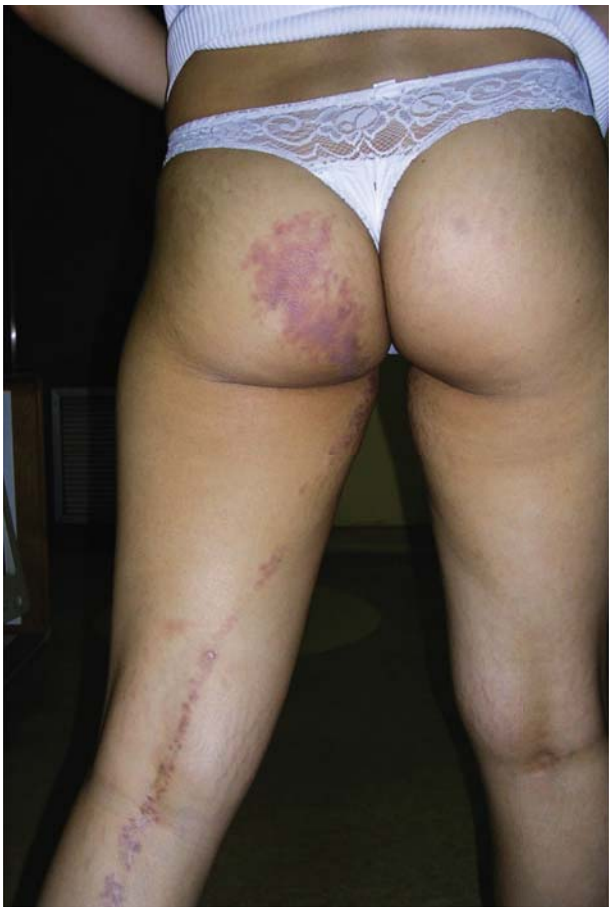

Figure 1. Clinical presentation before therapy: pink, coalescing scaly papules linearly distibuted following one BL down the left lower limb, with band broadening into plaque on the left buttock

Complete regression of the treated lesions was achieved twelve weeks after the last treatment. In the final phase of therapy, topical Contractubex® cream was indicated twice a day for a month (Figure 6). A systemic antihistamine (Desloratadine) was used to relieve itching.

Discussion

LS mostly shows a great confinement to Blaschko lines (BL) which are a manifestation of cutaneous mosaicism, a postzygotic genomic alteration, specifically a somatic mutation in which different groups of skin cells behave differently for unknown reasons; BL are believed to reflect the embryologic migration of these aberrant skin cells (1). Moreover, another theory proposing "epigenetic mosaicism" with transposable elements or retrotransposons has recently emerged: it has actually been hypothesized that these elements which are present in a large portion of the human genome, can activate or inactivate (via methylation or demethylation) the neighboring genes (6). A recent report on the unique simultaneous occurrence of LS in two related siblings (one suffering from recurrent otitis media) along the same BL, supports the infectious and genetic components in the development of LS (7). This report also supports the latter theory of epigenetic mosaicism, since this theory is based strictly on familial occurrence of LS, in contrast to the former, which supports somatic mutations with occurrence by chance, when familial incidence is improbable (7). Although familial occurrences are extremely rare, it seems most likely that different endogenous or exogenous factors may lead to the unmasking of tolerance to an abnormal keratinocyte clone in apparently healthy,

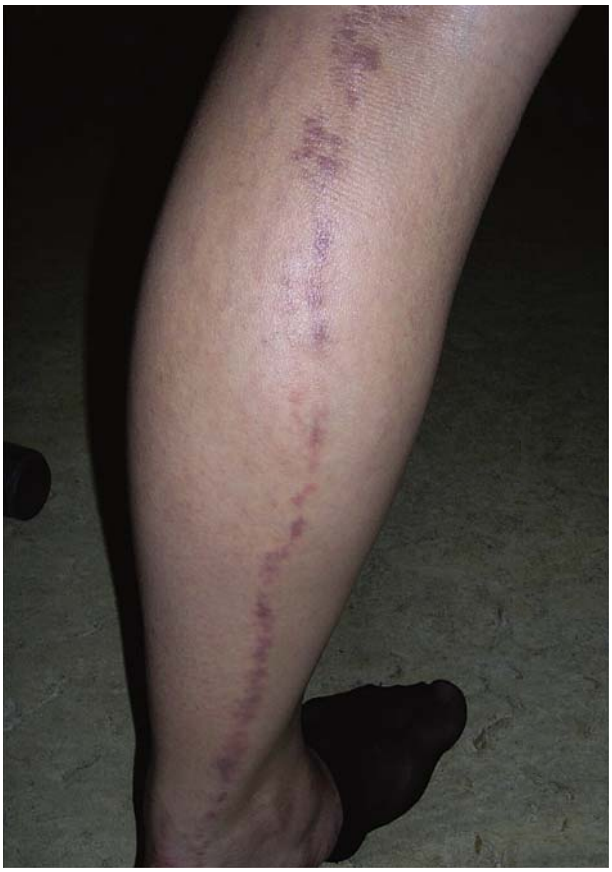

Figure 2. Clinical presentation before therapy: pink, coalescing scaly papules linearly distibuted following one BL down the lower limb to the ankle

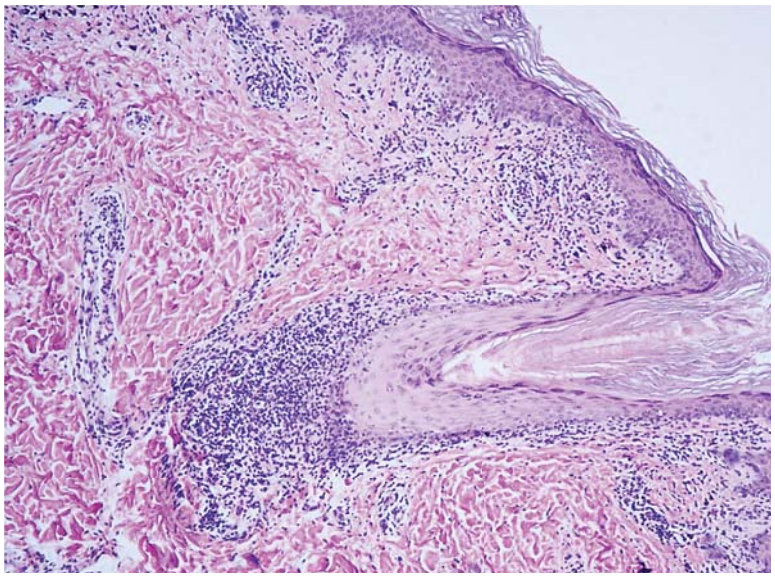

Figure 3. Histological analysis of the skin lesion revealed: the epidermis slightly hyperkeratotic, with rather deep invagination filled with keratin and vacuolar alteration of the basal layer showing very few necrotic keratinocytes; papillary dermis with a band-like infiltrate of lymphocytes admixed with some histiocytes and melanophages; the infiltrate spread into the deeper part of the epidermis, as well as perifollicular region (hematoxylin and eosin, x 40)

but genetically predisposed individuals. Based on current evidence, the endogenous triggering event in unmasking these clones is likely to be an aberrant cell-mediated immunologic mechanism. Thus, Racette et al., hypothesize that individuals with LS are predisposed with partially silenced genomic transposable elements which are methylated or demethylated by an immunologic reaction to an infection. The infection acts only as an initiator of the aberrant cell-mediated immune response by creating

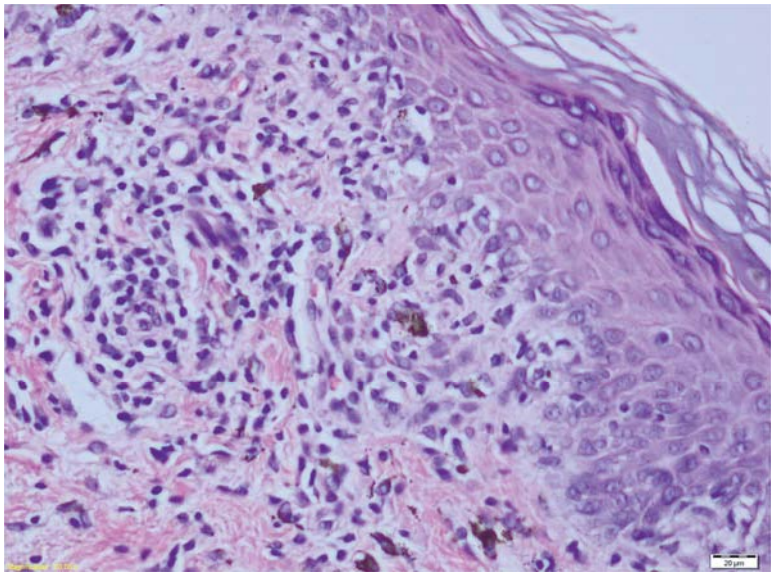

Figure 4. Higher magnification reveals: vacuolar degeneration of basal keratinocytes; chronic inflammatory infiltrate spreading from papillary dermis into the deeper part of epidermis; pigmented melanophages in the infiltrate (hematoxylin and eosin, x 200)

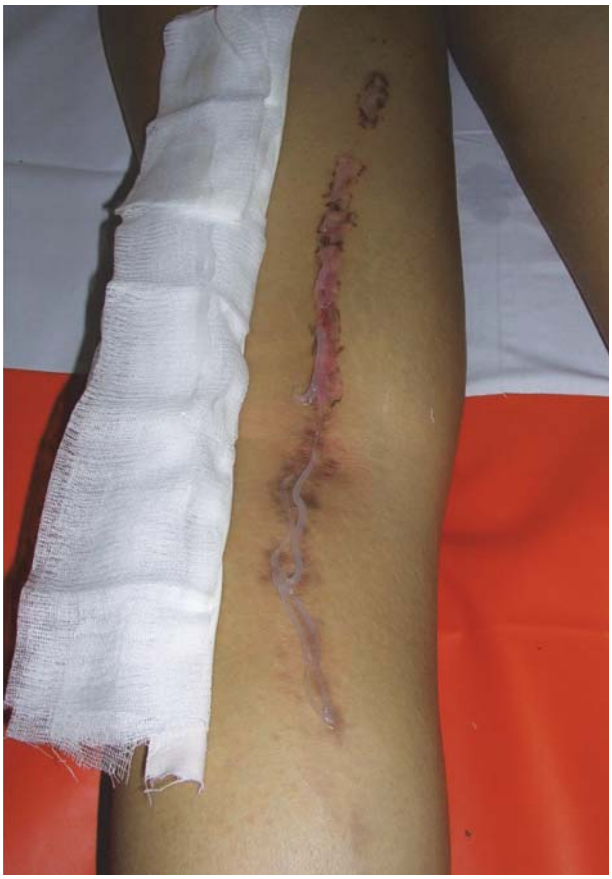

Figure 5. Clinical presentation two weeks after initiation of cryotherapy

a cellular alteration (7). Recently reported association of LS with Blaschkoid pityriasis rosea in the same location, also supports this concept (8). Moreover, the lack of viral particles in the lesions reported by some authors substantiates the hypothesis that infection or other exogenous triggers (e.g., environmental agents, cutaneous injury and hypersensitivity reaction) need only to initiate the cell-mediated immune response. The absence of prodromal symptoms in our patient as in most cases, does not exclude the possibility of asymptomatic illness triggering LS (7).

The occurrence of LS after allogenic stem cell transplantation was hypothesized to be an unusual form of localized, chronic graft-versus-host disease (9). This occurrence provided further support for the immunohistochemistry findings of necrotic keratinocytes bordered by CD8+T cells in LS (10), acting as cytotoxic lymphocytes eradicating mutant cells as probable target in LS.

Regarding aberrant cell-mediated immune mechanism acting as an endogenous triggering event in unmasking aberrant clones, this hypothesis could be substantiated by the higher association of atopy with LS reported by some authors (11). However, Taniguchi et all., have found an association between LS and personal history of atopy, which closely approaches the incidence of atopy in the general population (12). Thus, the association of LS with a positive personal or family history of atopy, like in our patient, is still unclear. The occurrence of LS three months after delivery reported here is also unclear, since it cannot be supported by similar literature data.

In our patient, the diagnosis of LS was made based on the: history of sudden development and rapid linear spread of lesions; clinical presentation of small pink, coalescing scaly papules without umbilication or Wickham's striae, with a linear distibution following

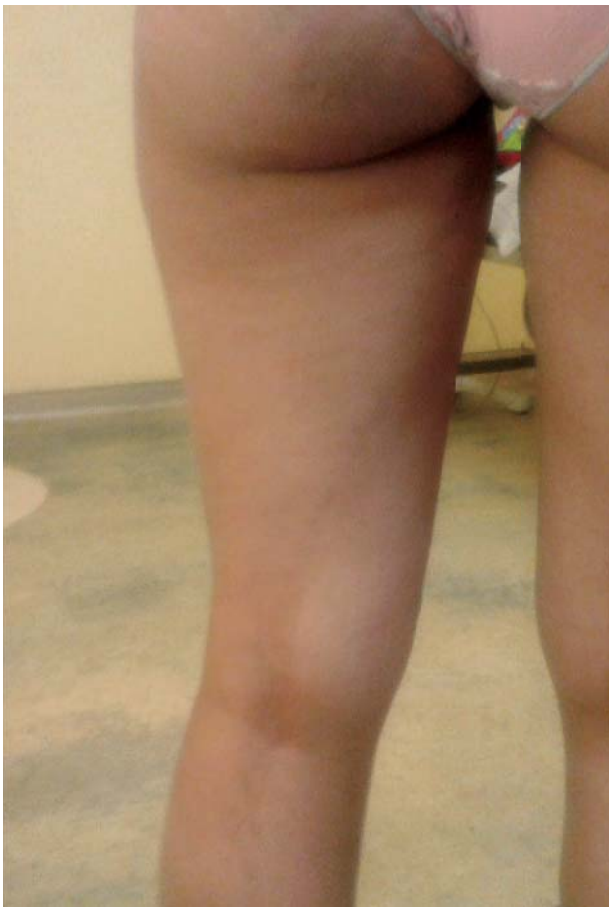

Figure 6. Clinical presentation twelve weeks after treatment

one BL down a lower limb to the ankle, with band broadening into plaque on the left buttock; histology showed some hyperkeratosis, lichenoid dermatitis similar to lichen planus, but with the presence of inflammatory infiltrate of lymphocytes admixed with some histiocytes and melanophages located in the papillary dermis as well as deeper in the perifollicular arrangement.

Several generalized dermatoses either occasionally follow BL, probably reflecting a clonal "susceptibility mutation" (linear lichen planus, porokeratosis, linear lichen nitidus, lichen striatus (eczema), segmental vitiligo, linear morphea nevoid psoriasis, Darier's disease, Hailey–Hailey disease, "adult Blaschkitis" - BLAISE (acronym for *B*laschko *l*inear *a*cquired inflammatory *s*kin eruption), or have also been reported in a linear or nevoid distribution (lupus erythematosus fixed drug eruption, chronic graft-versus-host disease and mycosis fungoides) (13). Probably, they all reflect genetic mosaicism, the former for multifactorial dermatoses with an autosomal dominant component, and the latter for potentially lethal dominant mutations rescued by mosaicism (13). They can can also be differed from inflammatory linear verrucous epidermal nevus (ILVEN) and child nevus, which occur at or soon after birth and usually persist lifelong, However, LS is considered to have a greater affinity to BL than any other condition. Some authors propose "adult Blaschkitis" a remitting and relapsing eruption of itchy inflammatory vesicles and papules occurring usually on the trunk in adults and adult version of LS to be the same entity (14, 15), while the others think BLAISE should perhaps be considered a description rather than a diagnosis (13).

Although LS has variable histologic presentations, histological analysis may be helpful. LS most closely resembles linear lichen planus and inflammatory linear verrucous epidermal nevus (ILVEN). Linear lichen planus and LS display the same histopathology as classical lichen planus, but LS may also show superficial or deep perivascular and/or periadnexal (perifollicular in our patient), localization of the infiltrate. The epidermal changes in ILVEN usually more closely resemble psoriasis than interface dermatitis, while the significant acanthosis and hyperkeratosis in verrucous ILVEN are absent in LS (4). The histology of "adult Blaschkitis" shows remitting and relapsing eruption of itchy inflammatory vesicles and papules most frequently localized on the trunk in adults, and it is more eczematous (spongiotic) than lichenoid. Lichen nitidus exhibits more histiocytic than lymphocytic lichenoid interface dermatitis with epidermis showing atrophy and parakeratosis (2). Perifollicular infiltrate in lupus erythematosus exhibits denser perifollicular lymphocytes and increased interstitial mucin deposits (2).

Standard treatment for LS is usually only observation, because of its benign, self limited course, and should be given for cosmetic or psychological reasons only (1). Not only rapid resolution of skin lesions but also complete resolution of pruritus was sustained in one series by combining a topical retinoid with a topical steroid (5). In order to achieve satisfying cosmesis in our patient responding her occupational demands, she was successfully treated with cryotherapy, which she tolerated well without any side effects.

Conclusion

Here we present a case of lichen striatus in an adult female as a Blaschko linear acquired inflammatory skin eruption successfully treated with cryotherapy. According to world literature available to us, this is the first report of successful treatment of LS with this therapeutic option.

Abbreviations

LS - lichen striatus
BL - Blaschko lines
BLAISE - Blaschko linear acquired inflammatory skin eruption

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Lichen striatus kod odrasle osobe lečene krioterapijom - prikaz slučaja

Sažetak

Uvod. Lichen striatus (sinonim – linearna lihenoidna dermatoza, LS) predstavlja linearnu inflamatornu dermatozu nepoznate etiologije. U najvećem broju slučajeva promene u LS se lokalizuju duž Blaškovih linija (engl. Blaschko lines, BL), ali faktori koji su odgovorni za linearni raspored lezija nisu dovoljno razjašnjeni. Oboljenje se javlja godinu dana nakon rođenja, najčešće kod dece uzrasta 5–15 godina. Javlja se i kod odraslih osoba u vidu linearne promene koja nastaje konfluencijom malih eritematoznih promena ili nepromenje boje kože papula koje nisu umbilikovane i na svojoj površini nemaju Vikamove (Wickham) strije ali mogu pokazivati laku deskvamaciju. Za LS je karakterističan iznenadni početak i brzo progresivno širenje tako da vrlo brzo promena u celini poprima linearni 2 mm do 2 cm širok trakasti izgled, neravnu površinu i različitu dužinu, od nekoliko centimetara pa do dužine celog ekstremiteta uz zahvatanje nokta. Oboljenje se može javiti na skoro svim delovima tela uključujući i lice. Multiple lezije su retke, bilateralno zahvatanje je izuzetno retko, ali su objavljeni slučajevi sa paralelnim linearnim trakastim ili zosteriformnim rasporedom; ne javlja se udruženo sa sistemskim poremećajima. Oboljenje u najvećem broju slučajeva protiče asimptomatski ali pruritus može biti u pojedinim slučajevima intenzivan.

Histološki, za LS su karakteristični znaci lihenoidnog dermatitisa ali se u pojedinim slučajevima u histološkoj analizi mogu detektovati promene za koje se pretpostavlja da su karakteristične za LS: psoriaziformna epidermalna hiperplazija, inflamatorni infiltrat u papilarnom dermisu, u kome se pored limfocita nalaze histiociti i melanofagi, perivaskularno i periadneksalno širenje infiltrata. Spontana rezolucija promena se može očekivati u periodu od 3 do 6 meseci, ali i duže.

Standardna terapija podrazumeva samo praćenje, u slučaju jačeg svraba ili, iz kozmetičkih i psiholoških razloga, mogu se u terapiju uključiti topikalni kortikosteroidi ili kalcineurinski inhibitori – takrolimus ili pimekrolimus.

Prikaz slučaja. Dvadesetsedmogodišnja ženska osoba, inače dobrog zdravstvenog stanja, po zanimanju stjuardesa, upućena je na pregled dermatologu zbog pojave eritematozne linearne promene na levoj nozi, koja je naglo nastala tri meseca posle porođaja, progredila veoma brzo da bi u roku od nedelju dana zahvatila dužinu cele noge i bila praćena osećajem slabog svraba. Promeni nije prethodila infekcija gornjih respiratornih puteva niti bilo koji drugi poremećaj, uzimanje lekova niti lokalna aplikacija bilo kakavih preparata. Lična anamneza za atopiju je bila negativna ali je njena majka bolovala i lečila se od alergijskog rinitisa.

Prilikom pregleda, na koži leve noge uočeno je prisustvo unilateralne, solitarne linearne oko 0,5–0,8 cm široke trakaste promene, neravne, orožale površine, nastale aglomeracijom sitnih, ružičastosmeđih papula, dijametra nekoliko milematara, na čijoj površini nije bilo Vikamovih figura već umerene deskvamacije. Promena je bila neravne, umereno orožale i deskvamirane površine, pratila je jednu BL i od plaka, veličine dlana ženske osobe, lokalizovanog na levom gluteusu, protezala se duž čitave fleksorne strane leve noge do unutrašnjeg maleolusa (slike 1 i 2). Osim kseroze, na koži nije bilo drugih promena niti znakova koji bi ukazivali na prisustvo atopijskog dermatitisa.

Od laboratorijskih analiza jedino je utvrđen povišen nivo imunoglobulina klase E koji je iznosio 700 IU/ml (referalna vrednost ≤ 100 IU/ml).

Histološka analiza isečka ledirane kože pokazala je sledeće: slabo izražena hiperkeratoza epidermisa sa vakuolnom degeneracijom i malim brojem nekrotičnih keratinocita u bazalnom sloju; linearni trakasti infiltrat u papilarnom dermisu sastavljen od limfocita, pigmentofaga i manjeg broja histiocita; inflitrat je pokazivao epidermalnu egzocitozu i perifolikulano nakupljanje (slike 3 i 4).

Na osnovu anamneze, kliničkog pregleda i patohistološke analize, postavljena je dijagnoza LS. Prvenstveno iz estetskih razloga, ordiniran je prvo lokalno kortikosteroidni krem (mometazon fuorat 0,1%) dvaput dnevno tokom dve nedelje. Ova terapija nije dala rezultat u smislu smanjenja ili regresije linearne promene – samo je ublažila svrab. Iz ovih razloga je preduzeta sekvencijalna krioterapija koja je sprovedena u duplom ciklusu zamrzavanja (double cycling freezeng). Korišćen je aparat Cry-Ac® (Brymill Cryogenic Systems, Brimill company, Ellington, USA). Tečni azot je nanošen na linearnu promenu u trajanju od 30 sekundi sa stvaranjem oko lezije haloa debljine 2 mm. Krioterapija je izvođena u dva navrata sa periodom oporavka između dva tretmana u trajanju od dve nedelje i tada je na tretirane površine aplikovan antibiotski krem (gentamicin) (Slika 5). Osim osećaja slabog pečenja i uobičajene postterapijske reakcije u vidu eritema i manjih plikova nastalih 48 časova posle kriotretmana, nije bilo drugih tegoba. Kompletna regresija tretiranih promena nastupila je dvanaest nedelja nakon poslednjeg tretmana. U završnoj fazi na tretiranu površinu je lokalno aplikovan Contractubex® krem dvaput dnevno tokom mesec dana (Slika 6). Osećaj svraba kupiran je sistemskom primenom antihistaminika (desloratadin).

Diskusija. Distribucija promena LS pokazuje veliki afinitet prema BL, koje predstavljaju izraz kutanog mozaicizma kod ljudi, postzigomatski genomski proces koji se verovatno odvija u obliku somatske mutacije u različitim ćelijama kože i čini da se ove ćelije ponašaju neuobičajeno iz za sada nepoznatih razloga. Pretpostavlja se da BL odražavaju put kojim ove aberantne ćelije migriraju za vreme embrionalnog perioda. Druga teorija promoviše epigenetski mozaicizam koji podrazumeva ulogu transpozomnih elemenata tzv. retrotranspozona za koje je utvrđeno da zauzimaju veliki deo genoma ljudske vrste. Ova teorija se zasniva na hipotezi da ovi elementi putem metilacije/demetilacije, izazivaju aktivaciju, odnosno inaktivaciju susednih gena. U prilog ovoj teoriji priključuje se i nedavno objavljena istovremena pojava LS duž iste BL kod dva rođena brata (kod jednog od braće pojavi LS prethodio je otitis medija), koja je podržala ulogu genetskih faktora i infekcije u nastanku LS. Štaviše, ovim je podržana i torija o epigenetskom mozaicizamu, s obzirom da se njome može objasniti familijarna pojava oboljenja, za razliku od somatskih mutacija koje se dešavaju slučajno, kada bi familijarna pojava oboljenja bila malo verovatna. Iako je porodična pojava oboljenja ekstremno retka (porodična anamneza kod naše pacijentkinje negativna) najverovatnije da u nastanku LS različiti endogeni ili egzogeni faktori mogu izazvati demaskiranje navedenih abnormalnih klonova keratinocita kod inače zdravih ali genetski predisponiranih osoba. Epigenetski mozaicizam promoviše hipotezu da se genetska predispozicija zasniva na metilaciji/demetilaciji retrotranspozona, koju izaziva imunska reakcija pokrenuta infekcijom. Pretpostavlja se da infekcija inicira aberantni ćelijski imunski odgovor, pošto izazove ćelijsku (keratinociti kože) aberaciju. Nedavno objavljena istovremena pojava unilateralno lokalizovane blaškoidne pitiriazis rozee (Pityriasis rosea) sa istostranim LS potkrepljuje ovu hipotezu da infekcija i/ili drugi egzogeni okidači (npr. spoljašnji činioci, trauma ili alergijske reakcije) iniciraju imunski odgovor, što istovremeno objašnjava zašto pojedini autori u lezijama LS nisu detektovali infektivne uzročnike (virusne partikule). Odsustvo prodromalnih simptoma kod naše pacijentkinje

kao i u većini slučajeva, ne isključuje mogućnost asimptomatske infekcije.

Na aberantni imunski odgovor ukazuje i signifikantna udruženost atopije sa LS koju su objavili pojedini autori. Značaj udruženosti LS sa pozitivnom ličnom ili porodičnom anamnezom o atopiji kao što je slučaj kod naše pacijentkinje, ostaje nedovoljno razjašnjen, s obzirom da su rezultati drugih autora ukazali da prevalencija atopije (anamnezni podaci) u LS ne odstupa od one u opštoj populaciji. Takođe pojava LS tri meseca nakon porođaja kod naše pacijentkinje zahteva potvrdu u radovima drugih autora.

Dijagnoza LS je kod naše pacijentkinje postavljena na osnovu sledećeg: anamneze o iznenadnoj pojavi i brzom širenju (tokom jedne nedelje) linearne promene; klinički izgled promene nastale aglomeracijom malih ružičastosmeđih papula na čijoj površini nisu bile prisutne Vikamove figure, već skvame, koja se sa lako hiperkeratotičnom i neravnom površinom linearno pružala u vidu trake od plaka na levom gluteusu do levog unutrašnjeg maleolusa, duž cele fleksorne strane leve noge; prisustvo hiperkeratoze i lihenoidnog dermatitisa u epidermisu i papilarnom dermisu ledirane kože, što je nalaz sličan sa nalazom za lihen planus, ali se za razliku od njega u infiltratu pored limfocita nalaze melanofagi i histiociti a infiltrat se širi dublje i lokalizuje i perifolikularno.

U diferencijalnoj dijagnozi na prvom mestu treba isključiti linearni lihen planus i inflamacijski linearni verukozni epidermalni nevus (engl. inflammatory linear verrucous naevus – ILVEN). Iako LS može imati različitu histološku prezentaciju koja se u pojedinim slučajevima ne može razlikovati od prezentacije karakteristične za lihen planus, ono što ih može razlikovati i što se smatra najkarakterističnijim histološkim nalazom lihen strijatusa jeste prisustvo infiltrata ne samo u površnim delovima dermisa nego i njegova lokalizacija periadneksalno, tj. perikrino ili perifolikularno kao kod naše pacijentkinje. Epidermalne promene u ILVEN u najvećem broju slučajeva podsećaju na one karakteristične za psorijazu, dok su znaci lihenoidnog dermatitisa odsutni. Lihen nitidus u infiltratu ima dominaciju histiocita a u epidermisu atrofiju i parakeratozu. Perifolikularni infiltrat karakterističan za lupus eritematozus, pored perifolikularnih limfocitnih infiltrata, sadrži u intersticijumu depozite mucina.

Zaključak. U ovom radu prikazan je slučaj odrasle ženske osobe kod koje je lihen strijatus, koji se pojavio naglo, tri meseca nakon porođaja, uspešno lečen krioterapijom. Prema nama dostupnoj literaturi, ovo bi bio prvi objavljen slučaj uspešnog lečenja ovim vidom terapije.

Ključne reči: Lichen sclerosus et atrophicus; Lihenoidne erupcije; Odrasli; Krioterapija; Ishod terapije; Prikazi slučajeva

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Painless Multidermatomal Herpes Zoster in an Immunocompetent Elderly Male: a Case Report

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Abstract

The varicella-zoster virus is the cause of both varicella and herpes zoster. The primary infection of varicella includes viremia and a widespread eruption, after which the virus persists in nerve ganglion cells, usually sensory. Herpes zoster is the result of reactivation of this residual latent virus. The first manifestation of zoster is usually pain, which may be severe and accompanied by fever, headache, malaise and tenderness localized to one or more nerve roots. The lymph nodes draining the affected area are enlarged and tender. Occasionally, the pain is not followed by eruption (zoster sine herpete).

We hereby report an 85-year-old otherwise healthy male patient with a 3-day history of a non-painful rash on the left side of abdomen, pubic and penile regions, left groin and the left leg. He denied any pain and/or abnormal sensations before the rash onset. On examination, there were closely grouped multiple vesicles over the anterior left abdominal wall, left groin, thigh, knee and left upper quarter of penis, involving the left T12, L1-L4 and S2 dermatomes. The patient reported no pain, fever, rigor or any other symptoms; he had no associated cervical, axillary or inguinal lymphadenopathy. He denied any abdominal pain, nausea, vomiting, any weakness or sensory changes in the limbs. There was no history of penile numbness, urinary retention, and increased frequency of micturition or constipation. The varicella-zoster virus serology test performed by Calbiotech VZV IgG ELISA Kit (Calbiotech, Spring Valley, Canada) was strongly positive. The human immunodeficiency virus serology test, as well as herpes simplex virus type 1 and type 2 serology tests performed by ELISA were all negative. The Tzanck smear, stained with Giemsa, demonstrated multinucleated giant cells. The patient responded well to valacyclovir with complete clearance of lesions within one week.

An extensive PubMed search revealed only few reports of painless herpes zoster.

We present a rather peculiar case of painless herpes zoster in an elderly patient with no apparent systemic immunosuppression, with severe involvement affecting multiple adjacent and one remote dermatome. We hereby propose the term ”herpes zoster sine algesia” in cases where eruption is not followed by pain.

Key words

Herpes Zoster; Immunocompetence; Aged, 80 and Over; Signs and Symptoms; Acyclovir; Treatment Outcome; Case Reports

Herpes zoster (HZ), also known as shingles, is a self-limited disease caused by reactivation of the varicella zoster virus (VZV). The virus can cause both varicella and herpes zoster. The primary infection of varicella includes viremia and a widespread eruption, after which the virus persists in sensory ganglia of the dorsal roots and cranial nerves. Herpes zoster is the result of reactivation of this residual latent virus. The term “zoster” refers to girdle-like skin eruption with segmental distribution which classically occurs unilaterally (1). The first manifestation of zoster is usually pain, which may be severe and accompanied by fever, headache, malaise and tenderness localized to one or more nerve roots. The lymph nodes draining the affected area are enlarged and tender. The dermatomes most frequently affected are the thoracic and cranial.

Less commonly, two or three adjacent dermatomes are affected. In individuals with immunodeficiency, but less commonly in immunocompetent persons, the lesions may involve multiple contiguous, noncontiguous, bilateral, or unusual dermatomes (2, 3, 4). The onset of disease is usually heralded by pain within the dermatome which precedes the lesions by 48 to 72 hours. Occasionally, the pain is not followed by eruption ("*zoster sine herpete*") (1).

Case report

We hereby report an 85-year-old otherwise healthy male patient with a 3-day history of a non-painful rash on the left side of his abdomen, the pubic and penile regions, the left groin and the left leg. He denied any pain and/or abnormal sensations before the rash onset. On examination, there were closely grouped multiple vesicles over the anterior left abdominal wall, left groin, thigh, knee and left upper quarter of penis, involving the left T12, L1, L2, L3 and L4 and S2 dermatomes (Figures 1 - 3). The patient reported no pain, fever, rigor or any other symptoms. He had no associated cervical, axillary or inguinal lymphadenopathy. He denied any abdominal pain, nausea, or vomiting. He also denied any weakness or sensory changes in the limbs. There was no history of penile numbness, urinary retention, increased frequency of micturition or constipation. The patient suffered from hypertension and received losartan; he had a surgical history significant for herniorraphy done for bilateral inguinal hernia in 2013, and cholecytectomy for gall bladder stones in 2014. The blood test revealed no abnormalities in the total and differential leukocyte counts, and the rest of the hemogram was unremarkable. The fasting blood glucose was 96 mg/dl, and post prandial level was 127 mg/dl. HbA1c was 6.4%. The varicella-zoster virus serology test performed by Calbiotech VZV IgG ELISA Kit (Calbiotech**,** Spring Valley, Canada) was strongly positive (8.35 IU/µl, negative < 0.9). The human immunodeficiency virus serology test, as well as herpes simplex virus type 1 and type 2 serology tests performed by ELISA were all negative. The Tzanck smear, stained with Giemsa, demonstrated multinucleated giant cells (Figure 4). The patient responded well to valacyclovir with complete clearance of lesions within one week. During this time he did not experience any pain.

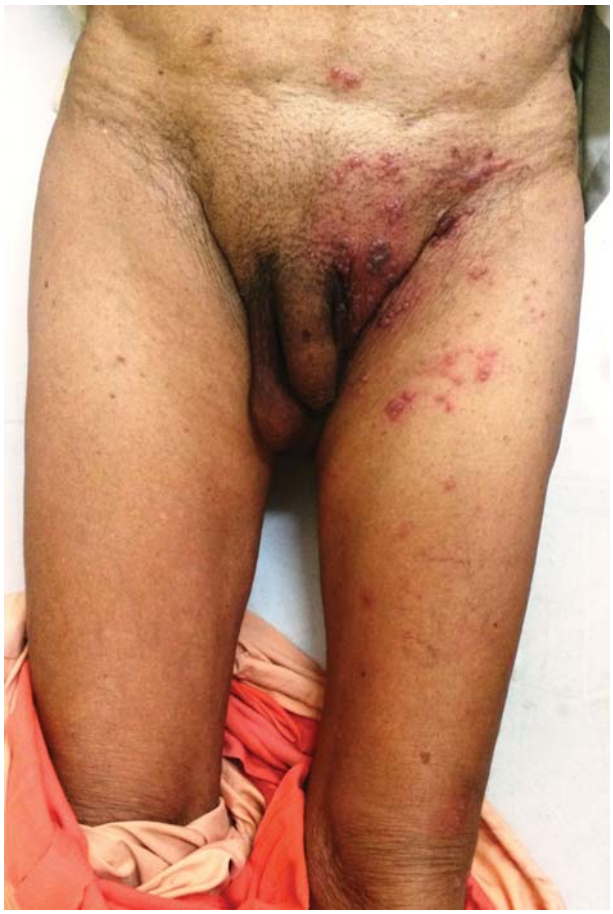

Figure 1. Closely grouped multiple vesicles over the anterior left abdominal wall, left groin, thigh, knee and left upper quarter of penis, involving the left T12, L1, L2, L3, L4, and S2 dermatomes

Discussion

Varicella-zoster virus (VZV) causes varicella or chicken pox as its primary presentation, usually in childhood. Only people who have previously had chicken pox are at risk of shingles. The risk and complications increase with age, due to a decrease in cell-mediated immunity to VZV (5). After primary presentation, the virus remains latent in sensory ganglia of the dorsal roots and cranial nerves. The virus is kept in this state of quiescence by a competent cell-mediated immune system. Any condition that compromises the immune system may cause reactivation of the virus which travel down axons, and manifest as cutaneous infection known as herpes zoster. Variations in the zoster syndrome depend on the dorsal root involved, intensity of its involvement, and extension of the inflammation into the motor root and

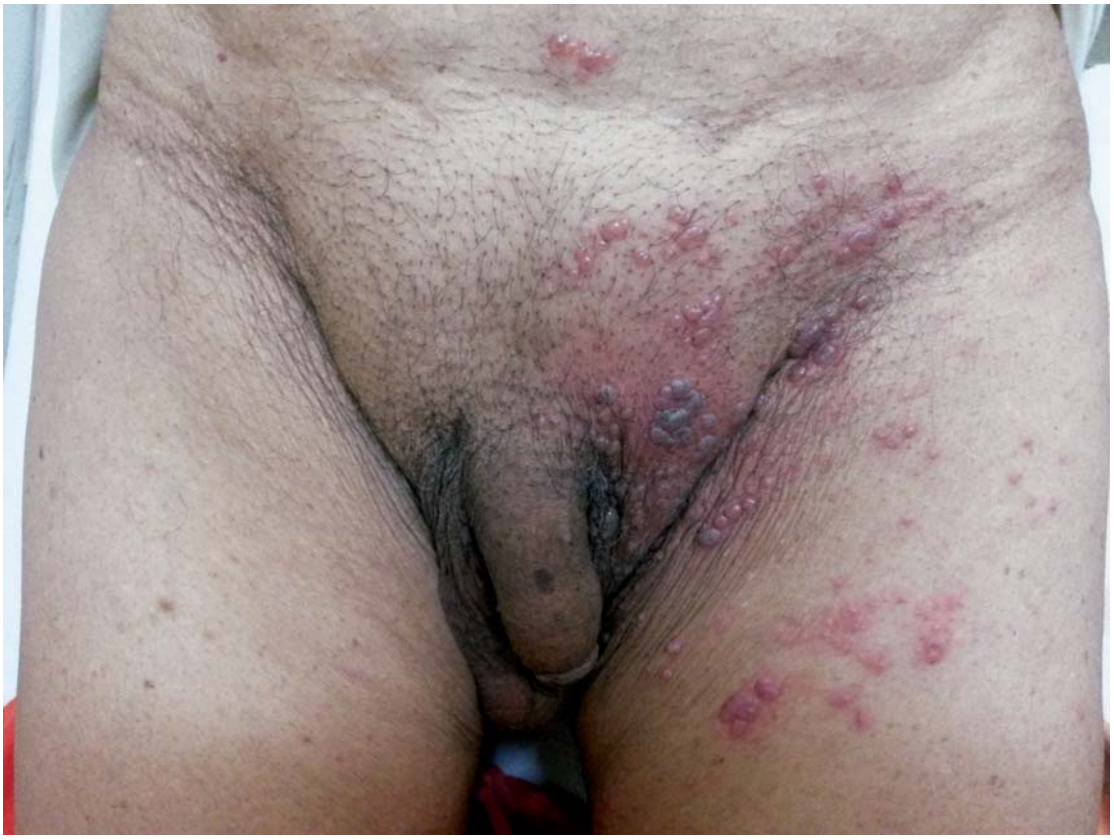

Figure 2. Closely grouped multiple vesicles over the anterior left abdominal wall, left groin, thigh, knee and left upper quarter of penis, involving the left T12, L1, L2, L3, L4, and S2 dermatomes

anterior horn cells (1). By an unknown mechanism, the virus reactivates in dorsal-root ganglia when immunocompetence declines due to: aging, long-term use of steroids, chemotherapy, infections e.g. with human immunodeficiency virus (HIV), lymphoma, cancer, or organ-transplantation. Age-related decline of the immune system is the main risk factor for cutaneous reactivation of VZV in the form of (HZ) (6). Upon reactivation, the virus replicates causing ganglionitis resulting in severe neuritis. The virus then migrates peripherally down the nerve to the skin producing radiculoneuritis, or migrates centripetally to the spinal cord and particularly in the immunocompromised, the brain, resulting in myelitis and meningoencephalitis. In rare cases, the virus may enter the circulation producing vasculitis that in turn causes stroke (7). The patient presented here did not have any underlying factors which would lead to immunosuppression. However, at his age, he most likely had a reduction in VZV-specific, cell-mediated immunity. Serological evidence for VZV infection exceeds 90% in growing adults meaning there is about 10% to 20% risk of developing herpes zoster in one's lifetime. With the increasing age, the incidence of herpes zoster rises and after the age of 75, it may exceed 10 cases per 1000 persons (8).

HZ characteristically presents with a prodrome of burning pain followed by an outbreak of vesicles distributed unilaterally within a single dermatome. In most cases, when lesions appear, the course of zoster remains unchanged. In some 16% of patients with zoster, vesicles develop beyond the dermatome primarily involved, within a few days of the local eruption. This is more common in the elderly, but in most cases only a few lesions appear and the course of the zoster stays unchanged. Rarely, in such cases, zoster may successively involve further dermatomes (1). More extensive skin involvement of several adjacent dermatomes is called multidermatomal zoster (3), whereas spread to a non-adjacent dermatome (in two non-contiguous dermatomes) is known as zoster

duplex, unilateral or bilateral (2, 4). In patients with lymphomas, or those otherwise immunocompromised, generalized varicella ("disseminated zoster") develops and may be hemorrhagic. Only few such cases, seen either in immunosuppressed or immunocompetent hosts, especially in elderly patients as in our case, were reported in the literature (2, 3, 4, 6).

HZ rash is usually confined to the area which was most heavily affected by varicella. Furthermore, but not surprising, the greater the extent of the rash or number of lesions, the more severe the pain would be. Severe involvement is categorized as more than 50 lesions over the dermatome involved (9). Our patient met the criteria for severe involvement, but did not experience any pain. Similarly to our patient, a 78-year-old male patient was reported by Akira Nishizawa in 2003, who also met the criteria for severe involvement but had no pain (6). Regarding patients with HZ and no accompanying pain, there are few reports in the literature. An extensive PubMed search revealed a case report in 1995 of painless HZ in two immunocompetent young Caucasian males who had HZ with no pain in their twenties. One of the patients claimed that he had relatives who also had herpes zoster without pain (10). Recently, in 2013, a case of almost painless HZ presenting with symptoms of cystitis, penile numbness and acute vestibular failure was reported (11). In one large series of 1.778 patients with varying degrees of skin involvement, 45% had severe rash of which 11% (or 5% of the total) complained of no pain. Moreover, when patients with severe rash and no pain were compared with patients with severe rash and varying degrees of pain (from mild to severe), the significant difference was that patients with severe rash and no pain, like our patient, were much less likely to have had a prodrome (defined as pain and/or abnormal sensations e.g. dysesthesia before the rash onset) (9). The weakness of these studies lies in the fact that acute pain severity was rated on a single occasion within a window period of 72 h after the rash onset (9, 12). For a considerable proportion of patients, however, acute pain may not have reached its maximum at this point;

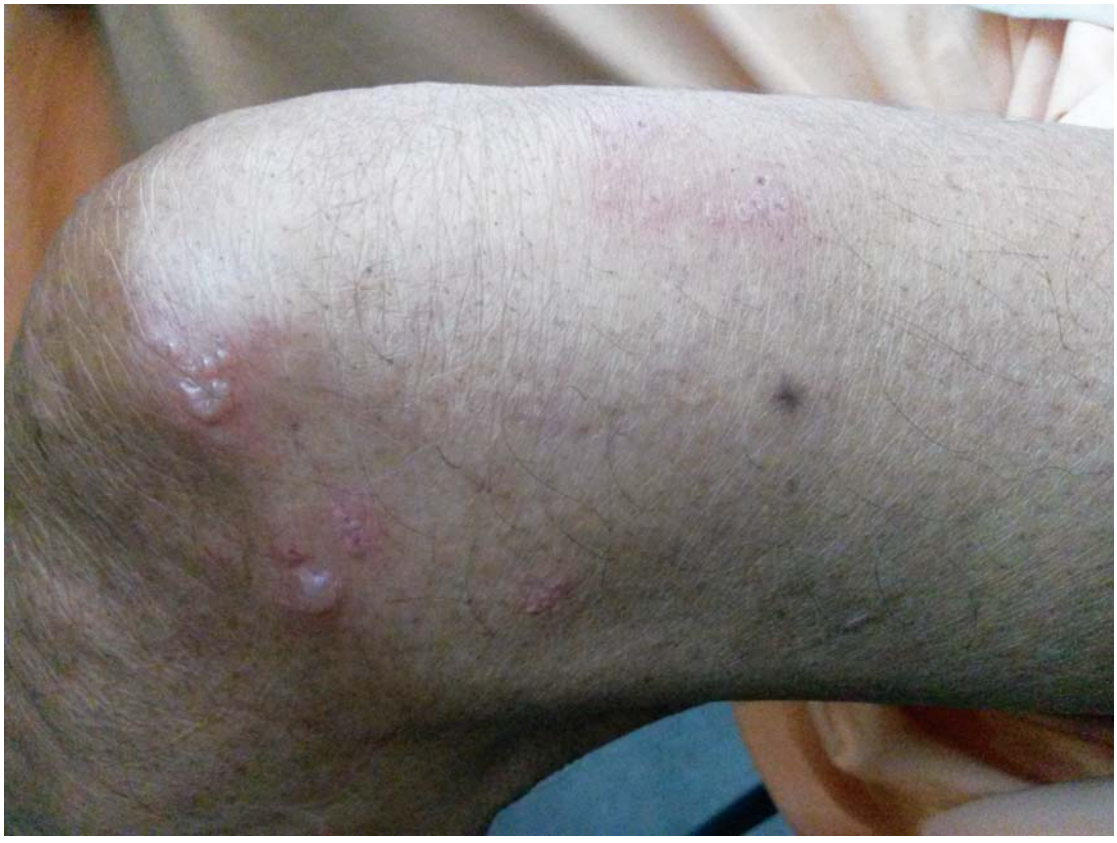

Figure 3. Closely grouped multiple vesicles over the anterior left knee, involving the left L4 dermatome

it was found to occur equally often before, at, and after the rash onset. Moreover, the relationship between rash duration and pain severity was significant, which reflected a greater likelihood of reports of no pain in patients with shorter rash duration (12). These results suggest that assessments of acute zoster pain that take into consideration its evolution over time, e.g. for a week following the rash onset, may have stronger relationships with demographic and clinical variables (12).

Regardless of whether it begins before or after the rash onset, acute pain is a prominent characteristic of HZ infection, and a large proportion of patients report that this pain is at least moderate in intensity. The lack of pain is unusual in HZ, particularly when the rash is extensive, as in our 85-year-old patient. The results of the logistic regression analyses previously conducted in the afore-mentioned large series of 1.778 patients, suggest that older age, female sex, greater rash severity, and presence of a prodrome are independently associated with moderate or severe acute zoster pain (12). Considering the etiology of the lack of pain, one can speculate that this might be due to extreme ganglionic destruction and possibly severe peripheral nerve damage. Zoster can cause some destruction of nerve fibers in the middle and lower dermis, detectable by silver-impregnation techniques (1). Considered together, these data provide further support for hypothesizing that age, rash severity, and acute pain severity in HZ do not simply reflect a single underlying process of infection severity, but instead reflect different aspects of the acute episode that each contribute independently to the pathogenesis of PHN (12). Thus, pain may not be present in some elderly individuals with herpes zoster (7).

In varicella, cells of the basal and spinous skin layers with ballooning of their cytoplasm by intracellular edema, and by distinctive nuclear changes, comprising eosinophilic inclusions and marginated chromatin are present. Some nuclei develop additional nuclear membranes which divide the nucleus into small

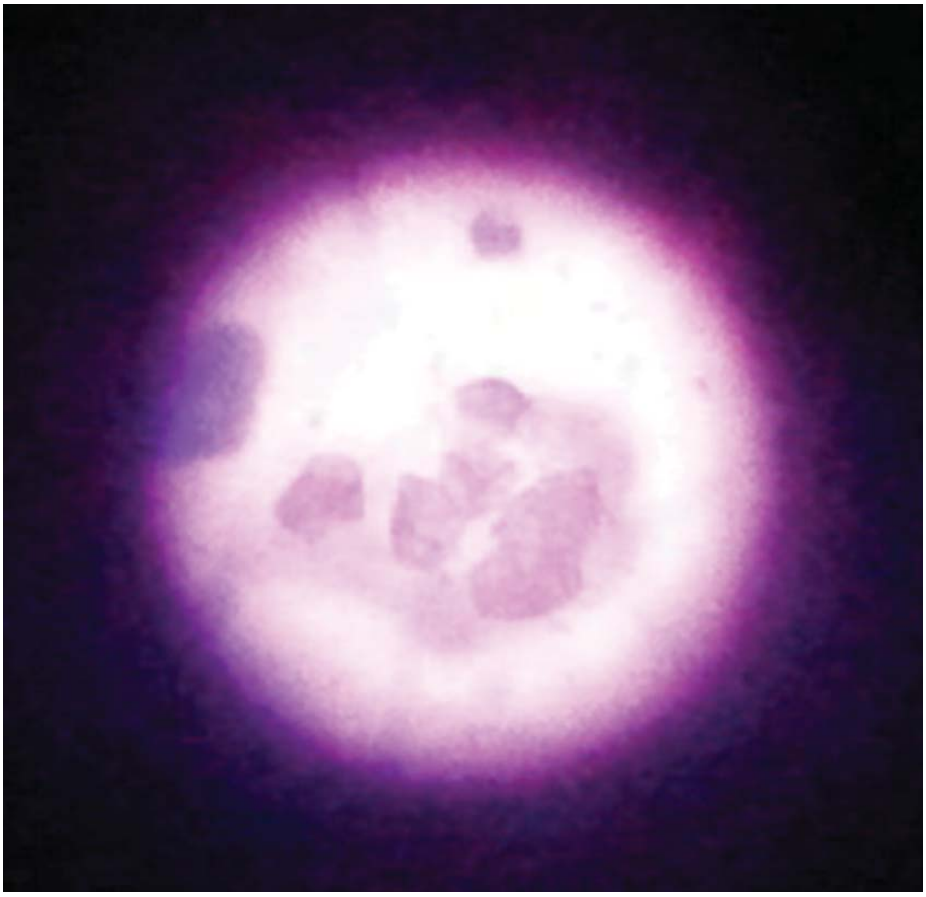

Figure 4. Cytology finding of the Tzanck smear from the buttom of a vesicle showed multinucleated giant cells

compartments. The multinucleate giant cells with up to 15 nuclei, which are a characteristic feature of infections with *Herpesvirus varicellae* and *Herpesvirus hominis*, are produced mainly by cell fusion. Intracellular edema combined with intercellular edema, forms a vesicle, the roof of which consists of the upper spinous and horny layers. A mild inflammatory reaction in the dermis later extends to the epidermis and a certain number of polymorphonuclear cells increase with ulceration (1).

The diagnosis of herpes zoster is mostly based on clinical findings. Laboratory test for suspected shingles is not routinely done (1, 8, 13). However, in atypical cases and in order to differentiate between herpes simplex and HZ, laboratory confirmation is done by: immunofluorescence microscopy of cells from the base of a vesicle for VZV; PCR testing of cells scraped from the base of a vesicle for VZV DNA, or real-time polymerase chain reaction (PCR), which can rapidly detect VZV DNA in skin lesion samples (1, 8, 13). Serological testing elicits VZV immune status, and it is useful in atypical cases and in patients without a rash but with pain, since IgG titers increase with reactivation, like in our case (1, 13). The appearance of HZ in our patient was quite clinically distinctive, thus the diagnosis of multidermatomal herpes zoster was made and supported by serology and cytology finding of elevated VZV IgG levels and multinucleated giant cells, respectively. Tzanck smear stained with Giemsa demonstrated multinucleated giant cells, known to be characteristic but not a pathognomonic feature, because they are also seen in varicella, herpes simplex and pemphigus (1). The differential diagnosis excluded herpes simplex due to zosteriform distribution, although, one would expect the latter to be associated with deep pain and regional lymphadenopathy (1), the clinical features that were not present in our patient; in addition, vesicles in herpes simplex are uniform within a cluster, the feature that was not seen in our case.

Valacyclovir was introduced, as an alternative to acyclovir, expected to have greater overall effectiveness, considering the clinical presentation, the age of the patient, as well as criteria for valaciclovir in patients with zoster (13). The patient responded well to valacyclovir with complete clearance of lesions within one week.

Conclusion

This is a rather peculiar case of painless herpes zoster in an elderly patient with no apparent systemic immunosuppression, with severe involvement affecting multiple adjacent and one remote dermatome. We hereby propose the term ”herpes zoster sine algesia” in cases where eruption is not followed by pain.

Abbreviations

HZ - herpes zoster
VZV - varicella zoster virus
ELISA - enzyme-linked immunosorbent assay
HIV - human immunodeficiency virus
PCR - polymerase chain reation

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Bezbolni herpes zoster sa zahvatanjem većeg broja dermatoma kod imunokompetentne starije osobe – prikaz slučaja

Sažetak

Uvod. Varičela zoster virus (VZV) može biti uzrok varičele ili herpes zostera (HZ). Primarna infekcija koja se manifestuje varičelom podrazumeva stanje viremije i diseminovane promene na koži i vidljivim sluznicama, posle čega virus perzistira u latentnom stanju u senzornim ganglionima spinalnih (dorzalni korenovi) ili kranijalnih nerava. Rezultat je reaktivacije latentnog virusa. Prva manifestacija HZ najčešće je bol, koji može biti jak i biti praćen groznicom, glavoboljom, slabošću i bolnom osetljivošću lokalizovanom u jednom ili više nervnih korenova. Regionalne limfne žlezde takođe mogu biti uvećane i bolne. U retkim slučajevima bol nije praćen erupcijom promena na koži i/ili sluznicama („zoster bez lezija").

Prikaz slučaja. U radu je prikazan slučaj osamdesetpetogodišnje, inače zdrave muške osobe, koja se javila na pregled dermatologu zbog promena na koži leve strane stidne regije, penisa, leve prepone leve natkolenice i levog kolena. Promene su se javile tri dana ranije i nisu bile praćene osećajem bola, kako u vremenu koje je prethodilo pojavi promena tako i za vreme njihovog izbijanja. Na pregledu, na koži levog donjeg dela prednjeg trbušnog zida, levog ingvinuma, leve gornje četvrtine penisa, kao i leve natkolenice i levog kolena, bile su prisutne multiple grupisane vezikule aglomerirane i delom konfluentne, distribuirane po T12, L1-L4, S2 dermatomima sa strogom poštedom središnje linije. Nije bilo osećaja svraba, groznice, ukočenosti, niti bilo kakvog drugog simptoma. Takođe regionalne limfne žlezde uključujući cervikalne, aksilarne i ingvinalne nisu bile uvećane. Pacijent je negirao prisustvo abdominalnog bola, muke povraćanja, osećaja slabosti i bilo koje druge senzacije u donjim ekstremitetima, bolne erekcije, gastrointestinalne ili urinarne tegobe. Serološkim testiranjem pomoću Calbiotech VZV IgG ELISA Kit (Calbiotech**,** Spring Valley, Canada), otkiven je povišen nivo IgG (8.35 IU/μl, negativan < 0.9) prema VZV. Serološko testiranje na virusom humane imunodeficijencije (HIV) i herpes simpleks virus tip 1 i tip 2 (HSV tip 1 i HSV tip 2) pomoću ELISA testa nije dalo pozitivan rezultat. Tzankovim citomorfološkim testom uzorka uzetog sa dna vezikule bojenog po Gimzi (*Giemsa*), utvrđeno je prisustvo multinuklearnih gigantskih ćelija. U terapiju je uključen valaciklovir i nakon sedam dana došlo je do potpune regresije svih promena na koži.

Detaljni *PubMed* pregled ukazao je na mali broj objavljenih slučajeva bezbolnog HZ u literaturi.

Diskusija. Varičela zoster virus (VZV) izaziva varičelu ili ovčije boginje kao primarnu prezentaciju, najčešće u detinjstvu. Samo oni koji su preležali varičelu imaju rizik od obolevanja od HZ. Rizik za nastanak HZ i njegovih komplikacija raste sa godinama, usled smanjenog celularnog imunskog odgovora na VZV. Nakon primarne infekcije, virus ostaje u latentnom stanju u senzornim ganglionima spinalnih (dorzalni korenovi) i kranijalnih nerava. Virus ostaje u fazi mirovanja pod nadzorom očuvanog ćelijskog imuniteta. Svako stanje koje dovodi do pada imuniteta može dovesti do reaktivacije virusa, koji tada putuje centrifugalno duž aksonskog vlakna do kože i manifestuje se kao HZ. Varijacije u kliničkoj prezentaciji zavise od toga koji je dorzalni koren zahvaćen, od intenziteta njegovog učešća i od prelaska inflamacije na motorne korenove i neurone prednjih rogova. Po još nepoznatom mehanizmu, virus se reaktivira u ganglijama dorzalnih korenova u trenutku kada imunitet opadne usled npr. starosti, dugotrajnog korišćenja steroida, hemoterapije, infekcija npr. virusom humane imunodeficijencije (HIV), malignih oboljenja ili posle transplatantacije organa. Relativno smanjenje funkcije ćelijskog imunskog odgovora koje se javlja sa starenjem, predstavlja glavni faktor rizika za reaktivaciju VZV u koži i nastanak HZ: nakon reaktivacije, virus se replicira u ganglionima izazivajući ganglionitis koji rezultira težim neuritisom; virus potom migrira periferno-centifugalno duž nerva do kože, izazivajući radikuloneuritis; takođe virus može da migrira centripetalno prema kičmenoj moždini, a kod imunokompromitovanih i do moždanog tkiva, izazvajući mijelitis ili meningoencefalitis. U retkim situacijama virus može ući u cirkulaciju i izazvati vaskulitis, a u ređim slučajevimai i infarkt – cerebralni inzult.

Pacijent čiji je slučaj HZ ovde prikazan, osim životnog

doba nije imao nijedan drugi faktor koji je mogao dovesti do imunosupresije. U opštoj populaciji odraslih, serološka pozitivnost na VZV premašuje 90%, što znači da rizik od nastanka HZ iznosi tokom života 10–20%. Sa starenjem godišnja incidencija HZ raste, i nakon 75. godine života može iznositi više od 10 slučajeva HZ na 1 000 odraslih osoba.

U najvećem broju slučajeva HZ karaktriše prodromalni stadijum u vidu osećaja peckanja, svraba a najčešće bola na mestu zahvaćenog dermatoma, sledi nalet unilateralnih linearno raspoređenih vezikula u okviru jednog ili dva susedna dermatoma. U većini slučajeva, kada se lezije pojave, dalji tok HZ ostaje nepromenjen, ali kod oko 16% pacijenata, vezikule se javljaju i izvan primarno zahvaćeneg dermatoma, npr. na susednom ipsilateralnom ili simetričnom kontralateralnom dermatomu. Ovo se dešava ćešće kod starijih osoba, ali u većini slučajeva pojavi se samo nekoliko (≤ 20) lezija i tok HZ ostaje dalje nepromenjen. Retko u ovakvim slučajevima, HZ može sukcesivno zahvatiti druge dermatome. Zahvaćenost većeg broja dermatoma izaziva tzv. multidermatomni HZ, dok je zahvaćenost nesusednih dermatoma opisana kao unilateralan ili bilateralan dvostruki HZ. Kod pacijenata sa limfomom ili koji su imunokompromitovani na drugi način, može se razviti generalizovana varičela („diseminovani zoster"). U literaturi je opisano nekoliko ovakvih slučajeva kod imunokompetentnih, naročito starijih osoba kao što je bio slučaj i sa našim pacijentom.

Poznato je da se promene u HZ lokalizuju na područje koje je prethodno bilo najteže pogođeno varičelom. Štaviše, ali ne i iznenađujuće jeste to da je i broj, izgled i bolnost promena na tim mestima veći. Težina kliničkog nalaza na koži karakteriše se u zavisnosti od broja lezija (papule, vezikule, pustule ili kruste) u dermatomu na sledeći način: blag – do 25 lezija, umeren 25–50 lezija, težak > 50 lezija. Naš pacijent je imao > 50 lezija u najjače zahvaćenom dermatomu, ali nije imao osećaj bola. Skoro indentično našem slučaju u literaturi je opisan 2003. godine slučaj bezbolnog HZ kod sedamdesetosmogodišnjeg muškarca koji osim životnog doba, takođe nije imao nijedan drugi znak koji bi ukazivao na stanje imunosupresije. U literaturi je objavljen mali broj ovakvih slučajeva. Godine 1995. objavljen je slučaj bezbolnog HZ sa više od 50 lezija u dermatomu kod dva imunokompetentna dvadesetogodišnja muškarca. U jednoj velikoj seriji od 1778 pacijenata sa različitim stepenom težine dermatološkog statusa, 45% je imalo najteži stepen (> 50), a 11% od njih (5% od ukupnog broja), nije imalo osećaj bola. Kada su ovi pacijenti poređeni sa onima koji su imali osećaj bola i isti stepen težine kliničkog nalaza na koži, jedina statistički značajna razlika sastojala se u pojavi prodromalnog stadijuma (definisan kao bol i/ili abnormalni osećaj npr. dizestezija, koji prethodne pojavi lezija) kod osoba kod kojih se potom javio bol. Kod našeg pacijenta nije bilo prodroma i nije bilo ni bola sve vreme trajanja HZ. Slabost ove studije leži u činjenici da je ozbiljnost akutnog bola procenjena na osnovu samo jedne evaluacije i to 72 h nakon početka pojave lezija na koži. Međutim, za značajan broj pacijenata akutni bol ne mora dostići svoj maksimum u tom momentu; utvrđeno je da se bol podjednako često javlja pre, za vreme izbijanja i nakon pojave lezija na koži. Utvrđena je značajna povezanost između dužine trajanja promena na koži i jačine bola, tako da je postojala veća verovatnoća prijavljivanja odsustva bola kod pacijenata sa kraćim trajanjem lezija na koži. Ovi rezultati ukazuju na potrebu za procenjivanjem postojanja ili odsustva akutnog bola kod HZ tokom dužeg vremenskog perioda, npr. tokom nedelju dana praćenja pacijenta od pojave prvih promena na koži, čime bi se mogla utvrditi jača povezanost bola sa demografskim ili kliničkim varijablama.

Bez obzira da li je počeo pre, za vreme, ili nakon pojave lezija na koži, akutni bol je upadljivo najčešća odlika HZ infekcije i veliki broj pacijenata ovaj bol opisuje kao bol umerenog intenziteta. Nedostatak bola je neuobičajen kod HZ, naročito kada su promene na koži obimne a pacijent stariji, kao što je to kod našeg osamdesetpetogodišnjeg pacijenta. Rezultat logističke regresione analize sprovedene u ranije pomenutoj velikoj seriji od 1 778 pacijenata, ukazali su da starije životno doba, ženski pol, veći broj lezija na koži i prisustvo prodroma predstavljaju nezavisne faktore rizika za pojavu umerenog ili jakog akutnog bola kod obolelih od HZ. S obzirom na etiologiju odsustva bola, može se spekulisati da se on možda ne javlja zbog ekstremne dekstrukcije gangliona i moguće ozbiljne neurogene lezije perifernih nerava. Ispitivanja su dokazala da HZ može izazvati destrukciju nervnih vlakana u srednjem i dubokom dermisu, koja se može detektovati pomoću impregnacionih tehnika srebrom. Ovi rezultati podržavaju hipotezu da životno

doba, težina kliničkog nalaza na koži i jačina akutnog bola kod HZ ne odražavaju jedan jedinstveni proces direktno odgovoran za stepen težine infekcije, nego različite aspekte akutne epizode koji svaki ponaosob nezavisno jedan od drugog, doprinosi patogenezi postherpetične neuralgije (bol u trajanju dužem od 3 meseca od pojave ili prestanka promena na koži). Na ovaj način se može dati objašnjenje zašto bol ne mora biti prisutan kod svih starih osoba sa HZ.

U koži, kod varičele/HZ, ćelije bazalnog i spinoznog sloja pokazuju baloniranu citoplazmu sa intraćelijskim edemom i karakteristične promene na jedru, uključujući prisustvo eozinofilnih inkluzija i marginalizaciju hromatina. Neka jedra razvijaju dodatnu membranu, koja deli jedro na veći broj manjih delova. Multijedarne gigantske ćelije sa do po15 jedara, koje su karakteristična pojava kod infekcije koju izazva *Herpesvirus varicellae* i *Herpesvirus hominis*, uglavnom nastaju ćelijskom fuzijom. Intracelularni edem kombinovan sa intercelularnim edemom formira vezikule, čiji se krov sastoji od gornjeg spinoznog i rožastog sloja. Blaga inflamatorna reakcija u dermisu kasnije se proširuje na epidermis i broj polimorfonuklearnih ćelija raste sa razvojem dubljih lezija i ulceracija.

Dijagnoza HZ se u najvećem broju slučajeva postavlja na osnovu kliničke slike. Laboratorijski testovi za dokazivanje HZV ne izvode se rutinski. Međutim, u atipičnim slučajevima i u slučajevima u kojima je potrebno napraviti diferencijalnu dijagnozu između herpes simpleks i HZ, koristi se imunofluoroscentna mikroskopija ćelija uzetih sa dna vezikule kojom se može dokazati prisustvo VZV, ili PCR tehnika brisa uzetog sa dna vezikule sa ciljem dokazivanja prisustva VZV DNA u lezijama, ili PCR u realnom vremenu, kojom se u kratkom vremenskom roku može brzo detektovati VZV DNA u kožnim lezijama. Serološki testovi mogu dokazati postojanje antitela prema VZV i mogu biti korisni kod atipičnih slučajeva i kod pacijenata sa kožnim lezijama a bez osećaja bola, kao što je to bio slučaj kod našeg pacijenta, pošto titar specifičnih IgG ponovo raste sa reaktivacijom HZV (za razliku od herpes simpleks virusa). Ispoljavanje HZ kod našeg paciijenta je bilo klinički karakteristično, a dijagnoza potkrepljena serološki i citološki pomoću ELISA testa i Tzankovog testa sa Gimza bojenjem, kojim je potvrđeno prisustvo povišenog nivoa VZV IgG u serumu, odnosno na dnu vezikula multijedarnih džinovskih ćelija, karakterističnih ali ne i patogmoničnih za HZ (mogu biti prisutne kod varičele, herpes simpleksa i pemfigusa). U diferencijalnoj dijagnozi smo isključili herpes simpleks sa zosteiformnom distribucijom, s obzirom da bi u tom slučaju promene u dubokom dermisu bile praćene bolom i regionalnom limfadenopatijom, kliničkim nalazom koji nije bio prisutan kod našeg pacijenta.

Imajući u vidu ispunjenje jednog od dva važeća kriteriterijuma za uvođenje valaciklovira u terapiju HZ, valaciklovir je uveden u terapiju kao bolja alternativa acikloviru zbog njegove veće efektivnosti, godina života našeg pacijenta i kliničke prezentacije oboljenja. Pacijent je dobro odreagovao na valaciklovir sa kompletnim povlačenjem promena na koži tokom sledećih sedam dana.

Zaključak. U radu je predstavljen nesvakidašnji slučaj bezbolnog herpesa zoster kod stare muške osobe, kod koje je bolest bez osećaja bola i bez drugih znakova sistemske imunosupresije, zahvatila veći broj susednih i jedan udaljeni dermatom. Predlažemo termin *herpes zoster sine algesia* za one slučajeve oboljenja u kojima erupciju kožnih promena ne prati osećaj bola.

Ključne reči

Herpes zoster; Imunokompetencija; Stari preko 80 godina; Znaci i simptomi; Acyclovir; Ishod terapije; Prikazi slučajeva

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Pityriasis Rubra Pilaris: A Report of Two Cases and Literature Review

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Abstract

Pityriasis rubra pilaris (PRP) is an idiopathic inflammatory hyperproliferative chronic dermatosis characterized by: perifollicular coalescing papules with central keratotic acuminate plugs gradually submerged in sheets of erythema; perifollicular erythema with islands of unaffected skin; palmoplantar keratoderma; diffuse desquamation which typically spreads from the head down to the feet. The cause of the condition is unknown, but possible etiological factors include: vitamin A deficiency, trauma, infections, autoimmune mechanisms, and malignancies. Taking into account different age of onset, clinical course, morphology and prognosis, there are six different types of the disease: two in adults (classical and atypical); three in children (classical, circumscribed and atypical); one in individuals infected with human immunodeficiency virus.

This paper presents two male patients with clinical symptoms of classical PRP, 53 and 69 years of age at the onset of the disease, with rapid generalized involvement, typical erythematous perifollicular papules, islands of unaffected skin, palmoplantar hyperkeratosis with a waxy appearance and nail changes. The diagnosis was based on clinical findings and histopathologic analysis. Apart from topical therapy with emollients, corticosteroids and keratolytics, they received systemic retinoids and corticosteroids, which resulted in improvement of skin lesions.

It is extremely important to consider the possible triggering factors, establish the diagnosis as soon as possible and begin proper treatment.

Key words

Pityriasis Rubra Pilaris + diagnosis + classification + therapy; Diagnosis, Differential; Case Reports; Dermatologic Agents; Treatment Outcome; Review

Pityriasis rubra pilaris (PRP) (synonyms - lichen ruber pilaris, lichen ruber acuminatus, Devergie's disease) (1), is an idiopathic inflammatory hyperproliferative dermatosis which is characterized by: follicular hyperkeratotic papules grouped into broad erythematous patches with islands of unaffected skin, palmoplantar keratoderma, diffuse follicular squamous papules of the scalp, and often present progressive exfoliative erythroderma (2, 3, 4). The name of the disease comes from Latin words for: redness (Lat. rubra), desquamation (Lat. pityriasis) and follicular inflammation (Lat. pilaris). It was first described in 1835 by Claudius Tarral, but he did not consider it to be a separate entity, but a variant of psoriasis (5). In 1856, Alphonse Devergie described "pityriasis pilaris" as a combination of follicular lesions and psoriasis palmaris, pityriasis capillitii and pityriasis rubra, naming Tarral's case as pityriasis pilaris (6), while in 1877 Richaud recognized it as a distinct entity (7). In 1889, Ernest Besnier named this condition - pityriasis rubra pilaris (8), whereas in 1910, De Beurmann first described the familial form of PRP (9).

The incidence of PRP is low: in the United States it has been reported to occur with 1: 3500 to 1 :

5000 patients presenting in dermatology clinics (10), in India, 1 case in every 500 new pediatric patients with a dermatologic disease (11). It occurs equally in male and female patients; in childhood, the male to female ratio is 3:2 (3). It affects members of all races, but it is less common in black people. Although PRP may occur at any age (10), it most commonly affects those in their first, second, fifth or sixth decades of life (1). Usually these are sporadic acquired forms, familial forms are rare, being rather transplacentally transmitted (1), than inherited in an autosomal dominant or autosomal recessive or X-linked fashion (3, 12).

Based on the age of onset, clinical course, morphology and prognosis, in 1980 Griffiths (13) classified PRP into five types: two adult types (classical and atypical) and three juvenile types (classic, circumscribed and atypical). In 1983, Larregue et al. (14) described a new variant, as a subtype of type III, acute or postinfection juvenile PRP (15). The characteristics of this type include: a) no familial occurrence; b) begins at early childhood, after the first year of life; c) previous infectious episode; d) scarlatiniform erythema followed by the appearance of follicular papules; e) no laboratory abnormalities, except for those derived from the infectious process; f) clinical appearance similar to classic juvenile PRP, and g) acute course with good outcomes, although resolution may be slow, and no tendency toward recurrence.

In 1994, Piamphongsant and Akaraphant (16) analyzed 168 patients with PRP and proposed a new classification that distinguished the following 4 types of PRP based on clinical appearance: 1. salmon-colored or erythematous thick plaques on the palms and soles, which extend beyond the dorsopalmar and plantar junctions; 2. circumscribed scaly erythematous patches on the elbows and knees; 3. patches involving large areas of the trunk which are not generalized; 4. exfoliative erythroderma associated with diffuse follicular plugging. However, in practice, Griffiths classification is still actual, although in 1995 (17) sixth type was added: PRP associated with human immunodeficiency virus (HIV) infection, which differs from other types in terms of clinical course and poor prognosis (18).

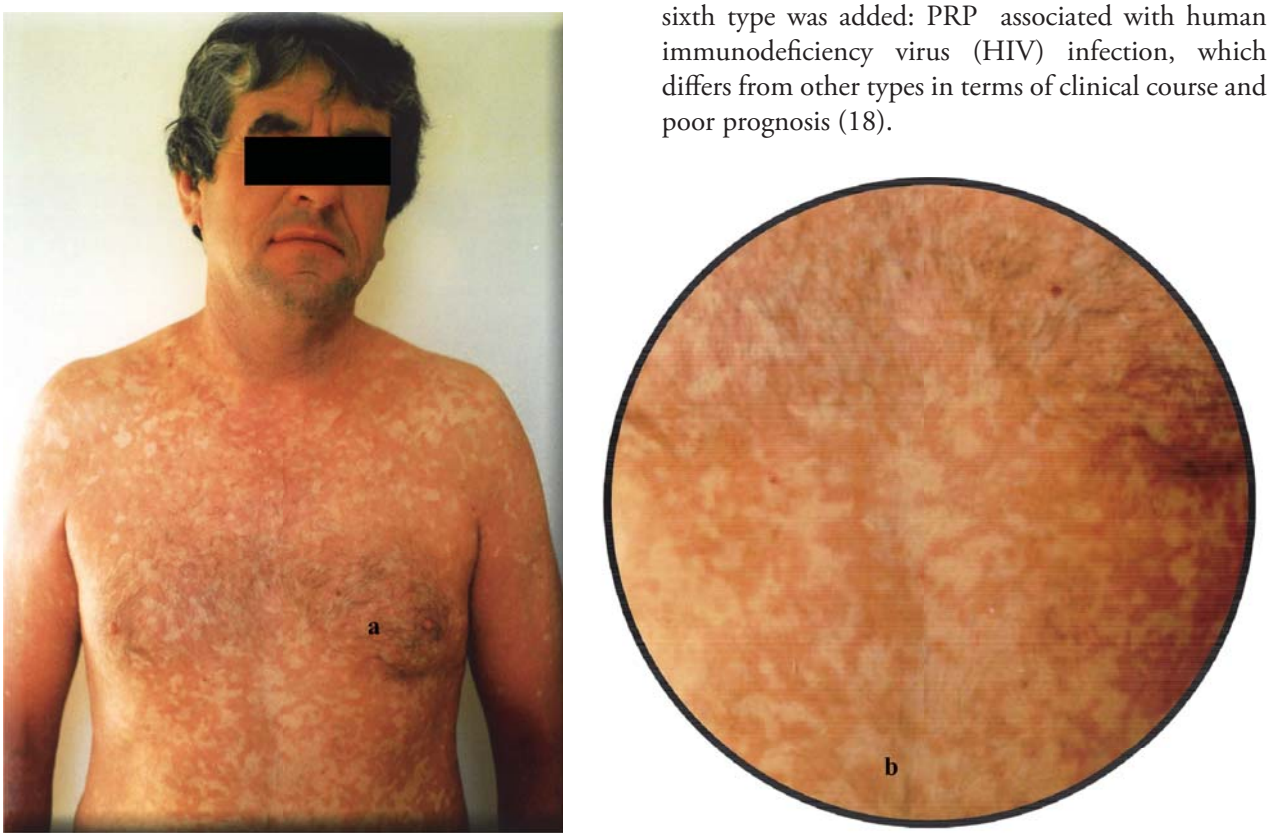

Figure 1. The skin of the abdomen: a) intense individual and coalescing erythematous plaques covered with thin whitish poorly adherent scales with well demarcated islands of unaffected skin; b) an enhanced detail

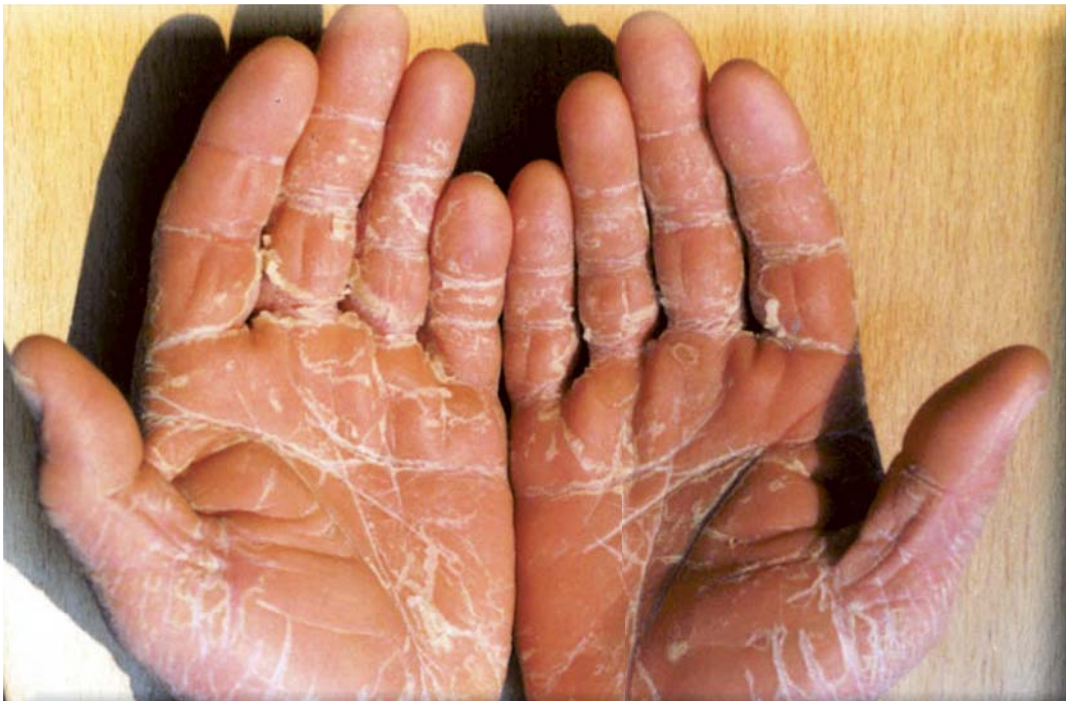

Figure 2. Palmar hyperkeratosis with a waxy appearance with shallow rhagades and a marked lamellar desquamation

Case reports

Patient 1. A 53-year-old farmer, with a diagnosis of erythroderma, was admitted due to skin changes that appeared 15 days earlier including redness and itching of the scalp, which soon spread to the whole body. His personal and family medical histories were unremarkable. The dermatological examination revealed: intense erythematous plaques on the whole body, especially on arms and legs, covered with thin whitish poorly adherent scales with well demarcated islands of unaffected skin (Figure 1); the skin of the face and scalp was erythematous with fine velvety desquamation; the hands and feet were edematous with palmoplantar hyperkeratosis and a waxy appearance, shallow rhagades and a marked lamellar desquamation mostly on the palms (Figure 2).

Laboratory test results

All relevant laboratory findings were within normal limits, except for slightly elevated cholesterol and triglyceride levels.

Histopathological analysis

Histopathological examination of the fully developed erythematous lesion showed a moderate to prominent orthokeratosis with alternating parakeratosis, mild acanthosis with short and broad rete ridges; a nonspecific perivascular infiltrate in the papillary and subpapillary dermis composed predominantly of lymphocytes (Figure 3).

Therapy

The patient received a systemic corticosteroid therapy for 15 days and after initial improvement, acitretin was initiated at a dose of 75 mg per day, which was gradually reduced to 25 mg per day; topical treatment included corticosteroids, emollients and keratolytics. On discharge, the patient showed a significant improvement of skin lesions.

Patient 2. A 70-year-old retired male patient, diagnosed with erythroderma, was admitted due to skin changes that began 6 months earlier on his right cheek with redness, itching and subsequent scaling. The skin lesions then spread to the chest, abdomen, shoulders and back, with intense itching. Almost from the beginning, the disease also affected the palms, soles and nails, with painful thickening. A month before admission, the patient developed burning in the eyes and his eyelids were stuck together in the morning. He received outpatient treatment without

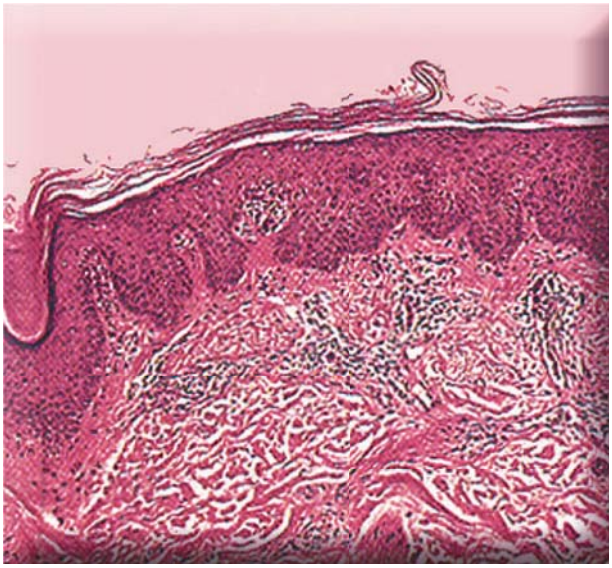

Figure 3. Fully developed erythematous lesion: moderate to prominent orthokeratosis with alternating parakeratosis in the epidermis, mild acanthosis with short and broad rete ridges; a nonspecific perivascular infiltrate in the papillary and subpapillary dermis composed predominantly of lymphocytes (HE stain, x 50)

significant improvement, and when the changes spread to the whole body, half a year after the onset of symptoms, he was referred to hospital for examination and treatment. Apart from elevated blood pressure, the patient's personal and family history were unremarkable; dermatological examination showed: pinhead-sized erythematous follicular papules on the chest and abdomen, single or coalescing, forming plaques with whitish pityriasiform scaling (Figure 4); red-orange lesions with diffuse thickening were found on the face, neck, back, arms and legs, covered with whitish scales with islets of healthy skin (Figure 5); the skin of both palms and soles was thickened, yellowish-brown with a wax appearance (Figure 6); the distal third parts of the nail plates of the fingers and toes were yellowish and thickened, with longitudinal ridging and subungual hyperkeratosis.

Laboratory test results

All relevant laboratory findings were within normal limits. After examination, the ophthalmologist diagnosed blepharoconjunctivitis, and 3% solution of boric acid eye drops was introduced, as well as chloramphenicol eye ointment.

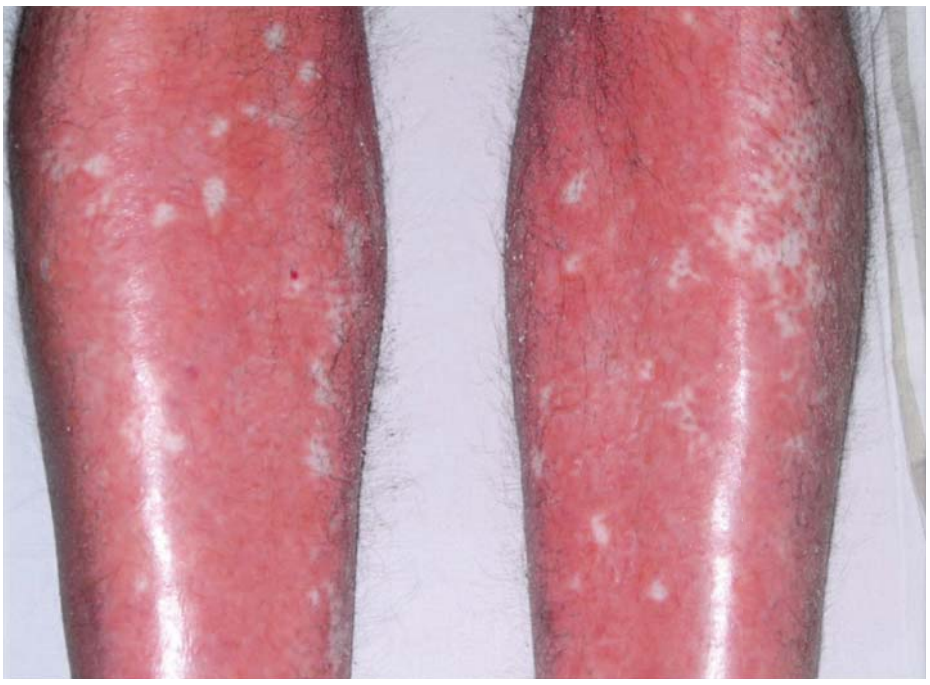

Figure 4. Red-orange lesions with diffuse thickening on the legs, covered with whitish scales with islets of healthy skin

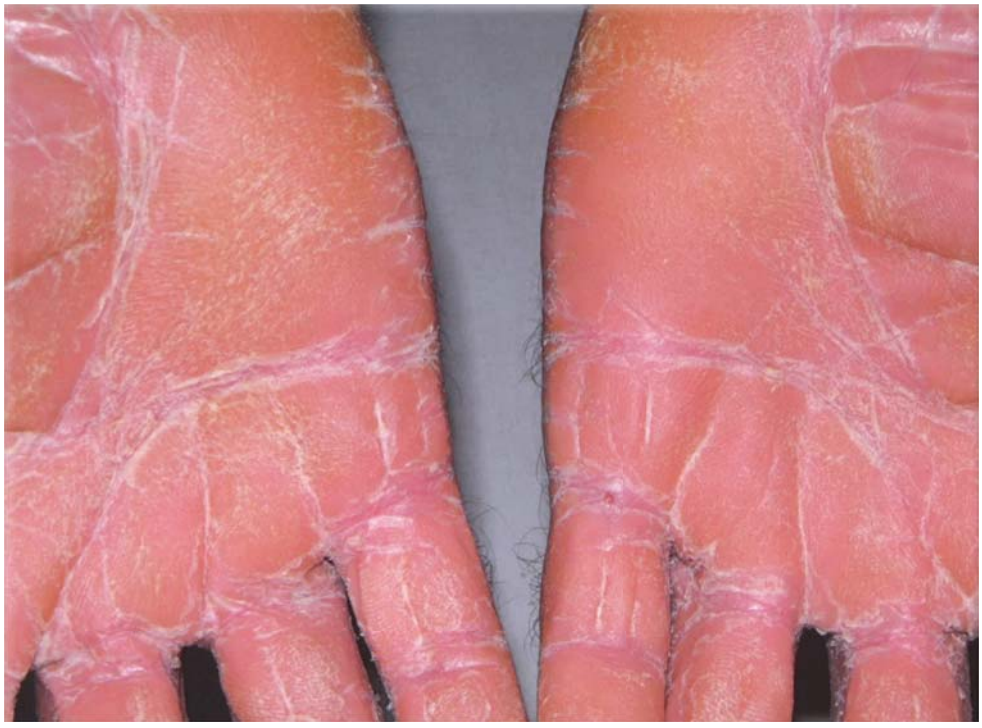

Figure 5. The skin of both palms and soles is thickened, yellowish-brown with a waxy appearance

Histopathological analysis

Histopathological examination of the areas corresponding to follicular papules showed: dilated infundibulum filled with orthokeratotic plug; the hairs were present, but reduced in volume (Figure 7); perifollicular parakeratosis; mild perifollicular lymphocytic infiltrate.

Therapy

The treatment was initiated with parenteral methylprednisolone (the initial dosage of 80 mg per day, with gradual reduction of the daily dose), and systemic antihistamines; topical treatment included corticosteroids, emollients and keratolytics. The patient was discharged in a much improved condition: reduced erythema, desquamation and infiltration of the skin, especially on the palms and soles.

Discussion and a Literature Review

PRP is rare heterogeneous dermatosis with unclear etiology and pathogenesis (19, 20). The skin lesions are the result of hyperproliferation of keratinocytes in the epidermis and inflammation in the dermis. In conjunction with the genetic background, different infectious, endogenous and environmental triggers, such as vitamin A deficiency, autoimmune, neoplastic, and traumatic have been sought, but none has been conclusively associated with the disease (1, 21, 22). Thus, no positive correlation between vitamin A deficiency and PRP has been established, whereas beneficial effects of vitamin A in PRP therapy are compared with its therapeutic efficacy in the treatment of dermatoses with follicular and nonfollicular keratosis, where no vitamin A deficiency has been determined. The potential etiological role of inadequate vitamin A transport due to lack of retinol-binding protein requires further verification. According to the National Organization for Rare Disorders, PRP may develop due to abnormalities in the way the body processes vitamin A (22). In the literature, some cases of PRP were preceded by upper respiratory tract infections, in children usually triggered by streptococcal superantigen (15, 23), varicella virus (24), cytomegalovirus (21), Epstein Barr virus (19), vaccination against diphtheria-tetanus-polio, flu vaccination, and vaccination against measles, mumps and rubella (25, 26). Cases associated with HIV infection have also been reported

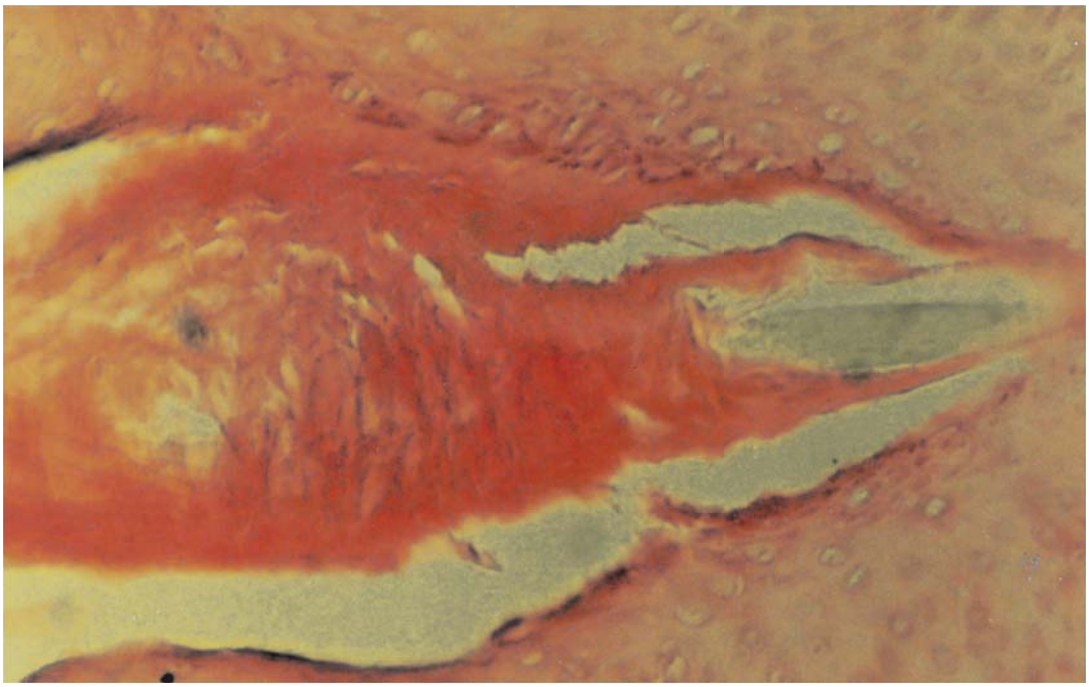

Figure 6. Areas corresponding to follicular papules show: dilated infundibulum filled with orthokeratotic plug; the hair is present, but reduced in volume (HE stain, x 400)

(17, 27). It seems that infections and other triggers act only as initiators of the aberrant cell-mediated immune response. The absence of prodromic symptoms in both our patients, as in most cases, cannot eliminate the possibility of an asymptomatic illness triggering PRP.

Besides acquired, sporadic cases, familial cases of PRP have been reported, most commonly with autosomal dominant inheritance (10). Mutations in the CARD14 gene on chromosome 17q25 (28), which encodes a group of interactive protein known as nuclear factor-kappa B (NF-kB), have been found in some families. NF-kB regulates the activity of multiple genes, including genes that control immune responses and inflammatory reactions; CARD14 gene mutations enhance the activation of NF-kB signaling pathway which causes an aberrant inflammatory response. The CARD14 protein is found in many of the body's tissues, but it is particularly abundant in the skin, where it appears to play important roles in regulating inflammatory reactions. Data obtained recently (28), demonstrate that autosomal-dominant PRP is allelic to familial psoriasis, which was recently shown to be caused also by mutations in CARD14 gene (29).

In PRP, skin, nails, mucous membranes, and eyes can be affected (10). The skin is typically orange-red or salmon-colored with scaly plaques, with sharp borders, with islands of unaffected skin not exceeding 1.5 cm in diameter. The nails show a yellow-brown discoloration, subungual hyperkeratosis, nail-plate thickening, and splinter hemorrhages. Lesions of the mucous membranes include white plaques confined to the palate, bilateral gray-white plaques with a rough surface in the buccal mucosa and erythematous lesions, even erosions (30). Complications may involve the eyes: ectropion, blurred vision and dry eyes.

Griffith's classification (13), which is generally used, gives precise descriptions of the PRP types.

Type I is classic adult pityriasis rubra pilaris which accounts for 50 to 55% of all cases (4). The onset is acute, it is sporadic and there are no familial cases. PRP is characterized by cephalocaudal progression. Scarring alopecia may also develop (31). It has the best prognosis: about 80% of patients have remission in an average of 3 years. One reported case resolved spontaneously after 20 years (32).

Type II is atypical, accounting for 5% of patients. It is characterized by: marked desquamation, thin hair, increased palmoplantar keratosis, ichthyosiform lamellar scales, alopecia, incomplete erythroderma,

sometimes with psoriasiform appearance, but never progresses to psoriasis, and has no cephalocaudal spread. It has a long-term chronic course (11), and lasts several years (10).

Type III is a classic juvenile type, and accounts for 10% of all patients with PRP (3); it has the same clinical picture as Type I, but its onset is within the first 2 years of life and the course is more favorable in children compared with adults. Classical juvenile type may progress into circumscribed form. Initially, it may resemble other superantigen-mediated diseases: staphylococcal scalded skin syndrome (SSSS), scarlet fever, toxic shock syndrome, and Kawasaki disease. It is featured by raspberry tongue, shiny, chapped lips, flexural (particularly perineal) erythema followed by peeling, palmo-plantar erythema, and generalized rash, whereas usual lesions appear days or weeks later. Symptoms spontaneously resolve within 3 years or earlier (10). In 6% of patients self-limitation occurs in the first year, and in 90% in three years.

Type IV is circumscribed juvenile PRP and it occurs in prepubertal children or young adults. This form accounts for about 25% of all cases. It is characterized by sharply demarcated areas of follicular hyperkeratosis and erythema of the knees and the elbows. Sometimes it is extremely difficult to distinguish it from psoriasis. The long-term outcome is unclear; it rarely progresses; it may resolve spontaneously, but may also be persistent and last for several years (33).

Type V is atypical juvenile generalized chronic PRP. Most familial PRP cases belong to this type (10). It accounts for 5% of patients with PRP, and it is characterized by diffuse ichthyosiform follicular lesions on the feet, with severe keratoderma, and sclerodermiform palmoplantar lesions, mostly without erythema.

Type VI is associated with HIV infection (17). It is characterized by follicular keratosis, acneiform, nodular and pustular lesions with elongated follicular plugs or lichen spinulosus–type lesions on the face and upper trunk, often with clear symptoms of immune deficiency (10). It significantly differs from other types of PRP, it is refractory to treatment and it has an increasing incidence (4).

The diagnosis of PRP is based on clinical and histological findings (10, 34). Our patients presented with clinical symptoms of classical PRP at the age of 53 and 69, respectively. Although there are no specific laboratory markers for PRP, all relevant laboratory and other tests were performed to detect the potential trigger factors (10). The test results of both patients were within reference values. Although histological features are not pathognomonic in PRP, they are useful to rule out other possible papulosquamous and erythrodermic disorders (10). In classical adult type, histopathological changes are distinctive, and vary depending on the stage and localization of lesions from which the biopsy is taken (1). It is characterized by hyperkeratosis with alternating ortho- and parakeratosis, focal and confluent hypergranulosis, follicular plugging with perifollicular parakeratosis forming a shoulder effect, short and broad rete ridges, and sparse superficial dermal lymphocytic perivascular infiltration (35). Acantholysis has been reported as an additional histological finding, and together with hypergranulosis, follicular plugs, dilated, but not tortuous dermal capillaries and absence of epidermal pustules, it may help to distinguish pityriasis rubra pilaris from psoriasis (35). Unlike psoriasis, the acanthotic epidermis in PRP is not thinned above the dermal papillae (1). Histopathological findings in type IV, circumscribed PRP differ from those in classical: lamellar hyperkeratosis with unchanged or increased granular layer; marked follicular hyperkeratosis; scarce acanthosis; rare cell infiltration (1). The classical type I PRP was histologically confirmed in both of our patients.

In early stages, many diseases, including PRP, may have similar symptoms, so the differential diagnosis includes a series of dermatoses. In adults they are: contact dermatitis, scabies crustosa, cutaneous T-cell lymphoma, Darier's disease, dermatomyositis, eczema, erythroderma, lichen spinulosus, phrynoderma, psoriasis, pityriasis versicolor, pityriasis lichenoides chronica, pityriasis rosea, pityriasis rosea-like drug eruption, psoriasis, subacute cutaneous lupus erythematosus, sclerodermiform dermatitis, dermatitis seborrhoica, secondary syphilis. In children, differential diagnosis includes: eczema, erythroderma variabilis, Kawasaki disease, lichen spinulosus, nummular dermatitis, phrynoderma (36). Sometimes it is difficult to differentiate these lesions from psoriasis (37). Unlike psoriasis, PRP

has the following features: bimodal age of onset; general state of the patient is good, even in those with erythroderma; the presence of islets of unaffected skin is easy to distinguish from areas of uninvolved skin in psoriatic erythroderma if we bear in mind that "islands of unaffected skin" in PRP do not exceed 1.5 cm in diameter; the primary lesion is papule with a hair in its center with no inclination to peripheral growth and fusion due to skin infiltration, but due to an ongoing erythematosquamous process when diffuse erythroderma is formed; brick-red or carrot-orange color; absence of infiltrates, lichenification, large lamellar scales; absence of onycholysis; palmoplantar hyperkeratosis without infiltration, with yellow-orange discoloration; rare seronegative arthropathy; variable response to methotrexate; hormonal therapy, primarily with corticosteroids, has no favorable effects; pure response to UVB therapy (1, 38).

Regarding complications of PRP, we should rather consider them as various associations of uncertain significance (1). PRP has been reported to be associated with: photosensitivity, increased susceptibility to herpes simplex eye infection, ectropion and vision disorders (39). Our older patient presented with eye irritation and watering; an ophthalmologist was consulted, but the patient did not develop ectropion. PRP is also associated with poor quality of life, depression, insomnia, suicidal ideation (40). Particular attention should be paid to the side effects of drugs used in the treatment of PRP, primarily retinoids (41).

The therapy is very diverse, with different results; treatment of children with PRP should be done with special caution and in most cases include topical agents only. Topical therapy involves the use of different agents such as emollients and keratolytics, creams with urea and lactic acid, corticosteroids, vitamin D analogues (calcipotriol), retinoids, imiquimod 5% (20, 22, 42, 43, 44). In systemic therapy results are unpredictable, although retinoids are widely considered the first-line treatment in the erythrodermic phase; methotrexate has been effective as an alternative or adjunct to oral retinoids but generally is less efficacious in PRP than in psoriasis; success and failure have been reported with cyclosporine, as well as with corticosteroids, high doses of vitamin A, vitamin E, antihistamines, azathioprine, biological agents such as infliximab, ustekinumab, adalimumab (18, 20, 22, 42, 44-47). Phototherapy (UVB, NB UVB, PUVA) can be effective as monotherapy, or combined with retinoids (48). Treatment of refractory juvenile PRP with synthetic retinoid-analogue bexarotene, has shown good therapeutic effects (49). Tumor necrosis factor alpha (TNF-α) inhibitors have been used with various success, but their long-term use may cause serious side effects (50, 51). Based on their experience and literature review, Muller et al., (46) found infliximab monotherapy as first-line treatment for adult-onset PRP (type I).

Our first patient was initially treated with systemic corticosteroids, but they were found ineffective. A systemic retinoid was initiated, as well as topical therapy with corticosteroids, emollients and keratolytics, and this treatment resulted in significant improvement. The second patient was treated with systemic corticosteroids with beneficial therapeutic effects.

Conclusion

We presented two adult males with classical clinical picture of type I PRP. The diagnosis was based on clinical appearance and histological findings, and both had a favorable response to treatment. It is of utmost importance to be familiar with potential triggers of the disease, make early diagnosis, and start proper treatment.

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Abbreviations

PRP - pityriasis rubra pilaris
HIV - human immunodeficiency virus
NF-kB – nuclear factor-kappa B
SSSS - staphylococcal scalded skin syndrome
UVB - ultraviolet B
NB UVB - narrow-band ultraviolet B
PUVA - psoralen and ultraviolet A
TNF-α - tumor necrosis factor alpha

Pityriasis rubra pilaris: prikaz dva slučaja i pregled literature

Sažetak

Uvod. *Pityriasis rubra pilaris* (PRP) (sinonimi *lichen ruber pilaris*, *lichen ruber acuminatus*, Divergijeva (*Devergie*) bolest jeste idiopatska inflamatorna i hiperproliferativna dermatoza koju karakterišu: folikularne hiperkeratotične papule grupisane u široke eritematozne plaže, između kojih se nalaze ostrvca neizmenjene kože, palmoplantarna keratodermija, difuzne skvame u kosmatom delu glave i, često, progresivna eksfolijativna eritrodermija.

Bolest se retko registruje u Americi – jedan oboleli na 3 500–5 000 novoregistrovanih slučajeva dermatoloških oboljenja među pacijentima koji se javljaju na pregled dermatologu. Kod odraslih bolest se javlja podjenako često kod oba pola, dok je kod dece češća kod dečaka (odnos dečaka prema devojčicama je 3 : 2). Obolevaju pripadnici svih rasa, nešto ređe crne rase. Iako se PRP može javiti u bilo kom periodu života, najčešće započinje u prvoj, drugoj, petoj ili šestoj dekadi. Najčešće su to sporadični stečeni slučajevi, dok je pojava PRP među pripadnicima iste porodice posledica najverovatnije transplacentarnog prenošenja, ređe autozomno dominantnog, autozomno recesivnog, ili nasleđivanja vezanog za X hromozom.

Zbog razlika u vremenu početka bolesti, kliničkom toku, morfologiji i prognozi, Grifits (*Griffiths*) je 1980. godine izvršio klasifikaciju PRP na pet tipova: dva tipa kod odraslih (klasični i atipični) i tri juvenilna tipa (klasični, cirkumskriptni i atipični). Larege (*Larregue*) i saradnici su 1983. godine opisali novu varijantu kao podtip tipa III, akutni ili postinfekcioni juvenilni PRP, što se retko navodi u literaturi. Karakteristike ovog tipa su: a) odsustvo porodičnog javljanja; b) početak u detinjstvu, posle prve godine života; c) prisustvo prethodne infekcije; d) skarlatiniformni eritem, sa kasnijom pojavom folikularnih papula; e) nema laboratorijskih abnormalnosti, sem onih u vezi sa infektivnim procesom; f) klinički sličan klasičnom juvenilnom tipu; g) akutni tok sa dobrom prognozom, mada rezolucija može biti spora, ali bez tendencije ponovnog javljanja.

Piamphongsant i *Akaraphant* su 1994. godine predložili novu klasifikaciju oboljenja na osnovu analize 168 pacijenata sa PRP koja razlikuje sledeća četiri tipa PRP na osnovu kliničkog izgleda promena: 1. eritematozni zadebljali plakovi na dlanovima i tabanima sa širenjem na dorzopalmarne i plantarne zglobove; 2. eritemoskvamozni plakovi na kolenima i laktovima; 3. eritemoskvamozni plakovi koji zahvataju široke areale na trupu, bez generalizacije; 4. eksfolijativna eritrodermija udružena sa difuznim

folikularnim čepovima. U praksi je međutim i dalje aktuelna podela Grifitsa na pet tipova, kojima je 1995. godine dodat i šesti tip: PRP udružen sa infekcijom virusom humane imunodeficijencije (HIV) koji se od ostalih tipova razlikuje po kliničkoj slici i lošijoj prognozi.

Prikaz slučaja. Slučaj 1. Bolesnik mušog pola, starosti 53 godine, po zanimanju zemljoradnik, sa uputnom dijagnozom eritrodermije, primljen je na bolničko lečenje zbog promena na koži, koje su počele 15 dana ranije sa crvenilom i svrabom na kosmatom delu glave, a ubrzo su se proširile na čitavo telo. Lična i porodična anamneza bile su bez osobenosti; dermatološki pregled je otkrio: na koži čitavog tela, naročito ruku i nogu, pojedinačne i većim delom slivene intenzivno eritematozne plaže prekrivene tankim beličastim slabo adherentnim skvamama, sa ostrvcima neizmenjene kože između njih (Slika 1); na koži lica i kapilicijuma eritem sa sitnom brašnastom deskvamacijom; na šakama i stopalima edemi, palmoplantarna hiperkeratoza voštanog izgleda, sa plićim ragadama i krupnom lameloznom deskvamacijom, naročito izraženom na dlanovima (Slika 2). U laboratorijskim nalazima, osim lako povišenih nivoa holesterola i triglicerida u serumu, svi ostali relevanti laboratorijski nalazi bili su u granicama normale. Histopatološki pregled eritematozne lerzije: u epidermisu umerena do jače izražena ortokeratoza i alternativna parakeratoza, blaga akantoza sa plitkim i širokim grebenima; u papilama i subpapilarno perivaskularno prisutan oskudan nespecifičan infiltrat sastavljen pretežno od limfocita (Slika 3). Posle sistemske kortikosteroidne terapije u prvih 15 dana, koja je dala početno poboljšanje, u terapiju je uključen acitretin u dozi od 75 mg dnevno, sa postepenim smanjivanjem na 25 mg dnevno; u lokalnoj terapiji primenjeni su kortikosteroidi, emolijensi i keratolitici. Bolesnik je otpušten na kućno lečenje znatno poboljšanog stanja kože.

Slučaj 2. Osoba muškog pola, stara 70 godina, po zanimanju penzioner, sa uputnom dijagnozom eritrodermije, primljen je na bolničko lečenje zbog promena na koži koje su počele 6 meseci ranije i to na koži desnog obraza u vidu crvenila i svraba, sa kasnijim perutanjem. Promene su zatim zahvatile kožu na grudima, trbuhu, ramenima i leđima, uz jak osećaj svraba. Skoro od samog početka bolesti nastale su promene na dlanovima, tabanima i noktima u vidu zadebljanja i bolne osetljivosti. Mesec dana pred prijem u bolnicu, javio se osećaj pečenja u očima i „slepljenost“ očnih kapaka u jutarnjim časovima nakon buđenja. Lečen je ambulantno bez znatnijeg uspeha, a kada su se promene proširile na čitavo telo, pola godine od početka bolesti, upućen je na hospitalno ispitivanje i lečenje. Osim podatka o povišenom krvnom pritisku, lična i porodična anamneza bile su bez relevantnih osobenosti; dermatološki pregled je otkrio: na koži prednje strane grudnog koša i trbuha folikularne eritematoznene papule veličine čiodine glave, pojedinačne i slivene, sa beličastim pitijaziformnim skvamama (Slika 4); na koži lica, vrata, leđa, ruku i nogu difuzno zadebljanje neravne površine crvenonarandžaste boje, prekriveno beličastim skvamama, sa ostrvcima zdrave kože (Slika 5); na koži oba dlana i tabana difuzno zadebljanje, žućkastosmeđe prebojeno – voštanog izgleda (Slika 6); u distalnim trećinama nokatnih ploča na prstima ruku i nogu žućkasobeličasto prebojena zadebljanja, sa uzdužnim grebenima i subungvalnom hiperkeratozom. Svi relevanti laboratorijski nalazi bili su u granicama normale. Histopatološki pregled folikularne papule: folikul dlake dilatiran, ispunjen ortokeratinskim čepom; dlaka je prisutna, ali redukovanog volumena (Slika 7); perifolikularna parakeratoza; oskudni limfocitni perifolikularni infiltrat. Lečenje je započeto sa parenteralnom primenom metilprednizona, u početnoj dozi od 80 mg dnevno, uz postepeno smanjivanje dnevne doze, i sistemskom primenom antihistaminika; u lokalnoj terapiji primenjeni su kortikosteroidi, emolijensi i keratolitici; pregledom oftalmologa postavljena je dijagnoza blefarokonjunktivitisa, a lečenje je sprovedeno rastvorom borne kiseline 3%, u vidu kapi za oči i aplikacijom hloramfenikol masti za oči. Bolesnik je otpušten na kućno lečenje u znatno poboljšanom stanju: redukovan eritem, deskvamacija i infiltracija naročito kože na dlanovima i tabanima.

Diskusija. *Pityriasis rubra pilaris* je retka u osnovi heterogena dermatoza sa nejasnom etiopatogenezom. Promene na koži su rezultat hiperproliferacije keratinocita u epidermisu i inflamacije u dermisu. Pored genetske predispozicije, različiti infektivni, endogeni i egzogeni ekološki faktori, npr.

nedostatak/disfunkcija A vitamina, autoimunski neoplazijski, traumatski činioci opisani su kao mogući pokretači PRP ali njihova uloga nije sa sigurnošću dokazana. Tako je dokazano odsustvo korelacije između deficijencije vitamina A i PRP, a potencijalni etiološki značaj neadekvatnog transporta vitamina A usled nedostatka retinol binding proteina, zahteva dalju proveru. Prema Nacionalnoj organizaciji za retke bolesti, PRP može nastati zbog abnormalnosti u načinu na koji telo procesuira vitamin A. U literaturi su opisani slučajevi PRP, kojima je prethodila infekcija gornjih respiratornih puteva, kod dece najčešće izazvane streptokokom (sa superantigenom u ulozi pokretača), virusom varičele, citomegalovirusom, *Epstein Barr* virusom, posle difterija-tetanus-polio vakcinacije, vakcinacije protiv gripa, posle vakcinacije ROR (fr. *rougeole-oreillons-rubéole*) vakcinom protiv morbila, parotitisa i rubeole. Posebno su opisani slučajevi udruženi sa infekcijom HIV-om. Pretpostavlja se da infekcija kao i ostali nabrojani činioci imaju ulogu pokretača oboljenja tako što pokreću aberantni celularni imunski odgovor. Odsustvo prodromalnih simptoma kod oba naša pacijenta kao i kod većine ostalih slučajeva opisanih u literaturi, ne isključuju mogućnost postojanja asimptomatskog oboljenja u ulozi pokretača PRP.

Osim stečenih, sporadičnih slučajeva, opisano je i porodično javljanje PRP, sa najčešće autozomno dominantnim načinom nasleđivanja. Kod nekoliko porodica nađene su mutacije CARD 14 gena na hromozomu 17q25 koji reguliše aktivaciju *nuklearnog faktora kapa B* (NF-kB), a preko njega reguliše se aktivnost multiplih gena, uključujući gene koji kontrolišu imunske i inflamatorne reakcije. Mutacije CARD 14 gena dovode do prevelike aktivacije NF-kB signalnog puta što izaziva aberantni inflamatorni odgovor. Podaci dobijeni u skorije vreme pokazuju da je autozomno-dominantna PRP alelski povezana sa porodičnom psorijazom, koju takođe mogu izazvati mutacije u CARD14 genu.

Promenama na koži, na noktima, mukoznim membranama i očima može da se manifestuje PRP. Na koži su tipični narandžastocrveni ili crvenkasto prebojeni skvamozni plakovi sa oštrim ivicama, između kojih se nalaze ostrvca neizmenjene kože koja po većini ne prelaze 1,5 cm u dijametru. Na noktima se može registrovati distalna žućkasto-smeđa diskoloracija, subungvalna hiperkeratoza, longitudinalne brazde, zadebljale nokatne ploče i hemoragije. Promene na mukoznim membranama su u vidu beličastih plakova, sivobelih papula ili plakova, eritema ili čak erozija na sluzokoži usta. Kao komplikacije na očima mogu nastati ektropion, nejasan vid i suvoća očiju.

Prema klasifikaciji Grifitsa koja je u opticaju i opšte korišćena, dati su preciznije opisi naznačenih tipova. Tip I je klasični tip koji se javlja kod odraslih i prisutan je kod 50% do 55% svih obolelih. Tip II je atipičan, javlja se u oko 5% pacijenata, praćen je izraženom deskvamacijom nekada psorijaziformnog izgleda, ali nikada ne prelazi u psorijazu. Tip III je klasični juvenilni tip; javlja se kod 10% od svih pacijenata sa PRP, ima istu kliničku sliku kao tip I, ali se javlja u prve dve godine života i ima povoljniji tok nego kod odraslih. U početku, klinički podseća na superantigenom izazvana oboljenja: šarlah, toksični šok sindrom i *Morbus Kawasaki*. Uobičejene karakteristike su malinast jezik, sjajne ispucale usne, fleksuralni (posebno perinealni) eritem koji prati ljuštenje, palmoplantarni eritem i generalizovani osip, dok se promene klasične PRP javljaju danima ili nedeljama kasnije. Tip IV je cirkumskriptni juvenilni tip koji se javlja kod prepubertetske dece i mlađih odraslih osoba. Nastaje kod 25% od svih bolesnika sa PRP. Karakterišu ga oštro ograničene skvamozne plaže folikularne hiperkeratoze i eritema na kolenima i laktovima. Tip V je atipična juvenilna generalizovana hronična forma. Najveći broj slučajeva PRP sa familijarnim javljanjem pripada ovom tipu. Nastaje kod 5% obolelih od PRP. Karakterišu ga difuzne folikularne lezije ihtioziformnog izgleda na nogama, sa značajnom keratodermijom, sklerodermiformnim promenama na palmarnim i plantarnim regijama i neretko eritem. Tip VI je udružen sa infekcijom HIV-om: promene su na licu i gornjem delu trupa u vidu folikularne keratoze, akneiformnih lezija nodularnih i pustuloznih, sa elongiranim folikularnim čepovima, lezijama sličnim lihen spinulozusu i često naglašenim znacima imunodeficijencije. Signifikantno se razlikuje od drugih tipova, refrakteran je na terapiju a incidencija mu je u porastu (4).

Dijagnoza PRP se postavlja na osnovu kliničkog

i patohistološkog nalaza. Kod naših pacijenata bolest je počela u 53. i 69. godini i manifestovala se kao klasični I tip PRP. Iako do sada nisu utvrđeni specifični laboratorijski markeri koji bi imali dijagnostički značaj, uradili smo sve relevantne laboratorijske i ostale analize radi otkrivanja/isključenja mogućih faktora okidača. Ni kod jednog od naša dva pacijenata nije bilo bitnih odstupanja od referalnih vrednosti relevantnih laboratorijskih analiza.

Histološke karakteristike nisu patognomonične u PRP, ali mogu da omoguće razlikovanje PRP od drugih papuloskvamoznih i eritematoznih dermatoza. Kod klasičnog tipa kod odraslih, patohistološke promene su upadljive, i razlikuju se prema stepenu bolesti i lokalizaciji promena sa kojih je uzeta biopsija. Karakteristična je hiperkeratoza sa naizmeničnom orto i parakeratozom, fokalna i konfluentna hipergranuloza, folikularni keratinski čepovi sa perifolikularnom parakeratozom, plitki a široki grebeni, limfocitna papilarna i subpapilarna infiltracija. Kao dodatna promena može se registrovati akantoliza, koja zajedno sa hipergranulozom, folikularnim čepovima, dilatiranim ali neizuvijanim dermalnim kapilarima i odsustvom epidermalnih pustula, omogućavaju diferencijalnu dijagnozu PRP u odnosu na psorijazu. Za razliku od psorijaze, akantotičan epidermis u PRP nije suprapilarno istanjen.

Za razliku od psorijaze PRP se odlikuje sledećim karakteristikama: doba javljanja je bimodalno; opšte stanje pacijenata je dobro, čak i kod eritrodermijskog oblika; prisustvo ostrvaca klinički nepromenjene kože čiji dijametar je manji od 1,5 cm; primarna lezija je papula iz čijeg centra izrasta dlaka i koja ne pokazuje tendenciju širenja putem infiltracije konfluiranja već putem eritemske deskvamacije; narandžasta boja se poredi sa bojom cigle, odnosno mrkve; odsustvo infiltrata, lihenifikacije, velikih lamelarnih skvama; odsustvo oniholize; palmoplantarna hiperkeratoza bez infiltracije, sa žućkastonarandžastom prebojenošću; seronegativna artropatija je retko prisutna; odgovor na metotreksat varijabilan; hormonska terapija, u prvom redu kortikosteroidima, ostaje bez željenog efekta; slab odgovor na UVB fototerapiju. Klasični tip I oboljenja potvrđen je patohistološki kod oba naša pacijenta.

Komplikacije kod PRP se mogu pre smatrati udruženim stanjima, komorbiditetima, a ne komplikacijama u užem slislu te reči. Opisani su slučajevi PRP udruženi sa povećanom predispozicijom za herpes simpleks infekciju oka, ektropion i smetnje sa vidom: kod našeg starijeg pacijenta manifestovali su se simptomi u vidu peckanja u očima i vlaženja, zbog čega je konsultovan oftalmolog, ali se nije razvio ektropion. Takođe može doći do znatnog pogoršanja kvaliteta života, sa depresijom, insomnijom, suicidnim idejama. Posebno treba obratiti pažnju na neželjena dejstva lekova koji se primenjuju za lečenje PRP, u prvom redu retinoida

Terapija može biti veoma raznovrsna sa nepredvidim rezultatima; kod dece treba biti oprezan i uglavnom primenjivati lokalnu terapiju. Lokalna terapija podrazumeva primenu agenasa kao što su: emolijensi i keratolitici, kreme sa ureom i mlečnom kiselinom, kortikosteroidi, analozi D vitamina (kalcipotriol), retinoidi, imikvimod 5%. Krajnji efekat sistemske terapije je nepredvidiv iako se retinoidi smatraju lekovima prvog izbora za lečenje PRP naročito u eritrodermijskoj fazi oboljenja; metotreksat može predstavljati alternative ili dodatak retinoidima, ali je njegova efikasnost kod PRP manja nego kod psorijaze; uspešna/neuspešna se pokazala i primena ciklosporina, kortikosteroida, visokih doza vitamina A i D, antihistaminika, azatioprina, bioloških lekova kao što su infliksimab, ustekinumab, adalimumab. Fototerapija (UVB, NB UVB, PUVA) može dati rezultate kao monoterapija ili u kombinaciji sa retinoidima. Lečenjem refrakterne juvenilne PRP sa abeksarotenom, sintetskim retinoid-analogom, postignut je dobar terapijski efekat. Inhibitori tumorske nekroze faktor alfa (TNF-α) upotrebljeni su sa različitim uspehom, ali njihova dugotrajna upotreba može dovesti do značajnih sporednih efekata. Miler (*Müller*) i saradnici, na osnovu svojih iskustava i pregledane literature, zastupaju stav da je monoterapija infliksimabom prva linija lečenja PRP kod odraslih (I tip).

U prvom slučaju opisanom u ovom radu, posle početne primene sistemskih kortikosteroida koji nisu pružili željeni efekat, uključen je sistemski retinoid nakon čega je uz lokalnu terapiju kortikosteroidima, emolijensima i keratoliticama došlo do značajnog poboljšanja; u drugom slučaju je povoljan terapijski

efekat postignt već nakon početne primene sistemskih kortikosteroida.
Zaključak. Prikazali smo dve odrasle muške osobe sa klasičnom kliničkom slikom PRP tip I, kod kojih je dijagnoza potavljena na osnovu kliničkog izgleda i patohistološkog nalaza i koje su povoljno reagovale na primenjenu terapiju. Izuzetno je važno poznavati mogućnost dejstva raznih mogućih okidača bolesti, na vreme postaviti dijagnozu i započeti adekvatno lečenje.

Ključne reči

Pityriasis rubra pilaris + dijagnoza + klasifikacija + terapija; Diferencijalna dijagnoza; Prikazi slučajeva; Dermatološki agensi; Ishod terapije; Pregled literature

Activities of the Dermatovenereology Section of the Serbian Medical Society in 2015

Four meetings were organized in 2015, and all of them were accredited by the Health Council of the Republic of Serbia.

The first meeting of the DVS was organized by the Clinic of Dermatovenereology, Clinical Center of Serbia on March 20, 2015.

The introductory lecture was delivered by Assist. Prof. Dr Dušan Škiljević: "The role of DNase I activity in the pathogenesis of lupus erythematosus". Also, 13 case reports were presented at this meeting:

1. Cytophagic histiocytic panniculitis. Dr. Srđan Tanasilović
2. Wells' syndrome in childhood. Assist. Dr. Mirjana Gajić-Veljić
3. Iatrogenic Kaposi sarcoma. Dr. Jovan Lalošević
4. Darier's disease – segmental type. Dr. Branislav Lekić
5. Pyoderma gangrenosum induced by propylthiouracil. Dr. Iva Maširević
6. Pemphigus herpetiformis. Assist. Dr. Jelena Stojković-Filipović
7. Porphyria cutanea tarda. Dr. Vesna Reljić
8. Recurrent PLEVA in 11-year-old child. Assist. Prof. Dr .Snežana Minić
9. Shulman's syndrome in a patient with lung carcinoma. Assist. Dr. Jelena Stojković-Filipović
10. Bowen's disease treated with imiquimod. Dr. Margita Mijušković
11. KID syndrome – report of two cases. Dr. Branislav Lekić
12. Rowell's syndrome. Dr. Lana Ćirković

The second meeting of the DVS was organized by the Clinic of Dermatology and Venereology, Military Medical Academy on April 24, 2015.

The introductory lecture was presented by Dr. Miroslav Dinić: "Comorbidities in psoriasis: cardiometabolic aspects". Also, 9 case reports were presented at this meeting:

1. Linear IgA bullous dermatosis. Dr. Miroslav Dinić
2. Cutaneous T-cell lymphoma. Dr. Zorana Kremić
3. Anti Jo-1 syndrome. Dr. Kristina Kostić
4. Non-Langerhans indeterminate histiocytosis. Dr. Aleksandra Vojvodić
5. Acne conglobata and vulgar psoriasis treated with acitretin. Dr. Lidija Cvetković Jordanov
6. Lichen planus pemhigoides. Assist. Dr. Tatjana Vukanović
7. Stevens Johnson/toxic epidermal necrolysis overlap syndrome. Dr. Dušan Šofranac
8. Linear IgA bullous dermatosis of childhood. Assoc. Prof. Dr. Lidija Kandolf Sekulović
9. Disseminated granuloma annulare. Assoc. Prof. Dr. Lidija Kandolf Sekulović

The third meeting of the DVS was organized by the Clinic of Dermatology and Venereology, Clinical Center Niš on May 9, 2015 in Prolom Banja.

The introductory lectures were delivered by Assist. Prof. Miljan Krstić: "Concerns of pathologist in the diagnosis of pigmented skin lesions", and Assist. Prof. Dr. Danica Živković Tiodorović: "Unusual clinical presentations of basal cell carcinoma".

Also, 8 case reports were presented at this meeting:

1. Syndrome Arndt Gottron – Scleromixoedema. Dr. Danijela Popović
2. Syndrome CREST. Dr. Vesna Jovanović
3. Dermatomyositis. Dr.Vesna Jovanović
4. Dermoscopy of cutaneous metastatic melanoma. Assist. Prof. Dr. Danica Živković Tiodorović
5. Brooke-Spiegler syndrome. Assist. Prof. Dr. Danica Živković Tiodorović
6. Sweet syndrome - acute febrile neutrophilic dermatosis. Dr. Zorana Zlatanović
7. Tularemia. Dr. Zorana Zlatanović
8. Sarcoidosis cutis et pulmonum. Dr. Sladjana Cekić

The fourth meeting of the DVS was organized by the *Clinic of Dermatovenereology, Clinical Centre of Vojvodina* on October 16, 2015 in Novi Sad.

The introductory lecture was delivered by

Prom. Dr. Siniša Tasić "A clinical-epidemiological and therapeutic aspects of dermatophyte infections scalp and glabrous skin in children and adolescents". Also, seven more lectures were presented at this meeting, five case reports:

1. Inflamed trichilemmal proliferating tumor. Assist. Dr. Milana Ivkov Simić
2. Granular cell tumor of the skin. Dr. Marijana Krstičević
3. "Rainbw pattern" on dermoscopy in nonvascular skin lessions. Assist. Dr. Tatjana Roš
4. Hereditary epidermolysis bullosa. Dr. Anamarija Pfau
5. Systemic lupus erythematosus. Assist. Prof. Dr. Aleksandra Petrović

The last two lectures were devoted to:

1. Reasons for the supplements in the "anti aging" treatment. Assist. Dr. Branislava Gajić
2. Reasons against the supplements in the "anti aging" treatment. Assist. Dr. Milana Ivkov Simić

Assist. Prof. Dr. Aleksandra Petrović
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2015 Annual Report on the Activities of the Dermatovenereology Section of the Society of Physicians of Vojvodina of the Serbian Medical Society Meetings of the Dermatovenereology Section of the Society of Physicians of Vojvodina

During 2015, there were three meetings of the *Dermatovenereology Section* of the *Society of Physicians of Vojvodina* and all of them were accredited by the *Health Council of the Republic of Serbia.*

The first Section meeting was held on March 27, 2015, in Novi Sad in the quarters of *Dermatovenereology Section* of the *Society of Physicians of Vojvodina*. The main topic: "Present experiences in the application of conventional systemic treatment of psoriasis" was delivered by Dr Ljubinka Matović. Also, six more lectures were given by doctors of the *Dermatovenereology Clinic* of the *Clinical Center of Vojvodina.*

1. Surgically treated Lichen striatus. Assoc. Prof. Dr. Slobodan Stojanović.
2. Pigmented warts - diagnostic problem. Assist. Prof. Dr. Zoran Golušin.
3. Delayed pressure urticaria – case report. Assist. Dr. Aleksandra Petrović.
4. Scoring the severity of psoriasis - holistic approach. Assist. Dr. Milana Ivkov-Simić.
5. Papuloeruptive Xanthomas. Assist. Dr. Ljuba Vujanović.
6. Roaccutane. Assoc. Prof. Dr. Slobodan Stojanović.

The second Section meeting was held on October 16, 2015, in Novi Sad in Conference Hall of Hotel "Park". It was a joint meeting of *Dermatovenereology Sections* of *Society of Physicians of Vojvodina* (SPV) and *The Serbian Medical Society* (SMS). Its professional part was carried out by doctors of the *Clinic of Dermatovenereology Diseases* in Novi Sad, *Clinical Center of Vojvodina.*

The introductory lecture: "A clinical-epidemiological and therapeutic aspects of dermatophyte infections scalp and glabrous skin in children and adolescents" was delivered by Prim. Dr. Siniša Tasić. Five more lectures were presented at this meeting as case reports:

1. Inflamed trichilemmal proliferating tumor. Assist. Dr. Milana Ivkov Simić.
2. Granular cell tumor of the skin. Dr. Marijana Krstičević.
3. "Rainbow pattern" on dermoscopy in nonvascular skin lesions. Assist. Dr. Tatjana Roš.
4. Hereditary epidermolysis bullosa. Dr. Anamarija Pfau.
5. Systemic lupus erythematosus. Assist. Prof. Dr. Aleksandra Petrović.

The last two lectures were dedicated to the topic: "For and against supplements in anti-aging treatment."

1. Reasons for the supplements in the "anti-aging" treatment. Assist. Dr. Branislava Gajić.
2. Reasons against the supplements in the "anti-aging" treatment. Assist. Dr. Milana Ivkov Simić.

After lectures and case reports, Full Prof. Dr. Marina Jovanović presented the monograph "Contact allergic dermatitis, decades of experience" of Serbian well known dermatovenerologist Full Prof. Dr. Mirjana Paravina.

The third Section meeting was held on November 27, 2015, in Novi Sad in the quarters of *Dermatovenereology Section* of the *Society of Physicians of Vojvodina*. Lectures were given by doctors of the *Dermatovenereology Clinic* of the *Clinical Center of Vojvodina.* The introductory lecture: "Treatment of Granuloma annulare – new guidelines" was delivered by Assist. Dr. Olivera Levakov. Eight more lectures were given:

1. Orf virus infection in humans – case report. Assoc. Prof. Dr. Slobodan Stojanović
2. Sarcoidosis as familial disease. Mr. sc. med. Dr. Milica Subotić.
3. Keratosis follicularis Darier. Assist. Prof. Dr. Ljuba Vujanović.

4. Erythema annulare centrifugum. Mr. sc. med. Dr. Ljubinka Matović.

5. Human dirofilariasis – two case reports. Dr. Jasmina Jovanović Ljubičić.

6. Tuberous sclerosis – case report. Prim. Dr. Novak Rajić.

7. Aplasia cutis congenita circumscripta. Mr. sc. med. Dr. Anica Radulović

8. Levocetirizine in the treatment of chronic urticaria. Assist. Prof. Dr. Aleksandra Petrović.

Participation of the members of the SPV *Dermatovenereology Section* at other professional meetings in the country and abroad:

As it has been planned, over the past year our members were actively involved in education, conferences and meetings in our country and abroad.

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A Report on the 24th Congress of the European Academy of Dermatology and Venereology, Copenhagen, 2015

The 24th Congress of the European Academy of Dermatology and Venereology was held in Copenhagen, October 7 - 11, 2015. During the Congress, the Scientific Programming Committee was introducing a new program format, with sessions of different teaching levels, which should enable participants to optimize their time to meet their professional needs and to maximize their learning outcomes. The intensive 4-day program included 180 stimulating sessions with more than 600 speakers.

Prof. Miloš Nikolić was the chair of the session "Autoinflammatory Disease" and delivered a lecture "Clinical and Pathological Spectrum of SCLE (subacute cutaneous lupus erythematosus) and SLE (systemic lupus erythematosus)".

Prof. Ljiljana Medenica delivered a lecture "The Pemphigus Group: Clinical Manifestations, Differential Diagnosis and Prognosis" in the session "Bullous Diseases".

Figure 1. Danica Tiodorović (Niš, Serbia) in the Entrance Hall

Figure 2. Dermatologists from Serbia in the exhibition space (standing, from left to right): Ljiljana Trklja, Ivana Binić, Zoran Nedić, Mirjana Milinković, Maja Mitrović, Zorica Mišić, Anica Radulović and Zoran Golušin

Figure 3. Session " The Autoinflammatory Disease": Miloš Nikolić (Beograd, Serbia) - the Chair, with the Co-Chair - Jorg Wenzel (Bonn, Germany

Assist. Prof. Mirjana Milinković was the chair of the session "Chronic Inflammatory Diseases" and delivered a lecture "Sarcoidosis".

Assist. Prof. Danica Tiodorović-Živković delivered a lecture "Rare Presentations of Basal Cell Carcinoma" in the session "Clinical Cases from Around Europe".

There were 14 E-posters from Serbia.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2015/2016

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
28-30 January, 2016	4th European School of Dermato-Oncology, Berlin, Germany	No abstract submission	www.dermato-oncology2016.org
28-31 January, 2016	IMCAS World Congress, Paris, France	28 December, 2015	www.imcas.com
10-12 February, 2016	5th Conference of the Hidradenitis Suppurativa Foundation, Berlin, Germany	31 December, 2015	www.ehsf2016.com
26-27 February, 2016	4th Symposium on Diagnosis and Treatment of Fungal Diseases, Belgrade, Serbia	20 December, 2015	www.dtfd.org
4 March, 2016	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Serbia, Belgrade, Serbia	No abstract submission	www.sld.org.rs
16-20 March, 2016	1st International Dermatology and Cosmetology Congress (INDERCOS), Istanbul, Turkey	31 January, 2016	www.indercos.org
7-8 April, 2016	1st Regional Congress on Youth Health, Belgrade, Serbia	20 January, 2016	www.kongres-zdravljemladih.org
12-14 April, 2016	Dubai Derma 2016, Dubai, UAE	30 November, 2016	www.dubaiderma.com
15 April, 2016	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Military Medical Academy, Belgrade, Serbia	No abstract submission	www.sld.org.rs
7 May, 2016	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Niš, Prolom Banja, Serbia	No abstract submission	www.sld.org.rs
19-22 May, 2016	13th EADV Spring Symposium, Athens, Greece	10 January, 2016	www.eadvathens2016.org
23-27 May, 2016	4th International Conference on Radiation and Applications in Various Fields of Research, Niš, Serbia	31 December, 2015	www.rad-conference.org
26-28 May, 2016	13th Congress of the European Society for Pediatric Dermatology, Paris, France	15 January, 2016	www.espd2016.com
11-15 June, 2016	Congress of the European Academy of Allergology and Clinical Immunology, Vienna, Austria	10 January, 2016	www.eaaci2016.org
13-15 June, 2016	7th European Dermatology Congress, Alicante, Spain	No submission deadline	www.dermatology.conferenceseries.com/europe

Prepared by: Dr. Tatjana Roš, Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia, E-mail: t.rosh@nscable.net

AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

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

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

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

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

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

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

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

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

1. Manuscript Preparation Guidelines

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

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

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

- A running title (limited to 30 characters);

- Authors' names and institutional affiliations;

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

1.2. Abstracts

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

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

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

1.3. A list of abbreviations

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

1.4. Cover Letter

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

2. Tables and illustrations

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

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

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

3. References

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

4. Additional information

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

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

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Cover figure: Christ Healing Ten Lepers, Christ's Miracles, 14th century, The monastery Visoki Dečani

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