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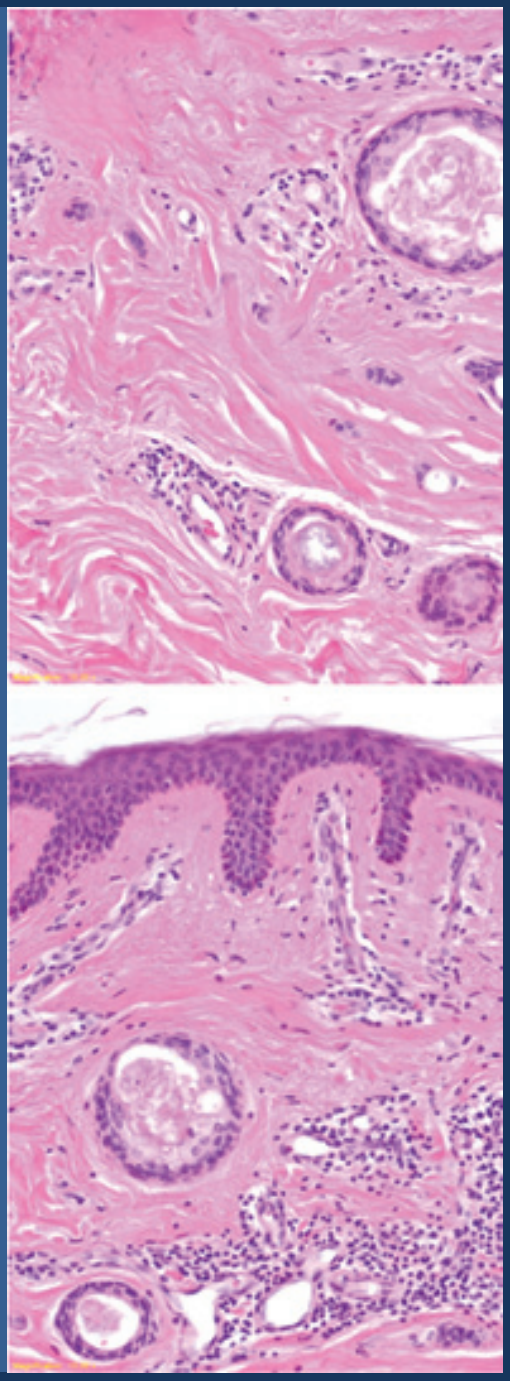

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Possible Influence of Oxidative Stress on Development of Raynaud Phenomenon in Patients With CREST Scleroderma Syndrome

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Abstract

CREST syndrome represents a form of scleroderma where the progressive autoimmune reaction is mainly manifested by the main symptoms, which make this acronym: calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly and teleangiectasia. Among the first affected organs is the skin followed by the excessive fibrosis manifested by the deposition of collagen in dermis. Reactive oxygen species (ROS) theory has been underlined as one of the main pathogenetic mechanisms and triggering factor in development of scleroderma. The present study was aimed at estimating the marker of lipid peroxidation products (MDA) in plasma of patients with CREST syndrome having manifested symptoms of both Raynaud syndrome and positive ANA antibodies. The lipid peroxidation (MDA) level was significantly higher in the patients who had CREST syndrome and Raynaud syndrome for less than 10 years compared to the patients suffering from Raynoud syndrome for more than 10 years ($p<0.05$). Both groups were found to have a significant MDA level increase ($p<0.001$) compared to the control healthy subjects. In conclusion, the relationship between lipid peroxidation (MDA level) and Raynaud syndrome appearance may emphasize the role of ROS produced by the ischemia-reperfusion injury as an early pathogenetic mechanism in CREST scleroderma syndrome.

Key words: CREST Syndrome; Scleroderma, Systemic; Raynaud Disease; Reactive Oxygen Species; Oxidative Stress; Lipid Peroxidation; Malondialdehyde

Introduction

Scleroderma represents a progressive autoimmune disease, where cutaneous and visceral fibrosis, together with vascular damage, lead to premature mortality. CREST syndrome represents a form of scleroderma where the autoimmune reaction is manifested by the main symptoms, which make this acronym: calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly and teleangiectasia. Among the first affected organs is skin and the excessive fibrosisis manifested by the deposition of collagen, followed by the infiltration of mononuclear cells in dermis (1-3). Increased thickening of small blood vessels is accompanied with the above mentioned symptoms. The pathological hallmark is the overproduction of the extracellular matrix (ECM). The main cells responsible for the excessive ECM synthesis are fibroblasts, myofibroblasts and perycites, stimulated mainly by transforming the growth factor-beta (TGF-β). Exctracellular matrix (ECM) proteins accumulated in dermis are the types I, III, IV, and VII of collagen and fibronectin. The extracellular glycosaminoglycans and proteoglycans are also found in ECM and in the intima of blood vessels (4, 5).

Reactive oxygen species (ROS) theory has been underlined as one of the main pathogenetic mechanisms and triggering factor in the development of connective tissue

diseases. The free oxygen radicals are liberated by activated inflammatory cells and may be results of ischemia reperfusion tissue damage. The association between oxidative stress and accelerated fibrosis may be a result of their interrelationship, where free oxygen radicals may stimulate fibroblasts migration, fibrous tissue synthesis and accumulation, while active fibroblasts may result in free oxygen radicals liberation (6, 7).

Lipid peroxidation represents a ROS action on unsaturated fatty acids, the main elements of phospholipids. Lipid peroxidation is finished by terminal reaction a production of malondyaldehyde (MDA). The polyunsaturated fatty acids of cell membranes and blood lipoproteins are particularly affected. Damaged cell membranes undergo a modification of their structure (altered fluidity), followed by the increased permeability and altered receptor function (8, 9).

Raynaud's phenomenon is a prominent symptom of CREST syndrome. It is a consequence of endothelial damage, followed by ischemia-reperfusion injury, vasospasm and the intimal proliferation (10). Dysfunction of blood vessels flow is accompanied with the procoagulant state, and because of the elevation of factor VIII-von Willebrand and thrombocytosis was documented. The observed changes are adrenergic and endothelin-dependent. Taken together, vasospasm, hypoxia and oxidative stress induce the ischemia-reperfusion injury. A pro-coagulant state and the impairment of endothelium-dependent relaxation are the main pathogenetic hallmarks due to the decreased bioavailability of nitric oxide-NO (11-13). The decreased NO bioavailability is the result of toxic peroxinitrite (ONOO) production, due to the excess of both NO and ROS and their rapid reaction (14).

The present study was aimed at estimating the marker of lipid peroxidation products (MDA) in plasma of patients with CREST syndrome having manifested symptoms of Raynaud syndome and anti-nuclear antibodies (ANA).

Patients and Methods

The study included 15 female patients with CREST syndrome, having the symptoms of Raynaud syndome for less than 10 years (4 patients) and more than 10 years (11 patients). Age-matched female healthy subjects (20) were used as control. The patients with CREST syndrome were diagnosed by the clinical and laboratory assessment according to the working classification of scleroderma (15). All patients were positive for ANA immune test. Raynaud phenomenon was documented by the recurrent spasms of small vessels, followed by the pallor, cyanosis and the reactive hyperemia in fingers and toes, triggered by cold or the emotional stress.

Results

Demographic characteristics of female patients are given in Table 1, which shows the duration of the disease and the appearance of Raynaud phenomenon. All patients were ANA

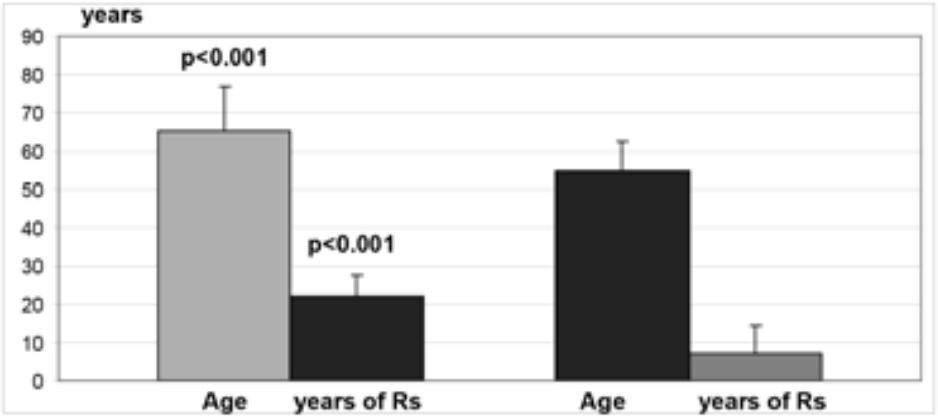

Figure 1. Age of patients and years of Raynaud syndrome duration in examined groups of patients with CREST syndrome

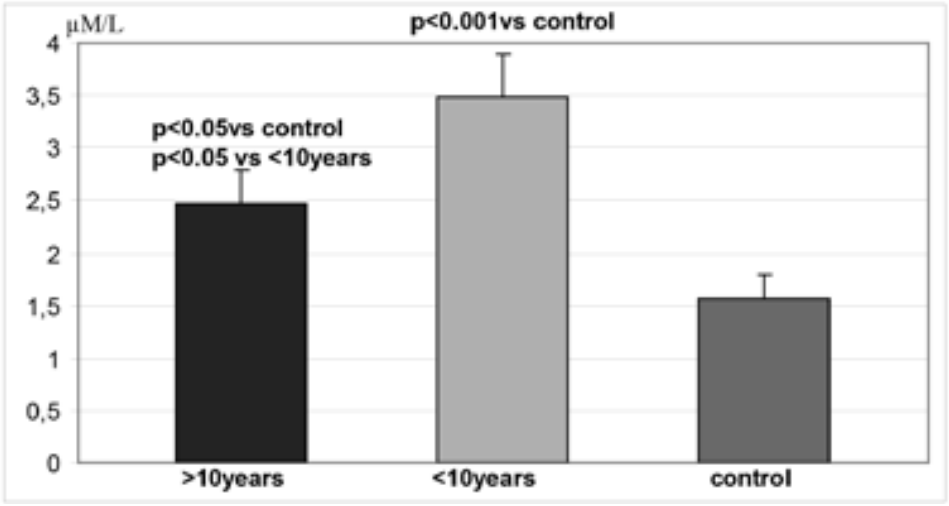

Figure 2. Lipid peroxidation (MDA) level in the examined groups of patients with CREST syndrome and the controls

positive. The level of MDA (μM/L) was almost two times higher in the patients suffering from scleroderma for less than 10 years than in the patients suffering from it for more than 10 years and in the control healthy subjects.

Discussion

In order to emphasize the importance of ROS in scleroderma development, some theories have been proposed regarding the increased ROS liberation (16). The main ROS are superoxide anion radical ($O2^{\cdot -}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\cdot}$) and peroxynitrite ($ONOO^-$) (17). ROS mechanism in the development of this disease seems to be the first triggering mechanism since the increased MDA level has been reported in the patients suffering from scleroderma for less than 10 years (Figure 1). In the period of limited blood flow intracellular protease activation is induced by prolonged ischemia, which may lead to interconversion of xanthine dehydrogenase to its ROS-producing form xanthine oxidase. Ischemia may induce a cell energy crisis followed by the accelerated degradation of ATP. Upon reperfusion with oxygen supply the last reaction catalyzed by xanthine oxidase is followed by the simultaneous liberation of uric acid and free radicals (superoxide anion radical and hydrogen peroxide) (18). Ischemia can also induce nitric oxide liberation (NO), which can react with superoxide anion radical, when the peroxinitre (ONOO) radical is formed, one of the ugliest ROS. In this way, the main pathogenetic mechanism of ROS liberation in CREST syndrome is the ischemia-reperfusion injury. The other mechanism of ROS liberation belongs to mitochondrial injury, where liberated superoxide anion radical in the mitochondrial respiratory chain can alter mitochondrial membrane permeability (19). Moreover, a very important enzymatic complex responsible for additional ROS production would be also NADPH oxidase (NOX) produced by phagocytic cells. The additional mechanism is the imbalance between pro and antioxidative defense with the decreased activity of the antioxidative defense enzymes, especially of catalase and superoxide dismutase (SOD) (13, 14, 20, 21). Increased oxidative stress can stimulate fibroblasts to produce ECM (accelerated fibrogenesis) and to secrete inflammatory cytokines. Liberated ROS can directly damage biomollecules, lipids, proteins and nucleic acids. Oxidativelly-modified unsaturated fatty acids derived from phospholipids proceed through the well-defined steps finally producing terminal product malondyaldehyde (MDA). The first step is the reaction of ROS with fatty acids and unstable fatty-acid radical production, peroxyl-fatty acid radical production and lipid peroxide. The process proceeds continually as a “chain reaction mechanism”. Membrane injury may cause cell apoptosis with subsequent tissue and organ injury (8, 9).

Conclusion

In conclusion, the inverse relationship of oxidative damage (MDA level) and disease appearance may reflect the role of ROS as an early pathogenetic mechanism of disease development and consequent ischemia-reperfusion injury in CREST scleroderma syndrome.

Abbreviations

ROS – reactive oxygen species
MDA – malondyaldehyde
TGF-β – transforming growth factor beta
ECM – extracellular matrix
NO – nitric oxide
ONOO peroxynitrite
NOx – NADPH oxidase (NOX)
SOD – superoxide dismutase

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Mogući uticaj oksidativnog stresa na razvoj Rejnoovog fenomena kod pacijenata sa CREST Skleroderma sindromom

Sažetak

CREST sindrom predstavlja jedan oblik skleroderme gde se progresivna autoimuna reakcija uglavnom manifestuje osnovnim simptomima koji čine akronim a to su calcinosis cutis, Rejnoov fenomen, ezofagealni dismotilitet, sklerodaktili i teleangiektazija. Među najugroženijim organima je koža, zatim prekomerna fibroza koja se mani-

festuje taloženjem kolagena u dermisu. Teorija o reaktivnim vrstama kiseonika (ROS – *reactive oxygen species*) navodi se kao jedan od osnovnih patogenih mehanizama i faktor okidač u nastanku skleroderme. Cilj ovog rada je procena markera produkata lipidne peroksidacije (MDA) u plazmi pacijenata sa CREST sindromom koji su ispoljili i simptome Rejnoovog sindroma i pozitivna ANA antitela. Nivo lipidne peroksidacije (MDA) bio je značajno viši kod pacijenata koji su imali CREST sindrom i Rejnoov sindrom manje od 10 godina nego kod pacijenata koji su patili od Rejnoovog sindroma duže od 10 godina ($p < 0,05$). U obe grupe pacijenata zabeležen je značajan porast MDA nivoa ($p < 0,001$) u poređenju sa zdravom kontrolnom grupom. Odnos između lipidne peroksidacije (MDA nivo) i pojave Rejnoovog sindroma može da naglasi ulogu reaktivnih vrsta kiseonika (ROS) koje stvori ishemijska reperfuziona povreda kao rani patogeni mehanizam CREST skleroderma sindroma.

Ključne reči: KREST sindrom; Sistemska skleroderma; Rejnaudova bolest; Reaktivne vrste kiseonika; Oksidativni stres; Lipidna peroksidacija; Malondialdehid

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Furuncular Botfly Myiasis – A Case Report

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Abstract

Botfly myiasis is an infestation of the skin or a body cavity by developing larvae of Dermatobia hominis, one of the most common flies that cause human infestation among the local population, in regions ranging from Mexico into South America and in travelers. The life cycle starts when a female fly glues the eggs to the vector, a blood-sucking arthropod, which carries the unhatched larvae to the susceptible host. A case of furuncular botfly myiasis in an 85 year-old female with recent travel to Belize is presented here to highlight the parasite life cycle and review the different treatment options.

Key words: Skin Diseases, Parasitic; Myiasis; Travel; Diptera; Scalp Dermatoses; Insects; Belize; Larva

Case Report

An 85 year-old Caucasian female presented to dermatology clinic for evaluation of a growing nodule on the scalp that was accompanied by intermittent stabbing and shooting pain. Prior to the onset of symptoms, the patient had traveled to India and Belize, returning to the United States just a few weeks prior to presentation. Initial examination in clinic showed a 1 cm subcutaneous nodule with overlying linear erosion and hemorrhagic crust (Figure 1A). The lesion was thought to be a cyst and thus she was scheduled for excision.

Examination in procedure clinic showed a 2.5 cm subcutaneous nodule with a central 1 mm “punched-out” opening. After the area was prepped and anesthetized, a standard fusiform incision was made over the subcutaneous nodule. Upon removal of the overlying skin, a 1.2 cm yellow striated larva was identified (Figure 1B). The larva was alive and moving at the time. The specimen was then sent to microbiology, and the larva was identified as *Dermatobia hominis* by the characteristic rows of posteriorly directed spines (Figure 2).

The patient was empirically started on cephalexin 500 mg twice a day for a total of ten days. A head CT was obtained and did not show evidence of skull or sinus involvement. At one week follow up, she was healing well and reported resolution of the stabbing and shooting pain over the area.

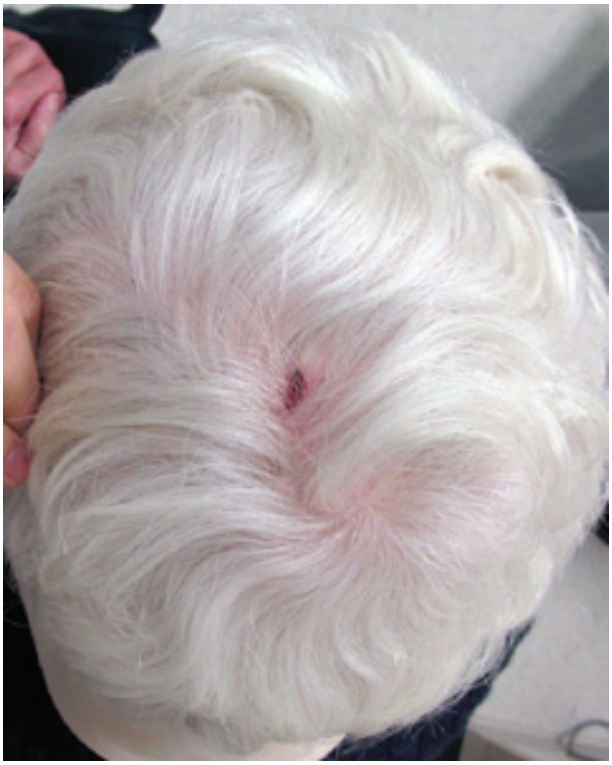

Figure 1A. 1 cm subcutaneous nodule with overlying linear erosion and hemorrhagic crust

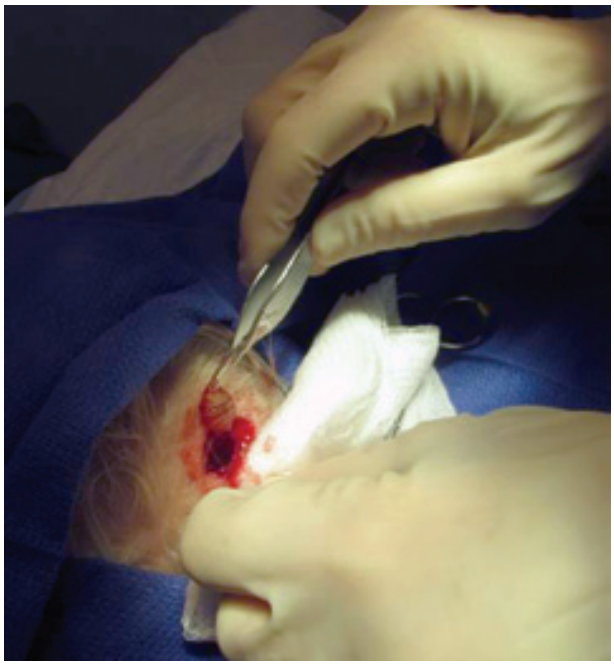

Figure 1B. Removal of a 1.2 cm yellow striated larva from fusiform opening

Discussion

Geographic locations of cutaneous myiasis are usually limited to the tropical and subtropical areas, including countries in Central America, South America, and Africa. It is very uncommon within the United States, and the majority of patients had recent travel to topical areas (1). *Dermatobia hominis* (human botfly) and *Cordylobia anthropophaga* (African tumbu fly) are the two most common causes of furuncular myiasis worldwide. Patients with open wounds can also develop wound botfly myiasis. Cavitary myaisis is possible in cases when larva is deposited near facial orifices, where it can then burrow deeper to involve the nearby sinuses (2).

Figure 2. *Dermatobia hominis* with characteristic rows of posteriorly directed spines

The life cycle of a botfly involves a blood-sucking arthropod as well as a warm-blooded host (mammal or avian). The adults of *D.hominis* are free living. During breeding, they lay eggs on the bodies of mosquitos, where they are cemented via a glue-like substance. Larvae develop within the eggs and remain there until the arthropod comes in contact with a warm-blooded host during feeding. Once in contact with the host, the larva penetrates into the skin and remains in a subdermal cavity for the next 5 to 10 weeks where it feeds on the host as it matures. Typically, these present as boil-like lesions with a central punctum which functions as a breathing hole for the larva. Once the larva matures, it burrows through the breathing hole and drops to the ground where it pupates and becomes a free living botfly (3).

During their course of maturation, botfly myaisis usually does not pose any danger to the host. Patients may experience pruritus, sensations of movement and lancinating pain, which may be explained by rotational movement of the larvae and its rows of hooklets (4). Secondary bacterial infections with *Staphylococcus* and Group B *streptococcus* have been reported (5, 6). Overall, furuncular myiasis is a self-limited infestation as the larvae will eventually leave the host; however, leaving the parasite to perform its natural cycle is generally not recommended (2).

There are several methods used for the extractions of the botfly larvae. Traditional folk remedy calls for a strip of bacon over the central punctum to suffocate the larvae, which forces it to surface for air over the course of several hours, at which point the larva can then be gently extracted with a forceps. This can also be accomplished using petroleum jelly, liquid paraffin, beeswax, or even nail polish (7). Other authors have advocated the use of 1% lidocaine to paralyze the parasite, and liquid nitrogen to stiffen the larvae for easier extraction (8, 9). In most cases, surgi-

cal excisions and extractions are unnecessary, but can be done under local anesthesia if other methods of extractions are unsuccessful (10). Antibiotics are recommended if there are signs or symptoms of secondary bacterial infection (2).

Conclusion

Botfly myiasis represents an interesting parasitic infection transmitted by blood-sucking arthropod. Its unique life cycle leads to delayed symptom onset and diagnosis. It is a common condition in tropical and subtropical continent though rarely seen in the more temperate climate except for travelers. We present this case of furuncular myiasis for clinical interest.

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Furunkularna botfly mijaza – prikaz slučaja

Sažetak

Botfly mijaza je infestacija kože ili telesne šupljine larvama Dermatobia homini, jedne od najčešćih muva koje izazivaju infestaciju kod lokalnog stanovništva, u regionima od Meksika do Južne Amerike i kod putnika. Životni ciklus počinje kada ženka položi jaja na vektor, insekt krvopiju, koji prenosi neizležene larve na podložnog domaćina. Ovde je prikazan slučaj furunkularne botfly mijaze kod žene stare 85 godina koja je nedavno putovala u Belize da bi se objasnio životni ciklus parazita i dao uvid u različite opcije lečenja.

Ključne reči: Parazitske kožne bolesti; Myiasis; Putovanja; Dvokrilci; Dermatoze kože glave; Insekti; Belize; Larve

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Inherited Epidermolysis Bullosa – A Case Report of Several Family Members in Three Generations

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UDC 616.591-002.1-056.7

Abstract

Inherited epidermolysis bullosa (IEB) is a genodermatosis transmitted in either autosomal dominant or autosomal recessive manner. The disease is characterized by the development of blisters, erosions, scars, nail dystrophy and scalp abnormalities. Our case report has included four members of one family in three generations with manifested disease. Our 25-year-old female patient presented with a few eroded, crusted, nummular lesions localized on the dorsal plate of interphalangeal joints of fingers, elbow and knee skin, while anonychia was found on her digits. Our youngest patient (her 3.5-year-old son) presented with the lesions in the form of blisters filled with serous fluid, erosions, recent scars and atrophy. Some atrophic scars on the elbow and knee skin were found in our patient's younger brother, aged 16. The 46-year-old mother of our female patient had nail dystrophy on her hands accompanied by the toenails absence. Pediatric geneticist created the pedigree chart which showed autosomal dominant inheritance pattern with complete expressivity and penetrance. Further diagnostics was not done because the family was not interested.

Key words: Epidermolysis Bullosa Simplex; Skin Diseases, Genetic; Skin Diseases, Vesicobullous; Signs and Symptoms; Case Reports

Introduction

Inherited epidermolysis bullosa (IEB) belongs to a group of genodermatoses transmitted in either autosomal dominant or autosomal recessive manner, characterized by blistering spontaneously or following minor trauma (1). It encompasses four major forms: simplex, junctional, dystrophic, Kindler syndrome and over 30 different clinical phenotypes (1-3). IEB can result from mutations within genes that encode structural proteins sited in epidermis, dermo-epidermal junction or uppermost papillary dermis, resulting in cleavage and blister formation (2). The disease is characterized by the development of blisters, erosions, scars, scalp abnormalities and nail dystrophy. The clinical manifestations of IEB vary in accordance with the type of disease, and diagnosis could be determined only by skin biopsy and immunofluorescence or electron microscopy (1).

Case Report

A 25-year-old female was referred for dermatologic examination with a suspicion of a drug allergy. On admission, a few eroded, crusted, nummular lesions localized on the dorsal plate of interphalangeal joints of fingers, elbow and knee skin were present. Besides, anonychia on the feet was also found (Figure 1). Her personal history revealed that the skin changes first appeared two days after birth. The skin lesions were localized on the right hand fingers, shins and around external malleolus of the ankles. The patient noted some improvement after the age of 10 when the blisters occurred more rarely; however, the condition deteriorated during summer. The oral cavity was not affected throughout the disease. The family history revealed that the same lesions were present in our patient's mother, younger brother and one son from her twin pregnancy. Out of the thirty members of the patient's great-grandmother's family, 13 suf-

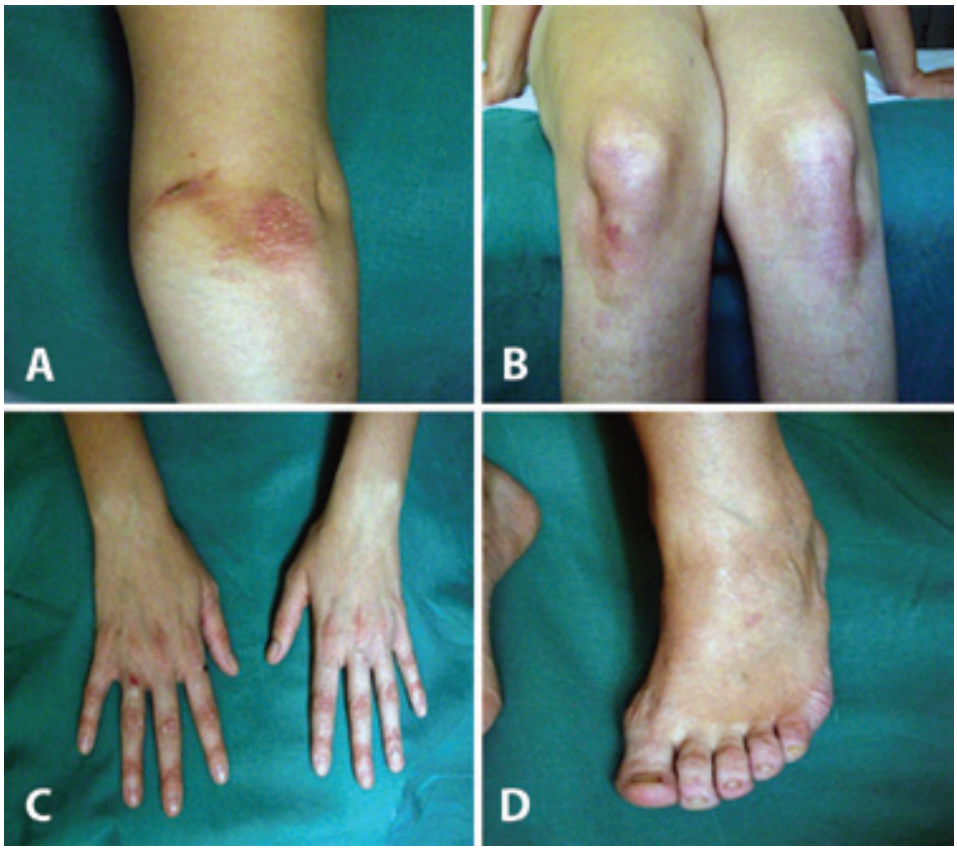

Figure 1. Our female patient: A) eroded and crusted lesions on the elbows; B) eroded and crusted lesions on the knees; C) eroded, crusted, nummular lesions localized on the dorsal plate of interphalangeal joints of fingers; D) anonychia on the feet

fered from EBS, while the rest of relatives had had atopic dermatitis. The relatives of our patient with similar skin condition were thoroughly examined. Her 3.5-year-old twin son presented with erythematous recent scars, having atrophic appearance. Similar lesions with scarring and ulcerations and blisters filled with serous fluid sized 2 cm in diameter were found on the right elbow. In addition, fresh erosions, crusts and milia on the feet and epithelized erosion on lateral malleolus were visible (Figure 2). Our patient's younger brother, aged 16, was found to have atrophic scars with slight central hypertrophy on the elbow and knee skin (Figure 3) with apparent anonychia. The mother of our patient, aged 46, presented with nail dystrophy on her hands accompanied by the toenails absence (Figure 4).

A pediatric geneticist constructed the pedigree chart in order to interpret autosomal dominant inheritance pattern with complete expressivity and penetrance (Diagram 1). The patient as well as the members of her family refused further diagnostics.

Discussion

Inherited epidermolysis bullosa was first described in 1870 by von Hebra, whereas the current title *epidermolysis bullosa hereditaria* was given by Koebner in 1886. Twelve years later, in 1898, Hallopeau identified a distinction between the clinical presentation of simplex and dystrophic forms. Furthermore, in 1962, Pearson established the precise characterization of three major forms (simplex, junctional, dystrophic) by means of transmission electron microscopy. In the following decades, due to the development in science, technology and technical achievements, additional IEB phenotypes were described. Moreover, monoclonal antibody studies suggest the existence

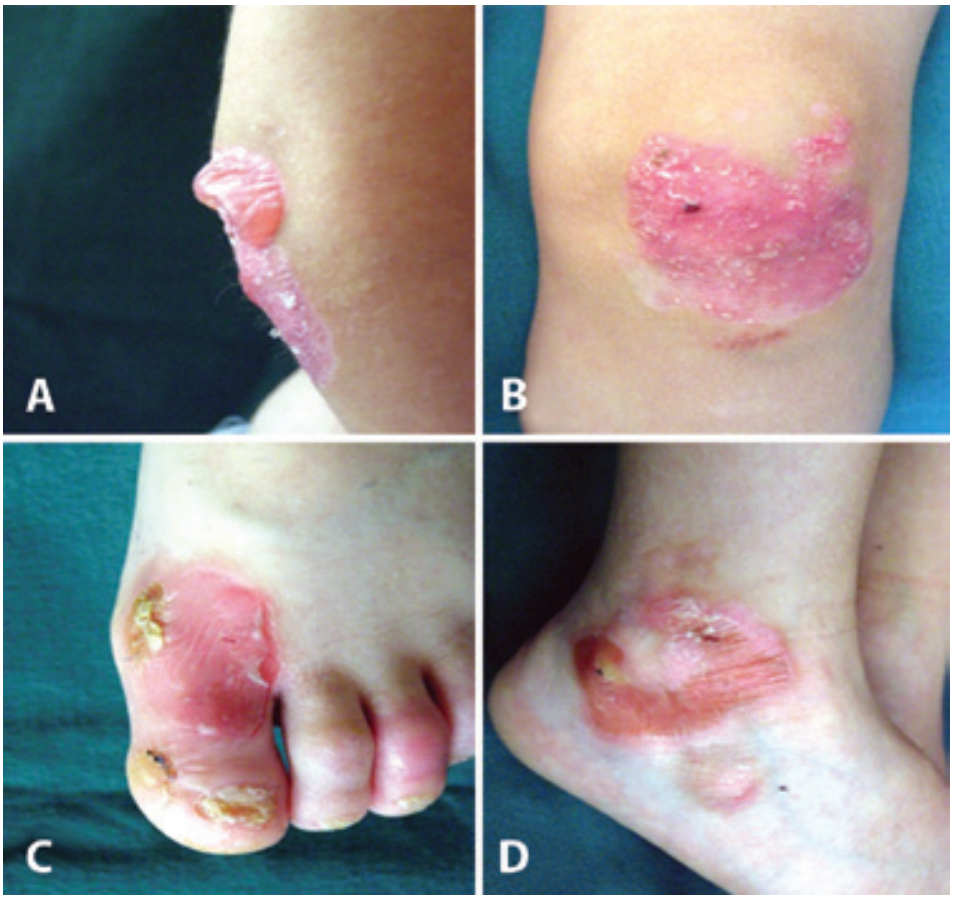

Figure 2. Her son: A) recent scars and ulcerations and blister filled with serous fluid sized 2 cm in diameter resided on the right elbow; B) recent atrophic scar on the knee and marginal milia; C) fresh erosions, crusts and milia on the feet; D) epithelialized erosion on the lateral malleolus

of specific protein defects in each type and subtype (2). Depending on the ultrastructural level of cleavage, the antigenic alteration in the skin, inheritance pattern and clinical features, IEB is divided in epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), dystrophic epidermolysis bullosa (DEB) and Kindler syndrome (2, 3).

EBS is transmitted in the autosomal dominant manner as it happened in our patient and her relatives. Besides, EBS could be inherited in the autosomal recessive manner resulting in a severe clinical form associated with muscular dystrophy and pyloric atresia. In addition to the generalized form known as Koebner subtype, there have been reports on the localized form named Weber-Cockayne subtype that presents most often with a milder form of IEB as well as EBS herpetiformis named Dowling-Meara subtype. In all subtypes, intraepidermal blisters are developed soon after birth. Because of the early appearance of blisters and generalized distribution of skin lesions in our patient as well as in other patients included in this case report, our opinion was that all of them might have suffered from Koebner subtype. However, milia were visible on the lower extremities in our youngest patient, the 3.5-year-old son of our female patient. For that reason and since no biopsy for histopathological examination had been performed, we considered other forms of IEB with clinical picture of milia. At first, we thought it was DEB that can be transmitted in either autosomal dominant or autosomal recessive manner (3), characterized by an early appearance of blisters with tendency of localization during maturation. Dominant dys-

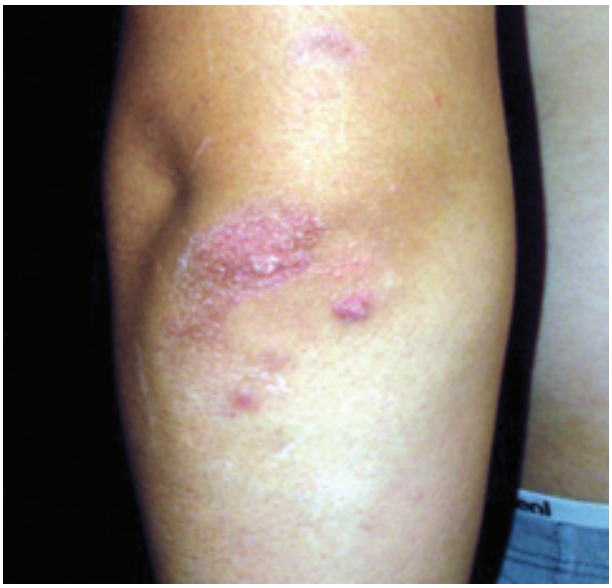

Figure 3. Her brother: atrophic scars with slight central hypertrophy on the elbow

trophic epidermolysis bullosa (DDEB) includes two subtypes, more often form, Cockayne-Touraine, with acral distribution of lesions and rarely affected oral cavity, and Pasini variant manifesting excessive oral lesions and severe blistering. Nail dystrophy or anonychia is common in both entities, with distinctive scarring: Cockayne subtype is characterized with hypertrophic scars, Pasini variant results in atrophic scars. Multiple milia as an isolated skin manifestation without a previous blister formation could be a primary manifestation of DDEB (4). Due to the fact that neither of our patients presented with oral lesions, and according to the literature data revealing the rare occurrence of atrophy and milia in Koebner subtype of EBS (5), we suggested the possible existence of this form of EBS. In this subtype, the wound almost always heals with no scarring, while the aggravation may develop in summer as it happened to our patient. Nail dystrophy may occur in severe forms of disease. Following the examination of all patients it may be concluded that clinical expressivity of lesions declines with years. The literature describes frequency of Koebner form with prevalence of about 2 per a million (6).

The diagnosis can be determined on the basis of anamnesis, clinical characteristics, histopathological analysis of the biopsy specimens (a recent blister) and by antigenic mapping and identifying specific agents responsible for pathogenic mutations (7). In addition to this, in their study, Tampoia et al. have suggested that the IL-6/IL-10 ratio can be used as a prognostic and predictive marker of the severity of IEB and it has been reported that this ratio is statistically higher in recessive DEB than in EBS and healthy subjects (8). Apart from immunofluorescence antigen mapping, immunohistochemistry staining could be used as a diagnostic method especially in resource-limited settings (9). Histopatho-

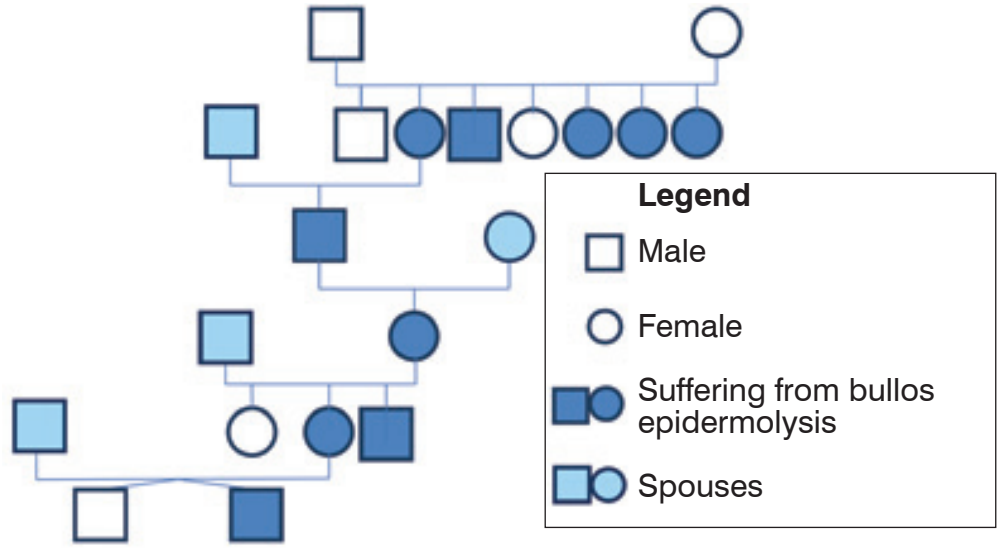

Diagram 1. Pedigree chart

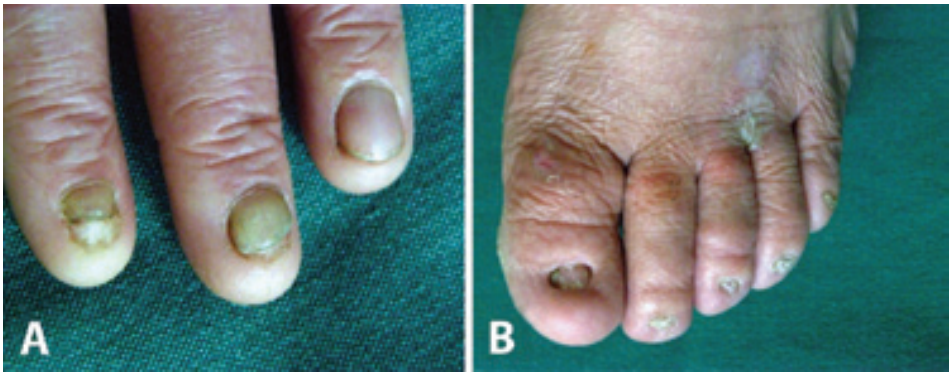

Figure 4. Mother: A) nail dystrophy on the hands; (B) anonychia on the feet

logical examination was not performed because the patient did not consent to it, therefore we do not have evidence of cleavage level, although it is known that EBS is characterized by intraepidermal blistering.

There is no specific therapy for any form of IEB. Treatment of IEB is focused on preventing mechanical trauma and infections (2). Treatment of newborns is managed by neonatologists and dermatologists in intensive care units. The aims of therapy are prevention of appearance of new lesions by intensive care, gentle manipulations, soft padding and adequate, easily removed clothes. A number of dressings are available for wounds. As a general rule, those that are non-adhesive and easily changed should be applied to the lesions (2). Topical and systemic antibiotics should be administered for short periods according to the recommendations in order to avoid bacterial resistance and sensitization (1). Patients suffering from severe forms require attentive monitoring and additional interventions such as different medical, surgical, dental, nutritive and psychological consultations (1). All potential parents with positive family history should be referred to genetic counselor so as to establish the diagnosis, type and subtype of IEB. EBS does not generally require invasive prenatal diagnosis. However, chorionic villus sampling is essential in recessive forms (3).

Conclusion

In spite of a small number of patients affected by inherited epidermolysis bullosa and low demand for examination of patients suffering from mild forms of the disease, the implementation of available diagnostic procedures is required. Monitoring, genetic counseling and support in emotional suffering, physical pain and economic burden must be provided to patients and their families.

Abbreviations

IEB – inherited epidermolysis bullosa
EBS – epidermolysis bullosa simplex
JEB – junctional epidermolysis bullosa
DEB – dystrophic epidermolysis bullosa
IL6 – interleukin 6
IL10 – interleukin 10

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Nasledna bulozna epidermoliza – prikaz nekoliko članova porodice iz tri generacije

Sažetak

Epidermolysis bullosa hereditaria je genodermatoza koja se nasleđuje autozomno dominantnim ili autozomno recesivnim putem. Bolest se manifestuje stvaranjem bula, erozija, ožiljaka, distrofijom nokatnih ploča i abnormalnostima skalpa. Prikazujemo četiri člana jedne porodice u tri generacije kod kojih se bolest manifestovala. Kod naše bolesnice (25 godina) postojale su erodovane, krustozne, numularne promene na dorzumima interfalangealnih zglobova prstiju šaka, na koži laktova i kolena, dok je na prstima postojala anonihija. Kod najmlađeg bolesnika (sin naše bolesnice, 3,5 godina) uočavale su se promene na mestima pritiska u vidu bula ispunjenih bistrim sadržajem, erozija, svežih ožiljaka i atrofije. Kod brata naše bolesnice (16 godina) bili su prisutni atrofični ožiljci na laktovima i kolenima. Majka naše bolesnice (46 godina) imala je distrofične nokatne ploče na šakama uz anonihiju na stopalima. Genetičar je izradio porodično stablo iz kog se vidi da se bolest nasleđuje autozomno dominantno uz potpunu ekspresivnost i penetrantnost gena. Dalja dijagnostika nije rađena, jer porodica nije bila zainteresovana.

Ključne reči: Bulozna epidermoliza simpleks; Genetske kožne bolesti; Vezikobulozne kožne bolesti; Znaci i simptomi; Prikazi slučajeva

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Indeterminate Cell Histiocytosis – Case Report and Review of Literature

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Abstract

Introduction. Indeterminate cell histiocytosis is a rare proliferative disorder of indeterminate dendritic cells, reported in only 50 case reports so far. It is clinically presented as yellow, red or brown papules and nodules that appear in otherwise healthy adult individuals. Indeterminate cells are distinct dendritic cells of the skin that have ultrastructural similarities to the epidermal Langerhans cells but do not contain the characteristic Birbeck's granules and they are also langerin-negative, unlike LCH. Indeterminate cell histiocytosis is an exceptional entity with variable clinical, histopathologic or immunohistochemical findings, sharing morphologic and immunophenotypic features with both Langerhans- and non-Langerhans cell histiocytoses. Case Report. We present a case of indeterminate histiocytosis in a 77-year-old man with 3-year history of asymptomatic, multiple reddish and brown papules and nodules over the entire body, including the oral mucosa. Skin biopsy was done, and histopathological analysis with immunohistochemistry was performed. The positive ICH staining of cells for CD68, CD1a, and S-100 enabled us to diagnose ICH in our patient. Also, *BRAF V600E* mutation was detected in tumor tissue. The treatment was started with methotrexate that was effective for 6 months, but due to the disease recurrence, further therapy with thalidomide was advised, without effect. Conclusion. Indeterminate histiocytosis is a rare disease, therefore no standardized treatment has been established and the treatment options are limited.

Key words: Histiocytosis; Dendritic Cells; Langerhans Cells; Skin Neoplasms; Rare Diseases; Treatment Outcome

Introduction

Indeterminate cell histiocytosisis is an extremely rare variant of cutaneous histiocytosis which can be distinguished from Langerhans cell histiocytosis by three important characteristics: the lack of Birbeck granules on ultrastructural study, the absence of epidermotropism on histopathology, and the lack of extracutaneous involvement. These cells evidently express both Langerhans cell and monocyte/macrophage markers (1). It is clinically characterized by multiple asymptomatic yellow, red, or reddish brown papules and nodules that can be found in otherwise healthy individuals (2).

Indeterminate cells may present as dendritic cells histologically and immunohistochemically resembling Langerhans cells because of their expression of CD1a and S-100, but without the definitive Birbeck granules (3). The real relationship between the two types of cells has been a matter of controversy since their original finding. Because of the fact that indeterminate cells migrate into the epidermis, some authors share an opinion that their organelles may modify and may become LC (1). On contrary, in cell culture, LC usually lose Birbeck granules, resembling indeterminate cells and therefore some authors have also postulated that finding of the indeterminate cells may represent a more mature form of LC (2-4). Because of their immunophenotypic similarity, indeterminate cells are considered to be related to Langerhans cells. By definition, they express S-100 protein and CD1a, but in contrast to LCh, they do not express langerin (CD207). Furthermore, these tumors do not express any of other histiocytic and dendritic specific markers including CD163, CD30, CD21, CD23, and CD35. They are variably positive for CD45, CD68, lysozyme, and CD4 (4-6).

ICHs are extremely rare neoplasms of indeterminate cells and have only been re-

ported in less than 50 cases. In most cases the patients have been presented with one or more papules, nodules, or plaques on the trunk, face, neck or extremities. Diagnosis is established based on the histopathological analysis of the lesion. In case of localized disease, further work-up with systemic CT scans and bone marrow biopsy is not indicated (5, 6). Treatment of the disease is not standardized due to its rarity. The treatment options include: systemic chemotherapy, PUVA, narrowband ultraviolet B phototherapy, thalidomide, pravastatin and low dose methotrexate. The disease course is usually not progressive. Recently, BRAF mutations were found in patients with certain forms of histiocytoses and treatment with BRAF inhibitors was found to be effective in some of these patients.

Case Report

A 77-year-old man presented with a 3-year history of asymptomatic multiple brown and reddish papules and nodules over the trunk and extremities and in the oral mucosa

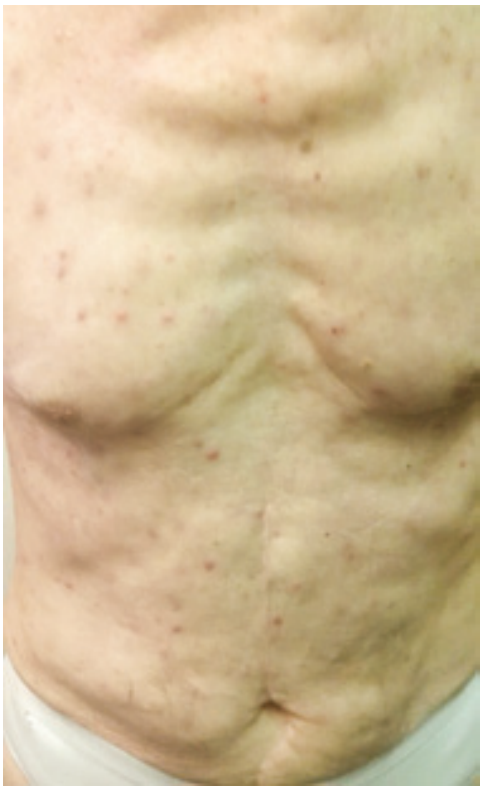

Figure 1. Asymptomatic multiple brown and reddish papules and nodules over the trunk

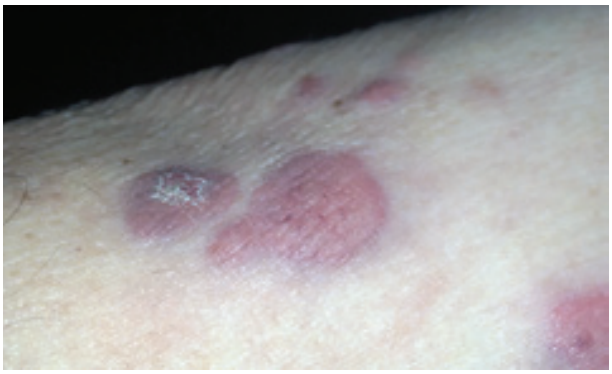

Figure 2. Reddish papules and nodules

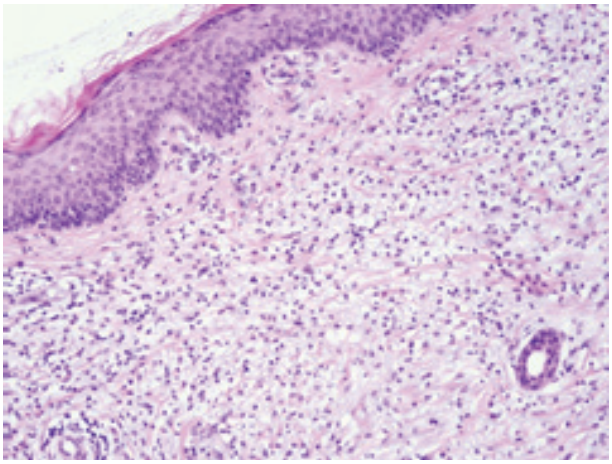

Figure 3. Histopathology revealed a diffuse, moderately mononuclear, monomorphous, nonepidermotropic infiltrate of large epithelioid cells in the upper dermis (stain type–Hematoxylin and eosin; original magnification: 100).

(Figures 1, 2, 3). The first skin biopsy was nonspecific with superficial dermal infiltrate of lymphocytes. The patient was treated with systemic corticosteroids and colchicine without response, and then with indometacin, desloratidine, dapsone and azathioprine, again without effect. The patient's history, physical examination, and routine laboratory tests did not show any systemic involvement. The erythrocyte sedimentation rate (ESR) was increased and the C-reactive protein was elevated *(*SE 125 mm/h; CRP 36,1 mg/l), as well as the level of lactate dehydrogenase (256 U/L). The results of serum protein electrophoresis (SPEP), ANA, anti-HIV antibody, complete blood count, total proteins, serum albumin, bilirubin, cholesterol, triglycerides,

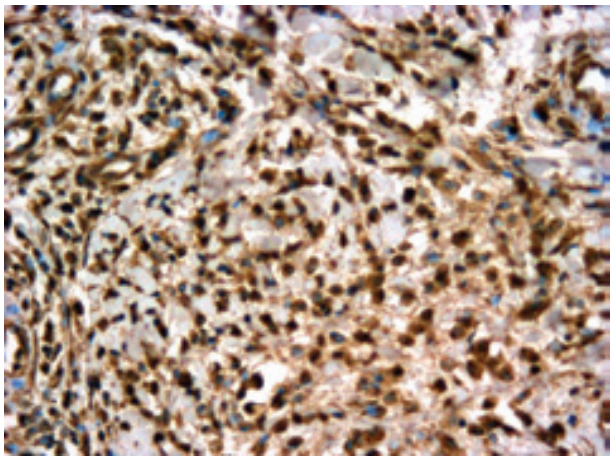

Figure 4. Immunohistochemical examination showed expression of S-100 (original magnification: 300)

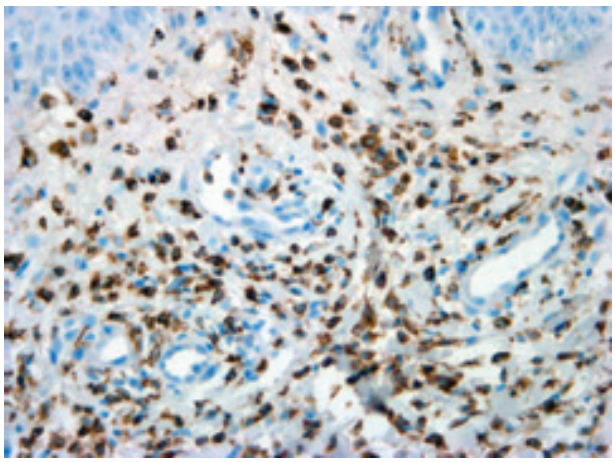

Figure 5. Immunohistochemical examination showed expression of CD 68 (original magnification: 300)

AST, ALT, CK, RF, a-CCP, IgM, IgA, IgG, C3, C4, PSA, f/t PSA were within normal range. Chest radiography, radiography of the joints of hands and feet, and ultrasound imaging of the abdomen and peripheral lymph nodes showed normal results. Skin biopsies were repeated and histological findings of the second and the third skin biopsies were also nonspecific, while diffuse, moderately active mononuclear infiltrate of small hystiocitic cells was found in the upper dermis on the forth biopsy. Histiocytes were kidney-shaped, segmented and partly with the light nucleus. Immunohistochemical examination showed histiocyte cell expression of S-100 protein and CD68, while no expression was found for

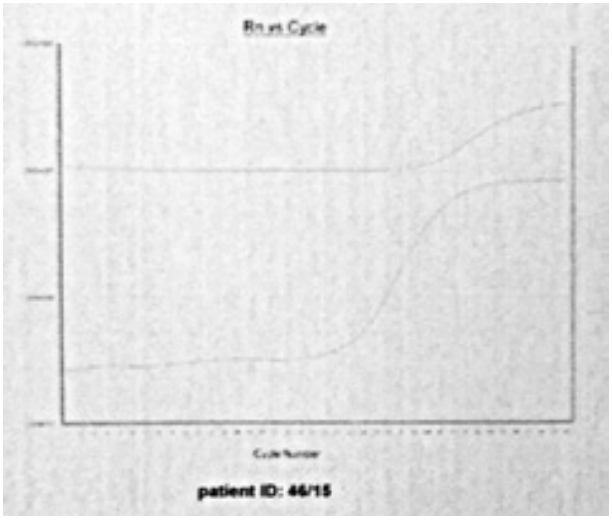

Figure 6. The genetic analysis of BRAF mutation was done using real-time PCR

CD3, CD4, CD8, CD10, CD20, CD30 and CD1a (Figures 4, 5). Also, somatic mutation in the *BRAF gene (BRAF^{V600E})* was identified (Figure 6). Bone marrow biopsy was done and showed normal result, and TCR and BCR rearrangement analysis revealed polyclonal pattern in the bone marrow. B clonality testing in the skin tissue showed IgH monoclonal B cell infiltrate, while it was polyclonal in the peripheral blood. TCR rearrangement in the skin and peripheral blood revealed polyclonal pattern. CT of the chest, abdomen and pelvis showed normal results.

The diagnosis of indeterminate cell histiocytosis was made based on clinicopathologic and immunohistochemical findings. The patient was treated with methotrexate with regression of skin lesions (Figures 7, 8). However, after six months, a new flare-up of generalized reddish nodules was evident, so the treatment with thalidomide was advised, but with no response. The patient was lost to follow-up and died one year later.

Discussion

Histiocytoses are a heterogeneous group of disorders characterized by the proliferation and accumulation of the cells of mononuclear-macrophage system and dendritic cells, originating from neutrophil/macrophage lineage CD34þ progenitor cells in the bone marrow (3-7). Langerhans cells (LC), the proto-

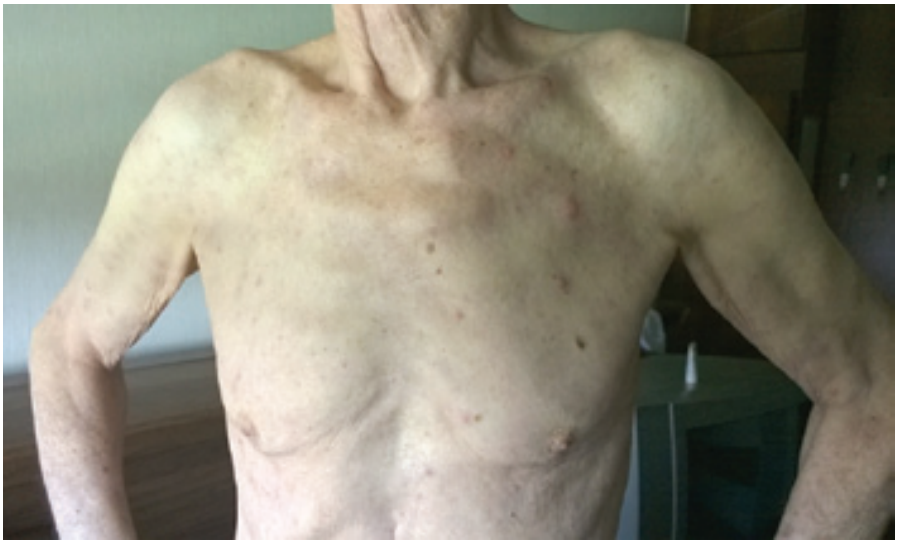

Figure 7. After treatment with methotrexate

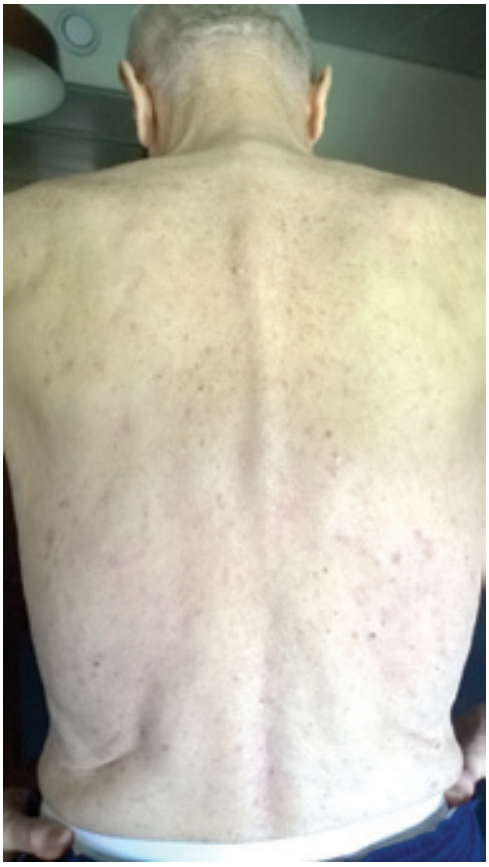

Figure 8. After treatment with methotrexate

type of dendritic cells are characterized by strong immunoreactivity for S100 protein and CD1a. In addition, they show Birbeck granules, a defining ultrastructural feature of LC. Monocytes/macrophages are defined by markers, such as KP1 (CD68) or Ki-M1p.2 Ultrastructurally, they show phagolysosomes, but no Birbeck granules. Occasionally, LC stain for KP1 (CD68), but then with less intensity than macrophages. Conversely, macrophages are usually negative for the LC markers, S-100 protein and CD1a. Various hypotheses regarding the relationship between LC and IC have been proposed – i.e. ICs are either immature precursors of LC and LC are precursors of IC or both are independent types of dendritic cells.

Less than 50 cases of ICH have been reported so far. The disease is a proliferative disorder of dendritic cells that has both immunophenotypic features of Langerhans cells (CD1a and S-100-positive) and macrophages (CD68-positive). Birbeck granules that characterize Langerhans cells cannot be detected by electron microscopy in ICH histiocytes. Nowadays, it is proposed that ICH could be a non-Langerhans' cell histiocytosis variant, but its pathogenesis has remained unknown (5-8).

Two theories on pathogenesis of this rare disorder have been presented in the literature. The first is in regard to the cases of ICH arising de novo. Since the cell of the origin is thought to be the Langerhans cell, it is believed that indeterminate cells are a phase in the development of the Langerhans cell. However, it is still uncertain whether or not the indeterminate cells are immature Langerhans

cells that have not developed Birbeck granules or that they are Langerhans cells that have lost their Birbeck granules in their migration towards a lymph node. The second theory relates to those cases evolving from a preexisting B cell lymphoma. Although the cell of origin in ICH is from the common myeloid progenitor lineage, some cases of ICH have arisen in association with low grade B-cell lymphoma, leading some authors to speculate that ICH may be the result of B-cell dedifferentiation, caused by a so far unknown mechanism (8, 9).

Histologically, there is a diffuse dermal infiltration of cells with irregular nuclear grooves and clefts that resemble Langerhans cells. These cells are without Birbeck granules on electron microscopy and desmosomes; however they contain cell processes. On immunohistochemistry, these cells are S100 and CD1a positive and are negative for CD21, CD23, CD35, langerin, and B and T cell markers (13). Although langerin immunostaining was not available at the time of diagnosis, the histopathological analysis with immunohistochemical profiling was consistent with the diagnosis of ICH in our patient.

Recently, a somatic mutation in the *BRAF gene (BRAF V600E)* was identified in Langerhans cell histiocytosis and Erdheim-Chester disease tissue infiltrates, suggesting a common origin of both histiocytoses and leading to the reclassification of these disorders (12-14). The presence of BRAF mutation in indeterminate cell histiocytosis was also described in case reports, as well as in our patient (5, 10).

ICH is a localized or generalized, and almost exclusively cutaneous disease (9-12). A study done by Ratzinger et al reported on 18 patients with indeterminate cell histiocytosis who were followed up from six months to seven years after their initial diagnosis. In this study, the majority of patients with the localized disease experienced complete resolution after excision. The disease tended to become stable in the patients having more widespread lesions, even without specific treatment. Only two patients developed a slow progression of skin lesions. Two patients in this cohort developed a systemic disease, one with lesions of the eye and the other with lesions of the bone. Neither deaths nor other serious illnesses were reported as related to ICH in this study, thus supporting the premise that ICH runs a benign course, regardless of the skin lesion distribution (solitary or diffuse variant). One case report documents the remission and recurrence without treatment but there are reports of remission and recurrence also with chemotherapy. Even though it is rare, there are cases with systemic involvement,

Table 1 Treatment modalities for ICH and their effects in previous case reports

Number of patients	Immunostaining of the dermal cell infiltrate	Treatment modality	Treatment efficacy	Reference
1	CD1, CD68, S100	nbUVB	Short term	Nogueira Zerbini MC, 2016. (20)
1	CD1, S100	nbUVB	Complete	Ishibashi M, 2008. (21)
1	S100-	nbUVB	Complete	Bard S, 2011. (22)
1	S100, CD68	methotrexate	Complete	Fornier J, 2011. (23)
1	S100, CD 1-	thalidomide	Complete	Toth B, 2012. (24)
1	CD1, S100, CD68	thalidomide	Complete	Ventura, 2010. (27)
1	CD1, S100	EBT+ 2-chlorodeoxyadenosine	Complete	Adam Z, 2017. (26)
1	CD1, S100	PUVA	Without effect	Adam Z, 2017. (26)
1	CD1, S100, CD68	pravastatin	Complete	Burns MV, 2011.(28)
1	S100, CD68	methorexate thalidomide	Short term Without effect	Vojvodic A, 2018.

Abbreviations: nbUVB- narrowband UVB, PUVA- psoralen and UVA, EBT- electron beam therapy

resistant to the chemotherapy with the lethal outcome. Our patient was treated for 6 months with methotrexate with a temporary resolution of skin lesions, but with a further relapse and unsuccessful treatment with thalidomide. He was lost to follow-up and he died a year later, and further details from his medical history were unavailable.

There is no standardized treatment for ICH (Table 1) (14-17). As ICH has a benign clinical course, conservative management is the best approach. In some cases, skin lesions were resolved spontaneously. Some treatments that have been used with various success include systemic chemotherapy, PUVA, narrowband Ultraviolet B, thalidomide, pravastatin and low dose methotrexate with a generally good therapeutic response. Chemotherapy must be used for aggressive cutaneous ICH, which involves over 50% of the body surface area and lasts for at least 6 months with no spontaneous resolution and new appearing lesions. There are four reports of ICH association with malignancies: one case of mast cell leukemia, another patient with myelomonocytic leukemia, and two cases with low grade B-cell lymphomas (8, 14, 18). Our case was not associated with hematologic malignancy, which was ruled out. Our patient's clinical history, physical examination and routine laboratory tests did not show any systemic involvement. TCR and BCR rearrangement analyses revealed polyclonal infiltrate in the bone marrow. Monoclonal IgH B cell infiltrate was found in a skin sample, while it was polyclonal in the peripheral blood, which was described previously in these entities (19).

Conclusion

Indeterminate cell histiocytosis is a rare disorder of cutaneous histiocytic/dendritic system development, but the true pathogenesis is still unknown. It can be found mostly in adults and must be diagnosed only on the basis of a thorough clinical investigation, repeated skin biopsies, histopathological, immunohistochemical and molecular analysis. In our patient, treatment with methotrexate led to transient resolution of lesions, while further thalidomide treatment was inefficient. Targeted inhibition of *BRAF-V600E* with combined *BRAF* and *MEK* inhibitors could be a good option and might be a promising therapy for patients with treatment resistant disease. Further research in these groups of rare disorders is needed to widen the treatment options for these patients.

Abbreviations

LCH, LC – Langerhans cells
Lh – Langerhans
ICH – Indeterminate cell histiocytosis
IC – Indeterminate cell

References

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Histiocistoza indeterminantnih ćelija – prikaz slučaja i pregled literature

Sažetak

Uvod. Histiocitoza indeterminantnih ćelija je retko proliferativno oboljenje histiocita koje je opisano u literaturi kao pojedinačni slučajevi kod oko 50 pacijenata. Javlja se u vidu žuckastih, crvenih ili smeđih papula i nodusa kod zdravih odraslih osoba. Indeterminantne ćelije su različite dendritične ćelije kože koje imaju ultrastrukturne sličnosti sa epidermalnim Langerhansovim ćelijama, ali ne sadrže karakteristične Birbekove granule, niti eksprimiraju langerin u poređenju sa Langerhansovom histiocitozom. Histiocitoza indeterminantnih ćelija je redak entitet sa promenljivim kliničkim, histopatološkim ili imunohistohemijskim nalazima, koji dele morfološke i imunofenotipske karakteristike histiocitoza Langerhansovih i non-Langerhansovih ćelija. Prikaz slučaja. Predstavljamo slučaj indeterminantne histiocitoze kod 77-godišnjeg muškarca sa trogodišnjom istorijom asimptomatskih, multiplih, crvenkastih i smeđih papula i nodula na celom telu, uključujući i oralnu mukozu. Histopatološkom analizom bioptata kože uz imunohistohemiju ukazao je na pozitivno bojenje ćelijskih infiltrata na CD68, CD1a i S-100 što je omogućilo postavljanje dijagnoze histiocitoze indeterminantnih ćelija. Osim toga, detektovana je *BRAF V600E* mutacija u tumorskom tkivu. Lečenje je započeto metotreksatom uz regresiju promena na koži, ali su se posle 6 meseci promene ponovo javile, te je savetovana terapija talidomidom, zbog nedostupnosti *BRAF* inhibitora. Zaključak. Indeterminantna histiocitoza je retka bolest, što onemogućava standardizovani pristup dijagnostici i terapiji.

Ključne reči: Histiocitoza; Dendritske ćelije; Langerhansove ćelije; Kožne neoplazme; Retke bolesti; Ishod Terapije

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DERMOSCOPY OF THE MONTH
Dermoscopic Finding of Pigment Network in Lesions of Eruptive Syringoma

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Abstract

Syringoma is a benign adnexal tumor derived from intraepidermal eccrine ducts. The usual presentation of syringoma is a small smooth skin-colored, yellowish or brownish papule with flattened or rounded top. Eruptive syringoma is a rarely reported form, where lesions are numerous and occur in successive crops. A case of a 57-year-old Caucasian male with a twenty four-year history of multiple asymptomatic, erythematous and brownish papules, predominantly over the anterior aspect of the trunk is presented. All lesions appeared after prolonged sun exposures within a few days and persisted without further changes afterwards. Contact non-polarized dermoscopy showed a fine light brown, regular pigment network on a light pink background, being the same in all lesions. History of the disease, clinical finding and dermoscopy were inconclusive, and biopsy was performed. Histopathology revealed signs of syringoma. Dermoscopic finding was thought to be intriguing and therefore is discussed in this paper.

Key words: Syringoma; Skin Neoplasms; Dermoscopy; Pigmentation Disorders; Skin Diseases; Case Reports

Introduction

The word syringoma is derived from Greek language syrinx meaning tube. Syringoma is a benign adnexal tumor derived from intraepidermal eccrine ducts (1, 2). Although the definition of syringomas as benign neoplasms of the eccrine duct is widely accepted, the pathomechanisms and the genuine neoplastic character of eruptive syringomas are controversial. As reported in two cases by Guitard et al., eruptive syringomas occur as a consequence of chronic inflammatory processes of the skin involving adnexal structures. The authors propose the term “syringomatous dermatitis” to outline the assumed underlying inflammatory reaction because the patients revealed eczematous dermatitis with residual lesions that could be histopathologically diagnosed as an eccrine syringoma (3, 4).

There are four major variants as proposed by Friedman and Butler: localized, generalized including eruptive and multiple, familial and associated with Down syndrome (1, 2). Syringoma usually occurs in the eyelid region in females during puberty or early adulthood, rarely later. Eruptive syringomas are a rarely reported form, where lesions are numerous and occur in successive crops (2, 5-12). Most studies emphasize that the diagnosis of syringoma, particularly of eruptive syringoma, have usually not been suspected clinically and the definitive diagnosis is made upon histological examination (4, 6-8, 11, 12). Rare forms and localization of syringoma such as plaque type, presenting as milia, linear, vulvar, penile, chondroid, scalp, acral and solitary over ankle are also reported (1, 2, 5-8).

Eruptive syringomas are rarely reported and dermoscopic findings are also sparse.

Case Report

A case of a 57-year-old Caucasian male with the twenty four-year history of generalized

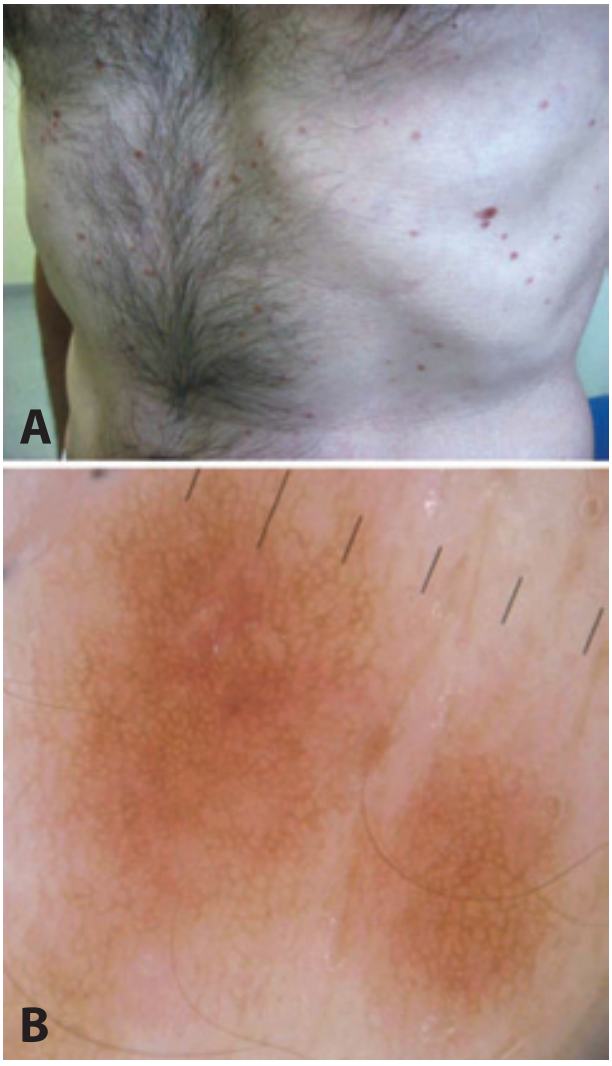

Figure 1. (A) Round to oval, erythematous to brownish papular lesions, slightly shiny, from 2-4 up to 7 mm indiameter, on the anterior abdomen. **(B)** On a light pink background, light brown regular pigment network as seen by dermoscopy on two nearby lesions (Delta Heine20, original magnification x10).

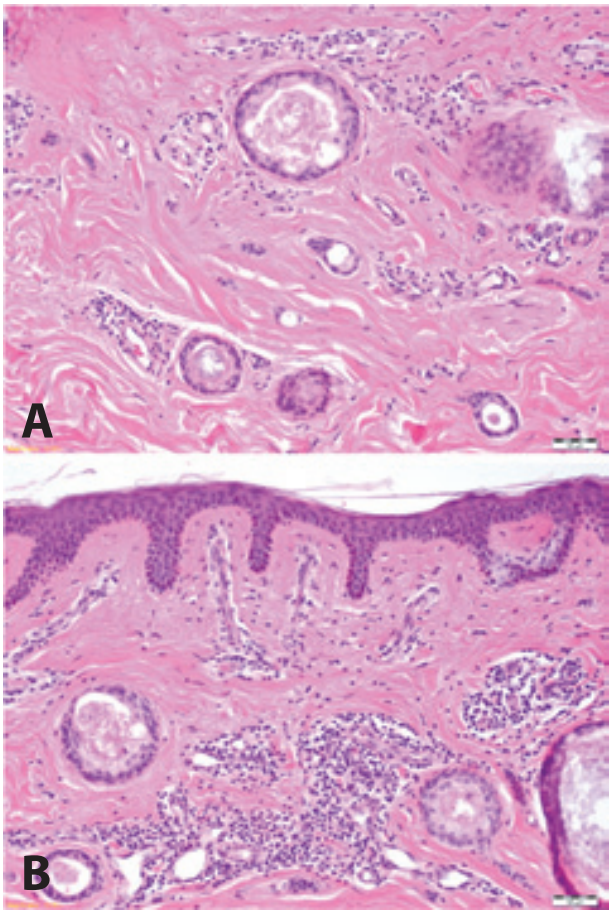

Figure 2. (A) Microphotograph of the skin with circumscribed small aggregates in the superficial dermis of cysts with at least two layers of cuboidal cell with regular nuclei. Some cystic ducts contain eosinophilic material in thelumina. On several ducts there is a visible tennis racket or tadpole process (hematoxylin-eosin stain;original magnification x100). **(B)** Characteristic microphotograph finding of syringoma, with melanin pigment prominent in the basal cellsof the epidermis (hematoxylin-eosin stain; original magnification x100).

eruptive syringoma is presented. All lesions appeared after prolonged sun exposure, without sunburns (e.g. blisters, and/or painful erythema following sun exposure) within a few days in the region of the anterior trunk without any subjective symptoms and persisted without further changes afterwards. He is Fitzpatrick skin type III. His previous medical history and basic laboratory findings were unremarkable. He denied use of any medication prior to the development of skin lesions. Family history was negative for similar skin lesions. Clinically we observed around fifty, erythematous-brownish papules, round to oval, their diameter being 2-4 mm (the largest one was 7 mm), slightly shiny on the skin of anterior trunk, axillae and upper arms (Figure 1a). Darier sign was negative. Contact non-polarized dermoscopy was performed with a hand-held Delta Heine 20 dermoscope. The only finding was a fine light brown, regular pigment network on a light pink background, being the same in all lesions (Figure 1b). Digital dermoscopy was performed. Dermoscopic

finding in our patient was intriguing, suggestive of urticaria pigmentosa. In the superficial dermis histopathology showed circumscribed small aggregates of multiple eccrine ducts lined by up to two layers of cuboidal cells with regular nuclei. Some cystic ducts contained eosinophilic material in the lumina. On several ducts a tennis racket or tadpole-like shape was visible (Figure 2a). Besides, melanin pigment was prominent in the basal cells of the epidermis, reveling signs of basal hyperpigmentation (Figure 2b), which could correspond to dermoscopic finding. It was the only pattern, which looked the same and was visible in all lesions observed in this patient. The patient was reassured about the harmless, benign nature of the condition, and he had not been treated since he had no discomfort or aesthetic problems.

Discussion

Our patient, except for his male gender, expressed characteristic features of generalized eruptive syringoma such as occurrence in crops, absence of subjective symptoms, distribution of lesions on the trunk and arms with stable course of lesions over time (6-8).

Prolonged exposure to the sun and heat as provocative factors is also in concordance with previous studies (7, 13, 14).

Dermoscopic finding in our patient was intriguing, suggestive of urticaria pigmentosa (15, 16). Pigment network on the light pinkish background was the only dermoscopic finding in our patient. Pigment network is a dermoscopic criterion for melanocytic lesions, but it can also be detected in non-melanocytic lesions such as mastocytosis, dermatofibroma, solar lentigo, pigmented seborrheic keratoses, accessory nipple, Kaposi sarcoma, and even healthy skin (15). Recent histopathological reports of syringomas showed basal hyperpigmentation in various but important percentages of lesions in addition to other features (5, 7, 8). Patrizi et al. noted hyperpigmentation in the basal layers in 12 (41.2%) patients, being more frequent in eruptive syringomas in 9 patients (5). Lee et al. analyzed 61 patients and reported basal hyperpigmentation in 26.2% of them (7). Ghanadan et al. reported cases of 34 patients with basal hyperpigmentation in 86.6% of localized syringomas and in 73.6% of the generalized form (8). In their case of unilateral linear syringoma Hayashi et al. observed on histopathological examination a slight thickening of the rete ridges with basal melanosis with characteristic features of syringoma in dermis. They connected dermoscopic finding of a very faint light brown color pigment network that was observed in their case with basal melanosis alone. They speculated that fibrotic stroma in syringoma might cause epidermal thickening and basal melanosis, which would correspond to a delicate pigment network, as often shown in dermatofibroma (11).

We share the opinion of Hayashi et al. that dermoscopic finding of regular light brown pigment is not likely to be the specific finding caused by tumor structure itself, but rather non-specific consequence of basal layer pigmentation that overlie deeper tumor structure. Moreover, that finding could potentially favor an underlying inflammatory reaction and proposed “syringomatous dermatitis” that is one of points of view to the proposed pathomechanisms of syringomas. Prolonged sun and heat exposure may have been provocative factors that triggered such an inflammatory reaction and resulted in eruptive syringomas in our patient.

Conclusion

We can conclude that eruptive syringoma can in some cases be included in the differential diagnosis of melanocytic lesions and non-melanocytic skin lesions with the dermoscopic appearance of a regular pigment network. Future reports and studies on this subject are needed.

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Dermoskopski nalaz pigmentne mreže kod lezija eruptivnog siringoma

Sažetak

Siringomi su benigni adneksalni tumori, porekla intraepidermalnog dela ekrinih žlezda. Najčešće su u vidu papula boje kože, žućkaste ili braonkaste, glatke, zaravnjene ili zaobljene površine. Eruptivni siringomi su ređe opisivani oblik siringoma. Kod ovog oblika se javljaju brojne lezije koje nastaju u „naletima“. Prikazujemo muškarca starosti 57 godina, bele rase. Promene na koži nastale su nakon dužeg izlaganja suncu, bez opekotina, u vidu eritematozno braonkastih papula dominantno na trupu, bez subjektivnih simptoma; od kada su nastale perzistiraju nepromenjene tokom 24 godine. Lezije su pregledane i kontaktnom dermoskopijom, pri čemu je uočena svetlobraon, delikatna, pravilna pigmentna mreža na svetloružičastoj osnovi. Anamneza, klinička slika i dermoskopski nalaz nisu doveli do definitivne dijagnoze, te je urađena biopsija lezije i histopatološki nalaz je ukazao na siringome. Dermoskopski nalaz je bio intrigantan i prodiskutovan je u radu.

Ključne reči: Siringomi; Kožne neoplazme; Dermoskopija; Poremećaji pigmentacije; Kožne bolesti; Prikazi slučajeva

Report on the 6th European School of Dermato-Oncology Berlin 2018

The 6th European School of Dermato-Oncology (ESDO) was held from January 18th to 20th, 2018 at the H4 Hotel Berlin Alexanderplatz, Germany. The ESDO is an annual event which invites experts in the field of dermato-oncology to give research update through lectures and debate on current aspects of dermato-oncology and to cover the entire spectrum of cutaneous malignancies starting from prevention and wide range of diagnostic options to novel therapies of skin cancers.

During three-day programme numerous participants from all over Europe were able to attend a total of 15 plenary lectures followed by a total of 8 courses. The attendees, who were divided into four groups, moved from one lecture room to another after the end of every course following the precise timetable. Thus, working in small groups every participant could take active part in discussions. A comprehensive overview of the prevention, early diagnostic, dermoscopy, treatment and follow-up of the patients with melanoma, non-melanoma skin cancer, cutaneous lymphomas, supported with the numoreus case reports was the main advatage of this type of meeting.

One of the courses, ''How to manage adverse effects of checkpoint inhibitors and targeted therapy'', was held by Prof. Lidija Kandolf Sekulović. This lecture, illustrated with numerous cases from our Department, was very useful.

We can warmly recommend the European School of Dermatooncology to all specialists and residents interested in dermato-oncology.

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Figure 1. Lidija Kandolf Sekulović, Tatjana Radević, Ivana Ilijin and Ljubica Jevremović at ESDO in Berlin

FORTHCOMING EVENTS

Dermatology and Venereology Events 2018

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
12-16 September, 2018	27th EADV Congress, Paris France	13 March, 2018	www.eadvparis2018.org
05-06 October, 2018	Pediatric Dermatology, Specialist Course, Lausanne, Switzerland	13 March, 2018	www.eadv.org
4-6 October, 2018	ESTRO School, Multidisciplinary management of non- melanoma skin cancer, Brussels, Belgium		www.estro.org
11-13 October, 2018	22ndBDD, Belgrade, Serbia	1 June, 2018	www.udvs. org
29-30 October, 2018	6th International Conference on HIV/AIDS, STDs and STIs, San Francisco, USA		www.hiv-aids-std.conferenceseries.com
6-9 November, 2018	14th Congress of the EADO, Barcelona, Spain	10 September, 2018	www.congresseado-melanomacenters2018.com
9-11 November, 2018	EADV Course- Skin Cancer, Trieste, Italy		www.eadv.org
14-17 November, 2018	CILAD 2018, Sao Paulo, Brazil	10 September, 2018	www.cilad2018.com
5-6 December, 2018	GA2LEN Global Urticaria Forum (GUF 2018), Berlin, Germany	10 September, 2018	www.globalurticariaforum.org

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AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

3. Review articles (limited to 10 pages) should provide systemic critical assessment ofliterature 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 are to be submitted to the **Editor in Chief: Prof. Dr. Lidija Kandolf Sekulović,** Clinic of Dermatovenereology, School of Medicine, Military Medical Academy, Crnotravska 17, Belgrade, Republic of Serbia, by mail to: serbjdermatol@gmail.com

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 ofthe article, which shouldbe 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 sho uld 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 nonstandard 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:// w*ww.bipm.fr/en/si/.

1.4. Cover Letter

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

2. Tables and illustrations

Tables should capture information concisely

and precisely. Including data in tables, rather than in the text, reduces the length of the article itself.

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

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3. References

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

4. Author's Statements

– Conflict of Interest

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