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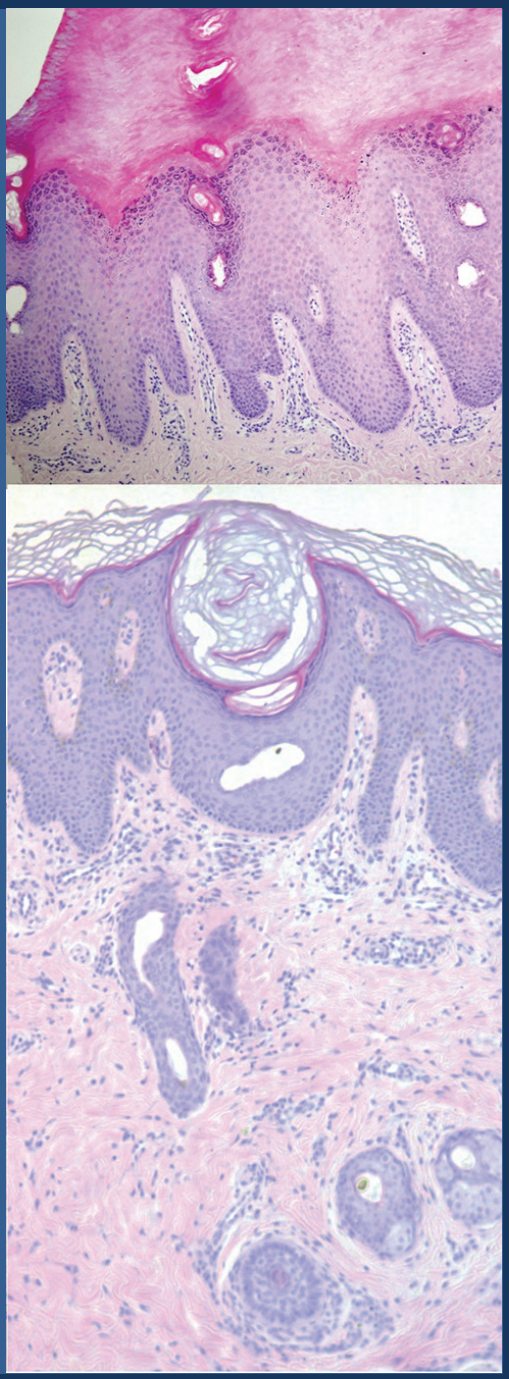

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Vojnomedicinska akademija, Klinika za kožne i polne bolesti, 11000 Beograd, Crnotravska 17
E-mail: serbjdermatol@gmail.com, serbjdermatol@mts.rs, Tel: +381 11 266 11 22; +381 11 266 00 20.
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Cutaneous Manifestations in HIV Infected Libyan Patients

Nabil A. ALJEHAWI, Omran O. BUGREIN, Azza GREW, Gamal Ahmed DUWEB

Dermatology and Community Medical Departments, Faculty of Medicine, Benghazi University, Benghazi, Libya

*Correspondence: Gamal Ahmed Duweb, Dermatology Department, Faculty of Medicine, Benghazi University, Benghazi, Libya, E-mail: drduweb@gmail.com

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Abstract

Cutaneous manifestations of human immunodeficiency virus (HIV) disease may result from HIV infection itself, or from opportunistic disorders secondary to the declined immunocompetence due to the disease. A total of 220 HIV positive patients, treated in the Benghazi Center of Infectious Diseases and Immunology over a period of 14 years (January 2003 to November 2016), were included in a retrospective study. The patients' age ranged from 7 to 46 years. The study was conducted by reviewing the patients' records using the management information system (MIS). Statistical analysis of the data was carried out by the t-test and Chi square test. Among the studied patients, 119 (54.1%) were males and 101 (45.9%) were females, and most of them (78.6%) were 10 – 19 years of age. The predominant mode of transmission was parenteral transmission, in 95% of patients, and positive family history was observed in 12% of patients. Among the total number of visits to dermatologists, 93% of patients had a single disease. Of the total number of skin diseases diagnosed during the visits, parasitic infestations were seen in 92 patients (21.0%), eczematous and related disorders in 78 patients (17.8%), viral infections in 71 patients (16.2%), bacterial infections in 41 patients (9.3%), and fungal infections in 35 patients (7.9%). Dermatophyte infections were the most common fungal infections recorded in 19 patients (4.3%), followed by Candida infection in 11 patients (2.5%). Warts were found in 5.9% of viral infections, followed by herpes zoster (4.1%). HIV positive patients should be examined for skin disorders, because early diagnosis and management of such problems improves the quality of life in these patients.

Key words: HIV; HIV Infections; AIDS-Related Opportunistic Infections; Retrospective Studies; Skin Diseases; Libya

Introduction

Acquired immune deficiency syndrome (AIDS), or acquired immunodeficiency, is a disease of the human Immune system caused by the human immunodeficiency virus(HIV) (1, 2, 3). About 39 – 46 million people in the world are currently living with HIV/AIDS, and HIV infection is among the main health problems worldwide. Since 1981, when the first reports about AIDS were published in the medical literature, skin and mucocutaneous diseases have played an important role in the clinical diagnosis of acquired immunodeficiency. Opportunistic infections of the skin and oral cavity, such as herpes simplex and candidiasis, were noted to be clinical markers of acquired immunodeficiency (2). Candida albicans infection, presenting as extensive oral thrush or recalcitrant monilial diaper dermatitis, is the most common and often the first manifestation of pediatric HIV infection. Bacterial infections, including severe forms of staphylococcal impetigo, ecthyma and furuncles, are also common (3). Extensive molluscum contagiosum, herpes simplex infection and plane warts are also common with lesions which are more widely distributed and very difficult to treat.

Non infectious/inflammatory dermatosis like seborrheic eczema and Kaposi's sarcoma, which are common in adults in whom they become more widespread and refractory to treatment as CD4+ T-cell count declines, are exceptional in children. Pruritic papular eruption (PPE) of HIV/AIDS is common in both adults and children with marked depletion of CD4+ T-lymphocytes (4).

Skin diseases are considered a major health problem among HIV positive patients presenting with a variety of dermatologic manifestations. In this study, our aim was to assess epidemiological and clinical cutaneous manifestations in Libyan HIV positive patients.

Table 1. Age distribution of patients

%	No	Age groups/years
0.5	1	9 -0
78.6	173	19-10
15.5	34	29-20
2.7	6	39-30
2.7	6	49-40

Material and Methods

This retrospective study included 220 HIV positive Libyan patients who visited the Dermatology Clinic of the Benghazi Center of Infectious Diseases and Immunology (BCIDI) on one or more occasions with different skin lesions over a period of 14 years (January 2003 to November 2016). The patients' age ranged from 7 to 46 years. The study was conducted by reviewing the patients' medical records and their data were collected by using the Management Information System (MIS). The records were screened for dermatological findings by thorough examination of patients' age, sex, residence, family history and date of HIV diagnosis, including the number of visits to a dermatologist, clinical findings, and diagnosis. The data were collected and processed according to a previously prepared procedure. Statistical analysis of the data was carried out using the Statistical Package for the Social Sciences (SPSS) (version 12) software and analyzed using the t– test and Chi square test.

Results

Among the 220 HIV positive patients included in this study, 119 patients (54.1%) were males and 101 (45.9%) were females. Their age ranged from 7 to 46 years (mean 16.5 years). A total of 189 patients (86%) were residents of Benghazi, whereas 31 patients (14%) were residents of rural areas. Positive family history for HIV was found in 12% of cases (5% were parents, 4.1% were sons or daughters, 1.8% were siblings and only in 0.9% there were more than one infected member). The age of onset was from 0 to 5 years of age in 66.3% of cases (146 patients), in 18.6% between the age of 6 and 10 years, and in the remaining cases the onset was at older age. The most affected age group was from 10 to 19 years, which accounted for 78.6% of patients (173 patients); the next most affected group accounted for 15.5% (34 patients) aged from 20 - 29 years; the older age groups were less frequently affected (Table 1).

The predominant mode of HIV transmission in our patients was parenteral transmission, found in 209 patients (95%), from child to mother (4.5%) where cracks in the nipple of lactating mother and the presence of oral erosions or ulcers in the child may facilitate the transmission of HIV by breast feeding. Ninety percent of patients were co-infected with at least one viral infection, and about 62.7% of them were co-infected with more

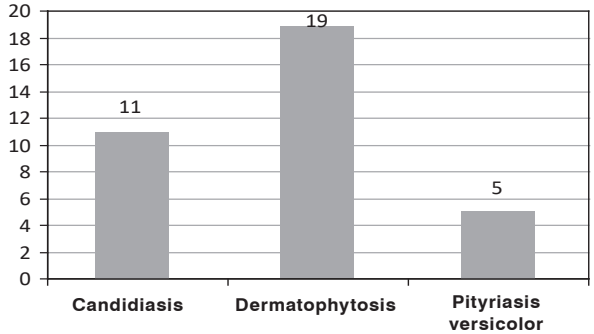

Figure 1. Fungal infections in the study sample

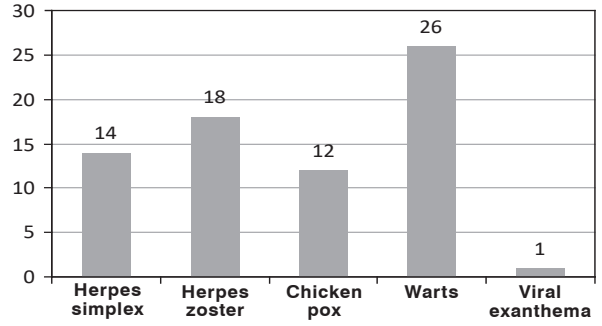

Figure 2. Viral infections in the study sample

Table 2. Common skin disorders in the study sample

Skin disorder	As a single skin disorder	With another skin disorder	All observations	% from all complaints
Parasitic infestations	86	6	92	21.0%
Eczema and related disorders	68	10	78	17.8%
Viral infections	60	11	71	16.2%
Bacterial infections	40	1	41	9.3%
Fungal infections	30	5	35	7.9%
Total	284	33	317	72.2%

than one viral agent. The most prevalent infection was cytomegalovirus found in 80.9%, followed by hepatitis C virus (46.8%), hepatitis B virus (22%), and uncommonly by toxoplasmosis (10%) and rubella only in 3.6%. The number of visits to dermatologists during this period was 408 (1.86 per patient) and the total number of complaints was 439 (2 per patient). Among the total number of visits to dermatologists, 93% of patients had a single disease, 6.1% had two diseases, and only 0.7% had three diseases.

Of the total number of skin diseases diagnosed during visits, parasitic infestations were seen in 92 patients (21.0%), eczematous and related disorders in 78 patients (17.8%), viral infections in 71 patients (16.2%), bacterial infections in 41 patients (9.3%), and fungal infections in 35 patients (7.9%) (Table 2). Dermatophyte infections were the most common fungal infections recorded in 19 patients (4.3%), followed by Candida infections in 11 patients (2.5%) (Figure 1). Warts accounted for 5.9% of viral infections, followed by herpes zoster (4.1%) (Figure 2). There were 41 patients with bacterial infections, 9 (2.1%) with impetigo, followed by ecthyma in 8 (1.8%), and furuncle in 7 patients (1.6%) (Figure 3). Eczematous disorders accounted for 11.5% of all complaints; atopic dermatitis, photodermatitis and seborrheic dermatitis were the most common disorders, found in 16 (3.6%), 9 (2.1%) and 8 (1.8%) patients, respectively (Figure 4). Insect bites and scabies were seen in 58 and 31 patients (13.2%, 7.1%), respectively. The total number of cases with other skin dermatoses was 122 patients (27.8%), including pityriasis alba in 40 patients and acne vulgaris and xerosis in 17 patients each (Table 3).

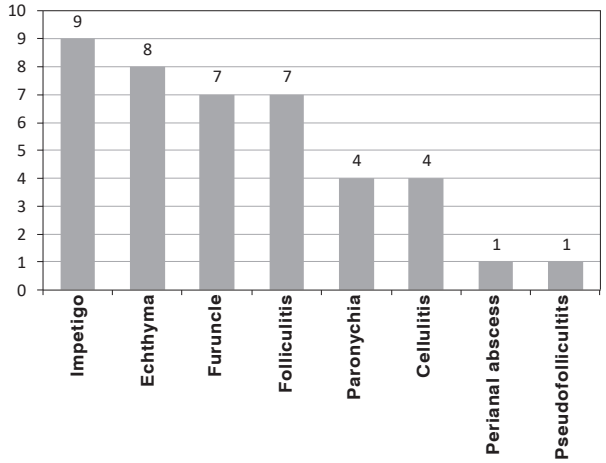

Figure 3. Bacterial infections in the study sample

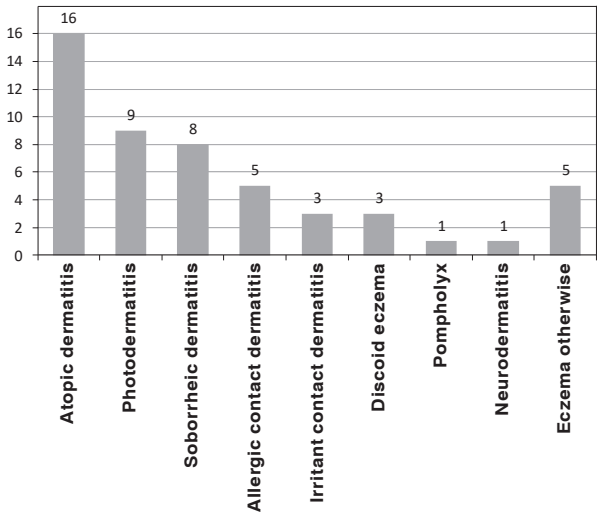

Figure 4. Eczematous dermatoses in the study sample

Table 3. Other skin disorders in the study sample

Skin disorder	As a single skin disorder	With another skin disorder	All observations	% from all complaints
Acne vulgaris	15	2	17	3.9%
Xerosis	11	6	17	3.9%
Aphthous ulcer	7	1	8	1.8%
Angular stomatits	5	2	7	1.6%
Cheilitis	4	1	5	1.15%
Dandruff	5	0	5	1.15%
Alopecia	4	0	4	0.9%
Psoriasis vulgaris	4	0	4	0.9%
Keratosis pilaris	4	2	6	1.4%
Pityriasis rosea	2	0	2	0.5%
Pityriasis amiantacea	1	1	2	0.5%
Acneiform eruption	1	0	1	0.2%
Callosities	1	0	1	0.2%
Chilblains	1	0	1	0.2%
Ichthyosis vulgaris	1	0	1	0.2%
Necrobiosis lipoidica diabeticorum	1	0	1	0.2%
Pityriasis alba	29	11	40	9.1%
Total	96	26	122	27.8%

Discussion

Cutaneous disorders may be the initial sign of HIV-related immunosuppression. Recognition of HIV-related skin changes may lead to the diagnosis of HIV infection in the early stages, providing timely initiation of appropriate antiretroviral therapy.

A variety of neoplastic, infectious, and noninfectious diseases may present with cutaneous manifestations throughout the course of HIV infection. The manifestations may occur more frequently than in persons without HIV infection and may be less responsive to usual treatment modalities (5). There is evidence in literature pertaining to the fact that prevalence and pattern of skin diseases vary from region to region (6, 7, 8). For instance, the prevalence rates of dermatologic problems established in Tanzania, Cameron, Thailand and Zambia were 41.7%, 68.8%, 95%, and 98.3%, respectively (8, 9, 10, 11).

In our study, at least one skin lesion was detected in 93% of patients and this is consistent with other studies, including Pitche et al. (82.5%), Sanadaj city in Iran (94.3%), Jeffrey et al. in 86% of their patients, whereas a South Western France study showed that it was somewhat lower (65.3%) (12, 13, 14). Results of the present study showed that 119 patients (54.1 %) were males and 101 patients (45.9 %) were females, which is relatively similar to another study in the tertiary care hospital in atribal (Bastar) region of Chhattisgarh in India, where of 137 patients, 83 (60.58%) were males and 54 (39.41%) were females (15).

Our patients were between 7 and 46 years of age (mean 16.5 years), and the most affected age group was from 10 to 19 years, accounting for 78.6% of all patients. This finding did not correlate with the findings of Bravo et al. (2006) who found that the most affected

age was the sexually active age group from 30 to 39 years (51%) (16). Also, the age of HIV onset in our patients was between the age of 0 - 5 years in 66.3% of cases (146 patients), 18.6% between the age of 6 - 10 years, and the remaining fewer cases were found at older ages. This may be explained by the fact that the predominant mode of HIV transmission in our patients was by parenteral abuse (95%), while they were admitted to Child Hospital in 1998, while the others were either mothers who got the infection from their children or through vertical transmission from mother to child (4.5%, 0.5%, respectively); however, other studies reported that the modes of transmission were by homosexual partners in 35.3%, intravenous drug use in 27.8%, and heterosexual partners in 24.4% of cases (14).

Among the total number of skin diseases diagnosed during the visits, parasitic infestations were found in 92 patients (21.0%), eczematous and related disorders in 78 patients (17.8%), viral infections in 71 patients (16.2%), bacterial infections in 41 patients (9.3%), and fungal infections in 35 patients (7.9%). Similar to Eichmann's study, eczema was common in our patients (17). Viral, bacterial and fungal infections were common in our study, which is consistent with other studies, where fungal, viral, bacterial infections and neoplasms were the most common findings (18, 19).

In comparison to other studies, oral candidiasis was observed only in 2.5% of our patients, whereas in other studies it accounts for 34.3% and 54.17% in Sivayathorn and Wiwanitkit reports, respectively (20, 21). Dermatophytosis accounted for 4.3% from all complaints, and this is not consistent with a study conducted in USA accounting for 34% of cases (11).

Regarding viral infections in the present study, warts were the most common accounting for 37% of all viral infections (5.9% from all complaints). This was not in line with the results of the study carried out at the Phramongkutkloa Hospital Skin Clinic, Bangkok, which showed herpes zoster as the most common viral infection (48.2%) of all viral infections and no cases of warts were reported. In our study, herpes zoster was observed only in 4.1%, which is very much lower than Sivayathor's report in which herpes zoster was found in 16.3% of cases (20). Also, herpes simplex was observed only in 3.2%, which is not consistent with the same study report where herpes simplex was found in 14.9% of cases (20). Although our and the other study reported low frequency of seborrheic dermatitis found in 1.8% and 4.7%, respectively, other international data reported higher percentage of seborrheic dermatitis (21% and 46.6%, respectively) (20, 21).

Abbreviations

AIDS - acquired immune deficiency syndrome
HIV - human immunodeficiency virus
PPE - pruritic papular eruption
BCIDI - Benghazi Center of Infectious Diseases and Immunology
MIS - Management Information System
SPSS - Statistical Package for the Social Sciences

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Kutane manifestacije kod libijskih pacijenata inficiranih HIV-om

Sažetak

Kutane manifestacije u vezi sa infekcijom virusom humane imunodeficijencije (HIV) mogu biti posledica same infekcije HIV-om, ili sekundarnih oportunističkih infekcija nastalih usled smanjene imunokompetentnosti pacijenta. U retrospektivnu studiju uključeno je ukupno 220 pacijenata pozitivnih na HIV, lečenih u Bengazijskom centru za infektivne bolesti i imunologiju u periodu od 14 godina (od januara 2003. do novembra 2016. godine). Starost pacijenata kretala se od sedam do 46 godina. Studija je sprovedena analizom istorija bolesti pacijenata koristeći menadžmenski informacioni sistem (MIS). Statistička analiza podataka izvedena je primenom t-testa i hi-kvadrat testa. Među ispitivanim pacijentima, bilo je 119 (54,1%) muškaraca i 101 (45,9%) žena, a većina njih (78,6%) bila je u starosnoj grupi od 10 do 19 godina. Glavni put prenosa HIV-a bio je parenteralni, kod 95% pacijenata, a pozitivna porodična istorija zabeležena je kod 12% pacijenata. Od ukupnog broja pacijenata koji su bili na pregledu kod dermatologa, 93% pacijenata imalo je samo jednu bolest. Od ukupnog broja kožnih bolesti dijagnostikovanih tokom pregleda, parazitsku infekciju imalo je 92 bolesnika (21%); ekcem ili neku srodnu bolest imalo je 78 pacijenata (17,8%); virusnu infekciju imao je 71 pacijent (16,2%); bakterijsku infekciju 41 pacijent (9,3%) i gljivičnu infekciju 35 pacijenata (7,9%). Dermatofitne infekcije bile su najčešće gljivične infekcije zabeležene kod 19 pacijenata (4,3%), zatim kandida kod 11 pacijenata (2,5%). Virusne bradavice su pronađene kod 5,9% infekcija, a zatim herpes zoster (4,1%). Potrebno je da pacijente pozitivne na HIV pregleda dermatolog jer rana dijagnoza i lečenje kožnih bolesti poboljšava kvalitet života ovih pacijenata.

Ključne reči: HIV; HIV infekcije; Oportunističke infekcije vezane za sindrom stečene imunodeficijencije; Retrospektivne studije; Kožne bolesti; Libija

DOI: 10.1515/sjdv-2017-0012

Pachyonychia Congenita - Can a Specific Phenotype be a Clue to a Genetic Defect? - a Case Report and Literature Review

Jovan LALOŠEVIĆ[1], Mirjana GAJIĆ-VELJIĆ[1,2], Jelena STOJKOVIĆ-FILIPOVIĆ[1,2], Martina BOSIĆ[2], Miloš NIKOLIĆ[1,2]

[1]Clinic of Dermatovenereology, Clinical Center of Serbia, Belgrade, Serbia
[2]University of Belgrade, School of Medicine, Belgrade, Serbia

*Correspondence: Javan Lalosevic, E-mail: drjovanlalosevic@gmail.com

UDC 616.596-003.87-056.7

Abstract

Pachyonychia congenita (PC) is a rare inherited disorder of keratinization characterized by hypertrophic nail dystrophy, painful palmoplantar blisters, cysts, follicular hyperkeratosis and oral leukokeratosis. These pathological clinical features are resulting from mutations in keratin proteins including KRT6A, KRT6B, KRT6C, KRT16, and KRT17. We present a 6-year-old girl with hypertrophic nail dystrophy, follicular hyperkeratosis, circumscribed plantar keratoderma and oral leukokeratosis. The features were consistent with the diagnosis of PC. The patient has been registered in the International Pachyonychia Congenita Research Registry (IPCRR) and is waiting for a detailed genetic analysis. The IPCRR has contributed to publication of numerous papers which emphasized the importance of the mutation type affecting various clinical presentations of PC. Based on recent data, a new classification system has been developed for PC, and it is gradually replacing the earlier classifications. It is based almost exclusively on the mutated genes. In this report we have raised the hypothesis that distinctive clinical features may be highly suggestive of a specific keratin mutation.

Key words: Pachyonychia Congenita; Child; Signs and Symptoms; Skin Diseases, Genetic; Mutation; Phenotype; Case Reports

Introduction

Pachyonychia congenita (PC) is a rare genodermatosis transmitted as an autosomal dominant trait, caused by mutations in at least one of 5 keratin genes. PC affects different ectodermal structures to variable extent. Most frequently, it is clinically characterized by nail dystrophy and painful focal plantar keratoderma. Additionally, PC may affect the palms, oral mucosa, tongue and teeth (1). Patients with KRT17 mutations are more likely to have natal teeth and develop steatocystomas, while patients with KRT6A mutations more commonly manifest oral leukokeratosis (2). Historically, based on the clinical features, two subtypes emerged: Jadassohn-Lewandowsky PC type 1, and Jackson-Lawler PC type 2 (3).

Case Report

We present a 6-year-old girl born to non-consanguineous parents, with normal developmental milestones for her age. The family history was unremarkable. On examination, the girl presented with subungual hyperkeratosis resulting in nail abnormalities on all fingers and toes. On the lateral aspects of her upper and lower extremities, as well as on the lower-anterior part of the trunk, she had disseminated follicular hyperkeratosis with a hedgehog-like appearance (Figure 1. A, B, E, F). Circumscribed plantar keratoderma was present on both soles (Figure 1. C). Mucosal examination revealed oral leukokeratosis (Figure 1. D). Due to a mild hoarseness, an ear-nose-throat specialist examined the child, and indirect laryngoscopy showed no signs of laryngeal involvement. Histopathology of the plantar keratoderma showed massive hyperkeratosis with discrete focal parakeratosis, thickening of the granular layer with large keratohyalin granules. Histopathology of the hyperkeratotic papules on the trunk showed mild acanthosis and lamellar hyperkeratosis,

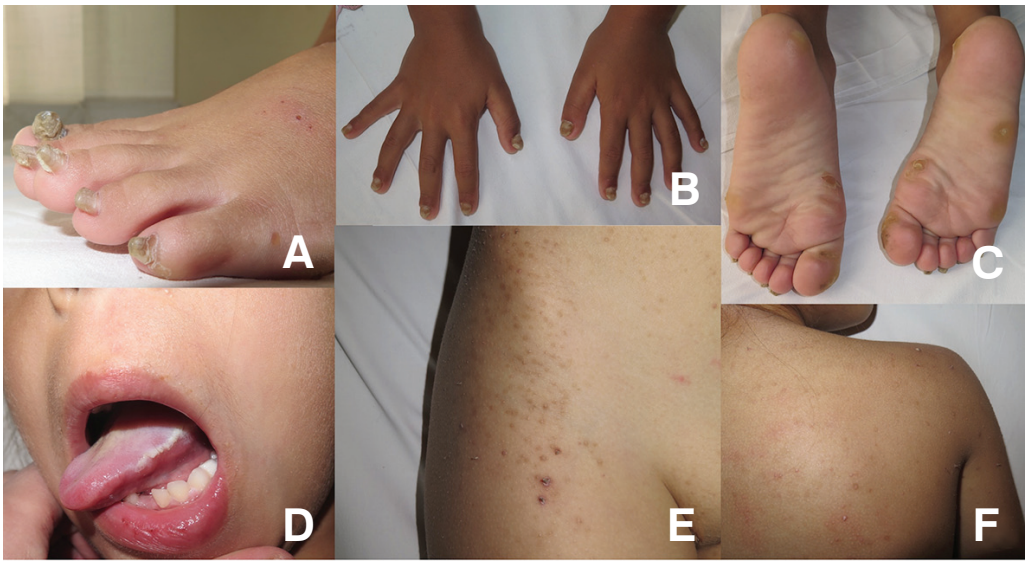

Figure 1. A, B. Subungual hyperkeratosis present on all fingernails and toenails, leading to wedge-shaped nail deformities; **C.** Circumscribed plantar keratoderma; **D.** Oral leukokeratosis, predominantly on the sides of the tongue; **E.** Follicular hyperkeratosis on lateral aspects of the trunk; **F.** Follicular hyperkeratosis with hedgehog spike formations

most intense in the follicular infundibulum (Figure 2).

Routine laboratory test results were normal. Since a large portion of the patient's trunk and extremities was covered with hyperkeratotic papules, oral isotretinoin at 0.6 mg/kg/day was introduced, as well as topical 40% urea ointment for plantar keratoderma. The patient has been registered in the International Pachyonychia Congenita Research Registry (IPCRR) (www.pachyonychia.org) and is waiting for a detailed genetic analysis. Because of frequent nose bleeds, oral isotretinoin had to be discontinued after two weeks, while the topical treatment was regularly applied. On a regular check up, 4 months after the initial admission, the girl showed a mild improvement.

Discussion

Pachyonychia congenita is an autosomal dominant genodermatosis caused by heterozygous mutations in any of the genes encoding the differentiation-specific keratins KRT6A, KRT6B, KRT6C, KRT16, or KRT17 (4). The main clinical features of the condition include painful and highly debilitating plantar keratoderma, hypertrophic nail dystrophy, oral leukokeratosis, and a variety of epidermal cysts (2). Although the condition has previously been subdivided into PC-1 and PC-2 subtypes, the phenotypic characterization of over 700 mutation-verified PC patients enrolled in the IPCRR, shows that there is a considerable overlap between these subtypes (1, 2).

Patients with type 1 PC (Jadassohn-Lewandowsky syndrome) are characterized by nail dystrophy since birth. This may be accompanied by painful paronychia, hyperkeratosis of palms and soles over the pressure sites, oral leukokeratosis, palmoplantar hyperhidrosis and follicular keratotic papules distributed through the body (5). Also, painful blisters can develop over the palms and soles. Additional finding is the presence of verrucous lesions over the elbows and knees, sometimes the gluteal area (2, 6). Furthermore, stridor and hoarseness can develop as severe leukokeratosis may produce laryngeal obstruction (7).

Patients with type 2 PC (Jackson-Lawler syndrome) have natal teeth and hair anomalies (including pili torti, unruly hair and bushy eyebrows). Oral leukokeratosis and palmoplantar keratoderma is milder in comparison to PC-1. Steatocystoma multiplex (epidermal cysts) is the hallmark of PC-2 (8).

The IPCRR was established in 2004 with the aim to collect clinical and molecular data from patients with PC worldwide. The IPCRR has collected data about more than 700 cases with genetically confirmed PC, and more than 100 different dominant mutations have been identified (no cases of confirmed recessive PC). Up to September 2016, 51 cases enrolled in the IPCRR have been identified without mutations in KRT6A, KRT6B, KRT6C, KRT16 or KRT17, but rather with mutations in other genes including GJB6, TRPV3, DSG1, DSP, KRT9, FZD6 or AAGAB. Although these patients do not suffer from PC, their clinical features are similar, even though they have completely distinct genetic mutations (9).

The IPCRR has contributed to the publication of numerous papers that emphasized the importance of the mutation type on various clinical presentations in PC patients (1, 2, 10, 11).

Eliason et al. conducted a large study including 254 PC patients in whom the keratin mutations were associated with their clinical presentations (1). Supported by the results, the authors proposed a new classification for PC based on the specific keratin gene mutation. Three clinical features that were reported in more than 90% of patients across all mutation subtypes were thickened toenails, plantar keratoderma and plantar pain (1). Patients with KRT6A mutations were more than 11-fold more likely to have all 10 toenails affected. Also, patients with these mutations had the earliest average onset of nail dystrophy (about 4 months). In regard to plantar keratoderma, they noted that patients with KRT16 and KRT6A, developed symptoms at a similar age, but significantly earlier than patients with KRT6B and KRT17 mutations. Furthermore, patients with KRT6B mutations appeared to have fewer fingernails affected on average, compared with those with other keratin gene mutations. Concerning mucosal involvement, KRT6A and KRT17 carriers had a significantly increased odds/ratio of earlier onset of oral leukokeratosis compared with KRT6B and KRT16 carriers. Pilosebaceous cysts and natal teeth were a hallmark of the previously described PC type 2, and in this cohort had a much higher likelihood of appearance in patients with KRT17 mutations (1).

Spaunhurst et al., used the IPCRR to describe clinical heterogeneity among patients with PC with genetic mutations in KRT6A and KRT16. They concluded that KRT6A carriers have more extensive nail involvement, which starts at much younger age than those with KRT16. Furthermore, oral leukokeratosis was reported in 94% of patients with KRT6A mutation, in comparison to only 56% of KRT16 carriers. Follicular hyperkeratosis was also more likely to be present in patients with KRT6A mutations than in patients with KRT16 (11).

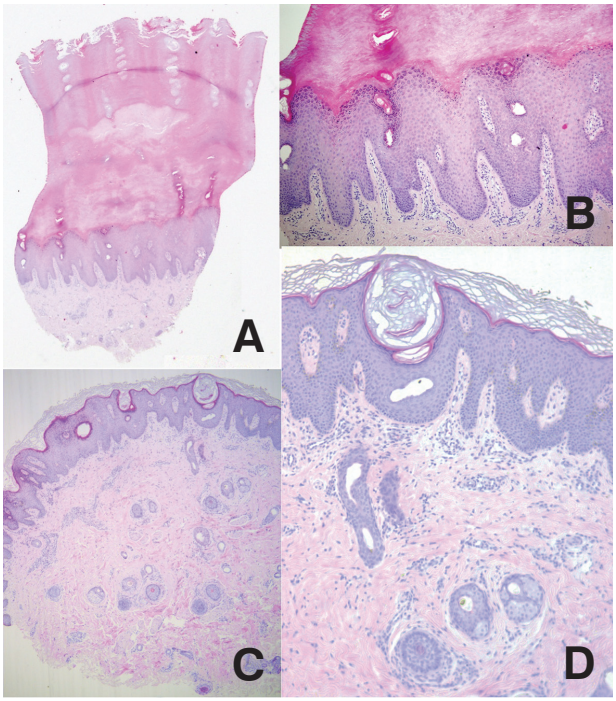

Figure 2. A, B. Severe hyperkeratosis with discrete focal parakeratosis, thickening of the granular layer with large keratohyalin granules; **C, D.** Mild acanthosis and lamellar hyperkeratosis, most intense in the follicular infundibulum

Genetic analysis has been a helpful predictive parameter in determining a potential response to a specific treatment. For example, a study confirmed that carriers of KRT6A and KRT16 mutations are more likely to benefit from keratolytics than carriers of KRT17 mutations (12).

The clinical classification of PC variants was first suggested by Kumer in 1935 (13), and it was intended to assist in the prognosis without genetic testing. After the discovery of the underlying cause of PC, genotype-phenotype analysis initially suggested that mutations in KRT6a/KRT16 and KRT6b/KRT17 were associated with type 1 and type 2 PC, respectively. A large amount of clinical and genetic

information, based on the data collected from the IPCRR, has become available in the last several years. This has provided the basis for a new classification system of PC, gradually replacing earlier classifications, and is based almost exclusively on the mutated genes. The new classification, revealing a broad spectrum of overlapping clinical and pathologic features, has closely correlated phenotype to the specific keratin genotype in PC patients. The new classification is as follows: (a) PC-K6a (caused by mutation of KRT6A); (b) PC-K6b (caused by mutation of KRT6B); (c) PC-K6c (caused by mutation of KRT6C); (d) PC-K16 (caused by mutation of KRT16); and (e) PC-K17 (caused by mutation of KRT17) (1, 2).

Conclusion

Taking into consideration our patient's clinical presentation, early onset of nail dystrophy, presence of follicular hyperkeratosis and plantar keratoderma, we may assume that she is a carrier of a KRT6A mutation. If this is the case, beneficial effects of treatment with keratolytics can be expected. A more promising future for our patient may reside in the genome-based therapy, but before that we are waiting for the findings of her genetic test results.

Abbreviations

PC - Pachyonychia Congenita
IPCRR - International Pachyonychia Congenita Research Registry

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Pachyonychia Congenita – Može li određeni fenotip biti ključ za genetski defekt? Prikaz slučaja i pregled literature

Sažetak

Pachyonychia congenita predstavlja grupu urođenih poremećaja keratinizacije za koju su karakteristične sledeće promene: zadebljale nokatne ploče, bolna palmoplantarna keratodermija, ciste, folikularna hiperkeratoza i oralna leukokeratoza. Ovi patološki nalazi posledica su mutacije na jednom od gena koji kodiraju keratine KRT6A, KRT6B, KRT6C, KRT16 ili KRT17. Prikazujemo devojčicu uzrasta šest godina sa hipertrofičnim nokatnim pločama, folikularnom hiperkeratozom, fokalnom plantarnom keratodemijom i oralnom leukokeratozom. Na osnovu kliničke slike, postavljena je dijagnoza *Pachyonychia congenita*. Pacijent je registrovan u *International Pachyonychia Congenita Research Registry* (IPCRR) i očekujemo nalaze genetskih ispitivanja. Sam IPCRR doprineo je objavljivanju velikog broja radova iz ove oblasti koji naglašavaju značaj tipa mutacije na razvoj specifične kliničke slike. Najnoviji podaci su pružili osnovu za postavljanje novog klasifikacionog sistema koji bi postepeno trebalo da zameni staru klasifikaciju i bazira se skoro u potpunosti na genima koji su mutirani. U ovom prikazu smo postavili hipotezu da određene kliničke karakteristike pacijenata sa dijagnozom *Pachyonychia congenita* mogu da ukažu na određenu mutaciju gena koji kodiraju keratin.

Ključne reči: Pachyonychia congenita; Dete; Znaci i simptomi; Genetske kožne bolesti; Mutacija; Fenotip; Prikazi slučajeva

Diffuse Cutaneous Mastocytosis in a Child - a Case Report

Svetlana POPADIĆ[1,2], Mirjana GAJIĆ-VELJIĆ[1,2], Biljana MARENOVIĆ[1], Miloš NIKOLIĆ[1,2]

[1]Clinic of Dermatovenereology, Clinical Center of Serbia, Belgrade, Serbia
[2]Department of Dermatovenereology, School of Medicine, University of Belgrade, Belgrade, Serbia

*Correspondence: Svetlana Popadić, scpopadic@gmail.com

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Abstract

Mastocytosis refers to a group of diseases characterized by a clonal proliferation and accumulation of mast cells in one or more tissues/organs with different clinical presentations. In children, limited cutaneous forms of mastocytosis are rather frequent, while systemic mastocytosis is rare. The diagnosis of cutaneous mastocytosis is based on clinical findings and histopathology. We present a patient who developed skin lesions at the age of 18 months. Clinical findings, confirmed by histopathology, were consistent with diffuse cutaneous mastocytosis. The follow-up period was 7 years. The treatment included oral antihistamines in combination with mast cell stabilizers, mild topical steroids and avoidance of friction. During the follow-up period, there were no signs of systemic involvement, and the quality of life was preserved, despite the large surface of affected skin. This case report should increase the awareness and knowledge of clinicians about this rare form of cutaneous mastocytosis in the pediatric population.

Key words: Mastocytosis, Cutaneous; Child; Diagnosis; Signs and Symptoms; Mast Cells; Dermatologic Agents; Treatment Outcome

Introduction

Mastocytosis is a rare disease that occurs both in children and in adults. In pediatric patients, mastocytosis is usually cutaneous and transient, while in adults the condition commonly progresses to a systemic form. Mastocytosis is a heterogeneous disorder characterized by clonal proliferation and accumulation of mast cells in one or more organs which may lead to different clinical pictures (1). Pathological accumulation of mast cells may affect the skin, bone marrow, liver, spleen and the lymph nodes.

Cutaneous forms are urticaria pigmentosa (UP), diffuse cutaneous mastocytosis (DCM), and cutaneous mastocytoma. UP and mastocytoma are more frequent forms during childhood and the lesions may be present at birth (1 - 3), while DCM is rare.

The treatment of cutaneous mastocytosis (CM) depends on the severity of lesions. The management is conservative and aimed at counteracting the symptoms due to mast cell mediator release, including avoidance of triggering factors such as cold water, friction, hot or cold air. In case of hypotension, epinephrine may be indicated, and in cases of frequent hospitalizations, imatinib mesylate (a type 2 kinase inhibitor) may be introduced (1).

Case Report

A 2-year-old boy was admitted to our Department of Pediatric Dermatology with a history of atopic dermatitis since the second month of life. The first cutaneous lesions and blisters on trunk and diaper area appeared at the age of 18 months. On admission, the boy presented with leathery thickened skin on the face, trunk and extremities (Figure 1). Approximately 80% of the body surface area was affected. He also had a marked dermographism and tense blisters in the friction zones (Figure 2). The Darier's sing was positive. Routine laboratory test results (CBC, biochemistry, and urinalysis) were all normal. The levels of serum tryptase were not measured, due to the lack of laboratory tests. Abdominal ultrasonography revealed normal findings of the spleen and liver. He had no lymphadenopathy, gastrointestinal or respiratory symptoms, but had a personal history of perinatal asphyxia with no complications, allergy to peanuts, home dust, orange, nuts and peach.

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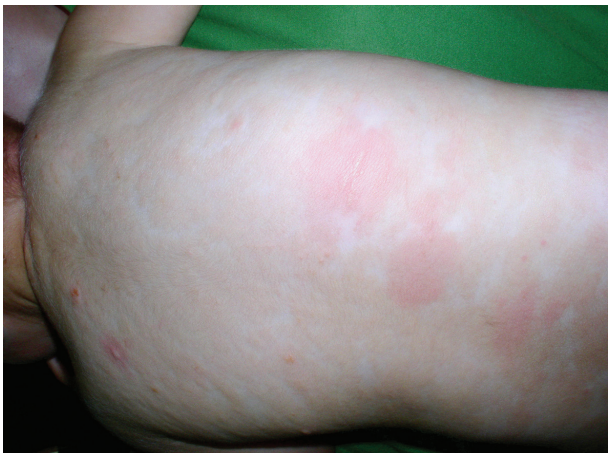

Figure 1. Leathery, erythematous thickened skin on the trunk in our patient at the age of 18 months

Histopathology of skin lesions revealed an increased number of mast cells in the papillary dermis, and mast cells aggregates around blood vessels (Figure 3. A; 3. B). Mast cell infiltrations were confirmed by toluidine blue staining (3. C).

The treatment included oral antihistamines in combination with mast cell stabilizers, mild topical steroids and avoidance of friction. During the following 7 years, the boy was followed up by a pediatrician and a dermatologist. There was no need for hospital treatment. The skin lesions were slowly regressing (Figure 4). The Darier's sign remained positive (Figure 5). He had no blisters since the age of 2 years. Oral and topical treatment was adjusted according to the clinical flares. During summer months, due to increased friction (sports activities, sweating), antihistamines and/or mast cell stabilizers were increased, while during autumn and winter months he was periodically without treatment. He developed no signs of systemic mastocytosis or growth retardation. However, the parents were advised to carry his medical records, just in case of skin manifestations worsening. The parents were also informed that radio contrast substances containing iodine, as well as drugs such as aspirin, NSAIDs, codeine, morphine, may be associated with exacerbations, and that they have to inform medical workers about DCM.

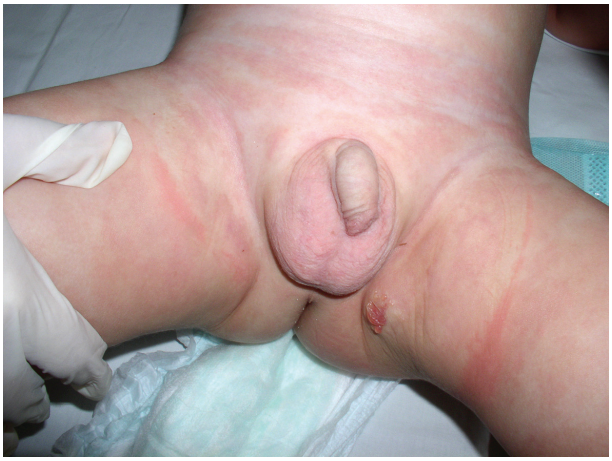

Figure 2. Erythema, marked dermographism and tense blisters in the diaper area

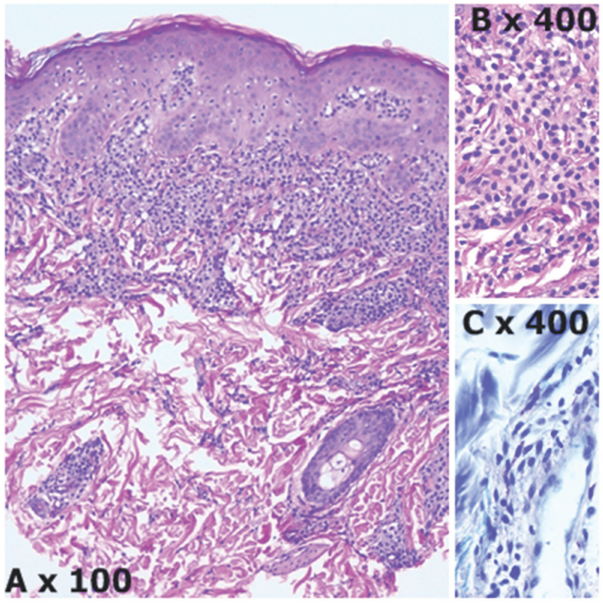

Figure 3 A, 3 B. Increased number of mast cells in the papillary dermis (x 100) and mast cell aggregates around the blood vessels (x 400); 3. C. Mast cells infiltrations confirmed by toluidine blue staining (x 400)

Discussion

Based on limited data, it is believed that males and females are equally affected by mastocytosis and that there is no racial predominance. In children, internal organ involvement is not frequent (4).

Our patient developed skin lesion before the age of 2, without systemic involvement. His initial presentations were in line with data published by other authors: pediatric-onset

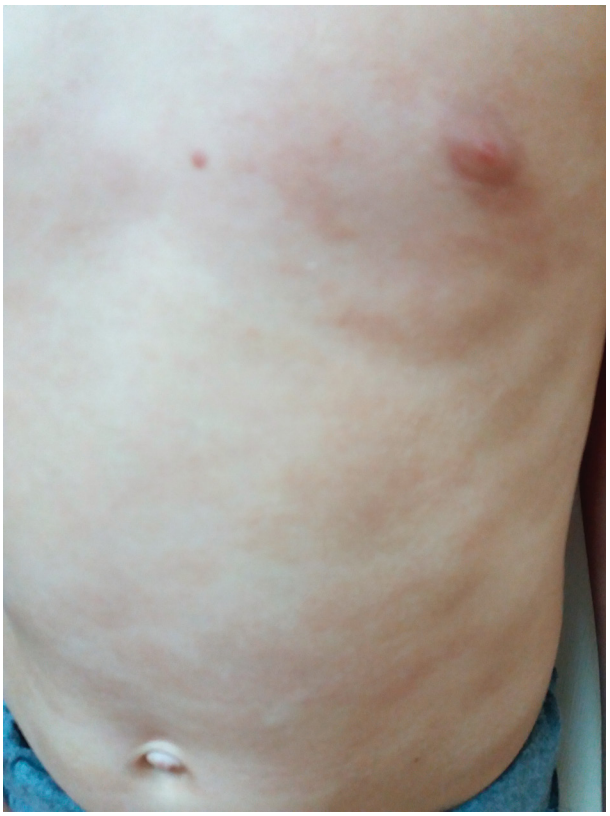

Figure 4. Slightly erythematous leathery skin on the trunk in a nine-year-old boy

of mastocytosis is commonly diagnosed prior to 2 years of age, and it is usually a cutaneous disease (4). Despite its clinical forms, the prognosis of mastocytosis depends on the age of onset. Therefore, the condition may be divided into childhood onset mastocytosis and adult onset mastocytosis (5 - 9). The age of mastocytosis onset is very important because it has prognostic implications (10). The majority of children with CM experience spontaneous resolution of skin lesions by adolescence, whereas adult-onset mastocytosis is chronic and tends to progress to the systemic form (7, 9, 10).

DCM is rare, but can present with more severe symptoms. It accounts for 1 – 3% of cases of CM, and it may involve the whole body, the central region and scalp being most affected. DCM can appear at birth (congenital and neonatal) or in early infancy (4). Blistering and bullae are the most common symptoms, and the blisters may be hemorrhagic. The skin may be leathery and thickened. Hyperpigmentation may persist into adulthood and with prominent dermographism (4). Due to the extent of the lesions and their severity, systemic symptoms can be present due to the large amount of mast cell mediators released locally and absorbed locally and systemically. Whole body flushing, pruritus, diarrhea, intestinal bleeding, hypotension, anemia, hypovolemic shock and deaths have been reported (11). Visceral involvement with lymphadenopathy and hepatomegaly may be present (12). DCM skin lesions often resolve by adolescence. In contrast, a small minority of patients with DCM and familial mastocytosis exhibit a chronic course with persistently elevated serum tryptase levels and extracutaneous mast cell infiltrates due to germline mutations in c-KIT (3, 14, 15).

During the 10-year period (2006 to 2015), 40 children with mastocytosis were hospitalized at our Department of Pediatric Dermatology. Among them, 30 patients (75%) had urticaria pigmentosa; 7 patients (17.5%) had mastocytoma, and 3 patients (7.5%) had DCM. Our data are in line with a retrospective study from Mexico that reviewed 71 cases of CM in children, of whom 53 had urticaria pigmentosa, 12 had mastocytomas, and 6 had DCM. A positive Darier's sign was found in 94% of patients. In the Mexican study, in 92% of cases the disease onset was recorded in the first year of life. About 80% of patients presented with an improvement or had a spontaneous resolution of the disease (15). Our patient did not have associated symptoms. In the Mexican study, associated symptoms and signs were absent in those with mastocytomas, except for itching.

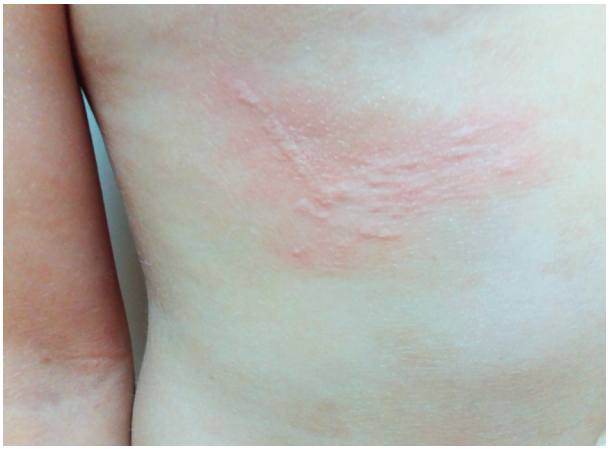

Figure 5. Positive Darier's sign in a nine-year-old boy

Diarrhea was seen in 7/36 cases of urticaria pigmentosa, and 2/5 cases of DCM (15).

In our patient the treatment was symptomatic and included oral antihistamines in combination with mast cell stabilizers, mild topical steroids and avoidance of friction. This approach is in the line with guidelines for diagnosis and treatment of CM in children (4). According to the guidelines, avoidance of triggering factors includes hot temperatures and to a lesser extent, cold temperatures, anxiety and stress. Systemic therapy in pediatric mastocytosis includes H1 antihistamines; combined treatment with H1 and H2 antihistamines; oral cromolyn sodium; oral methoxypsoralen therapy with long-wave psoralen plus ultraviolet A radiation (PUVA). The PUVA is most effective in non-hyperpigmented DCM. Nonetheless, there are some suggestions about peri-operative considerations since patients with mastocytosis have an increased mast cell burden and mast cells are implicated in the pathophysiology of anaphylaxis. Because of understandable concern about adverse reactions which may follow administration of pharmacologic agents in the peri-operative period, various opioids, muscle relaxants, analgesics, and anesthetics should be used with caution. The authors suggest administration of slow intravenous injections, rather than a single bolus of needed drugs (opioids, muscle relaxants) known to activate mast cells. So, the medically indicated drugs (opioids, muscle relaxants) should not be eliminated from therapeutic consideration in the perioperative period, unless there is a clear prior history of sensitivity (4).

Conclusion

Diffuse cutaneous mastocytosis is rare in pediatric patients and it is usually not associated with systemic manifestations. However, regular check-ups, including personal history of gastrointestinal manifestations and lymphadenopathy, should be adopted with caution. The serum tryptase level should be monitored, since it may indicate increased mast cell activation and instability.

Abbreviations

UP - urticaria pigmentosa
DCM - diffuse cutaneous mastocytosis
CBC - complete blood count
NSAID – non-steroidal anti-inflammatory drug
CM - cutaneous mastocytosis
PUVA - psoralen plus ultraviolet A radiation

Disclosure

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Difuzna kutana mastocitoza u dečjem uzrastu – prikaz slučaja

Sažetak

Mastocitoze predstavljaju grupu bolesti koje karakterišu klonalna proliferacija i akumulacija mastocita u jednom ili više organa/tkiva, sa različitim kliničkim prezentacijama. Kod dece su najčešće kutane forme mastocitoze, dok je sistemska mastocitoza retka. Dijagnoza kutanih formi mastocitoze postavlja se na osnovu kliničke slike i histopatološkog nalaza. Prikazujemo pacijenta kod koga su se prve promene na koži pojavile u uzrastu od 18 meseci. Klinička slika i histopatološki nalaz bili su karakteristični za difuznu kutanu mastocitozu. Period praćenja bio je sedam godina. Terapija je podrazumevala primenu H1 antihistaminika per os, stabilizatore membrane mastocita, blage kortikosteroidne preparate za lokalnu primenu i izbegavanje frikcije. Tokom perioda praćenja, postepeno je dolazilo do delimične regresije kožnih promena i poboljšanja kvaliteta života pacijenta. Ovaj prikaz slučaja treba da poveća svest i znanje kliničara o ovom retkom obliku kutane mastocitoze u dečjem uzrastu.

Ključne reči: Kutana mastocitoza; Dete; Dijagnoza; Znaci i simptomi; Mastociti; Dermatološki preparati; Ishod terapije

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Indolent Systemic Mastocytosis – a Case Report

Ljuba VUJANOVIĆ[1]*, Marina JOVANOVIĆ[1], Zoran GOLUŠIN[1], Olivera LEVAKOV[1], Aleksandra PETROVIĆ[2], Jasmina SEKULIĆ[3]

[1]Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia, University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia
[2]Løvåsen sykehjem Undervisningssykehjem, Bergen, Norway
[3]General Hospital "Đorđe Joanović" Zrenjanin, Serbia

*Correspondence: Ljuba Vujanović, E-mail: ljuba.vujanovic@mf.uns.ac.rs

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Abstract

Indolent systemic mastocytosis is a benign form of systemic mastocytosis characterized by an abnormal proliferation of mast cells either in the bone marrow or in numerous tissues. Case Report: A 27-year-old female patient was admitted to our department due to urticaria which started a month ago. Before the skin changes appeared, our patient suffered from a toothache, so she took various painkillers (nimesulide, ibuprofen, acetylsalicylic acid, paracetamol). During skin examination, individual hyperpigmented macules on the trunk and lower limbs were observed as incidental findings. The patient reported having them for the last two years. Darier's sign was positive. Following the examination, she was admitted due to suspected urticaria pigmentosa. Laboratory Findings: erythrocyte sedimentation rate: 9 mm/h; complete blood count, urine, blood glucose, total and direct bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, urea, creatinine, and uric acid were within normal ranges. Electrolytes: sodium, potassium, chlorine clearance, total calcium and calcium ionized, osteocalcin, and crosslaps were within normal ranges as well. Fibrinogen: 5.57 g/l; 5-Hydroxyindoleacetic acid: 49.8 umol/dU (10.4 - 31.2). Bone densitometry, chest x-ray and upper abdomen ultrasound findings were normal. The suspected clinical diagnosis of urticaria pigmentosa was confirmed by skin biopsy. Histopathological examination of the bone marrow showed moderately increased cellularity (60 - 70%). All three types of blood cells were slightly multiplied. Focal infiltrations were found in the perivascular area, consisting of elongated, oval cells with abundant eosinophilic granular cytoplasm. The nuclei were regular, oval shaped with finely granular chromatin and inconspicuous nucleoli. No nuclear atypia was found. These cells are highly CD117-positive. This finding strongly indicated bone marrow infiltration in systemic mastocytosis. The diagnosis was based on 'major' and 'minor' diagnostic criteria. The recommended therapy included H1 and H2 antagonists and topical corticosteroids. Conclusion: Regular follow-up was recommended in order to prevent complications and malignant alterations.

Key words: Mastocytosis, Systemic; Mastocytosis, Cutaneous; Urticaria Pigmentosa; Diagnosis; Signs and Symptoms; Histamine H1 Antagonists; Histamine H2 Antagonists; Dermatologic Agents; Case Reports

Mastocytosis is defined as a heterogeneous group of hematopoietic disorders characterized by increased accumulation of mast cells in one or more organs (1, 2). The classification of the World Health Organization (WHO) classifies it into cutaneous and systemic mastocytosis (3). The clinical presentations and the course of mastocytosis are variable, ranging from pure cutaneous mastocytosis (CM) to different forms of systemic mastocytosis (SM).

In 1869, Nettleship and Tay described a rare form of urticaria with pigmented papular lesions, later termed as urticaria pigmentosa by Sangster in 1878. After mast cells were described by Paul Ehrlich in 1879, the disease was classified as mastocytosis. Until 1949, it was believed that mastocytosis was only a cutaneous disease, but then Ellis described involvement of visceral organs as well (4).

Systemic mastocytosis is a disease of unknown etiology, characterized by abnormal proliferation of mast cells. Skin is the most commonly involved organ, but bone marrow, liver, spleen, lymph nodes and some other organs may be involved as well (5, 6).

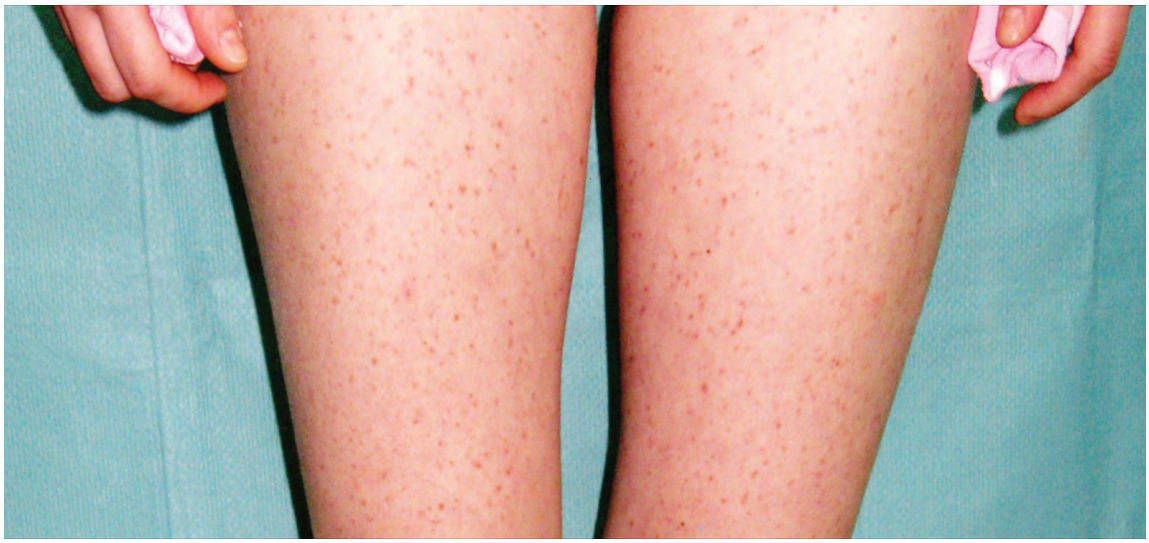

Figure 1. Hyperpigmented macules on the lower limbs

Case Report

A 27-year-old female patient was referred to a dermatologist due to onset of acute urticaria after taking non-steroidal anti-inflammatory drugs. During skin examination, individual hyperpigmented macules on the trunk and lower limbs were observed as an incidental finding. The patient reported having them for the last two years. Darier's sign was positive (Figure 1).

Relevant laboratory tests and diagnostic procedures were run, as urticaria pigmentosa was suspected. Laboratory findings: erythrocyte sedimentation rate (ESR): 9 mm/h; complete blood count (CBC), urine, blood glucose (BG); total and direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), urea, creatinine, and uric acid were within normal ranges. Electrolytes: sodium (Na), potassium (K), chlorine clearance (Cl), total calcium and calcium ionized; osteocalcin, crosslaps were within normal ranges as well. Fibrinogen: 5.57 g/l; 5-Hydroxyindoleacetic acid (5-HIAA): 49.8 umol/dU (10.4 - 31.2). Bone densitometry, chest x-ray and upper abdomen ultrasound findings were normal.

Histopathology of the skin showed diffuse hyperkeratotic epidermis. Perivascular infiltration of the upper dermis consisted of moderate mononuclear inflammatory infiltrates with increased number of spindle mast cells. Adnexal atrophy was observed. Sweat glands were of normal appearance and distribution (Figure 2, 3). Histopathology of the bone marrow showed increased cellularity (60 - 70%) with moderate reduction of fat tissue. All three types of blood cells were present, preserved continuity of maturation and distribution, slightly multiplied. Megakaryocytes were individual and polymorphic. The granulocyte lineage was moderately hyperplastic, without maturation disorders and with slight domination of neutrophil granulocytes. Erythrocyte lineage was formed of large normoblastic islands, with preserved maturation and morphology. Small round lymphocytes and plasmocytes had an interstitial distribution.

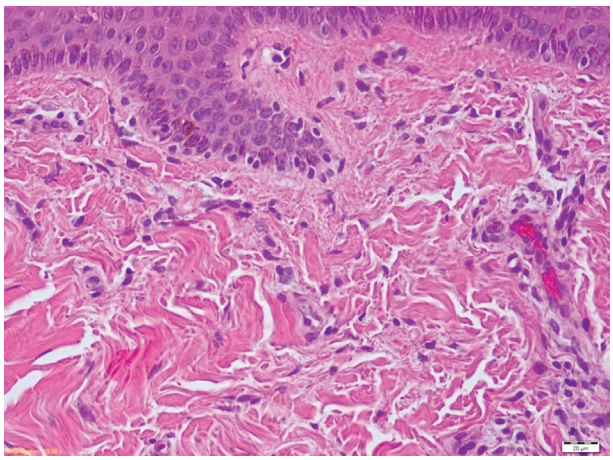

Figure 2. Perivascular infiltration of the upper dermis consisted of moderate mononuclear inflammatory infiltrate

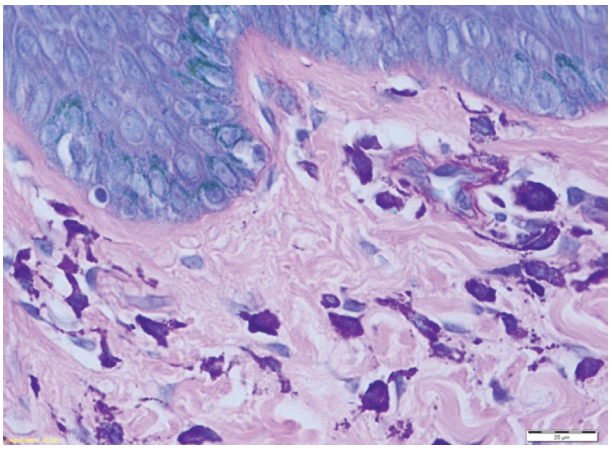

Figure 3. Perivascular infiltration of the upper dermis consisted of moderate mononuclear inflammatory infiltrate with increased number of spindle mast cells

A focal infiltration pattern was detected in the perivascular area, consisting of elongated, oval cells with abundant eosinophilic granular cytoplasm. The nuclei were regular, oval shaped with finely granular chromatin and inconspicuous nucleoli. No nuclear atypia was found. These cells were highly CD 117-positive. In addition to already described cells, morphologically, mastocytes, small round lymphocytes, eosinophils, and some plasmocytes were observed. This finding strongly indicated bone marrow infiltration in systemic mastocytosis. Oral antihistamines and topical corticosteroids were administered. The patient did not report for regular check up.

Discussion

In 2008, WHO classified mastocytosis as a subtype of myeloproliferative neoplasms. It was divided in two main types, cutaneous and systemic, and classified into different subtypes. Subtypes of cutaneous mastocytosis are urticaria pigmentosa, maculopapular cutaneous mastocytosis, diffuse cutaneous mastocytosis, and mastocytoma of the skin. Subtypes of systemic mastocytosis are indolent systemic mastocytosis, systemic mastocytosis with an associated hematologic non-mast cell lineage disease, aggressive systemic mastocytosis, mast cell leukemia, mast cell sarcoma, mast cell sarcoma and extracutaneous mastocytoma (3). For dermatologists, the points of interest are cutaneous mastocytosis without bone marrow involvement and indolent systemic mastocytosis, including bone marrow involvement and cutaneous symptoms (8). Mastocyte activation subsequently triggers pruritus, erythema, urticaria, abdominal pain, diarrhea, and psychiatric disorders (6, 8). Our patient complained of itching. Mastocyte degranulation is stimulated by heat, cold, pressure, bacterial toxins, drugs (aspirin, codeine, morphine) (6, 9). Our patient was taking various nonsteroidal anti-inflammatory drugs, including acetylsalicylic acid due to toothache. Systemic indolent mastocytosis is a benign form of systemic mastocytosis characterized by an abnormal proliferation of mast cells only in the bone marrow or in numerous tissues. In our patient mast cell proliferation was observed in the skin and in the bone marrow.

The diagnosis was based on diagnostic criteria (according to WHO classification). One major criterion was fulfilled (multifocal aggregates of mast cells in bone marrow biopsy specimen) and one minor criterion (atypical morphology in more than 25% mast cells in skin biopsy specimen). Also, the diagnosis can be established if at least three minor criteria are fulfulled - more than 25% of mast cells in the bone marrow or other extracutaneous organs show abnormal morphology or are spindle-shaped, KIT mutation at codon 816 in extracutaneous organs, KIT + mast cells in bone marrow show aberrant expression of CD2 and/or CD25 and serum total tryptase > 20 ng/ml (10).

The aim of mastocytosis therapy is to remove or reduce the symptoms. Since there is no specific therapy, and having pruritus as a main symptom, systemic antihistamines and topical corticosteroids were administered. Success of the therapy remained unknown, because our patient has not reported for regular check ups ever since. In addition to already described therapy, if the symptoms affect the quality of life, different therapeutic modalities may be applied, such as leukotriene antagonists, corticosteroids, PUVA therapy. A severe form of indolent systemic mastocytosis was treated by inhibitors of tyrosine kinase and imatinib mesylate with good therapeutic response (Marton et al., Akin et al., Hoffman et al., Ustun et al.) (7, 11, 12, 13). Although positive outcome of systemic mastocytosis is expected, extremely rare, aggressive form may develop.

Conclusion

This case report presents a female patient with a rare presentation of indolent systemic mastocytosis. Due to possible, although rare, development of aggressive forms of the disease, regular check ups, including upper abdomen ultrasound examination and serum tryptase level evaluation, as well as regular follow ups were recommended.

Abbreviations

CA - calcium
ESR - erythrocyte sedimentation rate
CBC - complete blood count
AST - aspartate aminotransferase
ALT - alanine aminotransferase
GGT - gamma-glutamyl transferase
Na - sodium
K - potassium
Cl - chlorine clearance
5-HIAA - 5-Hydroxyindoleacetic acid
WHO - World Health Organization
CM - cutaneous mastocytosis
SM - systemic mastocytosis
PUVA - psoralen and ultraviolet A

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Indolentna sistemska mastocitoza – prikaz slučaja

Sažetak

Indolentna sistemska mastocitoza je benigna forma sistemske mastocitoze za koju je karakteristična abnormalna proliferacija mast ćelija samo u koštanoj srži ili i u drugim organima. Bolesnica, stara 27 godina, došla je na pregled zbog urtikarije koja se javila mesec dana ranije. Pojavi kožnih promena prethodila je zubobolja zbog koje je koristila veći broj analgetika (nimesulid, ibuprofen, acetilsalicilnu kiselinu, paracetamol). Prilikom pregleda, kao usputan nalaz, uočavaju se pojedinačne hiperpigmentovane makule na trupu i donjim ekstremitetima. Anamnestički je dobijen podatak o pojavi ovih promena unazad dve godine. Darijerov znak je bio pozitivan. Hospitalizovana je zbog sumnje na urtikariju pigmentoza (*Urticaria pigmentosa*). Laboratorijski nalazi: SE: 9 mm/h, KKS, urin, ŠUK, bilirubini, AST, ALT, GGT, urea, kreatinin, ac. urikum u granicama referentnih vrednosti. Elektroliti: Na, K, Cl, Ca jonizovani, osteokalcin, Kroslaps u granicama referentne vrednosti, fi-

brinogen 5,57g/l; 5- HIAA: 49,8 umol/dU (10,4–31,2). Denzitometrija kostiju, RTG pluća, ultrasonografski nalaz gornjeg abdomena u granicama referentnih vrednosti. Patohistološki nalaz bioptata kože ukazivao je na klinički postavljenu dijagnozu – *Urticaria pigmentosa*. Patohistološki nalaz biopsije koštane srži: umereno povećane celularnosti (60–70%). Sve tri loze su lako umnožene. Perivaskularno, na par mesta postoji infiltrat koji se sastoji od izduženih, ovalnih ćelija, obilne, eozinofilne, diskretno granulirane citoplazme. Jedra su pravilna, ovalna, fino granuliranog hromatina, neupadljivog nukleusa, bez atipije. Ove ćelije su izrazito CD117+. Nalaz najviše odgovara infiltraciji koštane srži u sklopu sistemske mastocitoze. Dijagnoza je postavljena na osnovu major i minor dijagnostičkih kriterijuma. Terapija: H1 i H2 antagonisti i topikalno kortikosteroidi. Zaključak. Neophodne su redovne kontrole i praćenje bolesnika zbog mogućih komplikacija i maligne transformacije.

Ključne reči: Sistemska mastocitoza; Kutana mastocitoza; Urticaria pigmentosa; Dijagnoza; Znaci i simptomi; Histaminski H1 antagonisti; Histaminski H2 antagonisti; Dermatološki agensi; Prikazi slučajeva

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DERMOSCOPY CASE OF THE MONTH
Mammary Paget's Disease - a Case Report

Tatjana ROŠ[1,2], Marijana BADRKIĆ[2], Marijana MACANOVIĆ[2], Nenad ŠOLAJIĆ[2,3], Branislava GAJIĆ[1,2]

[1]Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia
[2]Faculty of Medicine, University of Novi Sad, Serbia
[3]Department of Pathology, Oncology Institute of Vojvodina, Sremska Kamenica, Serbia

*Correspondence: Tatjana Roš, E-mail: tatjana.ros@mf.uns.ac.rs

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Abstract

Mammary Paget's disease is a rare intraepithelial carcinoma of the nipple/areola complex often associated with ductal breast carcinoma. We report a case of a 55-year-old female patient with a classical form of mammary Paget's disease associated ductal ipsilateral breast carcinoma. Dermoscopy of Paget's disease revealed a whitish-pink area with polymorphous vessels organized in irregular nests separated by pale streak-like structures, with peripheral light brown diffuse pigmentation. Dermoscopic features described in this case are in agreement with rare previous reports and may contribute to better differentiation of mammary Paget's disease from clinically similar lesions.

Key words: Paget's Disease, Mammary; Skin Neoplasms; Diagnosis; Nipples; Breast Neoplasms; Dermoscopy; Case Reports

Introduction

Mammary Paget's disease (MPD) is a rare intraepithelial carcinoma of the nipple/areola complex frequently associated with ductal carcinoma *in situ* (DCIS) or invasive ductal breast carcinoma. MPD accounts for 1–5% of all breast carcinomas. It is most commonly diagnosed in postmenopausal women, in the sixth decade of life. Less frequently, MPD affects men, having a worse prognosis, although there is no evidence that the disease in men has a different course (1). Clinical presentation of MPD is often tricky and dermoscopic patterns are currently not defined. The diagnostic hallmarks of MPD are epidermal Paget's cells, but whether they originate from underlying ductal breast carcinoma or mutated keratinocytes is still debatable. Sometimes, even histological features are not distinct enough and ancillary diagnostic techniques are required.

Case Report

A 55-year-old female was referred for a dermatological assessment of an erythematous, slightly scaling asymptomatic plaque spreading irregularly from the left nipple to

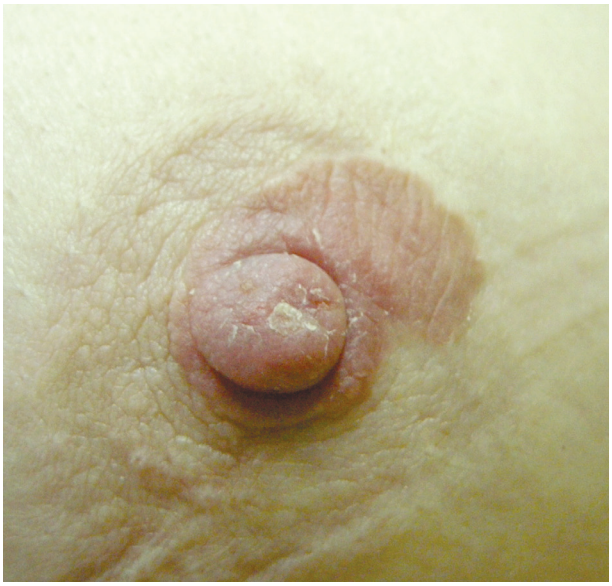

Figure 1. Erythematous, scaling plaque affecting the nipple/areola complex and the surrounding skin of the left breast

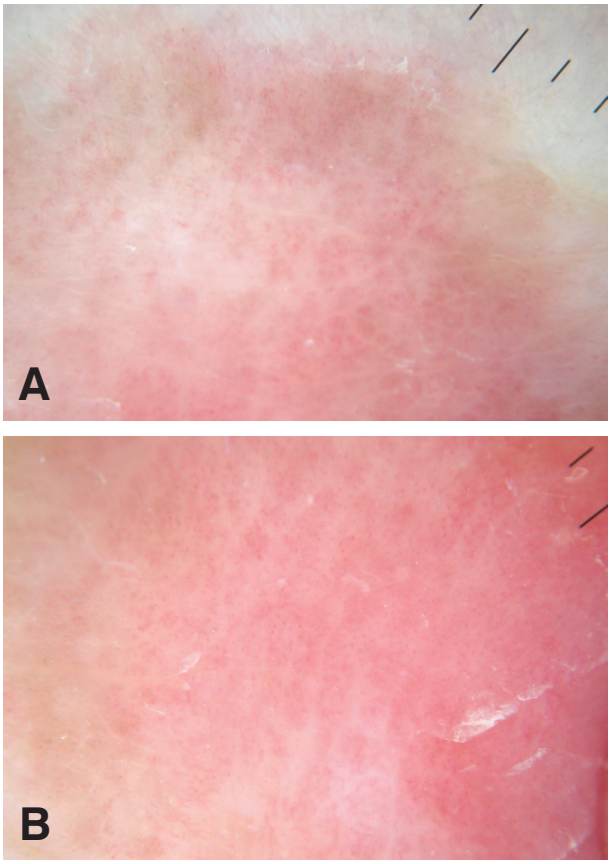

Figure 2 A, B. Dermoscopic examination (carried out with DermLite Pro HR; 3 Gen) shows a whitish-pink area with polymorphous delicate dotted and irregular linear vessels partially organized in irregular nests separated by pale streak-like structures, fine scales at the surface and light brown diffuse pigmentation at the periphery of the lesion

the areola and the surrounding skin for more than a year (Figure 1).

Dermoscopy revealed a whitish-pink area with polymorphous delicate dotted and irregular linear vessels organized in irregular nests and separated by pale streak-like structures, with light brown diffuse pigmentation at the periphery of the lesion (Figure 2. A, B).

The nipple/areola complex with the underlying breast tissue was excised, fixed in buffered formalin and sent to the Pathology Department for examination. Histopathological findings on standard hematoxylin-eosin (HE) sections revealed large atypical neoplastic polygonal epithelial cells infiltrating the epidermis and infundibular region of hair follicles. The neoplastic cells were arranged in small solid groups and rare adenoid formations haphazardly distributed throughout the epidermis. The dermis displayed reactive changes including telangiectasia and chronic inflammation (Figure 3. A, B). Along with Paget's disease, multifocal *in situ* and invasive ductal breast carcinomas were found. Since the sentinel lymph node biopsy was positive, subsequent left axillary dissection was performed. Histopathological examination revealed metastatic carcinoma in additional 5 lymph nodes. Hormonal receptor status of the primary ductal carcinoma was as follows: estrogen receptors positive, progesterone receptors negative and human epidermal growth factor receptor type 2 (HER2/neu) strongly positive (3+).

Discussion

MPD skin lesions are usually scaly, erosive or exudative eczema-like plaques of the nipple/areola complex, tending to spread to the surrounding skin and to cause destruction of the involved structures (1). Cases of pigmented MPD lesions have also been described. Patients may complain of itch or pain. Clinical presentation, therefore, poses a diagnostic problem since MPD may mimic a variety of inflammatory, microbial and neoplastic diseases, such as eczema, psoriasis, tinea, impetigo, lichenoid keratosis, erosive adenomatosis, Bowen's disease, basal cell carcinoma or even melanoma.

Besides the usual diagnostic procedures (a comprehensive history of the lesion, complete skin examination, microbial smear and culture from the skin lesion), it is advisable to use dermoscopy in further diagnostic work-up.

On dermoscopy examination, eczema and psoriasis present with yellowish to whitish scales and patchy or uniformly distributed dotted vessels, whereas Bowen's disease presents with scales and glomerular vessels (2, 3). In pigmented Bowen's disease, small brown globules regularly packed in a patchy distribution and structureless grey to brown pigmentation can also be seen (3). Errichetti et al. have reported dermoscopy findings in a case of erosive adenomatosis of the nipple: whitish/yellowish hyperkeratosis and sparse dotted vessels on a reddish-whitish background (4). The dermoscopic features of lichenoid keratosis vary, depending on the age

of the lesion, so pinkish background, annular granular structures, gray pseudonetwork and diffuse blue-gray dots can be seen (5).

Typical dermoscopic features of basal cell carcinoma and melanoma are numerous and well described, pointing to the histologic type, tumor thickness and other prognostic factors (6, 7).

Pigmented MPD is a rare subtype, but extremely challenging, since it is dermoscopically indistinguishable from melanoma. Reports of pigmented MPD describe diffuse brown pigmentation, reticular pigmentation, irregular black dots, blue-gray dots, scar like depigmentation and streaks (8 - 10).

Dermoscopic patterns of classical non-pigmented MPD are often described as non-specific. However, we have compared our observations to several other published cases (11 - 13) and noticed similarities among them, with correspondence to what we may expect in histopathology. Common features include a variable degree of pinkish background with polymorphous vessels that may represent dermal inflammation with irregular elongation of rete ridges and irregularly dilated capillaries typical for malignant neoplasms. Other common features are streak-like structures (described elsewhere as whitish reticulation, shiny-white streaks or chrysalis-like structures), separating aforementioned pinkish-vascular areas and giving a partially lobular look to the lesion. It is our assumption that clusters of Paget's cells are more translucent than keratinocytes, depicting nests in the dermoscopy images. Streak-like structures could be reflections of uninvolved epidermis or fibrosis in advanced stages of the disease.

Following a diagnostic algorithm, if a suspicion of neoplastic lesion remains, biopsy with histopathological examination is required. The diagnosis of MPD is based on the presence of large epidermal Paget's cells with clear and abundant cytoplasm, pleomorphic and hyperchromatic nuclei and prominent nucleoli. These cells are usually clustered into solid nests and occasionally into glandular structures, mainly but not exclusively confined to the basal half of the epidermis. Intracellular mucin and acinar formation are helpful histopathological features favoring MPD over melanoma and Bowen's disease, the two most frequent diagnostic pitfalls (1).

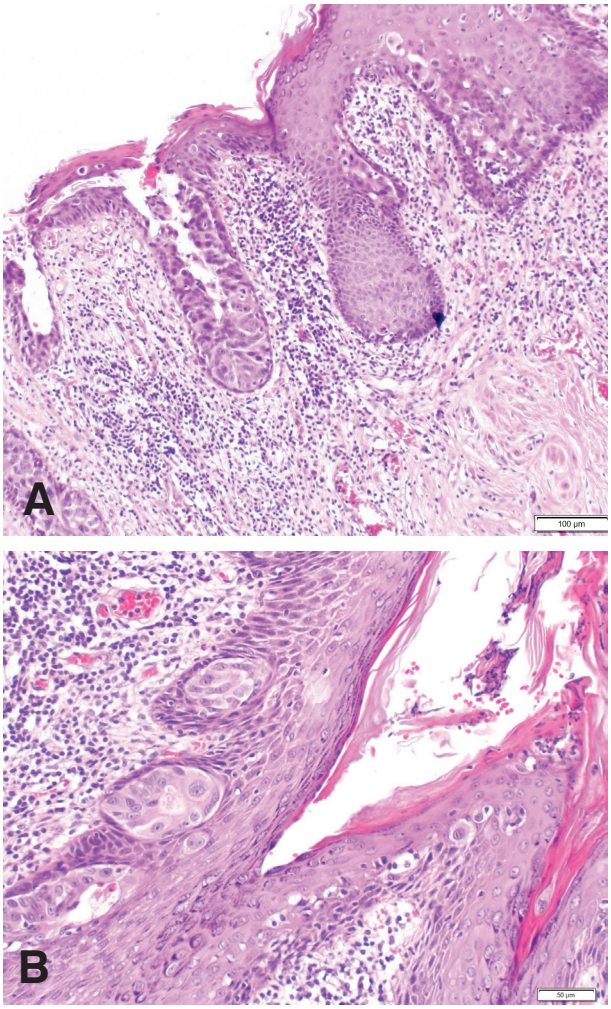

Figure 3 A. Histopathologic findings on standard hematoxylin-eosin sections (HE, × 100): neoplastic large atypical polygonal Paget's cells with clear cytoplasm infiltrating the epidermis, arranged in solid groups; telangiectasia and chronic inflammatory infiltrate in the dermis

Figure 3 B. Histopathologic findings on standard hematoxylin-eosin sections (HE, × 200): neoplastic large atypical polygonal Paget's cells with clear cytoplasm infiltrating the epidermis and infundibular region of hair follicles, arranged in small adenoid formations; telangiectasia and chronic inflammatory infiltrate in the dermis

Inability of standard histopathological examination to distinguish the aforementioned entities demands immunohistochemical staining. Paget's cells show overexpression of low molecular weight cytokeratins, especially cytokeratin 7, but it had been observed that MPD

has a similar immunohistochemical staining pattern and hormone receptor reactivity as that of the underlying breast carcinoma. The Paget's cells of the nipple are often HER2 positive (1, 14). Based on such findings, along with the presence of acinar arrangement of neoplastic cells, immunohistochemistry and receptor status of MPD were not performed in our case, since it would be irrelevant for the future therapeutic approach.

Conclusion

Timely recognition of MPD is of great importance, not only because it is a cancer, but because of a high probability of an associated, prognostically more serious ductal breast carcinoma. Dermatologists are usually first in line to face MPD, so they should use all the available tools in order to make a proper diagnosis. Dermoscopic features described in this case are in agreement with rare previous reports and may contribute to better differentiation of MPD from other clinically similar lesions. The spectrum of disorders entering the differential diagnosis can be narrowed by comparison of dermoscopic findings with other dermoscopically described entities and by clinico-dermoscopic correlation.

Abbreviations

MPD - mammary Paget's disease
DCIS - ductal carcinoma in situ
HE - hematoxylin-eosin
HER2/neu - human epidermal growth factor receptor type 2

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Padžetova bolest dojke – prikaz slučaja

Sažetak

Padžetova bolest dojke je redak intraepitelijalni karcinom koji zahvata strukture mamile i areole, često udružen sa duktalnim karcinomom dojke. Prikazujemo pacijentkinju staru 55 godina, sa klasičnim oblikom Padžetove bolesti i pridruženim duktalnim karcinomom iste dojke. Dermoskopskim pregledom uočeni su polimorfni krvni sudovi na beličastoružičastoj podlozi, organizovani u nepravilna gnezda koja su razdvojena bledim trakastim strukturama, a na periferiji lezije bledosmeđa difuzna pigmentacija. Dermoskopske karakteristike opisane u ovom slučaju u skladu su sa malobrojnim objavljenim prikazima i mogu doprineti boljoj diferencijaciji Padžetove bolesti dojke od klinički sličnih lezija.

Ključne reči: Padžetova bolest dojke; Kožne neoplazme; Dijagnoza; Bradavice; Neoplazme dojke; Dermoskopija; Prikazi slučajeva

A Report on the 14th EADV Spring Symposium, Brussels, 2017

The 14th Spring Symposium of the European Academy of Dermatology and Venereology was held in Brussels, Belgium from 25 to 27 May 2017. Prof. Jo Lambert was the President of the Congress.

The 3-day program covered the majority of exciting fields of dermatovenereology: inflammatory and infectious dermatology, dermatooncology and dermoscopy, cosmetic dermatology, dermatosurgery, dermatopathology, sexually transmitted diseases.

Plenary lectures reflected the diversity of pathology in skin diseases, main topics being the inherited mechanisms of atopic dermatitis, treatment of sexually transmitted infections, contact allergy, vitiligo and the role and value of histopathology. The title of the opening lecture was "Can we prevent ageing?" and master class was about the diseases of the hair and scalp.

The speakers came from 31 countries, including Serbia. Our country was represented by Prof. Miloš Nikolić who delivered a lecture titled: "How to manage chronic cutaneous lupus erythematosus" in the session "The spectrum of lupus erythematosus". Also, there were 3 e-posters from Serbia.

The next EADV Spring Symposium will take place in Budva, Montenegro in May 2018. In 2019, the World Congress of Dermatology will be held in Milan, so there will be no EADV Spring Symposium.

Dušan Škiljević
Clinic of Dermatovenereology,
Clinical Center of Serbia
Department of Dermatovenereology,
Faculty of Medicine,
University of Belgrade
E-mail: dusanskiljevic@yahoo.com

Legend: Prof. Dr. Miloš Nikolić, Dr. Emiliano Antiga and Prof. Dr. Stefan Beissert, the speakers at the "The spectrum of lupus erythematosus" session, with Prof. Dr. Martin Röcken, chairperson of the Scientific Program Committee

A Report on the 13th Congress of the EADO, Athens 2017

The 13th Congress of the European Association of Dermato-Oncology (EADO) was held from 3 - 6 May, 2017 in Athens (Greece) at the Megaron Athens International Conference Centre. Prof. Alexander J. Stratigos was the president of the Congress which has become a major interdisciplinary meeting for clinicians and basic scientists working in the challenging fields of melanoma and non-melanoma skin cancers. The 4-day rich scientific program covered all aspects of melanoma and skin cancers, from epidemiology, diagnosis and prevention to the results of the latest therapeutic trials in advanced tumors. The leading world experts presented up-to-date lectures and gave their opinions based on previous experience how to combine innovative treatment in metastatic melanoma. It was a successful meeting with 1266 delegates from 51 countries, and a total of 208 abstracts from authors coming from 39 countries. The program also featured 143 faculty members who contributed to a total of 36 scientific sessions, including 24 Symposia, 3 Free Communication Sessions, 2 Dermoscopy Courses, 2 Plenary Lecture Sessions, 2 Surgical Workshops and 3 Workshops.

Prof. Lidija Kandolf Sekulović was a session chair for the session "Melanoma in Difficult Situation" and delivered a lecture "Access to Innovative Medicines in Europe - an Overview" in the Special Session "Innovative Pathways for Innovative Treatments in Metastatic Melanoma". There were 8 poster presentations from Serbia. The EADO Congress is a key event, offering a variety of educational sessions dedicated to the latest clinical research and technological advancements and it was a privilege to participate in this meeting.

The next 14th EADO Congress and 9th World Meeting of Interdisciplinary Melanoma/ Skin Cancer Centers will take place in Palau de Congressos venue in Barcelona, from 6 - 9 November, 2018.

Teaching Assistant Dr. Tatjana Radević,
School of Medicine,
Military Medical Academy, Belgrade,
E-mail: tradevic@hotmail.com

Figure 1. Prof. Lidija Kandolf Sekulović (Serbia), Prof. Ana-Maria Forsea (Romania), Prof. Claus Garbe (Germany)

FORTHCOMING EVENTS

Dermatology and Venereology Events 2017/2018

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
13-17 September, 2017	26th EADV Congress, Geneva, Switzerland	16 March, 2017	www.eadvgeneva2017.org
27-30 September, 2017	6th Congress of Dermatovenereologists of Macedonia with International Participation, Ohrid, Macedonia	20 June, 2017	www.unet.com.mk/dermatology
27-30 September, 2017	47th Annual Meeting of European Society for Dermatological Research , Salzburg, Austria	31 May, 2017	www.esdr2017.org
13 October, 2017	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Vojvodina Novi Sad, Serbia	No abstract submission	www.sld.org.rs
13-15 October, 2017	ISD Regional Meeting, Sarajevo, Bosnia and Herzegovina	31 August, 2017	www.pso-simpozij.com
15-17 October 2017	9th World Congress on Itch, Wroclaw, Poland	31 May, 2017	www.itch2017.syskonf.pl
19-21 October 2017	17th ESPD Annual Meeting, Palma de Mallorca, Spain		www.espd.info
30 November - 2 December 2017	8th International Congress of Psoriasis - From Gene to Clinic 2017, London, United Kingdom	01 August, 2017	www.psoriasisg2c.com

Dr. Zorana Kremić, Clinic for Dermatology and Venereal Diseases, Military Medical Academy, Belgrade, Serbia, E-mail: kremicz@me.com

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 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 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.

– 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 proof. 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.

For further information please contact the Editorial Office (Tel: +381 11 3609183) or visit our web site: **www.udvs.org**.

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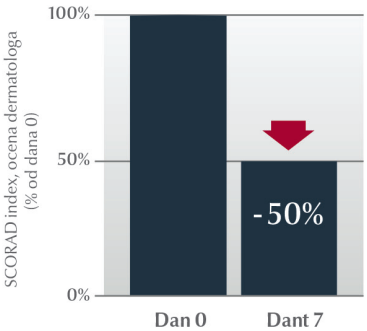

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