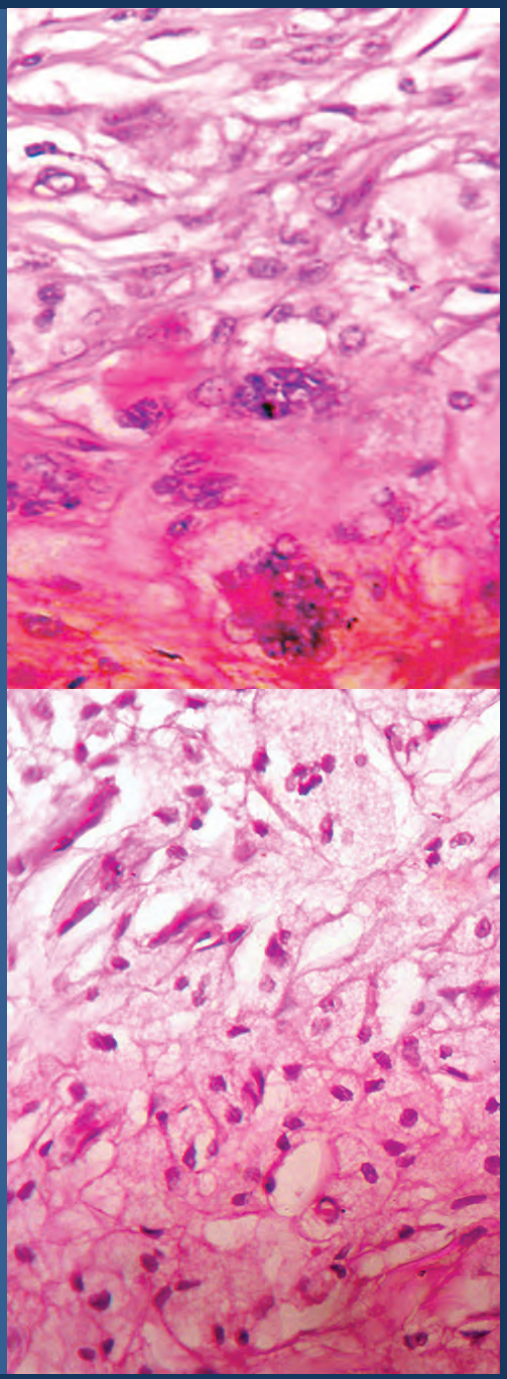
SERBIAN JOURNAL OF
Dermatology and Venereology

ISSN 1821-0902 ISSN 2406-0631 UDC 616.5(497.11) Volume 11, Number 1, March 2019



Published by the
Serbian Association of Dermatovenereologists

SJDV

The Journal is published four times a year with the circulation of 360. Manuscripts are to be submitted to the Editor-in-Chief: Prof. Dr. Lidija Kandolf Sekulović, Vojnomedicinska akademija, Klinika za kožne i polne bolesti, 11000 Beograd, Crnotravska 17
E-mail: serbjdermatol@gmail.com, Tel: +381 11 266 11 22; +381 11 266 00 20.
Open access: www.udvs.org

Published on behalf of The Serbian Association of Dermatovenereologists by Zlatni presek, Beograd

CONTENTS

Serbian Journal of Dermatology and Venereology 2019; 11 (1):1-40.

DOI: 10.2478/sjdv-2019-0001

Epidemiologic and Clinical Differences Between Classic and Hypertrophic Lichen Planus in Nigeria

Okpala CHIBUZOR IFEANYI[1], Adeolu OLADAYO AKINBORO[2], Ifeanyi OGOCHUKWU EZE-JOIFOR[3], Abel N. ONUNU[4] and Benson UCHECHUKWU OKWARA[4]

[1]Dermatology Unit, Department of Medicine, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State Nigeria.
[2]Dermatology Unit, Department of Internal Medicine, Ladoke Akintola University of Technology, Ogbomoso and LAU-TECH Teaching Hospital, Ogbomoso, Oyo State, Nigeria
[3]Dermatology Unit, Department of Medicine, Nnamdi Azikiwe University Nnewi Campus, Anambra State Nigeria.
[4]University of Benin and University of Benin Teaching Hospital, Edo State, Nigeria

*Correspondence: Adeolu Oladayo Akinboro, E-mail: deolusteve111@yahoo.com

UDC 616.516-036.22(669)

Abstract

Introduction. Lichen planus is a chronic inflammatory skin disease known to have several clinical variants with attended variable clinical outcomes. Certain complications have been observed in the hypertrophic type, which were not found in association with the classic variant. **Objective:** To identify the epidemiologic and clinical differences between the classic and hypertrophic lichen planus and clinical correlates. **Material and Methods**. Of 104 participants with lichen planus included in the study, 49 had classic and 55 hypertrophic lichen planus. Demographic and clinical information was obtained. Diagnosis of lichen planus was made clinically and confirmed with histology. The participants were screened for metabolic syndrome, hepatitis B, and C. **Results:** Mean age of all patients was 37.20±13.39 years, with no age and gender differences between the participants with classic and hypertrophic lichen planus. Classic lichen planus was more likely to be painful, (8.2% vs 0.0, p=0.046), generalized (95.9% vs 16.4%, p<0.001), involve the oral mucosa (38.8% vs 0.0, p<0.001), the nails (38.8% vs 1.8, p<0.001), present with kobnerisation (55.1% vs 5.5%,<0.001), Wickhiam striae (69.4% vs 16.4%,p<0.001), associated with Hepatitis B vaccination (16.3% vs 3.6%,p<0.028) and anti HCV positivity (16.3% vs 0.0%, p=0.002). Hypertrophic lichen planus was significantly associated with impaired glucose tolerance/diabetes mellitus (16.4% vs 2.0%, p=0.013), dyslipidemia (74.5% vs 40.8%, p=0.001) and saw- tooth histologic appearance compared to classic type. **Conclusion**: Hypertrophic lichen planus is more likely to be associated with metabolic complications compared to the classic type. Further studies are needed to loink this difference t chronic inflamation.

Key words: Lichen Planus; Comorbidity; Signs and Symptoms; Lichen Planus, Oral, Diabetes Mellitus; Diagnosis; Epidemiologic Studies; Nigeria

Introduction

Lichen planus (LP) is an idiopathic, inflammatory skin disease with unique clinical and histologic features (1–3). The LP commonly affects the skin and the mucous membrane but may also affect the nails and hair (1–3). Clinically, the classic LP is characterized by scaly, flat-topped, polygonal, shining and violaceous papules with reticular, lacy, white lines known as Wickham's striae; however, these papules may appear bluish-grey in individuals with dark skin (1–3). Lichen planus lesions may appear linearly, following the lines of trauma referred to as Koebner phenomenon (4); other variants of LP may include annular LP, atrophic LP, hypertrophic LP, vesiculobullous LP, erosive/ulcerative LP, LP pigmentosus, and lichen planopilaris. Other nomenclature of LP includes mucosal LP, nail LP, inverse LP, LP pemphigoides, lichen planus-lupus erythematosus overlap syndrome and drug-induced LP (1–5).

Classic LP (CLP) typically presents with the four P's: purplish, pruritus, polygonal, and papules and/or plaques. It is usually symmetric, and it favors flexural surfaces, sacral region, and oral mucosa; the scalp, hair, nails, and other mucosal surfaces could be involved

as well but the face is typically spared (1–3, 5, 6). The hypertrophic type of LP (HLP), however, is a distinct type of LP that presents with pruritic hyperpigmented thickened papules and plaques with a preference for the pretibial area of the lower extremities and the ankles (1–7). Typically, HLP is more chronic and pruritic and could rarely become generalized (7, 8). HLP could also infrequently become a disseminated disease (8). The etiology of HLP has been related to the eosinophils (9) and Koebner phenomenon (5). In recent time, HLP has been associated or called a mimicker of squamous cell carcinoma (10–12).

Few Nigerian studies have detailed the epidemiology of LP (13–17), but none has examined the differences or peculiarities of CLP and HLP. The main aim of this study is to research into any existing demographic, clinical and histologic differences between CLP and HLP and to determine the clinical correlates of both types of LP among patients attending the Dermatology Clinics of two Nigerian Teaching Hospitals located in southeastern and southwestern Nigeria.

Methodology

This cross-sectional study was conducted at the Dermatology Clinics of Nnamdi Azikiwe Teaching Hospital, Nnewi and LAUTECH Teaching Hospital, (LTH), Ogbomoso, Nigeria between December 2014 and February 2016. The study population consisted of 104 patients with CLP and HLP. The diagnosis of LP was made clinically and confirmed by histology via skin biopsies obtained from a fresh lesion. According to the inclusion criteria the sample included adult patients with clinical presentation in keeping with classic and hypertrophic types of LP and confirmed by histology. The patients below the age of 18 years, other variants of LP and those with history and clinical features suggestive of lichenoid drug eruptions and other types of LP were excluded. Ethical approval for the study was obtained from the ethical committee of Nnamdi Azikiwe and LAUTECH Teaching Hospitals and informed written consent was taken from all the patients before they were included in the study.

Data of all participants were obtained using an interview-administered questionnaire. The data collected included sociodemographic characteristics such as age, gender, occupation, marital status, and educational level attained. The survey also included the clinical history such as pruritus, pain, previous episode of LP, site of onset, treatment sought, smoking and alcohol intake. We asked for a family history of similar disease, hypertension, diabetes mellitus, and cardiovascular events.

Physical examination: The entire skin, hair, nails, and the mucous membrane were examined in bright daylight. The morphology, arrangement, distribution, and site of the lesions were documented. Wickham striae were examined after the application of mineral oil using the hand-held dermoscopy (RA Bock Diagnostic Pro-Physician 3.5V Dermatolight -LED) to observe the presence of Wickham striae. Other clinical signs, such as the Kobner phenomenon, were noted.

A localized lesion was defined as a LP lesion restricted to a portion of the skin while the generalized cutaneous LP disease was defined as the involvement of the skin of the trunk, the upper and the lower limbs. The participants' body weight was examined using a weighing scale, height was assessed using clinic stadiometer, and body mass index (BMI) was calculated using the formulae weight/height squared.

Laboratory: twelve milliliters of venous blood were collected after 12 hour overnight fasting, twelve milliliters of venous blood were collected from a vein in the antecubital fossa. Serum samples were sent for the detection of anti-hepatitis C virus (HCV) antibody, hepatitis B virus surface antigen (HBsAg), fasting lipid profile [total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein (LDL-c) and triglyceride], and fasting blood glucose using standard methods (18–22). The diagnosis of the metabolic syndrome and dyslipidemia was based on the National Cholesterol Education Program Adult Treatment Panel III working definition (23). Skin biopsy was performed in the consulting room after obtaining consent using an appropriate size punch biopsy needle. The samples were sent to the histopathology laboratory of NAUTH and LAUTECH Teaching Hospital for histology.

Table 1. Sociodemographic Characteristics of Lichen Planus Patients

Characteristics of Lichen Planus	Total	Classic LP N=49	Hypertrophic LP N=55	p-value
Mean age (years) ±SD	37.20±13.39	35.47±12.32	38.75±14.21	0.215
Gender				
Male	55 (52.9)	26 (53.1)	29 (52.7)	0.973
Female	49 (47.1)	23 (46.9)	26 (47.3)	
Occupation				
Civil Servant	29 (27.9)	13 (26.5)	16 (29.1)	0.023
Trading	32 (30.8)	14 (28.6)	18 (32.7)	
Clergy	5 (4.8)	5 (10.2)	0 (0.0)	
Schooling	4 (3.8)	1 (2.0)	3 (5.5)	
Artisan	2 (1.9)	2 (4.1)	0 (0.0)	
Unemployed	27 (26.0)	14 (28.6)	13 (23.6)	
Others	5 (4.8)	0(0.0)	5 (9.1)	
Marital Status				
Single	45 (43.3)	24 (49.0)	21 (38.2)	0.335
Married	56 (53.8)	25 (51.0)	31 (56.4)	
Separated	2 (1.9)	0 (0.0)	2 (3.6)	
Widowed	1 (1.0)	0 (0.0)	1 (0.0)	
Education				
None	3 (2.9)	3 (6.1)	0 (0.0)	0.016
Primary	6 (5.8)	0 (0.0)	6 (10.9)	
Secondary	31 (29.8)	17 (34.7)	14 (25.5)	
Tertiary	64 (61.5)	29 (59.2)	35 (63.6)	

Data analysis

All data of interest were analyzed using statistical package for social sciences (SPSS) version 18.0. Socio-demographic and clinical characteristics of the study participants were presented with simple descriptive statistics (including mean, mode and percentage). To compare continuous variables, Student t-test was used while the categorical variables were analyzed using chi-square test. All data of importance were represented in tables and bar chart. The p-values less than or equal to 0.05 were taken as significant level.

Results

One hundred and four participants with LP, 49 CLP, and 55 HLP, whose mean age was37.20±13.39 years, were enrolled into the study; there were no significant age, gender or the marital status differences among the patients having two clinical variants of LP. While most of the participants had attained at least secondary or tertiary education (p=0.016), the majority of them were civil servants, traders or unemployed (p=0.023) **(Table 1)**.

Although pruritus as a symptom was insignificantly commoner in HLP, CLP patients were more likely to present with a painful rash than HLP (p=0.046). The rate of treatment-seeking behavior from non-dermatologist was high (76.5%); there was no significant difference in the treatment-seeking behavior among CLP and HLP patients. Also, tobacco smoking, alcohol intake behavior, family history of hypertension, diabetes and cardiovascular events between the two groups were not different. The CLP is more likely to be generalised (95.9% vs 16.4%,

Table 2. Clinical Characteristics of Classic and Hypertrophic Lichen Planus

Characteristics of Lichen Planus	Total	Classic LP N=49	Hypertrophic LP N=55	p-value
Clinical history				
Pruritus	93 (89.4)	41 (83.7)	52 (94.5)	0.072
Pain	4 (3.8)	4 (8.2)	0 (0.0)	0.046
Previous history of lichen planus	12 (11.7)	8 (16.3)	4 (7.4)	0.159
Sought treatment from non-dermatologist	78 (76.5)	39 (79.6)	39 (73.6)	0.476
Smoking	4 (3.8)	2 (4.1)	2 (3.6)	1.000
Alcohol	31 (29.8)	15 (30.6)	16 (29.1)	0.866
Family history				
Family history of hypertension	24 (23.1)	11 (22.4)	13 (23.6)	0.866
Family history of diabetes	17 (16.5)	6 (12.5)	11 (20.0)	0.306
Family history of CVE	3 (2.9)	3 (6.1)	0 (0.0)	0.101
Body Area distribution				
Upper Limb distribution	77 (74.0)	47 (95.9)	30 (54.5)	<0.001
Lower Limb distribution	101 (97.1)	49 (100.0)	52 (94.5)	0.097
Chest distribution	21 (20.2)	19 (38.8)	2 (3.6)	<0.001
Abdomen distribution	29 (27.9)	26 (52.1)	3 (5.5)	<0.001
Generalized	56 (53.8)	47 (95.9)	9 (16.4)	<0.001
Sites of LP involvement: the skin, mucosa and nails				
Genital Mucosa	1 (1.0)	1 (2.0)	0 (0.0)	0.287
Oral Mucosa	19 (18.3)	19 (38.8)	0 (0.0)	<0.001
Nail Involvement	20 (19.2)	19 (38.8)	1 (1.8)	<0.001
Skin and nails	20 (19.2)	19 (38.8)	1 (1.8)	<0.001
Skin and Oral Mucosal	19 (18.3)	19 (38.8)	0 (0.0)	<0.001
Skin, Nail and Oral Mucosal	11 (10.6)	11(22.4)	0 (0.0)	<0.001
Clinical Signs				
Koebnerization	30 (28.8)	27 (55.1)	3 (5.5)	<0.001
Wickhiam Striae	43 (41.3)	34 (69.4)	9 (16.4)	<0.001
Hepatitis Screening result and Vaccination history				
Hepatitis B vaccination	10 (9.6)	8 (16.3)	2 (3.6)	0.028
Anti HCV positivity	8 (7.7)	8 (16.3)	0 (0.0)	0.002
HBsAg	5 (4.8)	2 (4.1)	3 (5.5)	1.000
Comorbid Conditions				
Systemic Hypertension	27 (26.0)	12 (24.5)	15 (27.3)	0.747
Diabetes Mellitus	10 (9.6)	1 (2.0)	9 (16.4)	0.013
Dyslipidemia	61 (58.7)	20 (40.8)	41 (74.5)	0.001
Obesity	21 (20.2)	10 (20.4)	11 (20.0)	0.959
Metabolic Syndrome	16 (15.4)	5 (10.2)	11 (20.0)	0.186

CVE – Cardiovascular event like Myocardial Infarction, stroke, HCV – hepatitis C virus infection, LP – Lichen planus

p<0.001), affect the upper limbs (95.9% vs. 54.5%, p<0.001), the upper torso: chest (38.8% vs. 3.6%, p<0.001); abdomen (52.1% vs. 5.5%), oral mucosa (38.8% vs.0.0%, p<0.001), and the nails (38.8% vs. 1.8%, p<0.001) compared to HLP. In term of multiple involvement of body sites, CLP is more likely to significantly affect the combinations of the skin and the nails (38.8% vs. 1.8%), skin and oral mucosa (38.8% vs 0.0%, p<0.001) and the skin, nails and the oral mucosa (22.4% vs 0.0%, p<0.001) compared to HLP **(Table 2)**. Similarly, Kobner's sign (55.1% vs. 5.5%, p<0.001) and Wickham's striae (69.4% vs. 16.4%, p<0.001) were significantly commoner in the patients with CLP compared to those with HLP. The patients with CLP had a history of Hepatitis B vaccination significantly more often (16.3% vs. 3.6%, p=0.028), and anti HCV positivity (16.3% vs. 0%, p=0.002) compared to HLP. However, diabetes mellitus (16.4% vs. 2.0%, p=0.013) and dyslipidemia (74.5% vs. 40.8%, p=0.001) were more likely to be associated with HLP **(Table 2).**

The peculiarities of lichen planus patients (classic and hypertrophic) were examined about mucosal and nails involvement. The involvement of the mouth or the nails in CLP and HLP had no association with the patients' age, metabolic syndrome, and dyslipidemia. Those LP patients with oral mucosa and nail involvement were more likely to have upper limb onset (p<0.001 respectively), generalised LP (p<0.001 respectively), kobnerization (p<0.001 respectively), Wickham's striae (p=0.002 and p<0.001 respectively), and classic type of LP (p<0.001 respectively. The lower limb onset of LP is less likely to be associated with oral and nail involvement, also, localized disease is likely to be associated with no nail and mucosa involvement **(Table 3).**

The histologic characteristics of CLP and HLP were not different in terms of the presence of dense band of lymphocytes infiltration, vacuolar degeneration of dermo-epidermal junction, hyperkeratosis, elongation of rete ridges, melanophage, and colloid body, but the presence of saw-tooth appearance (72.0% vs. 28.0%, p=0.028) which was significantly associated with HLP compared to CLP **(Figure 1).**

The clinical pattern of the nail involvement in LP patients is shown ih **Figure 2.** Twenty (19.23%) patients had nail changes. Longitudinal ridging was the most frequent pattern of nails affectation as above 18 (17.3%), followed in that order by melanonychia 7 (6.7%), nail thinning 4 (3.8%), and pterygium 2 (1.9%). The CLP was significantly associated with longitudinal ridging (34.7% vs. 1.8%, p<0.001) and melanonychia (14.3% vs. 0.0%, p=0.004) as shown in **Figure 3.**

Discussion

The present study shows that CLP is more likely to have upper limb onset, oral involvement, nail involvement and the presence of the eponymous signs of LP such as the Kobner's phenomenon, and Wickham's striae when compared with the HLP. The CLP is also the variant that may be associated with upper limbs, and torso distribution, HCV antibody positivity and

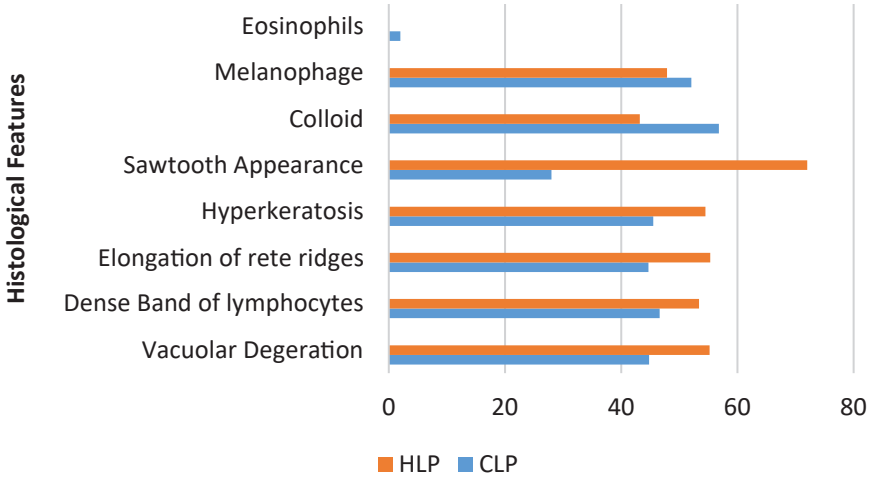


Figure 1. Histological Characteristics of Classic and Hypertrophic Lichen Planus

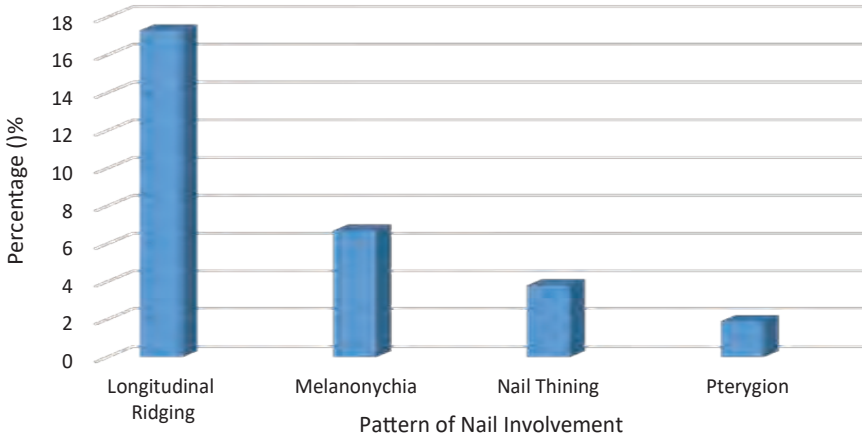


Figure 2. Pattern of Nail Involvement among Patients with Lichen Planus In Nigeria

presents as a generalized LP disease. Furthermore, the cases of HLP are more likely to originate in the lower limbs, confine to the lower legs and have a significant association with metabolic comorbidities such as diabetes mellitus and dyslipidemia compared to those with CLP.

The mean age of LP patients in the present study was 37.20±13.39 years, that being in accordance with the previously documented adult age range of 30-60 years (24, 25). Similarly, the mean age of patients with LP in this study was very close to 37.13±12.8 years as documented by Daramola et al. previously in a similar environment (15–17) and 38.8 years as documented in India by Bhattacharya et al. (26). There was no age difference between CLP and HLP patients. However, contrary to Daramola et al. (16) findings, the present study has not confirmed the female predominance of LP, as both sexes were almost equally affected by CLP and HLP. This observation is consistent with the findings of other studies as well (25, 26). Studies have described the CLP as a non-gender, non-racial prevalent disease with tendencies to involve the skin, nails, hair, and mucosal sites (5, 25). As found in the present study, limb onset of 93.2% of cases is higher than 55.6% as observed by Bhattacharya et al. (26). The CLP demonstrated tendencies to start in the upper limbs, to be widespread with the involvement of oral and nail sites (5). Nakamura et al. (27) showed that both oral mucosa and nail association in LP are manifestations of a disseminated LP disease.

Similarly, a positive antibody to HCV in the present study is significantly associated with CLP. Contrary to our finding, Daramola et al. found an increased frequency of association between HCV infection and HLP, as more than

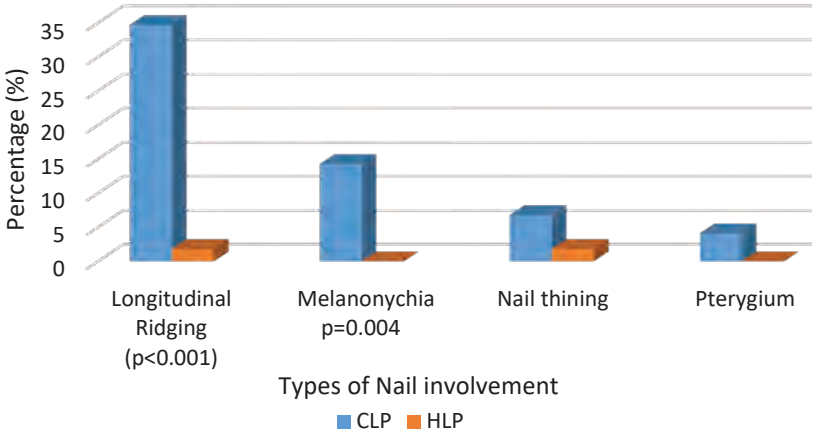


Figure 3. Pattern of Nail involvement: Classic and Hypertrophic Lichen Planus

Table 3. Peculiarities of lichen planus (classic and hypertrophic) in relation to mucosal and the nail involvement

Characteristics of Patients	Total N=104	Oral Mucosal Involvement Present N=19	Oral Mucosal Involvement Absent N=85	p-value	LP with Nail Involvement N=20	LP without Nail Involvement N=84	p-value
Mean Age (years) ± SD	37.44±13.88	34.10±11.45	37.89±13.75	0.267	33.55±15.46	38.07±12.80	0.176
Metabolic Syndrome	16 (15.4)	1 (5.3)	15 (17.6)	0.176	2 (10.0)	14 (16.7)	0.458
Dyslipidaemia	61 (58.7)	9 (47.4)	52 (61.2)	0.269	9 (45.0)	52 (61.9)	0.168
Onset of LP							
Predominantly Upper Limb onset	29 (27.9)	8 (40.0)	21 (25.0)	<0.001	8 (40.0)	21 (25.0)	<0.001
Predominantly Lower limb onset	68 (65.4)	7 (35.0)	61 (72.6)		7 (35.0)	61 (72.6)	
Predominantly Chest	3 (2.9)	3 (15.0)	0 (0.0)		3 (15.0)	0 (0.0)	
Predominantly Abdomen onset	4 (3.8)	2 (10.0)	2 (2.4)		2 (10.0)	2 (2.4)	
Extent of Lesion							
Localized	38 (36.5)	0 (0.0)	38 (44.7)	<0.001	0 (0.0)	38 (45.2)	<0.001
Generalized	66 (63.4)	19 (100.0)	47 (55.3)		20 (100.0)	46 (54.8)	
Clinical Signs							
Koebnerization	30 (28.8)	13 (68.4)	17 (20.0)	<0.001	15 (75.0)	15 (17.9)	<0.001
Wickhiam Striae	43 (41.3)	14 (73.7)	29 (34.1)	0.002	17 (85.0)	26 (31.0)	<0.001
Type of Skin Lesions							
Classic	49 (47.1)	19 (100.0)	30 (35.3)	<0.001	19 (95.0)	30 (35.7)	<0.001
Hypertrophic	55 (51.0)	0 (0.0)	55 (64.7)		1 (5.0)	54 (61.3)	

77.7% of their HCV antibody positive LP patients had HLP. It must be noted that HLP was the predominant variant of LP in their study and sampling method could have accounted for the difference observed. Despite numerous published studies, the link between LP and HCV remains controversial (16, 17, 28, 29). Some researchers demonstrated a positive relationship and recommended HCV screening tests for LP patients (29, 30), while others did not observe such association (17). The association between LP with HCV infection appears to be dependent on geographical heterogeneity (31). A previous study has shown the increased risk of HCV positivity in LP patients (30). We found no association between HBsAg positivity and LP like the Birkenfeld et al. (30) and a history of previous immunization against HBV appears predominant among CLP patients and might explain the protection against this virus.

Hypertrophic LP is a variant of LP also known as lichen planus verrucous or lichen planus hypertrophic whose etiology is not known (5). In the present study, we found no association between HLP and the Koebner phenomenon. A study found chronic rubbing of initial lesions following intense pruritus as implicated in the development of HLP lesions from papules to verrucous or plaques (5). Similarly, some authors have suggested that eosinophils play specific unknown roles in the etiology of HLP (5, 32). In the present study, eosinophils were seen in the histology of a single case of LP, which was diagnosed as CLP. A study has described rare or no eosinophil HLP similar to CLP and plenty eosinophil HLP that resemble lichenoid drug eruption and established no significant variation in the quantity of eosinophil in biopsies about the location of the lesions (9). We found the HLP is more likely to start and localize to the

lower limbs; this observation is in keeping with several isolated reports on HLP (8–12). The HLP involvement of the lower legs in the present study (94.5%) is close to 88.9% described by Alomari et al. (9). Some authors have attributed venous stasis as a possible reason for the high frequency of HLP in the lower limbs (2, 26). It is rare for HLP to present as a widespread disease, but a report of disseminated HLP has been documented in the literature (8).

Our study found significant associations between HLP and comorbidities such as diabetes mellitus and dyslipidemia, though no significant association was found with metabolic syndrome. Previous studies have shown an association among LP, dyslipidemia and glucose intolerance (32–34). Several studies have shown chronic induction of inflammation and generation of reactive oxygen species in LP as the link among dyslipidemia, glucose intolerance, and LP (32–35). The impaired fasting and diabetes were present (9.6%) in our study; this falls within the lower limit of 2.3-27.4% documented in previous studies (36, 37). Some studies established a close association between LP and carbohydrate dysmetabolism (36, 37). The insulin signaling effect of the inflammatory mediators and the inflammation-induced insulin resistance may be responsible for the development of the systemic insulin-resistant state in LP patients. Apart from dysmetabolism associated with the HLP, HLP has been associated with development of squamous cell carcinoma (SCC) (10–12). A study has shown an SCC incidence of 0.27% per annum in HLP lesions, and chronic inflammation (38, 39) explained the association between SCC and HLP.

There is a significant association between saw-tooth histologic appearance and HLP. Saw-tooth appearance is described as profound hyperplasia of the epidermis with invagination into the dermis. The classic pseudoepitheliomatous hyperplasia described in several reports (8–12) was not seen in the present histologic review. Other features of LP including a dense band of lymphocyte infiltration, vacuolar degeneration of dermoepidermal junction, granular hyperkeratosis, and the presence of melanophages were observed but there were no differences in their occurrence in the the variants.

Concerning the presenting symptoms, we found no difference between the frequency of pruritus in the patients with CLP and HLP, although HLP had an insignificantly higher rate of pruritus compared to CLP. HLP has been documented in previous observation as the most pruritic variant (5, 25, 26). We also observed that CLP was more associated with pain than HLP. Bhattacharya et al. also found that 19.6% of their patients with oral LP experienced burning or pain while eating hot or spicy meals (26). It is not unusual in our environment to have more than 70% of our patients to have sought help from non-orthodox sources or self-help because LP is an annoying disease with the capacity to impair quality of life.

The prevalence of nail involvement (19.23%) is close to 15.17%, as observed by Bhattacharya et al. in India. We noted that longitudinal ridging was the most frequent nail changes while pterygium was the least type pf involvement which was comparable with other published data (32). Longitudinal ridging of the nail characterizes nail involvement in LP, nail thinning, cuticular overgrowth (i. e., pterygium), atrophy of the nail bed, melanonychia, subungual keratosis, and hyperpigmentation (25).

Limitation and Conclusion

Limitations of the present study is that it is the observational single-center analysis. Also, the differences between two variants in metabolic markers and markers of chronic inflammation, thus limiting interpretation of results.

Finally, CLP is significantly associated with generalized LP disease, anti-HCV positivity, oral and nail involvement Kobner's phenomenon, and Wickham's striae. The HLP is more likely to start and be localized to the lower limbs compared to the CLP. Impaired glucose tolerance/ type 2 diabetes mellitus, dyslipidemia and histologic saw-tooth appearance were significantly associated with HLP compared to CLP. Further inferential studies are needed to elucidate the causal relationship between HLP/CLP, abnormal metabolism, and chronic inflammation.

References

1. Black MM. Lichen planus and lichenoid disorders. In: Champion RH, Burton JL, Ebling FJG, Rook AJ, Wilkinson DS. Textbook of dermatology. Vol. 3. 5th ed. Oxford: Blackwell Scientific Publications; 1992. p. 1675.
2. Boyd AS, Neldner KH. Lichen planus. J Am Acad Dermatol. 1991;25(4):593-619.
3. Usatine RP, Tinitigan M. Diagnosis and treatment of lichen planus. Am Fam Physician. 2011:84(1):53-60.

4. Katta R. Lichen planus. Am Fam Physician. 2000;62(8): 1786. Erratum for: Am Fam Physician. 2000;61(11):3319-24.
5. Weston G, Payette M. Update on lichen planus and its clinical variants. Int J Womens Dermatol. 2015;1(3):140-9.
6. Lukács J, Schliemann S, Elsner P. Lichen planus and lichenoid reactions as a systemic disease. Clin Dermatol. 2015;33(5):512-9.
7. Pickert A. Concise review of lichen planus and lichenoid dermatoses. Cutis. 2012;90(3):E1-3.
8. Jaime TJ, Jaime TJ, Guaraldi Bde M, Melo DF, Jeunon T, Lerer C. Disseminated hypertrophic lichen planus: relevant response to acitretin. An Bras Dermatol. 2011;86(4 Suppl 1):S96-9.
9. Alomari A, McNiff JM. The significance of eosinophils in hypertrophic lichen planus. J Cutan Pathol. 2014;41(4): 347-52.
10. Levandoski KA, Nazarian RM, Asgari MM. Hypertrophic lichen planus mimicking squamous cell carcinoma: the importance of clinicopathologic correlation. JAAD Case Rep. 2017;3(2):151-4.
11. Totonchy MB, Leventhal JS, Ko CJ, Leffell DJ. Hypertrophic lichen planus and well-differentiated squamous cell carcinoma: a diagnostic conundrum. Dermatol Surg. 2018;44(11):1466-70.
12. Dietert JB, Rabkin MS, Joseph AK. Squamous cell carcinoma versus hypertrophic lichen planus; a difficult differential diagnosis of great significance in approach to treatment. Dermatol Surg. 2017;43(2):297-9.
13. Nnoruka EN. Lichen planus in African children: a study of 13 patients. Pediatr Dermatol. 2007:24(5):495-8.
14. Alabi GO, Akinsanya TB. Lichen planus in tropical Africa. Trop Geogr Med. 1981;33(2):143-7.
15. Daramola OO, Ogunbiyi AO, George AO. Lichen planus following hepatitis B vaccination in an African girl. Trop Doct. 2002;32(2):117-8.
16. Daramola OO, Ogunbiyi AO, George AO. Evaluation of clinical types of cutaneous lichen planus in anti-hepatitis C virus seronegative and seropositive Nigerians patients. Int J Dermatol. 2003;42(12):933-5.
17. Daramola OO, George AO, Ogunbiyi AO. Hepatitis C virus and lichen planus in Nigerians: any relationship? Int J Dermatol. 2002;41(4):217-9.
18. Trinder P. Determination of blood glucose using 4-amino phenazone as oxygen carrier acceptor. J Clin Pathol. 1969;22(2):246-50.
19. Searcy RL. Quantitative determination of triglycerides by enzymatic endpoint colorimetric method. In: Searcy RL. Diagnostic biochemistry. New York: McGraw Hill; 1969. p. 115-21.
20. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem. 1974;20(4):470-5.
21. Burstein M, Mortin R. Quantitative determination of HDL-cholesterol using the enzymatic colorimetric method. Life Sci. 1969;8:345-7.
22. Friedewald WT, Levy RJ, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502.
23. Executive summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97.
24. Bilgili SG, Karadag AS, Ozkol HU, Calka O, Akdeniz N. The prevalence of skin diseases among the geriatric patients in eastern Turkey. J Pak Med Assoc. 2012;62(6):535-9.
25. Kyriakis KP, Terzoudi S, Palamaras I, Michailides C, Emmanuelidis S, Pagana G. Sex and age distribution of patients with lichen planus. J Eur Acad Dermatol Venereol. 2006;20(5):625-6.
26. Bhattacharya M, Kaur I, Kumar B. Lichen planus: a clinical and epidemiological study. J Dermatol. 2000; 27(9):576-82.
27. Nakamura R, Broce AA, Palencia DP, Ortiz NI, Leverone A. Dermatoscopy of nail lichen planus. Int J Dermatol. 2013;52(6):684-7.
28. Daoud MS, Gibson LE, Daoud S, el-Azhary RA. Chronic hepatitis C and skin diseases: a review. Mayo Clinic Proc. 1995;70(6):559-64.
29. Jubert C, Pawlotsky JM, Pouget F, Andre C, DeForges L, Bretagne S, et al. Lichen planus and hepatitis C virus-related chronic active hepatitis. Arch Dermatol. 1994;130(1):73-6.
30. Birkenfeld S, Dreiher J, Weitzman D, Cohen AD. A study on the association with hepatitis B and hepatitis C in 1557 patients with lichen planus. J Eur Acad Dermatol Venereol. 2011;25(4):436-40.
31. Song J, Zhang Z, Ji X, Su S, Liu X, Xu S, et al. Lack of evidence of hepatitis in patients with oral lichen planus in China: a case-control study. Med Oral Patol Oral Cir Bucal. 2016;21(2):e161-8.
32. Arias-Santiago S, Buendía-Eisman A, Aneiros-Fernández J, Girón-Prieto MS, Gutiérrez-Salmerón MT, Mellado VG, et al. Cardiovascular risk factors in patients with lichen planus. Am J Med. 2011;124(6):543-8.
33. Arias-Santiago S, Buendía-Eisman A, Aneiros-Fernández J, Girón-Prieto MS, Gutiérrez-Salmerón MT, Garcıa-Mellado V, et al. Lipid levels in patients with lichen planus: a case-control study. J Eur Acad Dermatol Venereol. 2011;25(12):1398-401.
34. Seyhan M, Ozcan H, Sahin I, Bayram N, Karincaoğlu Y. High prevalence of glucose metabolism disturbance in patients with lichen planus. Diabetes Res Clin Pract. 2007;77(2):198-202.
35. Lu R, Zhang J, Sun W, Du G, Zhou G. Inflammation-related cytokines in oral lichen planus: an overview. J Oral Pathol Med. 2015;44(1):1-14.
36. Petrou-Amerikanou C, Markopoulos AK, Belazi M, Karamitsos D, Papanayotou P. Prevalence of oral lichen planus in diabetes mellitus according to the type of diabetes. Oral Dis. 1998;4(1):37-40.
37. Romero MA, Seoane J, Varela-Centelles P, Diz-Dios P, Garcia-Pola MJ. Prevalence of diabetes mellitus amongst

oral lichen planus patients. Clinical and pathological characteristics. Med Oral. 2002;7(2):121-9.
38. Mehta NN, McGillicuddy FC, Anderson PD, Hinkle CC, Shah R, Pruscino L, et al. Experimental endotoxemia induces adipose inflammation and insulin resistance in humans. Diabetes. 2010;59(1):172-81.
39. Krasowska D, Kozłowicz K, Kowal M, Kurylcio A, Budzyńska-Włodarczyk J, Polkowski W, et al. Twice malignant transformation of hypertrophic lichen planus. Ann Agric Environ Med. 2012;19(4):787-9.

Epidemiološke i kliničke razlike između klasičnog i hipertrofičnog lihena planus u Nigeriji

Sažetak

Uvod. Lihen planus je inflamatorno oboljenje kože sa nekoliko kliničkih varijanti i različitim kliničkim ishodima. Primećene su neke komplikacije kod hipertofičnog tipa koje se ne nalaze kod klasične varijante. **Cilj** je bio da se ustanove epidemiološke i kliničke razlike između klasičnog i hipertrofičnog lihena planus i kliničke povezanosti. **Materijal i metode.** Od 104 ispitanika sa lihenom planus, 49 su imali klasični a 55 hipertrofični lihen planus. Skupljeni su demografski i klinički podaci. Lihen planus je dijagnostikovan klinički i potvrđen histološki. Ispitanici su pregledani na metabolički sindrom, hepatitis B i C. **Rezultati.** Prosečna životna dob svih pacijenata bila je 37,20±13,39 godina, bez starosnih i polnih razlika između ispitanika sa klasičnim i hipertrofičnim lihenom planus. Klasični lihen planus je češće bi bolan (8,2% vs 0,0, p = 0,046), generalizovan (95,9% vs 16,4%, p< 0,001), obuhvatao je usnu duplju (38,8% vs 0,0, p < 0,001), nokte (38,8% vs 1,8, p < 0.001), bio povezan sa vakcinom protiv hepatitisa B (16,3% vs 3.6%, p < 0,028) i anti-HCV pozitivnosti (16,3% vs 0,0%, p = 0,002). Hipertrofični lihen planus je bio značajno povezan sa poremećenom tolerancijom glukoze (16,4% vs 2,0%, p = 0,013), dislipidemijom (74,5% vs 40,8%, p = 0,001) i nazubljenim invaginacijama epiderma u derm na histologiji u poređenju sa klasičnim tipom. **Zaključak.** Hipertrofični lihen planus je uglavnom povezan sa metaboličkim komplikacijama za razliku od klasičnog tipa. Potrebno je izvesti dodatna istraživanja da se poveže ova razlika sa hroničnom inflamacijom.

Ključne reči: Lichen planus; Komorbiditet; Znaci i simptomi; Oralni lichen planus; Dijabetes melitus; Dijagnoza; Epidemiološke studije; Nigerija

Received 5.03.2019.
Accepted 9.07.2019.

DOI: 10.2478/sjdv-2019-0002

Use of Ustekinumab in the Treatment of Libyan Psoriasis Vulgaris Patients

Belkais BELTAMMER, Ali GARGOOM, Ghada TAEIB, Gamal DUWEB

Dermatology Department, Faculty of Medicine, Benghazi University, Benghazi-Libya

*Correspondence: Gamal Duweb, E-mail: drduweb@gmail.com

UDC 616.517-085.26:615.456(612)

Abstract

Introduction. Psoriasis is a relatively common chronic inflammatory disease. It clinically manifests as raised, well defined erythematous plaques with irregular borders and silvery scales. Psoriasis appears to be mediated by abnormal immune system functioning, including T lymphocyte and macrophage activation and release of various cytokins, such as interleukin 12 (IL-12) and IL-23. Recently a new biologic agent Ustekinumab has been used in the treatment of psoriasis. Our aim in this study was to assess the efficacy and tolerability of ustekinumab in moderate to severe psoriasis vulgaris and to observe and report any adverse reaction. **Material and Methods.** Thirty five psoriatic patients above the age of 18 years having moderate to severe psoriasis were included in this study. Ustekinumab is available in pre-filled syringe 45mg/0.5ml, 90mg/1.0ml for subcutaneous injection according to body weight at the intervals of 0, 4 weeks, and then every 12 weeks. It is given in hospital by a doctor or specialist nurse. The assessment of the patients' condition and improvement was carried out after administering each dose using PASI score. **Results.** Thirty five patients were included in this study. Baseline PASI score of our patients ranged from 11.4 to 39.8 (mean: 21.1).There was a dramatic response to treatment with ustekinumab in which PASI decreased to 6.7 after the second dose, followed by subsequent responses that reached 2.6 after the 6th dose . After the second dose, 61% of the cases had marked improvement and 11% had clearance of their skin lesions. After the last, sixth dose there was a marked improvement in 65% of cases and the percentage of complete clearance increased to 24%. Ustekinumab had positive effect on psoriatic nail changes as well-there was a significant improvement in 50% of cases and complete clearance (cure) in 24% of cases. **Conclusion:** Ustekinumab is effective in the treatment of severe and resistant cases of psoriasis vulgaris. It is well tolerated by the patients. No reactions or serious side effects have been reported.

Key words: Psoriasis; Ustekinumab; Dermatologic Agents; Biological Therapy; Treatment Outcome; Libya

Introduction.

Psoriasis is a relatively common chronic inflammatory disease that affects around 3% of the general population. The incidence is highest in males at the age between 20 and 39 years and in females aged from 40 to 59 years, with an equal male-to-female ratio (1, 2). Psoriasis vulgaris accounts for almost 90% of the dermatological presentation of the disease.

Psoriasis is presumed to be a multifactorial disease which is provoked in genetically predisposed individuals by various triggering factors (3). Psoriasis appears to be mediated by abnormal immune system functioning, including T lymphocyte and macrophage activation and release of various cytokins (4–6). These include interleukin 12 (IL-12) and IL-23. IL-12 induces differentiation of CD4+ T Cells into Th1 cells that produce type 1 cytokines such as interferon g and tumor necrosis factor α (7, 8). IL-23 induces the development of Th17 cells producing proinflammatory cytokine IL-17 (9, 10), which has recently been identified as mediating the tissue damage in psoriasis (11, 12). It has a very high negative impact on quality of life, requires a long-term treatment which usually has a high social and economic impact, and is also associated with a decreased life span (13, 14).

In psoriasis treatment, topical monotherapy remains the mainstay of treatment for most patients especially those with limited disease. However, 20 to 30% of people with psoriasis experience severe symptoms and may require systemic treatment such as methotrexate, cyclosporine, oral retinoids or pho-

totherapy (15, 16). The following biologic agents of the anti-TNFα group are currently available at the market: etanercept, infliximab, and adalimumab. Recently a new biologic agent, ustekinumab has been used in the treatment of psoriasis. Ustekinumab is a first-in-class, fully human interleukin -12/23 p40 monoclonal antibody has demonstrated high efficacy in treating moderate to severe plaque psoriasis (9, 17).

Our aim in this study was to assess the efficacy and tolerability of ustekinumab in the treatment of patients with moderate to severe psoriasis, any additional effect on psoriatic nail changes and to observe its adverse effects.

Material and Methods

Thirty five Libyan psoriatic patients above the age of 18 years with moderate to severe psoriasis attending the Psoriasis Clinic of the Dermatology Department, Benghazi, Libya were included in this study over a period of 3 years (April, 2014 to April 2017). All patients had given the signed written informed consent prior to participating in the study. Detailed disease history was taken for each patient and all of them underwent complete clinical examination. The disease severity was assessed by using PASI score at each first visit. Investigations including CBC and ESR, RFT, LFT, FBS, tuberculin test, chest X ray, serology test for HIV, HBV, and HCV, ANA and Anti dsDNA were done in all patients at the baseline visit and some were repeated at each visit. Clinical assessments included dermatological examinations, vital signs, concomitant medications, monitoring for adverse events, and measures of psoriasis activity (Psoriasis Area Severity Index) (PASI). Ustekinumab is available in pre-filled syringe 45 mg/0.5 ml, 90 mg/1.0 ml for subcutaneous injection according to the body weight at the intervals of 0, 4 weeks, and then every 12 weeks. It was given in hospital by a doctor or specialist nurse. Assessment of the patient's condition and improvement was carried out after each dose using PASI score. Any patient's compliant or unusual presentation or adverse reaction reported by a patient or doctor was recorded. Laboratory investigation included complete blood count, liver function test, renal function test fasting blood sugar which had been taken before administering the dose. When all data were collected, they were fed to the computer and processed using the statistical package for social sciences (for personal computer) SPSS-TC program version 11.5.

Results

Out of 35 psoriasis vulgaris patients included in our study, 72% were males and 28% were females. Their age ranged from 19 to 82 years, the mean age being 41.1 years and and their disease lasted from 3 to 25 years, the mean duration being 11.78 years. The body weight was <100 kg in 72% of our patients and >100 kg in 28% of them.

In 56% of our patients the disease was moderate, while in 44% of them it was severe and nail involvement was seen in 81% of our study cases. As for the previous treatment with systemic therapy including methotrexate, photochemotherpy, narrow-band UVB, cyclosporine and retinoids, the majority of our patients (78%) received either one, two or all of them. Twenty five patients (71.4%) received 45 mg of ustekinumab.

The baseline PASI score of our patients ranged from 11.4 to 39.8, the mean being 21.1. **Figure 1** illustrates one of the most severely affected patients with highest score. There was a dramatic response to treatment with ustekinumab in which PASI decreased to 6.7 after the

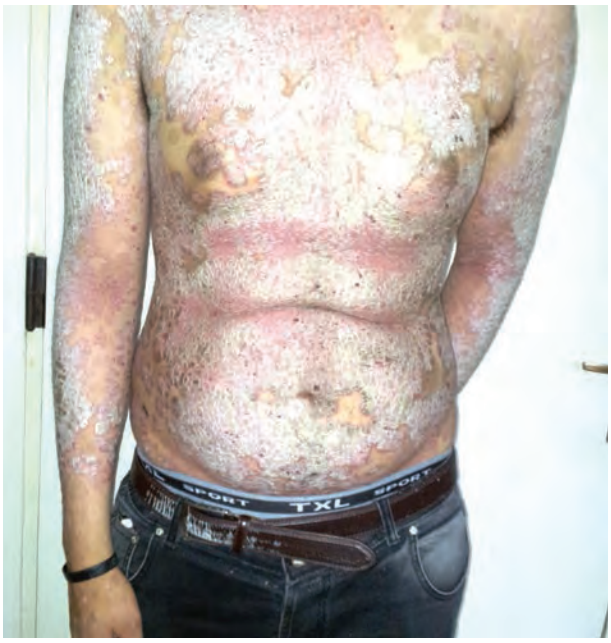


Figure 1. The patient before treatment

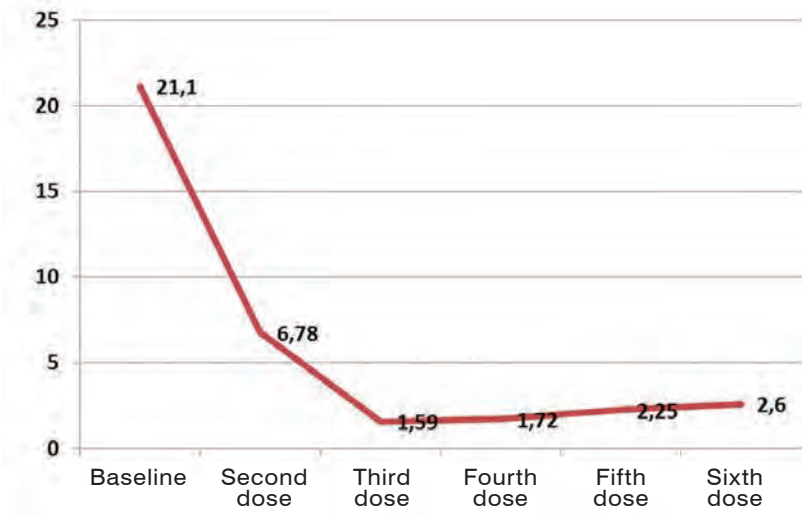


Figure 2. PASI changes during the treatment course

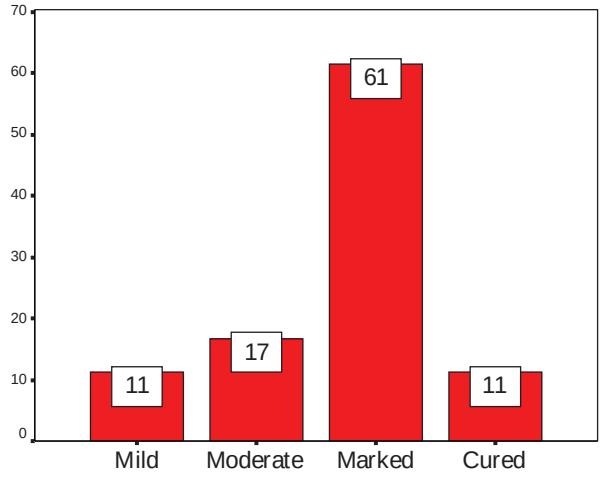


Figure 3. Improvement after the second dose

second dose, followed by subsequent responses that reached 2.6 after the 6th dose **(Figure 2)**. After the second dose 61% of the cases had marked improvement and 11% had clearance of their skin lesions **(Figures 3 and 4)**. Also the efficacy was great and 75% improvement was seen in 27 (78%) patients and 90% improvement was seen in 25 patients after the third dose. After the last, 6th dose, a significant improvement was observed in 65% of cases and the percentage of clearance increased to 24% **(Figures 5 and 6)**. An additional effect of ustekinumab was observed on the psoriatic nail and nail changes significantly improved in 50% of our cases and there was the complete clearance in 24% of them at the

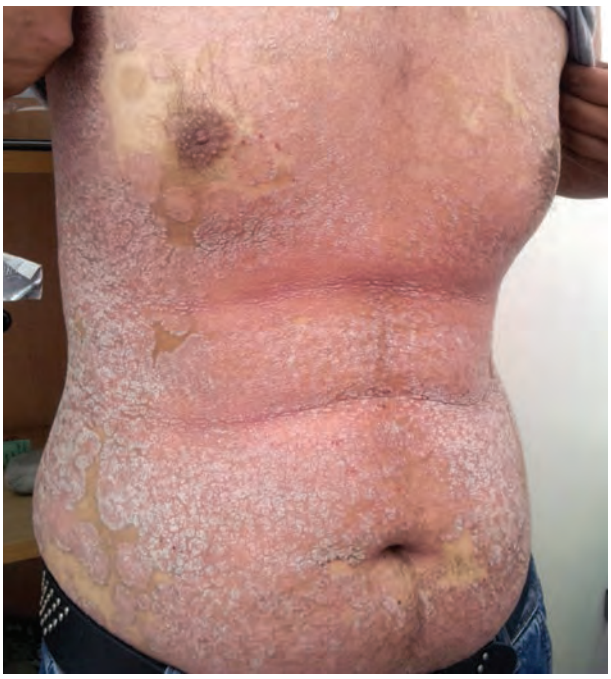


Figure 4. The photo of the same patient after the second dose

end of treatment. Out of 7 patients (25%) who had presented with joint pains, stiffness and/or swelling seen in our study, moderate to marked improvement was achieved in 4 patients. No side effects were reported either by the patients or the doctor.

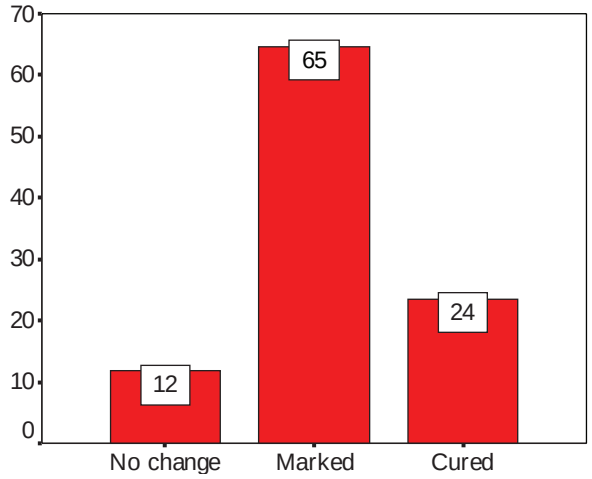


Figure 5. Improvement after the last, sixth dose

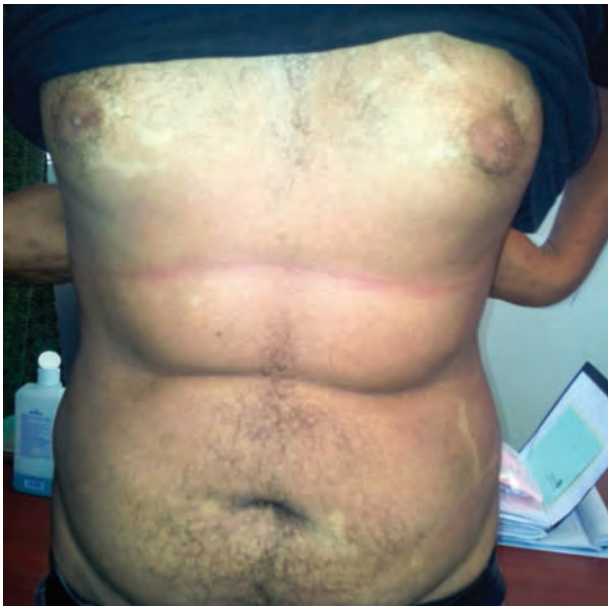


Figure 6. Clearance in the same patient after the last, sixth dose

Discussion

Psoriasis appears to be mediated by abnormal immune system functioning, including T lymphocyte and macrophage activation and release of various cytokins (4–6) such as interleukin 12 (IL-12) and IL-23. IL-12 induces differentiation of CD4+ T Cells into Th1 cells that produce type 1 cytokines such as interferon gamma and tumor necrosis factor α (7, 8). IL-23 induces the development of Th17 cells producing proinflammatory cytokine IL-1 (8–10). Therapy for moderate to severe or refectory psoriasis has been revolutionized with the introduction of biologics in the past 15 years (1821). The first US Food Drug Administration (FDA) biologic approved for plaque psoriasis was Alefacept in January 2003. Ustekinumab was approved in September 2009 (22). This study was designed to assess the clinical benefit and safety of ustekinumab monotherapy in patients with moderate to severe psoriasis. In 56% of our patients the disease was moderate while in 44% of them it was severe. The dose of 45 mg of ustekinumab was administered in 71.4% of our patients while 28.6% of them received 90 mg dose in contrast to the study by Leonardi CL (2008) where the 50% of cases received ustekinumab. The baseline PASI score of our patients ranged from 11.4 to 39.8 (mean: 21.1) where 50% of cases received ustekinumab 45 mg dose and the other 50% received 90 mg dose.

The dramatic response to ustekinumab, in which PASI decreased to 6.7 after the second dose, was followed by the subsequent response when it reached 2.6 after the sixth dose. After the second dose 50% improvement was seen in 27 patients (78%) and 90% improvement in 8 (22%) patients. The efficacy was also great after the third dose and 75% improvement was seen in 27 patients (78%) and 90% improvement was seen in 25 patients. A significant improvement was achieved after the last, sixth dose in 65% of cases and the percentage of clearance increased in 24%, as compared with the results of two trials carried by Leonardo CL, where he found PASI 75 improvement in more 50% of both ustekinumab groups at week 12 (67.1% and 66.7% in group 45mg and 66.4% and 75.7% in 90 mg group VS 3.1% and 3.7% for placebo respectively) (17, 18).

Similar response rates after crossover at week 12 from placebo to ustekinumab treatment were also found. Maximal efficacy was observed between weeks 20 and 24. In the PHOENIX1 trial, the patients who achieved PASI 75 were re-randomized at week 40 to continue or withdraw from treatment until psoriasis recurrence. Partial responders (week 28: PASI 50-74; week 40: <PASI 75 switched to dosing every 8 weeks (9, 17). PASI 75 response was better maintained up to at least 1 year in those receiving maintenance ustekinumab than in those withdrawn from treatment, suggesting that long-term therapy is necessary (9, 17).

In conclusion ustekinumab is effective in the treatment of severe cases of psoriasis vulgaris and well tolerated in patients with resistant, moderate to severe psoriasis vulgaris. Additional effects were seen on psoriatic nails and neither reactions nor serious side effects have been reported by the patients or their doctors.

References

1. Nestle FO, Kaplan DH, Barker J. Psoriasis. New Eng J Med. 2009;361(5):496-509.
2. Christiophers E, Henseter T. Psoriasis type I and type II as subtypes of non pustular psoriasis. In: Roenigk H, Maibach H, editors. Psoriasis. New York: Dekker; 1990. p. 15-21.
3. Vasků V, Bienertová Vasků J, Pávková Goldbergová M, Vasků A. Three retinoid x receptor gene polymorphism in plaque psoriasis and psoriasis guttata. Dermatology. 2007;214(2):118-24.
4. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58(5):826-50.
5. Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JY, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. J Am Acad Dermatol. 2008;58(5):851-64.
6. Boker A, Kimball AB, Rolz-Cruz G. Biologicals in the treatment of psoriasis. Curr Opin Investig Drugs. 2007;8(11):939-46.
7. Barlett BL, Tyring SK. Ustekinumab for chronic plaque psoriasis. Lancet. 2008;371(9625):1639-40.
8. Torti DC, Feldman SR. Interleukin-12, interleukin-23, and psoriasis: current prospects. J Am Acad Dermatol. 2007;57(6):1059-68.
9. Reddy M, Davis C, Wong J, Marsters P, Pendley C, Prabhakar U. Modulation of CLA, IL-12R, CD40L, and IL-2pα expression and inhibition of IL-12 and IL-23 induced cytokine secretion by CNTO1275. Cell Immunol. 2007;247(1):1-11.
10. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-wk result from a randomised, double-blind, placebo-controlled trial (PHOENIX1). Lancet. 2008;371(9625):1665-74.
11. Steinman L. A brief history of Th17, the first major revision in Th1/Th2 hypothesis of T cell-mediated tissue damage. Nat Med. 2007;13(2):139-45.
12. Asarch A, Barak O, Loo DS, Gottlieb AB. Th17 cells: a new therapeutic target in inflammatory dermatosis. J Dermatolog Treat. 2008;19(6):318-26.
13. Lebwohl M. Psoriasis. Lancet. 2003;361(9364):1197-204.
14. Naldi L, Gambini D. The clinical spectrum of psoriasis. Clin Dermatol. 2007;25(6):510-8.
15. Menter A, Griffiths CE. Current and future management of psoriasis. Lancet. 2007;370(9583):272-84.
16. Griffiths CE, Iaccarino L, Naldi L, Olivieri I, Pipitone N, Salvarani C, et al. Psoriasis and psoriatic arthritis: immunological aspects and therapeutic guidelines. Clin Exp Rheumatol. 2006;24 (1 Suppl 40);72-8.
17. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody in patient with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX2). Lancet 2008;371(9625):1675-84.
18. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58(5):826-50. SAME AS REF 3
19. Ellis CN, Krueger GG; Alefacept Clinical Study Group. Treatment of chronic plaque psoriasis by selective targeting of memory effecter T lymphocytes. N Engl J Med. 2001;345(4):248-55.
20. Papp KA, Carey W. Psoriasis care. New and emerging pharmacologic trends. J Cutan Med Surg. 2010;14 (3):119-29.
21. Weger W. Current status and new development in the treatment of psoriasis and psoriatic arthritis with biological agents. Br J Pharmacol. 2010;160(4):810-20.
22. Nelson AL, Dhimolea E, Reichert JM. Development trends for human monoclonal antibody. Nat Rev Drug Discov. 2010;9(10):767-74.

Upotreba ustekinumaba u lečenju libijskih pacijenata sa psorijazom vulagaris

Sažetak

Uvod. Psorijaza je relativno često hronično inflamatorno oboljenje. Klinički se manifestuje uzdignutim, jasno definisanim eritematoznim plakovima sa nepravilnim ivicama i srebrnastim krljuštima. Čini se da psorijaza nastaje usled nenormalnog funkcionisanja imunosistema, uključujući i aktivaciju T-limfocita i makrofaga i oslobađanje različitih citokina, poput interleukina 12 (IL-12) i IL-23. Odnedavno se u lečenju psorijaze koristi novi biološki agens ustekinumab. Cilj naše studije bio je da utvrdimo efikasnost i toleranciju na ustekinumab kod umerene do teške psorijaze vulgaris i da se prate i prijave neželjene reakcije. **Materijal i metode.** U ovu studiju uključeno je 35 pacijenata starijih od 18 godina sa umerenom do teškom psorijazom. Ustekinumab se može naći u već napunjenim špricevima od 45 mg/0,5 ml, 90 mg/1 ml za supkutano ubrizgavanje shodno telesnoj težini u periodu od 0,4 sedmice i posle svakih 12 sedmica. Daje ga doktor ili specijalizovana medicinska sestra u bolničkim uslovima. Procena stanja pacijenata i poboljšanja sprovedena je posle svake doze pomoću PASI skora (*Psoriasis Area and Severity Index* – površina psorijaze i indeks težine oboljenja). **Rezultati.** Ispitivanje je obuhvatilo 35 pacijenata. Početni PASI skor kod naših pacijenata varirao je od 11,4 do 39,8 (srednja vrednost 21,1). Došlo je do dramatične reakcije na lečenje ustekinumabom kada je PASI pao na 6,7 posle druge doze, što je praćeno kasnijim reakcijama kada je došao na 2,6 posle šeste doze. Posle druge doze, u 61% slučajeva došlo je do poboljšanja, a u 11% lezije su se povukle. Kod poslednje, šeste doze, došlo je do značajnog poboljšanja u 65% slučajeva a povećao se i procenat kompletnog povlačenja u 24% slučajeva. Bilo je vidljivo delovanje i na psorijatične promene na noktima i na kraju lečenja došlo je do značajnog poboljšanja u 50% slučajeva a do kompletnog izlečenja u 24%. **Zaključak.** Ustekinumab je efikasan u lečenju teških i rezistentnih slučajeva psorijaze vulgaris. Pacijenti ga dobro podnose. Nisu prijavljenje reakcije niti ozbiljnije nuspojave na lek.

Ključne reči: Psorijaza; Ustekinumab; Dermatološki preparati; Biološka terapija; Ishod terapije; Libija

Received 12.03.2019.
Accepted 19.03.2019.

DOI: 10.2478/sjdv-2019-0003

Superficial Genital Infantile Hemangiomas

Aleksandra MATIĆ[1,2], Milan MATIĆ[1,3], Sonja PRĆIĆ[1,2]

[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia
[2]Pediatrics Clinic, Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia
[3]Clinic of Dermatovenereology, Clinical Center of Vojvodina, Novi Sad, Serbia

*Correspondence: Aleksandra Matić, E-mail: aleksandra.matic@mf.uns.ac.rs

UDC 616-006.3-053.3-085:611.6

Abstract

Introduction. Superficial infantile hemangiomas (IH) are rarely localized in the genital region. **Case Report.** We present 8 infants with IHs in the genital region (3 boys and 5 girls). Our patients had only superficial IHs, their internal organs were not affected and there were no associated anomalies. In the boys, IHs were localized on the scrotum and the foreskin in 2 cases and 1 case, respectively. In the girls, IHs were on the labia majora and near the vaginal introitus. None of the IHs showed any IH-related complications. No therapy for IHs was administered in any of the presented infants, either because IHs were small and non-aggressive, or because their parents rejected the proposed therapy. **Conclusion.** Genital IHs have increased tendency for ulceration, so thorough examination and follow-up are of outmost importance. If therapy is indicated, oral propranolol is the treatment of choice for genital IHs.

Key words: Hemangioma; Infant; Scrotum; Genital Neoplasms, Female, Propronolol; Drug-Related Side Effects and Adverse Reactions

Introduction

Infantile hemangiomas (IHs) are the most frequent vascular tumors of infancy. The estimated incidence reported in the literature ranges from 4% to 5% during the first year of life (1–3).

The vast majority of IHs are benign, with no need for intervention (1, 2). However, substantial subset of IHs can be the cause of a variety of medical, functional and/or aesthetic adverse effects, which depends on the size and clinical characteristics of IH as well as its localization. Superficial IH can emerge on any part of the skin or mucous membranes; the genital region being no exception, although it is a rare localization of IHs (4).

The aim of this paper is to present a series of patients with superficial IHs with rather distinctive localization in the genital region, and to point to the clinical characteristics and management of this type of IH.

Case Reports

We present 8 infants with IHs in the genital region – 3 boys and 5 girls.

All the presented infants had only superficial IHs. On ultrasound, no IHs were revealed on the internal organs. Furthermore, none of our patients had any dysmorphic features or congenital anomalies. Each of the presented boys had a single IH, which was in the genital area. IHs were slow in growth, reaching the full size at the age of 2-3 months. The first signs of involution of IHs were noted at the age of 9-11 months. One boy was prematurely born; he received the resuscitation at birth and mechanical ventilation during first 10 days of life, and developed posthemorrhagic hydrocephalus, which was treated with ventriculo-peritoneal shunt. His IH was on the bottom of his right scrotum and was the biggest in size of all the three presented IHs in our male patients (**Figures 1a and 1b**). The other two boys were born at term. One of them had inconspicuous neonatal period (the other boy with scrotal IH – **Figure 2**), and the other one had minor respiratory problems. The most important characteristics of genital IHs in the presented boys are shown in **Table 1**.

All genital IHs in the presented girls were on the labia majora and/or near vaginal introi-

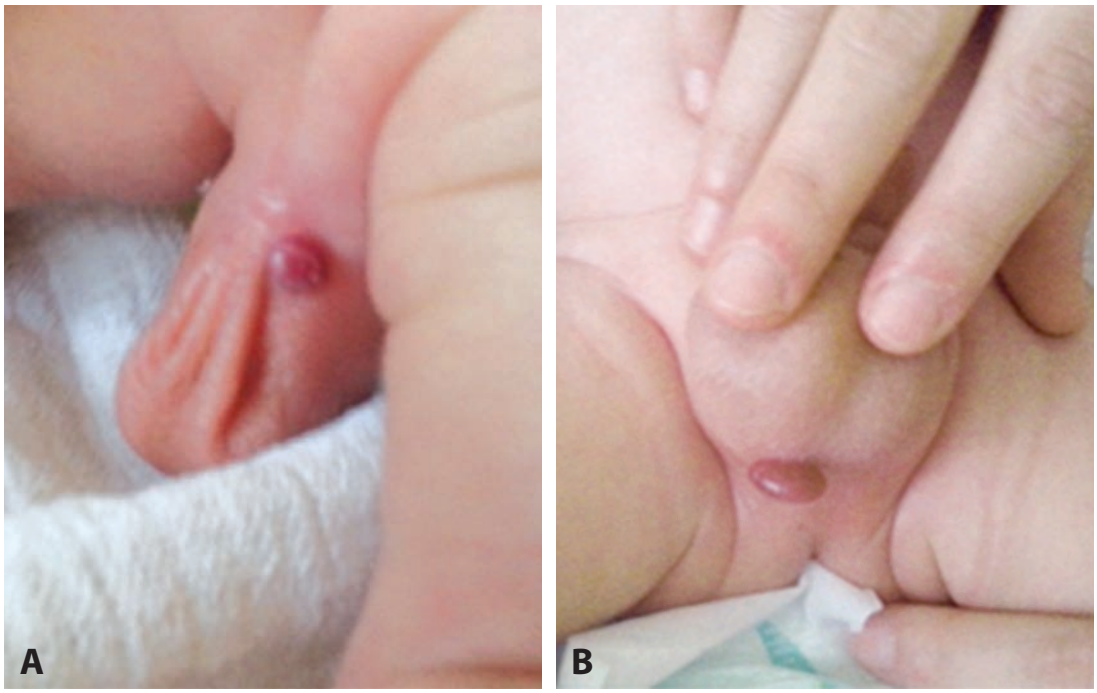


Figure 1. Case of a boy No 1: a preterm boy with globular superficial infantile hemangioma at the bottom of his right hemiscrotum A) at the postnatal age of 2 months, B) at the postnatal age of 3.5 months

tus. Two girls were found to have two genital IHs, and three girls had one genital IH. Two girls had just two IHs in the genital regions, with no additional IHs (**Figure 3**). In addition to one genital IH, each of the other three girls had 1 to 4 extragenital IHs, localized on the forehead, abdomen, and/or extremities. Once they appeared, all genital IHs grew very slowly until the age of 3 postnatal months. Afterwards genital IHs showed very little changes in size and appearance until the first signs of their involution, which were noted at the age of 9-10 postnatal months. Extragenital IHs showed a slightly more advanced growth comparing to the genital IHs in the same infant. Three of the presented girls were born preterm, while 2 were born at term. All the presented girls had some early morbidity after birth: respiratory distress, jaundice, urinary tract infection, early anaemia; hence their prolonged primary hospitalization after birth. The characteristics of genital and extragenital IHs in the presented girls are given in **Table 2**.

Neither ulceration nor any other IH-related complications were found in the presented cases, whether genital or extragenital ones. In addition, no therapy for IHs was administered in any of the presented infants, either because IHs were small and non-aggressive, or because their parents rejected the proposed therapy for IHs (boy No 1, with globular scrotal IH and girl No 3, who had 5 IHs in total).

Table 1. Common characteristics of genital IHs in the presented boys

	Preterm	Localization of genital IH	Description of genital IH	The largest diameter of IH	Extragenital IHs
Boy No 1	yes	scrotum	bright-red flattened globe with a smooth surface	9 mm	none
Boy No 2	no	scrotum	round bright-red, slightly elevated	5 mm	none
Boy No 3	no	prepuce	oval-elongated, bright-red, slightly elevated	5 mm	none

Table 2. Common characteristics of genital IHs in the presented girls

	Preterm	Number of genital IHs	Localization of genital IHs	Largest size of IHs	Appearance of genital IHs	Number of extragenital IHs	Localization pf extragenital IHs
Girl No 1	yes	1	labia majora	3 mm	oval - elongated, bright-red, flat	1	knee
Girl No 2	yes	2	labia majora, near vaginal introitus	10 mm and 5 mm	irregular shape and oval-elongated; both bright-red, smooth and almost flat	none	/
Girl No 3	yes	1	labia majora	5 mm	oval-elongated, bright-red, smooth, flat	4	forehead, scalp, abdomen, lower leg
Girl No 4	yes	1	near vaginal introitus	5 mm	oval, smooth, flat	1	upper leg
Girl No 5	no	2	labia majora	5 mm and 3 mm	oval, smooth, flat	none	/

All parents of the infants were advised to pay special attention to the hygiene of their child's genital region, especially in case of elevated/pendulated IHs, like it was the case with boy No 1.

Discussion

IHs are more often localized in some regions of the skin and mucous membranes for the reasons not known so far, while some other regions are rarely affected. Literature data show that only 1% of all IHs are in the anogenital region (4).

According to the depth of the affected tissue, IHs are classified as superficial (localized primarily on the surface of the skin), deep (within the deep dermis and subcutaneous tissue) or mixed – superficial and deep, also known as combined IHs (1, 5). All the presented infants had the superficial type of IHs. IHs localized in the genital region with a deep component are much more aggressive and with more complications. They can interfere with the sperm production in case of scrotal deep IH, through the direct involvement in the physical growth of developing testis as well as by increasing local temperature in the testicle because of the nearby IH (6, 7). In a scrotal as

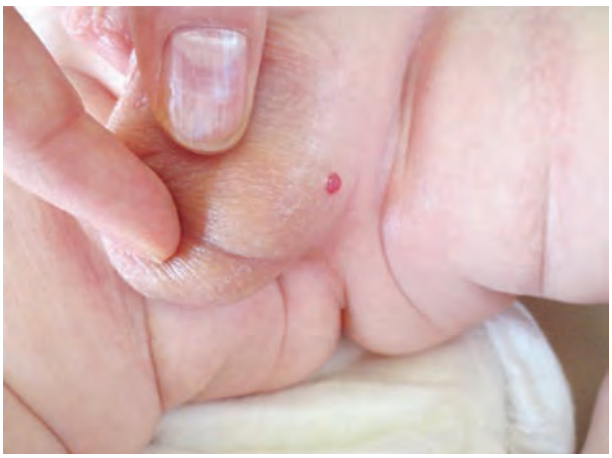


Figure 2. Case of a boy No 2: a term boy at the postnatal age of 3 months with round infantile hemangioma at the left hemiscrotum.

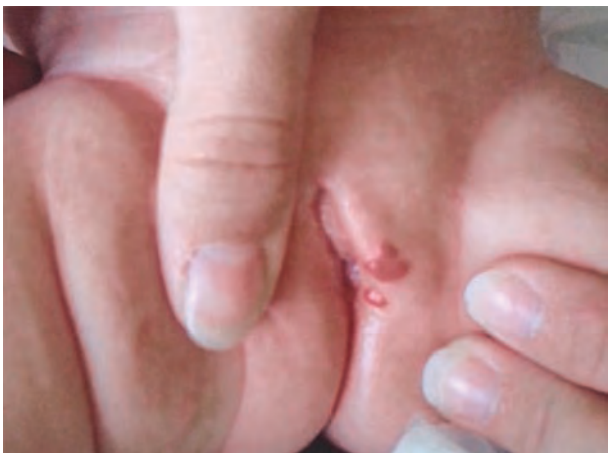


Figure 3: Case of a girl No 2: two superficial infantile hemangiomas at the labia majora and near vaginal introitus at the age of 3 months

well as penile deep IH, an important disfigurement and malfunction can occur (7). If an IH is purely superficial, these complications are rarely expected. In girls, genital IH can be the cause of recurrent vaginal bleeding (8) or redness, pruritus and pain (9). The thorough evaluation and follow-up of every genital IH is therefore very important. Furthermore, the detailed complete examination of the infant is necessary in order to look for the possible presence of dysmorphic features and associated anomalies. Particular attention should be paid to the anatomy of anogenital region in infants with large IHs in this area because of possible associated anomalies within PELVIS syndrome of varying degree (10).

Superficial IHs have a specific appearance, which is mainly sufficient for the correct diagnosis. In morphologically less obvious cases, imaging studies (ultrasound and MRI) and the typical clinical course are diagnostic clues for IH. (1, 2). Classical superficial IH is not visible at birth but appears at the age of several weeks or months. IHs are characterised by specific natural evolution, which implies proliferative phase and subsequent spontaneous involution. These features of IH are important elements of IH diagnosis. Typical appearance and clinical course were noted in all the presented cases of IHs.

As previously mentioned, the potential for adverse effects depends on morphology and growth rate, but also on localization of IH. Genital IHs are especially prone to ulceration, due to the irritating and macerating properties of stool and urine, frequent friction and occlusive effect of diapers (6, 11). The additional trigger for ulceration of IH in this anatomic area is decreased oxygenation of the surface of the hemangioma (6, 7). About 75% of total hemangioma ulcerations are found in the diaper area, out of which 26% in the gluteal region, 23% at the perineum, 18% around the anus, and 8% at the scrotum (12). Ulceration often develops at the height of the proliferative phase of IH evolution, especially in the cases of rapid growth. Generally, larger, more prominent and more granulated IHs are prone to ulceration (1, 2). Ulceration is among very important adverse effects of IHs because of accompanied pain and bleeding, as well as residual scarring with the potential for significant life-lasting disfigurement and functional impairment. For ulcerated IH oral propranolol is the treatment of choice.

In all the presented patients, genital IHs are superficial with very limited growth and relatively small final size – less than 10 mm. Therefore, we did not expect complications such as ulceration, bleeding or the harmful effect of the increased temperature of the hemangioma on the developing testicles in the presented boys with scrotal IHs. Furthermore, the majority of the presented infants were prematurely born with prolonged primary hospitalization and significant early morbidity, even with life-long serious consequences in our boy No 1. In such cases the parents are usually less willing to accept additional therapy. Complicated IHs – those which are life-threatening, function-threatening, ulcerated or with high risk thereof, or with acute and/or chronic disfigurement – must be treated. In complicated IHs the first line therapy is oral propranolol, and topical timolol only in special cases. The widely accepted indication for treatment with oral propranolol is also the presence of 5 or more IHs in the child (1), as it was the case with the presented girl No 3. The rational for introducing the treatment for IH is much wider than the above-mentioned and includes aesthetics as well as parents` concerns and wishes in non-complicated IHs (2, 13). One should have in mind that the involution of IH might be complete or with some permanent residuals in the form of telangiectasias, scarring, atrophic skin, fibrofatty tissue or changes in pigmentation (5). Anyhow, before the introduction of any IH therapy, detailed explanations of all the options should be provided to infants` parents. The final decision, except in very few life-threatening cases, should be made jointly between the attending doctor and the parents. After all, every therapeutic option requires full-cooperation with the parents, because of the necessity for long-term and regular administration of medications as well as monitoring of treatment effects and potential adverse events. When it comes to genital IHs, the therapy of choice would be oral propranolol (14, 15). It should be considered in large IHs (over 10 mm in diameter), those with fast growth, significantly raised above the surrounding skin and/or with significantly granulated surface. Oral propranolol has shown good effects with no adverse events in a series of 9 genital IHs cases (15). The topical therapy with timolol-maleate is less applicable

in this type of IH due to the increased potential for adverse effects. Occlusion effect of diapers as well as the proximity of the mucous membrane in some genital IHs are responsible for the increased systemic absorption of timolol and subsequent higher potential for adverse events such as bradycardia, hypotension, apnoea, hypothermia and sleep disturbances (14). There were attempts at applying topical timolol for IH localized on the labia majora under occlusion on everyday basis in ambulance settings (16), but it was for study purposes; for everyday practice it is rather inconvenient for infant and parents.

Conclusion

Genital IHs have the increased tendency for ulceration, so thorough examination and follow-up are of outmost importance. Furthermore, looking for dysmorphic features and anomalies (particularly of anogenital region), as well as for additional IHs on other body parts, are mandatory in such infants. Parents should be advised to pay special attention to the hygiene as well as daily examination of the genital area. If therapy is indicated, oral propranolol is the treatment of choice for genital IHs.

References

1. Krowchuk DP, Frieden IJ, Mancini AJ, Darrow DH, Blei F, Greene AK, et al. Clinical Practice Guideline for the Management of Infantile Hemangiomas. Pediatrics. 2019;143(1):e20183475.
2. Darrow DH, Greene AK, Mancini AJ, Nopper AJ; Section on dermatology, Section on otolaryngology-head and neck surgery, and Section on plastic surgery. Diagnosis and management of infantile hemangioma. Pediatrics. 2015;136(4):e1060-104.
3. Munden A, Butschek R, Tom WL, Marshall JS, Poeltler DM, Krohne SE, et al. Prospective study of infantile hemangiomas: incidence, clinical characteristics, and association with placental anomalies. Br J Dermatol. 2014;170(4):907-13.
4. Grantzow R. Treatment of genital infantile hemangiomas. In: Mattassi R, Loose D, Vaghi M, editors. Hemangiomas and vascular malformations. Milano: Springer; 2015. p. 151-4.
5. Vivar KL, Mancini AJ. Infantile hemangiomas: an update on pathogenesis, associations, and management. Indian Journal of Paediatric Dermatology. 2018; 19(4):293-303.
6. Patoulias I, Farmakis K, Kaselas C, Patoulias D. Ulcerated scrotal hemangioma in an 18-month-old male patient: a case report and review of the literature. Case Rep Urol. 2016;2016:9236719.
7. Chavan D, Javalgi AP. Scrotal hemangioma: a case report. J Clin Diagn Res. 2014;8(12):ND03-4.
8. Ganti AK, Ray J, Mooney KL, Zambrano E, Hillard PJA, Fok W. Unusual cause of pediatric vaginal bleeding: infantile capillary hemangioma of the cervix. J Pediatr Adolesc Gynecol. 2019;32(1):80-2.
9. Silva JMD, Calife ER, Cabral JVS, Andrade HPF, Gonçalves AK. Vulvar hemangioma: case report. Rev Bras Ginecol Obstet. 2018;40(6):369-71.
10. Girard C, Bigorre M, Guillot B, Bessis D. PELVIS Syndrome. Arch Dermatol. 2006;142(7):884-8.
11. Chen TS, Eichenfield LF, Friedlander SF. Infantile hemangiomas: an update on pathogenesis and therapy. Pediatrics. 2013;131(1):99-108.
12. Morelli JG, Tan OT, Yohn JJ, Weston WL. Treatment of ulcerated hemangiomas infancy. Arch Pediatr Adolesc Med. 1994;148(10):1104-5.
13. Semkova K, Marina S, Kazandjieva J. Topical treatment of infantile hemangiomas – where are we now? Serbian Journal of Dermatology and Venereology. 2011;3(4):145-52.
14. Frommelt P, Juern A, Siegel D, Holland K, Seefeldt M, Yu J, et al. Adverse events in young and preterm infants receiving topical timolol for infantile hemangioma. Pediatr Dermatol. 2016;33(4):405-14.
15. Tran C, Tamburro J, Rhee A, Golden A. Propranolol for treatment of genital infantile hemangioma. J Urol. 2016;195(3):731-7.
16. Moehrle M, Leaute-Labreze C, Schmidt V, Röcken M, Poets CF, Goelz R. Topical timolol for small hemangiomas of infancy. Pediatr Dermatol. 2013;30(2):245-9.

Površinski genitalni infantilni hemangiomi

Sažetak

Uvod. Infantilni hemangiomi su retko lokalizovani u genitalnoj regiji. **Prikaz slučaja.** Prikazujemo osmoro odojčadi sa infantilnim hemangiomima u genitalnoj regiji (tri dečaka i pet devojčica). Svi prikazani pacijenti su imali samo površne infantilne hemangiome, bez infantilnih hemangioma na unutrašnjim organima i bez pridruženih anomalija. Kod dečaka, infantilni hemangiomi bili su lokalizovani na skrotumu u dva slučaja i prepucijumu u jednom slučaju. Kod devojčica, infantilni hemangiomi bili su na velikim usnama i u blizini introitusa vagine. Nijedno prikazano odojče nije imalo komplikacije. Takođe, ni u jednom slučaju nije primenjena terapija za infantilne hemangiome, bilo zato što su bili mali i sporog rasta, ili zato što su roditelji odbili predloženu terapiju. **Zaključak.** Ge-

nitalni infantilni hemangiomi imaju povećanu tendenciju ka ulceraciji, te su detaljan pregled i redovno praćenje izuzetno važni kod ovakve dece. Ako postoji indikacija za terapiju, oralni propranolol je lek izbora za genitalni infantilni hemangiom.

Ključne reči: Hemangiom; Odojče; Scrotum; Neoplazme ženskih genitalija; Propranolol; Neželjena dejstva i reakcije na lekove

Received 17.03.2019.
Accepted 7.04.2019.

DOI: 10.2478/sjdv-2019-0004

Familial Hypercholesterolemia with Tendinous Xanthomas and Achilles Tendinitis – A Forgotten Dermato-Rheumatologic Association

Puspanjuli SAHU[1], Saritha MOHANAN[2], Carounanidy UDAYSHANKAR[2], Sankappa P. SINHASAN[2], Ramachandra V. BHAT

[1]Hi-Tech Medical College & Hospital, Rourkela
[2]Department of Dermatology, IGMC&RI, Puducherry

*Correspondence: Saritha Mohanan, E-mail: saritha_mohanan@yahoo.co.in

UDC 616.153.7-056.7-06:616.52 and 616.153.7-056.7-06:616-002.77

Abstract

Familial hypercholesterolemia (FH) is a disorder of lipoprotein metabolism with dermatological and rhematological manifestations. Tendinous xanthomata (TX) are a hallmark of this disease. They are associated with recurrent tendinitis and tendon damage, an aspect of the clinical presentation, which is not well-known among dermatologists. We report two cases of heterozygous familial hypercholesterolemia, where the patients started developing tendinous xanthomata early in their life, with progressive increase in the number and size of lesions. However, they presented late, only when the recurrent attacks of tendinitis became severe .We present these cases to highlight the rheumatologic features, which may be the first symptom of heterozygous familial hypercholesterolemia.

Key words: Hyperlipoproteinemia Type II; Xanthomatosis; Achilles Tendon; Heterozygote; Genetic Predisposition to Disease; Rheumatic Diseases

Introduction

Familial hypercholesterolemia (FH) is a familial metabolic disorder characterised by high serum concentration of low-density lipoprotein (LDL) cholesterol, corneal arcus, tendinous xanthomata (TX) and premature atherosclerosis (1). Rhematological manifestations, though not uncommon, are not usually highlighted in dermatology literature. Tendinitis, tenosynovitis, arthralgia, and migratory polyarthritis have been described in these patients (2). We report two cases with dermatological and rheumatic manifestations in order to stress the importance of awareness of the rheumatologic manifestations.

Case 1

A 41-year-old woman, born of third degree consanguineous marriage, was referred to Dermatology OPD with multiple painful skin-coloured nodules over the joints of the hands, elbows, knees and the ankle along with fever. The nodular lesions started developing in the second decade of her life, with progressive increase in the number and size of lesions. There was history of recurrent attacks (2-3 episodes/year) of inflammation of the nodules and nearby joints, associated with fever, from the third decade of her life. The attacks were mild and subsided with a short course of non-steroidal anti-inflammatory drugs.

Physical examination revealed multiple, skin coloured, firm to hard, subcutaneous nodules over the extensor aspect of the small joints of the hands and elbows (**Figure 1**), with larger lesions over the knee and pedunculated lesions over the hip joints. She also had xanthelasma palpebrarum and diffuse thickening of the bilateral Achilles tendons (**Figure 2**). There was warmth, swelling and focal tenderness over the nodules of hand and the Achilles tendon. The joints were normal. Systemic and ophthalmologic examinations were normal.

Her blood counts were normal. Erythrocyte sedimentation rate was elevated (110 mm/1st hr)

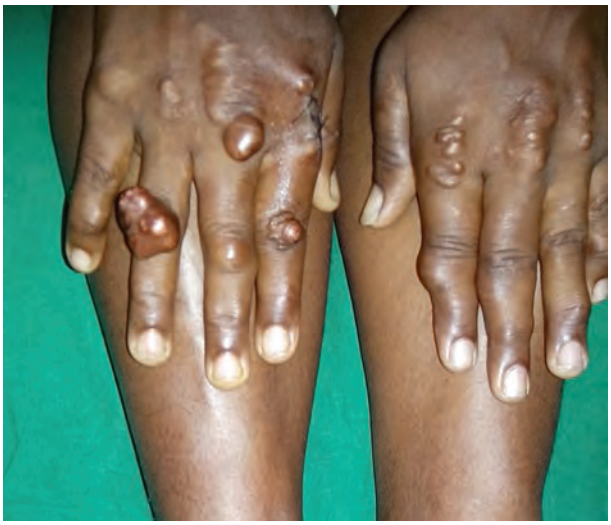


Figure 1: Multiple tendinous xanthomata on bilateral hands, elbows and feet of patient 1.

and C-reactive protein was positive. Antistreptolysin O titre, rheumatoid factor, antinucelar antibodies, and serum uric acid were within normal range. Fasting lipid profile was abnormal (**Table 1**). Radiography of the bilateral hands did not show any bone abnormality. Fine needle aspiration cytology (FNAC) revealed foam cells, touton and foreign body giant cells and mixed chronic inflammatory cells. Transthoracic echocardiography was normal. DNA testing was not done due to financial constraints. Histopathological examination of the subcutaneous nodule showed the *thinned out epidermis with well circumscribed co*llection of xanthomatous cells (foamy cells), few cholesterol clefts, touton cells and foreign body giant cells in the superficial dermis extending deep into dermis (*Figures 3,4*). Based on clinical examination and investigations, a diagnosis of FH with tendinous and tuberous xanthomata with acute tendinitis was made.

The patient was started on Atorvastatin 40mg and analgesics. Fever, pain and swelling of nodules improved within three days of treatment. The patient was examined in our OPD after 3 months. Xanthomas decreased in size and became soft, without episodes of tendinitis in the meantime.

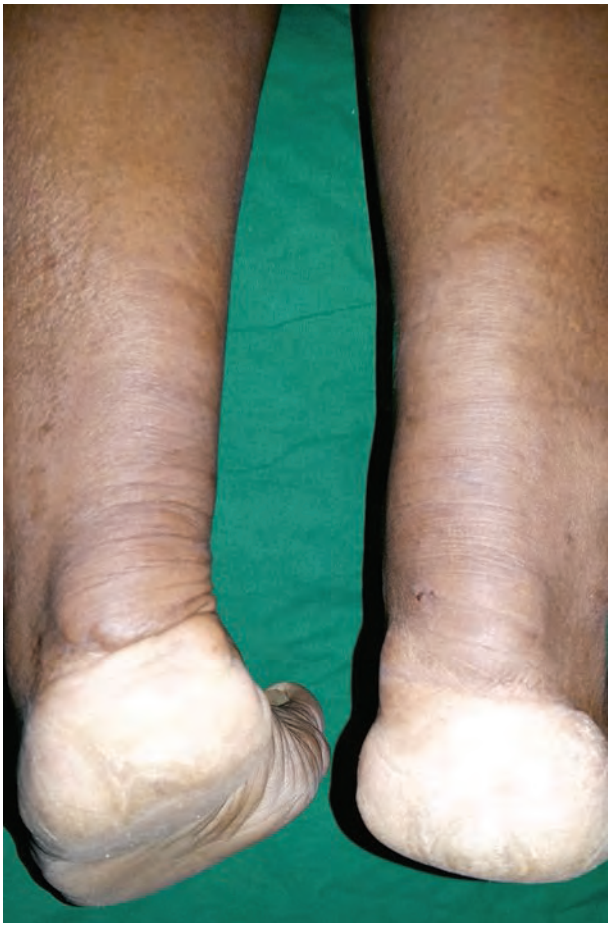


Figure 2. Diffuse thickening of Achilles tendons of patient 1

Table 1: Lipid profile of Patient 1 and Patient 2

Fasting lipid profile	Patient 1	Patient 2	Reference range
Cholesterol	524	562	130-240 mg/dl
Triglycerides	168	228	65-165 mg/dl
HDL Cholesterol	29	31	>35 mg/dl
LDL Cholesterol	351	531	130-159 mg/dl
Cholesterol/HDL ratio	18.07	18.13	0.0-0.0

HDL-High Density lipoprotein; LDL-low density lipoprotein

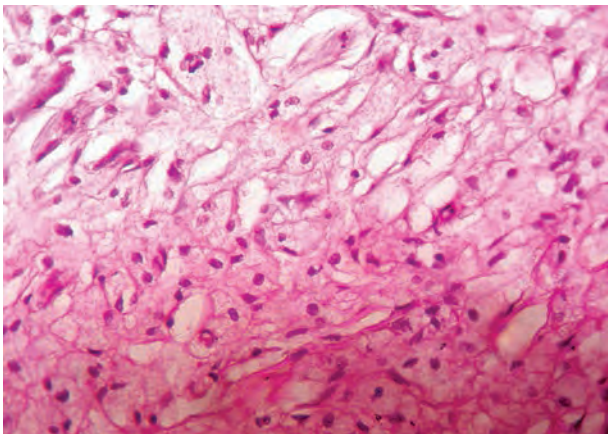


Figure 3. Xanthoma cells displaying foamy cytoplasm admixed with few cholesterol clefts (H and E stain, 40 X magnification)

Case 2

A 48-year-old female patient came to Dermatology OPD with similar complaints, along with ulceration of a larger pedunculated lesion over the left gluteal region. The nodules started appearing in the third decade of her life and during the last 5 years, she suffered from four to five episodes of swelling and pain over the lesions along with fever every year. There was a partial restriction of joint mobility during these episodes, which subsided within four to five days, without any residual joint problem. There was no similar history in other family members.

Physical examination showed similar features with ulcer of size 3 X 3 cm over the pedunculated lesion on the left gluteal region (**Figure 5**). FNAC revealed lipid laden foaming macrophages along with touton gaint cells, lymphocytes, plasma cells with fibrocollagenous stromal fragments. Fasting lipid profile was deranged (**Table 1**). Skin biopsy was not done as the patient did not give consent. She was prescribed atorvastatin 40 mg. She was lost to follow up after that.

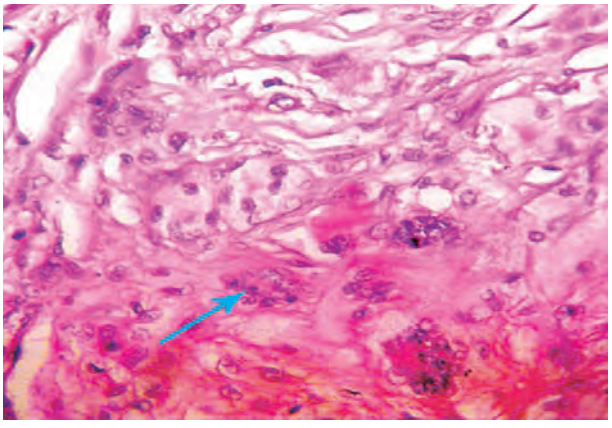


Figure 4. Presence of numerous multinucleated giant cells (arrow) admixed with xanthoma cells and cholesterol clefts (H and E stain, 40 X magnification)

Discussion

Familial hypercholesterolemia is a common autosomal codominant disease caused by defects in the LDL receptor gene (3). In the homozygous form of the disorder, LDL cholesterol levels are above 500 mg/dl and xanthomata appear during infancy and childhood. In the heterozygous form, LDL cholesterol levels are around 300 mg/dl, tendinous xanthomata (TX) appear in the second and third decades of life (2). In our patients, the lipid profile was suggestive of heterozygous type IIa hyperlipoproteinemia and xanthomata started appearing in the second and third decade of life respectively.

The dermatological manifestations occur in form of multiple types of xanthomas such as tendinous, tuberous, subperiosteal xanthomas, and xanthelasma. Intertriginous xanthomas are rare, but if present, they are pathognomonic of this disorder (4). In both of our patients, tendinous, tuberous xanthomas and xanthelasma palpebrarum were the typical manifestations. TX deposits are highly specific of FH, and current recommendations include them as an important clinical diagnostic criterion (5). In these subjects, LDL receptor defect results in the formation of oxidized LDL

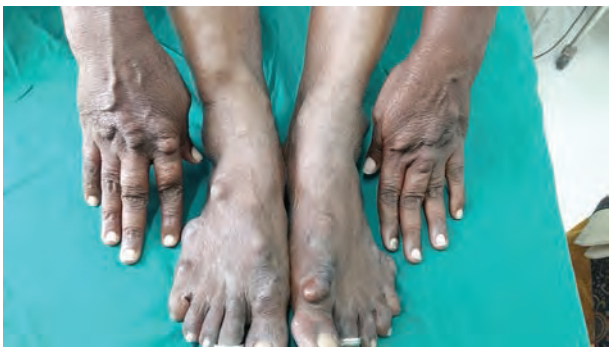


Figure 5. Multiple tendinous xanthomata on bilateral hands, elbows and feet of patient 1

(oxLDL), and uptake by the macrophage receptors, leading to massive lipid accumulation and foam cell formation (6).These foam cells, extracellular unesterified and esterified cholesterol and connective tissue are the main components of tendon xanthomas (7, 8).

The clinical expression of heterozygous FH is highly variable in terms of the severity of hypercholesterolemia, the presence of TX, and the age of onset and severity of CAD, even in subjects sharing the same LDL receptor gene defect (9). The macrophages from FH patients TX + have higher inflammatory response to oxLDL than those from FH subjects TX- and a resultant higher predisposition to form foam cells, due to differential expression of HLA-II and FccRIIb. In these cases, a strong upregulation of tryptase and a specific tryptase expression have been observed. They reduce the efflux of cholesterol from macrophages and activate peripheral mononuclear cells for the release of TNF-α, IL-6 and IL-1b, thereby mediating inflammation (10).

Among the different types of xanthomata, TX cause significant rheumatological manifestations. They are usually skin colored and hard due to fibrosis (4). Predilection sites of TX are Achilles tendons, tendons on the backs of the hands and fingers, as well as elbows, knees and heels (11). The rheumatologic manifestations include recurrent Achilles tendon's pain, acute mono-oligoarthritis and migratory polyarthritis (rheumatic fever type) (12). A typical attack of polyarthritis coincides with a slight but definite rise in the plasma cholesterol concentration (1). The articular manifestations in heterozygous FH are frequent, diverse, recurrent, incapacitating and short. The joints remains symptom free between attacks, and they never progress to articular damage or deformity as observed in the homozygous FH (2).

In our patients, rheumatologic manifestations were in form of acute tendinitis, not only of Achilles tendon, but almost all the tendons that were infiltrated with xanthomata. Repeated inflammation in the xanthomas caused fibrosis, leading to hard consistency mimicking calcinosis cutis. These cases can be mistaken for rheumatoid arthritis, tophaceous gout, psuedogout because the presentation is quite similar.

Systemic inflammation can cause lipid profile changes (13). Conversely, lipids can have a direct modulating effect on inflammation by increasing the circulatory inflammatory cells and proinflammatory cytokines TNF-α and IL-6 (10, 14). In our patients, a transient rise in plasma cholesterol concentration might have stimulated the genetically modified macrophages in TX and in peripheral blood; thereby producing a higher inflammatory response resulting in acute tendinitis and fever.

We report these cases of heterozygous FH because of its typical manifestation of various types of xanthomas and highlight the presentation of recurrent acute tendinitis along with fever as part of FH, which has not been discussed in literature on dermatology so far to the best of our knowledge.

References

1. Carroll GJ, Bayliss CE. Treatment of arthropathy of familial hypercholesterolaemia. Ann Rheum Dis. 1983;42(2):206-9.
2. Mathon G, Gagne C, Brun D, Lupien PJ, Moorjani S. Articular manifestations of familial hypercholesterolaemia. Ann Rheum Dis. 1985;44(9):599-602.
3. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science. 1986;232 (4746):34-47.
4. Braun-Falco O, Plewig G, Wolff HH, Winkelmann RK. Skin disorders caused by disturbances of lipid metabolism. In: Braun-Falco O, Plewig G, Wolff HH, Winkelmann RK. Dermatology. Berlin: Springer; 1991. p. 849-60.
5. Civeira F; International Panel on Management of Familial Hypercholesterolemia. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. Atherosclerosis. 2004;173(1):55-68.
6. Linton MF, Fazio S. Class A scavenger receptors, macrophages and atherosclerosis. Curr Opin Lipidol. 2001;12(5):489-95.
7. Kruth HS. Lipid deposition in human tendon xanthoma.Am J Pathol. 1985;121(2):311-5.
8. Tall AR, Small DM, Lees RS. Interaction of collagen with the lipids of tendon xanthomata. J Clin Invest. 1978;62(4):836-46.
9. Ferrieres J, Lambert J, Lussier-Cacan S, Davignon J. Coronary artery disease in heterozygous familial hypercholesterolemia patients with the same LDL receptor gene mutation. Circulation. 1995;92(3):290-5.
10. Artieda M, Cenarro A, Junquera C, Lasierra P, Martínez-Lorenzo MJ, Pocoví M, et al. Tendon xanthomas in familial hypercholesterolemia are associated with a differential inflammatory response of macrophages to oxidized LDL. FEBS Lett. 2005;579(20):4503-12.

11. Zak A, Zeman M, Slaby A, Vecka M. Xanthomas: clinical and pathophysiological relations. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2014;158(2):181-8.
12. Chakraborty PP, Mukhopadhyay S, Achar A, Pal M, Mondal PC. Migratory polyarthritis in familial hypercholesterolemia (type IIa hyperlipoproteinemia). Indian J Pediatr. 2010;77(3):329-31.
13. Myasoedova E, Crowson CS, Kremers HM, Roger VL, Fitz-Gibbon PD, Therneau TM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis. 2011;70(3):482-7.
14. Drechsler M, Megens RT, van Zandvoort M, Weber C, Soehnlein O. Hyperlipidemia triggered neutrophilia promotes early atherosclerosis. Circulation. 2010;122 (18):1837-45.

Porodična hiperholesterolemija sa tendinoznim ksantomima i Ahilovom petom – zaboravljena dermatovenerološka veza

Sažetak

Porodična hiperholesterolemija (PH) je poremećaj metabolizma lipoproteina sa dermatološkim i reumatološkim manifestacijama. Tendinozni ksantomi (TK) su obeležje ovog oboljenja. One su združene sa recidivnim tendinitisom i oštećenjem tetive, a to je aspekt kliničke prezentacije koji nije dobro poznat među dermatolozima. Prikazana su dva slučaja heterozigotne porodične hiperholesterolemije, u kojima su pacijenti počeli da dobijaju tendinozne ksantome rano u životu, a broj i veličina povreda su progresivno rasli. Međutim, oni su se javili kasno, tek kada su recidivni napadi tendinitisa postali teški. Prikazujemo te slučajeve da bismo objasnili reumatološke osobine, koje mogu biti prvi simptom heterozigotne porodične hiperholesterolemije.

Ključne reči: Hiperlipoproteinemija tipa 2; Ksantomatoza; Ahilova tetiva; Heterozigot; Genetska predispozicija prema bolesti; Reumatske bolesti

Received 24.03.2019.
Accepted 29.04.2019.

DOI: 10.2478/sjdv-2019-0005

DERMOSCOPY OF THE MONTH
Clinical, Dermatoscopical and Laboratory Essentials of Fish Tank Granuloma

Danijela DOBROSAVLJEVIĆ[1], Bojana LUKOVIĆ[2], Dimitrije BRAŠANAC[3], Olivera KOSOVAC[4]

[1]Clinic of Dermatovenereology KCS, Faculty of Medicine, Belgrade, Serbia
[2]Clinic of Pulmology, National Reference Laboratory for Mycobacteria, Department of Microbiology, KCS, Belgrade, Serbia
[3]Institute of Pathology, Faculty of Medicine, Belgrade, Serbia
[4]Kosovac Center for Plastic and Reconstructive Surgery, Belgrade, Serbia

*Correspondence: Danijela Dobrosavljević, E-mail: danijela_dobrosavljevic@yahoo.co.uk

UDC 616.5-006.44-076

Abstract

In immunocompetent individuals Mycobacterium marinum (M. marinum) infection usually presents with localized skin lesions, better known as “swimming pool granuloma” or “fish tank granuloma” (FTG). When establishing the diagnosis of FTG, doctors encounter several problems in the clinical practice: granulomas are detected in less than two thirds of biopsies and acid-fast bacilli are identified only in a minority of cases. Majority of disseminated and aggressive FTG forms are unrecognized at the beginning, and occur in immunosuppressed patients, including organ transplant patients. Functional impairment or even amputation of the extremity, visceral involvement and lethal outcome have been reported. Although more than one thousand cases of FTG have been reported worldwide, dermatoscopy of FTG, as a diagnostic aid, has not been reported yet. Presenting the case of FTG of recent onset where, guided by dermatoscopy, microorganisms were isolated and identified from the biopsy material, we summarize the essentials of clinical and laboratory diagnostics of M. marinum infection.

Key words: Granuloma; Diagnosis; Mycobacterium marinum; Skin Diseases, Bacterial; Dermoscopy; Immunocompromised Host

Introduction

In immunocompetent individuals Mycobacterium marinum (M. marinum) infection usually presents with localized skin lesions, better known as “swimming pool granuloma” or “fish tank granuloma” (FTG), due to fish-keeping hobby (1, 2). Several problems may occur during establishing the diagnosis of FTG. Granulomas are detected in less than two thirds of biopsies (3). With conventional Ziehl-Niellsen (ZN) staining, acid-fast bacilli are identified only in a minority of cases (4,5). In the absence of M. marinum identification, the patients are treated empirically. Majority of disseminated and aggressive FTG forms are unrecognized at the beginning, and occur in immunosuppressed patients (4-7), including organ transplant patients (8). Although more than one thousand cases of FTG have been reported worldwide, dermatoscopy of FTG, as a diagnostic aid, has not been reported yet. Presenting the case of FTG of recent onset where, guided by dermatoscopy, microorganisms were isolated and identified

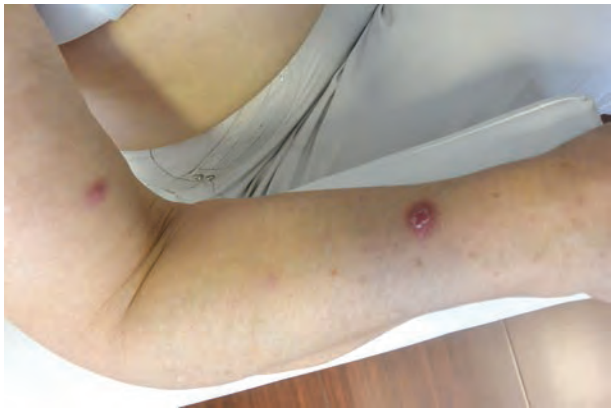


Figure 1. The clinical presentation. The livid nodule with annular scale was biopsied and histology of the excised lesion is presented in Figure 3.

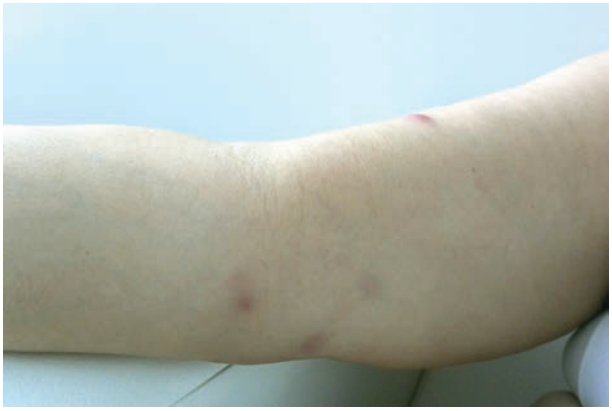


Figure 2. Multiple lesions on the upper arm. The biggest lesion on the upper arm with dermatoscopy images presented in Figure 4.It was biopsied and M. marinum isolated from the tissue (colonies/microorganisms are presented in Figure 5 and 6).

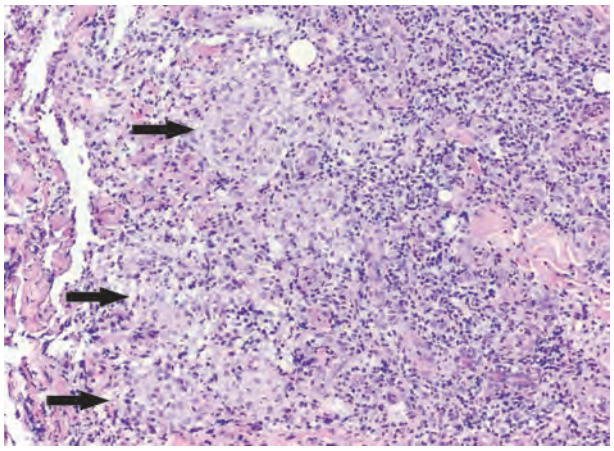


Figure 3. Microscopic analysis revealed mixed inflammatory infiltrate with proliferation of small blood vessels, and scattered epitheloid granulomas (arrows) (hematoxylin&eosin stain, original magnification 100x).

from the biopsy material, we summarize the essentials of clinical and laboratory diagnostics of M. marinum infection.

Case report

A 68-year-old woman, an aquarium owner, presented with sporotrichoid painless livid nodules of the skin and subcutaneous tissue on the right arm, ranging from 0.5 to 2 cm, present for 3 weeks **(Figures 1 and 2).** The largest distal nodule on the forearm with annular scaling was excised. Dermal non-caseating epitheloid granulomas surrounded by mixed inflammatory infiltrate, with the proliferation of small blood vessels were present **(Figure 3).** ZN

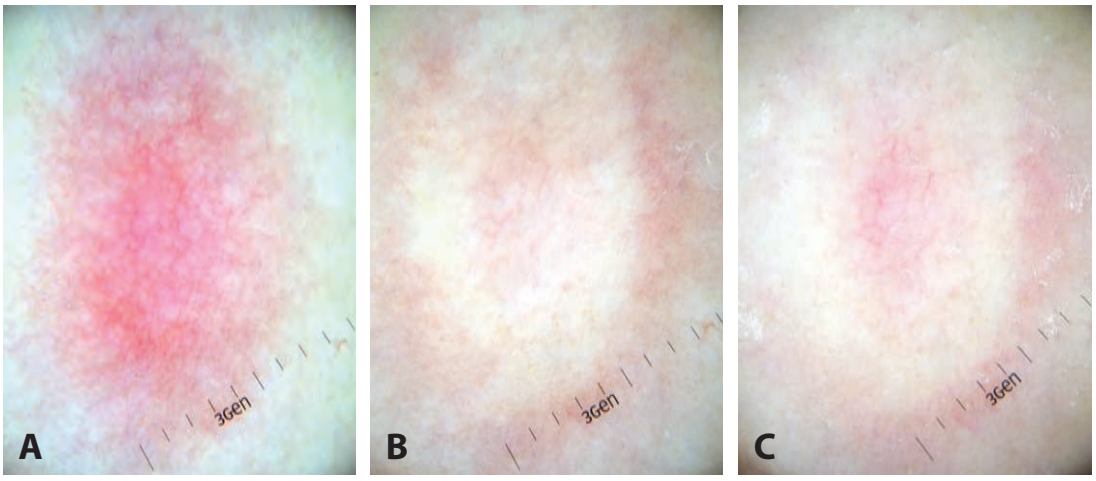


Figure 4. (4a) Dermatoscopy of the lesion that was subsequently biopsied and samples sent to laboratory for mycobacteria identification. Telangiectatic vessels on an erythematous base are present. (equipment: DermLite Hybrid M dermatoscope (3 GEN, San Juan Capistrano, CA, USA) in a polarized mode coupled with Nikon J1 camera (Nikon corporation, Tokyo, Japan) (4b) With increasing the pressure, erythema completely disappeared, leaving yellow background indicating a granulomatous disease. (4c) At the maximum pressure of the device, the yellow background color disappeared completely into a white color, depicting telangiectatic vessels in the center.

Figure 5. Tissue samples were decontaminated with N-acetyl-L-cysteine and cultured in parallel in liquid Mycobacteria growth indicator tube (MGIT) and solid Lowenstein-Jensen (LJ) media. One set was incubated at 30°C and another at 37°C up to 8 weeks. Yellow pigmented photochromogen M. marinum colonies growth on LJ at 30°C.

staining was negative for acid-fast bacilli. Subsequently, dermatoscopy of the remaining, clinically similar lesions, was performed. The lesions were depicted as telangiectatic vessels on an erythematous base. Only the largest nodule on the upper arm presented the persistence of the central vascular pattern at the maximum pressure **(Figure 4 a, b, c)** and was biopsied using two punch biopsies. Both Mycobacteria growth indicator tube (MGIT) and Lowenstein-Jensen (LJ) incubated at 37°C remained negative after 8 weeks, but, incubated at 30°C, yielded colonies on MGIT and LJ after 15 and 20 days, respectively. Colonies on LJ turned yellow upon the light exposure **(Figure 5).** ZN stain confirmed the cultured organism

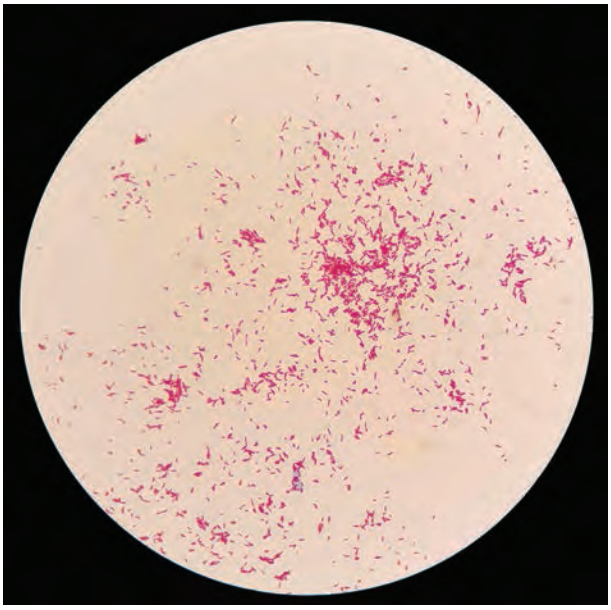


Figure 6. Acid-fast bacilli identified from the M. marinum colonies (Ziehl-Niellsen stain, light microscopy, immersion 1000x)

as acid-fast bacillus **(Figure 6).** Isolated colonies were identified as M. marinum with a GenoType Mycobacterium CM culture identification kit (Hain Lifescience, Nehren, Germany). The patient had positive Quanti FERON®-TB Gold test (interferon-gamma release assay).

All the lesions disappeared after 3 months of clarithromycin monotherapy and no recurrence was observed after 20 months of follow-up.

Discussion

Incubation period for cutaneous M. marinum infection ranges from 5 to 270 days (the median period being 21 days) (9). M. marinum low replication temperature and inhibition of growth at 37°C limits infection to the skin and subcutaneous tissue in the peripheral, cooler parts of the body. Skin lesions can be papular or plaque-like, eczema-like or can progress forming ulcers (1, 2, 7, 9). Locally invasive disease, including tenosynovitis, arthritis, and osteomyelitis is usually associated with delayed diagnosis or initially mistaken for rheumatoid arthritis, leading to prescription of tumor necrosis factor-α inhibitors or local steroid injections which aggravate the disease resulting in varying degrees of functional impairment or even amputation (5, 6). Polymorphous clinical presentation makes correct

diagnosis difficult, sometimes leading to visceral involvement (4), or lethal outcome (7). Tuberculin skin test and interferon-gamma release assay are often positive due to exposure to M. marinum, and can support the presumptive diagnosis of FTG (4, 5).

Tissue specimens should be incubated at 30 - 32°C, that being the temperature that promotes optimal growth of M. marinum, instead of standard 37°C, used for Mycobacterium tuberculosis and most other nontuberculous mycobacteria [4, 6-9].The long-acting bacterial cultures can be identified either by conventional biochemical testing [6, 7], nucleic acid amplification techniques (4, 8), or gas-liquid chromatographic analysis of cellular fatty acids (7).

The most important differential diagnosis of FTG are sporotrichosis, cutaneous leischmaniasis and deep mycoses. Dermatoscopically, in sporotrichosis, in the only reported case,generalized erythema, yellowish structurless areas with clustered pustules at the periphery, arborizing telangiectasia and white scar-like areas are present (10). In cutaneous leischmaniasis, there is generalized erythema, yellow tears, white starburst-like pattern and increased vascularity.Dermatoscopy of deep mycoses is limited to single case reports (11). Dermatoscopy of FTG, however, reveals different features comparing to the mentioned diagnoses and needs unique terminology (10, 12). Telangiectatic vessels on an erythematous base, and test with different pressure with the dermatoscope causing background colour change into yellow with persistence of the central vessel architecture at the maximum pressure have not been reported so far. According to our opinion, this pressure test might be important in order to find the best lesion for biopsy because the persistence of vessels at the highest pressure might point to well developed structures that are needed for histological and microbiological confirmation of the disease.

Conclusion

Further investigations of FTG dermatoscopy and the application of descriptive rather than metaphorical terminology will help to compare the reports and make more definitive conclusions. Collaboration with microbiologist is necessary for M. marinum successful cultivation, timely FTG diagnosis and treatment.

References

1. Aubry A, Chosidow O, Caumes E, Robert J, Cambau E. Sixty - three cases of Mycobacterium marinum infection: clinical features, treatment, and antibiotic susceptibility of causative isolates. Arch Intern Med. 2002;162(15):1746-52.
2. Veraldi S, Molle M, Nazzaro G. Eczema-like fish tank granuloma: a new clinical presentation of Mycobacterium marinum infection. J Eur Acad Dermatol Venereol. 2018; 32(5):e200-1.
3. Abbas O, Marrouch N, Kattar MM, Zeynoun S, Kibbi AG, Rached RA, et al. Cutaneous non-tuberculous Mycobacterial infections: a clinical and histopathological study of 17 cases from Lebanon. J Eur Acad Dermatol Venereol. 2011;25(1):33-42.
4. Macek P, Bodnarova M, Zavada J, Jezek P, Pavlik I, Slany M, et al. Mycobacterium marinum epididymoorchitis: case report and literature review. Urol Int. 2011;878(1):120-4.
5. Danko JR, Gilliland WR, Miller RS, Decker CF. Disseminated Mycobacterium marinum infection in a patient with rheumatoid arthritis receiving infliximab therapy. Scand J Infect Dis. 2009;41(4):252-5.
6. Nguyen HH, Fadul N, Ashraf MS, Siraj DS. Osteomyelitis infection of Mycobacterium marinum: a case report and literature review. Case Rep Infect Dis. 2015;2015: 905920.
7. Holmes GF, Harrington SM, Romagnoli MJ, Merz WG. Recurrent, disseminated Mycobacterium marinum infection caused by the same genotypically defined strain in an immunocompromised patient. J Clin Microbiol. 1999;37(9):3059-61.
8. Lau SK, Curreem SO, Ngan AH, Yeung CK, Yuen KY, Woo PC. First report of disseminated Mycobacterium skin infections in two liver transplant recipients and rapid diagnosis by hsp65 gene sequencing. J Clin Microbiol. 2011;49(11):3733-8.
9. Jernigan JA, Farr BM. Incubation period and sources of exposure for cutaneous Mycobacterium marinum infection: case report and review of the literature. Clin Infect Dis. 2000;31(2):439-43.
10. Dabas G, Kaur H, Vinay K, Kumaran MS, Shivaprakash MR, Saikia UN, et al. Dermoscopy in disseminated sporotrichosis. J Eur Acad Dermatol Venereol. 2019;33(1):e33-5.
11. Sławińska M, Hlebowicz M, Iżycka-Świeszewska E, Sikorska M, Sokołowska-Wojdyło M, Smiatacz T, et al. The role of dermoscopy in the diagnosis of deep mycoses and systemic mycoses with cutaneous involvement. Comment on “Dermoscopy in disseminated sporotrichosis”. J Eur Acad Dermatol Venereol. 2019; 33(1):e35-6.
12. Kittler H, Marghoob AA, Argenziano G, Carrera C, Curiel-Lewandrowski C, Hofmann-Wellenhof R, et al. Standardization of terminology in dermoscopy/dermatoscopy: results of the third consensus conference of the International Society of Dermoscopy. J Am Acad Dermatol. 2016;74(6):1093-106.

Serbian Journal of Dermatology and Venereology 2019; 11 (1): 31-35

Kliničke, dermatoskopske i laboratorijske karakteristike akvarijumskog granuloma

Sažetak

Kod imunokompetentnih osoba *Mycobacterium marinum (M. marinum)* infekcija se obično prezentuje lokalizovanim kožnim lezijama, poznatijim kao "bazenski granulom" ili "akvarijumski granulom" (engl. *Fish tank granuloma* (FTG)). U kliničkoj praksi, pri postavljanju dijagnoze FTG lekar se susreće sa nekoliko problema. Granulomi se mogu naći u manje od dve trećine biopsija, *acid-fast* bacili se identifikuju samo u manjem broju slučajeva. Većina diseminovanih i agresivnih formi FTG se ne prepoznaju na početku i javljaju se kod imunosuprimiranih, uključujući i pacijente kojima je transplantiran neki organ. Zabeleženi su funkcionalni ispadi ili čak amputacije ekstremiteta, visceralna diseminacija i smrtni ishod. Iako je objavljeno više od hiljadu slučajeva FTG širom sveta, dermatoskopija FTG, kao pomoć u dijagnostici, nije do sada publikovana. Prikazujući slučaj FTG sa skorašnjim početkom gde su, zahvaljujući dermatoskopiji, mikroorganizmi izolovani i identifikovani iz biopsijskog materijala, prezentujemo osnove kliničke i laboratorijske dijagnostike *M. marinum* infekcije.

Ključne reči: Granulom; Dijagnoza; Mycobacterium marinum; Bakterijske kožne bolesti; Dermoskopija; Imunokompromitovani domaćin

Received 26.05.2019.
Accepted 6.09.2019

FORTHCOMING EVENTS

Dermatology and Venereology Events 2019

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
17-19 January, 2019	7th EADO School of Dermato-Oncology, Berlin, Germany		www.eado.org
27-30 March, 2019	4th Dermatology and Cosmetology Congress with International Participants (NDERCOS 2019), Istanbul, Turkey	27 January, 2019	www.indercos.org
24-27 April, 2019	15th EADO Congress of Dermato-Oncology, Paris, France		www.esdoparis2019.com
10-15 June, 2019	24th World Congress of Dermatology, Milan, Italy	15 September, 2018	www.wcd2019milan.org
9-13 October, 2019	28th EADV Congress, Madrid, Spain		www.eadv.org
28 November - 1 December, 2019	3th National Medical Aesthetics Congress, Antalya, Turkey	25 September, 2019	www.mastder2019.org

Prepared by: Dr. Zorana Kremić, MD, Department of Dermatoveneorology Diseases, Military Medical Academy, Belgrade, Serbia

AUTHOR GUIDELINES

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

Categories of Manuscripts

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

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

3. Review articles (limited to 10 pages) should provide systemic critical assessment 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.

– 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. Author's Statements

– Conflict of Interest

To ensure fair and objective decision-making, authors must declare any associations that pose a conflict of interest (financial, personal or professional) in connection with evaluated manuscripts. If there are no conflicts of interest, the following statement should be included *before the References* (or at the end of the *Acknowledgments sectio*n):

Conflict of interest: Authors state no conflict of interest.

– Informed Consent

The protection of privacy is a legal right that must not be breached without individual informed consent. In cases where the identification of personal information is necessary for scientific reasons, authors should obtain full documentation of informed consent, including written permission from the patient prior to inclusion in the study.

The following (or similar) statement should be included *in the Methods section*:

Informed consent: Informed consent has been obtained from all individuals included in this study.

– Authorization for the use of human subjects

Manuscripts containing information related to human use should clearly state that the research has complied with all relevant national regulations and institutional policies and has been approved by the authors' institutional review board or equivalent committee. Copies of the guidelines and policy statements must be available for review by the Managing Editor if necessary. The editors reserve the right to seek additional information or guidance from reviewers on any cases in which concerns arise. All investigation with human subjects must have been conducted by following the tenets of the Helsinki Declaration, what is more authors must identify the committee or review board approving the experiments, and provide a statement indicating approval of the research. The following (or similar) statement should be included *in the Methods section*:

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

– Authorization for the Use of Experimental Animals

Manuscripts containing information related to animals use should clearly state that the research has complied with all relevant national regulations and institutional policies and has been approved by the authors' institutional review board or equivalent committee. Copies of the guidelines and policy statements must be available for review by the Managing Editor if necessary. The editors reserve the right to seek additional information or guidance from reviewers on any cases in which concerns arise. The research using animal subjects should be conducted according to the Principles of Laboratory Animal Care and similar documents. For manuscripts reporting experiments on live vertebrates or higher invertebrates, authors must identify the committee approving the experiments, and must confirm that all experiments were performed in accordance with relevant regulations. The following (or similar) statement should be included *in the Methods section*:

Ethical approval: The research related to animals use has been complied with all the relevant national regulations and institutional policies for the care and use of animals.

If the manuscript does not contain any study that requires human or animal ethical approval, the following statement should be included in the *Methods section*:

Ethical approval: The conducted research is not related to either human or animals use.

5. 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**.

CIP – Каталогизација у публикацији
Народна библиотека Србије, Београд

616.5(497.11)

SERBIAN Journal of Dermatology and Venerology / editor-in-chief Lidija Kandolf Sekulović. - Vol. 11, no. 1 (March 2019). - Belgrade (Pasterova 2) : The Serbian Association of Dermatovenereologists, 2019 - (Beograd : Zlatni presek). - 30 cm

Tromesečno
ISSN 1821-0902 = Serbian Journal of Dermatology and Venerology
COBISS.SR-ID 156525836

KOŽA SKLONA AKNAMA

UBLAŽAVA NEŽELJENE EFEKTE

NAJČEŠĆE KORIŠĆENIH LEKOVA U TERAPIJI AKNI

Eucerin® DermoPure Komplementarna umirujuća krema: razvijena sa ciljem povećanja komplijanse

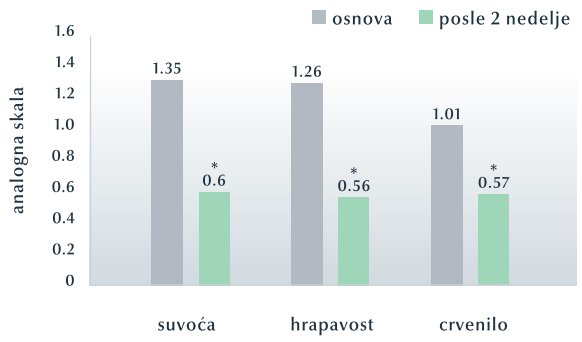
Preko 90% pacijenata na medikamentoznoj terapiji akni potvrđuje: preparat umiruje kožu i smanjuje osećaj zatezanja[1]

- Formulacija koja intenzivno hidrira
- Ceramidi jačaju barijernu funkciju kože i smanjuju gubitak vlage
- Likokalkon A deluje antiinflamatorno i smanjuje crvenilo kože
- Symsitive® ublažava iritacije direktno na mestu nastanka tako što smanjuje reaktivnost nerava

Kombinovati sa Eucerin® Oil control gel-kremom: zaštita od sunca namenjena za kožu sklonu aknama

Smanjenje suvoće, hrapavosti i crvenila kože[2]

Klinička procena posle 2 nedelje | *značajno poboljšanje



Symsitive® registrovana marka Symrise, Nemačka
(1) Samoprocena i (2) klinička procena n=58, žene i muškarci na medikamentoznoj terapiji akni (benzoyl peroxide, tretinoin, adapalene ili oralni isotretinoin), prosečne godine: 24 godine, 14 dana korišćenja preparata, dva puta dnevno, BDF podaci

Eucerin® NAUKA U SLUŽBI ZDRAVE KOŽE