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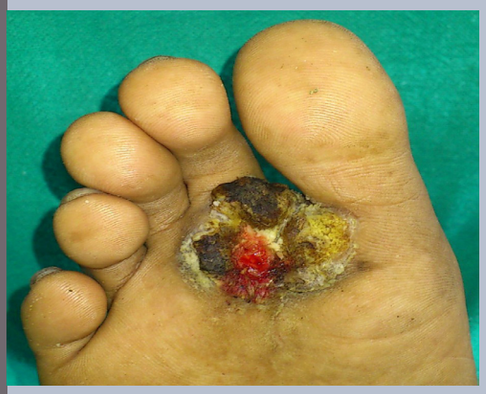

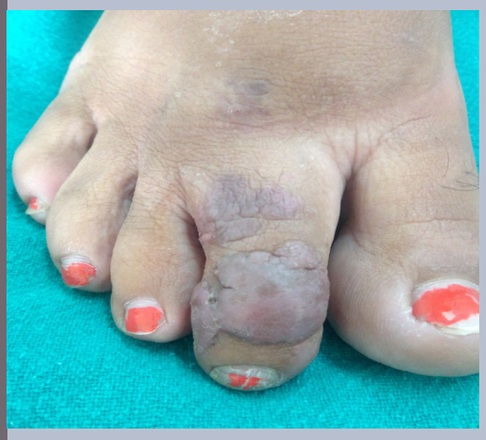

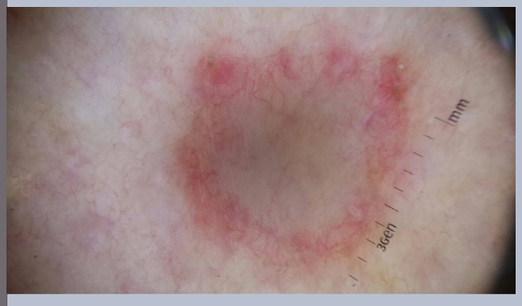

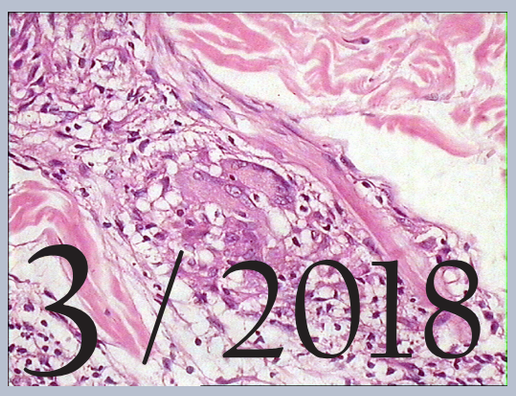

Editorial Pages

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Original Article

Interferon-gamma in patients with alopecia universalis

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ABSTRACT

Background: Alopecia universalis (AU) is an uncommon form of alopecia areata that involves the loss of all hear and body hair. The cause of AU is unknown, although most evidence supports the hypothesis that AU is a T-cell mediated autoimmune disease of the hair follicle and that cytokines play an important role. **Objective:** The aim of our study was to evaluate serum concentrations of interferon-γ (IFN-γ) in patients with AU and healthy subjects and also to asses a possible association between IFN-γ and duration of the disease. **Material and Methods:** Twenty two patients with AU and 20 healthy controls were enrolled in the study. Serum concentrations of IFN-γ were measured using enzyme-linked immunoassay techniques. **Results:** The serum concentration of IFN-γ in patients with AU was significantly higher than that in the control group (12.050 pg/ml *vs* 10.000 pg/ml, respectively; $p < 0.0001$). No correlations were found between duration of disease and the serum levels of IFN-γ ($p= 0.3048$). **Conclusion:** Our results have demonstrated the importance of determining IFN-γ concentrations in serum in patients with AU. This research could contribute to the interpretation of insufficiently well known views of the pathogenesis role and significance of IFN-γ in AU.

Key words: Alopecia universalis; Cytokines; Interferon-gamma

INTRODUCTION

Alopecia areata (AA) is a non-scarring inflammatory disease of the hair follicle. Although it usually presents as asymptomatic localized hair loss, it is a disese of very broad spectrum. Alopecia universalis (AU) is an uncommon form of AA that involves the loss of all haed and body hair and is estimated to account approximately 5% of all alopecia cases [1]. The cause of disease is unknown, although there is evidence to suggest that the link between lymphocytic infiltration of the follicle and the disruption of the hair follicle cycle in AA may be provided by a combination of factors, including cytokine release, cytotoxic T-cell activity, and apoptosis [2,3]. It is also considered that a disequilibrium in the production of cytokines, with a relative excess of proinflammatory and Th1 types, vs. anti-inflammatory cytokines may be involved in the persistence of AA lesions, as shown in human scalp biopsies [4]. The immune response presented in AU is associated with aberrant lesional expression of interferon-gamma (IFN-γ), interleukin-2 (IL-2) and IL-1β, and overexpression of ICAM-1 and MHC molecules on hair follicle keratinocytes and dermal papilla cells [5].

Interferon-γ (IFN-γ) is produced by perifollicular or follicular antigen presenting cells and among several actions it also deprives dermal papilla cells of their ability to maintain anagen hair growth [6]. The elevated serum levels of IFN-γ in AA patients may reflect the state of inflammation, especially in the extensive forms of the disease, and the measurement of serum IFN- γ may be useful in discriminating those who are likely to develop AU from the remaining local disease, or as a prognostic indicator [7].

Recent progress in the understanding of AU has shown that the regulation of local and systemic cytokines plays

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an important role in its pathogenesis. Therefore, the aim of our study was to evaluate serum concentrations of IFN-γ in patients with AU and healthy subjects and also to asses a possible association between IFN-γ and duration of the disease.

MATERIALS AND METHODS

Study Setting

This is a case-control study of serum concentration of IFN-γ in AU patients. The study was conducted in the Department of dermatovenereology at University Clinical Center Sarajevo, Sarajevo, Bosnia and Herzegovina.

Subjects

The study included 22 patients with AU (10 female and 12 male). A detailed history and examination were taken in all study subjects, including patients age, age at onset and duration of disease. The diagnosis of AU was made on clinical grounds. None of the patients had used any systemic medications for AU treatment for at least 6 months before the study. We excluded the patients with other types of illnesses, such as autoimmune diseases that could affect the outcome of the study.

Control group consisted of 20 generally healthy subjects (11 female and 9 male). They did not have any scalp lesions in their personal history or on clinical examination.

All subjects gave their informed consent in accordance with the requirements of the Institutional Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Serum Cytokine Determination

Serum concentrations of IFN-γ were measured by enzyme-linked immunosorbent assay (ELISA) technique, using Quantikine Human IFN-γ Immunoassay (R&D System, Minneapolis, USA), in accordance with the manufacturer's instructions.

Briefly, a monoclonal antibody specific for IFN-γ has been precoated onto a microplate. Standards and samples are pipetted into the wells and any IFN-γ present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for IFN-γ is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and colour develops in proportion to the amount of IFN-γ bound in the initial step. The colour development was stopped and the intensity of the colour was measured at 450 nm with a photometar (Rider Biotek Elx800).

Statistical Analysis

Statistical analyses were performed using MedCalc Statistical Software version 15.2.2. (MedCalc Software bvba, Ostend, Belgium). Statistical comparisons were performed using T test and Mann Whitney U test for independent samples. We used Spearman correlation coefficient rho for calculate relationship between duration of disease and serum levels of cytokines. Data were considered statistically significance at $p<0.01$.

RESULTS

The study group composed of 22 patients with AU (10 female and 12 male; the mean age of the patients was 33.96 years, ranging from 5 to 60 years), and 20 healthy controls (11 female and 9 male; the mean age 32.55 years, ranging from 6 to 63 years). There were no significant difference in age and female/male ratio between the patients and controls ($p>0.05$).The mean duration of AU was 27.59±29.95 (range 2-108 months). Dermographic data of patients and controls are shown in Table 1.

The serum concentration of IFN-γ in patients with AU was significantly higher than that in the control group (12 050 pg/ml *vs* 10 000 pg/ml, respectively) (Table 2, Fig. 1). Patients with longer duration of the disease had higher concentration of IFN-γ, but not significantly (Table 3).

Table 1: Demographic characteristics of patients and healthy controls

	Alopecia universalis (n=22)	Healthy controls (n=20)	p
Age (mean±SD)	33.96±15.65	32.55±16.12	0.889*
Range	5-60	6-63	
Sex (male/female)	12/10	9/11	0.7574**
Duration of disease (months) (mean±SD)	27.59±29.95	/	
Range	2-108	/	

*T test **Chi-squared test

Table 2: Serum concentrations of IFN-γ in patients and healthy controls

	Alopecia universalis (n=22) (pg/ml)	Controls (n=20) (pg/ml)	Mann-Whitney U	Z	p*
IFN-γ (med)	12.050	10.000	40.00	4.536	< 0.0001***
Range**	9.900-13.900	9.100-11.200			

*Mann-Whitney U test, **Range – min-max values,***Statistical significance (p<0.01)

Table 3: Relationship between duration of disease and serum levels of IFN-γ (Spearman rank test)

	Duration of disease			
	n	rho	95% CI	p
IFNγ	22	0.229	–0.213-0.594	0.3048

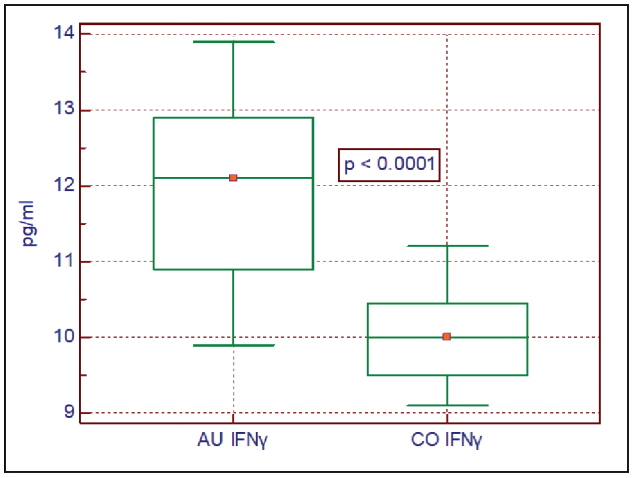

Figure 1: Median, minimum-maximum values of serum levels IFNγ in alopecia universalis (AU) patients and healthy controls (CO).

DISCUSSION

Although the cause of the disease is at present unknown, several studies have shown that within cascade of pathogenesis of AA, cytokines play a crucial role [8]. Hair loss may occur because proinflammatory cytokines interfere with the hair cycle, leading to premature arrest of hair cycling with cessation of hair growth [9]. This concept may explain typical clinical features of AA such as a progression pattern in centrifugal waves and spontaneous hair regrowth in concentric rings [10], suggesting the presence of soluble mediators within affected areas of the scalp.

IFN-γ is the main cytokine known to be aberrantly expressed in AA though a CD4+ Th1 mediated response. By using immunohistochemical and *in situ* hybridization studies to demonstrate the persistence of proinflammatory as well as apoptotic mechanisms in the skin biopsies from patients with chronic AA, Bodemer *et al.* have confirmed the presence of a cellular infiltrate in close contact with the hair follicle, producing IFN-γ in association with proinflammatory cytokine production [4].

Ito *et al.* reported that IFN-γ rapidly inhibited hair elongation in cultured human anagen hair follicles and induced morphological signs of catagen transformation after only four days of culture, faster than with other reported catagen-inducers [11]. Proliferation was inhibited, apoptosis was increased, and follicular melanogenesis was switched of in hair bulb keratinocytes treated *in situ* with IFN-γ.

To determine which cytokines may be involved with overexpression of ICAM-1 and MHC molecules on dermal papilla cells of affected hair follicles, Konig *et al.* were able to imitate the *in vivo* situation of AA [5]. They found that incubation with IFN-γ led to a time-dependent upregulation of the surface molecules, as well as to an overexpression of ICAM-1. Additionally, it has been proposed that an ectopic expression of MHC class I molecules on hair matrix and subinfundibular epithelium can be induced by IFN-γ [3], increasing the possibility of the destruction of the hair follicle immune privilege site.The breaking of tolerance in hair follicle and subsequent change in cytokine profiles leads to infiltration of lymphocites [12].

In addition, increased serum levels of IFN-γ in patients with AU compared with normal controls has been reported, further suggesting a role for this cytokine [13]. The results presented in our study demonstrate that the mean serum levels of IFN-γ were significantly elevated in AU patients in comparison to healthy subjects. These results are consistent with a clinical study performed by Arca *et al.* [14]. They compared the serum levels of IFNγ in patients with AA and the control group and also they investigated the difference between the localized form of the disease with the extensive form like AU. It has been shown that serum levels of IFN-γ are significantly higher in patients with AU compared to controls. In the study of Teraki *et al.* [15], they compared the serum levels of cytokines,including IFN-γ, TNF-a, IL-1a, IL-2, IL-4 and IL-6 in patients

with the localized form and the extensive form and found that the serum levels of IL-1a and IL-4 were significantly elevated in patients with the lokalized form. In contrast,the serum levels of IFN-γ and IL-2 were significantly elevated in patients with the extensive form. They said that these findings could be interpreted as an indication that Th1 type cytokines might be critical for the progression to the extensive form and that Th2 type cytokines may exert a more subtle influence on the inhibition of a cell-mediated attak on hair follicles. After that, Barahmani *et al.* analyzed serum cytokine profiles in 269 patients with AA and found it that increased IFN-γ levels is associated with AA regardless of disease severity [16].

The main limitation of the present work is the sample size. Nevertheless, the fact that alopecia universalis is the rarest and most severe form of alopecia areata reinforces our findings.

In conclusion, IFN-γ seems to be a useful indicator of the activity of AU and that it may play an important role in the development of this disease. Further investigations are required to clarify the pathogenic role and clinical significance of IFN-γ, and these findings may provide important clues to assist in the development of new therapeutic strategies for patients with AU.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

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Original Article

Vitamin D receptor gene polymorphism and risk of skin cancer patients of Kashmiri population (India): A case-control study

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ABSTRACT

Background: Vitamin D deficiency and Vitamin D Receptor (VDR) polymorphism, *Fok1*, is reported to be associated with the increased risk of several types of cancers through the regulation of various cancer related signaling pathways. We aimed to determine the effect of vitamin D deficiency and the association of *Fok1VDR* gene polymorphism with the risk of skin cancer in Kashmiri population. **Material and Methods:** A case-control study was conducted that include 68 histopathologically confirmed cases of skin cancer and 65 normal healthy controls from Kashmiri population. Vitamin D levels were estimated by automated chemiluminescent microparticle immunoassay. The *Fok1* genotyping was done by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique followed by sequencing of amplified PCR products. **Result:** We detected (T/C) polymorphism in the first potential start (ATG) codon in exon 2 of VDR gene. The frequencies of *CC*, *CT* and *TT* genotypes among the cases were 33.82%, 47.06% and 19.11% while in controls genotypic frequencies were 53.84%, 38.46% and 7.7% respectively. A significant difference was observed in variant allele frequencies (*CT*+*TT*) between the cases and controls with odds ratio=2.283; 95%confidence interval=1.133-4.597 (*P*=0.02). Interestingly, the association of *CT* and *TT* genotype was observed statistically significant among the squamous cell carcinoma (SCC) ($P<0.05$) and insignificant among basal cell carcinoma ($P>0.05$). The plasma 25(OH)D levels were significantly low among the cases as compared to healthy controls ($P<0.05$). **Conclusion:** We found the possible role of vitamin D deficiency and *Fok1 VDR* polymorphism with the increased risk of skin cancer. The *Fok1* polymorphism appears to be a strong risk factor for SCC development in Kashmiri population.

Key words: Vitamin Dkwd; *Fok1* polymorphism; Skin cancer; SMHS

INTRODUCTION

Globally, skin cancer is one the most commonly diagnosed type of cancer in humans [1]. It accounts for around 40% of cancer cases [2,3]. The rate of incidence is low in India as compared to the western world. However, due to its large population, the absolute number of cases is estimated to be significant [4]. The most common types of skin cancers may be categorized into two major groups: melanoma and non-melanoma. Non-melanoma type of skin cancer (NMSC) arises from keratinocytes and is further divided into two sub-types: basal cell carcinomas (BCC) and squamous cell carcinomas (SCC). Globally, BCC is the most common type of skin cancer accounting for approximately 70% of all malignant diseases of the skin [5]. Various studies have consistently reported that SCC is the most prevalent type of skin cancer in India [4,6-8]. Reports

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also indicate that skin cancer especially non-melanoma skin cancer (NMSC) is on rise in India [9]. However, clinical spectrum of skin cancer in Kashmir valley bears a different tale from the rest of the country due to its geography, climate, dietary habits and socio culture. The incidence of NMSC in Kashmir valley among males and females has been reported to be 2.7% and 2.8% respectively [10]. Genetic as well as environmental factors play an important role in the development of cancers [11- 13]. Strong associations has been observed between the deficient circulating levels of vitamin D and increased risk of various types of cancers like breast, colon, [14,15] and ovarian [16,17]. Kashmiri people are prone to vitamin D deficiency due different topographical, geographical and climatic conditions [18]. Association between vitamin D levels and risk of skin cancer have been examined in several studies and provide an insight into the positive role of vitamin D deficiency in the development of skin cancer especially NMSC.

Vitamin D modulates various cancer related signaling pathways and acts via binding to its intranuclear receptor vitamin D receptor (VDR) there by altering the gene expression of various proteins involved in the process of proliferation, differentiation and regulation of cell cycle [19]. VDR contributes to the signaling of hedgehog (Hh) and Wnt/β-catenin pathways that plays an important role in proliferation and differentiation of keratinocytes [20]. Several studies have reported that VDR gene is significantly associated with the frequency of occurrence of various types of cancers [19]. *VDR* is encoded by a large gene (>100kb) located on chromosome 12q12-q14 [21]. Whereas *Fok1* polymorphism, (rs2228570) is present at the first potential site start in exon 2 of the *VDR* gene [22-25]. This polymorphism alters an *ACG* codon that is located ten base pairs upstream from the translation start codon and results in the generation of an additional start codon. A change in the sequence from *C* to *T* allele in the translation site leads to generation of a polymorphic variant (*TT*). If the initiation of translation starts from this alternative site (thymine variant), the resultant product is three amino acid longer VDR protein of 247 amino acids that exerts less transcriptional activity as compared to the wild type (*CC*) [22]. Several studies report that there is a significant association between the *Fok1* polymorphism and the risk of various types of cancer [26]. The *Fok1* polymorphism is considered to be an independent risk marker as it has no Linkage Disequilibrium with any of the other *VDR* polymorphisms [27,28]. Keeping in view the role played by vitamin D and *VDR* gene in various cancers, we aim to assess the contribution of vitamin D and *Fok1* polymorphism and its association with skin cancer in Kashmiri population.

MATERIALS AND METHODS

A total of 68 histopathologically confirmed newly diagnosed skin cancer patients attending the Department of Dermatology, Government Medical College (GMC), Srinagar, were included in this study. A pool of 65 normal healthy controls were also recruited from the same hospital that belonged to the same geographical area, ethnic background and were of matching sex and age group. The controls did not have a previous diagnosis of any type of cancer and had maintained a healthy life style. The subjects included farmers, labours, employers, household, medical personals and students. A written informed consent was obtained from each recruited subject and the study was approved by the ethical committee of GMC, Srinagar. Among the cases, 55.88% were SCC, 39.70% included the BCC and 4.41% were melanoma. To avoid the experimental bias, melanoma type of skin cancer was excluded from the study. In cases, 58.82% were males and 41.17% females and the control consisted of 53.84% male and 46.15% female. Also, 60.3% cases were in the age group of greater than 50 and 39.7% of the cases were in age group of less than 50 years. In controls, 58.46% were in age group of greater than 50 and 41.53% were in the age group of less than 50. Out of 65 cases, 48.53% cases belonged to rural region and 51.47% cases belonged to urban region. In controls, 47.70% were from rural areas and 52.30% were from urban areas. Among the cases 25% had a family history of cancer. Blood sample (3ml) was collected in EDTA coated vials from both the study groups for plasma collection and DNA extraction. Sample collection was done from the month of March to October every year to avoid seasonal variation of Vitamin D levels.

Plasma vitamin D estimation

Vitamin D status was measured by estimating concentrations of 25-hydroxyvitaminD (25(OH)D) in the plasma. The circulating concentration of 25(OH) D in the range of 30-50ng/ml is considered necessary for optimal health [29]. The healthy controls whose 25(OH)D levels were in the range of 27-53ng/ml were included in the study. Plasma 25(OH)D levels

were estimated by automated chemilumnescent microparticle immunoassay (CMIA) method by ARCHITECT25-OH vitamin D assay (Abbott laboratories illino is, USA Ref 3L52-25).

Genotype Analysis

Genomic DNA was extracted from the blood samples by using Quick-gDNA™ MicroPrepkit (Zymo Research, The Epigenetics Company, USA) according to given protocol. The concentration of extracted DNA was measured in a spectrophotometer at 260nm wave length by using the formula: DNAμg/ml=A_{260}x50xdilution factor. The purity of DNA was checked by using A_{260}/A_{280}. *VDR Fok1* genotype was analysed by PCR-RFLP using specific primers Forward 5'-AGCTGGCCCTGGCACTGACTCTGCTCT-3'and Reverse 5'-ATGGAAACACCTTGCTTCTT CTCCCTC-3' for amplification of 265bp of DNA segment [30]. PCR amplification was carried out in a 50-μl volume containing 50-150ng genomic DNA; 1X PCR buffer containing 2mM $MgCl_2$ (Biotools, B&M Labs, S.A. Madrid, Spain); 0.2mM dNTPs (Biotools, B&M Labs, S.A. Madrid, Spain); 1.5Units of Taq polymerase; 2pmol/μl of forward and reverse primers (Eurofins Genomics India Pvt Ltd). The PCR cycle conditions were as follows: Initial denaturation at 94°C for 10 minutes followed by 35 cycles of denaturation at 94°C for 45 seconds, annealing at 60°C for 45 seconds, extention for 72°C for 45 seconds and final extention at 72°C for 5 minutes. PCR products were verified on 2% agarose gel and analysed under a UV illuminator. The amplicons were digested with FastDigest *Fok1* restriction enzyme (Thermo Scientific, (EU) Lithuania) (1U at 37°C for 15-20 minutes). DNA fragments were subjected to electrophoresis on a 3.5% agarose gel for resolution. Genotyping of the samples were confirmed via sequencing by Sanger method (SciGenom Labs Pvt Ltd, Cochin, Kerala).

Statistical Analysis

The vitamin D levels were analysed using independent t-test. The χ^2-test was used to compare the allelic and genotypic frequencies. The association of the *VDR* genotype with the risk of skin cancer were estimated by computing the odds ratios (OR) and 95%confidence intervals (95%CI). A p-value of <0.05 was considered as statistically significant. Statistical analysis was done using SPSS version16.0 (SPSS, Inc., Chicago IL, USA).

RESULT

Vitamin D levels and *Fok1* polymorphism in *VDR* gene were evaluated in skin cancer cases. The calculated mean age of the skin cancer cases was 52.5±8.7 years whereas it was 49.3±9.25 years among the controls. The general characteristics of the studied subjects are given in Table 1. Interestingly higher number of SCC cases (55.88%) followed by BCC (39.70%) were observed when the skin cancer cases were classified into groups. Further, age distribution of cases showed that there was high incidence of skin cancer in the age group of ≥50 years as compared to <50 years. The incidences of skin cancer were also found to be higher in males as compared to females. However, the

Table 1: General characteristics of study population (cases and controls)

Variables	Cases (n=68) (%)	Controls (n=65) (%)	P value
Gender			
Male	40(58.82)	35(53.84)	0.563
Female	28(41.17)	30(46.15)	
Age			
≥50	41(60.3)	38(58.46)	0.83
<50	27(39.7)	27(41.53)	
≥50			
Family History			
Yes	17(25.0)	11(17.0)	0.25
No	51(75.0%)	54(83.0)	
Dwelling			
Rural	33(48.53)	31(47.70)	0.92
Urban	35(51.47)	34(52.30)	
Skin Cancer			
SCC	38(55.88)		
BCC	27(39.70)		

P<0.05 is considered as statistically significant, by chi square test.

rates of incidences were comparable among of urban and rural cases.

Plasma vitamin D levels

The mean plasma 25(OH)D levels were significantly lower among skin cancer cases when compared to normal healthy controls (21.05±9.67ng/ml vs 38.88±7.29ng/ml, P<0.05, Fig. 1). However, no significant difference was observed in 25(OH)D levels between SCC and BCC type of skin cancer (Table 2). In cases, the plasma 25(OH)D levels were found significantly lower among the age group of ≥50 years as compared to <50 years (P<0.05). While, no significant difference in 25(OH)D levels was observed between the male and female cases (Table 2).

Table 2: Represents plasma 25(OH)D ng/ml levels in variables of skin cancer cases and controls

Variables	Mean±SD (range)		P-value
	Cases	Controls	
SCC	21.58±10.17(06-40) (n=38)	38.88±7.29(27-53) (n=65)	P<0.001
BCC	20.76±8.91(08-37.7) (n=27)	38.88±7.29(27-53) (n=65)	P<0.001
≥50	17.12±8.12(6to38) (n=41)	35.05±6.08(27to49) (n=38)	P<0.001
<50	27.12±8.61(8to40) (n=27)	44.65±4.71(34to53) (n=27)	P<0.001
Males	21.11±10.77(7to40) (n=40)	39.17±7.28(28to53) (n=35)	P<0.001
Females	20.96±8.02(6to36) (n=28)	38.55±7.42(27to50) (n=30)	P<0.001

Data are represented as mean±SD, independent t-test. P<0.05 is considered as statistically significant.

Genotype distribution

The distribution of genotypic and allelic frequencies of *Fok1* VDR polymorphism (C>T) were compared between the skin cancer cases (diagnosed ones) and controls. The alteration of *C* to *T* allele in the start codon of translation site created a restriction site in the amplified region which was digested by *Fok1* restriction enzyme. The *CC* homozygote (wild) shows only one fragment of 265bp, while the *TT* homozygote (variant) with *Fok1* restriction site generated two fragments of 196bp and 69bp. The heterozygous (*CT*) genotype displayed three fragments of 265bp, 196bp and 69bp (Fig. 2). The frequency of *CC*, *CT* and *TT* genotypes among the cases were 33.82%, 47.06% and 19.11% while in controls it was found to be 53.84%, 38.46% and 7.7% respectively Table 3. The genotypic frequency of *CC vs TT* and *CT+TT* was found statistically significant among the cases when compared with normal healthy controls with a p-value of 0.016 and P=0.02 respectively. The mutant *T* allele was found to be a risk factor for skin cancer with OR=2.018, 95%CI1.205-3.379, P=0.007. When the subjects were classified further into groups, it was observed that the frequency of *CC*, *CT* and *TT* genotypes in SCC type were 26.3%, 55.2% and 21% respectively and this pattern of distribution showed statistical significance among the SCC cases as compared to controls (P<0.05). While in BCC type the frequency of *CC*, *CT* and *TT* genotypes were 44.4%, 40.7% and 15% respectively. However no statistical significance was observed between the BCC

Table 3: Represents genotypic and allelic frequencies of Fok1 VDR gene among the skin cancer cases and controls and their association with risk of skin cancer

VDR Polymorphism	Cases (%)	Controls (n=65 (%)	OR (95%CI)	P value
Fok-1				
Genotype	*Skin*			
CC (FF)	*cancer (n=68)*	35(53.84)		
CT (Ff)	23(33.82)	25(38.46)	*1.00*	
TT (ff)	32(47.06)	5(7.7)	1.948(0.928-4.090)	0.077
CT+TT (Ff+ff)	13(19.11)	30(46.15)	3.957(1.243-12.594)	0.016
Allele	45(66.17)		2.283(1.133-4.597)	0.02
C (F)		95(73.07)		
T (f)	78(57.35)	35(27.0)	2.018(1.205-3.379)	0.007
Genotype	58(42.64)			
CC	*SCC(n=38)*	35(53.84)	1.00	
CT	10 (26.3)	25(38.46)	2.8(1.12-7.0)	0.025
TT	20 (55.2)	5(7.7)	5.6(1.5-21)	0.007
CT+TT	8 (21.0)	30(46.15)	3.567(1.367-7.8)	0.007
Allele	28 (76.6)			0.003
C		95(73.07)		
T	40(52.6)	35(27.0)	2.443(1.35-4.425)	
Genotype	36(47.3)			
CC	*BCC(n=27)*	35(53.84)	1.00	0.612
CT	12(44.4)	25(38.46)	1.283(0.5-3.371)	0.25
TT	11(40.7)	5(7.7)	2.33(0.537-10.14)	0.411
CT+TT	4(15.0)	30(46.15)	1.46(0.6-3.6)	
Allele	15(55.5)			
C		95(73.07)		
T	35(64.8)	35(27.0)	1.473(0.747-2.90)	0.262
	19(35.1)			

P<0.05 is considered as statistically significant, by chi square test.

cases and controls. When the age group of ≥50 years in cases of diagnosed subjects was evaluated, the frequency of mutant *T* allele was found to be 41.46% compared to 26.31% among controls with OR=1.983, 95%CI 1.01-3.89, P=0.045. While in age group of <50 years, no significant difference was found between the cases and controls. In females, the frequency of mutant *T* allele was 46.43% and 28.33% in cases and controls respectively and this observation showed a statistical significance of *T* allele among the cases when compared to controls (*P*=0.044). While, in males, no significant difference was observed between the cases and controls as shown in Table 4. Genotyping of the samples were confirmed via sequencing by Sanger method (SciGenom Labs Pvt Ltd, Cochin, Kerala) (Figs. 3 – 5).

DISCUSSION

Vitamin D plays an important role in various cancer related signaling pathways. Vitamin D induces transcriptional activation or repression of target genes by binding to the *VDR*. In the epidermis, Hh and Wnt/β-catenin are the two important vitamin D signaling pathways that play an important role in proliferation and differentiation of keratinocytes. VitaminD/VDR inhibits the Hh pathway in keratinocytes by suppressing the expression of Shhandgli1. In Wnt/β-catenin pathway, VitaminD/VDR binds to β-catenin and reduces its transcriptional activity. Therefore, VitaminD/VDR reduces the proliferation and induces the process of differentiation in keratinocytes thereby limiting their ability to induce tumors in the skin [20]. In keratinocytes, VitaminD/VDR regulates the proliferation in the basal layer of the epidermis and promotes sequential differentiation [31]. A low circulatory level of 25(OH)D is the main marker of

Table 4: Represents genotypic and allelic frequencies of *Fok1 VDR* gene in age and gender variables of skin cancer cases and controls and their association with risk of skin cancer

Variable	Cases	Control	OR (95%CI)	P value
Age ≥ 50	(n=41)	(n=38)		
Genotype	15(36.6)	21(55.26)	1.00	
CC	18(44)	14(36.84)	1.80(0.687-4.71)	0.23
CT	08(19.51)	03(8)	3.733(0.85-16.47)	0.0713
TT	26(63.41)	17(44.73)	2.14(0.87-5.27)	0.096
CT+TT				
Allele				
C	48(58.53)	56(73.68)		
T	34(41.46)	20(26.31)	1.983(1.011-3.89)	0.045
<50	(n=27)	(n=27)		
Genotype	8(29.6)	14(51.85)	1.0	
CC	14(52)	11(40.74)	2.23(0.689-7.20)	0.178
CT	5(18.5)	02(7.41)	4.375(0.68-27.98)	0.104
TT	19(70.37)	13(48.14)	2.56(0.835-7.83)	0.096
CT+TT				
Allele	30(55.5)	39(72.2)		
C	24(44.4)	15(28)	2.08(0.933-4.64)	0.0714
T				
Males	(n=40)	(n=35)		
Genotype	14 (35%)	19 (54.28%)	1.0	
CC	20 (50%)	14 (40%)	1.94(0.734-5.12)	0.1795
CT	06 (15%)	02 (5.71%)	4.071(0.71-23.26)	0.0982
TT	26 (65%)	16 (45.71%)	2.205(0.87-5.6)	0.0932
CT+TT				
Allele				
C	48 (60%)	52 (74.3%)		
T	32 (40%)	18 (25.71%)	1.926(0.96-3.87)	0.0641
Females	(n=28)	(n=30)		
Genotype	9(32.14%)	16(53.33%)	1.0	
CC	12(42.85%)	11(36.66%)	1.94(0.61-6.162)	0.26
CT	7(25%)	3(10%)	4.15(0.854-20.14)	0.068
TT	19(68%)	14(46.66%)	2.413(0.83-7.03)	1.034
CT+TT				
Allele				
C	30(53.57%)	43(71.66%)		
T	26(46.43%)	17(28.33%)	2.2(1.016-4.73)	0.044

*P<0.05 is considered as statistically significant, by chisquare test

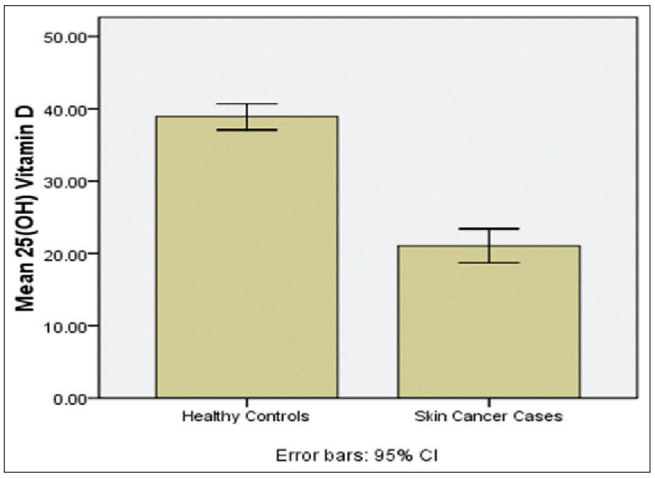

Figure 1: Represents the mean plasma 25(OH)D levels in skin cancer patients and controls.s Data are represented as mean±95% CI, independent t-test. P<0.05 is considered as statistically significant.

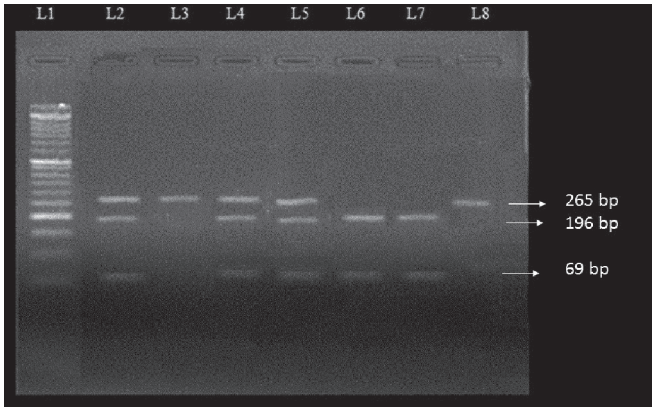

Figure 2: Representative gel picture showing PCR-based RFLP analysis of Fok1 VDR gene polymorphism on 3.5% agarose gel. Lane no. 1 represents the 50bp DNA ladder. Lane no. 2, 4, 5 represents heterozygous genotype (three bands 265bp, 196bp and 69 bp). Lane no. 3 & 8 represents homozygous wild genotype (one band 265bp). Lane no. 6 & 7 represents mutant homozygous genotype (two bands 196bp and 69bp).

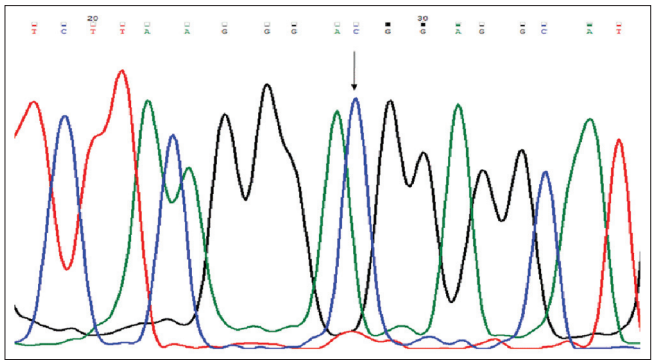

Figure 3: Representative electropherogram sequencing result of the *Fok1 VDR* gene polymorphism in exon 2, arrow indicates the presence of homozygous wild genotype (CC) at the polymorphic site.

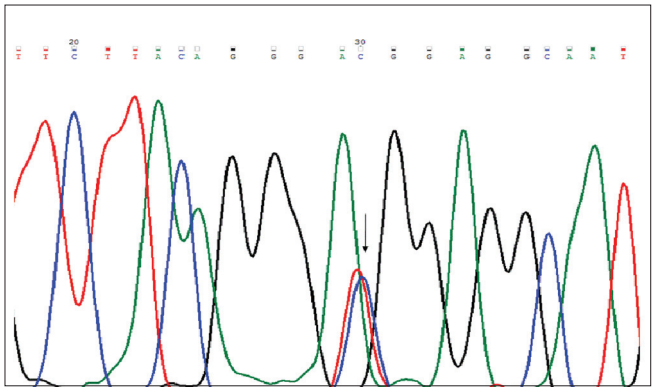

Figure 4: Representative electropherogram sequencing result of the *Fok1 VDR* gene polymorphism in exon 2, arrow indicates the presence of heterozygous genotype (CT) at the polymorphic site.

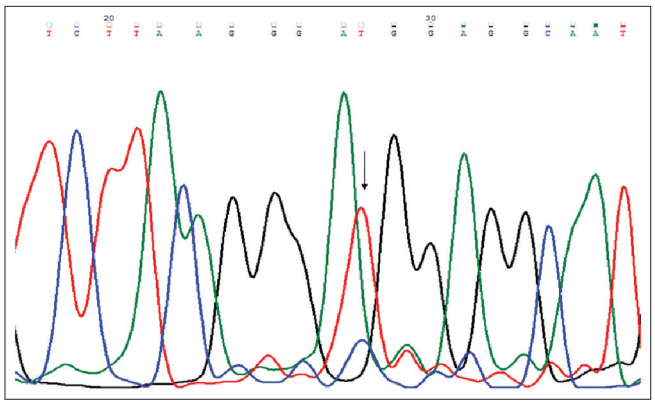

Figure 5: Representative electropherogram sequencing result of the *Fok1 VDR* gene polymorphism in exon 2, arrow indicates the presence of mutated homozygous genotype (TT) at the polymorphic site.

vitamin D deficiency. The limited exposure to sun is considered the main cause of vitamin D deficiency. However, prolonged sun exposure will not increase the vitamin D levels further, as Holick *et al* documented that human skin has the intrinsic ability of vitamin D production [32]. Harinarayan *et al* reported that the sunlight exposure between the hours 11a.m. to 2p.m. will promote adequate vitamin D formation in the skin [33]. Usually, 20-30 minutes exposure in the sun two to four times a week is enough to maintain adequate levels of Vitamin D. The prolonged exposure to sunlight increases the risk of skin cancer as ultraviolet radiation in sufficient quantity can damage DNA, causing genetic mutations and results in abnormal cellular proliferation [34]. People aged >50 years are prone to develop vitamin D deficiency due to various risk factors such as decreased dietary intake, diminished sunlight exposure, reduced skin thickness, impaired intestinal absorption and impaired hydroxylation in the liver and kidney [35]. In the present study the plasma 25(OH)D levels were found to be significantly lower among skin cancer cases when compared to healthy controls (21.05±9.67 vs 38.8±7.29, P<0.05). Several studies reported that the basal line of 25(OH)D levels were lower in skin cancer patients as compared to the control group. Asgari *et al*., reported an increased risk for BCC with higher prediagnostic serum 25(OH)D levels, adjusted for sun exposure, in a nested case control study [36]. Tang *et al*., reported that higher baseline 25(OH)D serum levels coincided with a decreased risk for NMSC [37]. Likewise Van der Pols *et al*., found that there is a reduced risk for SCC type of skin cancer, in those with a history of skin cancer and whose vitamin D levels >75nmol/L [38]. However, in the current study no significant difference was observed in plasma 25(OH)D levels between the SCC and BCC type of skin cancer. Plasma 25(OH)D levels were significantly lower among the cases of ≥50 years age group as compared to <50 years. Tang *et al*., reported that elderly men with 25(OH)D levels >75nmol/L were associated with the decreased risk for non-melanoma type of skin cancer (OR=0.53, P=0.026) [37]. In this study no significant difference was observed in the plasma 25(OH)D levels between the male and female patients. The rate of skin cancer incidence was observed higher in males as compared to female as unprotected sun exposure was found usually higher in males as compared to females. Several studies have evaluated the role of *Fok1 VDR* polymorphism in skin cancer and have found that *Fok-1 VDR* gene polymorphism is as an important mediator in the development of skin cancer. A study reported that the *Fok1 ff* genotype was positively associated with an increased risk for each type of skin cancer [38]. A meta-analysis conducted by Gandini *et al*., reported borderline significance with increased risk of *f* allele in NMSC while the *ff* genotype attributed to about 30% of the increased risk for the NMSC type of skin cancer [39]. Consistent with this studies, our

findings suggest that *Fok1 VDR* polymorphism was significantly associated with the risk of skin cancer. The frequency of homozygous mutant *Fok1 TT* genotype and *T* allele was found to be statistically significant among the skin cancer cases as compared to controls but statistical association was limited to SCC type. In SCC type of skin cancer, the genotypic frequency of both heterozygous *CT* and homozygous *TT* mutant *Fok1* polymorphism was found statistically significant in cases as compared to controls. This was consistent with a study conducted by Han *et al*., which showed the significantly positive association of *Fok1* polymorphism with SCC risk among the woman [40]. However, the association was found to be statistically in significant among BCC type of skin cancer. In ≥50 years of age group, the frequency of mutant *T* allele was observed to be statistically significant among the cases as compared to controls, while as, in <50 years of age group, no significant difference was found between the cases and controls. Similarly, among the males, no significant difference was found between the cases and controls, however, in females the frequency of mutant *T* allele was found statistically significant among the cases as compared to controls. The present study supports the notion that vitamin D deficiency and *Fok1 VDR* polymorphism may increase the risk of skin cancer and a strong association of *Fok1* polymorphism was observed with SCC type of skin cancer.

CONCLUSION

Vitamin D deficiency is found to be associated with different types of cancers including skin cancer. This study suggests a possible association of vitamin D deficiency and *Fok1 VDR* polymorphism in skin cancer development, especially for SCC. Our study gives a strong impression that vitamin D has a protective effect against the development of skin cancer. However, there is need of independently large population-based prospective studies to validate our findings and to facilitate rigorous analyses of subgroups.

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STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

STATEMENT OF INFORMED CONSENT

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Original Article

Two cases of disseminated superficial actinic porokeratosis (DSAP) and treatment literature review

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ABSTRACT

Background: Disseminated superficial actinic porokeratosis (DSAP) is characterized by asymptomatic multiple papules with annular keratotic rim distributed symmetrically on the sun-exposed areas. Many approaches have been proposed in the past for treating DSAP, but the therapy is still a challenge for every physician, mostly because of the frequent relapses of the disease and the multiplicity of the skin lesions. **Material and Methods:** Two case reports were reported emphasizing the challenges of treatment approach. Therefore, a systemic English literature review was conducted searching Medline database using PubMed Central and Ovid software as search interface to collect evidence based on the various treatment modalities for DSAP. **Results:** The initial search yielded 146 articles, but only the relevant case reports, case series and studies relating to the treatment of DSAP have been described and summarized in a table. For each different therapy the efficacy of each treatment, side effects, cost-effectiveness and authors' recommendations were reported. **Conclusion:** Several factors need to be considered prior to physicians' decision of the most appropriate treatment for each patient like age, the extent of body surface area involvement, patients' medical history and social situation, the available resources, the side effects and cost- effectiveness of each treatment. However, l the exact value of each treatment is difficult to determine owing to the lack of controlled studies evaluating their efficacy. Due to few incidences of squamous cell carcinoma, patients need to be followed up and monitored closely for any early detection of recurrence or possible onset of malignancies.

Key words: Porokeratosis; Keratinizing disorders; Lasers; Photodynamic therapy

INTRODUCTION

Disseminated superficial actinic porokeratosis (DSAP) was first described by Chernosky and Freeman [1]. Clinically, DSAP is characterized by asymptomatic multiple papules with annular keratotic rim distributed symmetrically on the sun-exposed areas, and facial involvement is a rare presentation[1]. Malignant degeneration has been described in 7% to 11% of porokeratoses cases, with squamous cell carcinoma being the most common [2-4]. Histological hallmark is the cornoid lamella, which is formed by clonal hyperproliferation of atypical keratinocytes [3]. Underlying the cornoid lamella, the granular layer is thinned or absent and keratinocytes are oedematous with spongiosis, and dermal lymphocytic infiltrate may also be evident [5]. Dermoscopy examination demonstrate single or double "white track" structure at the margin corresponding to the cornoid lamella, and the red dots, globules, and lines are enlarged capillary vessels that can be observed because the epithelium is atrophic [6].

Xia and colleagues using a genomewide search in a large Chinese family, identified a locus at chromosome 12q23.2-24. 1 responsible for disseminated superficial actinic porokeratosis [7]. Therefore, DSAP is an inherited dermatologic disorder with lesions appearing in genetically predisposed individuals after adequate exposure to ultraviolet radiation or immunosuppression in the third and fourth decades of life [8].

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A variety of approaches have been proposed to treat DSAP, but the therapy is still a challenge for every physician, mostly because of the multiplicity of the skin lesions and the frequent relapses of the disease [9]. Herein, we present two case reports with a great dilemma in treatment approach, following by an update literature review.

CASES

Case 1: An eighteen four-year-old man presented in our clinic with 6-month history of bilateral symmetrical erythematous skin lesions on the lower and upper extremities. The skin eruptions were associated with photosensitivity and moderate pruritus. The patient had a background medical history of hypercholesteremia, hypertension, ischemic heart disease, congestive heart disease, diabetes mellitus type 2, non-alcoholic fatty liver, chronic renal failure and glaucoma.

On examination bilateral erythematous scaly papules with annular configuration, well –demarcated borders and central atrophy were seen on the shins, thighs and forearm (Figs. 1a and 1b). Dermoscopy examination revealed a white like track structures at the periphery of the lesion with a mild hyperpigmentation in the inner side and with some red globules, and lines at the periphery (Fig. 2). On histological examination cornoid lamella was found in the stratum corneum with focal loss of granular layer, prominent lichenoid, superficial perivascular lymphocytic infiltrate and background elastosis (Figs. 3a and 3b).

Case 2: An eighteen one-year-old man with background history of diabetes mellitus type 2, bronchiectasis, asthma, ischemic heart disease, aortic stenosis and mitral insufficiency was examined in our clinic due to 3-year history of annular non-pruritic lesions on the shins. In the past, he was treated with steroid intralesional injections without any improvement.

On examination, there were multiple annular erythematous lesions with central clearing and elevated borders on the shins (Figs. 1c and 1d). Histological examination revealed cornoid lamella with absence of the granular layer. The intervening epidermis between the cornoid lamellae was thin and in the upper dermis there were perivascular mononuclear and lichenoid cells.

According to the clinical and histological presentation, both of our patients were diagnosed with disseminated superficial actinic porokeratosis. Their clinical presentation, risk of malignancy, medical history and their social situation was considered for choosing the most appropriate treatment for the patient.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

METHOD

A systemic English literature review was conducted in June 2017 searching Medline database using PubMed Central and Ovid software as search interface to collect

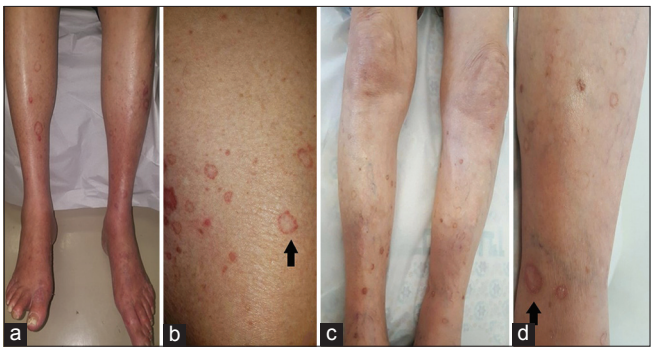

Figure 1: (a-d) Bilateral erythematous scaly papules with annular configuration on the shins, thighs and forearm with well – demarcated borders and central atrophy.

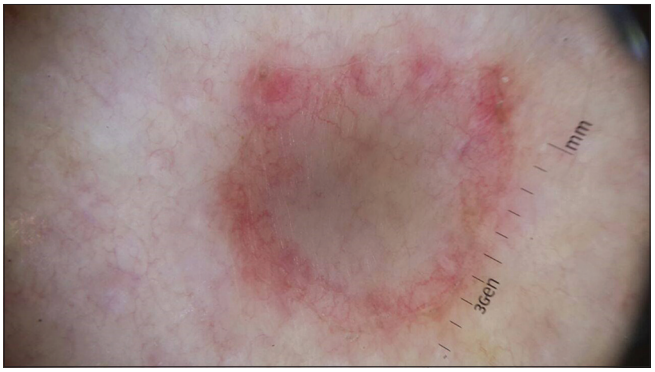

Figure 2: A "white track" structures can be identified at the periphery of the lesion with a brownish pigmentation in the inner side and with some red globules, and lines at the periphery.

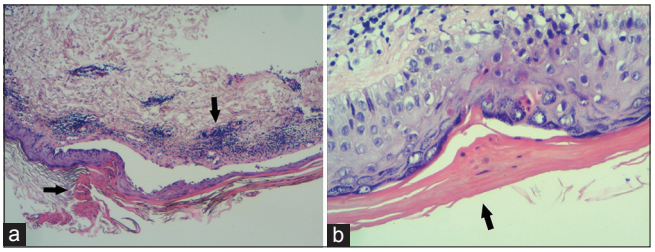

Figure 3: (a and b) Cornoid lamella was found in the stratum corneum with focal loss of granular layer, prominent lichenoid, superficial perivascular lymphocytic infiltrate and background elastosis. (Hematoxylin and Eosin, 40×, 400x).

Table 1: Review of treatments modalities. DSAP - Disseminated Superficial Actinic Porokeratosis; N/A – Non-Applicable. ;MAL-PDT - Methyl-aminolevulinate Photodynamic Therapy.; ALA-PDT- Aminolaevulinic acid Photodynamic Therapy; Nd: YAG - neodymium-doped yttrium aluminium garnet

Author	Type of study	Therapy	Number of patients	Age of patients	Mechanism of action	Efficacy	Side effects	Cost	Authors' recommendations
Topical treatment									
Vlachou *et al.*, 2008 10	Case series	Topical Diclofenac 3%	8	51-79	Diclofenac exerts its action via inhibition of prostaglandin synthesis by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), causing inhibition of arachidonic acid metabolism, thereby reduction of the tumorigenic effects of its metabolites	Completion of the therapy: 6/8 patients had no improvement and 2 had partial improvement	Pruritus Erythema	Inexpensive	A non-invasive, generally well tolerated and relatively safe topical therapy, but the results do not support its effectiveness on DSAP
Marks *et al.*, 2009 11	Open-label, multicenter pilot study		17	N/A		12nd weesk: 7/13 patients had a decrease in number of lesions, and 1 patient had a stable number of lesions on the target area Completion of the therapy (24th week): 3/10 patients had a decrease in number of lesions, and 1 patient had a stable number of lesions	Dermatitis Erythema		The data implies that the treatment provided some protection against disease progression, and it would be helpful in the absence of desirable alternatives
Otero-Rivas *et al.*, 2016 12	Letter to the Editor		1	82		Completion of the therapy (12nd week): almost all lesions had cleared and only some erythematous macules persisted	No side effects		It is a well-tolerated and safe topical therapy with excellent results in the treatment of DSAP and it could be useful in some selected patients
Arun, Pearson, Chalmers 2011 13	Case report	Imiquimod 5% cream	1	68	Toll-like receptor (TLR) agonist, stimulating the innate immune response by activating antigen-presenting cells to produce interferon and other cytokines and chemokines. It may suppress or switch off the abnormal mutant genes through its immunological effects	Completion of the therapy (8th week): slight superficial scarring and residual erythema, but no evidence of the original condition	Superficial scarring Residual Erythema	Inexpensive	It may be a useful treatment option, but it should be introduced cautiously, and an application frequency of three times a week should be used initially to avoid excessive inflammation
Riad *et al.* 2013 14	Case report		1	19		Completion of the therapy: only few lesions with a partial response and no relapse after 2 years	Erythema, Pruritus		N/A
Harrison, Stollery 1994 15	Letter to the Editor	Calcipotriol	3	68-85	Vitamin D3 analogs may induce genes critical for keratinocyte differentiation, such as transglutaminase or involucrin; and may inhibit proliferation by inducing sphingomyelin hydrolysis and modulation of protein kinase C activity	Completion of the therapy: improvement varied between 50 and 75%, which was maintained for up to 6 months in 2/3 patients	Skin irritation	Inexpensive	N/A
Bakardzhiev, Kavaklieva, Pehlivanov, 2012 16	Letter to the Editor	Calcipotriol	1	73		Completion of the therapy: after 6-month patient was free of lesions	Non-reported	Inexpensive	Good response of DSAP to calcipotriol has documented.

Contd...

Table 1: (***Continued***)

Author	Type of study	Therapy	Number of patients	Age of patients	Mechanism of action	Efficacy	Side effects	Cost	Authors' recommendations
Böhm, Luger, Bonsmann, 1999 17	Case report	Tacalcitol	1	40		Completion of the therapy: 5-month lesions had completely faded and only few invisible lesions were noticeable on palpation	Non-reported		Vitamin D3 analogs may help to reduce the long-term risk of malignant transformation.
Nakamura *et al*., 2014 18	Case report	Calcipotriol and adapalene	1	63		Completion of the therapy: after 3 months skin lesions improved substantially	Hyperpigmentation		The lack of significant adverse effects and clinical efficacy, indicates that the treatment may represent a useful option
Tchernev *et al*., 2017 19	Case report	Calcipotriol/ betamethasone gel	1	80		Completion of the therapy: after 2 months almost full resolution of the clinical symptoms and without the appearance of fresh lesions	No side effect		The lack of significant adverse effects in the patient, as well as the good tolerance and the significant clinical improvement, indicates that this treatment option is beneficial for the therapy of DSAP
Systemic Therapy									
Kariniemi, Stubb, Lassus, 1980 20	Case report	Aromatic retinoid	1	84	Vitamin A derivatives may participate in the differentiation of the epidermal cells and enhance keratinization, leading to reduction of the mitotic activity	Completion of the therapy: after the 40th day, the pruritus had stopped entirely, and the lesions had cleared so that the scaly thread-like border had disappeared	Mild cheilitis Hair loss	Inexpensive	N/A
Ludera-Zimoch, Rubisz-Brzezinska, 1989 21	Case report		1	55		Completion of the therapy: after the 3rd month, clinical improvement lasted for several months and their followed by less pronounced but progressive reappearance of clinical symptoms	N/A		N/A
Carmichael, Tan, 1990 22	Case report	Etretinate	1	55		Completion of the therapy: after the 2nd month marked improvement in the scaling, but treatment stopped due to side effects	Hair thinning Digitate keratoses		N/A
Photodynamic Therapy (PDT)									
Cavicchini, Tourlaki, 2006 9	Letter to the Editor	MAL-PDT	1	50	Topical methyl aminolevulinate (MAL), photosensitizing drug with appropriate light dose can result to highly reactive oxygen species leading to selective cell damage and indirectly stimulate inflammatory cell mediators	Completion of the therapy: after the 12th month, no new lesions occurred, and a striking clinical improvement was observed with only a slight residual hyperpigmentation	Burning sensation Hyperpigmentation	Expensive	MAL-PDT showed high efficacy and good cosmetic outcome with a high patient satisfaction level

Contd...

Table 1: (***Continued***)

Author	Type of study	Therapy	Number of patients	Age of patients	Mechanism of action	Efficacy	Side effects	Cost	Authors' recommendations
Fernandez-Guarino *et al.*, 2009 23	Letter to the Editor	MAL -PDT	6	55-74		Completion of the therapy: after 2 weeks: 2/6 showed no respond, 4/6 showed slight reduce roughness	No side effects were noted	Expensive	DSAP with MAL-PDT suggest that this treatment may not be promising for this dermatosis
Salas *et al.*, 2016 2	Case report		2	58,73		Completion of the therapy: after 10 months good results remained and no evidence of recurrence in the treated lesions	No side effects were noted		Two cases of DSAP treated successfully with daylight-PDT with no recurrence after 10 months
Nayeemuddin *et al.*, 2002 24	Case series	ALA-PDT	3	42-59	5-aminolaevulinic acid (5-ALA) is a pro-drug, which relatively selectively is taken up by some skin diseases and it has the same mechanism of action with MAL when combine with appropriate light dose	Completion of the therapy: After the second treatment 3/3 patients decided not to continue the treatment because 2/3 did not respond, 1/3 had post -inflammatory hyperpigmentation	Discomfort, Skin peeling Pigmentary changes	Expensive	The results of ALA-PDT in these three patients suggests that this treatment modality may not be suitable for DSAP
Boiy , de Witte, Roelandts 2010 25	Case report	Hypericin-PDT	1	54	Hypericin is a photo-active dye originating from the herb Hypericum perforatum (St. John's wort)	Completion of the therapy: After three treatments, little or no clinical improvement was noted	Erythema	Expensive	Topical hypericin-PDT does not emerge as a promising treatment for DSAP
Lasers and Lights									
Lolis , & Marmur, 2008 3	Case report	Q-switched ruby laser (694nm)	1	48	N/A	Completion of treatment: most of the lesions decrease	Erythema Hyperpigmentation	Expensive	Ruby laser (694 nm) has a great degree of penetration, allowing it to treat pigmented lesions which occur deeper in the dermis affecting mainly post –inflammatory hyperpigmentation of the lesion
Itoh, & Nakagawa, 2007 26	Case report		1	61	N/A	Completion of treatment: most of the lesions improved with no residual skin lesions	Hyperpigmentation		The Q-switched ruby laser (QSRL) may be useful for the treatment of DSAP
Lui , 2010 27	Case report	Q-switched Nd: YAG laser (532nm)	1	56	N/A	Completion of treatment: good improvement of most of the lesions with patient satisfaction and unchanged results after 9 months follow up	N/A		N/A
Rosenblum, 2013 28	Case report	Erbium and neodymium YAG lasers	1	62	N/A	Completion of treatment: good improvement of the majority of the lesions	Erythema		N/A

Contd...

Table 1: (***Continued***)

Author	Type of study	Therapy	Number of patients	Age of patients	Mechanism of action	Efficacy	Side effects	Cost	Authors' recommendations
Ross *et al.*, 2016 29	Case report	Fractional 1927nm thulium fiber lasers	2	46,65	N/A	Completion of treatment: No new lesions, decrease the thickness of remaining lesions	Edema Erythema	Expensive	It is convenient and safe with nearly no downtime or morbidity associated with pigment or textural defects. Conducting multiple treatments versus one and more aggressive treatment are needed due to the poor wound healing properties on the lower extremities
Chrastil *et al.*,2007 30	Case report	Fractional Photo-thermolysis	2	47,48	The stimulatory effects of fractional resurfacing on dermal collagen remodeling and epidermal regeneration, in addition to the reversal effects on photodamaged skin, are mechanisms that might explain the successful treatment of DSAP	Completion of treatment: greater than 50% improvement of the lesions was noted and full patient satisfaction	Erythema		N/A
Noborio , Morita, 2011 31	Letter to the Editor	CO2	1	83	N/A	Completion of treatment: majority of lesions disappear, satisfy patient and no recurrence on the follow up	N/A		CO2 laser therapy is mostly effective, but severe scarring is an occasional adverse effects of conventional CO2 laser irradiation
Kim *et al.*,2011 32	Case report	CO2+PDT	2	61,62	N/A	Completion of treatment: majority of lesions disappear with no recurrence on the follow up	Hyperpigmentation Aggravation of melasma		Overall, PDT was found to remove some of the remnant rims of DSAP following CO2 laser ablation, but the degree of improvement was not striking. Using MAL-PDT to CO2 laser vaporization, multiple sessions of treatment are required, and complications associated with PDT raised some concern
Ricci, Rosset, Panizzon, 1999 33	Case report	Grenz rays	1	77	X-rays are known to have antiproliferative activity by inhibition of the DNA synthesis, particularly in abnormal cells, apart from their potent anti-inflammatory effect	Completion of treatment: after two years they were excellent outcomes, no recurrence	Pruritus	Expensive	It may be a useful option in the management of elderly patients with DSAP

evidence based on the various treatment modalities for DSAP. In addition, studies that have been commonly cited in the literature and review articles were included as citation search engine to identify subsequent publications, which were relevant for the literature review. The following medical terms and text world were used: "Disseminated superficial actinic porokeratosis", "porokeratosis", "laser", "photodynamic therapy", "diclofenac", "calcipotriol", "imiquimod", "retinoid", "photodynamic therapy", "lasers". The keywords were combined using multiple combinations. Articles that did not mention treatment approaches, which were not published in English or were not available, have not been included for the purposes of this literature review. Any discrepancies about data evaluation of the selected articles were resolved after discussion between the authors.

RESULTS

The initial search yielded 146 articles, but only the relevant case reports, case series and studies relating to the treatment of DSAP have been described below and summarized in Table 1. For each different therapy the efficacy of each treatment, side effects, cost effectiveness and authors' recommendations were reported.

DISCUSSION

Traditional topical treatment approaches include topical treatments like diclofenac [10-12], imiquimod [13-14] and calcipotriol [15-19]. Oral retinoids [20-22] and cryotherapy [15] were used in the past with no any satisfied results. Newer treatment of photodynamic therapy (PDT) [2,9,23-25] and lasers [3,26-32] have been introduced in the recent years with some desirables results. A literature review was conducted five years ago assessing the level of evidence for some therapeutic modalities. However, still the exact value of each treatment is difficult to determine owing to the lack of controlled studies evaluating their efficacy [5].

Several factors need to be considered for choosing the most appropriate treatment for each patient, like the age, the extent of body surface area involvement, patients' medical history and their social situation, the available resources in dermatology departments, the side effects and cost effectiveness of each treatment approaches. Systemic treatment might not be an option if patients have complicated medical background and take multiple medications, due to possible interactions of retinoids with their regular medications. Expensive treatment like different types of lasers can be discussed with the patients but usually are not considered due to the high cost and lack of experienced centres. PDT therapy showed poor outcome in several studies (e.g. six out of nine patients had none or minimal response with MAL- PDT, all patients had no response with ALA-PDT and Hypericin-PDT), thus it is not recommended frequently [2,9,23-35].

Following a thorough discussion among physicians in our clinic, both patients started on topical treatment with calcipotriol/betamethasone gel with partial resolution. Patients are under follow up and they will be monitored closely for any possible onset of malignancies. In conclusion, there are several options available for treating DSAP, but always the best approach should be tailored to every patient. There is still a great need for further controlled studies with a greater sample size to draw conclusions on the effects of these novel treatments for DSAP.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Original Article

Association of serum hormone levels with acne vulgaris: Low estradiol level can be a pathogenetic factor in female acne

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ABSTRACT

Background: Acne vulgaris is a chronic disease with a multifactorial pathogenesis. Speculative data has been shown concerning acne vulgaris and hormones, obesity, inflammatory, metabolic disorders. Aims: Our study aimed to evaluate hormone levels, inflammatory, metabolic parameters of patients with acne vulgaris. **Materials and Methods:** 136(male/female:42/94) participants including 68 patients and 68 age and sex-matched controls were enrolled retrospectively. Age, gender, height, weight, body mass index (BMI), systolic (SBP) and diastolic (DBP) blood pressure, serum lipid profile (SLP), fasting blood sugar (FBS), C-reactive protein (CRP) and red cell distribution width (RDW) parameters were evaluated for patients and controls. Patients were questioned about the type and duration of acne, previous treatments, presence of acne vulgaris and other types of acne in first-degree relatives. Females(47patients,47controls) were evaluated for follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone (PRO), estradiol (EST), prolactin (PRL) and total testosterone (TT) levels collected on the early follicular phase of menstruative cycle. **Results:** There was no statistically significant difference between patients and controls regarding BMI, SBP, DBP, SLP, FBS, CRP, RDW parameters (all p values>0.05). Moreover, serum FSH, LH, PRO, PRL, TT levels showed no statistically significant difference between female patients and female controls (all p values>0.05). However, female patients had statistically significant lower levels of serum EST than female controls. **Conclusion:** Low serum EST levels can be observed in female acne patients. Further investigation is required to define the association between serum EST and acne. This may also bring a new approach to the treatment of female acne vulgaris by estrogen containing hormone therapies.

Key words: Acne vulgaris; Estradiol; Female; Hormone

INTRODUCTION

Acne vulgaris is one of the most common skin diseases affecting the pilosebaceous unit [1]. Multifactorial pathogenesis of acne vulgaris includes inflammation [2,3], dietary intake [4-6], hormones[7-9], especially androgens [2,3], metabolic imbalances, insulin resistance and obesity [10,11,12]. Genetic background [13] is also accepted to play a role in the pathogenesis of acne. Despite several studies on acne pathogenesis, possible relationships between predisposing and aggrevating factors are poorly understood. Recently, acne is suggested as a visible indicator of systemically exaggerated mammalian target of rapamycin complex 1 (mTORC1) signaling. mTORC1 is a protein complex which plays a crucial role in protein and lipid synthesis, cell growth and proliferation [14]. In acne vulgaris, metabolic deviation due to increased mTORC1 signal pathway occurs resulting in mTORC1-driven diseases, such as obesity, arterial hypertension, insulin resistance, type 2 diabetes mellitus, and even cancer and Alzheimer's disease [12,15].

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A probable association between acne and inflammation has long been postulated. *Propionibacterium acnes* (P. acnes), which is a bacteria involved in the pathogenesis of acne, can induce IL-1, IL-8, TNF-α leading to subsequent secretion of high amounts of CRP from the liver [16,17]. Thus, locally increased levels of inflammatory cytokines may lead to elevation of serum CRP levels. RDW is also an inflammatory biomarker which shows correlation with CRP. It is an independent risk factor in patients with coronary artery disease and heart failure probably reflecting an underlying chronic inflammation [18]; however, the link between acne and RDW remains uncertain.

Studies are able to show certain effects of BMI on acne vulgaris development and dietary interventions are proposed to play a role in the management of acne [19]. High-glycemic index diets play a role in the induction and exacerbation of acne contributing to overstimulation of sebum production, P. acnes overgrowth, biofilm formation while low-glycemic index diets reduce the severity of acne [5]. Furthermore, one of the diseases that particularly shows strong relation between BMI and acne is polycystic ovary syndrome (PCOS). Weight loss in PCOS patients is suggested as an effective method of restoring ovulation and menstruation by reducing androgen levels and thereby improving ovarian function. These effects are related to reduction of insulin levels and improvement of insulin resistance and thereby decreasing acne severity [20,21].

Human sebum is composed of triglycerides, diglycerides, free fatty acids, wax esters, squalene with some cholesterol and cholesterol esters [22]. Changes in the lipid content of sebum and increased sebum production have a role in the development of acne [23]. Whether serum lipids are elevated in patients with acne or not is still a matter of debate. The role of androgens in acne pathogenesis is evident, increase in androgen levels during puberty stimulates sebum production, increases size of the sebaceous glands, stimulates keratinocyte proliferation in sebaceous gland duct and acro-infundibulum[2]. Testosterone, an androgenic hormone, is converted to its more potent form called dihydrotestosterone (DHT) through the action of the enzyme 5α-reductase (5-ARD) causing an excess production of sebum [20]. Although the pathogenesis of acne is closely related with androgens, androgen levels were within normal ranges in many patients [24]. There is limited data about androgenic (testosterone) and non-androgenic hormones (FSH, LH, PRO, EST, PRL) on acne. FSH and LH which are secreted by the anterior pituitary gland stimulate gonads for androgen secretion. Especially, PCOS patients who have increased LH/FSH ratio have acne as a common clinical comorbidity [20]. Estrogens have several effects on sebum such as decrease in sebaceous gland sizes and sebum production in high doses [25,26]. Progesterone inhibits the activity of 5-ARD and prevents conversion of testosterone into DHT that probably help reducing sebaceous gland activity. Prolactin which is a hormone mainly involved in the milk production also increases the activity of 5-ARD.

The aim of the present study was to evaluate hormone levels, inflammatory and metabolic parameters of acne vulgaris patients. For this aim, age and gender characteristics, anthropometric measurements (height, weight and BMI), SBP and DBP, laboratory parameters of SLP, FBS, CRP, RDW were evaluated in all participants. Acne vulgaris type, duration of acne, previous acne treatments, presence of acne vulgaris and other types of acne in first-degree relatives were recorded in patients. Additionally, serum levels of FSH, LH, PRO, EST, PRL and TT were assessed in female patients and female controls.

MATERIALS AND METHODS

Study Protocol

A total of 136 participants; 68 acne vulgaris patients (M/F: 21/47) and 68 age and sex-matched controls (M/F: 21/47) who were older than 18 years of age were retrospectively enrolled for the study. Age and gender characteristics, anthropometric measurements including height (kg), weight (m), BMI (kg/m^2), systolic (normal 90-120 mmHg) and diastolic (normal 60-80 mmHg) blood pressure, laboratory analyses of SLP (total cholesterol, (TC, normal 0-200 mg/dl), high-density lipoprotein cholesterol (HDL-C, normal 40-60 mg/dl), low-density lipoprotein cholesterol (LDL-C, normal 0-99 mg/dl) and triglycerides (TG, normal 30-150 mg/dl)), FBS (normal 70-110 mg/dl), CRP (normal 0-5 mg/dl) and RDW (normal 11.6-14.6%) parameters were evaluated from all participants. Acne vulgaris type, duration of acne, previous acne treatments, presence of acne vulgaris and other types of acne in first-degree relatives were evaluated for each patient. Body mass index was calculated by using Quetelet index as dividing weight by the square of height [27]. Four categories are created based on the calculated BMI scores: 1. Underweight: Lower than 18.50; 2. Normal

range: 18.50-22.99; 3. Overweight: 23.00-24.99; 4. Obese: 25 or higher [28]. The recorded blood pressure values were measurements taken by a blood pressure monitor after at least resting 10 minutes (ERKA. The Original, VARIO, blood pressure monitor, Germany). Five ml of peripheral venous blood was collected from all participants by using biochemistry tubes (BD Vacutainer® SST II Plus plastic serum tube, 367955 - 13 × 100 mm × 5.0 mL, BD Diagnostics - Preanalytical Systems, USA) after 8 hours of fasting for evaluation of SLP, FBS, CRP (AU5800 Clinical Chemistry System; Beckman Coulter Inc., USA) and by using ethylenediaminetetraacetic acid (EDTA) tubes (EDTA. K3 GD020EK3 blood collection tube, 13 × 75 mm × 2.0 mL) for evaluation of RDW (Sysmex® XS-1000i Automated Hematology Analyzer, Sysmex America, Inc., USA). SLP, FBS and CRP levels were measured by photometric, hexokinase and turbidimetry methods, respectively.

Furthermore, female participants (n=94) including patients (n=47) and controls (n=47) were evaluated for serum FSH (normal 2.5-10.2 mIU/mL), LH (normal 1.9-12.5 mIU/mL), EST (normal 11-63 pg/mL), PRO (normal 0.15-1.40 ng/mL), PRL (normal 2.8-29.2%) and TT (normal 21-118 ng/mL) levels which were performed on the early follicular phase (2–5. days) of menstruative cycle. On the early follicular phase of menstruative cycle, 5 ml of peripheral venous blood was collected from female patients and female controls to analyze serum FSH, LH, PRO, PRL, EST and TT levels by using chemiluminescence enzyme immunoassay method (UniCel®DxI 800 Immunoassay System; Beckman Coulter Inc., Clinical Diagnostics Division, Brea, CA, USA).

Type of acne vulgaris was defined as comedonal, mild papulopustular, moderate papulopustular and nodulocystic [1]. The duration of acne disease was expressed as months. Patients were grouped under 5 categories for previous acne treatments (Group 1: No previous treatment, Group 2: Having previously received topical therapy alone. Group 3: Having previously received topical therapy and antibiotherapy. Group 4: Having previously received oral isotretinoin. Group 5: Having previously received both topical therapy, antibiotherapy and oral isotretinoin as combination or at different times). Menstruative cycle pattern of the female participants is examined in 7 groups: 1. Premenarche: No menarche before 16 years of age, 2. Primary amenorrhea: Menarche was not started after 16 years of age, 3. Secondary amenorrhea: The absence of menstruation for 180 days or more, 4. Oligomenorrhea: An average menstrual cycle of 42 to 180 days, 5. Polymenorrhea: An average menstrual cycle of 21 days or less, 6. Regular menstrual cycles: An average menstrual cycle of 22 to 41 days, 7. Irregular menstrual cycles with an average menstrual cycles of 22 to 41 days and two or more menstrual cycles with a length of less than 22 or more than 41 days during the past year [29].

Exclusion criteria for this study were pregnancy, lactation, cigarette smoking, presence of diabetes mellitus, hypertension, hyperlipidemia, atherosclerotic heart disease, systemic diseases affecting CRP levels (rheumatic disease, inflammatory bowel disease, cancer, chronic infections), anemia (defined as hemoglobin levels < 12.0 g/dL in women and < 13.0 g/dL in men according to the World Health Organization (WHO) [30]), systemic anti-inflammatory treatment for any reason in the past 1 month, presence of primary gonadal failure. Participants using medications known to affect hormone levels (ovulation induction therapies, high dose testosterone, PRO and estrogen treatments), lipid metabolism (statins, thiazide diuretics, estrogen and androgen preparations, selective estrogen receptor modulators, antidiabetics, orlistat, corticosteroids, cyclosporine, mitotane, isotretinoin, antipsychotics, antiretrovirals), sugar metabolism (oral antidiabetics, insulin, corticosteroids, barbiturates, thiazide diuretics, OCS, decongestants, niacin, olanzapine) and serum CRP levels (cyclooxygenase inhibitors, platelet aggregation inhibitors, lipid reducing drugs, beta adrenoceptor antagonists, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, vitamine E) were also excluded from this study. None of the patients received treatment for acne during the laboratory examination. Control group subjects were chosen from individuals without medical or family history of acne. All parameters used in the study were evaluated from the database of the hospital.

Data Analysis

Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 20.0 was used for all statistical analyses. Results were expressed as mean ± standard deviation (SD) and median ± interquartile range (IR). Shapiro-Wilk test was used to understand whether numeric variables distribute normally or not. When parametric assumptions were provided, independent sample t-test was used. Differences in numeric variables between independent groups

were analyzed by using Mann-Whitney U test when parametric assumptions were not provided. The ci-square test was used to determine whether there were differences in categorical variables between independent groups or not. Relationships between the quantitative variables were calculated by using the Pearson's and Spearman's correlation coefficient. Numeric variables which are not normally distributed were analyzed by Kruskal Wallis test while normally distributed numeric variables are examined by one-way analysis of variance (ANOVA) test. $p < 0.05$ was considered to be statistically significant.

Ethics Statement

The study protocol was approved by the Institutional Ethics Review Board at the Ankara Numune Training and Research Hospital with number of E-16-999 and was conducted according to the ethical principles of the Declaration of Helsinki.

RESULTS

Sixty-eight patients (M/F: 21/47) with acne vulgaris and 68 healthy controls (M/F: 21/47) were included in this study. Age, gender, height, weight, BMI, SBP, DBP, SLP, FBS, CRP and RDW parameters were evaluated for each individual. Acne vulgaris type, duration of acne, previous acne treatments, presence of acne vulgaris and other types of acne in first-degree relatives were recorded in patients. Female participants (n=94, 47 female patients and 47 female controls) were evaluated for their hormone profile consisting of serum FSH, LH, PRO, EST, PRL and TT levels which were collected on the early follicular phase of menstruative cycle. Comparisons of the parameters analyzed in this study are summarized in Table 1 and Table 2. Patient and control groups did not have any statistically significant difference according to age ($p > 0.05$). N=10 (14.7%) of the patients had comedonal, N=10 (14.7%) patients had mild papulopustular, N=34 (50%) had moderate papulopustular and N=14 (20.6%) had nodulocystic acne. N=35 (51.5%) patients had never been treated before for acne while N=10 (14.7%) of the cases used topical therapy alone, N=15 (22.1%) patients used topical therapy and antibiotherapy, N=7 (10.3%) patients used oral isotretinoin and one patient had both previous treatments of topical therapy, antibiotherapy and oral isotretinoin. The median duration of the acne disease was 24 ± 46.5 months (median ± IR, range: 0-264 months). Thirty of the 68 patients had history of acne in first-degree relatives. Seventy-eight (82.9%) of the 94 females had regular menstrual cycles taking place in group 6, 7 (7.5%) was in group 4, 3 (3.2%) in group 5, 6 (6.4%) in group 7, and no female had premenarche or secondary amenorrhea. Forty patients (58.8%) and 32 controls (47.1%) had BMI scores within normal ranges whereas 10 patients (14.7%) and 15 controls (22.1%) had scores greater than 25 indicating category 4 as obese. No statistically significant difference was detected between mean BMI scores of the patients and controls which were 22.4 ± 2.96 and 21.9 ± 4.65 kg/m^2, respectively ($p > 0.05$). Comparison of patient and control groups revealed that there was no statistically significant difference between SBP, DBP values and TC, TG, HDL, LDL, FBS, CRP, RDW levels (all p values > 0.05, Table 1). Moreover, serum FSH, LH, PRO, PRL and TT levels showed no statistically significant difference between female patients and female controls (all p values > 0.05, Table 2). However, female acne vulgaris patients had statistically significant lower levels of serum EST (median ± IR, 33.6 ± 16.62 ng/mL) than female controls (median ± IR, 43.3 ± 17.23 ng/mL) ($p = 0.015$, Table 2).

DISCUSSION

In this study, we showed that low serum EST levels can be expected in female patients with acne. BMI, SBP, DBP parameters and SLP, FBS, CRP, RDW, FSH, LH, PRO, PRL and TT levels did not show any association with acne vulgaris.

The effects of estrogens on acne pathogenesis is not very clear. Estradiol, the primary female sex hormone, is the evaluated form in this study and known as the major active estrogen form during human female reproductive years in terms of absolute serum levels and estrogenic activity. In general, while androgens contribute to the development of acne through increase in sebum production, estrogens, in sufficient amounts, have inhibitory effects on acne through suppression of sebum production [31]. The effect of estrojen on acne are through three different mechanisms, including opposition of androgens within the sebaceous glands, inhibition of gonadal androgen production via negative feedback mechanism on gonadotrophin release and effects on genes which play a role in sebaceous gland growth and lipid production [32]. But, estrogen effect on sebum production and acne development is not yet well understood since some women experience a deterioriation of acne during high estrogen periods like

Table 1. Clinical and laboratory findings of 68 acne vulgaris patients and 68 healthy controls.

Parameters	Patients (n=68) (mean±SD or median±IR)	Controls (n=68) (mean±SD or median±IR)	*p* value	Normal range
Gender (M/F)	21/47	21/47		
Age (years)	20.5±5	21.0±5	0.901	
Height (m)	1.65±7.7	1.67±8.3	0.249	
Weight (kg)	60.9±9.5	61.9±10.9	0.432	
BMI* (kg/m_2)	22.4±2.96	21.9±4.65	0.902	18.50-22.99
SBP (mmHg)	110±20	110±20	0.473	90-120
DBP (mmHg)	70±20	70±20	0.546	60-80
FBS (mg/dl)	97±10.8	97±12.8	0.976	70-110
CRP (mg/dl)	1.97±1.58	1.90±1.4	0.102	0-5
TC (mg/dl)	160.0±44.3	158.5±49.3	0.747	0-200
TG (mg/dl)	73±35.3	78±64	0.094	30-150
HDL-C (mg/dl)	52.0±21	53.5±17.8	0.403	40-60
LDL-C (mg/dl)	78.0±25.3	83.5±33.3	0.233	0-99
RDW-CV (%)	13.2±1.07	13.1±0.97	0.065	11.6-14.6

* Data is reported as mean±SD for BMI due to its normal distribution, Independent Samples t test. Apart from BMI, data are reported as median±IR, Mann-Whitney U test. SD=standard deviation; IR=Interquartile range; M=male; F=female; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; FBS=fasting blood sugar; CRP=C-reactive protein; TC=total cholesterol; TG=triglycerides; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; RDW-CV=red cell distribution width.

Table 2. Laboratory findings of 47 female acne vulgaris patients and 47 female healthy controls.

Parameters	Patients (n=47) (mean±SD or median±IR)	Controls (n=47) (mean±SD or median±IR)	*p* value	Normal Range
FSH* (mIU/mL)	6.92±1.54	6.79±1.91	0.724	2.5-10.2
LH (mIU/mL)	4.64±2.75	4.66±2.01	0.823	1.9-12.5
EST (pg/mL)	33.6±16.62	43.3±17.23	0.015	11-63
PRO (ng/mL)	0.54±0.42	0.53±0.33	0.832	0.15-1.40
PRL (%)	13.1±11.1	11.67±9.28	0.073	2.8-29.2
TT (ng/mL)	40.65±261.7	53.1±267.4	0.212	21-118

* Data is reported as mean±SD for FSH due to its normal distribution, Independent Samples t test. Apart from FSH, data are reported as median±IR, Mann-Whitney U test. SD=standard deviation; IR=Interquartile range; FSH=follicle-stimulating hormone; LH=luteinizing hormone; EST=estradiol; PRO=progesterone; PRL=prolactin; TT=total testosteron.

pregnancy. Moreover, in recent years, a new concept has emerged as adult female acne in which the disease is present after the age of 25 years in women and hormonal therapies containing estrogen preparates are highly effective for those via opposition of the effects of androgens on pilosebaceous units and sebaceous glands even in patients without hormonal abnormalities. Combined oral contraceptives, containing estrogen and progestin, are used for this purpose to inhibit ovarian androgen production, decrease activation of androgen receptors on sebaceous glands and increase sex hormone-binding globulin in the liver [32] which leads decrease in circulating levels of free testosterone. In studies regarding these patients, efficacy of hormonal therapy is based on improvement of acne evaluated by investigator and patient, reduction in lesion counts and severity of acne grades [33] and not based on hormone levels. But, it is known that serum estradiol and androgen levels will decrease in women receiving oral contraceptives. However, we don't know whether female acne patients who benefit from hormonal therapies have initially lower serum estrogen levels compared with those of female acne patients with normal serum estrogen levels. For this reason, studies are required to compare initial and final hormone levels in female acne patients who do and do not benefit from hormone therapies. The relationship between serum EST levels and acne was demonstrated by Wei et al. as serum EST levels was significantly different between female cases with acne and female controls except males. This data was also consistent with the report of Arora et al. [9] revealing that high serum EST levels protects females against the onset of adolescent acne [34]. In accordance with previous data, the current study showed significantly low serum levels of EST in female patients when compared to female healthy controls. The role of estrogen rich foods, drugs containing high amounts of estrogen such as pills, skin patches, topical agents in the treatment of acne may be speculative and contradictive. Similarly, the role of estrogen decreasing conditions such as aging, menopause and some drugs in acne may be questionable too.

Although androgen hormones significantly play a role in the pathogenesis of acne, serum androgen levels were found to be normal in many patients with acne [24]. In some reports, the effects of androgens on acne development is connected to the androgen receptors instead of its levels suggesting an increased receptor sensitivity to androgens in acne prone skin [35]. A study including 26 patients and 21 controls from Turkey stated that severe acne itself is not related with hyperandrogenism suggesting that it may not be necessary to measure serum androgens in women with severe acne in the absence of other manifestations of hyperandrogenism, such as hirsutism and menstrual irregularity [11]. However, the improvement of acne by anti-androgens [1], increased incidence of acne in patients with PCOS[20] and congenital adrenal hyperplasia who have higher levels of androgens indicate the role of androgens in the pathogenesis of acne. Hormonal therapies will also be useful for female acne patients both in those with hyperandrogenism and without hyperandrogenism [31]. The only androgen measured in this work was serum TT about which we were unable to find any significant differences in serum levels between two female groups at all. Serum TT level was detected on the early follicular phase, perhaps this was the reason why we could not have found any relation with its level and acne.

Testosterone is converted to its more potent form DHT by 5-ARD enzyme causing an excess production of sebum whereas PRO inhibits the activity of this enzyme and prevents turning testosterone into DHT. So, PRO itself might be expected to reduce sebaceous gland activity. But, PRO effect on acne still remains unclear. Although some studies show that PRO can reduce androgen effects by inhibiting 5-ARD enzyme or androgen receptors[36], the fluctuation of sebum production in women during menstrual cycle and premenstrual cyclic flare has partly been associated with PRO and some progestins lead an exacerbation of acne by interacting with androgen receptors [37,38]. Although PRO's unclear effect on acne, combined oral contraceptives which are used for female acne treatment include both an estrogen and a progestin product to decrease the risk of endometrial cancer associated with unopposed estrogens. Due to the fact that many progestins aggravate acne, new generation progestins with lower androgenic activity have began to be used for acne treatment [32]. The relationship between serum PRO levels and acne was demonstrated by Bakry et al. that no significant association between serum PRO levels and the severity of acne was found although a statistically significant difference in serum PRO levels between patients and controls was recorded [39]. Arora et al. also found higher serum PRO levels in patients than that in controls correlating with serum cholesterol levels supporting the fact that cholesterol is the precursor of PRO [40]. In our study, there was no statistically significant difference between female patients and controls in terms of serum PRO levels. This discrepancy between our study and other studies could be explained by analysis of hormone levels on different days of the menstruative cycle and the different profile of the target group.

No significant association was detected between serum FBS levels and acne in this study. Emiroğlu et al. showed that fasting blood glucose levels were not statistically different between 246 patients with acne and 156 healthy controls despite the fact that there was a highly significant difference in terms of fasting insulin levels between these groups suggesting insulin resistance in patients [10]. Furthermore, Kaymak et al. also indicated that there was no significant difference of serum glucose level between patients with acne and control subjects [41]. Contrarily, another study from Turkey showed that FBS levels were significantly higher in patients than that in controls [42].

Many studies have pointed out a possible link between BMI and acne [12]. Seleit et al. studied 60 patients with acne vulgaris and 40 subjects without acne to determine the association between acne severity and BMI [19]. In another study conducted by Tsai et al. on 3274 children, BMI values were significantly higher in patients with acne than that in non-acne group which have suggested that BMI is a risk factor for acne [43]. However, Lu et al. showed that BMI is negatively associated with the number of acne lesions in Taiwanese women with moderate to severe post-adolescent acne in those without PCOS probably advocating BMI and acne relationship varies by age [44]. Although several studies have revealed a link between BMI and acne, no association between those could be found in this study. These results could be considered as a contradictory to those previously published in the literature and this contradiction should be discussed in line with the methodology and target group. Whether serum lipids are elevated in patients with acne or not is also a matter of debate and controversy. In 2010, Arora et al. revealed that compared with controls, adult women with acne had higher levels of serum TC and LDL, lower levels of HDL [40]. In 2007, El-Akawi et al. indicated that patients with acne had significantly

low plasma HDL levels while TC and TG levels did not differ significantly [45]. As for our results, we have failed to show any significant differences of serum TC, TG, HDL, LDL levels between patients and controls.

Prolactin is a hormone mainly involved in milk production. In contrast to the effects of PRO, PRL increases the 5-ARD enzyme. Darley et al. found hyperprolactinemia in 45% of 38 women patients with late onset or persistent acne vulgaris [46]. 20 women with idiopathic hyperprolactinemia and acne were treated with bromocriptine by Peserico et al. in 1988. Both serum PRL levels and acne lesions showed a great improvement with this drug in this study [47]. In terms of serum PRL, we found no significant differences between female groups. This is a field that needs further investigation on larger number of cases with analyses performed on different days. The role of FSH and LH in acne vulgaris is also not well-documented. In a study from Italy, 6 women with acne and 6 women with hirsutism were treated by Faloia et al. with a GnRH analog which suppresses FSH and LH levels. During the treatment, clinical score for acne showed a significant reduction revealing the hypothesis that suppressing ovarian steroids by GnRH analogs might be an effective treatment in women suffering from acne [48]. Combined oral contraceptives which are particularly used for adult female acne treatment, inhibit FSH and LH release in the pituitary via negative feedback loops and thereby androgen production suppression and acne improvement [32]. Besides, PCOS patients may show increased LH/FSH ratio in which acne is a common clinical finding in these patients [20]. A study from Turkey on 60 patients with acne and 30 controls showed that serum FSH and LH levels measured on 5th day of menstruative cycle did not differ between groups [49]. In our study, no patient was diagnosed with PCOS and serum LH and FSH levels did not differ significantly between female cases and controls.

Limiting aspects of this study are its retrospective design, reliance on patient data registered on hospital system, restriction to a single center and being done on a young cohort. Effect of other androgens such as dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), androstenedione, DHT on acne and assessments performed on different days of menstruative cycle needs further evaluation. Despite the findings demonstrating a relation between serum EST levels and acne, the study limitations do not allow straightforward comment that estradiol is good for acne.

CONCLUSION

In conclusion, in this study we showed that the female acne patients may have low serum EST levels compared with those of female controls. Further investigation on this topic is required to define the association between serum EST levels and acne. This may also bring a new approach to the treatment of female acne vulgaris by estrogen containing hormone therapies. Further studies are needed to clarify the role of conditions which can decrease and increase EST levels on acne improvement and deterioriation.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Original Article

To study the relevance of inpatient dermatology referrals in a Teaching Hospital of North India

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ABSTRACT

Background: Dermatology is primarily considered to be an outpatient-centered specialty. However, several inpatient admissions to other specialties require dermatologic consultation for optimum management. **Aims:** The aim of this study was to evaluate the pattern of referrals sent to the dermatology department by other Departments and impact of dermatology consultation on patient management. **Materials and Methods:** The study included all inpatients referred to dermatology department of a tertiary care centre of North India during a two year period. The demographic details, specialties requesting consultation, cause of referral, and dermatological advice have been recorded and analyzed. **Results:** Dermatology consultation changed the dermatologic diagnosis and treatment. General medicine requested the maximum number of referrals, skin rash being the most common cause for referral. Accurate diagnosis on referrals was provided by only 25.23 % of non dermatologists. Common dermatological disorders were often misdiagnosed by these physicians, and dermatology referrals had significant impact on the diagnosis and subsequent management of these patients. **Conclusion:** While dermatologic referral leads to improved patient care, there is a need for better training of non dermatologists enabling them to recognize and treat common dermatoses.

Key words: Dermatology; Inpatient; Referral

INTRODUCTION

Dermatology practice takes place mainly in the outpatient setting. However, several inpatient referrals are made to dermatology departments by other specialties on a daily basis for proper patient management in the hospital settings [1]. The knowledge of dermatology among non-dermatologists is believed to be very poor [2-5]. Patients admitted to non-dermatology units may often have numerous skin lesions besides the systemic disease for which they are hospitalized [5,6]. The dermatoses may be associated with significant morbidity and at times mortality [7]. These inpatients with dermatoses often require expert dermatology consultation. The interdepartmental referral not only helps in patient care but also improves the diagnostic acumen and clinical knowledge of the clinician [6,7-11].

MATERIALS AND METHODS

This retrospective observational study, after obtaining approval from Institutional Ethics Committee, was carried out at tertiary hospital in North India assessing data over a period of 2 years. The Department of Dermatology at the hospital is responsible for all dermatological consultations for inpatients.

The data thus obtained has been statistically analyzed with respect to patient demography, frequency of referrals made by different specialties, causes of referrals (presumptive diagnoses made by non dermatologists), diagnostic accuracy of referring departments by comparing with the final dermatological diagnoses made by senior faculty members as the gold standard, and impact of dermatology consultations on the management.

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Specific investigations such as KOH examination, Gram's smear, Tzanck smear, slit skin smear, skin biopsy, and blood and radiological investigations were undertaken in selected cases, wherever deemed appropriate to substantiate the clinical diagnosis. All the patients were examined within 24 hours of request for referral.

RESULTS

During 2 year period, total of 817 referrals were received. Mean age of our patients was 35.95 (range- 1 day to 85 years) (Fig. 1). 82.7% of dermatological consultations were sought for patients > 20 years. There were 360 males (44.1%) and 457 females (55.9%), with a M: F ratio – 1:1.269. Majority of patients were in age group 21- 40 years (48.5%). Referral was most frequently sought by department of Internal Medicine, 339 patients(41.5%), followed by department of Obs & Gynae, 231 patients (28.3%), Pediatrics 73 patients (8.9%), department of Surgery 63 patients (7.7%) and Orthopaedics 52 patients (6.4%) (Table 1).

Unspecified "skin rash" was the most common dermatologic condition, for which skin referral was sought (335 cases 41%) followed by skin infections (145 cases 17.7%), vesiculobullous disorders (8.4%), drug rash (7%), oral and genital lesions and eczema (2.7%). All these diagnoses were made by the referring departments and mentioned on the referral sheets. The different conditions for which referrals were sought are tabulated in Table 2.

The different diagnoses were made by the dermatologists after examining the referred patients. Cutaneous infection and infestations were the most commonly diagnosed condition (55.3%), which included parasitic infections, 163 cases (20%), fungal infections, 142 cases (17.4%), viral infections, 126 cases (15.4 %) and bacterial infections, 21 cases (2.6%) (Fig. 2). Most of the cases of bacterial and fungal infections were referred from medicine department, however maximum cases of viral infections were from gynaecology department. This was followed by eczema, 112 cases (13.7%), drug reactions, 93 cases (10.2%), out of which 10 cases were of severe adverse drug reactions. Other dermatological diagnosis which were made are tabulated in Table 3. Dermatology consultation resulted in revised diagnosis in about 75% of instances of case referrals. (Fig. 3)

Table 1 Specialities requiring dermatological consultation

Department	Number of patients	Percentage of patients
Internal medicine	339	41.5
Gynaecology	231	28.3
Paediatrics	73	8.9
General surgery	63	7.7
Orthopaedics	52	6.4
Chest & tuberculosis	29	3.5
Psychiatry	25	3.1
ENT	2	0.2
Plastic surgery	2	0.2
Cardiology	1	0.1

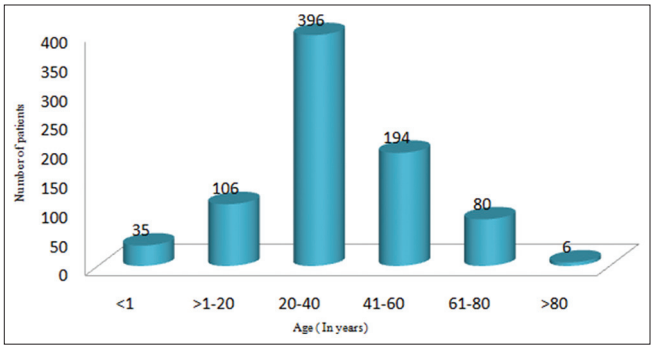

Figure 1: Age distribution of the study.

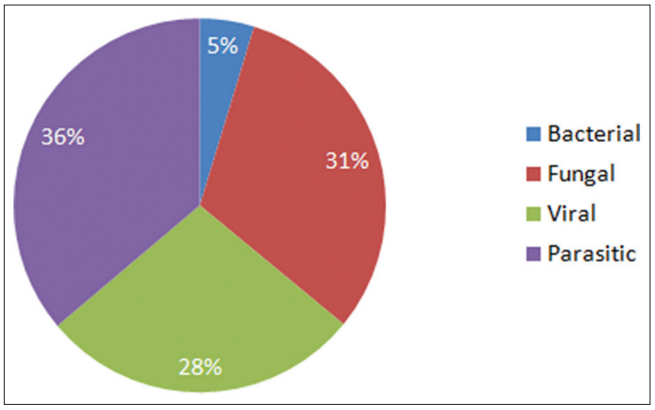

Figure 2: Cutaneous infections and infestations.

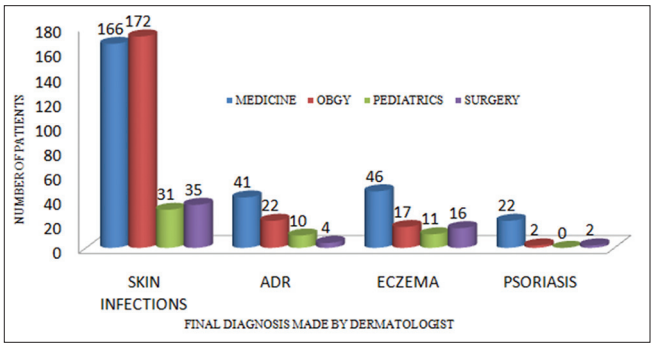

Figure 3: Final diagnosis made by dermatologist.

Table 2 Dermatological diagnoses by the referring departments

Provisional diagnosis	Number of patients	Percentage of patients
Skin rash	335	41
Skin infection	145	17.7
Vesiculobullous disorders	69	8.4
Drug rash	57	7.0
Oral/Perioral lesions	49	6.0
Pigmentary disorders	33	4.0
Non specific skin lesions	30	3.7
Genital lesions	27	3.3
Eczema	22	2.7
Skin ulcers	16	2.0
Skin swelling	8	1.0
Nail lesions	7	0.9
Purpuric rash/Vasculitis	7	0.9
Ischemic lesions	5	0.6
Connective tissue disorders	4	0.5
Psoriasis	3	0.4

Table 3 Final diagnosis made by dermatologist

Diagnosis	Number of patients	Percentage of patients
Cutaneous infections :		
Bacterial infections	21	2.6
Fungal infections	142	17.3
Viral infections	126	15.4
Parasitic infestations	163	20.0
Eczema/dermatitis	112	13.7
Cutaneous adverse drug reaction (non severe type):	83	10.2
Severe adverse drug reaction:	10	1.2
Psoriasis	32	3.9
Connective tissue disorder	19	2.3
Leg ulcers	13	1.6
Urticaria/angioedema	11	1.3
Genodermatoses	11	1.3
Vasculitis	9	1.1
Diabetic dermopathy	9	1.1
Immunobullous disorders	9	1.1
Disorders of sweat and sebaceous glands	9	1.1
Vitiligo	5	0.6
Miscellaneous :	33	4.0

DISCUSSION

In this study, we analysed 817 patients referred from various departments for dermatological consultation. In our study, most of the dermatology consultations were sought for patients >20 years (82.7%). In most of previously published works [12], males have outnumbered females while our study constituted 55.9% females. In the present study, internal medicine accounted for the highest proportion of dermatological consultations (41.5%). Internal medicine has been shown to send maximum dermatology referrals in most of the literature [12,13]; thus corroborating our findings. This might have occurred as many medical disorders are associated with dermatological manifestations which may serve as important clues for diagnosis of the underlying medical conditions. However, in some studies [11,14,15], neurology unit has accounted for a significant number of referrals after internal medicine. In an Indian study [3], from Secunderabad, surgery (29.8%) and internal medicine (29.7%) departments were responsible for more than half of the referrals to dermatologists.

Non specific skin rash constituted most of the dermatology referrals, 41%, followed by cutaneous infections in 17.7%. A similar finding was obtained by Walia and Deb [3] in India. However, in final diagnosis made by dermatologist, cutaneous infections and infestations accounted for 55.3% followed by eczema and adverse drug reactions in 13.7 and 10.2% patients respectively. Whereas, maximal referrals from various departments were sent for non specific skin rash i.e., 41%, cutaneous infections and eczema/dermatitis in 17.7% and 2.7% respectively. Most of the patients with tentative diagnosis of skin rash, after dermatology consultation came out to be of cutaneous infections. 13.7% patients had eczema/dermatitis in reality, however provisional diagnosis of eczema was kept in only 2.7% patients, suggesting its underdiagnosis by non dermatologists.

We found that nondermatologists could provide an accurate dermatological diagnosis only in 25.23% of cases. This rate is similar to another study from the USA [12], where the diagnostic accuracy was reported to be only 23.9% and lower when compared to another Indian study (39%) [13]. However, this figure is quite low when compared to 48% diagnostic accuracy in a study conducted by Falanga *et* al. [9].

This study also showed the inability of many non dermatologists to recognize simple cutaneous infections such as scabies and drug reactions. Dermatology is primarily a visual discipline. Most dermatoses can easily be diagnosed by a trained eye without expensive investigations that are often advised by non dermatologists. Non dermatologists usually tend to use combined topical preparations often containing steroids. This has led to modification of the original clinical picture, thus making subsequent accurate diagnosis difficult even by a trained dermatologist, as is commonly seen with topical steroid

abuse. Frequent inter-departmental referrals and interactive inter-departmental teaching and training programmes are essential, thus providing exposure to non dermatology residents regarding diagnosing and managing common dermatoses.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Original Article

Relationship between diet and seborrheic dermatitis

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ABSTRACT

Background: Seborrheic dermatitis is a chronic inflammatory skin disease that affects 1-10% of the general population. *Malassezia* yeasts, immune response and emotional stress have been implicated in the etiology of seborrheic dermatitis. However, the effect of diet on development of seborrheic dermatitis is still controversial. This study investigates the differences in the frequency of consumption of foods and food groups between patients with seborrheic dermatitis and healthy individuals. **Material and Methods:** Fifty-one patients with seborrheic dermatitis of the scalp (28 female, 23 male) and 50 healthy individuals within the control group (30 female, 20 male) have been included in this study. The mean age of the patients and control group were 30.6±11.4 years and 32.7±10.7 years, respectively (p=0.35). Dietary habits were evaluated by a questionnaire which includes frequency of intake of meat, processed meat, chicken, fish, egg, legume, milk, dairy products, fruit, vegetable, bread, tea, coffee, coke, fast food, sugar, pasta, rice, chocolate, cake, cookie and pie. The questionnaire included options like every day, 3-5 times a week, 1-2 times a week, twice a month, once a month and none. **Results:** The frequency of intake of foods in the questionnaire was simlar between patients and healthy individuals except for vegetables. Vegetable consumption was significantly more common among patients than healthy individuals (p=0.04). **Conclusions:** The results showed that dietary habits were not associated with increased risk of seborrheic dermatitis.

Key words: Dandruff; Diet; Seborrhea; Seborrheic dermatitis

INTRODUCTION

Seborrheic dermatitis is a chronic inflammatory skin disease which is characterised by erythematous scaly plaques on the sebaceous areas like forehead, eyebrows, glabella, nasolabial folds, scalp, chest, and back. The prevalence of seborrheic dermatitis among adults in the general population is 1-10%. It is more common in men than in women. The disease usually presents between the ages of 30 and 40 years [1]. The incidence of seborrheic dermatitis is similar between ethnic groups [2]. The exact cause of this condition remains unknown. However, numerous factros including *Malassezia* yeasts, sex hormones like androgens, sebum levels, immune response, neurogenic factors and stress have been implicated in the etiopathogenesis of seborrheic dermatitis [3].

Sebaceous glands are distributed all over the skin surface except palms and soles. However, the secretion of sebum from sebaceous glands is highest on the scalp, face, chest, and back [4]. Sebum has an important role in the pathogenesis of seborrheic dermatitis [5]. It maintainces epidermal barrier function, carries anti-oxidants to the skin surface and protects skin from microbial colonization. Sebum is composed of triglycerides, fatty acids, wax esters, sterol esters, cholesterol, cholesterol esters, and squalene. Lipids are used by *Malassezia* species for proliferation. They degrade sebum, free fatty acids and leave the unsaturates which cause inflammation, irritation and scaling in seborrheic dermatitis [4].

Insulin and insulin-like growth factor-1 (IGF-1) stimulate the lipogenesis of sebaceous glands by a transcription factor named sterol regulatory element-binding protein 1. It has been suggested that high carbohydrate intake leads to reactive hyperinsulinemia and increased IGF-1 production [6]. Zinc, riboflavin, pyridoxine and niacin deficiency can lead to seborrheic dermatitis-like lesions. Therefore, nutrition has been associated with an increased risk of seborrheic

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dermatitis [2]. However, no exact relation has been established yet [7].

The purpose of this study was to examine the frequency of consumption of foods in patients with seborrheic dermatitis and healthy subjects and determine the relationship between dietary habits and seborrheic dermatitis.

MATERIALS AND METHODS

This study included 51 patients with seborrheic dermatitis of the scalp and 50 healthy individuals within the control group. The exclusion criteria were having an inflammatory skin disease like psoriasis, lichen planus, having a chronic condition like diabetes, hypertension, renal insufficiency, hypothyroidism, hyperthyroidism, obesity, cancer, eating disorder, and requiring a special diet.

Dietary intake was evaluated by a food frequency questionnaire which consisted of frequency of intake of meat, processed meat, chicken, fish, egg, legume, milk, dairy products, fruit, vegetable, bread, tea, coffee, coke, fast food, sugar, pasta, rice, chocolate, cake, cookie and pie. The questionnaire included options such as every day, 3-5 times a week, 1-2 times a week, twice a month, once a month and none. All participants answered the questionnaire based on their eating habit for the last five years.

Statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago, IL). Continuous variables were defined as the means (±) standard deviations and categorical variables as percentages. Differences between groups were analysed by independent-samples t-test for numerical variables and chi-square test for categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

Fifty-one patients with seborrheic dermatitis (28 female, 23 male) and 50 healthy individuals within

Table 1: Information about the frequency of consumption of some foods among patients and control group

		Patient (n=51)	Groups	Control (n=50)		P-value
Meat	None	1	2%	0	0%	0.43
	Once a month	4	7.8%	4	8%	
	Twice a month	4	7.8%	4	8%	
	1-2 times a week	25	49%	16	32%	
	3-5 times a week	14	27.5%	21	42%	
	Everyday	3	5.9%	5	10%	
Milk	None	8	15.7%	5	10%	0.62
	Once a month	6	11.8%	7	14%	
	Twice a month	8	15.7%	9	18%	
	1-2 times a week	13	25.5%	14	28%	
	3-5 times a week	10	19.6%	5	10%	
	Everyday	6	11.8%	10	20%	
Fruit	None	0	0%	1	2%	0.68
	Once a month	2	3.9%	1	2%	
	Twice a month	3	5.9%	1	2%	
	1-2 times a week	3	5.9%	5	10%	
	3-5 times a week	17	33.3%	19	38%	
	Everyday	26	51%	23	46%	
Bread	None	2	3.9%	1	2%	0.93
	Once a month	0	0%	0	0%	
	Twice a month	1	2%	1	2%	
	1-2 times a week	5	9.8%	4	8%	
	3-5 times a week	8	15.7%	6	12%	
	Everyday	35	68.6%	38	76%	
Sugar	None	7	13.7%	10	20%	0.16
	Once a month	2	3.9%	4	8%	
	Twice a month	5	9.8%	4	8%	
	1-2 times a week	7	13.7%	5	10%	
	3-5 times a week	15	29.4%	5	10%	
	Everyday	15	29.4%	22	44%	
Vegetable	None	0	0%	0	0%	0.04
	Once a month	0	0%	2	4%	
	Twice a month	2	3.9%	2	4%	
	1-2 times a week	14	27.5%	3	6%	
	3-5 times a week	21	41.2%	26	52%	
	Everyday	14	27.5%	17	34%	

the control group (30 female, 20 male) were included in the study. The mean age of the patients and control group were 30.6±11.4 years and 32.7±10.7 years, respectively (p=0.35). The mean disease duration was 7.3±8.5 years. Dietary habits were similar between the two groups except for vegetable intake (Table 1). Consumption frequency of vegetable was everyday in 14 (27.5%) patients; 3-5 times a week in 21 (41.2%) patients; 1-2 times a week in 14 (27.5%) patients; twice a month in 2 (3.9%) patients. However, vegetable consumption frequency was everyday in 17 (34%) controls; 3-5 times a week in 26 (52%) controls; 1-2 times a week in 3 (6%) controls; twice a month in 2 (4%) controls and once a month in 2 (4%) controls. Vegetable consumption was significantly more frequent among patients than controls (p=0.04). There were no statistically significant differences between patients and healthy individuals in the frequency of intake of meat (p=0.43), processed meat (p=0.94), chicken (p=0.33), fish (p=0.70), egg (p=0.14), legume (p=0.53), milk (p=0.62), dairy products; yogurt (p=0.28), cheese (p=0.88), fruit (p=0.68), bread (p=0.93), tea, coffee (p=0.20), coke (p=0.13), fast food (p=0.79), sugar (p=0.16), pasta, rice (p=0.66), chocolate (p=0.34), cake, cookie and pie (p=0.98).

DISCUSSION

Seborrheic dermatitis is characterized byhyperkeratosis, parakeratosis, excess intercellular and intracellular lipids. Epidermal keratinocytes consist of lipid granules which play role in the skin permeability. However, sebaceous glands are the main source of lipids of skin surface [6]. Therefore, sebaceous secretions are considered to play a pathogenetic role in seborrheic dermatitis [8]. Sebaceous glands provide lipid substrates for the *Malassezia* growth. Sebum consists of 57.5% triglycerides, 26.0% wax esters, 12.0% squalene, 3.0% cholesterol esters and 1.5% cholesterol [6]. Sebaceous gland secretions metabolise to irritating unsaturated fatty acids by *Malassezia* [4]. The prevelance of the disease is directly correlated with increased sebaceous gland activity [8]. Predilection sites are sebaceous gland rich areas like face, ears, scalp and the upper trunk [6]. Patients with oily skin are prone to develop seborrheic dermatitis [9]. When hygiene is poor as occurs in neuropathic patients, the residual sebum on the skin results in growth of *Malassezia* and seborrheic dermatitis [10].

The effect of diet on increased sebum production has been reported previously. It has been suggested that dietary lipids like fatty acids, acetat and glucose may be the source for sebum synthesis [6]. Frequent consumption of carbohydrates with a high glycemic index can lead to hyperinsulinemia. It istimulates sebum secretion by increasing androgen levels [11]. Boelsma et al. investigated the effect of diet on the skin conditions including hydration, sebum content, and surface pH of the skin in 302 healthy subject. They assessed dietary intake with food frequency questionnaires and sebum content of the forehead with the sebumeter. No association between the nutrients in diet and sebum content of the skin have been found. However, increased serum vitamin A levels were related with decreased sebum content [12]. It has been suggested that caloric restriction can reduce sebum release. Pochi et al. evaluated sebaceous gland activity in obese patients following a four to eight week-long caloric deprivation. The study showed decrease in sebaceous gland secretion in all patients [13].

Dietary changes shown to be benefical in the treatment of skin diseases like psoriasis, scleroderma, acne, rosacea, herpes, pemphigus, and Refsum's disease [14]. Moreover, dietary recommendations have been reported in the treatment of dandruff which is regarded as a mild form of seborrheic dermatitis with scalp scaling [15,16]. Patients with dandruff were adviced to eat foods rich in vitamin B, shellfish, red meat, sunflower seeds, sardines, salmon, water based fruits and vegetables. In addition to this, the patients were adviced to avoid oily and greasy food products, sugar, junk foods, animal fats, flour, and seafood [16]. Faulty eating habits have also been reported to be related with seborrheic dermatitis [9]. In 1967, Bett et al. measured the sugar intake of 16 patients with seborrheic dermatitis and two groups of control subjects with a questionary. A control group included 16 healthy individuals and the other included 16 patients suffering from warts. The consumption of sugar by patients with seborrheic dermatitis was found to be significantly higher than two groups of control subjects [17].

However, the association between diet and seborrheic dermatitis has not been clearly established yet. There are no adequate number of studies in the literature. Therefore, frequency of food consumption of patients with seborrheic dermatitis and healthy individuals have been compared in this study. No significant differences have been observed between two groups except for frequency of vegetable intake. Vegetable consumption

was significantly more frequent among patients than controls. This study indicates that diet doesn't play role in production of sebum in patients with seborrheic dermatitis.

CONCLUSION

In conclusion, the results showed that dietary habits were not associated with increased risk of seborrheic dermatitis.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

STATEMENT OF INFORMED CONSENT

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Brief Report

Topical anesthesia in cosmetic dermatological procedures

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ABSTRACT

Background: Rapid increase in demand for fast, effective and painless cosmetic procedures has inspired the pursue for the ideal method of anesthesia. The aim of the study was to compare the effectiveness of different types of topical anesthetics most commonly utilized in dermatological procedures: EMLA cream, BLT cream, infraorbital nerve blocks with 2% lidocaine with epinephrine. **Material and Methods:** The study involved 12 patients with scheduled painful dermatological procedures intended to improve their facial and neck skin. Pain intensity was measured using 0-10 numeric scale (10 being the worst imaginable pain and 0 no pain). Patients were asked to assess their pain levels during fractionated CO2 laser treatment of the face. **Results:** Results demonstrated that patients subjected to treatment with the use of anesthetic EMLA and BLT creams still feel a considerable level of pain during the performed dermocosmetic procedures. Similar pain level concerned the group anesthetized with the infraorbital nerve block injection. **Conclusion:** Finding the ideal topical anesthetic is one of the greatest challenges of present-day cosmetic dermatology. The most desired method of anesthesia in this context would have to be easy to apply, display high clinical effectiveness over a short time period, be able to exert numbing effect on intact skin without systemic effects, cause nominal pain or discomfort during treatment with minimal to no side effects. According to the results of the reported study, the most effective method of anesthesia was proved to be the triple anesthesia involving of a combination of a painkiller drug, EMLA cream and infraorbital nerve block.

Key words: Topical anesthesia; EMLA; BLT; Nerve block; Lidocaine; Cosmetic procedures

INTRODUCTION

In recent decades cosmetic dermatology has experienced an unprecedented growth in popularity. Rapid increase in demand for fast, effective and painless cosmetic procedures has simultaneously inspired the pursue for the ideal method of anesthesia. Currently, the field of cosmetic procedures is increasingly being dominated by non-surgical (but nevertheless invasive and potentially painful) procedures, often described as 'quick and safe' alternatives to surgery. Patients thus expect quick yet spectacular results achieved through procedures that can be safely carried out within a span of a lunch-break. To meet their demand, dermatologists are constantly searching for anesthetics that would be most effective but also yield the least risk for a patient and bear minimal (if any at all), unwanted side-effects.

Anesthesia in Cosmetic Dermatology Practice

There are many types of anesthesia that are employed by dermatologists during cosmetic procedures. Out of the broad range of available options, local or topical anesthesia has become the preferred method of practitioners. The popularity of topical anesthesia during dermocosmetic procedures is undoubtedly linked to the unique nature of these procedures and the fact that they are usually associated with precise medical interventions that are however usually limited to very small areas of skin. At the same time, as many such procedures are typically carried out on the patient's face, the associated pain and the fear of pain and/or needles is an important factor that should be addressed while deciding upon the best method of anesthesia.

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Effective pain management strategies adjusted to the type of procedure planned for a given patient is critical to achieving the desired effect of the performed procedure while assuring a high level of overall patient satisfaction. Pain is a common barrier to cosmetic procedures, and therefore alleviating the fear of painful interventions is critical factor determining the patient's assessment of the procedure, the skill of the medical staff and the procedure itself. The level of pain associated with the given type of procedure may also be a defining element in patient's decision concerning the continuation of therapy, the choice of the type of further therapy and evaluation of the medical center. It should be also always considered that patients checking in for dermocosmetic procedures are prevailingly driven by the desire to improve their appearance, undergo corrections of psychical beauty defects or to simply look younger. This specific group of patients is thus mostly concentrated on achieving a certain aesthetical outcome of the chosen medical procedure and as they are not suffering from a medical condition they are less inclined to accept pain as part of their therapy. In may regards patients deciding to undergo a cosmetic dermatological procedure are perceiving these procedures as an extended (or rather – advanced) form of beauty treatment and as such are expecting them to be fast, effective and painless.

These patients' expectations along with the dynamic increase in popularity of cosmetic dermatology determine the need to search for the best ways of eliminating unwanted side-effects and relieve the pain and the stress related with the discussed types of procedures.

Local anesthesia is therefore broadly regarded as the most effective and convenient component of successful interventions in cosmetic dermatology. Its possible administration techniques and types of medications are varied, allowing for selecting the most appropriate type of anesthesia given the nature of the procedure and the patient in question.

Types of Topical Anesthetics

Local anesthetics alleviate pain by the inhibition of voltage-gated sodium channels which in turn prevents the depolarization of nerve cells and reversibly blocs nerve conduction [1,2]. Their operation therefore causes temporary loss of sensation in a limited area of application.

Chemical structure of all topical anesthetics is uniform; they contain a lipophilic aromatic group, an intermediate chain, and a hydrophilic amine group. The chemical group attached to the intermediate chain determines their classification as amide- (eg, lidocaine, bupivacaine, articaine, mepivacaine, prilocaine, levobupivacaine) or ester-containing (eg, procaine, proparacaine, benzocaine, chlorprocaine, tetracaine, cocaine). Epinephrine or another adrenergic agonist is often added to the local topical agent in order to prolong the anesthetic effects by increasing vasoconstriction and decreasing the rate of systemic absorption [3]. The role of epinephrine in this context is also to reduce surgical bleeding and increase the intensity of blocade.

These topical anesthetics can be administered in a multitude of methods, including topical sprays, patches, creams, ointments, peels and even injections. Duration of action of various formulations depends on the agent and chosen method. Their distinctive feature is that they noninvasively deliver anesthesia in locally required areas.

There are several clinical techniques of delivering anesthesia locally:

1) Topical, non-invasive administration by means of applying the drug through spray, ointment or cream
2) Topical refrigerants such as the cooling ethyl chloride spray
3) Infiltration anesthesia with the use of drugs intended for topical anesthesia
4) Block anesthesia for example - peripheral nerve block (as in the case of this study) which is an injection of a topical anesthetic in the vicinity of a peripheral nerve to anesthetize that nerve's area of innervations
5) Anesthesia through infiltrative tumescent technique.

The most often used method among practicing dermatologists is the EMLA cream. EMLA stands for Eutectic Mixture of Local Anaesthetics and is a mixture of lidocaine 25 mg/g, prilocaine 25 mg/g, arlatone 289 (emulgent), carbapol 934 (thickener) and distilled water in 1 ml cream.

EMLA cream has proven to have anesthetic efficacy in several clinical trials involving such dermatologic procedures as cryotherapy, pulsed dye laser treatment, and debridement of leg ulcers [4-7]. It is used worldwide, with proven safety and efficacy [8-10].

Other local anaesthetics that are used include: amethocaine patch, ethylchloride spray, lidocaine gel, lidocaine gel 10% + glycerrhetinic acid monohemiphtalate disodium (absorption promoter), lidocaine adrenaline tetracaine (LAT) gel, liquid nitrogen tetracaine adrenaline cocaine (TAC) gel, tetracaine cream.

In addition to the above, of the the most commonly used compounded topical anesthetics is the triple-anesthetic benzocaine/lidocaine/tetracaine cream (BLT gel/cream). When properly formulated the BLT gel can provide effective cutaneous anesthesia as early as 15 minutes after application without occlusion, reaching a maximum effect 30 minutes after application.

Aim of the Study

The aim of the study was to compare the effectiveness of different types of topical anesthetics most commonly utilized in dermatological procedures. The types of topical anesthesia subject to the study were: EMLA cream, BLT cream, infraorbital nerve blocks with 2% lidocaine with epinephrine. In several cases patients were additionally premedicated with ibuprofen 400 mg or ketoprofen 100 mg prior to the procedure. The goal of the assessment of the operation of these types of topical anesthetics was to establish the best choice for cosmetic dermatology procedures.

MATERIAL AND METHODS

The study involved 12 patients with scheduled painful dermatological procedures intended to improve their facial and neck skin. The planned procedures were: fractionated CO2 laser resurfacing-using ECO2 lutronic laser (6 patients) and micro needling using Dermapen (6 patients). Patients' pain levels during procedures were measured using numeric 0-10 scale (where 0 - no pain, 10 - most severe pain one can imagine). 6 patients were anesthetized topically with EMLA cream and 6 with BLT cream (compounded in local pharmacy). Additionally 2 out of 6 patients in each group had infraorbital nerve blocks with 2% lidocaine with epinephrine. 2ml of the local anesthetic was injected on each side to ensure better anesthesia of the peri oral and lip area. 1 patient in the infraorbital nerve block and 2 patients in the topical cream anesthesia only group were pre medicated with paracetamol 1000 mg, ibuprofen 400 mg or ketoprofen 100 mg-depending on the patient's preference.

RESULTS

In order to compare the results of the various types of anesthesia as well as combinations of different forms of anesthesia used, the patient self-report responses were disaggregated into the following 4 groups and 3 subgroups defined by the method of anesthesia applied:

Group 1 (topical EMLA only) – 3 patients
Group 2 (topical BLT only) – 3 patients
Group 3 (topical EMLA and infraorbital nerve block) -1 patient
Group 4 (topical BLT and infraorbital nerve block) – 2 patients
Subgroup 5 (topical EMLA and premedication-ketoprofen 100mg) -1 patient
Subgroup 6 (topical BLT and premedication ibuprofen 400 mg) -1 patient
Subgroup 7 (topical EMLA, infraorbital nerve block and ketoprofen 100 mg) -1 patient.

Pain intensity was measured using 0-10 numeric scale (10 being the worst imaginable pain and 0 no pain). Patients were asked to assess their pain levels during fractionated CO2 laser treatment of the face. The patient in subgroup 7 scored the lowest (4) while the results in group 1 (EMLA only) displayed the highest pain scores (8.6). Other groups/subgroups scores ranged from 6 to 9: group 2-(8), 3-(7), 4-(6), 5-(8), 6-(9).

The results of the study indicate that the application of topical anesthesia in the form of cream of gel (in this case the most commonly used EMLA and BLT creams were compared – groups 1 and 2) has only a very moderate anesthetic effect during painful dermocosmetic procedures. This method of anesthesia stands out as the easiest in administration and does not involve any pain at the stage of application. However, as a standalone anesthetic, these creams are not fully effective.

The numbing effect of the EMLA and BLT creams applied in combination with premedication by painkillers – ketoprofen and ibuprofen (groups 5 and 6) was also very limited. The study showed that the premedication by these substances failed to significantly reinforce the numbing effect of the creams alone. The comparison of mean pain level in groups with EMLA and BLT creams only (group 1 and 2) and groups applying the creams and premedicated (groups 5 and 6) are almost the same which questions the rationale behind the use of these drugs.

In groups 3 and 4 the anesthetic EMLA and BLT creams were applied in combination with an infraorbital nerve block injection. Both groups demonstrated similar pain levels, still considerably high and not significantly lower than the results for standalone application of creams.

The only noticeably lower pain level was associated with the patient in group 7, whose anesthesia consisted of three different methods: the topical application of EMLA, infraorbital nerve block and premedication with ketoprofen 100 mg. This triple anesthesia proved to be by far the most effective method from the range of methods assessed in the present study.

DISCUSSION AND CONCLUSIONS

Finding the ideal topical anesthetic is one of the greatest challenges of present-day cosmetic dermatology. One can assume that the most desired method of anesthesia in this context would have to be easy to apply, display high clinical effectiveness over a short time period, be able to exert numbing effect on intact skin without systemic effects, cause nominal pain or discomfort during treatment with minimal to no side effects [11,12].

The reported study demonstrated that patients subjected to treatment with the use of anesthetic EMLA and BLT creams alone, similarly to those who were previously premedicated with ibuprofen and ketoprofen still feel a considerable level of pain during the performed dermocosmetic procedures. The mean pain level in these groups was also very similar to patients who were anesthetized with the creams and infraorbital nerve block injection. The most effective method of anesthesia was proved to be the triple anesthesia involving of a combination of a painkiller drug, EMLA cream and infraorbital nerve block.

Of course, one has to keep in mind that the choice of which anesthetic to use depends on a number of factors, including personal patient factors, age, pregnancy status, state of health, history of allergies, other medical conditions such as renal or hepatic failure, cardiac problems, current medications, type of procedure being performed, its duration, body area where the procedure will be carried out, doctor's own preference, training and experience and the patient's preference including for example severe needles phobia.

Only after a careful consideration of all these factors and a detailed patient interview, the doctor will be able to make an informed decision about the choice of the best local anesthetic for the particular procedure planned.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Brief Report

Revisitation of an old antimalarial to combat Psoriatic Arthritis administering an antidote to Santonin to avoid xanthopsia or maculopathy

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ABSTRACT

Background: The mechanism of action of antimalarials in the treatment of patients with rheumatoid arthritis is hitherto unknown but is thought to involve changes in antigen presentation or effects on the innate immune system. **Material and Methods:** Patient with psoriatic artritis after ineffective therapy of three kinds of NSAIDs was used following therapy: chloroquine: 250 mg/day for one entire year; -ibuprofene: 600 mg/day for one entire year; thiamine: 1.6 mg/day. Was analyzed of Disease Activity Score (Das28 using three parameters, excluding the self evaluation, because of the problem of the subjectivity according to the method heralded by Van der Heijde DMFM, van't Hof MA, van Riel PLCM, van de Putte LBA. **Results:** At the beginning Das28 was 2.4 and at the end of the trial it was 1.00. **Conclusions:** The antidotes to santonine are limewater, chloral hydrate and thiamine. The antidotes Forecasts a novel re-introduction of this antimalarial in therapy against RA as it reveals a good improvement according to the Das28 method of evaluation of remission of complex symptoms of the same Reumatoid Arthritis.

Key words: Chloroquine; Antimalarial; Ibuprofene; Thiamine

INTRODUCTION

Since the the co-author of this paper had already complained the uncontrolled usage of TNFα inhibitors (that may result perilous and sometimes letal in peculiar cases for elder) to attempt to combat all kinds of Rheumatoid Arthritis (RA) and referred that this specific phaenomenon is extremely common in Italy where a well organised Mafia exists and numbers many supranational pharmaceutical companies and holdings among the acolytes and too many specialists among the adepts [1-3], the A, who will be the "patient" in this seat, would like to propose, together with his physician,who is the corresponding author, a canonical and ancestral therapy that has been often excluded from the orthodox protocols, because of the ocular toxicity of the main drug employed, that is chloroquine.

Given that the mechanism of action of antimalarials in the treatment of patients with rheumatoid arthritis is hitherto unknown but is thought to involve changes in antigen presentation or effects on the innate immune system [4].

The most important toxicities are on the eyes: corneal deposits, extraocular muscular weakness, loss of accommodation (and sensitivity to light), and a retinopathy that may progress to irreversible visual loss.

The very first complication provoked by chloroquine is xanthopsia [4], the same disease evoked by the prolonged assumption of digoxin or hydrochlorothiazide, but even by santonin (from semen contra extracted from Artemisa cina or absinth from Artemisia absinthium (AA), the former used as helminthic in many underdeveloped countries or in the same lands where

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the plant is native to and the latter is used as voluptuary beverage by maniacs and artists) [5].

The proposal of the employ of chloroquine in association with antidotes to semen contra is not peregrin or erratic, the AA deem and are to demonstrate that this hypothesis is not debatable.

MATERIALS AND METHODS

The report is represented by the co-author himself, who was diagnosed as having seronegative psoriatic artritis three years ago. He presented the typical manifenstations of chronic plaque psoriasis but even other peculiar symptoms as low back pain,conjunctivitis, swollen joints, morning stiffness,foot pain,fatigue and swelling of the toes and fingers.

He underwent to three kinds of NSAIDs, that is: celecoxib for 6 months, niflumic acid for six months, and indomethacin for the residual 6 months.

After 18 months of these types of therapy he, appealing to Sir Thomas Percival's rules on Medical Ethics, has decided to follow the suggestions of his physician (the corresponding Author) and so to self administer the following therapy:

- Chloroquine: 250 mg/day for one entire year,
- Ibuprofene: 600 mg/day for one entire year
- Thiamine: 1.6 mg/day (since the patient drinks generally black tea as voluptuary drink, Equisetum arvense as diuretic and anxiolytics in order to sleep well).

It is well known that some teas,anxiolytics,diuretics and barbiturates can cause the depletion of thiamine,for this the patient made up his mind to increase the daily dosage of vitamin, from 1.2 mg to 1.4 mg.

The patient has been avoiding to drink alcohol, smoke cigarettes or eat fresh shell fishes for the entire year of proof.

Thiamine is known to be an excellent antidote to santonin of semen contra since it has beneficial properties on extraocular muscles and on sensitivity to artificial or sun light.

For the sake of truth the patient and the corresponding A are not rheumatologists and for the fact that the co-author experimented the therapy on himself in corpore vili, he could not examine the observable results (joint pain,joint stiffness at the morning, joint redness and/or warmth,fatige,fever or weight loss since all of these are subjective remarks).

He could only state the amelioration relying on the Disease Activity Score (Das28 using three parameters, excluding the self evaluation, because of the problem of the subjectivity according to the method heralded by Van der Heijde DMFM, van't Hof MA, van Riel PLCM, van de Putte LBA. in 1993) [6], obtained resolving the following equation:

0,53938√ (Ritchie's index)+0,06465 (0.01285,idest the global number of swelling joints/28)+0,330 Ln (VES)+0,00722(GH).

For this, the patient has his own Das28 measured, at the very beginning of the four trials (celecoxib,niflumic acid, indomethacin and finally the synergic combiné chloroquine-anti-inflammatory-thiamine) and recorded all the scores.

All the values revealed after the three prior trials effectuated on himself in corpore vili:

1) Before assuming celecoxib 200 mg twice a day the Das28 was 4.8 and at the end of the proof was 3.9
2) Before assuming niflumic acid 100 mg pro day the Das28 was 3.9 and at the end of the proof was 2.8.
3) Before assuming Indomethacin 200 mg/day the Das28 was 2.8 and at the end of the proof was 2.4.

It is well established that when initial DAS28 value is >5.1 one assists at a moderate improvement when the DAS28 score falls down to >0.6 at the end of therapy (6 or 12 months) and all scores <1.2 are not valuable,that is that there has been no improvement in the recovery of illness.

When the initial Das28 is >3.2, there is a moderate improvement when after the cure the Das28 reaches a value comprised between >0.6 and 1.2.

When finally the original Das28 is <3.2 there is an excellent improvement when final Das28 will be >0.6, a moderate improvement when Das28 is <1.2 and no improvement at all when final Das28 is >1.2.

RESULTS

So when the patient and his physician decided to start with the therapy choroquine-ibuprofene-thiamine the co-author's Das 28 was 2.4 and at the end of the trial it was 1.00.

The patient had his visual field measured at the beginning of the trial and the scores were 100 degrees laterally, 60 degrees medially, 60 degrees upward, and 75 degrees downward.

The same results were obtained measuring the visual field at the end of the therapy.

No positive scotoma has been observed after 12 months of cure.

DISCUSSIONS

There is to object that the real value of Das28 at the very beginning of the series of therapies could not be taken for right in this work, as it should be clear that for a net observation of data it would be better if the measure of Das28 should have been effectuated without undergoing to the prior proofs with celecoxib,niflumic acid and Indomethacin.

But all this has been done on purpose, in order to describe a comparison of efficacies among the three common anti-inflammatory drugs and the antimalaric drug.

Knowing that when the difference between the initial score and the final is >1.2 the amelioration is valuable, when the difference is >0.6 the amelioration is moderate and when indeed is <0.6 no valuable improvement can be observed, the A can assert that the combiné chloroquine-anti-inflammatory-thiamine shows that the difference of initial and final Das28 is 1.4.

The difference in the case of celecoxib is 0.9, in the case of niflumic acid is 1.1 and in the case of Indomethacin is 0.4.

CONCLUSIONS

Chloroquine has been used for decades in last centuries to try to combat RA, but its employ in medicine was abandoned as the eye toxicity was serious, causing cataract, maculopathy and xanthopsia.

If the therapy with this antimalarial is associated with an antidote to santonin, the biological principle discovered in Artemisia cina by Kahler in 1830 in Düsseldorf, substance that used to evoke irrevocable xanthopsia in teenagers who were forced to assume it as anthelmintic, the eye disorders, it will be demonstrated, will not occur at all.

The antidotes to santonine are limewater, chloral hydrate and thiamine.

The antidotes forecasts a novel re-introduction of this antimalarial in therapy against RA as it reveals a good improvement according to the Das28 method of evaluation of remission of complex symptoms of the same RA.

It must be taken on serious account the problem of xanthopsia or eventual (even rare) problem of maculopathy or cataract.

For this reason a measuration of the visual field is adviced, almost every 12 months.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

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Our Dermatology Online

Case Report

A case of HIV, leprosy co-infection - presenting as immune reconstitution inflammatory syndrome

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ABSTRACT

Though leprosy was officially declared eliminated in India, new cases continue to be reported. Introduction of Highly Active Antiretroviral Therapy (HAART) for Human Immunodeficiency Virus (HIV) infection in 1996, caused emergence of a new condition called Immune Reconstitution Inflammatory Syndrome (IRIS), which is the paradoxical deterioration of clinical status following HAART initiation. A 49 years old male patient who came with the complaints of dry skin and numbness of limbs 3 weeks after starting HAART was found to have IRIS syndrome and started on (MB- MDT) after which he developed type 1 lepra reaction. He was managed with systemic steroids with prompt recovery. Case is being reported to create awareness of this condition as more and more number of patients may be put on HAART due to increasing HIV prevalence in the region which may in turn lead to increase incidence of IRIS.

Key words: Leprosy; HAART; IRIS; AIDS

INTRODUCTION

Leprosy has been a major public health problem in many developing countries for centuries. Though it was officially declared eliminated in India since December 2005, new cases have been reported with varying prevalence throughout the nation. Introduction of Highly Active Antiretroviral Therapy (HAART) in 1996, caused emergence of a new condition called Immune Reconstitution Inflammatory Syndrome (IRIS), which is the paradoxical deterioration of clinical status following HAART initiation [1]. First case of leprosy or its reaction as IRIS syndrome was reported in 2003 and there are not much case reports as well as etiolopathological investigatory studies in the subject so far.

CASE REPORT

A 49 yr old paramilitary officer on irregular HAART for 10 months was referred from Antiretroviral therapy (ART) clinic, for numbness and gradually progressive, non itchy, painless, dry skin lesions over the forearms and legs. There was swelling and pain of feet for one week. He was started on HAART with Zidovudine, Lamivudine and Nevirapine but was interrupted due to skin rashes. He was shifted to Efavirenz subsequently and he had taken HAART for an effective period of seven months before presenting to us. He was on oral hypoglycemic agents as well as twice daily clotrimoxazole for eight months.

On examination, approximately 10 large dry wrinkled, mildly shiny and scaly hyperpigmented plaques of varied morphology and imperceptibly merged margins was detected over forearms and legs (Fig. 1). Dry irregular scaly plaques were seen on gluteal region, while annular reddish yellow plaque with central clearing and mildly raised peripheral rim was seen on left mammary area; ill defined plaques over lower back were present (Fig. 2). Sensations were diminished in all skin lesions in varying degrees. Muscle power was normal, great auricular, radial-superficial and deep, ulnar nerves were enlarged but non tender. Common peroneal nerves were enlarged and mildly tender bilaterally.

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Hemogram was normal except for high ESR (110mm/1st hr). RBS, LFT, KFT, Urine R/E, Thyroid profile, G6PD levels, Hepatitis serology, chest X-ray were all in normal limits. CD4 counts were 147/cumm and 161/cumm before starting HAART and at the time of presentation respectively. Skin biopsy from the lesion on back showed mildly flattened epidermis, mild to moderate lymphocytic infiltration in papillary dermis with well formed epithelioid cell granulomas, peri-appendageal granuloma, lepra stain showed few acid fast bacilli; features which were consistent with diagnosis of Hansen's disease (BT type) (Fig. 3). Multibacillary multidrug therapy (MB-MDT) was started along with HAART.

Three weeks later he presented with tingling and numbness in whole body, pain over the thighs and arms for ten days and painful swelling of hands and feet for one wk. Increase in the size of existing skin lesions was noted. There was edema over bilateral hands and feet, claw hand was present. Ulnar, Common peroneal, Posterior Tibial nerves were thickened and tender. Paralysis was seen in small muscles of hands and foot. Diagnosis of type 1 lepra reaction was made and managed with oral Prednisolone 60mg/day. MB-MDT and HAART continued. He was lost to follow-up further. Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Immune Reconstitution Inflammatory Syndrome (IRIS) is defined as the occurrence or worsening of clinical and/or laboratory parameters despite favorable outcome in HIV surrogate markers (CD4 counts and viral loads) [1]. It was originally reported in mycobacterium avium complex in 1998 [2]. Subsequently many opportunistic infections like herpes zoster, warts, hepatitis, cryptococcosis, histoplasmosis, toxoplasmosis, pneumocystis carinii infections as well as non infectious conditions like sarcoidosis, various autoimmune and neoplastic disorders were reported. IRIS can occur even among HIV negative individuals with sudden recovery of neutrophil counts after stopping chemotherapy or long term immunosuppressive therapy.

First case of leprosy associated with IRIS syndrome was reported on 2003 only, by Lawn et al. [3]. HIV infection has not been reported to increase susceptibility to leprosy infection markedly or alter the pathological course of the disease. A retrospective study on 4025 leprosy patients in India described only 5 cases of co-infection with HIV [4]. Similarly, another common

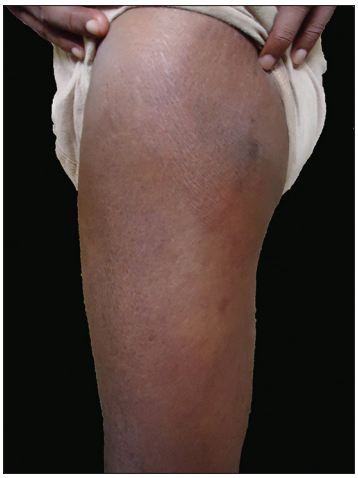

Figure 1: Shiny scaly plaque over lateral aspect of thigh.

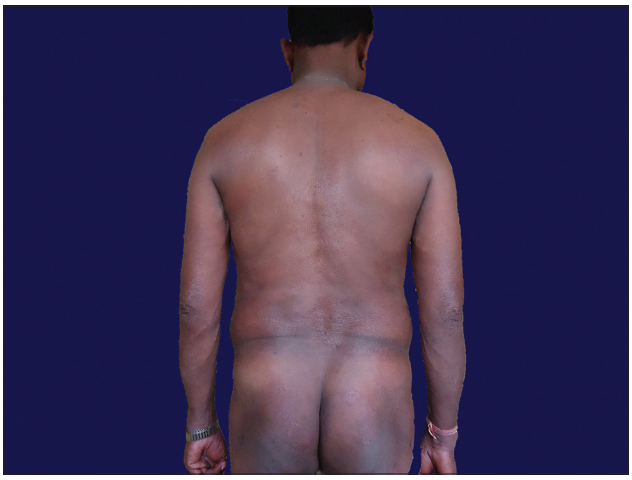

Figure 2: Shiny scaly plaques with imperceptively merged margins over back and gluteal region.

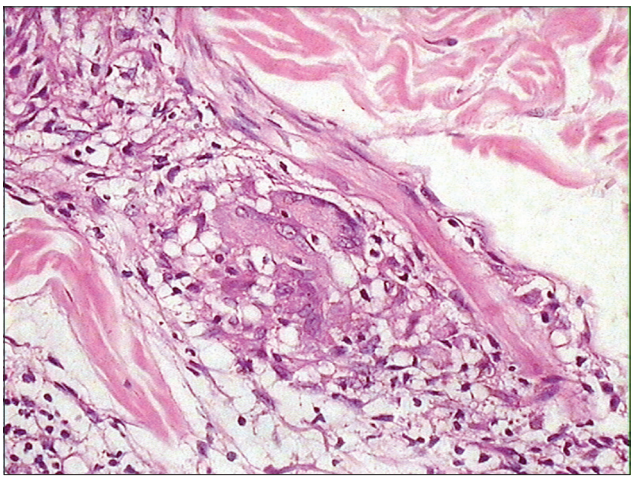

Figure 3: H.P.E (H&E, 10x) showing papillary dermis with mild to moderate lymphocytic infiltration and well formed epithelioid cell granulomas.

belief that HIV, by decreasing immunity may lead to increased incidence of lepromatous cases, also was rejected by systematic studies. Tuberculoid cases found to be favored in co-infection with HIV. In a cohort study conducted by Euzenir et al showed HIV infection is preferentially associated with the emergence of previously undiagnosed BT/PB leprosy. It also showed an improved immune status, a higher CD4+ counts and lower viral loads favors diagnosis of leprosy in HIV co-infected patients. This observation provides support for the reports suggesting leprosy as part of IRIS [5].

Though IRIS is a well discussed entity, an universally acceptable diagnostic criteria is still lacking. According to the proposal by Deps and Lockwood in 2010 diagnosis can be achieved from the following; 1) leprosy and/or type 1 reaction presenting within six months of starting HAART 2) advanced HIV infection 3) low CD4+ count before start of HAART and 4) CD4+ count increasing after HAART has been started [6]. Ideally, both viral load and CD4+ cell count should be used as diagnostic criteria. If data on viral load is not available, then should be an increase in CD+ count associated with starting HAART [7]. In our case, there is only a minimal increase in CD4+ count after starting HAART and viral load was not done due to un affordability. It has been found that even a minimal decrease in viral load in the absence of a significant rise in CD4+ cell count itself can precipitate IRIS [8]. However viral load was not tested in our patient before initiation of HAART due to non availability during that period and NACO (National AIDS Control Organization) consider it to be an optional test.

CONCLUSION

In HIV infected patients with low CD4+ counts <200/cmm, on HAART, if skin lesions with numbness appearing within first six months of initiation of the treatment, a differential diagnosis of leprosy in the form of immune reconstitution inflammatory syndrome should be made with priority in high endemic areas. A wide variety of atypical clinical presentations and serious reactions should be anticipated. More systematic studies are required to understand the immune and inflammatory mechanisms associated with the condition.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Tuberculosis verrucosa cutis masqerading as chromoblastomycosis - a case report

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ABSTRACT

Tuberculosis verrucosa cutis (TVC) also known as prosector's wart occurs due to exogenous inoculation of tubercle bacilli into the skin. A 52 year old female came with complaints of raised skin lesion over the left leg and foot since 20 years. Pain and discharge from the lesion was present since 15 days. History of swelling of the left leg since 2 weeks. Cutaneous examination revealed multiple well defined erythematous to flesh coloured soft nodules over left lower leg with surrounding hyperpigmented scaly plaque. A well defined hyperpigmented verrucous plaque with central depigmentation over left foot. Lupus vulgaris and chromoblastomycosis were the provisional diagnosis.Mantoux test was positive. Biopsy was suggestive of TBVC. Patient was treated with anti-tuberculous therapy. TBVC usually presents as a single verrucous lesion over exposed areas of the body. Our patient here presented with multiple nodules and hyperpigmented plaque over the left lower limb which was mimicking chromoblastomycosis.

Key words: Tuberculosis verrucosa cutis; Tubercle bacilli; Chromoblastomycosis

INTRODUCTION

Tuberculosis is one of the most established known illnesses with confirmation of the disease being found in the vertebrae of neolithic man in Europe and in Egyptian mummies. It was not until 1882 that Robert Koch discovered the causative agent Mycobacterium tuberculosis [1]. In 2007, India positioned first in terms of aggregate number of TB cases (2.0 million) globally. Cutaneous tuberculosis constitutes about 1.5% of all extra pulmonary tuberculosis [2]. Various clinical forms of the disease have been reported, many of which closely mimics of other common dermatoses in the tropics.

CASE REPORT

A 52 year old female came to dermatology OPD with complaints of multiple raised skin lesions over left leg and foot since 20 years. c/o discharge and pain over the lesion since 15 days. She initially developed a blister over left foot and swelling over left leg following trauma while cutting woods. The bulla spontaneously ruptured leaving an ulcer slowly healed and was recurrent which gradually developed into aymptomatic raised lesion over the left leg. No history of antituberculous therapy. No history of contact with open case of tuberculosis. On general examination left leg pitting pedal edema was present. Systemic examination did not reveal any abnormality. Cutaneous Examination revealed three well defined erythematous to pinkish soft nodules of size 1.5cm over anterior aspect of left lower leg with surrounding hyperpigmented scaly plaque (Fig. 1) and a well defined hyperpigmented plaque with central depigmentation with thick verrucous surface of size 5 x 3 cm over lower aspect of left leg. Diffuse swelling seen over the left leg with xerosis (Fig. 2). Diascopy was negative.

A provisional diagnosis of chromoblastomycosis and lupus vulgaris were made. Routine blood investigations were within normal limits except ESR which was 80mm. Serology, chest xray and USG abdomen were normal. AFB for sputum was negative. A 10% potassium hydroxide mount was done from the scraping obtained

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from the margin of the plaque was negative for mycelia/spores.

Mantoux Test – Positive (Figs. 3a and 3b).

To confirm the diagnosis an incision biopsy was taken from the nodule and the verrucous lesion (Figs. 1 and 2). The specimen was sent for Histopathological examination and fungal culture.

HPE of specimen A

PAS staining for fungus was negative. Culture for mycobacteria and fungi revealed no growth after 6 weeks.

Based on the clinical features and histopathology a diagnosis of tuberculosis verrucosa cutis was made (Figs. 1, 2 and 4).

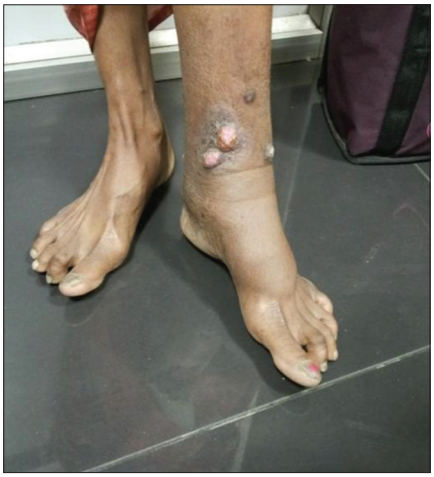


Figure 1: Three well defined erythematous to pinkish soft nodules of size 1.5 cm over anterior aspect of left lower leg with surrounding hyperpigmented scaly plaque.

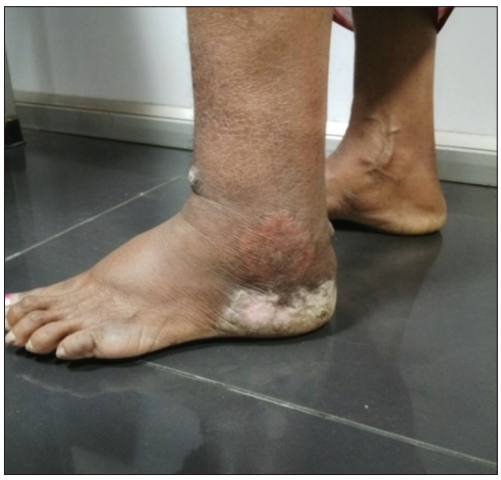


Figure 2: A well defined hyperpigmented plaque with central depigmentation with thick verrucous surface of size 5 x 3 cm over lower aspect of left leg. Diffuse swelling seen over the left leg with xerosis.

The patient was started on DOTS category 1 regimen comprising of:

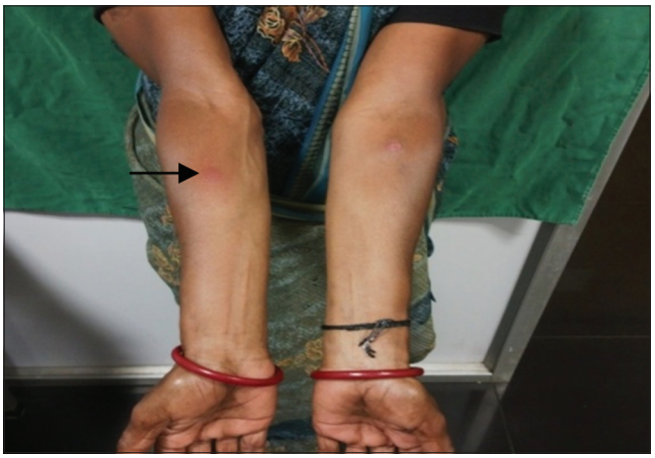


Figure 3a: Mantoux Test Positive.

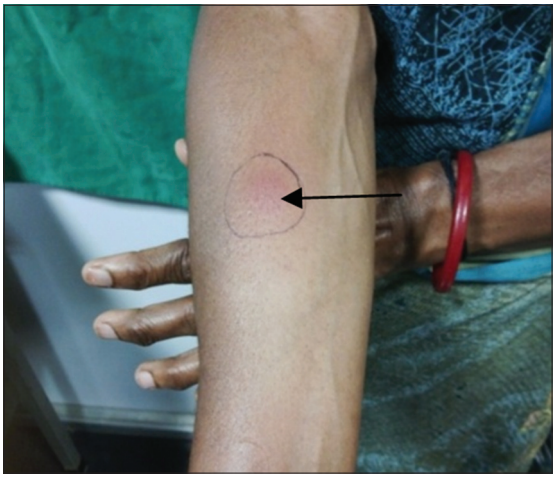


Figure 3b: Mantoux Test Positive.

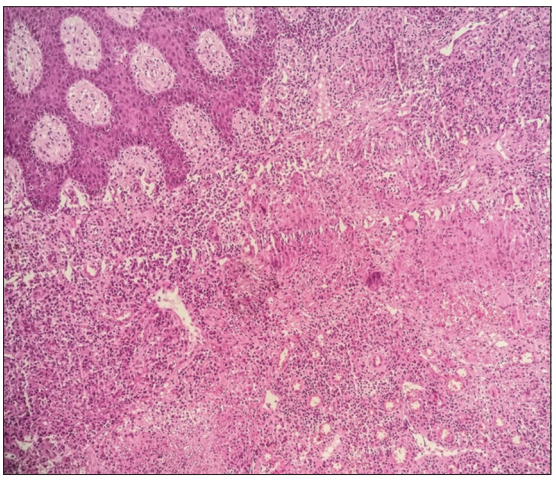


Figure 4: Histopathology showing Hyperkeratosis, acanthosis, papillomatosis, granulomas composed of lymphocytes, neutrophils, giant cells with central caseous necrosis.

(2)HRZE + (4)HRE (Intensive phase - Isoniazid, Rifampicin, Pyrazinamide and Ethambutol for 2 months+ continuos phase - Isoniazid, Rifampicin, Ethambutol for 4 months).

There was regression of size of the lesion and also the verrucosity after 6months of therapy.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Cutaneous tuberculosis forms a small proportion of extrapulmonary tuberculosis. Tuberculosis verrucosa cutis (TBVC) is a form of secondary (reinfection) tuberculosis occurring in presensitized individuals with a moderate to high degree of immunity.

Tuberculosis verrucosa cutis(TVC) also known as prosector's wart of Laennec [3], verruca necrogenica, anatomic tubercle, lupus verrucosus, and butcher's wart [4] is a paucibacillary form of cutaneous tuberculosis which occurs due to exogenous inoculation of tubercle bacilli into the skin in a previously sensitized patient [3] with a moderate to high degree of immunity [4]. The incidence of cutaneous tuberculosis has fallen from 2% to 0.15% [4]. TVC is frequently found on the hands and in areas prone to trauma. In tropical areas, the buttocks and lower extremities are commonly affected sites. The lesion starts as a papule or papulopustule also, gradually enlarges to form a verrucous plaque. It is much of the time misdiagnosed as a wart. Spontaneous healing may occur at the centre and the entire lesion may resolve after several months or years [5].

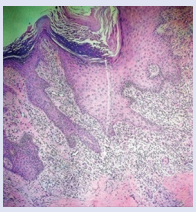
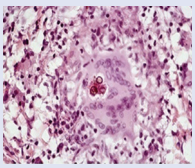
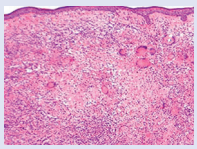
The histopathological features are characterized by marked pseudoepitheliomatous hyperplasia of the epidermis and the dermis show dense inflammatory infiltrates comprising of neutrophils, lymphocytes and giant cells [3].

Cutaneous tuberculosis still remains a puzzle to todays dermatologists as a result of the wide varieties in its clinical appearance, histopathology, immunology, and treatment response. In atypical variations of cutaneous tuberculosis, one needs to depend on examinations like histopathology, AFB examination, culture, or polymerase chain response (PCR) for confirmation [5].

Table. 1: Guidelines for TB treatment in India.
Legends: (H – Isoniazid, R- Rifampicin, P- Pyrazinamide,E-Ethambutol,IP– Intensive phase, CP- continuos phase) [6]

Type of Tuberculosis Case	Treatment regimen in IP	Treatment regimen CP
New	(2) HRZE	(4) HRE
Previously treated	(2) HRZES + (1) HRZE	(5) HRE

Table 2: Differentiating features of cutaneous tuberculosis and chromoblastomycosis

Tuberculosis verrucosa cutis	Chromoblastomycosis	Lupus Vulgaris
Hands – Europe Buttocks & elbows - Asia	Lower limbs	Buttocks, trunk – India Face - Europe
Solitary, small, symptomless, indurated papule or nodule with a verrucous surface	5 different forms: nodular, tumoral lesions, verrucous, plaque and cicatricial.	A single Soft erythematous Plaque with a gelatinous consistency
It slowly extends in a serpigenous manner producing an irregular reddish brown warty plaque	Nodular -fairly soft, moderately raised, pale pink or purple nodules, surface may be smooth/scaly/verrucous	On diascopy - Apple jelly nodules at the edge of a plaque
The centre involutes and leaves atrophic scar	Nodules gradually transform into bigger tumoral lesions	Extension of the plaque with areas of atrophy
		
Pseudoepitheliomatous Hyperplasia of the epidermis with diffuse or nodular granulomas in the dermis	Hyperkeratosis, parakeratosis, elongation of rete ridges/ pseudoepitheliomatoushyperplasis Granulomas in dermis Medland bodies or muriform bodies	Thin atrophic/hyperplastic epidermis with granulomas composed of giant cells, lymphocytes, plasma cells, epitheloid cells

Treatment and differentiating features of cutaneous tuberculosis was presented respectively in Table 1 and Table 2 [4,5,6-11].

CONCLUSION

Any patient presenting with multiple nodules and verrucous plaque a diagnosis of TBVC should never be missed.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

A report on primary tuberculosis of glans penis – rare presentation of a common disease

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ABSTRACT

Penile tuberculosis is an extremely rare form of genitourinary tract tuberculosis even in developing countries with higher tuberculosis prevalence. A 38-year-old married male without promiscuous behavior presented to dermatology outpatient department with a single, painful penile ulcer of 1.5×1cm size for last 2 years; which got mildly improved after on and off treatment from local practitioner, but without complete resolution. All workup in the line of sexually transmitted diseases were negative. Incisional biopsy revealed diffuse granuloma, however stain for AFB (TB) was negative. He also had positive mantoux test and raised ESR. On these bases, we started him on category I-anti tuberculosis therapy; which resulted into complete resolution of ulcer leaving behind fibrotic scar. Hence, in country like Nepal where the prevalence of tuberculosis is high, we should always suspect tuberculosis in case of non-healing chronic ulcers.

Key words: Chronic Ulcer; Genital tuberculosis; Glans penis

INTRODUCTION

Penile tuberculosis (TB) is an extremely rare form of genitourinary tract tuberculosis even in developing countries with higher tuberculosis prevalence. Here we are going to present a report on primary tuberculosis of glans penis for its rarity.

CASE REPORT

A 38-year-old married male presented to dermatology outpatient department with a painful penile ulcer for last 2 years; which got mildly improved after taking treatment from local practitioner, but without complete resolution. He didn't give history of promiscuous behavior. He was heterosexual and his wife did not have any genital problems. Local examination revealed single, 1.5×1cm, tender ulcer over glans penis with indurated, mildly fibrotic base (Fig. 1). There was no regional lymphadenopathy. All the investigations in the line of sexually transmitted diseases were negative. On laboratory investigation, he had raised ESR (35 mm/h), peripheral lymphocytosis and positive mantoux test (16 mm induration). Incisional tissue biopsy from the margin of ulcer showed diffuse granuloma composed of mixed inflammatory infiltrates, epithelioid cells and langhans giant cells, however stain for AFB (TB) was negative (Fig. 2). However, we could not find focus of tuberculosis in any other organs on thorough workup. After evaluation, we started patient on category I-anti tuberculosis therapy (ATT); which resulted into complete resolution of ulcer leaving behind fibrotic scar (Fig. 3). He does not have recurrence of the lesion till date (three years after completion of ATT) on telephonic follow up.

DISCUSSION

Though tuberculosis (TB) is one of the commonest infectious diseases in Nepal, frequently affected primary sites are lung and lymph nodes. Primary tuberculosis of the glans penis is extremely rare. Though it was little bit

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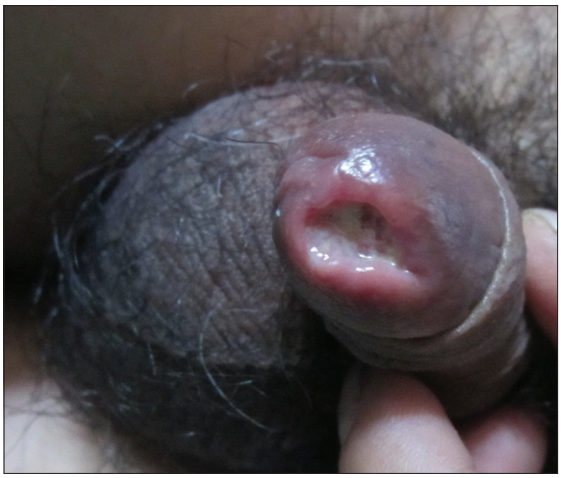

Figure 1: Ulcer over glans penis

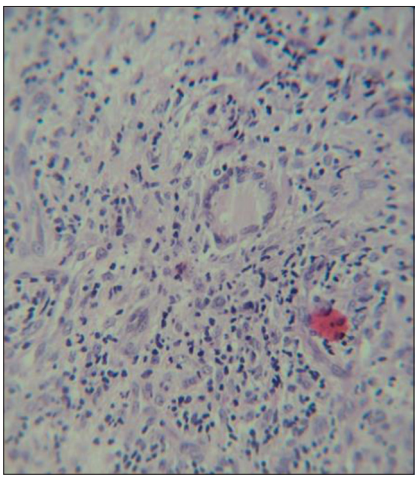

Figure 2: Granuloma comprising of mixed inflammatory infiltrates and multi-nucleated giant cell. H&E (40X)

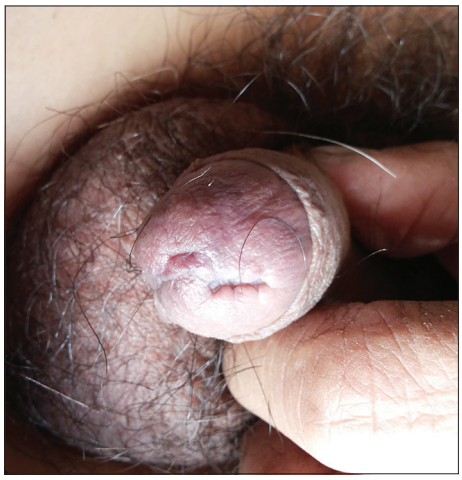

Figure 3: Post treatment scar

more common in 19th century with approximately 161 published cases [1]; it is interesting to observe primary TB of glans penis in the era of 21st century.

A study on non-venereal genital dermatosis from India did not find any cases of genital TB amongst 50 studied patients, showing its rarity even in TB prevalent country [2]. There are few recent case reports in the literature on penile tuberculosis with various presentations. A 45 year Indian male patient presented with multiple penile ulcer [3]. Similarly, another patient had ulcero-proliferative penile growth [4]. In a tertiary referral hospital of eastern Nepal, we could find similar case after a gap of 15 years [1]. This is also another evidence for its rarity.

TB glans may be either primary or secondary. Primary cases may be acquired during sexual intercourse, circumcision or from infected fomites. Friction induced epithelial breach facilitates bacterial inoculation in otherwise healthy and resistant mucosa [5]. In our case, infected clothing could be the possible source of infection. The secondary form of penile TB may be because of complication of lung or other organ tuberculosis.

Clinically, it may present as superficial ulcer, multiple asymptomatic penile papules or even cauliflower like growth [6,7]. Sometimes only glans penis may be involved as in our case, making diagnosis more difficult. Since many antibiotics also have some anti-tubercular action, there can be temporary partial improvement in the lesion, which further complicates diagnosis like in our patient.

In TB prevalent countries like Nepal, even positive mantoux test is not specific for the diagnosis of active tuberculosis [8]. Hence, a high degree of suspicion, supportive biopsy and therapeutic trial will be of great help for diagnosing penile TB as in the current case.

CONCLUSION

Unless the possibility of tuberculosis is not considered for affecting unusual sites, the diagnosis may be missed or delayed. So, in country like ours where the prevalence of tuberculosis is high, we should always suspect tuberculosis in case of chronic non-healing genital ulcers.

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Our Dermatology Online

Case Report

The first application of epiluminescence dermoscopy in erythema nodosum

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ABSTRACT

We reported an adult female with a clinical diagnosis of erythema nodosum. The patient declined lesional biopsy. We applied epiluminescence dermoscopy, which revealed features compatible with panniculitis. We managed conservatively. The rash remitted four weeks since rash onset, leaving only post-inflammatory hyperpigmentation. Dermoscopic examination cannot replace lesional biopsy for histopathology for a diagnosis of erythema nodosum to be properly confirmed. However, there are patients with clinical diagnoses of erythema nodosum who would not give consent for lesional biopsies, and patients presenting to dermatologists when the rash is already remitting. We thus described the dermoscopic findings of our patient in this report. The applicability of dermoscopy to patients with erythema nodosum and differential diagnoses of such is yet to be evaluated by further studies.

Key words: Contact dermoscopy; Cross-polarisation; Dermatoscope; Dermoscope; Digital epiluminescence dermoscope; Polarised light

INTRODUCTION

Epiluminescence dermoscopy (ED) is increasingly being applied to dermatological conditions other than cutaneous malignancies. We present here the first application of ED on a patient with erythema nodosum (EN).

CASE REPORT

A 32-year-old lady consulted us for more than two weeks' history of painful skin lesions over her lower limbs. She was also enduring frequent productive cough with purulent sputum. Her appetite was fair, but she reported no recent weight loss. She had no monoarthralgia and no polyarthralgia. She enjoyed good past health. Travel, contact, sex, and drug histories were unremarkable.

Our examination revealed a well and afebrile patient with no pallor and no jaundice. Multiple plaques were noted on the lower aspect of her thighs, latero-posterior and posterior aspects of her legs, and both ankles (Fig. 1). The lesions were discrete, erythematous to purple-coloured, subcutaneous, and slightly elevated. They were monomorphic but differed in sizes from 0.5 cm to 4 cm. The margins of lesions were not clearly demarcated. The lesions were not blanchable. All other skin surfaces including the external genitalia were uninvolved.

Her mucosal surfaces were unaffected. Her throat was inflammed, with tonsils being enlarged. No exudate was noted. There was no inguinal or other lymphadenopathy. Examination of her cardiovascular system, chest, abdomen, and musculoskeletal system revealed no abnormality otherwise.

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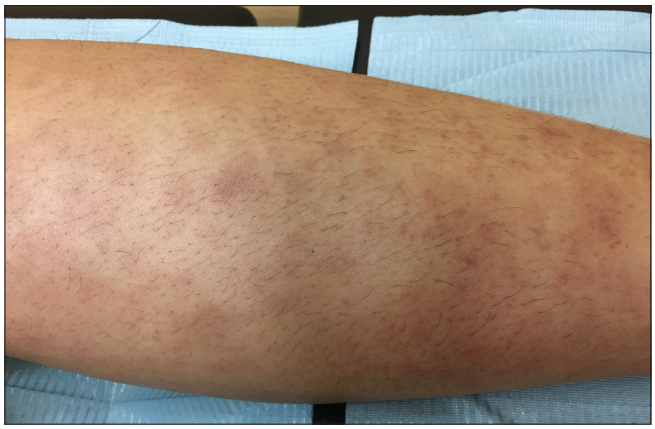

Figure 1: Multiple discrete purple-coloured macules on the anterior aspects of both legs of a patient with a clinical diagnosis of erythema nodosum.

Dermoscopic examination without cross-polarisation (Fig. 2a) revealed erythema in the lesional skin (centre in the figure) as compared to the normal skin (peripheral in the figure). The skin creases were largely uninterrupted from non-lesional to lesional surfaces. Examination under DED revealed one entire lesion comprising eight to nine lobules (Fig. 2b), compatible with the histopathology in EN. The separations between the lobules would correspond to inter-lobular septa in EN. Based on the setting of our ED device, we should be viewing features just beneath the dermis. This was also compatible with the depth of panniculitis in EN.

Results for her complete blood count, random glucose, liver function tests, and renal function tests were normal. ESR was elevated to 64 mm in the first hour. CRP was elevated to 98.4 mg/l (reference: less than 5 mg/l). Qualitative anti-streptolycin-O-titre was positive. Monospot test and serology against *Mycoplasma spp* were negative. Antinuclear autoantibodies and rheumatoid factor were negative. Chest X-ray revealed no evidence of acute chest infection, tuberculosis, or sarcoidosis. The patient declined a deep lesional punch biopsy.

We believed that the clinical findings and the findings in ED were adequate for making a diagnosis of EN, with streptococcal infection being a possible triggering factor. We prescribed oral cefuroxime 250 mg twice daily for one week, and oral diclofenic sodium 25 mg twice daily as necessary for the relief of pain. We also recommended compression hosiery. The patient attended us again two weeks later. Almost all skin lesions had remitted, leaving post-inflammatory hyperpigmentation only.

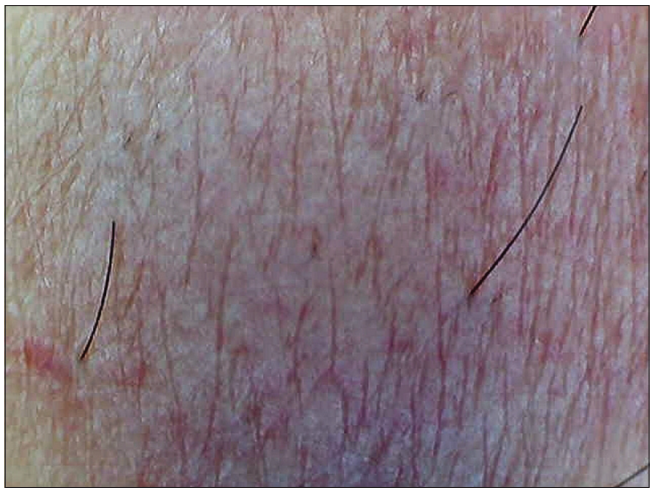

Figure 2a: Digital dermoscopic image with no cross-polarisation demonstrating one lesion. Erythema was noted. The skin creases were not interrupted. Apart from such, no additional information was provided.

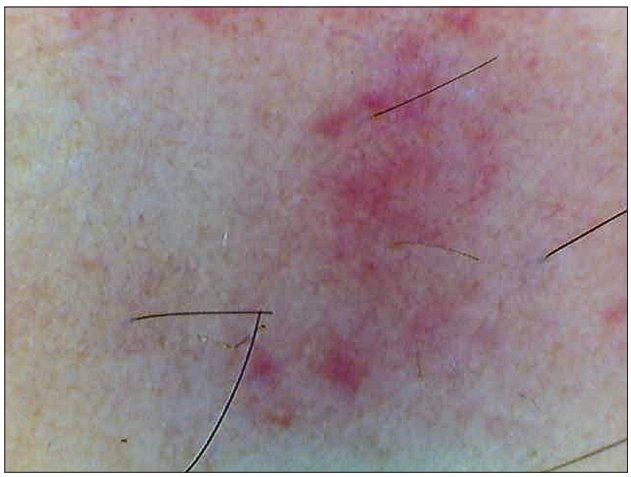

Figure 2b: Digital epiluminescence dermoscopy with the highest level of polarisation, showing the layer just deeper than the dermis. One entire lesion was depicted, composing of around eight erythematous lobules. These lobules substantiated the presence of lobular panniculitides. The separations between the lobules could represent the inter-lobular septa in erythema nodosum. Swollen blood vessels were noted, with no telangiectasia. Overall, these features were compatible with known features in erythema nodosum.

DISCUSSION

The configuration shown Figure 2b is spectacular. To our best knowledge, images akin to this figure has not been published. This was why we elected to submit this patient report despite our having findings on only one patient. However, we do not believe that our findings can be generalised to other patients, nor do we advocate dermoscopy replacing lesional histopathology as the proper substantiation in diagnosing EN.

Making a proper diagnosis of EN is important. First and foremost, underlying causes including

pulmonary tuberculosis, other infectious diseases, autoimmune diseases, malignancies, and drugs must be excluded [1-3]. Secondly, although EN is usually a self-limiting disease remitting spontaneously in six to eight weeks, the pain can affect the mobility of patients, thus affecting their schoolings or works. Thirdly, some patients will keep on developing crops of lesions, thereby progressing to chronic EN.

The management for EN would be to treat the underlying cause if identifiable. Otherwise, for recalcitrant EN, systemic corticosteroids might be indicated. However, one important differential diagnosis of EN is cellulitis. The bacterial infection in cellulitis will flare up if a wrong diagnosis of EN is made and systemic corticosteroids are administered.

EN is a panniculitis caused by delayed hypersensitivity responses to antigens. It belongs to the group of panniculitis which are septocentric and without vasculitis [4,5]. The histopathological changes of EN are those of septal and lobular panniculitis [4-6]. Septa would divide fat lobules. Perivascular and periadnexal lymphocytic, neutrophilic, and eosinophilic infiltrates are usually present.

Inspection with naked eyes or with a magnifying glass might not be adequate to explore the configuration of EN owing to (i) the skin creases distracting the view; (ii) the tissue changes being too deep; and (iii) the changes being too small for the visual acuity.

These directly echo the roles of ED. Against (i), cross-polarisation in ED ablates reflections from the skin service, rendering the skin creases invisible. Against (ii), some dermoscopes incorporate settings for adjusting the extent of cross-polarisation, thus allowing visualisation of the deep layers of affected fatty tissues. Against (iii), ED would magnify the images optically and digitally so that small details can be displayed.

Deep lesional biopsy is painful, can cause complications, and consumes time and expenses. For patients with a provisional diagnosis of EN but, like our patient, decline lesional biopsy, the application of ED might therefore substantiate the diagnosis to some extent. Moreover, there are patients with suspected EN whose rashes have already been largely remitted by the time they are referred to see a dermatologist. The need for lesional biopsy might also be lessened in such clinical scenarios.

However, our knowledge of dermoscopic changes in EN and important differential diagnoses of EN is still premature. Further studies are necessary to investigate the validity and reliability of applying ED in patients with EN or differential diagnoses of EN.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Unsusual manifestation of terra firme-forme dermatosis – upper eyelid and orbital rim

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ABSTRACT

Terra firme-forme dermatosis is a benign exogenous dermatosis found in all age-groups. The typical localizations include neck, face, trunk and ankles. Here we report on an 88-year-old male with a medical history of stroke and paraplegia of the legs who presented with asymptomatic, hyperkeratotic and slightly hyperpigmented lesions on his upper lids. Wiping of skin with alcohol pads completely removed the lesions confirming the diagnosis of terra firme-forme dermatosis of upper eyelids. Although affection of lower eyelids has reported before, the localization on upper eyelids only is very unusual.

Key words: Terra firme-forme dermatosis; Dirty dermatoses; Skin care; Hygiene; Dermatosis negelecta

INTRODUCTION

Terra firme-forme dermatosis is a benign skin disorder also known as dermatitis neglecta, unwashed dermatosis or Duncan's dirty dermatosis [1-3]. It is characterized by asymptomatic dirt-like plaques with typically localization on neck, face, trunk and ankles [4-6]. Its etiology is not completely understood. Retention of keratinocytes in combination of sebum, residues of ointments and dirt contribute to hyperpigmented lamellar and partially whorled orthohyperkeratosis [1]. All ages can be affected [3,7].

CASE REPORT

An 88-year-old male patient presented to the department for surgical correction of severe phimosis and secondary balanophosthitis. His medical history was positive for stroke and paraplegia of the legs. He lived in a nursery.

By clinical examination hyperkeratotic, slightly hyperpigmented plaques and scales were observed on his upper lids and orbital rim (Fig. 1). There was no pruritus or any other subjective symptom. There were no clinical signs of seborrheic dermatitis or tinea. The lesions could easily be removed by wiping with alcohol pads. The diagnosis of terra firme-forme dermatosis was confirmed.

DISCUSSION

Terra firme-forme dermatosis is an often overlooked, asymptomatic skin condition related to suboptimal hygiene and skin care [5,6,8]. Diagnosis is established by medical history, clinical examination and skin modified by alcohol rubbing test (SMART). SMART is performed using 70% isopropyl alcohol for wiping the skin. The commonly affected body parts are neck, face, trunk and ankles [4-6]. Eyelids are uncommonly involved. Panda et al. described three female cases aged 58 to 62 years with lower lid and periorbital presentation of terra firme-forme dermatosis after cataract surgery. Cleansing of skin was omitted for several weeks due to wound dressings. The lesions could be easily removed by soap, water or acetone [9].

Here, we describe the rare upper lid affection of an 88–year-old male patient with a positive SMART test. Because of the localization, other dermatoses need to be considered such as atopic and seborrheic dermatitis, contact dermatitis, psoriasis, rosacea and tinea [10].

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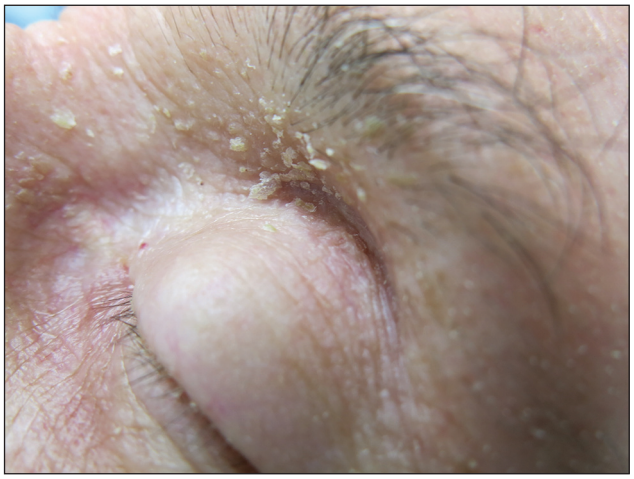

Figure 1: Terra firme-forme dermatosis of upper lid and orbital rim.

Although a rare localization, upper lids and orbital rim can be affected by terra firme-forme dermatosis. SMART test is an easy way to exclude other possible differential diagnoses.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Stewart Bluefarb syndrome: case report of a rare variant of acroangiodermatitis

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ABSTRACT

Stewart Bluefarb syndrome is a rare acroangiodermatitis which occurs due to presence of arteriovenous malformations. It presents at birth or during early childhood as an erythematous to violaceous plaques over the dorsum of foot or ankle. It's a benign condition but can mimic a malignant condition, Kaposi's sarcoma. Histopathological differentiation between these two conditions is important. Investigations like doppler ultrasound are required to establish the diagnosis. In long standing cases, complications like ulceration, bleeding and secondary infections can occur. Treatment includes surgical correction of underlying arteriovenous malformation.

Key words: Stewart Bluefarb syndrome; Acroangiodermatitis; Arteriovenous malformation; Kaposi's sarcoma

INTRODUCTION

Stewart Bluefarb syndrome is a variant of acroangiodermatitis, also known as Pseudo-Kaposi sarcoma. Acroangiodermatitis is an uncommon condition characterized by reactive proliferation of cutaneous blood vessels in response to chronic circulatory disturbance. It is often seen in association with various vascular anomalies such as venous insufficiency, arteriovenous shunts etc [1]. Stewart Bluefarb syndrome presents in young patients due to underlying arteriovenous malformation. It appears unilaterally, over the dorsum of foot, ankle or calf. Clinically, this condition presents as erythematous to violaceous, indurated plaques, usually located over lower extremities [2]. It may be associated with edema or hypertrophy of affected foot or limb. Although, it's a benign condition, it needs to be differentiated from a well known, imitating malignant condition, Kaposi's sarcoma. Due to rarity of this condition, we report a case of Stewart Bluefarb syndrome in a 25 year old female.

CASE REPORT

A 25 year old female patient presented to our dermatology outpatient department with complaints of swelling of second toe of right foot with presence of raised, violaceous lesions on the dorsum of same toe (Fig. 1). On enquiring further, patient revealed that these lesions are present since the age of 5 years and an increase in size of lesions was observed from last 4 years. There was history of swelling of affected toe and forefoot on walking. On examination, a single erythematous to violaceous, flat topped plaque of size approximately 6 x 3 cm was present over the dorsum of second toe of right foot sparing the nail. It was surrounded by few small, discrete plaques of similar appearance extending upto proximal part of dorsum of foot. On further examination, girth of affected toe was more as compared to rest of the toes with multiple dilated tortous blood vessels radiating out from proximal end of affected toe. On palpation, plaques were compressible and soft in consistency, blanchable and non tender. Pulsations in

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the affected toe were normal. Toe girth discrepancy was measured to be 2 cm and there was no toe length discrepancy. There was no audible bruit or palpable thrill. Routine investigatons including complete blood count, liver and renal function tests and urine complete examination were within normal limits. Enzyme linked immunosorbent assay (ELISA) for human immunodeficiency virus (HIV) was non reactive. No significant abnormality was detected on systemic examination. Arteriovenous doppler ultrasound (USG) revealed presence of high velocity monophasic arterialised flow beneath the plaque that suggested an arteriovenous malformation. Contrast enhanced magnetic resonance angiography revealed presence of dilated tortous blood vessels making a fistula beneath the plaque. Histopathological examination revealed an increased number of thick walled capillaries, present in a clustered pattern within thickened papillary dermis. These vessels were surrounded by mucin and sparse perivascular lymphocytic infiltrate. Moderate amount of hemosiderin deposits were seen around many of these vessels (Fig. 2). Dermoscopy revealed presence of blood filled lacunar spaces (Fig. 3). On the basis of history, clinical examination and investigations like doppler USG, magnetic resonance angiography and histopathology, diagnosis of Stewart Bluefarb syndrome was confirmed. Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

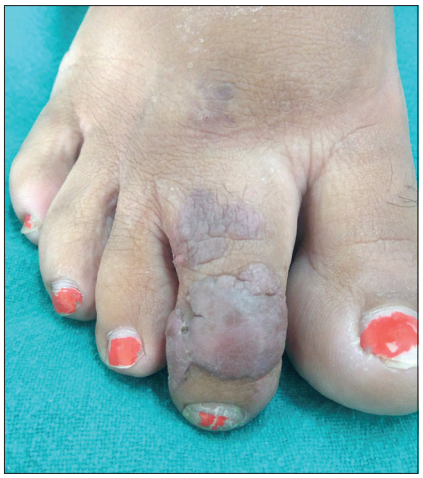

Figure 1: Violaceous plaque on dorsum of right foot second toe.

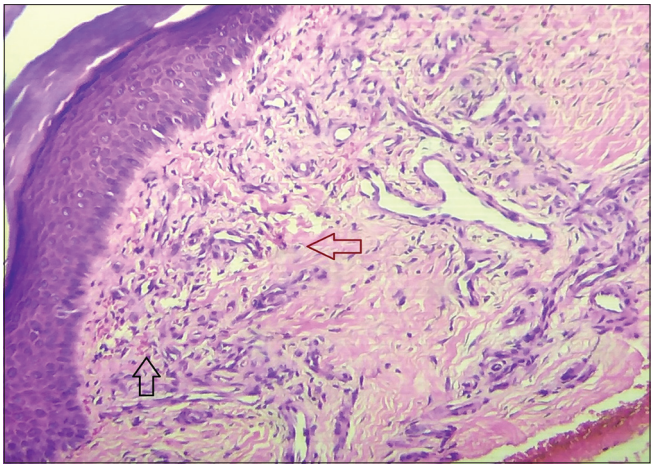

Figure 2: Histopathological picture showing proliferation of blood vessels in a cluster (red arrow) and presence of hemosiderin deposits (black arrow). (H&E, 100X).

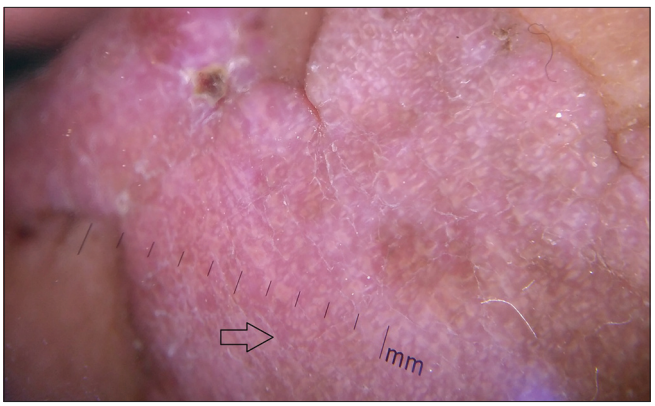

Figure 3: Dermoscopic picture showing blood filled lacunar spaces (black arrow).

DISCUSSION

Acroangiodermatitis or Pseudo-Kaposi sarcoma is an uncommon angioproliferative disease that can simulate many other conditions such as Kaposi's sacroma, hemangioma, lymphangioma, basal cell carcinoma etc. In the present case, on the basis of clinical examination, differentials taken into consideration were Kaposi's sarcoma, tufted angioma, verrucous hemangioma and eccrine syringofibroadenoma. On the basis of investigations, all other conditions were ruled out and diagnosis of Stewart Bluefarb syndrome was established. Acroangiodermatitis was first described by Kopf and Gonzale. There are 4 variants of acroangiodermatitis namely, Stewart Bluefarb syndrome (associated with arteriovenous malformations), Mali type (associated with chronic venous insufficiency), Dermite ocre of Favre (associated with first pregnancy) and in chronic renal failure over hemodialysis shunt [3]. Stewart Bluefarb syndrome was described by Bluefarb and Adam as an arteriovenous malformation with angiodermatitis [4]. Underlying arteriovenous malformation causes abnormal oxygen and carbon dioxide perfusion that leads to distal

ischemia. This ischemia is responsible for release of various endothelial proliferation growth factors causing hypertrophy and skin changes. This condition may occur at birth or during early childhood and clinically presents as soft, compressible, painful nodules or plaques, mostly located unilaterally on the dorsum of foot or ankle. It may also be associated with edema or hypertrophy of affected area. Stewart Bluefarb syndrome has been reported to be associated with other syndromes such as Klippel Trenaunay Weber syndrome [5]. Palpable thrill and audible bruit can be appreciated in some cases along with varicose veins. In the present case, hypertrophy of affected toe was observed but with absence of thrill or bruit. Magnetic resonance angiography revealing underlying arteriovenous malformation, acts as a diagnostic tool. In these cases, histopathological examination of affected skin should be done in order to differentiate it from a known malignant condition, Kaposi's sarcoma. On histopathology, in Kaposi's sarcoma, vessels with slits, Cluster of Differentiation 34 (CD34) positive spindle shaped and atypical cells proliferation is observed whereas in Stewart Bluefarb syndrome, no atypical cells and vascular slits are seen and cells are CD34 negative. In our case, CD34 immunohistochemical staining was not performed but other histopathological features such as absence of atypical cells and spindle shaped cells, absence of vascular slits, helped in establishing the diagnosis of Stewart Bluefarb syndrome. There are chances of misdiagnosis of this syndrome if relevant investigations are not performed and complications like ulceration, bleeding and secondary infections can occur. Hence, early diagnosis and management is important in such cases. Surgical correction of underlying arteriovenous malformation is the mainstay of treatment [6]. In the present case, patient was counselled regarding surgical correction of arteriovenous malformation.

CONCLUSION

Stewart Bluefarb syndrome is an uncommon variant of acroangiodermatitis which appears due to arteriovenous malformation beneath the affected area. This condition closely resembles Kaposi's sarcoma, hence histopathological differentiation is required. For early diagnosis, investigations like ultrasound doppler or magnetic resonance angiography should be performed and then, surgical correction of underlying malformation should be planned.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Frontal fibrosing alopecia and ulerythema ophryogenes as two entites that can transist one into another

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ABSTRACT

The authors report two clinical cases of progressive hair loss in frontoparietal area of the scalp accompanied by a total loss of eyebrows that occurred in mother and daughter. They are diagnosed with scarring alopecia which is a condition described in a wide group of diseases that cause diagnostic and classification problems. The symptoms that occurred in presented patients are characteristic for frontal fibrosing alopecia, a disease histologically similar to lichen planopilaris, typically appearing in women at postmenopausal age, and ulerythema ophryogenes, one of the keratosis follicular disorders that appears in early infancy and has familial occurrence. The authors hypothesize that these two diseases have much in common and are likely to evolve one into another.

Key words: Scarring alopecia; Frontal fibrosing alopecia; Ulerythema ophryogenes; Primary cicatrical alopecias

INTRODUCTION

There is a wide group of diseases that can result in scarring alopecia. Accoriding to clinical features they can be divided into 2 subgroups [1]. The first one is scarring follicular keratosis – a group of hereditary disorders with an early onset (usually occuring from early infancy). This group includes atrophoderma vermiculata (acne vermiculata, folliculitis ulerythematosa vermiculata), ulerythema ophryogenes (keratosis pilaris atrophicans faciei) and keratosis pilaris spinulosa decalvans. The second subgroup is lichen planopilaris consisting of entities histologically very closely related to lichen planus; namely frontal fibrosing alopecia, Graham-Little-Piccardi-Lassueur Syndrome and fibrosing alopecia in pattern distribution.

The diseases mentioned above have been described as clinically and histologically overlapping. All of them are characterized by inflammation and destruction of the hair follicle resulting in permanent alopecia. They are often described as one group under the name of primary cicatrical alopecias (PCA) [2]. The pathogenesis of PCA is still unknown, although there are some reliable hypotheses of immunopathological mechanisms. According to several reports, the damage of epithelial hair follicle stem, located at the bulge region of the arrector pilli muscle, seem to play an important role, as it's responsible for regenerative processes of the hair follicle and the hair cycle. The bulge region is surrounded by T-lymphocytes, Langerhans cells, macrophages and antimicrobial peptides and it is thought to be a place with immune privilege. The damage is caused by pro-inflammatory events like type-I interferon-associated cytotoxic inflammation, loss of hair follicle privilege, loss of immunosuppressive "no danger" signals. However; this concept doesn't explain other features like epidermal and sebaceous-gland atrophy, scalling, pustules, arrector pili muscle loss, which are characteristic for PCA [3].

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The cases reported below include inflammation of follicles and eyebrow loss, most characteristic clinical features occurring in both frontal fibrosing alopecia and ulerythema ophryogenes.

CASE REPORTS

Case 1

A 60-year-old woman presented with a loss of eyebrows and progressive loss of scalp hair (Figs. 1a and 1b). The onset of the disease is unknown, however both patients claimed that their eyebrows have always been "weak". Case history revealed no other complaints. The scalp examination revealed follicular hyperkeratosis and scarring alopecia over frontal area of the scalp with marked recession of the frontal hairline. The complete eyebrow loss was also observed. The patient was treated with potent topical steroids (clobetasol propionate) and prescription liquid with 10% tinctura capsici and 1% chloramphenicol. After a 3-year follow-up, in addition to former symptoms, subungual keratosis was observed. Yet again, moderate steroid (mometasone furoate) and liquid with tinctura capsici plus chloramphenicol were administered. The patient presented 4 months later; the treatment revealed good control of progressive scarring alopecia and inflammatory changes of follicles, whereas hyperkeratotic papules on the scalp were only partially treated. The treatment with tinctura capsici and chlorampfenicol was continued.

Case 2

This 36-year-old woman, the daughter of patient 1, presented with progressive loss of hair and eyebrows(Figs. 1c and 1d). She was diagnosed with Raynaud disease 2 years earlier. There are no other diseases in the patient's medical history. The physical examination disclosed keratosis pilaris on the skin of the upper cheek areas and the scalp, inflammation of the follicles, scarring alopecia over the frontal area of the scalp with marked recession of the frontal hairline, eyebrow hair loss. Topical steroids (mometasone furoate), adapalene, the prescription liquid mentioned above were prescribed.

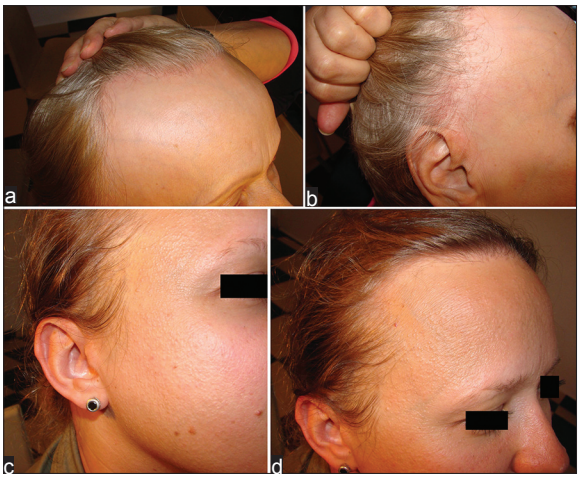

Figure 1: a and b Patient one. Please notice the loss of eyebrows and noticeable loss of scalp hair accompanied with cicatrical skin lesions. c and d Patient two. The follicular keratosis is associated with the onset of hair and eyebrows alopecia.

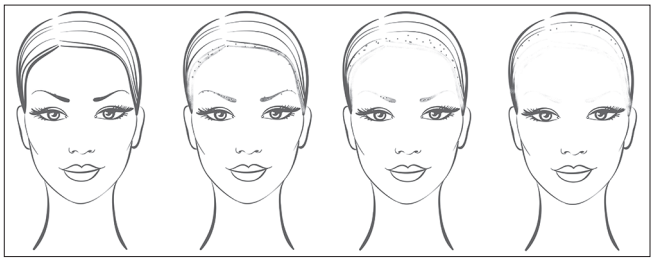

Figure 2: The hypothetical transition of UO into FFA. Areas affected by follicular keratosis marked red. Please note the disappearance of the keratosis followed by hair loss in affected areas.

DISCUSSION

Frontal fibrosing alopecia (FFA) was first described in 1994 by Kossard [4], hence its other name - the Kossard's disease. Clinically it is characterized by frontoparietal recession of the hairline, often accompanied by eyebrow loss. Histological features like perifollicular fibrosis and lymphotic inflammation around the follicles suggest a substantial resemblance to lichen planopilaris [5], although no skin lesions characteristic for lichen planus are seen on the skin in FFA. FFA was first described in postmenopausal women and a hormonal background was considered [4]; however, according to some recently published case reports, it may also occur in men and premenopausal women. No genetic role in pathogenesis of FFA has been proven [6]. Nevertheless, certain cases that could suggest it have been described [7-10]. The hair loss is irreversible as in all scarring alopecias. No treatment has been found to significantly reverse the progressive changes. The use of topical or systemic antibiotics, corticosteroids or, antimalarial agents has no significant effects. According to some authors, the 5-alfa-reductase inhibitors (finasteride, duatasterid) and intralesional triamcinolone have produced several positive outcomes [10,11]. Others have described relevant results of the application of prescription liquid

with tinctura capsici with 1% chloramfenicolum if administered alternated with superpotent steroids. Such treatment may prevent recurrence of the disease and has also been found effective in other types of cicatricial alopecia [12]. The efficacy of treatment is difficult to prove due to potential spontaneous stabilization in some patients [4].

Ulerythema ophryogenes (UO), also known as keratosis pilaris atrophicans faciei (KPAF) or folliculitis rubra, was first described in 1878. The name derives from the Greek-"ule", which means scar and "orphys", which means "eyebrow". UO is a variant of keratosis pilaris characterized by erythematous follicular papules of the eyebrows and cheeks followed by a gradual loss of hair. Some follicles are affected by inflammatory changes that lead to their destruction as well as to alopecia and plain scars of a honeycomb-like structure. The honneycomb pattern, however suggests a different cicatrical disease – atrophoderma vermiculatum [13]. According to the authors, UO typically appears in childhood and its' progression usually stops after puberty. It has been described as inherited in autosomal dominant pattern with variable penetrance although sporadic prevalence is also possible. UO is considered a rare and often misdiagnosed syndrome [14]. The frequent delay in diagnosis of the disease may be attributed to a fact that patients fail to notice it or do not consider it a problem (e.g., due to common eyebrow make up routines and depilation). In fact, it may be more common than it has been described. Treatment is similar to other variants of scarring alopecia. There is no perfect cure. The hair loss is irreversible. Steroids, antibiotics and retinoids have been administered without notable effects.

The study presents two cases of cicatricial alopecia occurring in mother and daughter that can be best described as FFA. Familiar occurrence of this disease has been described before. Nevertheless, the clinical picture of the 36 years old daughter includes follicular keratosis found in UO. Therefore authors hypothesize that these two diseases may have more in common than it was thought before.

Ulerythema ophryogenes usually appears in childhood with follicular keratosis of the eyebrows eventually leading to their irreversible alopecia. The problem is frequently ignored, especially by women who often change the shape of their eyebrows to obtain a satisfactory cosmetic effect. Many women also use the eyebrow pencil or pomade to define the shape of their eyebrows. If the clinical picture of both patients described shows the same disease, further alopecia, involving the frontal area of the scalp at this time appears two – three decades after the loss of the eyebrows. Moreover, in the area where the eyebrows were the follicular keratosis eventually disappears, but it is present on the forehead and the border of the scalp, at least until permanent alopecia. In severe cases there is no visible follicular keratosis. Authors suggest that lack of follicular keratosis in advanced UO (or FFA) can be explained by the fact that if all follicles have been destroyed by the disease process there is no longer room for follicular keratosis. Alopecic skin is atrophic and lacking skin appendices; the only area with possible visible keratosis is the border between alopecic skin and the remaining hair. The considerable time interval between eyebrow loss and scalp alopecia leads to the conclusion that ulerythema ophryogenes and frontal fibrosing alopecia are two different diagnoses, while authors suggest that these two may have some connection to each other. The hypothetical transition of UO into FFA has been proposed in figure 2.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Lipschütz ulcer: a rare diagnosis to keep in mind

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ABSTRACT

Lipschütz ulcer (LU) is a rare condition that usually affects prepubertal and pubertal girls. It can be misdiagnosed as a sexually transmitted disease or even as a sign of child abuse, causing great anxiety to patients and their families. We describe a case of 15-year-old girl who developed a painful genital ulcer that healed spontaneously within 3 weeks. The pathophysiology remains unknown. However, there is some evidence of a possible link with several non-veterinary infections, including mainly acute Epstein-Barr virus infection. Differential diagnosis should be made with other sexually transmitted diseases, Behçet's disease and Crohn's disease. This rarely benign but disabling entity should be known by dermatologist and gynecologist to avoid unreasonable treatment and reassure patients and family about sexual transmission

Key words: Genital ulcer; Lipschütz´s ulcer; Epstein–Barr virus

INTRODUCTION

Acute genital ulcer or Lipschütz ulcer is a rare and little known entity. It is characterized by the sudden onset of genital ulceration, of non-venereal origin, affecting mainly girls and adolescents before the start of their sexual activity. We report a typical case of a girl of 15 years old who has evolved well under symptomatic treatment.

CASE REPORT

Miss O. H. is a 15-year-old girl who never had sexual relationships, and said she was a virgin. She was admitted with an extremely painful and debilitating vulvar ulcer, which had appeared suddenly five days earlier, preceded by fever, chills and odynophagia. The patient had no particular medical history, particularly no recurrent oral or genital aphthaosis and was not receiving any treatment. Examination of the vulvar mucosa found significant edema of the large right lip (Fig. 1a), with a large ulceration of 3 cm. This ulceration was hollow, necrotic, fibrinous, purulent, non-indurated, and surrounded by an inflammatory halo (Fig. 1b). The examination of other organs had revealed pharyngitis as well as small bilateral infra-centimetric inguinal lymphadenopathies. Syphilis, hepatitis, EBV, HIV1 and HIV2, as well as p24 antigenemia were negative. The biopsy showed a polymorphic inflammatory infiltrate rich in neutrophils associated with macrophages, small lymphocytes and a few rare plasma cells. Analgesic treatment as well as local treatment and antibiotic therapy based on amoxicillin-clavulanic acid were administered. The evolution was quickly favorable. The lesion healed in 20 days without any sequelae (Fig. 2), making it possible to retain the diagnosis of acute Lipschütz ulcer.

DISCUSSION

Acute ulcer of the vulva is a rare entity, initially described by Lipschütz in 1913 [1]. It usually reaches young virgin girls even before the beginning of their sexual life [2] as was the case in our observation. The etiology is most often unknown, but it is most often a contemporary episode of an infection. Primary EBV infection is most often reported, but this is not systematic [3].

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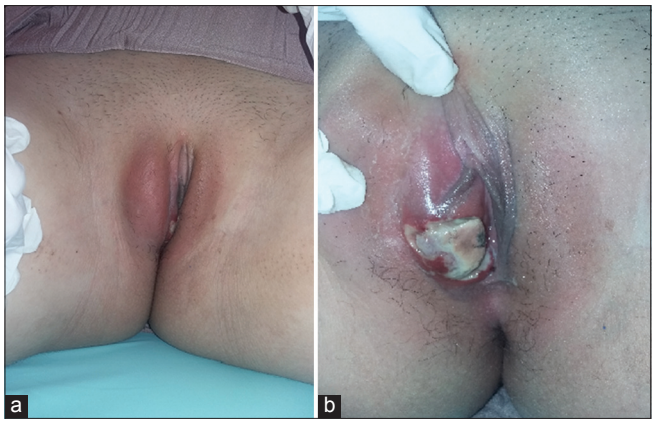

Figure 1: (a and b) Clinical aspect of genital ulcer.

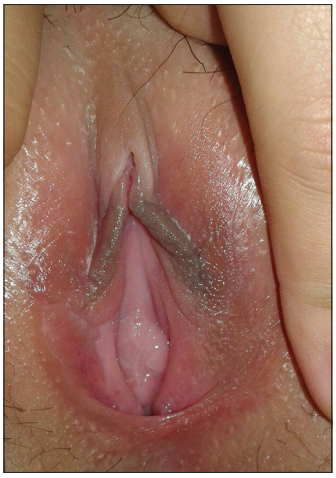

Figure 2: Total healing of the lesion.

Clinically, it takes the aspect of a deep, hyperalgic and often unique acute vulvar ulceration, usually preceded by a flu-like syndrome in 70% of cases [4] as in our patient. The histological aspect is not specific [5,6]. The diagnosis of Lipschütz ulcer remains a diagnosis of elimination often carried retrospectively, in front of a spontaneously and rapidly resolving evolution without subsequent recurrences. However, it is imperative to rule out other causes of more frequent genital ulcers, particularly a sexually transmitted disease, and to discuss the main differential diagnoses such as Behçet's disease, idiopathic aphtosis or cutaneous localization of Crohn's disease [2-6].

Therapeutic management is symptomatic and does not require systematic hospitalization. It is based on local care, analgesics or sometimes a short general corticosteroid therapy. Healing occurs within two weeks without a scar [7].

CONCLUSION

Lipschütz's vulvar ulcer is a rare and very impressive clinical entity due to the deleterious, extremely painful and disabling ulcerations. Its diagnosis should not be ignored because of its benignity and its simple therapeutic management.

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CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Primary leiomyosarcoma of the psoas in a patient with Neurofibromatosis type 1

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ABSTRACT

Neurofibromatosis Type 1 (NF1) is an autosomal dominant disorder that reduces the effectiveness of the neurofibromin tumor suppressor, resulting in an increased risk for benign and malignant soft tissue tumors. Leiomyosarcoma has been infrequently observed in NF1 patients. This case adds to the limited number of leiomyosarcomas reported in NF1 patients. This particular malignancy presented in a highly unusual location. A 15-year-old male with a previous diagnosis of NF1 presented a 3-month history of right-sided lumbago. Pelvic MRI revealed a large parenchymatous mass (69x66x115mm) in contact with the right psoas muscle. A biopsy guided by the scanner was performed. Histological examination with diffuse positivity of tumor cells for immunohistochemical muscle markers revealed high-grade leiomyosarcoma. A neoadjuvant chemotherapy was started based on Fluorouracil. The evolution was marked by the death of the patient 04 months later. To our knowledge, this is the first report of an NF1 patient who developed a primary leiomyosarcoma of the psoas. These rare tumors should be further evaluated. A careful follow-up of these patients is essential.

Key words: Neurofibromatosis type 1; Leiomyosarcoma; Psoas

INTRODUCTION

Neurofibromatosis Type 1 (NF1) is an autosomal dominant disorder that reduces the effectiveness of the neurofibromin tumor suppressor [1]. Mutations result in a predisposition to developing a variety of tumors of the central and peripheral nervous systems, as well as other malignancies. However, the occurrence of malignant tumors unrelated to the nervous system is rare [2]. Patients with NF1 can develop leiomyosarcoma less frequently than other malignancies. We report an NF1 patient who developed a leiomyosarcoma of the psoas. To our knowledge, this is the first report of an NF1 patient who developed a primary leiomyosarcoma of the psoas.

CASE REPORT

A 15-year-old male with a previous diagnosis of NF1 presented a 3-month history of right-sided lumbago. He had no history of recent trauma. On exam, the skin overlying the affected digit was intact; the palpation of the right flank was very painful. Routine blood tests and tumor markers in the blood were normal. Initial pelvic tomography revealed a soft tissue mass measuring 62x62x105 mm (Fig. 1). Pelvic MRI revealed a large parenchymatous mass (69x66x115mm) in contact with the right psoas muscle, showing inhomogeneous structure and containing necrotic areas (Fig. 2). A biopsy guided by the scanner was performed. Histological examination with diffuse positivity of tumor cells for immunohistochemical muscle markers (H-Caldesmon) revealed high-grade leiomyosarcoma (Fig. 3). The decision to omit the resection was made by the operating physician due to the specific location and the size of the lesion. A neoadjuvant chemotherapy was started based on Fluorouracil. The MRI monitoring showed an extension of the lesion despite 4 sessions of chemotherapy with a serious deterioration of the general condition of the patient. The evolution was

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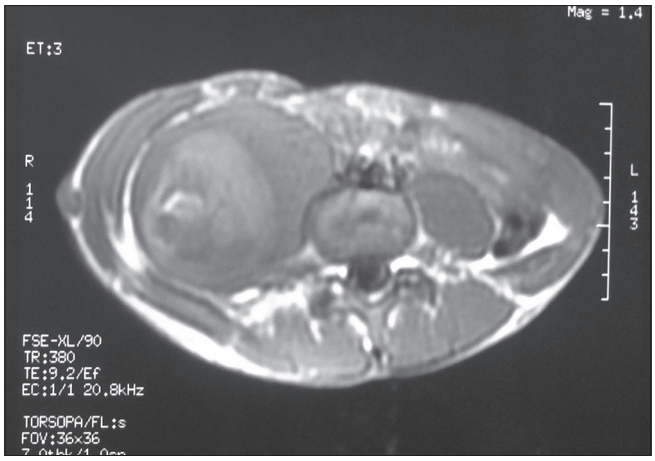

Figure 1: Pelvic tomography revealing a soft tissue mass (62x62x105 mm).

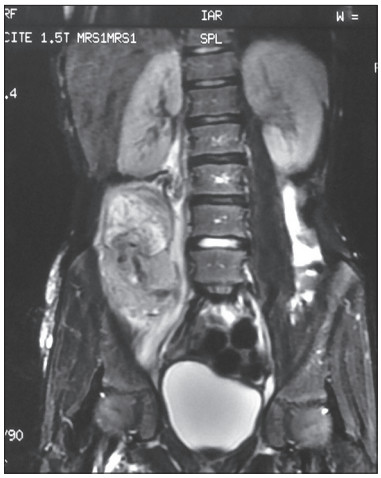

Figure 2: Pelvic MRI revealing a large parenchymatous mass (69x66x115mm).

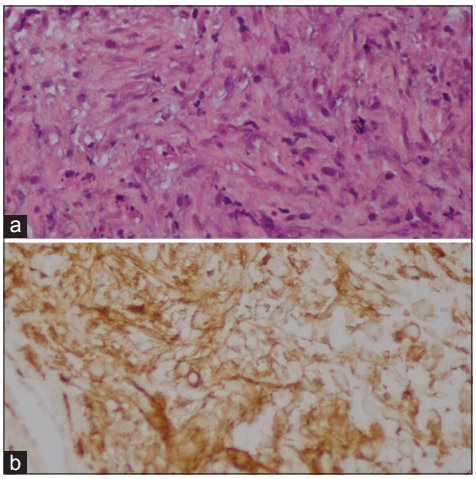

Figure 3: Histopathology. (a) spindle cell proliferation forming rough bundles and fascicles, spindle cells with cigar shaped nuclei, cytologic atypia and mitotic figures. (b) positivity of tumor cells for immunohistochemical muscle markers (H-Caldesmon).

marked by the death of the patient 04 months later. Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Patients with NF1 are predisposed to the development of benign and malignant neoplasms, particularly those of neurogenic or neuroendocrine origin [2]. Zöller et al. reported a fourfold increase in the risk of developing a malignancy in patients with NF1 (24%); when compared to the general population [3].

Soft-tissue sarcomas represent about 8% of all malignant tumours of children and adolescents with NF1 [4]. Leiomyosarcomas arise from smooth muscle and represent 10-20% of all diagnosed sarcomas [5]. Leiomyosarcoma is uncommon in NF1. Zöller found two cases of leiomyosarcoma among 70 patients with NF1 [3]. The different localizations of leiomyosarcomas reported in NF1 patients are [6]: the sciatic nerve, the liver, the bladder, the pelvis, intracranial and the hand [7]. Low-grade malignant peripheral nerve sheath tumor with smooth muscle differentiation has also been reported in the literature [6]. The Leiomyosarcoma of the psoas in NF1 has never been reported. This different localizations illustrates the need to be aware of potential leiomyosarcoma in NF1.

Leiomyosarcomas are often unresponsive to chemotherapy and radiation; thus, wide margin surgical removal has proven to be the most accepted treatment method [8]. New approaches to the treatment of these rare malignancies and the genetic interaction of the NF1 gene should be taken into consideration. A careful follow-up of these patients is essential.

CONCLUSION

This study adds to the limited number of cases of leiomyosarcomas that have been reported in NF1 patients. As NF1 patients may die at a young age after the onset of an associated malignancy, it is important to examine routinely these patients in order to have an early diagnosis and treatment for a better outcome.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Multiple and giant perforating pilomatrixoma: a case report

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ABSTRACT

Pilomatrixoma is benign skin tumor that originates from the pilosebaceous follicle. In most cases it presents as a solitary asymptomatic and a firm subcutaneous nodule on the head, neck or upper extremities. Herein, we report a case of 27-year-old patient who presented with a history of multiple tumors of the upper back, the left arm, the forearms, the proximal third of the right thigh and the scalp. The biopsy showed a benign tumoral proliferation on the dermis and hypodermis with a transepidermal elimination of shadow cells islands on the perforated lesion. Pilomatrixoma is an adnexal skin tumor which may be difficult to diagnose due to different clinical and cytological findings. This diagnosis must be evoked in every patient presenting with a firm subcutaneous tumor of the head, neck or upper extremities. The histological examination confirms the diagnosis and the treatment is surgical excision.

Key words: Pilomatrixoma; Multiple; Perforating

INTRODUCTION

Pilomatrixoma, also termed pilomatricoma, trichomatricoma or calcifying epithelioma of Malherbe, is a benign skin tumor that originates from the matrix of the hair root. It's a relatively rare condition [1] which is frequently misdiagnosed clinically and the correct diagnosis is only histological [1,2]. This tumor presents as a solitary asymptomatic, firm, and skin-colored faint blue/red nodule in the deep dermis and subcutaneous tissue, with an average size of 0.5 to 3.0 cm [3]. However, giant pilomatrixomas (more than 5 cm) have been reported in a few cases [4]. Pilomatrixoma is most commonly seen on the head and neck region followed by the upper extremities [5]. Although it can be seen in all ages and sexes; it is most often encountered in first two decades of life and females [1,4-9].

CASE REPORT

A 27-year-old white man, presented with a history of multiple tumors of the upper back, the left arm, the forearms, the proximal third of the right thigh and the scalp. He reported first noticing of these masses on the left arm, approximately one year earlier, since then, this lesion had rapidly increased in size and other lesions had progressively appeared.

He denied any history of trauma, and reported some discomfort in the left arm secondary to the size of the lesion in this area. His past medical history was unremarkable. Physical examination revealed a dome-shaped, polypoïd, stony and movable tumor measuring 10 × 8 × 3 cm, on the distal third of the left arm with a blue-red overlying skin showing telangiectatic vessels and stretch marks (Fig. 1). Besides, examination showed four painless and freely-movable, firm subcutaneous nodules ranging from 0,5 to 2 cm in diameter on the right upper back, the posterior forearms and the occipital region of the scalp. The overlying skin was normal. We also found a well-demarcated large area of thick, keloid, blue-red skin, measuring 7cm in largest diameter and presenting a firm ulcerated, crumbly and spontaneously bleeding tumor on the

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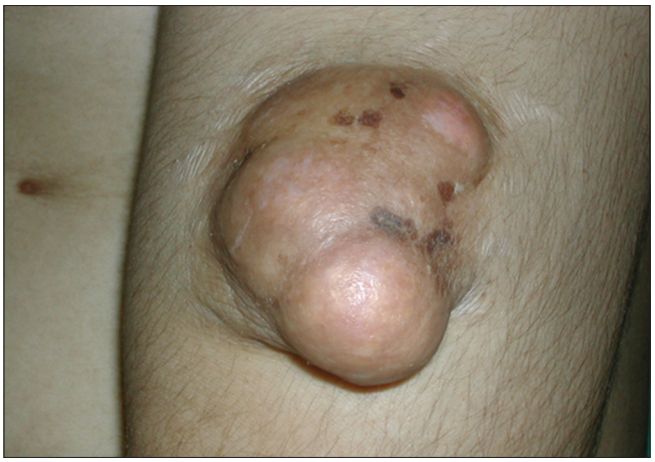

Fig ure 1: Dome-shaped, polypoïd, stony and movable tumor measuring 10 × 8 × 3 cm, on the distal third of the left arm.

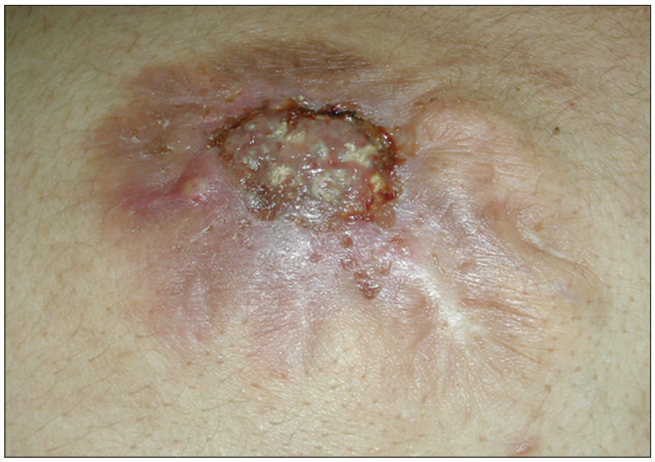

Figure 2: Ulcerated, crumbly and spontaneously bleeding tumor on the upper back.

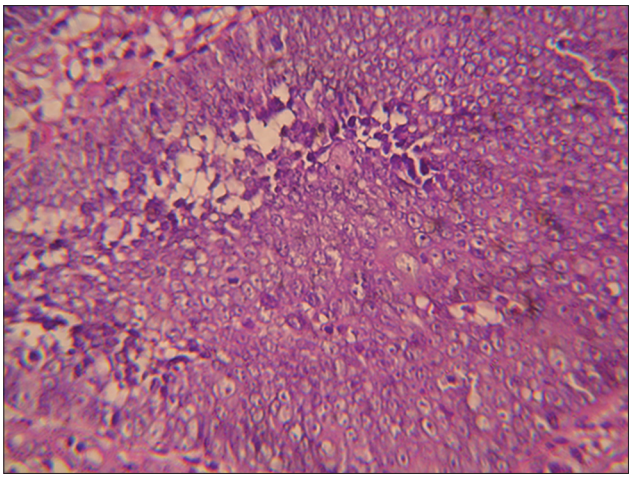

Figure 3: Scattered foci and islands of basophilic and shadow cells in the dermis and hypodermis.

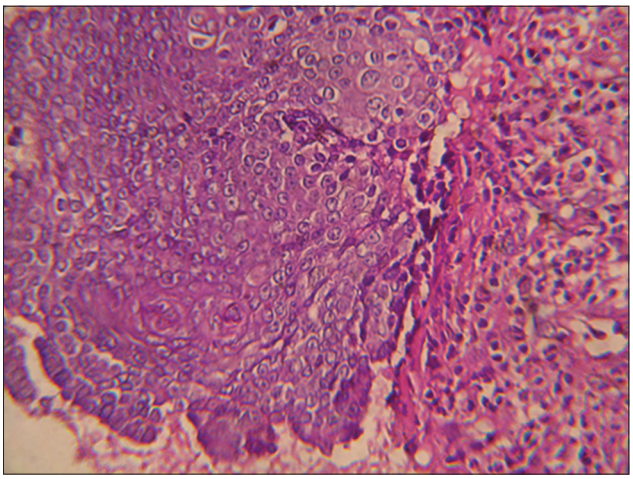

Figure 4: Trans epidermal elimination of shadow cells islands.

upper back (Fig. 2). Histopathologic examination found a benign tumoral proliferation in the dermis and hypodermis which was composed of scattered foci and islands of basophilic and shadow cells in an inflammatory stroma with a granulomatous reaction with foreign body giant cells (Fig. 3). The perforated lesion shows a trans epidermal elimination of shadow cells islands (Fig. 4). Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Pilomatrixoma is a relatively rare benign skin tumor. In fact, it has been reported to be the most common cutaneous adnexal tumor in patients younger than 20 years [8]. Up to 40% of pilomatrixomas arise before the age of 10 years and more than 60% of cases in the first two decades [6,8,9]. Most studies report a slight preponderance in females [1,4,7] and it seems that this tumor occurs usually in Caucasians when compared with Asians and African-Americans [4,8].

The head and the neck followed by upper extremities are the most frequent localizations of pilomatrixoma with up to 40 % of cases occurring on the head [6,8,10] perhaps due to the higher hair follicle density in the scalp.

Clinically, pilomatrixomas present as solitary, firm to hard, painless, dermal or subcutaneous nodules ranging from 0,5 to 3 cm; although pilomatrixomas over 10 cm in diameter have rarely been reported in literature [1,4,10]. Multiple or recurring pilomatrixomas are rarely seen and can be associated with myotonic dystrophy, Gardner syndrome, Turner syndrome, trisomy 9, spina bifida or sarcoidosis [6]. The overlying skin may be normal or have a reddish or bluish hue in 24% of cases [1,3,8].

The diagnosis may be reached by physical examination, imaging and cytology; however, there is a large number of misdiagnosis [1,3,6]. The differential diagnosis includes dermoid cysts, branchial cleft remnants, pre-auricular sinuses, sebaceous cysts, hemangiomas or malignant soft tissue tumors [1,3]. Pilomatrixoma do not regress or disappear spontaneously and transdermal elimination has rarely been reported as perforating or ulcerating pilomatricoma and this was noted in our patient [4].

The present case report is consistent with the published literature in terms of incorrect provisional diagnosis, and it's original in terms of the age of first appearance of the disease, the number of lesions, their various appearance, some atypical localizations [2,3] and the perforating histological feature.

CONCLUSION

Pilomatricoma is an adnexal skin tumor which may occur at any age especially in the two first decades. This diagnosis must be evoked in every patient presenting with a firm subcutaneous tumor of the head, neck or upper extremities. The histological data confirm the diagnosis and the treatment is surgical.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Pseudokaposi's sarcoma: a diagnostic dilemma

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ABSTRACT

Acroangiodermatitis of mali also called as pseudokaposi s sarcoma is a very rare, benign condition which clinically presents as purple-colored patches, plaques or nodules, mostly on the extensor surfaces of lower extremities in patients with chronic venous insufficiency and arteriovenous malformations. It resembles clinically with conditions like Kaposi's sarcoma and hence requires histopathological examination for its diagnosis. We report one such case of acroangiodermatitis. 45 year old male presented with multiple violaceus colored plaque with ulceration on the left extensor aspect of the leg, with associated venous insufficiency of same limb. On histopathology it showed proliferating small vessels associated with clusters of spindle cells showing numerous extravasated red blood corpuscles (RBCs), scattered plump to ovalendothelial cells with dark nuclei in the centre. Patient was treated with oral erythromycin and lesions improved in 3 weeks.

Key words: Venous insufficiency; Pseudokaposi s sarcoma; Immunohistochemistry; Klippel-Trenaunay syndrome

INTRODUCTION

Acroangiodermatitis is a reactive angiodysplasia of cutaneous blood vessels associated with venous insufficiency or with vascular anomalies such as Klippel-Trenaunay syndrome or stump dermatosis in amputees. Exaggerated stasis dermatitis begins as violaceous macules and patches that gradually develop into papule, nodules, or indurated plaques often bilateral, and usually located on the lower extremities with edema. Rarely it can present with ulceration also. Although benign, it may mimic malignant conditions like Kaposi's sarcoma and therefore requires histopathological examination for its diagnosis and differentiation.

Here, we report one such case presenting with nodulo-ulcerative lesions, with histological features of acroangiodermatitis, emphasizing the importance of histopathology and immunohistochemistry in differentiating this from similarly presenting condition.

CASE REPORT

A 45 year old male presented with multiple ulcerated lesions over the left leg with associated discharge since 6 months. It started spontaneously, gradually spreading to involve other areas of left leg. No history of trauma, asoociated pain. The discharge was minimal, non foul smelling. No history of any grain like discharge. Patient is a known case of alcoholic liver disease. No other systemic illness or major surgery in the past.

On examination

1. Single deep ulcer measuring about 1*1 cm, well defined margins, sloping edges, base formed by granulation tissue, non tender with minimal purulent discharge present over the medial aspect of left leg.
2. Single subcutaneous mass measuring about 5*3 cm over the medial malleolus with overlying small ulcer covered with healthy granulation tissue (Fig. 1).
3. Multiple hyperpigmented plaque of varying size with few showing surrounding violaceous hue over the extensor aspect of left leg.

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4. Non pitting odema of the left leg till the mid calf was present. Superficial varicosites were visible. Right leg was normal.

Based on this a differential diagnosis of mycetoma, Kaposi s sarcoma, pseudokaposi's sarcoma, bartenlosis was considered.

On investigating, all routine haematological and biochemical investigations were normal, ELISA for HIV was negative. KOH was negative, gram stain showed few pus cells, gram positive cocci in singles and pairs, occasional gram negative bacilli were present. AFB was negative.

.On histopathological examination epidermis showed psoriasiform acanthosis, papillomatosis, increased vascular proloiferation with cluster of spindle cells showing numerous extravasated RBCs (Fig. 2). Immunohistochemistry was positive for CD 31 and factor VII, confined to vessels and endothelium.

Venous doppler of left limb showed incompetent sapheno femoral junction.

Final diagnosis of pseudokaposi s sarcoma was made.

Patient was treated with oral erythromycin 500 mg QID and compression stockings was advised (Fig. 3).

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Acroangiodermatitis (Synonyms: pseudo-Kaposi's sarcoma, acroangiodermatitis of Mali-Kuiper, gravitational purpura, stasis purpura) was first coined by Mali in 1965 [1]. It is a proliferation of pre-existing vasculature seen in chronic venous insufficiency, arteriovenous malformation, or acquired iatrogenic arteriovenous (AV) fistula. A variety of vascular conditions giving rise to this venous pathology include Klippel-Trenaunay syndrome, stump dermatosis in amputees, paralyzed limb, and intravenous drug abuse. It is rarely reported in hereditary coagulation defects (carrier of the thrombophilic 20210A mutation in the prothrombin gene and homozygous activated protein C resistance) [2,3]. Most of the cases of acroangiodermatitis have been associated with some signs of venous insufficiency however Barbar et al. reported no venous insufficiency in 9 of their 10 case of acroangiodermatitis [4] and few cases of spontaneous presentation have also been reported [5].

There are various variants of acroangiodermatitis:

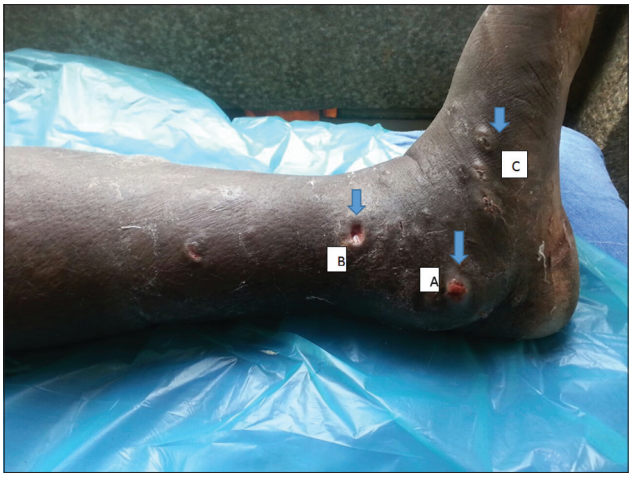

Figure 1: Single subcutaneous mass over the medial malleolus with overlying small ulcer covered with healthy granulation tissue (A), single deep ulcer with minimal purulent discharge present over the medial aspect of left leg (B) and multiple hyperpigmented plaques (C).

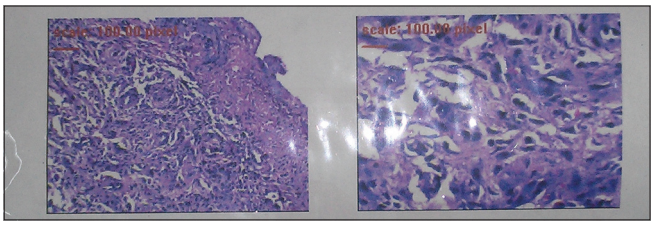

Figure 2: Histopathology showing psoriasiform acanthosis, papillomatosis, increased vascular proloiferation with cluster of spindle cells showing numerous extravasated RBCs.

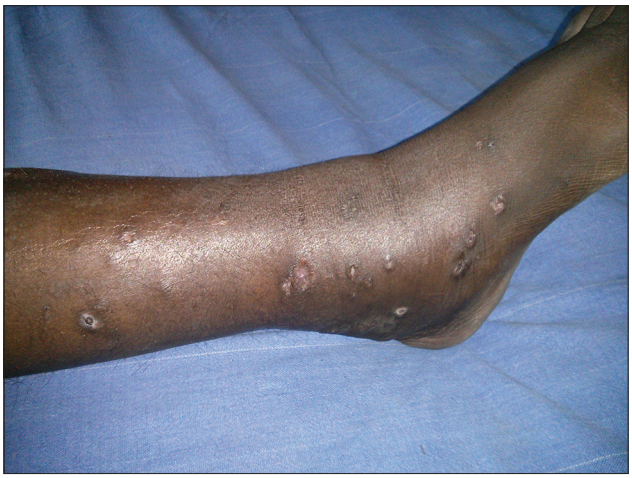

Figure 3: Lesions improved after treatment with oral doxycycline and compression stockings.

- Stewart-Bluefarb syndrome is a congenital arteriovenous malformation of the lower leg with multiple arteriovenous shunts. It begins early in life unilaterally over lower extremities with painful purple papules and macules, which may ulcerate. The affected limb may show increased warmth with varicose veins and a palpable thrill can be felt [1].
- Mali type is an exaggerated stasis dermatitis seen in elderly patients, usually bilateral with chronic venous insufficiency on dorsum of feet, hallux, and second toe or on medial aspect of lower legs. The lesions begin as violaceous macules and patches that develop slowly into soft, non tender, red to purple papules and nodules or indurated plaques [1].
- Dermite ocre of Favre (gravity purpura): Venous varicosities with first pregnancy [6].
- Angiodermatitis occurring after placement of the arteriovenous shunt for hemodialysis in chronic renal failure [5].
- Although precise etiology is unknown, it is postulated that severe chronic venous stasis with insufficiency of the calf muscle pump elevates the capillary pressure and leads to chronic tissue hypoxia from chronic edema which induces neovascularisation and fibroblast proliferation.
- Chronic pressure changes with the vessel proliferation in the upper and mid-dermis andextravasation of red blood cells produce a combination of purplish papules and plaques on the edematous skin [7].
- Severe chronic venous stasis with insufficiency of the calf muscle pump elevates the capillary pressure and leads to chronic tissue hypoxia from chronic edema. and this in turn to neovascularisation and fibroblast proliferation.
- Clinically it presents clinically as multiple papules, nodules and plaques, sharply defined reddish-brown, sometimes in bizarre configurations, generally localized on the dorsal aspect of the foot and the lower aspect of the shin, usually associated with edema.
- Histopathological examination shows proliferation of endothelial cells, newly- formed vessels with thick walls, often in a lobular pattern and surrounded by pericytes in the dermis.
- Extravasation of red blood cells, hemosiderin pigment deposition, superficial perivascular infiltrate of lymphocytes, histiocytes and occasional plasma cells are also found and may resemble Kaposi's sarcoma.
- Immunohistochemical staining with Cluster of differentiation (CD34) antiserum helps to distinguish between acroangiodermatitis and Kaposi's sarcoma, because in the former, an absence of perivascular CD34 is noted, unlike in the latter (CD34 staining on the endothelial cells as well as the perivascular spindle cells)
- Various medical modalities of therapy have been tried with favorable results, but options are limited.
- Oral erythromycin 500 mg four times a day or dapsone 50 mg twice a day for 3 months in combination with compression therapy has been tried with good results [3].
- Topical therapy with local corticosteroid preparations is often useful [6].

CONCLUSION

This case report is to emphasize the importance of histopathology and immunohistochemistry to differentiate this benign condition from other similar presentation of malignant conditions.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Epithelioma cuniculatum arising on a preexisting wart

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ABSTRACT

Epithelioma cuniculatum is a rare, well-differentiated variant of verrucous carcinoma, arising almost exclusively on foot, with a minimal incidence of metastasis. Clinically, it presents as a non-verrucous, slow growing, exophytic plaque or tumor of the plantar region with a penetration in the deep tissues. Histological examination shows a proliferation of well-differentiated keratinocytes. Conservative treatment and local excision have been utilized, but high recurrence rates have been observed. We report a case of epithelioma cuniculatum arising on the plantar aspect of foot in a 60-year old male, which arose at the site of a preexisting wart, which was managed by surgical excision.

Key words: Epithelioma cuniculatum; Squamous cell carcinoma; Verrucous carcinoma; Carcinoma; Human papilloma virus

INTRODUCTION

Epithelioma cuniculatum refers to verrucous carcinoma found almost exclusively in the foot. It is a rare, well-differentiated variant of squamous cell carcinoma. Its clinical presentations are variable, but usually it presents as a slow growing, exophytic, low-grade and with minimal dysplasia. The tumor rarely metastasizes but it is capable of a slow and progressive invasion of the deeper tissues, i.e. subcutaneous fat and bone [1]. Most commonly, it is unilateral but bilateral cases have also been reported [2]. Herein, we report a case of epithelioma cuniculatum arising on the plantar aspect of foot in a 60-year old male, which arose at the site of a preexisting wart.

CASE REPORT

A 60-year old male presented to us with the chief complaints of a gradually progressive, large exophytic growth with seropurulent discharge on the plantar aspect of the right foot for the last five years. The patient gave a history of a plantar wart at the same site for the last eight years for which he had undergone radiofrequency ablation twice. Presently, the lesion was gradually increasing in size and was associated with pain and blood stained discharge for the last one year. There was no history of prolonged fever, loss of appetite, weight loss, chronic cough, family or personal history of tuberculosis. Cutaneous examination revealed a single verrucous lesion measuring 3 × 3 cm on the plantar aspect of right foot associated with a blood stained discharge (Fig. 1). There was no associated lymphadenopathy and the systemic examination was also normal. Routine hematological, biochemical and serological investigations were within normal limits. X-ray examination of the right foot revealed soft tissue swelling. Mantoux's test was negative and chest X-ray was also normal.

The differential diagnoses of tuberculosis verrucosa cutis, epithelioma cuniculatum and giant plantar wart were considered and a marginal incisonal biopsy was performed. Histopathology of the lesion revealed hyperkeratosis, papillomatosis, parakeratosis and elongated rete ridges with keratinocyte hyperplasia. There was formation of multiple large keratin-filled cysts and crypts with burrow like invaginations. The keratinocytes appeared well differentiated without any signs of atypia or loss of polarity. The histological features confirmed the diagnosis of epithelioma cuniculatum and the patient was advised a wide surgical

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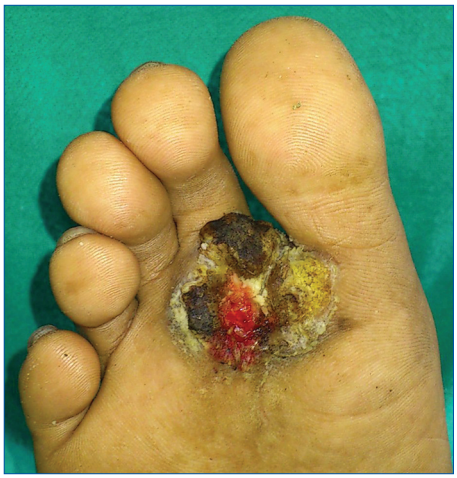

Figure 1: Large exophytic growth on the plantar aspect of the foot.

excision. Regular post-surgery follow up was done for six months and the patient remained well with no tumor recurrence.

DISCUSSION

Epithelioma cuniculatum, first described in 1954 by Professor Ian Aird, refers to verrucous carcinoma found almost exclusively in the foot. It is rare tumor with only about 100 cases reported so far. It occurs in older patients, usually during the 5th-6th decade, and with a higher prevalence in men as compared to women [2]. Etiolgically, chronic and repeated plantar trauma, slowly repairing bone fracture or osteomyelitis, local infiltration of corticosteroids, chronic decubitus ulcer and chronic inflammatory diseases have been hypothesized to play a role in its development [2,4]. Chronic infection by human papillomavirus 1-4, 6, 11 and 18 has also been hypothesized to play a role in pathogenesis due to their weak oncogenic potential.

The gross clinical appearance of epithelioma cuniculatum is characteristic and distinctive, presenting as a warty, keratotic tumor with crypts and sinuses that drain a malodorous exudate. The lesion is almost always single and bilateral lesions have been described only in a few patients. The anterior weight bearing area of the foot is more commonly involved than the heel or the arch [3]. The diagnosis is usually made at a later stage as the lesion is very often misdiagnosed at first as a wart or corn, which grows progressively despite topical treatments. The tumor rarely metastasizes but the delay in diagnosis allows the invasion to the underlying bones [1,2,4].

Histopathology of the tumor is characterized by a well-differentiated squamous cell carcinoma with low-grade cytological atypia and burrowing sinus tracts, often filled with keratinous debris, descending to the subcutaneous fat and sometimes infiltrating the bone [4].

Patients with verrucous carcinoma usually have a favorable prognosis with 5-year survival rates of 75%. Wide local excision with at least a 5-mm tumor-free margin remains the treatment of choice. Other modalities like electrodessication, cryotherapy, and laser ablation, are not advisable as they often result in tumor recurrence. Amputation is necessary when the tumor is too extensive or recurs after multiple attempts of local excision [1,2].

In conclusion, epithelioma cuniculatum is a rare tumor with low intrinsic metastatic potential. However, it is often misdiagnosed which may lead to invasion of the underlying bone which requires amputation, thus leading to substantial morbidity. Therefore dermatologists should be aware of the condition and should have a better knowledge of this uncommon carcinoma.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

A novel dermoscopic feature in traumatic onycholysis

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ABSTRACT

Dermoscopy has certainly had a profound impact on the clinical diagnosis and management of both pigmented and nonpigmented skin lesions. Over the years, there has been much emphasis on the use of dermoscopy for the diagnosis of onychopathies. Traumatic onycholysis has been considered as one of the most common onychopathies. Although history and clinical examination remain the most crucial steps, dermoscopy apppears to be a rapid and effective tool in establishing the diagnosis of traumatic onycholysis. Here, we present two cases of traumatic onycholysis with classical and novel dermoscopic findings.

Keywords: Trauma; Onycholysis; Dermoscopy

INTRODUCTION

The nail plays an essential role in appearance. Moreover, the nail provides a barrier and protects the distal phalanx [1,2]. Traumatic nail diseases are a common group of nail disorders. Among them traumatic onycholysis is one of the mostly encountered one, which has been defined as the traumatic separation of the nail plate from the nail bed due to disruption of the onychodermal band [1,3,4]. Although history and clinical examination remain fundamental steps, dermoscopy has offered a new approach in the diagnosis of traumatic onycholysis [5-7]. Here, we present two cases of traumatic onycholysis with classical and novel dermoscopic features.

Case 1

A 19-year-old woman came to our outpatient clinic with a six months' history of thickened toenails. She had a history of working as a saleswoman and wearing pointed toed high heeled shoes for long periods of time. Dermatological examination of the patient revealed subungual hemorrhage, subungual hyperkeratosis and onycholysis in the right second toenail and bilateral great toe nails. Beau's lines also observed in the left great toe nail. Nail plate dermoscopy showed homogenenous pigmentation with peripheral fading and satellite globules, linear edged onycolytic areas and horizontal grooves (Figs. 1 and 2). Moreover, distal free edge dermoscopy of the left great toe nail revealed red and black filamentous structures in the subungual area (Fig. 3).

Case 2

A 59-year-old woman came to our outpatient clinic with a two months' history of separation of the right great toenail plate from the nail bed. She had a history of regular long distance walking for physical activity. Dermatological examination revealed distal onycholysis in the right great toenail. Nail plate dermoscopy demonstrated distal onycholysis with a linear proximal border. In addition, distal free edge dermoscopy of the right great toenail revealed reddish-black globules, black dots, red and black filamentous structures (Figs. 4- 6). Based on history, clinical and dermoscopic findings we made the diagnosis of traumatic onycholysis in both of our patients. Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Onycholysis is a common problem encountered by dermatologist. Greatest majority of cases are caused by

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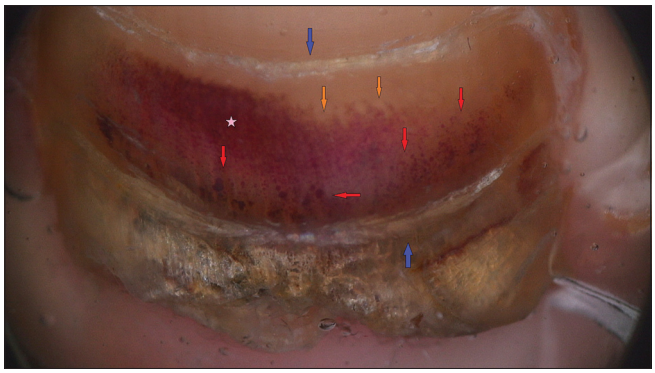

Figure 1: Nail plate dermoscopy showing reddish-purple homogeneous pigmentation (pink star) with peripheral fading (orange arrows) and satellite globules (red arrows), note linear edged distal onycholysis and horizontal grooves, which correspond to Beau's lines (blue arrows) (x20).

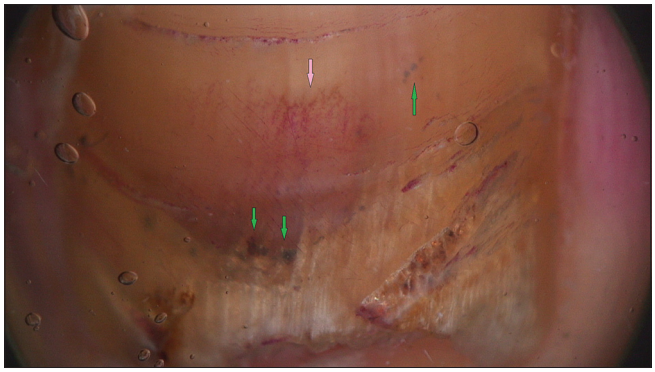

Figure 2: Dermoscopy demonstrating destruction of the nail plate and distal onycholysis. Note black globules (green arrows) and brownish red dots (pink arrow) corresponding to subungual hemorrhage (x20).

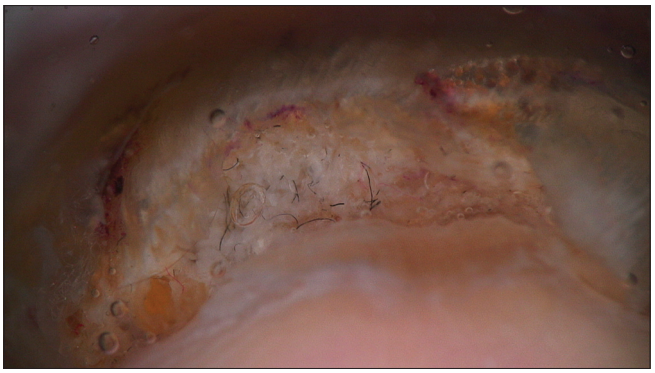

Figure 3: Dermosocpy of the distal free edge revealing subungual hyperkeratosis and red and black filamentaous structures in the hyperkeratotic area (x30).

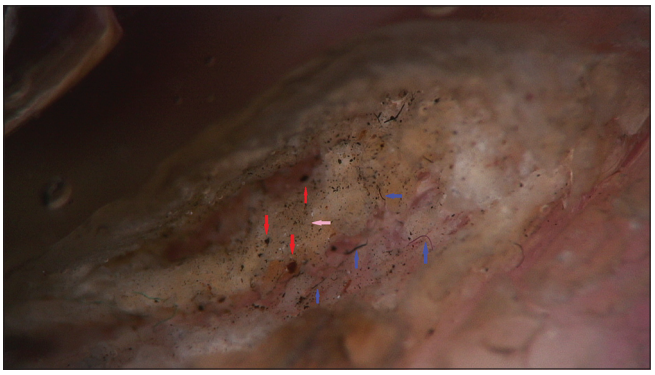

Figure 4: Distal free edge dermoscopy of the right great toenail showing subungual hyperkeratosis, reddish-black globules (red arrows), black dots (pink arrow), red and black filamentous structures (blue arrows) (x40).

physical trauma. Generally patients are asymptomatic until they notice the whitish appearance of the transparent onycholytic nail plate [4]. "Roller coaster nails" has been defined as the typical presentation of onycholysis. This appearance describes linear edged onycholytic nail plate with an oscillating pattern [1]. Dermoscopy has been shown to be a reliable tool in differentiating traumatic onycholysis from other causes of onycholysis, which mainly include psoriasis and onychomycosis. In traumatic onycholysis the line of detachment of the plate from the bed is linear, regular and smooth and is surrounded by a normally pale pink bed. Whereas, in onychomycosis the line of detachment has a jagged appearance with sharp indentations, which are called as spikes. In psoriasis, the edge of the detachment is surrounded by an erythematous border [6,7].

In traumatic lesions not only onycholysis, but also other signs of trauma are detected. Generally, dermoscopy also reveals hemorrhagic spots and streaks, which are the main clues of subungual hemorrhage [6-8]. Onycholysis and subungual hemorrhage were the main findings in our patients. Therefore, the major dermoscopic features were linear edged onycolytic areas and homogenenous pigmentation with peripheral fading and satellite globules. On the other hand, we noticed a peculiar feature in both of our patients. Distal free edge dermoscopy of traumatic nails of the patients revealed red and black filamentous structures. In one of our patients we also observed reddish-black globules and black dots.

The nail unit has a complex and abundant vascular network. It has been shown that the superficial capillary network of this complex microvasculature varies according to specialized areas of the nail unit. The hyponychium, the most distal region of the nail bed, is a specialized area, which seals the subungual space and allows the nail plate to physiologically detach from the nail bed. The subungual region of the nail unit is supplied by distal and proximal subungual arcades. The nail bed has numerous capillary loops arising from a deeper regular arrangement of sagittally aligned, parallel rows of vessels. The size of the capillary loops becomes longer and gets more inclined distally, with the longest capillary loops seen at the hyponychium [2,9,10].

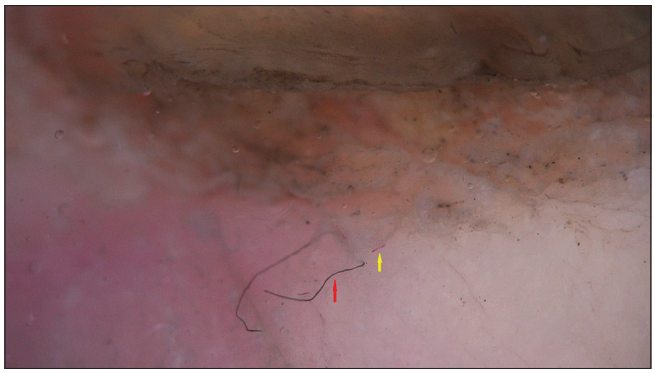

Figure 5: Dermoscopy of the hyponychium demonstrating juxtaposing black (red arrow) and red (yellow arrow) filamentous structures, note that the central region of the black filamentous structure is underneath the surface (x40).

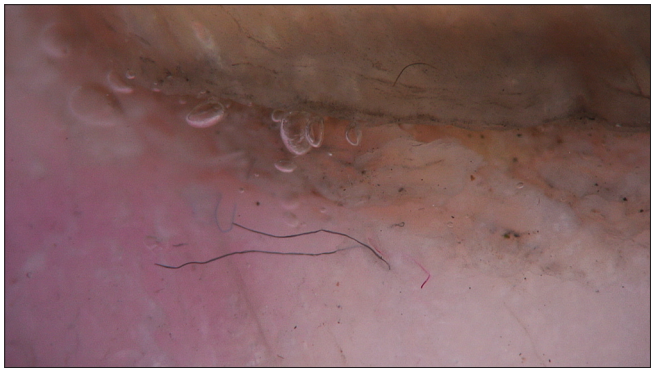

Figure 6: Altered orientation of the black filamentaous structure with changing the camera probe position, note juxtaposing red filamentaous structure (x60).

In our opinion, red and black filamentous structures, that we detected on dermoscopy, correspond to subungual capillary remnants of this complex microvasculature. In a recent study, it has been demonstrated that identical dermoscopic features are found in nail bed psoriasis [11]. Nail psoriasis is characterized by increased hyponychial capillary density. Dilated, tortuous hyponychial capillaries are found in psoriatic patients [11,12]. Traumatic onycholysis is another nail disorder, in which damaged capillaries are exposed in the hyponychial area. Moreover, as it is seen in Figure 4, we have detected dots and globules. We suggest that these dots and globules represent the tops of the capillary loops, which are perpendicular to the surface, reclining vertical to the plane of the nail bed.

Here, we present two patients with traumatic onycholysis. Other than classical features, we have described a novel dermoscopic finding. Dermoscopy has opened new perspectives in the diagnosis of countless number of dermatological diseases. There is a growing body of literature on the use of dermoscopy as a diagnostic tool in everyday practice. On the other hand, further studies are needed to better characterize unusual dermoscopic findings.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Hereditary benign intraepithelial dyskeratosis: Is this the first African case?

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ABSTRACT

Inherited benign intraepithelial dyskeratosis (IBID) is a rare genodermatosis, affecting both the oral and conjunctival mucosa. We report a new case of a 10-year-old girl with clinico-histological manifestations of IBID and melkersson rosenthal syndrome. IBID manifests itself by whitish, painless, spongy papules or plaques of varying sizes sitting mainly at the side edges of the tongue. The Melkerson Rosenthal syndrome is a rare disease, to be evoked in the framework of pathologies of the big lips. The association of these two pathologies is unusual.

Key words: Inherited Benign Intraepithelial Dyskeratosis; Genodermatosis; Melkerson Rosenthal Syndrome

INTRODUCTION

Inherited benign intraepithelial dyskeratosis (IBID) is a rare genodermatosis. It is an autosomal dominant disorder affecting both the oral and conjunctival mucosa. IBID is characterized by elevated epithelial plaques on the ocular and oral mucous membranes. It has been reported primarily, but not exclusively, in individuals of American Indian heritage in North Carolina. The melkersson rosenthal syndrome (MRS) is a rare disease, to be evoked in the framework of pathologies of the big lips [1]. This sign is sometimes found in isolation. We report a new case combining both clinical and histological features of IBID and MRS

CASE REPORT

a 10-year-old girl with first-degree inbreeding with no history of tuberculosis, sarcoidosis or chronic inflammatory bowel disease. It presented from the first days after its birth, a tearing, a photophobia as well as an ocular redness. At the age of 3, her parents noticed the appearance of whitish patches at the two lateral edges of the tongue, followed later at age 7 by increasing the size of the lower lip as well the tongue. Clinical examination found macrocheilitis (Fig. 1a) of the lower lip evolving by thrust and incomplete remission, and macroglossia (Fig. 1b) surmounted at the lateral edges by multiple whitish, linear, spongy, painless and undulating plaques (Fig. 1b). The ophthalmologic examination noted superficial corneal neovascularization (Fig. 1c), as well as two small bilateral whitish opacities (Fig. 1d) . In view of this clinical manifestations, an IBID was strongly suspected. Two biopsies at the tongue and lower lip were performed, showing signs for IBID and epithelioid and gigantocellular granulomas with no fibrinoid necrosis or caseins leading to MRS. An exhaustive assessment of tuberculosis and sarcoidosis was without anomalies.

DISCUSSION

IBID is a hereditary condition, the symptoms of which appear in early childhood and predominantly affecting descendents of Haliwa-Saponi Native Americans [2]. They appear as whitish, painless, spongy papules or plaques of varying sizes, reaching any part of the

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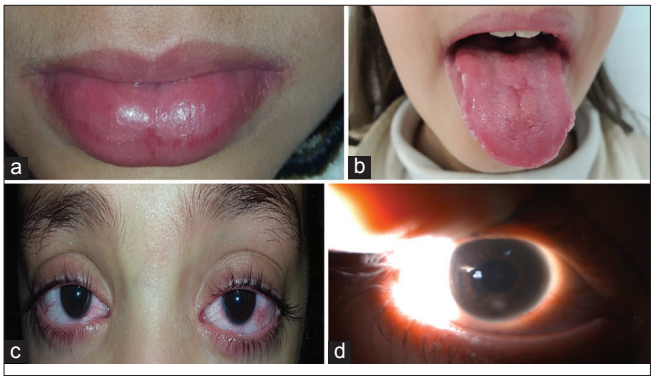

Figure 1: a: Macrocheilitis, b: Macroglossia and multiple whitish, linear, spongy, painless and undulating plaques, c: Superficial corneal neovascularization, d: Corneal opacity

oral cavity. Ocular lesions are typically bilateral, associated with tearing, photophobia, and corneal neovascularization as well as corneal opacities. The affection of the oral and conjunctival mucosa shows the same clinical aspect: Dyskeratosis, parakeratosis and acanthosis of the stratified squamous epithelium. Cells appearing to be engulfed by normal cells, "cell-whithing-cell" pattern can also be seen [3]. The genetic study makes it easy to retain the diagnosis (duplication 4q35), but is not essential [4]. Several medical and surgical treatments have been proposed, but none has proved quite effective [2]. MRS is a rare disorder consisting of a triad of persistent or recurrent orofacial edema, relapsing facial paralysis and fissured tongue. It is rarely possible to observe all aspects of the classical triad at the same time, since these symptoms may appear in different times of life cycle [5]. In our case, we retained the diagnosis of MRS because of the association of macrocheilitis and granulomatous macroglossia. The question of a link between the MRS and the IBID is mentioned in our patient.

CONCLUSION

According to our knowledge, we report the first case of association of IBID and MRS. Is it a rare association, or an entity in its own right?

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CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Unilateral nevoid hyperkeratosis of the nipple and areola in a Saudi female

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ABSTRACT

Nevoid hyperkeratosis of the nipple and areola (NHNA) is a rare, benign condition of unknown origin that is characterized by a hyperpigmented, hyperkeratotic verruca plaque over the nipple and/or areola. NHNA usually occurs bilaterally, but is sometimes present unilaterally. We present a case of a 21-year-old Saudi female who presented at dermatology outpatient clinic with a 3-year history of skin darkening and thickening of the left nipple, associated with moderate itching. The patient was diagnosed with unilateral NHNA on the basis of clinical presentation and skin-punch biopsy findings of epidermal orthokeratotic hyperkeratosis, mild papillomatosis, basal-layer hyperpigmentation and irregular filiform-pattern epidermal acanthosis. To the best of our knowledge, this case represents the first report of NHNA with unilateral presentation in a Saudi female.

key words: Nevoid hyperkeratosis; Nipple; Areola

INTRODUCTION

Nevoid hyperkeratosis of the nipple and areola (NHNA) was first described by Taber in 1932 [1]. Hyperkeratosis of the areola and nipple was classified by Levy-Franckel into three types: type 1 is characterized by an extension of the epidermal nevus; type 2 occurs secondary to another form of dermatosis; and type 3 is the idiopathic, isolated form [2]. However, Pérez-lzquierdo et al. suggested an alternative classification that distinguished just two types of nipple hyperkeratosis: either idiopathic (nevoid) or occurring secondary to other cutaneous conditions [3].

Nevoid hyperkeratosis of the nipple and areola is characterized by a hyperpigmented, hyperkeratotic verruca plaque that involves the nipple and/or areola [3,4]. This condition is rare, and most frequently occurs bilaterally, although unilateral cases have also been reported [5–7].

NHNA is a clinical entity that tends to be diagnosed on the basis of the exclusion of other conditions. The patient who presents with hyperkeratosis of the nipple and/or areola must be examined carefully for the presence of other underlying cutaneous diseases, including epidermal nevi, ichthyosis, acanthosis nigricans, Darier disease, and cutaneous T-cell lymphoma. If no other diagnosis is suggested by the clinical findings, then a diagnosis of NHNA can be made.

Here, we report a case of unilateral NHNA in a 21-year-old female from Saudi Arabia. The patient presented with a left-nipple hyperpigmented, hyperkeratotic verruca plaque with a histopathological finding of orthokeratotic hyperkeratosis and papillomatosis, with mild epidermal acanthosis. Diagnosis was made on the basis of clinical presentation and histopathological findings, as well as the exclusion of other diagnoses.

CASE REPORT

An otherwise healthy, 21-year-old, single Saudi female presented to the outpatient dermatology clinic with a 3-year history of progressive skin thickening and darkening of the left nipple, associated with moderate

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itching. The patient had no history of nipple discharge or bleeding, breast pain or masses, skin lesions at other sites of the body, drug use, personal or family history of atopy or family history of a similar skin condition.

On physical examination, asymmetry was observed between the patient's breasts, with normal appearance of the right breast, but a diffuse, brown, hyperpigmented, hyperkeratotic verruca plaque over the left nipple and areola (Figs. 1, 2A and 2B). Bilateral examination of the breasts found no mass, tenderness or discharge. There was no evidence of lymphadenopathy. An examination of the skin of the neck, axillae and other intertriginous areas showed no increase in pigmentation or thickening. Similarly, the nails, hair and skin covering other areas of the body were normal. A 4-mm skin-punch biopsy was performed. Examination of the skin punch biopsy indicated the presence of epidermal orthokeratotic hyperkeratosis, mild papillomatosis, basal-layer hyperpigmentation and an irregular pattern of epidermal acanthosis with elongated rete ridges (Figs. 3 and 4).

The diagnosis of unilateral NHNA was made on the basis of the clinical and the histopathological findings. In addition, secondary causes of nipple hyperkeratosis, such as acanthosis nigricans, seborrheic keratosis, mammary Paget's disease, atopic dermatitis, superficial basal-cell carcinoma and mycosis fungoides, were excluded. Using the Levy-Franckel classification, our patient was classified as having type III (i.e., idiopathic) NHNA.

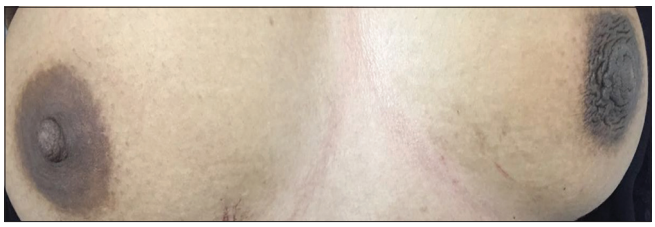

Figure 1: Photograph of the patient, showing unilateral nevoid hyperkeratosis of the nipple and areola on the left breast, compared with the normal tissue of the right breast.

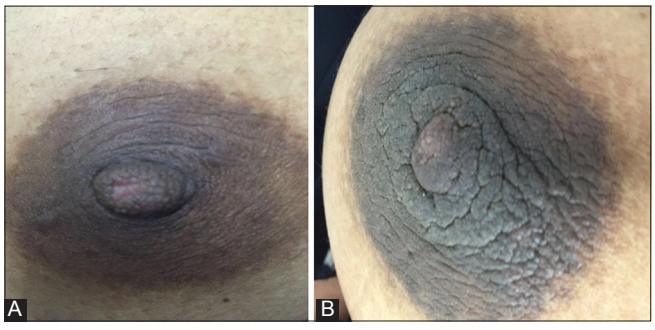

Figure 2: A magnified view showing (A) the normal right breast and (B) the verrucous, hyperpigmented thickening of the left areola and nipple.

The patient was treated with calcipotriol (synthetic vitamin D3) cream daily for 6 months, at the end of which she was satisfied with the cosmetic result, reporting the disappearance of itching and a 50% decrease in skin thickening of the left nipple and areola. There was no treatment-related skin irritation.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

The present case report identified a Saudi female with idiopathic hyperkeratosis of the nipple and areola. Notably, 80% of 45 cases identified in a Review of NHNA had occurred in female patients [8].

Although the exact cause of NHNA remains unknown, it has been postulated that some cases could arise from

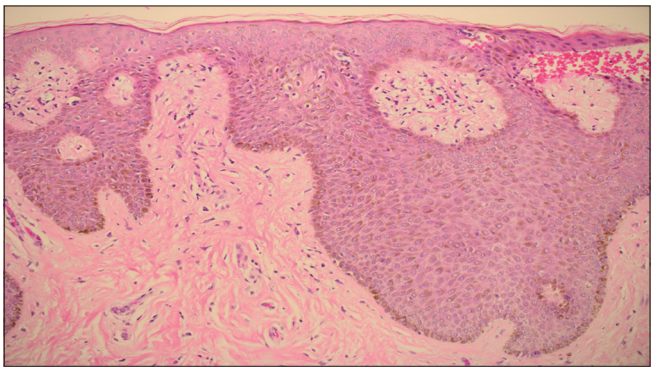

Figure 3: Skin biopsy from the patient's left breast , stained with hematoxylin and eosin and, 400x original magnification, showing orthokeratotic hyperkeratosis, basal-layer hyperpigmentation and irregular pattern acanthosis with elongated rete ridges.

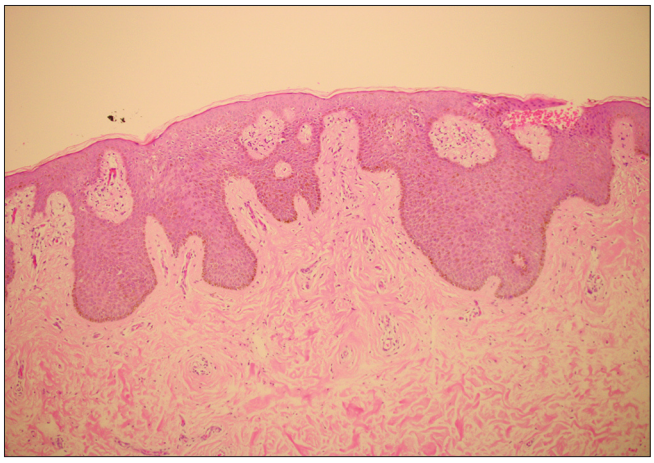

Figure 4: A skin biopsy from the patient's left breast , stained with hematoxylin and eosin and presented at 100x original magnification, to show irregular filiform epidermal acanthosis with elongated rete ridges.

an alteration in estrogen levels [9]. In support of this hypothesis, two cases of NHNA have been reported in an elderly male who received estrogen therapy for prostatic adenocarcinoma [8]. Another patient developed NHNA during pregnancy [10]. In a study of female patients with NHNA, six of the seven cases examined had occurred among women of reproductive age, who were in the second or third decade of life [3]. Similarly, our patient had started to develop symptoms 3 years before she first presented to the dermatology clinic at 21 years old.

More than half of the cases of NHNA occur bilaterally, but unilateral cases have been reported [5–7]. Our patient presented with the less common unilateral type of NHNA.

Histopathological findings of NHNA include epidermal orthokeratotic hyperkeratosis, papillomatosis and occasional keratin plugging with irregular filiform-pattern epidermal acanthosis. The basal layer of epidermis is hyperpigmented, without melanocyte proliferation, and the dermis may show mild perivascular lymphocytic infiltration [3,4,6,7,11]. Our case was diagnosed clinically and confirmed with a left-nipple histopathological finding of epidermal orthokeratotic hyperkeratosis, mild papillomatosis, basal-layer hyperpigmentation and an irregular pattern of epidermal acanthosis with elongated rete ridges.

Different therapeutic options have been used to manage NHNA, with varying results. The use of topical calcipotriol (a synthetic form of vitamin D3) has been reported to be effective and to produce a rapid outcome [5]. Topical calcipotriol combined with topical tacrolimus (an immunosuppressant) has previously been used to treat NHNA in a 19-year-old female, with improvement noted after 2 months of treatment [12]. Low-dose oral acitretin (a second-generation retinoid) has also been combined with topical calcipotriol for the treatment of NHNA, with no relapse after 2 years of follow-up [13].

The mechanism of action of topical calcipotriol in NHNA could involve inhibition of cellular proliferation and induction of keratinocyte differentiation. Topical calcipotriol is considered a very safe drug when used in amounts up to 100 g per week. The most important adverse effect of topical calcipotriol is skin irritation, but it also has a potential effect on calcium hemostasis [14]. Our patient was treated with topical calcipotriol cream daily for 6 months, and she experienced disappearance of skin itching, and a 50% decrease in skin thickening of the left nipple.

Acceptable cosmetic results have been obtained after the treatment of NHNA with a topical retinoid [15]. Cryotherapy has also been used successfully in the treatment of NHNA, with improvement noted after five sessions (with 20 s of cryotherapy per session) in a female patient who failed to respond to topical keratolytic agents [16]. In addition, surgical treatment modalities have been described, including radiofrequency surgery [17].

To the best of our knowledge, this case provides the first report of unilateral NHNA in Saudi Arabia. Although this condition is benign, it is considered distressing for the patient because of a disfigured appearance and of concern to doctors because of its similarity to mammary Paget's disease.

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CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Opinion Article

The demonstration that amongs myriads of palliative anticancer plants, there is one that is endowed by a synergical action: The Chenopodium album, that avoids the biotranformation of a benign skin tumor to malignant

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ABASTRACT

The corresponding Author has experimented upon himself, that is, in corpore vili, the capacity of a common herb (retrievable in all Europe and Americas), the Chenopodium album, the treatment of an abscissed spitz nevus (he had on his shoulder) and has had magnificient results. This herb is endowed by two types of biological principles that can act synergically:the plant is effiecient both for prevention and cure itself of a Spitz nevus and could be proposed for the treatment of other types of skin melanomas in the future.

Key words: Spitz nevus; Chenopodium album pulvis; ELM; Venetian talc; Polyphenols

Physiologically, the hormones carry messages to all cells in Man organism, triggering the cells to take action. These messages are carried by blood through the vascular system (arteries, veins and capillaries). The blood carries the other things that cells need to function too. Cells need oxygen and glucose to keep them alive, for example. Blood vessels also carry away waste products and oxygen-poor blood once the cells have used the oxygen in the blood. The lymphatic system helps to clean and drain what we do not need. The lymphatic system is a part of Man's body's defense system, and it drains away bacteria and germs and all cancerous cells (cells where the DNA became foolish and irresponsible) that tend to create growths and then tumors or cancers.

When the lymphatic system is not upset, cellular DNA and all that concerns normal health is regular but cells become abnormal if their DNA – and therefore their "knowledge" – becomes damaged. As long as there are very few abnormal cells and they are kept under control by the immune system, they will not harm man and thus these kinds of "anomalies" may be clinically defined "benign tumors". It is only when these cells start to divide uncontrollably, forming lumps or growths, that it is poissbile to number have one of the more than 200 diseases called cancer. Growths like this are called tumors. The main differences between malignant (cancerous) and benign (non-cancerous) tumors are that malignant ones can:

- spread into the surrounding tissue,
- destroy the surrounding tissue, and
- cause other tumors to develop.

Malignant tumors can be life-threatening. But there are also some kinds of cancer that develop so slowly in older people that they do not lead to any problems in their lifetime.

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Benign tumors usually do not cause much damage and are not normally life-threatening. But there is no guarantee: benign growths can become dangerous if they grow a lot, or they might become malignant after a certain amount of time.

If cancer cells start replicating, they do not behave like normal cells. For example, they do not know when to stop replicating and when to die. And they do not always stick together, so they might break away and move through the vascular or lymphatic system and start growing somewhere else in the body.

The Spitz nevus is a rare type of skin mole that usually affects young people and children, but even often elder. Although it can look like a serious form of skin cancer called melanoma, a Spitz nevus lesion isn't considered cancerous, even if in case of immunodeficiency or other pathological conditions, it could grow malignant.

The first step a physician should do is to effectuate the biopsy of the Spitz nevus and control if the nevus is going to become, because of certain causes, malignant.

The biopsy for almost all types of nevi is conducted by the aids of the ELM (Epiluminescence Microscope), ointing the part that is suspected.

If it is completely benign, the second pace is to remove it (abscission).

Afterwards it is important to care that the abscissed nevus (a liminal lesion remains always) can grow malignant anyway.

Apart shamans and sorceresses who may promise the inhibition of the passage from a tumor to become from benign to malignant owing to manifold antiquate and traditional herbs, some of these plants reflects a very important role in this conditions, thanks to the co-presence of many biological principles as polyphenols or tannins or glycosides, that can guarantee the impossibility of the tumor to grow malignant, but anyway these constitute a fancy repertoire, that has no scientific approval.

We could observe that the usage of some herbs can be reputed palliative and help to slow the growth of the tumor.

Chenopdium album, amongst many plants containing polyphenols, catechins and tannins, that are reputed antioxidant and sometimes cytotoxic, contains two important principles: an important glycoside:the xyloside and another biological active (see below).

Moreover polyphenols make a major contribution to free radical scavenging capacities. There was a direct relationship between antioxidant activity and total phenolics content in selected herbs, vegetables. *Chenopodium album* leaves had a relatively high level of total phenolics and extractable condensed tannins which consisted of predominantly procyanidins and prodelphinidins with 2,3-cisstereochemistry. Tannins extracted from leaves, twigs and stem bark all showed very good DPPH radical scavenging activity (IC50 of 56.86, 62.31 and 54.80 μg/ml) and ferric reducing power (4.28, 3.74 and 4.49 mmol AAE/g dried tannins).

The aglycone of this glycoside (xyloside) consists of a hydrophobic compound which aids in carrying the sugar moiety to the Golgi membrane where GAG synthesis takes place, as Proteoglycan (PG) synthesis is initiated by the transfer of D-xylose from UDP-xylose to a serine residue in core proteins. This natural primer acts as a template for the assembly of heparin sulfate, heparin, chondroitin sulfate, and dermatan sulfateside chains, depending on the tissue. However, in 1973 it was determined that synthetic B-D-xylosides can prime glycosaminoglycan (GAG) synthesis by substituting for the core xylosylated protein, meanwhile the aglycone moyety is able to stop this process and avoid the growth of dermal cells that could create ex abrupt growth and lumps.

When a malignant tumor is contained within one area and has not spread to the surrounding tissue, the medical term is "carcinoma in situ." If this tumor does not keep growing, that means it is just lying there quietly ("dormant cancer cells"). It is not likely to cause harm unless it starts growing.and eveniences are coexistent.

To keep growing, these tumors start to create their own blood vessels to supply them with the extra oxygen, glucose and hormones they need to survive and keep getting bigger. That process of developing a blood supply system is called angiogenesis (the growth of new blood vessels). Once a tumor does this, it can start to invade the surrounding tissue. This is called an invasive cancer, and it is possible to observe an excrescence, especially in skin carcinomas or nevi.

Moreover manifold lines of evidence suggest that carnosol, contained in the same Chenopodium album, holds the promise of preventing certain types of cancer,

especially skin melanomas. A remarkable progress has been made in delineating the biochemical mechanisms underlying the chemopreventive effects of carnosol. Results from in vitro cell culture studies as well as animal model experiments have revealed that carnosol inhibits experimentally induced carcinogenesis and exhibits potent anti-oxidative, anti-inflammatory, antiproliferative and apoptosis inducing properties. Moreover, carnosol enhances the sensitivity of chemoresistant cancer cells to chemotherapeutic agents [1].

When a suspect amount of melanocytes or chloasma is detected, the employ of Chenopodium extract could be efficient, but this must be scientifically ascertained in a next future.

It is well known that even in islamic medicine chenopodium was recognized as anticancer remedy [2].

It must stressed that Cancer is an unbeaten health challenge for the humankind. After striving for decades to find a cancer cure, attention has now been shifted to reduce the morbidity and mortality from cancer by halting the course of tumor development. Numerous bioactive phytochemicals, especially those present in edible and non-edible plant species, have been reported to reduce the risk of many cancers. Multiple lines of evidence suggest that carnosol, a phenolic diterpene contained in Chenopodium album, holds the promise of preventing certain types of cancer. A remarkable progress has been made in delineating the biochemical mechanisms underlying the chemopreventive effects of carnosol. Results from in vitro cell culture studies as well as animal model experiments have revealed that carnosol inhibits experimentally induced carcinogenesis and exhibits potent anti-oxidative, anti-inflammatory, antiproliferative and apoptosis inducing properties. Moreover, carnosol enhances the sensitivity of chemoresistant cancer cells to chemotherapeutic agents.

Epidemiological, clinical and laboratory studies have implicated solar ultraviolet (UV) radiation in various skin diseases including premature aging of the skin and melanoma and nonmelanoma skin cancers. Chronic UV radiation exposure-induced skin diseases or skin disorders are caused by the excessive induction of inflammation, oxidative stress and DNA damage, *etc*.. The use of chemopreventive agents, such as plant polyphenols, to inhibit these events in UV-exposed skin is gaining attention. Chemoprevention refers to the use of agents that can inhibit, reverse, or retard the process of these harmful events in the UV-exposed skin. A wide variety of polyphenols or phytochemicals, most of which are dietary supplements, have been reported to possess substantial skin photoprotective effects. Presently the photoprotective agents from some selected polyphenols, are considered as valuable, like green tea polyphenols, grape seed proanthocyanidins, resveratrol, silymarin and genistein, on UV-induced skin inflammation, oxidative stress, and DNA damage, *etc.*, with a focus on mechanisms underlying the photoprotective effects of these polyphenols. The laboratory studies conducted in animal models, suggest that these polyphenols have the ability to protect the skin from the adverse effects of UV radiation, including the risk of skin cancers. It is suggested that polyphenols may favorably supplement sunscreens protection, and may be useful for skin diseases associated with solar UV radiation-induced inflammation, oxidative stress and DNA damage.

Cancer of the skin is characterized by an imbalance towards too little apoptosis, or too much cell proliferation and survival in the epidermis [3,4]. Although UV radiation is the leading cause of skin cancer, other causative agents include viruses, mutagens in food, mutagens in chemicals and genetic susceptibility [5,6]. Skin cancer can be prevented by controlling, or eliminating these causative agents. Skin cancer can be effectively removed by hindering blood supply to the tumor (anti-angiogenesis), which curbs tumor growth and enhances patient survival. Most cancer cells develop ways to evade apoptosis, or exhibit defective apoptosis mechanisms, thus allowing uncontrollable cell development [2]. The apoptosis process is therefore the major target of anti-cancer chemotherapeutics or natural drugs (Box 1).

Finally laboratory studies conducted in animal models, suggest that these polyphenols have the ability to protect the skin from the adverse effects of UV radiation, including the risk of skin cancers. It is suggested that polyphenols may favorably supplement sunscreens protection, and may be useful for skin diseases associated with solar UV radiation-induced inflammation, oxidative stress and DNA damage.

The Spitz nevus was discovered on right shoulder by in Martini and since We are doctor and can follow the Sir Percival ethical rights (that permits the experimentations on oneself with no consense of whichever medical ethical committee) We underwent to a ELP biopsy and have the melanoma abscissed.

After two days We began the following treatment:

Quercetin, Kaempferol, EGCG, Apigenin, β-carotene, Fucoxanthin, Vitamin C, Ganoderma lucidum extract, Coriolus versicolor extract, Resveratrol, Curcumin, Sulforaphane, Melaleuca alternifolia extract, Zingiber officinale extract, Withaferin A from Withania somnifera, Eupatilin from Artemisia, Galangin from Alpinia officinarum, Kaempferol, Apigenin, Vitamin A, Vitamin C, Vitamin D, Vitamin E, Ganoderma lucidum extract, Coriolus versicolor extract, Hypericum perforatum extract, Melaleuca alternifolia extract, Calendula officinalis extract, Emodin from Aloe, Eupatilin from Artemisia, Alpinia oxyphylla extract, Alpinia galangal extract, Amentoflavone, Hinokiflavone, β-carotene, Fucoxanthin, Resveratrol, Sulforaphane, Withania somnifera extract, Viscum album extract, Calendula officinalis extract, Carnosol from Chenopodium album, Ursolic acid from Rosmarinus officinalis.

Box 1: List of drugs.

a powder made of 50% chenopodium album pulvis and 50% venetian talc.

The treatment has lasted 14 days.

After this period We have prayed a friend of mine (dermatologist) to observe by a dermascope (Dino-Lite) to state the condition of my skin.

No lesion or shadow of past scare was visible at all.

No itching, no redness and no skinmanifestation was detectable.

Notwithstanding the avalanche of herbs that promise the prevention and the complete cure of a skin melanoma, I propose Chenopodium album pulvis to avoid that a tumor (considered after a biopsy by ELP benign) becomes malignant.

Even rosemary (Rosmarinus off. contains great percentages of carnosol, but does not contain absolutely the xyloside.

One is excellent to prevent and the other is exceptional to treat eventual transformation of a benign skin cancer to malignant.

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Our Dermatology Online

Review Article

Micronutrients in hair loss

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ABSTRACT

Alopecia is a common dermatological complaint. Affected patients are often distressed and attempt to arrest the hair loss by taking various over the counter nutritional supplements containing vitamins and minerals. The evidence supporting their efficacy however is limited. Moreover, there are toxicity reports. We reviewed the literature about the normal levels and the daily dietary needs of the most common micronutrients, their role in the hair follicle cycle as well as their use in the hair loss treatment. 4 independent researchers reviewed a total of 119 papers, and 92 articles published in the English language within the last 30 years were included. Telogen effluvium and alopecia areata have been associated with lower iron, zinc and vitamin D levels. Androgenetic alopecia has been associated with lower iron and vitamin D levels. Both lower and increased vitamin A levels can result in telogen effluvium, but lower levels are associated also with hair breakage. Vitamin C insufficiency results in hair shaft abnormality (cork screw hairs). No data exist about hair loss associated with abnormal biotin levels. The role of micronutrients for the hair follicle function is not completely understood. Empiric treatments of hair loss with micronutrients without confirmed deficiencies have not shown utility.

Key words: Alopecia; Supplements; Vitamins; Iron

INTRODUCTION

Hair follicle cells have a high turnover and active metabolism, requiring a good supply of nutrients and energy. A caloric deprivation or deficiency of several macro and micronutrients, such as proteins, minerals, essential fatty acids, and vitamins, can lead to hair loss [1]. Patients with hair loss, particularly with hair shedding are often distressed by their condition and attempt to arrest the shedding taking multivitamins, minerals and herbal products. While considered helpful by patients the consumption of these products may not be supported by evidence [2,3]. Moreover, reports exist of worsening of hair loss as well as liver toxicity [4].

MATERIALS AND METHODS

In order to assess the current evidence about the role of micronutrients for hair loss and hair growth, we reviewed the major database sources PubMed and Medline by using the key words hair, hair loss, alopecia, telogen effluvium and the names of most common vitamins and minerals listed as ingredients in the commercial "hair" and "hair and nails" supplements. We reviewed the literature about the normal levels and the daily dietary needs for optimal hair growth of the most common micronutrients, their role in the hair follicle cycle as well as their use in the hair loss treatment. A total of 119 papers were reviewed by 4 independent researchers, and 92 articles published in English language within the last 30 years were selected for inclusion. All articles were peer-reviewed with available full-text texts in English or Spanish, providing primary data. Also data from the World Health Organization (WHO) and Institute of Medicine (US) about Dietary Reference Intakes and Recommended Dietary Allowance were included.

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RESULTS

Our results are summarized in Table 1.

1. Iron

Iron participates in the structure of many molecules in the body, such enzymes, cytochromes and transcription factors, and is involved in many critical physiologic processes. It is a catalyst in oxidation-reduction reactions and can control DNA synthesis in dividing cells.

Serum ferritin is the standard test for assessing iron stores because it is one of the most sensitive and specific markers of iron deficiency. It is directly related to intracellular ferritin and total iron reserves [5,6].

Normal levels

The Recommended Dietary Allowance (RDA) for men of any age and for postmenopausal women is 8 mg/day; and for premenopausal women is 18 mg/day.

A cut-off of 41 ng/L of the ferritin's serum level has sensitivity and specificity of 98% in detecting iron deficiency [7]. Serum ferritin values < 12 ng/l suggest absent iron stores and it is considered diagnostic for iron deficiency anemia [8]. The proposed optimal ferritin level for hair regrowth is 70 ng/L [7,9,10].

It must be considered that ferritin is an acute phase protein, and in neoplasia, infections and inflammatory diseases it may be falsely elevated despite of the low iron reserve. C Reactive Protein levels or erythrocyte sedimentation levels can be used in such cases to rule out false negative results [11].

Causes of deficiency

Iron deficiency is the most common nutritional deficiency in the world. Data from the Third National Health and Nutrition Examination Survey (NHANES III; 1999-2000) indicated that iron deficiency anemia was present in 1 to 2 percent of adults. Iron deficiency without anemia was found in 9-16% of females aged 12-49 years and it was two times higher in non-Hispanic American women. The prevalence of iron deficiency in males aged 16-69 years was 2% [12].

In premenopausal women, the most common causes of iron deficiency anemia are menstrual loss and pregnancy, whereas gastrointestinal blood loss and malabsorption are most common in men and postmenopausal women [6]. Also, borderline iron deficient diets such as vegetarian and vegan diets are another common cause. Good food sources of iron include red meat, egg yolks, green leafy vegetables, lentils, and beans; however, non-animal foods provide less bioavailable-ingested iron. Iron is absorbed mainly in the epithelium of distal duodenum and proximal jejunum [13].

Many patients with iron deficiency and even anemia are asymptomatic. When present, clinical symptoms include hair loss, cheilitis and koilonychia [9].

Iron and hair

Currently, the role of iron on the hair follicle biology is not completely understood and the exact mechanism by which iron deficiency affects hair is also unclear.

It is believed that decreased iron bioavailability may impair the proliferation of the follicular matrix cells. Dividing cells require higher levels of ferritin. An abnormal balance between cellular ferritin and free iron has been suspected as a mechanism for abnormal hair growth [14].

In 2008, Du et al. described iron-dependent genes in the hair follicle bulge whose mutation causes high levels of hepcidin, a liver protein that decreases iron absorption [15]. In 1963, Hard first suggested the role of iron as etiological factor in diffuse hair loss in iron deficient non-anemic women [16]. Since then various studies have evaluated the association; most of them have addressed only women with non-cicatricial alopecia. Data are contradictory and difficult to compare due to discrepancy in the study designs, the variables assessed and the population included (Table 2). Kantor et al proposed the "Threshold hypothesis", stating that decreased iron stores can lower the threshold to develop different type of alopecia depending on the genetic predisposition and the family history [14].

Treatment recommendation

The recommended oral daily dose for the treatment of iron deficiency in adults is in the range of 150-200 mg/day of elemental iron. It can be given by mouth, under forms of ferrous sulfate, gluconate or fumarate. Better bioavailability of elemental iron per tablet is derived from the fumarates (33% of elemental iron, versus 20% and 12% for sulfate and gluconate respectively) [12], but there is no evidence that one is more effective than the others. Sulfates are worst tolerated as they can cause gastrointestinal upset and constipation. The daily dose can be divided in order to

Table. 1 Micronutrients in hair loss association and treatment

Nutritient	Laboratory test	Normal level	Hair loss association	Recommended supplementation
Iron	Serum Ferritin	>40 ng/l	CTE ATE AA AGA	150-200 mg/day of elemental iron. Ferritin tests at 3 months interval and continue oral iron therapy for 3-6 months after the iron deficiency is corrected
Zinc	Serum Zinc (Zn)	>10,7 mmol/L	TE AA	50 mg Zn Gluconate daily for 12 weeks or 5 mg/kg/day Zn Sulphate for 3 months
Vitamin D	Serum 25(OH) D2	>30 ng/mL Insufficiency: < 30 ng/mL Deficiency: < 20 ng/mL	CTE FPHL AA	50,000 IU once a week for 1-3 months. Maintenance dose of 800-2000 IU to avoid recurrences
Biotin	Urinary excretion of biotin/organic acids and Carboxylase activity in peripheral blood lymphocytes	Deficiency: Biotin urinary excretion low 20ug/L or 25 ug/24 hours	No evidence of hair loss association	No evidence for biotin supplementation for hair loss treatment
Vitamin C	Serum vitamin C	>11mmol/L or 0,6-2.0 mg/dL	Cork screw hairs	300-1000 mg daily of oral vitamin C for 1 month
Vitamin A	Serum Retinol concentration	Deficiency below 20 mcg/dL	Deficiency: TE and hair breakage Overload: TE	In deficiency: 200.000 IU, single dose monthly for 1-6 months

TE: telogen effluvium, CTE: chronic telogen effluvium, ATE: acute telogen effluvium, AA: alopecia areata, AGA: androgenetic alopecia, FPHL: female pattern hair loss

Table 2. Iron deficiency and hair loss.

Author	Type of Alopecia	Type of Study	Results
Hard S. (1963)[16]	Diffuse Hair Loss	Cross-sectional, followed by prospective cohort	100% regrowth in 18/96 (18.8%) non-anemic women with iron deficiency (measured by serum iron) and DH treated with oral iron therapy
Rushton DH, Ramsay ID, James KC, Norris MJ, Gilkes JJ. (1990)[17]	Diffuse Androgen dependent alopecia	Case control study	72% of 50 premenopausal women with DA had serum ferritin levels less than 40 mg/L.
Rushton DH, Norris MJ, Dover R, Busuttil N. (2002)[18]	CTE	Cross-sectional study	65% of 200 healthy women with increased hair shedding had ferritin levels less than 70 ug/L.
Rasheed H (2013) [19]	TE, FPHL	Prospective case control study	Serum ferritin levels were significantly lower in TE and FPHL compared to control patients.
Olsen EA 2010[20]	CTE, FHPL	Case control study	There was no statistically significant increase in the incidence of iron deficiency in premenopausal or postmenopausal women with FPHL or CTE versus control patients
Kantor J, Kessler LJ, Brooks DG, Cotsarelis G. (2003)[14]	TE, AGA, AA, AU, AT	Case control study	Serum ferritin levels were significantly lower in women with AGA (37.3 ug/L) and AA (24.9 ug/L) compared to control patients.
Boffa MJ, Wood P, Griffiths CE (1995)[21]	AA	Cross sectional study	No increased incidence of iron deficiency in patients with AA compared with general population.
Sinclair R (2002)[22]	DTHL	Prospective cohort study	There is no clear association between low serum ferritin and CTE

AGA: androgenetic alopecia; AA: alopecia areata; AT: alopecia totalis; AU: alopecia universalis; CTE: chronic telogen effluvium; DA: diffuse alopecia; DH: diffuse hair loss; DTHL: diffuse telogen hair loss; FPA, female pattern alopecia, DTE: diffuse telogen effluvium

improve the tolerance and absorption.

Concomitant treatment with ascorbic acid, 500-1000 mg per day and L-Lysine 1000 mg per day, may also enhance the absorption [18]. It is recommended to repeat ferritin tests at 3 months interval and continue the oral iron therapy for 3-6 months after the iron deficiency is corrected [6,7,11].

2. Zinc

Zinc is an essential trace mineral that participates in

the structure and function of proteins, such as enzymes, transcription factors, hormonal receptor sites, and biologic membranes throughout the body. It is also involved in signal transduction, gene expression, and plays a regulatory role in apoptosis [23]. Zinc is crucial for the proper function of lymphocytes, neutrophils and Natural Killer cells in the immune response, as well as for the skin barrier [24].

Serum or plasma zinc level is the standard test for assessing zinc status [25].

Normal levels

RDA for zinc is 11 mg and 8 mg per day for men and women respectively [26]. The lower limit of normal (morning) fasting plasma zinc has been set at 10.7 mmol/L (700 mg/L) [27].

Causes of deficiency

Severe zinc deficiency has been documented in patients on parenteral feeding without adequate zinc intake and in cases of acrodermatitis enteropathica, an inherited disorder of zinc absorption caused by a mutation in a zinc transporter [28].

Acquired zinc deficiency can also be caused by insufficient uptake from food, intestinal malabsorption syndromes or pregnancy. Long-term alcohol consumption is associated with impaired zinc absorption and increased urinary zinc excretion [21]. Avoidance of red meat by young women can be a cause of concomitant iron and zinc deficiency [29]. The first source of zinc from diet is red meat; other good sources are beans, nuts, crab and lobster. Phytates present in cereals and legumes inhibit the zinc absorption [30].

Cutaneous manifestations present as impaired wound healing and an increased susceptibility to infections, paronychia, periorificial dermatitis, diffuse alopecia [31], and hair color and texture changes [25].

Zinc and hair

The exact role of zinc in the function of the hair follicle is unclear. Zinc has been considered a hair growth modulator and immunomodulator because the DNA polymerase is zinc dependent and zinc acts in multiple aspects of T-lymphocyte activation, signal transduction and cellular apoptosis [24,32]. Zinc deficiency has been related to alopecia areata [33-36], and telogen effluvium [35,37].

Some studies have found lower zinc serum levels in patients with alopecia areata comparing with controls. It has also been shown in alopecia areata that the disease duration, severity and resistance to therapies are correlated inversely with low serum zinc levels [38].

Treatment recommendations

There is scarce evidence on the proper zinc supplementation and the therapeutic response in alopecia areata. Zinc Gluconate dosed as 50 mg daily for 12 weeksproduced regrowth in 15 patients with alopecia areata who had low serum zinc level. Positive therapeutic effects were observed in 9 out of 15 patients (66.7%) although this was not statistically significant [33]. The most recent and the only double blind, cross over study used Zinc Sulphate in a dose of 5 mg/kg/day for 3 months in patients with alopecia areata which resulted in hair regrowth for 60% of the group receiving treatment [34].

Zinc can be supplemented using several forms such as zinc gluconate, zinc sulfate and zinc acetate with different elemental zinc contribution [39]. There are no data about the differences in the efficacy.

3. Vitamin D

Vitamin D is a fat-soluble vitamin belonging to the family of steroid hormones that plays an important role in the calcium homeostasis and musculoskeletal health.

Vitamin D consists of 2 bioequivalent forms, Ergocalciferol (vitamin D2) and Cholecalciferol (vitamin D3). The main source in the body is the endogenous synthesis in the skin as a result of the action of ultraviolet B radiation on 7-dehydrocholesterol, which results in the formation of vitamin D3. The skin is the only organ capable of synthesizing and activating Vitamin D, in addition to expressing its receptor [40].

Vitamin D can be obtained exogenously from few foods like fatty fish, fish liver oil, egg yolk and some mushrooms. Ingested and cutaneous produced vitamin D needs 2 hydroxylation steps, first in the liver, turning into Calcidiol or 25-hydroxyvitamin D, and then in the kidneys to turn into its active metabolite, Calcitriol or 1,25- (OH) 2 D [41].

The most stable form of the vitamin D in the serum is 25 hydroxyvitamin D or 25(OH) D, which is routinely

measured to assess the vitamin D status. Besides being the predominant circulating form, it also has a longer half-life [42].

Normal levels

The optimal 25(OH)D serum level is 30 ng/ml (75nmol/L) [43,44]. In 2003, the World Health Organization (WHO) defined vitamin D insufficiency as serum 25(OH) D below 20 ng/ml [45]. Other authors define Vitamin D deficiency as serum 25 (OH) D less than 20 ng/ml and insufficiency below 30 ng/ml [46,47].

Causes of deficiency

Conditions associated with vitamin D deficiency are malnutrition, intestinal malabsorption, especially affecting the proximal small intestine, obesity and some paraneoplasic syndromes [42]. Vitamin D deficiency in healthy adults has been estimated to affect up to 30% of the population [48-50].

Among the risk factors are dark skin, very low sunlight exposure, atmospheric pollution, and multiple within short interval pregnancies, vegetarian diet and some medications such anticonvulsants, rifampicin, antiretroviral agents and corticosteroids [51].

Vitamin D and hair

The action of 1,25- (OH) 2 D is mediated by its binding to the Vitamin D receptor (VDR) which is a member of the nuclear receptor superfamily. VDR distribution on the body is not restricted to organs involved in calcium and bone metabolism but also in the cells of the immune system [42], and in appendageal structures such as the hair follicles [52].

In the hair follicle, the VDR is expressed in the mesodermal dermal papilla cells and the epidermal keratinocytes depending on the stage of the hair cycle. VDR expression in the hair follicle is increased during late anagen and catagen, correlating with proliferation and differentiation of the keratinocytes in preparation for the new hair cycle [53]. Lack of VDR in the keratinocytes as opposed to the dermal papilla would cause its dissociation from hair bulb by the end of catagen, leading to defective initiating of subsequent anagen phase [41,54]. VDR therefore exerts a regulatory role on the hair cycle, independent of the vitamin D binding [55].

Patients with mutations in the VDR, such as hereditary vitamin D-resistant rickets (Vitamin D-dependent rickets type IIA) have normal hair at birth due to the normal hair cycle in the fetus; however, they develop alopecia totalis between 1 to 3 months of age, after the first hair is shed [56,57].

It has been shown among 80 women with chronic telogen effluvium and female pattern of hair loss that the serum vitamin D level was significantly lower compared to controls [18].

A significant lower serum 25 (OH) D level (below 20 ng/ml) were observed in patients with alopecia areata compared with a healthy control group [49, 58-60].

Disease severity in alopecia areata is inversely correlated with the serum levels of vitamin D [49].

Treatment recommendations

People with normal serum level of 25(OH) D are advised to take a supplement containing 800 IU of vitamin D per day to maintain a normal level [40,47].

D2 (ergocalciferol) and D3 (cholecalciferol) are available as dietary supplements. Both seem to be effective in preventing or treating vitamin D deficiency. The longer half-life of D3 suggests that less frequent dosing may be needed. Supplements of vitamins D2 and D3 should be taken with a meal containing fat to ensure maximum absorption [61].

There are no accepted guidelines for treating vitamin D deficiency and insufficiency. A recent review recommends the use of vitamin D3 over vitamin D2 [62]. One time dose of vitamin D3 of at least 300,000 IU is most effective in improving vitamin D status for up of 3 months. However, the most widely used mode of supplementation is an average weekly dose of 50,000 IU (cholecalciferol) for 1-3 months, depending on the severity of Vitamin D deficiency. A maintenance daily dose of 800 to 2000 IU or more will be needekd to avoid recurrent deficiency [40,52,61].

Vitamin D topical analogues have been tested in mice with congenital alopecia with positive response [63]. In human studies, topical calcitriol has shown to prevent alopecia induced by chemotherapy agents (paclitaxel and cyclophosphamide) [56].

4. Biotin

Biotin is an essential nutrient; a water-soluble vitamin classified as a B-complex vitamin. Biotin serves as a coenzyme for carboxylation reactions on fatty acids,

aminoacids and glucose metabolism and has an essential role in gene regulation [64,65].

The main source of biotin is the diet; it is widely distributed in foods like egg yolk, cereals and vegetables. Evidence suggests that dietary biotin is 100% bioavailable. It is also synthetized by normal intestinal microflora, but it is unknown how much this source contributes to the biotin status [66].

To achieve its active form and to be absorbed in the intestine, biotin is subjected to a proteolysis. Biotinidase is a critical enzyme in this process. There are hereditary disorders of biotinidase deficiency that can be detected with a newborn screening [66].

Normal levels

There is no conclusive data on validated markers for assessing the biotin status. Measuring urinary excretion of biotin and organic acids such 3- Hydroxyisovaleric and quantifying biotinylated carboxylases in lymphocytes have been utilized. The latter has shown to be the most reliable marker [67]. A low plasma biotin concentration is not a sensitive indicator of inadequate biotin intake.

Deficiency of Biotin has been defined as urinary excretion less than 20ug/L or 25 ug/24 hours [68]. The adequate intake (AI) for biotin is 30 μg/d in men and women [69].

Causes of deficiency

Real biotin deficiency can be observed only in rare and specific conditions: a diet that contains raw egg whites, patients receiving parenteral nutrition without biotin supplementation, and treatments with anticonvulsants such primidone, and carbamazepine [70,71]. Cutaneous findings include severe dermatitis, dry skin, seborrheic dermatitis, fungal infections, macular rash, fine and brittle hair and hair loss [54].

Biotin and hair

There is no evidence regarding direct effect of biotin on the hair follicle development and cycle. There is no data that biotin is related to hair disorders either.

Treatment recommendations

There are no published data supporting the evidence that biotin supplements can be an effective treatment of hair loss.

5. Vitamin C

Vitamin C is a water-soluble vitamin and an essential micronutrient. It is a potent antioxidant and is required for the biosynthesis of collagen, specifically procollagen triple helix and also is needed in the synthesis of catecholamines [72]. It also plays an important role in immune function and modulates iron absorption, transport, and storage [73].

Normal levels

Recommended daily intake in adults is 90 mg in men and 75 mg in women [69].

Measuring the plasma vitamin C levels assesses the vitamin C status. Normal plasma level is in the range of 0,4- 0,9 mg/dL. Vitamin C deficiency is defined as plasma level less than 0,2 mg/dL [74].

Causes of deficiency

According to NAHNES 2003-2004, 7.1% of the total population suffers from vitamin C deficiency, with the smokers being at the most risk. The principal cause of deficiency is the minimal consumption of fruits and vegetables [75]. The clinical presentation of Vitamin C deficiency is scurvy, with skin manifestations due to decreased and altered collagen production [76,77].

Vitamin C and hair

Vitamin C promotes hair shaft elongation in cultured human hair follicles and triggers hair growth in mice by progression from telogen to anagen. This has been achieved by increasing the Insulin Growth Factor 1 (IGF1) production in the dermal papilla cells [78].

Treatment recommendations

The recommended treatment for Vitamin C deficiency is 300-1000 mg daily of oral vitamin C for 1 month [79,80].

6. Vitamin A

Vitamin A is a fat-soluble vitamin. There are two main forms of vitamin A: 1) retinoids or preformed vitamin A and 2) carotenoids or provitamin A. Retinoids are the active form. The common food sources for retinoids are animal derived food (eggs, chicken, fish, and meat). Leafy greens, orange and yellow vegetables and nuts are good sources of carotenoids. Vitamin A has a role in growth, vision, epithelial differentiation, immune function and reproduction. The most common symptom of vitamin A deficiency is xerophthalmia with night blindness [81].

Normal levels

The retinol RDA for adults is 3,000 IU for men and 2,300 IU for women [18]. Serum retinol concentration is the most common method used to evaluate vitamin A status. Other methods such as dose response tests and isotope dilution assays attempt to evaluate liver reserves of vitamin A but are not feasible on daily basis.81 Vitamin A deficiency is defined as retinol serum level below 20μ/dL [83].

Causes of deficiency

Vitamin A deficiency is rare in developed nations but remains a concern in developing countries, particularly in areas with poor nutrition. Several factors such as malnutrition and fat malabsorption can lead to vitamin A deficiency. Hypervitaminosis A is seen with long-term supplementation and oral retinoid treatments [84].

Vitamin A and hair

There is genetic evidence that the alfa retinoid nuclear receptor forms a dimer with Vitamin D receptor and plays a major role in controlling hair cycling [85]. Retinoids play a crucial role for the anagen initiation, and depletion of vitamin A results in epidermal interfollicular hyperplasia with keratinocyte hyperproliferation and aberrant terminal differentiation, accompanied by an inflammatory reaction of the skin [86].

Vitamin A deficiency causes ichthyosis-like skin changes and is often associated with telogen effluvium and fragility of the hair [87,88].

Iatrogenic retinoid-induced hair loss is frequently observed in clinical practice. It has been shown that retinoids can inhibit hair shaft formation during anagen and induce premature catagen [89]. Telogen effluvium can occur with isotretinoin therapy (mostly in doses over 0.5 mg/kg/24 h) [90]. This generally occurs after 3 to 8 weeks of treatment and stops 6 to 8 weeks after stopping it. However, telogen effluvium is more common with acitretin treatment in doses of 25 mg or more daily [91]. Isotretinoin - associated telogen effluvium may also be attributed to an effect on the biotinidase activity [90,92].

Treatment recommendations

In vitamin A deficiency, a single dose of 200,000 IU is given by mouth every 4-6 months [82]. Telogen effluvium in the course of systemic isotretinoin treatment has a benign reversible nature and usually requires no treatment.

CONCLUSION

Our results show that the role of micronutrients for the hair follicle function and the mechanisms by which deficiency could lead to hair loss are not completely understood. Empiric treatments of hair loss conditions without confirmed deficiencies have not shown utility.

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Clinical Image

Giant neurofibroma: a localization palpebral

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A 4-year-old child with asymptomatic upper right eyelid mass, observed by the mother since the age of one year, having progressively increased in size. A physical examination revealed a mass of 4 cm taking the upper right eyelid (Fig. 1), of soft consistency with ptosis (Fig. 2). Moreover, the child presented more than 6 coffee milk spots> 5 mm long axis, axillary lentigines without palpable adenopathies (Fig. 3). had confrmed that it was a plexiform neurofibroma associated with a dysplasty of the great right sphenoidal wing. the child was referred to the ophthalmology department for the management of his palpebral neurofibroma.

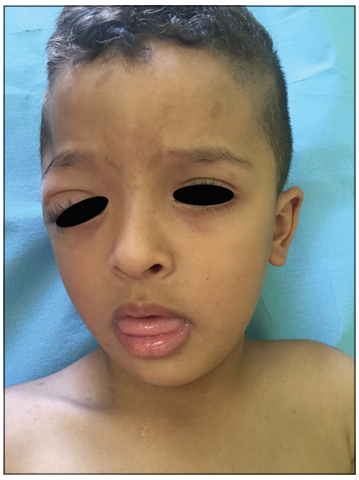

Figure 1: A 4 cm mass involving the upper right eyelid.

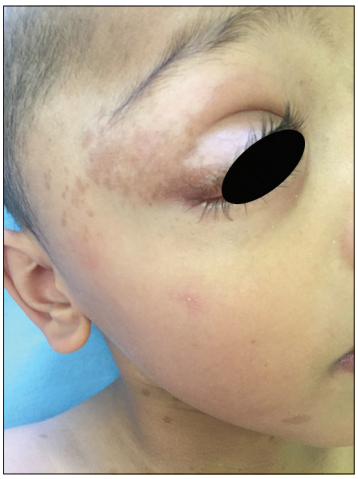

Figure 2: Profile view revealing ptosis.

Neurofibroma is a manifestation of neurofibromatosis type 1 (NF1) or Von Recklinghausen disease, who is an oncogenic condition with an autosomal dominant inheritance pattern [1]. His incidence in children with NF1 is less than 10%. It is identified within the first few years of life. It follows the distribution of the trigeminal nerve [1]. It is manifested by a firm or soft palpebral mass with concomitant eyelid edema and it can lead to a ptosis or strabismus. Plexiform neurofibroma mostly occurs on the trunk and proximal extremities and presents as an occasionally pigmented, bag-like mass [2]. It is associated with pigmented spots (coffee coloured) in the skin, commonly seen on the back, abdomen and limbs (café au lait spots). Axillary freckling and lisch nodules may be present [3]. Magnetic resonance imaging (MRI) of the brain and orbits is needed to confirm diagnosis and to define its extent. The

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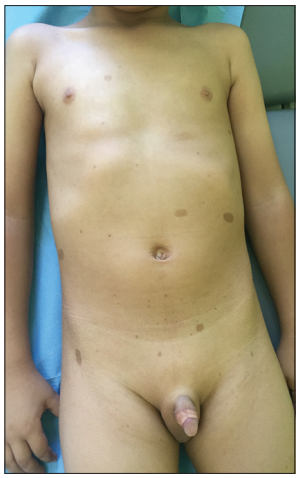

Figure 2: Multiples coffee milk spots > 5 mm long axis.

treatment is mainly surgical, it must be practiced early in order to avoid intraorbital extension and esthetic damage in children.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Letter to the Editor

A Vietnamese case of dyskeratosis congenita

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Sir,

Dyskeratosis congenita (DC) is an inherited bone marrow failure (BMF) syndrome characterized by abnormal skin pigmentation, nail dystrophy, oral leukoplakia, and cancer predisposition, with increased risk of squamous cell carcinoma and hematolymphoid neoplasms. This is a rare disease with an estimated annual incidence of < 1 in 1 million [1]. To the best of our knowledge, there is no report of DC in Vietnam in PubMed or Vietnamese Dermatology literature. Here, we report a case of DC in a Vietnamese man with the classic triad of signs.

A 22-year-old Vietnamese man presented to our hospital with hyperpigmentation and nail dystrophy. The patient had no history of alcoholism, smoking, chewing tobacco, or chronic drug use. He had white and thickened patches in the mouth since birth but had noticed asymptomatic skin pigmentation all over the body, predominantly on the chest, trunk, and arms since 10 years of age. In addition, he had noticed nail deformity when he was 15 years old. Although his sister had no abnormal skin pigmentation or nail dystrophy, his cousin (maternal side) had similar skin symptoms, including hyperpigmentation, nail dystrophy, and leukoplakia.

Clinical examination revealed fine, reticular, grey-brown pigmentation over the whole body, particularly on the neck, chest, arms, and thighs (Fig. 1a). All of the patients nails exhibited dystrophy (Fig. 1b). Leukoplakia was present on the tongue (Fig. 1c). He also had epiphora and hyperhidrosis. Blood pressure and body temperature were within normal ranges. Chest X-ray and abdominal ultrasound revealed no abnormality.

Laboratory examination found a normal white blood cell count (6,350/μL) with 69.9% neutrophils (4,400/μL). However, a low red blood cell count (3,120,000/μL), a low level of hemoglobin (116 g/L), and a low platelet count (38,000/μL) were detected. In addition, bone marrow histology further supported BMF. Histopathology of a skin biopsy obtained from the lesion with pigmentation revealed no abnormal findings, with an increasing amount of melanin and number of melanocytes within the epidermis. However, melanophages and perivascular lymphocytic infiltrates were detected within the dermis (Fig. 1d). We diagnosed DC and the patient has been advised to follow-up every 3 months with a dermatologist and hematologist.

DC is characterized by a triad of nail dystrophy, skin pigmentation, and leukoplakia. It can be associated with BMF, as presented in this case. The skin pigmentation and nail changes usually appear first, before the age of 10 years, and then BMF often develops before the age of 20 years, which was similar to our case [2]. Because a higher prevalence is found in men than in women, with a ratio of 13:1 reported for DC [3], X-linked recessive conditions are suggested to be related to the pathogenesis of this disease. Considering that the patient's cousin had a similar clinical appearance, we should still take the genetic background into account in our case.

Many studies have demonstrated that DC is principally a disease of defective telomere maintenance [1,4]. DC patients normally have very short telomeres, which could be related to the fact that some DC patients are reported to have mutations in different genes encoding components of the telomerase complex [2,4,5]. Previous

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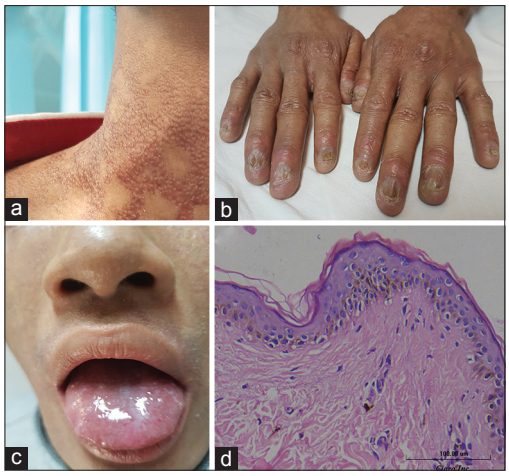

Figure 1: Clinical manifestations and histopathology of the patient. (a) Reticular, grey brown pigmentation on the neck and chest. (b) Nail dystrophy. (c) Oral leukoplakia. (d) Skin histopathology shows increased melanin and melanocytes in the epidermis and melanophages and perivascular lymphocytic infiltrate in the dermis.

electron microscopy studies revealed that cells isolated from DC patients have an embryonic immature nucleus, which could induce malignant transformation [6]. Cancer usually develops after the third decade; the most frequent solid malignancies are head and neck squamous cell carcinomas [7]. Although we have not detected any malignant changes, we need to follow-up with this first case of DC in Vietnam regularly.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Letter to the Editor

Renbök phenomenon: Alopecia areata sparing psoriasis plaques

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Sir,

Researchers have tried to elucidate the poorly understood mechanisms underlying localization of skin lesions leading to dermatoses-specific clinical presentations from some interesting phenomena such as of "co-localization" or "co-existence", "Wolf's isotopic phenomenon", "Koebner's (isomorphic) phenomenon" and recently described "Renbök phenomenon" having only few cases reported as yet.

A 45- year-old man presented with progressively increasing asymptomatic patchy scalp hair loss of sudden onset for one month. He had plaque psoriasis involving scalp and extensors for the last 7 years with infrequent relapses. The lesions used to clear following treatment with topical coal tar 3% solution and shampoo. His family and medical history, and laboratory investigations (complete blood counts, hepatorenal and thyroid function tests, anti-thyroid and antinuclear antibody profile) were unremarkable. Cutaneous examination showed psoriatic plaques localized over vertex and fronto-temporal region and multiple patches of alopecia areata involving the occipital scalp (Fig. 1). The psoriasis plaques were well delineated, confluent and stopped short of alopecia areata patches without any encroachment and showed normal hair growth. The hair loss in patches of alopecia areata was total and spared psoriatic plaques reflecting Renbök phenomenon. He did not consent for skin biopsy. He was prescribed twice daily topical application of betamethasone dipropionate 0.05% lotion and to follow-up regularly.

The phenomenon of "co-localization" or "co-existence" of psoriasis or alopecia areata appearing over vitiligo-affected skin is not uncommon. While structural similarities between anti-stratum corneum antibodies and anti-melanocyte antibodies, and a common neuropeptide have been speculated possible causative factors for co-localization of psoriasis on vitiligo, the melanocyte-derived antigens (melanocyte epitopes) released in pathogenesis of vitiligo are postulated to act like auto-antigens inducing hair loss in co-localizing alopecia areata [1]. The "Wolf's isotopic phenomenon" describes occurrence of a new skin disease at the site of another, unrelated and already healed skin disease and is different from "isomorphic response" described by Koebner as early as 1876 [2]. The "Koebner's (isomorphic) phenomenon" means appearance of clinicopathologically identical skin lesions of an existing dermatosis at the site of injury [3]. While psoriasis remains its classic prototype, this phenomenon also characterizes lichen planus as well as vitiligo. Interestingly, Koebner's phenomenon of psoriasis aggravation over sites of alopecia areata too has been described [4]. Its

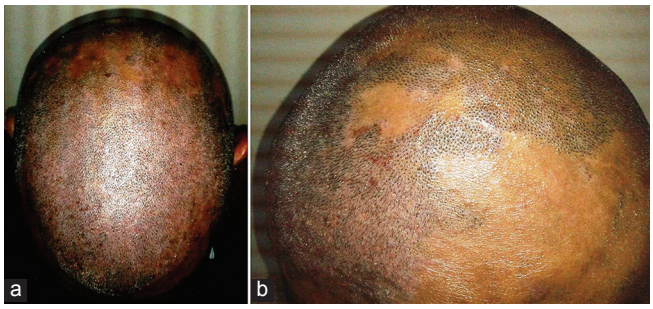

Figure1: (a) Psoriasis lesions with normal hair growth and involving vertex and fronto-temporal scalp stopping just short of alopecia patches. (b) Patches of alopecia areata devoid of hair present over occipital scalp sparing psoriasis lesions.

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pathogenetic mechanisms are poorly understood and immunologic, vascular, dermal, enzymatic, inhibitory, neural, growth, genetic and hormonal factors have been implicated [3]. Contrarily, inverse of Koebner's phenomenon is seen when an area of psoriasis clears or re-pigmentation of vitiligo lesion occurs following trauma (electrodessication, dermabrasion, surgery) [5].

Renbök phenomenon, a reverse of 'Koebner' phenomenon, is a relatively recent term coined by Happle et al [6]. It was considered peculiar to patients with psoriasis having alopecia areata wherein hair growth over psoriatic plaques is normal [7]. Later, its application was expanded to include alopecia areata similarly sparing nevus flammeus or congenital nevus [4]. Its pathomechanism is unknown and it has been hypothesized that in psoriasis (Th-17 mediated dermatoses) and alopecia areata (Th-1 mediated disorder) T-cell subsets by cytokine production enhance their own response through positive feedback while antagonizing the other responses in the affected areas [4,8]. Hence, only a single subset of inflammatory response is seen at a particular site. Criado et al [7] also proposed that the microenvironment of high levels of TNF-α in psoriasis is not favorable for the development of inflammatory response in alopecia areata producing characteristic Renbök phenomenon. However, its exact pathogenesis remains poorly elucidated for paucity of reported cases.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Letter to the Editor

Dermoscopic description of trichoepithelioma in the skin of colour

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Sir,

Skin colored flat topped lesions on the face more often than not pose as a diagnostic dilemma to the treating physician. Establishing the diagnosis in such a case depends generally on the clinical presentation history and invasive diagnostic techniques like histopathology, which however is not very popular on the face owing to the risk of scarring. In recent years dermoscopy is gaining appreciation in the diagnosis of various skin diseases where diagnosis is made by better visualization of the surface and sub surface structures, the permutation and combination of which leads to specific diagnosis.

A 28year old lady presented to the outpatient dermatology department with complaints of asymptomatic raised lesions on the face of 15 months duration (Fig. 1). Although asymptomatic they were slowly increasing in size and extent for which no treatment was taken in the past. The lesions were localized over the centrofacial area. History did not reveal any seasonal variation with regards to the size of the lesions. Medical, family and past history was non-contributory in the patient. Clinical examination revealed multiple, discrete 3mm to 6 mm skin colored flat topped to dome shaped papular lesions localized over the area. The differential diagnosis considered at this stage included syringomas, eccrine hydrocystomas, trichoepithellioma and papular sarcoidosis.

Dermoscopic examination of the lesions revealed a whitish background, in focus arborizing vessels, few lesions in addition demonstrated milia like cysts while others showed rosettes (Fig. 2).

Histopathological examination revealed, well circumscribed dermal tumour with branched nests if basaloid cells, small keratin cysts and a dense collagenous stroma with fibroblasts suggestive of trichoepithelioma.

A diagnosis of trichoepithelioma was established on the basis of clinical examination, dermoscopy and histopathological evaluation.

Trichoepitheliomas are not so common benign hamartomatous tumours of the pilosebaceous unit

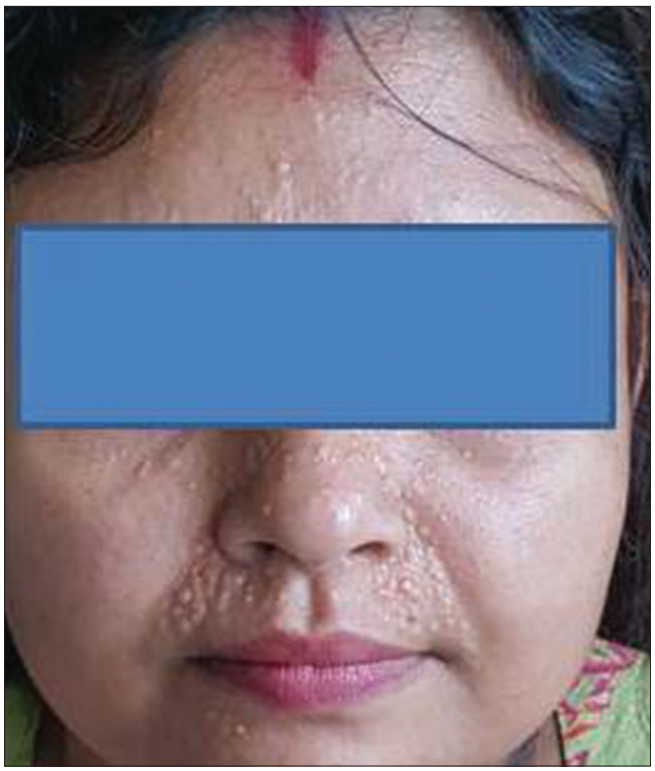

Figure 1: Asymptomatic skin colored flat topped papular lesions on the face in a centrofacial distribution.

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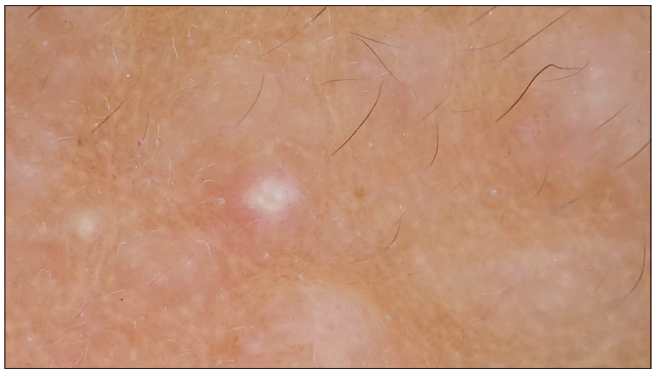

Figure 2: Dermoscopy showing a whitish background, in focus arborizing vessels, few lesions in addition demonstrated milia like cysts while others showed rosettes

which when present cause minor cosmetic concern to the patient. Multiple familial trichoepithelioma constitute an autosomal dominant disease characterized by the appearance of multiple flesh-colored, symmetrical papules, tumors and/or nodules located in the central face and occasionally on the scalp [1]. They may cause functional impairment when present on vital areas like periocular. Although most of the times clinical examination may clinch the diagnosis to a trained eye, it may more often than not pose a diagnostic challenge to many. Dermoscopy forms a non invasive diagnostic technique, the findings of which when interpreted correctly improves the accuracy of diagnosis. While evaluating a papular lesion the parameters evaluated include the back ground colour, vascular pattern, presence of pigmentary network, white shiny structures in the form of milia like cysts or rosettes. Although a facial papule displaying arborizing vessels and shiny white structures under dermoscopy is highly suggestive of basal cell carcinoma, the patient's clinical history and the presence of numerous identical lesions raised the clinician's suspicion for multiple familial trichoepithelioma [2]. Dermoscopy in our patient revealed arborizing vessels, milia like cysts. However most of the lesions in our patient demonstrated the presence of rosettes.

Vascular pattern depicting arborizing vessels or linear vessels suggest the lifting up of overlying skin with vascular proliferation. The background colour whether erythematous or whitish will depend on proliferation of fibroblasts and presence of collagenous material or an underlying inflammatory pathology. The milia like cysts on dermoscopy correspond to the keratinous cysts on histopathology [3]. Rosettes are peculiar structures only observed with polarized dermoscopy and are defined as four white points, arranged as a four leaf clover [4]. Another view suggests that they arise from Interaction of the polarized light with narrowed or keratin filled adnexal openings [5].Others suggested that rosettes correspond to an alternating focal hyperkeratosis and normal corneal layer and keratin filled openings [6]. Haspeslagh et al in their study stated that rosettes are an optical effect of crossed polarization by concentric fibrosis or horny material and hence are not lesion-specific [7]. Also these structures are more commonly seen in actinic skin. This probably explains the demonstration of rosettes in our case of trichoepithelioma where concentric fibrosis was seen on histopathology and also the lesions being located in the actinic area of face.

To the best of our knowledge there is no documentation of rosettes in trichoepithelioma in the skin of color. However continuous observations require to be made and documented in order to suggest rosettes as a consistent finding in trichoepitheliomas in the skin of colour.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Letter to the Editor

Giant vulvar ulcers in the course of adult onset cyclic neutropenia

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Sir,

Genital ulcers may be associated with a variety of clinical disorders such as infectious conditions (streptococcal, staphylococcal infections), syphilis, immune disorders such as lupus erythematosus or scleroderma as well as tumors (squamous cell carcinoma etc). Other conditions such as Behcet or Crohn disease have been associated with genital ulcers.

A 73 year old female was admitted to the Internal Medicine Unit of our hospital for fever, malaise, fatigue that started a week before admission. She complained of lesions on her genitalia that provoked difficulty in urination and reported similar episodes for which she had been hospitalized in a Gynecology Departement but no specific diagnosis has been made. On admission she had fever 39 Celsius and the skin examination revealed two giant ulcers on both right and left inner side of the thighs with raised erythematous sharp demarcated borders and purulent center, as well post -inflammatory healing lesions on the lower part of the abdomen (Fig. 1).

The day of the admission WBC count was 900/mm^3, with neutrophils count 400/mm^3 with Hgb7,6gr/dl and Hct24,7%. Because of the fever a broad spectrum antibiotic combination was started associating ceftriaxone and aminoside. The WBC count had gradually restored to normal with WBC 1900/mm^3 and neytrophils 900/mm^3 the 3rd day of her hospitalization and WBC 2500/mm^3, RBC 4120000M/μl, Hgb9,1gr/dl and Hct 28,7% the sixth day of her hospitalization. Bone marrow examination was performed and proved normal apart a focal increase of lymphocytes. Differential diagnosis of the genital ulcers include infectious diseases, such as syphilis, neoplastic disorders, Chrohn disease, Behcet disease and other. Serology of syphilis, Herpes 1 and 2, HIV 1 AND 2, Ebstein Barr, Cytomegalovirus, Parvovirus B19 were performed and were negative. Hemocultures taken during the feblile period yielded no bacteria or fungus A biopsy taken from the borders of the ulcer found non specific inflammation and no signs

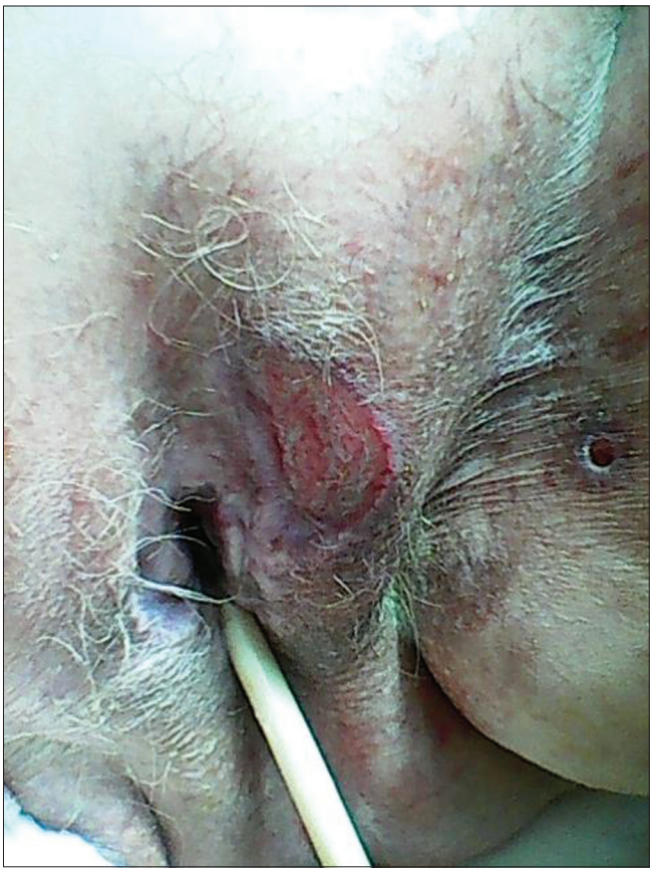

Figure 1: Giant genital ulcer in patient with adult onset cyclic neutropenia.

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of vasculitis,therefore eliminating Behcet disease. Although no symptoms from the digestive tract were present a colonoscopy was performed. This revealed an ulcer in the terminal colon and a biopsy had been taken. The findings were similar with that of the skin biopsy showing non specific inflammation and no signs of vasculitis, enabling to exclude the diagnosis of Chrohn disease. The hematological findings, the decrease in the total WBC count and neutrophils, the progressive restoration to their normal levels within six days, the increase of lymphocytes in the bone marrow and the same repeated episodes in the past confirm the diagnosis of adult -onset neutropenia.

Cyclic neutropenia is a rare benign hematological disorder of very low frequency of 1:1000000 one in one million in the general population [1]. Decrease of white blood cell and neutrophil count occur at monthly intervals five or six times a year with restoration to normal levels within a week. Two types of the disease have been described one occurring in children with more severe course and a milder one in adulthood. Pathogenesis of the disease involves reduced neutrophil production due to accelerated apoptosis of neutrophil precursors. Most patients with cyclic neutropenia experience oral ulcerations, gingivitis, lymphadenopathy, pharyngitis, tonsillitis, sinusitis otitis media as well as skin infections [1,2]. The disease has a chronic course although spontaneous remissions have been described. Diagnosis is based on past medical history, on serial measurements of the absolute neutrophil count and on clinical findings. Treatment consists of administering antibiotics and G-CSF (granulocyte-colony stimulating factor) which reduces the duration of the neutropenic episodes as well as the risk of bacterial infection and improves quality of life.

Although adult onset cyclic neutropenia is a rare clinical condition the presence of genital ulcerations associated with fever should alert the physician towards this rare disorder in order to recognize it in time and avoid infectious complications such as bacterial or even fungal infections during the neutropenic phases. A thorough and detailed past medical history should accompany a meticulous clinical examination.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Letter to the Editor

Usage of unsaturated esters of retinol to defeat Hopf's acrokeratosis verruciformis in hands and feet of a young man

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Sir,

Hopf's Acrokeratosis verruciformis is a rare genodermatosis with an autosomal dominant mode of inheritance. Acrokeratosis verruciformis is a disorder of keratinization characterized by multiple flat-topped, skin-colored keratotic lesions resembling plane warts typically observed on the dorsum of the hands and feet. Hopf first suggested the name acrokeratosis verruciformis in 1931 [1].

Lesions identical to those of acrokeratosis verruciformis are also observed in many patients with acral Darier disease (also termed keratosis follicularis) or even in relatives of individuals with Darier disease. Considerable controversy surrounds the nature and relationship of acrokeratosis and Darier disease and whether they are manifestations of one genetic abnormality. Some authors suggest that acrokeratosis verruciformis of Hopf and Darier disease are distinct entities, while others maintain that they are variable expressions of the same disease, with the former being a mild expression or a forme fruste of the latter. Recent genetic studies review show these may be distinct entities that are allelic variants [2].

Darier disease (keratosis follicularis) is the most important disorder to be distinguished from acrokeratosis. Darier disease, acrokeratosis verruciformis, epidermodysplasia verruciformis, plane warts, and seborrheic keratoses can be differentiated on the basis of histologic examination findings from biopsy samples from individual lesions. The hard nevus of Unna can be differentiated clinically on the basis of its late onset [3].

Acrokeratosis verruciformis is usually present at birth or manifests in early childhood. Onset may be delayed until the fifth decade of life.

Lesions tend to persist throughout life and become more prominent following prolonged sun exposure.

The only effective treatment is superficial ablation. Treatment is not generally recommended, but medical and surgical treatments have been tried. Applications of retinoids [4] have been helpful in some individuals. Oral natural vitamin A derivatives have also been reported to have some success. Destruction of the lesions with cryotherapy or laser, especially destructive lasers such as a carbon dioxide laser, may be used. Untreated lesions persist and become more noticeable after prolonged sun exposure because of darkening.

We describe the case of a 21-year-old man who came in our clinic with skin-coloured, flat, warty papules localized to the dorsum of the hands and feet. Both clinical and histological findings were compatible with acrokeratosis verruciformis.

Skin biopsy was performed and histological examinations showed acanthosis with mild papillomatosis.

There was also hyperkeratosis marked at the edge of the lesions with slight hypergranulosis and a very thin film of orthokeratosis.

The circumstant dermis was infiltrated with mild inflammatory cells surrounding the vessels.

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Both clinical and laboratory findings hadshowed the presence of a real Hopf's Acrokeratosis verruciformis.

Patient was treat the case with retinoids, but not retinyl palmitate or acetate, but the unsatured one:the linoleate, cause it has been demostred that even in the diet the usage of unsatured acids is preferable to saturated acids to combat all types of dermatities [4]. We suggested to him to take every day of the treatment even a food supplement (capsules containing 10,000 International Units of Retinyl palmitate).

The applications were to be done three times pro day for 12 days and we have repeated the clinical and the lab tests after 12 days. We observed that skin-coloured, flat, warty papules localized to the dorsum of the hands and feet were fully disappeared,idest we repeated the skin biopsy and now the histological examinations showed no more acanthosis and/or papillomatosis. We did not notice hyperkeratosis at the edge of the lesions and hypergranulosis was absolutely absent. No types of inflammatory cells surrounding the vessels were noticeable.

Many researchers have revealed that the stratum corneum penetration (called Emax) tends to increase with the octanol solubilities of the fatty acids to be spreaded onto skin and decrease with their lipophilicities [5].

Unsaturated acids are less lipophilic (minor octanol partition coefficient) than saturated ones and since Emax of solid fatty acids has been shown to depend on their melting points, linoleic acid presents a melting point lower (-5°C) than acetic (16.6) or palmitic acid (62.9) [6].

The lipophilic lotion we have applied by our patient was retinyl linoleate (15%) in sesamum indicum oil.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

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Letter to the Editor

Eccrine hidrocystoma: A brief report

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Sir,

A 48 year old female presented to us with multiple asymptomatic papules around eyes since 15 days. She had similar complaints from past 4 years. She gave history of exacerbation of these lesions in summer season and spontaneous remission in rainy season. There were no systemic complaints. On cutaneous examination, multiple translucent dome shaped papules of nearly 0.5 cm were present in peri orbital area (Fig. 1). Systemic examination was normal. Simple puncture of a papule with a sterile needle exuded small amount of serous clear fluid. Routine investigations were under normal limits. Histopathology suggested unilocular dermal cystic lesion lined by two layers of cells lined by cuboidal cells. The features were suggestive of Eccrine Hidrocystoma.

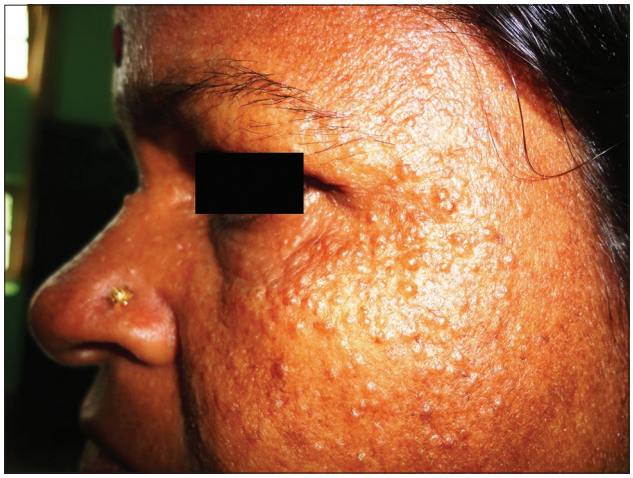

Figure 1: Multiple dome shaped translucent papules in periorbital area.

Hidrocystomas are rare benign cystic skin tumours. They are classified as Eccrine and apocrine Hidrocystomas. While the former represent retention cysts of the Eccrine duct, the latter arise from the apocrine secretory coil [1]. Eccrine Hidrocystomas (EC) are of two types; the classic Robinson type (multiple type) named after his first discovery of EC in women with multiple facial lesions who were working in hot and humid environment and the Smith and Chernosky type (solitary type) named after Smith and Chernosky who reported patients with a solitary lesion [2]. They are seen predominantly on face, usually in periorbital area as cystic papules of about 1-3mm in diameter. However head, trunk and popliteal fossae may also be affected [2]. It is prevalent in adults between 30 and 70 years of age and shows predilection for females, more so with the multiple type [3]. The peculiarity of EC is that the lesions worsen in summer and remit in winter. Its exact pathogenesis is not elucidated. However the hypotheses proposed are poral closure causing secondary dilatation of sweat duct or adenomatous proliferation of the excretory duct [4]. Although apocrine hidrocystomas (AH) can mimic EH clinically, there are certain differences to be noted. The cysts in AH are usually larger, with a diameter of 3 to15mm, darker blue in colour and they are more often seen along the eyelid margin near the inner canthus rather than the periorbital region. Unlike EC, no seasonal variation is seen and they are usually solitary at presentation although there are reports of multiple lesions over face, forearms, anterior chest, axillae and labia majora [5]. Histopathology aids in confirming the diagnosis. AC are multilocular cysts in the dermis lined by myoepithelial cells and secretory columnar cells with decapitation secretion. The cysts have papillary projections and periodic acid Schiff (PAS) positive and diastase–resistant granules in secretory cells. EC usually

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have a single cystic cavity lined by two layers of cuboidal cells. They do not feature myoepithelial cells, papillary projections, decapitation secretion and PAS positive diastase resistant granules [6]. Treatment options include simple needle puncture which gives temporary improvement, microdermabrasion, electrodessication. There are few reports of improvement with topical atropine and scopolamine, pulsed dye laser and botulinum toxin A [7].

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Letter to the Editor

Dermosccopic features of progressive cribriform and zosteriform hyperpigmentation

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Sir,

Progressive cribriform and zosteriform hyperpigmentation (PCZH), first described by Rower et al. in 1978, is a distinctive clinicopathological pigmentary disorder of the skin [1]. PCZH refers to an asymptomatic dermatosis consisting of a single area of uniformly tan, cribriform, macular pigmentation in a zosteriform distribution; histological pattern consisting of mild increase in melanin pigment in basal cell layer and complete absence of nevus cells. It had onset well after birth with no reported systemic associations. Di Lernia et al. [2], suggested that PCHZ should be considered as a part of spectrum of Linear and Whorled Nevoid Hyperpigmentation (LWNH) as apart from later age of onset, there was no difference between the two disorders clinically and histopathologically. They also proposed the terms 'Diffuse LWNH' for previous reported cases of LWNH and 'Localized-form' for PCZH [3].

An otherwise healthy 30 year old lady presented to the dermatology outpatient department of with a four-year history of asymptomatic dark patches confined to the right side of her arm. Brownish macules with a cribriform configuration extended linearly from the lower part of right upper arm to the fore arm area on the dorsal and ventral side (Fig. 1). Examination of her hair, nails, and mucosae did not reveal any abnormality. The lesions had first appeared over the upper arm, four years earlier, and had gradually progressed in linear fashion to their present extent. There was no history of trauma, inflammation, or use of any topical application on the involved areas prior to development of the lesions. Past medical history and family history were non-contributory. Our clinical differential diagnoses included lichen planus pigmentosus, verrucous epidermal nevus, reticulate pigmentary disorder,non hypertrichotic variant of Becker's nevus and linear and whorled nevoid hypermelanosis.

Overview of the dermoscopic image reveals small islands of accentuated pigment (Fig. 2). Dermoscopy

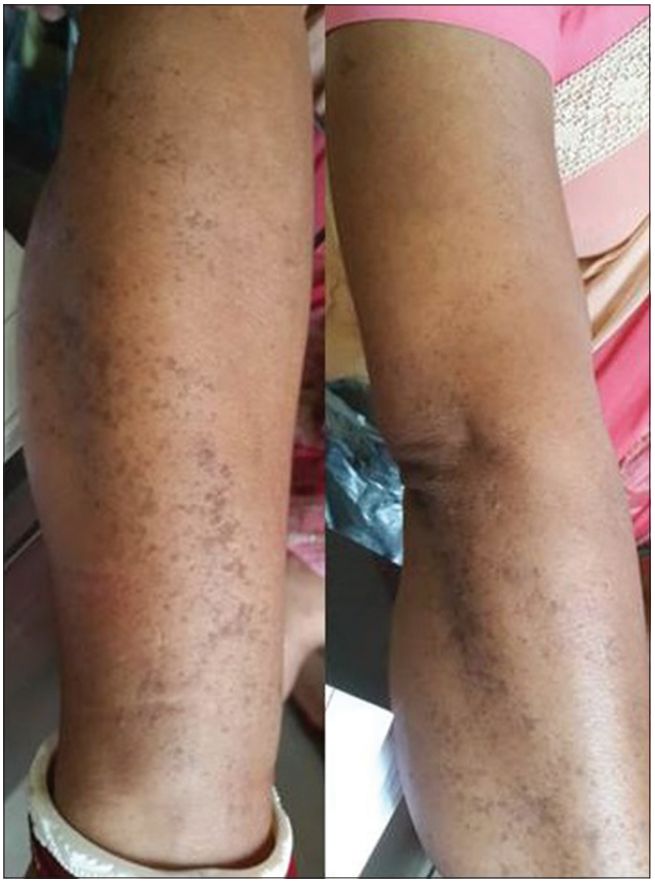

Figure 1: Brownish macules with a cribriform configuration extended linearly from the lower part of right upper arm to the fore arm area on the dorsal and ventral side

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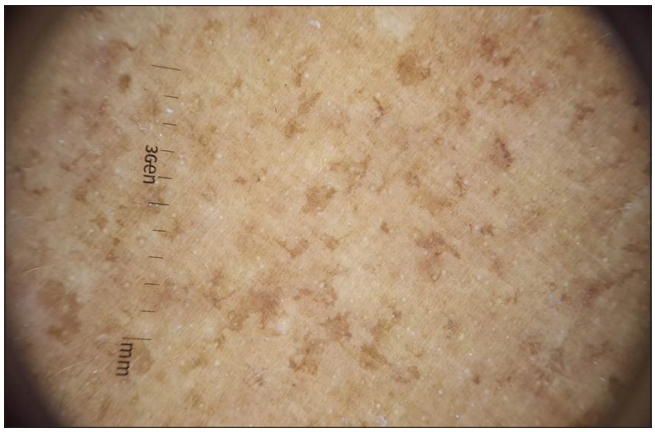

Figure 2: Dermoscopic overview showing small islands of accentuated pigment

Figure 3: Dermoscopy of the hyperpigmented areas revealed accentuation of melanin network, areas with greyish homogenous hyperpigmentation and brown dots and globules

of the hyperpigmented areas revealed accentuation of melanin network, areas with greyish homogenous hyperpigmentation and brown dots and globules (Figs. 3 and 4a). Hyperpigmented lesions may show finger print like structures (Fig. 4b). Rosettes were noted occasionally.

A skin biopsy from a representative forearm lesion revealed elongated epidermal rete ridges with hypermelanisation of the basal layer. Pigmentary incontinence was noted in focal areas. Melanophages, and dermal inflammatory infiltrate were not seen. Also, nevus cells were completely absent. Lichen planus was ruled out based on the absence of basal layer degeneration and interface dermatitis. Epidermal nevus could be reliably excluded due to the lack of characteristic epidermal changes.

Based on clinicodermoscopicpathological correlation, we made a diagnosis of progressive cribriform and zosteriform hyperpigmentation.

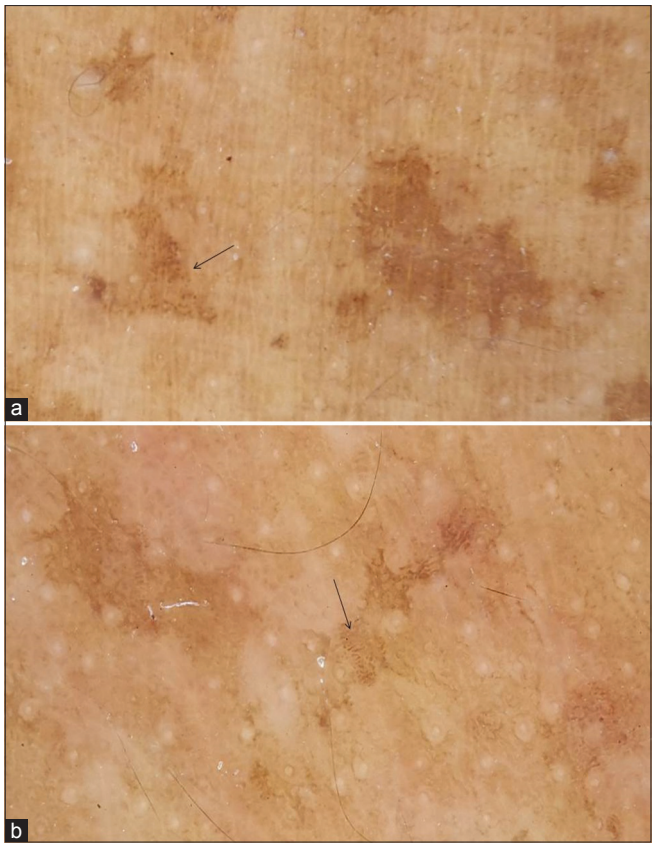

Figure 4: (a) Dermoscopy of the hyperpigmented areas revealed accentuation of melanin network, areas with greyish homogenous hyperpigmentation and brown dots and globules, (b) Hyperpigmented lesions showing finger print like structures

This distinctive pigmentary dermatosis has five diagnostic criteria: (a) uniformly tan cribriform macular pigmentation in a zosteriform distribution, (b) histology showing an increase in basal layer melanin along with complete absence of nevus cells, (c) absence of history of rash, injury, or inflammation to suggest post-inflammatory hyperpigmentation, (d) onset well after birth with gradual extension, and (e) lack of other associated cutaneous or internal abnormalities [1,4].

The etiopathogenesis of progressive cribriform and zosteriform hyperpigmentation is possibly related to somatic mosaicism that develops during embryogenesis [5]. Another hypothesis postulated stated that clonal migration and proliferation of embryonic melanoblasts along the Lines of Blaschko could be the underlying mechanism behind this condition.

Histopathological correlate of hypermelanisation of rete ridges points towards the dermoscopic accentuation of the melanin network. Areas of greyish homogenous pigmented areas correlates with areas of

pigment incontinence. Pigment incontinence has been reported in 13/30 cases by Cho et al [6]. The occurrence of rosettes could be attributed to the actinic area of distribution of lesions. This can be differentiated from lichen planus pigmentosus where the melanin network remains uncharacterized and pigmentary pattern is characterized by the presence of brown dots and globules with either diffuse or mixed pattern of pigmentation.

The dermoscopic description of this entity has not been described in literature so far and doesnot find its position even in the diagnostic criteria. We propose that a constellation of accentuation of melanin network, areas with greyish homogenous hyperpigmentation, finger print like structures along with clustered brown dots and globules could provide a clue towards this entity.

To the best of our knowledge this is the first ever time that the dermoscopic description of this entity is being reported and we request continuous observations of these findings in different skin type and further documentation of the same to establish it as one of the diagnostic criteria for this uncommon entity.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Historical Article

Dermatology Eponyms – sign –Lexicon (S). Part I

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ABSTRACT

Eponyms are used almost daily in the clinical practice of dermatology. And yet, information about the person behind the eponyms is difficult to find. Indeed, who is? What is this person's nationality? Is this person alive or dead? How can one find the paper in which this person first described the disease? Eponyms are used to describe not only disease, but also clinical signs, surgical procedures, staining techniques, pharmacological formulations, and even pieces of equipment. In this article we present the symptoms starting with (S) and other. The symptoms and their synonyms, and those who have described this symptom or phenomenon.

Key words: Eponyms; Skin diseases; Sign; Phenomenon

Saber Shin sign

The sharp delimitation characteristic of a syphilitic skin lesion and Scars on the mouth following the healing of lesions in congenital syphilis [1]. Anterior bowing of the tibia, seen in some children with congenital syphilis (Fig. 1). Also known as Fournier's sign.

Jean Alfred Fournier

French dermatologist, 1832-1914 (Fig. 2). He specialized in the study of venereal diseases. In 1876 he was appointed chef de service at the Hôpital Saint-Louis, and in 1880 became a member of the Académie de Médecine. His main contribution to medical science was the study of congenital syphilis, of which he provided a description of in 1883. In his numerous publications he stressed the importance of syphilis being the cause of degenerative diseases. His name is associated with the following three medical terms: Fournier's gangrene: Gangrene caused by infection of the scrotum and usually associated with diabetes. Although the condition is named after Fournier, it was first described by a physician named Baurienne in 1764. Fournier's sign, Fournier's tibia [2].

Sabia sign

South America fever and bleeding caused by the zoonotic Brazilian hemorrhagic fever *Arenaviridae virus* [3].

Sacral sign

Pitting oedema over the sacrum [4].

Saint Gervasius's sign

During the Middle Ages, "St. Gervasius' disease" became a popular name for any rheumatic affliction.

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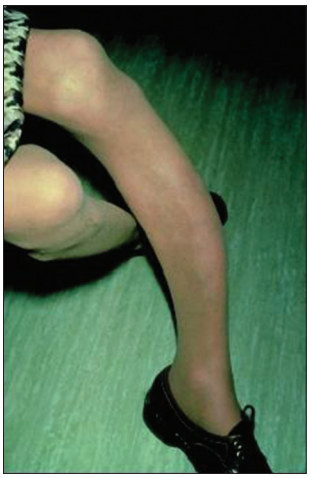

Figure 1: Saber Shin sign.

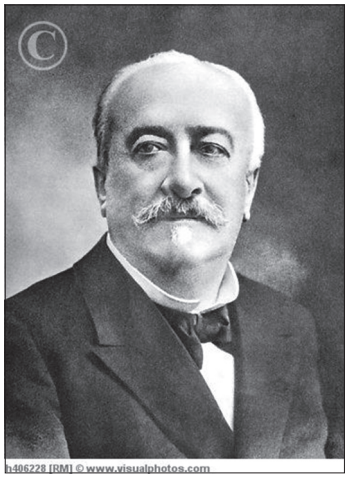

Figure 2: Jean Alfred Fournier.

During the Middle Ages, "St. Gervasius' disease" became a popular name for any rheumatic affliction. St. Gervais-les-Bains has been a well-frequented spa on the Bon-Nant River in Southeast France since Roman times. It would be hard to ascertain if the disease was named after the saint or the town. Benjamin Lee Gordon, the medical historian, noted that the eponym was derived from the Babylonian and Persian. According to the St. Andrew Daily Missal, Sts. Gervase and Protase, sons of St. Vitalis and St. Valeria, "were martyred under Nero at Milan (first century). Gervase was beaten to death and Protase, after having been scourged, was beheaded." Whether St. Gervase was afflicted with a rheumatic disease is not revealed [5].

Saint Giles's sign

The epicentre of the Great Plague of 1665 was also the location of London's primary medieval leprosy hospital. To the likes of Samuel Pepys, Nell Gwynn and Charles II, St Giles in the Fields was London's largest outer parishes. Close to the capital's burgeoning playhouses, it was a dirty, disorganised and poverty-stricken suburb of ramshackle tenements (just under 2000 households in total) and narrow streets, containing inns, brothels, butchers, watchmakers, booksellers, beltmakers, justices of the peace and nobility. Cosmopolitan and heavily populated, at its centre was the parish church of St Giles in the Fields, rebuilt in the late 1620s/early 1630s upon the site of the medieval original. It was a place that became synonymous with plague and the deaths of tens of thousands of Londoners.

In the early twelfth century, the space that the London parish of St Giles in the Fields would later occupy was a green expanse of open fields and fresh air, well outside the capital. The only sign of habitation came from a newly-built hospital or 'leprosarium', that provided sanctuary for 'lepra' sufferers, away from the populous of London. At the time of the hospital's foundation, the word 'lepra' (from the Latin 'scaly') was a catch-all term used to describe those suffering from a range of debilitating skin conditions, such as eczema, psoriasis, skin cancer. As well as being one of the earliest in England, St Giles was also the first leprosarium associated with London. St Giles was positioned on the main throughway to London from the west. The arrival of The Black Death in 1348, and its undeniably contagious nature, led to a fear – for the first time – that leprosy might also spread through miasma (the Galenic idea of 'bad air'). St Giles was no exception. In 1542, a burial ground was annexed to the church. As London swelled, the village of St Giles grew in tandem and became the parish of St Giles in the Fields. By 1665, it had transformed into an overcrowded London suburb, notorious for its poverty and crime, and the burial place of over three thousand plague victims [6].

Saint Giles's Black sign

Saint Giles (c. 650 AD – c. 710), is a Patron Saint of Breast Cancer (Feast Day - September 1st) [7].

Saint Guy's sign

Dancing in wild delirium often for many hours accompanied with an irrational fear of demons and drowning in blood, as well as, sometimes visions of heaven and the Savior enthroned with the Virgin Mary. An indication of ergot poisoning. Also known as chorus sancti viti, the lascivious dance, choromania, tanzplage,

and orchestromania. Most commonly called Dancing Madness Sign [8].

Saint Job's sign

In the 15th and 16th centuries, people sought to protect themselves against a new disease that the physician Gaspare Torella (1452-1520) named the scourge of God. In seeking comfort in faith and prayer for God's forgiveness, the supplicants prayed to the saints to intercede on their behalf to help them recover from this new disease of syphilis, which was identified variously by the saints' names. Syphilis became known as Saint Mevenno disease, Saint Minus disease, Saint Mento disease, Saint Maino or Saint Job disease [9]. Saint Job disease (male de Yob or Giobe disease, Giobbe disease, or le fiebres Sainck Yob) refers to the biblical Job, who paiently accepted all the plagues that affected him.

Saint Lazare's sign

Synonym of Leprosy. The Military and Hospitaller Order of St. Lazarus of Jerusalem (OSLJ) is a religious/military order of chivalry which originated in a leper hospital founded by Knights Hospitaller in the twelfth century by Crusaders of the Latin Kingdom of Jerusalem. Sufferers of leprosy regarded the beggar Lazarus as their patron saint and usually dedicated their hospices to him. His name corresponds to Hebrew רזעלא 'el' azar ("God saved") [10].

Saint Louis headache sign

Fever, headache, disorientation, coma, encephalitis with cerebellar involvement, can progress to mortality. Caused by the bite of a mosąuito infected with the zoonotic St. Louis encephalitis flavivirus [11].

Saint Main's Evil sign

The sign of a patient suffering from scabies. Also called Saint Main's disease.

Saint Rochs sign

Synonym of plague [12]. Saint Roch is a patron saint of plague victims.

Saint Semen's sign

Synonym of sypliilis.

Saldana sign

Fever, pancytopenia, hepatosplenomegaly, caused by the zoonotic transmission of a protozoal Leishmania species by the bite of phlebotomine sand flies. The disease can exist in visceral, cutaneous, and mucosal forms [13,14].

Salt sign

A form of enzootic marasmus due to a cobalt deficiency [15].

Saluting sign

The "allergic crease" together with the "allergic shiner" (darkening of the lower eyelid) and the "allergic salute" constitute the three facial hallmarks of these patients. This is the characteristic habitual gesture of wiping and/or rubbing the nose in an upwards or transverse manner with the fingers, palm, or back of the hand. It is termed a salute because the upward movement of the hand acts as an unintentional gesture [16].

Samitz's sign

Dystrophic and ragged cuticle seen in dermatomyositis is called as Samitz sign [17,18].

Sandal sign

The gap between the first and second toes is a typical finding in trisomy 21 (Fig. 3). The feet are broad and short. The plantar surfaces are creased with a deep long furrow (ape-line) between the first and second toes [19]. Also called as "thong sign".

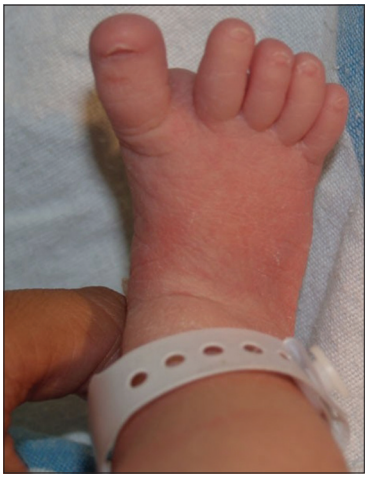

Figure 3: Sandal sign

Sandwich sign

In dermatophytosis, fungi are present in the horny layer between two zones of cornified cells, the upper being orthokeratotic and lower consisting partially parakeratotic cells (Fig. 4) [20].

Sandworm sign

Inflammation and spiral erythema on the inner side of the sole [21,22].

Schönlein's sign

Purpura rheumatica (Fig. 5). Also called Schönlein's disease [23-25].

Johann Lukas Schönlein

German physician, 1793-1864 (Fig. 6). Johann Lukas Schönlein is reckoned among the most important medical secientists of the Biedermeier Zeit, the period following the Napoleonic wars, 1815 to 1858, in Germany. The work of Schönlein contributed greatly to the establishment of medicine as a natural science and, above all, to the development of modern methods in the teaching and practice of clinical medicine.

Schönlein grew up in a Bamberg which was one of the cradles of German hospital medicine. His interests however, were not in medicine, but in natural knowledge, which experienced a period of scientific advances in the beginning of the nineteenth century.

In 1811 he began his studies of the natural sciences, particularly under Georg Augustin Bertele at the University of Landshut. Schönlein changed his course to that of medicine, and already whilst a student he sought beyond the ordinary medical curriculum and concerned himself with comparatory anatomy, particularly under Friedrich Tiedemann. One of his other important teachers in the main curriculum was Martin Muenz. In 1813 Schönlein went to Würzburg to continue his education. His special field of interest was the anatomy of the brain, which was the topic for his doctoral thesis in 1816, Von der Hirnmetamorphose - an unusually long dissertation of 140 pages that clearly demonstrates his inclination towards natural philosophy. After reciving his doctorate, Schönlein in 1816 left Würzburg, still not considering a clinical career. Hoping for a position with the Dutch East India Company, to have the opportunity to undertake studies in natural history.

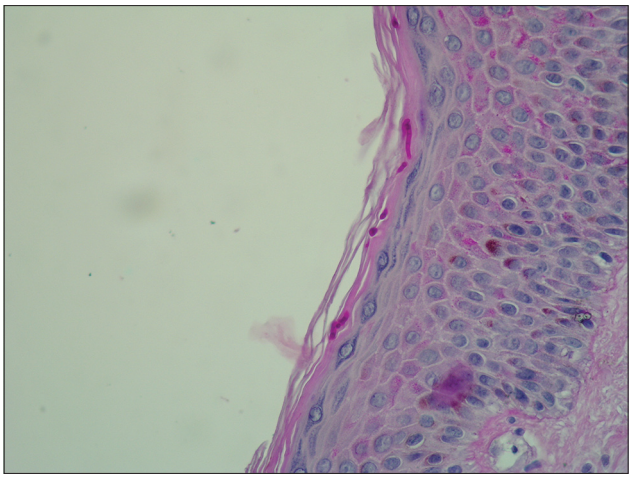

Figure 4: Sandwich sign.

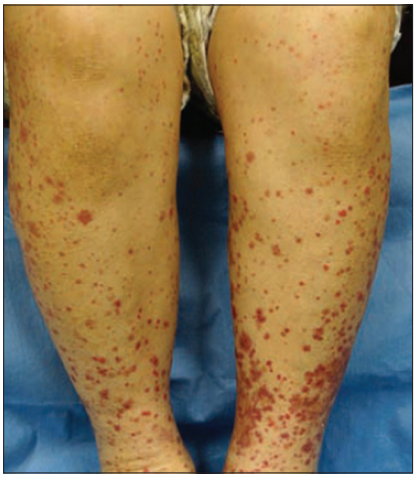

Figure 5: Schönlein's sign.

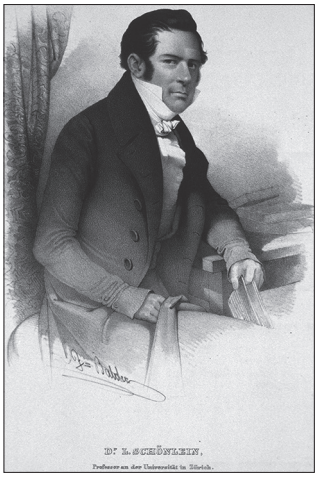

Figure 6: Johann Lukas Schönlein.

In the autumn of 1817, by the support of Döllinger, Schönlein was habilitated as Privatdozent at the University of Würzburg. In the spring of 1818 he commenced lecturing on pathological anatomy,

later also on diseases of the eye, children's diseases (1818/1819) and public health.

Because of his liberal political views Schönlein was fired from his academic position in 1832. Instead of accepting a transfer to Passau as Kreis-Medicinalrath, he quit his job. Due to the Frankfurt Attentat he feared arrest and fled to Switzerland, where in 1833 he became the first professor of medicine at the newly founded Hochschule in Zurich. In 1839 he returned to Prussia to take over the chair of clinical medicine in Berlin, entering this position in 1840. He was also appointed personal physician to king Frederick William IV (reigned 1840-61). Schönlein was the founder of the natural historic school of studies and classification of medicine, introducing methods equivalent to those used in botany and zoology. He enjoyed the reputation of an exceptionally competent teacher among his students; he laid the foundation for this reputation while in Würzburg, and it would follow him through the rest of his teaching career. At the Berlin Charité he was the first to lecture on medicine in German rather than in Latin and introduced into Germany modern methods of clinical investigations like percussion and auscultation, and he was the first to use the microscope in conjunction with chemical analyses of urine and blood for diagnosing diseases. His introduction of bedside teaching was a novelty that quickly enhanced his reputation as a teacher. A number of positions that had previouslyy been reserved for military physicians, under Schönlein were given to civilian physicians.

Schönlein conducted his clinical teaching in much the same way that patients are presented to the students today, with a presentation of case history, chemical, physical and microscopic findings. He would control these findings and instigate a discussion towards a diagnosis, then discuss etiology and therapy with the students. If the patient died, there would be a discussion of the pathological findings and errors in the diagnosis.

Schönlein wrote relatively little - his doctoral thesis and two papers of 1 and 3 pages respectively. Still, despite his lack of enthusiuasm for writing, it was Schönlein who introduced the terms haemophilia and tuberculosis (1839). The word "tuberculosis" was derived from "tubercle", a word introduced by the English physician Richard Morton (1637-1698) in 1689 to describe the characteristic lesions of consumption.

Schönlein's description of purpura rheumatica was written down by his students and published in Allgemeine und specielle Pathologie und Therapie, a work containing true empirical medicine. In it he descriebes the peteccies and the associated joint troubles - Schönlein's purpura [26].

Screwdriver Teeth sign

There are depressions or notching of the incisal edges of the labial surfaces of the permanent incisors (Fig. 7). A sign of congenital syphilis [27]. Also called Hutchinson's Incisor sign or Teeth sign.

Sir Jonathan Hutchinson

English surgeon and pathologist, 1828-1913 (Fig. 8). In 1851 he studied ophthalmology at Moorfields and was an ophthalmologist to the London Ophthalmic Hospital. He was also venereologist to the Lock

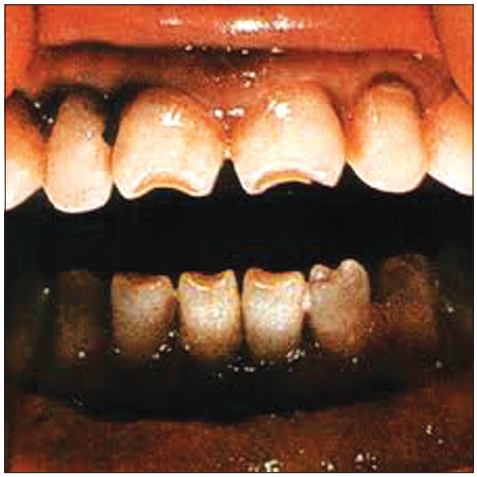

Figure 7: Screwdriver Teeth sign.

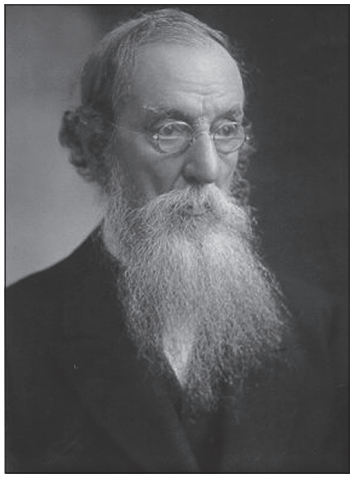

Figure 8: Sir Jonathan Hutchinson.

Hospital, physician to the City of London Chest Hospital, and general surgeon to the London and Metropolitan Hospitals. From 1859 to 1883 he was surgeon to the London Hospital, and he also worked at the Blackfriars Hospital for Diseases of the Skin, being elected to the staff in 1867 and becoming senior surgeon. Hutchinson developed a special interest in congenital syphilis, which was common in London in his time, and he was responsible for delineating the natural history of the disorder. It is said that he saw more than one million patients with syphilis in his lifetime. Hutchinson had a vast clinical experience and he published his observations in more than 1,200 medical articles. Despite his busy practice he produced the quarterly Archives of Surgery. For a brief period of time he was the editor of the British Medical Journal. In England the term morbus Hutchinson-Boeck has been used for benign lymphogranulomatosis, now commonly known as Boeck's sarcoid. In January 1869, a 58 year-old coal-wharf worker, John W, attended Jonathan Hutchinson at the Blackfriars Hospital complaining of purple skin plaques, which had gradually developed over the preceding two years, somewhat symmetrically on his legs and hands. They were neither tender nor painful and did not ulcerate. Hutchinson considered that the skin lesions were in some way related to the patient's gout. His name is associated with: Bernard-Horner syndrome (Claude Bernard), Hutchinson's angina, Hutchinson's dehidrosis, Hutchinson's disease, Hutchinson's facies, Hutchinson's freckle, Hutchinson's mask, Hutchinson's melanotic disease, Hutchinson's patch, Hutchinson's prurigo, Hutchinson's pupil, Hutchinson's sign 2 (Sir Jonathan Hutchinson), Hutchinson's teeth, Hutchinson's triad, Hutchinson-Gilford disease [28].

Scrub Typhus sign

Mite bites followed with severe headache, shivering, and rash. A sign of Scrub Typhus fever, also called Mite fever [29].

Schultz-Charlton reaction

Schultz-Charlton reaction phenomenon [30,31]. The specific blanching of a scarlatinal rash at the site of intracutaneous injection of scarlatina antiserum. Also called Rash-extinction sign.

In 1918, Schultz and Charlton1 first reported that the intracutaneous injection of from 0.5 to 1 cc. of normal or scarlet fever convalescent serum would blanch the rash of scarlet fever at the site of injection. They also showed that the blanching substance was present in serum taken after the fourteenth day of scarlet fever, but that serum taken earlier in the disease did not have blanching power. Plain horse serum or diphtheria antitoxin failed to blanch the rash. Schultz and Charlton also made injections of a dilute solution of epinephrine hydrochloride intracutaneously, and found that the rash blanched within a few minutes. This blanching lasted five or six hours. In contrast, the reaction produced by scarlet fever convalescent serum appeared only after five or six hours and lasted several days. Schultz and Charlton expressed the belief that human serum contained some vasoconstricting factor which counteracted the vasodilating effect.

Scratch sign

This sign is to be elicited in patients having pityriasis versicolor, wherein the barely perceptible scales are made to stand out by scratching the lesion with fingernail [32]. Also calles as coup d'ongle sign, Besnier's sign or stroke of the nail.

Seat Rash sign

Sign from IndoChina, c. 19th century. Described urticarial buttocks lesions on French soildiers, caused by the zoonotic *Strongyloides stercoralis* roundworm [33].

Seeping sign

Just after birth a seemingly healthy child begins to bleed from the mucous surfaces and from the navel [34]. A sign of syphilis haemorrhagic neonatorum. The first survey was made by Mraček, who described a series of cases of syphilis haemorrhagica neonatorum and demonstrated the pathologic changes in blood vessels and capillaries. In 1875 Bälz described 3 cases of hemorrhagic syphilis. One patient suffered from a papulosquamous syphilid with capillary bleeding combined with hemorrhage from different points and in the lungs.

Seoul Fever sign

Rapid fever, kidney failure, severe back pain, and bleeding rash which progresses to death in 15 percent of victims [35]. Caused by a zoonotic hantaviral infectious process known as hemorrhagic fever with renal syndrome disease.

Septic sign

A disease which arises from the development of pyogenic or putrefactive organisms [36].

Serpent sign

Keratolysis or deciduous skin, a condition in which the whole skin is cast off like a snake in huge contiguous pieces. Also called Preston's sign. Deciduous skin can be defined best as continuous, periodic or seasonal shedding or peeling of the epidermal layer of the skin of more or less generalized distribution [37].

Setting sun sign

The setting-sun phenomenon is an ophthalmologic sign in young children resulting from upward-gaze paresis. In this condition, the eyes appear driven downward, the sclera may be seen between the upper eyelid and the iris, and part of the lower pupil may be covered by the lower eyelid. Pathogenesis of this sign is not well understood, but it seems to be related to aqueductal distention with compression of periaqueductal structures secondary to increased intracranial pressure.1 However, it can also be transiently elicited in healthy infants up to 7 months of age by changes of position or removal of light (benign setting-sun phenomenon). The benign form might represent immaturity of the reflex systems controlling eye movements.When persistent, this sign is one of the most frequent markers of elevated intracranial pressure, appearing in 40% of children with hydrocephalus (of any cause) and in 13% of patients with ventriculoperitoneal shunt dysfunction. It is an earlier sign of hydrocephalus than enlarged head circumference, full fontanelle, separation of sutures, irritability or vomiting. Consequently, this sign is a valuable early warning of an entity requiring prompt neuroimaging and urgent surgical intervention [38].

Shaven Beard sign

Peyer's patches seen post mortem due to typhoid fever [39].

Shawl sign

Oedematous-erythematous lilac coloured skin lesions may be also present in the skin of decolletage and shoulders as the shawl sign (Fig. 9) [18,40].

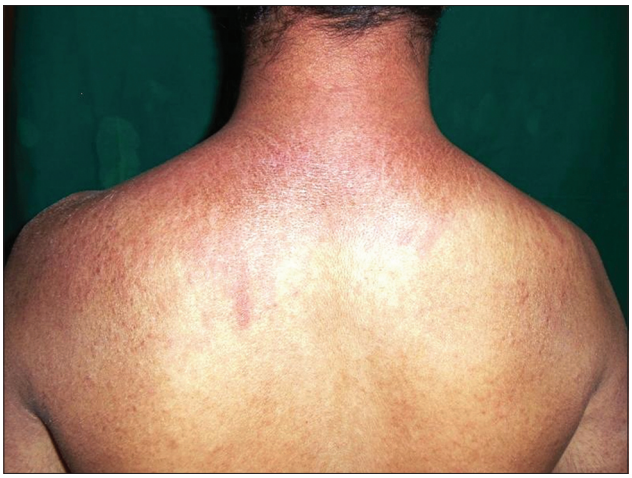

Figure 9: Shawl sign.

Sheep Dip sign

Severe spreading stomach pain with possibly vomiting black from soot or blue from indigo. Intense thirst, cramps, and coma [41]. Also known as Arsenic sign (acute) and Paris Green sign.

Shelly's sign

A sago like eruption on the palate and the lips [42]. A sign seen in influenza.

Sheklakov sign/False Nikolskiy sign

This sign is positive in subepidermal blistering disorders, like bullous pemphigoid, cicatricial pemphigoid, herpes gestationis, dermatitis herpetiformis, linear IgA bullous dermatotis, epidermolysis bullosa acquisita, junctional and dystrophic epidermolysis bullosa, porphyrias and bullous SLE.

This involves pulling the peripheral remnant of a roof of a ruptured blister, thereby extending the erosion on the surrounding normal appearing skin. It is called the "false Nikolskiy" sign because it is a subepidermal cleavage occurring in the perilesional skin.The erosions thus induced are limited in size, do not exhibit tendency to subsequent spontaneous extension and heal rapidly [43,44].

Nikolay Dmitriyevich Sheklakov

Russian dermatologist (1918-1989), (Fig. 10), who was Professor and Chairman of the Department of Dermatology and Venereology at the Moscow School of Dentistry, Moscow, Russia (then the Union of Soviet Socialist Republics), described the sign of perifocal

subepidermal separation ("false Nikolskiy sign"), which is also known in the modern dermatologic literature published in Russian as the Sheklakov sign. In contrast to the true Nikolskiy sign, perifocal subepidermal separation is induced at the periphery of blisters with a subepidermal location by pulling the remnant from the blister roof or wall. The induced erosions are limited in size, do not have a tendency to subsequent spontaneous extension, and heal fast [45].

Ship-fever sign

Epidemic typhus (Fig. 11) (also called "camp fever", "jail fever", "hospital fever", "ship fever", "famine fever", "putrid fever", "petechial fever", "Epidemic louse-borne typhus" and "louse-borne typhus") is a form of typhus so named because the disease often causes epidemics following wars and natural disasters. The causative organism is Rickettsia prowazekii, transmitted by the human body louse (Pediculus humanus corporis) [46-48].

Figure 10: Nikolay Dmitriyevich Sheklakov.

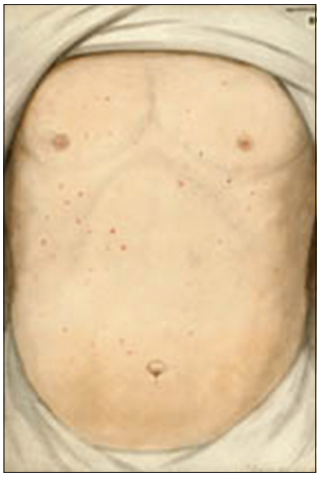

Figure 11: Ship-fever sign

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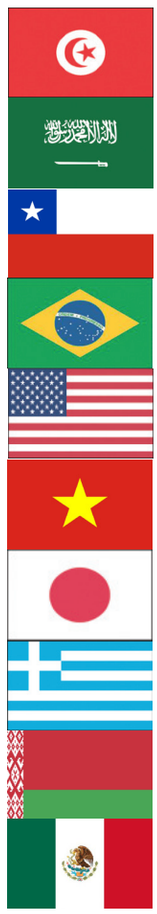

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