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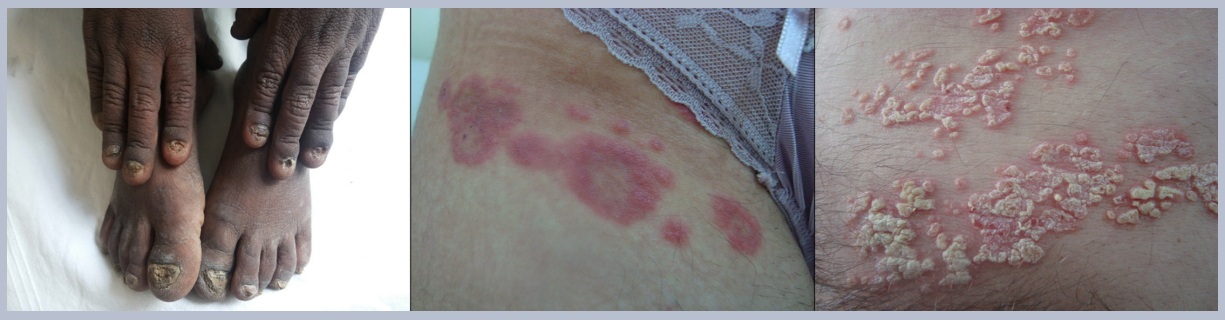

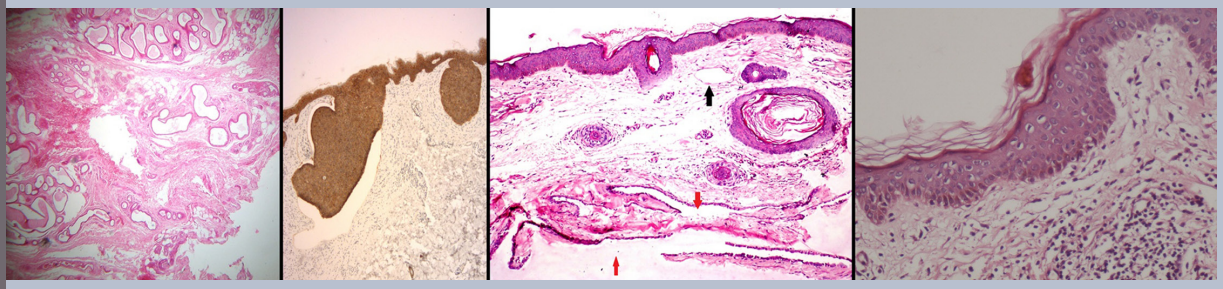

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Editorial Pages

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Our Dermatology Online

Original Article

Pruritus in hemodialysis patients: Results from Fresenius dyalisis center, Banja Luka, Bosnia and Herzegovina

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ABSTRACT

Introduction: Uremic pruritus (UP) is a common and distressing complication of end-stage renal disease (ESRD). A global cross-sectional study of 18,000 hemodialysis patients reported a 42% prevalence of moderate or extreme UP, which was strongly associated with sleep disturbance, depression, impaired quality of life, and mortality. Pruritus is commonly encountered in individuals with end-stage renal disease (ESRD) on hemodialysis (HD). **Materials and Methods:** This cross-sectional study was performed in order to find out the prevalence of pruritus in patients on regular maintenance hemodialysis (HD) as well as to analyze its relationship to age, sex of the patient, duration of hemodialysis in months per patient, serum levels of phosphate, PTH, KT/V (index of dialysis dose), parameters in the beggining of the study and six months after. The data were analyzed by descriptive statistics-Wilcoxon Signed Rank Test and Chi-square test with Yates correction factor. **Results:** Sixty and two patients with ESRD (age ranging from 31 to 87 years) free from systemic, skin or psychiatric disorders and other secondary causes attributable to pruritis, undergoing maintenance HD (duration on HD 4-348 months; mean 86.97 and median 79,5 months) at Fresenius dialysis center, Banja Luka, Bosnia and Herzegovina were evaluated for pruritus. Pruritus has been discovered in 21 out of 34 males (54,8%) and 6 out of 28 females (22,2%). Our study as many others showed that pruritus is very common (45.2%) in HD patients. Applying χ^2 test with Yates correction factor is highly statistically significant ($\chi^2 = 8.003$, $p = 0.005$) by gender. Research of the gender revealed that pruritus appeared more in men analysis. There were no significant differences between other measured markers: to age, duration of hemodialysis in months per patient, serum levels of phosphate, PTH, KT/V (index of dialysis dose) in patients with pruritus and in patients without pruritus. **Conclusions:** This first cross-sectional study describes key features UP in Republic of Srpska (Bosnia and Herzegovina) and results that the UP is significantly more common in men. This study demonstrates that the serum level of PTH and phosphate isn't associated with the incidence of pruritus in HD patients.

Key words: Uremic pruritus; End-stage renal disease; Hemodialysis

INTRODUCTION

Pruritus, defined as an unrestricted and uncomfortable sensation that elicits the desire to scratch, has been well recognized as a common complication in patients with chronic Renal failure [2-6]. It has been found that 15%-49% of patients with predialysis chronic renal failure and 50%-90% of those on hemodialysis or CAPD have pruritus [7].

In 2012, over 2500 patients received hemodialysis (HD) in the Bosnia and Herzegowina [17], in USA about 384,000 [7], and in Germany about 63,300 patients per year depend on HD [8]. It is estimated that worldwide

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more than 2 million people suffer from end-stage renal disease (ESRD) that requires HD.

Pruritus may be localized or disseminated and is the most common symptom of ESRD. It occurs in about 53% of these patients, causing great harm to their quality of life [2,10,11]. It is not associated with other primary or systemic skin diseases, psychological disorders or acute renal failure. The pathogenesis is not fully known, but there is a relation with hyperparathyroidism, xerosis, hypervitaminosis A, iron deficiency anemia, and elevated serum levels of magnesium, calcium, phosphate, aluminum and histamine, though the latter may be associated with allergic sensitization to components in dialysis membranes. Pruritus contributes to the appearance of perforating injuries by the Koebner phenomenon [12-16].

Moreover, there is no relationship between the plasma level of PTH and dermal Cell proliferation, nor is there a difference in the number of mast cells or the levels of PTH between patients with or without pruritus.

The pathophysiology of pruritus is multifactorial. Until now, studies reported significant association between serum parathyroid hormone (PTH) and the itching; some other studies have found no specific relationship between pruritus and hyperparathyroidism, hypercalcemia, hyperphosphatemia, and level of PTH [5,9,14,23].

PATIENTS AND METHODS

This cross-sectional study was conducted on sixty and two patients with ESRD (age ranging from 31 to 87 years) free from systemic, skin or psychiatric disorders and other secondary causes attributable to pruritis, undergoing maintenance HD at Fresenius dialysis center, Banja Luka, Bosnia and Herzegovina were evaluated for pruritus and included in a study during period from December, 2013 to May, 2014. Duration of each session was 4 hours.

Those with history of dermatologic disease or chemical exposure were excluded. Patients were asked to report the severity of their pruritus.

Blood samples were taken from all patients for assessment of serum levels of phosphate, PTH, KT/V (index of dialysis dose), parameters at the beginning of the study and six months after.

Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study and they were fully informed about the drug and its side-effects.

Statistical Analyses

Descriptive data were compared as a mean±standard deviation (range). Mann-Whitney U test and T-test was used to compare means between patients with and without pruritus.

Wilcoxon Signed Rank Test and Chi-square test with Yates correction factor were used for relationship of quantitative data and comparison of qualitative variables respectively. The level of significance was $p<0.05$.

RESULTS

The overall prevalence of pruritus in the present study is 45,2%.

Pruritus has been discovered in 21 out of 34 males (54,8%) and 6 out of 28 females (22,2%).

Applying χ^2 test with Yates correction was highly statistically significant (χ^2 = 8.003, p = 0.005) by gender. Analysis of the gender revealed that pruritus was significantly more detected in men, as shown in Table 1.

According to patients' age no significant differences were found (applying T-Test (Independent Samples), t = - 0.443, p = 0.659).

Applying the Mann-Whitney-U test, there was no statistically significant difference in the duration HD/months/by groups of patients with pruritus (n = 27, Md = 84.00) and those without pruritus (n = 35,

Table 1: Pruritus in relation to patients' gender

Gender of the patients	Patients		Total
	Patients with pruritus	Patients without pruritus	
Male			
N	21	13	34
%	77.8	37.1	54.8
Female			
N	6	22	28
%	22.2	62.9	45.2
Total			
N	27	35	62
%	100.0	100.0	100.0

Md = 75.00), U = 421.00 z = -0731, p = 0.465, r = 0.092 (Table 2).

Using the Mann-Whitney-U test, there was no statistically significant difference in KTV1 by groups of patients with pruritus (n = 27, Md = 1.56) and patients without pruritus (n = 35, Md = 1.65), U = 339.50, z = -1889, p = 0.059, r = 0.239), the laboratory determined the start of the study as shown in Table. 3.

Using the T-test for independent samples there was no statistically significant difference (t = - 1.166, p = 0.248) in KT/V2 examined groups of subjects, measured at the end of the study.

Using the Mann-Whitney-U test, there was no statistically significant difference of level Phosphate 1 in serum by groups of patients with pruritus (N = 27, Md = 1.42) and patients without pruritus (N = 35, Md = 1.33), U = 371.50, z = -1.434, p = 0.151, r = 0.182. The laboratory determined the start of the study as shown in Table 4.

Using the Mann-Whitney-U, test there was no statistically significant difference of level Phosphate 1 in serum by groups of patients with pruritus (N = 27, Md = 1.26) and patients without pruritus (N = 35, Md = 1.30), U = 456.50, z = -0.227, p = 0.820, r = 0.029, measured at the end of the study.

Using the Mann-Whitney-U test, there was no statistically significant difference in PTH 1 by groups of patients with pruritus (N = 27, Md = 194.50) and patients without pruritus (N = 35, Md = 245.80), U = 453.00, z = -0.277, p = 0.782, r = 0.035 as shown in Table 5.

Using the Mann-Whitney-U test, there was no statistically significant difference in PTH 2 by groups of patients with pruritus (N = 27, Md = 218.20) and patients without pruritus (N = 35, Md = 214.70), U = 455.00, z = -0.248, p = 0.804, r = 0.031.

By applying the Wilcoxon test of paired couples there was no statistically significant difference in patients with pruritus neither in the change of KT/V2 and KT/V1 (z = 0.000, p = 1.000), nor in the change of Phosphates2 and Phosphates (z = -1.261, p = 0.207) nor in the change of PTH2 and PTH2 (z = -0,505, p = 0.614)., that is the measured laboratory value at the beginning of the study as shown in Table 6.

By applying the Wilcoxon test of paired couples there was no statistically significant difference in patients without pruritus neither in the change of KT/V2 and KT/V1 (z = -1.720, p = 0.085), nor in the change of Phosphates2 and Phosphates ((z = -0.377, p = 0.706), nor in the change of PTH2 and PTH2 (z = -0.419, p = 0.675). measured at the end of the study as shown in Table 7.

DISCUSSION

We conducted the first study of uremic pruritus in Republic of Srpska (Bosnia and Herzegovina).

Table 2: HD duration (months)

Group	N	Min.	Max.	Range	Median	Mean	Std. Dev.
Patients with pruritus	27	19	348	329	84.00	89.33	63.901
Patients without pruritus	35	4	299	295	75.00	85.14	70.801
Total	62	4	348	344	79.50	86.97	67.371

Table 3: Comparison of values KT/V 1 (index of dialysis dose)

Group	N	Min.	Max.	Range	Median	Mean	Std. Dev.
Patients with pruritus	27	1.24	1.99	0.75	1.5600	1.5552	0.19964
Patients without pruritus	35	1.28	2.44	1.16	1.6500	1.6820	0.25395
Total	62	1.24	2.44	1.20	1.6000	1.6268	0.23865

Table 4: Comparison of Phosphate 1 level in serum

Group	N	Min.	Max.	Range	Median	Mean	Std. dev.
Patients with pruritus	27	0.53	3.27	2.74	1.4200	1.4370	0.48337
Patients without pruritus	35	0.69	2.37	1.68	1.3300	1.2889	0.31249
Total	62	0.53	3.27	2.74	1.3400	1.3534	0.39938

Table 5: Comparison of PTH 1 level in serum

Group	N	Min.	Max.	Range	Median	Mean	Std. Dev.
Patients with pruritus	27	31.1	1885.0	1853.9	194.500	355.287	437.6542
Patients without pruritus	35	30.7	2150.0	2119.3	245.800	335.447	388.8529
Total	62	30.7	2150.0	2119.3	197.150	344.087	407.4530

Table 6: Comparisons within groups

Patients with pruritus	KT/V 2 – KT/V 1	Phosphate2 - Phosphate1	PTH 2 - PTH 1
z	0.000[b]	–1.261[c]	–0.505[c]
p	1.000	0.207	0.614

[a]Wilcoxon Signed Ranks Test, [b]The sum of negative ranks equals the sum of positive ranks, [c]Based on positive ranks

Table 7: Comparisons within groups

Patients without pruritus	KT/V 2 – KT/V 1	Phosphate2 - Phosphate1	PTH 2 - PTH 1
z	–1.720[b]	–0.377[c]	–0.419[b]
p	0.085	0.706	0.675

[a]Wilcoxon Signed Ranks Test, [b]Based on positive ranks.[c]Based on negative ranks

Our study as many others showed that pruritus is very common (45.2%) in HD patients.

The overall prevalence of pruritus among our study population is 45,2 % and it is comparable with the published reports [1,3-5,14,17-19,20-22,24].

Pruritus has been detected in 21 out of 34 males (54,8%) and 6 out of 28 females (22,2%).

Analysis of the gender revealed that pruritus was significantly more shown in men, and previous studies have shown no difference in gender [24].

Men in the DOPPS I and I Studies had UP more often than women. In contrast, Snit M. et al. report that UP occurred statistically significantly more often in women, independent of method of renal replacement therapy [1,14].

In our study, we did not find any relationship between pruritus and duration of dialysis as seen in some previous studies [14,21,23,24].

Like most of other studies, we could not find any relationship between serum levels of phosphorus and UP in the patients' [24].

Hyperparathyroidism has been proposed by some authors as a cause of uremic pruritus [24]. Hyperparathyroidism can stimulate mast cells to release histamine and can promote microprecipitation of calcium and magnesium salts in the skin. On the other hand, all of the patients with severe hyperparathyroidism do not have pruritus. Moreover, there is no relationship between the plasma level of PTH and proliferation of dermal cell, and there is no difference in the number of mast cells and the levels of PTH between patients with or without pruritus. On the other hand, a direct role for parathyroid hormone as a cause of uremic pruritus has been questioned because of the failure of intradermal injections of PTH analogs to produce pruritus, and because of negative immunohistochemical studies for PTH in the skin biopsy specimens [24].

Furthermore, no correlation between PTH levels and itching intensity was found in most studies [14,21,23].

In our study, we did not find any relationship between pruritus and the plasma level of PTH.

CONCLUSIONS

This first cross-sectional study describes key features UP in Republic of Srpska and results that the UP is significantly more common in men.

This study demonstrates that the serum level of PTH and phosphate isn't associated with the incidence of pruritus in HD patients.

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

Immunohistochemical evaluation of E-cadherin expression in basal cell carcinoma of the skin

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ABSTRACT

Introduction: E-cadherin is important cell-cell adhesion molecule, that plays a crucial role in the maintenance of tissue microarchitecture. In many human malignancies, reduced or loss of E-cadherin production in neoplastic cells correlates with tumor dedifferentiation and acquisition of the invasive and metastatic potential. In contrast to most other cancers, basal cell carcinoma (BCC) of the skin possess some unique features, such as slow local growth, strong stroma-dependency, and virtual absence of metastases. **Aim**: In the present study, we immunohistochemically evaluated expression of E-cadherin in a set of cutaneous BCCs. **Material and methods**: Study group consisted of 41 primary BCCs cathegorized into non-infiltrative subroup (superfical and nodular subtypes) and infiltrative subroup (nodular-infiltrative and infiltrative subtypes). **Results**: E-cadherin was expressed in all tumor specimens with variable quantitative range and intensity. There were 19 cases (46.3 %) with preserved and 22 cases (53.7 %) with reduced E-cadherin expression. In superficial, nodular, nodular-infiltrative and infiltrative BCC subtypes, reduced E-cadherin immunoreactivity was found in 40 % (2/5), 56.2 % (9/16), 54.5 % (6/11) and 55.5 % (5/9), respectively. We did not confirm a significant correlation between expression of E-cadherin and both given, non-infiltrative and infiltrative BCC subgroup. None of the tumors examined showed apparent decreasing immunostaining intensity in tumor tissue with increasing depth of invasion. There were not convincing differences either between the central and peripheral parts of tumor mass, or in the vertical dimension. **Conclusions**: Reduction of E-cadherin expression *per se* does not seem to directly contribute to the acqusition of more aggressive phenotype in cutaneous BCC. This may represent another peculiarity, by which BCC differs from the most other epithelial malignancies and reflect a distinct tumor biology.

Key words: Basal cell carcinoma; E-cadherin; Immunohistochemistry

INTRODUCTION

Basal cell carcinoma (BCC) of the skin is histomorphologically and phenotypically very heterogeneous neoplasia. In contrast to most other cancers, it possess some unique features, such as slow local growth, strong stroma-dependency, and virtual absence of metastases [1-5]. Although mortality rates are very low, some BCCs may grow aggressively causing extensive tissue destruction and repeated recurrences after treatment [1-4]. Therefore, based on different biological behaviour and prognosis we distinct two BCC subgroups: Indolent subtypes (superficial and nodular), and aggressive subtypes (infiltrative, micronodular BCC and metatypical carcinoma) [1,3]. Recently, there is not definitively explained, whether they are a part of a continuous spectrum of tumorigenesis, starting with indolent and ending with aggressive forms, or they represent separate developmental lines [6].

Untill now, various biomarkers have been identified in cutaneous BCC involved in the mechanisms of cancer evolution and progression, some of which have or could have a great importance in predicting further clinical outcome [6]. Among them, E-cadherin has been studied in several papers [7-12] giving diverse or contradictory conclusions. Cadherins comprise a large family of transmembrane or membrane-associated

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calcium-dependent glycoproteins that mediate specific cell-cell adhesion and function as a key molecule in the histogenesis of various organs. They play a crucial role during embryogenesis and morphogenesis, as well as in the maintenance of adult tissue microarchitecture [14]. Intracellulary, they interact with several proteins, collectively termed catenins, which link them to the actin-based cytoskeleton. The cadherin family consists of at least five major subfamilies, i.e. "classical" cadherins of type I (including the best known epithelial E- cadherin, neural N-cadherin and placental P-cadherin), closely related cadherins of type II, desmosomal cadherins, protocadherins, and a variety of cadherin-related molecules [13]. The prototype of all cadherins is generally considered E-cadherin because it belongs to the most important molecules in cell-cell adhesion in epithelial tissue and has probably been studied in most detail, both in normal and pathological conditions [13,14].

The human E-cadherin gene CDH1 plays (besides other functions) a major role in tumor development and progression [14]. The suppression of E-cadherin production is regarded as one of the main molecular events responsible for dysfunction in cellular adhesion and tissue integrity, that help in local tumor invasion. Therefore, loss of function of E-cadherin or inactivation of cadherin-catenin complex correlates with dedifferentiation and acquisition of the invasive and metastatic potential of tumor cells, resulting in it being referred to as the "suppressor of invasion" gene [14]. In biopsy specimens, reduced or loss of E-cadherin expression correlates with epithelial cancer cells dedifferentiation and was found as an indicator of unfavourbale prognosis in many human malignancies, for example in oral squamous cell carcinoma [15], oesophageal carcinoma [16], carcinoma of the breast [17], ovarian carcinoma [18], pancreatic adenocarcinoma [19], rectal carcinoma [20], or non-small cell lung cancers [21]. Thus, these observations suggest that E-cadherin is implicated in the acquisition of invasive and metastatic potential of human cancer cells. Among skin malignancies, reduced expression of E-cadherin has been well documented in squamous cell carcinoma [22,23]. However, in cutaneous BCC, although it is the most common malignancy in humans, this relationship is still unclear. As mentioned above, several studies have been published to date dealing with this issue in human BCC, some of which provided conflicting results. Whereas some authors [9-12] demonstrated that expression of E-cadherin in BCC cells was quite frequently reduced and its decrease or loss was associated with more aggressive tumor biology, the results of other studies [7,8] did not confirm such assumption. Therefore, we focused on immunohistochemical analysis of E-cadherin expression in BCC to elucidate these discrepancies and to throw light on its potential role in the pathogenesis of this cancer.

MATERIAL AND METHODS

Tissue Specimens

Biopsy samples from 41 chosen cases of cutaneous BCCs of different histological types from various anatomical locations were enrolled into this study. They were obtained from 33 subjects (22 men, 11 women) in the age range 35 - 91 years (mean age 73.4 years). Topographical distribution of the tumors was as follows: head and neck (n = 32), trunk (n = 5), and extremity (n = 4). All patients were treated at the clinical departments of the Faculty Hospital in Zilina (Slovakia) and biopsy specimens were histopathologically investigated at the Department of Pathology in Faculty Hospital in Zilina during year 2014. For the purpose of this study, we deliberately selected a set of representative samples of cutaneous BCCs included four basic histomorphological subtypes: superficial, nodular, mixed nodular-infiltrative and infiltrative. We aimed to achieve two separate subgroups comprising roughly the same number of tumors. Thus, the first subgroup consisted of 21 indolent (non-infiltrative) BCC subtypes (5 superficial, 16 nodular) characterized by expansive growth pattern with clearly visible peripheral palisading. The second subgroup consisted of 20 BCCs with (at least focal) infiltrative growth pattern (11 nodular-infiltrative, 9 infiltrative subtypes), which was characterized by strands, cords or small separate tumor clusters without peripheral palisading, that invaded adjacent stroma. Metatypical BCC cases were exluded due to their intermediate features with squamous cell carcinoma. Only samples with enough tumor tissue in the paraffin-embedded blocks to harvest appropriate slides for immunohistochemistry were chosen.

Immunohistochemistry

Tissue specimens were routinely processed and immunohistochemical stained for E-cadherin. Briefly, representative 4-μm tissue sections applied on silanized slides were baked for 2 hours in an oven at 56 °C. Then the sections were deparaffinized in xylene for 2 x 15 minutes, rehydrated in series of descending

ethanol concentrations and treated with microwaves in a 0.01 M citrate buffer (pH 6.0) for 15 minutes. The endogenous peroxidase activity was blocked with 3 % hydrogen peroxide for 10 minutes, followed by incubation with TBS (tris-buffered saline) solution (pH 7.6). Subsequently, specific monoclonal mouse anti-human antibody against E-cadherin (clone NCH-38, code M3612, DAKO, dilution 1: 50) was used for staining. After overnight incubation at ambient temperature, post primary antibody (rabbit anti mouse IgG and anti rabbit Poly-HRP-Ig containing 10 % animal serum in TBS, Leica Biosystems) was applied and an immunoreaction was visualised by means of the DAB (3,3'-diaminobenzidine) detection chromogen solution (Leica Biosystems) according to manufacturer's instructions. Slides were counterstained with Weigert's hematoxylin, dehydrated, mounted and finally evaluated in the light microscope.

Immunohistochemical Interpretation

According to study previously published by Pizzaro et al. [9] we classified the intensity of immunostaining in tumour cells as (+ +) when as strong as the normal epidermis, (+) when weak, and (-) when cells were not stained. After including a total percentage of immunolabelled tumor cells, as proposed Pizzaro et al. [9] we differed following four cathegories: a) BCC with preserved E-cadherin expression (more than 75% of the tumour cells were strongly (+ +) stained), b) BCC with slightly reduced E-cadherin expression (more than 25% of the tumour cells were positively stained but less than 75% of the tumour cells were strongly (+ +) stained), c) BCC with severely reduced E-cadherin expression (more than 75% of tumor cells were not stained), and finally d) BCC with absent E-cadherin expression (immunostaining was completely lost). In addition, we qualitativelly differed homogeneous and heterogeneous pattern of E-cadherin immunoreactivity. Homogeneous pattern was characterized by virtually the same staining intensity (regardless strong or weak) throughout the whole immunolabeled tumor tissue. In heterogeneous pattern, tumor areas with variable intensity of the immunolabeled cells (strong *versus* weak) were clearly visible.

Statistical Analysis

Data were collected in a databank, using a software SPSS Statistics. For the statistical analysis, chi-square test was employed and P value < 0.05 was considered to indicate statistical significance.

Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study and they were fully informed about the drug and its side-effects.

RESULTS

E-cadherin was expressed in all tumor specimens with variable quantitative range and intensity showing a linear pattern around the periphery of the cancer cells. A faint diffuse cytoplasmic staining was also observed in a minority of cases. No nucler immunoreactivity was detected. Overall, there were 19 cases (46.3%) with preserved (Fig. 1) and 22 cases (53.7%) with reduced E-cadherin expression, of which 15 cases were slightly and 7 cases severely reduced. None of the tumors investigated showed a completely negative staining. In superficial, nodular, mixed nodular-infiltrative and infiltrative BCC subtypes, reduced E-cadherin immunoreactivity was found in 40% (2/5), 56.2% (9/16), 54.5% (6/11) and 55.5% (5/9), respectively. Among them, severely reduced expression (< 25 % of entire tumor tissue) was seen in 40% of superficial BCCs (2/5), in 18.7% of nodular BCCs (3/16), in 9.1% of nodular-infiltrative BCCs (1/11), and 14.2% of infiltrative BCCs (1/7) (Fig. 2). We did not confirm a statistically significant correlation between immunohistochemical expression of E-cadherin (preserved *versus* reduced) and both given, non-infiltrative and (at least focally) infiltrative BCC subgroup ($p = 0.8$). In general, among four histological subtypes, diminished E-cadherin expression occured most commonly in nodular-infiltrative BCCs. However, when we precisely analyzed microarchitecture in all 11 cases we have found that in both structural components, virtually the same immunostaining intensity was seen in eight cases (72.7%) (Fig. 3). Only one tumor showed a weaker immunoreactivity in the infiltrative component and surprisingly, in the remaining two cases, tumor areas with infiltrative growth seemed to have a stronger immunopositivity compared to nodular component. As for spatial distribution, indolent (non-infiltrative) BCC subgroup usually showed a widely homogeneous staining positivity (16/21, 76.1%) throughout the tumor mass regardless of whether preserved or reduced E-cadherin expression. On the other hand, in infiltrative BCC subroup, a heterogeneous staining positivity (16/20, 80.0%) was more commonly seen. We confirmed a significant correlation between immunoreactivity pattern of E-cadherin and tumor

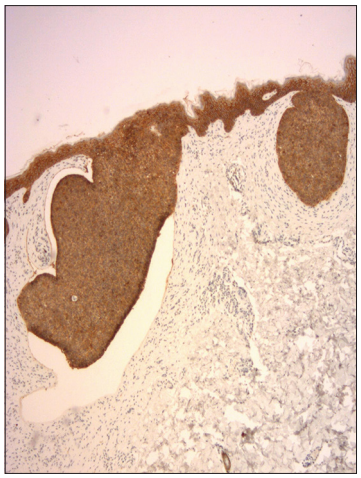

Figure 1: Preserved expression of E-cadherin with homogeneous staining pattern in superficial BCC (clone NCH-38, DAKO, original magnification 120x).

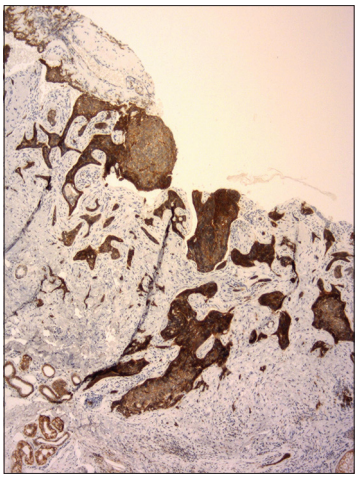

Figure 3: Preserved expression of E-cadherin with heterogeneous staining pattern in mixed nodular-infiltrative BCC (clone NCH-38, DAKO, original magnification 120x).

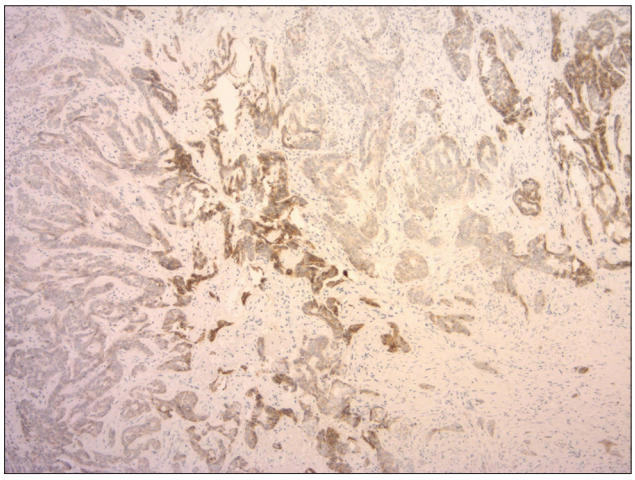

Figure 2: Severely reduced expression of E-cadherin with heterogeneous staining pattern in infiltrative BCC. Some parts of tumor are completely negative (clone NCH-38, DAKO, original magnification 120x).

growth microarchitecture in terms of more frequent heterogeneous pattern in BCCs with infiltrative growth features ($p < 0.003$). Further, while homogeneous pattern was more commonly associated with membranous E-cadherin positivity solely (18/20, 90%), heterogeneous pattern was mostly associated with mixed cytoplasmic-membranous positivity (15/21, 71.4%). In spite of this qualitative diversity of E-cadherin expression, none of the 41 cacinomas examined manifested apparent decreasing staining intensity in tumor tissue with increasing depth of invasion. Although BCCs having heterogeneous E-cadherin pattern exhibited mixed, weak and strong positive areas, as well as population of negative cells intermingled with clusters of positive cells, there were not convincing differences either between the central and peripheral parts of tumor mass, or in the vertical dimension. Interestingly, some BCCs belonging to infiltrative subgroup showed much more pronounced E-cadherin expression at the invasive fronts of tumor mass, which invaded deeply into the corium or subcutis (Fig. 4). Moreover, one of them also exhibited a multiple perineural tumorous infiltration (Fig. 5), which is a sign of aggressive tumor behaviour. There was not found a statistical correlation between E-cadherin expression and tumor ulceration ($p = 0.1$) or gender ($p = 0.7$). A summary of the morphological characteristics and immunohistochemical findings in our set of BCCs divided into two subgroups described above is presented in Table 1 and 2.

DISCUSSION

This paper describes immunohistochemical expression status of cell-cell adhesion molecule E-cadherin in a panel of 41 human BCCs of the skin. As pointed above, we found reduced E-cadherin expression in 53.7% cases investigated, indicating a relatively common phenomenon. More importantly, we did not shown significant association of decreasing production of E-cadherin with more aggressive tumor growth. It should be noted, however, conflicting views have been reported on the role of E-cadherin status in BCC carcinogenesis and biological behaviour until now. For example, some authors [7,8] immunohistochemically analysed E-cadherin in cutaneous BCCs and found, it was strongly expressed in most cases examined. From the results of their studies they suggested, virtually no metastatic potential of cutaneous BCC may be due to retention of high levels of E-cadherin production in tumor cells.

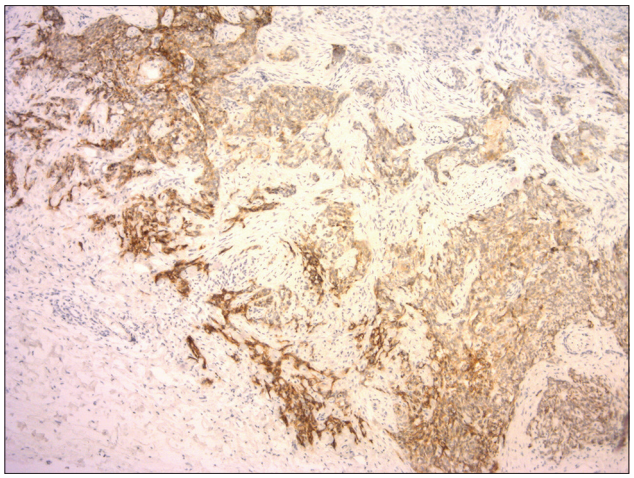

Figure 4: Slightly reduced expression of E-cadherin with heterogeneous staining pattern in mixed nodular-infiltrative BCC. Invasive front of tumor mass (left) consisting of infiltrative component exhibited stronger immunopositivity compared to nodular component (right) (clone NCH-38, DAKO, original magnification 120x).

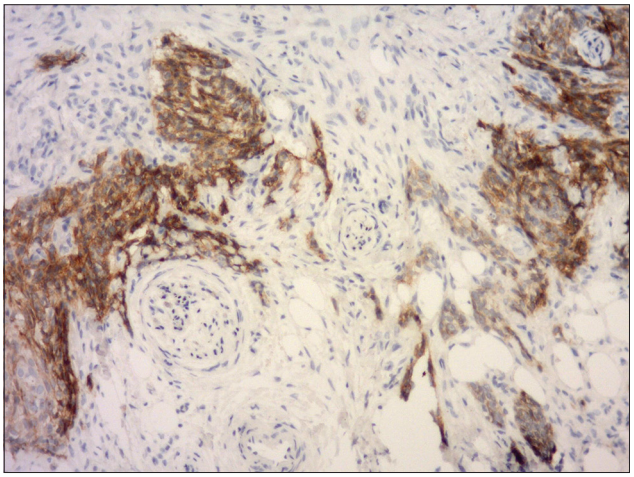

Figure 5: Predominantly strong expression of E-cadherin in the invasive edges of infiltrative BCC, that grow deeply into subcutaneous tissue and exhibit perineural tumor infiltration (clone NCH-38, DAKO, original magnification 240x).

However, another group of authors claimed [9-12] that intensity of E-cadherin expression in BCC is variable and depends on tumor histomorphology, being weaker or even absent in the infiltrative (morpheaform) subtypes. Two decades ago Pizzaro et al. [9] analysed 31 cutaneous BCCs and found, E-cadherin expression was preserved in all specimens of superficial and nodular BCC, but 66.6 % of the infiltrative BCCs showed decreased expression. Statistical analysis showed a significant association between reduction in E-cadherin expression and the infiltrative growth pattern. Based on these observations they stated, E-cadherin status may contribute to the growth pattern and the local aggressive behaviour of BCC. Remarkably, none of the tumors in their series showed completely negative immunostaining. Therefore, there are quite surprising results in a recent work published by Papanikolau et al. [10] who observed completely absent membranous E-cadherin immunoreactivity in 71 out of 100 BCC cases. In addition, they recorded a preserved membranous E-cadherin expression only in 8% of all cases examined. Nevertheless, a decrease in membranous E-cadherin expression correlated significantly with infiltrative BCC variant, as well as depth of tumor invasion. Additional controversial results are given by Uzquiano et al. [8] who analysed a set of 32 cutaneous BCCs including 12 nodular subtypes, 10 infiltrative subtypes, and 10 metastatic forms. They found E-cadherin expression in almost the same proportion of nodular (66. %) and infiltrative BCCs (70%). However, it was demonstrated in all (100%) metastatic BCCs, of which all but one exhibited infiltrative growth features. There was a statistically significant difference in expression of E-cadherin between metastatic BCC as compared to nodular BCC, being increased in metastases. These observations are interesting and call into question a relationship between decline of E-cadherin production in BCC cells and acquisition of more aggressive tumor biology.

The results of our study suggest that aggressive growth features of BCC are not directly associated with a decrease of E-cadherin production in epithelial tumor cells. This view is supported by several facts. Firstly, reduced E-cadherin expression was observed in similar percentage of all BCC subtypes investigated, moreover, without a statistical significance between non-infiltrative and (at least partially) infiltrative growth variants. Secondly, there was observed no "vertical gradient" of decreasing staining intensity in cancer tissue with increasing depth of invasion. Thirdly, in most cases of mixed nodular-infiltrative BCCs, both structural components exhibited about the same immunostaining intensity. Finally, cases accompanied by severely reduced E-cadherin expression occured most frequently in superficial and nodular BCC, while they were uncommon in pure infiltrative BCC subtype. Therefore, we are of the opinion, decrease or loss of production of this cell-cell adhesion molecule *per se* is not directly implicated in the acquisition of invasive potential of BCC cancer cells. More intriguingly, we showed a correlation between pattern of E-cadherin immunoreactivity and tumor growth microarchitecture, being homogeneous more frequently in non-infiltrative subtypes and heterogeneous predominantly in

Table 1: The morphological and immunohistochemical findings of 20 tumors included in the infiltrative BCC subgroup (Ulcer – tumor ulceration, + present, – absent)

Topographical location	Histological subtype	Ulcer	E-cadherin expression	E-cadherin pattern
Nose	Nodular-infiltrative	+	Preserved	Heterogeneous
Forehead	Nodular-infiltrative	+	Preserved	Homogeneous
Nose	Nodular-infiltrative	+	Preserved	Homogeneous
Face	Nodular-infiltrative	–	Preserved	Homogeneous
Medial kantus	Nodular-infiltrative	+	Preserved	Heterogeneous
Cheek	Nodular-infiltrative	+	Slightly reduced	Heterogeneous
Forehead	Nodular-infiltrative	+	Slightly reduced	Heterogeneous
Face	Nodular-infiltrative	+	Slightly reduced	Heterogeneous
Auricle	Nodular-infiltrative	+	Slightly reduced	Heterogeneous
Auricle	Nodular-infiltrative	+	Slightly reduced	Heterogeneous
Scalp	Nodular-infiltrative	+	Severely reduced	Heterogeneous
Scalp	Infiltrative	+	Preserved	Heterogeneous
Nose	Infiltrative	+	Preserved	Heterogeneous
Scalp	Infiltrative	–	Preserved	Heterogeneous
Auricle	Infiltrative	+	Preserved	Homogeneous
Shoulder	Infiltrative	–	Slightly reduced	Heterogeneous
Eyelid	Infiltrative	–	Slightly reduced	Heterogeneous
Forehead	Infiltrative	+	Slightly reduced	Heterogeneous
Back	Infiltrative	+	Slightly reduced	Heterogeneous
Forehead	Infiltrative	+	Severely reduced	Heterogeneous

Table 2: The morphological and immunohistochemical findings of 21 tumors included in the indolent (non-infiltrative) BCC subgroup (Ulcer – tumor ulceration, + present, – absent)

Topographical location	Histological subtype	Ulcer	E-cadherin expression	E-cadherin pattern
Back	Superficial	–	Preserved	Homogeneous
Neck	Superficial	–	Preserved	Homogeneous
Back	Superficial	–	Preserved	Homogeneous
Forehead	Superficial	–	Severely reduced	Homogeneous
Face	Superficial	–	Severely reduced	Homogeneous
Nose	Nodular	+	Preserved	Homogeneous
Shoulder	Nodular	+	Preserved	Homogeneous
Eyelid	Nodular	–	Preserved	Homogeneous
Arm	Nodular	–	Preserved	Homogeneous
Scalp	Nodular	+	Preserved	Homogeneous
Back	Nodular	+	Preserved	Homogeneous
Forehead	Nodular	+	Preserved	Homogeneous
Eyelid	Nodular	+	Slightly reduced	Heterogeneous
Upper lip	Nodular	+	Slightly reduced	Heterogeneous
Abdomen	Nodular	–	Slightly reduced	Heterogeneous
Eyelid	Nodular	+	Slightly reduced	Heterogeneous
Under auricle	Nodular	+	Slightly reduced	Heterogeneous
Neck	Nodular	+	Slightly reduced	Homogeneous
Hand	Nodular	–	Severely reduced	Homogeneous
Nose	Nodular	–	Severely reduced	Homogeneous
Behind auricle	Nodular	+	Severely reduced	Homogeneous

BCCs with infiltrative growth features. This may indicate that qualitative aspects of E-cadherin expression have a greater importance in biological behaviour of cutaneous BCC and should be taken into account at the histopathological examination and biopsy report interpretation. For instance, such relationship has already been revealed in carcinoma of the rectum. Kanazawa et al. [20] studied 43 primary rectal cancers and found that heterogeneous E-cadherin immunostaining pattern, when compared to homogeneous one, was significantly associated with poorer differentiation of tumors and a presence of lymph node metastases. Therefore, a presence of tumor areas with notably different E-cadherin expression may suggest a cancer progression and evolution of polyclonal neoplastic cell population with unstable genotype and thus, accompanied by higher tendency for more aggressive growth. In practical terms, nodular cutaneous BCC with severely reduced E-cadherin expression, however, with homogeneous pattern of

immunolabelled tumor cells would not have such aggressive biological behaviour as infiltrative BCC with only slightly reduced expression, but heterogeneous staining.

One limitation of our study is a relatively small number of cases investigated. Anyway, this number is larger than those published by Pizzaro et al. [9] and Uzquiano et al. [8] who found their observations statistically relevant. We can assume that the discrepancy with the results among individual authors may be related, at least in part, to the different proportion of BCC subtypes included in their series. The controversies may be also due to the distinct anatomic location of tumors examined, since it can not be excluded that some topographic-related factors, for example intensity of solar exposition, may influence pathogenetic mechanisms and consequently molecular phenotype of BCCs.

Recently, there is growing evidence that invasiveness and tendency of more aggressive BCC growth are largely influenced and modified by adjacent peritumorous stroma [5,24]. Some authors [5] identified a specific molecular profile of fibroblasts isolated from the surrounding peritumorous tissue in human BCCs when compared to those extracted from other epithelial malignancies. These results suggest unique molecular phenotype of cancer-associated fibroblasts in BCC possibly accounting for diseae-specific pathological roles including stroma-dependency and "non-metastatic" behaviour. In addition, BCC cells alone exhibited some mesenchymal markers with contractile properties, such as α-smooth muscle actin or calponin [8,25], which are unsusual for epithelial origin and are considered to be specifically involved in the epithelial-mesenchymal transition and cancer progression.

In conclusion, E-cadherin expression in BCC of the skin is variable and its decline within tumor cells is a relatively frequent finding. There is no doubt, this important cell-cell adhesive molecule is implicated in BCC development and carcinogenesis. However, reduction of E-cadherin expression *per se* does not seem to directly contribute to the acqusition of more aggressive phenotype in cutaneous BCC. This may represent another peculiarity, by which BCC differs from the most other epithelial malignancies and reflect a distinct tumor biology.

ACKNOWLEDGMENTS

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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

Pathogenesis of Molluscum Contagiosum: A new concept for the spontaneous involution of the disease

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ABSTRACT

Background: Molluscum contagiosum is a common viral skin disease that usually has a self-clearing course. **Objectives:** to study the process of involution of molluscum contagiosum through utilizing histological examination. **Patients and Methods:** Different sizes and stages of evolution of lesions from 50 patients with molluscum contagiosum were included. Deep shave biopsies were taken from each patient for histopathological examination. **Results:** All lesions showed a single punctum and this was confirmed by histopathological examination. Each individual lesion showed an epidermal hyperplasia consisting of many lobes which subdivided into lobules that contain the molluscum bodies. The intra-cytoplasmic molluscum inclusion bodies increase in the number and size as the cells differentiate toward the surface of the epidermis to accumulate at a central meeting point equivalent to the clinical sign of umblication at which the infected cells undergo cytocidal disintegration releasing its viral contents into the skin surface. The general histological architecture resemble that of keratoacanthoma. **Conclusion:** The central umblication represent the site of the future involution that contains the final growth phase of the infected epidermal cells where it ends by a process of cellular death and disintegration releasing its viral contents into the surface of the skin at the craterform opening which is called punctum. This process of self-involution may resemble that of keratoacanthoma where there are many similar pathological features in both conditions.

Key words: Molluscum contagiosum; Molluscum body; Keratoacanthoma

INTRODUCTION

Molloscum contagiosum (MC) is a common cutaneous viral disease that caused by pox virus [1]. It can affects both children and adults through direct contact or indirectly via fomites, swimming pools and towels in addition to the sexual transmission which can occurs in adults [2].

Clinical presentation starts by the appearance of a single or multiple, small, pearly white, discrete papules that located anywhere on body but especially on the face or genital region [3].Central umblication is considered to be a characteristic feature of MC lesions through which a cheesy white material can be evacuated mechanically [4]. Some authorities proposed a follicular pattern of MC disease where the virus has the tendency to infect the follicular epithelium (Fig. 1) [5].Spontaneous clearance usually occurs during the natural course of the disease [6]. However,

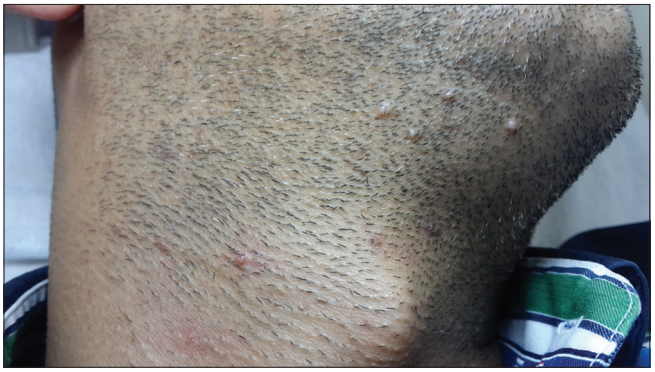

Figure 1: Follicular molluscum contagiosum affecting the beard of a young man.

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till now there is no explanation for this self-limiting fate and there is no comment about the feature of MC umblication and its relation to the pathogenesis of the disease. It has been reported that the mean duration of the single lesion of MC is 2 months while the mean duration of the infection process can last from 8 months to more than one year [7].

During our routine clinical and histopathological work, we noticed that early MC lesions are usually umblicated papules that become gradually larger and eventually involute and clears up spontaneously with a characteristic histopathological picture. Hence we arranged for the present work to correlate the different clinical stages of MC evolution with its corresponding pathological appearance so that we can discuss the spontaneous resolving course of the disease with emphasis on the pathogenesis of a single MC lesion.

MATERIAL AND METHODS

This prospective case series study included 50 patients, 29 males and 21 females with clinical diagnosis of molluscum contagiosum between February-December 2013 in Department of Dermatology, Baghdad Teaching Hospital - Baghdad College of Medicine. Their ages ranged from 1-46 years with a duration of their disease ranged from 1-14 months. All patients had no history of immunosuppressive diseases. All patients were checked up for the presence of punctum or so called umblication by the naked eye with or without using magnifying lens.

Deep shave biopsies were taken from lesions in 50 patients at different stages of evolution of MC disease, from very early papular lesion to mature large lesion. These were stained with hematoxylin and eosin (H & E) stain for the dermatopathological evaluation. The study was approved by the departmental ethical committee and the patients were informed about the nature of the study where they gave their consent to participate in this scientific work. Statistical analysis was done using scientific calculator.

Prior to the study, every patient gave written consent to the examination and biopsy after having been informed about the procedure and aim of the study. The study design was accepted by the Institutional Review Board of the Department of Dermatology, University of Baghdad- College of Medicine.

RESULTS

All lesions whether large or very small lesions had a single punctum using naked eye with or without using magnifying glass and these punctae had been confirmed by histopathology assessment in all lesions.

The results of the histological picture of MC lesions at its different stages of evolution were as follow:

Each single MC lesion consisted of many lobes of acanthotic hyperplastic epidermal tissue that descend downward into the dermis and each lobe made up of many lobules that separated from each other by distinct basement membrane (Fig. 2).

The infection of keratinocytes started usually at the base of the lobule causing swelling of the cells and forming intracytoplasmic inclusion bodies (MC bodies) that pushed the nucleus to the periphery of the keratinocytes. These MC bodies enlarge in size and increases in its number as the cells differentiate toward the stratum corneum where all the lobules meet at a central meeting point corresponding clinically to the punctum (Fig. 3). At this umblicated point, the cells from all lobules accumulate as a large bulky cells filled with viral particles and then attempt cytocidal degeneration where the lobules get rid of the necrotic material into the surface of the skin through the punctum (Fig.4). There was no obvious infiltration of inflammatory cells in the infected epidermis or in the surrounding dermis. The general histopathological architecture is similar to that of keratoacanthoma where both of them had epidermal hyperplasia, epidermal shouldering at the periphery of lesion and a central depression as a crater that opens to the surface (Fig. 5).

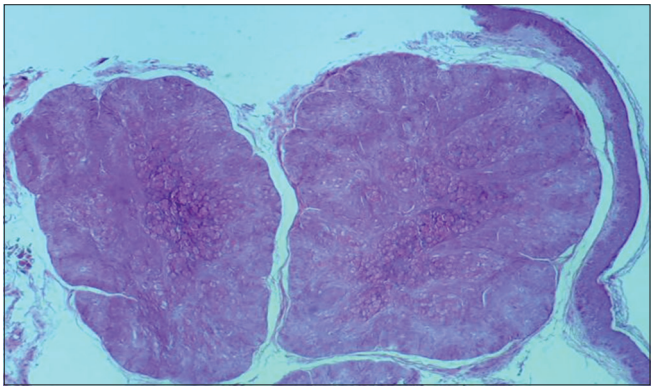

Figure 2: Histopathology of a single Molluscum contagiosum lesion composed from epithelial lobes that subdivided into many lobules separated from each other by clear basement membrane zone (H & E) ×40.

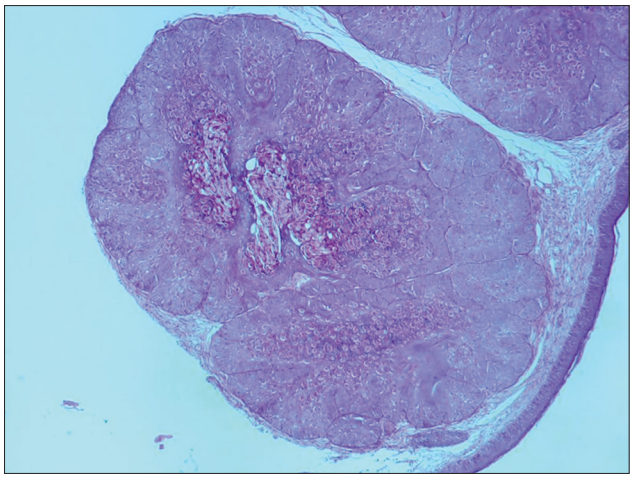

Figure 3: Cross section of MC lobe showing the umblication point as a central channel draining the intracytoplasmic MC inclusion bodies from all lobules to meet at the corresponding clinical punctum (H & E) ×100.

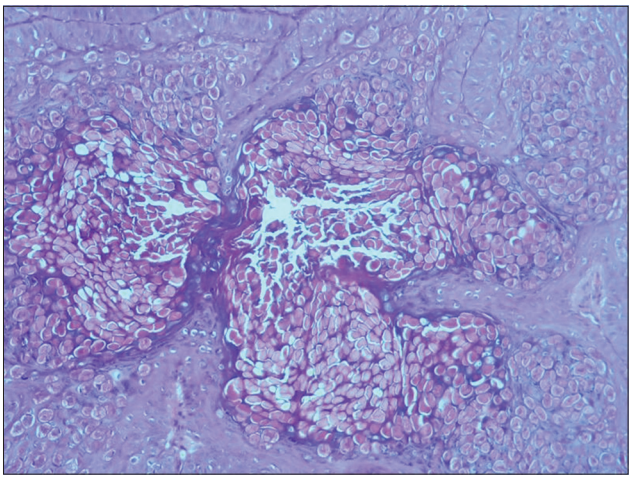

Figure 4: The central umblication point at a closer view demonstrating the final growth phase of the infected keratinocytes with its degeneration releasing the viral content (H & E) ×400.

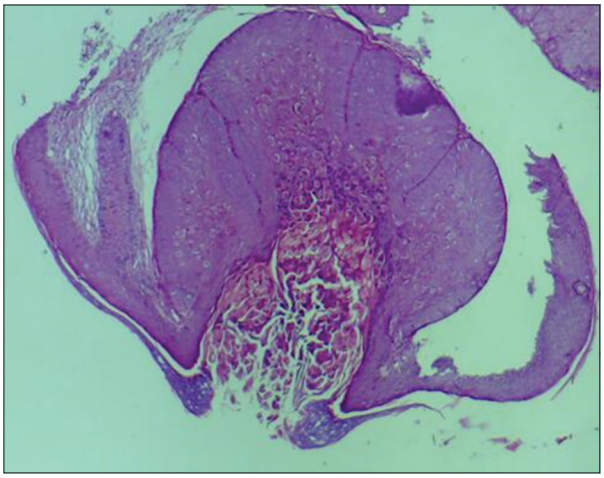

Figure 5: Molluscum contagiosum histological architecture resembling that of keratoacanthoma with a cup shape epidermal hyperplasia and shouldering of the epidermal surface and craterform opening at its center (H & E) ×40.

In some sections, the general pattern of MC lesion showed an acanthotic epidermis simulating that of the hair follicle where its ostium like opening filled with degenerated keratinous material and molluscum bodies (Fig. 6).

DISCUSSION

Molluscum contagiosum is a self-healing disease and many medical authorities don't recommend any treatment for it especially in children [8]. Clinical inflammation has been observed as preliminary step for spontaneous regression of some MC lesions [9].

A study by Vermi and colleagues presented evidence of brisk immunological response as a mechanism of self-resolution of the inflammatory MC lesions [10]. Meanwhile, not all involuting MC lesions have a preceding clinical inflammation to complete its resoluting course [11]. Also, no well explanation for the spontaneous resolution of the disease exists in the medical literature relating the presence of umblicaton to the pathogenesis of MC infection.

The present study that included 50 cases of MC lesions of different size and evolutions showed no inflammatory reaction. This finding encouraged us to think about alternative theory to explain the resolution of lesions especially the non-inflammatory MC disease.

Although punctum could not be seen clinically by naked eye in all cases of MC lesions, the present work showed the presence of punctum histopthologically in all cases of MC lesions regardless the size or stage of development.

Ianhez et al demonstrated the presence of punctum in 204 MC lesions out of 211 (96.68%) through using dermoscopy while they were able to diagnose the presence of punctum by clinical examination only in half of their cases [12].

Hence, punctum must be present as a channel through which the virion loaded keratinocytes discharge its content as they reach into the cutaneous surface. Meanwhile the individual MC lesion ends spontaneously via the same process of degeneration of the infected epidermal cells at the umblication point.

Accordingly, punctum represent the site of death of MC lesions and at the same time is a source of viral infection spread (Fig. 7). These results suggest that

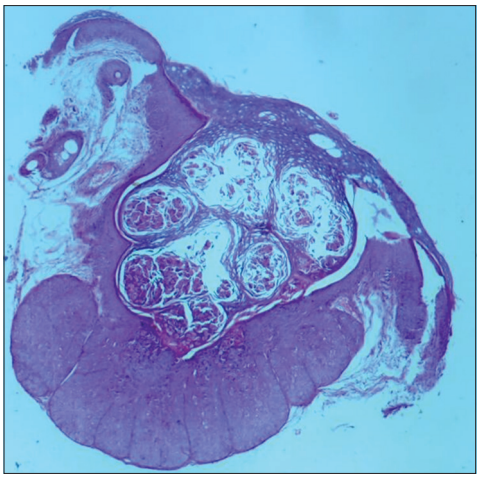

Figure 6: Histopathological patteren of molluscum contagiosum lesion showing epidermal acanthoma similar to hair follicle with central ostium full with viral particles and keratinous debris ready to be discharge to the outer surface (H & E) ×40.

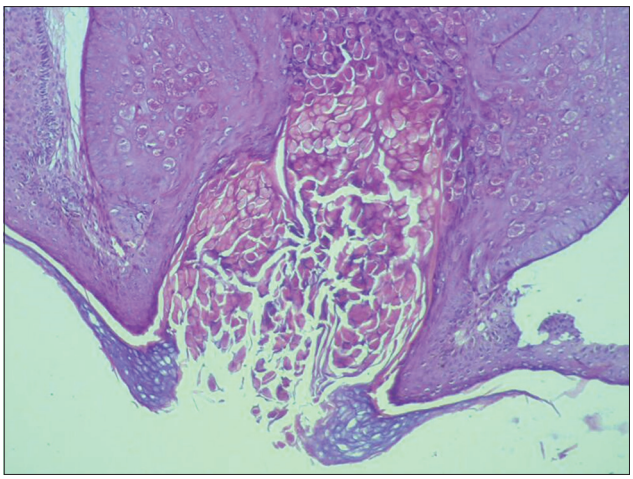

Figure 7: The craterform opening of molluscum contagiosum lesions discharges its degenerated cells and the viral particles into the surface of the skin (H & E) ×400.

the self-healing process of MC disease is not related to the size of the lesion where punctum was present in all cases regardless the stage of development of MC disease. Individual single MC lesion can persist an average period of 2 months,however the patient can still develop new lesions by inoculation via trauma or scratching for up to 8-12 months or even longer [7].

From these results, we can hypothesize the nature of the regressing course of MC as the viral infection stimulate the lobulated hyperplasia of the epidermis which contain the intracytoplasimic virion until it reaches the central meeting point of all lobules at the umblication point to undergo cytocidal degeneration where it discharges its content into the cutaneous surface. This hypothesis might explain many cutaneous diseases that heal spontaneously like keratoacanthoma (KA) as the present study demonstrated some similarities between the pathological pattern of MC and KA. The process of involution in KA could simulate that of MC in the following points;

- The etiology of KA is unknown but viral theory is suggested [13].
- In both conditions there are rapid proliferation of epidermal tissue followed by involution which is well demonstrated by the presence of cellular degenerations, apoptosis and disintegration of cells at the craterform opening [14].

The general pattern of MC growth mimics that of follicular neogenesis where the pale palisading basal cells of the MC lobules resemble the cells of the outer root sheath of the hair follicle and the central punctum of MC lesion simulate the ostium of the hair follicle [15]. The similarity of MC lesion to the hair follicle, the holocrine secretion of MC bodies into the surface, their ability to produce immune-modulators and the affinity of the virus to infect the follicular epithelium support our speculation to adopt the follicular stem cell theory as alternative one for the involution of the MC disease especially the non- inflammatory MC lesions. We can suggest that the infection originate in the hair follicle where the virus will prompt release of growth factors that induce rapid proliferation of epidermal cells producing a picture similar to anagen phase of hair follicle, subsequently the growth phase might end by involution and degeneration of keratinocytes similar to telogen phase of hair growth cycle. Further support of the follicular theory comes from a recent study that reported resolution of MC lesions by just pricking them with a sharp needle producing a cure rate of 82% where this new treatment proposed that trauma to MC lesion may induce growth arrest similar to the catagen and telogen phase of the hair cycle or alternatively the pricking action may break the barrier allowing the exposure of the hidden MC antigen to the local immune system [16].

In conclusion, the present study hypothesizes a new speculation of the growth and involution of MC lesions where each single MC lesion runs a uniform fixed course of infection that started with lobulated hyperplasia of the epidermis with central umblication producing a follicular pattern of growth. The central crater represents the area of viral discharge into the surface of the skin and the site of future involution of MC lesions.

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

Doctors' Support - An important part of medical therapy and quality of life

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ABSTRACT

Introduction: The correct patient - doctor relationship is important in shaping the whole process of treatment. The scientific studies highlight the various irregularities in this relationship and its negative impact on the effectiveness of medical treatment. The purpose of this study was to assess the relationship between levels of doctors' support and attitude to certain aspects of the treatment process and quality of life among patients with psoriasis. **Material and Methods:** The study was conducted on 50 patients with psoriasis aged from 21 to 78 who are treated in dermatological clinics. *The Psoriasis Area and Severity Index (PASI)*was used to assess the severity of psoriatic skin changes. The patients completed a questionnaire for the assessment of receive doctors' support, and its relationship with the attitude towards the disease. The research tool was developed based on literature review. **Results:** The level of doctors' support had a direct impact on the patients' attitude the disease, including attitudes towards the treatment and medical personnel, as well as adherence to medical recommendations; and indirectly on satisfaction with the treatment and the quality of life. **Conclusions:** Results of this study have shown clear evidence the importance of the level of doctors' support in psoriasis which could help to improve the overall functioning of these patients. The level of doctors' support indirectly affects the quality of life in patients with psoriasis.

Key words: Doctors' Support; Quality of life; Psoriasis; PASI; Treatment

INTRODUCTION

The Health Related Quality of Life (HRQOL) is emphasized as a factor associated with the assessment of the effectiveness of medical treatment in recent publications. It is particularly importance in dermatology. The dermatological diseases are characterized by a significant impact on psychosocial functioning of the patients, which may affect their attitude the disease [1-3].

Psoriasis is a chronic disease characterized by a genetically determined inflammatory lesions of skin with periods of relapse and remission. The etiology of this disease is very complex. Four major factors contribute to the development of this disease: autoimmune, genetic, hormonal and psychosomatic. It is diagnosed on the basis of observable skin changes and its treatment is one of the most difficult dermatological challenges. Psoriasis typically manifests as red scaly rashes and itching. The treatment is generally external (specific and nonspecific), general (including retinoid, immunomodulating and cytostatic drugs)and physical (including photo chemotherapy, phototherapy, heliotherapy)[4-5].

The scientific reports suggest that the quality of life of patients with psoriasis is largely dependent on a number of clinical parameters, include severity of skin changes [6-8]. The greater the number and severity of skin changes, the worse the quality of life is. The effectiveness of the dermatological therapy may has a positive impact on improving the overall psychosocial functioning. The relationship between the severity of symptoms associated with chronic dermatological diseases and HRQOL is well documented [1-3,6-7]. It is important, to focus on the existence of factors which both directly and indirectly affecting the effectiveness

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of treatment of patients with psoriasis, and thus their quality of life.

In recent years, there is an emphasis on the biopsychosocial model of disease and identify a variety factors which may be important during the medical therapy. One of these factors is the patient – doctor relationship. The correct communication between the patient and doctor can significantly affect the patient's attitude towards: (1)the disease, (2)the process of treatment and (3)medical workers. This may be associated with the quality and quantity of showing doctors' support and the degree of understanding of the needs or/and patients' problems [9,10]. Avoiding the patients' depersonalization and increasing the empathy, at the same time, could develop a positive attitude towards the patients' disease and the treatment process. The attitude towards the disease consists of three components: cognitive, emotional and behavioral. Changing of one of these factors may change the other components, thereby to change the attitudes towards the disease. Causing changes in affective state could influence the extent of behavioral activity of patients which is takes with respect to his/her disease [9-11].

The correct patient - doctor relationship is important in shaping the whole process of treatment. The scientific studies highlight the various irregularities in this relationship and its negative impact on the effectiveness of medical treatment. In many cases, the doctors believe that professional approach to the patient is limited to the diagnosis and the selection of appropriate pharmacotherapy. In contrast, the empathic approach to patients' problems, both medical as well as psychological, often is treated very superficially. The doctors do not give these problems a lot of time. The multi-faceted approach to reported intrapsychic problems may be particularly important in dermatology [9-11].

The skin is an important element of non-verbal communication, which affects the quality of interpersonal communications, e.g. through the expression of emotions. The severity of skin changes may contribute to reducing the frequency of interpersonal contacts undertaken, as well as a negative impact on mental state and quality of life [13,14]. Consequently, the support of dermatologist becomes particularly therapeutic relevance.

The purpose of this study was to assess the relationship between levels of doctors' support and attitude to certain aspects of the treatment process and quality of life among patients with psoriasis. The following research questions were formulated based on the literature review:

1. What is the level of doctors' support among psoriasis' patients?
2. What is the level of quality of life in patients with psoriasis?
3. Is there a relationship between the current level of doctors' support and the patients' attitude the treatment process?
4. Is there a relationship between the current level of doctors' support and the attitude of patients to adhere to the medical recommendations?
5. Is there a relationship between the current level of doctors' support and the attitude of patients to medical staff?
6. Does the current level of doctors' support affects patient's satisfaction of the currently treatment?
7. Does the current level of doctors' support affects the quality of life of patients with psoriasis?

MATERIALS AND METHODS

The study was conducted on 50 patients with psoriasis aged from 21 to 78 who are treated in dermatological clinics. The mean age was 38.4 years (SD = 14.2). The group of subjects consisted of 30 women and 20 men. The empirical data was collected from January 2013 to December 2013. All patients who were participating in the study had a medical care. The subjects were recruited from patients who were:
1)over 18,
2)with diagnosed psoriasis,
3)subject to ongoing therapy,
4)and gave informed consent to be part of the study.

All patients gave informed consent.

Patients were examined dermatologically. *The Psoriasis Area and Severity Index (PASI)*was used to assess the severity of psoriatic skin changes. The PASI can range from 0 to 72 (where 0–lack of severity of symptoms and 72– severe of severity of symptoms) [15]. The currently used anti-psoriatic medication and the age at first diagnosis of psoriasis (years of life)were analysed.

The patients completed a questionnaire for the assessment of receive doctors' support, and its relationship with the attitude towards the disease. The research tool was developed based on literature

review. The patients assessed retrospectively the level of doctors' support during diagnosis by a 5-point scale (where 1-complete lack of support, 2-small, 3-medium, 4-large, 5-very large). Before responding to the above question, we have asked to patients if they remembered how dermatologist gave them information about their diagnosis.

Then, the respondents were asked to indicate the current level of doctors' support according to 5-point scale (where 1-complete lack of support, 2-small, 3-medium, 4-large, 5-very large). Subsequently, the participants of this study assessed the relationships between the current level of doctors' support and various aspects of treatment, such as treatment process, adherence to medical recommendations, self-advancing our knowledge about psoriasis, well-being, the attitude towards the disease, the attitude towards the doctor and the treatment process. The respondents assessed the above dimensions of the attitudes toward the disease used by a 5-point scale, where -2-very negative influence, -1-negative influence, 0-neutral effect, 1-positive impact, 2-very positive impact.

The data were analysed statistically using Stat Soft Statistic 9.0 software. The $p \leq 0.05$ criterion of statistical significance was adopted. Since nominal, ordinal and interval scale data were analyzed, both parametric and nonparametric statistics were applied. Correlations between variables were analysed using the Spearman's rank-order coefficient.

The statistical package IBM® SPSS® Amos 18 was used to developed a relationship models between the current level of support from the doctor, treatment satisfaction and quality of life of patients

Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study and they were fully informed about the drug and its side-effects.

THE RESULTS

The study group was diverse in terms of marital status - 25.5% of patients declared free marital status, 59.0% were married and 15.4% were divorced. The age of onset of diagnosed psoriasis in the studied sample was between 9 and 45 (M=21.9, SD=13.2). Duration ranged from 1 month to 47 years (M=16.2;SD=11.9). The PASI score in the entire sample ranged from 0.5 to 26.6 (8.86±0.8).

The body weight of patients was ranged from 48 to 120kg. The average value of weight in the analyzed group was 73.03kg (SD = 19.2). The BMI remained well within from 17.21 to 36.23kg/m 2 (Table. 1).

The quality of life of patients who were participating in the study was mediocre (Me = 3.00) (Table. 2). The largest percentage of respondents considered that their quality of life was average (35.9%). The slightly less patients felt that their quality of life was poor (30.8%) or good (25.6%). Only 5.1% of respondents admitted that their quality of life was very good, while 2.6% felt that it was very bad.

The initial level of doctors' support during discussing diagnosis was assessed by patients as a small (Me =2.00). The current level of doctors' support was also small (Me = 2.00) (Table.2). Changing the level of this support, which was assessed retrospectively, did not change during treatment of psoriasis (Z = 0.10; p = 0.92).

There was no correlation between the BMI and the level of quality of life in patients with psoriasis (rho = - 0.19, p = 0.12). It has been shown a negative relationship between the level of quality of life and the value of the PASI coefficient (rho = - 0.90, p = 0.01). In the next step of statistical analysis, we have assessed relationship between the change of the current level of doctors' support and the length of psoriasis treatment. The statistical analyzes showed a positive relationship between those variables by use of the Spearman coefficient (rho = 0.32; p = 0.05).

The subjective assessment of the impact of current doctors' support on the various aspects of the treatment process had been made from the perspective of the patient. The current doctors' support has no effect on treatment process (Me=3.00), well-being (Me=3.00), attitude towards to the disease (Me=3.00), and medical personnel (Me=3.00)in the opinion of the patients. The received doctors' support, according to the

Table 1: The anthropometric parameters in the analyzed group

	The body weight [kg]	The growth [cm]	BMI [kg/m^2]
M	73.03	168.13	25.33
SD	19.27	12.10	5.21
Min.	48	110	17.21
Max.	120	190	36.23

M - average, SD - standard deviation, Min.- minimum value, Max- maximum value

respondents opinion, did not affect adherence to medical recommendations (Me=3.00)and attitude towards the treatment (Me=3.00), as well as the self-exploration of knowledge about the disease (Me=3.00)(Table. 3).

The relationship between the current doctors' supportand the various aspects of the treatment process, from the perspective of patients, were assessed in the present study which are presented in Table 4.

The level of received doctors' support at the time the diagnosis was positively correlated with the attitude towards the medical personnel (rho=0.30, p=0.03). There ware no such a compound in the case of the self-exploration of knowledge about the disease, the adherence to medical recommendations, the attitude towards the treatment and disease, as well as well-being (Table 4).

The current level of received doctors' support has a positive relationship with the adherence to medical recommendations (rho = 0.61; p = 0.01), well-being (rho = 0.34; p = 0.02)and attitude towards the treatment (rho = 0.40; p = 0.01), the disease (rho = 0.32; p = 0.02) and medical personnel (rho = 0.43; p = 0.01)(Table 4).

It was also shown a positive relationship between the change of the level of doctors' support and the adherence to medical recommendations (rho=0.47; p=0.01). The correlational dependencies have not observed in the case of the self-exploration of knowledge about the disease and the attitude towards the process of treatment, the disease and medical personnel (Table 4).

The evaluation of the relationship between the current level of doctors' support and treatment satisfaction on one hand, and quality of life on other hand was assessed using analysis of structural equation modeling (SEM). The standardized regression weights assessing the strength of relationship between the variables showed a positive value for the level of doctors'

Table 2: The level of quality of life and the doctors' support among patients with psoriasis

	M	Me	Mo	The cardinality of Mo	Min.	Max.	SD	The confidence interval –0,95%	The confidence interval +0,95%
The level of quality of life	3.00	3.00	3.00	14	1.00	5.00	0.95	0.77	1.22
The initial level of doctors' support	2.59	2.00	1.00	11	1.00	6.00	1.43	1.17	1.84
The current level of doctors' support	2.56	2.00	1.00	12	1.00	6.00	1.47	1.20	1.89

M - Average, Me – Median, Mo- Moda, Min.- minimum value, Max- maximum value, SD - standard deviation

Table 3: Impact of doctors' support on selected dimensions the attitudes towards the disease

The subjective impact of support from a dermatologist on	X	Me	Mo	The cardinality of Mo	Min.	Max.	SD	The confidence interval –0,95%	The confidence interval +0,95%
The treatment process	2.85	3.00	3.00	18	1.00	5.00	0.96	0.79	1.24
The adherence to medical recommendations	3.03	3.00	3.00	20	1.00	5.00	0.99	0.81	1.27
The self-exploration of knowledge about the disease	3.38	3.00	3.00	19	1.00	5.00	1.04	0.85	1.34
Well-being	2.72	3.00	3.00	19	1.00	4.00	0.92	0.75	1.18
The attitude towards the treatment	3.00	3.00	3.00	19	1.00	5.00	0.83	0.68	1.07
The attitude towards the disease	2.56	3.00	3.00	21	1.00	4.00	0.82	0.67	1.06
The attitude towards the medical personnel	2.51	3.00	3.00	19	1.00	5.00	1.07	0.88	1.38

M - Average, Me – Median, Mo- Moda, Min.- minimum value, Max- maximum value, SD - standard deviation,

Table 4: The relationship between the level of doctors' support and selected elements of attitudes towards the disease

	The current assessment of treatment process	The adherence to medical recommendations	The self-exploration of knowledge about the disease	Well-being	The attitudes towards		
					Treatment	Disease	Medical personal
The level of support during the first visit							
rho	0.24	0.01	–0.05	0.19	0.20	0.19	0.30
p	0.07	0.47	0.39	0.12	0.11	0.12	0.03
The current level of support							
rho	0.68	0.61	0.25	0.34	0.40	0.32	0.43
p	0.01	0.01	0.06	0.02	0.01	0.02	0.01
Changing the level of support during treatment - a subjective assessment							
rho	0.29	0.47	0.23	0.08	0.15	0.05	–0.01
p	0.04	0.01	0.08	0.32	0.18	0.37	0.49

support and the attitude of the patient to treatment and medical personnel, as well as adherence to medical recommendations. The attitude toward the treatment was characterized by a direct relationship with adherence to medical recommendations, which directly affect the satisfaction of the actual treatment. The attitude toward the medical staff has showed a direct correlation with the degree of satisfaction with the treatment, and the attitude the treatment - intermediate with a degree of satisfaction with the current treatment. The level of satisfaction with the treatment had a direct impact on the quality of life of patients with psoriasis. The analysis of structural equation modeling has showed that the level of doctors' support had a direct impact on the patients' attitude the disease, including attitudes towards the treatment and medical personnel, as well as adherence to medical recommendations; and indirectly on satisfaction with the treatment and the quality of life (Fig. 1).

DISCUSSION

The results of this study showed that the level of doctors' support has a direct in affect on the patients' attitude towards the treatment process and adherence to medical recommendations. Numerous scientific reports have confirmed the relationship between the level of social support and good physical health [16-19]. A significant part of the studies concern the level of patients' social support, centered around the family and the environment of live. The perspective of patient - doctor relationship is slightly less analyzed. These results suggest that the skills to show adequate levels of support may be important in the success of therapy.

The diagnosis of the disease is a stressful situation which could cause shock and loss of a sense of security. Researchers who had analyzed human functioning in stressful situations - such as somatic illness - often referred to the theory of social support [6,20]. The skills for coping with a difficult situation is associated with a number of:

(1) psychological mechanisms, such as: cope with stress or defense mechanisms,
(2) situational factors - current expression of the emotions and the level of social support. The social support is one of the most studied the trait stress resistance [20-23].

Informing about diagnosis is associated with stressful situation which could be partially reduced by correct communication doctor – patient; especially through an adequate level of doctors' support, as well as the quality and quantity of information provided [21].

The cognitive psychology researches have shown the specificity of cognitive functioning - including memory, concentration, attention, perception - in a stressful situation [22]. This suggests that a minimum level of demand for information about disease determines the balance in the patient's psyche. The affective aspect is also important among patients and doctors. The level of perceived severity of stress, affective state and cognitive processes may significantly affect the reception of the information provided by doctor and the desire to obtain the proposed medical treatment [22-23].

Restoration of patients' sense of security may have a positive relationship with his attitude towards the disease process, treatment and adherence to medical recommendations [9, 24]. The empathic approach, doctors' support and the ability to identify the patient's expectations could play an important role in the restoration of patients' sense of security [9]. The useful clinical tool in the assessment of the

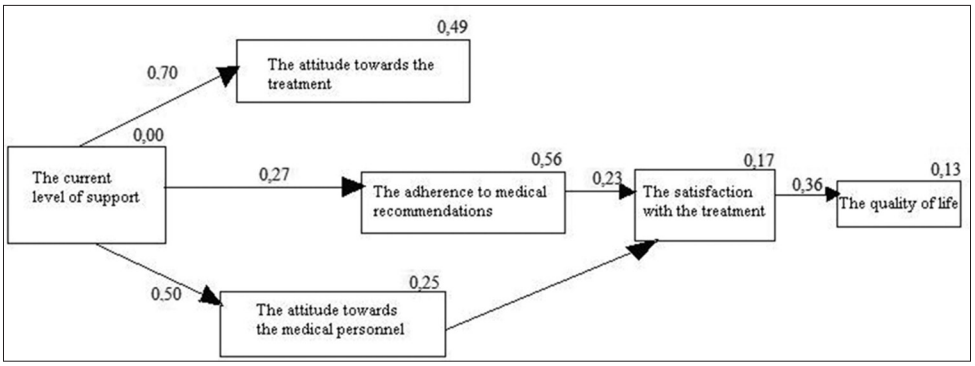

Figure 1: A model of the relationship between the level of doctors' support and selected aspects of attitudes toward the disease in patients with psoriasis (χ^2 (8) =3.72; p >. 05 (p = 0. 88); CFI=1.00 and RMSEA=0. 00; being removed the tracks that are not statistically significant).

needs of the patient could be an motivational interviewing (MI).

Doctors' Support influences not only on the attitude of the patient to the treatment process, but also to adherence to medical recommendations. The lower the level of support, the less medical recommendations adherence by patients. This highlights the importance of proper communication in the doctor-patient relationship during clinical practice.

It should be emphasized that the presented results of the study have a number of limitations that should be included during further empirical studies. Among other things, it is the small size of the group, which was not randomly selected. These limitations suggest caution in the interpretation of the data.

CONCLUSIONS

Results of this study have shown clear evidence the importance of the level of doctors' support in psoriasis which could help to improve the overall functioning of these patients. The level of doctors' support indirectly affects the quality of life in patients with psoriasis.

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

The relationship of body mass index and hirsutism in adult females

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ABSTRACT

Introduction: Hirsutism is a common clinical condition that usually has a benign course but extremely distressing symptom for women. Hirsutism is a perplexing issue, having variable presentations including different severity of hirsutism, with menstrual history regular or irregular, body mass index (BMI) within normal range or obese or overweight and yet some have a family history of hirsutism. Hirsutism may be associated with obesity, insulin resistance, diabetes, polycystic ovary syndrome (PCOS), hypertension, infertility, and menstrual irregularities. Studies suggested that it affects between 5 percent and 15 percent of women, varying according to characteristics and at least 5 percent of women of reproductive age suffer from this problem. Body mass index (BMI) classifications were developed based on associations between BMI and chronic disease and mortality risk in healthy populations. **Aim:** This study was designed to investigate the relationship between body mass index (BMI) and hirsutism. **Material and methods:** All patients were examined clinically, then interviewed and detailed questionnaires were completed for each of them. The study involved 300 individuals; 150 hirsute patients and 150 healthy people as control group. Hirsutism was determined by the Ferriman-Gallwey scoring system. Height and weight were measured by a physician mechanical scale. Body mass index was calculated weight/height^2 (kg/m^2), and collected data were analyzed by Microsoft excel-chi-square statistical test. **Results:** There were no significant differences between the two groups regarding age and height. However, BMI and weight were significantly higher in the cases group than the control group ($P < 0.05$). The chi square test revealed significantly higher differences between the case and control groups regarding BMI ($P < 0.001$). **Conclusion:** Our study clearly establishes that hirsute women had higher body mass index and moderate hirsutism was more prevalent among hirsute women.

Key words: Body Mass Index (BMI); Hirsutism; Obesity; Ferriman-Gallwey scoring system

INTRODUCTION

Hirsutism is defined as excessive terminal hair that appears in male pattern (i.e. sexual hair) in women. Hirsutism affects 5% to 10% of women [1]. What constitutes hirsutism is difficult to define, as it depends on a variety of cultural and racial factors, media-driven perceptions of normality, and the perceptions of the individual physician and patients. Not surprisingly, therefore, estimates of the frequency of hirsutism in the female populations have varied widely. In London, 1.2 percent of women were significantly hirsute. Other studies have reported frequencies of up to 18 percent [2]. Even the criteria for the definition of hirsutism used by physicians vary widely. In order to resolve this issue, different groups have evolved different grading schemes for body hair growth. The scheme employed in the study by Ferriman and Gallwey, which has become the standard grading system, defined hirsutism purely on quantitative grounds. Hirsutism is graded as numerical scores beyond an upper limit of twice the standard deviation from the mean. Scoring can be on global basis assessing 8-11 body sites, or it can be based on a single site [3].

Obesity and a BMI of more than 30 kg/m^2 are associated with decreased lung function, respiratory symptoms

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and cardiovascular diseases such as arteriosclerosis, ischaemic heart disease, stroke and hypertension, type 2 diabetes and metabolic syndrome [4].

With worldwide rates of obesity increasing steadily, the National Institutes of Health (NIH) and the World Health Organization (WHO) recently adopted similar body weight guidelines for overweight and obesity. Values of body weight adjusted for height, referred to as body mass index (BMI; in kg/m^2), in excess of 25 and 30 are considered to indicate overweight and obesity, respectively. A lower healthy BMI limit of 18.5 was also identified by both organizations. These body weight guidelines are useful for practitioners when screening patients for excessive adiposity and when prescribing treatment for overweight patients [5].

Androgen-dependent growth areas affected include the upper lip, cheeks, chin, central chest, breasts, lower abdomen, and groin. This altered growth pattern of the hair may be associated with other signs of virilization, which include temporal balding, masculine habitus, deepening voice, clitoral hypertrophy, and amenorrhea [6].

Most common causes of hirsutism are polycystic ovarian syndrome (PCOS) and idiopathic hirsutism. Other causes include late onset congenital adrenal hyperplasia and Cushing's syndrome. Pituitary, ovarian and adrenal tumors are rare causes of hirsutism [7].

Interestingly, serum androgens are positively associated with BMI not only in PCOS, but also in women with simple obesity. It seems that hirsutism is more common in people with simple obesity. The relation between obesity and hirsutism may be modified by racial and ethnic characteristics of different populations. for example in a retrograde 2 year cohort study by Khalil et al. of adult Saudi populations the associations between obesity and certain skin diseases such as hirsutism, dry skin, pruritus, and planter keratosis were all nonsignificant [8].

The sensitivity of the hair follicle to androgens is largely governed by the alpha reductase activity in the skin, which is responsible for the conversion of testosterone to dihydrotestosterone. The severity of hirsutism does not correlate well with the level of androgens, because the response of the androgen dependent hair follicle varies considerably within and between individuals. The source of testosterone in a female is the ovaries and the adrenals. Androgen dependent hirsutism may be caused by disorders affecting the adrenals or ovaries, exogenous administration of androgens or a combination of these factors [9].

Hirsutism must be distinguished from hypertrichosis—generalized excessive hair growth that occurs as the result of either heredity or the use of medications such as glucocorticoids, phenytoins, minoxidil, or cyclosporine. Hypertrichosis, in which hair is distributed in a generalized, nonsexual pattern, is not caused by excess androgen (although hyperandrogenism may aggravate this condition) [10].

MATERIAL AND METHODS

This is a cross sectional case control clinical trial. The study was conducted in Tikrit Teaching Hospital during the period from November 2012 to the end of May 2013. All patients were examined clinically, then interviewed and detailed questionnaires were completed for each of them. The study involved 300 individuals; 150 hirsute patients and 150 healthy people as control group. The participants' ages were between 15 to 45 years. Demographic data were collected by a questionnaire.

Height was measured without shoes and weight with light clothing and without shoes on a platform scale with a 1.5 kg subtraction to correct for clothing weight.

Height and weight were measured by a physician mechanical scale. Body Mass Index was calculated by dividing the body weight with the square of height (kg/m^2). According to the guideline proposed by the World Health Organization, the normal range of BMI is between 18.5 and 24.9, and values below18.5 imply underweight, while overweight is defined by a BMI over 25 and obesity over 30 kg/m^2 [11].

Ferriman and Gallwey, used a scoring system loosely based on that of Garn, evaluating 11 body areas, including the upper lip, chin, chest, upper back, lower back, upper arm, forearm, upper and lower abdomen, thighs and lower legs. A score of 0–4 was assigned to each area examined, based on the visual density of terminal hairs, such that a score of 0 represented the absence of terminal hairs, a score of 1 minimally evident terminal hair growth, and a score of 4 extensive terminal hair growth. Terminal hair hairs can be distinguished clinically from vellus hairs primarily by their length (i.e., 0.5 cm), coarseness, and pigmentation. In contrast, vellus hairs generally measure, 0.5 cm in length, are soft and non-pigmented [12].

Collected data were analyzed by Microsoft excel-chi-square statistical test.

Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study and they were fully informed about the drug and its side-effects.

RESULTS

The mean age and the mean height of cases and control are shown in Table 1. There were no significant differences between the two groups regarding age and height. However, BMI and weight were significantly higher in the case group than the control group ($P < 0.05$) as shown in the Table 1.

Frequency of distribution of BMI is shown in Table 2. The chi square test revealed significantly higher differences between the case and control groups regarding BMI ($P < 0.001$).

Among hirsute women it was found that, 61.54 % with moderate hirsutism, 37.69% of patients had mild hirsutism, while one patient with severe hirsutism as shown in the Table 3.

Table 1: BMI, weights, age, and heights in cases and controls groups

	Numbers	Cases (Mean±SD)	Control (Mean±SD)	P-value
Age	130	28.46±6.97	29.28±8.18	Not significant
Weight	130	78.75±16.32	68.10±13,31	Significant (<0.05)
Height	130	158.67±14.38	159.42±7.01	Not significant
BMI	130	30.58±5.77	26.71±5.54	Significant (<0.05)

Table 2: BMI frequency of distribution in cases and controls groups

WHO		Cases		Control		All	
BMI	(Kg\m²)	Nr	%	Nr	%	Nr	%
Underweight	<18.5	0	0	3	2.31	3	1.15
Normal	18.5-24.9	18	13.84	48	36.92	66	25.38
Overweight	25-29.9	49	37.7	45	34.62	94	36.15
Obese	>30	63	48.46	34	26.15	97	37.31
Class 1	30-34.9	31	49.2	19	55.9	50	51.54
Class 2	35-39.9	23	36.5	13	38.23	36	37.1
Class 3	>40	9	14.29	2	5.9	11	11.34
Total		130	100	130	100	260	100

The two-tailed P value is less than 0.0001. Statistically significant

Table 3: Ferriman-Gallwey score of hirsutism

Hirsutism score		Number	%
Non hirsute	<8	0	0
Mild	8-16	49	37.69
Moderate	17-25	80	61.54
Severe	>25	1	0.76
Total		130	100

DISCUSSION

In the current study hirsutism was more common in patients with increased BMI. In this sample there was a positive relation between body mass index and hirsutism. This may be a sign of an underlying metabolic disorder, which will lead to the greater risk of the development of cardiovascular disease and type-2 diabetes.

There were no significant differences between the two groups regarding age and height. However, Body Mass Index and weight were significantly higher in the case group than the control group. The chi square test revealed significant differences between the case and control groups regarding Body Mass Index ($P < 0.001$).

Hirsutism causes significant anxiety and lack of self-esteem in women. Although it is itself a benign condition, it is often the sign of an underlying and possibly serious endocrine condition. The diagnosis begins with a detailed history and physical examination, with laboratory testing and imaging as needed to confirm or rule out underlying causes [13]. As part of the physical examination, the clinician should also look for other cutaneous signs of hyperandrogenism, such as acne, androgenetic alopecia, and seborrhea. Acanthosis nigricans is a sign of insulin resistance. Height and weight should be measured and the body mass index calculated [14].

In this study the prevalence of overweight and obesity was higher among hirsute women than non hirsute women. In the study carried out in various hospitals of Lahore found that 20% were overweight among hirsute women [15].

In other study carried out in India found that girls with hirsutism were overweight 46.03%. The same study showed association of BMI with hirsutism, subjects with normal BMI were 6.78% shows signs of hirsutism, whereas subjects with BMI of more than 25 were 46.03% showed signs of hirsutism [16]. There is no evidence of association of hirsutism and abnormal BMI value in the study carried out in Tirana university students [17].

The prevalence of obesity in patients with hirsutism is different in various populations. Obesity was found in 63 patients (48.46) of our sample cases. This is similar to reported figure of 51% in Saudi Arabia [18].

In the instant study, a total of 49 (37.69%) patients had mild hirsutism, 80 (61.54%) had moderate and remaining one (0.76%) patients had severe hirsutism. In our study moderate hirsutism was more prevalent than mild and severe form. These observations were similar to study by Adams *et al*; Ram Krishan Gautam New Delhi -India; our findings were in disagreement with studies by Ansarin *et al*.who reported mild hirsutism in 65%, moderate in 32.5%, and severe in only 2.5% of their patients [19].

Our study clearly establishes that hirsute women had higher body mass index and moderate hirsutism was more prevalent among hirsute women.

This is likely to be due to hyperandrogenemia which will promote the development of hirsutism. This will add to our understanding of hirsutism and may help us in a precise targeted approach for management of such patients.

Considering the side effects of obesity and significant relationship between BMI and hirsutism, weight loss of obese and overweight is strongly recommended. Height and weight should be measured and the body mass index calculated.

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

Comparison of intralesional triamcinolone and intralesional verapamil in the treatment of keloids

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ABSTRACT

Introduction: Keloid is an abnormal fibrous tissue outgrowth which extends beyond the borders of the wound. Intralesional triamcinolone acetonide is the most commonly used corticosteroid in the treatment of keloids. Intralesional Verapamil is an emerging treatment modality. Both of these drugs were compared to guide us towards better management of keloids by choosing the more appropriate treatment. **Material and Methods:** This was a randomized controlled single blind study conducted in the outpatient department of Dermatology unit II, Mayo Hospital Lahore, Pakistan. Eighty patients (40 in each group) were enrolled. Group A was given Intralesional Verapamil injection 1ml (2.5 mg) every month and group B was given Intralesional Triamcinolone acetonide (40mg) monthly. Patients were assessed at the beginning of the treatment and at the end of 3th injection. The clinical assessment of the scar was based on the Vancouver Scar Scale. Mean decrease in total score was calculated and patient's keloid were photographed with a high quality digital camera, with consent. **Results:** Eighty patients, 42 (52.5%) male and 38 (47.5%) female were enrolled. The age of patients ranged from 12 to 40 with a mean age of 25.96 (±6.982) years. Most of the patients were between 21 to 30 years of age group. After the completion of study 58.28% reduction in the baseline score was seen in the triamcinolone group as compared to 36.75% in the verapamil group. Adverse drug reactions observed were pain in almost all patients, hypopigmentation in five patients and irregular menstrual cycles in two females with Triamcinolone. While only pain was observed with intralesional Verapamil. **Conclusion:** Intralesional verapamil can be used in the treatment of keloids but intralesional triamcinolone acetonide is better. Intralesional verapamil can give better results when used in combination

Key words: Keloid, Triamcinolone, Verapamil

INTRODUCTION

Keloid is an abnormal fibrous tissue outgrowth which extends beyond the borders of the wound. It does not usually regress spontaneously and possesses high chances of recurrence after excision. Keloids grow faster and become raised and thickened within 3 to 4 weeks [1]. They can occur anywhere on the body but the most common sites are sternum, shoulders, earlobes, and cheeks [2]. They are caused by minor trauma to the skin like ear piercing, abrasion, tattooing, burns, and at the site of injection [3]. It may occur after acne formation or chickenpox infection and sometime keloids can be formed spontaneously in sternal area in susceptible individuals [4].

Treatment of keloids is a difficult and challenging job. It has a high recurrence rate. Different modalities are in practice but none of them either single or in combination give promising results when used [5]. Compression bandages, silicone gel, flavonoids, intralesional corticosteroids injection, Cryotherapy, scar revision surgery, radiotherapy, intralesional interferon injection, bleomycin, 5-FU, methotrexate and laser therapy are used for the prophylaxis and treatment of keloids.

Intralesional triamcinolone acetonide is the most commonly used corticosteroid in the treatment of keloids, which suppresses the inflammatory process in the wound, diminishes collagen and glycosaminoglycan

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synthesis, inhibits fibroblast growth factors and enhances collagen and fibroblast degeneration [7,8].

Verapamil, an anti-hypertensive, is also used in the treatment of keloids. When administered intralesionally, it reduces extracellular collagen production and stimulates synthesis of collagenases, thus promoting the breakdown of collagen as well [6].

To the best of our knowledge, this was the first study in our country to compare intralesional Verapamil with intralesional Triamcinolone acetonide. The purpose of this study was to compare the efficacy and safety of both the drugs, to guide us towards better management of keloids by choosing the more appropriate treatment.

MATERIAL AND METHODS

This was a randomized controlled single blind study. Sample size of 80 cases (40 in each group) was taken by purposive non-probability technique. Mean decrease in score in both the groups was calculated through Vancouver scar scale. The power of the test was 80% and confidence interval was 95%.

The inclusion criteria for the study were patients from either sex, presented between 10 and 40 years of age; size of keloid more than 1 centimeter to 5 centimeters and on any site of the body; duration of keloid less than five years and baseline Vancouver scar score of 5 or above. The exclusion criteria were pregnancy or lactation; family history of keloids; Patients having diseases like acromegaly, diabetes mellitus and congestive cardiac diseases on the basis of history, physical examination and investigations like blood sugar level, and ECG; presented after thyroidectomy and patients on isotretinoin and anabolic steroids.

Patients having keloids presented to Outpatient Department of Dermatology, Mayo Hospital, Lahore and fulfilled the inclusion criteria were enrolled. Informed consent was taken and the graphic data (name, age, Sex, telephone contact number and address) was charted.

Patients were divided in two groups. Group A was given Intralesional Verapamil injection 1ml (2.5 mg) every month and group B was given Intralesional Triamcinolone acetonide (40mg) monthly. Patients were assessed at the beginning of the treatment and at the end of 3th injection. Administration of the drugs was continued till the keloid flattened or for a maximum period of three months. The patients were followed up three months after the administration of last injection to look for any recurrence.

The clinical assessment of the scar was based on the Vancouver Scar Scale which is universally accepted, standard scale used for scar assessment. The scars were assessed on four parameters namely pigmentation, vascularity, pliability and height

Mean decrease in total score was calculated and patient's keloids were photographed with a high quality digital camera, with consent.

Data was entered and analyzed in the SPSS version 12. Quantitative variables like age, baseline Vancouver scar score, Vancouver scar score after treatment at three months were calculated in the form of mean +/- S.D. Qualitative variables like gender were presented in the form of frequencies and percentages. t-test was used to compare the mean decrease in Vancouver scar score in both groups. P-value of <0.05 was considered as statistically significant.

Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study and they were fully informed about the drug and its side-effects.

RESULTS

Eighty patients, 42 (52.5%) male and 38 (47.5%) female were enrolled in the study from the outpatient department of Dermatology unit II, Mayo Hospital Lahore. All of the patients completed the study.

The age of patients ranged from 12 to 40 with a mean age of 25.96 (±6.982) years. Most of the patients were between 21 to 30 years of age group. The tabulation of age groups and sex distribution is given in Table I.

Patients were randomly divided into two equal groups A and B. The gender wise group distribution is shown in fig 1. Intralesional Verapamil was given in a dose of 1ml (2.5mg) to group A and group B was put on intralesional Triamcinolone acetonide, 1ml (40mg). Maximum of three doses, one month apart were given and patients were followed three months after the completion of treatment.

Keloids were assessed by Vancouver scar scale before, at the completion and three months after the completion of treatment in both the groups. After the completion of study 58.28% reduction in the baseline score was seen in the triamcinolone group (Figs 2 and 3) as compared to 36.75% (Figs 4 and 5) in the verapamil group. The mean decrease in score after the completion of treatment was calculated and compared. The descriptive statistics of the mean decrease in both the groups is plotted in Table 2.

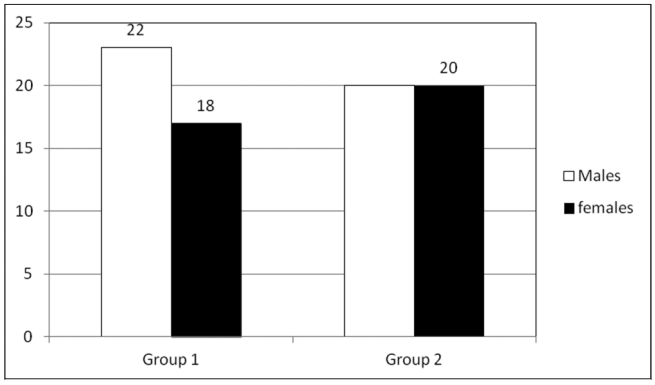

Figure 1: Gender distribution with respect to Group.

Adverse drug reactions observed were pain in almost all patients, hypopigmentation in five patients and irregular menstrual cycles in two females with Triamcinolone. While only pain was observed with intralesional Verapamil.

Patients were followed for three months after the completion of treatment in both the groups. No recurrence in keloid scar was noticed in any patient.

DISCUSSION

Keloid is basically the disease of young age. It occurs most commonly in people younger than 30 years, with peak age between 10 and 20 years. Its occurrence is also influenced by elevated hormone level in the

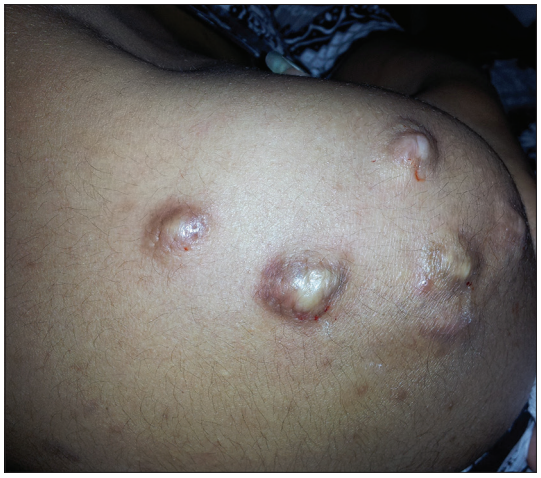

Figure 2: Before Intralesional Triamcinolone Inj.

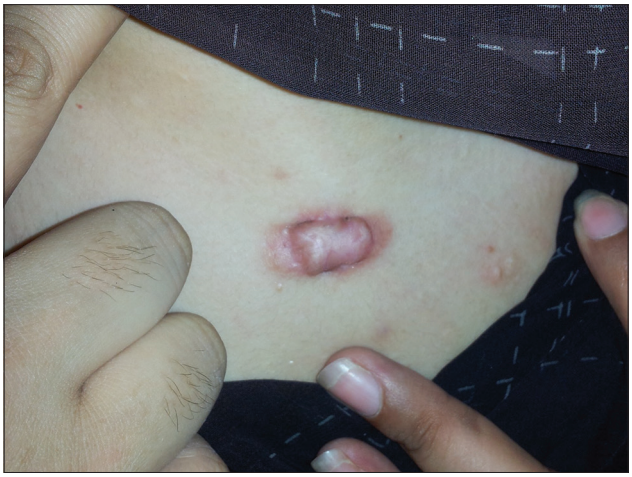

Figure 4: Before 1st Inj. of Verapamil.

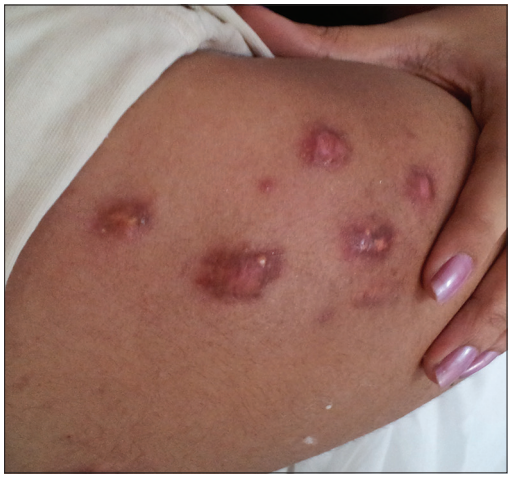

Figure 3: After 3rd injection of Triamcinolone.

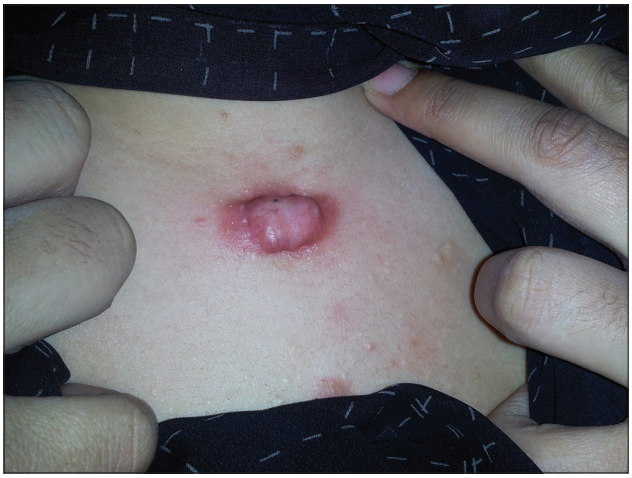

Figure 5: After 3rd Inj. of Verapamil.

body, especially during puberty and pregnancy. There is almost equal sex distribution. A slight female predominance may be related to the higher rate of earlobe piercing. Management of keloid is difficult as well as challenging. A lot of treatments have been advocated and claimed to be effective but cure is rarely achieved. Multiple measures have been used for prevention as well as treatment of keloids.

This is the first comparative study of its kind, to compare intralesional Triamcinolone with intralesional Verapamil in Pakistan.

Total of eighty patients, equally divided in groups A and B and were enrolled in our study. Group A was put on Verapamil, 1ml (2.5mg) and Triamcinolone acetonide 1ml (40mg) was given to group B. In our study 52% patients were males while 47% were females. Internationally the occurrence of keloids has an almost equal sex distribution[2], which is in contrast to our study. The reason behind this may be the social setup in our country, in which less number of females with keloids report to the hospitals. Another reason may be the lack of epidemiologic studies of keloids in Pakistan, there may be difference in sex distribution of keloids in this part of the world.

The mean age was same in both the groups. The majority of patient enrolled in our study were below 30 years of age with a peak between 20 and 30 years which is compatable with studies, carried out in other parts of the world. Bermain B. *et al* [9] reported that most patients having keloids were younger than 30 years of age. Gauglitz G.G [8] also found that the highest incidence of keloids was in the 2nd and 3rd decade of life. In another study conducted in Iran[10], the keloids were more prevalent between 15 to 30 years of age.

Dhanraj P [11], *et al* in their study published in 2008, for the first time compared intralesional verapamil with intralesional triamcinolone acetonide in the treatment of keloids. They performed their study on 54 patients (27 in each group) and followed them for one year. They reported that verapamil was equally effective. Their results were in contrast to our findings.

The sample size in their study was small, i.e 54 as compared to 80 in our study. Another reason may be that we used maximum three doses, one month apart and followed the patients for three months, while Dhanraj P. *et al* [11] injected the drugs for a maximum of six doses, one month apart and followed them for one year.

D'Andrea F.*et al* [12] in their study, conducted on 44 patients concluded that verapamil hydrochloride showed poor results when used in the treatment of already formed keloids even when compared to topical steroids. However when intralesional verapamil injection was combined with surgical excision and topical silicon application, 54% cure rate was seen.

The reason that verapamil hydrochloride is less effective than corticosteroids may be that corticosteroids has an additional anti-inflammatory effect on the scar tissue along with inhibition of collagen and glycosaminoglycan synthesis and degeneration of fibroblast/collagen as compared to verapamil.

Internationally intralesional verapamil is used as an adjuvant therapy to surgery in majority of studies in the prevention as well as the treatment of keloids.

Lawrence [13] combined intralesional verapamil and pressure earrings with excisional surgery and reported 55% cured earlobe keloids in 52% of the patients after an average of 28 months of follow-up.

Copcu E, Sivrioglu N, Oztan Y [14] in a case series, surgically treated 22 keloid patients followed by 5 treatments of intralesional verapamil at 2.5mg/ml over a 2-month period. When evaluated at 2 years follow up, an average patient satisfaction score of 6.4 was reported on a scale from 1 to 10.

Side effects were seen more with intralesional triamcinolone as compared to intralesional verapamil. Pain was observed by all patients in triamcinolone

Table 1: Cross tabulation of age groups and sex

Age group in years	Sex		Total
	Male	Female	
0-15	4	1	5
16-20	5	7	12
21-25	8	15	23
26-30	14	7	21
31-35	5	4	9
36-40	6	4	10
Total	42	38	80

Table 2: Descriptive statistics

Groups	(n)	Mean decrease in score	Standard deviation	Difference of means	95% confidence interval of the difference	
					Lower	Upper
Group A	40	2.50	0.716			
Group B	40	4.35	0.700	−1.850	−2.165	−1.535

P value=0.00

group while hypopigmentation in five and menstrual abnormalities in two females.

This shows that intralesional triamcinolone acetonide is the drug of first choice in the treatment of keloids, when given in proper dose according to the size of the lesion. It results in rapid reduction in size as well as the symptoms of keloids. The adverse effects with triamcinolone injection can be reduced if the injection is given neither too deep nor too superficial.

Verapamil hydrochloride gives good results when used as an adjuvant therapy to surgery.

CONCLUSION

Keloids are difficult to treat and their management is still emerging. Intralesional verapamil can be used in the treatment of keloids but intralesional triamcinolone acetonide is better. Intralesional verapamil can give better results when used in combination with other modalities like surgical intervention. Further large randomized controlled double blind studies are needed to establish the role of intralesional verapamil in the treatment of keloids.

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

Comparison between the effects of Daivonex cream alone and its combination with narrowband ultraviolet B in treatment of psoriasis

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ABSTRACT

Introduction: Psoriasis is a chronic immune disorder that multiple factors are involved in its creation. Psoriasis is not curable but a large number of local and systemic treatments for psoriasis are available that can reduce symptoms and recurrence of the disease. Treatment is selected based on severity of illness, associated comorbidities, patient preference[including costs and convenience], and evaluation of the effectiveness of patient response to treatment. **Methods:** 94 cases included from patients admitted to the Sina dermatology clinic with diagnosis of psoriasis. They were randomly divided in two groups. First group treated with Calcipotriol alone while the second group treated with calcipotriol and NBUVB phototherapy. **Results:** According to the results of our study the subjects in the two groups in terms of sex, age, weight, height, history of systemic disease, duration of psoriasis, site of involvement and the extent of the lesions were not significantly differ. An average improvement in lesion thickness, erythema and scaling and investment, and improve overall recovery of waste per week in the fourth, eighth and twelfth week after treatment, In the second group were significantly higher than the first group. **Conclusion:** Daivonex cream in combination with NBUVB phototherapy has a faster and more recovery in a given time. Daivonex with NBUVB phototherapy can be used to provide better results.

Key words: Psoriasis; Daivonex cream; NBUVB phototherapy

INTRODUCTION

Psoriasis is a chronic, relapsing inflammatory skin disease with silver plaques, Shell transition, and erythematous condition. Psoriasis is a polygenic disease that can occur at any age. Although in more than 75% of patients, the first symptoms are manifested before the age of 40 [1,2]. Furthermore, the association between psoriasis and inflammatory and metabolic disorders have also been reported. Several factors are involved in causing psoriasis such as trauma, infections, lifestyle, such as obesity, smoking and certain medications such as beta-blockers, and lithium, antimalarial drugs [3], nonsteroidal anti-inflammatory drugs,also Corticosteroid dose reduction noted in people who are genetically prone to cause disease [4,5].

From NBUBV In combination with Calcipotriol is also used to treat psoriasis. Studies that have evaluated the combined effect of Calcipotriol and NBUBV have offered varying results [6,7]. In this study, we attempt to evaluate the effectiveness of the cream Daivonex alone and to combine this method with phototherapy with NBUBV and to Choose an appropriate method that can, cause the greatest improvement in shortest time And can be more effective and safe therapy for the treatment of these patients.

METHODS AND MATERIALS

All the patients referred to the dermatology department of the sina hospital from October 2013 to March 2014 witch had been diagnosed with psoriasis, we chose the

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study cases totally random. To determine the sample size we used Rim Jh and colleagues study.In this study, the changes in the intensity of the thickness (induration) was considered as the primary outcome 94 individuals.

During the process of collecting samples from individuals who have less than 10% BSA or had limited psoriasis, if other criteria were matched they referred to responsible resident to be reviewed. The patients were randomly divided into 2 groups of 47, with no age limit. Anthropometric characteristics such as height and weight were determined for each individual. Duration of illness in patients was determined and patients were categorized according to the type of medication or unit weight in mg doses and duration of drug use. And each group was been treated with one of the 2 therapy methods as follows: All the patients underwent routine tests before starting treatment. Those in the treatment group of Daivonex.

Cream used 5.0 mg every 12 hours to the surface of the body used the palm of a hand to measure it. Patients used creams with Behestan Behdasht (under license Leo pharma, Denmark) brand. Those in the treatment group witch treated with cream Daivonex with NBUVB 2 times a week using Dermapal 800 Davlin machine made in United States of America with a primary energy of 2.0 joules per square centimeter were under phototherapy. In the next sessions 1/0 joules per square centimeter on the amount of energy was added by the system. These patients were similar to the previous group witch were using cream with the difference that in the days of phototherapy, the cream used after PHOTOTHERAPY. All patients at baseline and 4, 8 and 12 weeks after starting treatment were visited and the improvement of erythema, scaling, thickening (induration) lesion (no = 0, less than 30% = low, 30 -60% = average, over 60% = high) and the response to treatment was assessed and defined in to grades according to the following Table 1.

For 12 weeks, according to previous studies, it was enough for patients and patients relapse after completion of the study were not examined.

Table 1: Grades evaluation of treatment

Percent	Grade criterion	Recovery
5-20	Poor improvements	Erythema and desquamation decreased
20-50	Average recovery	The relative flattening of plaques, erythema and scaling low
50-95	Considerable improvement	Flat plate with a margin of almost all palpable, no erythema and scaling
95>	Clear	The flattening of all plaques with or without hyper pigmentation

To eliminate bias in the study some inclusion criteria were determined.

Inclusion criteria for this study include:

1. Having mild psoriasis
2. The non-glare
3. No other systemic diseases
4. Lack of lupus erythematous or derma Pygmantvzvm
5. No history of melanoma
6. No other skin malignancies
7. Arsenic consumption
8. Pregnant women or lactation
9. Willingness to participate in the study
10. Do not use other treatments in the last month.

Exclusion criteria:

Failure to comply with any of the criteria for inclusion

This study is registered with registration number IRCT138903294207N1 in database of registered clinical trials.

Findings

In this study 85 patients, 47 males (55.3%) and 38 females (44.7 %) participated. 24 males (55.8%) and 19 women (44.2%) participated in group A treated with Daivonex cream alone, 23 men (54.8%) and 19 females (45.2%) participated in group B treated with Daivonex cream and ultra-violet with narrow band B (NBVUB),the frequency of sex differences in the two groups was not statistically significant (P=0.923).

The duration of the disease, patients in group A, with an average 4.16±4.45 years and group B with an average of 5.37±7.82 years. Statistically significant differences

Table 2: Frequency of results of two group treatment

	Group A	Group B
Erythem		
4th week	0.76±2.12	0.90±2.67
8th week	1.04±2.77	0.85±3.40
12th week	1.12±3.14	0.56±3.79
Scaling		
4th week	0.76±2.19	0.87±2.76
8th week	0.98±2.81	0.70±3.50
12th week	1.05±3.19	0.50±3.81
Thickness		
4th week	0.63±1.30	0.85±1.83
8th week	0.92±1.95	0.88±2.74
12th week	1.21±2.60	0.86±3.55

Group A: group under treatment of Daivonex only, Group B: Group under treatment of Daivonex with NBUVB

between the groups in duration of disease was observed (P=0.387).

Among the most affected areas of the body, legs. Statistically no significant differences showed in the place of the lesions between the two groups (P=0.594).

Due to the significant chi-square value of P=0.842, there is no significant difference in the extent of lesions between the two groups.

According to the results presented by sex, age, weight, height, history of diabetes, duration of psoriasis, the involvement of problem and size difference between the two groups A and B was not significant. In comparing the recovery of patients in groups A and B, of erythema, scaling and thickness investment (induration) at weeks 4, 8 and 12, the following information was obtained:

About Improving in the levels of erythema 4 grades including, no erythema = 4, (low) less than 30% = 3, (average) 30-60% = 2 and (much) more than 60% = 1, coded and measured.

All patients in both groups at baseline were with high erythema (60%). The mean improvement in erythema at different is described weeks in Table 2.

About Improve in the investment of Scaling, 4 grades including, no scaling = 4, (low) less than 30% = 3, (average) 30-60% = 2, and (much) more than 60% = 1 encoded and measured.

All patients in both groups at baseline had more scaling investment. The mean improvement in the scaling investment (Table 2) is visible. In group B recovery were greater and faster than in group A.

About Improving in thickness (induration) four levels including, no abnormal thickness = 4, (low) less than 30% = 3, (average) 30-60% = 2 and (much) more than 60% = 1 encoding and measured.

In All patients of both groups at baseline lesions were too thick. Average improvement in thickness described in Table 1. Five levels in recovery including: no recovery = 0, low recovery in scaling or erythema less than 20% = 1, average recovery with smooth scaling and erythema (20-50%) = 2, nice smooth complete recovery with a palpable edge of the crust and no erythema (50-95%) = 3 and full recovery (over 95%) = 4 is defined and measured.

Improvement Process at week 4 in Group A was 1.19± 0.76 and in group B was 1.76±0.93. Due to the significant level of p=0.002 in the recovery of group A and B at 4 weeks of treatment, there was a statistically significant difference.

In group A, the mean recovery in week 8 was 1.86±1.06 and in group B was 2.71± 0.94. Due to the significant level of P=0.000 in the recovery of group A and B at 8 weeks of treatment, there was a statistically significant difference.

In group A, the mean recovery in week 12 was 2.56±1.18 and in the group B was 0.86 ± 3.55. Due to the significant level of P=0.000 in the recovery of group A and B at 12 weeks of treatment, there was a statistically significant difference.

In both groups recovery was observed but in group B recovery was more and faster than in group A. So that at the end of the study the group witch used cream Daivonex had 30.2% of complete recovery but patients in group B witch treated by phototherapy with narrowband ultra violet and Daivonex cream in the combination 73.8% of complete recovery was observed.

DISCUSSION

According to the results of our study subjects in the two groups in terms of sex, age, weight, height, history of diabetes, duration of psoriasis, the plight and size differences were not significant The mean improvement in erythema and crust investment and improve in lesion thickness overall recovery of lesion in the fourth week, eighth and twelfth after starting treatment in patients who were treated with creams and phototherapy were Significantly higher than the group that used the cream alone. The results of our study show that the use of cream in combination with phototherapy Daivonex Phototherapy with faster and more recovery at a time can be used to provide better results [8]. It can be concluded that patients can improve the speed of treatment side effects, including cumulative effects of phototherapy dose reduction That the matter should be further investigated in other comparative studies. Similar to Noborio et al study in 2006 concluded that the therapeutic effects of Calcipotriol is higher than other drugs in combination with phototherapy [9]. The results of our study showed that Calcipotriol in combination with phototherapy increase the speed and the amount of improvement.

As a study done by Jong-Hyun Rim et al [10] in our study, the use of Calcipotriol cream in combination with phototherapy with an appropriate treatment was introduced to accelerate and enhance recovery.

As a study done by Takahashi et al [6], the results of our study showed that the combination of Calcipotriol Ointment with NB-UVB twice a week, compared to other treatments, the rate and extent of psoriasis of lesion can be further improved.

As a study done by Rogalski et al [7] as well as a study done by Roussaki-Schulze et al [11], in our study group Calcipotriol alone received less improvement than the other groups showed. This could indicate an increased therapeutic effect in combination with other treatments is Calcipotriol, or excimer laser, or narrowband ultraviolet radiation.

Unlike our study Karakawa et al as "the period of remission treated with narrowband ultraviolet B in psoriasis vulgaris" did And retrospectively studied the factors that influence the duration of remission after photo chemotherapy so we compared [8]. The two methods together, to achieve a therapeutic effect that is the most efficient and lowest paid.

CONCLUSION

The results of our study show that the use of cream Daivonex in combination with phototherapy By creating more and faster recovery time can be as a treatment that can be used to provide better results So that in the group treated with cream Daivonex, at the end of the study 30.2% of patients achieved complete remission, while the combination of cream and ultra violet Daivonex narrowband cure rate was 73.8 percent.

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

Brief Report

Balanoposthitis as a cutaneous marker of diabetes mellitus in an apparently healthy male

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ABSTRACT

Background: Balanoposthitis inflammation of the glans penis, which often involves prepuce is a common condition and are usually managed symptomatically without considering a possible association diabetes. Acquired balanoposthitis may be the first clinical presentation of undiagnosed diabetes mellitus. **Methods:** We enrolled 100 subjects with balanoposthitis with no history of diabetes mellitus in the past. Random blood sugar was done in all subjects, those with random blood sugar more than 140 mg/dl underwent fasting and 2 hour post prandial blood sugar estimation. **Result:** Out of 100 patients having balanitis,7 patients were detected to have diabetes mellitus for the first time, while another 4 patients were found to have impaired glucose tolerance for the first time. **Conclusion:** In conclusion, we must bear in mind that balanoposthitis may be the first clinical sign of diabetes mellitus in males and hence appropriate blood glucose testing should be carried out when assessing men with balanoposthitis.

Key words: Balanitis; Balanoposthitis; Diabetes mellitus

INTRODUCTION

Diabetes mellitus is a major public health problem in India and its incidence is rapidly increasing and it has had an increasing impact on urological practice. Balanitis defined as inflammation of the glans penis, which often involves prepuce (known as balanoposthitis) is a common condition and are usually managed symptomatically without considering a possible association diabetes. Acquired balanoposthitis may be the first clinical presentation of undiagnosed diabetes mellitus [1].

AIMS

To establish the incidence of undiagnosed diabetes mellitus in men presenting with balanitis.

MATERIALS AND METHODS

Study was conducted in the period 01.01.2014 to 31.10.2014. Patients were enrolled in the study if they met following criteria:

1. Age 20-70 years.
2. Clinical findings consistent with the diagnosis of Balanoposthitis.
3. No History of Diabetes Mellitus in the past.

A total of 100 patients were enrolled in the study who met the above mentioned criteria. Each eligible patient then underwent thorough physical examination and local examination of Genital region. Patients were then subjected to laboratory investigations CBC, Random Blood Sugar and complete urine analysis. Those patients with abnormal Random blood sugar (more than 140 mg/dl) underwent Fasting and 2 hour post prandial blood glucose estimation on subsequent day. Diabetes Mellitus and Impaired Glucose Tolerance was diagnosed as per ADA guidelines.

Balanoposthitis was treated by personal hygiene, oral fluconazole 150 mg once a week for 2 week, cefpodoxime 200 mg twice daily for five days and metronidazole 400 mg thrice daily for five days. Newly detected Diabetic patient were given medication for diabetes as per ADA guidelines.

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Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study and they were fully informed about the drug and its side-effects.

RESULT

Baseline demographic characteristics of 100 enrolled patients are summarized in (Table I). Mean age was 43-72 years. Maximum number of patients (38) were in the age group 40-49 years, followed by 27 in age group 50-59 years. Out of 100, Eleven patients had increased random blood sugar levels and these eleven patients underwent fasting and post prandial blood sugar estimation. Out of eleven patients with increased random blood sugar,7 patients were newly detected to have Diabetes Mellitus (Fasting Blood Glucose > 126 mg/dl and/or Post prandial blood glucose >200 mg/dl) and 4 patients were detected to have impaired glucose tolerance(Post prandial blood glucose 140-199 mg/dl). Maximum number of newly detected diabetic patient (03) were in age group 40-49 years (Tabl. 1).

Thus Type 2 Diabetes Mellitus was newly diagnosed in 7% men presenting with balanitis and no history of a glycaemic disorder in past. A further 4% were diagnosed with impaired glucose tolerance. Urine analysis was positive for glucose in all new diagnoses of glycaemic disorders.

DISCUSSION

Balanitis is defined as inflammation of the glans penis, which often involves the prepuce (balanoposthitis). Balanitis can occur at any age, but the prevalence of specific etiologies is age dependent. It is a common condition affecting 11% of male genitourinary clinic attendees [1] and it can be a recurrent or persistent condition. Etiology is usually fungal or bacterial, but remains undetermined in a large proportion of patients. Balanitis symptoms often evolve over three to seven days. The condition may present as pain, tenderness, or pruritus associated with small erythematous lesions on the glans and/or the prepuce (Fig.1). These lesions can be ulcerated or scaly (Fig.2). Thick foul smelling purulent exudate is often produced. Edema may develop if symptoms are allowed to progress without treatment. The combination of inflammation and edema can result in adhesions, with adherence of the prepuce to the glans. Persistent inflammation may result in scarring of the foreskin. Treatment of Balanitis is often empirical, and involves use of antifungal and antibiotic agents. If not properly treated, this process can evolve into a tightening of the prepuce, known as phimosis.

It is well established that diabetes is related to balanoposthitis and acquired phimosis [2]. Acquired balanoposthitis can be the first clinical sign of DM in uncircumcised males. In a recent study from Britain,

Table 1: Demographic charecteristics and incidence of newly detected diabetes patients in study group

Age group (years)	Total no. of patients with balanitis	Mean age (years)	Number of newly detected DM patients (%)	Number of patients with Impaired Glucose Tolerance (%)
20-29	03	25	00	00
30-39	18	33.5	01 (5.5)	01 (5.5)
40-49	38	45.5	03 (7.89)	02 (5.26)
50-59	27	52.8	02 (7.4)	01 (3.7)
60-69	14	61.8	01 (7.14)	00
Total	100	43.72	07	04

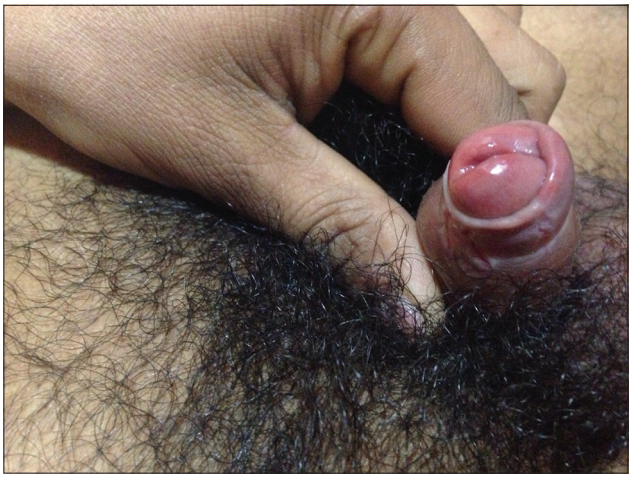

Figure 1: Patient with balanitis

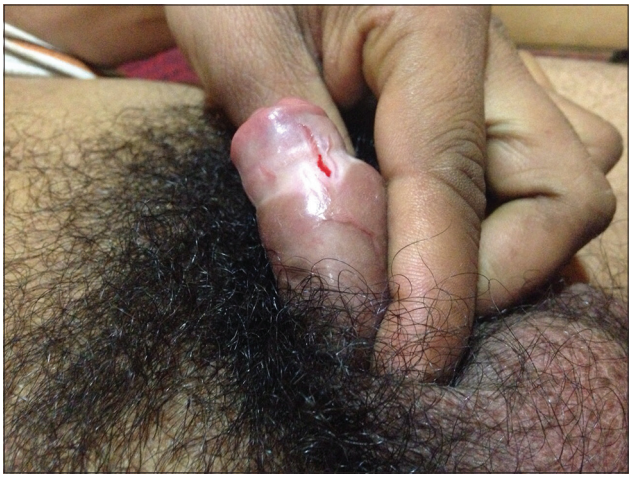

Figure 2: Patient with ulcerative balanits

26% of adult patients with balanitis were found to suffer from type II DM [3]. The diagnosis of DM was made for the first time in 8% of these patients which means that balanoposthitis in an apparently healthy male is a cutaneous marker of DM. Another 15% of males had impaired glycemic control. Diabetes caused balanoposthitis is more of a problem in India than sexually acquired balanoposthitis. In our study of 100 patients with balanitis, Type 2 Diabetes Mellitus was newly diagnosed in 7% men presenting with balanitis and no history of a glycaemic disorder in past. A further 4% were diagnosed with impaired glucose tolerance. These findings are consistent with previous studies.

Chih-Chun Ke et al reported that a volcano-like appearance of balanoposthitis with generalized erythema, a dry glazed appearance, acquired phimosis and surrounding fissures may be a typical finding in diabetic balanoposthitis [4]. The presentation may be more severe in patients with underlying diabetes mellitus than those without, with edema and fissuring of the foreskin, which may become non-retractile [5]. Preputial fissures, a hallmark of this condition, can be explained by the accumulation of advanced glycation end products (AGEs) in the foreskin [6]. AGEs content is increased in particular by inadequate glycemic control in diabetics. AGEs impair production of collagen and extracellular organization that is associated with a lowered hydroxyproline content and superoxide dismutase activity. In addition, this causes deleterious effects such as a greater impairment and alteration of biomechanical properties of the skin, namely, elasticity and hydration. There is also loss of surface lipids of skin due to impairment of sebaceous gland function and a tendency of reduced hydration in the stratum corneum. Repeated retracting the stiff foreskin during urination or sexual intercourse can be responsible for vertical fissuring of the foreskin, and this can further lead to fibrosis in the form of phimosis.

Balanoposthitis should be viewed as a manifestation of an immunocompromised state, which can occur at any age [7], and need not be limited to sexually active men.

Numerous studies have reported the growing impact of diabetes on dermatological practice with erectile dysfunction, voiding dysfunction and urinary tract infections all more common in diabetic than non-diabetic patients [8]. In 2006 Drivsholm et al have found that abnormal thirst (63%), fatique (61%), frequent urination (53.9%), unintended weight loss (34.8%), general itching (27.2%) and balanitis (12%) were the most common prediagnostic symptoms in diabetic patients [9]. These clinical conditions might be the initial presentation of previously undiagnosed diabetes. It is important to recognize this condition early to avoid later complications.

CONCLUSION

In conclusion, we must bear in mind that balanoposthitis may be the first clinical sign of diabetes mellitus in males. Diagnosing Diabetes in these men may not only reduce operative complications, but also prompt appropriate diabetic management and reduce long term complications. Therefore it is important that appropriate blood glucose testing should be carried out when assessing men with balanoposthitis.

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

Study of Cryotraphy results in warts in patients referring to Dermatology Department of Sina Hospital, Iran

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ABSTRACT:

Introduction: Warts can occur at any age, but the disease prevalence is mostly between the ages of 12-16 years. 23% of warts remit within two months, 30% of warts remit within 3 months, 78-65 % remit within two years. People with a history of infection are most likely to get involved with the recurrent infection than those who had never been infected with warts. In this study, the results of cryotherapy treatment for refractory warts have examined. Refractory warts are which remain more than 2 years or with no response to routine karyolitic treatments. **Methods and Material:** This study is a descriptive and analytical study. It is done on patients referred to the Dermatology Department of the Sina Hospital in Tabriz witch diagnosed with refractory warts. This study was conducted on a group of 30 patients. The checklist has been prepared and was completed for each patient separately. **Results:** The patients response to treatment in patients who had warts in hands and foot in 11 were poor, in 8 were moderate and in 4 were good. The response in patients who had warts in oral and congenital area in 2 were poor, in 3 were moderate and in 1 were good also in patient with warts in head, face and neck the response was good. 19 patients (63.3%) of patients were female and 11 (36.7%) were male. The mean age of patients were 11.18 ± 26.97 years old (8-54 years). **Conclusion:** Our study shows that cryothrapy is less effective for treating refractory warts and the most frequent side effects between the others. Improvement in plantar and foot warts was almost high that may because of almost high number of individuals referring with these anatomic locations warts.

Keywords: Cryothrapy; Warts; Skin diseases

INTRODUCTION

The human papilloma virus-induced tumors, warts, which can be polymorphic lesion of skin and mucosal areas such as hands, feet, face, trunk, genital mucosa, mouth, larynx and also involve the cervix. They are actually benign proliferation of skin and mucous membrane [1,2]. This is a fairly common condition and more than 100 different species of this viruses has had been known.

Warts can occur at any age, but the disease prevalence is mostly between the ages of 12-16 years [3]. The most common types of warts is" common warts" and the most common sites are the hands [3], 23% of warts remit within two months, 30% of warts remit within 3 months,78-65 % remit within two years. people with a history of infection are most likely to get involved with the recurrent infection than those who had never been infected with warts [4].

Since different types of warts and various parts of the skin and mucous membranes are involved as well, depending on the number of lesions in different parts of the body, treatments for warts is different. It should be emphasized that none of the methods of treatment has definite response, and recurrence of warts is common [5].

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Mostly warts treatment methods are aggressive and effective anti viral (HPV) treatment is not available and treatments which are effective on lesions that can be viewed or induce immune system stress [6] several therapies are used to treat warts, but resistance to many of them have been observed. In this study, the results of cryotherapy treatment for refractory warts have examined. Refractory warts are which remain more than 2 years or with no response to routine karyolitic treatments.

METHODS AND MATERIAL

This study is a descriptive and analytical study. It is done on patients referred to the Dermatology Department of the Sina Hospital in Tabriz witch diagnosed with refractory warts. This study was conducted on a group of 30 patients. The checklist has been prepared and was completed for each patient separately.

Location of study was Dermatology Clinic of Sina Hospital affiliated with the University of medical sciences of Tabriz. The study lasted 12 months. Collecting data was done in 2013-2014, the evaluation and analysis of the data was done in 2014.

Age and gender, number and extent of lesions, duration of wart were recorded on the questionnaire for each patient. Also, for more accuracy the wart lesions were photographed before treatment and all these steps after completion of therapy in each patient was assessed again.

For statistical analysis descriptive statistics (frequency, percentage, mean ± SD) were used and also Spss 17th statistical software was tested with the latest version available. Individuals in 6 session once in a two week were under cryothrapy treatment and they were followed up as point of side effects and recurrence of warts for 6 months.

Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study and they were fully informed about the drug and its side-effects.

RESULTS

19 patients (63.3%) of patients were female and 11 (36.7%) were male. The mean age of patients were 11.18 ± 26.97 years old (8-54 years). Concerned with The distribution of the marital status of patients 15 person equals 50% were single and 15 person equals 50% were married. The frequency distribution of the number of warts was 11.07±9.55. patients had warts average 17.47±14.66 months, minimum time getting refractory warts from initial diagnose was 1 months and maximum was 120 months.

The distribution of the anatomic location of the warts in 23 person warts were observed in hands and foot in 6 patient were observed in Oral and genital are and in 1 were observed in servicofacial.

Frequency distribution of treatment effects 1 with no side effects were observed 8 with pain, 1 with blister, 2 with Erythema and swelling, 2 with Erythema and pain, 10 with Pain and blisters and 6 with Hyperpigmentation, scarring, pain and blistering were observed. Frequency of healing in treatment session are as written in below: 1.03±0.18 patients showed improvement in first session, 1.07±0.28 patients showed improvement in second session, 1.17±0.48 patients showed improvement in third session, 1.33±0.60 patients showed improvement in forth session, 1.5±0.73 patients showed improvement in fifth session And 1.77±0.77 patients showed improvement in sixth session. the recurrence of refractory warts in this study after 6 months were reported in 8 patients (26.6%).

The patients response to treatment in patients who had warts in hands and foot in 11 were poor, in 8 were moderate and in 4 were good.

The response in patients who had warts in oral and congenital area in 2 were poor, in 3 were moderate and in 1 were good also in patient with warts in head, face and neck the response was good.

DISCUSSION

Warts is a common clinical problem for patients and dermatologists and an effective treatment without pain and scarring, especially in refractory cases is required [5]. Cryotherapy has traditionally been used for plantar warts. However, clinical trials report low rates of cure and it results in significant pain and blistering, reducing mobility for up to several weeks. A meta-analysis of trials of cryotherapy (with liquid nitrogen or any other substance which induces cold damage to warts, e.g. dimethyl ether and propane [DMEP]) [6]

showed that freezing of cutaneous warts located on the hands or feet was with less effective and mostly with side effects than others. Studies of combination treatment of cryotherapy with additional topical salicylic acid application for refractory do not support the idea that this treatment is better than salicylic acid alone [7,8]. Cryotherapy for plantar warts is therefore a non-evidence based intervention, associated with significant morbidity. N.B. Cryotherapy is less effective for treating plantar warts due to the thickness of the stratum corneum in this area. It may be more effective for treating warts in other body sites, e.g. anogenital warts [9].

In our study 63.3% of patients were female and 36.7% were male. The mean age of patients were 11.18 ± 26.97 years old (8-54 years). The frequency distribution of the number of warts was 11.07±9.55.

The treated area is likely to blister within a few hours. Sometimes the blister is clear and sometimes it is red or purple because of bleeding (this is harmless) [10]. Treatment near the eye may result in a puffy eyelid, especially the following morning, but the swelling settles within a few days [11]. Within a few days a scab forms and the blister gradually dries up. Concerned with Frequency distribution of treatment effects 1 with no side effects were observed 8 with pain, 1 with blister, 2 with Erythema and swelling, 2 with Erythema and pain, 10 with Pain and blisters and 6 with Hyperpigmentation, scarring, pain and blistering were observed. So in our study among 30 individuals only we had one with no side effects (3.3%) and 29 patients (96.7%) showed different side effects which was convey pain, blister,scar, the most frequent side effects were pain and blister.

The patients response to treatment in patients who had warts in hands and foot in 11 were poor, in 8 were moderate and in 4 were good. The response in patients who had warts in oral and congenital area in 2 were poor, in 3 were moderate and in 1 were good also in patient with warts in servicofacial the response was good. Thus totally in this study among 30 individuals 13 cases (43.3%) had a poor response, 11 cases (36.6%) had a moderate response and finally 6 cases had a good response (20%), these results obtained after 6 session of cryothrapy treatment.

Cryothrapy in refractory warts is a less effective which include different side effects on patients. And it has aggressive procedures. In comparison of anatomical locations of refractory warts, the servicofacial had a good response to cryothrapy treatments, due a thick hypoderm of plantar and foot wart had e resistance in cryothrapy which causes more side effects and due to this it takes more time of treatment and more treatment sessions.

CONCLUSION

Our study shows that cryothrapy is less effective for treating refractory warts and the most frequent side effects between the others. Improvement in plantar and foot warts was almost high that may because of almost high number of individuals referring with these anatomic locations warts.

Due this descriptive and analytical study, is suggested a clinical trial study to compare different methods of treatments for refractory warts.

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

Ustekinumab successfully treated a patient with severe psoriasis vulgaris with primary failure to infliximab and secondary failure to adalimumab

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ABSTRACT

Biologic drugs have been recently used to treat psoriasis. However, some patients do not respond or lose therapeutic benefit with first-line use of tumor necrosis factor (TNF) antagonists. We report a case of psoriasis vulgaris, that failed to respond to TNF antagonists, infliximab and adalimumab, completely disappeared after treatment with ustekinumab, a therapeutic agent for biologically blocking p40 protein of interleukin (IL) 12 and 23. This report highlights anti-TNF agents only inhibited the TNF-α/inducible nitric oxide synthase (iNOS)-producing dendritic cells (TIP-DCs), but the plasmacytoid-DC-derived psoriatic response was re-initiated. On the other hand, ustekinumab may inhibit both the TIP-DCs and the plasmacytoid-DC-derived inflammatory response.

Key words: Ustekinumab; psoriasis; psoriasis vulgaris; infliximab; adalimumab

INTRODUCTION

Psoriasis is a common, chronic inflammatory skin disease [1,2]. Patients with psoriasis experience a significant reduction in quality of life and psychosocial disability; this emphasizes the need for prompt, effective treatment and long-term disease control [2]. Recently, psoriasis has been treated with biologic agents that selectively block specific steps in the inflammatory cascade [2]. For example, tumor necrosis factor (TNF) antagonists, including infliximab and adalimumab, have proven to be highly effective in treating psoriasis, because TNF-α plays a central role in the inflammation underlying psoriasis [3]. However, some patients do not respond or lose therapeutic benefit with anti-TNF antagonists [4]. Ustekinumab is a fully humanized monoclonal antibody that binds to the shared p40 subunit of interleukin (IL) 12 and 23. Ustekinumab was recently approved by the National Institute for Health and Clinical Excellence for first-line use or for treatment after failure with an anti-TNF antagonist [4]. Here, we describe a patient with severe psoriasis that was successfully treated with ustekinumab after responding poorly to two TNF antagonists, infliximab and adalimumab.

CASE REPORT

A 46-year-old female (weight, 51 kg) was referred to our department with refractory psoriasis that had lasted 7 years. Previous unsuccessful treatments included topical therapies, including topical corticosteroids and vitamin D3, and a systemic cyclosporine. Before TNF antagonist treatment, her assessment of the condition of psoriasis was as follows: psoriasis area and severity index (PASI): 11.2 (Fig. 1); physician's global assessment (PGA): 3; and Dermatology Life Quality Index (DLQI): 17. Clinical and laboratory investigations were performed to exclude active tuberculosis and possible systemic infections. The hepatitis B (HB) core antibody (HBcAb) test was positive, but HBV surface antigen, HBV e-antigen, and HBV DNA tests were negative. Aspartate aminotransferase and alanine aminotransferase levels were within normal

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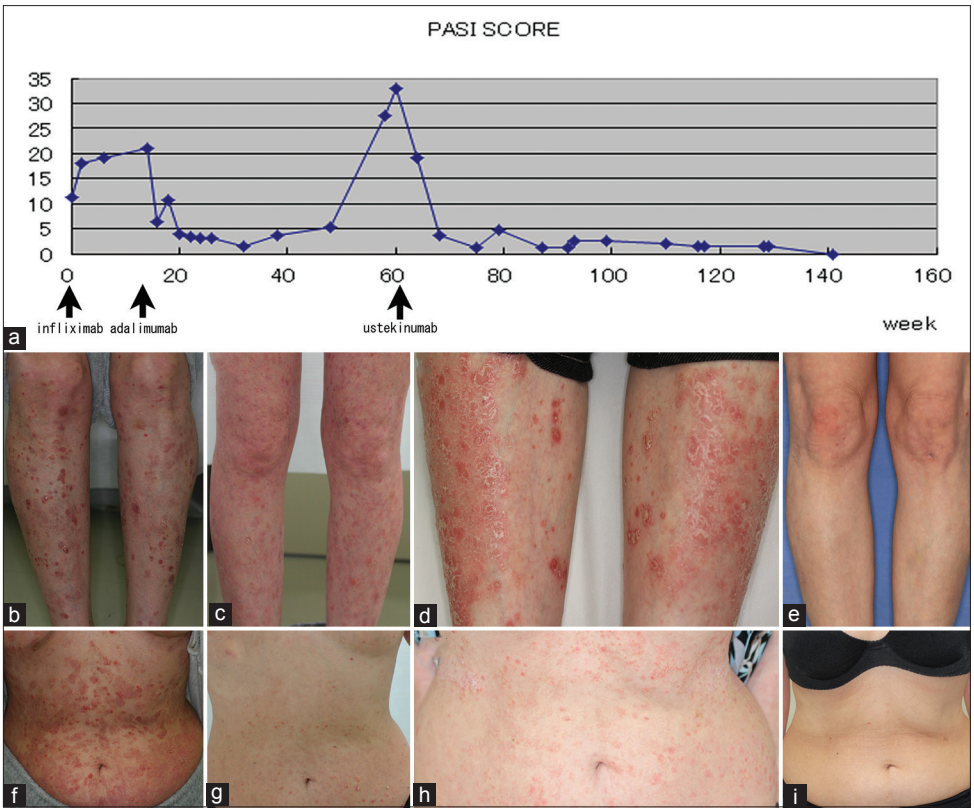

Figure 1: (a) Psoriasis Area and Severity Index (PASI) scores throughout the time course (b) (f) Psoriatic plaques on the lower extremities (b) and the abdomen (f) before infliximab (c) (g) Skin lesions on the lower extremities (c) and the abdomen (g) before adalimumab (d) (h) Flare-up of new plaques with severe scales on the lower extremities (d) and the abdomen (h) before ustekinumab (e) (i) Complete clearance of psoriasis on the lower extremities (e) and the abdomen (i) at 77 weeks after starting ustekinumab.

ranges. In March 2010, we administered intravenous infusions of infliximab (5 mg/kg) at 0, 2, and 6 weeks. At 14 weeks, she achieved a partial response, but exhibited PASI: 21, PGA: 4, and DLQI: 21 (Fig. 1). Therefore, we decided to withdraw infliximab therapy. In June 2010, we initiated subcutaneous adalimumab (40 mg) injections every 2 weeks. Twice, she received 80 mg of adalimumab, but then she declined 80 mg and reduced the amount to 40 mg due to its high cost. After 48 weeks, the psoriatic skin lesions worsened, with PASI: 33, PGA: 4, and DLQI: 24. In June 2011, we switched to ustekinumab because we considered secondary failure of adalimumab (Fig. 1). Ustekinumab (45 mg) was injected subcutaneously at 0 and 4 weeks. At week 4, the patient achieved a PASI 75. She continued ustekinumab treatment with injections every 12 weeks. She achieved PASI 90 and PGA: 0 after the third treatment. Her psoriasis remained well-controlled for 3.5 years. HBV DNA has remained negative.

DISCUSSION

Biologic agents that selectively block steps in the inflammatory cascade can control severe psoriasis. These agents have increased our understanding of the immunologic and pathophysiological basis of psoriasis. Psoriasis is driven and maintained by multiple components of the immune system. Although long been assumed to be a disorder in T helper type 1 (Th1) cells, recent evidence indicated that psoriasis pathophysiology also involves TNF-α, inducible nitric oxide synthase (iNOS)-producing dendritic cells (TIP-DCs), and Th17 cells. This was highlighted by the remarkable clinical efficiency of anti-TNF antagonist and anti-IL-12/23-p40 antibodies in treating psoriasis. Nevertheless, the TIP-DC-Th17 cell theory cannot explain the unique clinical finding, known as the paradoxical side-effect, where psoriasiform and pustular eruptions develop during anti-TNF therapy [5]. Therefore, it was proposed that plasmacytoid DCs were also involved in psoriasis pathophysiology [1]. Plasmacytoid DCs initiate psoriasis through production of interferon-α (IFN-α) [1]. TNF inhibits plasmacytoid DC generation and also inhibits IFN-α release by plasmacytoid DCs [1]. The TIP-DCs are inhibited by anti-TNF agents, but the plasmacytoid-DC-derived psoriatic response may be re-initiated [5]. The presented case demonstrated that ustekinumab could effectively treat severe psoriasis

that was unresponsive to anti-TNFα preparations. We hypothesized that anti-TNF agents only inhibited the TIP-DCs, but the plasmacytoid-DC-derived psoriatic response was re-initiated; thus, ustekinumab may inhibit both the TIP-DCs and the plasmacytoid-DC-derived inflammatory response. Further studies are needed to evaluate these treatments and to determine the role of ustekinumab in psoriasis management.

CONSENT

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

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Our Dermatology Online

Case Report

Intraepidermal and subepidermal blistering with skin necrosis, possibly caused by etanercept in treatment of a patient with psoriasis

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ABSTRACT

Background: Etanercept is often used for treating patients with plaque psoriasis and psoriatic arthritis. **Case report:** A 78 year old Caucasian female recently treated with Etanercept for plaque psoriasis developed necrotic patches and plaques on several areas of the body. Skin biopsies for hematoxylin and eosin (H&E) histology and immunohistochemistry(IHC), as well as direct immunofluorescence (DIF) were taken. **Results:** H&E review revealed necrotic areas in the epidermis, with both intraepidermal and subepidermal blisters. Dilated dermal blood vessels with a perivascular infiltrate of lymphocytes, histiocytes and neutrophils were seen. DIF revealed anti-stratum corneum reactivity involving multiple immunoglobulins and complement factors, as well as deposits of fibrinogen and complement/C3c complexes at the basement membrane zone and in upper and intermediate dermal neurovascular areas. IHC review demonstrated an overexpression of von Willembrand factor, positive CEA in the stratum corneum. Focal BCL-10 and P53 overexpression on the basaloid and spinous layers of the epidermis was also noted. CD15 and myeloperoxidase expression were noted in the blisters as well as CD8 and CD45 expression around the upper dermal blood vessels. **Conclusions:** We present a case of intraepidermal and subepidermal blistering with skin necrosis and document the presence of multiple immunoreactants in these lesions, possibly clinically linked to Etanercept.

Keywords: Etanercept, blistering diseases, medication adverse events, severe adverse events, autoimmunity, necrosis, von Willembrand factor, vascular degeneration.

Abbreviations and acronyms: Immunohistochemistry (IHC), direct immunofluorescence (DIF), hematoxylin and eosin (H&E), tumor necrosis factor (TNF); basement membrane zone (BMZ), medication-related adverse drug reactions (ADRs), severe adverse events (SAEs).

INTRODUCTION

Enbrel© (Etanercept) is a biologic medical product that is used to treat autoimmune diseases by interfering with tumor necrosis factor (TNF; a soluble inflammatory cytokine) by acting as a TNF inhibitor [1]. Etanercept has U.S. FDA approval to treat rheumatoid, juvenile rheumatoid and psoriatic arthritis, plaque psoriasis and ankylosing spondylitis [1]. Etanercept is a fusion protein produced by recombinant DNA. It fuses the TNF receptor to the constant end of the IgG1 antibody [1]. On May 2, 2008, the FDA placed a black box warning on Etanercept, due to a number of complications associated with the drug in post-marketing reports of serious infections and sepsis, including fatalities. Tumour necrosis factor (TNF)-α is a proinflammatory cytokine that may induce anti-apoptotic proteins and endothelial cell activation factors in psoriasis, and therefore is commonly used in dermatology practices. It has also being proposed that Etanercept may inhibit neovascularisation in psoriatic lesions

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CASE REPORT

A 78 year old Caucasian female had been recently treated with Etanercept for plaque psoriasis. A week later the patient presented excoriated, necrotic patches and plaques on the face, buttocks, chest, abdomen and extremities. Skin biopsies for hematoxylin and eosin (H&E) and immunohistochemistry (IHC) review, as well as direct immunofluorescence (DIF) were obtained. The Etanercept administration was halted, and topical steroids were given to the patient resulting in improvement of the necrotic lesions.

MATERIALS AND METHODS

For DIF, we incubated 4 micron thickness tissue sections on slides with secondary antibodies, as previously described [2-15]. We utilized FITC conjugated rabbit anti-total IgG (Dako, Carpinteria, California, USA) at dilutions of 1: 25. The samples were run with positive and a negative control. We also utilized FITC conjugated rabbit antisera to human IgG, IgA, IgM, IgD, IgE, complement/1q, complement/C3, fibrinogen and albumin. Our anti-human IgA antiserum (alpha chain) and anti-human IgM antiserum (Mu chain) were obtained from Dako. Our anti-human IgE antiserum (epsilon chain) was obtained from Vector Laboratories (Burlingame, California, USA). Our FITC conjugated anti-human IgD antibodies were obtained from Southern Biotechnology(Birmingham, Alabama, USA). The slides were then counterstained with 4',6-diamidino-2-phenylindole(Dapi; Pierce, Rockford, Illinois, USA). Mouse anti-CD31/PECAM was utilized to stain dermal vessels (Invitrogen, Carlsbad, California, USA), and was specifically utilized with a secondary donkey anti-mouse IgG (heavy and light chains) conjugated with Alexa Fluor 555 (Invitrogen).

Immunohistochemistry (IHC)

We performed IHC utilizing multiple monoclonal and polyclonal antibodies, all from Dako (Carpinteria, California, USA). For all our IHC testing, we used a dual endogenous peroxidase blockage, with the addition of an Envision dual link to assist in chromogen attachment. We then applied the chromogen 3,3-diaminobenzidine(DAB), and counterstained with hematoxylin. The samples were run in a Dako Autostainer Universal Staining System. Positive and negative controls were consistently performed; our studies were specifically performed as previously described [2-15]. The following antibodies were utilized: monoclonal mouse anti-human vascular endothelial growth factor (VEGF) Clone VG1, monoclonal mouse anti-human BCL-10 protein, Clone 151, monoclonal mouse anti-human von Willebrand Factor, Clone F8/86, monoclonal mouse anti-human CD8, CD15, and CD45 and Myeloperoxidase (all from Dako), and Factor XIIIa (Novocastra, Chicago, Illinois, USA)).

RESULTS

Microscopic Description

A: Examination of the H&E tissue sections demonstrated focal, confluent parakeratosis within the stratum corneum. In addition, scattered collections of neutrophils were seen within the stratum corneum. Overall, the epidermis displayed minimal psoriasiform hyperplasia; the stratum granulosum was focally attenuated. Some focal epidermal spongiosis was seen. In focal areas, the epidermis was also ulcerated, with collections of neutrophils and serum scale crust present within the ulcer bases. Both intraepidermal and subepidermal blisters and clefts were seen. Dermal cellulitis is not present. Within the dermis, a mild, perivascular infiltrate of lymphocytes, histiocytes and neutrophils was present. Eosinophils were rare. No evidence of a neoplastic process was seen. Special stained slides were reviewed; the positive controls stained appropriately. The Gram special stain revealed collections of Gram positive, bacterial coccal organisms within the serum scale crust areas.

Direct immunofluorescence(DIF)

Demonstrated the following results: IgG (+, diffuse epidermal stratum corneum); IgA (+, diffuse epidermal stratum corneum); IgM (+, diffuse epidermal stratum corneum); IgD (+++, diffuse epidermal stratum corneum); IgE (+, Lower papillary dermal perineural); Complement/C1q(-); Complement/C3 (+, diffuse epidermal stratum corneum and blood vessels in the middle dermis); Complement/C4 (+, diffuse epidermal stratum corneum); CD31/PECAM(+, overexpressed dermal vascular endothelial); Kappa light chains (+, diffuse epidermal stratum corneum); Lambda light chains(+, diffuse epidermal stratum corneum) albumin (+, diffuse epidermal stratum corneum) and fibrinogen (+++, diffuse epidermal stratum corneum, and focal linear shaggy basement membrane zone (BMZ) (Fig. 1).

Immunohistochemistry (IHC)

As expected, myeloperoxidase and CD15 were very positive in the blister, around the edges of the blisters and in the crust material. CD45 was positive in some areas of the epidermal corneal layer, within the blisters and around upper dermal blood vessels. CD8 was positive mainly around the upper dermal inflammatory infiltrate. In the upper and intermediate dermal blood vessels, some markers such VEGF and von Willembrand factor seemed to be overexpressed. We also noted that P53 and BCL-10 were positive in the epidermis, but with strong expression around the blister edges and in some focal BMZ areas. Factor XIIIa was positive around the edges of the blisters (Fig. 1).

DISCUSSION

Etanercept has been successfully utilized in the treatment of multiple diseases, including psoriasis and autoimmune skin blistering diseases; however, multiple secondary reactions involving the skin and other organs have been documented [16-29]. Some adverse reactions and conditions include primary thyroid marginal zone B-cell lymphoma, sinusitis, herpes zoster, herpes simplex, antiphospholipid antibodies, cerebral ischemic damage, hypertension, carcinoma cuniculatum (verrucous squamous cell carcinoma), urticaria, angioedema-like reactions, nodular fasciitis, *Coxiella burnetii* infection(Q fever), erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, tuberculosis, apoptotic enthreopathy, pyogenic granuloma, alopecia, lichen striatus, alterations in sperm quality, a possible cerebral venous thrombosis, lymphopenia, neurosarcoidosis, systemic sarcoidosis, lichen planus, acute transverse myelitis, rosacea, salmonella septic arthritis, *Staphylococcus aureus* colonization and injection site reactions[16-29]. Other documented adverse reactions include generalized pustular psoriasis, for which a differential diagnosis of acute generalized examthematous pustulosis(AGEP) should be considered.

Multiple autoimmune diseases and syndromes have also been reported to develop after the use of TNF-alpha inhibitors including vasculitis, lupus erythematosus and interstitial lung diseases [16-29]. Some studies have also shown that a predisposing sensitivity of patients to TNF-alpha inhibitors could be genetically determined, and may be due to genetic polymorphisms in selected genes. Some authors have demonstrated seroconversion with development of positive anti-ANA/dsDNA of the IgG subtype in patients receiving TNF-alpha inhibitors, as well as describing the onset of lupus/vasculitis [16-29]. Autoimmune induced renal disorders have also been described following TNF-alpha inhibitor use, including glomerulonephritis associated with systemic vasculitis, glomerulonephritis in a lupus-like syndrome and isolated autoimmune renal disorders [16-29].

Our findings indicate that Etanercept did possibly trigger the patient's secondary blistering and ulceration reaction due to involvement of the dermal vasculature. Moreover, this medication could not stop the anti-corneal antibodies that were still being seen on the DIF. Given the fact that we observed some superinfection with Gram positive cocci in the ulcers, Etanercept

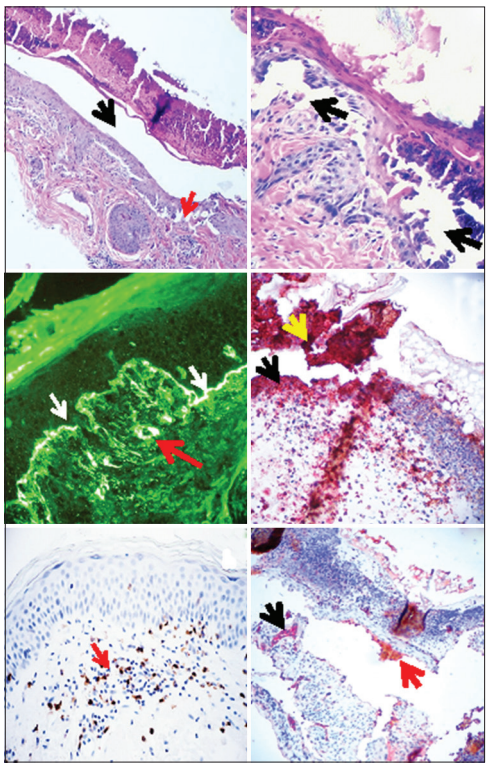

Figure 1: (a and b) H & E stain showing the epidermal corneal layer with necrosis and a subcorneal blister (black arrow), and also some subepithelial blisters (red arrows), (100X), In b, higher magnification of a, showing the subepithelial blisters (black arrows) (200X). c. DIF, using anti-human FITC conjugated fibrinogen antibody positivity, with pseudo-basement membrane deposits in a serrated manner (white staining; white arrows) as well as staining against the upper dermal blood vessels (white staining; red arrow). d. IHC double staining, using anti-human CD15 in brown and anti-CD45 in red. The photomicrograph highlights an amalgamation of the positivity of both markers in the crust (yellow arrow), as well as on the blister floor (black arrow). e. IHC staining with CD8 antibody, showing positive staining in an upper dermal perivascular infiltrate (brown staining; red arrow). f. IHC double staining, using anti-human myeloperoxidase in brown and anti-von Willembrand factor in red. The photomicrograph highlights damage to dermal blood vessels and (red staining; black arrow) and the presence of myeloperoxidase in the crust(brown staining; black arrow).

could have some immunosupressant role in the psoriatic plaques. Other notable observations are that the BCL10 and P53 markers seem to play some role in development of the blisters, possibly by some apoptotic regulatory role that remains unknown.

Given our data, it is important to consider that there are other anti-TNF monoclonal antibodies similar to Etanercept, including Infliximab®, Adalimumab®, Certolizumab®, Golimumab® and Pegsunercep®. Thus, these medications may act as putative triggers in some secondary reactions in patients treated for plaque psoriasis.

CONCLUSIONS

We report an unknown reaction, possibly triggered by Etanercept and featuring intraepidermal and subepidermal blistering with skin necrosis. The incidences of inflammatory skin reactions due and/or related to Etanercept need to be considered when patients are using this medication suddenly develop dermatologic side effects, including those described here.

CONSENT

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

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Our Dermatology Online

Case Report

Embolis cutis medicamentosa, a rare preventable iatrogenic complication

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ABSTRACT

Embolis cutis medicamentosa is an uncommon iatrogenic complication characterised by variable degree of skin and tissue necrosis, likely to follow intramuscular injection. Intense pain and purplish discoloration of overlying skin, with or without reticulate pattern subsequently followed by tissue necrosis and scarring is highly specific for this syndrome. It has also been reported following intravenous, intra-articular and subcutaneous injections. Herein we are reporting two cases of this rare preventable entity.

Key words: Embolia cutis medicamentosa; tissue necrosis; intramuscular; diclofenac

INTRODUCTION

Embolia cutis medicamentosa also known as Nicolau syndrome, livedoid dermatitis characterised by severe painful local necrosis at the site of injected medicament [1,2]. Intense pain and purplish discoloration of overlying skin, with or without reticulate pattern subsequently followed by tissue necrosis and scarring is highly specific for this syndrome. Initially described by Nicolau and Frudenthal as an adverse effect with use of bismuth salts intramuscularly in syphilis patients [3]. Clinically, patient manifests with intense pain at the injection site, followed by bluish discoloration of overlying skin assuming reticulate pattern, referred as non-inflammatory retiform purpura, livedo-like dermatitis.[2] In later stages, discoloured area undergoes necrosis and ulceration may involve subcutis and underlying muscles.

CASE REPORTS

Case 1

A 50 year old male presented with non healing ulcer over the left buttock of one month duration. Patient had fever and generalized body ache one month back, for which he was administered intramuscular injection of diclofenac in outer aspect of left buttock. Immediately after the injection, patient experienced intense pain along with redness followed by bluish discoloration of the overlying skin after two days. Later the entire skin became black with necrosis which eroded over a week. On examination, a solitary well defined ulcer measuring 10×5 cm in size, covered with necrotic tissue (Fig. 1) was noted over the outer aspect of left buttock. Patient was treated with oral and topical antibiotics, without much improvement. Patient was admitted, wound was debrided, and was started on systemic antibiotics. Routine investigations including bleeding time, clotting time were normal. Following daily dressings and systemic antibiotics, wound was covered with healthy granulation tissue in about 2 weeks. Split skin grafting was done to hasten the healing.

Case 2

A 45 year old female presented with chronic non-healing ulcer of one month duration over the outer aspect of right buttock. Patient had received intramuscular

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injection of diclofenac for joint pain 3weeks back. Immediately following injection she developed intense pain and blanching of skin. Later over a period of 2 weeks entire blanched area becomes ulcerated and necrotic. On examination, a solitary well defined ulcer measuring 4×6 cm in size, localized to outer aspect of right buttock covered with necrotic tissue was noted (Fig. 2). Patient was admitted and wound debridement was done. After daily dressings and antibiotics, ulcer showed signs of healing. Finally after 2 weeks it healed with scar formation.

DISCUSSION

Embolia cutis medicamentosa or Livedoid-like dermatitis (Nicolau syndrome) is an uncommon iatrogenic complication characterised by variable degree of skin and tissue necrosis, likely to follow intramuscular injection [2]. Cases have been reported following intramuscular injection of vitamin-K [4], diclofenac [5], bismuth [6], benzathine penicillin [7], gentamycin [8] and vaccination [9]. It has also been reported following intravenous polidocanol 1% [10], intra-articular corticosteroids [11], subcutaneous injections of pegylated interferon-α [12] and sclerotherapy for pyogenic granuloma [13].

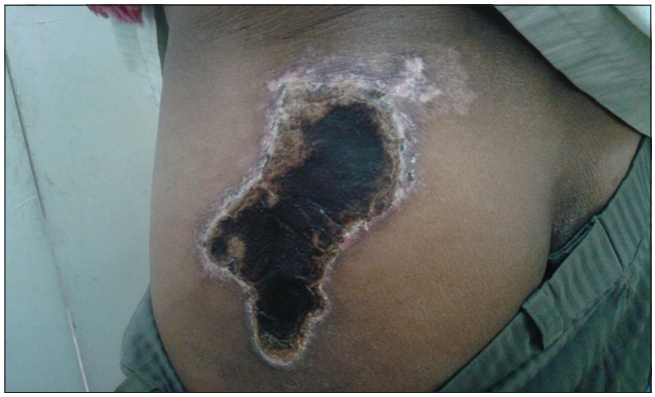

Figure 1: Case 1 showing well defined ulcer measuring 10×5 cm in size, covered with necrotic tissue.

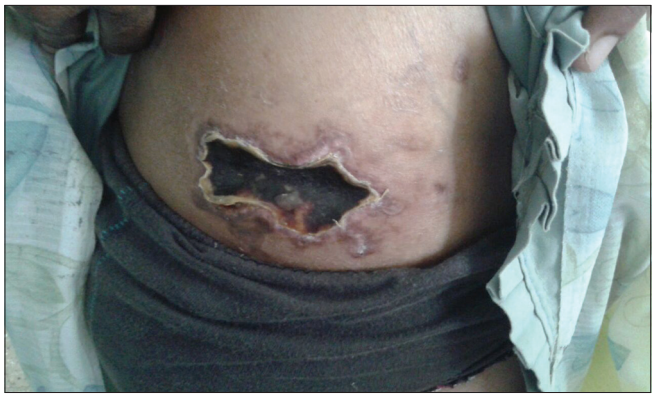

Figure 2: Case 2 showing well defined ulcer localized to outer aspect of right buttock covered with necrotic tissue.

The exact etio-pathogenesis of this syndrome is not known. Probable explanations for the ischemic necrosis of the skin and deep tissues seen in this syndrome includes, vasospasm secondary to needle prick, pressure of material placed around vessel and embolization of the injected material [7]. Cutaneous necrosis seen following bismuth salt injections in syphilis patients were thought to be due to high viscosity of salts causing blockage arterioles. Application of cold compresses can aggravate necrosis [14].

Complications like paralysis of limb has been reported which is attributed to embolization of medication into the internal iliac vessels [15]. Late complications such as contractures and deformities can occur due to scarring process that needs surgical correction [6]. Soft tissue sarcoma can occur as a rare complication at the site of tissue necrosis [16].

Diagnosis is mainly clinical. Nicolau syndrome has to be differentiated from necrotising fasciitis. In the latter, there is rapidly spreading infection of the subcutis and fascia due to haemolytic streptococci and other anaerobes. Necrotising fasciitis usually occurs following surgery or after a deep penetrating injury and manifests with intense pain with erythema of the skin later becomes purplish and ulcerates. On X-ray there is often presence of air in the tissues. Ultrasound and magnetic resonance imaging often helpful to delineate the extent of damage in the tissues [2].

Early institution of treatment has been reported to avert the extent of necrosis. Measures to improve the vascularity such as pentoxyphylline, hyperbaric oxygen, intravenous alprostadil and thrombolysis with heparin has been tried in the immediate post-event period [2]. Surgical debridement and systemic antibiotics play pivotal role in controlling infection. Since it can occur to common drugs it is very important for the Dermatologists to be aware of this rare iatrogenic disfiguring 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

Manifestaciones mucocutáneas debidas a la infección por Mycoplasma pneumoniae. Reporte de 3 casos [Muco-cutaneous manifestations due to Mycoplasma pneumoniae infection: Report of 3 cases

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ABSTRACT

Mycoplasma pneumoniae, one of the most frequent agents of community-acquired pneumonia worldwide, can affect different organs besides the lung, causing skin lesions in 25% of patients. The spectrum of dermatological features include macules, papules, purpura, target lesions and even well stablished conditions as erythema multiforme, Stevens-Johnson's Syndrome and toxical epidermal necrolysis. We present 3 pediatric patients with erythema multiforme and toxical epidermal necrolysis in which Mycoplasma pneumoniae was considered as the etiological agent.

Key words: Mycoplasma pneumoniae; erythema multiforme; toxic epidermal necrolysis

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Manifestaciones mucocutáneas debidas a la infección por Mycoplasma pneumoniae. Reporte de 3 casos [Muco-cutaneous manifestations due to Mycoplasma pneumoniae infection: Report of 3 cases

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RESUMEN

El Mycoplasma pneumoniae, uno de los más frecuentes agentes etiológicos de neumonía adquirida en la comunidad alrededor del mundo, puede afectar además del pulmón, a varios órganos causando lesiones en piel en el 25% de los pacientes. El espectro de lesiones dermatológicas incluye máculas, pápulas, púrpuras, lesiones en diana e incluso cuadros bien establecidos de eritema multiforme, síndrome de Stevens-Johnson y necrólisis epidérmica tóxica. Presentamos 3 casos de pacientes pediátricos con eritema multiforme y necrólisis epidérmica toxica en los cuales el Mycoplasma pneumoniae fue considerado agente etiológico.

Palabras clave: Mycoplasma pneumoniae; eritema multiforme; necrolisis epidérmica toxica

INTRODUCCIÓN

Mycoplasma pneumoniae es una bacteria de pequeño tamaño que se caracteriza por carecer de pared celular. Es el agente responsable del 20 al 50% de las neumonías adquiridas en la comunidad, siendo la infección por este agente endémica en la mayor parte del mundo, con epidemias que ocurren a intervalos de 4 a 7 años [1-3].

Sus manifestaciones más frecuentes son las infecciones del tracto respiratorio, pero se han descrito otras muchas formas de presentación, como cuadros cutáneos, neurológicos, gastrointestinales, hematológicos, cardiacos, incluso artralgias y artritis. El mecanismo de producción de estas patologías no se ha aclarado hasta la fecha, sosteniéndose que podrían ser desencadenadas por la acción de autoanticuerpos, por toxinas del microorganismo, o por lesión directa del mismo a distintos órganos [1-5].

El compromiso cutáneo-mucoso aparece en alrededor del 25% de todos los casos que presentan infección por M. pneumoniae, pudiéndose observar una gran variedad de lesiones dermatológicas como máculo-papulares, vesiculares, urticariales, purpúricas en general de evolución autolimitada, y en algunos casos cuadros establecidos de eritema multiforme, síndrome de Stevens-Johnson (SJS) o incluso necrólisis epidérmica tóxica (NET). También puede manifestarse como eritema nodoso, vasculitis, pitiriasis rosada, angioedema aunque en un menor porcentaje [1-3].

El diagnóstico requiere de hallazgos serológicos los cuales presentan una alta sensibilidad y especificidad, siendo

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la histopatología un arma útil en especial en los casos en que la clínica de las lesiones no es muy clara [1-3].

CASOS CLÍNICOS

Presentamos a 3 adolescentes varones con cuadros de eritema multiforme mayor en dos casos y necrólisis epidérmica tóxica (NET) en un caso. Los pacientes con diagnóstico de eritema multiforme acudieron a la consulta dermatológica, mientras que el paciente diagnosticado de NET acudió a la consulta pediátrica de donde debido a la gravedad del cuadro fue ingresado a la Unidad de Cuidados Intensivos. Las características clínicas de los pacientes se detallan en la Table 1.

Todos los pacientes presentaron confirmación histopatológica del diagnóstico clínico (figs 4). En el caso del paciente número 3, se destaca el papel del M. pneumoniae como agente causal-potenciador de la NET, dado el antecedente de dicho paciente de consumo de difenilhidantoína y considerando a los anticonvulsivantes como agentes frecuentemente involucrados en su patogenia.

Se obtuvo el consentimiento informado del paciente.

Antes del estudio, el paciente dio consentimiento escrito para el examen y la biopsia, tras haber sido informado sobre el mismo y el objetivo de éste.

DISCUSIÓN

Mycoplasma pneumoniae es un patógeno respiratorio frecuente que produce una amplio rango de patologías que van desde una leve infección de las vías respiratorias superiores a una neumonía atípica severa. Constituyen los agentes bacterianos más pequeños con capacidad patogénica para el hombre, pertenecientes a la familia Mycoplasmataceae [1-3].

Este microorganismo se caracteriza además por producir un amplio espectro de manifestaciones extrapulmonares, y hasta un 25% de pacientes infectados pueden presentar manifestaciones dermatológicas, haciendo de éstas una de las complicaciones más frecuentes de la infección. La presencia de cuadros exantemáticos en el curso de infecciones neumónicas causadas por Mycoplasma, son relativamente frecuentes, de hecho, la asociación de neumonía y exantema, sugiere la infección por este agente etiológico y se ha observado en el 17% de los casos [1-4,6].

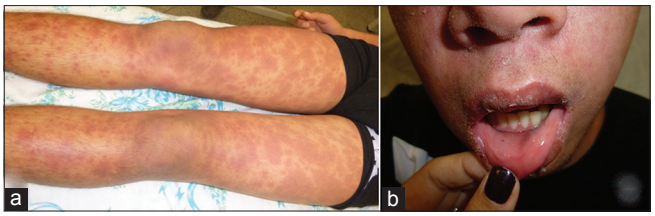

Figure 1: Caso 1. A: Placas eritemato-purpúricas en abdomen, tronco y miembros. B: Erosiones en mucosa oral.

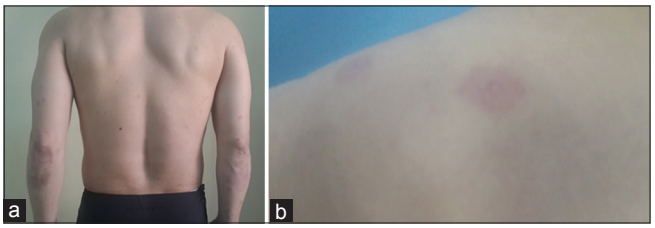

Figure 2: Caso 2. A y B: Placas eritematosas con pápula central (en diana) en abdomen, espalda.

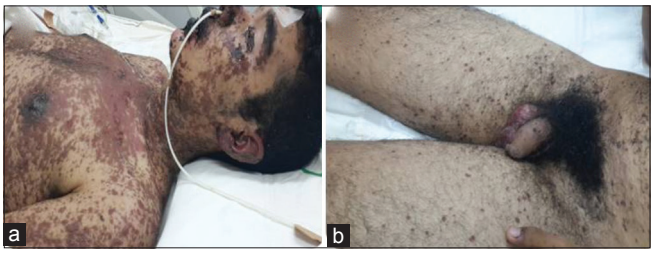

Figure 3: Caso 3. A y B: Múltiples ampollas y pápulas eritemato-púrpuricas generalizadas. Erosiones a nivel de piel y mucosas. Costras hemáticas en labios. Afectación de mucosas oral, ocular, nasal y genital.

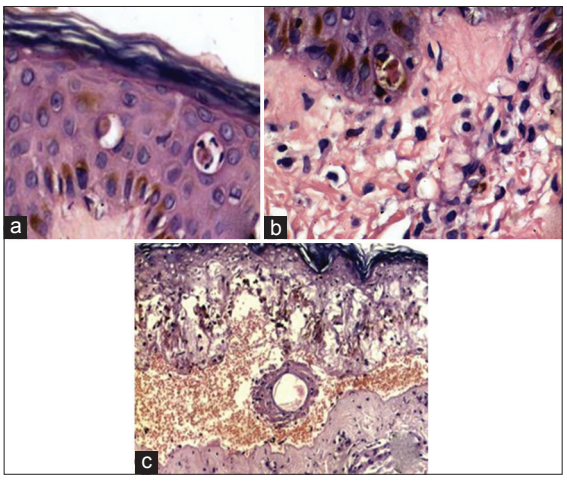

Figure 4: Histopatología. A y B: Erupción liquenoide con numerosos disqueratocitos. Corresponde a un Eritema Multiforme (casos 1 y 2). C: Ampolla subepidémica pauciinflamatoria con necrosis queratinocitica en el techo de la misma (caso 3)

Las manifestaciones dermatológicas pueden presentarse antes, durante o después de una infección pulmonar, e incluso en ausencia de la misma, como lo observado en nuestro caso número 1. El compromiso muco-cutáneo

Tabla 1: Características clínicas y tratamiento de 3 pacientes con manifestaciones mucocutáneas asociadas a la infección por Mycoplasma pneumoniae

	CASO 1	CASO 2	CASO 3
Edad	15 años	16 años	15 años
Sexo	Masculino	Masculino	Masculino
Días de evolución	5	7	3
Antecedente de ingestión de fármacos	No	No	Difenilhidantoína desde hace 3 semanas
Patologías de base	Ninguna	Ninguna	Síndrome convulsivo en estudio
Compromiso cutáneo	Maculas eritemato- purpúricas Placas en "diana" (figura1)	Placas en "diana" en tronco y espalda (figura 2)	Maculas y pápulas eritemato-purpúricas Erosiones y ampollas en más del 30% de la superficie corporal (figura 3)
Compromiso mucoso	Oral, perianal	Oral	Oral, genital, nasal, conjuntival
Compromiso respiratorio	No	Rinorrea y tos seca	Tos seca previa al cuadro cutáneo Neumonía de base derecha
IgM para M.pneumoniae	+	+	+
IgM para Herpes Simple I y II	-	-	-
Antibiótico recibido	Claritromicina	Claritromicina	Claritromicina
Uso de corticoesteroides	No	Tópico (betametasona)	No
Uso de Inmunoglobulinas endovenosas	No	No	Si
Diagnóstico histopatológico	Eritema Multiforme	Eritema Multiforme	SJS/NET
Diagnóstico final	Eritema Multiforme Mayor	Eritema Multiforme Mayor	Necrolisis epidérmica toxica
Evolución	Buena , sin complicaciones	Buena, sin complicaciones	Alta. Sinequias oculares

se presenta típicamente como un exantema macular o maculo-papular, generalmente auto limitado, pudiendo presentarse además, aunque en un porcentaje menor, eritema multiforme, síndrome de Stevens-Johnson, eritema nodoso, vasculitis, entre otros [1-3].

Los mecanismos exactos por los cuales el M. pneumoniae produce una variedad de manifestaciones cutáneas está poco dilucidado. La mayoría de las lesiones se cree son causadas por la respuesta del huésped a los antígenos del microorganismo. Además se ha postulado que mecanismos de respuesta inmune como la mediada por inmuno complejos, la mediada por células T citotóxicas y mecanismos autoinmunitarios juegan un rol crucial en el desarrollo de las lesiones en piel [1-3,7].

El eritema multiforme, el síndrome de Stevens- Johnson y la necrólisis epidérmica tóxica representan diferentes manifestaciones de un mismo espectro de graves reacciones cutáneas a fármacos y en menor medida, a agentes infecciosos. El eritema multiforme es en el 90% de los casos secundario a la infección por virus del herpes simple y por Mycoplasma pneumoniae. Se caracteriza por la aparición de lesiones maculo-papulares con centro rojo y rodeadas por un halo pálido y un tercer anillo externo más oscuro las que se denominan "lesiones en diana" que se distribuyen por el tronco, palmas, plantas y extremidades. Se presenta frecuente compromiso mucoso en particular de la mucosa oral, evidenciado en nuestros pacientes 1 y 2, y en ocasiones lesiones ampollares [3,4,8].

El *Eritema multiforme* es una patología de baja morbilidad con una resolución completa en el período de 1 mes. Ya desde la segunda mitad del siglo 20, existía una fuerte sospecha de la participación del M. pneumoniae en la patogenia del eritema multiforme [8-9].

El *SSJ* tiene una incidencia de 0,4 a 1,2 casos por millón de habitantes por año y la NET de 1,2 a 6 casos por millón de habitantes por año. Ambos se diferencian solo por el porcentaje de compromiso de la superficie corporal (<10% en SSJ y > 30% en la NET). Tanto en el SSJ como en la NET se encuentra gran cantidad de macrófagos y linfocitos CD8 en la epidermis y estos se cree reaccionan frente a antígenos o a fármacos. Los queratinocitos normales expresan en su superficie el antígeno soluble CD95 (Fas) que se une a un ligando de Fas (s Fas L) generando la apoptosis normal. En los pacientes con NET se han encontrado concentraciones normales de Fas, pero grandes cantidades de s-Fas L en los queratinocitos; originándose así una intensa apoptosis epidérmica [3,10-12].

El M. pneumoniae es una causa bien conocida de SJS, que afecta usualmente a niños y adultos jóvenes y ha sido reportado como la causa infecciosa más frecuente, evidenciándose además que en algunos casos de infección recurrente por M. pneumoniae se vio recurrencia del cuadro de SJS. Casi todos los pacientes presentan compromiso de la mucosa oral y aproximadamente 2/3 presentan afectación ocular. Varios estudios han reportado que el SJS inducido por M. pneumoniae se asocia con complicaciones más

leves comparando con los desencadenados por otras causas [3,10,11].

Numerosos estudios han descripto a pacientes con SJS "atípico" que presentaban infección activa por M. pneumoniae y severa mucositis sin afección cutánea. Dado que las lesiones cutáneas, son primordiales para el diagnóstico del SJS, algunos autores recomiendan denominar a esta entidad como "Mucositis asociada a Mycoplasma pneumoniae" [3,12,13].

La mayoría de los pacientes con SJS, NET e infección por M. pneumoniae frecuentemente han recibido antibióticos u otras drogas en los estadios tempranos de la enfermedad previamente a la aparición de lesiones muco-cutaneas por lo que en muchos casos es difícil determinar la precisa etiología o si se trata de un sinergismo entre ambos agentes [3,11].

La *NET* es la expresión más grave de este proceso inmunológico; inicialmente se aprecia la piel enrojecida semejante a una quemadura, apareciendo luego lesiones en diana y ampollas, provocando un desprendimiento de la epidermis lo que origina grandes pérdidas proteicas, desequilibrio hidro-electrolítico, alteraciones en la termo-regulación y favoreciendo las sobre-infecciones [3,10].

En la literatura se describe además casos de *púrpura de Schönlein- Henoch* relacionados a la infección por Mycoplasma pneumoniae. Una complicación de esta presentación es la Glomerulonefritis, la cual es una grave manifestación que debe ser pesquisada durante y después de la infección activa y tratada con agentes inmunosupresores [3,4].

Raramente la infección por M. pneumoniae presenta como complicación a la *vasculitis cutánea*. Existen pocos casos reportados con confirmación serológica de la infección presentándose la vasculitis asociada a una poliartritis. En pacientes adolescentes y adultos jóvenes se recomienda la pesquisa de la infección por M. pneumoniae en casos de cuadros de vasculitis y poliartritis [2,3,14].

El *eritema nodoso* es una manifestación secundaria a muchas patologías infecciosas y es causada por el M. pneumoniae en un 8% de los casos. Otros cuadros menos frecuentes reportados son el angioedema no episódico y el exantema ampolloso [2-4].

El diagnóstico de infección por M. pneumoniae es difícil en la fase aguda y presenta mayor sensibilidad en la fase de convalecencia. Los anticuerpos IgM específicos contra Mycoplasma aparecen en suero de los pacientes a los 7 días de comenzar los síntomas de la infección, con un pico en la titulación entre los 10 y 30 días después, posteriormente los títulos caen lentamente, hasta hacerse indetectables entre las semanas 12 y 26 del inicio de la infección. La respuesta inmunológica a M. pneumoniae es variable de una persona a otra, lo que condiciona el daño tisular; a mayor vigor en la respuesta inmune mediada por células e interleuquinas, mayor es el daño tisular [2,3].

En la actualidad se utilizan formas nuevas y más rápidas para detectar la infección por M. pneumoniae en diferentes tejidos y secreciones de los pacientes, como los métodos de detección directa del antígeno por enzimoinmunoanálisis (Ag-EIA) y técnicas de reacción en cadena de la polimerasa (PCR) [2,3].

El M. pneumoniae es susceptible a antimicrobianos que actúan en la síntesis proteica, como son macrólidos, tetraciclinas y quinolonas. En la actualidad se recomienda el uso de macrólidos nuevos como claritromicina o azitromicina, por su cómoda posología y mejor tolerancia digestiva. Los corticosteroides, en aplicación tópica como sistémica, son indicados en los casos de eritema multiforme. En la NET el uso de Inmunoglobulinas endovenosas sería beneficioso, ya que, proporciona anticuerpos contra el Fas, bloqueándolo y por lo tanto deteniendo la intensa apoptosis queratinocitica [1-4].

En resumen, destacamos el papel del Mycoplasma pneumoniae en la patogenia de los cuadros dermatológicos presentados, siendo importante que el dermatólogo tenga en cuenta a este microorganismo como responsable de un amplio espectro de lesiones cutáneas, en especial algunas graves como el eritema multiforme, el síndrome de Stevens-Johnson y la necrólisis epidérmica tóxica donde se impone el diagnóstico diferencial de otras etiologías ya sean farmacológicas o infecciosas más frecuentes.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Our Dermatology Online

Case Report

O'Brien's Granuloma in a 50-year-old Chinese male

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ABSTRACT

O'Brien's actinic granuloma is clinically characterized by grouped red papules that may coalesce into annular plaques on sun damaged skin such as the head and neck, chest, and arms. There is no gender predilection, and patients tend to be middle-aged or older giving the association with significant actinic damage. We presented a 50-year-old male with multiple annular lesions on the neck of four years duration, associated with prolonged sun exposure. A biopsy confirmed the clinical suspicion of O'Brien's granuloma and excluded other possibilities.

Key words: O'Brien's; granuloma; actinic

INTRODUCTION

O'Brien's granuloma is a rare skin disease that presents clinically by grouped red papules that may coalesce into annular plaques on sun damaged skin. The annular plaques have raised erythematous borders (3-5 mm)and slightly atrophic center [1].The hypo pigmented central regions are distributed mainly in sun-exposed areas. The sites of predilection include the neck, face, chest and arms. Early on, skin-colored or pink papules may be identified singly or in small groups before they coalesce into annular plaques. Individual lesions measure 1-10 cm in diameter. A single plaque lasts for months to years, after which spontaneous remission may occur, leaving mottled dyspigmentation or normal-appearing skin [2].

O'Brien's granuloma must however, be differentiated from granuloma annulare which is a distinct entity. Lesions of granuloma annulare occur most commonly on the dorsa of the hands and feet. Interestingly, a variant of granuloma annulare has been described in which the lesions occur on the sun-exposed areas [3].

CASE REPORT

A 50-year-old male presented with multiple annular lesions on the neck of four years duration, associated with prolonged sun exposure.

Since four years ago, the patient started to develop small erythematous papules on the back of the neck, which increased in size and healed centrally to form many annular lesions on the back and the sides of the neck, at sun exposure area.

Exposure to the sun followed by erythema and mild itching but no pain.

The patient was otherwise healthy. He had no past history of skin diseases or medical diseases, no family history of skin or medical diseases. Drug history was negative. No application of any topical agents was found. The patient exposed to the sun several hours daily for many years.

Physical examination showed pink papules arranged into annular form with slightly atrophic center. There were several rings on the back and sides of the neck ranging between one to five centimeters in diameter. The surface of the lesions was smooth, shiny and firm (Figs 1-a, b and c).

A full blood count, ESR, routine biochemistry and urinalysis were normal. Angiotensin converting enzyme levels were within normal limits and antinuclear antibodies were negative. The intradermal tuberculin test was nonreactive. A chest X-ray did not reveal any abnormalities.

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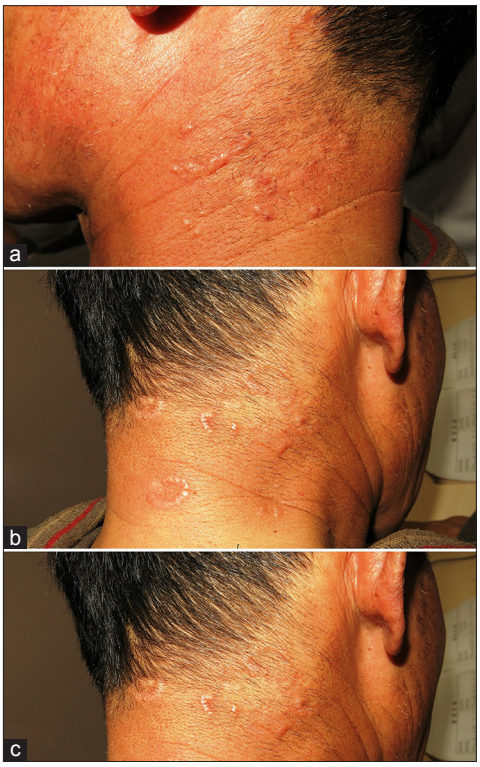

Figure 1: The clinical pictures of O'Brien's granuloma: Fig.1a and 1b: small erythematous papules on the back of the neck, which increased in size and healed centrally to form many annular lesions. There were several rings on the back and side of the neck ranging between one to five centimeters in diameter on the back and the side of the neck. Fig.1c: Close up view revealed significant pink papules arranging into annular form with slightly atrophic center. The surface of the lesions was smooth, shiny and firm.

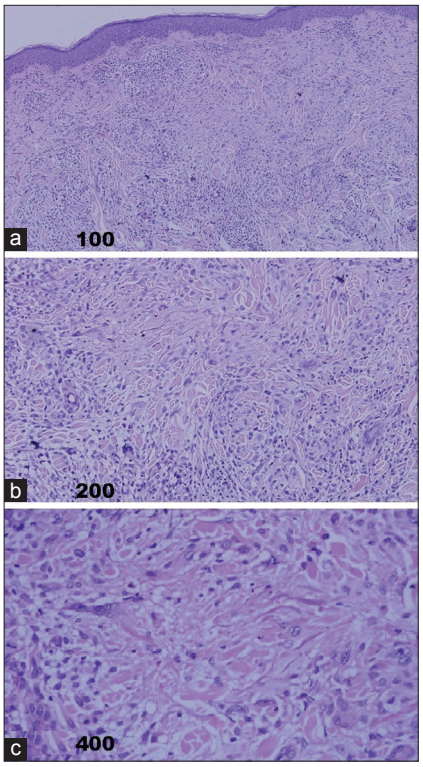

Figure 2: (HE stain)In dermis, there were granulomas composed of histiocytes and a few multinucleated giant cells, (Fig.2a×100). The histiocytes and multinucleated giant cells showed no typical palisading pattern in the periphery of the granuloma. Rarely, mild collagen degeneration could be found in the center of the granuloma, (Fig.2b×200; Fig.2c×400).

Biopsy of a plaque on the neck showed histological changes consistent with the diagnosis of O'Brien's granuloma. In the dermis, there were granulomas composed of histiocytes and a few multinucleated giant cells which arranged with no typical palisading pattern in the periphery as seen in granuloma annulare. Occasionally mild collagen degeneration in the center of the granuloma could be seen (Figs 2-a, b and c). Alcian blue staining showed no significant mucin deposition in the center of granuloma (Fig. 3). Decreased and broken fragments of elastic fibers could be found in the center of granuloma. However, Elastophagocytosis was not seen (Fig 4).

Based on the history especially the lesions are associated with sun light and the special location, a diagnosis of actinic granuloma was established.

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

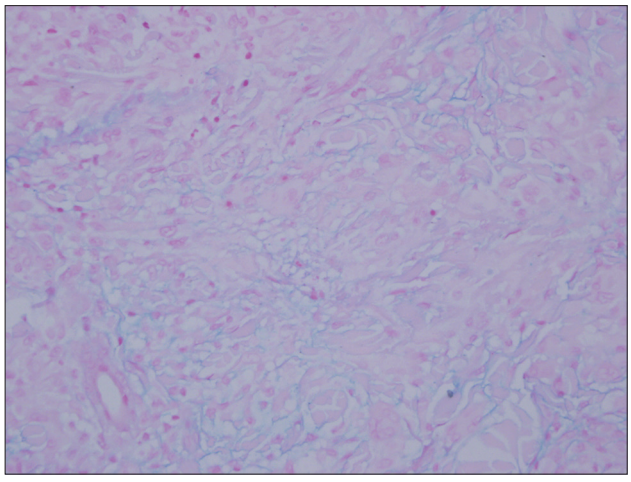

Figure 3: (Alcian blue staining)showed no mucin deposition in the center of granuloma.

DISCUSSION

O'Brien granuloma is a rare disorder develop in an area of solar elastosis [4]. O'Brien used'actinic' in the name of this disorder because he believed that its etiology was linked to ultraviolet and infrared radiation. This theory was rejected by Hanke et al [5], whose patients did not

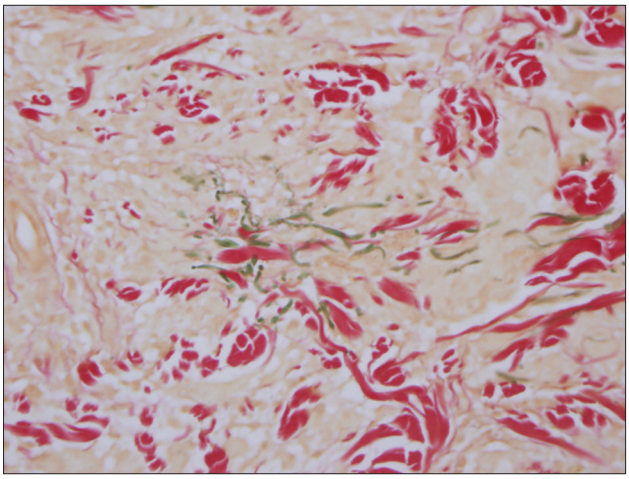

Figure 4: (Masson stain): there were a few broken fragments of elastic fibers in the center of granuloma.

all demonstrate significant solar elastosis histologically but otherwise fit O'Brien's clinical and histopathologic descriptions. These authors coined the descriptive term annular elastolytic giant cell granuloma in 1979. Upon review of the literature, both O'Brien and Hanke realized that the diseases they were describing had previously been reported under other names, including atypical necrobiosis lipoidica of the face and scalp [6],

O'Brien's granuloma is an annular inflammatory reaction with giant cell dermal infiltrate, which is characterized clinically by lesions develop in the exposed skin [7]. They start insidiously as small, pink papules, which progress slowly to form an annular, firm, superficial, smooth dermal thickening, the ring may expand up to 6 cm in diameter with slightly atrophic center, usually asymptomatic [4].

The pathology shows three distinct zones in the dermis. In the external 'normal' skin, there is actinic elastosis. In the thickened edges, there is a histiocytic and giant cell inflammatory reaction in relation to elastotic fibers, and in the center, within the annulus, little or no elastic tissue remains [8]. The cellular infiltrate slowly expands outwards, leaving behind a central area from which elastic fibers have been removed by 'elastoclasis'. The epidermis may be normal or it may show signs of actinic damage [9-11].

O'Brien's granuloma must, however, be differentiated from granuloma annulare which is a distinct entity. Lesions of granuloma annulare occur most commonly on the dorsa of the hands and feet. Interestingly, a variant of granuloma annulare has been described in which the lesions occur on the sun-exposed areas [2]. However, granuloma annulare is characterized by foci of necrobiotic collagen surrounded by palisades of histiocytes which are not features of actinic granuloma. In further contrast with lesions of actinic granuloma, elastosis and elastoclastic giant cells are absent and mucin deposition is usually more obvious from granuloma annulare [12].

Annular elastolytic giant cell granuloma was characterized clinically by erythematous papules and plaques which may arise anywhere on the body, but the diagnosis is usually reserved for those that occur on areas without severe actinic damage. They may often be annular in appearance. Most patients are over 40 years old, and children are almost never affected. Histologically there are dermal granulomas with prominent multinucleated giant cells. Elastophagocytosis is a common feature. Necrobiosis and mucin deposition are absent, and there should not be a significant degree of palisading. As the lesions progress, more elastic fibers are destroyed eventually leading to a complete absence of elastic fibers in affected areas. An elastin stain will highlight the elastic fibers and help identify elastophagocytosis [1].

O'Brien argued that actinic granuloma to Miescher's granuloma of the face, atypical necrobiosis lipoidica of the face and scalp, and granuloma multiforme were, in fact, the same, although distinct from granuloma annulare. He speculated that they resulted from a common sequence of events in which primary elastin damage was followed by a giant-cell-mediated phagocytic repair process. It is generally accepted, however, that at least some of the conditions do represent true variants in the well-recognized necrobiosis lipoidica-granuloma annulare spectrum of granulomatous reactions. Specific disease entities might result from different types of dermal injury, with some degree of overlap [13].

Granuloma multiforme is a chronic granulomatous skin condition, characterized clinically by firm papules aggregated into plaques or forming the edges of annular lesions mainly occurring in middle Africa, and histologically by focal areas of necrobiosis, with loss of elastic tissue, surrounded by histiocytes. Multinucleated giant cells are usually a prominent feature. There is a perivascular lymphocytic infiltrate with variable numbers of plasma cells and eosinophils [14,15].

CONCLUSION

We presented a 50-year-old male with O'Brien's actinic granuloma, who present clinically as multiple annular lesions on the neck of four years duration, associated with prolonged sun exposure. Our patient was compatible with the aforementioned clinical and histopathologically features of O'Brien's granuloma and excluded other possibilities. This is further supported by the fact that the condition is more common in sunny countries and in fair-skinned and actinically damaged individuals.

CONSENT

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

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Our Dermatology Online

Case Report

Miescher granulomatous macrocheilitis: A case report

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ABSTRACT

Cheilitis granulomatosa (CG) is a chronic swelling of the lip due to granulomatous inflammation. It is a rare inflammatory disorder first described by Miescher in 1945. It is a monosymptomatic form or an incomplete variant of Melkersson-Rosenthal syndrome. As the etiology remains unknown, treatment of CG is challenging. We present a case of CG in a 20-year-old male patient presented to us with diffuse swelling of the lower lip of seven years duration. On examination, there was gross enlargement of his upper-lip. A histopathological specimen from the lower lip showed non-caseating granulomas. We treated our patient with intralesional triamcinolone acetonide and oral clofazimine. The present case highlights the importance of thorough clinical examination, history & investigations in the diagnosis of this lesion as the findings mimic many other granulomatous conditions in dermatology.

Key words: Cheilitis granulomatosa; Upper lip swelling; Melkersson-Rosenthal syndrome

INTRODUCTION

Miescher granulomatous macrocheilitis (cheilitis granulomatosa) is a mono-symptomatic form of Melkersson-Rosenthal Syndrome (triad of recurrent labial and/or recurrent facial edema, relapsing facial paralysis, and fissured tongue) [1]. The complete classical presentation of Melkersson-Rosenthal syndrome is considered to be rare, occurring in only 25 to 40 percent of cases [2]. The condition was first described by Miescher in 1945 [3]. Orofacial granulomatosis is a unifying terminology showing similar clinical features and a broad spectrum of non-necrotizing granulomatous inflammation in the oral and facial region [4]. Other entities that need to be considered in the differential diagnosis of orofacial granulomatosis include sarcoidosis, Crohn disease, and infectious disorders (e.g., tuberculosis).

CASE REPORT

A 30-year-old male was brought to our outpatient department with the chief complaint of gross swelling and deformity of the upper lip of two years duration. Initially the swelling over the upper lip was minimal and gradual progression in nature which was persistent for two years of after single honey bee bite episode. There was no significant past history for tuberculosis, crohn disease, sarcoidosis. On detailed examination, our patient showed massive enlargement and protuberance of the upper lip (Fig. 1). The lips were firm and rubbery in consistency on palpation. No regional lymph gland enlargement was present. There was no other mucosal abnormality.

The initial investigations revealed a normal complete blood count. The levels of serum urea and creatinine, electrolytes, serum proteins and albumin, serum calcium and serum angiotensin-converting enzyme were normal. Urine and stool analyses were normal too. VDRL tests for syphilis were negative. Chest radiograph was normal. Tuberculin skin test and abdominal ultrasound was normal.

Histopathological examination of the tissue biopsy obtained from the mucosal surface of the upper lip revealed The sections show stratified squamous epithelium with atrophy at places. The dermis has focal dense superficial perivascular inflammatory infiltrate composed of lymphocytes and a few plasma cells. Occasional epithelioid cells are also seen in the

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present sections. In summary, in appropriate clinical settings, these histologic findings are suggestive of granulomatous cheilitis (Figs. 2 and 3).

The patient received systemic steroids 40 mg per day for 15 days then in tapering doses till next 2 months along with oral clofazimine 100 mg three times a day (pre treatment and post treatment Figs. 1 and 4).

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

DISCUSSION

Granulomatous cheilitis is clinically characterized by diffuse and painless swelling of the lips. [5]. When associated with fissured tongue and facial palsy it is known as Melkersson-Rosenthal syndrome More Details [5,6]. Isolated granulomatous cheilitis, also known as Miescher granulomatous cheilitis, is sometimes considered a monosymptomatic variant of Melkersson-Rosenthal syndrome [5]. Histopathological features consist of epitheloid cell granulomas with Langhans giant cell in a mononuclear inflammatory background [7].

Cheilitis granulomatosa is considered a form fruste of Melkersson-Rosenthal syndrome. The cause is not known in the majority of the cases. But there may be genetic predisposition with increased incidence in siblings [8]. A few cases represent localized form of sarcoidosis or extraintestinal manifestation of Crohns disease [9,10]. Infective agents implicated in the etiology of granulomatous cheilitis are Toxoplasma

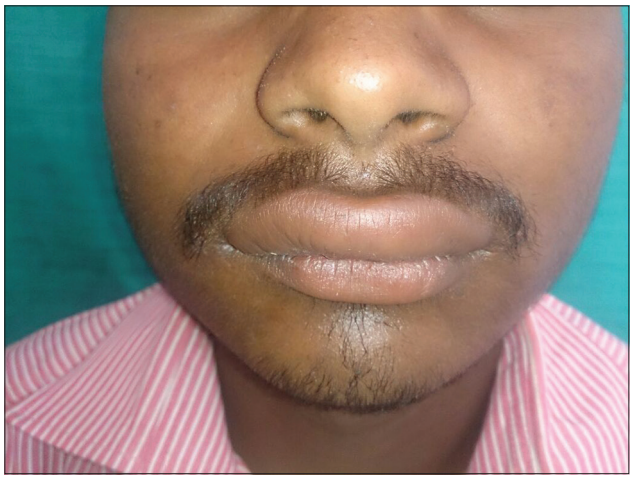

Figure 1: Massive enlargement and protuberance of the upper lip.

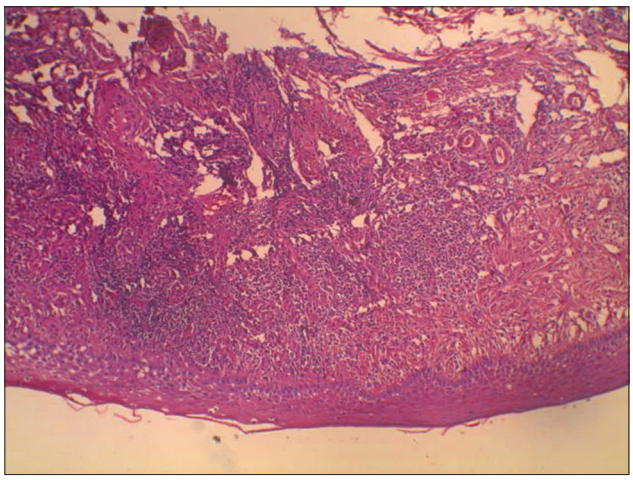

Figure 2: Epidermis showing stratified squamous epithelium with atrophy at places. The dermis has focal dense superficial perivascular inflammatory infiltrate composed of lymphocytes and a few plasma cells. Occasional epithelioid cells are present. (H &E stain at 10x magnification).

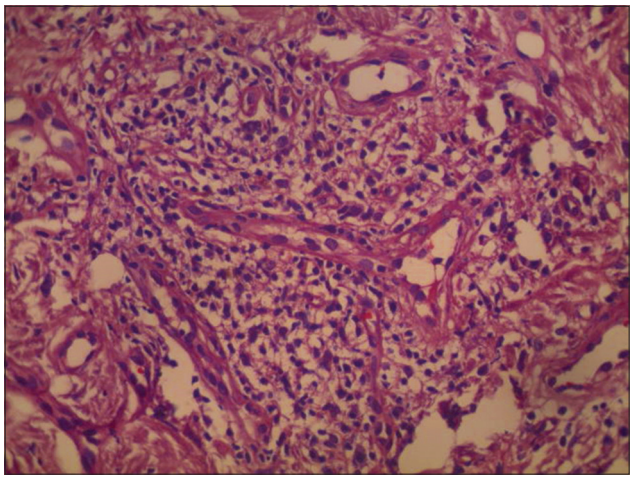

Figure 3: The dermis showing dense superficial perivascular inflammatory infiltrate composed of lymphocytes and a few plasma cells with few epitheloid cells.(H &E stain at 40x magnification).

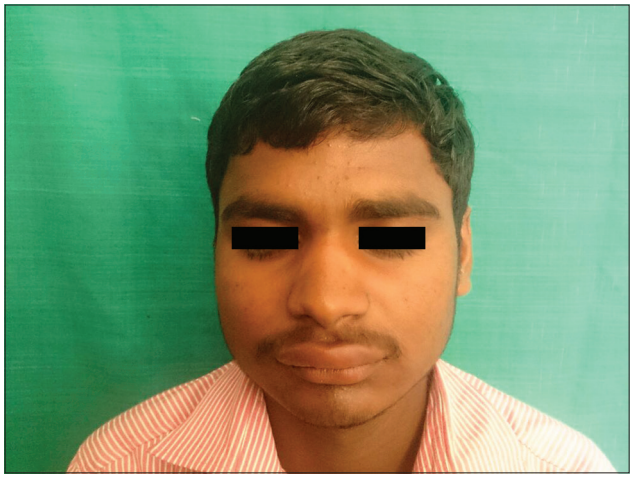

Figure 4: Post treatment photograph.

gondii, Treponema pallidum, Mycobacterium tuberculosis, Mycobacterium leprae, Herpes simplex and Borrelia burgdorferi [8].

Cheilitis granulomatosa usually presents with recurrent and episodic swelling of the upper lip (common), which subsides in a matter of a few hours. Hence it is commonly mistaken for angioedema without undergoing for thorough investigations for patient. Gradually, the frequency of painless lip swelling increases and leads to a more persistent and firm swelling of both lips. Compression of lymphatics by the enlarging granulomas leads to an aggravation of swelling.

The differential diagnosis of acquired swelling of the lips are as following Acute causes – trauma, insect bite reaction, angioedema, anaphylaxis, drug reaction, erythema multiforme, urticaria. And chronic causes - Cheilitis granulomatosa, Sarcoidosis, Crohn disease, Melkersson-Rosenthal syndrome, Leprosy, Leishmaniasis, Syphilis, Tuberculosis, Rhinoscleroma, Malignancy, Actinic cheilitis, Cheilitis glandularis, Acromegaly, Amyloidosis, Cl esterase deficiency, foreign body granuloma.

Diagnosis of cheilitis granulomatosa relies on the typical history, clinical features and supportive evidence of non-caseating granulomas on histopathology. Two types of histology have been described for cheilitis granulomatosa (i) the sarcoid type with non-caseating granuloma consisting of epithelioid cells (histiocytes), lymphocytes, plasma cells, macrophages, and diffuse edema within the interstitial connective tissue and the (ii) lymphedematous type showing lymphatic distension, lymphedema, and plasma cell infiltration [11]. Our patient had the sarcoidal type of granulomatous inflammation present in the upper and mid dermis with edema, which corresponded to the massive swelling of his lower lip. However, no perilymphatic pathology was seen on pathology.

Treatment of cheilitis granulomatosa is a challenge for dermatologist. There are many drugs, which are reported to be useful in the management of cheilitis granulomatosa. Intralesional triamcinolone acetonide with lignocaine 2 percent is the first line of treatment for cheilitis granulomatosa [12]. Intralesional triamcinolone acetonide (10-20 mg/ml) in the volume of 1.0-1.5 ml into each side of the lip leads to prompt resolution of inflammatory granulomas. However, the response to intralesional steroid is of short duration and requires frequent painful injections. Other drugs that have been successfully used in cheilitis granulomatosa include dapsone, clofazimine [13], metronidazole [14], and roxithromycin [15]. Because of a similar pathogenesis of cheilitis granulomatosa and Crohn disease, the TNF antagonist (infliximab) has been reported to be successful in the management of cheilitis granulomatosa [16]. Owing to similar clinical and pathological features of cheilitis granulomatosa and sarcoidosis, hydroxychloroquine might prove useful in the treatment of cheilitis granulomatosa [17]. Treatment resistant and disfiguring cases of cheilitis granulomatosa need surgical intervention in the form of surgical reduction and cheiloplastic procedures with adjuvant intralesional steroid injection to prevent relapse [18,19].

CONCLUSION

We have presented a case of cheilitis granulomatosa (Miescher granulomatous macrocheilitis) secondary to honey bee bite and patient showed remarkable improvement with systemic steroids and clofazamine.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Case Report

A confusing cutaneous lymphoma

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ABSTRACT

Blastic plasmacytoid dendritic cell neoplasm previously called CD4+CD56+ haematodermic neoplasm or blastic NK cell lymphoma is a rare and clinically aggressive hematologic malignancy, derived from plasmacytoid dendritic cells. It is characterized by a skin tropism and co-expression of CD4 and CD56. We report the case of a 57 year old man who had lesions papulonulaires back and lower limbs associated with multiple lymph nodes. The diagnosis was made by histological examination and immunohistochemistry.

Keywords: CD4; CD56; Immunophenotype; Lymphoma; Skin

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Our Dermatology Online

Case Report

Un lymphome cutané déroutant

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RÉSUMÉ

La tumeur à cellules plasmocytoïdes dendritiques blastiques anciennement appelée hématodermie CD4/CD56 ou lymphome NK blastique est une hémopathie maligne rare et cliniquement agressive, dérivée à partir des cellules plasmocytoïdes dendritiques. Elle est caractérisée par un tropisme cutané et une co-expression de CD4 et CD56. Nous rapportons le cas d'un homme âgé de 57 ans qui présentait des lésions papulo-nodulaires du dos et des membres inférieurs associées à des adénopathies multiples. Le diagnostic positif était histologique et immunohistochimique.

Mots clés: CD4; CD56; Immunophenotype; Lymphome; Peau.

INTRODUCTION

La tumeur à cellules plasmocytoïdes dendritiques blastiques (TCPDB) anciennement appelée hématodermie CD4/CD56 ou lymphome NK blastique est actuellement une entité distincte classée par l'OMS 2008 dans le groupe des leucémies myéloïdes aiguës [1]. C'est une hémopathie maligne rare et cliniquement agressive, dérivée à partir des cellules plasmocytoïdes dendritiques. Un tropisme cutané et une co-expression de CD4 et CD56 à l'exclusion des autres marqueurs spécifiques des lignées définies, caractérisent cette tumeur.

CASE REPORT

Un homme, âgé de 57 ans, consultait en dermatologie pour des lésions papulo-nodulaires du dos et des jambes, évoluant depuis trois mois.

L'examen clinique trouvait des plaques infiltrées, érythémato-violacées, arrondies, bien limitées, fixes et indurées (Fig. 1). Ces lésions siégeaient au niveau du dos, du membre inférieur gauche et du cuir chevelu et mesuraient entre 1 et 5 cm de grand axe.

Des adénopathies inguinales bilatérales et cervicales mesurant entre1 et 3 cm étaient trouvées.

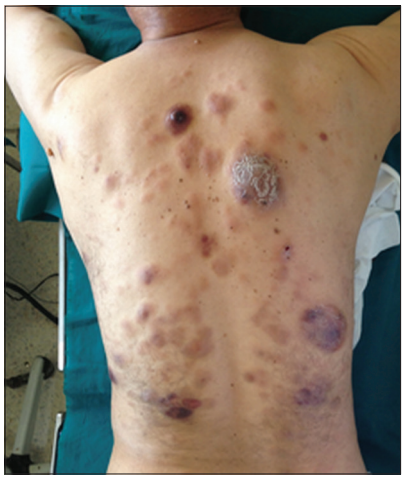

Figure 1: Plaques infiltrées, érythémato-violacées, arrondies, bien limitées du dos

Une biopsie de l'une des lésions était réalisée. A l'examen histologique, le derme était habité par une prolifération d'allure lymphoïde maligne présentant une architecture nodulaire et diffuse étendue jusqu'au niveau de l'hypoderme et respectant l'épiderme dont elle était séparée par une Grenz zone (Fig. 2). Cette prolifération était faite de cellules d'allure lymphoïde, de taille le plus souvent moyenne, présentant un noyau hyperchromatique, rond et volumineux. Le cytoplasme était peu abondant (Fig. 3). Il n'a pas été vu d'angiotropisme.

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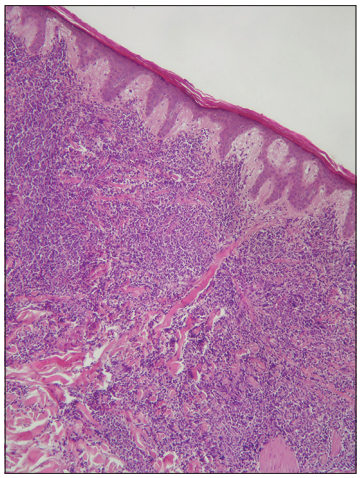

Figure 2: Prolifération lymphomateuse dermique séparée de l'épiderme par une Grenz zone.

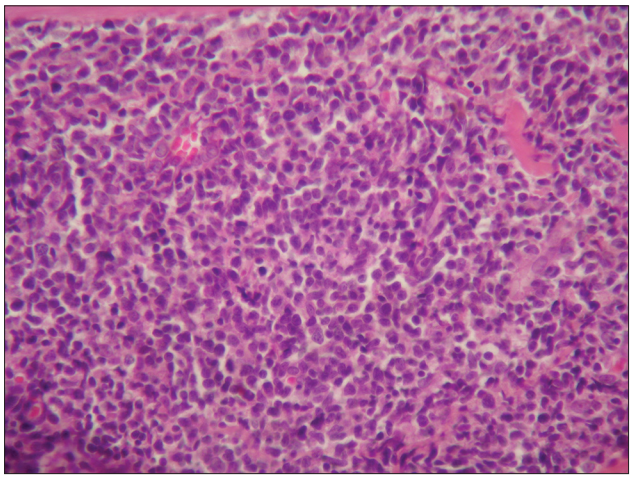

Figure 3: Cellules d'allure lymphoïdes de taille moyenne, présentant un noyau hyperchromatique, rond et volumineux.

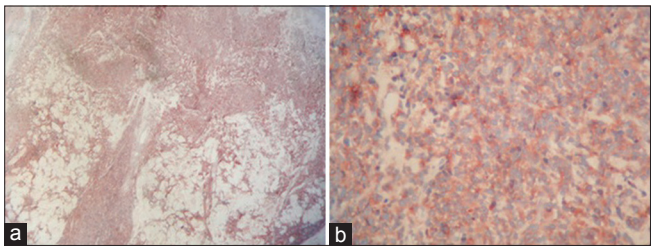

Figure 4: Positivité intense et diffuse du CD4 (a) et du CD56 (b).

L'étude immunohistochimique montrait une positivité intense et diffuse des cellules tumorales au CD4 (Fig. 4a), CD56 (Fig. 4b) et bcl2. Le CD20, le CD3 et le CD8 avaient marqué quelques lymphocytes réactionnels.

Une biopsie de l'une des adénopathies inguinales était réalisée montrant la même prolifération d'allure lymphoïde ainsi que le même profil immunohistochimique qu'au niveau des lésions cutanées.

Quel est votre diagnostic?

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

DISCUSSION

Tumeur à cellules plasmocytoïdes dendritiques blastiques (Hématodermie CD4/CD56)

La tumeur à cellules plasmocytoïdes dendritiques blastiques (TCPDB) anciennement appelée hématodermie CD4/CD56 ou lymphome NK blastique est actuellement reconnue par l'OMS 2008 comme entité distincte appartenant au groupe des leucémies myéloïdes aiguës [1]. Il s'agit d'une hémopathie maligne rare et cliniquement agressive, dérivée à partir des cellules plasmocytoïdes dendritiques (CPD). La TCPDB est caractérisée par un tropisme cutané et une co-expression de CD4 et CD56 à l'exclusion des autres marqueurs spécifiques des lignées définies.

Cette tumeur affecte essentiellement les sujets âgés, avec prédominance masculine. De rares cas pédiatriques ont été rapportés [2].

Dans plus de 90% des cas, la maladie se manifeste au début par une atteinte cutanée [3]. Les lésions sont solitaires ou localisée à l'apparition de la maladie, puis elles deviennent multiples et disséminées. Il peut s'agir d'un érythème, de papules, de nodules, de plaques, de lésions ulcérées ou ecchymotiques ou d'un hématome. Une atteinte ganglionnaire associée, comme dans notre cas, est observée dans un tiers des cas. L'intervalle de temps entre l'apparition des lésions cutanées et la dissémination leucémique varie généralement entre quelques semaines et plusieurs mois.

L'examen histologique montre, comme dans notre cas, un infiltrat dermique dense, diffus, fait de cellules monomorphes, de taille moyenne et à cytoplasme réduit. Elles ont un noyau arrondi ou ovalaire, légèrement irrégulier, à chromatine fine " d'aspect blastique ". Les mitoses sont fréquentes. Cet infiltrat est séparé de l'épiderme par une Grenz zone. L'angioinvasion et la nécrose sont rares.

Le profil phénotypique de la population tumorale est très caractéristique. En effet, les cellules tumorales se caractérisent par la co-expression du CD4 et du CD56 et l'expression des marqueurs des CPD (CD123,

CD303 et TCL1). L'expression du CD2 et CD7 est variable. Le CD3 est négatif. Le CD68, le CD43 et la Tdt peuvent être positifs dans certains cas [1].

Le diagnostic différentiel se pose essentiellement avec les lymphomes CD3 - et CD20 - pouvant atteindre primitivement ou secondairement la peau tels que les lymphomes T de phénotype nul (prolifération T CD30+), les lymphomes lymphoblastiques avec perte antigénique, les lymphomes NK/T, et les localisations cutanées des hémopathies myéloïdes (leucémie myélomonocytaire et sarcome granulocytaire). Parmi les lymphomes NK, les diagnostics différentiels principaux sont représentés par les localisations cutanées d'un lymphome T/NK de type nasal ou d'un lymphome/leucémie agressif à cellules NK. Sur le plan histologique, ces tumeurs présentent un angiotropisme et une angiodestruction avec des plages de nécrose, qui sont généralement absents dans l'hématodermie CD4/CD56. Néanmoins, ces lésions ne sont pas toujours visibles sur les biopsies cutanées de lymphome NK/T de type nasal cutanés. Sur le plan immunohistochimique, les cellules tumorales expriment CD56 mais n'expriment pas CD4. L'élément phénotypique essentiel est la mise en évidence des marqueurs de cytotoxicité.

Au cours du lymphome/leucémie agressif à cellules NK, l'atteinte cutanée est possible mais le tableau clinique est généralement différent de celui de l'hématodermie CD4/CD56.

Concernant les localisations cutanées des leucémies myéloïdes ou myélomonocytaires, elles expriment généralement le CD4 et peuvent exprimer le CD56. Par ailleurs, elles peuvent exprimer également HLADR, CD2, CD7, CD36 ou CD38.

Initialement, l'origine NK des cellules tumorales a été proposée en raison de l'expression du CD56. Actuellement, la forte expression du CD123 et de la chaine alpha du récepteur à l'interleukine-3 (IL-3R- alpha) suggère une origine à partir des cellules plasmocytoïdes dendritiques [1].

Plusieurs attitudes thérapeutiques ont été proposées, mais les résultats étaient décevants. Une meilleure réponse, bien que faible, a été obtenue avec l'association de chimiothérapie agressive et de radiothérapie suivies de greffe de moelle osseuse [5].

Le pronostic de la TCPDB est médiocre même chez les patients manifestant une rémission complète. La médiane de survie varie entre 12 et 27 mois [6]. Les résultats d'études récentes montrent l'absence de signification pronostique de l'extension de l'atteinte cutanée et la valeur pronostique des marquages de CD303 et du Ki-67 [1]. Notre patient est décédé un mois après le diagnostic de sa maladie.

En conclusion, la TCPDB est un lymphome rare, de très mauvais pronostic. Devant l'absence d'un traitement efficace, un diagnostic précoce ainsi qu'une thérapie initiale agressive comme la greffe de moelle osseuse sont justifiés.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Case Report

An interesting uncommon side effect of topical corticosteroids-hidradenitis suppurativa

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ABSTRACT

There are many local and systemic side-effects of topical corticosteroids. To the best of our Knowledge, Hidradenitis Supportive (HS) due to topical corticosteroids has not been reported previously. We report a 39-year old, male patient who started himself a topical corticosteroid Pander Plus cream because of itching, scaly lesions over groins and buttocks since 6 months. After 4 months of topical treatment, he developed pus discharging sinuses over both groins and buttocks. Based on patient history, clinical and laboratory findings and the exclusion of other diagnoses, HS points out the use of topical corticosteroids. The case well highlights this unusual condition and represents the first case reported in India to our best of the knowledge. Having performed thorough literature search I would like to discuss in this report the evidence for this relation and stress the importance of appropriate usage of topical corticosteroids.

Key words: Hidradenitis; pus; sinus discharge; skin atrophy; striae; topical steroid

INTRODUCTION

Topical corticosteroids have now been in use for treating skin disease for over half a century, since the introduction of compound F or hydrocortisone (cortisol) in 1952 [1].Many local and systemic side effects have become more prevalent since the uncontrolled use of high potency topical corticosteroids. The most common local side effects are atrophy, acneiform eruptions, erythema, folliculitis, hyper pigmentation, hypertrichosis, hypo pigmentation, Purpura, Striae, susceptibility to infections and Telangiectasia [2]. Here in, we report a case of HS due to using a topical corticosteroid cream.

CASE REPORT

A 39 year-old male patient reported to our department with complaints of pus discharging sinuses over both groins and buttocks since 2 months duration, past history of uncontrolled use of topical corticosteroid cream for itching over groins and buttocks for a period of 4 months. It was prescribed by friend initially and he got it over the counter sale. According to his history he did not have any systemic disease. He had only itching scaly skin lesions over groins and buttocks. He used topical corticosteroid cream by himself uncontrollably for improvement of itching without consulting dermatologist. Recently he underwent surgical excision of abscess over buttocks in private hospital. Physical examination was normal. Laboratory investigations revealed leucocytosis raised ESR, normal Liver function tests and Kidney function tests.

On Local examination:

1. Longitudinal striae over supra pubic area and flanks, hypopigmentation over both groins (Fig. 1);
2. Skin atrophy over both groins and pubic area (Fig. 2);
3. Multiple discharging sinuses with healed scars over buttocks and hypertrichosis (Fig. 3);
4. Circular shaped crusted lesion over the left medial aspect of the thigh and multiple discharging sinuses over left groin with pus (Fig. 4).

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Based on the patient's history, clinical and laboratory findings and the exclusion of other diagnoses, the HS associated with the use of topical corticosteroids cream was diagnosed. Pus culture and sensitivity was done. In Gram stain of pus culture showed staphylococcus aureus and anaerobic streptococci. It showed Sensitivity to Vancomycin, Tecoplanin and Gatifloxacin.

DISCUSSION

Supportive hidradenitis is a chronic relapsing inflammatory disease originating in apocrine gland follicles, which may become chronic and often indolent due to subcutaneous extension with induration, scarring, destruction of skin appendages and sinus formation [3].

Comedonal occlusion of the "apocrine gland follicle" unit therefore obstructs the outflow of the apocrine gland in addition to that of the sebaceous gland, and is believed to be the initiating event in hidradenitis.

Friction and pressure accentuate the inflammatory changes that invade the fat and cause further granulomatous change extending widely over the buttocks and thighs. Persistent perineal sinuses are frequent, and deep lesions cause anal fistulae.

Keratin Plugs are identified in apocrine gland follicles, leukocyte inflammatory cells in ducts of glands. As the apocrine gland extends well below the dermis into the less supportive subcutaneous tissue, the suppuration readily breaks through the gland and extends under the skin.

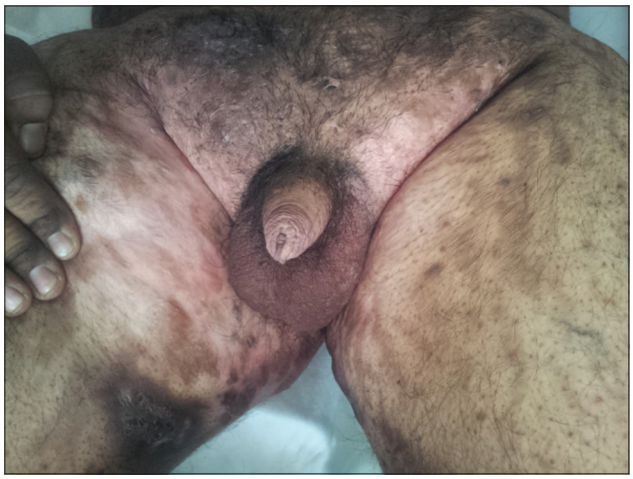

Figure 1: Multiple striae over anterior abdomen,flanks and thighs. shows multiple discharging sinuses over pubic area, few with crusting.

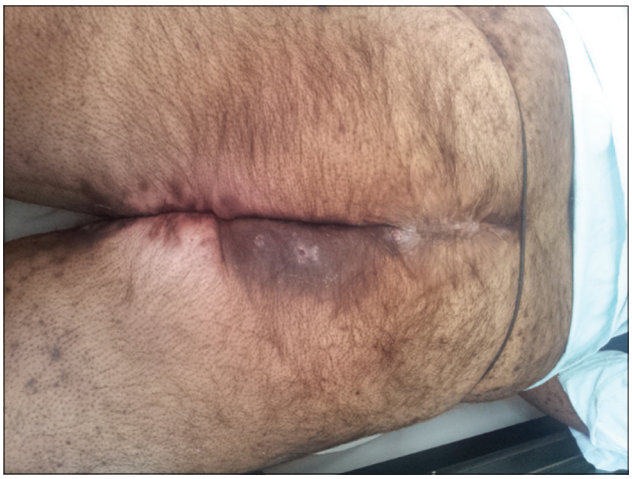

Figure 3: Multiple discharging sinuses over inter gluteal region, scar and hypertrichosis.

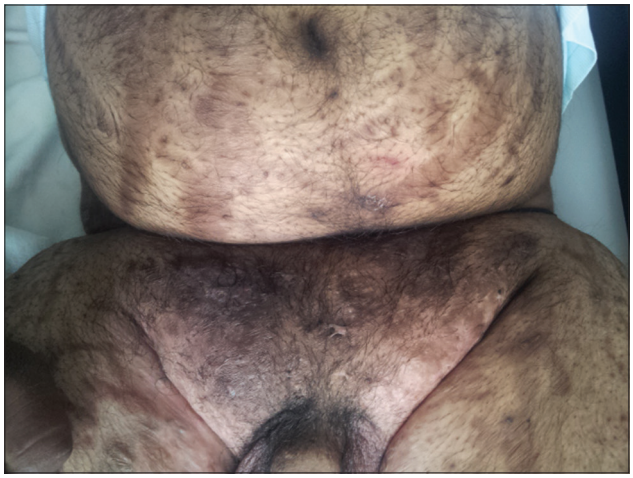

Figure 2: Skin atrophy over both groins and pubic area.

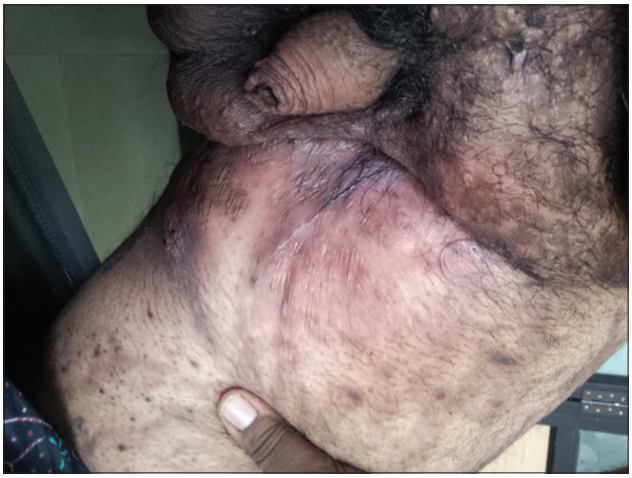

Figure 4: Multiple discharging sinuses over left groin with pus.

Laboratory investigations show higher yield of potential pathogens Staphylococcus aureus, anaerobic streptococci and, notably, the microaerophilic organisms Streptococcus milleri from purulent disease and abscesses.

Topical corticosteroids are classified according to their potency into mild, moderate, potent, and very potent categories. It is recognized that topical corticosteroid preparations can be absorbed through the skin and may result in suppression of hypothalamo-pituitary-adrenal (HPA) axis and may cause Cushing's syndrome. Prolonged steroid use is associated with myriad side effects. Androgen levels were on average increased compared with controls, but were normal in many individual patients. The application of topical corticosteroids on thin and damaged skin, on the elderly or paediatric population or under occlusion, intertriginous areas or moisture areas increases risk of side effects [4].

Corticosteroids can cause virilization in females and feminization in males. And also corticosteroids may increase muscle mass as well as hypertrophy of the penis, accentuate scrotal folds and stimulate sebaceous glands in men.

Corticosteroids once absorbed stimulate sebocyte proliferation [5] and aggravates sebaceous gland activity by its stimulatory effects on proliferation and differentiation in the presence of growth factors [6]. Friction and pressure accentuate the inflammatory changes that invade the fat and cause further granulomatous change extending widely over the buttocks and thighs.

Following atypical sites already noted in dermatological literature, areola, infra- mammary and inter-mammary fold, [7] abdomen, scalp, [8] external auditory meatus, ear lobes, retro auricular fold [9], abdomen and chest [10].

In our case report patient continually applied ointment, which combines a potent topical steroid and an antifungal agent, twice daily to the intergluteal folds, pubic area and both groins. The occlusive nature of this anatomical location had led to an increase in the potency of the steroid.

CONCLUSION

In conclusion, this is the first case of Hidradenitis Suppurativa due to topical corticosteroids. The clinicians should be aware of an unusual complication caused by topical corticosteroids.

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Our Dermatology Online

Case Report

Hidradenitis suppurativa in Down's syndrome: A case report

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ABSTRACT

Of the many dermatological conditions thought to be linked with Down's syndrome, hidradenitis suppurativa presents a peculiar manifestation. This brief case report summarises the clinical features and possible genetic basis for this fascinating association.

Key words: Hidradenitis suppurativa; Down's syndrome; genodermatoses; genetic basis of skin disease; clinical dermatology

INTRODUCTION

The association of hidradenitis suppurativa with Down's syndrome has long been suspected. First proposed in 1992 by Spanish authors [1], the connection came under the spotlight again more recently in a correspondence article published in the *British Journal of Dermatology* [2]. Including the five cases given in that article, there have only been ten such cases recorded worldwide to date, but the actual incidence of hidradenitis in Down's syndrome may be much higher. Here the author presents another case.

CASE REPORT

A 20 year old female Paralympian swimmer with Down's syndrome, presented to emergency with a progressively enlarging and tender right groin lump of several weeks duration. The patient reported the finding to her mother on the same day and was brought into emergency because of the size and appearance of the lesion. The lump had started to cause the patient considerable pain more recently but she had been afebrile and well otherwise. There had been no preceding trauma or any other specific inciting event. Further questioning revealed that the patient suffered from spontaneously recurring flexural abscesses and cysts up to three times a year. They first started happening when she was in primary school and affected only her axillary and groin regions – a search of her hospital record showed that she had indeed been repeatedly diagnosed with axillary 'abscess' and 'cellulitis' in past visits to emergency. Some of these attacks were more severe than others and she once had to complete four courses of oral broad spectrum antibiotics before her axillary lesions settled. The patient could only recall having ever had one incision and drainage operation for a persisting axillary abscess. With this history, a clinical diagnosis of hidradenitis suppurativa was made. There was no significant family history of the disease.

On examination, a fairly large ellipsoid and erythematous lump measuring 40 by 20 mm was seen in the right groin crease (Fig. 1). It was firm and tender to touch and appeared to be slightly indurated superficially. A small break in the skin was noted in close vicinity to the lump but there was no purulent discharge or bleeding. The left groin was clear and there were no obvious sinus tracts or signs of scarring in the region. Minimal grade scarring was seen in both axillae but there were no active lesions present (Fig. 2). Other dermatological features of Down's syndrome that were noted during the examination included, mild to moderate xerosis, a fairly large and fissured tongue (lingua plicata), and multiple facial

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syringomas that were clearly appreciable infraorbitally on the right side. There was no palmoplantar hyperkeratosis, alopecia, vitiligo, or signs of elastosis perforans serpiginosa on the examined skin. The patient denied a history of eczema, cheilitis, or any other significant skin eruptions. Her white cell count turned out to be normal and so she was discharged with oral flucloxacillin and asked to return to emergency the following morning for an ultrasound scan of her right groin.

The ultrasound scan the next day showed simple abscess formation only, and by this time, the lesion had already reduced in size and redness (Fig. 1). Even so, it was incised and drained under Entonox analgesia and the small amount of pus that was extruded was sent off for microscopy and culture. The wound was left open to aid further drainage and the patient was advised to avoid swimming while it healed. After educating the patient and her mother on the condition she was advised of the possible association with Down's syndrome. Since the history and examination findings suggested a relatively mild case of hidradenitis, the patient was asked to avoid triggers, and to present to her general practitioner in the event of a new breakout. Expert dermatological input could then be organised as required.

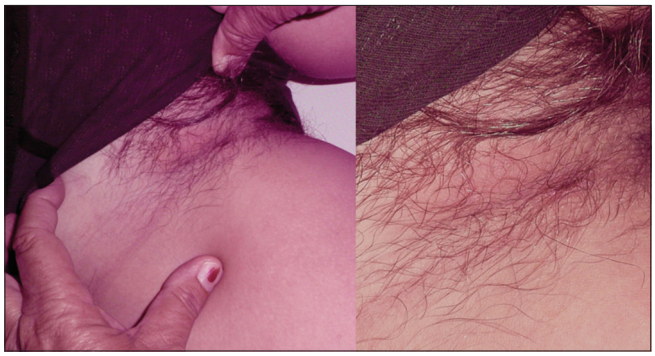

Figure 1: The patient's right groin abscess as seen from above (left) and closer up (right). The original lesion was much more florid and erythematous. These pictures were taken when the patient returned for her ultrasound the following day – she had already commenced taking antibiotics at this stage. The patient's mother (hands) helped to show us the lesion. Images reproduced with kind permission from the patient and her mother.

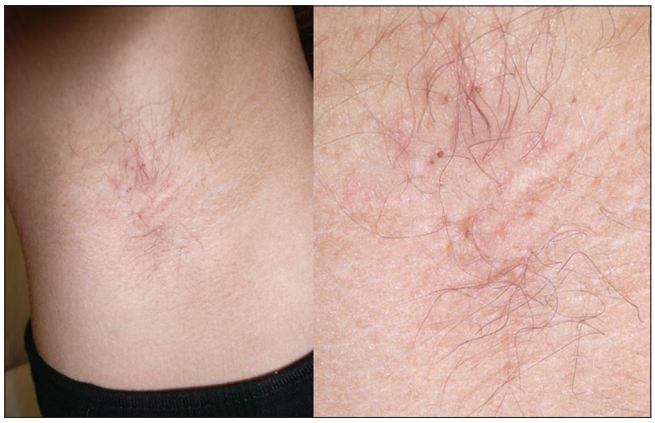

Figure 2: The patient's right axilla showed minimal grade scarring from previous attacks of hidradenitis.

DISCUSSION

Although the exact pathogenesis of hidradenitis suppurativa remains to be understood, the development of the condition appears to be greatly influenced by a number of genetic and environmental factors. Notch pathway signalling defects brought on by loss of function mutations in gamma-secretase proteins like presenilin enhancer 2 (PSENEN), presenilin-1 (PSEN1), and nicastrin (NCSTN)are known to be associated with familial cases of the disease [3], and similar deficiencies have been implicated in follicular and skin appendage abnormalities in mice [4]. Activated innate immunity is also prolonged by Notch signalling defects, and this correlates with the chronic inflammatory nature of the disease [4]. All this indicates that Notch pathway signalling defects are central to the pathogenesis of hidradenitis suppurativa, but is there any causal explanation for such defects in Down's syndrome?

A convincing answer to this question was given by Blok and colleagues in June of last year [2], when they hypothesised that the missing link between hidradenitis suppurativa and Down's syndrome (Trisomy 21) may in fact be explained by the potential overexpression of amyloid precursor protein (APP), whose gene is located on chromosome 21. In line with the 'gene dosage effect' hypothesis – that is that the phenotypical features of Down's syndrome result from the overexpression of specific genes on chromosome 21 [5]–, the authors suggest that excess APP levels in the epidermis could engender the hyperkeratosis and follicular plugging typical of hidradenitis suppurativa. Furthermore, they show how a functional decline in Notch signalling can be brought on by excess APP as it competes against Notch receptors for active binding sites on gamma secretase. The contributions of obesity and Down's syndrome induced immune dysregulation are also listed as possible causal associations in these patients.

Our patient was not obese. She had mild mental retardation and a history of recurrent ear infections. She also had acquired hypothyroidism related to her Down's syndrome but there was no other significant

medical history. Although her symptoms were relatively mild, the case further supports the possibility of a real association between hidradenitis suppurativa and Down's syndrome. It was only through curiosity that this association was questioned and given the relative triviality of such considerations in emergency and other generalist departments, one wonders if there haven't been many other cases like this one which have gone by undiagnosed and therefore unreported.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Our Dermatology Online

Case Report

Dermoscopy of shagreen patch: A first report

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ABSTRACT:

The name is derived from French phrase peau chagrinee which is usually found on lower back, buttock and thigh. The major manifestations of Tuberous sclerosis include skin lesions in more than 95%, mental retardation in approximately 50%, autism, seizures in approximately 85%. The incidence at birth is estimated to be 1 in 5800. We report case of shagreen patch in a 27 year female which is present since birth. However there is no history of seizures or consanginous marriage in our case. Associated features are naevus comedonicus and naevus collagenosis, facial angiofibroma. Shagreen patch are present in mandibular area of face. Although, diagnosis is easy, it can be mistaken for inflammatory verrucous epidermal nevus, plaques of other inflammatory skin conditions. Diagnosis is usually on clinical background. Sometimes biopsy is necessary to confirm the diagnosis. Dermoscopy, a non-invasive, in vivo technique for the microscopic examination of pigmented skin lesions, has the potential to improve the diagnostic accuracy. Dermoscopy of Shagreen patch showed reddish-brown strands with white dots giving a cobblestone appearance It can be utilized as a diagnostic aide in the diagnosis of Shagreen patch. Authors evaluated the dermoscopic patterns of Shagreen patch and hence, it is useful in diagnosis.

Key words: Dermoscopy; Shagreen patch; Tuberous sclerosis; Reddish-brown strands, White dots

INTRODUCTION

Shagreen patch (SP) was first described by Hallopeau and Leredde in 1895. Since then it has been reported to be present in 20-50% of cases of tuberous sclerosis [1].

SP is a connective tissue nevus that presents as a firm to rubbery irregular hyperpigmented rough plaque ranging in size from 1 to 10cms. The surface may resemble the surface of an orange peel. It is commonly located over the back, buttocks, thighs and nape of neck [1,2].

Although, diagnosis is easy, it can be mistaken for inflammatory verrucous epidermal nevus, plaques of other inflammatory skin conditions. Diagnosis is usually on clinical background. Sometimes biopsy is necessary to confirm the diagnosis [3].

Dermoscopy, a non-invasive, in vivo technique for the microscopic examination of pigmented skin lesions, has the potential to improve the diagnostic accuracy [4]. It can be utilized as a diagnostic aide in the diagnosis of SP. Authors evaluated the dermoscopic patterns of SP and hence, it is useful in diagnosis.

CASE REPORT

A 22 year unmarried female patient presented with skin lesions. Patient was born from non-consanguineous parents. Lesions appeared at the age of 2years on right ramus of mandible and pre-auricle. Examination revealed a thick brownish-black pigmented plaque measuring 7x4 cm extending from right ramus of mandible to the upper part of the neck on right side (Fig. 1). There were angiofibromas on the face. There were no periungual fibromas, café-au lait macules, forehead plaques or hypopigmented patches. She had a normal psychomotor development and there was no history of convulsions, mental retardation. Magnetic resonance imaging was performed to exclude other potential manifestations of tuberous sclerosis (TS). Provisional diagnosis of tuberous sclerosis was made.

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Dermoscopy of SP showed reddish-brown strands with white dots giving a cobblestone appearance (Fig. 2 and 3). Skin biopsy was taken from mandibular lesion and histopathology showed papillomatosis and dense collagen bundle in the dermis (Fig. 4).

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

DISCUSSION

Dermoscopy patterns in inflammatory, melanocytic, non-melanocytic lesions correspond very much to the histological features [5].

It was utilized only for evaluation of melanoma in the past. Recently usage of dermoscopy in the diagnosis, differential diagnosis and monitoring of ectoparasitic, infectious and inflammatory skin diseases has been documented [6,7].

Hence, dermoscopic study of skin lesions will reveal histopathological changes with specific pattern and therefore, are helpful in the diagnosis of skin condition.

Cutaneous lesions are very characteristic and help in the early diagnosis of TS which is an autosomal dominant disorder characterized by seizures, mental retardation and skin findings, including congenital hypomelanotic macules and facial angiofibromas and SP [1].

SP is one of the major diagnostic features of the disease. Its frequency is less as compared to facial angiofibromas [8]. SP represents a collagenoma.

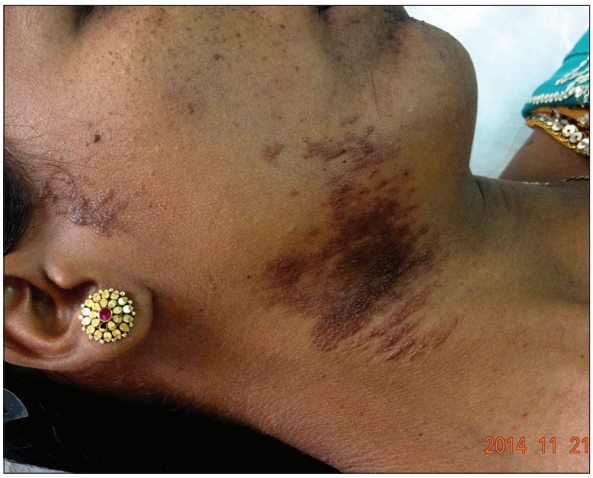

Figure 1: Clinical image of shagreen patch on the right ramus of mandible.

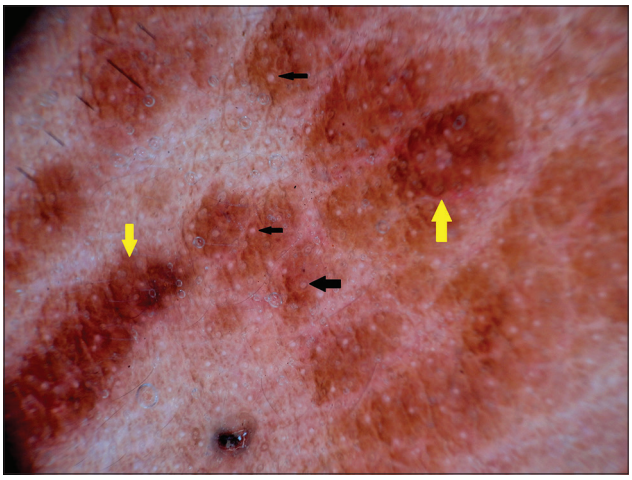

Figure 3: Dermoscopy showing white dots (black arrows) studded in reddish-brown strands (yellow arrows).

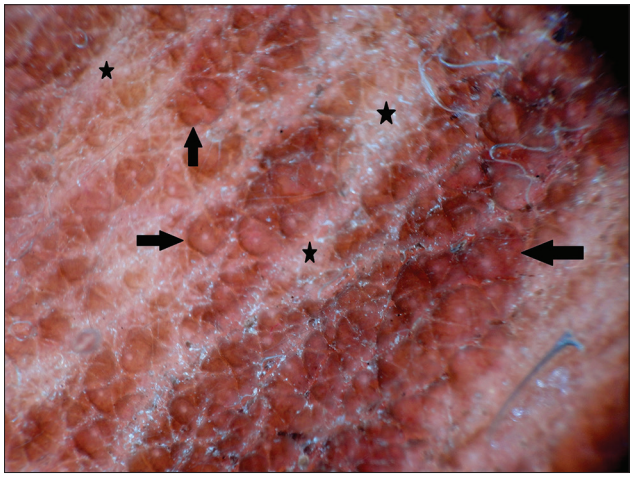

Figure 2: Dermoscopy showing linearly arranged reddish-brown strands (black arrows) with whitish lines in between (black stars) giving a cobblestone appearance.

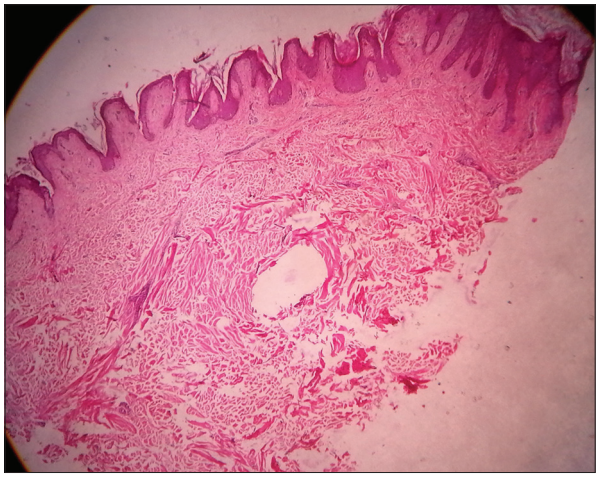

Figure 4: Histopathology showing papillomatosis, dense collagen bundles in the dermis. Acanthosis was present at some places, (H & E, x10).

Dermis is replaced by thick collagen bundles and elastic fibers are typically absent. Fibroblasts are large and morphologically atypical [1]. Diagnosis of SP becomes impossible especially when it occurs in rare site without other signs of TS. In one report, authors observed SP in daughter and her mother over the face [9]. Therefore, SP occurring on rare sites makes it difficult to diagnose. In the present report, SP was situated on right mandible and on pre-auricle. In such scenario, biopsy is a must to prove the diagnosis. Dermoscopy can be used to diagnose SP. Till now dermoscopic patterns of SP are not described in the literature.

In the present study, authors observed reddish-brown strands on the ridges of skin lines appearing as cobblestone. They were arranged linearly with whitish lines in between which correspond to furrows of skin lines The linear strands were studded with regularly spaced white dots. The reddish-brown strands correspond to papillomatosis as well as dense collagen bundles in the dermis. White dots correspond to eccrine sweat duct openings on skin surface. Hence, dermoscopic patterns are specific and correspond well to histopathological changes of SP.

To conclude, dermoscopy shows specific patterns in SP and these patterns corresponds to the histological changes. Hence, dermoscopy enables dermatologist to diagnose SP without doing biopsy. To the best of our knowledge, this is first report of dermoscopic pattern in SP in the literature.

CONSENT

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

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Source of Support: Nil, **Conflict of Interest:** None declared.

Our Dermatology Online

Case Report

Dermoscopy of apocrine hydrocystoma: A first case report

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ABSTRACT

Apocrine hydrocystoma (AH) is a translucent, skin-colored to bluish dome shaped cyst on the face. AH mimics basal cell carcinoma (BCC), blue nevus, amelanotic melanoma requiring histopathological confirmation. Dermoscopy shows specific patterns in skin conditions. Dermoscopy of AH is not described in the literature. Authors evaluated dermoscopic patterns in AH and observed characteristic patterns corresponding to histological features. To the best of our knowledge, it is a first report in literature.

Key words: Dermoscopy; Apocrine hydrocystoma; Whitish strands; Histopathology; Patterns

INTRODUCTION

Apocrine hydrocystoma (AH) typically presents a translucent, skin-colored to bluish dome shaped cyst on the face, although it occurs in other sites [1]. It is not uncommon and occurs in adult life with no predilection for particular age group. Males and females are equally affected [2]. AH mimics basal cell carcinoma (BCC), blue nevus, amelanotic melanoma requiring histopathological confirmation [3].

Dermoscopy, a non-invasive technique shows specific patterns in skin conditions corresponding to histopathological changes and hence can be utilized in the diagnosis of melanocytic and non-melanocytic lesion [4]. Dermoscopy of AH is not described. Here, we evaluated dermoscopy of AH which showed characteristic patterns corresponding to histological features. To the best of our knowledge, it is a first report in dermatology literature.

CASE REPORT

A 56yr female presented with asymptomatic skin lesion on the right cheek since 6months. Examination revealed skin colored translucent nodule measuring about 1x1 cm. Consistency was soft to firm (Fig. 1). Systemic examination was unremarkable. Blood analysis was within normal limits. Provisional diagnosis of AH, nodular BCC, pilomatricoma was made. Dermoscopy of the lesion was done using polarized dermoscopy and it demonstrated arborizing telengiectasia, brown pigment globules and whitish strands across the tumor (Figs. 2 and 3). Excisional biopsy was done and histopathology showed cystic dilatation of tumor and dilated blood vessels in the dermis. Cyst wall was lined

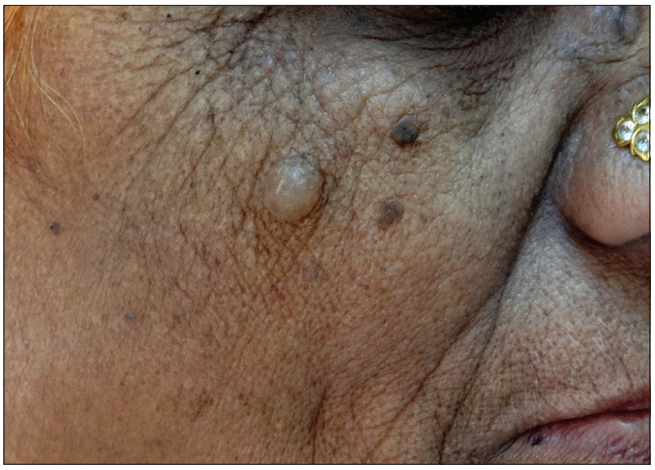

Figure 1: Skin colored translucent tumor on the right cheek.

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by cuboidal cells with decapitation secretion into the lumen (Figs. 4 and 5). The histopathological features were consistent with AH.

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

DISCUSSION

Dermoscopy is a noninvasive diagnostic technique and it was being employed for the purpose of diagnosis as well as screening of melanoma in a melanocytic lesion. Recently, its applications are expanded and it is being utilized in infectious, parasitic and inflammatory skin conditions [5].

As AH mimics other benign and malignant skin tumors including basal cell carcinoma and malignant melanoma, early diagnosis and treatment is of great importance.

In present study, dermoscopy of AH showed brown pigment globules arranged in a haphazard pattern, arborizing telengiectasia and whitish structures traversing across the tumor resembling tree branches.

Brown pigment globules observed under dermoscopy correspond to the melanin in the rete ridges or in the epidermis and they follow a particular pattern in each condition. In melanocytic nevus, globules are in network pattern, in BCC, there is absence of pigment network and regression of pigment is observed in melanoma [6]. However: in AH, it was not following

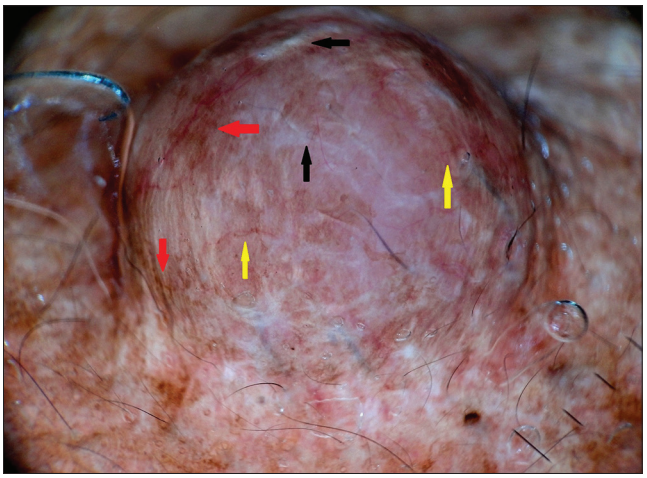

Figure 2: Dermoscopy showing brown pigment globules (red arrows), telengiectasia (yellow arrows) and whitish strands (black arrows).

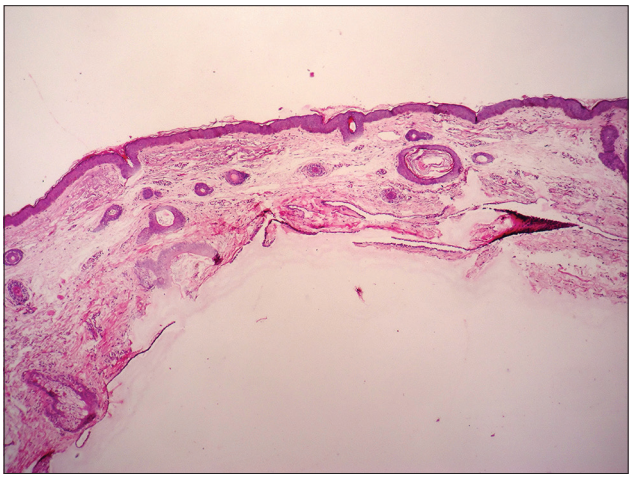

Figure 4: Histopathology showing cystic dilatation of tumor (H& E, 4x).

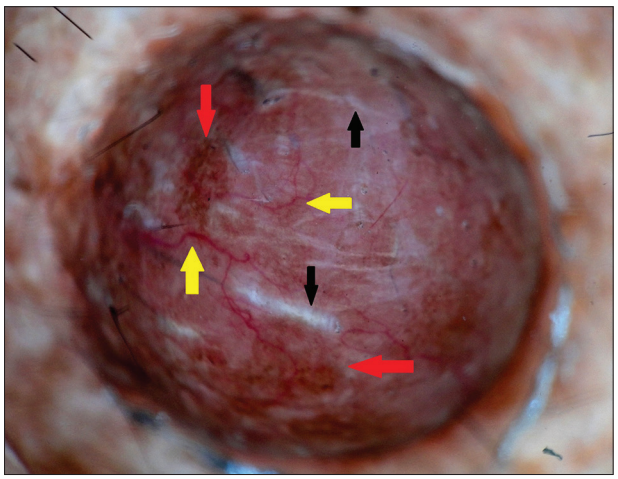

Figure 3: Dermoscopy showing haphazard arrangement of brown pigment globules (red arrows), arborizing telengiectasia (yellow arrows) and horizontal whitish strands across the tumor (black arrows).

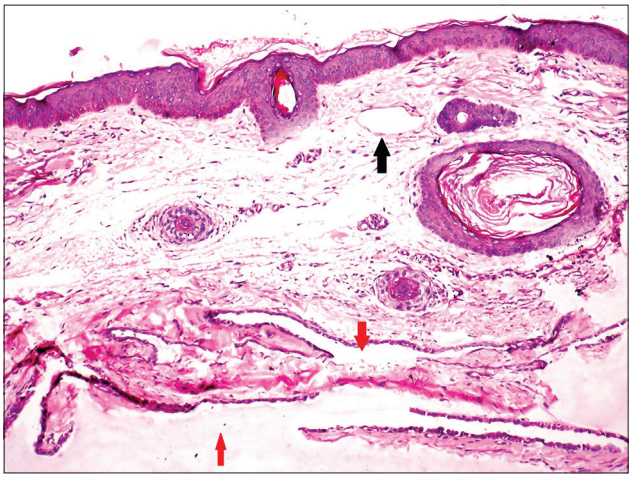

Figure 5: Histopathology showing cyst is lined by cuboidal cells with decapitation secretion (red arrows) and dilated blood vessels (black arrow) (H&E, 10x).

any specific pattern. Authors believe that irregular pattern of globules in AH may be because of stretching of epidermis as a result of cystic dilatation of tumor.

Telengiectasia represent dilatation of blood vessels in the dermis [7]. In AH, they were arborizing from base of tumor. Arborizing telengiectasia are also a feature of BCC. However other dermoscopic features such as leaf-like structures, milia-like cysts, erosions and blue-grey nests are characteristic of BCC [8]. They appear as 'hair-pin' pattern in keratinized lesion like warts [6]. And they are referred as 'crown vessels' because of their location in sebaceous hyperplasia due to pushing of vessels to the periphery by hypertrophic sebaceous glands [8]. Hence, dermoscopic patterns of blood vessels give a clue to the diagnosis.

Whitish strands or white chrysalis strands represent either fibrous septa or dense collagen in the dermis [6]. In pyogenic granuloma, whitish strands are in 'white rail lines' fashion surrounding reddish homogenous areas [9]. In dermatofibroma, they follow 'star burst' appearance at the centre [6]. In morphea and lichen sclerosis et atrophicus whitish structures are seen as chrysalis strands [10]. Therefore dermoscopy depicts the histological process. Furthermore, it indicates possible histological changes and enables clinical visualization with appropriate color and pattern.

CONCLUSION

Dermoscopy is a rapidly evolving diagnostic method in dermatology practice. Though, it is a simple technique, it adds dimensions in clinical diagnosis making better dermatologists. Dermoscopy of AH demonstrates specific patterns which are helpful in diagnosis. Hence, authors recommend use of dermoscopy in daily practice. However, it is first observation; further studies involving large sample size are recommended.

CONSENT

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

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Source of Support: Nil, **Conflict of Interest:** None declared.

Our Dermatology Online

Case Report

Nevoid acanthosis nigricans: a rare case with late onset

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ABSTRACT

Nevoid acanthosis nigricans is a rare variant usually presents as a localized hyperpigmented velvety plaque at birth or before puberty. However, unlike other variants, it is neither localized to the neck or flexures nor associated with metabolic disturbances, syndromes, drug toxicity, endocrinopathy or malignancy. Only a few cases of nevoid acanthosis nigricans have been reported in the literature. This 17-year-old male presented with a gradually progressive hyperpigmented, velvety plaque of nevoid acanthosis nigricans over the midline of the abdomen having a late onset.

Keywords: Nevoid acanthosis nigricans; Acanthosis nigricans; Epidermal nevus

INTRODUCTION

Acanthosis nigricans is a disorder of keratinization classically characterized by hyperpigmented velvety plaques localized mainly over neck, axillae and the inguinal folds. Depending upon the underlying systemic abnormality it has been classified as obesity-associated, benign, syndromic, malignant, acral, unilateral, drug-induced and mixed-type acanthosis nigricans. The nevoid acanthosis nigricans is a rare form which presents at birth or before puberty as a solitary well-defined hyperpigmented velvety plaque, usually localized to body areas other than those involved by classic AN and is not associated with any underlying disorder [1]. The described case is of classic nevoid acanthosis nigricans localized over the abdomen with a late onset.

CASE REPORT

A 17-year-old boy presented with a gradually progressive, asymptomatic, hyperpigmented plaque over the midline of abdomen for three months. The lesion had begun as a small hyperpigmented plaque initially over the epigastrium that gradually increased in size and progressed to reach the mid abdomen. The patient was a second child of non-consanguineous parentage and had no family history of similar lesion. He was not obese (BMI 21.4) and had no past or concurrent history of diabetes mellitus, drug intake or other associated systemic complaints. Clinical examination showed a well-defined hyperpigmented, velvety plaque with irregular margins, measuring 12 x 5 cm over abdomen extending between epigastrium and supra umbilical area with predominant left-to-midline localization (Fig. 1). There were no other lesions of similar morphology present over neck or the flexural folds. A few acneiform lesions were noted over chest. Examination for hair, nails, mucous membranes and other systems was unremarkable. Laboratory investigations including blood counts, blood glucose levels, hepato-renal function tests, thyroid function tests, growth hormone assays and urinalysis were normal. X-rays for chest, skull and long bones, and abdominal ultrasonography revealed no abnormality. A skin biopsy from the lesion revealed hyperkeratosis, papillomatosis and mild acanthosis in the epidermis (Fig. 2). There was mild mixed inflammatory infiltrate in the upper dermis. In view of these clinicopathologic features, a diagnosis of nevoid acanthosis nigricans was made. He was prescribed topical 0.05% tretinoin gel for once daily application. The lesional thickness and

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DOI:10.7241/ourd.20153.90

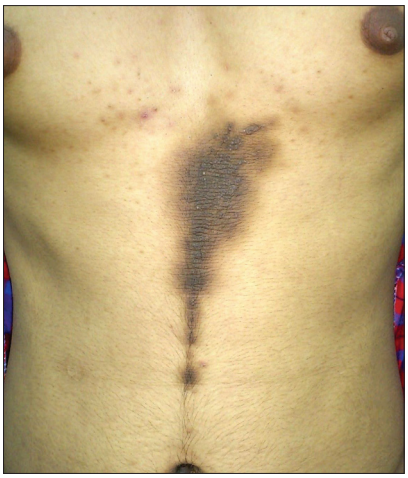

Figure 1: A well-defined hyperpigmented, velvety, plaque of typical nevoid acanthosis nigricans over abdomen extending between epigastrium and supra umbilical area with predominant left-to-midline localization.

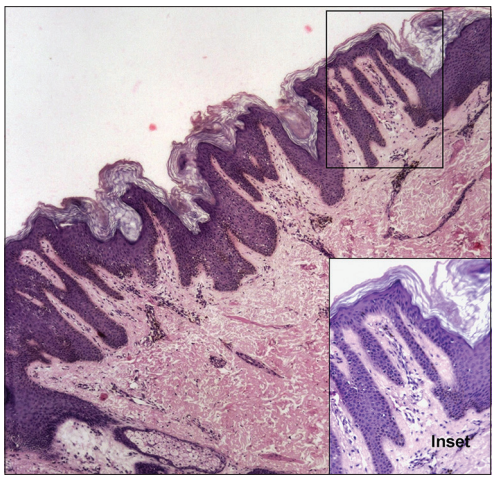

Figure 2: Epidermis shows mild hyperkeratosis with basket weave appearance, mild acanthosis, elongated rete ridges and prominent papillomatosis with minimal inflammatory cell infiltrate in papillary and upper dermis, (H&E, x10, Inset x40).

pigmentation decreased to some extent after 2 months of therapy. He did not turn up further.

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

DISCUSSION

Nevoid acanthosis nigricans is a rare dermatosis usually presenting as a solitary, localized lesion over body. It may present at birth, during childhood or appear at puberty. The exact underlying pathomechanism in the development of nevoid acanthosis nigricans remains speculative. It has been postulated to be inherited irregularly as an autosomal dominant trait and the mosaic expression of activated growth factor receptors in keratinocytes has been hypothesized to play a role in its pathogenesis [1-3]. Clinically, it appears as a well-defined hyperpigmented, velvety plaque resembling classic acanthosis nigricans without any flexural predisposition while chest, abdomen, umbilicus, retroauricular area and the submammary area being the predominant sites of involvement in most cases [1-5]. Occasionally it presents along the lines of Blaschko. It may enlarge initially but tends to remain stable or may even regress over time. The closest differential diagnosis is epidermal nevus but acanthosis nigricans lesions are usually more velvety and histologically show mild compact hyperkeratosis, papillomatosis, and limited acanthosis as compared to epidermal nevi. The affected individuals often seek treatment for cosmetic reasons. However, no therapeutic recommendations exist. Some workers have noted efficacy of topical tretinoin that largely remains unevaluated for paucity of cases [1,5]. This patient exhibited more or less similar clinical and histologic features of typical nevoid acanthosis nigricans exhibiting partial improvement with topical tretinoin before he stopped follow up.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Case Report

Pachyonychia Congenita type 1 – A peerless entity

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ABSTRACT

Pachyonychia congenita (PC) is a rare Autosomal dominant genodermatosis characterized by hyperkeratosis affecting the nails and palmoplantar areas, oral leucokeratosis, and cystic lesions. Although classically subdivided into two major variants, PC-1 (Jadassohn-Lewandowski syndrome) and PC-2 (Jackson-Lawler syndrome), according to the localization of the mutations in the KRT6A/KRT16 or KRT6B/KRT17 genes, respectively. We report a 10 year-old male patient with a history of thickened, discoloured nails, raised spiny skin lesions all over the body since birth with focal plantar keratoderma and absence of natal teeth.

Key words: Jadassohn-lewandowsky syndrome; keratins; nails; pachyonychia congenita; palmoplantar keratoderma

INTRODUCTION

Pachyonychia congenita (PC) describes a group of rare autosomal dominant skin disorders characterized predominantly by dystrophic, thickened nails and painful and highly debilitating palmoplantar hyperkeratosis [1,2]. With a base on phenotypes, PC is classified in four types: PC I to III and PC tarda [3,4]. The objective of this case report is to describe the clinical features of PC-I.

CASE REPORT

A 10 year-old male born at preterm to non consanguineous parents was referred to our outpatient clinic for evaluation of thickened nails starting at the age of 6 months.

The boy had been born prematurely at 34 weeks' gestation after premature contractions and prolonged rupture of membranes. No maternal fever, tachycardia, chorioamnionitis, or other complications had occurred. The boy had stayed in neonatal intensive care for 4 weeks because of feeding issues, and he had been transiently on nasal continuous positive airway pressure therapy, from which he was weaned to room air after 3 days of life. He was discharged at 38 weeks' gestation. He presented with history of pinhead-sized yellowish spiny skin lesions all over body noted at birth that had slowly grown during the first year of age and abnormalities nails. No history of natal or neonatal teeth. The patient intelligence was normal. No similar complaints in family.

Physical examination showed

1. All 20 nails were thickened, yellowish discolouration with increased curvature and subungual hyperkeratosis (Fig 1).
2. All toe nails were thickened, dystrophy, yellowish discolouration and subungual hyperkeratosis (Fig. 2).
3. Skin: Multiple follicular discrete papules present over the face, neck and upper chest (Fig. 3).
4. Multiple hyperkeratotic papules present over the back of neck, back of chest , buttock and elbow (Fig. 4).
5. Focal plantar keratoderma (Fig. 5).

There were no abnormalities in examination of otolarynx and ophthalmology.

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DOI: 10.7241/ourd.20153.91

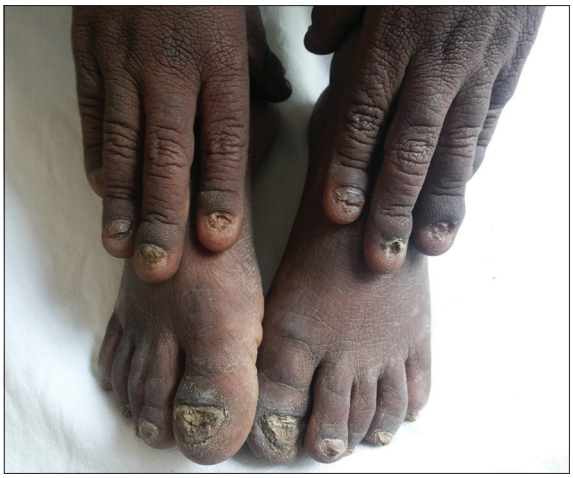

Figure 1: 20 thickened nails, yellowish discolouration with increased curvature and subungual hyperkeratosis.

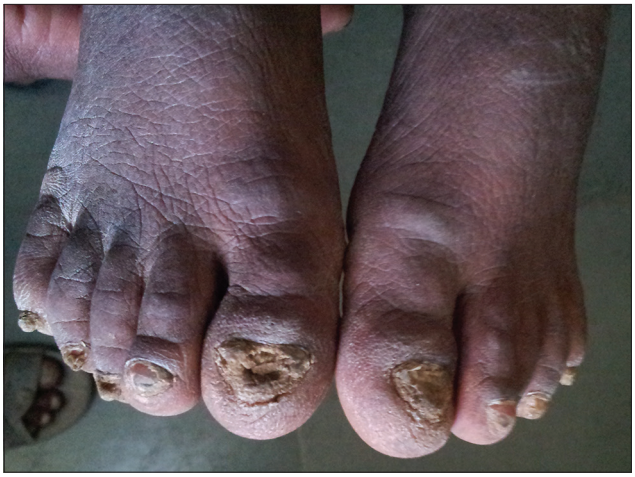

Figure 2: 20 thickened nails, yellowish discolouration with increased curvature and subungual hyperkeratosis.

Figure 3: Multiple follicular discrete papules present over the face, upper chest, buttock, elbow, knees and flexures.

All laboratory investigations were within normal limits. KOH mounts of toe and finger nails were negative for fungal elements. Histopathology examination of

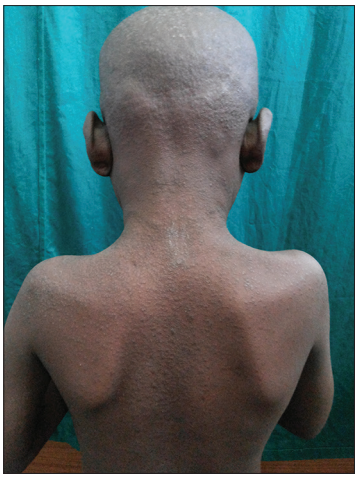

Figure 4: Multiple follicular discrete papules present over the face, upper chest, buttock, elbow, knees and flexures.

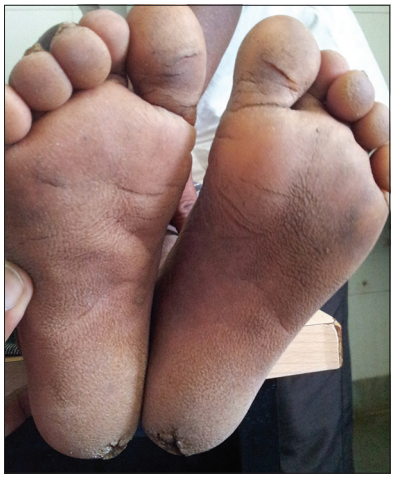

Figure 5: Focal plantar keratoderma.

Follicular keratotic papule showed follicular plugging, hyperkeratosis and acanthosis. Skin biopsy of Sole showed marked hyperkeratosis, acanthosis, moderate hyper granulosa's and minimal dermal inflammatory infiltration. Based on characteristic clinical findings and histopathology features, diagnosis of pachyonychia congenital type1 or Jadassohn - Lewandowsky syndrome.

Pachyonychia congenita (PC) is a rare, autosomal dominant disorder characterized by triad of subungual hyperkeratosis with accumulation of hard keratinous material beneath the distal portion of the nails, lifting the nails from the nail bed, keratosis palmaris et plantaris with thick callosities, especially on the soles and thick white areas on the oral mucosa [5]. Other associated features which may occur include keratosis pilaris, hyperkeratotic follicular papules on the sites of friction, hair abnormalities and hyperhidrosis of the

palms and soles. These disorders have been suggested to be due to mutations in paired keratins, K6a/K16 (in PC1) and K6b/K17 (in PC2). According to these mutations, various clinical variants have been described:

PC-I or Jadassohn - Lewandowsky syndrome (MIM #167200) is a common entity characterized by onychogryposis on all the digits (100%), hyperkeratosis of the palmo plantar (50-90%) and of extensor areas, follicular keratosis (37%), oral (50-75%) or laryngeal (6-15%) leukokeratosis, acral hyperhidrosis (20-75%) and blisters (36%) [2-7,8,9].

In patients with PC-II or Jackson- Lawler syndrome (MIM #167210) main changes are natal or neonatal teeth (15-50%), cutaneous cystic lesions (25%), disorders in scalp and eyebrow hairs (9-25%), in addition to corneal dystrophy (8%); moreover, the nail hyperkeratosis is less accentuated in PC-II than in PC-I [3,6,7,8,9].

PC-III (Schafer-Brunauer syndrome) shows ccombined features of type 1 and 2 with angular cheilosis, cataract and corneal dyskeratosis. [4]. Despite recent advances in genetic analysis, Misdiagnosis can occur because same mutations may show diverse features [10].

A fourth variant, PC *tarda*, has also been described and is characterized by a later onset that ranges from late childhood to middle ages.

Other rare variants include pachyonychia congenital with only nail involvement. Patients with PC often present at birth or soon after with the characteristic hypertrophic toenail dystrophy [11].

Pathogenesis

Keratins are structural proteins that promote the integrity of epithelial cells. As a result mutations in the genes encoding keratins lead to cell fragility [1,12]. The skin expresses the largest number of keratin genes of any organ in body. PC is caused by mutations in 5 keratin genes *KRT6a*, *KRT6b*, *KRT6c*, *KRT16* and *KRT17*which are expressed only in palmo plantar skin, the nail bed, pilosebaceous unit and oral mucosa, leading to selective involvement of these sites in PC [1,13,14].

Genetic Diagnosis

PC is an autosomal dominant disorder, which has been reported worldwide with approximately equal prevalence in males and females. More than 45% of cases appear spontaneously with no family history of PC [11]. Given the overlapping clinical presentation with other genetic disorders, only genetic testing can confirm the PC diagnosis.

With nearly 100 distinct PC mutations now identified, correlating the signs of PC with specific mutations and genes has led to a new classification system of PC. While in the past, PC has been classified according to phenotypic features into PC-l and PC-2, the disorder is now classified into 5 subgroups corresponding to the underlying genetic defect: PC-K6a, PC-K6b, PC-K6c, PC-K16 and PC-K17 [11,13].

Histological Findings

Histological examination of plantar hyperkeratosis plaques reveals an acanthosis epidermis with parakeratosis and orthokeratosis compatible with rapid keratinocyte proliferation and differentiation. Cytologic atypical is not seen.

Immunostaining shows positive immune staining of K14, as would be expected along with K6, K16, K17 in the basal cell layer. In the supra basal layers, K6, K16, K17, and K14 staining persists and K10 staining appears [14,15].

Electron microscopy on palmar or plantar plaques shows thickened and clumped intermediate filaments, as well as enlarged keratohyaline granules. In the broadened granular layer, thick masses of monofilaments and large, irregular keratohyaline granules are present. In the spinous layer, thick masses of monofilaments are found at the periphery of the cells.

Complications like respiratory distress due to laryngeal leucokeratosis and acroosteolysis, malignant changes in palmoplantar lesions can occur in pachyonychia congenital.

Treatment

Treatment options for PC fall into four broad categories:

1. Non- invasive (mechanical) e.g. abrasion with some hand tool
2. Invasive (surgical) e.g. electrofulgration, excision
3. Chemical methods using urea, propylene glycol, alpha hydroxy acid
4. Pharmacological (vitamin A, retinoid), all basically targeted at reducing the hyperkeratosis involving different sites [16].

When the familial mutation is known, genetic counselling can be done and if required, prenatal diagnosis can be done at early stage of pregnancy by chorionic villi biopsy. In our case we advised keratolytics and oral isotretinoin.

CONCLUSION

PC is a rare genetic disorder for which there are very few therapeutic options are available. Free genetic testing is provided to each patient through the International Pachyonychia Congenita Research Registry(IPCRR) sponsored by the PC Project (www.pachyonychia.org) which is a non-profit USA public charity, supports clinical and research activities related to the treatment of pachyonychia congenital. By building a patient community through the IPCRR and a physician and researcher community through the IPCC, PC Project is moving research forward to better understand the condition and to develop effective treatments.

In India we don't have such projects working on PC. With this case, we intend to draw attention to this condition and the role of the dermatologist in the diagnosis. To our best of the knowledge this represents the first report of isolated PC in siblings with healthy parents.

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CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Case Report

Infantile Haemangioma – An unusual location

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ABSTRACT

Infantile haemangiomas (IH) are benign vascular neoplasms that have a characteristic clinical course marked by early proliferation and followed by spontaneous involution. Haemangiomas are the most common tumours of infancy and usually are medically insignificant. Cutaneous haemangiomas at particular sites is more common at Head and neck followed by Trunk and Extremities. Extra cutaneous haemangiomas were more common in Liver, Gastrointestinal tract, Larynx, Central nervous system, Pancreas and Lungs. We represent an 8-month-old boy presented with a small but growing, strawberry-colour tumour over the right groin since birth.

Key words: Cutaneous vasculature; Groin; Haemangiomas; Vascular malformations

INTRODUCTION

A "haemangioma"(Greek for blood-vessel-growth) of Infancy is a benign overgrowth of blood vessel cells in the skin. It is also known as proliferative haemangioma because it is due to proliferating endothelial cells; these are the cells that line blood vessels. The incidence ranges from 1% in neonates to 12% [1]. These are known to appear soon after birth, proliferate for 8-18 months, and then slowly regress over the next 5-8 years, leaving behind normal or slightly blemished skin [2,3].

Haemangiomas are common birthmarks which are usually red or purple. They mostly occur on the head and neck areas and develop shortly after birth.One in 10 babies will develop a haemangioma and it is more common in girls.In literature of Dermatology, groin has been cited unusual site of occurrence.

CASE REPORT

An 8-month-old boy presented with a small but growing, strawberry-colour tumor over the right side of the groin. The mass had been present since birth, now measuring approximately 4 × 3 cm of Circular in shape. The parents were concerned about the tumours growth and appearance.

The boy had been born prematurely at 34 weeks' gestation after premature contractions and prolonged rupture of membranes. No maternal fever, tachycardia, chorioamnionitis, or other complications had occurred. The boy had stayed in neonatal intensive care for 4 weeks because of feeding issues, and he had been transiently on nasal continuous positive airway pressure therapy, from which he was weaned to room air after 3 days of life. He was discharged at 38 weeks' gestation. When the child had reached approximately 6 months of age, he had begun to scratch the haemangioma and rub it against toys and other items, resulting in severe ulceration of the lesion. The parents were anxious about the tumour's rapid growth, and bleeding from minor trauma.

On admission, a thorough physical examination showed tumours growth of oval to circular in shape with diameter of 4 × 3 cm with red in colour over the right side of groin (Figs 1 and 2). Single linear ulcer with well defined borders of size 1cm was seen over tumourous growth. No other areas of body affected.

The possible differential diagnoses are
1. Cherry Haemangioma
2. Cobb Syndrome
3. Lipomas
4. Capillary Malformation

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5. Lymphangiomas
6. Lobular Capillary Haemangioma)

Routine Laboratory investigations followed by electrocardiogram, chest x-ray and local ultrasonography of the lesion using a high frequency probe. Laboratory investigations were within normal limits.

After discussing with parents and with their consent, Punch biopsy was performed.

Histopathological examination of the specimen showed the Para keratinised stratified Squamous epithelium of varying thickness and the fibrous connective tissue with numerous endothelial lined capillaries of varied size and few blood vessels, which were yet to be lumenized (Figs 3-5). Tumour of the blood vessels of capillary calibre (no elastic fibres nor smooth muscle within the wall, size is variable) and undifferentiated endothelia. Diagnosis of capillary haemangioma was confirmed.

After evaluating the boy and noting the haemangioma location and because of parent's anxiety and apprehension the boy was referred to paediatric surgery.

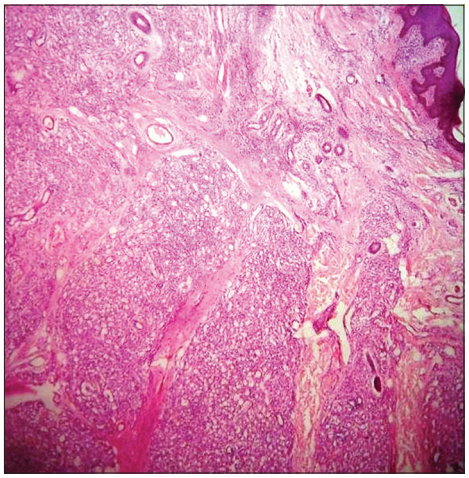

Figure 3: Para keratinised stratified Squamous epithelium of varying thickness and the fibrous connective tissue with numerous endothelial lined capillaries of varied size.

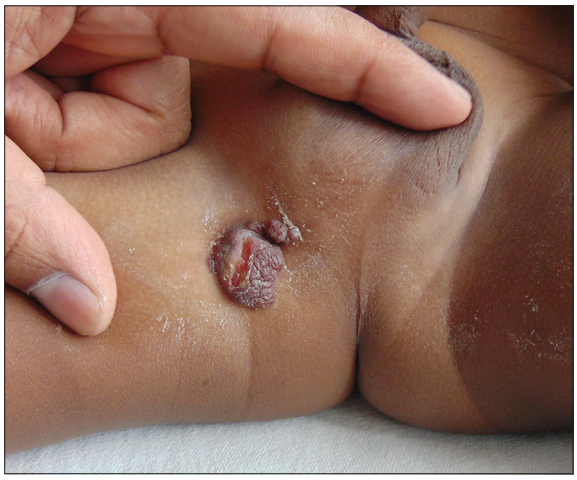

Figure 1: Multiple tumorous growth over right side of groin

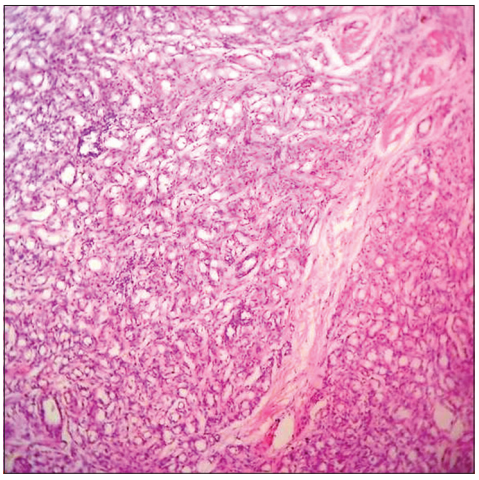

Figure 4: Fibrous tissue in between capillaries.

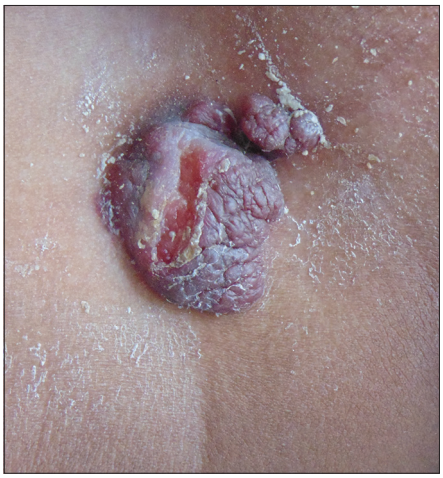

Figure 2: Linear ulcer with well-defined border over tumorous growth.

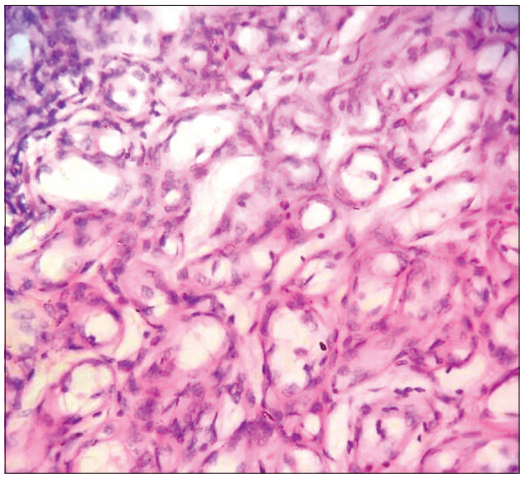

Figure 5: Endothelial cells lining capillaries.

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

DISCUSSION

IH is a benign, self-involuting tumour of endothelial cells that usually appears during the first weeks to months of life [4]. It is one of the most common birthmarks among newborns. Most infantile haemangiomas reach a maximum size of 0.5-5 cm, but they can range from the size of a pinhead to greater than 20cm in diameter. Most infantile haemangiomas remain well circumscribed and focal. Haemangiomas are found in up to 10% of children by the age of 1 year and are more common in girls and premature infants. Their cause is unknown. In very rare instances, they may run in families, but they generally are not inherited.

Infantile haemangiomas are classified as superficial, deep or mixed lesions.

- The superficial infantile haemangiomas is also called capillary haemangioma, capillary naevus, strawberry haemangioma, strawberry naevus, and haemangioma simplex. The blood vessels in uppermost layers of the skin are dilated.
- Deep infantile haemangiomas are also called cavernous haemangiomas and are more deeply set in the dermis and sub cutis. They appear as a bluish soft to firm swelling.
- Both types of haemangiomas may occur together in mixed angiomatous naevi. A strawberry naevus overlies a bluish swelling.

Another variant is the infantile haemangioma with minimal or arrested growth (IH-MAG). These have been previously referred to as abortive, reticular, or telangiectatic IH. This variant has been seen in association with underlying vascular and other extracutaneous congenital anomalies PHACE and PELVIS syndromes [5].

Regulators of haemangioma growth and involution are poorly understood. During the growth phase, two major proangiogenic factors are involved: basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) [6]. Potential explanations for the therapeutic effect of propranolol (a non-selective beta-blocker) on IH include: vasoconstriction, which is immediately visible as a change in colour, associated with a palpable softening of the haemangioma; decreased expression of VEGF and bFGF genes through the down regulation of the RAF-mitogen -activated protein kinase pathway [7]. The response of IH to propanolol has been reported by Léauté-Labrèze et al [8].

IH usually involutes over time: 30% resolve by 3 years of age, 50% by 5 years of age, and 80% to 90% by 9 years of age. More than half of haemangiomas heal with excellent cosmetic results without treatment. Nevertheless, some haemangiomas require treatment, such as when a vital organ (e.g. eye, ear, trachea) is involved; when bleeding, ulceration, crusting, or infection is present; or when their rapid growth leads to deformity of surrounding tissues. IH in certain areas, particularly the face (especially the nose and lips), body folds, and groin, have a higher risk of complications.

The vast majority of IH do not require any medical or surgical intervention. Medical care of clinically significant IH has been limited to a few medications, including glucocorticosteroids (topical, intralesional and oral), interferon alfa [9] and, rarely, vincristine and topical Imiquimod [10]. Beta-blockers, most specifically propanolol, [11] have serendipitously been shown to induce involution of IH [8,12] Pulse dyed laser surgery, [13] other lasers frequency-doubled ND: YAG, and KTP lasers.

Certain benefits to early surgical excision include saving a life or preserving vision if it is near to eye and decreasing the negative psychosocial effects associated with a cosmetically disfiguring lesion during early childhood.

CONCLUSION

To our best of knowledge, this is the first reported case of a capillary haemangioma occurring in this location. We describe case of capillary haemangiomas, concluding that despite the rarity of these lesions, they should be considered in the differential diagnosis of lesions in the groin region.

CONSENT

Written informed consent was obtained from the patient guardian for publication of this case report and any accompanying images. The examination of patients is conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Slim belt induced morphea-Price paid for a slimmer look

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ABSTRACT

Morphea, also known as localized scleroderma, encompasses a group of distinct conditions characterized by sclerosis of the skin and the underlying tissues. Many triggering factors have been implicated in the development of morphea like trauma, immobilization, bacille Calmette–Guérin (BCG) vaccination, injections of vitamin K, mechanical compression from clothing, etc. but slim belt as a cause of morphea has not been previously reported to the best of our knowledge. We report a 28 year old married obese woman who developed a shiny brownish indurated plaque over the abdomen after three months of use of a slim belt for her obesity. Skin biopsy was consistent with the diagnosis of morphea. She was prescribed topical tacrolimus 0.1% ointment and improved with course of time.The present case illustrates the first description of morphea as a result of use of slim belt which has not been previously reported in the literature.

Key words: Localised scleroderma; Indurated plaque; Morphea, Slim belt; Tacrolimus

INTRODUCTION

Morphea is a rare, chronic inflammatory disease of the skin and underlying tissues characterized by sclerosis of the skin, subcutaneous tissue, and in some cases involves the underlying fascia, muscle, or bone [1,2]. Although the specific etiology of morphea is unknown, several triggering factors have been recognized in the literature which include trauma [2], immobilization [3], bacille Calmette–Guérin (BCG) vaccination [4], injections of vitamin K [5], mechanical compression from clothing [6], previous radiotherapy [7], etc. The use of slim belts for abdominal obesity is becoming common in the society due to advertisements on television, newspapers, etc. Slim belt use as a cause of morphea has not been stated in the literature yet to the best of our knowledge.

CASE REPORT

A 28 year old married obese woman presented to our dermatological department with a chief complaint of shiny brownish indurated area on the left upper abdomen of one month duration. There is history of use of slim belt for her abdominal obesity for the last three months. The lesion started insidiously and progressed during this month to attain the size of four to five centimeters. It was associated with mild pruritis initially which resolved of its own. There is no history of application of any topical medication. She didn't give history of any trauma to the affected site nor any sequential colour changes of digits on exposure to cold. The patient was not taking any medication prior to this lesion and was advised by some relative to use the slim belt for her obesity. She used to wear the slim belt over abdomen for 12-16 hours a day.

On physical examination, she looked obese with a body weight of 82Kg, height 162 cm with a body mass index (BMI) of 31.29 and her waist circumference was 92 cm confirming her obesity. Review of systems was unremarkable. Dermatological examination revealed a single, shiny, 4 × 5 cm, ill-defined, brownish hyperpigmented, indurated plaque over left upper

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abdomen (Fig. 1). There was loss of appendages in the plaque. Nail fold capillaroscopy did not reveal any abnormal capillaries. Punch skin biopsy was taken from the edge of the lesion to involve the normal skin to act as control. Histopathological examination revealed atrophic epidermis with loss of rete ridges. Dermis showed mild to moderate chronic mononuclear cell inflammatory infiltrate with loss of skin appendages while deeper dermis showed bundles of dense collagen which was consistent with the diagnosis of morphea. With such a history and clinical presentation and further supported by histopathological findings, a diagnosis of morphea secondary to the use of slim belt for obesity was made. Her laboratory investigations like complete blood counts (CBC), erythrocyte sedimentation rate (ESR) and anti-nuclear antibody (ANA) were unremarkable. She was advised to avoid the use of slim belt and to use alternative treatment for her abdominal obesity. She was prescribed topical tacrolimus 0.1% ointment twice daily. Over a follow up of three months, no new lesions appeared with reduction in the skin thickening, induration and hyperpigmentation of the plaque.

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

DISCUSSION

The cause of morphea is unknown. Various triggering factors have been documented in the literature viz., trauma, immobilization, bacille Calmette–Guérin (BCG) vaccination, injections of vitamin K, previous radiotherapy [2-5,6]. In 2006, Mutsuko Ehara et al, described two female patients with generalized morphea-like lesions, whose distribution was confined to areas mechanically compressed by underclothes [6]. How did the use of electronic slim belt cause morphea in our patient is still not clear. We speculate that the constant pressure and irritation caused by the slim belt on the abdominal skin together with the generation of local heat in the electronic slim belt may have caused morphea in our patient. There are many treatment options for limited plaque morphea which include topical tacrolimus, narrowband ultraviolet light (NB-UVB) therapy, ultraviolet light A1 (UVA1) phototherapy, psoralen plus ultraviolet A light phototherapy (PUVA), topical imiquimod and combination of calcipotriol with betamethasone dipropionate [8,9]. Kroft et al studied the efficacy of topical tacrolimus 0.1% in the plaque type morphea in a randomized, double-blind, emollient-controlled study. They found that topical tacrolimus effectively decreased skin thickness, induration, dyspigmentation and atrophy when applied twice daily for duration of 12 weeks [10]. Our patient was similarly prescribed topical tacrolimus 0.1% ointment twice a day. After a follow up of three months, the plaque showed reduction in skin thickening, induration and hyperpigmentation. This is probably the first case of plaque type morphea secondary to the use of abdominal slim belt and may be in future more cases come out due to its use.

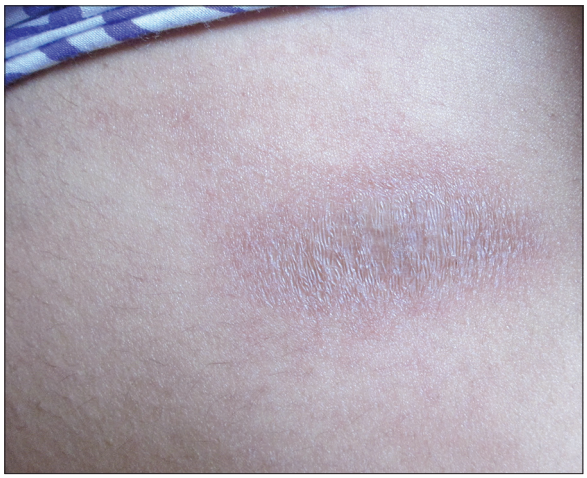

Figure 1: Morphea showing a shiny, hyperpigmented, indurated plaque over left upper abdomen

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article and any accompanying images.

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Our Dermatology Online

Review Article

Melanocytes and melanogenesis

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ABSTRACT

Pigmentation is heritable and is regulated by genetic, environmental and endocrine factors. During embryogenesis, specific cells (melanoblasts) migrate from the neural crest into the basal epithelium of the epidermis, hair bulbs of the skin and specific areas of the eye, ear and brain. There are 3 types, viz.eumelanosome, pheomelanin, neuromelanin. They have special staining methods: antigens as well as antibodies.

Key words: Eumelanosome; pheomelanin; neuromelanin

INTRODUCTION

Pigmentation is heritable and is regulated by genetic, environmental and endocrine factors [1]. Skin colour results from [1-3]:

1. Concentration and admixture of the types of melanins in melanocyte (most important),
2. carotenoid pigments,
3. the number of blood vessels in the cutis, the colour of blood in them.

EMBRYOLOGY

During embryogenesis, specific cells (melanoblasts) migrate from the neural crest into the basal epithelium of the epidermis, hair bulbs of the skin and specific areas of the eye, ear and brain [2].

Slac2-a simultaneously interacts with Rab27A on the melanosome and with an actin-based motor myosin Va, the resultant tripartite protein complex (Rab27A-Slac2-a-myosin Va) mediates actin-based melanosome transport. After actin-dependent melanosome transport, the second Rab27A effector Slp2-a promotes the anchoring of melanosomes to the plasma membrane of melanocytes through direct interaction of the C2A domain with phosphatidylserine. Melanosomes are attached to a framework of microtubules and are transported up the dendrites on ladders of actin. The little "feet" that walk up the actin fibers are called myosin 5. Melanin is transferred through dendritic processes from melanocytes to basal keratinocytes, where it is first stored and later degraded. The greater number of melanin is present in Basal keratinocytes than in the melanocytes and often basal cells at the tips of Rete ridges are preferentially more melanized. 10% of cells in basal layer are melanocytes. Each melanocyte supplies 36 keratinocytes with melanin, forming Epidermal-Melanin unit [2-4].

ANATOMY

They are located in the Basal layer of epidermis, Hair bulb and Outer root sheath of hair follicles [2-7].

Melanocytes in epidermis

Epidermal have round to oval, dark stained nuclei, smaller than those of basal keratinocytes. A clear halo of surrounding cytoplasm.

Melanocytes in hair

Melanocytes are diffentiated into

1. Differentiated melanocytes, located in the hair matrix region
2. Melanocyte stem cells, located at the lower portion of hair follicle.

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Differentiated melanocytes

They express

1. Sox 10 (Sry-related HMG box/sex determining region box 10),
2. kit,
3. mitf (micropthalmia associated transcription factors),
4. Pax 3 (paired bx 3),
5. Dct (Dopachrome tautomerase)

Melanocyte stem cells

They express only Pax 3 and Dct.

Ear

Melanins are found in Striae vascularis of Inner ear.

Eye

Melanocytes are also present in the Iris stroma in the front of Iris, Iris pigment epithelium on the back of Iris, Retinal pigment epithelium.

Adrenal glands

They are also seen in Medula and Zona reticularis.

Others

Melanin is also found in heart, liver, muscles and intestine.

TYPES OF MELANIN [4-7]

1. Eumelanin (dark brown)
2. Pheomelanin (pale red or yellow)
3. Neuromelanin (produced in dopaminergic neurons of the human substantia nigra).

Phaeomelonosomes

- They spherical in shape
- they lack TRP1, TRP2 and p-protein (TRP = tyrosine related proteins)
- they have 1/3rd the level of tyrosinase as eumelanosomes.

Eumelanosomes

- They are oval-shaped melanosomes,
- they have TRP1, TRP2, p-protein,
- they have 3 times the tyrosinase as compared to phaeomelanosomes.

Neuromelanin

Sites

1. dopaminergic neurons of Substantia nigra,
2. locus ceruleus,
3. dorsal motor nuclei of vagus nerve,
4. median raphe nucleus of Pons.

They are located in the lysosomes and are made from oxy-radical metabolites of mono-amines neurotransmitters such as Dopamine and Norepinephrine.

LABORATORY METHODS FOR STAINING OF MELANIN

1. Fontano-masson method

Melanin granules reduce ammoniacal silver nitrate to metallic silver [6-14].

2. Schmorl's method

Melanin has ability to reduce Ferricyanide to Ferrocyanide which in presence of Ferrous ion forms Prussian blue [6-14].

3. Dopa-oxidase method [6-14]

This is the Most specific test, based on action of Dopa-oxidase upon Dopa.

4. Bleaching technique

Using strong oxidising agents like KMnO4 or Hydrogen peroxide [6-14].

5. Formaldehyde-induced fluorescence

Formalin fixation imparts a strong yellow fluorescence to unstained tissues with biogenic amines [6-14].

6. PAS (Periodic acid schiff)

Pseudomelanin (melanosis coli) is PAS +ve while true melanin is PAS –ve [6-14].

ANTIGENS AND THEIR RESPECTIVE ANTIBODIES

Antigens are [7-13]:

a. S-100 proteins
b. gp 100

c. Melan-A/MART-1
d. Tyrosinase
e. PNL 2 Antigen
f. MITF

Antibodies are [7-13]:
a. Anti-S-100
b. HMB 45
c. A 103/M2-7C10
d. T 311
e. PNL 2 Antibodies
f. D 5

Melanogenesis

TYR Gene (located in the long arm of chromosome 11 i.e chr 11 q 14 - q 21) is involved in melanogenesis [13-17].

Genes involved in development of melanoblast

The genes/transcription factors involved in melanogenesis are Pax3, Sox10, Mitf, Edn3(endothelin 3), Ednrb (endothelin receptor B), Kit (c-Kit tyrosine kinase receptor), Kitl (Kit ligand/asSCF/steel factor) and Snai2 (also called as Slug) [13-17].

Sites of melanogenesis

Melanosomes are synthesised in [13-18]:
1. mammalian skin melanocytes,
2. choroidal melanocytes,
3. retinal pigment epithelial (RPE) cells in the eye.

Steps of melanin synthesis

The survival and migration of neural crest-derived cells [13-19]

It is dependent on interactions between specific receptors on the cell surface and their extracellular ligands. For example, FGF, steel factor, formerly known as mast cell growth factor, KIT ligand or stem cell factor (SCF), binds the KIT receptor on melanocytes and melanoblasts. Mutations in the KIT gene decrease the ability of the KIT receptor to be activated by the steel factor.

Differentiation of melanoblasts into melanocytes [13-19]

When melanoblasts reached epidermal-dermal junction, it is differentiated into melanocytes at around sixth month of fetal life.

Survival and proliferation of melanocytes [13-19]

Melanocytes have been identified within fetal epidermis as early as 50 days of gestation. Dermal melanocytes decrease in number during gestation and virtually disappear by birth. Epidermal melanocytes established at the epidermal-dermal junction continue to proliferate and start to produce melanin.

Formation of melanosomes and production of melanins [13-19]

Melanocytes start producing melanosomes, highly organized elliptic membrane-bound organelles in which melanin synthesis takes place.

BIOCHEMICAL EVENTS

The Tyrosine, under the influence of Tyrosinase and CU^{2+} forms DOPA and then Dopaquinone. This Dopaquinone with the help of Cystathione or Cysteine, forms Cysteine-L-Dopa which further forms pheomelanin. When Cysteine is depleted, the Dopaquinone forms Leucodopachrome which ultimately forms eumelanin. The ratio of these two types of Melanin determines visible pigmentation. The variation in skin color among various races is determined mainly by the number, melanin content and distribution of melanosomes produced and transferred by each melanocyte to a cluster of keratinocytes surrounding it [17-21].

STAGES OF MELANOSOMES

Stage 1

Melanosomes are spherical endosomal vacuoles lacking tyrosinase (TYR) activity (the main enzyme involved in melanogenesis) and have no internal structural components. No melanin is present yet. They contain the melanosomal protein Pmel17, which is sorted into intraluminal vesicles (ILVs) within the organelle. A partial clathrin coat is seen which is involved in sorting proteins into ILVs of vacuolar endosomes. The presence of Pmel17 gives rise to the structurally important intraluminal fibrils that characterise stage II melanosomes [13-20].

Stage 2

Melanosomes are ellipsoidal, around 0.5 micro-mm diameter. At this point, the presence and correct processing of Pmel17, an important melanosomal structural protein, determine the transformation

of stage I melanosomes to elongated, fibrillar organelles known as stage II melanosomes. They contain MELANOSOMAL enzymes tyrosinase TYRP1. They exhibit minimal deposition of melanin. Melanin is deposited within cross-linked longitudinal filaments. Enzymes activity is localised in surrounding membrane. Tyrosinase and TYRP1 are trafficking to melanosomes from early endosomes. They are present in tubular endosomal domain.Tyrosinase- and TYRP1-positive endosomal membranes have buds that are coated with the adaptor proteins AP1 or AP3, which play roles in sorting tyrosinase and TYRP1 to melanosomes [13-20].

BLOC1 and BLOC2 (protein complexes) plays important role in the regulation of endosome-to-melanosome transport.

a. BLOC1 –They are located in the tubular regions on early endosomes and control the exit of cargo from early endosomes.
b. BLOC2 – They regulate subsequent step i.e. the direction of cargo to maturing melanosomes.

Stage 3

Melanosomes are ellipsoidal. Melanin deposition increases by enzymatic activity and non-enzymatic polymerization. The pigment is uniformly deposited on the internal fibrils [13-20].

Stage 4

Melanosomes are ellipsoidal. Melanosome is fully developed and is filled with electron-opaque organelles. Melanin production is through polymerization.

Key protein involved in melanosome assembly is NCKX5, encoded by the gene SLC4A5 [13-20].

FACTORS INFLUENCING MELANOGENESIS

1. Genetics and endogenous factors

Migration, proliferation, differentiation and survival of melanocytes is influenced by tyrosine kinase receptor KIT and its ligand stem cell factors [7-9,11-16].

Microphthalmia transcription factor (MITF) is a nuclear protein involved in:

1. embryonic development of melanocytes,
2. regulation of transcription of genes involved in melanin synthesis e.g 'mi' gene located at chromosome 3p

The two Rab27A effectors are Slac2-a (also called melanophilin) and Slp2-a; they are abundantly expressed on melanosomes and sequentially regulate melanosome transport in melanocytes. TGF-beta suppress melanogenesis by inhibiting activation of Pax3. P 53 promotes melanogenesis by suppressing TGF- beta, upregulation of alpha-MSH and KITL. E-cadherin (mediating cell-to-cell interaction) also regulates melanocytes. Dermal fibroblast is also involed in regulation of melanocytes. Notch signalling in melanocytes, an essential cell-to-cell interaction mechanism, regulates processes such as cell proliferation, cell fate decision, differentiation or stem cell maintenance [7-9,11-16].

2. Environmental or exogenous factors

(A) UV Rays

UVA Cause immediate dark pigmentation within minutes and persists for several hours. Followed by persistent pigment darkening, which occurs within several hours and lasts for several days. UV exposure leads to increase expression of MITF (master transcriptional regulator of pigmentation) and its downstream melanogenic proteins, including Pmel 17, MART-1, TYR, TRP-1,Dct. Thereby, leading to increase in melanin content. It also increases levels of PAR 2 (Protease activated receptor) in keratinocytes which increases uptake and distribution of melanosomes by keratinocytes in the epidermis. It also increases Alpha-MSH, endothelin and ACTH which upregulate MC-1R, thereby enhancing melanocytes response to melanocortins. It also incre ases IL-1 secretion by keratinocytes, stimulating secretion of ACTH, Alpha-MSH,SCF, NGF Endothelin-1 and hFGF by keratinocytes. UV-R also causes peroxidation of lipids in cellular membranes, leading to generation of ROS, which may stimulate melanocytes to produce excess melanin [7-9,11-17].

(B) Retinoic acid

It upregulates differentiation and proliferation of melanocytes through melanocortins receptors.

(C) Other exogenous factors

- vitamin D metabolites - retinoids
- forskolin (extract from Indian coleus plant)
- cholera toxin

- isobutyl-methyl-xanthines
- di-acylglycerol and its analogues

3. Endocrine factors

The endocrinal products and substances responsible for melanogenesis are CRH (Corticotropin-releasing hormones), UROCORTINS (CRH-like neuro-peptide), POMC (Pro-opio-melanocortin), ACTH, alpha-MSH And beta-ENDORPHIN [7-9,11-16].

Mechanism of action of melanocytes

Melanocyte acts on Melanocyte-receptors thereby activating signaling pathways [7,9,11-16,19-21].

1. Melanocyte-receptors are:
   - MC1R,
   - Melatonin receptor,
   - G-protein-coupled receptors – Frizzled 5
   - Receptor Tyrosine kinase- c-Kit,
   - Hepatocyte Growth factor (HGF).
2. Signalling pathways involved in actions of melanocytes
   - RAS/RAF/MEK/ERK pathway,
   - PI3K/AKT pathway,
   - Notch signalling pathway.

Role of melanocytes

Melanocytes or melanin [4,7,8,10,12-16,21,22].

- Gives skin colour,
- Protects skin from UV-induced skin damaged and skin cancer,
- Development of striae vascularis of cochlea and production of Endocochlear potential thereby helping hearing function,
- Absorb toxic substances in the inner ear,
- Maintain proper hair colour,
- Role in eye color,
- In CNS, different stressors, like chemicals, oxidative damage and high temperature are also suppressed by melanin,
- Melanocortins have effects on appetite and sexual activities.

Deleterious effects

In vitro studies, melanin reacts with DNA and is known to act as photosensitiser. In contrast to eumelanin, pheomelanin is prone to photodegradation and contribute to damaging effects of UVR because it can generate Hydrogen peroxide and superoxide anions and may cause mutations in melanocytes. Pheomelanin is associated with higher rates of apoptosis after UVR. Pheomelanin increases release of Histamine, thereby contributing to sun-induced erythema and oedema. Pheomelanin is UVA sensitiser that cause cell death [4,7,8,10,12-16,21,22].

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Our Dermatology Online

Clinical Image

A case of Hailey-Hailey disease

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We report a 48 year-old man with a family history of hailey-hailey disease who had outbreaks of rashes and blisters of the neck, axillary (Fig. 1) and inguinal folds. These lesions were recurrent every year. The histological examination of skin biopsy revealed intraepidermal and suprabasilar acantholysis (Fig. 2). Elongated papillae extend into lacunae, and a single layer of basal cells lines the villi (Fig. 3). The diagnosis of Hailey-Hailey disease was retained and the patient was treated by disulone.

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

Hailey–Hailey disease, or familial benign chronic pemphigusor familial benign pemphigus is a rare hereditary blistering skin disease. It can occur at any age but usually appears in the third or fourth decade. Clinically, it typically begins as a painful erosive skin rash in the skin folds. The lesions may come and go and usually heal without scarring. Common sites include the armpits, groins, and neck, under the breasts and between the buttocks. The genetic defect responsible has now been identified on a gene called *ATP2C1* found on chromosome 3q21-24. Usually Hailey-Hailey disease is diagnosed by its appearance and the family history. Diagnosis may require a skin biopsy. There is no specific treatment and the underlying genetic defect cannot be altered;

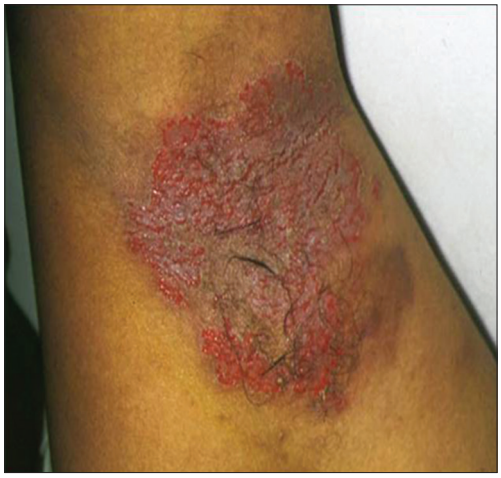

Figure 1: Erythematous and cracked plaques of the armpit.

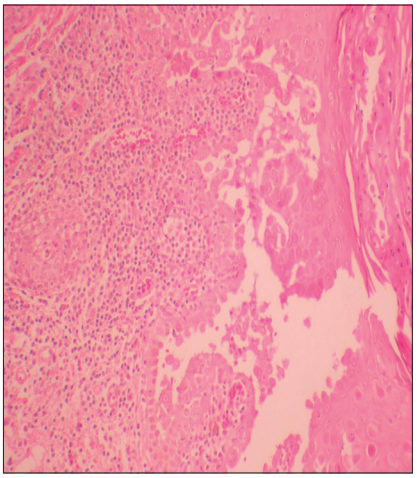

Figure 2: Intraepidermal and suprabasilar acantholysis, (HE x 20)

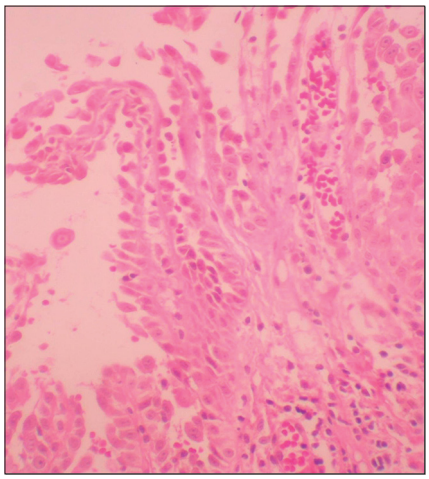

Figure 3: Elongated papillae or villi lined by a single layer of basal cells, (HE x 40)

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however, treatment does help and long remissions are common.

CONSENT

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

Source of Support: Nil, **Conflict of Interest:** None declared.

Clinical Image

Carcinoma sebace palpebral: un dilemme diagnostique [Palpebral sebaceous carcinoma: a diagnostic dilemma]

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Nous rapportons l'observation d'un homme âgé de 43 ans qui a eu une exérèse d'un nodule palpébral récidivant, diagnostiqué initialement comme un chalazion et traité par antibiothérapie pendant 3 mois sans aucune amélioration. Une exérèse de la lésion a été pratiquée. L'examen histologique de la pièce montrait une muqueuse conjonctivale massivement infiltrée par une prolifération carcinomateuse faite de lobules et d'amas séparés par un stroma fibreux, richement vascularisé, hyalinisé par endroits (Fig. 1). Les cellules tumorales étaient de grande taille, aux noyaux irréguliers parfois en mitose et au cytoplasme abondant (Fig. 2). Au centre des lobules on notait une différenciation sébacée avec de nombreuses cellules au cytoplasme vacuolisé (Fig. 3) PAS négatif. En périphérie, les cellules étaient d'aspect basaloide avec focalement une différenciation malpighienne. En immunohistochimie, la kératine 7 était diffusément positive. Le diagnostic d'un carcinome sébacé palpébral envahissant la conjonctive a été retenu.

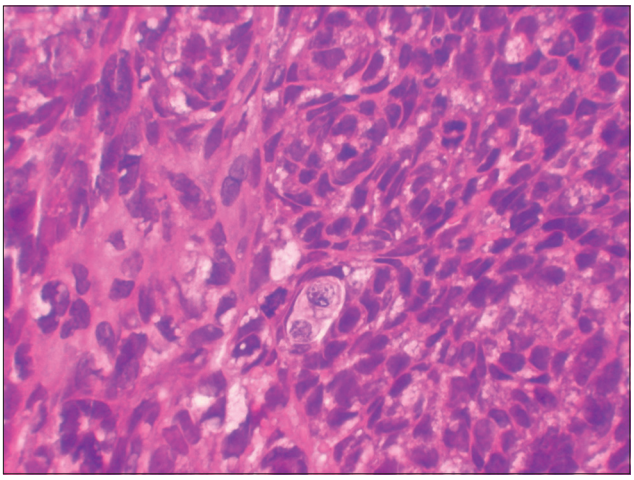

Figure 2: Les cellules tumorales sont de grande taille, aux noyaux irréguliers parfois en mitose et au cytoplasme abondant, (HE x 40)

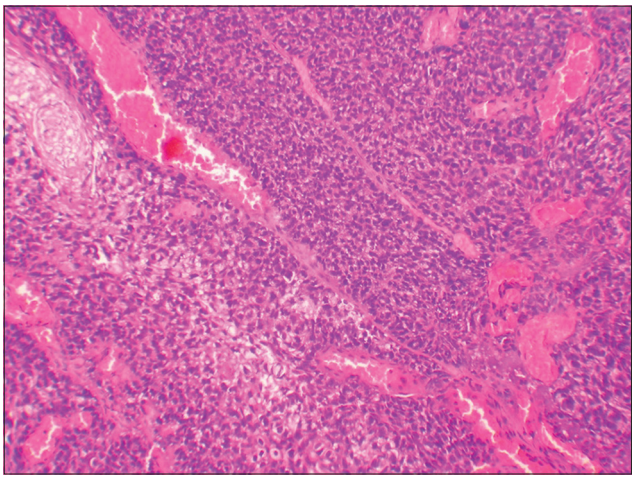

Figure 1: Prolifération carcinomateuse faite de lobules et d'amas séparés par un stroma fibreux, richement vascularisé, (HE x 20)

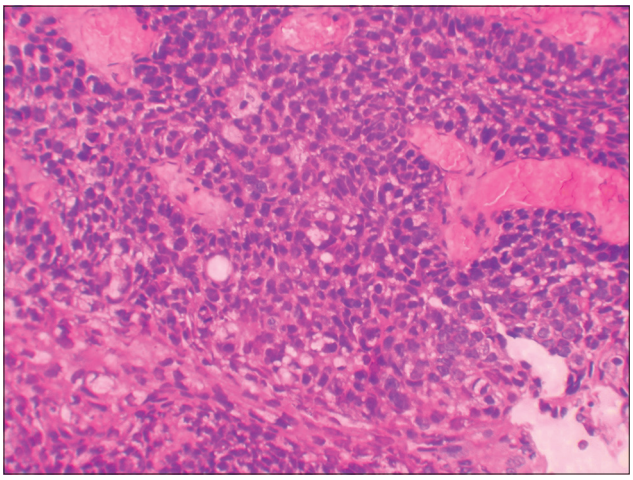

Figure 3: Différenciation sébacée des cellules qui ont un cytoplasme vacuolisé, (HEx40)

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

Bien que rare, l'atteinte palpébrale constitue un siège classique du carcinome sébacé qui doit être suspecté, en particulier devant un " chalazion " trainant et résistant au traitement médical. Le carcinome sébacé touche volontiers chez la femme avec un âge moyen de 60 ans.

La tumeur siège surtout sur la paupière supérieure sous forme d'un nodule indolore rarement ulcéré. Il peut s'agir aussi d'une lésion inflammatoire simulant un chalazion ou une blépharo-conjonctivite chronique.

Le diagnostic positif est donné par l'examen anatomopathologique des biopsies effectuées au niveau de la lésion.

Cet examen montre une prolifération organisée en lobules situés dans le derme profond et l'hypoderme sans connexion avec l'épiderme. Les cellules tumorales ont un cytoplasme clair avec un fin réseau enserrant des gouttelettes lipidiques. Les noyaux sont volumineux atypiques et mitotiques.Des cellules moins bien différenciées sont présentes en périphérie des lobules.

Histologiquement cette tumeur peut faire discuter un carcinome epidermoide ou un carcinome basocellulaire à différentiation sébacée.

Le traitement de choix est l'exérèse chirurgicale large associée à un curage ganglionnaire en cas d'adénopathie palpable.

Le carcinome sébacé est une tumeur agressive, à potentiel métastatique ganglionnaire et viscéral. Le diagnostic précoce et l'exérèse complète peuvent en améliorer considérablement le pronostic.

CONSENT

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

Source of Support: Nil, **Conflict of Interest:** None declared.

Our Dermatology Online

Clinical Image

Tubular apocrine adenoma of the axilla: A rare adnexal tumor

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We report a 52-year-old woman who presented with a painless mobile nodule of the axilla of unknown duration. The physical examination found a small, mobile, painless and circumscribed nodule of the axilla. There was no associated regional lymphadenopathy. The patient had a simple excision of the nodule.

Gross examination revealed a well-circumscribed nodule measuring 1 cm of diameter. Histologically, the tumor was composed of lobules of well-differentiated dilated tubular structures situated in the dermis and the subcutis (Figs. 1 and 2). The tubules were double-lined by an inner layer of typical apocrine epithelial cells and an outer layer of myoepithelial cells (Fig. 3). A focal ductal differentiation was noted. The intervening stroma was scanty and fibrous with minimal inflammatory cells (Fig. 1). There was no evidence of comedolike channels, hyaline, or clear cell differentiation. The diagnosis of tubular apocrine adenoma was retained. The patient received no further therapy and was well during the 3 months period after excision.

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

Tubular apocrine adenoma also called apocrine adenoma, tubulopapillary hidradenoma and papillary tubular adenoma is a rare benign tumor. It predominates in women with a sex ratio of 2:1. The wide age distribution ranges between 18 and 78 years. The scalp is most commonly affected although lesions have been described at a variety of other sites including the face, eyelid, axilla, leg, and genitalia. In the scalp, lesions often arise in a background of nevus sebaceus and may be associated with syringocystadenoma papilliferum. Clinically,the tumor generally presents as a dermal nodule 1–2 cm in diameter or pedunculated lesion, frequently of many years duration. Histologically, tubular apocrine adenoma presents most often as lobules of well-differentiated tubular structures located

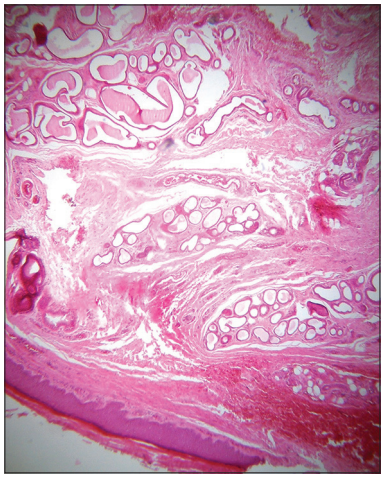

Figure 1: Lobules of well-differentiated dilated tubular structures situated in the dermis and separated by a scanty fibrous stroma

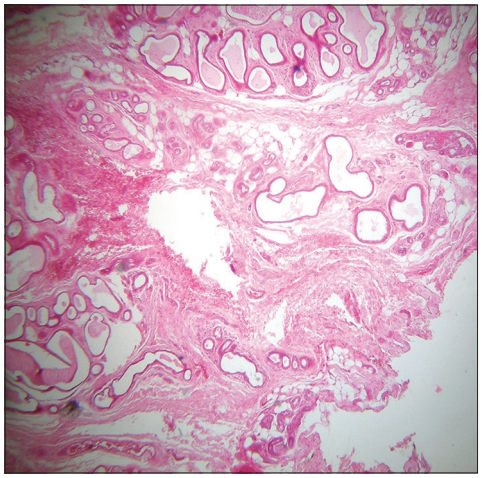

Figure 2: The tubules structures reach the subcutis

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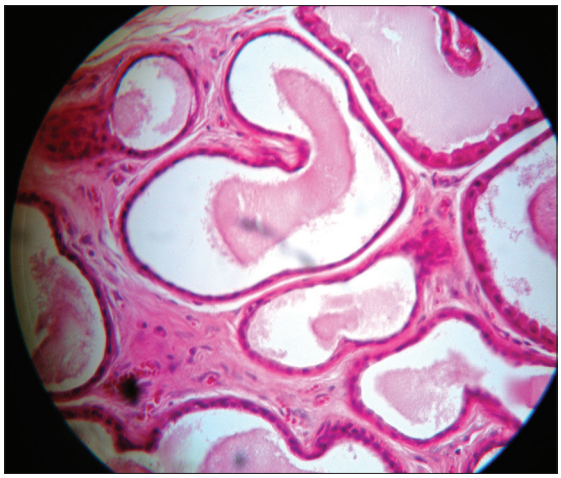

Figure 3: The tubules are double-lined by an inner layer of apocrine cells and an outer layer of myoepithelial cells

in the dermis and sometimes the subcutis. The tubules are lined by an inner layer of tall columnar cells, which show decapitation secretion, and frequently show an outer layer of cuboidal cells. Comedo-like channels that extend into the epidermis and connect with some of the tubular structures are occasionally seen. The stroma is composed of fibrous tissue with few inflammatory cells. This is in contrast to syringocystadenoma papilliferum, which contains numerous inflammatory cells in the stroma.

The tubular adenoma is benign and recurrence following excision is uncommon.

CONSENT

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

Source of Support: Nil, **Conflict of Interest:** None declared.

Our Dermatology Online

Letter to the Editor

Solitary neurofibroma

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Sir,

58 year old female with no significant past medical or family history incidentally observed to have a growth on her left fifth toe. It was soft, skin-colored, and compressible (Figs. 1 and 2). The rest of the physical examination was within normal limits.

The patient reported that five years ago she noticed that the fifth left toe starting becoming "thick" and that in the last year and a half it had increased in thickness and length, covering the entire digit. She states that it does not cause discomfort and no family members have any similar lesions.

Past medical and family history: negative.

With this clinical data, the diagnosis of a soft tissue tumor was made and the patient underwent biopsy of the lesion.

Biopsy of the lesion at scanning power shows laminar hyperkeratosis of the epidermis, slight irregular acanthosis, and a perivascular lymphocytic inflammatory infiltrate in the papillary and superficial reticular dermis (Fig. 3), in the mid reticular dermis there is an unencapsulated, poorly defined neoplasm, consisting of a symmetrically arranged proliferation of wavy spindle cells in fascicles, immersed in a fibromyxoid matrix (Fig. 4) also observed are nerve bundles which surround the subcutaneous tissue and are indeed the origin of the lesión. Higher magnification demonstrates an abundant fibromyxoid stroma, with unorganized spindle cells with wavy nuclei, basophils, and indistinct cytoplasmic borders (Fig. 5). Higher magnification shows that the wavy spindle cells are actually Schwann cells and perineural fibroblasts, interspersed with mast cells and axons in a myxoid stroma (Fig. 6).

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

This clinical case is interesting because it is a solitary neurofibroma without neurofibromatosis.

Neurofibromas are soft, rubbery, pink to skin-colored benign tumors of the peripheral nerve sheath that invaginate when central pressure is applied, known as the "buttonhole" sign [1-3]. Solitary neurofibromas

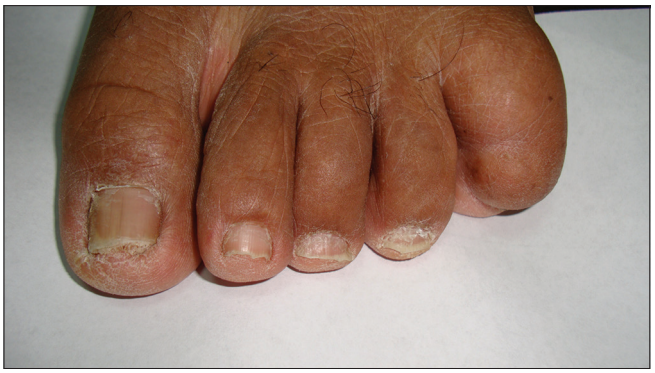

Figure 1: Panoramic view of the lesion

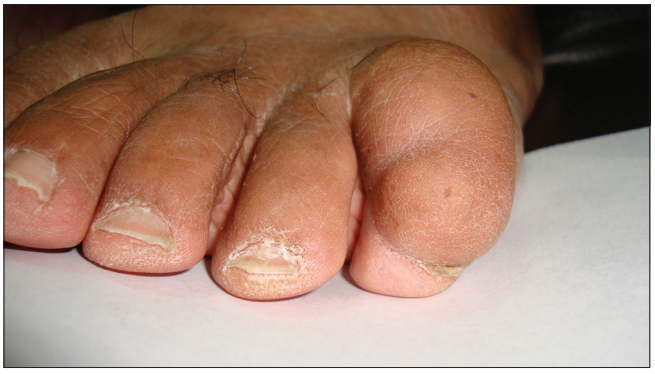

Figure 2: Closer inspection demonstrates a soft, skin-colored neoplasm spanning the length of the 5th toe

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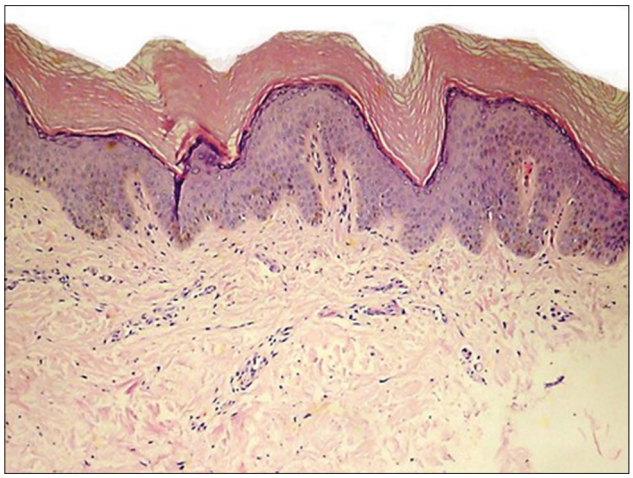

Figure 3: At scanning power, there is laminar hyperkeratosis of the epidermis, slight irregular acantosis, and a perivascular lymphocytic inflammatory infiltrate in the papillary and superficial reticular dermis

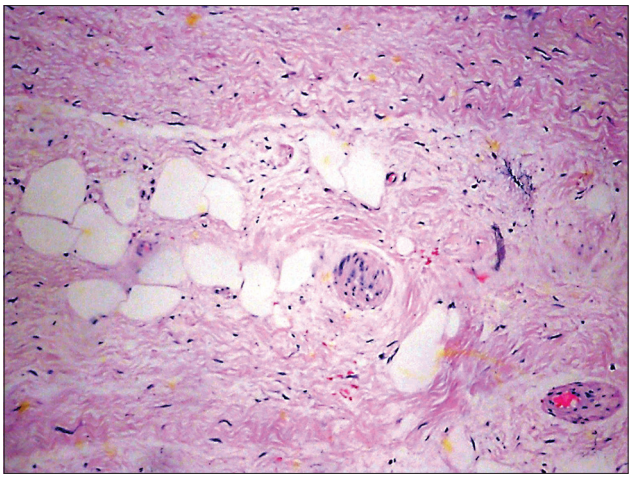

Figure 5: Nerve bundles which surround the subcutaneous tissue and are indeed the origin of the lesión. Higher magnification demonstrates an abundant fibromyxoid stroma, with unorganized spindle cells with wavy nuclei, basophils, and indistinct cytoplasmic borders

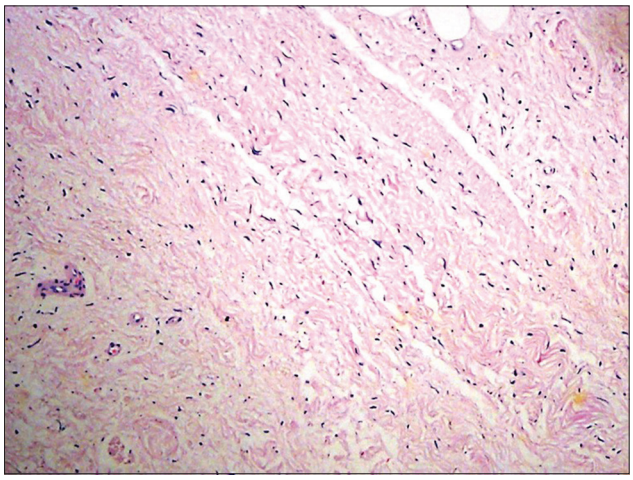

Figure 4: In the mid reticular dermis is an uncapsulated poorly defined neoplasm consisting of a symmetrically arranged proliferation of wavy spindle cells in fascicles, immersed in a fibromyxoid matrix

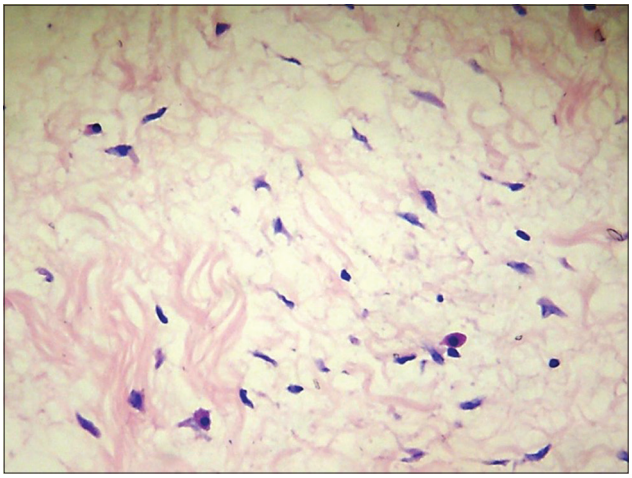

Figure 6: Higher magnification shows that the wavy spindle cells are actually Schwann cells and peri-neural fibroblasts, interspersed with mast cells and axons in a myxoid stroma

typically arise in the second or third decade of life as asymptomatic, slowly-enlarging, soft growths [4]. They may present as papules or nodules, become pedunculated over time, and more than one is present in 10% of cases. They are most commonly found on the skin of the head and neck [5]. The presence of one or two solitary neurofibromas is not usually a cause for concern, however, the diagnosis of neurofibromatosis should be considered if three or more are present. On the other hand, one plexiform neurofibroma, which mostly occurs on the trunk and proximal extremities and presents as an occasionally pigmented, bag-like mass, is pathognomonic for Neurofibromatosis 1. Neurofibromatosis types 1 and 2 are autosomal-dominantly inherited neurocutaneous disorders with a significantly increased risk of tumors in various organs.

Type 1 is more common of the two, mainly affecting the skin, skeletal, and peripheral nervous systems. Neurofibromatosis 2 on the other hand, is a very rare disorder with a low incidence of skin manifestations and a classic association with bilateral acoustic neuromas [3,6]. On biopsy, solitary neurofibromas demonstrate wavy, spindled nuclei, fine collagen fibers, and a myxoid stroma with an abundance of mast cells. Histological appearance varies according to the amount of mucin and myxoid tissue present. Cholinesterase activity, S-100, vimentin, and myelin basic protein are positive markers. Histologically and clinically, neurofibromas are identical in behavior, regardless of whether or not they are occurring as part of neurofibromatosis [7,8]. Clinically, 90% manifests

as solitary, soft, small, skin-colored, neoplasms, occasionally exceeding 6 cm in size [8]. While the clinical differential diagnosis includes dermal melanocytic nevus, schawannoma, soft fibroma, and fibrolipoma, the diagnosis of neurofibroma should be considered for all slow-growing, soft or rubbery swellings on the skin, regardless of the location [2,9]. Interestingly, there have been a handful of case reports of subungual neurofibromas, in which the differential diagnosis includes glomus tumor. Glomus tumors, however, can be distinguished from neurofibromas by the symptoms of hypersensitivity to cold, paroxysmal severe pain, and point tenderness in the involved finger or toe [10]. In addition to the skin, numerous cases of head and neck neurofibromas have been reported, including one report in the palatine tonsil. While solitary cutaneous neurofibromas are almost always benign, those of the head and neck are typically deep-seated, and have a 5-12% chance of malignant transformation [11]. Treatment of neurofibromas is indicated if symptomatic, and generally consists of surgical excision [1]. However, if the tumor is soft and small, better cosmesis may be obtained by extruding the tumor through a small punch hole [2].

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Letter to the Editor

Escherichia coli: an uncommon cause of severe urticarial vasculitis

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Sir,

Urticarial vasculitis is an uncommon clinicopathological entity with a reported prevalence of 5% wherein episodes of urticaria are accompanied by leukocytoclastic vasculitis that may be normo-complementemic or hypo-complementemic (low C1q and C4 levels, and variably decreased C3 levels) [1,2]. Bacteremia may present as leukocytoclastic vasculitis via septic emboli, immune complex injury or via bacterial seeding of vessels that causes necrosis through direct bacterial action. *Escherichia coli*, a rare cause of leukocytoclastic vasculitis, is not a well described cause of urticarial vasculitis among reported cases.

A 46-year-old male was hospitalized with widespread, intensely pruritic deep dusky red lesions, edema of hands/feet, painful left knee for 4days and no fever. Historically, a week earlier he had developed an increasing painful scrotal swelling, fever and chills. He had coalescing, dusky red and ecchymotic lesions, few having dusky erythematous wheals and central pallor, widely distributed over trunk and extremities while sparing the palms, soles and scalp (Fig. 1). His left knee had mildly painful movements without swelling. Scrotal swelling was firm, tender, and non-transilluminant. He was put on intravenous ceftriaxone (1gm twice daily), oral doxycycline (100mg twice/d), and cetirizine 10mg/d with the provisional diagnosis of epididymo-orchitis and urticarial vasculitis. Except for leukocytosis (total leukocyte count 12,900/cmm), lymphopenia (18%) and monocytosis (16%), his laboratory investigations including serum biochemistry, VDRL, HIV serology, smears from urethra and vesiculopustular lesions, chest and knees x-rays were essentially normal. Abdominal ultrasonography (USG) revealed mild hepatomegaly with prominent portal vein. Scrotal USG showed mild left hydrocele and swelling of skin overlying left testis. He became febrile (temperature 39°C) and developed fresh wheals with dusky erythema. Histology showed unremarkable epidermis, mild dermal edema and inflammatory cell infiltrate in papillary and upper dermis, and inflammatory infiltrate comprising lymphohistiocytes, neutrophils and occasional eosinophils and focal vascular endothelial swelling, fibrin deposition and nuclear dust (Fig. 2). Throat swab culture, Widals' test, ASO titre, antibodies for hepatitis A, B and C, serum cryoglobulins and complements (C3, C4), antinuclear antibodies, and rheumatoid factor were normal. He improved symptomatically after addition of prednisolone (60mg/d). Tab nitrofurantoin (100mg twice/d) was

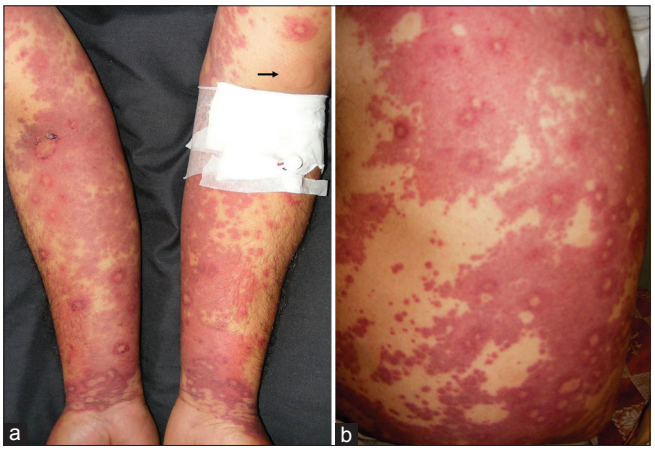

Figure 1: (a) Deep red to brown colored, coalescing, ecchymotic lesions with characteristic dusky erythema and central pallor are involving the trunk. (b) Dusky erythematous, ecchymotic, coalescing lesions with central pallor are seen over forearms. Arrow indicates typical urticarial wheal while other lesions are in various stages of resolution.

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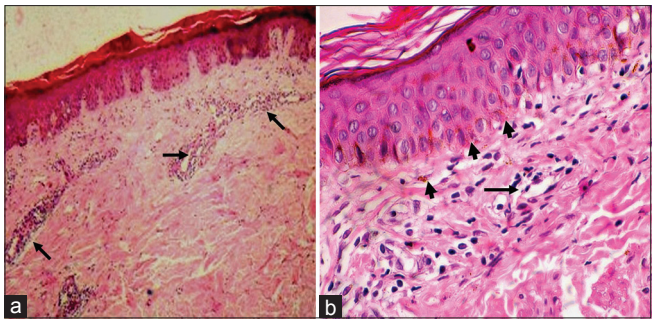

Figure 2: (a) Histology shows unremarkable epidermis, mild dermal edema and inflammatory cell infiltrate in papillary and upper dermis especially around the vessels (arrows) (H&E, x10). (b) Cell infiltrate comprises lymphohistiocytes, neutrophils and occasional eosinophils. Vessel walls show focal endothelial swelling, fibrin deposition, nuclear dust (thin arrow) and hemosiderin deposition in epidermodermal areas (thick arrows) (H&E, x40).

added after the urine culture showed *E. coli* sensitive to it. Pus culture sensitivity from surgical incision/drainage of scrotal swelling after it became fluctuant showed growth of *E. coli* sensitive to cefoperazone/sulbactum (administered intravenously 1gm twice/d for 7 days). Prednisolone was tapered off over next 2weeks as new lesions stopped. The scrotal wound was closed by secondary suturing after another 2weeks. No recurrences reported on follow up visit at 3 weeks.

Urticarial vasculitis mostly remains idiopathic or may occur secondary to connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome), serum sickness, neoplasia (leukemias, or breast, pituitary, thyroid, colon and pancreatic tumors), drugs (diltiazem, cimetidine, ACE inhibitors, antibiotics, interferon, NSAIDs, potassium iodide), and infections (hepatitis B, hepatitis C, HIV, syphilis, infectious mononucleosis, upper respiratory infections) [1,3]. Clinically, the wheals last for 48-72 hours, associated with burning, pain or tenderness, and foci of purpura and induration. Angioedema-like swelling of lips, tongue, eyelids, and hands is seen in 40% cases [2]. Resolution occurs usually with purpura or hyperpigmentation [1]. All these features distinguish urticarial vasculitis from true urticaria. Fever, malaise, myalgia, fatigue, and specific organ involvement (arthralgia, arthritis, serositis, glomerulonephritis, interstitial nephritis, Raynaud's phenomenon) are common accompaniments especially in hypo-complementemic variety [2]. Conjunctivitis and episcleritis may also occur [4]. Although response to therapy is unpredictable, antihistamines or nonsteroidal drugs (ibuprofen, naproxen) may suffice in normo-complementemic or idiopathic cases. Patients with organopathy or more severe cases may need systemic corticosteroids, hydroxychloroquine, colchicine, dapsone, azathioprine or cyclophosphamide [4]. Complications such as skin ulcers or multiorgan damage (lungs, eyes, kidneys) occur often in secondary or hypo-complementemic variety [3]. Prognosis is generally good in normo-complementemic or idiopathic cases. Spontaneous recovery may occur but some cases require intermittent treatment lasting for several years. However, the overall prognosis is often dictated by the prognosis of the underlying disease.This patient was normo- complementemic and recovered completely without recurrence after *E. coli* infection was eradicated.

CONSENT

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure. The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Source of Support: Nil, **Conflict of Interest:** None declared.

Our Dermatology Online

Letter to the Editor

Superficial thrombophlebitis mimicking cutaneous polyarteritis nodosa as an early and sole cutaneous manifestation of Behçet's disease

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Sir,

A 32-year-old woman presented to us with multiple painful nodules and erythema on her ankles which had appeared two weeks previously. She had a mild fever for previous half a year and experienced blurred vision and conjunctival hyperemia for a month, which was diagnosed as iridocyclitis. On physical examination, her ankles were swollen and tender, and irregularly-shaped erythema with unclear borders was observed (Fig. 1). Laboratory findings revealed leukocytosis in her peripheral blood and a slightly increased C-reactive protein level (5.3 mg/dl). Myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA), proteinase-3 (PR3)–ANCA, and antiphospholipid antibody were all negative. Histological examination of the erythema revealed a thrombus of a subcutaneous vessel (Fig. 2) along with dense infiltration of neutrophils, lymphocytes and their nuclear dust in the vessel wall and deposition of fibrin on the wall as well as diapedesis of red blood cells (Fig. 3). Both Elastica-Masson and Elastica–van Gieson staining showed signs of non-circumferential single-layered elastic fibers along the inner cavity of the vessel and intravascular lumen being compressed (Fig. 4). Later, we interviewed her in detail and found that she often got aphthous stomatitis. We made a conclusive diagnosis of incomplete-type Behçet's disease.

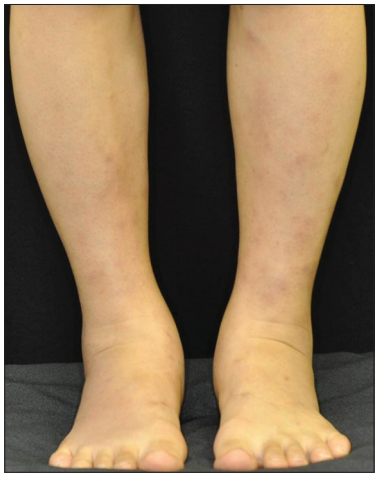

Figure 1: Irregularly shaped erythema with unclear borders on the ankles.

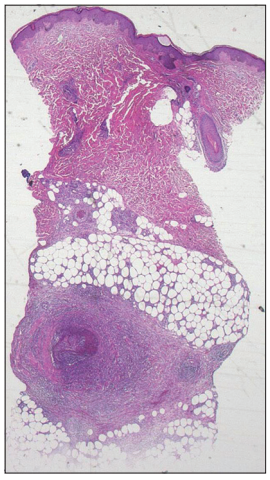

Figure 2: A thrombus of a subcutaneous vessel.

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

Our case presented with multiple painful nodules on the bilateral lower limbs. At first, we clinically diagnosed her as having cutaneous polyarteritis nodosa (cPN), and histological features were suggestive of vasculitis.

How to cite this article: Hiraiwa T, Yamamoto T. Superficial thrombophlebitis mimicking cutaneous polyarteritis nodosa as an early and sole cutaneous manifestation of Behçet's disease. Our Dermatol Online. 2015;6(3):367-368.

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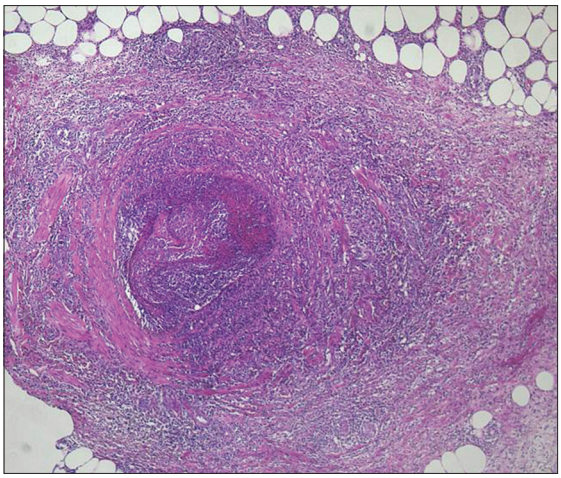

Figure 3: Infiltration of neutrophils, lymphocytes and their nuclear dust in the vessel wall with deposition of fibrin on the wall as well as diapedesis of red blood cells.

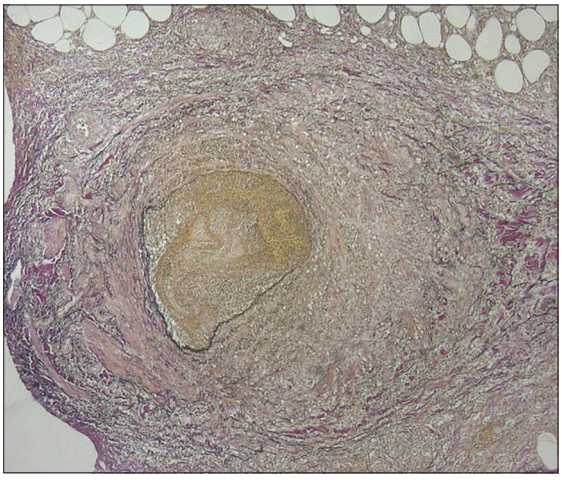

Figure 4: Non-circumferential single-layered elastic fibers along the inner cavity of the vessel and compressed intravascular lumen was revealed by Elastica-Masson and Elastica–van Gieson staining.

However, detailed examination revealed a thrombus with severe perivascular infiltration of inflammatory cells in the subcutis, and Elastica–van Gieson staining detected concentric bundles of elastic fibers between smooth muscles in veins. Prior to the onset of the cutaneous lesions, the patient had been diagnosed as having iridocyclitis. Thrombophlebitis was observed as the sole cutaneous sign, unaccompanied by aphthae, erythema nodosum, or folliculitis. Thus, we diagnosed our patient as having incomplete-type Behçet's disease.

Thrombophlebitis sometimes mimics cPN not only clinically but also histologically and is therefore easily misdiagnosed as cPN [1,2]. Chen [3] reported the main reasons for misdiagnosis, i.e. i) subcutaneous veins in the lower legs have a thick muscular layer that resembles that of the muscular veins, ii) tissue sections obtained vertically show a concentric muscular layer with a round luminal appearance, which resembles an internal elastic lamina in the muscular layer of the arteries, and iii) subcutaneous veins in the lower legs reveal intimal elastic fiber proliferation, resembling that of the arteries. Although the differential diagnosis is sometimes difficult, thrombophlebitis should be considered when diagnosing cPN in order to avoid misdiagnosis and overtreatment.

CONSENT

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

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Letter to the Editor

Inflammatory linear verrucous epidermal nevus syndrome

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Sir,

A 26-year-old male patient, who was a born of a nonconsanguineous marriage came to our outpatient clinic with a lifelong history of pruritic red, scaly lesions over left side of his body, left upper and lower limbs. His past medical and family history were unremarkable except the fact that he had been prescribed for skin lesions for several times without improvement. Upon dermatological examination, we observed multiple erythematous scaly papules coalescing into linear plaques following the lines of Blaschko on the left side of his trunk, medial aspect of his left arm and elbow, also medial aspect of his left leg down to the plantar region (Figs 1-3). The scale was obviously adherent and silvery at some points while semi-adherent in other regions (Fig. 3). It was also noticed that on the plantar region the lesion was more likely a verrucous plaque with an irregular serpiginous outline and an erythematous border. Clinical assessment of the patient implied that he had neuropsychological problems particularly mental retardation. However, the patient did not accept neither any laboratory and medical imaging procedures, nor the neurological consultation. Histopathological examination of the lesional skin biopsy revealed hyperkeratosis, acanthosis and elongation of the rete ridges with mild spongiosis in the epidermis (Fig. 4). Although we could not perform further evaluation, based on clinical and histopathological findings we made a diagnosis of ILVEN syndrome and prescribed topical keratolytics and topical corticosteroids.

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

Inflammatory linear verrucous epidermal nevus (ILVEN), is a type of epidermal nevus which is characterized by psoriasiform papules coalescing to form linear plaques following the lines of Blaschko. It is fourfold more likely to occur in females than males and although occasional isolated adult cases have been described, ILVEN most commonly appears during the first five years of life [1-3]. The etiology of ILVEN is obscure. Many hypotheses brought forward including that ILVEN is nothing but a mosaic form of psoriasis [4], and that ILVEN reflects the action of a retrotransposon which is actually a transposable DNA element that is partly expressed and partly silenced at an early developmental stage [5]. The histopathological resemblance of ILVEN to psoriasis is striking. Indeed, ILVEN appears as psoriasiform papules and plaques in a Blaschko-linear distribution. Lesions are generally on a limb, most frequently left lower extremity, although rare bilateral and widespread involvements have been described. Moreover, since CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) is characterized by unilateral erythematous verrucous lesions, infrequent reports of limb reduction in association with ILVEN have prompted the idea that ILVEN represents a forme fruste of CHILD syndrome [2,3].

On the other hand, ILVEN has been considered as a specific group within the epidermal nevi and since in about one third of cases with epidermal

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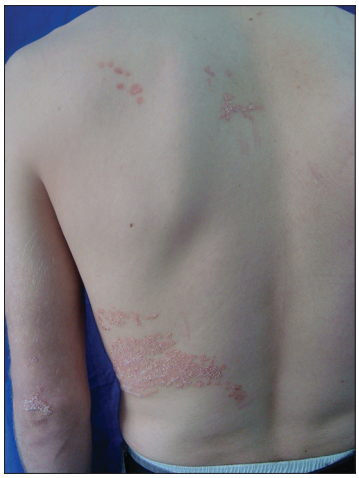

Figure 1: Erythematous papules coalescing into linear plaques following the lines of Blaschko

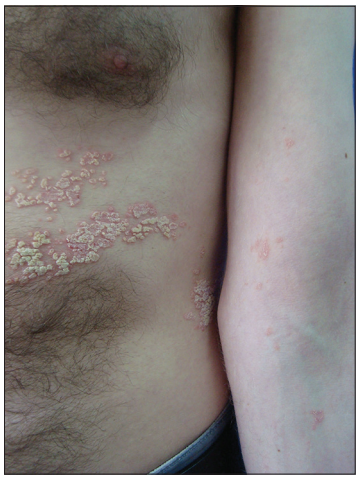

Figure 2: Psoriasiform papules and plaques in a Blaschko-linear distribution

nevi have extracutaneous manifestations, ILVEN may display other organ defects and present as a component of an epidermal nevus syndrome [6-8]. Cerebrovascular malformations, skeletal abnormalities, visceral anomalies of eye, heart and kidney have been reported in patients with ILVEN syndrome. However, CNS complications are the most common extracutaneous manifestation and among the other neurological abnormalities like hydrocephalus, cortical atrophy hemiplegia, cranial nerve palsies, intracerebral calcification and hemimegalencephaly, mental retardation is the most common one as in our case [1,6,8,9].

CONSENT

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

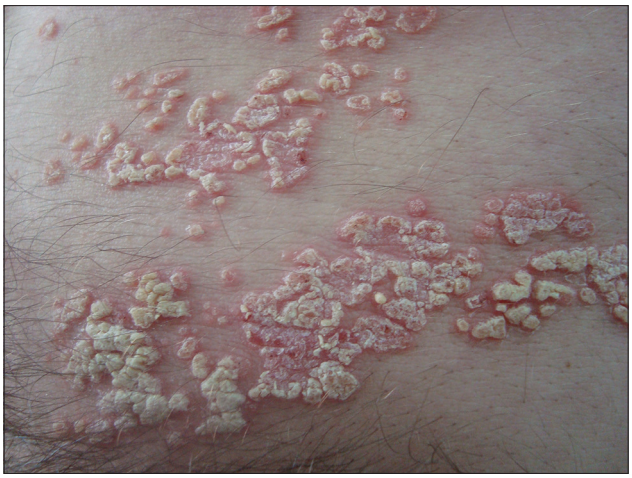

Figure 3: Blaschkoid papules in a closer view

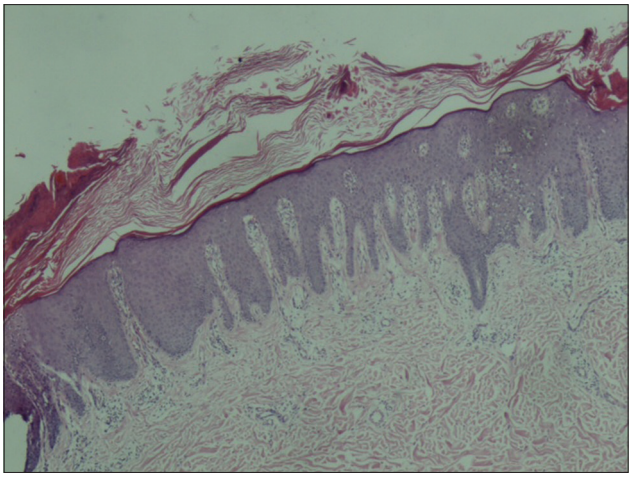

Figure 4: Histopathological findings, (H&Ex40)

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Letter to the Editor

A case of pityriasis rosea of vidal accompanied by neurofibromatosis type 1

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Sir,

A 23-year-old woman came to our outpatient clinic with a two-weeks history of pruritic reddish lesions on her armpits and groins. Her past medical history was consistent with neurofibromatosis type 1 (NF-1), for which she was under routine follow-up. Upon dermatological examination we observed multiple erythematous to violaceous coalescent and infiltrative plaques with central clearing which were annular and polycyclic in shape on bilateral proximal femoral regions (Figs 1-3) and erythematous papules tending to merge into smaller plaques on left axillary area (Fig. 4). Dermatological examination also disclosed several café-au-lait macules, one of which was greatest in diameter on left lateral brachial region and axillary freckling which was more marked on the left side (Fig. 4). A lesional skin biopsy from erythematous plaques revealed extravasation of red blood cells in dermis, dermal perivascular lymphocytic infiltration and focal spongiosis in the epidermis (Figs 5-7). Based on history, clinical and histopathological findings a diagnosis of pityriasis rosea circinata et marginata of Vidal (PRV) accompanied by NF-1 was made. The patient was prescribed topical corticosteroids and at the one month follow up visit, the lesions were significantly improved.

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

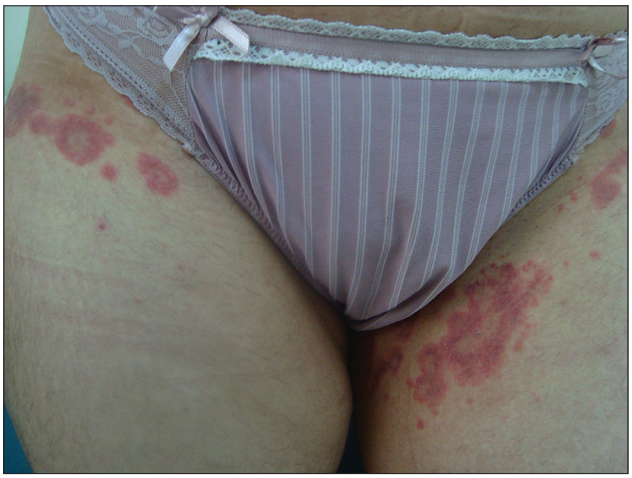

Figure 1: Erythematous to violaceous papules and confluent annular, polycyclic plaques with central clearing

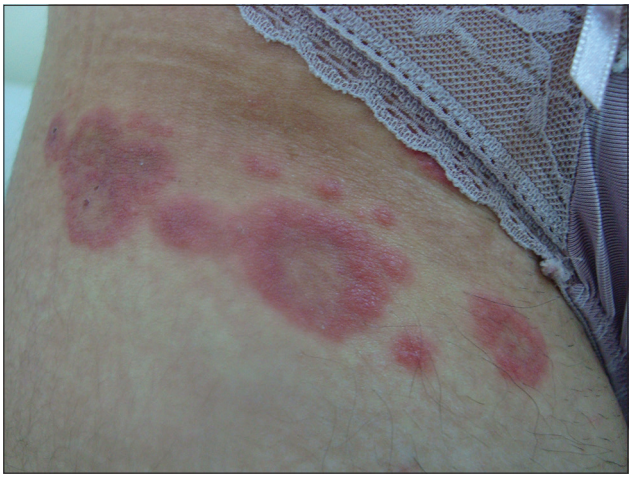

Figure 2: Coalescent plaques with indurated borders and paler central areas

Pityriasis rosea (PR) is a self-limited, acute exanthem of uncertain etiology mostly affecting children and young adults [1]. NF-1 is a common genodermatosis characterized by café-au-lait macules, neurofibromas,

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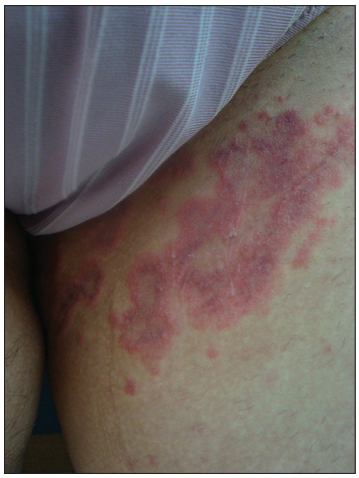

Figure 3: Confluent plaques with central paling and a fine scale in the middle of the largest plaque

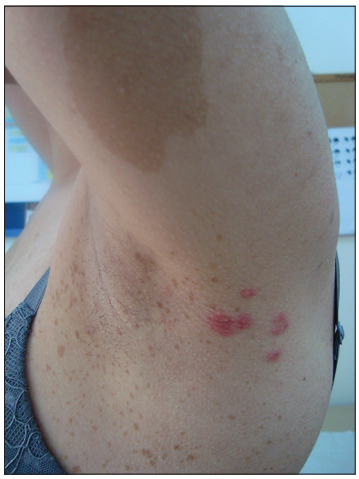

Figure 4: Erythematous papules merging into plaques, a large sized café-au-lait macule and axillary freckling

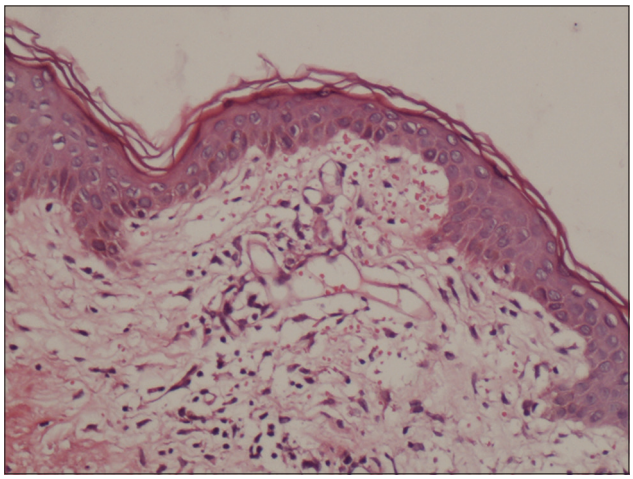

Figure 5: Erythrocyte extravasation within the dermis and superficial dermal perivascular infiltration, (H&E x200)

freckling in the axillae and groin, pigmented iris hamartomas, and skeletal abnormalities. The

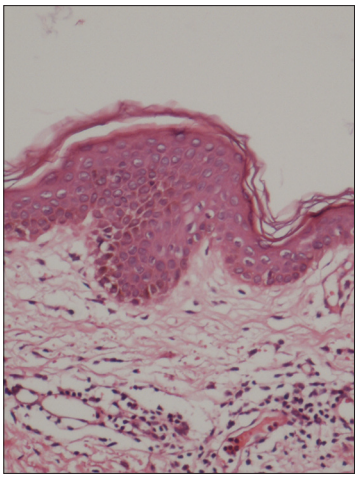

Figure 6: Focal spongiosis in the epidermis (H&E x200)

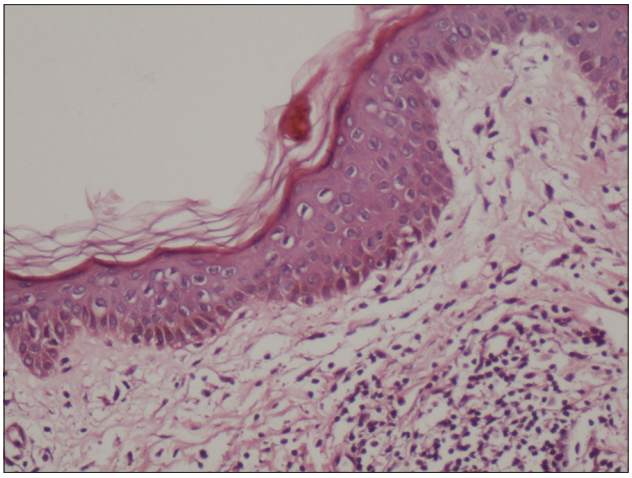

Figure 7: Small foci of parakeratosis and dermal perivascular lymphocytic infiltration, (H&Ex200)

clinical spectrum of NF is broad and the diagnosis is made on the basis of clinical manifestations [2]. On the other hand, PR has several clinical variants, each with a distinct presentation of morphology, configuration and distribution pattern of the lesions. PRV is an uncommon variant of PR, characterized by large oval or annular plaques around the axilla and / or groins. Affecting exclusively axilla and groin, PRV must be considered in the differential diagnosis of dermatophytosis, secondary syphilis and invers psoriasis [1,3,4]. Herein, we report a case of 23-year-old woman with PRV accompanied by NF Type 1.

CONSENT

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

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Comment to the Article

A case of pityriasis rosea of vidal accompanied by neurofibromatosis type 1

by Ahu Yorulmaz, Ferda Artuz, Sezer Kulacoglu, Elif Sen

COMMENT

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The association of *pityriasis circiné et marginé* and neurofibromatosis type 1

COMMENTS

We read with pleasure the case report by Yorulmaz A *et al* on the occurrence of *pityriasis circiné et marginé* which is a variant of pityriasis rosea (PR) in a 23-year-old lady with known neurofibromatosis type 1 (NF-1) [1].

We agree to both diagnoses [2-4]. Both diseases are uncommon, but definitely not rare. We have no data on the prevalence of NF-1 in Turkey. In the United Kingdom, the prevalence is around 1:4560 [5], with the prevalence at birth being 1:2699 [5]. The prevalences of NF-1 for six-year-old German children, and 9-11 year-old children in Cuba, are 1:2996 [6] and 1:1141 [7] respectively. The prevalence of PR is around 1:167 [8]. This means that if a clinic follows 200 patients with NF-1, and sees them once every year, around 1.20 patient with PR would be expected to be seen.

While reporting them concomitantly in one individual, we might consider exploring the mechanisms as to whether these two diseases: (1) are merely co-incidental; (2) are being innocent bystanders (NF-1); (3) are related to the same confounder(s), and (4) have underlying immunopathogenetic connections, which could be risk factors, precipitating factors, or be genuine causal relationships.

For patient with NF-1, the immunological system is compromised to various extents [9-12]. The processes are not comprehensively known, although it is likely that multiple immunological pathways and cellular mechanisms reduce the antigen-processing and antigen-presenting cells in NF-1 [12].

Moreover, large groups of immune function genes in human Schwann cells are down-regulated in NF-1 [13]. Acute phase reactants such as interleukins are reported to be adversely affected in NF-1 [13]. Other than systematic effects, topical immunological responses could also be compromised [11], which might facilitate the inoculation of viruses at the herald patch, a postulation not yet substantiated.

A simplified immunopathological sequence would be: primary viral infection in childhood, the body then launches a primary and non-specific immunological response, then clonal expansion of T-cells (*memory cells*), then life-long latent infection of the virus in the peripheral blood mononuclear cells, then physical or psychological stresses together with NF-1 weakening the immunity, then endogenous reactivation of the viruses, then secondary immunological response (mainly by cell-mediated immunity), then the visible PR rash. The immunological basis for the predilected sites of lesions in bilateral axillae and groins in *pityriasis circiné et marginé*, however, is completely unknown.

For other paraviral exanthems, eruptive pseudoangiomatosis was reported to be associated with hospitalisations and treatment for cancers [14]. It was postulated that relative immunocompromisation is the missing link. We have reported the association of Gianotti-Crosti syndrome – another paraviral exanthem – and hyperimmunoglobulinaemia E syndrome (Job's syndrome), which is a congenital immunodeficiency disease [15]. Whether relative immunocompromisation is associated with other paraviral exanthems, such as asymmetric periflexural exanthem (unilateral laterothoracic exanthem) and papular-purpuric gloves and socks syndrome, is yet to be investigated.

Finally, we congratulate Yorulmaz A and his colleagues for such an outstanding piece of work which can be applied to patients immediately. We humbly recommend Yorulmaz A *et al* and other investigators to explore the possible associations between relative immunocompromisation and PR or other paraviral exanthems.

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Letter to the Editor

Tuberous sclerosis associated with a renal angiomyolipoma

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Sir,

A 27 year-old male hospitalized in the department of urology awaiting left nephrectomy, after presenting with a four month history of feeling a mobile mass in his left abdomen. CT angiography of the bilateral kidneys showed the following: the right kidney is of normal dimensions with multiple lipomas no greater than 7mm, while the left kidney is enlarged, with multiple heterogeneous lipomas in the cortex and medulla, most likely representing an angiomyolipoma (Fig. 1).

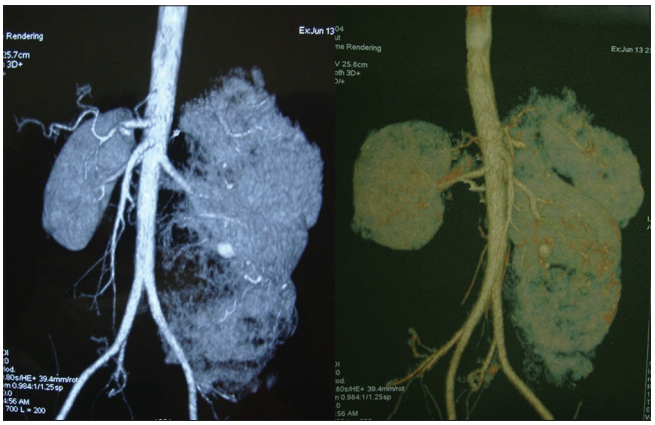

Figure 1: CT angiography of the bilateral kidneys showed the following: the right kidney is of normal dimensions with multiple lipomas no greater than 7 mm, while the left kidney is enlarged, with multiple heterogeneous lipomas in the cortex and medulla, most likely representing an angiomyolipoma

A through dermatologic examination demonstrated pink neoplasms in the proximal nail fold of the first, second, third and fourth toes of the left foot (Figs. 2 and 3), dermatoscopic view of the pink neoplasms of the proximal nail folds (Figs. 4ab and 5ab) and multiple, skin-colored neoplasms of the central face (Fig. 6). The remainder of the examination was within normal limits.

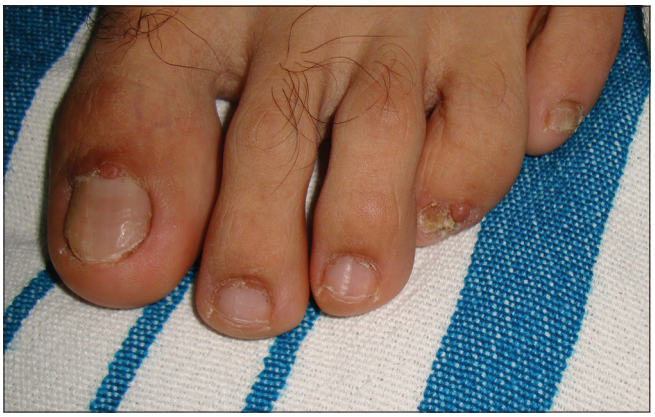

Figure 2: Pink neoplasms in the proximal nail fold of the first, second, third and fourth toes of the left foot

The patient reported that he has had the lesions on the face and left foot since he was very young. No other family member affected.

Past medical history and family history: negative and not consanguinity

With this clinical data, it was determined that the renal mass in this patient was associated with a diagnosis of tuberous sclerosis

The renal mass was surgically removed. Macroscopic and histological images of the kidney are observed on its outer surface, note the increase in size and abnormal appearance (Fig. 7a) Cut surface of the macroscopic and histological images of the kidney are observed on its

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outer surface and at both poles, with some observable normal renal parenchyma (Fig. 7b), the microscopic image of the tumor shows that it is composed of neoplastic adipose tissue, smooth muscle and blood vessels, correlating well with the gross image (H & E 10X) (Fig. 8) Increased magnification of the neoplasm shows a group of adipocytes surrounded by prominent blood vessels and bundles of smooth muscle (H & E 40X) (Fig. 9).

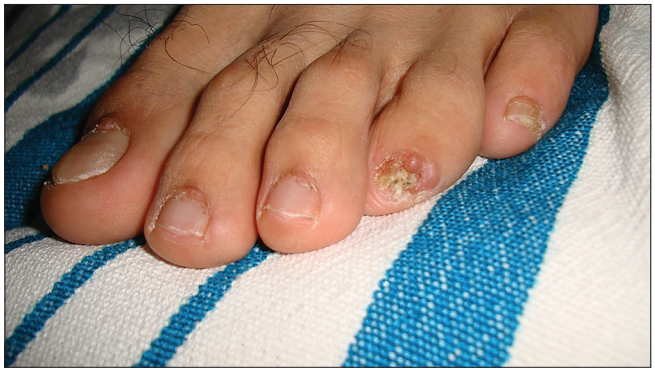

Figure 3: close up of the Koenen´s tumors of the proximal nail fold

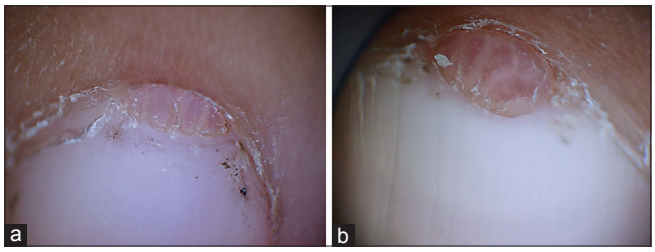

Figure 4: (a and b) Dermatoscopic view of the neoplasms of the proximal nail fold

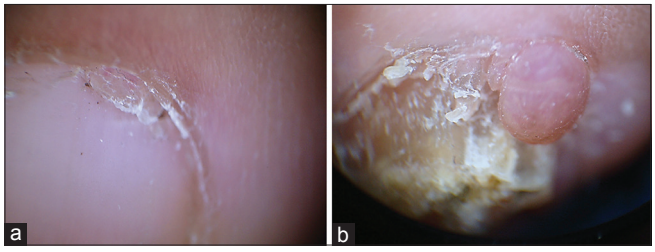

Figure 5: (a and b) Dermatoscopic view of the neoplasms of the proximal nail fold

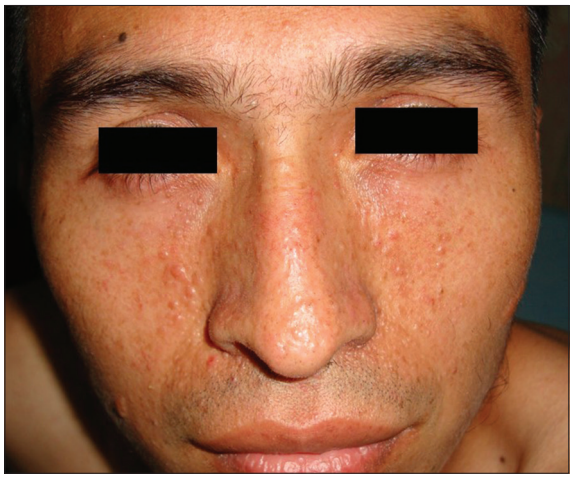

Figure 6: Angiofibromas of the face

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

What is interesting about this case is the association of tuberous sclerosis with a renal angiomyolipoma, which is not a very common clinical presentation.

Tuberous sclerosis is an autosomal dominant genodermatosis, historically characterized by epilepsy,

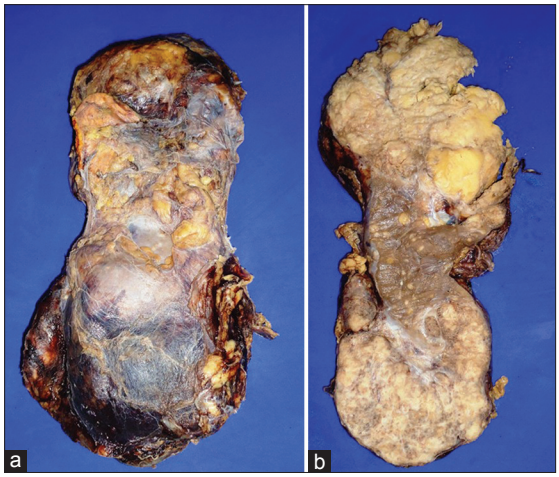

Figure 7: (a) Macroscopic and histological images of the kidney are observed on its outer surface and increase in size and abnormal appearance (b) Macroscopic and histological images of the kidney are observed on its outer surface and at both poles, with some observable normal renal parenchyma

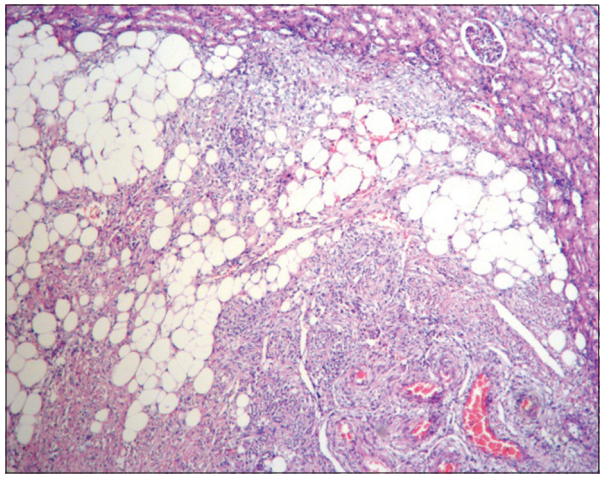

Figure 8: The microscopic image of the tumor shows that it is composed of neoplastic adipose tissue, smooth muscle and blood vessels, correlating well with the gross image (H & E 10X)

Table 1: Different manifestations of the tuberous sclerosis

Skin/nails	Renal	Neurological	Cardiovascular	Ocular	Oral cavity	Pulmonary
Facial angiofibroma	Angiomyolipoma	Cortical tuber	Rhabdomyoma	Retinal hamartoma	Gingival hyperplasia	Pulmonary lymphangioleio myomatosis
Shagreen patch	Cystic disease	Giant cell astrocytoma		Optic nerve hamartoma	Oral papillomatosis	
Hypomelanotic macule	Fibroadenoma	Subependymal nodule			Enamel pitting	
Periungual fibroma	Mixed tumor					
	Renal cell carcinoma					

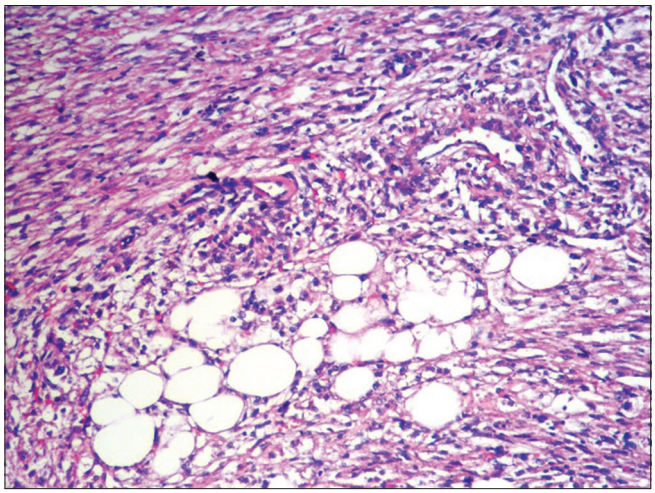

Figure 9: Increased magnification of the neoplasm shows a group of adipocytes surrounded by prominent blood vessels and bundles of smooth muscle, (H & E 40X)

low intelligence, and hamartomatous lesions in many organs, including facial angiofibromas. Although reported as roughly 1 in 10,000, the exact prevalence of this disease is unknown, due to the fact that the classic triad mentioned above is only found in a minority of cases, making the diagnosis difficult [1]. Clinically, greater than 90 percent of affected patients have one or more classic skin finding, including facial angiofibromas, hypomelanotic macules, periungual fibromas, and Shagreen patches [2]. The percent of patients with tuberous sclerosis that present with the above-mentioned lesions are 90, 85, 50, and 40, respectively. Facial angiofibromas, or adenoma sebaceous, tend to first appear around four years of age, and are usually found symmetrically on the cheeks, nose, and forehead. They consist of 1-3 mm yellowish-red, discrete, waxy papules. Ash leaf, or hypomelanotic macules, may range in number from 1 to 100, commonly present in the first few decades of life, and tend to fade in late adulthood. "Knobby" patches or plaques of connective tissue, Shagreen Patches usually develop in the first decade of life. They vary in size from 1 to 8 cm in diameter, and are most found on the trunk, particularly the lumbosacral area. Periungual fibromas, also called Koenen tumors when associated with tuberous sclerosis, are small digitate, protruding neoplasms that tend to manifest during adolescence or adulthood, and despite their name, can be periungual and/or subungual (Table 1) [1,3]. In addition to cutaneous involvement, the kidneys are often affected in Tuberous Sclerosis. In one study, renal lesions were found in 80% of patients, with roughly 80% of those being angiomyolipomas (AML), 20% renal cysts, and 25 case reports of an associated renal cell carcinoma. It is a mutation in a tumor suppressor gene, either TSC1 or TSC2, which causes tuberous sclerosis. In general, both alleles of a tumor suppressor gene must be mutated to lead to disease, and hamartomas in tuberous sclerosis patients typically demonstrate this loss of heterozygosity. Interestingly, angiomyolipomas and renal cysts are more commonly associated with mutations in the TSC2 gene than the TSC1 gene. The diagnosis of tuberous sclerosis is usually suspected clinically, with confirmation by genetic testing. However, evidence of a mutation in TSC1 or TSC2 confirms the diagnosis even in the absence of physical findings. Biopsy is rarely needed, and is usually performed when the clinical picture is not classic for the disease [1,3,4]. When considering alternative diagnoses, the presence of multiple facial papules may indicate other genodermatoses, such as Cowden, Brook-Spiegle, or Birt-Hogg-Dubé syndrome [3]. Schaffer et. al describe a case of a patient with Birt-Hogg-Dubé syndrome, a rare autosomal dominant genodermatosis with an increased risk of renal tumors, whose major presenting sign was multiple facial angiofibromas [5]. Historically, surgery was considered to be the only viable option for treating the cutaneous lesions of tuberous sclerosis. More recently, topical rapamycin has been shown to improve the appearance of subungual fibromas and facial angiofibromas, lessening the need for surgery and subsequent scarring. In addition to topical treatment, systemic everolimus, approved for patients with tuberous sclerosis who have subependymal giant-cell astrocytomas or renal angiomyolipomas, has also proven to have positive effects on skin lesions [1,3,6,7].

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Letter to the Editor

Tasleem's water jet sign - A new sign in dermatology

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Sir,

The field of dermatology is known by various signs many of which bear clinical importance while others provide academic assistance to the postgraduate scholars. A number of signs have been mentioned in dermatology and many more are being introduced as a result of meticulous work going on in this field of medical science. With the advent of Dermoscopy, many new signs have been introduced in the recent past. In this article, the authors have mentioned their observation while working with the management of cutaneous warts and have introduced a new sign in dermatology which has been named as " Tasleem's Water Jet Sign".

During the treatment of warts in dermatosurgery theatre, the authors observed a peculiar phenomenon. In our dermatosurgery unit, we mostly treat warts by radiofrequency ablation. While giving local anesthesia to the site of wart, we observed that sometimes the local anesthetic spills out back through the verrucous surface of the wart like a jet of water which has been referred to as 'Water Jet Sign'. Many times this jet of local anesthetic directly aims the face including the eyes of the treating doctor. However, those dermatologists wearing spectacles or protective glasses, the water jet of local anesthetic may directly strike these protective shields sparing the eyes. One of the authors has the experience of this jet striking his spectacles several times during the procedure.

Why this jet of local anesthetic comes out back needs to be explained. Before we explain the possible genesis of this sign, the basic histopathology of a wart needs to be revived. Histopathologically, common and palmoplantar warts are characterized by hyperplasia of all layers of the epidermis. There is marked hyperkeratosis with associated parakeratosis. Both the stratum granulosum and stratum spinosum are conspicuously thickened. There is steeply sloping "church spire" papillomatosis. Epidermal rete ridges are elongated and flattened and are bent inwards towards the centre of the wart [1,2]. So from this pathological description, it becomes clear that in a wart, there are vertical columns of dense papillomatosis and some of which may be separated from each other by potential weaker spaces. When a local anesthetic solution is injected into the base of the wart, the incoming solution of anesthetic doesn't find a sufficient space in tissues like palms, soles, etc where the skin is tough and less yielding which is also contributed by the dense hyperkeratosis of the wart itself. As a result, the local anesthetic solution is held under a high pressure at the base of the wart which tries to negotiate through any weaker area. When more anesthetic solution is being injected, the pressure at the base of the wart increases as the solution is now held in a tight unyielding space. The dense hyperkeratosis of the wart, tough connective tissue of the palms and soles and the elongated rete ridges which are bent inwards towards the centre of the wart do not allow the anesthetic solution to escape through the bottom and sideways. As a result when more anesthetic solution is injected, intracompartmental pressure increases more and more and draws the solution through the narrow channels present in between the columns of dense papillomatosis away from the base of wart and comes out of it as a jet of water.

The water jet sign is usually seen in the palmoplantar warts where the skin is tough and unyielding. We didn't observe this sign in verruca plana and at areas with loose skin like axillae, scrotum, neck, eye lids, etc. This sign has some importance. Firstly, a dermatologist dealing with warts must be wearing eye protection to avoid chances of getting the jet of local anesthetic into the eyes during

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the procedure. Secondly, when this sign is present, it can augment the diagnosis of warts. Lastly, it adds to the academic armamentarium of postgraduate scholars.

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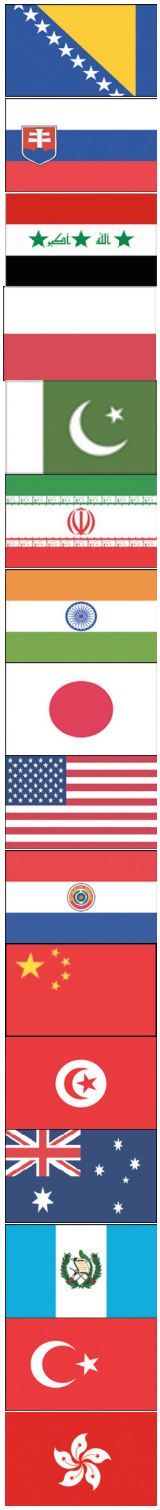

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