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DERMATOLOGIA E VENEREOLOGIA

OFFICIAL JOURNAL OF THE SOCIETÀ ITALIANA DI DERMATOLOGIA MEDICA, CHIRURGICA, ESTETICA E DELLE MALATTIE SESSUALMENTE TRASMESSE (SIDeMaST)

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Case reports. These give a description of particularly interesting cases. The text should be 2000-3000 words (6 to 8 typed, double-spaced pages) not including references, tables, figures. No more than 30 references will be accepted. The article must be subdivided into the following sections: introduction, case report or clinical series, discussion, conclusions. It is suggested to the authors to follow the guidelines reported by the CARE statement (www.care-statement.org).

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Letters to the Editor. These may refer to articles already published in the journal or to a subject of topical interest that the authors wish to present to readers in a concise form. The text should be 500-1000 words (1 to 3 typed, double-spaced pages) not including references, tables, figures. No more than 5 references will be accepted.

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Articles should include an abstract of between 200 and 250 words. For original articles and therapeutical notes, the abstract should be structured as follows: *aim* (aim of the study), *methods* (experimental design, patients and interventions), *results* (what was found), *conclusion* (meaning of the study). Key words should refer to the terms from Medical Subject Headings (MeSH) of MEDLINE/PubMed. No abstracts are required for editorials or letters to the Editor.

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- Short title, with no abbreviations.
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- Dates of any congress where the paper has already been presented.
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Articles should include an abstract of between 200 and 250 words. For original articles and therapeutical notes, the abstract should be structured as follows: *aim* (aim of the study), *methods* (experimental design, patients and interventions), *results* (what was found), *conclusion* (meaning of the study). Key words should refer to the terms from Medical Subject Headings (MeSH) of MEDLINE/PubMed. No abstracts are required for editorials or letters to the Editor.

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Identify methodologies, equipment (give name and address of manufacturer in brackets) and procedures in sufficient detail to allow other researchers to reproduce results. Specify well-known methods including statistical procedures; mention and provide a brief description of published methods which are not yet well known; describe new or modified methods at length; justify their use and evaluate their limits. For each drug generic name, dosage and administration routes should be given. Brand names for drugs should be given in brackets. Units of measurement, symbols and abbreviations must conform to international standards. Measurements of length, height, weight and volume should be given in metric units (meter, kilogram, liter) or their decimal multiples. Temperatures must be expressed in degrees Celsius. Blood pressure must be expressed in millimeters of mercury. All clinical chemistry measurements should be expressed in metric units using the International System of Units (SI). The use of unusual symbols or abbreviations is strongly discouraged. The first time an abbreviation appears in the text, it should be preceded by the words for which it stands.

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If figures are in color, it should always be specified whether color or black and white reproduction is required.

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CONTENTS

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Vulvar melanoma: a 33 years single Italian center experience

C. CATALANO [1], A. DE MAGNIS [1], T. KANNINEN [2], G. SISTI [1], A. SISTI [3], F. SORBI [1], I. TURRINI [1], N. PIMPINELLI [4], M. FAMBRINI [1]

Aim. **Vulvar melanoma is a rare disease with a poor prognosis. The purpose of this study was to report our experience on vulvar melanoma.**

Methods. **This is a retrospective study on patients with primary melanoma of the vulva admitted to our hospital during the last 33 years. Clinical characteristics, surgical therapy and follow-up are reported. Patients were classified following the 2009 edition of the melanoma staging system.**

Results. **The predominant symptom was pain; five patients reported ulceration and one patient presented bleeding from the vulvar lesions. The average age at diagnosis was 61.4 years. Surgical treatment was performed: radical vulvectomy in five cases, emivulvectomy in three cases, large regional excision in one case. Average time to follow-up was 50.2 months. In four cases (44.4%), regional recurrence occurred and the patients died as a result of the tumor; one patient died of other causes; four patients were still alive at the time of the study.**

Conclusion. **Current treatment protocols have moved towards less aggressive treatment in view of the current available evidence. Sentinel lymph node biopsy and adjuvant therapy are still under debate. Our study confirms the overall poor prognosis for vulvar melanoma.**

KEY WORDS: Vulva - Melanoma - Prognosis.

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Melanomas are commonly encountered malignant tumors arising from melanocytes. The most common type of melanoma is cutaneous melanoma. Sun exposure is a well-known causative risk factor and as such these malignancies usually arise from sun-exposed areas of the body. Importantly, melanocytes are located in other non sun-exposed areas of the body, such as the vulva, vagina, eye, leptomeninges and internal organs [1] and many times cancer of these melanocytes have a worst prognosis than its manifestation in more traditional areas.[1]

Unlike common cutaneous melanoma, which is estimated to be the sixth most common cancer in the United States among women,[2] vulvar melanomas are rare. Vulvar melanoma represents 5-10% of all vulvar cancers, with an overall incidence of 0.1 per 100,000 women every year. It represents the second most common vulvar malignancy. With cutaneous melanomas differences in regard to ethnicity are well documented (higher frequency in white women),[3] lifetime risks of cutaneous melanoma varies by histological subtype and race/ethnicity in the United States.[3]

This ethnic difference seems not to be apparent with vulvar/vaginal melanomas.[4] The lack of ethnic differences may be a reflection of the insurgence of this cancer in areas not exposed to ultraviolet radiation,[5] where the protective nature of melanin may provide minimal benefit. Given this difference, other

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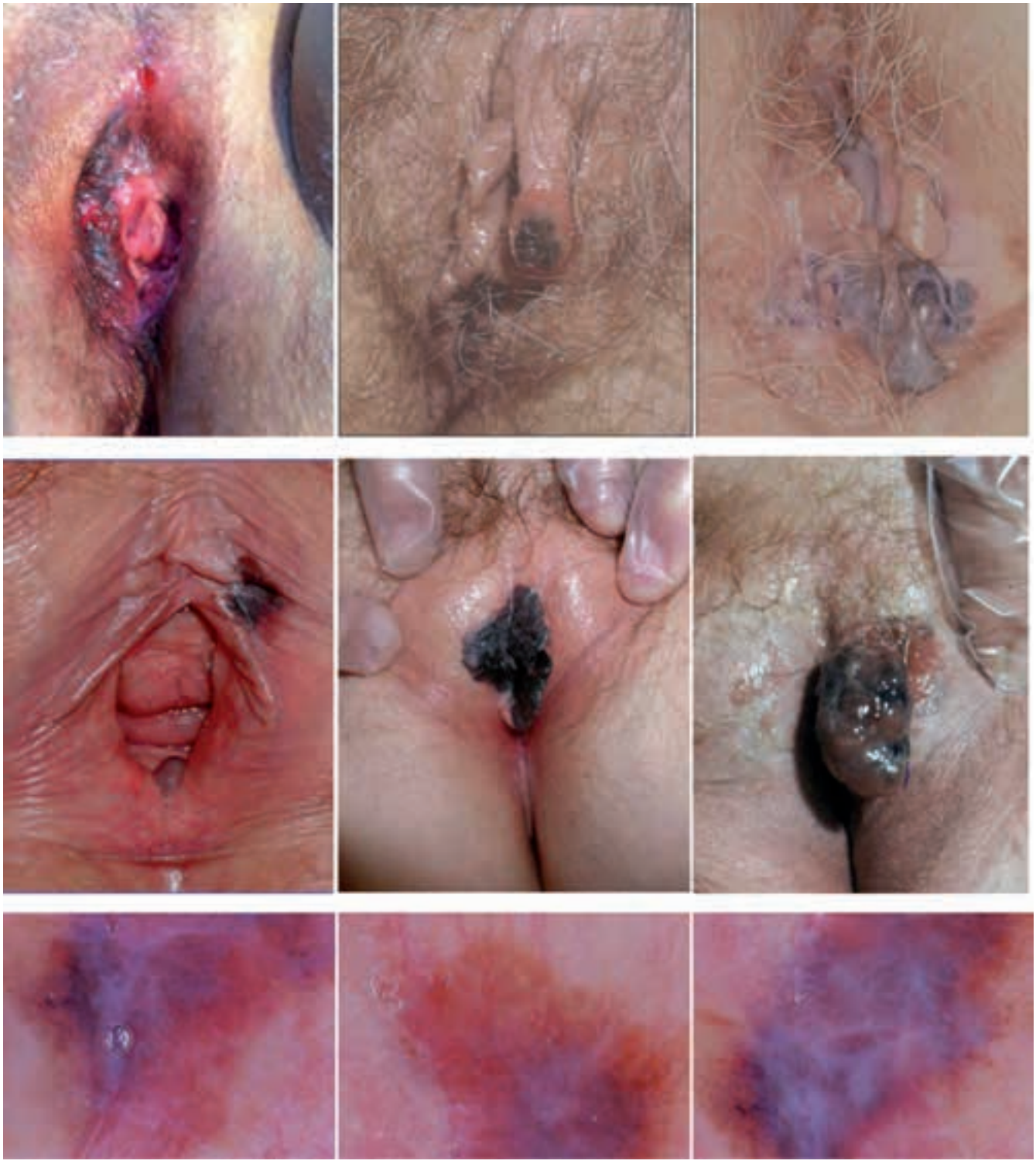

Figure 1.—Vulvar melanoma gross appearance and dermoscopic features.

TABLE I.—*Clinical and pathological characteristics, surgical data and clinical course of the 9 patients included in the study.*

Patient	Age (years)	Initial symptom	Staging (AJCC 2009)	Infitration depth	Vulvar surgery	Inguinal treatment	Local recurrence	Time until recurrence (months)	Follow-up (months)	Status
1	46	Pain, vulvar lesion	III B	Breslow 3 mm	Left emivulvectomy	UIL	-	-	6	AWD
2	45	Vulvar lesion	II C	Breslow 4.6 mm	Right emivulvectomy	-	-	-	5	AWD
3	48	Pain	III C	Breslow 6 mm	Radical vulvectomy	UIL	Iliac	3	12	DFD
4	85	Blood, pain	II C	Breslow 4.3 mm	Radical vulvectomy	BIL	-	-	21	AWD
5	64	Vulvar lesion	missing data	Missing data	Right emivulvectomy	BIL	Vaginal, forchetta vulvare	15	60	DFD
6	77	Pain	II B	Breslow 2, 5 mm	Radical vulvectomy	BIL	-	-	48	AWD
7	63	Pain	III A	Breslow 4 mm	Radical vulvectomy	BIL	Periurethral, iliac	10	38	DFD
8	69	Vulvar lesion	I A	Breslow 0.5 mm	Large regional excision	-	-	-	12	DOC
9	56	Pain	III C	Breslow 3 mm	Radical vulvectomy	BIL	Vaginal	235	250	DFD

UIL: unilateral inguinal lymphoadenectomy; BIL: bilateral inguinal lymphoadenectomy; AWD: alive without disease; DFD: dead for the disease; DOC: dead for other causes.

etiological factors have been considered to be implicated in the onset of disease, for example chronic inflammation or viral infections.[6]

However, ethnicity has been demonstrated to effect prognosis, with blacks suffering poorer outcome. Overall 5-year survival for vulvar/vaginal melanoma has been reported at 11.4%, survival for vaginal melanoma being worse than vulvar melanoma.[7]

Diagnosis is largely late, which may account for its negative prognosis, and late in life. Unsatisfactory pelvic exams are frequently preformed ignoring the vulvar and vaginal areas and benign pigmented lesions of the vulva are often confused with malignant melanomas.[8, 9]

Vulvar melanoma can also present as amelanotic, friable, fungating mass and in this case it can be easily mistaken for other malignancies, however this presentation is very rare.[10, 11] Common symptoms are pruritus, local ulceration, bleeding, insurgents mainly on *labia minora* or clitoris.[12]

Given, its similarities to cutaneous melanoma classic Clark and Breslow [13] staging methods have been utilised, however an ideal staging system is not known at this point.[4]

In the current study we examined the vulvar/vaginal melanoma incidence and outcome in our regional hospital localised in Tuscany, Italy between the years 1981 and 2013.

Materials and methods

Nine patients with primary melanoma of the vulva were admitted to Careggi Hospital from January 1981 to December 2013. The patients' records were reviewed and all patients were staged in accordance with the American Joint Committee on Cancer Staging 2009. Clinical characteristics, histopathology, surgical therapy and follow-up were analyzed.

Data about patients include: age, initial symptom, staging, type of vulvar surgery performed, inguinal treatment, presence of local recurrence, time until recurrence, time of follow-up, current condition.

Results

The predominant symptom was pain, five patients reported ulceration and one patient presented bleeding from vulvar lesions. The average age at diagnosis was 61.4 years. Two patients reported history of melanoma in the family. The primary location was labium major in two cases, labium minor in four cases, both labia major and labia minor in three case (Figure 1). Dermatoscopy revealed pigmented lesions with multiple colours, irregular vascularity and broad network (Figure 1).

Surgical treatment was performed in all patients, in five cases with radical vulvectomy, in three cases with emivulvectomy and in one case with large regional excision. Sentinel lymphonode (LN) technique was not preformed in any case.

Stage III was detected in four cases, three cases were detected as stage II and one case presented as stage I. The depth of infiltration was more than 2.26 mm in 7 patients (Breslow score 4-5), concordant with poor prognosis achieved by these patients. LN

metastases were detected in 4 patients, 3 of these died from the disease, 2 developed regional recurrence.

The average time of follow-up was 50.2 months. In four cases (44.4%) regional recurrence occurred and the patients died as a result of the tumor; one patient died of other causes; four patients were still alive at the time of the study.

Mean time until recurrence was 65.75 months, the reappearance of disease involved iliac, periurethral and vaginal regions.

Surgical treatment for regional recurrence was performed in all 4 patients, leading to a mean postoperative survival of 40.2 months.

Only one of the four patients died from primary disease underwent unilateral inguinal lymphadenectomy, the other three patients were subjected to bilateral lymphadenectomy.

Discussion

Vulvar/vaginal melanoma is a rare clinical presentation and carries a substantial negative prognosis, as confirmed in our study. Staging for prognosis and treatment management for vulvar/vaginal melanoma has generally followed the classic Clark and Breslow [13] staging methods created for cutaneous melanoma given, its similarities. However an ideal staging system is not known at this point. The American Joint Committee on Cancer (AJCC) staging system 2002 revision [19] and 2009 AJCC Melanoma Staging and Classification [20] have been suggested to be valid systems in regard to primary vulvar melanoma. The 2002 AJCC staging system takes into consideration not only thickness and dermal penetration of the tumor but also presence of ulcerations and lymphnode involvement, 2009 7th edition of melanoma staging system includes some other more criteria like the mitotic rate and the immunochemical detection of nodal metastases.

Final prognosis of this cancer is better if compared to patients with mucosal melanomas that occur in other sites of the body. The worst prognosis is in the nasal/palate/oral melanoma subtype [1, 21-23]

and it seems to be poorer in black women.[4] Survival rate of patients included in our study was 33.3%, in agreement with the data in the literature. Recently, it has been suggested that breast cancer radiotherapy might play a role in the onset of primary vulvar melanoma.[24]

Five-years mean survival rate range of vulvar melanoma is only 36%; chemotherapy and radiotherapy is still mainly experimental.[13, 14]

Primary treatment in vulvar/vaginal melanoma is surgery and though radical surgery was promoted traditionally, recent emphasis on local satisfactory excisional surgery seems to have demonstrated similar outcomes in respect to more radical approaches.[15-17] Sentinel LN biopsy technique has been advocated to avoid LN dissection and negative patient sequelae, but the intervention benefits are still under debate.[18] Currently there are no guidelines in regard to adjuvant treatment in vulvar/vaginal melanoma, with the sole FDA approved adjuvant treatment being Interferon-alpha.[7].

In our series of patients there was no association with other cancers or treatment protocols. More studies are needed to further examine the association of this cancer with other diseases.

Given the rarity of malignant melanoma of the vulva and vagina treatment protocols have followed those set for cutaneous arising melanomas. Surgical resection has been the mainstay of treatment and more recent studies have supported a more limited approach as compared to radical resection in consideration of the similar outcomes in the two groups.[15, 16]

Recently, Janco *et al.*[7] provided further evidence supporting the lack of necessity to conduct radical surgical procedures for vaginal and vulvar melanoma,[14, 15, 25-27] though one report showed the opposite result.[28]

The role of elective lymphnode dissection in patients with vulvar melanoma remains controversial. The morbidity associated with an inguinofemoral lymphadenectomy (infections, edema and inflammatory sequelae) is significant.[17]

Furthermore a clear benefit to the procedure has not been demonstrated in the available literature.[29]

Sentinel LN preoperative technique with vulvar/vaginal melanoma treatment is debated and considered experimental. Its use has been suggested as only useful in studies of melanomas of intermediate thickness.[18]

There are few published papers on sentinel LN in relation to vulvar melanoma and there is insufficient evidence for their routine use. Within our study we did not perform this technique in our nine patients.

Pharmacological treatment as an adjuvant and

neoadjuvant option in vulvar/vaginal melanoma holds promise but has largely been experimental to date. The sole FDA approved adjuvant treatment for melanoma is IFN-alpha, and specifically geared treatment toward vaginal/vulvar melanoma is lacking.[7]

Currently limited available evidence does not suggest any difference in overall survival for patients treated with adjuvant chemotherapy or immunotherapy.[7, 30]

Recently, clinicians at the Mayo Clinic have reported initial success with neoadjuvant therapy, mainly in promoting decreased tumor size to favor complete surgical removal.[7]

Conclusions

Our data confirms the highly negative prognosis of having lymph nodal metastasis and being classified in stage III. All patients with stage III disease, were deceased at follow-up except one with the shortest follow up (6 months). Stage II patients were all alive at follow-up without signs of primary disease recurrence. These current data reinforces the importance of an early diagnosis. Unfortunately, our data underlines the negative effect of tardy diagnosis either by neglected importance given to them by the elderly patients and/or superficial and poor investigation by physicians.

Given its rarity vulvar/vaginal melanoma staging, prognosis and treatment protocols are limited in number. Our data further confirms the overall poor prognosis for vulvar melanoma and provides further data on the regional outcomes in our patient population.

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Immunohistochemical assessment of endothelin-1 axis in psoriasis, basal cell carcinoma and squamous cell carcinoma

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***Aim*. Endothelin-1 is an autocrine growth factor for keratinocytes, an effect controlled by its A and B receptors, with no previous comparison of endothelin axis expression in inflammatory and neoplastic skin diseases showing keratinocyte proliferation. The aim of the study was to investigate endothelin-1 axis expression in skin lesions of psoriasis, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC).**

***Methods*. This study included 40 subjects (8 patients with SCC, 12 patients with BCC, 10 patients with psoriasis, and 10 healthy controls). Biopsies from lesional skin of patients and normal skin of controls were examined immunohistochemically for endothelin-1 and its receptors A and B frequency and grade of expression.**

***Results*. Endothelin-1 and receptor A were detected in all patients with SCC and psoriasis, with a higher frequency and grade of expression than controls and BCC. The frequency of receptor B expression was significantly lower while higher staining grade was found in BCC (8.3%) rather than other studied groups.**

***Conclusion*. A comparable higher frequency and grade of expression of endothelin-1 and its receptor A are documented in psoriasis and SCC than in BCC and controls denoting their involvement in keratinocyte proliferation in both diseases. Receptor A is the predominately expressed receptor in psoriasis and SCC.**

KEY WORDS: Carcinoma, basal cell - Endothelin-1 - Receptors, endothelin - Psoriasis.

Endothelin (ET)-1, ET-2 and ET-3 in humans are a family of 21-amino-acid peptides that were originally identified as potent vasoconstrictors.[1] The effects of ETs are mediated by two major receptor subtypes: ETA receptor (ETAR) that binds ET-1 and ET-2 with high affinity and ET-3 with low affinity, and ETBR, that non-selectively binds all ET isopeptides with equal affinity.[2] The ETs and their receptors are referred to as the ET-axis.[3]

ET-1 is a potent mitogen for a variety of cell types and tumor cells of epithelial origin.[4-6] ETAR mediates mitogenic and additive proliferative effect of ET-1.[7] ETBR is proposed to negatively regulate the activity of ET-1.[8]

In normal human skin, ET-1 is mainly expressed in blood vessel walls, hair follicles, and sweat glands.[9] It is secreted by human keratinocytes and is involved in the regulation of melanocyte proliferation and pigmentation [10] through a paracrine action by binding to ETBR.[11] It also acts as an autocrine growth factor for keratinocytes through binding to ETAR [4] and possibly also to ETBR.[12]

ET-1 could be involved in inflammatory mechanisms.[13] Increased keratinocyte proliferation can occur in some inflammatory diseases as psoriasis.[14] It

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can also occur in tumors as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).[15]

Within the ET axis, different predominant expression of its receptors ETAR and ETBR were found in distinct tumor types.[16-19] Even more, in SCC, the predominantly expressed receptor differs in different sites.[3, 20-23] The increased production of ET by keratinocytes may function as a growth factor and potential mitogen, and may accelerate the proliferation in BCC.[24]

Considering the different expression patterns of ET receptors in different cancers and lack of studies on their tissue expression in psoriasis, cutaneous SCC, and BCC; with absence of reports of comparative expression of ET axis in inflammatory and neoplastic skin diseases showing keratinocyte proliferation, we aimed in this study to investigate ET-1 axis expression in skin lesions of psoriasis, BCC, and SCC.

Materials and methods

Study population

This case-control pilot study included 40 subjects, 24 males and 16 females, aged 15-78 years. They included 8 patients with cutaneous SCC (5 males and 3 females aged 19-75 years), 12 with BCC (8 males and 4 females aged 45-78 years), and 10 with chronic plaque psoriasis (6 males and 4 females aged 15-55 years), agreeing to participate in the study. We excluded patients on topical treatment within two weeks or on systemic treatment within one month prior to biopsy taking, and also patients with any other associated dermatological or systemic disorders. Ten healthy subjects (5 females undergoing cosmetic surgery for breast reduction and 5 males undergoing face lift aged 29-64 years) were included as controls. Subjects were randomly recruited from the Dermatology and Plastic surgery clinics of Ain Shams University Hospitals, and the National Research Centre. All subjects gave informed consent to participate in this work. The study was approved by the research ethics committee, National Research Centre.

Methods

Sampling

Five millimiter punch biopsies were taken from lesional skin of patients with SCC, BCC, and psoriasis and from controls. Four micron thick sections from the paraffin embedded biopsies were stained by Haematoxylin and Eosin to verify the clinical diagnosis and by immunohistochemical staining for ET-1, ETAR, and ETBR.

Immunohistochemical staining

Immunohistochemical staining was performed using rabbit polyclonal antihuman ET-1antibody, rabbit polyclonal ETAR antibody and rabbit polyclonal ETBR antibody (1:200 dilution; Abcam, San Francisco, CA, USA; for all markers used). Avidin-Biotin immunoperoxidase complex technique was used by applying the super sensitive detection kit (Biogenex, CA, USA). Tissue sections were deparaffinized with graded concentrations of xylene and ethanol, and washed with 0.6% H_2O_2 in methanol for 30 minutes to block endogenous peroxidase activity. Tissue was then incubated with 5% normal bovine serum for 10 minutes to reduce nonspecific background staining and then with the primary antibody. Slides were then incubated with biotinylated secondary antibody then with avidin and biotinylated horseradish peroxidase complex. Peroxidase activity was visualized by a diaminobenzidine. Sections were counterstained with hematoxylin. Appropriate positive and negative controls were included for the slides. As a positive control for ET-1, human internal mammary artery sections with preserved endothelial cell layers were used; for ETAR, human placenta was used as positive control; and for ETBR, human intestinal cancer tissue was used.

Expression of the markers

Immunostaining for ET-1, ETAR, and ETBR was recorded according to the staining intensity, distribution in cytoplasm, and percentage of positive cells. Expression of proteins was graded semi quantitatively from 0 to 3 using the scoring method by Zeiher *et al*.:[25] grade 0 indicated absence of any staining; grade 1, positivity in <10% of the cells; grade 2, positivity in 10% to 30% of the cells; and grade 3, positivity in >30% of the cells. Grading was performed independently by two of the investigators.

Statistical analysis

Data was analyzed using the Statistical package for Social Science (SPSS 15.0.1 for windows; SPSS

Inc, Chicago, IL, USA). Descriptive statistics was presented as mean, standard deviation (± SD) for numerical data; and as frequency and percentage for non-numerical data. Chi-square test was used to examine the relationship between two qualitative variables. Fisher exact test was used when applicable. Independent-samples *t*-test was used to compare two group means. ANOVA test was used to compare more than two group means. Once a difference existed among the means by one-way ANOVA, post hoc range tests and pair wise multiple comparisons were used to determine which means differ. P≤0.05 was considered significant.

Results

After examining 20 randomly recruited subjects in each group, eight patients with SCC, 12 with BCC, 10 with psoriasis, and 10 healthy subjects confirmed eligible after excluding those subjects not matching our inclusion criteria, and were included in the study. Analysis of results was completed for all eligible subjects. Statistically insignificant difference was found between the studied groups (control, BCC, SCC, and psoriasis) regarding the sex distribution (P>0.05). Patients with psoriasis showed significantly younger mean age (36±15.47 years) than those having BCC (59.08±7.91 years) and SCC (53.87±18.79 years) (P<0.05), while patients with BCC and SCC showed no significant difference (P>0.05). Mean age showed no significant difference between different disease groups and controls (47.9±10.5 years).

ET-1 showed positive expression in 30% of the controls, 50% of BCC, and 100% of SCC and psoriasis patients. ETAR showed positive expression in 50% of the controls, 33.3% of BCC, and in 100% of SCC and psoriasis patients. ETBR showed positive expression in 80% of the controls, 25% of BCC, 87.5% of SCC, and 70% of psoriasis patients.

Comparison of the frequency of endothelin axis markers expression between disease groups and controls

There was a significantly higher frequency of ET-1 expression in psoriasis and SCC compared with controls (P<0.05), while the difference between BCC and controls was not significant (P>0.05). Compared with controls, psoriasis showed a significantly higher frequency of ETAR expression (P<0.05), while BCC showed a significantly lower frequency of ETBR expression (P<0.05). The difference between the other groups and controls regarding the expression of different markers was not significant (P>0.05).

Comparison of the frequency of endothelin axis markers expression between different disease groups

Psoriasis and SCC were 100% positive for ET-1 and ETAR. There was an increased frequency of ET-1 expression in psoriasis (significant, P<0.05) and SCC (not significant, P>0.05) compared with BCC, while the frequency was significantly higher in the two diseases compared with BCC regarding ETAR (P<0.05). There was an increased frequency of ETBR expression in SCC (significant, P<0.05) and psoriasis (not significant, P>0.05) compared with BCC; while the difference detected between SCC and psoriasis was not significant (P>0.05).

Comparison of the endothelin axis markers grade of staining between disease groups and control

Psoriasis and SCC showed a significantly higher grade of staining for ET-1 and ETAR than control (P<0.05) (Figures 1, 2). Additionally, both BCC and SCC showed a significantly higher grade of staining for ETBR than the control group (P<0.05) (Figure 3). On the other hand, no statistically significant difference was found between BCC and controls regarding the grade of staining for ET-1 and ETAR, or between psoriasis and controls regarding ETBR grade of staining (P>0.05) (Table I).

Comparison of the endothelin axis markers grade of staining between different disease groups

A significantly higher grade for ET-1 expression was found in SCC than BCC (P=0.05), and in psoriasis than BCC and SCC (P<0.05) (Figure 1). Regarding ETAR, SCC and psoriasis showed a significantly higher grade of staining than BCC (P<0.05), with no significant difference between SCC and psoriasis (P>0.05) (Figure 2). ETBR staining grade was significantly higher in BCC than SCC (P<0.05) with no significant difference comparing each of SCC and BCC with psoriasis (P>0.05) (Figure 3) (Table I).

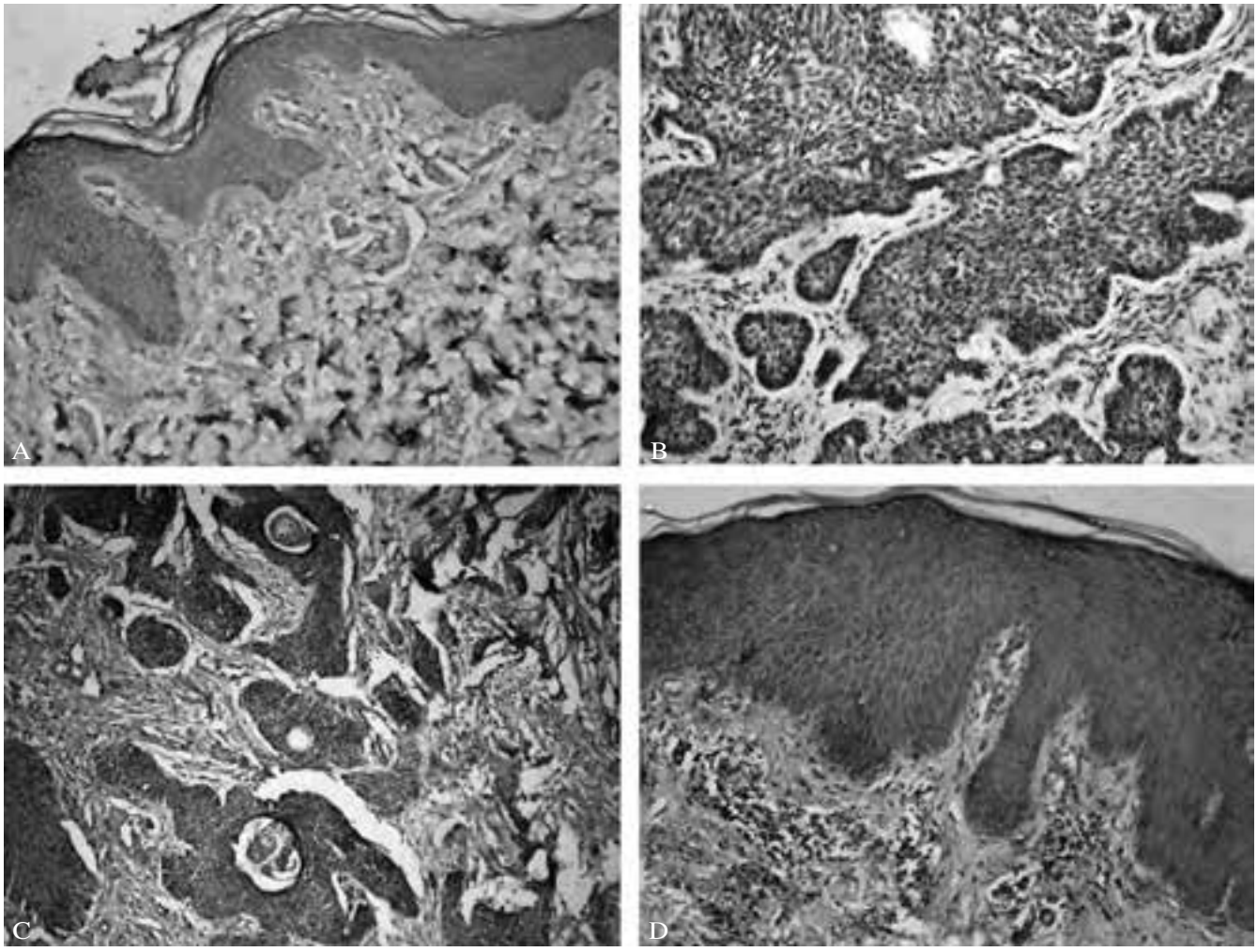

Figure 1.—Endothelin-1 immunohistochemical staining showing in: A) positive expression in the epidermis of normal skin of grade 2 immunostaining (x200); B) positive expression in basal cell carcinoma of grade 1 immunostaining (x200); C): positive expression in squamous cell carcinoma of grade 3 immunostaining (x200); D): positive expression in psoriasis of grade 3 immunostaining (x200).

Discussion

In this work we aimed to study the differential expression of ET axis markers in psoriasis, BCC, and SCC. The higher frequency together with the higher grade of expression of both ET-1 and ETAR in psoriasis and SCC found in this work compared with the control group imply their involvement in these disease entities. Increased keratinocyte proliferation and neo-angiogenesis are important pathogenic events in psoriasis [6] and SCC.[15] ET-1, being mitogenic for endothelial cells and keratinocytes, could participate in the pathogenesis of both diseases through these actions.

The higher frequency and grade of ET-1 expression in the epidermis of psoriasis and SCC compared with BCC denotes a higher proliferative rate of keratinocytes in the two former groups. Moreover, the significantly higher frequency and grade of ETAR expression in both groups compared with BCC together with the above mentioned findings underlines the importance of this receptor in me-

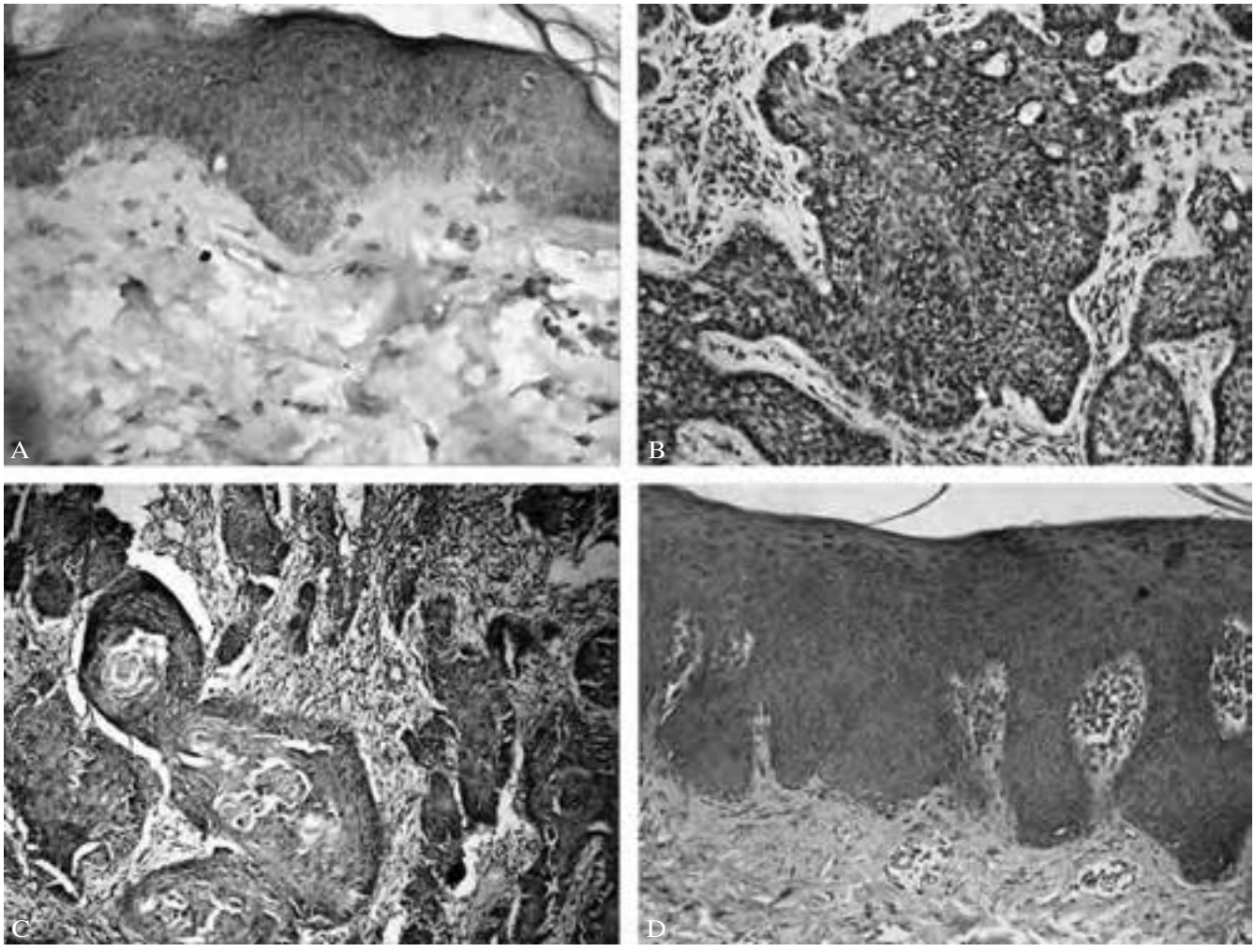

Figure 2.—Endothelin-A receptor immunohistochemical staining showing in: A): positive expression in epidermis of normal skin of grade 2 immunostaining (x200); B): positive expression in basal cell carcinoma of grade 2 immunostaining (x200); C): positive expression in squamous cell carcinoma of grade 3 immunostaining (x200); D): positive expression in psoriasis of grade 3 immunostaining (x200).

diating the proliferative effect of ET-1 on keratinocytes in these diseases. Both diseases seem to have comparable epidermal proliferation as the expression of ET-1 and its receptor A was detected in all their studied cases. Previous reports, however, show contradictory results, with some demonstrating a proliferation rate in SCC>BCC> psoriasis>normal skin,[15] and others reporting a higher proliferation index in psoriasis than SCC and in SCC than in BCC.[26] These contradictory results might be attributed to the use of different markers in evaluating the epidermal proliferation, where some of them could have additional effects that variably contribute to the disease process.

As interleukin 8, which is involved in the pathogenesis of psoriasis,[27] can possibly induce ET-1 production,[28] this could explain the significantly higher grade of expression of ET-1 in psoriasis compared with SCC. ET-1 could be possibly involved in inflammatory mechanisms in psoriasis by stimulating neutrophil chemotaxis.[13] Increased ET-1 and IL-8 in psoriatic lesional skin extracts were previously

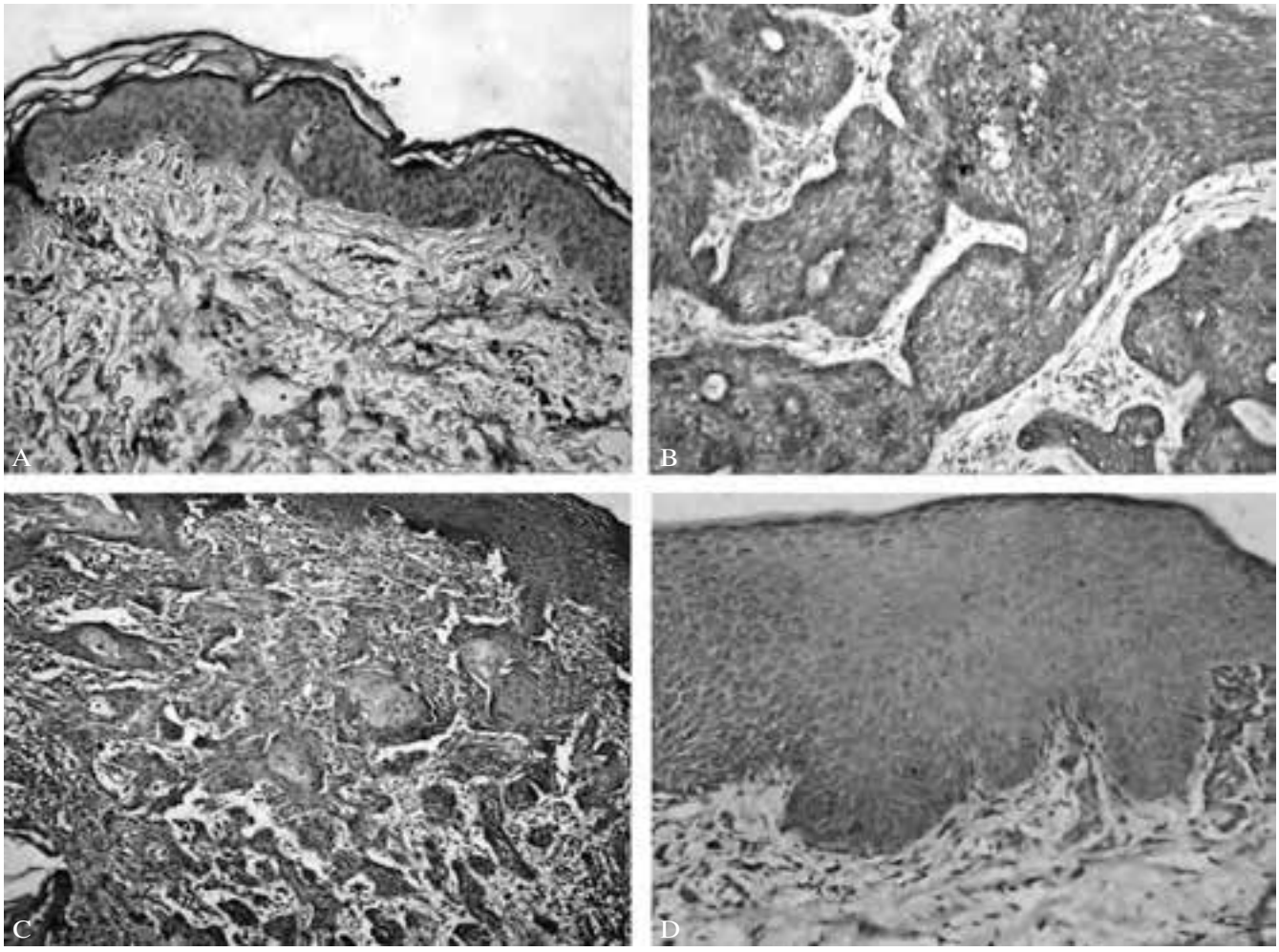

Figure 3.—Endothelin-B receptor immunohistochemical staining showing in: A): positive expression in epidermis of normal skin of grade 1 immunostaining (x200); B): positive expression in basal cell carcinoma of grade 3 immunostaining (x200); C): positive expression in squamous cell carcinoma of grade 2 immunostaining (x200); D): positive expression in psoriasis of grade 2 immunostaining (x200).

reported.[29] Moreover, tumor necrosis factor, which is as an important mediator in psoriasis, is an ET-inducible cytokine.[12]

The type of ET receptor mediating its keratinocyte proliferative effect is variably reported; with some studies demonstrating the involvement of ETBR in such a role,[12] while others reporting ETAR involvement.[20] However, the type of ET receptor expressed in psoriatic skin was not previously investigated. In this work, ETAR was detected in all psoriasis patients while ETBR was detected in only 70% of cases, with concomitant expression of ET-1 in all cases. This signifies a predominant role for the A receptor in the disease pathogenesis.

Although increased plasma ET-1 level in BCC was reported to be a probable result of and/or reason for the accentuated hyperkeratinization, hyperpigmentation, and keratinocyte proliferation,[24] the significantly lower frequency and grade of expression of ET-1 and ETAR in BCC compared with other disease groups in our work seems to exclude an important proliferative action of ET axis in this locally malignant tumor. This is supported by absence of significant differences in the frequency and grade of

TABLE I.—*Comparison between the studied groups as regards the grade of staining for endothelin-1, endothelin receptor A, and endothelin receptor B.*

		Groups							
		Control (3)		BCC (12)		SCC (8)		Psoriasis (10)	
		N.	%	N.	%	N.	%	N.	%
Endothelin-1	Grade 0	7	70.0%	6	50.0%	0	0.0%	0	0.0%
	Grade 1	0	0.0%	1	8.3%	0	0.0%	0	0.0%
	Grade 2	3	30.0%	3	25.0%	4	50.0%	0	0.0%
	Grade 3	0	0.0%	2	16.7%	4	50.0%	10	100.0%
P value	*vs.* control			0.59		**0.002***		**<0.0001***	
	BCC *vs.* SCC					**0.05***			
	BCC *vs.* Psoriasis							**<0.0001***	
	SCC *vs.* Psoriasis							**0.02***	
Endothelin receptor A	Grade 0	5	50.0%	8	66.7%	0	0.0%	0	0.0%
	Grade 1	2	20.0%	0	0.0%	0	0.0%	1	10.0%
	Grade 2	3	30.0%	3	25.0%	5	62.5%	4	40.0%
	Grade 3	0	0.0%	1	8.3%	3	37.5%	5	50.0%
P value	*vs.* control			0.48		**0.01***		**0.007***	
	BCC *vs.* SCC					**0.009***			
	BCC *vs.* Psoriasis							**0.003***	
	SCC *vs.* Psoriasis							0.79	
Endothelin receptor B	Grade 0	2	20.0%	9	75.0%	1	12.5%	3	30.0%
	Grade 1	8	80.0%	1	8.3%	0	0.0%	3	30.0%
	Grade 2	0	0.0%	1	8.3%	7	87.5%	4	40.0%
	Grade 3	0	0.0%	1	8.3%	0	0.0%	0	0.0%
P value	*vs.* control			**0.03***		**<0.0001***		0.53	
	BCC *vs.* SCC					**0.001***			
	BCC *vs.* Psoriasis							0.07	
	SCC *vs.* Psoriasis							0.14	

SCC: squamous cell carcinoma; BCC: basal cell carcinoma. *: significant.

expression of ET-1 and its A receptor with even a significantly lower frequency of B receptor expression in this tumor compared with controls. As such, enhanced ET-1 expression in BCC could be related more to the development of hyperpigmentation (a finding not present in our patients) than hyperproliferation in this tumor, supporting the previous findings of Lan *et al*.[30] In contrast to our results, Zhang *et al.*[31] found the ET signaling pathway, especially ET-1, to be activated in BCC, with no significant increase in expression in SCC.

Our finding of a significant difference in the staining grade of ETBR in BCC versus SCC, with higher grades of staining found only in BCC (although in small frequency 8.3%) could be explained as a reflection of a negative regulatory effect on ET-1,[8] and this might clarify the absence of a significant difference in the grade of expression of ET-1 and ETAR in BCC cases compared with controls. However, the exact reason for such a finding could not be elucidated and needs further research work. Another possible explanation for the presence of higher grade of ETBR staining in BCC is its up regulation in response to other types of ET as ET-2, whose mRNA was recently reported to be over expressed in BCC.[32] Despite the recent report of BCC origin from the interfollicular epidermis,[33] this tumor is commonly believed to originate from the basal cells of the hair follicle.[34] This could alternatively account for the different staining pattern of ET-1 axis in BCC compared with psoriasis and SCC. Relation of the presence of some strong ETBR expression with different clinicopathological types of BCC needs further research.

ET-1 may participate in SCC development or progression by autocrine or paracrine action on neoplastic and surrounding stromal cells [35] by either promoting cell proliferation or protecting cells from apoptosis, and by influencing angiogenesis and signaling of several growth factors.[16] The predominant type of ET receptor expressed in SCC differs in different sites and have diverse prognostic implications.[3, 20, 23, 36, 37] The type of ET receptor in cuta-

neous SCC was not previously investigated. In the present work, cutaneous SCC expressed ETAR in all cases and ETBR in only 87.5% of cases. Further studies are needed to assess the relation of both receptors with the invasiveness, metastatic potential, and tumor progression in cutaneous SCC.

The coexpression of ETBR with ET-1 and ETAR in 87.5% and 70% of patients with SCC and psoriasis respectively could reflect a regulatory action of this receptor on the ET-1 induced keratinocyte proliferation.

In view of the findings in the current work, a better understanding of the ET axis can ultimately lead to the development of novel therapeutic measures for such cases. Considering the presence of selective antagonists for ETAR and ETBR,[18, 20, 38] it would be useful to evaluate them as possible beneficial treatment options in psoriasis and SCC. Agonism of ETBR has also been proposed as an alternative approach to block the effects of ETAR [39] and should be assessed in this context.

Limitations of the study

The limitation in this study is the relatively small number of patients included. Further research on a larger scale is required for proper representation of each disease category. Correlating the findings of the present work with ET axis activity on molecular level should be targeted in future work.

Conclusions

In conclusion, this work shows a comparable higher frequency and grade of expression of ET-1 and its receptor A in psoriasis and SCC than in BCC and controls denoting their involvement in keratinocyte proliferation in both diseases. ETAR is the predominately expressed receptor in psoriasis and SCC. The potential role of the interplay of ETs and their receptors in benign and malignant proliferative keratinocyte diseases is intriguing and needs to be further elucidated.

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Clinical efficacy of two topical corticosteroids in the management of chronic hand eczema

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Aim. **The aim of this study was to evaluate efficacy, tolerability and safety of a combination treatment with fluticasone propionate 0.05% cream and clobetasole ointment 0.05% in patients suffering from chronic hand eczema.**

Methods. **The study examined 30 patients with a clinical diagnosis of chronic hand eczema.**

Results. **The treatment with topical corticosteroids resulted effective and topical corticosteroids proved their efficacy in mild and moderate hand eczema.**

Conclusion. **In according to the severity of the disease, authors suggest two different clinical strategies in the management of hand eczema.**

KEY WORDS: Eczema - Adrenal cortex hormones - Dermatitis.

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Hand eczema, also called hand dermatitis, is a common inflammatory skin disorder of the hands. It has often a chronic and relapsing course, interfering with the quality of life of the patient. Typical clinical manifestations include scaling, fissures, erythema, vesicles, papules, hyperkeratosis, pruritus, and pain.[1, 2]

It is common, with an annual prevalence of hand eczema (HE) in the general population estimated to be between 7% and 12% in Northern Europe.[3, 4] Recent epidemiological data in Italy confirmed the high incidence and prevalence as shown by international studies.[5] One of main Italian study on 981 patients, HE was chronic in 83.5% of patients. Among them, 21.3% were severe, 62% of these patients being refractory to standard therapy.[6] The social impact on patients affected by HE as well as on their quality of life is considerable. The lesions involve a highly visible part of the body that has an important role in communication and interpersonal relations. It represents one of the most common occupational skin disorder causing loss of wellbeing and productivity. The economic impact of HE is daunting, with both direct and indirect costs.[2, 6, 7]

The treatment is challenging. Although it would seem logical to assume that identifying and eliminating the causative factor could represent the first line treatment to get HE remission, this feat is rare in the daily practice because of the multifactorial causes of the disease, especially when the HE becomes chronic.[8]

The most common cause of HE is contact with mild irritants (*e.g.*, water and soaps), causing irritant contact dermatitis, followed by allergic contact dermatitis and atopic dermatitis. In many patients, HE has more than one cause.

Avoidance of irritants (and allergens, if relevant), frequent application of emollients, and personal protective equipment are important non pharmacological interventions. However, the use of topical glucocorticoids represents the first-line treatment in this challenging disease.[8-10]

The treatment is recommended and has to be prompt to avoid that HE becomes a chronic condiction.[11] Current treatment strategies are largely based on clinical experience and may differ from country to country.[8, 12-14]

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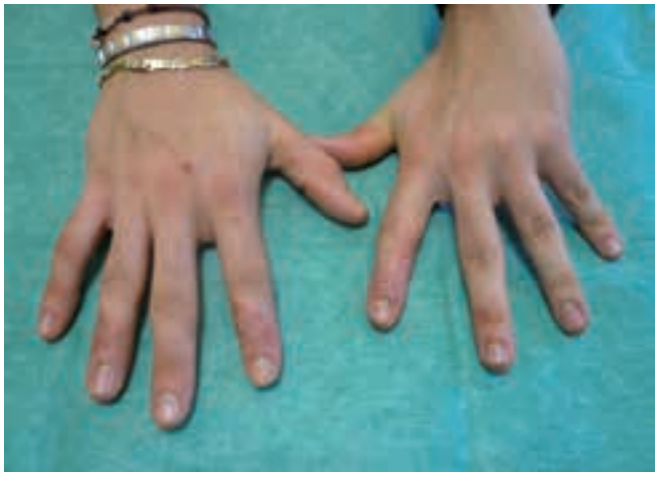
Figure 1.—Clinical condition at the beginning of treatment.

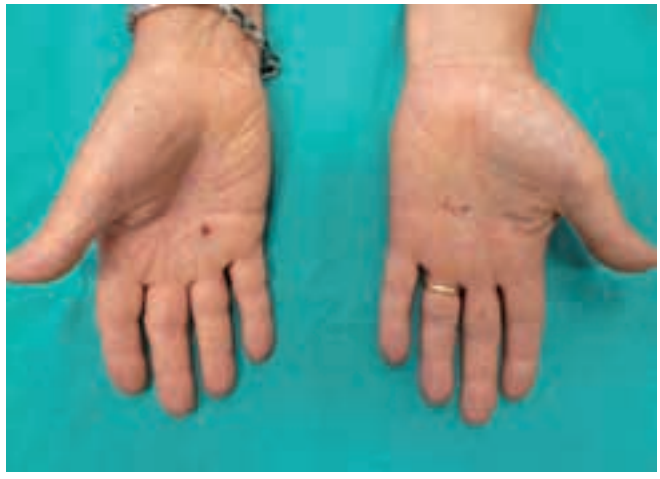
Figure 2.—Clinical improvement at the end of treatment.

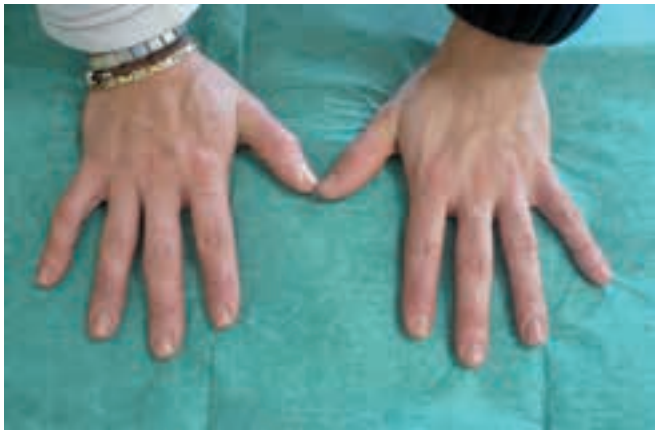
Figure 3.—Clinical condition at the beginning of treatment.

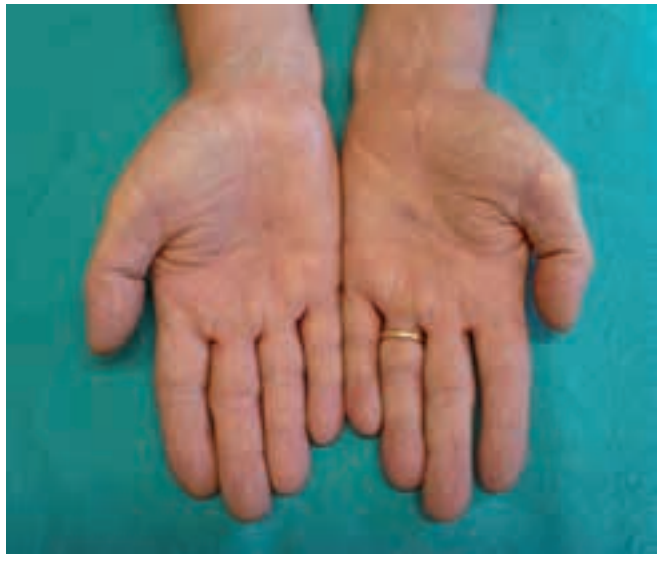
Figure 4.—Clinical improvement at the end of treatment.

Unfortunately literature data from randomized trials on the benefits of these first-line treatment are limited, especially about the use of potent topical glucocorticoids.[8, 15-18]

Aim of the study was to evaluate efficacy, tolerability and safety of combination treatment of fluticasone propionate 0.05% cream with clobetasole ointment 0.05% in the short- and long-management of chronic HE. Topical treatments were used in combination with daily use of emollient cream.

Materials and methods

The study examined 30 patients with a clinical diagnosis of chronic HE. Inclusion criteria were: age older than 18 years, duration of disease more than six months or more than two flares within the last twelve months, use of preventive measures, no use of topical or systemic treatments in the last three weeks. Exclusion criteria were: allergic contact dermatitis of current relevance, diabetes, hypertension and pregnancy.

The patients were divided in two groups according to the severity of the disease assessed with the physicians global assessment (PGA) scale.

Group 1 included 18 patients with mild to chron-

ic HE, treated with fluticasone propionate cream 0.05% once a day for two weeks. The use of emollient cream at least twice a day was also prescribed. After the two-week treatment patients continue with only emollient cream three times a day for 6 weeks.

Group 2 included 12 patients with moderate to severe chronic HE, treated with fluticasone propionate cream 0.05%, once a day for 4 weeks. Then clobetasol ointment 0.05% was prescribed twice a week for four weeks.

The use of emollient cream was always recommended for the whole observation period to be used at least two times a day.

The compounds of emollient cream were: aqua, *Olea europaea* fruit oil, glycerin, pentylene glycol, *Elaeis guineensis* oil, *Olus* oil, hydrogenated lecithin, squalane, betaine, palmitamide MEA, sarcosine, acetamide MEA, hydroxyethylcellulose, sodium carbomer, carbomer, xanthan gum.

A follow-up of the hand was carried out after 2 (T1) and 8 (T2) weeks. During these follow-ups clinical pictures have been recorded and the safety and tolerability of the products have been registered (Figures 1-4). The protocol is reported in Figure 5.

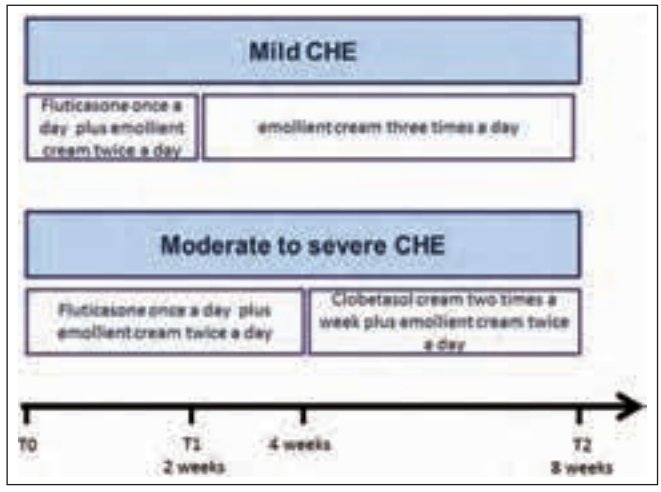

Figure 5.—Treatment protocol.

Results

The severity of chronic HE was mild in 18 patients, moderate to severe in 12. After 8 weeks (T2) 12 of 18 patients of group 1 presented a score of clear (PGA score), 6 patients were almost clear.

Among 12 patients with moderate to severe chronic HE (group 2), 9 of these presented a relevant improvement (PGA clear or almost clear). In 3 patients (10%) suffering from moderate to severe HE, there was no significant improvement and a relapse occurred after the first two weeks of treatment.

Considering all the 30 patients, at T2, 27 patients presented with a significant improvement (the PGA was clear in 14 patients, and almost clear in 13).

Discussion

Chronic HE is a common skin disease. Due to different etiologies, severity levels, lack of classification system, and chronic course, it presents a challenge for dermatologists.[1, 13]

Nowadays, it is recommended that treatment be adapted to the severity of the disease.

Some national and European guidelines and Consensum on the management of this disease have been published.[11, 19, 20] No evidence based guidelines have been published yet. According to the published guidelines, topical corticosteroids are the first-line therapy for HE. As reported by a German study corticosteroid treatments (72.6%) are the most commonly prescribed by private practice physicians.[13]

HE is a challenging condition that can become chronic and unresponsive to the topical treatment. For these reasons treatment of HE should be prompt and effective.

Despite the common use of the topical corticosteroids, papers dealing with this issue and the modality of use of these topical drugs in according to the severity of chronic HE are scanty. Furthermore, also a long-term management should be carried out in this disease.[16-18]

Thus we decided to study these two approaches in according to the severity of the disease. The treatment with topical corticosteroids resulted effective in the management of chronic HE within the two-week treatment (Figures 1-4).

As reported in a Consensus statement [19] topical corticosteroids have been proved to be very effective in the short term, but due to their inhibition in reparation of the stratum corneum they may interfere with recovery in the long term.

In our study, the combination with an emollient cream in mild to moderate cases and the proactive

use (2 times a week) in the moderate to severe cases allowed us to consolidated the results.

These results are consistent with a few others published in the literature.[15-19, 21] Despite new treatments have been introduced in the dermatological armamentarium,[11, 14] further larger studies are needed to better define the use of topical corticosteroids in the short- and long term-management of HE, either alone or in combination with other topical or systemic treatments.

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Efficacy of an emollient dermoprotective cream in the treatment of elderly skin affected by xerosis

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Aim. ***Xerosis cutis*** **is a frequent condition in the elderly and the topical treatments are aimed to maintain a balance between the physiological components of the epidermis and an optimal moisturization. The aim was to evaluate the efficacy of a dermoprotective cream, glycerol and paraffin-based, in the treatment of individuals affected by senile xerosis.**

Methods. **The patients were recruited at the Professional Dermatology and Allergology Outpatient Clinic of the San Gallicano Dermatological Institute of Rome, between 1st January 2013 and 30th September 2014. To assess the efficacy of the cream, two different areas of treatment were identified in each patient upper the limbs. All patients were staged at baseline (T0) and evaluated after 14 days (T1) and 28 days (T2) of topical treatment, using five clinical parameters: scaling, sensation of skin tightness, presence of fissuring and excoriations from scratching and erythema. The itching degree was also evaluated using a 10-steps analogical scale.**

Results. **Fifty patients with xerosis, 25 with a severe and 25 with a moderate form, over 60 were recruited and evaluated. Median age was 65 years (IQR=61-70). After 28 day of topical administration of the cream, the 54.0% of patients showed the absence of signs of xerosis, the 44.0% a mild form and the 2.0% (one patient) a moderate form. Consistently, a progressive and significative reduction of itching and transepidermal water loss (TEWL), and an improvement in skin hydration was also measured. A good profile of tolerability and no episodes of undesirable side effects, was also observed.**

Conclusion. **The topical daily use of a cream glycerol and paraffin-based, seem to able to control the xerosis in elderly patients, with a significant reduction of all associated signs and symptoms. Further additional data should be collected to better confirm the role of the topical treatment in the control of disease.**

KEY WORDS: Aged - Evaluation studies as topic - Skin diseases.

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Xerosis cutis is a frequent condition in the elderly. Though this is a common dermatological disorder, few epidemiological data are available. Some studies, mostly conducted in elderly resident in nursing homes, reported prevalence rates ranging from 30.0% to 75.0%.[1-8]

The aetiology of senile xerosis is associated with several factors, particularly with: 1) changes in the keratinisation process or in the content of epidermal lipids; 2) use of drugs for concomitant chronic disorders; and 3) environmental aggression.[9]

At clinical examination, the skin affected by xerosis is characterised by fissuring and scaling with a tendency to the enlargement. Among elderly people, the anatomical areas commonly affected by xerosis are the upper and lower limbs and the back. These lesions are often cause of intense itching and related scratching, which are itself cause of excoriations and risk of super-infections.[10]

A large epidemiological studies showed that xerosis and severity of its signs and symptoms are associated with female sex, age of patient, dry skin and history of atopia, concomitant use of drugs that can inducing xerosis, and itching during sweating.[11]

Up to date, the treatment of xerosis was mainly based on the topical administration of molecules

able to induce a persistent moisturization, also by the restore of the physiological balance between the different components of the corneous and the dermal stratus of the epidermis.

The purpose of this study was to evaluate the efficacy of a dermocosmetic cream, containing ingredients with a moisturising (glycerol satured) and filmogen/protective (soft white paraffin, liquid vaseline) effect, in the treatment of xerosis cutis in elderly individuals. The study evaluation was conducted using a clinical and instrumental approach.

Materials and methods

Individuals with different degrees of xerosis were recruited at the Professional Dermatology and Allergology Outpatient Clinic at the San Gallicano Institute of Rome, between 1st January 2013 and 30th September 2014.

The study participants were selected according to the following criteria: to be older than 60 years; to be in a good psycho-physical health state (Karnowsky >80); to have a negative history of familial severe skin disorders; not use of anti-inflammatory drugs of the class of FANS; not use of active drugs on the SNC; not use of drugs for cardiovascular pathologies; not use of emollient cosmetic treatments and commitment not to modify their normal daily routines (working and/or domestic).

We decided to conduct a 4-weeks observational evaluation study of the cream by the comparison of the characteristics of affected skin of participants under topical administration. Due to the well-known moisturizing effect of the cream's ingredients, a short observation period of 28 days was determined as appropriate to observe possible measurable outcomes.

All the enrolled patients were informed about the aims of the study and after consent they were educated by the dermatologist on the modalities of application of the cream, two times per day, upon the affected areas. The participants were treated exclusively with the above described cream. After the baseline evaluation (T0) at the enrolment, all the patients were invited to undergo two successive evaluation visits at 14 days (T1) and 28 days (T2).

To evaluate the degree of xerosis of participants at enrolment and at evaluation visits, five different clinical parameters were identified and utilized: scaling, sensation of skin tightness, presence of fissuring, presence of excoriations and erythema. Each parameter was evaluated using a four-level scale of severity: absent (0), mild (+), moderate (++) or severe (+++). In particular, as severe xerosis was defined a condition with a severe degree for at least three different clinical parameters. As moderate xerosis was defined a condition with a severe and moderate degree for at least one and two parameters, respectively. As mild xerosis was defined a condition with a degree equal or less than mild for at least three of five parameters. The average of itching was self-assessed from participants with an analogical scale of values within 0 (no itching) and 10 (severe itching).[12]

Two different areas of affected skin (*i.e.*, calf and forearm) were identified in all participants to conduct the standardized administration of the cream and the clinical and instrumental measurements.

The degree of hydration of the selected skin areas of skin under evaluation, was assessed at T0, T1 and T2, using a TewameterTM 300® (CK Electronic, Cologne, Germany) to obtain a measure of the water evaporation rate in g/h/m^2 (*i.e.*, Transepidermal Waterloss - TEWL). At the same time, the water content of the corneous layer was determined from the same skin areas, using a Corneometer CM 820® (CK Electronic, Cologne, Germany).

Statistical analysis

Descriptive statistics were used to describe the patients' characteristics. Proportions are presented as numbers and percentages. Mc Nemar paired test was performed to evaluate changes in proportion of scaling, skin tightness, fissuring, excoriation and erythema, before and after the application of a dermocosmetic cream. For continuous data measurement (*i.e.*, TEWL, level of water in layer and itching level) the comparison of measures obtained at different time points in the same patients was performed by Friedman test and Wilcoxon adjusted paired test. The level of significance was set at $P \leq 0.05$. All data analysis were conducted using SPSS+ statistical package (SPSS version 21.0, SPSS Inc., Chicago, Illinois, USA).

Results

During the study period 50 individuals over 60 were recruited and 27 (54.0%) of these were women.

At baseline, twenty-five (50.0%) and twenty-five (50.0%) patients were affected by a severe and moderate form of xerosis, respectively. Thus, one third of participants showed a severe degree of scaling (N.=17, 34.0%) and excoriations (N.=15, 30.0%) of the xerotic lesions. Moreover, the 26.0% of patients (N.=13) showed a severe degree of fissuring at level of the limbs, and from 48% to 66% of participants have a moderate degree of severity for all the five parameters (Table I).

At baseline, the median of itching average was elevated (median=8, IQR=6-9) among all participants and higher among men and among over 65. Moreover, elevated rates of TEWL (median=12.2 g/h/m^2) and a low presence of water in the corneous stratum (median=44.0 CAU) was also recorded in all elderly patients (Table II).

At the first follow-up visit, after 2 weeks of daily topical administration of the cream, the clinical evaluation of the treated areas (*i.e.* limbs) showed a significative reduction in the degree of severy of all parameters the disease in the majority of patients. In particular 14 out 15 (93.3%) and 16 out 17 (94.1%) of patients no longer present a severe degree of excoriation and scaling, respectively, and none of the patients no longer present a severe degree of fissuring or sensation of skin tightness. Further improvements were also assessed in each severity degree of the parameters. After 14 days of treatment, 23 out of the 50 enrolled patients with a severe or moderate xerosis, showed a mild degree of disease (Table I). At T1, the clinical improvement of the affected skin of participants was also confirmed by the significative decrease of measure of itching, particularly among older ones, and of TEWL and of water content in corneous layer, improved, from the baseline, of the -20.0% and +21,6% (P<0.001), respectively, without differences by gender or age-group (Table II).

The tendency to an improvement in the patients in all clinical parameters was confirmed and amplified at T2. After 28 day of topical administration of the cream, the 54.0% of patients showed the absence of signs of xerosis, the 44.0% a mild degree of disease severity and only one patient (2.0%) a moderate degree. In particular, at T2 none of the enrolled patients showed a severe or moderate degree of scaling, fissuring, skin tightness or erythema. Similar trend were also obtained after treatment for the parameter "excoriation" (*i.e.*, at T2 severe, moderate, mild and absent, respectively in 0.0%, 4.0%, 40% and 56.0% of patients).

In Figure 1 the distribution of participants by stag-

TABLE I.—*Clinical evaluation of the study participants at baseline (T0), after two weeks of treatment (T1) and at the end of observational study period (T2).*

Clinical parameter	Degree	T0 (N.=50)	T1 (N.=50)	T2 (N.=50)	P value
XEROSIS	Absent	0	0	27 (54)	<0.0001
	Mild	0	23 (46)	22 (44)	
	Moderate	25 (50)	25 (50)	1 (2)	
	Severe	15 (50)	2 (4)	0	
Scaling	Absent	0	2 (4)	30 (60)	<0.0001
	Mild	4 (8)	30 (60)	20 (40)	
	Moderate	29 (58)	17 (34)	0	
	Severe	17 (34)	1 (2)	0	
Tightness	Absent	1 (2)	1 (2)	35 (70)	<0.0001
	Mild	11 (22)	44 (88)	15 (30)	
	Moderate	33 (66)	5 (10)	0	
	Severe	5 (10)	0	0	
Fissuring	Absent	1 (2)	3 (6)	34 (68)	<0.0001
	Mild	10 (20)	33 (66)	16 (32)	
	Moderate	26 (52)	14 (28)	0	
	Severe	13 (26)	0	0	
Excoriation	Absent	1 (2)	3 (6)	28 (56)	<0.0001
	Mild	8 (16)	29 (58)	20 (40)	
	Moderate	26 (52)	17 (34)	2 (4)	
	Severe	15 (30)	1 (2)	0	
Erythema	Absent	0	5 (10)	46 (92)	<0.0001
	Mild	26 (52)	44 (88)	4 (8)	
	Moderate	24 (48)	1 (2)	0	
	Severe	0	0	0	

TABLE II.—*Median values of itching, TEWL and corneometry by gender and age-group in the three phases of the study (T0, T1, T2).*

		T0 (50)	T1 (50)	T2 (50)	P value (T0 *vs.* T1 *vs.* T2)
		Median (range)	Median (range)	Median (range)	
Itching*	Total	8 (6-9)	5 (2-8)	1 (0-5)	<0.0001
	Men	8 (6-9)	6 (3-7)	2 (0-5)	<0.0001
	Women	7 (6-9)	5 (2-8)	1 (0-5)	<0.0001
	P (men *vs.* women)	0.07	0.12	0.15	
	60-65	7 (6-8)	4 (3-6)	0 (0-3)	<0.0001
	66-75	8 (6-9)	5 (2-7)	1 (0-4)	<0.0001
	>75	8 (8-9)	6 (4-8)	3 (0-5)	<0.0001
	P (60-65 *vs.* 66 *vs.* >75)	<0.0001	<0.0001	<0.0001	
TEWL**	Total	12.2 (9.3-14.0)	9.7 (7.6-11.8)	6.8 (5.8-8.3)	<0.0001
	Men	12.0 (9.7-14.0)	9.7 (7.6-11.7)	6.5 (6.0-7.6)	<0.0001
	Women	12.2 (9.3-14.0)	9.7 (8-11.8)	7 (5.8-8.3)	<0.0001
	P(men *vs.* women)	0.85	0.99	0.35	
	60-65	11.7 (9.3-13.4)	9 (7.6-11.0)	6.6 (5.8-7.6)	<0.0001
	66-75	12.6 (9.7-14.0)	10.0 (8.0-11.8)	6.8 (6.0-7.6)	<0.0001
	>75	12.5 (10.5-14.0)	10.0 (8.3-10.7)	7.3 (6.0-8.3)	<0.0001
	P (60-65 *vs.* 66 *vs.* >75)	0.07	0.09	0.13	
Water Corneous Layer***	Total	44 (39.0-48.5)	53.5 (42.0-58.5)	62.0 (55.0-65.0)	<0.0001
	Men	42.5 (39.0-48.5)	52.5 (42.58.5)	62.5 (55.0-65.0)	<0.0001
	Women	44 (39.0-48.0)	54.5 (42.5-58.5)	61.5 (57.5-65.0)	<0.0001
	P (men *vs.* women)	0.31	0.63	0.62	
	60-65	44.5 (40.5-47.0)	53.0 (45.0-58.5)	62.5 (59.5-64.5)	<0.0001
	66-75	44.0 (39.0-48.0)	54.0 (44.0-57.5)	61.5 (58.5-65.0)	<0.0001
	>75	42.0 (39.0-48.5)	56.0 (42.0-58.5)	62.0 (55.0-65.0)	<0.0001
	P (60-65 *vs.* 66 *vs.* >75)	0.47	0.83	0.63	

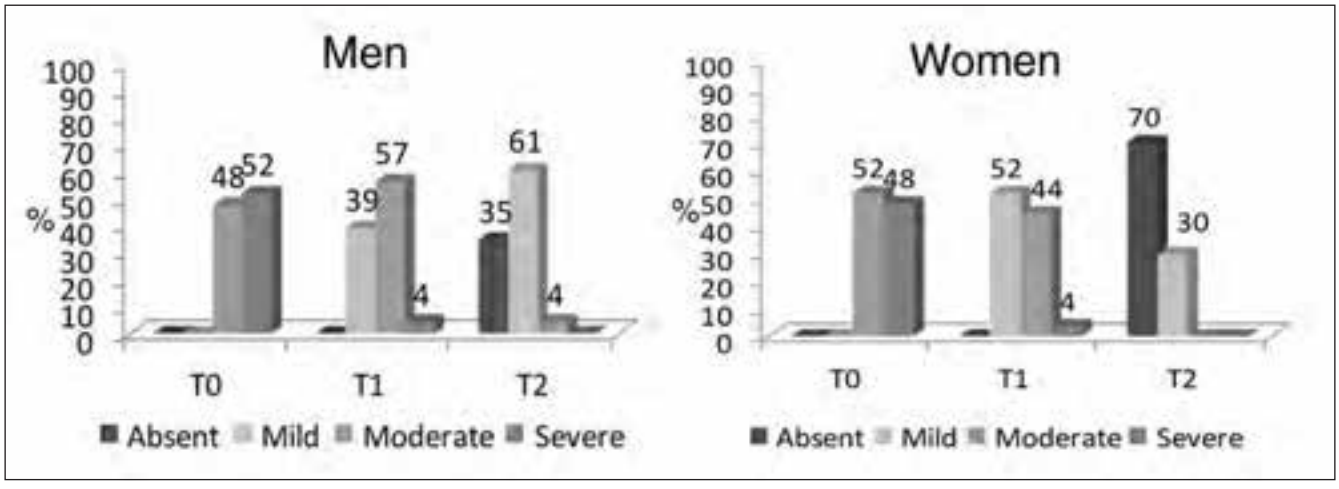

Figure 1.—Proportions of enrolled patients by degree of severity of xerosis by gender in the three phases of the study.

ing of xerosis and evaluation visits showed that, after 28 days of treatment a better global response in females was observed. In fact, while all the participants showing similar staging at enrolment, in T2

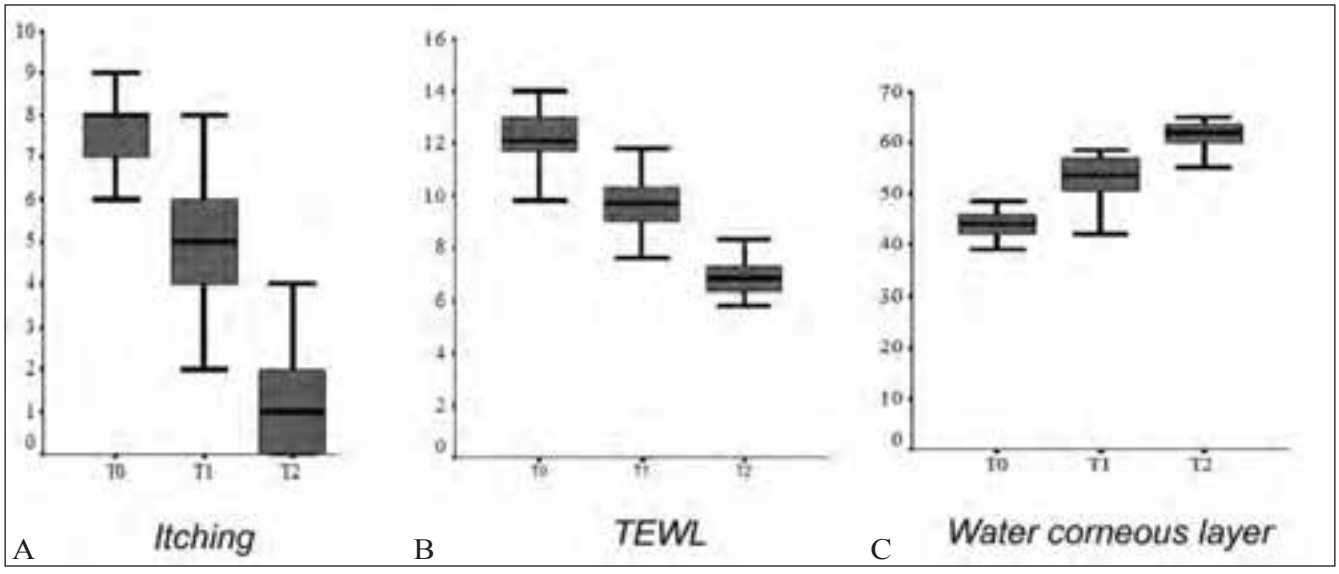

Figure 2.—Graphical representation *(box plot)* of itching (A), TEWL (B) and corneometry (C) median values at time zero (T0), after 14 days (T1) and at 28 days (T2).

the proportion of women who not have signs of xerosis was significantly higher than those among males (70.0% *vs.* 35%, P<0.01) and that the proportion of males with a moderate form of xerosis was twice of that among female (61.0% *vs.* 30.0%, P<0.01).

The instrumental measuring of skin moisturization showed a median value of the TEWL at baseline and T2 of 12.2 g/h/m^2 and 6.8 g/h/m^2, respectively (P<0.001). At T2 the median value of TEWL was slightly lower in men than among women (6.5 g/h/m^2 *vs.* 7.0 g/h/m^2, data not shown), without significant differences by age group. The same evaluation by the Corneometer® showed that the water content in the corneous layer among participants, tend to increase significantly from 44.0 in T0 to 62.0 in T2 (P<0.001), after treatment. No differences by gender and age-group were observed also for the water content in the corneous layer (Table II).

Consistently, among all patients the median value of itching index passed from 8 at baseline to 1 in T2, and a best improvement among under 66 year.

Globally, during the 28 days of follow-up, a progressive and significative reduction of itching and transepidermal water loss (TEWL), and an improvement in skin hydration was measured (Figure 2).

Finally, no mild or severe adverse effects among the treated patients were recorded during the study period or observed in T1 or T2.

Discussion

The xerosis cutis is a frequent dermatological disorder in old ages and among both sexes. The characteristics of chronicity and the worsering course of this disease represents additional factors of disability and decrease of quality of life (QoL) in the elderly. For this reason we decided to evaluate, by a clinical and instrumental observational study, the efficacy of a easy-to apply topical treatment, to reduce the signs and symptoms of xerosis cutis in a population of over 60.

The findings of the trial were collected using a study design without a control study group and based on a brief observation period (4 weeks). This choice was justified by the already well-known moisturizing effect of the cream's ingredients in other disorders and by the use of accurate instrumental measurements of hydration, reliable also in repeated short time assessments.

The data analysis showed that the daily administration (*i.e.*, 2 times) of the dermocosmetic cream, seem to determine a significative reduction of all clinical parameters of severity of xerosis, of the associated itching and to induce a progressive and measurable hydration of the treated skin. All the improvements, were assessed and observed already after the first two weeks of administration of the cream

and were continuous and progressive until the end of the study observation. Notably, all the participants have completed the study and no case of worsening of clinical status from baseline occurred during the entire period of 28 days.

The cream evaluated, based on glycerol satured (15.0%) and paraffin (10.0%), proved to act effectively on skin barrier integrity and on moisturization, probably due to the synergic effect of the two well-known ingredients. In fact, the glycerol has a fast moisturising and smoothing action on the skin and tend to accelerates barrier repair process, improving degradation of corneodesmosomes and restoring of normal keratosis.[13] Differently, the paraffin has a direct effect by the limitation of loss of transepidermal water. The importance of the combination of these two active ingredients has been proven in several studies in which the occlusive properties of paraffin were enhanced in the presence of glycerol when formulated in oil/water emulsions.[14]

Conclusions

The literature provides few studies on senile xerosis and on the efficacy of specific treatments for this pathology and no standardized guidelines for treatment are yet available. This study has demonstrated, using a not invasive clinical and instrumental approach, how the daily twice use of a topical dermocosmetic, based on glycerol and paraffin ingredients, is able, in a well tolerated way, to control xerosis cutis, itching and all the other clinical associated manifestations. To support our data, further prospective studies, conducted on larger sample of patients are needed, also to confirm the persistence of therapeutic effects and tolerability in the long period.

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A comprehensive health impact assessment and determinants of quality of life, health and psychological status in acne patients

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***Aim*. Acne adversely affects all aspects of quality of life (QoL). Although many papers assessed acne-specific QoL impairment, there are few data on its impact on general health and psychological status. Apart from acne severity, little is known about determinants of a worse QoL. The aims of this paper were to measure acne impact on QoL, health and psychological status and to analyze the relationship between socio-demographic variables, disease severity and mental status on QoL of acne sufferers.**

***Methods*. Acne cases were selected from a survey conducted in 2010. The Short-Form 12-Item Health Survey and the Skindex-29 were used to assess health status and QoL. The 12-Items General Health Questionnaire was used to identify individuals at risk for non-psychotic psychiatric disorders (GHQ-positive). Physician (PhGA) and patient global assessments were obtained. We investigated the variables involved in the QoL through a logistic regression analysis.**

***Results*. One hundred ninety-five cases were analyzed. Twenty-six percent were GHQ-positive; acne's impact on health status was worse compared to other chronic diseases. A GHQ-positive status (Skindex-29 overall: OR 2.6; 95% CI 1.20-5.60, P<0.05, functioning: OR 2.5; 95% CI 1.17-5.44, P<0.05, symptoms: OR 3.0; 95% CI 1.36-6.53, P<0.01; emotions: OR 2.55; 95% CI 1.19-5.46, P<0.05) and having a severe/very severe PhGA (Skindex-29 overall: OR 3.4; 95% CI 1.20-10.38, P<0.05) were associated with a poor QoL. Age of onset >25 was linked to being GHQ-positive (OR 2.92; 95% CI 1.2-7.1, P<0.05) controlling for gender, marital status and educational level.**

***Conclusion*. Acne is not a minor disease in comparison with other chronic conditions. Age of onset is capable to influence GHQ status which in turn affects QoL.**

KEY WORDS: Acne vulgaris - Quality of life - Health impact assessment.

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Although neither life threatening nor physically debilitating, acne can severely affect social and psychological functioning in addition to the physical problems it causes.[1] Acne is usually considered to be unimportant and a trivial problem compared to other diseases, but its presence has been implicated in psychiatric and psychological processes more often than most other dermatological conditions.[2] Measures of clinical severity of acne used by dermatologists do not assess the psychosocial effects on patients and are therefore useless to guide clinicians towards the most useful treatment for a given patient. On the other hand there is an increasing recognition of the patient's point of view as an important component in the assessment of healthcare outcomes. The use of self-reported measures of health status reflects the importance of considering the patients' point of view and the multidimensional nature of health.[3] In fact, quality-of-life instruments measure other constructs and not only disease severity. We therefore obtained acne patients' generic and dermatology-specific quality of life (QoL), self-reported disease severity and psychological status, in order to gain a comprehensive assessment of patient's perception of health status.

Materials and methods

Patients

Data concerning acne patients were obtained from an outpatients survey on QoL conducted at the Istituto Dermopatico dell'Immacolata, Roma (IDI-IRCCS), an Italian research hospital which acts as national reference center for dermatological diseases on March 2010.[4] The study was approved by Institutional ethical committee.

For three weeks QoL questionnaires were provided by front-office personnel to all patients asking for a dermatological examination, while three research assistant nurses in the waiting rooms explained the purpose of the study and collected the signed written informed consent forms. Filled questionnaires were then given back by the patient to dermatologist who added on the same form the clinical diagnosis and his/her evaluation of the clinical severity. Inclusion criteria were: age >18 years, ability to understand and read Italian, and signed written informed consent. We analyzed only patients with a clinical diagnosis of acne.

Assessment instruments

All outcome measures were collected using self-reported questionnaires. Patients were assessed for Skin-specific QoL via the Skindex-29,[5] and for health status through the Short-Form 12-Item Health Survey (SF-12) questionnaire.[6] Skindex-29 consists of 29 items, which are combined to form three domains: symptoms, emotions, and functioning. The symptom scale measures the physical burden of the disease, the emotion scale measures the psychological effects of the disease and the functioning subscale focuses on the changes to daily life. For some analysis we also used the overall score of the Skindex-29 even if the validity of the overall score as such is controversial. The domain scores and the overall score are expressed on a 100-point scale, with higher scores indicating a lower level of quality of life. The SF-12 is a generic short form health survey, developed from the original Short Form (SF-36) Health Survey. It produces two summary measures evaluating physical and mental self-perceived health that are identical with those from the SF-36: the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores. High values indicate a better health status. Apolone et al. have conducted local equivalence studies and found that the SF-12 is suitable for use in Italy.[6]

In addition, answers from the basal General Health Questionnaire-12 (GHQ-12), a reliable instrument for detecting current non-psychotic psychiatric disorders, were obtained. Health Survey GHQ-12 has been used and validated in a dermatological setting.[7] For this study, it was scored in a binary method (*i.e.*, 0-0-1-1) yielding a range of values of 0-12 as screening for psychiatric, non-psychotic disorders. Values greater or equals than 4 were considered as positive (i.e. at risk of anxiety and depression), values lower than 4 were considered negative.

For each patient, we obtained also the Physician Global Assessment (PhGA) and the Patient Global Assessment (PtGA), consisting of the questions "In your opinion, compared with other patients with the same condition, how severe is the disease of this patient?" and "In your experience, how severe is your disease?", respectively. Answers were given on a five-point scale: very mild, mild, moderate, severe and very severe.

Data analysis

For analysis purposes, some continuous variables were grouped by median values: the cut-off was 25-year for age, 30.7 for overall score of the Skindex-29, 42.5 for emotions, 16.7 for functioning and 33.9 for symptoms, 47.5 for MCS, 56 for PCS. To compare PhGA and PtGA, we created 3 categories: "agreement": PhGA equal to PtGA; "patient overestimates": PhGA lower than PtGA; and "patient underestimates": PhGA higher than PtGA. Cohen k was calculated to measure the agreement between the evaluations of severity by patients and by physicians. A value of 1 indicates perfect agreement, whereas a value of 0 indicates that agreement is no better than chance. A logistic regression was used to examine how sociodemographic variables (sex, age of onset, marital status, education, GHQ status), and clinical disease severity as assessed by PtGA, each considered as an independent variable may influence the overall score of the Skindex-29 and its scales as well as MCS or PCS. In another logistic regression model sex, disease age of onset, marital status, education were assessed for influencing GHQ status. Finally a politomic logistic regression was used to identify

determinants of patient overestimation/concordance/underestimation of disease severity. A P value <0.05 was considered statistically significant.

Kruskal-Wallis test for continuous variables and the Chi-squared test for dichotomous variables were applied. Data were analyzed using the Stata software, release 11 (StataCorp LP, College Station, TX, USA).

Results

One hundred ninety five patients suffering from acne were recruited. Characteristics of study's population, Skindex-29 and SF-12 scores are summarized in Table I. Male patients and those with age of acne onset after 25 year-old reported higher values in functioning. Concerning symptoms, married patients scored worse than unmarried; we observed a reduction in symptoms as education level increased. Patients classified as being GHQ positive performed worse in all Skindex-29 scales and in MCS score. PCS was slightly higher (i.e. better health status) among GHQ positive.

Overall score of the Skindex-29, emotions and symptoms were better when patients underestimated their disease (Table I). Considering PtGA all Skindex-29 scales (P<0.01) and MCS (P<0.05) scores were worse as PtGA increases (Table II). More than the half GHQ positive patients were found among those affected with a mild disease as reported by PtGA; on the other hand no differences were found stratifying patients by PhGA (Table II). Spearman correlation coefficient was -0.73 between GHQ and MCS score (P<0.001) whereas it was 0.23 between GHQ and PCS (P<0.001). The correlation coefficient didn't changed after adjusting for age of onset. Cohen's kappa between PtGA

TABLE I.—*Characteristics of patients for variables of interest (median values).*

	N. (%)	Skindex-29				SF-12	
		Overall	Emotions	Functioning	Symptoms	MCS	PCS
Overall	195	30.7	42.5	16.7	33.9	47.5	56.0
Sex							
Male	33 (17%)	39.4	45.0	22.9	39.3	51.2	55.7
Female	162 (83%)	29.6	42.5	**15.6***	28.6	46.0	56.0
Age of onset							
≤25	96 (49%)	31.3	40.0	12.5	35.7	47.3	56.1
>25	98 (51%)	30.3	45.0	**20.8****	32.1	48.6	55.9
Marital status							
Unmarried	165 (88%)	30.5	42.5	15.6	32.1	45.7	56.0
Married	23 (12%)	36.4	46.2	20.8	**50.0****	52.0	55.9
Education							
≤8 years	16 (9%)	39.5	48.7	15.6	42.9	52.5	55.4
High school	105 (56%)	31.2	40.0	14.6	35.7	46.5	55.8
University	64 (35%)	28.4	42.5	18.7	**28.6****	47.7	56.2
Occupation							
Student	86 (46%)	29.8	40.0	12.5	30.4	44.2	56.8
Employed	66 (36%)	33.9	45.0	20.8	35.7	49.4	55.9
Unemployed	33 (18%)	32.2	47.5	20	30.4	49.7	55.5
GHQ status							
Positive	50 (26%)	41.6	55.0	32.3	39.3	30.2	57.7
Negative	143 (74%)	**26.9***	**40.0***	**14.6***	**28.6***	**51.4***	**55.9****
Concordance between Physician and Patient Global Assessment							
Patient overestimates	36 (21%)	38.0	55.0	26.1	39.3	44.7	56.6
Agreement	72 (41%)	33.0	45.0	18.7	33.9	50.2	55.9
Patient underestimates	66 (38%)	**26.0****	**40.0****	12.5	**28.6***	50.1	56.0

Totals may vary because of missing values
Values in bold denote statistically significant results (*P<0.01; **P<0.05)
GHQ: 12-Items General Health Questionnaire; SF-12: 12-item Medical Outcomes Study Short Form questionnaire; MCS: Mental Component Summary Score; PCS: Physical Component Summary Score.

TABLE II.—*Quality of life, health and psychological status in acne patients stratified for disease severity as assessed by patients and by dermatologists (median values).*

		Skindex-29				SF-12		GHQ status	
	N. (%)	Overall	Emotions	Function-ing	Symptoms	MCS	PCS	Positive	Negative
Patient Global Assessment									
Mild	92 (51)	24.5	35.0	8.3	25.0	50.4	56.0	25 (13.9%)	67 (37.0%)
Moderate	66 (36)	34.9	45.0	17.8	35.7	48.0	55.9	10 (5.5%)	56 (30.9%)
Severe	23 (13)	**49.1***	**63.9***	**41.7***	**42.9***	**40.6****	56.6	12 (6.6%)	**11*** (6.1%)
Physician Global Assessment									
Mild	79 (42)	26.6	37.5	16.7	28.6	49.2	56.0	18 (9.7%)	61 (32.8%)
Moderate	88 (47)	31.5	45.0	16.7	33.9	49.1	55.6	25 (13.5%)	61 (32.8%)
Severe	21 (11)	39.8	52.5	31.8	39.3	43.7	56.6	6 (3.2%)	15 (8.0%)

Totals may vary because of missing values
Values in bold denote statistically significant results (*P<0.01; **P<0.05)
SF-12: 12-item Medical Outcomes Study Short Form questionnaire; GHQ: 12-Items General Health Questionnaire; MCS: Mental Component Summary Score; PCS: Physical Component Summary Score.

and PhGA was 0.19 with a 51% of agreement (P<0.0006). Skindex-29 as well as MCS score values stratified according to the PtGA classes were statistically different (respectively P<0.0001 and P<0.019), whereas PCS did not.

In a politomic logistic regression patient's female gender has an odds of disease severity underestimation of about 1.17 times greater than the males (regression coefficient: 1.17; 95% CI 0.08-2.3, P<0.05) controlling for marital status, age of onset, educational level or GHQ status. In another logistic regression using gender, disease age of onset, marital status, educational level, PtGA and GHQ status as covariate and MCS, PCS, overall score of the Skindex-29 and its scales as primary independent variables a negative GHQ status was associated with a better QoL in each analysis performed (Overall score of the Skindex-29: OR 2.6; 95% CI 1.20-5.60, P<0.05, functioning: OR 2.5; 95% CI 1.17-5.44, P<0.05, symptoms: OR 3.0; 95% CI 1.36-6.53, P<0.01; emotions: OR 2.55; 95% CI 1.19-5.46, P<0.05) whereas no statistical significant predictors of a better health status as measured by MCS and PCS were recognized. Being affected by a severe/very severe rather than a mild/very mild disease as assessed through PhGA was significantly associated with a poorer QoL (Overall score of the Skindex-29: OR 3.4; 95% CI 1.20-10.38, P<0.05). With regards to psychological status determinants, individuals with age of onset greater than 25-year-old have an odds of being GHQ-positive about 2.9 times greater (OR 2.92; 95% CI 1.2-7.1, P<0.05) controlling for gender, marital status and educational level.

Discussion

Our study tried to comprehensively assess QoL among outpatients with acne of an Italian dermatological referral centre. We used just two questions to evaluate patient's and clinical disease severity and a few questionnaires for psychological status, generic and dermatology-specific QoL, taking patients a short time to answer. Acne resulted having a considerable impact on patients' health status and QoL. Adding a generic to a dermatology-specific health profile is advisable [8] since it measures individuals' health status in generic terms thus allowing a comparison between other non-dermatological diseases. The overall median MCS value among acne patients was 47.5, a worse value compared to those reported for other chronic diseases in Italy. In fact Italian normative values for MCS was 47.7 for diabetes, 48.5 for hypertension, 48.6 for osteoarthrosis/arthritis.[6] Furthermore about a quarter of patients, *i.e.* those GHQ positive, reported a MCS of 30.2. PCS values reported by our patients were not different from the Italian normative values adjusted by age.

Acne sufferers are easily subject to anxiety and depression.[9] Among our patients 26% were GHQ positive, *i.e.* at risk for non-psychotic psychiatric disorders, whereas in another study using GHQ-28 this percentage reached 41%.[10] With this regard, we found that the psychological impact of disease as assessed by GHQ was affected by the disease age of onset. Patients with a greater age of onset have of a worse GHQ status

We are aware of just two studies used Skindex-29

to assess QoL in acne patients. The first by Lasek *et al.*[11] reported slightly lower values compared to those we herein report. Values from the other study by Jones-Caballero *et al.*,[12] which selected mild to moderate affected patients, reported instead the highest values for functioning.

Many papers recognized that acne severity alone does not affect QoL changes and other factors might play a role.[3, 9, 12] Our correlation factor between dermatologist versus patient disease severity assessment was significant but weak, thereby giving further evidence of this impression. Dermatology-specific QoL instruments have been reported to be more sensitive to changes assessing acne severity than generic measures.[12, 13] Our study was cross-sectional but both overall score of the Skindex-29 and MCS varied according to PtGA stratification, confirming the capability of generic measure of capturing patient's severity perception.

Analysis of sociodemographic characteristics showed that in our study married patients complained more about items regarding symptoms. Moreover males, rather than female,[10, 12, 14, 15] had worst QoL for functioning. We are aware of just one study reporting such contradictory results among Egyptians,[16] possibly due to cultural and social factors. This finding was somewhat unexpected because females are known to be more concerned with their looks. It may mean that the problem exceeds the looks issue. Nevertheless, this finding is possibly hampered by the small size of this group because the female effect on QoL disappeared in the logistic model.

Female gender underestimated their disease severity. considering overall dermatological disease among outpatients at our referral centre women have instead more chance of overestimating their disease, regardless of the diagnosis.[17]

Apart from clinical disease severity, being GHQ positive per se is the most significant factor behind patients' low perception of their health status, as previously reported (7). Our results highlight the importance of recognizing and addressing psychiatric comorbidity in acne patients.

Two limitations of this study merit attention. First, we have limited information about the response to treatment of the study population. It has been reported in fact that an effective treatment can effectively reversed the disability caused by acne (14). Second, another potential bias could be represented by the selection of an adult population i.e. patients older than 18. This can reflect a possible selection bias as suggested by the higher than expected patients with older acne age of onset and women percentage, since adult acne is more common in females.[18]

Assessment of acne should not be limited to objective acne severity measures but also include patients' perception of their disease. QoL measures are best for this purpose. This may, in turn, help dermatologists in deciding which treatment is most appropriate for the particular patient. GHQ status should not be ignored when making treatment decisions.

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Quality of life in patients with scalp psoriasis

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Aim. **The aims of this study were to describe the quality of life (QoL) in patients suffering of scalp psoriasis and to assess the impact of the socio-demographic and clinical features of this condition on patients' health-related QoL, using general and specific QoL scales.**
Methods. **This research is a cross-sectional study. The study involved 55 patients attending their first examination at the Dermatology Clinic of Padua University over the course of one year (April 2010-March 2011). The outcome was quality of life analyzed by means Scalpdex and SF-36 questionnaire.**
Results. **The sample's mean Scalpdex score was 43.60±17.52, while the mean SF-36 score was 68.28±20.32. The SF-36 identified statistically significant differences between the psoriasis patients and the Italian general population in two domains, *i.e.* general health (P=0.0075) and emotional role (P=0.0048). The severity of patients' scalp lesions emerged as a factor associated with a reduced QoL in these patients, irrespective of the severity of their disease as a whole. Sex, age, schooling and other socio-demographic factors also characterized patients' perceived QoL.**
Conclusion. **Patients with scalp psoriasis suffered from a lower QoL relating to the highly visible site of their psoriatic lesions. Specific supportive measures should be dedicated to these patients by health care workers.**

KEY WORDS: Scalp - Psoriasis - Quality of Life.

Psoriasis is ubiquitous worldwide with a prevalence of about 2-3%, representing one of the most important dermatological issues. The disease affects up to 5% of the European population,[1] and a recent study estimated its prevalence in Italy at 3%.[2]

Although psoriasis is generally not considered a serious disease, it often causes huge psychological and social problems [3] with a more negative fallout on the patient's health-related quality of life (QoL) than other, more serious diseases.[4] Psoriasis-related psychological and social impairments severely affect patients' QoL. It has also been demonstrated that such psychological and social impairments can influence patients' performance at work, giving rise to lower incomes and higher rates of absence from work and unemployment, adding to the economic burden of the disease in addition to the costs of its treatment.[5] In this scenario, assessing the severity of the disease is a complex process that also demands the patient's psychological assessment.[6, 7] The psychological and social consequences of psoriasis have been the object of several studies, that have highlighted the heavy impact on overall health and well-being in patients with moderate-to-severe disease.[8, 9]

The scalp is one of the body districts affected by psoriasis with the greatest impact on patients' image of themselves, and consequently a cause of severe

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psychological and social impairment. The scalp is the skin area most frequently affected by the disease,[10] with a highly variable clinical presentation that ranges from minimal signs of mild scaling to very severe disease with crusted plaques covering the whole scalp.[11] One of the most relevant aspects of psoriasis, which has a heavy impact on patients' QoL, is the visibility of the lesions, that may advance in many cases beyond the hairline onto the facial skin. Only a few studies have examined the specific effect of scalp psoriasis on QoL, and some have shown that physicians tend to underestimate the effect of such a condition on patients' lives, prompting the need for standardized QoL tools for this particular disease.[12]

The aims of this study were to describe the QoL in patients suffering from scalp psoriasis and to assess the impact of their socio-demographic and clinical features in these patients' health-related (HR) QoL, using generic and specific QoL scales.

Materials and methods

Design

The study design was cross-sectional, observational, with descriptive and analytical purposes.

Setting and population

The study was conducted at the Dermatology Clinic of Padua University Hospital, formally identified as the regional specialist center for the treatment of psoriasis. The study was conducted over a period of one year, from February 2010 to March 2011.

The eligible population consisted of 55 consecutive patients suffering from scalp psoriasis attending the psoriasis outpatients service at the Dermatology Clinic. Inclusion criteria included: age above 18 years and a sufficient comprehension of the Italian language. Exclusion criteria were: pregnancy and the use of neuroleptic drugs. Enrolment was on a voluntary basis and one patient refused to take part in the study.

Instruments and procedure

The tool used for data collection consisted of two sections, the first completed by the researcher and the second by the patient. The first part included: patients' personal and clinical details, and their assessment using the Psoriasis Area and Severity Index (PASI). The second part contained the Scalpdex Questionnaire (a specific tool for assessing QoL for patients suffering from scalp psoriasis), and the SF-36 Questionnaire (a widely-used generic scale for measuring QoL).

The PASI is a tool for grading psoriasis in terms of the extent of the skin lesions on the body areas affected and the severity of the signs (erythema, induration and desquamation of the skin lesions). The score for each symptom ranges from 0 to 4 and the score for the involvement of skin area ranges from 0 to 6. The total score gives an index ranging from 0 to 72. Psoriasis is defined "mild" when PASI index is below 10, "moderate" when it is between 10 and 20 and "severe" when PASI>20.[13]

The clinical severity of the disease was defined using Italian guidelines or those of the Efficacy Working Party of the EMA (European Medicines Agency), classifying the severity of psoriasis as follows: very mild (PASI Score <3), mild (PASI Score >3 and <7), moderate (PASI Score >7 and <12), severe (PASI Score >12 and <20) and very severe (PASI Score >20).[14]

The Scalpdex is a tool for assessing QoL in patients with scalp dermatitis, based on the Skindex scale used to assess the impact of all skin diseases on QoL. The questionnaire contains 23 items, assessed on a 5-point Likert Scale. The possible answers of each items are scored on a scale from 0 to 100 (0 indicates never; 25 rarely; 50 sometimes; 75 often; 100 all the times). The final scores of symptoms, emotions and functioning are calculated by the average of the item scores that pertain to the single scale. According to this model, the higher is the score the worse is the quality of life of the patients proportionally. This tool was translated into Italian by a group of experts (nurses and dermatologists) and tested on a group of patients to ascertain its comprehensibility, reproducibility and sensitivity.[15]

The SF-36 is a questionnaire that investigates the influence of health on QoL, developed in US starting in the 1980s.[16] The tool is generic and multidimensional, and contains 36 questions that refer to eight health domains, *i.e.* physical functioning, role-physical, bodily pain, general health perceptions, vitality, social functioning, role-emotional, and mental health. For each of the eight domains an aggregate percentage score is produced. The percentage scores

range from 0% (lowest or worst possible level of functioning) to 100% (highest or best possible level of functioning). Therefore higher scores on the SF-36 indicate better QoL. For Italy, this instrument was translated and culturally adapted by the IQOLA (International Quality of Life Assessment) project. This questionnaire can be completed by the patients themselves, and provides complementary information in synergy with other, specific tools, contributing to the evaluation of the global health status of patients with psoriasis.[17]

Data collection was done by one of the authors, a nurse actively involved in the research (MB).

The study was approved by the Ethical Committee of Padua University Hospital (Prot. N. 2089P). Patients signed an informed consent form before joining the study. Data protection requirements were observed throughout the study.

Statistical analysis

The data management and statistical analysis were performed using Office Excel 2007® and STATA software 8.1®. Variables were analyzed using descriptive statistical methods, reporting means and standard deviations for continuous variables, and absolute and relative frequencies (proportions) for categorical variables. The t-test was used to test the differences in SF-36 scores between patients with scalp psoriasis and Italian general population "normality" scores. The Italian sample analyzed to evaluate the "normality" scores nearly overlaps the one reported in the present study in terms of age classes, gender differences and years of schooling.[18] A stepwise linear regression analysis (with entry/exit probabilities of 0.10/0.05) was applied to evaluate the variables associated with the scores obtained in the QoL questionnaires. The demographic covariates entered in the models were as follows: sociodemographic variables, *i.e.* gender, age group (18-35 years, 36-59 years, ≥60 years), marital status (single, married), education (primary school, intermediate school, high school, university), occupation (public employee, private employee, unemployed), household dependents (yes, no). The clinical variables considered were: smoking (number of cigarettes), BMI class (≤25, 25-30, ≥30), family history of psoriasis (yes, no), psoriasis in other parts of the body (yes, no), severity of scalp psoriasis (mild, moderate, severe), severity of psoriasis generally (mild, moderate, severe), comorbidities (yes, no), psoriatic arthritis (yes, no), duration of history of psoriasis in years (mean±SD). All tests were conducted considering a 5% significance level ($P<0.05$).

Results

The sample consisted mainly of males and patients between 36 and 51 years of age; 48.15% were unemployed; and the majority were well educated (more than 59% had at least a high school diploma). The 54 patients involved in the study generally had long-standing psoriasis (a mean 12.44±10.59 years having elapsed since it was first diagnosed). Concerning disease severity, their scalp condition was mild in 25.93%, moderate in 29.63% and severe in 44.44% of cases, while their generalized psoriasis was mild, moderate and severe in 35.19%, 40.74% and 24.07% of patients, respectively. The sample's mean PASI score for the scalp lesions was 1.82±1.11, while for the patients' whole skin surface it was 5.11±4.02 (Table I).

The mean Scalpdex Score was 43.60±17.52, and the mean SF-36 score was 68.28±20.32. The SF-36 domains in which psoriasis patients differed statistically from the Italian general population were: general health ($P=0.0075$) and role-emotional ($P=0.0048$) (Table II).

Table III shows the results of stepwise linear regressions on the Scalpdex domains.

Data seem to indicate that middle age patients (36-59 years) tend to have lower functioning scores than younger while married, schooled subject and individuals with moderate severity of the disease tend to have higher functional scores. Symptoms and emotions seem to be influenced negatively by high levels of education while emotional domain have been influenced by the severity of scalp disease and by the presence of psoriatic lesions in other parts of the body. The Scalpdex Score as whole resulted strongly worsened by the high level of education and by the severity of scalp lesions.

The results of the stepwise linear regression models for the scores obtained in the SF-36 domains are given in Table IV. In general, considering the SF-36 Score as a whole, data suggest that severity of psoriasis and scalp psoriasis, smoking habits and the presence of other comorbidities significantly worsen the QoL perception of patients while male gender seem to be associated with better results in QoL scores.

TABLE I.—*Sample characteristics.*

		N.	%
Sociodemographic variables			
Gender	Female	24	44.44
Age group	18-35 y	18	33.33
	36-59 y	26	48.15
	≥60 y	10	18.51
Marital status	Single	20	37.04
	Married	34	62.96
Education	Primary school	7	12.96
	Intermediate school	15	27.78
	High school	22	40.74
	University	10	18.52
Occupation	Public employee	12	22.22
	Private employee	16	29.63
	Unemployed	26	48.15
Household dependents	yes	25	46.30
Clinical variables			
Smoking	Never smoked	24	44.44
	Former smoker	13	24.07
	Current smoker	17	31.48
BMI	≤25	30	55.56
	25-30	17	31.48
	≥30	7	12.96
Positive family history	yes	32	59.26
Psoriasis in other parts of the body	yes	12	22.22
Severity of scalp psoriasis	mild	14	25.93
	moderate	16	29.63
	severe	24	44.44
Severity of psoriasis (total)	mild	19	35.19
	moderate	22	40.74
	severe	13	24.07
Comorbidity	yes	19	35.19
Psoriatic arthritis	yes	4	7.41
		Mean	SD
Duration of disease (years)		12.4	10.6
PASI scalp		1.82	1.11
PASI total body		5.11	4.02

Discussion

This study showed that scalp psoriasis patients fared worse than the general population in terms of role limitations due to emotional problems and general health domains in QoL scales. It also demonstrated that most of the QoL domains (influenced by psoriasis?) are associated with both sociodemographic and clinical variables.

The low scores reflecting role limitations due to emotional problems in scalp psoriasis patients presumably relate to the psychological implications of the disease, particularly when the lesions affect the scalp. Other studies have analyzed the role of psoriasis in cases of depression and death wish,[19, 20] and a recent study reported that scalp dermatitis was a cause of depression in 19.6% of patients and a cause of embarrassment in 27.5%.[15] The results of our regression analyses also suggest that the severity of scalp lesions was an independent clinical factor (even after adjusting for the severity of the patient's psoriasis as whole) associated with role limitations due to emotional problems and the scores obtained in the vitality domain of the SF-36, and with the scores on the emotional subscale of the Scalpdex questionnaire. Moreover, although the clinical severity of the conditions does not always correlate with patients' reported levels of impairment,[21] the clinical severity of scalp lesions - after adjusting, here again, for the severity of the patient's psoriasis as whole - was as-

TABLE II.—*Scalp psoriasis patients' scores in QoL questionnaires.*

	Mean±SD
Scalpdex Score	
Symptoms	39.20±18.64
Functionality	45.00±24.99
Emotions	44.01±18.33
Total Scalpdex Score	43.60±17.52
SF-36	
SF-36 Physical functioning	86.48±18.27
SF-36 Role-physical	73.15±34.93
SF-36 Bodily pain	73.29±27.97
SF-36 General health	56.57±22.86*
SF-36 Vitality	58.98±21.51
SF-36 Social functioning	72.69±24.65
SF-36 Role-emotional	59.88±40.63*
SF-36 Mental health	65.19±19.61
SF-36 Physical health	69.69±20.58
SF-36 Mental health	65.92±24.02
SF-36 Total score	68.28±20.32

*Statistically significant difference (P<0.05) vis-à-vis Italian normative sample [SF-36 general health score in Italian normative sample =65.22; SF-36 Role-emotional score in Italian normative sample =76.16].

TABLE III.—*Stepwise linear regression for Scalpdex Index.*

		β	95%CI LL	95%CI UL	p
Functioning					
Age group (ref group 18-35)	Group 36-59	-23.47	-43.92	-3.01	0.025
	Group ≥60	-23.70	-49.20	1.80	0.068
Severity of scalp psoriasis (ref mild)	Moderate	13.96	2.93	24.99	0.014
Marital status (ref single)	Married	34.55	14.28	54.82	0.001
Psoriasis in other parts of body (ref no)	Yes	11.62	-1.03	24.27	0.071
Education (ref primary school)	Intermediate school	18.66	0.17	37.14	0.048
	high school	30.44	11.26	49.63	0.003
	university	21.74	1.55	41.94	0.035
Symptoms					
Gender (ref female)	Male	-15.13	-22.05	-8.20	0.000
Smoking	N° of cigarettes	0.37	-0.05	0.79	0.081
Education (ref elementary)	High school	9.42	2.68	16.16	0.007
Emotions					
Age group (ref group 18-35)	Group 36-59	-6.95	-13.74	-0.16	0.045
Severity of scalp psoriasis (ref mild)	Moderate	14.66	6.17	23.14	0.001
Severity of scalp psoriasis (ref mild)	Severe	14.94	4.13	19.75	0.004
Severity of psoriasis (ref mild)	Moderate	-5.85	-12.34	0.64	0.076
Psoriasis in other parts of body (ref no)	Yes	8.85	0.72	16.97	0.034
Education (ref primary school)	Intermediate school	24.28	10.16	32.39	0.000
	high school	25.38	15.38	35.38	0.000
	university	18.85	7.05	30.66	0.002
Total Scalpdex score					
Education (ref primary school)	Intermediate school	15.93	5.31	26.54	0.004
	high school	23.20	13.25	33.14	0.000
	university	13.89	2.28	25.50	0.020
Psoriasis in other parts of body (ref no)	Yes	7.02	-0.77	14.81	0.076
Severity of scalp psoriasis (ref mild)	Moderate	13.25	4.96	21.63	0.003
Severity of scalp psoriasis (ref mild)	Severe	9.54	1.83	17.25	0.016

TABLE IV.—*Stepwise linear regressions for SF 36 domains.*

		β	Lower L.	Upper L.	P
Physical functioning					
Household dependents (ref no)	Yes	-8.63	-17.3	0.04	0.51
Gender (ref female)	Male	10.33	1.83	18.83	0.018
Positive family history	Yes	8.83	-0.31	17.98	0.058
Arthritis (ref no)	Yes	-20.78	-36.83	-4.72	0.012
Other comorbidities (ref no)	Yes	-9.10	-18.26	0.06	0.051
Role-physical					
Age group (ref group 18-35)	Group 36-59	18.02	0.11	35.93	0.049
Other comorbidities (ref no)	Yes	-24.21	-42.95	-5.48	0.012
Bodily pain					
Gender (ref female)	Male	21.49	7.52	35.47	0.003
Other comorbidities (ref no)	Yes	-12.70	-27.52	1.83	0.085
General health					
Psoriasis in other parts of body (ref no)	Yes	-15.29	-29.32	-1.25	0.033
Severity of scalp psoriasis (ref very mild)	Moderate	-14.83	-27.61	-2.05	0.024
Vitality					
Gender (ref female)	Male	10.01	0.04	19.99	0.049
Education (ref. primary school)	Intermediate school	-18.57	-35.08	-2.06	0.028
	high school	-24.61	-40.32	-8.60	0.003
	university	-16.95	-34.63	0.72	0.060
Smoking	Number of cigarettes	-1.34	-2.02	-0.67	0.000
Household dependents (ref no)	Yes	-14.63	-25.45	-3.80	0.009
Severity of scalp psoriasis (ref very mild)	Moderate	-17.76	-28.34	-7.17	0.002
Severity of psoriasis (ref very mild)	Moderate	8.60	-1.50	18.70	0.093
Psoriasis in other parts of body (ref no)	Yes	-11.29	-23.76	1.18	0.075
Other comorbidities (ref no)	Yes	-11.81	-22.98	-0.64	0.039
Social functioning					
Age group (ref group 18-35)	Group 36-59	29.83	1.24	58.42	0.041
	Group ≥60	33.88	1.38	66.38	0.041
Duration of disease	Years	0.63	0.00	1.25	0.049
Marital status (ref single)	Married	-32.07	-62.92	-1.22	0.042
Arthritis (ref no)	Yes	21.65	-4.29	47.60	0.100
Other comorbidities (ref no)	Group 36-59	-16.99	-32.17	-1.82	0.029
Smoking	Number of cigarettes	-0.86	-1.89	0.17	0.099
Role-emotional					
Employ (ref cat public employee)	Private employee	18.65	-1.70	39.00	0.071
Age group (ref group 18-35)	Group ≥60	23.43	3.46	43.41	0.023
Gender (ref female)	Male	24.71	6.23	43.19	0.010
Smoking	Number of cigarettes	-2.52	-3.77	1.27	0.000
Household dependents (ref no)	Yes	-30.16	-51.68	-8.64	0.007
Severity of scalp psoriasis (ref very mild)	Moderate	-20.93	-41.38	-0.48	0.045
Severity of psoriasis (ref very mild)	Severe	-45.97	-68.32	-23.62	0.000
Arthritis (ref no)	Yes	39.63	4.02	75.23	0.030
Mental health					
Household dependents (ref no)	Yes	-9.96	-20.32	0.39	0.059
Psoriasis in other parts of body (ref no)	Yes	-9.97	-21.68	1.73	0.093
Gender (ref female)	Male	10.26	0.28	20.25	0.044
Smoking	Number of cigarettes	-0.89	-1.52	-0.21	0.011
Severity of scalp psoriasis p (very mild)	Moderate	-13.59	-24.08	-3.11	0.012
Total SF score					
Age group (ref group 18-35)	Group ≥60y	10.07	-0.50	20.65	0.061
Severity of scalp psoriasis (ref very mild)	Moderate	-12.83	-23.43	-2.22	0.019
Gender (ref female)	Male	14.31	4.56	24.06	0.005
Household dependents (ref no)	Yes	-12.91	-24.21	-1.62	0.026
Smoking	Number of cigarettes	-0.97	-1.63	-0.31	0.005
Other comorbidities (ref no)	Yes	-10.57	-20.95	-0.19	0.046
Severity of psoriasis (ref very mild)	Severe	-11.85	-23.16	-0.53	0.041

sociated with the scores both on the functional subscale of the Scalpdex questionnaire and on the physical health subscale in the SF-36 questionnaire. These findings go to show that scalp lesions are a cause of impaired physical and psychological health regardless of the severity of a patient's psoriasis on other parts of the body. Other factors were found to affect the psychological wellbeing of our patients (as well as the severity of their scalp lesions and psoriasis as a whole), including certain socio-demographic factors, such as gender, education and having a household dependent.

Our data indicated that males reported a better perception of QoL regarding to their bodily pain, vitality, role limitations due to emotional problems, mental health and physical health (in the SF-36), and symptoms (in the Scalpdex) than females, after adjusting for many other covariates. The more limited impairment in perception of QoL in males than in female relating to bodily pain (in SF-36) and symptoms (Scalpex) is broadly consistent with the results of previous studies on numerous different diseases, and gender-related differences in the experience of pain have been widely reported.[22] To be more specific, females are at greater risk of developing several chronic pain disorders, and women exhibit a greater sensitivity to noxious stimuli than men. Several mechanisms have been suggested to explain gender-related differences in the experience of pain, which are often broadly characterized as psychosocial or biological. Psychosocial factors such as beliefs concerning the role of the sexes, strategies for coping with pain, mood, and pain-related expectations, may underlie these differences. There is also evidence to support the impression that familial factors can alter pain responses, and such intergenerational influences may differ between the two genders. Sex hormones are also known to affect pain responses, and may also mediate the gender-related differences.[23] Be that as it may, gender was associated not only with symptom awareness, but also with mental and physical health scores, and total general QoL scores. These finding are consistent with the results of another study reporting a statistically significant greater deterioration in the QoL of females because of their greater perception of the disease compared to men,[24] though a review conducted by deKorte *et al.* found no association between gender and QoL.[25]

Our results also indicate that patients who were better educated had more severe impairments of their mental health and total QoL scores in both questionnaires. While the literature gives the impression that, in the general population, better-educated people have a higher quality of life,[26] some studies on people suffering from chronic diseases found QoL more impaired in those with more years of schooling.[27]

The social impact of psoriasis can be far-reaching and debilitating, as explained in the report from Fortune *et al.*[28] In particular, the problem for patients suffering from psoriasis who have household dependents is an issue generally not considered in the literature, though Eghlileb *et al.* showed that the QoL of members of psoriatic patients' families can also be influenced by the disease: they reported that family members and partners felt a greater psychological pressure and experienced disruptions in their social life as a result of the related embarrassment or the time spent on helping to care for the patient.[29] Our study showed instead that patients with family dependents suffered in terms of their vitality. The burden of caring for a family could be tiring for chronic patients, and their awareness of the psychological pressure on the family caused by their disease could be distressing.

The present study has some limitations. The first relates to the Scalpdex, in that the Italian version was translated officially by a group of experts and tested on a group of patients, but there are still no publications on its validation. Another limit concerns the sample size, which could be increased in future studies, preferably conducted jointly by several centers and including patients admitted to hospital. In addition, our patients complained that it took too long to complete all the questionnaires, indicating the risk of their reflecting too briefly before answering the questions. Another potential bias stems from the fact that a dedicated room was not used to complete the questionnaires and patients may have been distracted in a noisy waiting room.

Conclusions

This study shows that scalp psoriasis could produce not only physical but also psychological and emotional implications. During visits would be necessary a globally assessment of conditions in psoriasis patients and possibly offered tailored treatment pathways with different health care workers, including physician, nurses, psychologists and this coop-

erative team, taking care of these patients, tackle all of their problems, for all course of this long-standing chronic disease.

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Gluten-free diet as a therapeutic approach in psoriatic patients: if yes, when

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Since most of the studies are mainly confined to cases reporting coincidence of psoriasis and celiac disease, the authors want to underline the utility of investigating the possible presence of an underlying celiac disease in normal practice for a better approach to the patient. It is necessary to carry out controlled studies on a large number of patients to evaluate the association between these two diseases and the benefits of a gluten-free diet, even when the intestinal symptomatology is not evident.

KEY WORDS: Psoriasis - Diet, gluten-free - Celiac disease.

Several studies have reported an association between psoriasis and celiac disease with improvement of psoriasis with a gluten-free diet.[1-7] These two immune-mediated diseases seem to be related in a significant number of cases, around 4.34% of psoriatic patients also suffer from celiac disease *vs.* 1-2% of the general population.[2]

Psoriasis is a chronic, relapsing dermatosis characterized by erythema, plaques, scaling and sometimes pustules localized in typical body areas. Psoriasis can also involve joints and give psoriatic arthritis. Several predisposing genetic factors have been recognized to determine psoriasis together with environmental factors that are responsible for "triggering" an immunologic reaction mainly executed through T cells. Structural and functional abnormalities in the gastrointestinal tract, such as degenerative and dystrophic changes in epithelial cells and inflammatory stromal infiltration of the gastric and duodenal mucosa, have been identified in psoriatic patients.[4, 9]

Celiac disease (CD) is a chronic gluten-sensitive enteropathy occurring in genetically predisposed individuals, and caused by a permanent intolerance to gluten.[9] It is now recognized to occur in 1% of the population.[10, 11] The gastro-intestinal inflammation is substained by Gut-Associated Lymphoid Tissue (GALT), the largest and most important part of mucous-associated lymphoid tissue (MALT). CD manifests clinically with intestinal malabsorbtion and its histopathological abnormalities include small intestinal mucosal injury, including villous atrophy with crypt hyperplasia and an intraepithelial lymphocytosis, numerical increase of plasma cells in the lamina propria.[12] In some cases the skin is also involved with herpetiform dermatitis.[13-15] The most common symptoms of CD are diarrhea, abdominal distension, as well as anemia, weakness, fainting, osteoporosis and arthritis, which belong to the extraintestinal manifestations of CD.[10, 16, 17] A gluten-free diet is sufficient to solve both intestinal and cutaneous manifestations.[13-16] Co-occurrence of autoimmune diseases in CD patients has been found (N.=356) in increased

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rates compared to the non-CD group of patients (N.=234). Specifically, autoimmune thyroiditis with a prevalence of 10.34% *vs.* 0.4%, systemic lupus erythematosus (1.1% *vs.* 0%), insuline-dependent diabetes mellitus (2.2% *vs.* 1.7%) and psoriasis (13% *vs.* 5.5%).[9] The study of Iqbal *et al.* (2012) confirmed a recent observation that CD appears to be a risk factor for the development of psoriasis.[9]

Possible pathogenesis

In addition to the hypothesis of an association between these two diseases, some authors have seen, more interestingly, a correlation between psoriasis and a latent sensitivity to gluten.[18-22] Troncone and Jabri suggested that psoriasis could be considered as a part of gluten sensitivity at least in a subgroup of patients. In these patients, the site of immunization against gluten may be extraintestinal and transglutaminase (TG) is most likely not the main target antigen.[23] Higher levels of anti-gliadin IgG/IgA have been observed among psoriatic patients compared to healthy individuals. In fact, both diseases share genetic polymorphism in several immunoregulatory genes (for example, the gene that codes for interleukin-23 receptor).[24] Patients with psoriasis who had raised levels of IgG and/or IgA anti-gliadin antibodies in the absence of anti-TG antibodies showed clinical improvement and a significant reduction of anti-gliadin antibodies in a trial with gluten-free diet.[17] However, this regimen did not improve the disease in those patients without specific antibodies.[18, 25]

Skavland *et al.* (2012) [26] provided evidence for a possible role of wheat proteins in the pathogenesis of psoriasis. The authors conducted a pilot preliminary study based on the analysis of the *in vitro* effect of various wheat proteins or peptides on peripheral blood mononuclear cells (PBMCs), thus identifying a specific antigen with T cell activating properties in a subgroup of patients with psoriasis. PBMCs from 37 patients were exposed in vitro with various concentrations of wheat proteins/peptides: total albumins, α-amylase inhibitor and the synthetic peptides, p31-43, p57-68 and p62-75, based on celiac-active sequences of α-gliadin. Both the albumin fraction and the α-amylase inhibitor induced, in a few subjects, the expression of the skin homing receptor CLA on either CD4+ or CD8+ mononuclear cells, which further supports the suggestion that wheat proteins or degraded products could be involved in psoriasis through specific activation of T cells. This study indicated, but did not prove, that especially the p62-75 wheat peptide may be a relevant psoriasis-specific antigen in a subgroup of patients.[26] They did not find significant role of p57-68 and p31-43 in the lymphocytes proliferation but further investigations can give more insights in their role.

An epidemiological study conducted by Ludvigsson *et al.* (2011) analyzed the risk of patients affected by CD of developing psoriatic lesions. Forty-two percent of all psoriasis in patients with CD could be attributed to the underlying CD.[5]

Several hypotheses have been formulated in an attempt to explain the correlation between psoriasis and positivity to anti-gliadin antibodies (AGA).[3] The following different approaches were proposed: patients with latent sensitivity to gluten have an anomalous intestinal permeability after gluten intake that could act as a "trigger factor" for psoriasis. This increase in intestinal permeability is small and transient in non-CD intestinal tissue, but large and persistent over time in CD intestinal tissue.

Lammers *et al.* (2011) [27] suggested that PT-gliadin is a potent agonist of IL-8 and other cytokine production irrespective of the clinical condition. Since IL-8 is a chemotactic cytokine with proinflammatory and growth-promoting activities involved in the pathogenesis of psoriasis, it is rational to think that a gluten-sensitivity condition may worsen psoriasis manifestation.[27]

In CD, gliadin induces a sensitivity of CD4+ T cells that participate in the formation of psoriatic skin lesions.

Moreover, stimulation by inflammatory cytokines (IL-2, IFN-γ) induced by the AGA can be found in both psoriasis and CD.

Finally, psoriatic lesions could be caused by vitamin D deficiency, a condition present in both diseases.

Gluten-free diet as a therapeutic approach in psoriatic patients

The association between psoriasis and CD is endorsed by the fact that skin lesions of patients suffering from psoriasis and with positivity for anti-gliadin, have regressed significantly after following a gluten-free diet. Many authors have seen a significant improvement of the skin condition of AGA-pos-

TABLE I.—*Research that has investigated gluten-free diet as a therapeutic approach in psoriatic patients.*

	Number of patients with psoriasis and CD	Type of study	Number of patients with psoriasis improved after 3 months of gluten-free diet (GFD)	Remarks	Correlation between severity of psoriasis and antibody levels	References
1	33	Small prospective	30	AGA positive patients with psoriasis enrolled. 2 out of 33 AGA positive patients had IgA antibodies to endomysium (EmA). Significant decrease in mean PASI after GFD was observed. AGA positive patients with psoriasis may improve on a GFD even if they have no EmA or if the increase in duodenal intraepithelial lymphocytes is slight or seemingly absent.	Not provided	Michaelsson *et al.* (2000) [18]
2	1	Case report	1	CD patient with psoriasis not responding to specific anti-psoriatic therapies. Regression of skin lesions after GFD.	Not provided	Addolorato *et al.* (2003) [19]
3	28	Small prospective	N/A	Immunohistological aspects of psoriatic and non-psoriatic skin were evaluated. Ki67+ cells in involved dermis were highly significantly decreased after GFD even in patients without increased intraepithelial lymphocytes. Tissue transglutaminase was highly overexpressed in involved skin in the papillary endothelium, and decreased by 50% after GFD.	Not provided	Michaelsson *et al.* (2003) [22]
4	Review	Review	N/A	Further investigations are needed to clarify the role of a GFD and underlying mechanisms on psoriasis in gluten sensitivity.	Not provided	Wolters *et al.* (2005) [25]
5	Review	Review	N/A	Randomized, controlled studies on the use of GFD in the treatment of psoriasis are warranted.	Not provided	Ricketts *et al.* (2010) [28]

itive psoriatic patients that underwent only a gluten-free diet (Table I).[18, 19, 22]

Montesu *et al.* (2010) have reported a reduction in transglutaminase titre in psoriatic patients using a gluten-free diet that had positivity for AGA and high transglutaminase titres[3]. Another study conducted by Michaelsson *et al.* (2000) highlights the advantages of a gluten-free diet in patients suffering from both diseases.[18] Thirty out of thirty-three AGA-positive psoriatic patients included in the study showed a significant average decrease of the Psoriasis Area and Severity Index (PASI) after following a gluten-free diet. Some authors, also consider that gluten-free diet could have positive effects in the treatment of psoriasis for patients not necessarily AGA-positive (Table I).[28]

Conclusions

Since most of the studies are mainly confined to cases reporting coincidence of the two conditions, it is necessary to carry out controlled studies on a large number of patients to evaluate the association between psoriasis and CD, even when the symptomatology is not evident.

The genes that are common to CD, multiple other antibody mediated autoimmune diseases and psoriasis remain to be identified.

With this paper, the authors want to underline the utility of investigating the possible presence of an underlying CD in normal practice for a better approach to the patient.

Regarding the fact that treatment with a gluten-free diet helps a subgroup of patients with psoriasis that have specific antibodies to gluten, it would be rational to consider suggesting 3-6 months of gluten-free diet in psoriatic patients with IgG/IgA gliadin positivity, in order to possibly improve the patient's cutaneous and systemic condition.

Wheat proteins and peptides might be another antigen/trigger worth exploring in the pathogenesis of psoriasis.

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Antibiotic therapy in the management of atopic dermatitis

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Atopic dermatitis (AD), also known as atopic eczema, is a syndrome characterized by a chronic eczematous dermatitis, with associated pruritus, characteristic age-specific morphology and distribution of lesions and recurrent nature. Secondary infections in patients with AD are very common and difficult to treat. *S. aureus* colonizes almost all eczematous lesions in atopic patients and releases several super-antigens and exotoxins (*i.e.*, toxic shock syndrome toxin-1, enterotoxins A-D, etc.), which sustain inflammatory reactions and promote tachyphylaxis. The topical antibiotics most commonly prescribed for mild/moderate secondary infections are gentamicin, fusidic acid and mupirocine. This article reviews existing therapeutic options and provides guidance for the management of secondary skin infection among patients with AD.

Key words: Dermatitis, atopic - Skin infections - Fusidic acid - Antibacterial agents.

Atopic dermatitis (AD), also known as atopic eczema is a syndrome characterized by a chronic eczematous dermatitis, with associated pruritus, characteristic age-specific morphology and distribution of lesions and recurrent nature. Key features of the disease is skin barrier defect and hyper-reactivity. Given its strong association with lung hyper-reactivity, Wise e Sulzberger, proposed the adjective atopic to define this particular form of dermatitis in 1932.

AD onset usually occurs during early infancy, yet the disease may present later in adolescence or adulthood in few cases. AD prevalence in children and adults is 15-20% and 1-3% respectively.[1] A family history of allergic disorders has been reported to be a strong predictor for the development of AD, which is usually the first manifestation of atopic disease.[2]

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Clinical features, diagnosis and management of AD

AD is characterized by the development of small erythematous papule or papulo-vesicle which eventually evolve into eczematous papules and plaques. The papules coalesce to form erythematous plaque that may display weeping, crusting or scale, depending on the chronicity of the lesions.[2] The primary and most distressing symptom of AD is itch. These features and symptoms and their associated consequences, such as sleep disturbance and the social stigma of a visible skin disorder, may significantly impact the quality of life of these patients and their family.[3, 4] Additionally AD's patients are frequently susceptible to a variety of secondary cutaneous infections (most frequently caused by *Staphylococcus aureus)* such as impetigo or folliculitis. Both com-

monly cause exacerbations of the underlying eczema.

Hanifin and Rajka criteria are the current gold-standard for the diagnosis of AD. Differential diagnosis include scabies, contact dermatitis, psoriasis or other pruritic conditions.[5, 6]

The optimal management of AD requires a multi-treatment approach including both short-term and long-term treatments. Flares and infections require immediate management while longer-term strategies are designed to reduce relapses and mitigate symptoms.[7, 8] Such treatments include emollients, topical steroids, topical antibiotics and topical calcineurin inhibitors (TCIs).[9-12] Even though current medication options are effective in reducing symptoms and controlling the frequency of relapses, they cannot remove the underlying causes of the disease. As such sensible health care decision making should be modulated on disease presentation and pathogenesis.

Management of secondary infections in patients with atopic dermatitis

S. aureus colonizes almost all eczematous lesions in atopic patients [13] and releases several super-antigens and exotoxins (*i.e.*, toxic shock syndrome toxin-1, enterotoxins A-D, etc.), which sustain inflammatory reactions and promote tachyphylaxis. Super-antigens secreted by *S. aureus* are able to activate *T. lymphocytes via* a non-specific pathway and to penetrate the deep layers of the dermis where they interact with different immune-system cells.[14] As a consequence the use of topical antibiotics with antimicrobial properties against this pathogen is indicated in the management of AD flares.[15-17] On the contrary, formal evidence on beneficial effects of topical antiseptics is lacking: a recent Cochrane review did not find any benefit for antibacterial soaps (1 trial, 50 participants), or antibacterial bath additives (2 trials, 41 participants), or topical antibiotics/antiseptics (4 studies, 95 participants).[18]

Additionally, it has been shown that the colonization density of *S. aureus*, a parameter strongly correlated with the severity of cutaneous inflammation, can reach up to 10^7 CFU*cm^{-2} without signs of infections in patients with AD [14] and, conversely, that treatment with anti-inflammatory drugs may reduce *S. aureus* colonization density.[19] For this reason topical antibiotics are often formulated in association with corticosteroids in the attempt to increase effectiveness and improve treatment acceptability compared to the administration of the two products separately. Since therapy adherence is a key factor of effectiveness in all chronic conditions, and especially in pediatric health-care, integrating patients' preferences in clinical decision making is particularly important.[20]

Given the interplay between immunologic factors and colonization density of *S. aureus*, it has been suggested that topical antibiotics may be prescribed even with no overt sign of infection. Despite the association of antibiotic therapy and corticosteroids has been shown to be safe and effective in reducing colonization density and clinical severity scores,[21] antibiotics treatment of eczema presenting no signs of secondary infection, signs of beta-hemolytic streptococci colonization or visible *S. aureus* superinfection, had no effect in regards to clinical improvement and sparing of steroids and should not be carried out.[19]

A further point to consider in clinical decision making is that recolonization is a very common outcome in patients with AD even when a complete eradication in the skin occurs immediately after therapy.[14] Even if systemic antibiotics are effective in treating the infection and reducing flare severity,[14] several studies have shown that sustained eradication is very unlikely and might be impossible because anatomical reservoirs (*i.e.*, the nose, anogenital region, etc.) may not be completely eradicated even with systemic therapy and contacts (*i.e.*, parents and relatives, friends, teachers, etc.) may vehicle transmission since colonization of *S. aureus* is very common in the general population.

Additionally a recent Cochrane review has shown that the clinical significance of the reduction in *S. aureus* colonization achieved with topical therapies is still uncertain [22] and the chronic use of topical antibiotics may promote bacterial resistance. Given that the worldwide spread of antibiotic resistance and the risk of sensitization of repeated use of most common topical antibiotics is a raising concern of dermatologists, the choice of the topical antibiotic is key.

Topical antibiotics prescribed for mild/moderate secondary infections most commonly are gentamicin, fusidic acid (FA) and mupirocine.[23, 24] Gentamicin is an antibiotic of the aminoglycosides class along with neomycin, streptomycin and kanamycin and tobramycin. Aminoglycosides are tradition-

ally adopted for the treatment of infections caused by aerobic gram-negative bacteria. Mupirocine is a mixture of several pseudomonic acids and belongs to the monoxycarbolic acid antibiotic class which was originally isolated from Pseudomonas fluorescens. Conversely FA belongs to a unique class of antibiotics. The fusidanes have antibiotic properties and are derived from the fungus *Fusidium coccineum* but they also have been isolated from *Mucor ramanniianus* and Isaria kogana.

Several efficacy studies have shown that the association of FA and corticosteroids may achieve eradication rates of 98% [25] and is equally or more effective than FA alone, or the associations gentamicin/betamethasone, miconazole/hydrocortisone, neomycin/betamethasone, and clioquinol/betamethasone in infected atopic dermatitis.[26-30] However, FA presents a better safety profile (*i.e.*, very low sensitization potential) and a favorable drug-resistance profile compared to other topical antibiotics.[31]

Contrary to neomycin, gentamycin, mupirocin, beta-lactams, and macrolides FA penetrates both damaged and intact skin resulting in antimicrobial concentrations at deep layers of the epidermis or dermis. FA bactericidal activity (MIC90) has proven to be superior to that of gentamicin and mupirocin both in methicillin-resistant and methicillin-susceptible strains of *S. aureus.*[31]

Additionally, FA steric form strongly reduces the likelihood of contact sensitization, a very important feature in patients with AD who may need repeated use of topical antibiotics in their disease career. As a consequence, sensitization rates are extremely low in adult and pediatric patients treated with FA.[31] On the contrary, in our clinical experience neomycin sensitization was common in children with a history of frequent use of antibiotic creams and ointments containing neomycin or gentamicin for AD or other skin diseases.[32] Similarly sensitization and cross-sensitization rates are high for other aminoglycosides such as gentamicin, framycetin and kanamycin, polypeptides (*i.e.*, bacitracin and polymyxin B), chloramphenicol, oxytetracycline and benzoyl peroxide.[31]

Finally, unnecessary use of topical antibiotics also contributes to antibiotic resistance. *S. Aureus* is particularly efficient in developing resistance to common antibiotics.[33] It has been reported that 40% of *S. aureus* strains are methicillin-resistant in our country. Besides the well-known methicillin-resistant strains, reduced sensitivity to macrolides, aminoglycosides, β-lactam antibiotics and mupirocin [33-36] has been observed early after the introduction of these molecules in clinical practice. Contrary to gentamycin, FA has proven excellent efficacy against methicillin-resistant strains (32% *versus* 93% respectively).[37] Additionally, resistance of methicillin-resistant *S. aureus* to mupirocin increased from 1.6% to 7% between 1995 and 2004 [36] while FA resistance is steadily below 3% in Italy.[38]

Pediatric population

Despite most considerations about AD management in adult patients hold valid in pediatric populations, there are few peculiar aspects of child care which must be taken into account. Despite the well-documented safety of corticosteroids even among children, both pediatricians and parents are sometimes reluctant to administer systemic or topical corticosteroids to young patients with AD in the fear of adverse events.[39] Additionally methicillin-resistant strains of *S. aureus* (MRSA) are increasingly prevalent among children with AD.[40] Finally, pediatric patients are particularly prone to sensitization and the choice of the topical antibiotic should minimize such risk. Given that clinical severity is associated with skin colonization,[41] treatment of super-infected areas is a key aspect of care. Management strategies should include antimicrobial agents that are effective against MRSA and sensibly manipulate corticosteroid dosage to maximize their immune-modulatory potential while minimizing the risk of non-adherence due to corticophobia or skin-related side effects which is associated with new-onset antibiotic resistance.

It has recently been shown that a combination of diluted bleach, topical antibiotics and corticosteroids reduces *S. aureus* skin colonization and clinical severity.[41] As such, the adoption of a combination of diluted bleach, topical antibiotic with a medium potency corticosteroid like betamethasone in the acute phase followed by diluted bleach, topical antibiotics plus low potency corticosteroids such as hydrocortisone in the maintenance stage of flare management might be a sensible strategy in such population. Additionally, the use of low potency corticosteroids such as hydrocortisone in association with topical antibiotics may be better accepted by parents than betamethasone for applications on the face, the neck and skin folds. At the moment, only FA is available

in combination with both betamethasone and hydrocortisone for topical usage and may represent a convenient and effective association with low potential for sensitization and a favorable antibiotic-resistance profile.

Conclusions

The management of bacterial colonization is a key aspect of care for patients with AD. S. Aureus is the most common species isolated from superinfected skin lesions in patients with AD and colonization density is strongly correlated with clinical severity scores. Strong evidence also suggests that chronic inflammation sustains *S. aureus* colonization, a pattern establishing a vicious circle which is difficult to manage. As such the combined used of systemic (*i.e.*, for severe cases) or topical antibiotics (*i.e.*, for mild/moderate cases) with topical corticosteroids is indicated to manage clinically detectable superinfections in patients with AD. Given the high risk of contact sensitization and resistance rates in these patients, the choice of topical antibiotics is key to achieve sustained clinical improvement on the long term. Overall, FA efficacy, safety, sensitization potential, resistance profile and spectrum selectivity make it a first-choice option in the treatment of clinically detectable super-infections in patients with AD.

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Dialysis-associated pseudoporphyria successfully treated with vitamin D

Report of two cases

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Pseudoporphyria refers to a rare bullous dermatosis characterized by the clinical and histological features of porfiria cutanea tarda without abnormalities in porphyrin metabolism. The pathogenesis is heterogeneous and several exogenous factors may promote the bullous lesion formation, including medications, end stage renal disease, dialysis and tanning beds. Regarding treatment of this condition, in literature different therapy have been reported, such as glutathione and his precursor N-acetylcysteine, which presents anti-oxidant properties; however even more toxic drugs, such as chloroquine, are used. Moreover, in patients with drug-induced PP discontinuation of the offending agent, if possible, is a crucial aspect of the clinical management. We report two cases of dialysis patients presenting blisters on extremities, which healed with the avoidance of UV exposure and oral Vitamin D supplementation. Interestingly Vitamin D despite the lack of antioxidant properties led to a completely resolution of PP in both our patients within 30 days. A possible explanation of this finding is that Vitamin D, playing a key role in the regulation of serum Ca^{2+}, can modulated cadherin–cadherin interactions and led to healing of pseudoporphyria bullous lesions. Finally we highlight the prominent role of UV-exposure in PP elicitation thus a good photoprotection is essential for all patients with pseudoporphyria.

KEY WORDS: Vitamin D - Skin diseases - Porphyria cutanea tarda.

Pseudoporphyria (PP) is a vesiculobullous skin disorders that occurs predominantly in patients with renal failure undergoing dialysis therapy. In order to differentiate PP from porphyria cutanea tarda (PCT) it is important to make a full porphyrin investigation of plasma, stool and urine, although this may be difficult in anuric patients. As a matter of fact, PP is an uncommon photodistributed vesciculobullous skin disorder that clinically and histologically resembles PCT, but lacks the biochemical porphyrin abnormalities.[1] The pathogenesis is heterogeneous and not fully understood. A number of exogenous factors may promote bullous lesion formation, including dialytic treatment, that is a well known factor implicated in the activation of PP, especially after UV-ray exposure. In literature several treatment has been reported, including glutathione and his precursor N-acetylcysteine, and more toxic drugs such as chloroquine.[1-3] We report two cases of dialysis patients presenting blisters on extremities, which healed within 30 days thanks to restriction of sun exposure and vitamin D supplementation.

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Case report

A 65-year-old woman presented with a two-weeks history of bullous lesions on her fingers and toes who had been

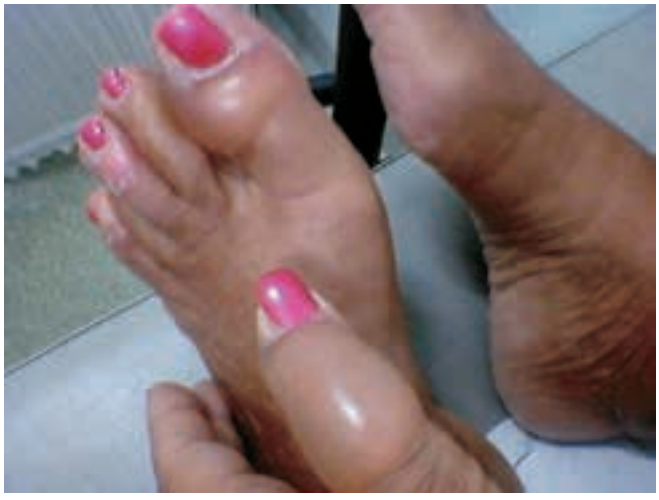

Figure 1.—Bullous lesions on first fingers and first toes, arisen after UV light lamp exposure, in a 65-year-old woman. On other toes are present scaly lesions outcomes of the blister's rupture.

receiving peritoneal dialysis for one year for end stage renal disease (ESDR) secondary to nephroangiosclerosis. These blisters had arisen after UV light lamp exposure for a nails reconstruction treatment. There was no history of photosensitivity, liver disease or excessive alcohol consumption. Family history was unremarkable. Her therapy consisted in ACE-inhibitors, ANG II-receptor antagonists, erythropoietin and cardioaspirin. She had had several episodes of peritonitis treated with teicoplanine and ceftazidime through peritoneal infusion. Clinical examination revealed multiple blisters on fingers and toes, some of which has just broken and were scaly (Figure 1). The level of serum and faecal porphyrins were within normal range. A urine sample was not available because of her ESRD. Result of routine laboratory examinations were within normal limits, except for vitamin D deficiency (7 pg/mL). Skin biopsy was not performed because of the unsuitable localization of the lesions. The cytological examination showed normal cells without any acantholytic cell. The patient was invited to avoid UV exposure and underwent to vitamin D supplementation (1000 UI daily) without changing therapy, although some of the drugs she assumed could be implicated in the PP pathogenesis. The blisters disappeared during the first month. No relapses were observed at 1 year follow-up.

The second patient was a 55-year-old woman who had been on regular hemodialytic treatment for 4 years for ESDR of undetermined origin presented bullous lesions on feet fingertips of the first and the second toe (Figure 2). There was a history of recent excessive sun exposure during the summer months. She did not consume alcohol and had negative serological tests for hepatitis B and C viruses. Family history was unremarkable. Result of routine laboratory examinations showed only a slight normochromic normocytic anemia (haemogobin: 11.2 g/dL) and vitamin

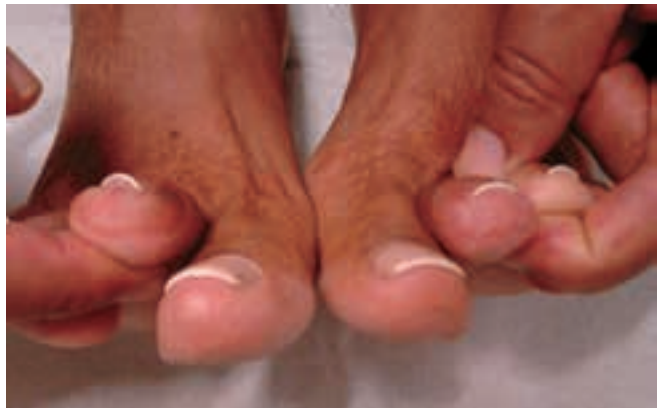

Figure 2.—Bullous lesion on the second fingertips in a 55-year-old woman.

D deficiency (10 pg/mL). Level of plasma and faecal porphyrins were normal. Her therapy consisted in erythropoietin and cardioaspirin. A skin biopsy was not feasible in this patient, too. Cytological examination revealed just scattered lymphocytes. Only vitamin D was prescribed (1000 UI daily) and after 25 days we observed healing of bullae with scarring, without relapses at 1 year follow-up.

Discussion

PP is a rare bullous dermatosis characterized by the clinical and histological features of PCT in the absence of abnormalities in porphyrin metabolism. Patients typically present with skin fragility, bullae, milia, and scarring on the dorsum of the hands and other sun-exposed areas.[1] Although we did not perform a skin biopsy we excluded, in both of our cases, other possible differential diagnosis by cytological examination: in fact the acantholytic cells, typical of pemphigus, were absent as well as the eosinophilic infiltrate consistent with bullous pemphigoid. Moreover, the clinical improvement of the lesions occurred independently of corticosteroid therapy, which was not applied. Although pathogenesis is not fully clear PP has been associated with ESRD, peritoneal dialysis and hemodialysis, and tanning beds. Even several drugs have been implicated in its arising including diuretics, antibiotics, antifungal, retinoids, finasteride as well as alcohol consumption. Also erythropoietin, assumed by both of our patients, is listed as a medication that may elicit pseudoporphyria. Moreover, patients with ESRD are especially prone to oxidative stress due to reduced levels of glutathione in plasma

and circulating erythrocytes, which may increase their susceptibility to the effect of UV exposure even at normal porphyrin levels; this is more pronounced in sun-exposed skin, which may further increase the likelihood of photo-oxidative cutaneous damage. In fact different treatment reported in literature such as glutathione and his precursor N-acetylcysteine have been proposed thanks to their antioxidant properties. In patients with drug-induced PP, discontinuation of the offending agent is also recommended.[1-3]

We propose treatment with oral Vitamin D since its role in the regulation of serum Ca^{2+}; in fact cadherin–cadherin interactions are gated by extracellular Ca^{2+} and it is well known that cadherins play a key role in the dynamics of cell–cell contact formation and remodeling of junctions.[4] Moreover, several data suggest that Vitamin D deficiency has reached a pandemic status and in dialysis patients this condition is almost universal.[5] Interestingly in our patients the avoidance of UV exposure and the vitamin D supplemention led to a complete resolution of lesions that came after only one month, although the resolution of clinical manifestations is usually slow. In fact patients normally can expect a gradual improvement with a decrease in blistering and skin fragility over a period which ranges from months to years.

According to our experience, we highlight the prominent role of UV-exposure in PP elicitation, UV-exposure appears indeed to be more decisive than drugs in its induction, thus a good photoprotection is essential for all patients with pseudoporphyria and should continue at least until resolution of the symptoms. Regarding vitamin D role in PP treatment, controlled investigations are needed, but it is possible that vitamin D thanks to its Ca2+ regulation is a important element for a rapid healing.

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Photodynamic therapy for the treatment of microinvasive squamous cell carcinoma of the lower lip: a case report

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Photodynamic therapy (PDT) with methyl aminolevulinate (MAL) is approved in Europe for the treatment of actinic keratosis and Bowen's disease, both intraepithelial forms of squamous cell carcinoma (SCC). A therapeutic effect of MAL-PDT has been recently suggested for superficial, microinvasive and well-differentiated cutaneous SCC. We describe the successful use of MAL-PDT in a recently observed patient with microinvasive SCC of the lower lip and review published data on the use of PDT with MAL or d-aminolevulinic acid (ALA) in cutaneous microinvasive SCC. A patient with a biopsy-proven recurrent microinvasive SCC of the lower lip was treated with 2 cycles of MAL-PDT. Complete clinical, dermoscopic and histopathological clearance was obtained after 2 cycles of MAL-PDT with an excellent cosmetic result and a sustained remission after 24-month follow-up. A review of the few studies reporting on the use of MAL-PDT or ALA-PDT for cutaneous microinvasive SCCs was carried out. MAL-PDT might represent a non-invasive treatment option for microinvasive SCC of the lower lip if patients are not eligible for surgery. Post-treatment histopathological confirmation and a long-term follow-up are strictly recommended.

KEY WORDS: Skin neoplasms - Carcinoma, squamous cell - Therapeutics.

Squamous cell carcinoma (SCC) is the second most common malignant skin tumor in adults that mainly affects sun-exposed areas. The lower lip vermilion is a frequently affected site due to its direct exposure to sunlight. Surgical excision is the gold standard treatment for SCC of the lower lip although it is often associated with a risk of unsightly scarring.

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Photodynamic therapy (PDT) using either d-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) is a well-established therapeutic modality for the treatment of basal cell carcinoma and intraepithelial forms of SCC such as actinic keratosis (AK) and Bowen's disease, being highly effective and offering excellent cosmetic outcomes.[1] According to recent guidelines, topical PDT is currently not recommended for the treatment of primary cutaneous invasive SCC due to its metastatic potential and to low PDT efficacy rates.[1] However, current evidences suggest the possible application of topical PDT in the treatment of cutaneous microinvasive SCCs, defined as SCCs confined to the papillary dermis, in selected groups of patients who are poor candidates for surgery or with large or multiple lesions in surgically difficult areas.[2-7]

We describe the effectiveness of MAL-PDT in the treatment of a patient with an histopathologically confirmed recurrent microinvasive SCC of the lower lip and review published data on the use of PDT with MAL or ALA in cutaneous microinvasive SCC.

Case report

A 70-year-old white man was referred to our clinic in October 2009 because of a persistent non-healing lesion

located on the lower lip. He was non-smoker with heavy sun exposure over the last 10 years. The patient reported that he underwent surgical excision of a microinvasive SCC of the lower lip two years earlier. On physical examination, we observed a crusty, hyperkeratotic and ulcerated plaque involving almost 50% of the lower lip (Figure 1A). Dermoscopic examination revealed an unspecific pattern with ulceration, scales and whitish scar-like areas (Figure 1B). Microscopic examination of a skin biopsy from the most representative area of the lesion confirmed the presence of a microinvasive SCC, with marked cytologic and architectural changes extending to the superficial portion of the lamina propria (Figure 2A, B). Nodal metastases were ruled out by ultrasonography of the regional lym-

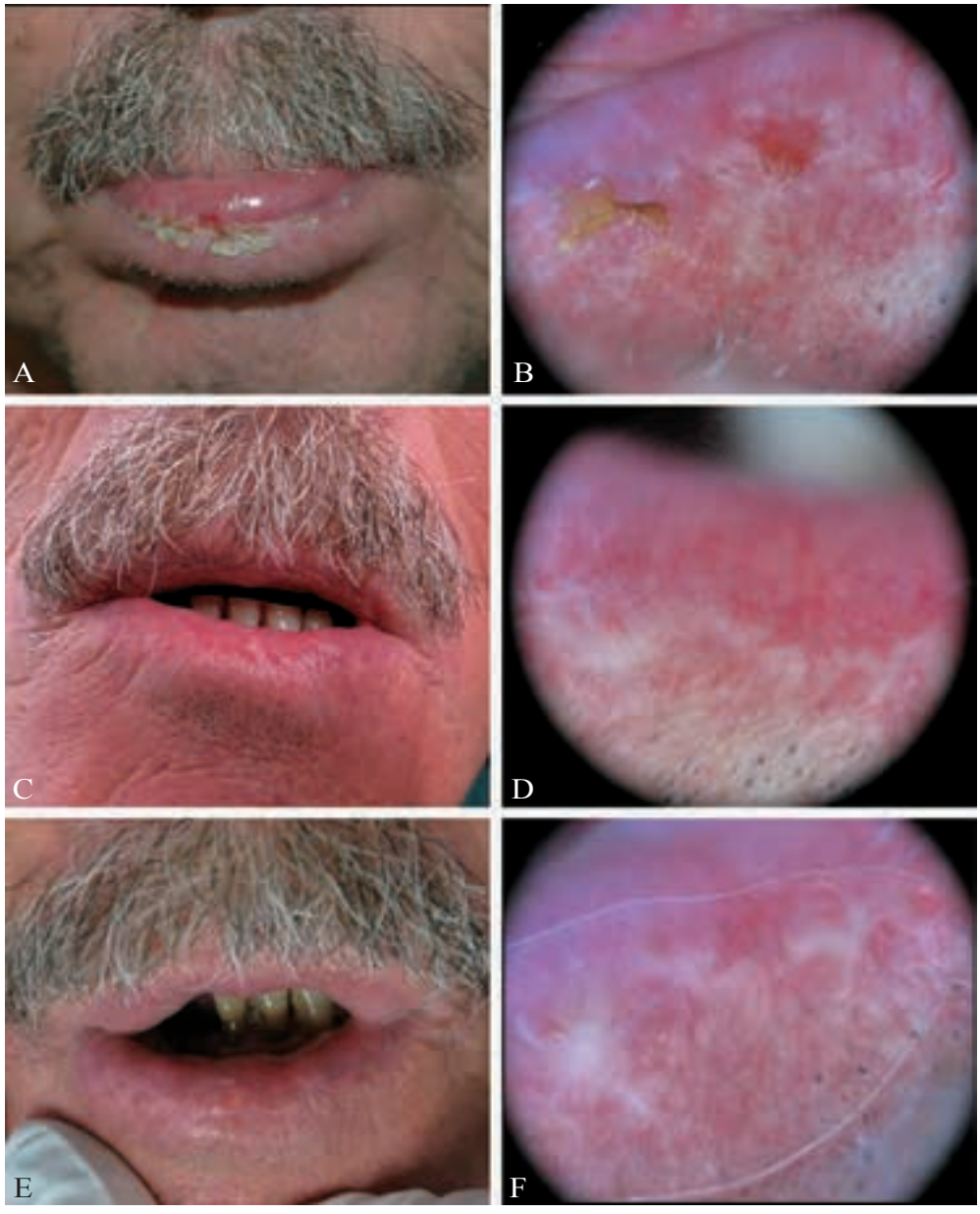

Figure 1.—Clinical images and dermoscopic features of a recurrent microinvasive SCC of the lower lip before and after MAL-PDT treatment. A) Clinical features of the microinvasive SCC; B) dermoscopy shows an unspecific pattern with ulceration, scales and whitish scar-like areas; C-D) clinical e dermoscopic remission after 1 cycle of MAL-PDT and E-F) after 2 cycles of MAL-PDT.

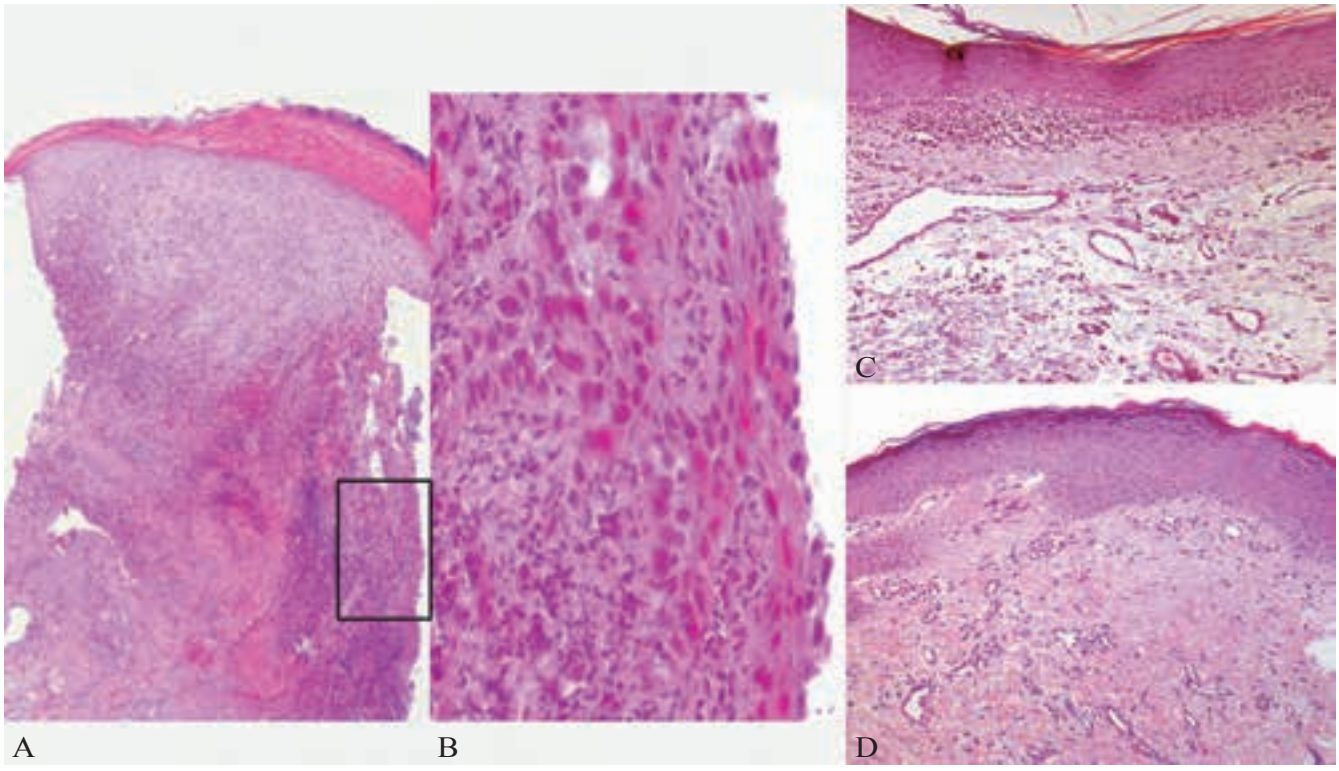

Figure 2.—Histopatological features before and after MAL-PDT. A) Histopathological examination of a skin biopsy before treatment showing a microinvasive SCC characterized by enlarged and elongated rete ridges, exhibiting marked cytologic and architectural changes, with loss of cell polarity, extending to the lamina propria superficially (40X;Hematoxylin/Eosin); B) a detail (black square) at higher magnification, showing the extent of downward growth and angulation of the rete to the superficial compartment of the lamina propria, and the proliferation of atypical keratinocytes with marked nuclear hypercromatism and pleomorfism (200X;Hematoxylin/Eosin); C) mild keratinocytic dysplasia confined to the lower third of the epidermis, with focal inflammatory infiltrate after 1 cycle of MAL-PDT (100X;Hematoxylin/Eosin); D) complete remission after 2 cycles of MAL-PDT (100X;Hematoxylin/Eosin).

phnodes. Since the patient declined surgical procedures, we performed a cycle of MAL-PDT with two sessions at 1-week interval after obtaining patient's written informed consent. MAL (Metvix cream®, Galderma, Paris, France) was applied over the entire lower lip under occlusion for three hours after gentle removal of crusts and scales and the lesion was then illuminated with red (635±18 nm) light at a dose of 37J/cm^2 from a diode lamp (Aktilite® CL128; Photocure ASA, Oslo, Norway) for 7 minutes and 40 seconds at the distance of 8 cm. Managing of the PDT-related pain was obtained by local intralesional anesthesia with mepivacaine 1%. After treatment, the patient experienced transient mild edema and erythema, followed by appearance of erosions and crusting with healing within 1 week. At the 3-month follow-up visit, clinical and dermoscopic examination showed complete regression of the SCC (Figure 1C, D), however, a post-PDT biopsy specimen from the most suspicious area revealed mild keratinocytic dysplasia confined to the lower third of the epidermis, with focal inflammatory infiltrate, consistent with a residual actinic cheilitis (Figure 2C). The lesion was treated with a second PDT cycle requiring local anesthesia, with complete response based on clinical (Figure 1E), dermoscopic (Figure 1F) and histopathological assessment (Figure 2D). After 24 months of follow-up, the patient remains free of disease with no clinical signs of recurrence and regional metastasis.

Discussion

This is the first published observation on the successful use of MAL-PDT for microinvasive SCC of the lower lip. In our patient, complete clinical, dermoscopic and histological clearance was obtained after 2 cycles of MAL-PDT with an excellent cosmetic result and a sustained remission after 24-month follow-up.

The use of PDT for microinvasive SCC has been addressed in a few open-label, uncontrolled trials

TABLE I.—*Clinical trials investigating the use of topical PDT in superficial, microinvasive SCC.*

Author	No. of lesions	Photosensitizer	Light source	Primary complete response % (N.)	Pre-treatment histopathology	Post-treatment histopathology	Complete response after follow-up % (months)
Kennedy *et al.*, 1990[2]	NA*	ALA	Visible light (red light)	100%	Yes	NA	NA
Wolf *et al.*, 1993[3]	6	ALA	Visible light (full spectrum and red light)	83.3% (5/6)	Yes	Yes§	NA
Calzavara-Pinton, 1995[4]	12	ALA	Dye laser	91.6% (11/12)	Yes	Yes¶	83.3%⁇ (10/11) (24-36 months)
Fink-Puches *et al.*, 1998[7]	35	ALA	Visible light (full spectrum or filtered, >515, >570, >610 nm)	54.3% (19/35)	Yes	Yes‡	31% (5/16) (3-47 months)
Fritsch *et al.*, 1998[5]	28	ALA	Visible light	NA	NA	No	62-100% (12-24 months)
Calzavara-Pinton *et al.*, 2008[6]	40	MAL	Red Light	80.0% (32/40)	Yes	No	57.5% (23/40) (24 months)

PDT: photodynamic therapy; SCC: squamous cell carcinoma; ALA: d-aminolevulinic acid; NA: not available; MAL: methyl aminolevulinate
*The Authors report treatment of a total of 6 SCCs either *in situ* or early invasive with no more details.
¶One month after treatment, 8 of 11 superficial SCC showing complete clinical regression were surgically removed. One of 8 lesions showed tumor remnants.
⁇Percentage of complete responses either controlled with histology or after long-term follow-up
‡After therapy, biopsies were performed to confirm the response, recurrence or both in 5 clinically ambiguous cases. In addition, the entire tumor tissue was examined after surgical excision in 4 recurrent lesions. A total of 9 superficial SCC were examined histologically.
§Punch biopsies were performed in cases with uncertain clinical assessment with no further details.

with controversial results, as summarized in Table I.

Calzavara-Pinton *et al.*[6] reported the efficacy, tolerability and cosmetic outcome of MAL-PDT in patients affected by microinvasive SCC achieving a complete response rate of 80.0% at 3 months and 57.5% at the 24-month-follow-up with a good to excellent cosmetic outcome in the majority of the lesions. The degree of cell atypia was the only statistically significant independent predictor of the outcome with higher response rates for well and moderately differentiated SCCs. In this study, all recurrences appeared within 12 months of the treatment with no additional recurrence in the second year of follow-up.

Treatment of microinvasive SCCs with ALA-PDT has been reported in 6 studies achieving complete response in 54-100% of the cases. The outcome of the use of ALA-PDT for microinvasive SCC is difficult to compare, since different methods, treatment schedules and evaluation criteria of clinical benefit have been used. After a follow-up period ranging from 3 to 47 months in the different studies, a sustained complete regression was reported in 31% to 100% of the cases.[2-5,7]

Conclusions

The case described herein suggests that MAL-PDT might represent an alternative option for the treatment of microinvasive SCCs of the lower lip, although it should be proposed exclusively to patients not eligible for surgery. In view of the metastatic potential of lip SCC, assessment of cellular differentiation before treatment, post-treatment histopathological confirmation of clinical clearance and a long-term clinical follow-up are strictly recommended. Large controlled studies are indeed required to confirm the efficacy and to standardize the treatment regimen for the management of initial stages of SCCs.

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Bullous pemphigoid-like eruption subsequent to scabies: bullous scabies or bullous pemphigoid?

TO THE EDITOR: Scabies commonly presents as classic burrows, pruritic papules, and inflammatory nodules, and in rare instance, it may mimic impetigo, psoriasis, contact dermatitis, urticaria, Darier's disease, dermatitis herpetiformis, and bullous pemphigoid-like eruption (bullous scabies [BS]).[1-4] Bullous pemphigoid (BP) subsequent to scabies has been reported rarely.[2] We here describe a case of BP subsequent to BS.

A 78-year-old woman had been hospitalized in a nursing ward for 8 months because of cerebral infarction. Three-month ago, papules appeared on her trunk which increased in numbers and spread the whole body rapidly. Hereafter, discrete nodules presented over her trunk and extremities, and isolated tense blisters with clear fluid, which were hard to rupture, were also present after weeks. Itchy papules with nocturnal predominance occurred on three of her paramedics. The lesions had poor response to antihistamines and topical steroids. Finally, the mites and eggs of *S. Scabiei* were detected by scraping from the papules. The woman and her paramedics had excellent response to topical 10% sulfur ointment.

Two weeks after the disappearing of the previous lesions, a few new bullae, except papules and nodules, relapsed over the hands, lower abdomen and inguinal folds, which didn't respond to sulfur ointment and antihistamines. Neither her relatives nor paramedics had similar eruptions or pruritic lesions this time.

Cutaneous examination showed a few discrete tense blisters filled with clear fluid measuring 0.5-1 cm in diameter over the hands, lower abdomen and right inguinal fold, as well as erosion area after bullae ruptured (Figure 1). The Nikolsky sign was absent. Hyperpigmentation macules and nodules were also noted. Laboratory work-ups showed normal urinalysis and serum chemistries. Complete blood counts showed hyperleukocytosis (12.8×10^9/L, normal range: $4.0\sim10.0\times10^9$/L) and eosinophilia (4.0×10^9/L, normal range $0.1\text{-}0.3\times10^9$/L). Blister fluid cultured for microorganisms was negative. Biopsy from a blister showed epidermal spongiosis, subepidermal cleft with infiltration of many eosinophils, neutrophils, and fibrin. A superficial perivascular and interstitial inflammatory infiltrate composed of small lymphoid cells and eosinophils was present in the dermis (Figure 2A, B). No scabies mites or eggs were noted within the overlying stratum corneum. Direct immunofluorescence of peri-bulllous skin revealed mild band-like deposition of IgM along the basement membrane zone (BMZ), but negative for IgA, IgG, C3 and fibrinogen.

The patient was diagnosed as BP. Because of lung infection, 250 mg of tetracycline four times daily combined with 300 mg of nicotinamide thrice daily were injected by gastrogavage. After 3 weeks of treatment, the blisters disappeared completely leaving behind only hyperpigmentation. The medications were then tapered gradually until stopping. The bullae relapsed after lesions free for 9-month, which presented as bullae initially, denuded area subsequently (Figure 3) and healing spontaneously. After signing informed consent by her guardian, the second biopsy showed linear deposition of IgG and C3 along the BMZ. Using Western blotting, the serum reacted with both 180 kDa (BP180) and 230 kDa (BP230) antigens (Figure 4). Finally, the patient died of pulmonary aspergillosis.

BP-like eruptions may develope concurrently with, or after, the occurrence of scabietic lesions; such conditions may be BS or scabies-induced BP, though both are excep-

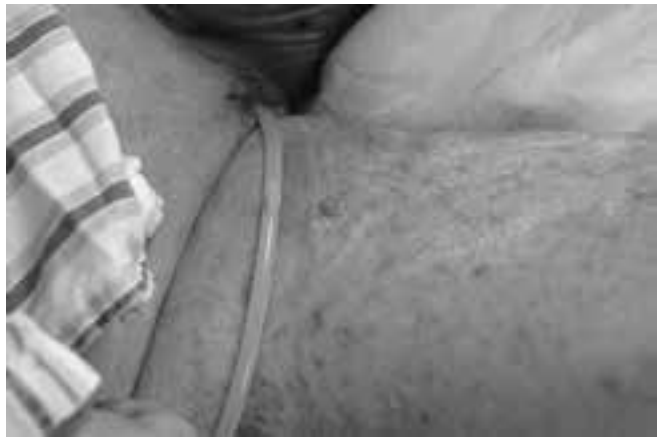

Figure 1.—Tense blister with clear fluid and erosion area on the right inguinal region.

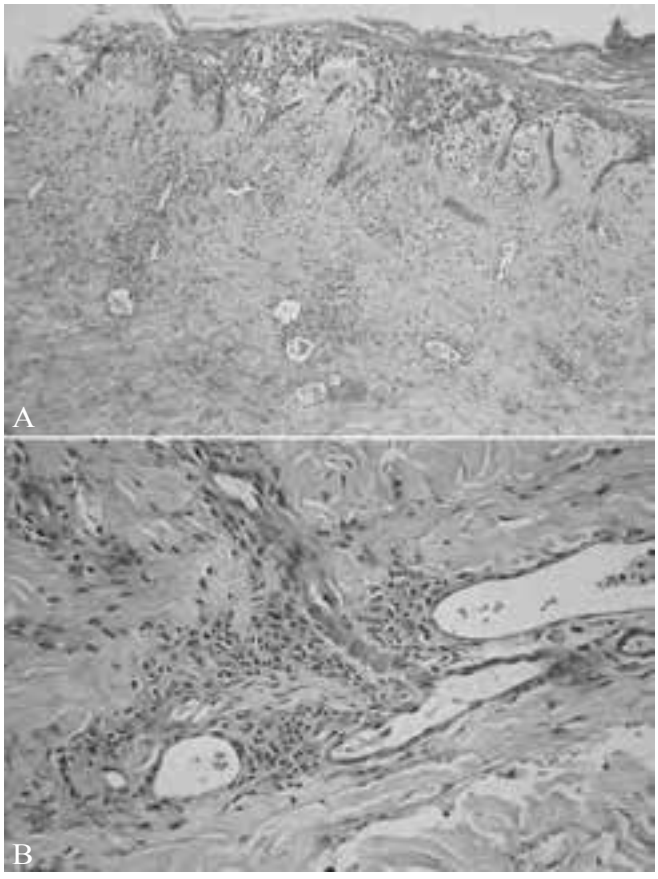

Figure 2.—Spongiosis and subepidermal split along with various inflammatory infiltrate in the superficial dermis (A), the infiltrate cells include neutrophils and many eosinophils (B) (HE staining, a×150, b×400).

tionally rare.[1, 2] The present patient had typical lesions and detecting of scabies mites initially, and the prior bullae had excellent response to sulfur ointment, BS can be concluded. The subsequent blisters were non-contagious and localized distribution, shared the same features of BP including circulating antibodies against both BP180 and BP230, and had poor response to antihistamines and sulfur ointment, but excellent response to tetracycline combined with nicotinamide, BP but not BS can be concluded, though recurrent BS had been described before.[3]

To our knowledge, 41 BS, including 4 Chinese, have been described. It always afflicts the elderly (median age: 70 years) with male predilection (unpublished data. BS shares the similar clinical and histological features of BP,[1-4] and both entities are indistinguishable based on histopathology and direct immunofluorescent studies. Because their therapies are quite different and missing the diagnosis of scabies may result in a risk of outbreak among healthcare workers, it is urgent and necessary to differentiate the two entities.

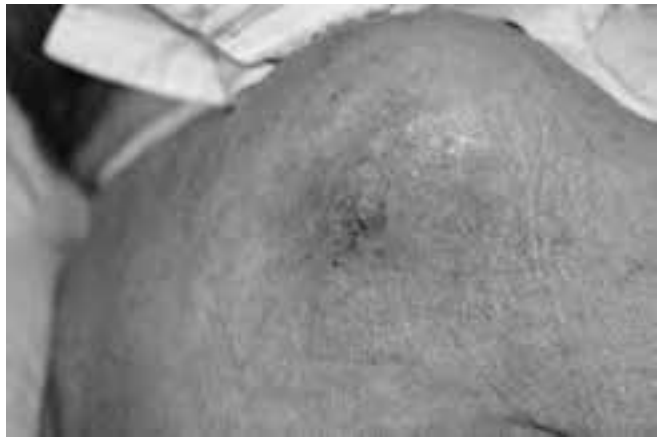

Figure 3.—The denuded area after bullae rupturing.

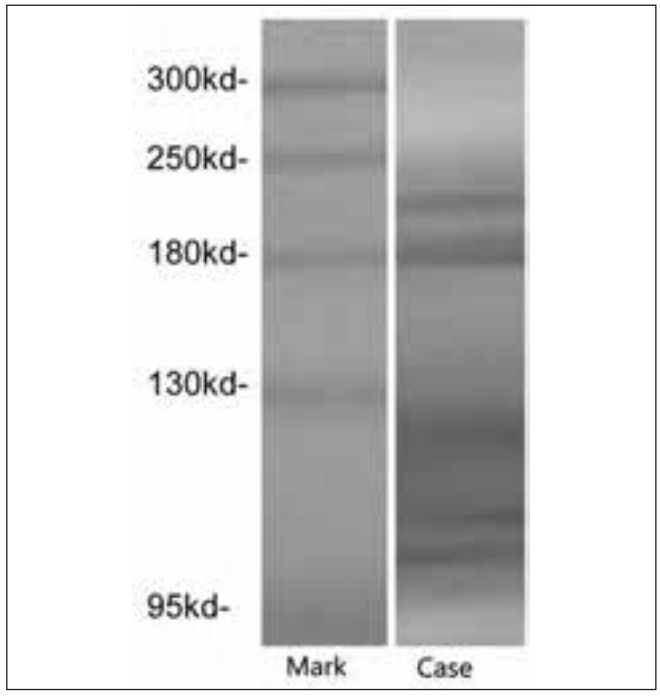

Figure 4.—Western blotting study of serum from the case shows positive for both BP180 and BP230.

As there are no defined diagnostic criteria for BS at present, we propose a practical approach for its diagnosis: the typical scabietic lesions with contagiosity; the bullae occur concurrently with, or after, the occurrence of scabies, and respond well to scabicides, but poorly to anti-histamines and/or topical steroids. If the blisters have poor response to scabicides but good to steroids or immunosuppressants, BP should be considered. We also consider that the differential diagnosis depends upon, in majority, whether the

lesions are contagious and/or have good or poor response to scabicides. In confused condition, diagnostic treatments and detecting of antibodies against BP180 and BP230 can help make the correct diagnosis. The dermatoscopy is also considered a valid tool helping find the scabies mites which is not found by traditional microscopic examination or is not localized in the characteristic zones.[5]

The mechanism of bullous formation in scabies remains unelucidated, although different theories have been suggested which include the induction of BMZ reactive autoantibodies caused by injury of scabies mites, cross-reaction of the mite antigens with BMZ antigens, and id reaction to scabietic mite.[1-4] However, such theories are still hard to explain that the antiscabietic agents can clear both the infestation and the bullous eruptions while steroids or immunosuppressants show no response or even make the lesions worse,[4] which provides a strong evidence that mites may play important rules in bullae formation of BS.[3] As circulating antibodies against BP180 or/and BP 230 had been detected in scabietic patients with bullae,[2] which suggested that some scabies with bullae are true BP, although the exact mechanism remains unknown. For the present BP, we speculate that scabietic mites, as a trigger factor, might activate the production of BMZ reactive autoantibodies that remained in the blood after the removal of the mites, and caused the lesions. Considering the respective frequencies of the two entities, the possibility of fortuitous associations cann't been excluded yet.

The physician should be aware that bullae subsequent to scabies may be BS, BP, or even the both in subsequence.

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Dr. Huang and Dr. Li contributed equally for the present work.

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Hutchinson-Gilford progeria

TO THE EDITOR: Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare genodermatosis characterized by premature ageing starting in the postnatal period that belongs to laminopathies, which affect nuclear lamins. In literature less than 200 cases have been reported and the causative genes have been found to be LMNA and ZMPSTE24. The most common mutation in subjects with HGPS is a *de novo* single-base pair substitution, G608G (GGC>GGT), within exon 11 of LMNA. We present here the case of a 6-month-old boy with a *de novo* p.G608G mutation showing a classic phenotype of HGPS.

A 6-month-old boy referred to our center for failure to thrive and translucent skin. He was the first child born to non-consanguineous parents with no significant family history. He was born at 38 weeks gestation weighting 3 kg after a non-complicated pregnancy without any dysmorphic features. The pediatric control made at 1 month did not reveal any clinical problems. Postnatal growth development has been regular until 4th month of life, when growth parameters started decreasing till reaching the 3rd percentile.

Physical examination showed translucent skin with prominent subcutaneous venous reticle that parents reported to be present since birth, slowly decreased subcutaneous fat in the scalp region and scalp veins easily visible (Figure 1). In addition, the child had fine hair with a peculiar disposition, upswept hairline and alopecia in the temporo-parietal regions. Facies was characterized by frontal bossing, glyphic nose and malar hypoplasia (Figure 2). Neurological and psycophysical development was normal.

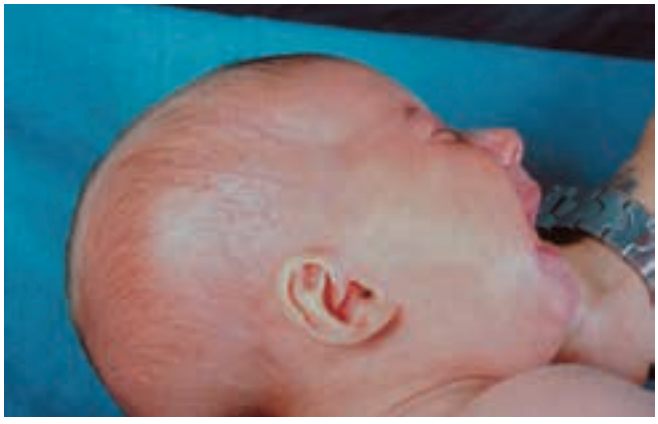

Figure 1.—Translucent skin with evident subcutaneous venous reticle.

By the age of 13 months the patient showed absent teeth eruption and skin anomalies became more marked, with thin and tense skin revealing capillary brittleness whereas at the abdominal region and at his buttocks irregular bumps were noted (Figure 3). He was failing to thrive with a weight of 7.2 kg and a height of 68 cm, both below the 3rd percentile.

A skin biopsy from areas of abnormal skin on the abdomen has been performed, showing mild hyperkeratosis with an increase of melanin in the basal layer. Collagen fibers were sparse, thickened and hyalinized while elastic fibers were unremarkable.

Clinical characteristics induced us to suspect a Hutchinson-Gilford progeria, so we performed a molecular genetic testing. The patient had a *de novo* heterozygous mutation in exon 11 of LMNA gene, with a single-base substitution at nucleotide 1824 (G608G) of the coding sequence.

Hutchinson-Gilford progeria syndrome (HGPS, OMIM 176670) is a rare genetic disease, characterized by several clinical features that develop in the childhood and cause a premature aging condition. Its incidence is estimated of 1 per 4-8 million live births.[1-3] Affected children appear normal at birth but before 1 year of age they present failure to thrive with low weight and short stature and prominent scalp veins. Characteristic facies, alopecia, loss of subcutaneous fat, short stature, stiffness of joints, osteolysis and premature abnormal tightness of the skin over the abdomen and upper thighs usually become apparent by 18 to 24 months of life. Motor and mental development is normal, as well as intelligence, and represents the only index of the patient's real age. Death occurs prematurely in teenage years due to cardiac or cerebrovascular complications due to premature atherosclerosis.[1, 2]

Diagnosis of Hutchinson-Gilford progeria syndrome (HGPS) can be based upon clinical and radiological features, additionally to molecular analysis.

HGPS is caused by different mutations in LMNA or ZMPSTE2 genes, which are involved in a common process of conversion and processing, respectively, of lamin A.

Since 1886, when the first case of HGPS has been found, less than 200 cases have been reported in literature: amongst these, only 48 have been described with their molecular diagnosis.[3, 5]

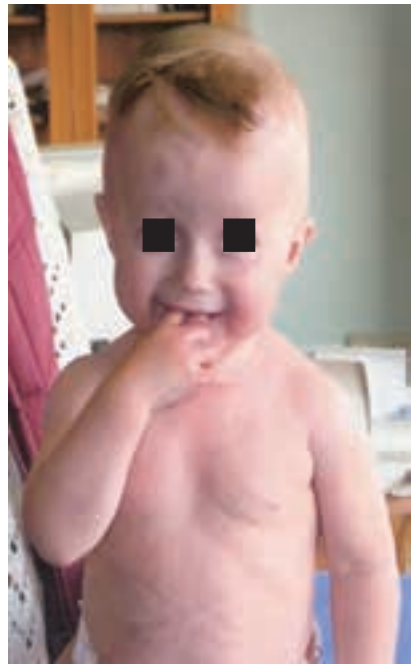

Figure 2.—Facies characterized by frontal bossing, glyphic nose and malar hypoplasia.

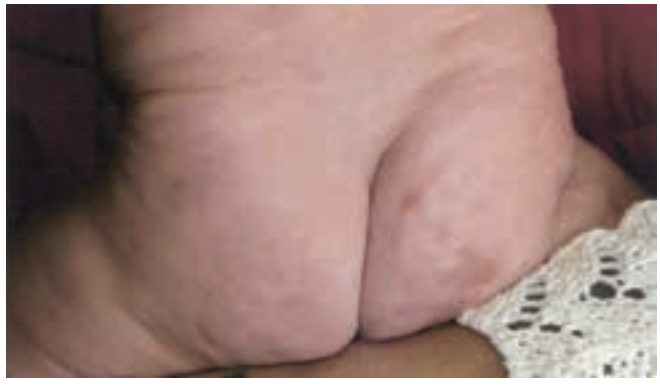

Figure 3.—Sclerodermic skin and irregular bumps at the child's buttocks at 13 months of life.

The disease is frequently caused by a *de novo* heterozygous point mutation at position 1824 in LMNA. This mutation activates a cryptic splice site in exon 11, resulting in the production of progerin, a mutant lamin A with an internal deletion of 50 aminoacids close to the C terminus, including the second ZMPSTE24 cleavage site. Progerin accumulates as a function of cellular age and its increase

amount correlates with the progressive changes in nuclear shape and in nuclear architecture.[5]

Affected children carrying this mutation show a classical phenotype of HGPS, although more severe cases with the same mutation have been occasionally described.[5]

Our index patient shows a classic phenotype of progeria and is affected by the most common mutation in HGPS. This genodermatosis is very rare and clinical features allows a certain diagnosis: nevertheless, since these children look normal at birth, recognition of phenotype may be delayed leading to a mean age at diagnosis of 2.9 years.[3]

We are reporting this case in order to focus on this syndrome and to evidence the slight skin anomalies already present at birth and the ones developing shortly after, to help pediatrics and neonatologists making the correct diagnosis within 1 year of age of the patients. In spite of the fact that this is a "classical" case of progeria, it is very important to highlight this extremely rare syndrome in order to make a right diagnosis the earliest as possible.

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Eosinophilic cellulitis

TO THE EDITOR: A 63-year-old farmer presented recent onset of intense itching in the groin and perineum. The physical examination showed gray-slate plaques, indurated and indolent to the pressure (Figure 1). Laboratory investigations including hemoglobin and total leukocyte counts were normal. Absolute eosinophil count was 600 cells/mm^3 (normal: 40-440 cells/mm^3). Random blood sugar, liver and renal function tests, urinalysis, chest X-ray, and antinuclear antibodies were normal. Histopathologic examination from a biopsy taken from the plaque showed moderately dense superficial and deep perivascular and periappendageal infiltrate of eosinophils and lymphocytes (Figure 2). Several eosinophils in granulomatous figures ("flame figures", Figure 3) were scattered in the interstitium of reticular dermis, around degenerating *fibrillae*, and around the deep vascular plexus. The papillary dermis showed moderate edema. Based on the clinical presentation and the histopathology, a diagnosis of Wells syndrome was made. The patient was given oral prednisolone 75 mg/day in tapering dose over 4 weeks. These lesions initially subsided within 20 days, leaving mild hyperpigmentation. After five weeks from discontinuation of therapy, the patient complained of itch exacerbation with appearance of annular plaques in the same side. So we treated the patient with topical calcineurin inhibitors (tacrolimus-oinment 0.1%), paying attention to the mucous sides, once a day for 2 weeks. No new lesions appeared during treatment and 4 months of follow-up. Wells syndrome is a rare, idiopathic dermatosis with recurrent, erythematous, urticarial plaques that become more indurated and subsequently heal with mild pigmentation. George Wells was the first to describe this syndrome in 1971 as a recurrent granulomatous dermatitis with eosinophilia. Afterwards, in 1979, Wells and Smith introduced the term "eosinophilic cellulitis". This syndrome is characterized clinically by an acute dermatitis resembling cellulitis and histopathologically by dermal eosinophilic infiltration. The course of the disease is mild despite occasional constitutional symptoms. Wells syndrome is usually sporadic, rarely familial. There is

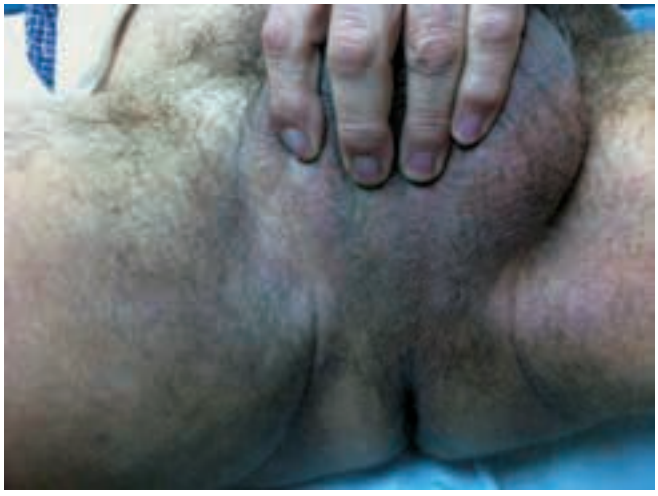

Figure 1.—Eosinophilic cellulitis of perineum.

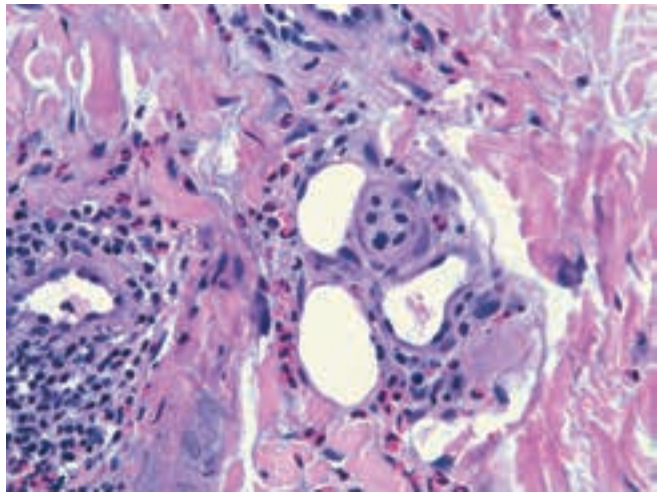

Figure 2.—Histology. Dermal perivascular and perifollicular infiltrate of eosinophils and lymphocytes, also present in the interstitial side.

a wide polymorphism in the clinical and histological presentation of the disease, depending on the nature and location of the infiltrate. Blood eosinophilia can be found.[1, 2] The diagnosis of the Wells syndrome is based on the clinical features and the course of the disease, especially its recurrences and the histopathologic features of eosinophilic infiltration of the dermis. Histopathologically, a dermal infiltrate of histiocytes, eosinophils, and eosinophilic granules occurs between collagen bundles, which form the classic "flame figures", even if these are not unique to the Wells syndrome and can be found in any disorder with a eosinophil-rich infiltrate such as insect bites, pemphigoid and Churg-Strauss syndrome. The flame figures may disappear after the acute stage with the granulomatous infiltrate becoming more evident. The pathogenesis of Wells syndrome is still uncertain: it appears to be the cause of dysregulated tissue eosinophilia. Peripheral T-cell immunophenotyping studies have shown an increased proportion of $CD3^+$ and $CD4^+$ T cells. These lymphocytes spontaneously release significant amounts of interleukin 5 (IL- 5) which is involved in the pathogenesis of blood and tissue eosinophilia. The eosinophils then degranulate in the dermis, causing edema and inflammation. With immunofluorescent stains, eosinophil major basic protein is identified in the granules of the flame figures. The relationship of Wells syndrome to other idiopathic disorders with eosinophils is unknown.[3] Wells syndrome usually improves dramatically with low-dose systemic glucocorticoids. Dapsone, interferon-alpha, cyclosporine, antihistamines, or minocycline have also proved effective. Systemic corticosteroids are the most effective treatment, but they may lead to corticosteroid dependence or resistence, in these cases we can include an use of topical calcineurin inhibitors.[4] Tacrolimus (FK-506) is a strong immunosuppressant, which also downregulates the high-affinity IgE receptor

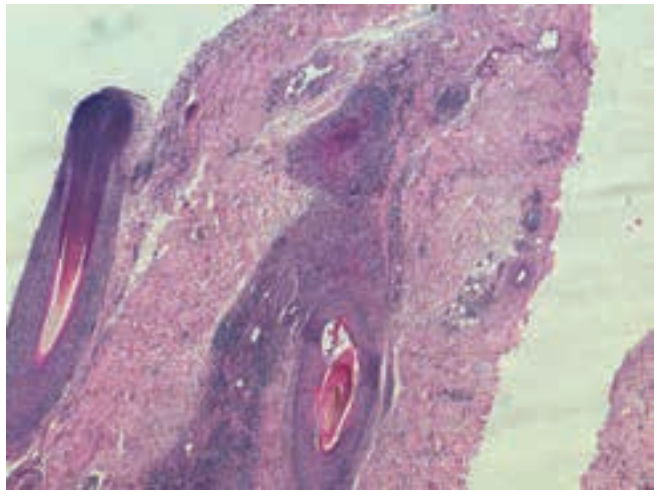

Figure 3.—Histology: flame figures.

I (FcRI) expression on Langerhans cells, a pathogenic event in the formation of flame figures.[5] We report this case for its rarity, in fact this disease is difficult to recognize and sometimes not easy to treat.

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Isotretinoin-induced regression of Fordyce spots in a patient with acne: the first report

TO THE EDITOR: Fordyce spots or granules are common variations of normal sebaceous gland occurring in 70% to 80% of the adult population. They are located in the vermillion border of the lips and oral mucosa. Due to its high frequency in normal population, it may be of cosmetic concern for some patients, especially when they are located on lower lips and come to attention. Here, we report a patient with Fordyce spots who was treated with isotretinon for acne but coincidentally, his Fordyce spots completely disappeared, only after a short period of isotretinoin treatment.

A 27-year-old man with moderate acne for 10 years presented to the clinic. Due to inadequate response to topical therapy and systemic antibiotics, oral isotretinoin at a dose of 10 mg per day was started. The patient also had multiple Fordyce spots in his upper lip area up to 0.5 mm in size, that were easily noticed. Two months after receiving isotretinoin, his acne was under control with no activity, and 1 month later the Fordyce spots disappeared completely. The isotretinoin dose was reduced to 10 mg every other day with no recurrence of Fordyce spots. The patient continues to receive isotretinoin, showing no relapse.

Fordyce spots have been considered ectopic sebaceous glands, histologically associated with no hair follicle. They are often located in the vermillion border of the lip and the oral mocusa, but free sebaceous glands can also be found on the eyelids, areola, labia minor and prepuce. They are usually multiple yellow white papules, 1-2 mm in size, and puberty seems to stimulate their development.

Isotretinoin is a naturally occurring compound resulting from vitamin A metabolism in the body. It is the only retinoid among natural and synthetic retinoids, that can significantly suppress sebum production. This phenomenon explains its dramatic effect on acne and sebaceous glands. Isotretinoin can also induce cell cycle arrest and apoptosis of sebaceous gland cells through RAR-independent mechanism via other pathways or with its metabolite or isomers.[1]

Neutrophil gelatinase associated lipocalin (NGAL) which is involved in the apoptosis of murine B lymphocytes and also innate defense mechanisms, has been recently shown to mediate isotretinoin-induced sebocyte apoptosis. Isotretinoin upregulates NGAL in the patient's sebocytes and can lead to apoptosis in patient's as well as human cultured sebocytes. Tretinoin and alitretinoin do not posses these effects.[2] This sebocyte inhibitory effect may explain the possible mechanism through which isotretinoin can cause the regression and complete disappearance of Fordyce spots.

To the best of our knowledge, this is the first report of a systemic medication that can be used in the treatment of Fordyce spots. They are only rare reports indicating the use of carbon dioxide laser, photodynamic therapy and bichloracetic acid in the management of Fordyce spots.[3-5] All of these remedies seem to be somewhat aggressive for a skin condition, which is regarded as a normal variant by some. Based on our observation, isotretinoin can be an alternative and fairly simple and safe treatment for Fordyce spots in patients who find this entity cosmetically unacceptable. However, further studies with more patients and with long-term follow-ups after discontinuation of isotretinoin is recommended to better demonstrate the effectiveness of isotretinoin in the treatment of Fordyce spots.

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A "monster" case of sarcoidosis

TO THE EDITOR: An 81-year-old woman presented with a 20-year history of multiple, erythematous papules, nodules and plaques on the face and the scalp. The patient was previously diagnosed with chronic discoid lupus erythematous and treated, for some years, with topical corticosteroid and oral hydroxychloraquine without clinical improvement. Her family and personal histories were both negative for cutaneous or systemic diseases. No type of traumatic trigger was reported.

The physical examination revealed multiple, erythematous nodules and plaques, a single ulcerated lesion on the right side of the face, and scarring alopecia of the scalp (Figures 1-4). Routine laboratory tests, including calcium, hepatic and renal function tests were normal. Serologic tests including C-reactive protein, rheumatoid factor, antinuclear antibodies, antimitichondrial antibodies, smooth muscle antibodies, antibodies to native DNA were negative. The serum angiotensin converting enzyme (ACE) level was 115 IU/L (normal: 18-55 IU/L). Erythrocyte sedimentation rate was 52 mm/h (normal: 0-15 mm/h).

A skin biopsy showed "non-caseating epithelioid granulomas with giant cells in the dermal layer".

Detection of acid-fast bacilli was negative in the biopsy sample.

A chest radiography showed "moderate and diffuse accentuation of the pulmonary texture".

Pulmonary function tests revealed a normal ventilatory pattern. High-resolution CT (HRCT) of chest (with and without contrast), showed "sublingual, right over-clavecular, jugular-digastrich, nuchal and para-aortic lymphadenopathy". Sputum for acid-fast bacilli and tuberculin skin test were negative. Ophthalmologic evaluation, revealed normal findings. Based on the clinical, serological, radiological and histological findings, a new diagnosis of cutaneous sarcoidosis with the involvement of pulmonary lymph nodes was made.

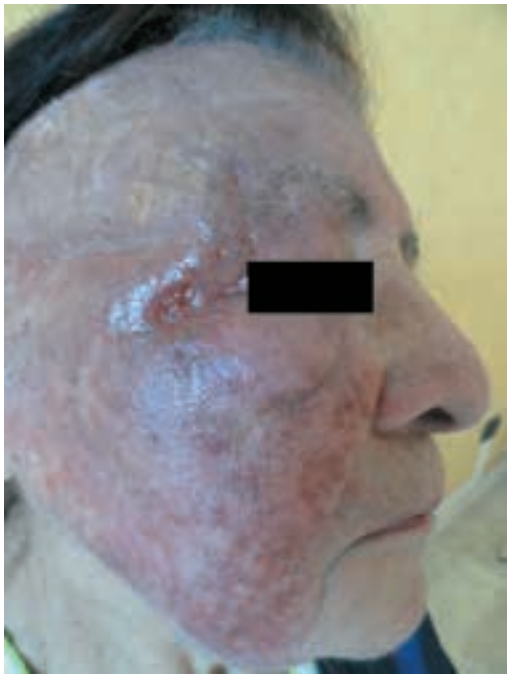

Figure 1.—Multiple, erythematous papules, nodules and plaques and a single ulcerated lesion on the right side of the face.

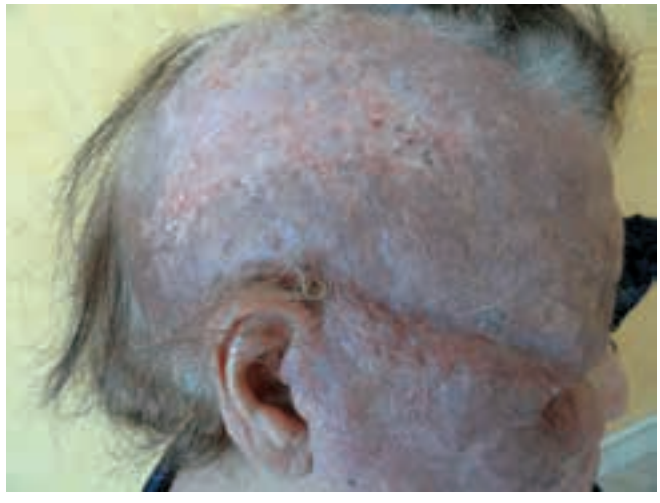

Figure 2.—Extensive scarring alopecia of the scalp.

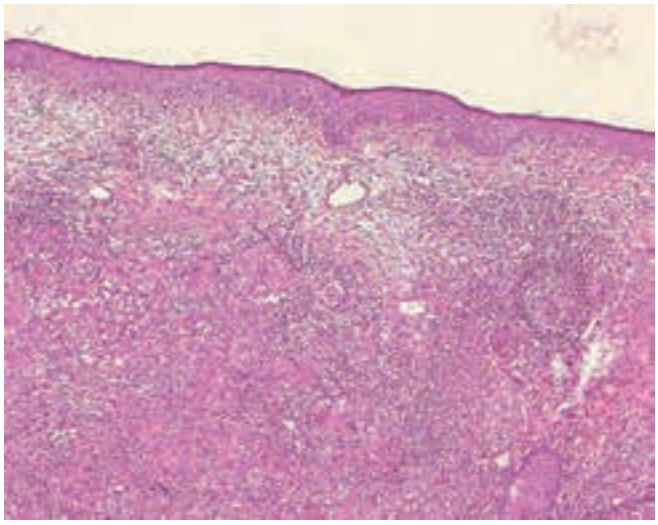

Figure 3.—Punch biopsy of scalp demonstrating numerous uniform circumscribed nests of non-caseating granulomas in the dermis (H&E x30).

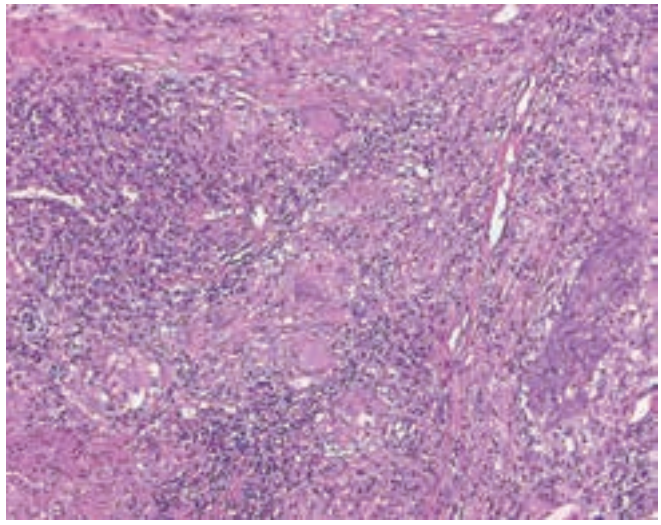

Figure 4.—Higher power of scalp biopsy reveals epithelioid cells with pink citoplasm, limphocites and Langhans giant cells (H&E x150).

The patient was treated with systemic steroids (40 mg/day of oral prednisolone for 4 weeks and gradually reduced over the next month), with visible clinical improvement, resolution of ulcerated lesion and arrest of the progression of scarring alopecia.

Sarcoidosis is a multysistemic disease of unknown etiology histologically characterized by non-caseating epithelioid cell granulomas. The disease may affect any organ. It affects all races, ages and both sexes but is more common and more severe in blacks.[1]

The current concept is that the pathogenesis of sarcoidosis involves the T-helper-1-mediated immune response to environmental antigens in a genetically susceptible host.[2]

Cutaneous involvement in sarcoidosis occurs in about one-quarter of the patients and is generally observed at the onset of the disease.[3]

Skin lesions may be classified in specific when histology shows typical non-caseating granulomatous inflammation or non specific, in presence of reactive process without granulomas.

Specific lesions can include maculopapules, nodules, plaques, subcutaneous nodules, infiltration of scars and lupus pernio. Non-specific lesions include erythema nodosus, calcinosis cutis, prurigo, erythema multiforme and nail changes.

Involvement of the scalp and ulcerative form are two rare manifestations of cutaneous sarcoidosis. The initial presentation of the involvement of the scalp is often a red or flesh-colored patch or plaque of scarring alopecia that may be clinically indistinguishable from discoid lupus erythematous, lichen plano-pilaris and scleroderma. The surface may be scaly or smooth. Over time, the hair loss expands to cover large areas of the scalp and the skin becomes shiny and atrophic.[4] Local destruction and scarring of the follicles in sarcoidosis may lead to permanent hair loss, which resembles pseudopelade of Brocq, a peculiar end-stage process of irreversible scarring alopecia.[5] The ulcerative type of sarcoidosis is the result of skin breakdown of atrophic plaques, often from trauma. As lesions can assume a vast array of morphologies, cutaneous sarcoidosis is known as one of the "great imitators" in dermatology.[3]

The histopathologic changes in specific skin lesions can consist of dermal nests, clusters of non-caseating epithelioid granulomas with minimal inflammatory cells, and variable giant cells. Necrobiotic collagen and necrosis are absent with sparse lymphocytic infiltrate concentrated peripherally around the non-caseating granulomas.

The diagnosis of sarcoidosis is established on the basis of compatible clinical and radiological findings, supported by histological evidence in one or more organs of non-caseating epithelioid cell granulomas in the absence of other potential causes (such as infections). The differential diagnosis with other skin disease, such as discoid lupus erythematosus, lichen planopilaris, scleroderma, pseudopelade of Brocq, folliculitis decalvans, acne keloidalis and dissecting cellulitis of the scalp make accurate diagnosis challenging. Moreover, the cutaneous manifestations of sarcoidosis often represent just the tip of the iceberg often revealing the presence of a multisystem involvement. Therefore, every patient with cutaneous sarcoidosis should receive an initial work-up for systemic involvement, followed by periodic screening. A baseline work-up should include a complete history and physical examination, baseline laboratory testing, chest radiography, pulmonary function testing and an ophthalmologic evaluation.[1] An-

giotensin converting enzyme (ACE) levels are elevated in 60% of patients with sarcoidosis. Unfortunately, while elevated ACE levels are suggestive, no single lab test can prove the diagnosis. Without a definitive diagnostic imaging study, fluid analysis, or blood test, sarcoidosis remains a diagnosis of exclusion.

The treatment of cutaneous sarcoidosis is often frustrating because lesions may be refractory to treatment and often recur after successful treatment.

Many patients with a limited cutaneous disease may require no treatment. Alternatively, cosmetic cover, potent topical corticosteroids or intralesional corticosteroids may be useful. In localized disease, both surgery and radiotherapy have been reported as helpful for some patients. Oral corticosteroids remain the drug of first choice commonly requiring daily doses of 30 to 40 mg of prednisolone for 6 to 12 weeks. Doses are then reduced according to clinical response and treatment is continued for 6 to 12 months.

The prognosis of patients with cutaneous sarcoidosis depends mainly on the extent of systemic involvement. However, it is important to remember that the extent of cutaneous lesions does not correlate always with that of systemic involvement and their prognostic value remain unclear.

We present the case of cutaneous sarcoidosis because of the rare location to the scalp including, the presence of unilateral ulcerative and necrotic lesions on the left side of the face. The difficult differential diagnosis that is extensive and unfortunately for this patient, caused a mistaken diagnosis for an extended period of time. This caused an additional social burden which severely limited her quality of life.

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Rowell syndrome

TO THE EDITOR: A 42-year-old woman presented with a two-week history of widespread, itching, erythematous, scaly papules and plaques. Her family history was negative. Her medical history revealed a two-year history of discoid lupus erythematosus (DLE) previously treated with hydroxychloroquine sulfate (200 mg/day). No history of infectious or pharmacologic triggers was reported. Physical examination revealed multiple, erythematous, scaly, confluent papules and plaques, some of them with annular pattern on the face, neck, trunk, upper and lower limbs. No oral, genital, ocular or palmoplantar lesions were noted (Figures 1, 2).

Laboratory tests showed mild leukopenia ($3.5x10^9/L$), positive antinuclear antibodies (ANA 1:320) with a speckled pattern, erythrocyte sedimentation rate (ESR) 45 mm/l/h and positive rheumatoid factor (RF). Anti-Ro and anti-La antibodies were negative. Antibodies antiherpes simplex virus (HSV), varicella zoster virus (VZV), human herpes virus (HHV6, HHV7) and antimycoplasma pneumoniae were negative. A chest X-ray, abdominal ultrasound and gynecological examination were unremarkable.

Histological examination of a skin biopsy showed a combination of basal cell hydropic degeneration and keratinocyte apoptosis accompanied by a superficial dermal lymphohistiocytic infiltrate associated with lymphocytic exocytosis and satellite cell necrosis. Apoptotic keratinocytes were rounded, intensely eosinophilic and anucleate. Marked basal cell hydropic degeneration resulted in subepidermal vesiculation (Figures 3, 4). Direct immunofluorescence (DIF) of a skin lesion was negative.

Based on the clinical, serological and histological findings, a diagnosis of Rowell syndrome was made.

The patient was treated with systemic steroids (1 mg/kg/day of oral prednisolone for 1 week and subsequently 0.5 mg/kg/day for 3 weeks) associated with synthetic antimalarials (hydroxychloroquine sulfate 400 mg/day) with complete resolution of the lesions after 1 month of treatment.

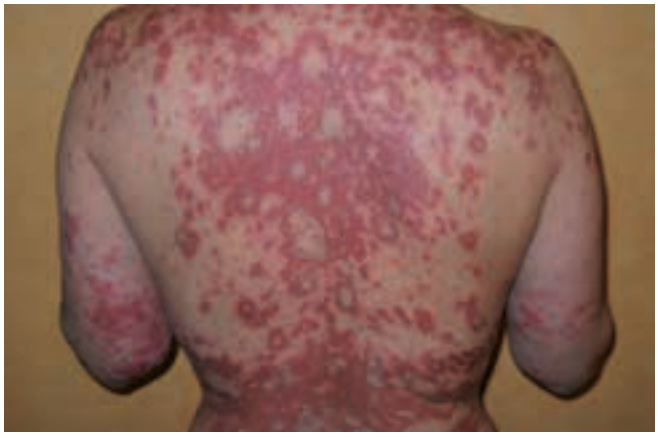

Figure 1.—Multiple, erythematous, scaly, confluent papules and plaques on the trunk.

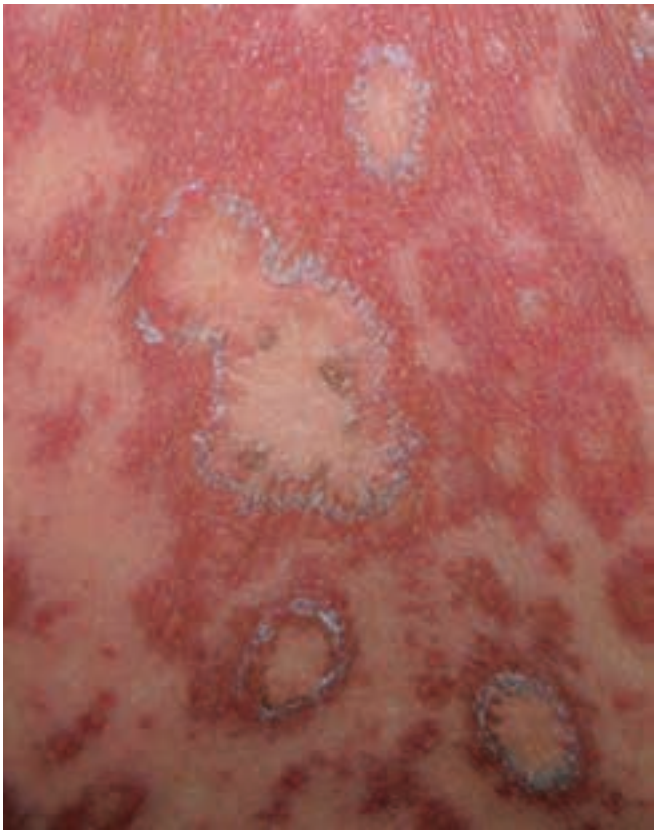

Figure 2.—Detail of the lesion with annular pattern on the trunk.

Rowell Syndrome (RS) is a rare entity originally proposed in 1963 by Rowell *et al.*[1] who described the coexistence of DLE with erythema multiforme (EM) associated with a characteristic immunologic pattern consisting of ANA in a speckled pattern, positive RF and antisaline extracts of human tissues (anti-SjT) antibodies (Table I). Since then, a small number of cases of RS have been reported in literature.[2] However, most reports did not show all diagnostic criteria firstly proposed by Rowell.[2] For this reason, several authors have questioned the existence of RS as an unique clinical entity. It has been considered variably as a distinct entity, the random co-occurrence of EM and LE, or a subpattern of subacute cutaneous lupus erythematosus (SCLE).[2, 3] Several reviews of the literature have been reported and proposed different diagnostic criteria for RS.

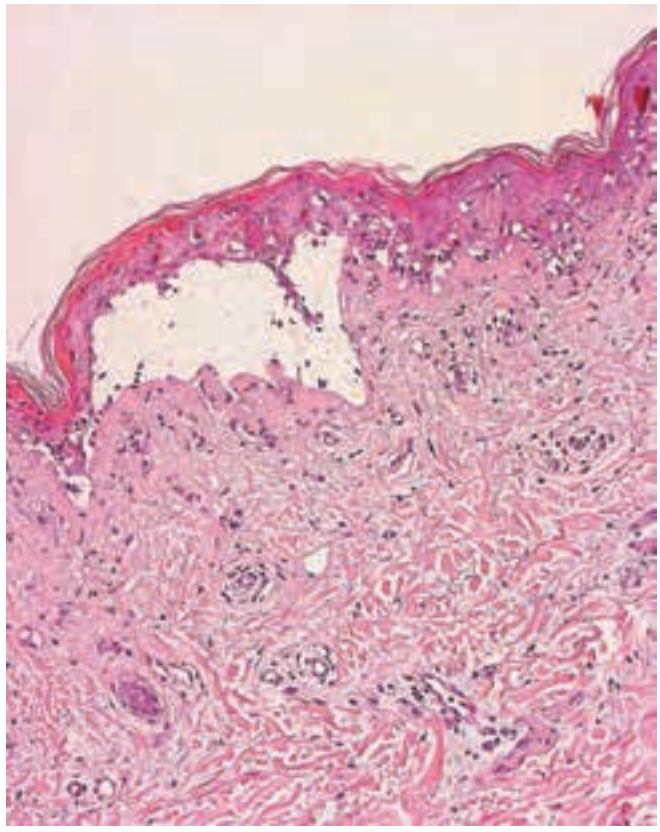

Figure 3.—Skin biopsy showed basal cell hydropic degeneration and keratinocyte apoptosis accompanied by a superficial dermal lymphohistiocytic infiltrate. Subepidermal vesiculation was also evident (H&E 100x).

Lee *et al.*[4] in 1995 suggested the inclusion of chilblain as a diagnostic feature (Table I). Zeitouni *et al.*[5] in 2000 proposed expanding the syndrome to include all forms of LE (systemic, discoid or subacute) (Table I).

A recent retrospective study of Torchia *et al.*[2] concluded that RS is a chronic cutaneous lupus erythematosus (CCLE) subtype within the spectrum of LE-specific skin disease. They suggested to maintain the eponym "Rowell syndrome" and proposed new diagnostic crite-

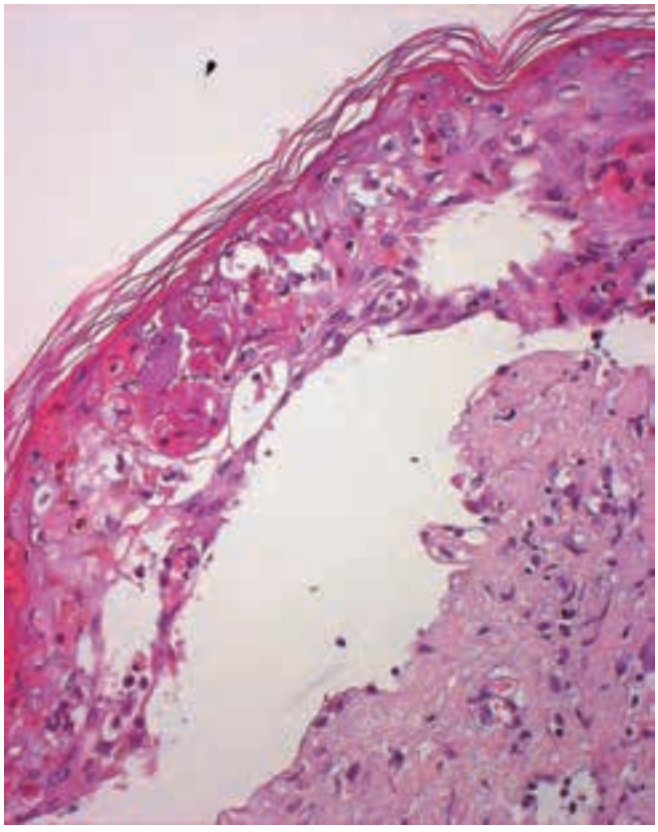

Figure 4.—Apoptotic keratinocytes were rounded, intensely eosinophilic and anucleate (H&E 200x).

ria (Table I). Major criteria include negative direct immunofluorescence (DIF) on lesional EM-like lesions that excludes the diagnosis of subpattern of SCLE. Minor criteria exclude true episodes of EM in patients with DLE ruling out the diagnosis of random association between DLE and EM. RF, included in previous diagnostic criteria for RS, was not considered to be a reliable diagnostic feature because it was positive in less than two thirds of the cases and would not probably add any significant diagnostic value.

In our case we made a diagnosis of RS according with new diagnostic criteria of Torchia *et al.* because all 4 major criteria and 2 minor criteria were present.

Therapeutic options are not well documented. Several therapeutic regimens are known, including corticosteroids, methotrexate, dapsone, hydroxychloroquine, azathioprine and cyclosporine A.

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TABLE I.—*Diagnostic criteria.*

Rowell *et al.*[1] (1963)	– LE – EM-like lesions (without any precipiting factors) – ANA in a speckled patter – Anti-SjT antibody – Positive RF
Lee *et al.*[5] (1995)	– Le – EM-like lesions (without any precipiting factors) – Chilblains – ANA in a speckled pattern – Anti-La/SSB antibody – Positive RF
Zeitouni *et al.*[6] (2000)	Major criteria – SLE, DLE, or SCLE – EM-like lesions (with/without involvement of mucous membrans) – ANA in a speckled pattern Minor criteria – chilblains – Anti-Ro/SSA or anti-La/SSB – Positive RF Diagnosis: 3 major + 1 minor criteria
Torchia *et al.*[3] (2012)	Major criteria – CCLE (DLE and/or childblain) – EM-like lesions (typical or atypical targets) – At least one positivity among speckled ANA, anti-Ro/SSA, and anti-La/SSB antibodies – Negative DIF on lesional EM-like lesions Minor criteria – Absence of infectious or pharmacological triggers – Absence of typical EM location (acral or mucosal) – Presence of at least one additional ARA criterion for diagnosis of SLE besides discoid rash and ANA and excluding photosensitivity, malar rash, and oral ulcers Diagnosis: 4 major + 1 minor criteria

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