CONTENTS

1
ORIGINAL ARTICLES
Psoriasis awareness among Italian patients: results of a nationwide survey

9
Laser surgery in rhinophyma
Bassi A., Campolmi P., Dindelli M., Bruscino N., Conti R., Cannarozzo G., Pimpinelli N.

17
Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL): a possible pathogenic role in chronic plaque psoriasis

25
Dermatological approach to vemurafenib skin toxicity: a single centre experience
Fava P., Marra E., Astrua C., Brizio M., Cavaliere G., Quaglino P., Fierro M. T., Savoia P.

32
Evaluation of efficacy and tolerability of four weeks bifonazole treatment after nail ablation with 40% urea in mild to moderate distal subungual onychomycosis
Piraccini B. M., Bruni F., Alessandrini A., Starace M.

37
Health-related quality of life in adult atopic dermatitis and psoriatic patients matched by disease severity
Chernyshov P. V.

44
REVIEWS
New insights into immune mechanisms of vitiligo
Boniface K., Taieb A., Seneschal J.

55
Paraneoplastic skin disorders: a review
Miyashiro D., Sanches J. A.

77
Treatments of advanced basal cell carcinoma: a review of the literature
Peris K., Tambone S., Kostaki D., Varrassi E., Fargnoli M. C.

87
Women and acne: any difference from males? a review of the literature
Skroza N., Tolino E., Proietti L., Bernardini N., La Viola G., Nicolori C., Pampena R., Zuber S., Balduzzi V., Soccodato V., Mancini M., Potenza C.

93
SPECIAL ARTICLES
Doctors and baldness: a five thousand year old challenge
Campo D., D’acunzo V.
CASE REPORTS

102
The rope sign: a case of interstitial granulomatous dermatitis with arthritis
Savoia F., Stinchi C., Gaddoni G., Patrizi A., Odorici G., Tengattini V., Cataleta P., Zago S.

106
Gianotti-Crosti syndrome associated with Ebstein-Barr virus and Parvovirus B-19 coinfection in a male adult: case report and review of the literature
Stojkovic-Filipovic J., Skiljevic D., Brasanac D., Medenica L.

CORRESPONDENCE

112
Hidradenoma papilliferum: diagnostic challenge

114
Annular lichen planus on the mammary areola: an unusual localization
Palleschi G., Bruscino N., Corradini D., Bassi D., Vega P., Pimpinelli N.

116
Diagnosis of pemphigoid nodularis with serological assay
Zhiliang L., Peiying J., Suying F.

118
Misleading mycosis fungoides: perichondritis
La Selva R., Fava P., Savoia P.

119
Linear basal cell carcinoma: clinical significance and better surgical approach
Palleschi G. M., Corradini D., Bruscino N., Maio V.

122
Bullous pemphigoid induced by escitalopram in a patient with depression
Caccavale S., Mea E. E., La Montagna M.

123
Rosacea and abatacept: the first report of a possible correlation
Lo Schiavo A., Tirri R., Peccherillo F., Abbondanza C., Russo B., Caccavale S.

124
Diagnosis of high risk multisystemic Langerhans cell histiocytosis: the practical use of cytology in dermatology
Caccavale S., Del Vecchio M., Brancaccio G., Caccavale T., La Montagna M., Ruocco E.

126
Classic erythema ab igne: still possible?
Greco A., Bassi A., Difonzo E. M., De Martino M.

127
Idiopathic atrophoderma of Pasini-Pierini associated with morphea: the same disease spectrum?
Ing X. L., Shi X.

129
An unusual manifestation in a patient with Neurofibromatosis type 1
Miraglia E., Iacovino C., Cantisani C., Calvieri S., Giustini S.

130
Primary idiopathic anetoderma
Grandi V., Mori M., Mariotti G., Gunnella S., Maio V.
Psoriasis awareness among Italian patients: results of a nationwide survey

Federico BARDAZZI 1, Paolo AMERIO 2, Giuseppe AMORUSO 3, Anna CAMPANATI 4, Andrea CONTI 5, Clara DE SIMONE 6, Paolo GISONDI 7, Giulio GUALDI 8, Claudio GUARNERI 9, Francesco LOCONSOLE 10, Annamaria MAZZOTTA 11, Maria L. MUSUMECI 12 Stefano PIASERICO 13, Concetta POTENZA 14, Luigia SCUDELLER 15* for the Alphard study group 2

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ABSTRACT

BACKGROUND: This was a prospective, multicentre study conducted in 14 Italian psoriasis referral centres (January-June 2014) with the objective of identifying factors associated with different levels of patient awareness on psoriasis.

METHODS: Overall, 298 patients (119 females, mean age 49.4 years, range 20–88) with a diagnosis of psoriasis (median of 14.1 years) were enrolled. Patients were more knowledgeable about the pathogenic nature of their condition compared with the other parameters (diagnosis, clinical course, prognosis, effect on QoL). Variables associated with significantly higher awareness, included years of education (the higher the education the greater awareness), internet usage, other family member with the disease, diet rich in fruit/vegetables, cigarette smoking and bone and joint involvement.

RESULTS: Older age, diabetes, and alcohol abuse were inversely associated.

CONCLUSIONS: Having established factors that affect awareness in our patients we can now go on to devise educational interventions to address these needs.


Key words: Psoriasis - Questionnaire - Awareness.

In modern medical practice, healthcare professionals spend an increasing amount of time and resources in the management of chronic diseases. According to the World Health Organization (WHO), 75% of the general population suffers from at least one chronic condition. Care for the chronically ill constitutes more than 75%
of all health care expenses in the USA, with over 25% of those living with a chronic illness, reporting that their condition significantly limits their daily activities.\textsuperscript{1, 2} Although psoriasis — a common, chronic, recurrent, multisystem immune-mediated disease — is not intrinsically life-threatening, it is associated with serious comorbidities, including psoriatic arthritis, depression, malignancy and cardiovascular conditions and it can have profound psychological and social implications.\textsuperscript{3-5} People with psoriasis experience reduced quality of life (QoL) as well as impaired physical, social, and occupational functioning.\textsuperscript{3} In one study, patients with psoriasis reported comparable disability to that observed with cancer, arthritis, hypertension, heart disease, diabetes, and depression.\textsuperscript{6} Despite these well-documented negative effects, the effectiveness of new treatments for psoriasis has been historically based on objective measures of the extent and severity of the disease on the skin alone.

More recently there has been a paradigm shift in dermatology in general and psoriasis in particular, from a physician-centred approach concentrated on diagnosis and therapy, to a patient-centred approach.\textsuperscript{7} This involves patients taking a more active part in their disease management by focusing on aspects that are important to them – physical, psychological, and social functioning and well-being – rather than physician dependent tools or standards. It is now generally accepted that psoriasis should be managed by ensuring that the patient, not the physician, determines the severity of his/her disease and that choice of the most appropriate therapeutic strategies are based on effective communication between the multidisciplinary team in order to meet the overall needs of the patient. The challenge for dermatologists is to endeavour to bring about long-lasting remittance of physical symptoms as well as improving QoL. The problem is that in order for patients to take a more active part in their disease management, they need to have the requisite tools to do so – for example they need to be equipped with the knowledge about their condition, its symptoms, life-style implications and available therapy options. Knowledge is power and there is evidence that empowering patients with information about their condition can have positive knock-on effects on self-management skills and QoL.\textsuperscript{8-10} Crucial to this process however, is the need for a reliable, reproducible tool with which the effects of a given intervention, such as an educational programme, can be quantitatively and effectively determined.\textsuperscript{11, 12}

Our group designed and validated a questionnaire investigating, in patients with psoriasis, awareness about their disease.\textsuperscript{13} Here we report the results of a large-scale cross-sectional study in psoriasis referral centres across Italy, to assess patients’ awareness on all aspects of their condition from pathogenesis and diagnosis to their information sources on psoriasis. The objective of the study was to identify factors associated with lower levels of awareness on psoriasis with the ultimate aim of devising and improving implementation of educational interventions in the clinical setting.

Materials and methods

Study design

This was an observational, cross-sectional, multicentre study conducted over a six-month period (January 2014 and June 2014) in 14 psoriasis referral centres across Italy. The local ethics committee of each centre approved the study and it conformed with the Declaration of Helsinki 1975 (revised in 1983).

Study population

Consecutive patients attending their assigned centre for routine evaluation in the week selected for conducting the study were enrolled if they met the following eligibility criteria: were aged >18 years, had a confirmed diagnosis of psoriasis and gave written informed consent to participate in the study. Patients who had previously taken part in the questionnaire validation study were not eligible for inclusion.

Sample size

The anticipated sample size was 300 (25 patients for each of 14 centres aimed at measuring an anticipated 60 points mean awareness (SD 10) with 95% confidence intervals ±5% (power 80% and alpha 5%), with intraclass correlation coefficient assumed 0.15.

Questionnaire

The patients awareness of psoriasis (PAP) questionnaire was developed in a previous study using standard questionnaire development techniques.\textsuperscript{13} This was
a self-administered questionnaire for patients with psoriasis consisting of 23 questions (in Italian) covering a wide range of subjects including knowledge of the pathogenesis and diagnosis of psoriasis, prognostic factors influencing its clinical course (addressing common misunderstandings in clinical practice) and sources of information of their condition (including a question with seven sub-items). The items and answers were then coded – each item allowed for a 4-point Likert scale (scoring 0-3, from low to high awareness: 0=wrong answer, 1=unsure but wrong, 2=unsure but correct, 3=correct answer), apart from one item that was coded as yes/no and for question 23 for which none or 1 “yes” was coded 0; 2 or 3 “yes answers” were coded 1; 4 or 5 were coded 2 and 6 or 7 were coded 3. The questionnaire was designed for self-administration and patients received a coding-free version, to avoid influencing their responses. Scoring of the questionnaire within each domain was calculated by adding up individual items’ scores standardized on the highest possible score for that domain, and multiplied by 100 for readability; for items with a missing answer, a zero was inputted (i.e. “no awareness”).

Data collection and management

Patients were requested to complete the questionnaire before their scheduled outpatient visit, after giving written consent to participate. The allocated time was 15 minutes (±10 minutes if necessary). In the follow-up medical examination physicians completed the patient case form including demographic data, history, clinical features, co-morbidities, lifestyle and treatment. The Dermatology Life Quality Index (DLQI) questionnaire was administered during the visit as well as the Psoriasis Area and Severity Index (PASI) ref su DLQI.14 Data were entered into specially designed database by dedicated personnel; data monitoring and quality checks ensured that missing, inconsistent and invalid data were resolved on a continuous basis.

Statistical analysis

Descriptive statistics were obtained for all variables: mean and standard deviations (or median and interquartile range) for continuous variables, absolute frequencies and percentages for categorical variables. Groups were compared with parametric or nonparametric tests, according to data distribution, for continuous variables, and with Pearson’s χ² test (Fisher exact test where appropriate) for categorical variables. Multilevel mixed linear regression was used for univariate and multivariate models to assess factors associated with awareness. Clinical Centre was the random effect, and patients’ characteristics were the fixed effects. Intra-class correlation coefficient (ICC) (i.e. the proportion of total variability in awareness explained by belonging to a clinical centre) was calculated to estimate the influence of centres on patients’ awareness. For fixed effects, at multivariate analysis, only variables significant at the 0.1 level at univariate analysis, or those acting as confounding factors for others, were included (forward fitting); significance of each variable included in the models was assessed by means of likelihood ratio test (P value for significance =0.05). Stata computer software version 13.0 (Stata Corporation, 4905 Lakeway Drive, College Station, Texas 77845, USA) was used for statistical analysis.

Results

Study population

In total, 298 patients were enrolled at the 14 participating centres with a median number of 22 patients per centre (IQR 17-36, min-max 10-50). The mean age of patients was 49.4 years (range 20-88 years; SD 13.9) and 119 (39.9%) were females. The majority of patients were of Italian origin (294, 98.6%). Patients had been diagnosed with psoriasis for a median duration of 14.1 years (IQR 6.6-24.9). Overall 45% of the sample had completed high school and 16% were educated to degree level (Table I). The median Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) scores were 4 (3-22) and 6 (0-10), respectively (Table I). The most common co-morbidities were hypertension (32%) and dyslipidaemia (29.5%) with 17.45% of patients defined as obese (Table I).

Patients’ awareness

Patients’ responses to the awareness questionnaire are shown in Figure 1. Mean awareness (adjusting for clinical centre) was 61.7 (95% 58.3-65.03). ICC was 0.14 (95%
<table>
<thead>
<tr>
<th>Category</th>
<th>N.</th>
<th>%</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td>Coefficient</td>
<td>95% CI</td>
</tr>
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<td>Age in years</td>
<td></td>
<td></td>
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<td>-0.2</td>
</tr>
<tr>
<td>Female gender</td>
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<td></td>
<td>-0.548</td>
<td>-5.771</td>
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<tr>
<td>Nationality</td>
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<td>-24.524</td>
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<td>School years</td>
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<td></td>
<td>4.14*</td>
<td>2.62-5.658</td>
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<tr>
<td>Geographical area</td>
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<td>-2.77</td>
<td>-24.524</td>
</tr>
<tr>
<td>Housing</td>
<td></td>
<td></td>
<td>-1.578</td>
<td>-6.681</td>
</tr>
<tr>
<td>Average sunlight hours per day</td>
<td>3</td>
<td>(2-5.3)</td>
<td>0.472</td>
<td>-1.191</td>
</tr>
<tr>
<td>Average fruit servings per week</td>
<td>7</td>
<td>(5-14)</td>
<td>0.335</td>
<td>0.046-624</td>
</tr>
<tr>
<td>Average vegetable servings per week</td>
<td>7</td>
<td>(4-10)</td>
<td>0.373</td>
<td>0.026-721</td>
</tr>
<tr>
<td>Months from symptoms onset to diagnosis</td>
<td>4.5</td>
<td>(0-19.6)</td>
<td>0.022</td>
<td>-0.057</td>
</tr>
<tr>
<td>Years from symptoms onset to enrolment</td>
<td>15.8</td>
<td>(8.2-28.7)</td>
<td>0.058</td>
<td>-0.213</td>
</tr>
<tr>
<td>Years from diagnosis to enrolment</td>
<td>14.1</td>
<td>(6.6-24.9)</td>
<td>0.013</td>
<td>-0.215</td>
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<tr>
<td>Dermatology Life Quality Index (DLQI) score</td>
<td>Median IQR</td>
<td>6</td>
<td>(3-22)</td>
<td>0.263</td>
</tr>
<tr>
<td>Psoriasis Area and Severity Index score (PASI)</td>
<td>Median IQR</td>
<td>4</td>
<td>(0-10)</td>
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<td>Living arrangements</td>
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<tr>
<td>Alone</td>
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<td>9.4</td>
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<td>With family</td>
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<td>88.59</td>
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<td>Internet usage</td>
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<td>Another member of the family affected</td>
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<td>Skin</td>
<td>282</td>
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Table I.—Description of the study population, univariate and multivariate analysis of factors associated to awareness (Data are N. [%] unless otherwise specified.

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Topical 102 36.3
Systemic 179 63.7
Phototherapy 39 13.88

IQR: interquartile range; SD: standard deviation.
*per each additional year of education.
was important in the clinical course of their condition and less than half felt that smoking and drinking alcohol could influence their disease. Similarly patients’ awareness of disease prognosis was limited with 40%, answering correctly “do you think you can definitely recover from your condition and does your condition cause your fingernails and toenails to fall off”. Furthermore, 75% of patients did not give the correct answer regarding hair loss while the majority of patients (60%) were not aware of the possible psychological effects of psoriasis and how it could influence mood and overall QoL.

Over 80% answered question 1, correctly (contagious nature of condition) while 45%, 35% and 55%, respectively provided correct answers to the other questions regarding pathogenesis (2, 8 and 14). Regarding the four questions on diagnosis the percentages of patients giving correct answers was lower with 55%, 35%, 40% and 40% providing correct answers to questions 4, 5, 15 and 19, respectively. Only 40% answered the following question correctly “Are there other diseases that can be associated with psoriasis”. Likewise, only 22% considered that diet was important in the clinical course of their condition and 0.06-0.32), indicating that between 6 and 32% of patient’s awareness is due to the influence of the clinical centre. Concerning the awareness/knowledge in each of the six areas investigated by the PAP (pathogenesis, diagnosis, clinical outcomes, prognosis, quality of life, and source of information) (Table II), the highest levels of awareness/knowledge was on pathogenesis (mean 80.4%) while the lowest was for source of information (mean 38.8%).

Over 80% answered question 1, correctly (contagious nature of condition) while 45%, 35% and 55%, respectively provided correct answers to the other questions regarding pathogenesis (2, 8 and 14). Regarding the four questions on diagnosis the percentages of patients giving correct answers was lower with 55%, 35%, 40% and 40% providing correct answers to questions 4, 5, 15 and 19, respectively. Only 40% answered the following question correctly “Are there other diseases that can be associated with psoriasis”. Likewise, only 22% considered that diet was important in the clinical course of their condition and less than half felt that smoking and drinking alcohol could influence their disease. Similarly patients’ awareness of disease prognosis was limited with 40%, answering correctly “do you think you can definitely recover from your condition and does your condition cause your fingernails and toenails to fall off”. Furthermore, 75% of patients did not give the correct answer regarding hair loss while the majority of patients (60%) were not aware of the possible psychological effects of psoriasis and how it could influence mood and overall QoL. In general patients also had limited knowledge of available treatments for their conditions, and in the main were not involved/aware of patient associations or other useful sources of information.

A number of variables were associated with significantly higher awareness/knowledge, including years of education (the higher the educational levels the greater awareness), internet usage, other family member with
the disease, bone and joint involvement, diet rich in fruit/vegetables, cigarette smoking and, bone and joint involvement. In contrast older age, diabetes, and alcohol abuse were inversely associated (Table I).

Discussion

The importance of an effective partnership between the patient and the multidisciplinary team, particularly in patients with chronic disease, is well established. Increased awareness/knowledge about a given condition not only allows patients to feel more in control but also enhances their ability to cope with symptoms and can also improve QoL and clinical outcomes. Renzi et al. recently reported that patients with good knowledge of their condition more frequently reported complete satisfaction with their care compared with patients with poor knowledge. In our patient cohort, we found, against an overall sufficient awareness, sizeable differences and significant disparities in patients’ knowledge of their condition. This finding was not entirely unexpected: although few studies have been published in this area, results of a recent similar study conducted in Norwegian patients showed similar variations. In our study, we found that the influence of the clinical centre (i.e. of the clinicians) on patient’s knowledge is sizeable, possibly accounting for up to one third of overall variation. The results of our study reiterate the important role of healthcare professionals in general and dermatologists in particular in getting important messages across to patients. The mean awareness score for pathogenesis and other areas was fair-to-high despite the low score for “source of information”: in our opinion this indicates that patients still rely on their treating physician as source of information about their disease. Results of our study also reflect the influence of the Internet as a source of information on diagnosis and treatment of clinical conditions with 63% of patients getting information from the Internet. In addition, probably reflecting the genetic nature of the condition, many received information from family/friends while for only for a minor proportion radio was a source of information.

Interestingly, a substantial number of patients were not aware of the detrimental effects that diet and alcohol can have on psoriasis and therefore they did not consider that their dietary habits and lifestyle could have a negative effect on the severity of their condition. In medicine in general, and in patients with psoriasis in particular, one of the most difficult things to convince patients to do is to change their lifestyle – stop smoking, improve their diet, increase physical activity. They feel that their treating physician should be able to prescribe therapeutic agents to effectively treat their condition without the need for them to make substantive lifestyle changes. One practical and easy way to would to request dietologists to be present when the dermatologist discusses diagnosis and treatment with patients. In fact, a recently published study, conducted by an Italian group, to assess the impact of a dietary intervention combined with physical exercise for weight loss in improving psoriasis in overweight or obese patients, showed that a 20-week dietetic intervention associated with increased physical exercise, reduced psoriasis severity (PASI score reduction of ≥50% significantly differed between study arms – 49.7% with dietary intervention vs. 34.2% with information only, P=0.006) in systemically treated overweight or obese patients with active psoriasis. Given that in our study 30% of patients had dyslipidaemia and 17.5% were obese, such an intervention would probably have benefitted a proportion of our patients.

The fact that patients included in the study had been suffering from psoriasis for a number of years and that median PASI/DLQI scores were low indicates that the disease was controlled by treatment strategies and had low impact on QoL. As expected, awareness increased with education years, and was also associated to internet usage, other family member with the disease, and diet rich in fruit/vegetables (i.e. with an healthier diet which in a Mediterranean Country is also associated to higher educational levels). Also, cigarette smoking was associated to a somewhat higher awareness, possibly reflecting the fact that in Italy the proportion of smokers among the most educated people is still quite relevant despite antismoke campaigns. Patients with bone and joint involvement had a somewhat higher awareness; we feel this is due to the fact that patients more compromised in their daily activities also seek more information. Unsurprisingly older age and diabetes were inversely associated to knowledge.

Strength of our study are the large sample size of consecutive patients in a high number of clinical centres across the entire Nation, the use of a validated questionnaire detailing a number of areas of knowledge and the estimate of patient’s knowledge unbiased by physician’s
suggestions (the questionnaire was administered BEFORE the clinical visit); in fact, some patients were at their first visit and had a “not known” answer to some clinical issue. Its biggest limitation is its cross-sectional design, which hinders us from inferring on causation (e.g. the higher knowledge of patients accessing the web is very likely reverse causation, that is patients with higher knowledge/education seek more information on the web).

There is evidence that even a single educational intervention may be helpful in improving psoriasis knowledge and give psychological relief to patients. Educational interventions aimed at one or more of the areas that showed lower scores in our study (prognosis, QoL, and source of information) may represent a cost-effective way to motivate patients thereby improving efficacy of therapeutic strategies. However, confirmatory, larger-scale studies involving a variety of patient subtypes are necessary to allow recommendations on educational interventions to be made.

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Rhinophyma is a benign, disfiguring disorder characterized by a progressive thickening and hypertrophy of the nasal skin and soft tissues. It is much more common in men, with a male:female ratio varying from 5:1 to 30:1, occurring mainly in Caucasian people. Although it is commonly referred to as the end-stage of severe rosacea, rhinophyma can also be caused by chronic, edematous, sebaceous and connective tissue hypertrophy. Clinically, the nose shows erythema, telangiectasia and thickening of the skin, with prominent pilosebaceous structures. Rhinophyma is the most common disorder; however, other variants have been reported in current literature: gnatophyma (chin), metophyma (forehead), otophyma (ears) and blepharophyma (eyelids).

In the past, this deformation of the nose has been described with the term “whisky nose.” Although facial flushing is caused by vasoactive substances such as alcohol and caffeine which may exacerbate the condition, in the literature there is no evidence for a causal relationship between chronic alcoholism and rhinophyma. The psychological impact is an important aspect of this disease, thus the use of treatment options that yield high patient satisfaction is highly recommended. This disease, however, is not solely an esthetic problem; in severe cases of rhinophyma, secondary nasal airway obstruction have also been observed.

Possible treatment options for rhinophyma are typically divided into two broad categories, i.e. nonsurgical and surgical (Table I). Among the non-surgical treatment options, antibiotics (mainly tetracycline and macrolides) and retinoids (isotretinoin) are the most widely
used. They have an anti-inflammatory and sebaceous gland-reducing activity; yet limited results have been shown with the aforementioned treatment modalities.6

Surgical treatment of rhinophyma has the main benefit of reducing nose’s dimension significantly. The surgical approach can be performed via a complete or non-complete excision, followed by re-epithelialization. The complete excision is less preferred, due to the formation of significant scarring, inexact color and texture matching, and essentially poor cosmetic results; moreover, it also presents some other disadvantages, like a limited depth control, which makes it difficult to recreate the aspect “natural nose”. Better results are obtained via incomplete excision techniques, such as cryosurgery, dermabrasion, electrosurgery, and laser surgery.7, 8

Laser options to treat rhinophyma consist of argon laser, Er:YAG, and CO2 laser. The formation of atrophic scarring and hyperpigmentation, however, has limited the use of argon. The use of Er:YAG laser is limited due to its lacking capacity to coagulate during the surgical procedure, resulting in a difficult vision of the surgical field.9

Our aim in the current study was to demonstrate that CO2 laser is a superior technique compared to other laser techniques and surgical methods, mainly because it produces minimal bleeding, thus allowing more precise and controllable esthetic and functional results.

Materials and methods

Patients

A total of 24 Caucasian patients with rhinophyma (20 males and 4 females; range of age 50-83 years; Fitzpatrick skin types I-IV, mainly II-III) were treated in our institution’s Outpatient Clinic from April 2003 to April 2013. The patients were treated after obtaining a detailed personal history (clinical manifestations, general health conditions, previous medications, and life-style). Exclusion criteria consisted of patients who underwent isotretinoin therapy six months prior to laser surgery. The study design was approved by the local Institutional Review Board, according to the Helsinki Declaration, and informed consent was obtained from each patient. Cutaneous biopsies were also taken in order to exclude the presence of any disease possibly mimicking rhinophyma.10, 11

A three-severity stage classification of rhinophyma was used: 1) minor rhinophyma (telangiectasias and mild thickening or textural change on the nose); 2) moderate rhinophyma (nasal thickening and early formation of lobules); and 3) major rhinophyma (presence of both nasal hypertrophy and prominent lobules).12 We enrolled 3 patients with minor, 7 with moderate, and 14 with major rhinophyma.

The patients were treated for a maximum of 4 months, receiving a mean of 4-laser sessions (range 2-6) with a 3-week interval.

Photographs were taken with a Canon digital camera and a polarized flash (Anthology System, DEKA-M.E.L.A, Calenzano, Florence, Italy) before and after each session, and 3, 6, and 12 months after the final treatment. The pictures were standardized using the same camera, shooting setting, twin flash, ambient light and chin holder to guarantee the same distance.

Six months after the last session, the results were independently scored by 3 dermatologists who had not taken part in the treatments. They assessed the performance of this CO2 laser by means of 3 categories of improvement (high, >75%; moderate, 50-75%; and low,
<25%), based on disappearance rate of teleangectasias, lobules, sebaceous glands hyperplasia and nasal iper-trophy.

Laser treatment

\[
\text{CO}_2 \text{ laser surgery was performed under local anesthetic with a 1% lidocaine solution (Xilocaine®). A 10,600-nm CO}_2 \text{ pulsed laser (Smart Xide}^2 \text{laser DEKA-M.E.L.A., Calenzano, Florence, Italy) was used in all patients with the following parameters: starting power of 5-25 Watt, continuous mode (CW). Then change to a pulsed mode (DP) with a starting power of 5 W with a frequency of 80-50Hz until a power of 1W with a frequency of 10Hz. We preferred to work with low power setting in order to avoid collateral effect such as atrophy and loss of cutaneous adnexals. The operator using CO}_2 \text{ laser performed a gradual removal of hypertrophic tissue, making sure that the natural nasal profile was maintained. The endpoint of the ablation was achieved upon the appearance of a honeycomb aspect leaving residual sebaceous glands to allow re-epithelization (Figure 1). There was a continuous vacuum suctioning of the smoke during the procedure through a suction device system. All patients were medicated with topical antibiotic cream under a simple dressing. They were also told to wash the wound and apply the cream on a daily basis for 15 days.}
\]

Results

Six months after the last laser session all the patients showed global improvement of their clinical conditions: 19 (79.1%) showed high improvement (>75%), 4 (16.7%) moderate improvement (50-75%), and 1 (4.2%) low improvement (<25%) (Figure 2).

The re-epithelization started days immediately after laser treatment and was completed within 3 weeks. Initially, formation of serous exudates and significant erythema was observed, yet fading in a few weeks. No major side effects, such as bacterial infection, scarring, and hyperpigmentation, were reported in any of our patients (Figures 3-5).

Discussion

Rhinophyma may be clinically diagnosed. In our opinion, however, it is better to make a skin biopsy to confirm the diagnosis. It can become very important in order to rule out the presence of cutaneous lymphoma (Figure 6), angiosarcoma, sebaceous carcinoma or other malignant lesions which can mimic rhinophyma.\(^{13}\) In this way, the physicians are able to approach the lesions more safely, without taking potential legal risks due to a wrong diagnosis and consequent treatment’s choice.

Several techniques have been reported to be useful in treating rhinophyma such as excision, dermabrasions, dermal abrasion, cryosurgery, and dermal shaving, but currently we have no clear consensus on the best one.\(^{14}\) Using the aforementioned techniques the physicians have several disadvantages pertaining to side effects such as excessive bleeding and unsatisfactory esthetic results.
Figure 3.—First example: rhinophyma before treatment (A, C, E) and after five sessions of CO$_2$ laser (B, D, F).
Figure 4.—Second example: rhinophyma before treatment (A, C, E) and after four session of CO₂ laser (B, D, F).
Figure 5.—Third example: rhinophyma before treatment (A, C, E) and after five session of CO₂ laser (B, D, F).
In the treatment of rhinophyma, it is fundamental to preserve follicular epidermal tissue in the deep layers of tissue where re-epithelization occurs.

The best approach permitting us to avoid this problem is CO\textsubscript{2} laser, which allows a bloodless operative field upon each treatment. In this way, we can also obtain a perfect visualization of the treatment area and decide to stop vaporization at the right moment.\textsuperscript{15} More important, even patients with severe rhinophyma can be successfully treated with this method, as demonstrated by our study. Other important advantages of CO\textsubscript{2} laser are that it only requires local anesthesia, and has a short healing time.\textsuperscript{16} In our study, re-epithelization of the nasal surface treated with CO\textsubscript{2} laser was obtained in a few (3-4) weeks. Usually if decortications are very deep, collateral effects may occur: we suggest to use a low power setting in a pulsed mode (DP) in order to avoid the scar formation and a “plastic nose” effect (Figure 7).
The CO₂ laser emits a wavelength absorbed by water, thus resulting in efficient evaporation and minimal thermal damage to closer tissue, offering a precise surgical tool for rhinophyma ablation leading to excellent cosmetic results with no scarring as seen in our study.

Our study, in fact, demonstrates that carbon dioxide laser allows a very careful nasal surface ablation and the remodeling of the hypertrophic areas, with an excellent cosmetic result, a very short healing time and virtually no side effects. CO₂ laser, as shown by our clinical results, can indeed be considered the gold standard therapy for rhinophyma, since it is a safe, efficient and reliable technique. One possible drawback in this application could derive from the experience which is required to achieve good results. In fact, even though this particular technique is widespread, not many physicians have the required skills to obtain such striking results.

The psychological rebound of patients with rhinophyma is another important aspect that we must take in consideration. Rhinophyma can carry a strong psychological impact due to its effect on one’s personal appearance. Patients seek effective cures because of the unsightly appearance of nose enlargement. This condition can generate a lack of confidence and isolation, that can be remedied by a treatment able to give a greater quality of life even in the long term. Besides the psychological problems, this condition is often characterized also by functional negative consequences like obstruction in breathing and vision. The rhinophyma therapeutic correction must take the dignity of a relevant intervention which overshoots the simple cosmetic problems. Nowadays a laser operation through only four sessions allows us to limit breathing and vision troubles, as documented by the patients subjective evaluations.

Conclusions

In our series, CO₂ laser treatment revealed to be the most effective approach if compared with previous therapeutic options received by patients. Of course, further studies are needed to improve protocols and settings in this kind of application.

References

Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL): a possible pathogenic role in chronic plaque psoriasis

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\(^1\)These authors contributed equally to the study.

ABSTRACT

BACKGROUND: Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) is a cytokine member of the tumour necrosis factor (TNF) family. Its role has been investigated in skin cancers and some inflammatory and/or immune-mediated skin diseases. An involvement of TRAIL in psoriasis pathogenesis has recently been hypothesized. We investigated the expression and localization of TRAIL and its receptors in psoriatic skin and measured serum TRAIL. The intracellular pathways activated by TRAIL were assessed to investigate its potential role in the pathogenesis of psoriasis.

METHODS: Twenty-four consecutive patients with plaque psoriasis and age- and sex-matched healthy subjects were recruited. Serum TRAIL was measured by means of an enzyme-linked immunosorbent assay (ELISA). TRAIL and TRAIL receptors were evaluated by reverse transcription – polymerase chain reaction (RT-PCR) (RNA of lesional and non-lesional psoriatic skin) and by immunohistochemistry (lesional skin). Caspase 8 and NF-kB immunohistochemistry were also evaluated by immunohistochemistry.

RESULTS: RT-PCR demonstrated increased synthesis of TRAIL and its receptors in lesional vs. non-lesional skin. Immunohistochemistry showed a strong staining of TRAIL and TRAIL receptors both in the epidermis and in the dermal infiltrate. Finally, a correlation emerged between caspase 8 and TRAIL immunohistoexpression in the dermis.

CONCLUSIONS: Our findings suggest an involvement of TRAIL in psoriasis pathogenesis, probably through an action at the site of the inflammatory infiltrate, likely via caspase 8.


Key words: TNF-related apoptosis-inducing ligand - Psoriasis - Pathogenesis - Enzyme-linked immunosorbent assay.
mediate the apoptotic signal due to lack of the intracellular signalling death domain.\textsuperscript{1-3} DcR1 and DcR2 have been hypothesized to antagonist decoy receptors, actually conferring resistance to TRAIL.\textsuperscript{3, 8} Recent studies suggest that TRAIL, besides its principal apoptosis-inducing action, may also have a proinflammatory role. In fact, TRAIL signalling through DR4 and DR5, as well as through DcR2, has been shown to activate nuclear factor (NF)-kB, mitogen-activated protein kinase (MAPK) and protein kinase B (PKB), which are capable of triggering an inflammatory cascade and anti-apoptosis pathways.\textsuperscript{9, 10} TRAIL also has an inhibitory soluble receptor, osteoprotegerin, commonly known as decoy receptor of the receptor activator for NF-kB ligand (RANKL), which is involved in osteometabolism. A role for it in the TRAIL system has been hypothesized but not completely elucidated.\textsuperscript{11}

TRAIL is highly expressed in several normal tissues including skin, especially the epidermis. Since it has been documented that chronic UV exposure is associated with diminished cutaneous levels of TRAIL, and that malignant epithelial neoplasms are associated with reduced TRAIL expression,\textsuperscript{12} it can be assumed that TRAIL retains a protective role in the development of skin cancer. TRAIL has also been investigated in a number of inflammatory and/or immune-mediated skin diseases.\textsuperscript{13, 14} TRAIL has been recently implied in the pathogenesis of psoriasis.\textsuperscript{15, 16} Zaba et al. have characterized a population of inflammatory dermal CD11c+ CD1c- myeloid dendritic cells (DCs) infiltrating cutaneous psoriatic lesions, producing multiple cytokines and inflammatory mediators (e.g. TNFα, IL23p19, IL12/IL23p40).\textsuperscript{17} A microarray analysis identified, among others, different TRAIL expression in those cells, compared to normal control, suggesting its possible role in psoriasis pathogenesis.\textsuperscript{15}

Our study was designed to investigate the expression and localization of TRAIL and its receptors in psoriatic skin. In addition, we also tested TRAIL serum levels. Since death receptor activation can induce caspase-mediated apoptosis and activate non-apoptotic proinflammatory pathways, such as NF-kB-mediated pathway, we assessed caspase 8 and NF-kB immunohistochemical expression in lesional skin to investigate the potential role of TRAIL and its receptors in psoriasis. Finally, we looked for any associations between laboratory findings and the clinical features of the disease.

Materials and methods

Patients and methods

Twenty-four consecutive patients presenting between March 2012 and December 2013 at the Department of Dermatology, “Sacro Cuore” Catholic University, Rome, Italy, with histologically proven plaque psoriasis, and 25 age- and sex-matched healthy subjects (6 biopsies, 25 blood samples) were enrolled after written informed consent was obtained. Disease severity was measured by Psoriasis Area and Severity Index (PSI) score and the disease duration was also recorded. Patients with erythrodermic, guttate or inverse psoriasis and those with psoriatic arthritis were excluded; all the patients in the study followed a wash-out period of 1 month for topical therapy and 3 months for traditional and/or biological systemic treatment.

For each patient and each healthy subject a blood sample was collected; serum was extracted and stored at -20 °C. In psoriasis patients, two biopsies from lesional, non-UV-exposed tissue and one from unaffected non-lesional skin were collected for each psoriasis patient. One lesional sample was fixed in formalin, embedded in paraffin and processed for histopathological and immunohistochemical evaluation; one lesional sample and the non-lesional specimen were stored at -80°C in RNAlater (RNA Stabilization Reagent, QIAGEN GmbH, Hilden, Germany), which immediately stabilizes RNA in tissue to preserve gene expression profile.

Clinical disease was assessed in the plaques where the biopsy specimens had been collected, using the Psoriasis Severity Index (PSI) as reported previously.\textsuperscript{19} Briefly, each plaque was evaluated for degree of erythema, infiltration and scaling using a 5-point scale (0: absent; 1: slight; 2: moderate; 3: severe; 4: very severe). The maximum score was 12.

The study was approved by the Ethics Committee of “Sacro Cuore” Catholic University, where patient recruitment was conducted.

Enzyme-linked immunosorbent assay (ELISA)

Serum TRAIL levels were measured by an ELISA (Human TRAIL/TNFSF10 Quantikine® ELISA, R&D Systems, Minneapolis, MN, USA) according to the
manufacturer’s instructions. Briefly, serum samples stored at -20 °C were thawed once and analysed in duplicate using a commercially available kit in the same day without dilution.

A 450 nm/540 nm or 570 nm wavelength spectrophotometer Spectrmax Plus384 (Molecular Devices, Sunnyvale, CA, USA) was used for the readings and results were given as pg/mL by interpolation using the SoftMax Pro software (Molecular Devices).

RNA extraction, reverse transcription – polymerase chain reaction (RT-PCR)

Total cellular RNA was extracted using Trizol (Invitrogen, Carlsbad, CA, USA) from skin biopsies stored in RNA later according to the manufacturer’s instructions. RNA concentration, purity and integrity were measured by spectrophotometrical analysis. 1 µg total RNA was retrotranscribed with the QuantiTect Reverse Transcription Kit (QIAGEN GmbH, Hilden, Germany) according to the manufacturer’s recommendations. Primers for TRAIL, TRAIL-DR4, TRAIL-DR5, TRAIL-DcR1, TRAIL-DcR2 and the housekeeping genes were designed using AlleleID (PREMIER Biosoft International, Palo Alto, CA, USA) and IDT SciTools (Tema Ricerca, Bologna, Italy). Special care was devoted to primer length, annealing temperature, base composition and 3’-end stability. Primer details, and the amplicon length of each gene examined are reported as Supplementary Material. The PCR amplification program was as follows: initial denaturation at 95 °C for 5 minutes, followed by 30 cycles of denaturation at 95 °C for 30 seconds, annealing at 60 °C for 30 seconds and 72 °C for 30 seconds, extension and a final step at 72 °C for 10 minutes. All the RT-PCR was performed three times. Products were subsequently run on 2% agarose gel stained with ethidium bromide. Densitometric analysis were performed to determine the fold induction of each gene.

Immunohistochemistry

Immunohistochemical staining for TRAIL and its receptors, NF-kB p65, and caspase 8 was performed in lesional skin samples, to investigate the localization and potential site of action of TRAIL in psoriasis. In particular, expression of TRAIL-DR4, TRAIL-DR5, TRAIL-DcR1 (TNFRSF10C), TRAIL-DcR2 (TNFRSF10D), TRAIL (TNFSF10), NF-kB p65, and caspase 8 was detected in 4 µg-thick tissue sections using the biotin–avidin (LSAB) immunoperoxidase method, as previously described. Antibodies used were: DR4 (dilution 1:250) and DR5 (dilution 1:200; by Novus Biologicals, Cambridge, UK); DcR1 (dilution 1:100), DcR2 (dilution 1:100) and TRAIL (dilution 1:250; all by AbNovo, Heidelberg, DK); and NF-kB p65 (dilution 1:100) and caspase 8 (dilution 1:100; both by Spring Bioscience Pleasanton, CA, USA). Finally slides were counterstained with haematoxylin. For staining intensity grading, baseline protein expression in normal control tissue (spleen) was taken as a reference and scored as 1+. Antibody expression was then evaluated in the entire tissue specimen. No staining and staining intensity less than or equal to that observed in control tissue was graded as 0 and 1+, respectively; a 3+ score was assigned for very high intensity, and a score of 2+ for intermediate levels of intensity. A score was assigned for the whole specimen and respectively for the dermis and the epidermis.

Sections were examined blindly and independently by two pathologists (VA and IP); those involving discordant scores were reviewed jointly in a multi-headed microscope until an agreement was reached.

Statistical analysis

Quantitative variables were expressed as median (interquartile range, IQR) and mean (±SD), qualitative variables as absolute and relative frequencies. The possible association between serum TRAIL level and presence of psoriasis was tested with the Mann-Whitney test, which was also applied to seek a relationship between TRAIL expression (RT-PCR data) and psoriasis. An association between TRAIL immunohistochemical data and expression of caspase 8 and NF-kB was sought by applying the χ² or Fisher’s exact tests. Spearman’s correlation was used to find an association between serum TRAIL levels and disease severity (PASI score) and duration. Finally, an association between PASI score and the expression of TRAIL and its receptors was sought using Spearman’s correlation (RT-PCR data) and the Mann-Whitney test (immunohistochemical data).

Analyses were performed using SPSS software (12.0 for Windows). Statistical significance was set at P=0.05.
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February 2016

(9/24), 67% (16/24) and 37.5% (9/24) respectively; the proportion of positive agreement of trail co-expression was 75%, 56%, 78% and 55% with trail-dr4, trail-dr5, trail-dcr1 and trail-dcr2 respectively. TRAIL was significantly overexpressed in lesional skin compared with unaffected non-lesional skin (P<0.05). The expression of trail-dr4, trail-dr5 and trail-dcr1 was also increased in lesional compared to non-lesional skin; however only trail-dcr1 gene expression was statistically increased in lesional skin compared to non-lesional skin (P<0.01). Finally, the expression of trail-dcr2 was similar in lesional and non-lesional samples.

The densitometric analysis data of RT-PCR band intensities are shown in Figure 1 as mean ± SD of TRAIL and TRAIL receptor mRNA, normalized to housekeeping gene mRNA expression.

Immunohistochemistry

TRAIL and its receptors were investigated only in lesional skin. TRAIL was expressed in 18/24 (75%) of psoriatic lesional skin samples. Interestingly, TRAIL immunoreactivity was found equally throughout the epidermis and in the dermal infiltrate. Staining was predominantly cytoplasmic in all cells (Figure 2); the staining intensity score ranged between 1+ and 2+.

Results

Characteristics of patients and controls

Overall 24 patients with plaque psoriasis and 25 age- and sex-matched healthy subjects (6 biopsies, 25 blood samples) were enrolled. Patients’ age ranged from 18 to 80 years (median=53; IQR=33); 17 (70.8%) were male. Their median PASI score was 14.8 (IQR=17.5) and their median PSI score was 7.0 (IQR=3). Disease duration ranged from 0.5 to 43 years (median=20; IQR=21.5). The age of control subjects ranged from 20 to 78 years (median=50; IQR=23); 16 (64%) were male.

ELISA

All sera from psoriasis patients and helathy subject were screened for TRAIL concentration. Although the mean serum concentration of TRAIL was 82.78 pg/mL (±36.7) in patients and 67.81 pg/mL (±25.9) in healthy subjects the data did not reach statistical significance (P=0.227).

RNA extraction, RT-PCR

The expression profiles of TRAIL and its receptors were studied by comparing mRNA from paired biopsy specimens of psoriatic skin and non-lesional skin (N.=24 pairs). All experiments yielded similar. The frequency of TRAIL, TRAIL-DR4, TRAIL-DR5, TRAIL-DcR1 and TRAIL-DcR2 expression in psoriatic skin samples was 75% (18/24), 58% (14/24), 37.5% (9/24), 67% (16/24) and 37.5% (9/24) respectively; the proportion of positive agreement of TRAIL co-expression was 75%, 56%, 78% and 55% with TRAIL-DR4, TRAIL-DR5, TRAIL-DcR1 and TRAIL-DcR2 respectively. TRAIL was significantly overexpressed in lesional skin compared with unaffected non-lesional skin (P<0.05). The expression of TRAIL-DR4, TRAIL-DR5 and TRAIL-DcR1 was also increased in lesional compared to non-lesional skin; however only TRAIL-DcR1 gene expression was statistically increased in lesional skin compared to non-lesional skin (P<0.01). Finally, the expression of TRAIL-DcR2 was similar in lesional and non-lesional samples.
DR4 and DR5 were detected in 100% and 95.8% of lesion samples, respectively, with staining intensity scores of 2+ or 3+ both in the epidermis and in the dermis (Figure 3). The findings for DcR1 and DcR2 were fairly similar: epidermal staining for both receptors was seen in 100% of patients, and dermal staining in 87.5% (DcR1) and 70.8% (DcR2), all with cytoplasmic localization. Staining intensity scores were 1+ and 2+, both in the epidermis and in the dermis.

Strong NF-kB expression was detected in all psoriasis skin specimens, both in the epidermis and in the dermis. However no association between NF-kB and TRAIL or its receptors expression was found (data not shown). Due to a technical problem caspase 8 was evaluated in only 23 of 24 samples; caspase 8 epidermal staining was found in 100% of the samples; while dermal staining was found in 17/23 (73.9%). Comparison of these data with the immunohistochemical expression of TRAIL (Table I) and its receptors (data not shown) highlighted an association (P=0.045) between

<table>
<thead>
<tr>
<th>Caspase 8 staining status</th>
<th>Negative TRAIL staining (N=6)</th>
<th>Positive TRAIL staining (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>2 (33.3%)</td>
<td>14 (82.4%)</td>
</tr>
<tr>
<td>Negative</td>
<td>4 (66.7%)</td>
<td>3 (17.8%)</td>
</tr>
</tbody>
</table>
the expression of caspase 8 and of TRAIL in the dermis.

Correlations between clinical and laboratory findings

No significant association emerged between PASI score and serum TRAIL level, or between PSI score and expression of TRAIL and its receptors as evaluated by RT-PCR or immunohistochemistry (data not shown) within the skin samples. In contrast, Spearman’s correlation demonstrated a strong association (P=0.002) between serum TRAIL level and disease duration (Figure 4).

Discussion

TRAIL, a cytokine member of the TNF family, has been mainly investigated in skin tumours for its major apoptosis-inducing action. Low TRAIL expression has been described in basal and squamous cell carcinoma and in chronically UV-exposed skin of elderly individuals. Increased TRAIL-DR4 and TRAIL-DR5 expression has been found in melanocytic tumours compared with benign naevi, suggesting a possible therapeutic role for TRAIL receptor–activating agents skin neoplasm treatment.

Besides its involvement in a range of neoplasms, TRAIL has also been suggested to play a role in the pathogenesis of several inflammatory skin diseases with various mechanisms. It has been hypothesized to have a proapoptotic action in vitiligo, where it seems to be cytotoxic for melanocytes. Mounting evidence also suggests a proinflammatory role in cutaneous lupus erythematosus. However, TRAIL may actually work as an anti-inflammatory agent, inducing IL-1 receptor antagonist expression in cultured human keratinocytes from atopic dermatitis.

The role of TRAIL in psoriasis has been only recently investigated, with suggestive but not univocal results. According to Zaba et al., it may be considered as a marker able to differentiate inflammatory dermal DCs in psoriatic skin. In the same paper TRAIL-positive cells were localized in the papillary dermis and at the dermal-epidermal junction in lesional, but not in non-lesional psoriatic skin; moreover, DR4 and DcR2 expression was found in basal keratinocytes and dermal cells in lesional and non-lesional skin, whereas DR5 was not expressed in either type of sample. Most recently, Peternel et al. examined the immunohistochemical localization of TRAIL, DR4 and DR5 in 10 psoriasis patients and in healthy subjects. In contrast with the results of Zaba and co-workers, Peternel et al. described significantly enhanced staining for DR4, DcR2 and DR5 both in lesional and in non-lesional skin, particularly in the dermis.

Our findings support the findings of Peternel et al. suggesting a pathogenic role for TRAIL in psoriasis. In fact, we discovered higher gene expression levels of the cytokine in lesional compared with non-lesional skin and a higher protein plasma level in psoriasis patients and in healthy controls. In this latter case, the absence of statistical significance could be the result of a high variability of PASI and PSI scores within the patients. In addition, increased synthesis of TRAIL receptors was demonstrated by RT-PCR in lesional vs. non-lesional skin. Immunohistochemistry showed an evident TRAIL and TRAIL receptor expression in lesional epidermis, as well as in the dermis. This is worthy of note because previous studies have already shown in non-lesional and healthy skin a costitutive expression of TRAIL and its receptors mainly in the epidermis. As stated by Zaba et al., the higher expression of TRAIL receptor in the dermis may suggest that TRAIL somehow induces the recruitment of inflammatory myeloid DCs, typically present in dermal inflammatory infiltrate.

We thought that the correlation between dermal caspase 8 and TRAIL immunoexpression could be of interest, in view of the fact that dermal caspase 8 could have
a role other than the proapoptotic action exerted in the epidermis. At the dermal level, the activation of caspase 8 through the binding of TRAIL to its receptor TRAIL-DR5, would then have a predominantly proinflammatory role, as noted by Chattergoon et al.25

Conclusions

All of these data suggest that TRAIL may be involved in psoriasis pathogenesis; TRAIL may have a proinflammatory role, even though no correlation between TRAIL expression and global (PASI score) or local (PSI score) disease severity has emerged from our study. On the other hand, TRAIL might have a proapoptotic role mediated by caspase 8, compensating for the typical hyperplasia of psoriasis. In this case further studies would eventually confirm that hypothesis, TRAIL could be a natural guardian of keratinocytes, preventing unrestricted proliferation and malignant transformation in psoriatic epidermis as already suggested by Peternel et al.16 The strong association (P=0.002) between serum TRAIL levels and disease duration that was highlighted in our study, strongly suggests the “guardian” role of TRAIL.

Limitations of this study include the lack of RT-PCR data in healthy skin and IHC data in healthy and non-lesional skin. This was due to avoid other skin biopsies to the enrolled subjects and based upon the presence of these data in the literature.

In conclusion, our findings confirm an involvement of TRAIL in the pathogenesis of psoriasis, probably through an action at the site of the inflammatory infiltrate, likely via caspase 8. Further studies are needed to clarify its complex role and the scope for its utilization in treating this common disease.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Dermatological approach to vemurafenib skin toxicity: a single centre experience

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ABSTRACT

BACKGROUND: Targeted therapies have recently changed the approach to advanced melanoma. RAF inhibitors represent the emerging standard of care for metastatic BRAF mutated melanomas. Cutaneous reactions are the most common side effects during vemurafenib treatment, and affect the quality of life. The aim of this study was to provide some practical advices to manage the drug related cutaneous reactions.

METHODS: A cohort of BRAF-mutated metastatic melanoma patients treated at our institution included 20 female and 21 male patients; median age was 56 years (32-87 years). All patients were treated at a dose of 960 mg b.i.d. orally.

RESULTS: After a median treatment duration of 7 months (range 0.5-25.2), 29/39 patients (74.4%) developed cutaneous toxicities. We identified 22 cases of maculo-papular rash (56%) and 18 of warts (46%); in a total of 10 cases we observed alterations of keratinization (25.6%), while 6 of our patients presented photosensitivity (15%). Six patients developed keratoacanthomas; no second melanomas were observed.

CONCLUSIONS: Skin involvement during vemurafenib treatment is frequent but in the majority of cases cutaneous side effects are self-limiting and easy to manage. Moreover, sun protection is mandatory in vemurafenib treated patients, and should be started together with BRAF inhibitor in order to minimize the impact of photosensitivity on quality of life.


Key words: Melanoma - PLX4032 - Toxicity - Skin.

Targeted therapies have recently changed the management of metastatic melanoma. Anti-CTLA-4 mono Abs (Ipilimumab) and RAF inhibitors are the earlier examples of this new kind of drugs, the firsts approved with both overall survival and progression-free survival benefit in respect of the current standard of care dacarbazine.1-5 Since its approbation in 2012 a new spectrum of skin toxicity has emerged, as the drug has become more widely used. Cutaneous reactions are the most common side effects described during vemurafenib treatment, and affect significantly on the quality of life.9-13 However dermatological studies on this topic are scanty.

As expected from the experience collected with others targeted therapies, skin toxicity seems to be related to the alteration of the cell-signaling pathway in response to BRAF inhibition in wild type BRAF cells.13

In this paper, we report our experience on cutaneous side effects collected by the treatment of 39 BRAF-mutated melanoma patients, with the aim to provide a practical guide to manage these common findings.
Materials and methods

A total of 41 BRAF-mutated metastatic melanoma patients were treated with vemurafenib at our Institution. Twenty patients were female, 21 male; median age was 56 years (32-87 years). Four patients showed a skin phototype I, 30 a phototype II and seven patients a phototype III. The study was approved by the committee on research ethics at the institution in which the research was conducted and any informed consent from human subjects was obtained as required.

All patients were treated at a dose of 960 mg b.i.d. orally. Median treatment duration was 7 months (range 0.5-25.2 months). Treatment regimen was stopped if a disease progression was detected. Three patients required a dose reduction as a consequence of cutaneous side effects, one patient stopped treatment due to skin toxicity.

Results

Two of the 41 patients discontinued treatment after a few weeks due to personal decision, withdrawing informed consent. These patients were excluded from data analysis. Cutaneous toxicities developed in 29/39 patients (74.4%); 5/39 patients experienced only one skin side effect; 8/39 two different kinds of cutaneous toxicity, 11/39 three, 4/39 four kinds. In one patient only we observed six different events. Taken together, cutaneous side effects developed during vemurafenib treatment were 64. The different types of adverse skin reactions are reported in Table I. No differences in distribution and type of side effects were found among sex and age.

Rash

Rash was the most early and frequent cutaneous side effect during vemurafenib treatment (56% of treated patients of our series). It was characterized by the onset of maculae and follicular papules mainly distributed on trunk and limbs (Figure 1); head was generally uninvolved. Rash appeared after a median time of 18 days...

Table I.—Number and median time of onset of cutaneous side effects related to vemurafenib treatment.

<table>
<thead>
<tr>
<th>Cutaneous side effect</th>
<th>Number of affected patients (%)</th>
<th>Median time of onset (range, days)</th>
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<tbody>
<tr>
<td>Maculopapular rash</td>
<td>22 (56%)</td>
<td>17 (5-55)</td>
</tr>
<tr>
<td>Warts</td>
<td>17 (44%)</td>
<td>50 (15-140)</td>
</tr>
<tr>
<td>Plantar hyperkeratosis</td>
<td>7 (18%)</td>
<td>87 (9-442)</td>
</tr>
<tr>
<td>Effluvium</td>
<td>6 (15%)</td>
<td>103 (55-201)</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>6 (15%)</td>
<td>59 (25-97)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>5 (13%)</td>
<td>162 (5-562)</td>
</tr>
<tr>
<td>Hand edema</td>
<td>4 (10%)</td>
<td>20 (14-27)</td>
</tr>
<tr>
<td>Follicular hyperkeratosis</td>
<td>2 (5%)</td>
<td>31 (9-53)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2 (5%)</td>
<td>47 (12-82)</td>
</tr>
<tr>
<td>Hair changes</td>
<td>2 (5%)</td>
<td>181 (159-202)</td>
</tr>
<tr>
<td>Milia</td>
<td>1 (3%)</td>
<td>85 (n.a)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1 (3%)</td>
<td>37 (n.a)</td>
</tr>
</tbody>
</table>
(range 5-55 days). In the majority of cases it was asymptomatic, even if some patients reported pruritus. Rush spontaneously resolved after a median of 21 days from the onset (range 2-69).

In our experiences, emollients were usually able to control cutaneous symptoms; topical steroids could be used to manage pruritus if present.

Warts

Viral warts represent the second most frequent cutaneous side effect under vemurafenib treatment and developed in 17 patients (44%); median time of onset was 50 days (range 15-140). Warts affected mainly head and neck areas, less frequently trunk and limbs (Figure 2A, B).

In 10.3% of our patients, viral warts were the first cutaneous side effect; whereas in 20.5% of patients it was the second effect, in 10.3% it was the third and in 5.1% it was the fourth.

From a histologic point of view, warts were indistinguishable from common viral warts; standard wart treatments (e.g. cryosurgery, keratolytic solutions, diathermic coagulation) resulted effective.

Hyperkeratosis

Hyperkeratosis was detected in a total of ten patients. Six developed plantar hyperkeratosis, occurring mainly in areas under physical pressure; 2 showed diffuse hyperkeratotic follicular papules that were observed mainly on lower limbs and forearms. One case of palmo-plantar hyperkeratosis was observed (Figure 3). The median time of onset was 87 (range 9-442).

Figure 2.—Viral warts. A) Hypertrophic warts on neck area; B) hypertrophic warts on trunk developed near an erythematous area resulting from a previous cryosurgery.

Figure 3.—Bilateral plantar hyperkeratosis on pressure areas; it is also visible a bullous lesion near the external malleolus due to sun exposure.
After 85 days of treatment, one patient developed milia on perioral and frontal regions (Figure 4). Lesion begin to regress a few days after treatment discontinuation due to a massive disease progression.

Topical keratolytic and emollient treatment can reduce hyperkeratosis, even if a complete resolution of this side effect was observed only after vemurafenib discontinuation.

Photosensitivity

Even if all our patients were encouraged to use sunscreen and avoid direct sun exposure during Vemurafenib treatment, sunburns were observed in 5 patients (13%). The median time of onset was 162 days, but sunburns can occur also after a few days of treatment (Figure 5). All patients who developed sunburns during Vemurafenib treatment showed a photo type II.

In two other patients we observed also an actinic conjunctivitis. In one patient this was an early side effect and developed after only twelve days of treatment, whereas in the other patients conjunctivitis was observed as very late manifestation and arises after than 82 days from the beginning of treatment.

Effluvium and hair changes

Hair change was a late phenomenon. Effluvium occurred in 6 patients (15%), after a median time of 103 days (range 55-201). No complete hair loss was observed.

Moreover two patients, after respectively 159 and 202 days from the beginning of treatment, experienced a curling and ticking of the hair.

Hands edema and urticaria

Four patients showed a bilateral, localized hand edema, that developed as an early side effect within one month from the beginning of the treatment (median 20 days, range 14-27). Laboratory tests did not show renal toxicity or hypoalbuminemia, and no other sign of edema diffuse or localized was present.

Moreover, we report the case of a patient with a personal history of atopia that experienced two urticarial episodes during the vemurafenib treatment. Both episodes spontaneously resolved without drug suspension, thus a clear relationship between vemurafenib and urticaria remains to ascertain.

Skin cancer

Despite the high incidence of skin tumors previously described during vemurafenib treatment, no patient of our series developed invasive cutaneous carcinomas or
Discussion

Even if vemurafenib is a safe and well tolerated drug, cutaneous adverse events are the most common toxicity with an important impact on quality of life.

In this paper we analyzed data collected from our experience in the use of vemurafenib with the aim to provide to dermatologists and other physicians a practical tool for the management of skin related cutaneous adverse reactions.

The vemurafenib skin toxicity profile seems to be changed since first reports obtained from Phase I-III and expanded access studies. These studies focused on squamous cell carcinoma observed in up to 31% of patients. In our experience the incidence of keratoacanthomas and SCC is lower than that reported in literature, even if a central pathology review of all lesions excised in phase II study revealed that 90% of reported SCC were keratoacanthomas and the remaining 10%, well-differentiated squamous cell carcinomas. More recent reports stated that incidence of SCC a keratoacanthomas is 14% and 18%, respectively.

Recently literature data hypothesized that keratoacanthomas and SCC is lower than that reported in literature, even if a central pathology review of all lesions excised in phase II study revealed that 90% of reported SCC were keratoacanthomas and the remaining 10%, well-differentiated squamous cell carcinomas. More recent reports stated that incidence of SCC a keratoacanthomas is 14% and 18%, respectively.

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anthomas and cutaneous carcinomas develop as a consequence of pre-existing precancerous RAS mutations in keratinocytes of sun exposed areas that are activated by vemurafenib exposure through a paradoxical up-regulation of MAPK signaling. These mechanisms explain also the keratinocytes proliferation that could lead to keratosis pilaris like lesions, palmo-plantar hyperkeratosis and hair changes that are common in vemurafenib treated patients, similarly to what observed during the treatment with sorafenib and MEK inhibitors.

In our experience, keratosis pilaris like lesions and palmo-plantar hyperkeratosis can be managed by regular use of topical emollient and/or keratolytics (such as urea, salicylic acid or lactic acid); topical steroid could also be useful in the presence of inflammatory or symptomatic lesions. In literature the use of systemic retinoid as chemopreventive for cutaneous squamous cell carcinomas has been reported in patients treated with vemurafenib. In our experience, also topical retinoid can significantly reduce the hyperkeratosis, with lower side effects. Moreover, keratolytics can be used in the treatment of warts, together with commonly used surgical procedures.

According to literature data, reporting the onset of a maculo-papular eruption in about 50% of treated patients, also in our experience rash represents a frequent, early and generally self-limiting toxicity. From a clinical point of view, this rash could be similar to other drug related exanthemas. However, in the majority of our patients, vemurafenib related rash is characterized by a diffuse presence of papular follicular lesions; macule can coexist, but usually are less represented. Cases that underwent skin biopsy showed an inflammatory lympho-histiocytic lichenoid infiltrate at histological examination, even if a keratinocytes activation should play a role. The origin of this maculo-papular eruption is still unclear; however these features can explain the usefulness of topical steroids, as well as the anecdotic finding that rash did not occurred in patient receiving concomitant steroids for other medical conditions.

Because of the self-limiting nature of this side effect we encourage the routinely use of topical emollients; steroids use should be limited to symptomatic cases. Patients should be also informed to the frequency and the benignity of this rash; persistent or clinically atypical exanthemas should be referred to an experienced dermatologist to avoid the risk of SJS/TEN.

Photosensitivity is another common phenomenon in vemurafenib treated patients. Molecular basis of this phenomenon are still unclear. Even if this side effect do not represent a life threatening condition, it can impact on quality of life and could be difficult to manage both by patients and physicians. Painful sunburns are an early phenomenon and may occur after few minutes of sun exposure; UVA component seems to play a larger role than UVB. Patient photo-type and intensity of sun exposure can concur in the onset of this phenomenon.

Sun protection is mandatory in vemurafenib treated patients, and should be started together with BRAF inhibitor. In our experience, the photosensitivity occurred in a lower percentage of cases than what is reported in literature, probably as a consequence of the fact that all of our patients were informed about the risk of sunburns and encouraged to use routinely an adequate sun screen. Peculiar was the case of a patient that of his own will has suspended the sun screen use to check if the medical advice was reliable; her picture is shown in Figure 5.

Conclusions

In conclusion, vemurafenib treatment is generally well tolerated; cutaneous side effects are common but, in the majority of cases they do not require dose reduction or treatment discontinuation. Skin toxicity may represent a consequence of the direct interaction of vemurafenib with the RAS/RAF/MEK/ERK pathway on cutaneous targets. This fact can explain also the short time of onset of the majority of these side effects and their quick resolution after drug suspension.

A correct patient education is mandatory to prevent and better manage this spectrum of skin toxicity, that is often asymptomatic and self-limiting. Moreover the Dermatologist role is crucial in the management of these challenging patients in order to early distinguish skin side effects potentially severe, from those benign and self-limiting, avoiding inappropriate treatment interruptions or discontinuations.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Evaluation of efficacy and tolerability of four weeks bifonazole treatment after nail ablation with 40% urea in mild to moderate distal subungual onychomycosis

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ABSTRACT

BACKGROUND: The aim of this study was to verify efficacy and tolerability of sequential therapy with 40% urea paste followed by 1% bifonazole urea in mild to moderate distal subungual onychomycosis of the toenails.

METHODS: It was an seven weeks open study. Sequential patients affected by mild to moderate distal subungual onychomycosis of the toenails agreed to apply on the affected nail 40% urea paste in occlusion overnight for the first three weeks, with gentle scraping with a spatula the following day, followed by1% bifonazole cream once a day for 4 weeks. Efficacy evaluation was based on mycology, clinical photography and investigator and patient assessment. Tolerability assessment included subjective and objective evaluations.

RESULTS: The ten patients enrolled (mean age 57.5 years) completed the study. Onychomycosis was caused in nine cases by dermatophytes and by Scopulariopsis brevicaulis in one patient. At the end of the study, mycological examination was negative in all 10 patients. Clinical photographs showed a reduction of the percentage of the nail affected by onychomycosis in 8 cases, cure in 2 and considerable reduction of the nail thickness, already evident after 7 days. All patients reported to be satisfied by the treatment, which was judged easy to perform and well tolerated.

CONCLUSIONS: Treatment with urea and bifonazole is effective and well tolerated, and easy to do also by elderly patients.

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Key words: Onychomycosis - Bifonazole - Urea - Nails.

Onychomycosis is a common condition, affecting about 5% of the general population, and particularly the elderly, where it accounts for 50% of the toenail dystrophies. The prevalence of onychomycosis is steadily rising in recent years, probably due to the increase in the old population and because of changes in the life-style. Predisposing factors include, in fact, old age, together with diabetes mellitus, peripheral vascular diseases, peripheral neuropathies, hyperhidrosis and foot trauma.

The most common type of onychomycosis is distal subungual onychomycosis, which usually involves one or two toenails and causes onycholysis, subungual hyperkeratosis and white-yellow discoloration of the nail plate. Fungi reach the nail from the plantar skin and invade the horny layer of the nail bed, inducing nail plate detachment and a more or less severe hyperkeratotic reaction of the nail bed. Proximal progression of fungi beneath the nail causes the discoloration. The nail plate is often thickened and uplifted and the patient complains of pain, spontaneous or when wearing shoes, with difficult walking. Toenail pain caused by onychomycosis is one of the factors reported to reduce the quality of life of the affected patients, other factors being the fear to transmit the infection to others or to other skin sites and the cosmetic impairment.2
Treatment of distal subungual onychomycosis includes systemic antifungals, administered for 2-3 months, which are indicated in patients with involvement of several nails or with invasion of the proximal nail plate, and topical antifungals in lacquers or creams, which require 6 to 12 months of use. Topical treatment is often preferred especially in the elderly, who are undergoing chronic therapies for systemic conditions, in order to avoid the risk of drug interactions.

The clinical improvement induced by systemic and topical antifungals appears very slowly, as the toenail grow rate is very low, about 1 mm/month, and elimination of the affected part of the nail plate is required to obtain an healthy nail. For this reason, clinical symptoms induced by mechanical traumas by shoes to the nails thickened by onychomycosis persist for a long time after starting treatment for onychomycosis and patients often require podiatrist treatment in order to decrease foot pain and be able to walk properly.

The sequential treatment with 40% urea paste and 1% bifonazole cream has the goal to first induce nail plate maceration and softening, improving the subjective symptoms and increasing the penetration of the active antifungal that, applied in the 2nd phase, is able to penetrate deeply into the nail plate and act against fungi.

The aim of this study was to verify the efficacy and tolerability of sequential therapy with 40% urea paste followed by 1% bifonazole urea in mild to moderate distal subungual onychomycosis of the toenails.

**Materials and methods**

This open study, approved by the ethics committee, had duration of 7 weeks and enrolled sequential patients affected by distal subungual onychomycosis of the toenails consulting our outpatient consultation for nail diseases. Inclusion criteria included: age between 18 and 75 years, distal or disto-lateral subungual onychomycosis involving 20-70% of the nail confirmed by positive KOH and culture, willingness to sign the informed consent for participation in the study and interruption of any topical or systemic antifungal in the 60 days prior to enrollment. Exclusion criteria were: malignant tumors or severe systemic diseases, dermatological diseases including psoriasis and lichen planus, allergy of any of the components of the two products.

On the day of enrollment in the study each patient received a sample of 40% urea paste to utilize for the first three weeks (phase 1) and was instructed on the correct application of the topical. Forty per cent urea paste was applied once a day on the target nail (1 toenail), preferably after a hot footbath, and then covered with the plastic wrap included in the package, shaped for easy adhesion to the digit. The medication was removed after 24 hours and the spatula contained in the package was used to gently scrape the nail plate surface and remove the macerated part. This treatment was repeated every day for 3 weeks. At the 3-week control visit the patient received a sample of 1% bifonazole cream to be applied on the affected nail once a day for 4 weeks (2nd phase). Patients were followed up weekly in the 1st phase of the study (3 visits in total), while the 4th visit was carried out at the end of the 2nd phase of the treatment, after 7 weeks of combined therapy.

Mycological evaluation (KOH and culture) was performed in the beginning and in the end of the study. Clinical evaluation included standardized photography of the target nail and patient and investigator assessment. Clinical parameters utilized to monitor the clinical outcome included: reduction of the percentage of the nail affected by onychomycosis, complete cure, and reduction of the nail thickness. The investigator assessment was performed at every visit, scoring the response to treatment in the following way: worsening (0), no change (1), improvement (2) cure of onychomycosis (3). A similar evaluation was asked to the patient, who at the end of the 7-week study had also to express his/her satisfaction of treatment (not satisfied, satisfied, very satisfied). At every visit the patient was inquired about any problem with the topical application, the onset of side effect and the overall tolerability of the treatment.

**Results**

The ten patients enrolled completed the study. They include 4 females and 6 males, ageing from 41 to 75 years (mean age 57.5 years), affected by mild to moderate distal subungual onychomycosis (percentage of affected nail <50%: 2 patients, >50% 8 patients). *Trichophyton rubrum* was the causative agent in 5 cases, *Trichophyton interdigitale* in 4 and *Scopulariopsis brevicaulis* in 1 patient. At the end of the study, mycological examination (KOH and culture) was negative in all 10 patients. Clinical photographs showed a reduction
periungual inflammation was noticed during both phases of the treatment period.

Discussion

The possibility to combine a topical antifungal with urea at high concentrations in the treatment of onychomycosis was first suggested in the 90s, where several studies proved the efficacy and tolerability of a topical combination containing urea and bifonazole.2-7 In Germany and other countries of the European Community the combined formulation of urea and bifonazole for the treatment of onychomycosis has been on the market since then. In these studies urea and bifonazole were applied on the affected nail in a single topical formulation and it was therefore impossible to distinguish the effects of each component.
In 2013, Tietz et al.\(^8\) proved the effectiveness of the sequential treatment of onychomycosis with urea and bifonazole, performing a double blind study that allowed evaluation of the effects of the single components. They treated patients with distal subungual onychomycosis involving 20-50% of the nail, following a 3 phase protocol: 1) phase 1: topical application of 40% urea paste in occlusion once a day for 14-28 days, until the nail plate become soft; 2) phase 2: topical application of 1% bifonazole cream (or placebo) once a day for 14-28 days; 3) phase 3: control visit performed 6 months after the end of therapy. The higher efficacy of urea+bifonazole therapy was already evident 2 weeks after the end of the treatment period, were 54.8% of the treated patients were cured, compared with 42.2% of the patients using placebo. The higher efficacy of urea+bifonazole was also proven by an increased number of mycological cures.

Our study repeated phase 1 and 2 of Tietz’s study, without placebo controls. The results are extremely satisfying, as we obtained mycological cure in all patients after 7 weeks of combined therapy. At that time, clinical cure was seen in 2 patients with mild distal subungual onychomycosis, and great improvement in the other 8 patients, who were affected by a more severe onychomycosis, involving >50% of the nail. These patients presented persistence of onychomycosis in the distal part of the toenail, due to the fact that the short duration of the study did not allow the nail plate to grow enough to eliminate all the diseased part. They are continuing therapy with 1% bifonazole cream and the next follow-up visit, 3 months after the end of the study period, is likely to reveal complete clinical cure. We decided to enroll patients with different severity of onychomycosis, including mild and moderate degrees, as we wanted...
to test the efficacy of the combined treatment in the most common types of onychomycosis, i.e. those with involvement of 40-50% of the nail.

Sequential treatment with 40% urea and 1% bifonazole proved to be effective and well tolerated. Patients particularly liked the softening activity of urea in occlusion, reporting clinical improvement of the symptoms already after 6-7 days of application, with a softer and more transparent nail plate, easy to cut and not painful in the shoe. The first phase of the treatment, with daily application of 40% urea paste in collusion, induces in fact a progressive chemical avulsion of the part of the nail invaded by fungi, resulting in a softer and more flexible nail plate, as the thickened part is removed by gentle scraping with the spatula included in the package. The effect of urea on the nails with onychomycosis has been evaluated by a study with Scanning Electron Microscopy (SEM),9 that showed that urea selectively destroys the part of the nail invaded by fungi, causing a gradual disintegration of corneocytes that starts in the superficial layers and gradually reaches the deep portions of the nail. The structure of the nail becomes grossly altered, with marked enlargement of the intercellular spaces. Similar effects may be obtained also in healthy nails, but it requires a much longer time of contact with urea. Application of 40% urea in occlusion on the nail affected by onychomycosis induces rapid nail plate softening, decreasing the pain induced by shoes, and allows the removal of the diseased part of the nail by the spatula. This causes clinical improvement of the nail aspect, and is especially helpful in preparing the nail for the application of the topical antifungal, which is easily absorbed by a macerated nail. Urea has also been shown to have an inhibitory activity on dermatophyte growth in vitro,10 so that the first phase of therapy not only induces nail maceration, but also has an antifungal effect.

Conclusions

Bifonazole is an imidazole derivative with broad-spectrum antifungal activity against dermatophytes, yeasts and non-dermatophyte molds. Bifonazole in cream at 1% concentration exerts its antifungal effects on all the layers of the nail and needs only 1 application per day, differently from other antifungals.11 Bifonazole also possesses anti-inflammatory and antibacterial activities, the latter particularly important in the nails with onychomycosis, where bacterial superinfection is common.

Our study confirms the data present in the literature about efficacy and tolerability of topical sequential treatment with urea and bifonazole in onychomycosis, and adds data about effectiveness on forms with moderate nail involvement (50-70%) and caused by non-dermatophytes. One of our patients was in fact affected by onychomycosis due to Scopulariopsis brevicaulis, which was considerably improved clinically and with negative mycology at the end of the 7-week study (Figure 3).

Treatment with urea and bifonazole is effective and well tolerated, and easy to do also by elderly patients.

References


Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.


PIRACCINI

BIFONAZOLE TREATMENT IN DISTAL SUBUNGUAL ONYCHOMYCOSIS

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36
Health-related quality of life in adult atopic dermatitis and psoriatic patients matched by disease severity

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ABSTRACT

BACKGROUND: Atopic dermatitis (AD) and psoriasis have significant negative impact on patients’ lives. Objective of this study was to compare the impact of psoriasis and AD in adult patients matched by disease severity and to perform further validation of the Ukrainian versions of the DLQI and Skindex-16 in these skin conditions.

METHODS: Sixty-three adult AD and 63 psoriatic patients matched by disease severity according to SCORAD and PASI were enrolled. Patients completed the Ukrainian versions of the DLQI and Skindex-16 questionnaires. Cronbach’s alpha was used to measure internal consistency of the Ukrainian versions of the DLQI and Skindex-16.

RESULTS: All three scales of Skindex-16 and the DLQI were internally reliable. Mean DLQI was 10.63±6.15 for AD patients and 11.59±7.18 for psoriatic patients (P=0.43). The highest scored question of the DLQI concerned symptoms tends the highest scored item for Skindex-16 was “frustration about skin condition”. The DLQI item on treatment was scored higher by psoriatic patients (1.32±0.98 and AD = 0.73±0.79, P<0.001). “Functioning” scale of Skindex-16 was assessed higher by psoriatic patients in all clinical subgroups and “Emotions” scale in subgroup with mild disease severity. Skindex-16 item on itching was assessed higher by AD patients (3.65±2.03 for AD and 2.92±1.95 for psoriatic patients, P=0.05) meanwhile, two other separate Skindex-16 items had higher impact on psoriatic patients: the effect of skin condition on desire to be with people (3.51±2.18 for psoriatic patients and 2.29±2.09 for AD patients, P<0.05) and skin condition making it hard to show affection (3.51±2.18 for psoriatic patients and 2.24±2.09 for AD patients, P<0.05).

CONCLUSION: Psoriasis has higher effect on desire to be with people, showing affection and cause more problems with the treatment, meanwhile in AD itching cause higher negative impact on QoL. Even psoriatic patients with mild disease often may have large negative effect on their QoL that is not typical for AD patients.

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Key words: Dermatitis, atopic - Psoriasis - Adult.

A topic dermatitis (AD) and psoriasis have a major negative impact on the lives of patients because of symptoms, secondary psychological and social consequences and treatment.1-3 Moderate-to-severe psoriasis has a profound negative impact on the employment capacity of patients.4 Substantial number of AD patients had abstained from a specific education or a job due to AD.5 To avoid uncontrolled psoriasis or eczema participants chose an approximately 40% shorter life expectancy. This indicates that severe chronic inflammatory skin diseases may be considered as severe as angina pectoris, chronic anxiety, rheumatoid arthritis, multiple sclerosis or regional oesophageal cancer.6 In psoriasis and AD, hospitalization effectively improved quality of life (QoL) and clinical disease severity.7 For patients with either AD or psoriasis, clinical status and physical symptoms of itching scarcely affected psychological distress. Instead, higher levels of fatigue, perceived
helplessness and less social support best predicted psychological distress in patients with both skin diseases in multiple regression analyses. Health-related (HR) QoL instruments are questionnaires consisting of a number of items, or questions, most often to be answered by choosing one of the response options. Dermatology-specific HRQoL tools are specifically developed for the assessment of HRQoL in skin diseases. They assess domains and aspects of HRQoL particularly important to patients with skin conditions. Dermatology-specific instruments should be applicable in skin diseases, thereby allowing comparison between them. For clinical practice purposes the European Academy of Dermatology and Venereology Taskforce on QoL recommends using a dermatology-specific instrument as generic instruments might fail in the assessment of important dermatology-specific aspects.

The Dermatology Life Quality Index (DLQI) and Skindex are widely used dermatology-specific QoL instruments. The DLQI was the first dermatology-specific QoL instrument and is still the most commonly used. The DLQI consists of 10 questions with simple tick-box answers. The mean answer time is two minutes. The DLQI has been used in 33 different skin conditions in 32 countries and is available in 55 languages. A 61-item prototype version of Skindex was created and tested in a series of studies that demonstrated it to be reliable and to have substantial evidence of validity as a measure of the effects of skin disease on quality of life. Shortened versions of Skindex: questionnaire – Skindex-29 and Skindex-16 are currently available and translated into different languages. Ukrainian versions of the DLQI, Skindex-29 and Skindex-16 were created. Test-retest reliability, discriminant validity, and sensitivity of the questionnaires to change over time and to successful therapeutic intervention were checked. Ukrainian versions of the DLQI and Skindex-16 were used in a comparative study of HRQoL in psoriatic patients from Lithuania and Ukraine.

The objectives of this study were: 1) compare the impact of psoriasis and AD in adult patients matched by disease severity and 2) perform further validation of the Ukrainian versions of the DLQI and Skindex-16 in these skin conditions. For the first time for comparison of the impact on HRQoL psoriatic and AD patients are well matched by severity of clinical manifestations. This study may aid insight into what extent the consultation process of patients with psoriasis and AD correspond; do psoriatic and AD patients with equal clinical severity have the same needs for active treatment, psychological help and education? This issue is especially important for the efficient organization of high quality but busy out-patient clinics.

Materials and methods

Subjects

Adult AD and psoriatic in-patients and day care center patients were matched by disease severity (equal number of patients with mild, moderate and severe disease) were recruited from the clinics of the department of Dermatology and Venereology, National Medical University, Kiev (Table I). Disease severity was measured by SCORAD for AD patients and by PASI for psoriatic patients. AD with a SCORAD higher than 40 was regarded as severe, whereas AD with a SCORAD below 20 was regarded as mild. Psoriasis with a PASI higher than 20 was regarded as severe, whereas psoriasis with a PASI below 10 was regarded as mild. Patients were invited to complete the DLQI and Skindex-16 questionnaires on admission to the clinic before starting treatment. Ethical permission for the study was granted from the local research Ethics Committee.

Instruments

The DLQI questionnaire is designed for use in adults. It is self explanatory and can be simply handed to the patient who is asked to fill in without the need for detailed explanation. The DLQI has 10 questions, each with four possible answers. The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. Following meaning of DLQI scores have been proposed: no effect (score 0-1), small effect (score 2-5), moderate effect (score 6-10), very large effect (score 11-20) and extremely large effect on patient’s life (score 21-30). The DLQI can also be expressed as a percentage of the maximum possible score of 30. The DLQI can be analyzed under six headings as follows: symptoms and feelings; daily activities; leisure; work and school; personal relationships; treatment. The scores for each of these sections can also be expressed as a percentage of either 6 or 3. If two or more questions are left unanswered the questionnaire is not scored.
TABLE I.—Clinical characteristic of patients with AD and psoriasis.

<table>
<thead>
<tr>
<th>Atopic dermatitis</th>
<th>Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (total N.)</td>
<td>63</td>
</tr>
<tr>
<td>Severe (N.)</td>
<td>21</td>
</tr>
<tr>
<td>Moderate (N.)</td>
<td>29</td>
</tr>
<tr>
<td>Mild (N.)</td>
<td>13</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>28.55±10.72</td>
</tr>
<tr>
<td>Sex Male</td>
<td>27</td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
</tr>
</tbody>
</table>

TABLE II.—Internal consistency of the Ukrainian version of Skindex-16.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Emotions</th>
<th>Symptoms</th>
<th>Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>0.89</td>
<td>0.84</td>
<td>0.89</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>0.87</td>
<td>0.83</td>
<td>0.89</td>
</tr>
</tbody>
</table>

The Skindex-16 is also self explanatory. It has 16 questions, each with seven possible answers. All responses are transformed to a linear scale of 100, varying from 0 (no effect) to 100 (effect experienced all the time). Each item can have a minimum score of 0 and a maximum score of 100. The higher the score, the more quality of life is impaired. It can be analyzed under 3 scales: emotions, symptoms (including one item on itch) and functioning. A scale score is the mean of a patient’s responses to the items in a given scale. Studies to aid interpretation of Skindex-16 scores have not yet been performed. Permissions for validation and use of the DLQI and Skindex-16 questionnaires were received from Prof. A.Y. Finlay (UK) and Prof. M.M. Chren (USA).

Statistical analysis

Data is presented as mean ± standard deviation of the mean. Unpaired t test with Welch correction, two-sided Fisher’s exact test and Spearman nonparametric correlation (Spearman r) were used. The results were considered significant if P<0.05. Cronbach’s alpha was used to measure internal consistency of the Ukrainian versions of the DLQI and Skindex-16.

Results

A total of 63 patients with AD and 63 with psoriasis were recruited, their clinical characteristics are given in Table I.

Scale scores for the Ukrainian version of Skindex-16 were internally reliable (Table II). Cronbach’s alpha of the Ukrainian DLQI version was 0.81 for AD and 0.86 for psoriatic patients.

The mean DLQI for AD patients was 10.63±6.15 and 11.59±7.18 for psoriatic patients (P=0.43). There was no statistically significant difference in distribution of the overall DLQI scores according to banding between AD and psoriatic patients. However, 11 psoriatic patients and 4 AD patients (P=0.09) had DLQI scores indicating an extremely large effect on their life. Only one DLQI question, “how much of a problem has the treatment of patient’s skin been” was assessed higher by psoriatic (1.32±0.98) than AD patients (0.73±0.79, P<0.001).

Analysis of three Skindex-16 scale scores showed that the “Functioning” scale was assessed higher by psoriatic patients (51.04±36.34) than for AD patients (40.51±34.67, P<0.01).

The Skindex-16 item on itching was assessed higher by AD patients (3.65±2.03) than for psoriatic patients (2.92±1.95, P<0.05). Two other Skindex-16 items scored higher in psoriatic patients than AD patients: “the effect of skin condition on desire to be with people” (psoriasis=3.51±2.18, AD=2.29±2.09, P<0.05) and “skin condition making it hard to show affection” (psoriasis=3.51±2.18, AD=2.24±2.09, P<0.05).

Even though summing a total score is not generally recommended for Skindex it was calculated in order to correlate Skindex and DLQI scores. They correlated well in AD (r=0.66, P<0.001) and psoriasis (r=0.71, P<0.001).

The age of patients with AD was significantly correlated with 6 separate Skindex-16 items: skin condition
burning or stinging (r=0.41, P<0.05), persistence/reoccurrence of skin condition (r=0.43, P<0.01), being annoyed about skin condition (r=0.40, P<0.05), feeling depressed about skin condition (r=0.51, P<0.01), the effect of skin condition on desire to be with people (r=0.36, P<0.05) and skin condition making it hard to show affection (r=0.39, P<0.05) and three separate DLQI items: how much the skin affected social or leisure activities (r=0.33, P<0.05), how the skin prevented working or studying (r=0.30, P<0.05) and how much of a problem the skin affected social or leisure activities (r=0.33, P<0.05), how the skin prevented working or studying (r=0.30, P<0.05) and how much of a problem the skin affected social or leisure activities (r=0.33, P<0.05), how the skin prevented working or studying (r=0.30, P<0.05) and how much of a problem the skin affected social or leisure activities (r=0.33, P<0.05), how the skin prevented working or studying (r=0.30, P<0.05).

There was no significant correlation between age and the DLQI scores or separate DLQI and Skindex-16 items in psoriatic patients.

Neither the mean DLQI nor its separate items correlated with PASI. Only three separate Skindex-16 items significantly correlated with PASI: the appearance of skin condition (r=0.65, P<0.01), the effect of skin condition on desire to be with people (r=0.55, P<0.01) and skin condition making it hard to show affection (r=0.40, P<0.05).

The highest scored question of the DLQI concerned symptoms tends the highest scored item for Skindex-16 was “frustration about skin condition”.

Comparative analysis of HRQoL in subgroups of AD and psoriatic patients matched by disease severity showed no difference in total mean DLQI scores. Only in the psoriasis subgroups with mild and severe disease was the DLQI item on “how much of a problem has the treatment of patient’s skin been” scored higher than AD patients (mild psoriasis=1±1, mild AD=0.3±0.48, P<0.05; severe psoriasis=1.9±0.86, severe AD=1.05±0.86, P<0.01).

The “Functioning” scale of Skindex-16 was assessed higher by psoriatic patients in all clinical subgroups (P<0.05) and the “Emotions” scale was assessed higher by psoriatic patients in the mild subgroup (psoriasis=55.01±35.17, AD=43.01±30.67, P<0.05).

Psoriasis patients with mild disease severity were more worried about their skin condition (that it will spread, get worse, scar, be unpredictable, etc.) than AD patients (psoriasis=4.31±1.44 AD=2.69±1.70, P<0.05). AD patients in the subgroup with moderate disease severity were more bothered with persistence/reoccurrence of their skin condition than psoriatic patients (psoriasis=2.52±1.86, AD=3.55±2.01, P<0.05). Psoriatic patients from this subgroup assessed two other Skindex-16 items higher than AD patients: the effect of skin condition on desire to be with people (psoriasis=3.37±2.04, AD=1.83±1.93, P<0.01) and skin condition making it hard to show the affection (psoriasis=3.17±1.97, AD=1.72±1.87, P<0.01). Psoriatic patients with severe disease also assessed the Skindex-16 item “skin condition making it hard to show the affection” higher than AD patients (psoriasis=4.86±1.56, AD=3.62±1.91, P<0.05).

Discussion

Good internal consistency was confirmed for the Ukrainian versions of the questionnaires in both skin conditions. Cronbach’s alpha was higher than 0.7, the minimal requirement for an instrument to be internally consistent, for all three Skindex-16 scales and the DLQI.

Despite the many studies on HRQoL impairment in AD and psoriasis it is not clear which of these diseases has more severe impact, with some reports of no difference and other reports of higher HRQoL in psoriatic patients.

Lundberg et al., demonstrated higher willingness to pay for a cure in psoriatic patients than in patients with AD. Willingness to pay correlated with DLQI scores and disease activity, but not with SF-36 scores. However, total DLQI score and all DLQI dimension scores except “Treatment” were higher in AD patients, though not significantly. Patients in that study were not matched by disease severity and participants with AD probably had more severe disease.

Only one scale (Functioning) of Skindex-16 scored higher by psoriatic than AD patients. However, it was assessed higher by patients with all degrees of severity and this might be attributed to peculiarities of the impact of psoriasis on the life of patients. Two items from Skindex-16 “the effect of skin condition on desire to be with people” and “skin condition making it hard to show affection” had higher impact on psoriatic patients. Both these items correlated with age and did not correlate with disease severity in AD patients but correlated with disease severity and did not correlate...
with age in the psoriasis patients. This may indicate that these aspects of QoL get worse with the age in AD and with more severe symptoms in psoriasis. The study by Leibovici et al.31 also demonstrated more severe psychopathology, a more passive attitude towards life, and a greater loss of meaning in life in psoriatic patients compared with AD patients. It may be that even adult AD patients think that they may “grow out of” their skin condition. However, as the years pass they become less optimistic. In contrast, the impact of several aspects of psoriasis is greater the more severe the disease, independent of age.

Meanwhile itch is a prominent characteristic feature of AD 32 according to the classic textbook description, psoriasis does not itch. Even in middle 80th itch was considered as occasional and not a major complain of the psoriatic patients.33 However, in a survey of members of the National Psoriasis Foundation (NPF), itch was the second most common symptom reported by 79% of respondents.34 In our study and others 35, 36 AD patients were highly affected by itching. Grob et al.37 reported that “physical discomfort” was greater in AD than in psoriasis. However, in our study subjective symptoms other than itch did not differ significantly between AD and psoriasis.

The greater reporting of problems caused by treatment of psoriatic patients than by treatment of AD might be explained in part by differences in compliance with treatment between psoriatic 38, 39 and AD 40 patients. Adherence to treatment negatively correlates with HRQoL impairment,41 but patients with mild psoriasis and those with a DLQI of 5 or less adhered less to the therapy.42 Adherence to the treatment may therefore be worse in psoriatic patients who experience either a small or a large effect on their life and may be better in patients who experience a moderate effect on their life. In our study psoriatic patients with mild and severe psoriasis reported more problems with treatment than AD patients. Psoriatic patients with moderate psoriasis did not show significant difference compared to AD patients. Zaghloul and Goodfield 43 reported higher adherence in psoriatic patients on topical than in those on systemic therapy. However, recent study reported higher adherence on systemic therapy.43 Psoriatic patients in our clinics more often received systemic treatment but in our study they reported more problems with treatment than AD patients. Direct comparison of the adherence to treatment in these skin diseases should be further investigated.

Psoriatic patients with mild disease severity may worry more than AD patients about their skin condition (that it will spread, get worse, scar, be unpredictable, etc.) because of information from the popular literature, the internet and from other psoriatic patients with more severe disease. They may have particular concerns about lifetime course, incurability, potential nail and joint involvement and progression of psoriasis. AD patients with mild disease severity usually receive information that it is possible to control their disease and if they avoid provoking factors AD will rarely become worse. This difference in patient information may also explain why AD patients with moderate disease severity were more bothered with persistence/reoccurrence of their skin condition than psoriatic patients. Patients with AD may not understand why their “allergy” did not disappear if they leave their house and/or work place, were hospitalized and received treatment. Failure of attempts to identify provoking allergens may even increase this problem.

Conclusions

It is possible to make several conclusions. The Ukrainian versions of the DLQI and Skindex-16 questionnaires are internally consistent in both AD and psoriasis. The DLQI and Skindex-16 did not simply duplicate the results of each other but when used together were a source of additional information. If we had used only one of these instruments several important aspects of HRQoL impairment would have been missed.

Psoriasis has higher effect than AD on the desire to be with people or on showing affection and more problems are caused by its treatment. In AD itching caused a higher negative impact on QoL than in psoriasis. There are also several peculiarities of HRQoL impairment related to the age and disease severity in AD and psoriasis.

The educational aspects of consultations should not be identical in AD and psoriasis. Psoriatic patients with mild disease often report a large negative effect on their QoL: that is not typical for AD patients.

Studies concerning adherence to treatment in AD and psoriasis may give some insight into explaining why psoriatic patients experience a higher impact on their life caused by treatment.
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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

New insights into immune mechanisms of vitiligo

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ABSTRACT
Vitiligo is the most common depigmenting disorder, affecting 0.5% of the population. This stigmatizing disease has a major social impact with high unmet needs, and no real curative intervention has been reported so far. Vitiligo is characterized by the development of white macules resulting from a loss of epidermal melanocytes, which can result from cell destruction through melanocyte-specific cytotoxic immune response and melanocyte detachment through a defective adhesion system. Multiple mechanisms have been suggested to be involved in melanocyte disappearance: genetic predisposition, environmental triggers, metabolic abnormalities, altered inflammatory and immune responses. The autoimmune and inflammatory theory is the leading hypothesis. Indeed, vitiligo is often associated with autoimmune diseases; genome-wide association studies and functional pathway analyses have shown that most vitiligo susceptibility loci encode components of the immune system; and immune cells are found in the perilesional margin of actively depigmenting skin of vitiligo patients. However, studies support melanocytes intrinsic abnormalities in vitiligo associated with increased melanocytes stress leading to the release of dangers signals important for the activation of the immune system. This review aimed to overview the link between cellular stress, melanocyte function, and the abnormal inflammatory immune response in vitiligo. The involvement of innate and adaptive immune cells in the pathomechanisms leading to melanocyte loss observed in vitiligo will be discussed.

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Key words: Vitiligo - Autoimmunity - Inflammation.

Vitiligo is an acquired chronic depigmenting disorder of the skin resulting from a selective loss of melanocytes. The estimated prevalence of vitiligo is around 0.5% of the world population.1, 2 The two sexes are equally affected, and there are no apparent differences in rates of occurrence according to skin type or race. Non segmental vitiligo or generalized vitiligo (“vitiligo” is now the proposed name by international consensus) is the predominant form of the disease, characterized by symmetric and bilateral white macules. A loss of epidermal melanocytes, the cells responsible for skin pigmentation, is the pathogenic hallmark of vitiligo. Factors involved in the initiation of vitiligo remain largely unknown, including genetic and environmental factors. However, the pathomechanisms leading to the loss of melanocytes are still in debate. Several theories have been proposed. Melanocyte-intrinsic abnormalities in vitiligo leading to impaired melanocyte degeneration and/or proliferation support the hypothesis that the disease could be due to a primary defect of melanocytes.3 However, other observations strongly support the role of the autoimmune system, particularly in the chronic and progressive phases of vitiligo.4-9 Genome-wide association studies (GWAS) have shown that 90% of vitiligo susceptibility loci encode components of the immune system.10 Furthermore, vitiligo is often associated with autoimmune diseases, and both innate and adaptive immune cells are found in patients’ affected skin. Since neither immune nor non immune mechanisms in isolation can sufficiently explain all parts of the disease, a convergence of combined biochemical, environmental and immunological factors in genetically predisposed patients has been proposed as a unifying background to the pathophysiology of vitiligo.11 In this review, we will summarize the scientific evidence linking melanocyte
biochemical and metabolic abnormalities to the exaggerated response of the immune system in vitiligo.

The link between cellular stress and the immune response

Several *in vitro* and *in vivo* studies have shown evidence of an altered redox status, with the presence of oxidative stress in cultured melanocytes coupled with an increased susceptibility to pro-oxidant agents. Increased levels of reactive oxygen species (ROS) have been observed in lesional and non-lesional skin of vitiligo. An external stress, such as ultraviolet (UV) radiation exposure or chemical damage (monobenzone or other phenols), leads to increased ROS production in melanocytes. In addition to their role in the alteration of the antioxidant system, the function and/or the proliferation of melanocytes, ROS can also create a pro-inflammatory environment leading to the activation of the immune system. Accordingly, a recent observation showed that melanocytes exposure to chemicals agents (4-TBP and MBEH) known to trigger vitiligo induces the disruption of the folding machinery of the endoplasmic reticulum, leading to the accumulation of immature proteins and resulting in the activation of the unfolded protein response (UPR). As a consequence, a high production of pro-inflammatory cytokines, such as interleukin (IL)-6 and IL-8, via the inositol-requiring enzyme-1 (IRE1)–X-box-binding protein 1 (XBP1) arm of the UPR machinery, was demonstrated. XBP1 is a transcription factor that modulates several downstream UPR targets. Supporting a role for the UPR pathway in vitiligo, a XBP1 polymorphism with increased risk of developing vitiligo has been published. More recently, it has been shown that vitiligo melanocytes present abnormalities of signal transduction pathways compatible with a condition of stress-induced premature senescence-like phenotype, which is characterized by the production of many proteins among the senescence-associated secretory phenotype, as the pro-inflammatory cytokine IL-6 (Figure 1).
Damage-associated molecular patterns and other endogenous pro-inflammatory signals

Beside the role of increased ROS levels to induce the secretion of pro-inflammatory cytokines, ROS can also modulate the innate immune system through the activation of pathogen recognition receptors (PRRs). These receptors are originally specialized in the detection of pathogens through pathogen-associated molecular patterns (PAMPs) which have a lipidic, proteic or nucleic acid origin. However, under some circumstances, in a genetically predisposed patient, the discrimination of pathogen-derived from host-derived (self) nucleic acids could be impaired. Host-derived self-DNA and/or self-RNA from damaged cells recognized by these nucleic acid receptors could lead to skin inflammation such as that found in vitiligo. Recently several new receptors have been identified, leading to a much more complex view of the machinery of nucleic acids recognition. Nucleic acid receptors are commonly divided in two subgroups based on their endosomal or cytosolic distribution. In the endosomes, these receptors include Toll-like receptor (TLR) 3, TLR7, TLR8, and TLR9. In the cytosol, nucleic acid receptors include the retinoic acid-inducible gene I (RIG-I)-like receptors, the cytosolic DNA sensors and receptors involved in inflammasome formation. All these receptors are involved in the recognition of nucleic acids and induce the production of proinflammatory cytokines to initiate the immune response. In endosomes, TLR9 senses the presence of CpG-containing DNA whereas TLR7 and TLR8 recognize single strand (ss) RNA, and TLR3 recognizes double strand (ds) RNA, leading to the transcription of pro-inflammatory cytokines like tumor necrosis factor (TNF)-α, IL-6 or type I Interferon (IFN) α/β. In addition to endosomal recognition, cytosolic receptors can sense the presence of nucleic acids in the cytoplasm. The gamma-IFN-inducible protein IFI16 and the IFN-inducible protein AIM2 (absent in melanoma-2) sense dsDNA and recruit the adaptor protein ASC (apoptosis-associated speck-like protein containing CARD) to form an inflammasome complex that activates caspase 1, leading to the processing and release of IL-1β and IL-18. Several inflammasomes have been described and defined by the NOD-like receptors protein that they contain: the NLRP1 (NALP1) inflammasome, the LRP3 (NALP3) inflammasome and the IPAF (NLRC4) inflammasome. Our group has previously demonstrated an increased expression of NLRP1 and IL-1β in peripheral skin of vitiligo that was associated with disease progression (Figure 1).

Moreover, a major focus of interest has been the stimulator of interferon gene (STING), which is a transmembrane protein of the endoplasmic reticulum, that upon activation induces type I IFN production. Several DNA sensors that include IFI16, the DNA-dependent activator of IFN-regulatory factors (DAI), and cyclic GMP-AMP synthase (cGAS) can activate the STING pathway. Beyond the recognition of dsDNA, dsRNA are also recognized by others cytosolic recognition receptors such as RIG-like receptors (RLRs) which belong to a superfamily including RIG-I, melanoma differentiation-associated protein 5 (MDA-5) also called IFI1H1, and laboratory of genetics and physiology 2 (LGP2). These sensors, upon recognition of RNA, induce activation of the nuclear factor kB (NF-kB) pathway, leading to the production of pro-inflammatory cytokines and IFN-β. New DNA helicases have been added in this complex machinery, such as Ku70, that recognizes the presence of plasmid DNA, DHX9 and DHX36 that are able to sense CpG DNA in the cytosol.

As already suggested, in a genetically predisposed patient, a self-molecular pattern released during sterile inflammation in damaged cells can lead to the release of pro-inflammatory cytokines and induce skin inflammation as shown in vitiligo. Again, recent GWAS have revealed multiple genetic risk factors for vitiligo associated with these PRRs. For example, it has been reported association of vitiligo with genes encoding NLRP1, MDA-5, the Toll-like receptor adaptor molecule 1 (TICAM1), important for TLR signalling, and caspase 7, a protein activated by inflammasome complex. Therefore the discovery of the association of vitiligo with these susceptibility loci link vitiligo to the innate immunity and nucleic acid sensing receptors.

In addition to nucleic acid recognition, it has been shown that the NLRP3 inflammasome is activated in response to excessive ROS production and mitochondrial stress. Moreover, heat shock proteins (HSPs) are protein-folding chaperones induced in response to cellular stress and UPR activation. They can activate TLR2, TLR4 and others PRRs. Inducible HSP (HSPi) is induced in chemical-induced stress in melanocytes and in vitiligo. Interestingly, it was recently demon-
HSP70i can stimulate the proliferation and cytotoxicity of natural killer cells (NKs), enhance leukotriene secretion by mast cells, induce maturation and type-1 polarizing cytokine production by dendritic cells (DCs) and stimulate cross-priming of CD8+ T cells. HSP70i induces antigen-specific immunity by promoting uptake, processing, and presentation of HSP70i-chaperoned proteins and peptides to antigen presenting cells. Altogether, these observations suggest that HSP70i targeting could be a promising approach in vitiligo. High-mobility group box 1 (HMGB1) is an important DNA binding protein that is present in the nucleus of cells where it regulates DNA accessibility to transcription factors. However, in response to stress, CRT can also translocate to the melanocyte surface when these cells undergo H2O2-mediated oxidative stress, increasing melanocyte immunogenicity and adding a new link between oxidative stress, cell death and immune reactions. Surface CRT then directs the contact of ROS-stressed melanocytes to DCs, followed by the activation of downstream immune responses, leading to the development of the disease. CRT also induces the expression of proinflammatory cytokines like IL-6 and TNF-α, enhancing the immunogenic potential of melanocytes (Figure 1).

**Innate immune cells in vitiligo**

Stimulation of PRRs by various mechanisms induces the activation and recruitment of innate immune cells to promote adaptive immune responses. In vitiligo, various innate immune cells have been observed in perilesional or lesional skin. First, a recent study found increased NK cells gene expression in both lesional and non-lesional skin compared to healthy controls. The presence of NK cells was then confirmed using immunofluorescence. NK cells respond to various cellular signals released by cells under stress, and can be activated through ligands binding to their receptors NKG2D. Besides their cytotoxic function, NK cells influence antigen presentation, stimulate function, survival and maturation of DCs through the release of the proinflammatory cytokines IFNγ and TNFα, and drive the Th1 (Th1) polarization of T cells. Another innate immune cell subset involved in the progression of vitiligo is composed of pDCs. Our group has previously found an accumulation of pDCs in perilesional skin of progressive vitiligo as compared to stable or slowly progressive vitiligo and healthy controls. This accumulation of pDCs was associated with local production of type I IFN cytokine as demonstrated by local expression of MxA (a specific intracellular protein induced by type I IFN), leading to the recruitment of CXCR3+ Th1 cells, probably through the response of CXCL9 and CXCL10 ligands expressed by keratinocytes. As shown in other skin inflammatory disorders such as psoriasis, pDC activation may result of the release of epidermal or melanocyte-derived nucleic acids leading to the activation of PPRs. Future studies will be important to investigate signals important for activation and recruitment of pDCs in vitiligo.

At the interface between the innate and the adaptive immune response, DCs are important for the promotion of the adaptive immune response. CD11c+ myeloid dermal DCs were found in increased numbers in perilesional skin of vitiligo, particularly mature CD11c+CD1c+ cells which might be important actors in vitiligo. Langerhans cells (LCs), which are the antigen presenting cells localized in the epidermis could be also important players in the activation of the immune response. In vitiligo, lesional skin LCs appear to be more expanded and show morphological alterations. These observations are correlated with higher number of in-
filtrating cells especially CD8+ T cells and Th17 cells, suggesting that LCs may be an important component of vitiligo pathophysiology.

Adaptive immune cells in vitiligo

The importance of the adaptive immune system in vitiligo is indirectly supported by GWAS that identified an association of both major histocompatibility complex (MHC) class I and II loci with vitiligo,37-39 suggesting a role of both cytotoxic CD8+ T cells and CD4+ T cells in disease pathogenesis. Contradictory results have been published regarding the ratio of circulating CD4+/CD8+ T cells during disease.40, 41 However, these cells are consistently found in the perilesional margin of actively depigmenting skin of vitiligo patients.4, 42 Furthermore, several studies have reported an altered proportion and/or function of effector and regulatory T cells (Tregs) in vitiligo (Figure 1).43

Cytotoxic CD8+ T cells

Accumulating evidence support a direct role for cytotoxic T cells in melanocyte loss in vitiligo. The proportion of circulating CD8+ T lymphocytes expressing granzyme B, perforin, and IFNγ is higher in vitiligo patients than in healthy controls.44 Such activation of CD8+ cytotoxic T cells correlates with impairment of Tregs. Importantly, CD8+ T cells in the skin are more abundant in patients with active disease9, supporting the involvement of a cytotoxic response to melanocytes. CD8+ T cells specific for melanocytes antigens, such as MelanA/MART-1, gp100, and tyrosinase, have been detected in the peripheral blood and perilesional skin of patients with vitiligo, although conflicting results have been reported.45-51 The progression of vitiligo might be directly related to circulating melanA-specific CD8+ T cells.45, 46 However, the functionality of circulating melanA-specific T cells in vitiligo was raised.49 Recently, Maeda et al. showed that Tregs can render self-reactive CD8+ T cells hypoproliferative and cytokine hypoproducing. In the same study, anergic CD8+ T cells reactive with MelanA antigen were identified in the blood of healthy individuals.52 Upon self-antigen stimulation and in the absence of appropriate Tregs number and/or function, as observed in vitiligo, such cells may become activated and may be involved in the development of abnormal autoimmune responses.

The first direct evidence of cytotoxic T cell responses causing skin depigmentation came from melanoma patients, where the majority of T cells infiltrating melanoma tumors are reactive to MelanA and gp100.53, 54 Interestingly, CD8+ T cells isolated from perilesional skin of vitiligo patients recognize melanocyte antigens, express granzyme B, the proinflammatory cytokines IFNγ, TNFα, IL-17, and induce autologous melanocyte apoptosis in normally pigmented skin in vitro.50, 51, 55, 56 The association of autoreactive cytotoxic T lymphocytes with depigmentation is also supported in vivo in disease-prone mouse models.57-60 However, one has to keep in mind that most the existing mouse models of vitiligo focus on depigmentation of the hair rather than the epidermis (because of the natural location of fewer melanocytes in mouse epidermis, e.g. the tail) and thus may not fully represent human disease. In addition those models feature sensitization steps which have not been validated in naturally occurring vitiligo, and are more relevant to melanoma-associated depigmentation.

CD4+ T cells

Although multiple studies are pointing out the role of cytotoxic CD8+ T cells response in vitiligo, the involvement of autoreactive CD4+ T cells in melanocyte loss is less clear. Different subsets of CD4+ effector T cells have been identified, i.e. Th1, Th2, Th17, or the more recently identified Th22 and Th9 subsets.61, 62 These polarized CD4+ T cells are able to produce a large panel of effector and inflammatory cytokines driving immune responses to pathogens or self-antigens. Th1 cells express CXCR3 and produce large amount of IFNγ, Th2 cells express CCR4 (chemoattractant receptor of Th2 cells) and secrete high levels of IL-4, IL-5, and IL-13, whereas Th17 cells are defined by expression of CCR6, CD161, IL-23 receptor and by a specific cytokine signature profile consisting of IL-17 (aka IL-17A), IL-22, and IL-17F.61, 63 This cell subset also produces elevated levels of IFNγ and TNFα. Lastly, Th22 cells produce IL-22 but no IL-17 or IFNγ, and Th9 cells mainly produce IL-9.

Dysregulation of adaptive immune responses with excessive production of these cytokines represents a common feature of a wide range of inflammatory and
autoimmune diseases. It is now well documented that Th1 and Th17 cells play a critical role during development of autoimmune and inflammatory diseases, including skin inflammatory disorders such as psoriasis. Indeed, dysregulation of CD4+ T cells function is often observed in autoimmune diseases, and these cells may play an important role in the autoimmune pathogenesis of vitiligo. Early reports revealed that, in vitiligo, both CD4+ and CD8+ T cells produce mainly IFNγ and TNFα,51 which is the characteristic of a Th1/Tc1 cell polarization. An increase of the Th17-derived cytokine IL-17 both in blood and perilesional skin of vitiligo patients has also been reported.8,64,65 CD4+ T cells are well known for their major role in coordinating the immune response through their effects on other lymphocytes, and seem important for the generation of cytotoxic CD8+ T cells.57 Studies using melanocyte-specific T cell receptor (TCR) transgenic mouse models suggest that CD4+ T cells are involved in depigmentation.66-68 However, the precise role of CD4+ T cells in melanocyte disappearance remains to be fully investigated.

Regulatory T cells

The balance between inflammatory and regulatory factors is critical to prevent tissue damage during infection and in the control of detrimental responses to self-antigen. The exact mechanism involved in the loss of tolerance in vitiligo is not fully understood, but likely involves a defect in Tregs. Tregs are the most important regulators of the immune homeostasis, suppressing pathological immune responses against self and foreign antigens. Two different subsets have been described, natural Tregs (nTregs) and induced Tregs (iTregs). nTregs develop in the thymus whereas iTregs are generated via antigen stimulation and in the presence of high levels of transforming growth factor (TGF)-β in humans. These cells are characterized by the expression of CD4, CD25 and FOXP3, while negative for CD127 (IL-7Rα). FOXP3+ Tregs decrease inflammation via multiple mechanisms: 1/deprivation of necessary signals for effector T cells activation: production of IL-10 and TGF-β or in a contact dependent manner via cytotoxic T lymphocyte antigen-4 (CTLA-4), 2/ killing or inactivation of antigen presenting cells.69 The lack or altered function of Tregs has been reported in a number of autoimmune diseases, and animal studies have shown that the rescue of Tregs number and function can prevent or ameliorate disease.70 We and others have shown genetic polymorphisms of FOXP3, CTLA-4, IL-10 and TGFβ receptor in vitiligo,10,37,43 which corroborates the results of several studies showing alterations in Tregs number and/or function in vitiligo.43 The number of Tregs expressing transcription factor FOXP3 is significantly reduced in the skin of vitiligo patients.71,72 The almost complete absence of Tregs in the skin contrasts with the presence of functional Tregs in the circulation of vitiligo patients.72 In addition, levels of serum TGF-β are decreased in patients with active vitiligo and are negatively correlated with the extent of body area involvement.73,74 Impairment of Tregs function could also be involved in the loss of tolerance in vitiligo since lower suppressive activities of Tregs towards CD8+ T cells together with an increase in IFNγ and TNFα production have been reported in affected patients.44,75 In accordance with this hypothesis, adoptive transfer of Tregs or treatment with rapamycin (known to increase the number and function of Tregs) can efficiently halt the depigmentation process in disease-prone mice.76

Skin resident T cells

With the better understanding of the skin immune system, and more particularly the recent concept of resident memory T cells (TRM),77,78 it is now critical to understand the role of memory T cells locally in this organ during autoimmunity. The human skin contains 20 billion T cells, representing twice more than in the entire blood volume, and most of them are resident T cells.79 These cells have the propensity to rapidly respond to pathogen or foreign antigens that attempt to breach skin epithelium, independently of T cell recruitment from the circulation. These skin resident T cells are non-recirculating memory T cells, express high levels of skin-homing receptors such as cutaneous lymphocyte antigen (CLA) and the chemokine receptor CCR4 and are characterized by expression of CD69. Therefore, inadvertent activation of these skin TRM must be tightly controlled and we have shown in a different context that a skin resident population of Tregs can locally proliferate and dampen skin effector memory T cell responses.80 In a predisposed patient, dysregulation of TRM could be very harmful in the context of inflammatory disorders, such as vitiligo. To date, the involvement of autoreac-
tive skin T<sub>RM</sub> cell subsets in vitiligo has never been investigated but assessing their phenotype and function would undoubtedly add a better understanding of the specific immune memory response in this disease.

Cytokines involvement in vitiligo

As mentioned above, a bias toward pro-inflammatory cytokines upregulation has been identified in vitiligo.

**TNFα**

TNFα has been largely described for its dual role as both a pro-apoptotic and a pro-inflammatory cytokine. Anti-TNF therapies have proven efficacy in a number of autoimmune and inflammatory disorders, in particular in the field of dermatology, rheumatology, and gastroenterology. It was then reasonable to foresee a role of this cytokine in an autoimmune disease like vitiligo. If conflicting results have been reported regarding a deregulation of TNFα production in peripheral mononuclear cells and sera from vitiligo patients, an increased expression in patients’ skin samples both at the gene and protein levels has been consistently observed; highlighting the pathophysiological relevance of characterizing the effects of targeted cells and their related soluble factors locally in the tissue. These findings are reinforced by genetic studies that identified polymorphisms associated with TNFα gene in vitiligo. Regarding TNFα secreting cells in patients, cytotoxic CD8<sup>+</sup> and CD4<sup>+</sup> T cells have been described as potent producers, yet keratinocytes, fibroblasts, and even melanocytes could be other sources of this cytokine under inflammatory conditions. Regarding the possible involvement of TNFα in vitiligo pathophysiology, in vitro studies revealed direct effects of this pro-inflammatory cytokine on melanocyte function. Indeed, TNFα inhibits the expression of microphthalmia associated transcription factor (MITF), essential for melanocyte development, survival, and function, of tyrosinase and tyrosinase related protein 1 (TRP-1), two enzymes involved in melanogenesis through a nuclear factor κ B (NFκB) dependent mechanism. Recently, Wang et al. showed that TNFα upregulates production of melanoma mitogens CXCL1 and IL-8 in melanocytes while suppressing genes of the pigmentation pathway. Furthermore, TNFα could enhance T cell trafficking to the skin through upregulation of intercellular adhesion molecule-1 (ICAM-1) expression both in melanocytes and keratinocytes. ICAM-1 is important in the initiation of inflammation and has been detected in melanocytes around active vitiligo patches.

Taken together, data from the literature strongly support a major role of TNFα in vitiligo. However, the limited evaluation of anti-TNF therapies in vitiligo suggests that blocking TNFα is effective at best in halting disease progression but does not induce significant repigmentation.

**IFNγ/Th1 pathway**

IFNγ is the most important cytokine related to the Th1 immune response. Binding of this cytokine to its receptor induces the Janus kinase (JAK)/Signal transducer and activator of transcription (STAT) pathway, in particular JAK1-2 and STAT1 activation, and regulates the expression of genes/proteins involved in a number of processes, such as defense against pathogens, proliferation, survival/apoptosis, immunomodulation, and leukocyte trafficking. Interestingly, the CXCR3 ligands CXCL9 (aka monokine induced by IFNγ, MIG) and CXCL10 (aka IFNγ-inducible protein-10, IP-10) and CXCL11 (aka IFNγ-inducible protein-9, IP-9) were identified as chemokines induced by IFNγ in various cell types, including immune and epithelial cells. CXCR3 and its ligands are well documented for their involvement in T cell trafficking and function during inflammation. In inflamed tissues, Th1 cells produce high levels of IFNγ and TNFα, which in turn induce CXCL9 and CXCL10 secretion, therefore amplifying inflammation.

The expression of IFNγ, CXCL9, CXCL10, and CXCR3 is increased in the skin of patients with vitiligo. Comparison of the transcriptional profile of lesional vitiligo skin with healthy skin revealed an IFNγ specific signature in vitiligo. During disease, IFNγ is produced by cytotoxic CD8<sup>+</sup> and CD4<sup>+</sup> T cells, although expression by other immune cells and skin cells is not excluded and has to be assessed. Functional studies performed in mice support a critical role in depigmentation of a IFNγ, CXCR3, and CXCL10 pathway in vivo. Moreover, accumulation of CD8<sup>+</sup> T cells in mouse skin is dependent on IFNγ and CXCR3. Thus, IFNγ could amplify the immune and inflamma-
IL-17, in combination with IL-1β IL-6, can directly or indirectly downregulate melanin production and gene expression of melanogenic and antiapoptotic molecules in melanocytes. The indirect effect of IL-17 would be through the induction of IL-1β and TNFα production by epidermal keratinocytes and dermal fibroblasts. More recently, Wang et al. showed that while IL-17 had little effects on melanogenesis, but that it could enhance TNFα inhibitory activities on pigmentation signaling, as shown by the downregulation of MITF, c-kit, dopachrome tautomerase (DCT), and melanocortin 1 receptor (MC1R) genes expression. In addition, these two cytokines (TNFα and IL-17) can act in synergy to upregulate pro-inflammatory chemokines production in melanocytes. Hence, Th17 cells and their related cytokines could regulate melanocyte function and/or survival directly or indirectly in vitiligo, as previously suggested in melanoma. Th17 cells were proposed to mediate a direct cytotoxic activity on melanoma cells, or indirectly, by facilitating the recruitment of effector immune cells, such as CD8+ T lymphocytes, through the increase of chemokine ligands levels in the tumor environment necessary for the migration of effector cells.

Conclusions
The recent development of our understanding of immune pathomechanisms in the pathophysiology of vitiligo opens interesting perspectives for innovative treatment strategies. The proof of concept in humans of targeting the IFNγ/Th1 pathway is much awaited. However, other major targets such as Tregs, and possibly the Th17 pathway, need to be investigated more in depth. The link high levels of cellular stress-immune responses noted in vitiligo but also in other immune-mediated inflammatory disorders suggest in addition several other strategies looking at limiting type I interferon activation pathway as background stabilizing therapies. For all strategies, the need to think in terms not only of inflammation/immunity but in addition in terms of regenerative medicine to compensate melanocyte losses, complicates the problem. However, in conclusion, the status of vitiligo is hopefully changing from a neglected non-medical problem to a big challenge at the high end of modern translational medicine with real perspectives for cure via specific drug development.
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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript. Article first published online: October 29, 2015.
The skin is the most accessible organ of the human body. Patients with internal malignancy often exhibit cutaneous lesions. These lesions can be specific, in the case of skin metastases or infiltration by leukemic/lymphomatous cells; and may be non-specific, when inflammatory skin changes are caused by cytokines produced by tumor cells. Another group of conditions associated with cancer correspond to genetic syndromes, in which there is an increased risk of developing benign and malignant neoplasms. Approximately 1% of internal malignancies are suspected from initial skin manifestations.

Paraneoplastic disorders are manifestations of internal malignancies without the direct action of the tumor. Its pathogenesis involves production of substances that interfere with cellular activity of distant tissues. Paraneoplasias may be the first sign of cancer, and clinicians should be familiarized with its manifestations in order to perform an early diagnosis of the underlying neoplasm. The aim of this review was to describe most common paraneoplastic skin diseases.

**ABSTRACT**

Paraneoplastic disorders are manifestations of internal malignancies without the direct action of the tumor. Its pathogenesis involves production of substances that interfere with cellular activity of distant tissues. Paraneoplasias may be the first sign of cancer, and clinicians should be familiarized with its manifestations in order to perform an early diagnosis of the underlying neoplasm. The aim of this review was to describe most common paraneoplastic skin diseases.

**Key words:** Paraneoplastic syndromes - Neoplasms - Skin manifestations.

In this review, we will discuss just the conditions that are considered truly paraneoplastic.

Criteria proposed for paraneoplastic skin conditions (modified from Curth) are shown in Table I.

<table>
<thead>
<tr>
<th>Table I.—Criteria proposed for paraneoplastic skin conditions.</th>
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<tr>
<td>Skin lesions and neoplasm begin simultaneously</td>
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<td>They run parallel courses</td>
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<tr>
<td>The dermatosis is not associated with a genetic syndrome</td>
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<tr>
<td>A specific dermatosis accompanies a specific tumor</td>
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<td>The cutaneous disease is uncommon in general population</td>
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<td>There is a high frequency of association between the dermatosis and the neoplasm</td>
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Malignant acanthosis nigricans, tripe palms and florid cutaneous papillomatosis

Introduction

Acanthosis nigricans is a prevalent skin condition, often associated with obesity and insulin resistance. The term was proposed by Unna in the “Internal Atlas of Rare Skin Diseases”, in 1890: “acanthus” comes from the Greek, and means “thorn”; “nigricans”, from the Latin, means “becoming black”. Pollitzer and Janovsky independently described the first reports of acanthosis nigricans in patients with digestive tract cancers in the book edited by Unna.

When associated with malignancies, it is called malignant acanthosis nigricans (MAN).

Tripe palms (TP) was described in 1977 by Clarke. It is considered a form of MAN involving palmo-plantar areas.

Florid cutaneous papillomatosis (FCP) is a very rare and obligate paraneoplastic syndrome, first described by Schwartz and Burgess in 1978.

Clinical manifestations

Clinically, MAN may resemble benign acanthosis nigricans, starting with brownish discoloration, followed by the typical thickening and velvety hyperpigmented surface on skin folds of axillary, groin and cervical regions (Figure 1). Overlying acrochordons may be present, as well as pruritus in varying degrees of intensity (Figure 2). Mucosal involvement is reported, affecting lips and oral cavity (tongue, palate, and retrocomissural areas), esophagus, larynx, eyes, anal and genital mucosa. Sometimes, MAN can be the first sign of malignancy. High degree of suspicion must be done when atypical topography is found (nipples, periumbilical, oribucular, labial), when appearance of the lesions is sudden, and when extensive areas of the skin are affected, especially in elderly.

TP and FCP are paraneoplastic conditions that may occur in association with MAN or alone.

In TP, a velvety appearance of the palmar surface, skin ridging and sharp demarcation of dermatoglyphics are found.

FCP is similar to warts, with diffuse and extensive verrucous papules. This term is used to distinguish it from viral warts. Also associated with malignancies, sometimes is observed in patients with MAN.

Some authors consider TP as clinical variation of MAN; others suggest these entities should be described as separate disorders, existing on a continuum.

TP may be associated with MAN in 77% of cases. The presence of these conditions must raise the suspicion of occult malignancy, and appropriate investiga-
tion is imperative, especially if they occur in elderly patients with a history of weight loss and familiar history of cancer.\(^4\)

**Histology**

Skin biopsy of MAN, TP, and FCP are characterized by hyperkeratosis, papillomatosis, and acanthosis, sometimes difficult to differentiate from HPV infections.\(^12\) Hyperpigmentation of basal layer is usually seen.\(^9\)

**Associated neoplasms**

The most common malignancies associated with MAN are abdominal cavity adenocarcinomas (90%), with half of these cases corresponding to gastric adenocarcinomas. Rarely, it may be associated with ovarian, endometrial, breast, prostatic, pancreatic and lung adenocarcinomas, and epithelial carcinomas. Rare studies report the association with hematologic malignancies.\(^10\)

The underlying neoplasm usually is in an advanced stage, with metastasis.\(^4\)

Most of the times (61.3%), the skin lesions occur concomitantly with the diagnosis of the neoplasm, but occasionally they can occur before (17.6%) or after (21.1%) cancer is diagnosed.\(^12\) This association highlights the importance of close follow-up of these patients to identify early manifestations of malignancy, in patients with suspected lesions of MAN.\(^10\)

TP is more associated with lung cancer, followed by gastric adenocarcinoma.\(^6\) However, it has also been related to nonmalignant conditions: bullous pemphigoid, psoriasis, erythroderma and pruritus.\(^9\)

Gastric adenocarcinoma is the most common malignancy associated with Leser-Trélat sign.\(^12\)

**Pathogenesis**

Evidence indicate the role of transforming growth factor α (TGF-α) and epidermal growth factor receptor (EGFR) in the pathogenesis of MAN lesions.

TGF-α plays an important role in keratinocytes hyperproliferation, as it binds to EGFR, leading to the activation of the mitogen-activated protein kinase (MAPK) and the extracellular-signal-regulated kinase (ERK). These pathways are implicated in keratinocytes proliferation and differentiation. EGFR is constitutively expressed in the basal cell layer of the epidermis, but, in MAN, it was shown to be present in basal and suprabasal keratinocytes. Also, ERK activity was increased within keratinocytes from MAN skin samples.\(^13\)

Production of insulin-like growth factor 1 by neoplastic cells, leading to the skin changes, as seen in the benign form of acanthosis nigricans has also been reported.\(^14\)

**Treatment**

Successful treatment of the neoplasm with surgical excision, radiotherapy or chemotherapy leads to remission of skin lesions.\(^10\) When the lesions do not improve with cancer treatment, or when they recur, search for unresponsive, progressive or recurrent disease must be done.\(^12\)

Pruritus may be treated with antihistamines, photochemotherapy with psoralen plus ultraviolet A (PUVA), systemic retinoids or gabapentin, with varying degrees of response.\(^15\)

**Acrokeratosis paraneoplastica (Bazex Syndrome)**

**Introduction**

**Acrokeratosis paraneoplastica**, or Bazex Syndrome, is a rare paraneoplastic disorder with a psoriasiform and hyperkeratotic aspect of skin lesions, affecting acral areas. This skin condition was first described by Gougerot and Grupper in 1922,\(^16\) but only in 1965 Bazex *et al.* recognized the skin lesions as a paraneoplastic entity, in a patient with laryngeal carcinoma.\(^17\)

**Clinical aspects**

Non-pruritic erythematous and violaceous scaly plaques with hyperkeratosis in a honeycomb appearance affect ear helices, nasal tip, fingers, toes, and nails (longitudinal streaks, subungueal hyperkeratosis, onycholysis and, onychomadesis) (Figures 3-5).\(^18\) Palmar and plantar lesions occur predominantly on pressure points.\(^18\) Penis, chest, and back may rarely be affected by hyperkeratotic papules and plaques.\(^19\) When the onset of the lesions is acute, within days, vesicles may appear.\(^20\)

Bazex and Griffiths described three stages of the dis-
ease. In the first stage, lesions affect distal regions of fingers, toes, nose and ear helices. Hyperkeratosis of the periungueal region and dystrophy of the nails with associated onycholysis is observed. The neoplasm has no clinical manifestations in this phase (precede cancer symptoms by 2 to 6 months). In the second stage, lesions spread centrifugally, affecting, palms, soles and other areas of the face, and the neoplasm starts to manifest initial symptoms. In the third stage, lesions spread to the knees, elbows, and trunk, and the neoplasm is highly symptomatic.\textsuperscript{21}

Histology

Histology shows hyperkeratosis with parakeratosis, acanthosis, mild spongiosis, vacuolar degeneration of the basal cell layer, with apoptotic keratinocytes and pigment incontinence. In the dermis, there is perivascu-
lar lymphohistiocytic infiltrate, and eosinophils may be present.\textsuperscript{18} Direct immunofluorescence is usually negative, but may show positivity for C3 and fibrin in basement membrane zone.\textsuperscript{22}
Associated neoplasms

Squamous cell carcinomas of the upper aerodigestive tract (oral cavity, pharynx, larynx, esophagus) correspond to nearly half of associated malignancies. Other sites include: lung, stomach, prostate, vulva, bladder, ovaries, breast, colon, liver, thymus, sarcomas, and hematological malignancies (Hodgkin’s disease, cutaneous lymphomas, multiple myeloma). Sometimes, lymphnode metastasis is found, with no primary site detectable. In 67% of the cases, acrokeratosis paraneoplastica precedes the diagnosis of neoplasm with an average of 11 months; in 18% they are concurrent; and, in 15%, skin lesions occur after the diagnosis of cancer.

Valdivielso et al. suggested an investigative protocol for patients with Bazex Syndrome. It includes: detailed anamnesis with complete physical examination, including ear, nose and throat evaluation; complete blood count, erythrocyte sedimentation rate, basic chemistry profile, tumor markers, stool guaiac, chest X-ray, colonoscopy, upper gastrointestinal endoscopy, computed tomography of chest, abdomen and pelvis. If no alterations are found, clinical reevaluation and basic laboratory tests should be repeated every 3 months.

Pathogenesis

Pathogenesis is unclear. Hypothesis are: autoantibodies against tumor antigens crossreacting with keratinocytes antigens of the basement membrane zone; neoplastic cells inducing epidermal proliferation with the release of epidermal growth factor, TGF-α or insulin-like growth factor 1; zinc and vitamin A deficiency.

Treatment

Treatment of the underlying malignancy is essential for skin improvement, but skin lesions may persist even after successful treatment of the tumor. Skin-directed therapies with topical corticosteroids, keratolytics, phototherapies with psoralen-UVA, and oral retinoids are palliative and offer minimum relief.

Dermatomyositis

Introduction

Dermatomyositis (DM) is an autoimmune disease that comprises the skin and striated muscles. It is provided in adult-onset or juvenile DM. Stertz, in 1916, described a patient with inflammatory myositis and gastric cancer. Since then, the association of DM and polymyositis with malignancies has been discussed. The most recent systematic review show incidence of cancer in 7% to 30% of the patients with adult-onset DM. The association of juvenile DM and malignant diseases is considered anecdotal.

Clinical aspects

Clinical findings of paraneoplastic DM resemble those from classical DM, with violaceous and poikilodermatous rash in sun-exposed areas (face, upper trunk, extensor surfaces of the upper limbs), heliotrope (erythema and edema around the eyelids), and Gottron papules (Figure 6). Pruritus, skin necrosis (crusted and eroded plaques) and nail involvement (dystrophia and periungueal erythema) can also be found (Figure 7). The central area of the mid back is usually spared; and calcinosis, a common feature observed in juvenile DM, is not seen. Myopathy is characterized by symmetrical proximal weakness, with or without elevation of creatine kinase (CK). It leads to difficulties in climbing the stairs and combing the hair. Swallowing difficulties may also be present.

Many studies addressed the relationship between clinical and laboratory findings, and risk of malignancy in DM. Chen et al. reported an association of age (>45 years of age) and male sex with increased likelihood of cancer. Cutaneous necrosis, dysphagia, elevated cre-
Electromyography and magnetic resonance imaging show nonspecific alterations, but are useful to indicate myopathic changes, guide muscle biopsy and monitor disease activity.\textsuperscript{33}

**Histology**

DM histology shows epidermal atrophy, interface dermatitis with vacuolar degeneration of the basal layer, necrotic keratinocytes, melanin incontinence, edematous papillary dermis, dilated blood vessels in the superficial dermis, perivascular infiltrate with mononucleated cells, and mucin deposition.\textsuperscript{36} Direct immunofluorescence shows deposits of IgG and C3 at the dermal-epidermal junction in 5 to 67\% of patients.\textsuperscript{33} These findings are identical to lupus erythematosus; thus, histopathology and immunopathology are not diagnostic tests; rather, they should be used to support the diagnosis when clinical aspects suggest DM.\textsuperscript{33}

Muscle biopsy is the gold standard diagnostic test to inflammatory myopathies. In DM patients, it shows loss of capillaries, altered morphology of capillaries, capillary necrosis, muscle infarcts, perifascicular atrophy, lymphocytic infiltrate and complement deposition in the vessel wall.\textsuperscript{36}

**Associated neoplasms**

Most malignancies associated with DM are breast and ovarian cancer in women; lung, prostate and rectum cancer in men.\textsuperscript{26} In Asian countries, higher frequency of nasopharyngeal carcinomas are reported.\textsuperscript{37} Other associations are liver, bladder, and kidney carcinomas, non-Hodgkin lymphomas, gastric and pancreas adenocarcinomas, and uterine cervix squamous cell carcinoma.\textsuperscript{30}

Prognosis is related to the underlying neoplasm, and sometimes, cancer is diagnosed already with metastatic disease.\textsuperscript{36} DM can precede (40\%), be concomitant (26\%), or follow diagnosis of cancer (34\%).\textsuperscript{29}

In adult-onset DM, extensive work-up is needed, including: detailed anamnesis and physical examination, laboratory investigation with tumorous markers such as CA125 for women, PSA for men, transvaginal ultrasonography, mammography, chest x-ray, computed tomography scan of thorax, abdomen and pelvis, colonoscopy, and gastroscopy. If no malignancy is detected,
it is recommended to repeat the screening once a year for the first three years, as the highest risk of cancer occurs during the first year after diagnosis of DM. In a cohort study from China, of 60 patients with DM and cancer, 65% of patients developed malignancies within one year after DM diagnosis; 21.7% during the second year; and 13.3% during the third year.

Pathogenesis

Hypotheses to the development of DM in patients with underlying malignancies are: crossover immunity due to common antigens expressed by cancer, skin, and muscle tissues; altered immune system causing myositis and onset of cancer; bioactive products from neoplastic cells stimulating immune reactions against skin and muscle; carcinogenic antigens which trigger immune reactions and induce malignancy; changes in the extracellular matrix surrounding the tumor, causing changes in the extracellular matrix of non-tumoral tissues, with mucin deposition, edema and atrophy.

Treatment

Treatment of paraneoplastic DM requires treatment of the underlying malignancy, with a good correlation of antineoplastic treatment efficiency and skin and muscle response. Systemic corticosteroids in the dosage of 1mg/kg/day are usually the first choice for DM without malignancy. Methotrexate with doses between 7.5 and 15mg per week may be used if there is no response to systemic corticosteroids or if prolonged treatment is required. Topical treatment with steroids, emollients and sunscreens may be associated. These treatments have little impact on the improvement of the disease, but may result in symptomatic relief. Recurrence of skin eruption and muscle weakness may be early indicative of cancer relapse.

Erythema gyratum repens

Introduction

Erythema gyratum repens (EGR) was first described in 1952 by Gammel in a woman who presented a peculiar skin eruption, with a “knotty cypress wood grain” appearance, and metastatic breast cancer. Skin lesions disappeared after successful treatment of cancer. EGR is classified with the figurate erythemas. “Gyratum” means coiled or winding around a central point, and “repens,” from the Latin, means to crawl or creep.

Clinical aspects

Multiple erythematous and serpiginous bands, with a hyperkeratotic scale at one edge, resembling a geographical map or a wood grain, are the typical cutaneous presentation. These lesions migrate 1cm per day centrifugally, with new lesions appearing within the existing ones. More pronounced in intertriginous areas of axillae and groin, may affect the trunk and extremities, often sparing the face. Palmoplantar keratosis, onychodystrophy, and ichthyosis may be present. Severe pruritus may be a debilitating symptom. Cases evaluating to erythroderma have been described.

Histology

Histopathology shows nonspecific findings, but it is useful to rule out other differential diagnoses. Hyperkeratosis, focal parakeratosis, acanthosis, mild spongio-
sis, and superficial perivascular lymphocytic infiltrate are seen.\textsuperscript{46}

Direct immunofluorescence shows granular deposits of IgG, C3 and fibrin at the basement membrane zone, and IgM deposition in colloid bodies.\textsuperscript{43} Indirect immunofluorescence is negative. IgG and C3 deposits at the basement membrane zone of lung epithelium may be present.\textsuperscript{43}

**Associated neoplasms**

In a recent systematic review, Rongioletti et al. evaluated the association of EGR with malignancies and non-malignant conditions. Seventy percent was associated with an underlying neoplasm, whereas 30% was associated with other conditions that may mimic EGR clinically.\textsuperscript{44}

Of the malignant diseases, bronchial cancer was the most prevalent, affecting 46.5%. Gastric cancer was responsible for 8.6% of cases, and 6.9% had esophagus cancer. Breast cancer and unknown primary site were present in 5.2%. Other described neoplasms are cervix, pharynx, kidney, anus, tongue, bowel, pancreas, bladder, prostate, uterus, multiple myeloma, Hodgkin’s lymphoma, and essential thrombocytopenia.\textsuperscript{43} EGR precedes the diagnosis of malignancy in 87.9% of the patients, with mean time of 7 months; it is concurrent in 8.6%; and is diagnosed after malignancy in 3.4% of the cases.\textsuperscript{44} The underlying neoplasm may be diagnosed with metastatic disease.\textsuperscript{41}

Other diseases that may mimic EGR are: lupus erythematosus, mycosis fungoides, bullous dermatoses (linear IgA dermatosis, bullous pemphigoid, pemphigus vulgaris), urticarial vasculitis, neutrophilic dermatoses, leukocytoclastic vasculitis, erythrodermatous variabilis, erythema annulare centrifugum, erythema annulare of infancy, Sjögren Syndrome.\textsuperscript{46} Two cases of EGR associated with interferon alfa for chronic hepatitis C, a case associated with azathioprine,\textsuperscript{44} and a case of EGR lesions in a patient with psoriasis treated with acitretin were described.\textsuperscript{47}

**Pathogenesis**

The deposition of IgG and C3 in the basement membrane zone of the skin and bronchial epithelium of the tumor raises the hypothesis of an immune reaction. Skin antigens may be the target of antibodies produced against tumor antigens, or against altered molecules from the tumoral stroma, in a cross-reaction process.\textsuperscript{43} Molecules produced by neoplastic cells or immunocomplexes made by the interaction of tumor antigens and antibodies may selectively deposit on the skin, leading to the inflammatory reaction.\textsuperscript{43}

**Treatment**

Treatment of tumor leads to resolution of skin lesions. In metastatic disease, lesions may persist despite appropriate treatment if the tumor is unresponsive to chemotherapy or radiotherapy.\textsuperscript{43} Topical and systemic steroids may be associated, with partial and transient relief of skin lesions and pruritus.\textsuperscript{41}

**Erythroderma**

**Introduction**

Described by Hebra in 1868, erythroderma is a cutaneous condition characterized by diffuse erythema and scaling affecting more than 90% of the body surface area. It is an inflammatory condition caused by several etiologies. Classically, it is associated with pre-existing dermatoses (psoriasis, eczema, pityriasis rubra pilaris, pemphigus foliaceous), drug reactions (carbamazepine, phenytoin, phenobarbital, allopurinol), cutaneous lymphomas (mycosis fungoides and Sézary Syndrome), infections (dermatophytosis, crusted scabies). Rarely, it may represent a paraneoplastic condition.\textsuperscript{48}

**Clinical aspects**

Generalized erythema and desquamation may be associated with palmoplantar keratoderma, onycho dystrophy, non-scarring diffuse alopecia, lower limbs edema, weight loss, pruritus, lymph node enlargement and fever (Figure 9).\textsuperscript{48} Erythroderma is a potentially serious condition, as it leads to altered skin barrier function, causing water loss, electrolyte and thermoregulatory disturbances, and increased risk of infections. Clinical support is important to avoid these severe complications.\textsuperscript{49}

An extensive investigation, with comprehensive anamnesis and clinical examination, extensive laboratory work-up, and detailed histopathologic evaluation are required. To exclude cutaneous lymphomas, search for monoclonality of lymphocytes in the skin biopsies.
and peripheral blood by polymerase chain reaction or Southern blot is essential. Papuloerythroderma of Ofuji is a distinct clinical entity characterized by coalescent papules, leading to erythroderma. It typically spares skin fold areas (“deck chair” sign). Often associated with hematological malignancies, patients with this condition should undergo extensive work-up to find associated neoplasm, similar to erythrodermic patients.51

**Histology**

Skin histopathology of paraneoplastic erythroderma shows nonspecific features. Hyperkeratosis, parakeratosis and acanthosis, spongiosis, mild perivascular lymphohistiocytic infiltrate in the upper dermis are common findings. Eosinophils may be present.52

**Associated neoplasms**

Due to the rarity of paraneoplastic erythroderma, studies report isolated cases associated with Hodgkin’s lymphoma, diffuse large B-cell lymphoma, anaplastic large T-cell lymphoma, renal cell carcinoma, breast cancer, gallbladder adenocarcinoma, lung, tongue, Langerhans cell histiocytosis, carcinoma of colon, prostate, thyroid, fallopian tubes, larynx, esophagus, liver, acute and chronic leukemia, sarcoma. Erythroderma may precede or be concomitant to cancer diagnosis, and recurrence of erythroderma is associated with recurrence of malignancy.48, 53-56

**Pathogenesis**

Pathogenesis of erythroderma is unknown, but some evidence suggested a Th2 cytokine profile leading to generalized skin inflammation, with eosinophilia and increased serum IgE levels.57 Interaction of interleukins 1, 2, and 8, intercellular adhesion molecule-1, and TNF may also act in erythroderma pathogenesis, increasing epidermal turnover rate.53

**Treatment**

Treatment is directed to the underlying tumor, but topical and systemic corticosteroids may relieve symptoms.56

**Hypertrichosis lanuginosa acquisita**

**Introduction**

Hypertrichosis lanuginosa acquisita (HLA) was first described by Turner, in 1865, in a female patient with breast cancer.58

**Clinical aspects**

Hypertrichosis is defined as an increase of pilification with lanugo, vellus or terminal hair. The increase of lanugo hair can be congenital or acquired.59 Lanugo-type hair is observed in utero, with thin, nonpigmented hair, which shed during the last month of pregnancy.59

Hypertrichosis lanuginosa congenita occurs in premature neonates. It is a variation of normality, as lanugo hair goes into a shedding phase before birth, in utero. Within few days or weeks, these hairs shed, and the condition is resolved.59 In HLA, mature hair follicle produces this embryonic hair.60

HLA may be secondary to endocrine disorders, adverse drug reactions (ciclosporin, penicillamine, psoralens, glucocorticosteroids, diazoxide, interferon, minoxidil, phenytoin, cetuximab), and may be a sign of internal malignancy.59

![Figure 9.—Erythroderma — Generalized erythema and scaling.](image-url)
Isolated reports show association with prostate, Ewing’s sarcoma, bladder, kidney, ovary, pancreas, uterus, gallbladder, liver, parotid gland, lymphoma, leukemia, melanoma, and gastric carcinoma. Malignancy can be diagnosed before, concomitantly or after skin eruption, and the prognosis is usually poor. Most commonly, the malignancy is diagnosed in the metastatic phase. Work-up should include a detailed anamnesis and physical examination, blood tests, chest X-ray, colonoscopy, and mammography.

Pathogenesis

Pathogenesis is unclear, but production of a non-recognized humoral factor by tumoral cells, causing a prolongation of the anagen phase of vellus hair follicles, is the most accepted theory. Other laboratory alterations, such as elevated cortisol and other hormones, were reported, but with no consistent association with HLA. The association of HLA and acanthosis nigricans suggests the involvement of TNF-α and insulin-like grown factor.

Treatment

Successful treatment of malignancy leads to resolution of HLA within weeks.

Leser-Trélat sign

Introduction

The sign of Leser-Trélat, described by Holländer in 1900 refers to the occurrence of multiple eruptive seborrheic keratosis. Léser, a German surgeon, and Trélat, a French surgeon, reported concomitantly the occurrence of multiple eruptive angiomas in patients with underlying malignancies. Posteriorly, its association was found to be untrue, with seborrheic keratosis as the lesions associated with cancer. Due to the historical importance of the first authors, the name of the sign persists.

A group from the Mayo Clinic suggested differentiation of sign and syndrome of Leser-Trélat. “Sign” should be used when there are eruptive multiple lesions of seborrheic keratosis, with or without association with malignancy. On the other hand, “syndrome” should be used when there is a diagnosis of underlying malignancy with the skin lesions.
Clinical aspects

The existence of the association of eruptive seborrheic keratosis and malignancies is still controversial, as some authors argue that seborrheic keratosis lesions are extremely common, and occur predominantly in elderly, when the risk of cancer is increased. This hypothesis is weakened, as there are some reports of lesions occurring in young adults. Multiple seborrheic keratoses may develop in erythrodermic patients, and investigation of the cause of erythroderma is imperative, as lymphoproliferative diseases may be associated with Leser-Trélat sign and erythroderma.

Involvement of the trunk is found in 76% of the patients, followed by extremities in 38%. Christmas tree pattern has been described (Figure 11). In a person with numerous seborrheic keratoses, Leser-Trélat sign must be considered if there is a rapid increase in size and number of the lesions, and it has been associated with TP in 10% of the cases.

Nonmalignant disorders may present multiple eruptive seborrheic keratoses: HIV infection, heart transplant, and acromegaly.

Histology

Histopathology is consistent with seborrheic keratosis, with hyperkeratosis, acanthosis and papillomatosis in the epidermis. Sometimes, pseudohorned cysts are found.

Associated neoplasms

It is most often associated with adenocarcinomas of the stomach and colon, lymphoproliferative disorders (leukemia and lymphomas), and rarely with breast, lung esophageal, liver, bladder, kidney cancer, and with melanoma. Most cases have more advanced stage neoplasms, with metastases. The sign may occur before, concomitantly or after the diagnosis of cancer.

Pathogenesis

Immunohistochemical studies showed elevated expression of epidermal growth factor receptor (EGFR) in all layers of the epidermis, except in the stratum corneum, in the seborrheic keratosis lesions of patients with associated malignancies. In normal skin, EGFR is expressed only in the basal keratinocytes. Transforming Growth Factor-α (TGF-α) has also been implicated as an important mechanism in Leser-Trélat sign. Ellis et al. described a possible role of TGF-α in Leser-Trélat sign, acanthosis nigricans and multiple acrochordons. Heaphy et al. suggest TGF-α induces epidermal changes in different cutaneous regions. Thus, flexural areas would develop acanthosis nigricans whereas exposed cutaneous surfaces would respond with the development of seborrheic keratoses lesions.

Treatment

Treatment of cancer leads to decrease and disappearance of the lesions.

Necrolytic migratory erythema

Introduction

Becker et al. described a patient with a distinctive skin eruption and pancreatic cancer, in 1942. McGavran et al. reported a case of a female patient with a functional alpha-cell pancreatic neoplasm, elevated glucagon levels, and bullous and eczematoid rash, in 1966. But only in 1977, Mallinson et al. defined the glucagonoma syndrome, characterized by necrolytic migratory erythema (NME), stomatitis, weight loss, anemia, and diabetes mellitus, in nine patients with pancreas tumors.
acanthosis, spongiosis and mild perivascular lymphocytic infiltrate in the superficial dermis. Intraepidermal cleft and subcorneal accumulation of neutrophils may be present.\textsuperscript{70}

The pancreatic tumor shows sheets of small and polygonal cells with eosinophilic cytoplasm and vesicular nuclei, and few mitotic figures. Immunohistochemistry stains for the vasoactive intestinal polypeptide, chromogranin, synaptophysin, somatostatin and glucagon.\textsuperscript{73}

**Differential diagnoses**

Zinc deficiency (acrodermatitis enteropathica), pelagra, pemphigus vulgaris, psoriasis, seborrheic dermatitis, contact eczema.\textsuperscript{70}

**Associated neoplasms**

The underlying neoplasm is, commonly, an alpha-cells adenocarcinoma of the pancreas.

Most of the patients have a metastatic disease by the time of diagnosis.\textsuperscript{70} Skin lesions usually appear before the diagnosis of malignancy is made, and identification of NME must raise the suspicion of a pancreatic neoplasm.\textsuperscript{72}

Association with other conditions was described, but it is very rare. These conditions include celiac disease, chronic pancreatitis, jejunal adenocarcinoma, hepatic cirrhosis or other pancreatic cancers, and these conditions are termed “pseudo glucagonoma syndromes”.\textsuperscript{74}
Paraneoplastic pemphigus

Introduction

In 1990, Anhalt et al. described five patients with a distinctive mucocutaneous disorder and underlying neoplasm. He suggested the term “paraneoplastic pemphigus” (PNP) for this condition.79

Clinical aspects

PNP affects mucosa and skin. Mucosal lesions are reported in 94% of the patients.81 Severe oral lesions, with painful erosions affecting more than 10% of the mucosal area is the most characteristic feature (Figure 14).82 These erosions may extend to pharyngeal, laryngeal, esophageal and bronchial mucosa.81 Ocular and genital lesions are observed in 80% and 66% of the patients, respectively (Figure 15).82

Pathogenesis

Pathogenesis of NME is unknown. Glucagon is a catabolic hormone and acts in glucose, fat and protein metabolism. It promotes hepatic gluconeogenesis and glycogenolysis; proteolysis of muscle tissue, increasing the source of alanine and glutamine, necessary to hepatic gluconeogenesis; and lipolysis of triglyceride due to activation of lipase, increasing free fatty acid delivery for hepatic ketogenesis.75 When a functional tumor of the pancreas secretes glucagon, diabetes mellitus is observed, as well as important weight loss and cachexia, due to increase in serum glucose with depletion of glycogen stores, muscle tissue and fat mass.75

Evidence support the role of glucagon in the pathogenesis of NME lesions. Improvement of skin rash is rapidly achieved when successful treatment of the malignancy is done, with a rapid decrease in glucagon levels. Even in metastatic disease, treatment with somatostatin analogs, a glucagon inhibitor, leads to significant improvement.75 Evidence suggest the role of glucagon in releasing inflammatory cytokines, such as arachidonic acid, which lead to superficial necrolysis of the skin.76 Hyperglucagonemia causes nutrients and vitamin B deficiencies, probably contributing to the appearance of skin lesions.77 Thus, the association of hyperglucagonemia, nutrients deficiency (zinc, amino acids, fatty acids, vitamins), cytokine release and liver dysfunction may lead to pathogenesis of NME.77

Treatment

There is a good association of the resolution of skin lesions and the decrease in glucagon concentrations.75 Thus, excision of pancreatic cancer leads to rapid resolution of skin lesions, within few days. Postinflammatory hyperpigmentation persists for a few months.73 When metastatic disease is diagnosed, palliative treatment with somatostatin (glucagon inhibitor) and interferon-α is effective.75 A transient improvement of skin lesions and pruritus is achieved with topical or systemic steroids, but rapid relapse occurs when the drug is withdrawn.70 Supplementation with zinc, amino acids, and essential fatty acids are adjuvant treatments.78

Figure 14.—PNP — Extensive erosions on the tongue.
Children and adolescents may be affected by PNP, with similar clinical features from adult PNP. However, in children, lichenoid lesions are more frequent, with few blisters, contrasting with the common association of blistering and lichenoid lesions in adults. Lung involvement has been reported with variable frequencies, from 17% to 93% of patients. Bronchiolitis obliterans is the most frequent cause of respiratory symptoms, with dry cough and dyspnea.

**Histology**

Histopathology is characterized by lichenoid infiltrate, with vacuolar degeneration of the basal cell layer, apoptotic keratinocytes, band-like infiltrate of lymphocytes in the superficial dermis, and melanophages. Anantholysis may also be found. Direct immunofluorescence shows deposition of IgG and C3 in epidermal intercellular spaces, along the basement membrane zone, or in both. Indirect immunofluorescence using monkey esophagus or rat bladder epithelium shows the same pattern observed in direct immunofluorescence, but may be negative in 20% to 25% of cases. Immunoblotting, immunoprecipitation and ELISA are used to identify the target antigens. Enoplakin (lower band of 210-kDa), periplakin (190-kDa), desmoplakin 1 (250-kDa), desmoplakin 2 (upper band of 210-kDa), bullous pemphigoid antigen 1 (230-kDa), α2-macroglobulin-like-1 molecule (170-kDa), desmoglein 1 (160-kDa), and desmoglein 3 (130-kDa) are the recognized antigens.

**Associated neoplasms**

Most common associated neoplasms are non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, Castleman’s disease, thymoma and follicular dendritic cell sarcoma. Associations with some carcinomas and other hematologic disorders (Hodgkin’s disease, myeloproliferative disorders, Waldenström disease, dysgammaglobulinemia) may be found. In children and adolescents, Castleman’s disease is the most common associated neoplasm. One-third of the cases of PNP shows mucocutaneous manifestations before the diagnosis of cancer; two-thirds shows PNP lesions after diagnosis of cancer.
Pathogenesis

It is suggested that a cytotoxic lichenoid eruption promotes exposure of self-antigens, leading to the development of humoral autoimmunity with the production of autoantibodies. Thus, lesions would be caused by the association of both lichenoid reaction/interface dermatitis and anti-plakin family members antibodies. Zhang et al. demonstrated the production of antibodies against plakin family antigens by Castleman’s tumor cells. This was not observed in thymoma and follicular dendritic cell sarcoma cells, suggesting different autoimmune mechanisms. Epitope spreading is another proposed explanation for the wide distribution of epitopes in plakin family members in PNP.

Treatment

Treatment should be adapted to disease severity, to limit adverse effects, such as infections. Treatment of the neoplastic disease is essential to the improvement of PNP. High-dose systemic corticosteroids (1 to 1.5 mg/kg/day) and association with other immunosuppressive drugs (azathioprine, rituximab) are used. Topical corticosteroids may be associated. Spontaneous remission has been described.

Acquired ichthyosis

Introduction

The term “ichthyosis” comes from the ancient Greek word “ichthys”, which means “fish”, because of the clinical aspect of the skin, similar to the scales from a fish. It can be congenital or acquired. Acquired ichthyosis (AI) can be a manifestation of numerous conditions, such as malignancies, inflammatory disorders, and malnutrition. Malignancies correspond to half of the causes of AI.

Clinical aspects

Clinically it is characterized by scaling affecting extremities and trunk, more prominent on the extensor surfaces of the limbs, with varying color and size of scales (Figure 19). Palmoplantar keratoderma and eczematropion may be present. Usually, patients with AI associated with malignancies have other symptoms, like weight loss, fever, and lymphadenopathy.

Histology

Hyperkeratosis with orthokeratosis, absence of the granular cell layer, or reduced granular cell layer is a common feature. No or mild perivascular infiltrate of lymphocytes may be seen in the papillary dermis.

Cutaneous T-cell lymphomas, mainly mycosis fungoides, and sarcoidosis are disorders associated with AI which the histological aspect shows epidermotropism of atypical lymphocytes (in MF), and granulomas (in sarcoidosis), raising the question whether these diseases have an ichthyotic specific manifestation, or if AI is an associated condition.

Associated neoplasms

Most associated malignancies are lymphoproliferative disorders, but solid neoplasms have been described. Half of the cases have Hodgkin’s disease. HTLV-1, a retrovirus related to adult T-cell leukemia/lymphoma (ATLL), may cause AI. Thus, patients with ATLL may present with AI and other skin lesions and constitutional symptoms typical of the neoplasm. Inflammatory disorders associated with AI are lupus erythematosus, dermatomyositis, sarcoidosis, eosinophilic fasciitis.
Pathogenesis

Pathogenesis is unclear, but some authors suggest the action of metabolites from neoplastic cells leading to altered function of the complex pool of enzymes necessary to normal keratinization of the stratum corneum. Deficiency in vitamin A absorption and altered lipid profile are other proposed pathogenic mechanisms.89

Treated

Treatment must be directed to the underlying disorder, but the use of humectants (glycolic acid) and keratolytics (salicylic acid) may relieve dryness.89

Hyperthrophic osteoarthropathy

Introduction

Digital clubbing, Hippocratic fingers, watch-glass nails, or drumstick fingers, was described by Hippocrates in a patient with empyema, in 400 BC.91 Hypertrophic osteoarthropathy (HOA), or pachydermoperiostitis, is characterized by digital clubbing, periostitis and arthritis.92 Primary HOA is an autosomal-dominant disease. Secondary HOA has been associated with malignant, cardiac, and congenital diseases.91

Clinical aspects

Primary HOA starts in childhood, with clubbing, periostitis, thickening of the skin of the face and scalp, coarsening of facial features, hyperhidrosis, and seborrhea.91 In secondary HOA, unilateral digital clubbing is associated with neurologic or vascular diseases; if bilateral, there is a strong association with pulmonary neoplasms. First, perungueal erythema occurs, with a spongy sensation on palpation due to softening of the nail bed. Then, an increase in the 160° angle between the nail bed and proximal nail fold occurs. This leads to increasing convexity of the nail. In malignancy-associated HOA, periostitis of lower extremities is common, associated with synovitis of the knees and ankles. Incomplete forms may show isolated findings.91

Histology

Histology of fingertip skin lesions shows vascular alterations: endothelial hyperplasia with partial occlusion of the capillary lumen by platelet clusters, pericapillary lymphohistiocytic infiltrate, thickening of collagen fibers, sebaceous and eccrine hypertrophy. Vasculitis of small vessels and arteries may be present.91

Associated neoplasms

HOA is associated with primary or metastatic lung cancer in 80% of cases. Other associated malignancies are: intrathoracic Hodgkin’s disease, nasopharyngeal carcinoma, mesothelioma, pleural tumors, kidney, esophageal, gastric, and pancreatic cancer, breast phylloides tumor, melanoma, thyroid cancer, osteosarcoma, and intestinal lymphoma.91

Cystic fibrosis, tuberculosis, endocarditis, syphilis, AIDS, congenital heart diseases, hepatic cholestatic diseases, inflammatory bowel disease, are other diseases associated with HOA. In primary lung cancer, HOA is present in 4 to 32% of the cases.91

Periostitis and HOA can precede malignancy by several months.92

Pathogenesis

Megakaryocytes are usually fragmented into platelets in the lungs. Disruption of normal pulmonary circulation would allow whole megakaryocytes to enter the systemic circulation. Due to their large size, they would impact in distal fingertip circulation, leading to the release of platelet-derived growth factor (PDGF), promoting growth, vascular permeability and monocyte and neutrophils chemotaxis, increasing the number of vascular smooth muscle cells and fibroblasts. Vascular endothelial growth factor (VEGF) is also increased in patients with lung cancer and HOA, contributing to vascular hyperplasia.91

Prostaglandin E is a potent bone formation stimulator, and its use has been associated with the development of periostitis and clubbing.92

Treatment

Treatment of cancer with surgery or chemotherapy may improve digital clubbing. Pain can be relieved by nonsteroidal anti-inflammatory drugs. Some studies report reduction of pain with pamidronate, probably due to its antitumor and anti-inflammatory actions. Octreо-
tide inhibits the production of VEGF, decreasing endothelial proliferation and relieving pain. Gefitinib and colchicine may be used for periostitis.\textsuperscript{92}

**Paraneoplastic pruritus/prurigo**

*Introduction*

Patients with chronic pruritus without concomitant skin changes have a higher incidence of renal, liver and thyroid disease, diabetes, depression, and anxiety. Chronic pruritus may also be associated with hematological malignancies and cholangiocarcinoma.\textsuperscript{93}

*Clinical aspects*

Patients with paraneoplastic pruritus, by definition, have varying degrees of pruritus, but with no direct action of neoplastic cells in the skin by invasion or compression. Thus, most patients exhibit only excoriations and, less frequently, ichthyosiform or eczematous lesions. Severe paraneoplastic pruritus significantly decreases patient’s quality of life.\textsuperscript{94}

*Prurigo nodularis* is characterized by hyperkeratotic nodule, with a predilection for extensor surfaces of the limbs. Crusting and excoriations, with port-inflamatory hyperpigmented and hypopigmented macules, may be present. *Prurigo nodularis* may be considered a pathological reaction secondary to pruritus and scratching, and may be present in patients with paraneoplastic pruritus.\textsuperscript{95}

If lymphnode enlargement, hepatosplenomegaly, B symptoms (fever, night sweats, weight loss) are present, search for hematological malignancies is mandatory. If jaundice, weight loss, and abdominal pain are detected, cholangiocarcinoma must be investigated.\textsuperscript{93}

*Associated neoplasms*

Hematological malignancies and cholangiocarcinomas are the associated neoplasms. Thirty percent of patients with Hodgkin’s lymphoma have chronic pruritus.\textsuperscript{93}

*Pathogenesis*

Malignant cells in hematological malignancies may release histamine, leukopeptidases, bradykinin and IL-31, leading to pruritus. In cholangiocarcinoma, pruritus occurs due to hyperbilirubinemia.\textsuperscript{93}

**Treatment**

First-line agents include oral antihistamines, oral antidepressants such as doxepin, and corticosteroids. Second-line agents include UV light exposure (UVB or PUVA), capsaicin (induces itch and burning sensation). Third-line include cyclosporine, thalidomide, naltrexone.\textsuperscript{95} Off-label use of aprepitant, a neurokinin 1 receptor antagonist has been described to reduce pruritus in a patient with Hodgkin’s lymphoma.\textsuperscript{94}

**Paraneoplastic vasculitis**

*Introduction*

Vasculitis is a specific pattern of inflammation of the blood vessel wall. It affects any organ, and may be caused by drugs, systemic infections, and connective tissue diseases. In 3.8% to 8% of the cases, vasculitis is associated with internal malignancies. The association of malignancy and cutaneous vasculitis was made by Longley \textit{et al.} in 1986 who suggested that malignant neoplasms might produce antigens and consequently cause paraneoplastic vasculitis.\textsuperscript{96}

*Clinical aspects*

As cutaneous involvement occurs almost exclusively with vasculitis of small and sometimes medium vessels, the major clinical feature is palpable purpura. Urticarial vasculitis and erythema elevatum diutinum are less commonly observed. Arthritis, hematuria, abdominal pain, oral ulcers, pericarditis and polyneuropathy due to vasculitis in other organs are reported.\textsuperscript{96}

Cytopenias and immature peripheral blood cells are present in hematologic malignancies associated with cutaneous vasculitis. Anemia, bicytopenia (anemia and leukopenia), and pancytopenia may be present. ANA, rheumatoid factor, and cryoglobulins may be present at low titles.\textsuperscript{96, 97}

Comparing paraneoplastic vasculitis and other cutaneous vasculitis, older age, longer duration of skin lesions, and constitutional symptoms were more frequent in patients with underlying malignancy. In patients with unexplained vasculitis, especially with advancing age,
investigation for the presence of neoplasm is mandatory. Death occurs due to neoplasm complications rather than vasculitis.\textsuperscript{96, 97}

**Histopathology**

Histopathology shows neutrophilic infiltration with leukocytoclasis, erythrocyte extravasation, and fibrinoid necrosis into the vessel wall of arterioles, capillaries, and post-capillary venules. Most patients show histologic features consistent with small-vessel leukocytoclastic vasculitis, rarely medium-sized vessels are involved.\textsuperscript{97}

**Associated neoplasms**

Hematologic disorders are the most common associated neoplasms: myelodysplastic syndrome, plasma cell myeloma, B-cell lymphoma, chronic lymphoid leukemia, multiple myeloma, acute myelogenous leukemia, Hodgkin’s disease, non-Hodgkin lymphoma. Less commonly, solid tumors are associated: non-small cell lung cancer, prostate, colon, renal, breast, gastric, head and neck and endometrial cancer.\textsuperscript{97}

Skin lesions are commonly the first clinical manifestation of malignancy, preceding 2 to 4 years the clinical manifestations of the tumor.\textsuperscript{96}

**Pathogenesis**

Circulating antigens bind to immunoglobulins, causing the formation of immune complexes, which deposit within vascular walls. These immune complexes fix complement, activate neutrophils, interact with lymphocytes provoking the release of cytokines, causing vascular tissue damage. Moreover, the immune complexes interact with the endothelium through their Fc receptor, induce the release of tissue plasminogen activator (t-PA), which causes the activation of the fibrinolytic system, increasing vasodilation and vasopermeability. Fibrinolysis is increased in the early phases of the disease and reduced in the late phases. The reduction of endothelial t-PA release and the increased levels of plasminogen activator inhibitors (PAI-1 and PAI-2) causes the reduction of fibrinolytic activity, leading to intravascular deposition of fibrin, with consequent microvascular thrombosis and necrosis, increasing tissue damage.

Other proposed mechanisms for the pathogenesis of paraneoplastic vasculitis are: production of immunoglobulins directed to not only the abnormal tumor cells but also the normal endothelium; release of cytokines, causing endothelial injury; the induction of a delayed hypersensitivity reaction to deposition of cancer proteins on vessel walls. Concomitant precipitating events (drugs, infections) may also cause an immune complex-mediated disorder that can be observed even at the beginning of the neoplastic disease.

All pathogenetic mechanisms lead to vasopermeability and vasodilation, with erythema and edema, endothelial cell dysfunction, neutrophilic infiltrate, platelet aggregation, and fibrin deposition, characteristics of cutaneous vasculitis.\textsuperscript{96}

**Treatment**

Successful treatment of the underlying malignancy leads to resolution of skin lesions in the majority of patients. Systemic treatments available are: corticosteroids, non-steroidal anti-inflammatory drugs, colchicine, dapsone, stanazolol (fibrinolytic agent), immunosuppressive drugs such as cyclophosphamide, methotrexate, azathioprine and cyclosporine A; intravenous immunoglobulin; recombinant tissue plasminogen activator (rt-PA).\textsuperscript{96}

**Sweet’s Syndrome**

**Introduction**

Sweet’s syndrome was described by Robert Douglas Sweet in 1964, and it was defined as an acute febrile neutrophilic dermatosis.\textsuperscript{98} There are three types of Sweet’s syndrome: classical, malignancy-associated, and drug-induced.\textsuperscript{99} Here we will focus on the malignancy-associated Sweet’s Syndrome.

**Clinical aspects**

Skin lesions are characterized by painful erythematous and edematous papules and plaques affecting the face, neck, and upper extremities. Vesicles and ulceration occur due to the intense edema. Fever is a common feature, and pathergic phenomena may be seen.
Pyoderma gangrenosum, swelling of the tongue, and periorbital cellulitis are associated cutaneous findings. In up to 50% of malignancy-associated Sweet’s Syndrome, an extracutaneous disease is present. It affects bone, joint, muscles, central and peripheral neural system, eyes, kidney, intestine, liver, heart, lung, and mouth. Anemia is a frequent finding, affecting 82-83% of malignancy-associated Sweet’s Syndrome, and is rare in classical type. Leukocytosis and neutrophilia are commonly observed, but neutropenia may rarely be seen.100

**Trousseau’s Syndrome**

**Introduction**

First described by Armand Trousseau in 1865, migratory thrombophlebitis, or Trousseau’s syndrome is a paraneoplastic syndrome characterized by recurrent, migratory thrombophlebitis. After two years of the first description, Dr. Trousseau diagnosed the syndrome on himself, due to gastric cancer.96

**Clinical aspects**

Recurrent erythematous rash over the course of a superficial vein, with migratory and tender aspects, are the typical features of migratory thrombophlebitis. Less frequently, disseminated intravascular coagulation, pulmonary embolism, thrombotic endocarditis, and diffuse bleeding are present.96

**Associated neoplasms**

Approximately 21% of Sweet’s Syndrome is associated with subsequently or already diagnosed malignancy. The most common underlying neoplasm is acute myeloblastic leukemia, but other hematologic diseases have been implicated: myeloproliferative neoplasms, diffuse large B-cell lymphoma, Hodgkin’s disease, myelodysplastic syndrome, myelofibrosis, and polycythemia vera. Eighty-five percent of associated neoplasms are hematological disorders. Solid malignancies correspond to 15%, commonly carcinomas of the breast, gastrointestinal or genitourinary tracts, lung and prostate.100

Sweet’s Syndrome has a good correlation with the course of malignancy, as skin eruption indicates recurrence or onset of a new malignancy.100

It is important to review all medications, once many drugs commonly used for oncologic treatments are associated with Sweet’s Syndrome (granulocyte-colony stimulating factor, antineoplastic agents, immunomodulating drugs, differentiation-inducing agents).100

**Pathogenesis**

Pathogenesis is unknown, but the hypothesis for Sweet’s syndrome associated with malignancies is the overproduction of cytokines (IL-1, IL-3, IL-6, IL-8, G-CSF, GM-CSF), or a hypersensitivity reaction against tumor antigens.100

**Treatment**

Treatment of the underlying malignancy can result in complete remission of skin lesions. Systemic corticosteroids, 1 mg/kg/day, is the gold standard treatment. If there are few lesions, topical or intralesional corticosteroids may be used. Potassium iodine and colchicine are other effective agents. Dapsone and cyclosporine are second line agents, and may be associated with systemic corticosteroids in refractory cases. Indomethacin, clofazimine, chlorambucil, cyclophosphamide, antime tabolites, immunoglobulins, interferon-alfa, infliximab, and thalidomide are used if other agents did not reach good response.100
of P- and L-selectins causing platelet microthrombotic processes; inflammatory cytokines produced by neoplastic cells, activating the endothelium and inducing the expression of adhesive molecules such as V-CAM and E-selectin; high concentrations of tissue factor (a primary cellular initiator of fluid-phase blood coagulation); and activation of factor X of coagulation by products from the malignant cells are some proposed hypotheses.\(^\text{96}\)

**Treatment**

Treatment of the underlying malignancy is imperative. Anticoagulant therapy must be used for embolic symptoms. Low molecular weight heparin is the treatment of choice, as unfractionated heparin may be strongly inhibited in the presence of some cancer cells. If tissue factor (TF) is increased, anti-TF agents, including recombinant tissue factor pathway inhibitor are being tested.\(^\text{96}\)

**Conclusions**

Studies of paraneoplastic dermatoses are essential in order to disseminate knowledge of these disorders for the population of dermatologists, clinical oncologists, hematologists and general practitioners so that they can perform the initial suspicion and the proper screening tests. More studies are needed to better understand its pathogenesis and its treatment, especially in cases where the cancer is at an advanced stage, when remission of paraneoplastic skin disease is very difficult, since the treatment of malignant disease becomes palliative.

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Treatments of advanced basal cell carcinoma: a review of the literature

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ABSTRACT

Advanced basal cell carcinoma (aBCC) encompasses locally advanced BCC (laBCC) and metastatic BCC (mBCC), two variants of BCC with a limited prevalence worldwide. Treatment of aBCC is still very challenging for the lack of randomized controlled trials/guidelines and the scarcity of available therapeutic options. Based on current data, surgical procedures and radiotherapy are considered the treatments of choice for aBCC although often associated with substantial morbidity and/or deformity. Alternatively, systemic chemotherapy and electrochemotherapy can be used but standardized treatment schedules and randomized clinical trials are not available for both treatments. In recent years, novel tumor-specific and pathogenesis-based molecules have been developed for the treatment of aBCC. A number of clinical trials have recently demonstrated the efficacy and tolerability of vismodegib, the first novel systemic, anti-Smo target cancer therapy for aBCC. Additional molecules currently investigated in phase I-III clinical trials include other Smo antagonists and itraconazole. The contribution of a multidisciplinary team composed of dermatologists, surgeons, oncologists, pathologists, radiologists and radiotherapists is required to deal with the spectrum of issues that emerge from managing patients affected by aBCC.

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Basal cell carcinoma (BCC) is the most common malignant epithelial neoplasm in white, middle-aged individuals, representing 80% of all non melanoma skin cancers (NMSC).

Recent epidemiologic studies have estimated that the incidence of BCC is increasing worldwide by up to 10% per year, particularly in individuals under the age of 40.1-5 These data clearly highlight the growing public health care burden and expenditure for BCC.

The most significant risk factors for BCC are genetic predisposition and exposure to ultraviolet radiation other than male sex, fair skin, old age and immunosuppression, particularly after organ transplantation.6-11

Several clinico-pathologic variants of BCC ranging from very superficial to deeply invasive and life-threatening tumors are currently recognized.3 Nodular BCC is the most common subtype of BCC, clinically appearing as a smooth, translucent papule or nodule with prominent telangiectasia, which in time increases in size while central ulceration and pigment deposit may occur. Nodular BCC has been related to chronic sun exposure with the head and neck region being the preferential anatomical location. The second most common subtype is superficial BCC, which is clinically characterized by a well defined plaque that slowly enlarges over years. Large lesions often have scattered erosions and hemorrhagic crusts.

Most BCCs can be easily diagnosed on the basis
that mBCC is extremely rare, with an incidence varying from 0.0028% to 0.5% 21, 22, 24, 28, 29. Such a wide range has been attributed to the high variability in data collection and sources, in surgical procedures and in pathology reports among the different studies. Less than 300 cases of mBCC have been described so far with the majority of them reported only in the last three decades probably due to increased prevalence of NMSC due to sun exposure, increased surveillance, more effective treatments, and higher academic interest.18-27

Risk factors for mBCC include: i) tumor size (>3 cm: 2% risk; >5 cm 25% risk; >10 cm 50% risk); ii) multiple primary tumors on the head and neck or genitalia; iii) aggressive histologic types (e.g. basosquamous pattern); iv) significant tumor depth and perineural invasion; v) recurrent BCC lesions, and vi) neglected lesions.29, 30

The most frequent sites of metastases include regional lymph nodes (40-83%), lungs (in the form of disseminated small nodules) (35-53%), bones (20-28%), distant skin with ulceration (18.5%), and liver (9%).

Diagnosis of mBCC should be made on the presence of the following criteria: i) the primary lesion must originate in the skin, ii) spread must be to a distant site and not represent simple extension, iii) similar histologic appearance of primary and metastatic lesions, and iv) no squamous cell features should be present.28, 31, 32

The estimated median survival after metastases range from 6 to 14 months.

Staging of BCC as well as of SCC and other cutaneous malignant neoplasms is performed according to the International Union Against Cancer (UICC) - TNM classification of malignant tumors, which unfortunately has several limitations regarding its clinical application in BCC as the T category is too broad while N and M are infrequent (Table I).

The goals of BCC therapy are to eradicate the tumor minimizing the risk of metastasis and to preserve the surrounding normal tissues with the best cosmetic result.

There are numerous therapeutic approaches for managing BCC. Surgical excision is the standard treatment while non-surgical techniques (e.g., radiotherapy) are preferred when surgery is not appropriate or
contraindicated. Characteristics of the lesion and patient-specific factors are the cornerstone which generally lead the choice of a specific treatment.33-36 Characteristics of the lesion to be considered are the number (single versus multiple), size and location, histological subtype and primary versus recurrent lesion. Patient-specific factors include previous therapy, coexisting serious medical conditions, use of anti-platelet or anticoagulant medications, immunosuppression (e.g., organ transplant recipients), patient’s adherence as well as patient’s choice and expectation. Moreover, local availability of specialized services as well as specialist skill and preference are further crucial issues in the final treatment decision.

Therapy of aBCC includes surgery, radiotherapy, different chemotherapy regimens and electrochemotherapy.29, 33-37 In contrast, cryotherapy (syn cryosurgery), electrodebsiccation and curettage, and carbon dioxide (CO₂) laser as well as photodynamic therapy and topical therapies (e.g. imiquimod and 5-FU) are not recommended in aggressive types of BCC, and there are no data on their use to treat aBCC.33-35, 38

Surgical techniques

Incisional biopsy

Although primary excision is the preferred treatment since it provides tissue for diagnosis as well as eradication of the tumor, there are a number of conditions in which a preliminary incisional or punch biopsy has to be considered.33 In detail, a punch biopsy may be required when a definite diagnosis cannot be made and whenever the tumor type or pattern of growth might direct or determine the choice of a specific treatment. Single or multiple biopsies can also be performed in large BCC lesions on the face prior to extensive surgery or when the tumor is supposed to be multifocal. In addition, a biopsy is needed to assess the pattern of differentiation and is mandatory before initiation of radiotherapy.

Surgical excision

Surgical excision is the most effective treatment for primary BCC, which allows to obtain high rates of disease control and good overall cosmetic results. The size of peripheral margins may vary from 3 mm to >10 mm depending on the type and location of BCC. The majority of small primary BCCs, i.e. <2 cm in diameter, can be successfully treated with a 3 mm peripheral surgical margin, achieving clearance rate up to 85% of cases and long-term control. A 4-5 mm peripheral margin has a higher likelihood (95%) of complete tumor removal and cure.39, 40 Wide surgical margins (i.e., 10-15 mm) are recommended when dealing with morpheiform and large BCCs since they display an aggressive behaviour and often extend beyond the apparent clinical margins.34, 35, 41

Dermatoscopy has proven to increase the diagnostic accuracy of BCC and it has recently shown to be useful to better determine the peripheral margins of BCC lesions, thus providing a complete and optimal surgical excision compared to clinical evaluation alone.42 In contrast to peripheral margins, very few data report the adequate deep margins; excision through the subcutaneous fat is recommended depending on the anatomical location of the lesion.39, 43, 44
Excision with margin controls may be performed using Mohs micrographic surgery (MMS) as well as the “Tubingen torte” or the “Munich” method, which are characterized by highly accurate removal of primary BCC with maximal preservation of normal tissues.\textsuperscript{45-48} In addition, MMS is indicated for recurrent BCC, for BCCs with poorly defined borders, aggressive histology and/or perineural or perivascular invasion. Several studies reported very high cure rates especially in high risk facial lesions, with 97-99% overall cure rate for primary BCC and 93-98% for recurrent lesions.\textsuperscript{49, 50} A recent study showed that the 5-year recurrence rates after MMS were 2.1% for primary BCCs and 5.2% for recurrent BCC suggesting that MMS should be offered to all patients with aggressive and recurrent facial BCCs in which preservation of esthetics and function is important.\textsuperscript{51} Although MMS is cost-effective compared to surgical excision with predetermined margins and micrographic surgical techniques are very popular in the USA and some European countries, these surgical procedures have the disadvantages to be time-consuming and to require specific laboratory processing and microscopic examination.

Incompletely excised BCCs, that are lesions with one or more positive histological margins, have been reported more frequently in morpheaform, infiltrative and aggressive variants and therefore mainly in BCC lesions histologically characterized by sclerosis, ulceration, infiltration and perineural invasion.\textsuperscript{41} The rate of local recurrence for incompletely excised BCC has been reported as 30-67% of the cases, with 82% of recurrences occurring within the first 5 years after treatment and 18% in the 6-10 years post-treatment period.\textsuperscript{34, 35, 52, 53} Since several retrospective and prospective studies demonstrated that not all tumors will recur, management of incompletely excised BCCs may include three options: 1) re-excision; 2) radiotherapy; or 3) observation. There is evidence that the risk of recurrence is higher in lesions in which deep rather than lateral margins are histologically positive (33% versus 17% risk of recurrence) and when the surgical excision was carried out for a recurrent BCC, especially after radiation therapy.\textsuperscript{54} Re-excision, using standard or stepwise surgical procedures, is the preferred treatment for incompletely excised BCCs when the lesions are located on the midfacial site or show an aggressive histological subtypes, when the deep surgical margin is involved or the surgical defect has been repaired using skin flaps or skin grafts.\textsuperscript{53, 55, 56} Radiotherapy may be an alternative to re-excision for patients who are unwilling or unable to undergo further surgery.\textsuperscript{54} Observation alone should always be discouraged and might be confined to few selected patients with low-risk BCC in whom neither surgery nor radiotherapy can be performed.

Recurrent BCCs are difficult to cure and their management may result in significant morbidity and disfigurement. Recurrent BCCs most often include large (≥ 2 cm) lesions located on the central face and periauricular area, and aggressive (infiltrative, ulcerated, morpheaform) subtypes. Cure rates for recurrent BCC seem to be inferior to those observed for primary BCC lesions\textsuperscript{52} and, indeed, recurrent BCCs have a 50% higher risk of further local recurrence compared to untreated lesions. Wide peripheral margins (up to 15 mm) as well as micrographic techniques are the recommended treatment modalities in such cases.

Other surgical procedures

Electrochemotherapy

Electrochemotherapy (ECT) combines the administration of poorly permeant chemotherapeutic agents, \textit{i.e.} bleomycin and cisplatin, with the use of high-intensity electric pulses to facilitate drug delivery into the cells and increase their anti-tumoral toxicity. Cell cycle arrest, apoptosis and mitotic cell death are the mechanisms implicated in bleomycin-caused cytotoxic activity and cell death. Several studies have demonstrated the effectiveness of ECT in melanoma and head/neck SCC but only a few reports have focused on BCCs so far.\textsuperscript{57, 58} The administration of intravenous or intralesional bleomycin followed by electric pulses delivered by needles or plate electrodes has shown to provide complete regression in 98% of sporadic BCCs, in 87% of BCC lesions of NBCCS patients and in single cases of mBCC.\textsuperscript{37, 59, 60} Pain, erythema and edema at the treated site occur within 24-48 hours after treatment, followed by ulceration and scale-crust; complete wound healing is achieved 4-6 weeks after treatment. Muscle spasms and myoclonus are often recorded. Several ECT treatment sessions are feasible and may provide complete response in BCC lesions which had an initial partial response.\textsuperscript{37} More studies and longer
follow-up on the use of ECT for treatment of aBCC are still needed.

Radiotherapy

Radiotherapy (RT) currently employed for treatment of BCCs includes megavoltage electrons (MeV) and photons generated by linear accelerators, and brachytherapy while superficial X-rays units are no longer used.

RT is a valid treatment option in selected patients with primary, recurrent and aBCC in which surgery is inappropriate because of tumor size or location, in patients with underlying comorbidities that make surgery inappropriate, or in patients who refuse surgery. In such cases, RT offers the advantage to treat large BCC lesions with deep tissue infiltration. Prior to radiotherapy, a biopsy is required to confirm the diagnosis and type of BCC.

Control rates achieved with RT are 95-99% at 5 years to 93-95% at 10 years for BCC <2 cm (T1 stage) while are 60% at 5 years and 50% at 10 years for BCC with tumor invasion beyond subcutaneous tissues (T4 stage). A randomized study, in which surgery was compared to radiotherapy, showed the efficacy of RT (total dose 40–60 Gy, single doses between 2 and 5 Gy) but the higher 4-year recurrence rate (7.5%) of RT compared to surgery (0.7%). A recent retrospective study described an estimated 5-year recurrence rate of 8.2% for nodular BCC, 26.1% for superficial BCC and 27.7% for the sclerosing type suggesting that the sclerosing type is a risk factor for recurrence after radiotherapy. In addition, some authors believe that surgery may be more difficult in cases of recurrent BCC after RT because of fibrosis induced by radiation. Cosmetic outcome of RT has been proven inferior to surgery with medium and long term side effects including pigmentation, telangiectasia, radiodermatitis and necrosis.

There are a number of studies in which RT, although not representing the ideal treatment, has been successfully employed for treatment of some BCC variants. Among these, good results have been described in BCCs with perineural invasion located on the head and neck region, treated with RT alone or combined with MMS. In addition, a retrospective study including 905 patients affected by BCC or SCC of the eyelids or nose, demonstrated that the 5-year cure-rate was 96.4% for eyelids lesions and 92.4% for lesions located on the nose. The percentage of relapse was 5.47. An hypofractionated irradiation schedule (>2 Gy per fraction) has been proposed in elderly patients affected with aBCC and several comorbidities, achieving a high local control rate in a shorter period of time but a worse cosmetic result compared to conventional RT.

Adjuvant RT following surgery should be restricted to patients with poor prognosis, i.e. patients with advanced tumors (T4) or with multiple or multifocal recurrences, and in BCCs with positive surgical margins or perineural invasion, and in node-positive BCCs.

Absolute contraindications to RT include patients with connective tissue diseases, patients affected with NBCCS or XP because of the high recurrence rate after treatment and the high risk to develop further BCC lesions, and young patients, because of potential carcinogenesis and tendency toward cosmetic deterioration overtime.

Brachytherapy (BT), which consists of placing sealed radioactive sources very close to or in contact with the target tissue represents the best treatment option for BCC lesions located on curved anatomical sites, for which curative surgery with adequate margins can not be offered without mutilation or extensive reconstructive surgery. With doses of 60 - 65 Gy, local control is excellent for T1 - T2 skin cancers. In addition BT can also be used after external beam radiotherapy to deliver additional dose to primary T2 - T3 tumors. BT can not be delivered in tumors involving bony structures or tumors located on the upper eyelid. Five-year recurrence rates range from 1 to 5% for NMSCs of the nose and nasal vestibule, eyelids, and pinna.

High dose rate (HDR) Electronic BT, which is based on the use of electrons instead of radioactive source as in the traditional BT, has been recently applied to NMSC achieving good efficacy, safety and cosmetic outcome.

Finally, helical tomotherapy (HT), that delivers photons to the target tumor tissue ensuring high protection to adjacent tissues, has shown efficacy and tolerability in a series of advanced NMSC, including 8 BCCs, with CR in 88% of cases and limited, grade I-II adverse events. High costs and time required to perform the procedure are still great limitations for a wider, more common use of HT.
**Systemic chemotherapy**

The use of systemic chemotherapy for both advanced local disease and metastatic lesions has been addressed only in case reports while there are so far no standard treatments, randomized controlled trials (RCT) or large case series available.

Various chemotherapeutic agents, including cyclophosphamide, 5-FU, vincristine, bleomycin and methotrexate, had been used with no significant response until 1980, when cisplatinum-based chemotherapy, alone or in combination with other therapeutic modalities, has been introduced and shown as the most effective medical treatment for aBCC.81

The efficacy of cisplatinum containing regimens has been reported in patients with aBCC achieving overall response rates (ORR) in up to 77% of the cases with complete response in up to 45%.82 A review of all studies published until 1996 on the efficacy of platinum containing regimens for treatment of localized, recurrent and metastatic BCCs showed an ORR in 82% of mBCCs with complete remission (CR) achieved in 45% of mBCC and in 30% of local disease and a median time to progression of 24 months.83

In a series of 12 patients affected by aBCC, the combination of cisplatin with doxorubicin, as single therapy or as neoadjuvant therapy followed by surgery, resulted in 4/12 complete responses and partial and no response in 5 and 3 patients, respectively.84 An excellent response with cisplatin and adriamycin ± cyclophosphamide has been reported in a small number of patients with large BCCs.85

The association of cisplatinum, bleomycin and fluorouracil has been reported in one case of laBCC on the head and neck with CR and in one case of mBCC on the genitalia with partial remission (PR). The combination of cisplatin and bleomycin has been proposed as neoadjuvant treatment in less than 20 cases of NMSC with only a few BCCs included in the series.86

In recent years, paclitaxel has been used in combination with cisplatin and/or carboplatin and/or capecitabine to treat mBCC providing rapid symptomatic response and manageable toxicity.87-89

In published reports, dosage of cisplatinum greatly varied from 20 to 100 mg/m² also depending on whether it was used as monotherapy or in combination with other agents, and the number of courses varied from 2 to 12.

Further RCT on chemotherapy regimens with survival benefit data are needed to guide the management of aBCC.

**Target therapy**

**Cetuximab**

Cetuximab is a chimeric murine/human monoclonal antibody that acts as an epidermal growth factor receptor (EGFR) antagonist, preventing activation of the receptor. To date, cetuximab has been used in less than 10 BCC patients with controversial results. Three patients affected by locally destructive BCC (2) and mBCC (1) were treated with intravenously administered cetuximab at the weekly dosage of 250-400 mg/m² with stable disease (SD) or mixed response.90, 91 Four additional patients with mBCC (1) and NBCCS (3) were treated at the initial weekly dosage of 125 mg/m² later escalated to 300 mg/m², with CR in 2 patients and PR in the remaining two patients. Although after a follow-up of 12 months all four patients were alive, the median survival data were not available.92

More studies are warranted to establish the efficacy of cetuximab as a treatment option for advanced BCC.

**Vismodegib (GDC-0449)**

Vismodegib is an oral inhibitor of the Hedgehog (Hh) pathway approved in the USA for the treatment of adults with laBCC or with mBCC that have recurred following surgery or who are not candidates for surgery or radiation therapy. Vismodegib selectively binds to and inhibits Smoothened (Smo), one of the key molecules of the Hh signaling pathway which is known to play an important role in the regulation of cell differentiation and organ formation during normal embryonic development. Hh pathway is usually quiescent in most adult tissues, with the exception of hair, skin and stem cells, and it is abnormally activated in >90% of BCCs through an activating mutation in the Smo gene or functional loss of the Patched gene93 (Figure 2).

Vismodegib has been and is being investigated in a number of phase I-II trials for treatment of aBCC both in sporadic cases and in the context of NBCCS patients.

The initial phase I trial enrolled 33 patients with mBCC (18) or with laBCC (15) treated with escalating doses (150 mg, 270 mg and 540 mg/day) of oral
vismodegib for a median period of 9.8 months. The ORR was 60% in patients with laBCC including 2 CR, 7PR, 4SD and 2PD and 50% in patients with mBCC including 9PR, 7SD and 2PD. Most common adverse events were fatigue, hyponatremia, muscle spasms, dysgeusia and weight loss. The mean time of treatment duration was 9.8 months and the mean duration of clinical response was 8.8 months.94

In a subsequent multicentre, single-arm, two-cohort, open-label phase II trial, 104 patients with mBCC or laBCC received vismodegib 150 mg once daily until disease progression, unacceptable toxicity or withdrawal from the study. The response rate for the mBCC cohort (33 patients) was 30.3% (by independent review); an additional 64% had SD while progression was seen in 3% of patients. The response rate for the laBCC cohort (63 patients) was 42.9% (by independent review), 38.1% of patients had SD and 12.7% had progressive disease. The median duration of response was 7.6 months in both cohorts. The most common adverse events were: muscle cramps, hair loss, dysgeusia or taste loss, weight loss and fatigue.95

A randomized, double blind phase II trial on 41 patients with NBCCS treated with vismodegib for at least 8 months (range: 1-15 m) showed a significant decrease of newly developed BCCs in NBCCS patients compared to the placebo group (2 vs 29 per group per year). In addition, a significant decrease of the size of existing BCCs (mean 65% vs 11% in the placebo group) was achieved. About 50% of patients discontinued treatment because of side effects.

The recurrence of BCC as observed in some patients approximately 3 months after discontinuation of vismodegib treatment, might have several explanations: i) drug-tolerant tumor cells with “cancer stem cell” characteristics may be present within BCC lesions, ii) residual tumor cells may occur in clinically regressed tumors accounting for the regrowth of tumors after stopping treatment or iii) a small number of morphologically normal (histologically unrecognizable) dormant tumor cells remain after examination of random histologic sections.96

Recently, the metabolic changes observed with 18-FDG PET/CT in 14 patients with mBCC treated with vismodegib have been correlated with the clinical response suggesting the valuable role of this procedure in the management of patients with aBCC.97

In conclusion, there are several evidences that vismodegib provides substantial clinical benefit for patients with aBCC and NBCCS, with mild to moderate adverse events. Phase III trials are currently ongoing.

Figure 2.—Representation of the Hedgehog signalling pathway (HhP). A) Inactive Pathway. In the absence of Hh ligand (Sonic Hh, Shh), the PTCH receptor inhibits the function of a transmembrane protein named Smoothed (Smo), by preventing its translocation to the cell membrane. Without Smo activation, Gli family transcription factors (Gli1/Gli2/Gli3) are processed with SuFu into a repressor form (Gli3); Gli3 translocates to the nucleus and blocks transcription of Hh target genes; b) active pathway. Hh pathway activation occurs when Shh ligand binds to PTCH, that in turn stops inhibiting Smo, which then migrates on the cell membrane. Smo activates a cytoplasmic complex that releases the transcription factor Gli1/Gli2, that translocates into the nucleus allowing transcription of Hh target genes.
LDE225

LDE225 is an additional molecule that targets the Hh pathway action inhibiting Smo; it is formulated as a cream and therefore it is topically administered. A double-blind randomized, intra-individual study of 8 patients with NBCCS presenting 27 BCCs were treated twice daily with 0.75% LDE225 cream vs. vehicle for 4 weeks. Three of 13 patients showed complete response, 9 partial response and 1 no response with an excellent safety profile.98

Itraconazole

Itraconazole is a triazole antifungal drug that targets the enzyme 14α-lanosterol demethylase (14LDM), which is involved in cholesterol biosynthesis in mammalian cells, and in the synthesis of ergosterol in fungi. In contrast to other antifungal agents, itraconazole has been recently shown to inhibit the Hh pathway both in vivo and in vitro 99 and, in particular, the mutated form of the Smo protein (SMOD477G) which might confer resistance to vismodegib and LDE225 treatment.100 Data available so far are promising for the future development of new therapeutic approaches in patients who develop resistance to treatment with Smo inhibitors.

Conclusions

Treatment of aBCC (laBCC and mBCC) is still very challenging for the lack of RCT/guidelines and the scarcity of available therapeutic options. In addition, most of the patients with aBCC are elderly individuals with co-existing comorbidities or taking several drug medications. The contribution of a multidisciplinary team composed of dermatologists, surgeons, oncologists, pathologists, radiologists and radiotherapists is required to deal with the spectrum of issues that emerge from managing these patients.

Therapy of aBCC includes surgery, radiotherapy, different chemotherapy regimens and electrochemotherapy. Recently, several clinical trials have demonstrated the efficacy and tolerability of vismodegib, the first novel target cancer therapy for aBCC. In addition, a number of new agents (e.g., Smo inhibitors other than vismodegib and irraconazole) are currently in development or being studied for treatment of aBCC.

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Women and acne: any difference from males?  
a review of the literature

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ABSTRACT

INTRODUCTION: The attention to the impact of gender differences in acne is needed and, at the moment, lacking. The aim of this paper was to perform a systematic review on gender differences in acne.

EVIDENCE ACQUISITION: A review of the literature was performed using the PubMed and Ovid literature search engines, using a variety of combined search terms including “acne”, “gender”, “sex”, “females”, “males”. The search extended until July 2013.

EVIDENCE SYNTEIS: Gender differences in acne highlight hormonal interactions as a major target for which more research is needed to translate current findings to clinically significant diagnostic and therapeutic applications. In addition, female patients are more likely to develop anxiety and depression due to their condition, and acne improvement positively influences quality of life.

CONCLUSIONS: The patient’s sex should not radically alter diagnostic or therapeutic efforts, although gender differences could be necessary to set up clinical management, monitoring also the psychological aspect.

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Key words: Acne vulgaris - Gender identity - Sex - Male - Female.

Gender medicine was born in the ’90s to evaluate the impact of gender on physiology and pathophysiology. During the last thirty years, the interest in gender differences has been increasing for what concerns both the pathogenesis and the treatment of several skin diseases. Object of this paper is acne, a very common skin condition, with an estimated prevalence of 70-87% in adolescents.1-2 Few studies can be found in literature about the relation between gender and acne; the first study, by Cunliffe et al. in 1985, showed that inflammatory response is more competent and effective in women than in men, leading to the development of milder forms of acne observed in girls.3

Great part of the data we have are extracted from studies that not originally intended to focus on gender differences in acne, in terms of pathophysiology, clinical course and response to treatment. Aim of this article is to evaluate if acne in females is different from what we observe in males and how these characteristics influence therapeutic management.

Evidence acquisition

Data for this review were gathered from the PubMed and Ovid literature search engines, using a variety of combined search terms including “acne”, “gender”,...
“sex”, “females”, “males”. The search extended until July 2013. A total of 667 articles were screened to exclude duplicates and papers not relevant. Forty-nine (49) articles were finally considered for the review.

**Gender and clinical aspects**

The anatomical substratum of acne is represented by the pilosebaceous unit, which can be found mostly on the face and the upper trunk, the areas primarily affected by acne. Acne can be subdivided into non-inflammatory, such as open and closed comedones, and inflammatory lesions, including papules, pustules, nodules and cysts. Draining sinuses and scars are consequences of the most severe forms of acne.4 Male patients usually suffer from more severe forms of acne than females5 and, compared to girls, boys are significantly more likely to have retentional and inflammatory acne lesions.6, 7

A premenstrual flare of acne is observed in a high percentage of girls, probably related to the cyclic changes of surface lipid composition, hydration, molecular structure of keratins or prostaglandin effects through its vasoactive properties.8 Conflicting data are reported about the age of onset of acne in males and females, since either boys or girls are reported to be more precociously affected in the different studies; what is known is that acne onset is during puberty in the great majority of patients from both sexes.5, 7 The course of the disease is different, significantly shorter in boys than girls.5, 7 In pediatric population, acne seems to be the most frequent dermatosis among females, as reported in Turkey.9

**Gender and pathogenesis**

The pathogenetic events that lead to the development of acne include hyperkeratosis of the infra-infundibulum and sebaceous duct, hyperactivity of sebaceous glands with consequent hyperseborrhea, hyperproliferation of *P. acnes* and inflammatory host reactions. Many factors can influence these pathogenetic steps, and they can be divided into endogenous (hormonal and genetic factors) or exogenous (environmental factors).

**Hormones**

Hormonal influences on sebum production and seborrhea are probably the key to understand pathogenetic differences between the two sexes. It is known that sebum secretion is stimulated by androgens and that sebum itself increases the production of androgens and their activity on sebocytes and keratinocytes, thus leading to follicular plugging, inflammation and *P. acnes* growth.10, 11

The different hormonal levels between the sexes likely contribute to the higher rate of sebum secretion observed in adult men than in adult women.11 Serum concentration of hormones is not necessarily related to acne severity, since sebocytes have different expression of sex-steroid-receptors and are able to autocrine production of androgens. It is not known if gender differences exist in the expression of sex-steroid-receptors in sebaceous glands, between males and females.12-14 Two further studies weren’t able to find a direct relationship between severity of acne and other markers of androgenicity leading to the conclusion that peripheral hormone metabolism is probably independent from the central endocrine regulation.5, 15

Sebum secretion levels, measured with Sebumeter®, as well as major facial pores showed a positive correlation with male gender.16

Ikaraocha et al. found no differences in the expression of skin surface lipids between the two sexes, observing a progressive significant increase of triglycerides from controls to acne patients and a progressive decrease of free fatty acids, squalene, wax ester and diglycerides.17

Although in most of the facial area of each gender, pH does not influence on the development of acne lesions it seems that the decrease of PH in male acneic patients could contribute of the development of inflammatory lesions, as reported by Youn et al.11

As expected, the menstrual cycle further stresses the differences in hormonal expression between males and females, leading to a periodic change in skin lipid composition. Sebum output levels are significantly higher during the menstrual phase, while pores are larger during ovulation.18 A decrease in SHBG levels is commonly observed in patients with acne; that is why oral contraceptive treatment, which increase SHBG and decrease DHEA-S, can improve acne.19

Acne in women can also be observed in the course of endocrine diseases; among them, polycystic ovary syndrome (PCOS) is the most common, characterized by hyperandrogenism, chronic anovulation, polycystic ovaries, peripheral insulin resistance and hyperinsulinemia. Acne...
can be diagnosed in 70% of PCOS cases. Insulin resistance could be considered as a new risk factor for men, probably playing a role in the development of acne in those not responding to common therapies.

**GENETICS**

Twins offer a good model to understand the relative weight of genetic and environmental factors in the pathogenesis of acne. A study on a large population of monozygotic and dizygotic female twins showed that 81% of the variance of the disease is attributable to genetic subsets, and the remaining 19% is attributable to environmental factors. A Chinese study on polymorphism and acne demonstrated that the frequency of CYP17-34T/C homozygote and C allele in severe acne male group were significantly higher than that in the control, suggesting that CYP17-34T/C homozygosis may increase the risk of developing severe acne in males; on the contrary, no significant differences were observed between female patients, mild and moderate male patients and their controls. Androgen receptor polymorphism could be considered as an alternative predictor for male acne susceptibility; a relationship between the polymorphism of CAG repeat coding and the onset of acne in males from Han population was documented. No significant clinical differences were found between male and female patients that have IGF-I (CA) polymorphism, that is significantly related to acne severity.

**ENVIRONMENTAL FACTORS**

Environmental factors play a significant role in the pathogenesis of acne. It is difficult to quantify the contribution of single factors, such as smoke, diet or other everyday habits, for the presence of bias in the analysis of qualitative variables.

Contrasting data regarding the role of smoke exist: cigarettes have resulted to worsen or prevent acne, depending from the studies. Different authors affirm that smoking may result protective in the development of inflammatory facial acne, in girls but not in boys; others believe that the incidence of severe forms of acne is significantly higher in smoking than not-smoking females. Last, no association between acne and smoking was demonstrated.

A higher Body Mass Index (BMI) seems to be related to severe forms of acne, with a more pronounced effect in males than in females; no gender differences are reported for what concerns the impact of single foods on development of acne.

Only one study considered the link between zinc and acne, showing that women, whether diseased or healthy, have significantly lower serum zinc level than men; in more severe grades of acne, both men and women have a significantly lower level of zinc if compared to the corresponding control group.

**Treatment**

Treatment of acne, as suggested by the guidelines from the Global Alliance to improve outcome in acne, consists in topical and systemic therapy mostly in association, depending on severity and type of acne. Each pathogenetic factor involved in acne as follicular hyperkeratinization, sebum excess, P. acnes proliferation and inflammation, that is present at different degrees in the two sexes, should be targeted from therapy. Few studies focused on gender differences during therapy and most of them revealed no variations in acne treatment and therapeutic responses.

**TOPICAL THERAPY**

Topical retinoids, such as adapalene, tretinoin or tazarotene, are the first-line treatment in acne, alone or in association with antimicrobials. Prescription of retinoids seems lower in male patients. Yu Zu et al. did not evidence difference between males and females who underwent to tazarotene 0.1% topical application. Clinical improvement, measured as lesions count, from clindamycin and benzoyl peroxide combination was found to be greater in adolescent girls than in boys of the same age. The response to dapsone 5% gel also appears to be influenced by gender, with female patients experiencing a significantly greater reduction in acne lesion count and a significantly higher clinical success rate following 12 weeks of treatment.

**SYSTEMIC THERAPY**

It is proven that male acneic patients under systemic isotretinoin treatment deal with a higher risk of side effects, such as severe flare with systemic signs simulating acne fulminans. Leyden reported that this com-

Clinical success of oral contraceptives for acne treatment in women is well-known; In general, combined estrogen/progesterone preparations have been useful to treat symptoms of androgenization, which is usually associated with PCOS. Patalski et al. investigated pituitary function in male acne patients and serum levels of dehydroepiandrosterone sulphate (DHEA-S), sex hormone binding globulin (SHBG) and other biochemical parameters in patients from both sexes before and after treatment with an oral contraceptive. Oral contraceptive treatment induces an increase in SHBG and decrease in testosterone; female acneic patients showed a decrease in SHBG and increase in DHEA-S levels when not treated with oral contraceptive. Oral contraceptive treatment induces an increase in SHBG and decrease in DHEA-S and obviously improves acne.

It is also known that Westerners and Asians respond differently to hormone therapy: K. Sato et al. examine the efficacy and safety of oral spironolactone used to treat acne in Asians and data showed that treatment was less efficacious for the males than for the females.

The management of acne vulgaris is a long-term process that must be individualized to each patient. Two studies found relevant factors influencing treatment, including the age and gender of the patient, the severity and extent of disease, the efficacy and tolerability of prior interventions, and the degree of compliance with recommended therapies. Medication non-adherence is generally prevalent among young acne patients, but it is difficult to measure and rates reported by patients often overestimate actual adherence. Patients cite lack of time as a common reason for no adherence to topical medications.

Bernard McEvoy et al. found missed appointments as major problem in healthcare delivery, and are one element of patient compliance with treatment. No significant differences were observed between males and females.

Gender and quality of life

Acne has a great impact on patients’ quality of life, deeply affecting their own self-esteem and human relationships. Several studies tried to quantify this psychological burden: results are conflicting but most of authors believe that women are more involved than men.

In different papers severity of acne resulted similar between the two sexes but quality of life was more impaired among girls than boys. Khan found a greater incidence of depression in female acneic patients. Factors responsible for the worse perception of disease by women with acne seem to be acne duration and AP-SEA (Assessment of the Psychological and Social Effects of Acne) score before treatment; Tan JK furtherly observed that a greater impairment in quality of life is associated with older age, female gender, and longer acne duration (>5 years).

Data from non-western countries such as China, Japan and Egypt, even if obtained using different evaluation tools (Cardiff Acne Disability, Mental Health Inventory and DLQI), confirm that women are more psychologically susceptible to acne than men.

Three studies from Scotland, New Zealand and Turkey showed no gender differences in patients’ quality of life and perception of disease; on the contrary, only one study reported that males tend to overestimate their acne more than females.

Berg et al observed that a higher percentage of female patients resulted under treatment with isotretinoin although clinically graded as moderate, probably because women perception of disease plays a role in physician’s choices. Treatment seems to be more effective on the quality of life of those patients, mostly females, that report more depressive symptoms at baseline showing that quality of life (QoL) can be enhanced through successful acne treatment.

Evidence synthesis

It is no more adequate to discuss on acne without taking into consideration the gender differences that exist in terms of severity, time of onset, pathogenesis, treatment and psychological impact.

As reported, females suffer from milder forms of acne, with fewer retentional and inflammatory lesions than males. As hypothesized by Holland et al. this could be related to a more competent immune response in female patients to the acne assault. These authors reported an earlier increasing of blood levels of leucocytes and inflammatory mediators (complement C3, CRP, alpha 2 macroglobulin and immunoglobulin levels) in female
than in male acne patients. Although further studies should clarify these findings. Characteristic female hormonal subset is responsible for the cyclic flares of acne. Endocrine diseases, such as PCOS, cause the persistence of acne in women older than 25 as well as the late onset of acne. No differences are demonstrated in the expression of receptors for sexual hormones in sebocytes, but diverse hormonal levels and peripheral susceptibility contribute to the lower rate of sebum secretion observed in adult women.

Topical treatments seem to be more effective in females, independently from the drug used; the risk for systemic isotretinoin side effects is lower in women than in men. Data on drug efficacy are not enough to express a final statement and influence therapy. What is known is that females with acne are more likely to develop anxiety and depression due to their condition, and acne improvement positively influences QoL.

Conclusions

In conclusion, gender-oriented evaluation of data is needed in future to better understand acne and guide a targeted therapy, in order to improve both clinical and psychological aspects.

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SPECIAL ARTICLE

Doctors and baldness: a five thousand year old challenge

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The history of trichology follows a thread that continually intersects with that of the history of medicine in general. Even Hippocrates believed that the approach to baldness should be of a medical nature. This confrontation between doctors and hair loss, which has lasted for five thousand years, begins with the invocations of the head physicians in the Egyptian era and ends with the recent institution of postgraduate Master’s degrees at Faculties of Medicine and Surgery. The biggest names in medicine concerned themselves with trichology beginning with Hippocrates, who dealt with the topic in his most famous work: the Aphorisms. Even the most celebrated doctors of the Roman era, such as Galen and Pliny the Elder, did not disdain considering hair loss, leaving important scientific contributions before passing on the baton to their distinguished colleagues of the Byzantine Empire. The narrative then flows through the most prestigious institutions of the Middle Ages, such as the Salerno School of Medicine and the Siena Accademia del Fisiocritici where, at the end of the 1600s, the distinguished anatomical describer Marcello Malpighi also taught trichology, and left his contribution to “Hair Science” with a fine description of the hair follicle in the pages of his Opera Posthuma. At the turn of the late Middle Ages and the early modern era, barbers formed the primordial nucleus of surgery and at the same time became the ones to concern themselves with hair loss. In the 1800s, several doctors published the first texts dealing with the anatomy and physiology of the hair and taking into account the principal forms of alopecia, but at the therapeutic level did not yet propose anything scientifically valid. Until a few decades ago trichology still lent itself to various commercial speculations. It was not until the twentieth century that the pathogenetic mechanisms of baldness were clarified in a scientific manner. With this knowledge, the pharmaceutical industry has been able, then, to develop the necessary drugs, and doctors have become willing and able to reappropriate treatments to counteract conditions that lead to hair loss.

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The history of trichology started at the same time as the history of medicine. The symbolic meaning given to hair by man meant that as soon as the man-doctor realised that with some procedures you could remedy some illnesses, he immediately tried to find a cure for baldness too.

Head doctors in ancient Egyptian civilization

In the highest civilization of antiquity, the Egyptian, the first prescriptions for alopecia areata and hair loss in general were drawn up. Egyptian medicine was based on very intelligent practices, even if incantations and invocations were included among the remedies. The Greek historian Herodotus (c. 450 BC) wrote: “Each physician is a physician of one disease and no more; there are physicians of the eyes, others of the head, others of the teeth, others of the affections of the stomach, and others of the more obscure ailments.” Obviously, trichology was under the influence of the head doctors. The oldest writings about hair date back to the Ebers Papyrus (XVIII Dynasty 1540-1293 BC), in which many remedies were proposed for many diseases; particular attention was paid to hair and skin diseases, in particular remedies to cure baldness and greying. In an attempt to hypothesise the aetiology of common baldness it emphasises the importance of the scalp blood vessels. Ebers is the name of the European buyer who
purchased the papyrus in 1874; it is a 20 metre roll, 30 centimetres high, and consists of 110 columns, which contain 877 instructions written in hieroglyphics. Currently, it is preserved in the library of the University of Leipzig.1

Hippocrates: “Eunuchs cannot become bald”

Later, when the cradle of civilization took up residence in classical Greece, medical knowledge also flourished there. The father of western medicine, Hippocrates of Kos (460-377 BC), did not fail to turn his attention to trichology in fighting his own battle against baldness, creating topical preparations made from opium, beetroot, horseradish, pigeon droppings and various spices.2 These remedies may make us smile, but it should be noted that Hippocrates was the first to have had the idea that hair loss in men was related to hormonal stimuli. In his Aphorisms, in fact, he wrote: “Eunuchs do not get gout, nor become bald” (XXVIII); he had observed that in the Persian army, among the eunuchs to guard the king’s harem there was not one who manifested hair loss.3 Later, two great doctors of the nineteenth and twentieth centuries, Sabouraud and Hamilton, resumed the same concept.

Galenic preparations for the hair of the Roman emperors

In the Roman Empire between 129 and 199 BC, the physician of the Emperor Marcus Aurelius, Galen of Pergamum, argued that hair growth was linked to the mood of the individual and hypothesized that moods, just like hair, came from our skin, as “consequences of the exhalation of bodily mood.” In this age there were remarkable developments in medicine, particularly anatomy and physiology, attributable to Celsus (14 BC-37 AD) and Galen. The latter, among other things, developed medical therapies with the institution, in fact, galenic preparations, but despite this progress, substances to treat baldness still had compositions with unlikely effectiveness.4

Pliny the Elder (23-79), in his “Naturalis Historia” (“Natural History”), refers to a useful mixture used to regrow hair recommending to “wipe with soda the part where the hair has fallen out, then apply an infusion of wine, saffron, pepper, vinegar, Lasерpitium and mouse droppings, while the ashes of a donkey’s penis sprinkled on the hair was used to thicken and prevent grey hair”. At the same time he suggested, perhaps already knowing firsthand the power of these remedies, to use wigs made using methods handed down from the Egyptians and still current at that time.5

The last doctor worthy of mention from the Roman period is Pedanius Dioscorides, physician, botanist and pharmacist, a native of Cilicia, who lived in the first century AD (40-90). Also of Greek origin, he practiced in Rome at the time of the Emperor Nero and became famous for the publication of his vast work in five books, “De Materia Medica” (“About Medical Matters”), which remained the reference of botanical medicine until modern times. In it were collected descriptions of more than five hundred plants, from the most common to the most rare and exotic; some of these referred to use in the treatment of alopecia and hair loss. It talks about using reed bark mixed with vinegar and applied to the head to treat alopecia. It also reported the use of labdanum with wine, myrrh or myrtle oil for healthy hair, the juice of Brassica sativus, nasturtium seed oil, and aloe with wine and maidenhair combined with myrtle oil, all to be used as a compress on the scalp.5

The Byzantine medical school remedies for baldness

Historically, the development of knowledge has invariably followed the fortunes of the power of civilization and so, in 324, when Constantine transferred his capital from Rome to the Bosphorus, the primacy of medical knowledge became the prerogative of the Byzantine school until 1453, when Byzantium fell to the Turks. From this period there are a group of doctors who drew their medical knowledge from the Hippocratic, Hellenic and Roman, and then Galenic traditions, handing down evidence of ancient treatises, for the most part lost, enriched by their own experiences. Oribasius of Pergamum (fourth century), Alexander of Tralles (sixth century), Paul of Aegina (seventh century), and Theophanes Chrysobalantes (tenth century) enriched medical knowledge in many fields, but devoted particular attention especially in the field of dermatology, leaving important treatises on the treatment of various skin pathologies, including herpes, leprosy, cancer, vitiligo, psoriasis and alopecia. They provided valuable cosmetic advice on body care and the preservation and improvement of the appearance of hair and eyebrows.
Among these, Oribasius of Pergamon, a physician and compiler, lived in the fourth century. In the ninth book of his compendium of medicine “Synopsis” (“Compendium”), dedicated to his son Eustace, in the chapters “De Alopecia e Oftasi” (“About Hair Loss and Ophiasis”) (XXII) and “De Capillis Fluentibus” (“About Hair Loss”) (XXIII), he recommends many preparations for the treatment of baldness, for the most part containing a fern named Adiantum, or maidenhair.

Another remedy cited by Oribasius contained labdanum, wine, myrtle oil and maidenhair, to be applied as a compress after bathing. Other preparations, containing mainly aloe, were considered useful to eliminate harmful moods. The compresses were applied to the skin after shaving. Oribasius is cited, amongst other things, for the description of a technique for the recovery of lost hair: candle wax, tar and glue (lithocolla) mixed with a heated metal cannula creating a soft sticky compound which was used to reattach the hair: this method could well be considered as the first use of “hair extensions” in history! Alexander of Tralles believed that the causes of hair loss were many, and were recognisable by the colour of hair: among these, lack of nutrients for the hair, too many or too few pores. Among the many remedies mentioned in the first chapter of his treatise “De Alopecia” (“About Alopecia”) and the second “De Capillis” (“About Hair”) he advised moderate bathing and a special diet, with some prohibitions: salt, fatty foods, and excesses of wine or sex. He also prescribed various herb compresses similar to those prescribed by Oribasius.

Paul of Aegina in the third book of his work, “De Arte Medendi” (“The Art of Healing”), defined hair loss as being due to the absence of liquid, just as plants that lose their leaves wither for lack of water, alopecia was due to the alteration of moods and required body purification before specific treatment. To thicken the hair, especially in baldness, Paul quotes a medication from the first book of a work by Crito, a physician from Trajan, his treatise in four volumes which has unfortunately been lost: “Ad Græbraetam et Capillorum Augmentam, ex Commentariis Critonis” (“Hair Growth and Hair Growth Loss, from Crito’s Commentary”). The treatment consisted of a mixture of a dried rabbit stomach with various herbs (myrtle bud leaves, rose hips, maidenhair fern and acacia flowers and leaves) all finely chopped and filtered, with the addition of bear or seal fat. This compound was kept in a lead container and applied as a compress. In the section “Quibus Conferentur Capillis” (“What it is Beneficial for Hair”) to prevent hair loss, a compress consisting of the following is advised: maidenhair, labdanum, wine and myrtle oil or crushed anemone flowers in olive oil. To thicken the hair a massage was suggested with a bathing of medicinal althea seed or with olive oil in which these seeds had been steeped or boiled. Theophrastes, or Theophrastus of Eresus (“Theophrastus”), a physician of the time of Emperor Constantius Porphyrogenitus, begins his book “Epitome de Curatione Morborum” (“Compendium about Disease Treatment”) with a chapter entitled “De Capillis Fluentibus.” He follows the prescriptions of the physicians Oribasius and Alexander, and also mentions a preparation by the ancient physician Archigene (1 century BC) which consisted of labdanum and mint in equal quantities. Another drug that was used as a lotion on the head was made with “An equal amount of laudanum and absinthe, ten juniper berries, beaten together and wrapped in a linen cloth for five days.” Left soaking to steep, when ready the head would be anointed with these (“Ladani & absinthii par moles, grana juniperi decem, trita in linctorium inuoluuntur et per dies quinque macerantur, his que tande caput illinitur et nec capilli defluent neq furfures aderunt.”). The author confirms that “no more hair will fall out and no more dandruff will be formed.”

A little light illuminates hair in the darkness of the Middle Ages

At this point, the history of trichology is lost for several centuries and we take up the story again in the twelfth century in the Salerno School of Medicine. This prestigious institution based its knowledge on ancient medical treatises in Latin, Greek, Arabic and Hebrew. It was the most important medical school in Europe in the Middle Ages, and the concept of the modern university came from here. Its trichology high point was in the eleventh century. A woman at that time headed the chair of medicine: the famous Trotula di Ruggiero (1050-1097). The daughter of a noble family from Salerno, Trotula left important medical treatises, especially dedicated to women, even writing a treatise on cosmetics “De Ornatu Mulierum” (“About Female Embellishments”). Her medicine was not based on magic potions or special prayers or rituals, but the use of products from more than three hundred healing plant species grown in the Minerva Gardens, and animal fats.
Expanding our view to the European Middle Ages, around 1500, lotions to combat hair loss were prepared using sulphur powder and saffron: someone had the idea that sulphur, already used to treat headaches and nausea, could have the same beneficial effects on the hair and scalp; in fact, a few centuries later it would be shown that sulphur has a natural disinfectant action and fights the causes that lead to the formation of dandruff.

Important texts on medieval medical science such as “Theatreum Sanitatis” [“Health Theatre”] written between 1052 and 1063, and then completed in the fifteenth century,12 or the “Health Treasures” by Durante cite, for example, the onion, rich in sulphur: “Such as it is beneficial for the tonsils if the onion is rubbed on the throat, the juice rubbed on the baldness makes hair regrow”13.

In the France of King Louis XIII, however, the problem of baldness would be addressed in a more expeditious way with the use of important wigs, as he was also forced to wear, to camouflage thinning hair. Followed by the other members of the Court, the use of the wig soon became fashionable and giant hairpieces began to be seen more and more frequently.14

At the end of the Middle Ages the treatment of baldness changed management: the exclusive property of the priests of primitive religions, it would pass, after having been taken in charge for several centuries by monks in monasteries, to the authority of the barbers who would form themselves into the initial cell of medicine, and above all, surgery.

The start of trichology as a medical science in 18th century Italy

To continue the story in the academic world, we should remember that the first Trichology Symposium, entitled “Discorzo de Capelli e Peli” [“Discussion on Head Hair and Body Hair”], was held in Italy on 23 December 1696, at the “Accademia dei Fisiocritici” in Siena. The keynote speaker, Doctor Ambrogio Anton Domenico Visconti, suggested some hypotheses to explain the difference between male and female hair: “It is these seeds, spread all over the body under the skin, which at the correct time send forth their germ, that is to say when all the body takes its nourishment. This does not happen in the female because they begin with their menstruation at the same age that men begin to grow a beard, so women remain without a beard. Furthermore, because the skin of the head is fatter than elsewhere, hair grows more and in a greater amount as it is supplied with more nutrients and vessels”. A manuscript, which reports the proceedings, is still consulted in the library of the Accademia.15 It is likely that the Bolognese doctor Marcello Malpighi also took part in the work of this convention from which there remains, by the way, some treatments on these subjects in an illustrated table (XVI) entitled “De Pilis Observationes” (Figure 1) which is part of his famous “Opera Posthuma”.16

First publications dedicated to medical trichology

In 1859 in New Bedford, Massachusetts, Bela Perry wrote “A Treatise on human hair and its diseases”. This was undoubtedly the first medical-scientific publication on the theme of trichology!17 In 1872 in Philadelphia, Benjamin Godfrey published a book titled: Diseases of hair. In this text, Seborrhea microbes were cited as the etiopathogenesis of common baldness as, later, Sabouraud’s microbacillus would be.18

In Europe in 1902, Raymond Sabouraud (1864-1938), the famous French dermatologist who headed the microbiology laboratory in the “Saint Louis” dermatological hospital in Paris from 1894 to 1897, issued “Maladies du cuir chevelu” [“Diseases of the scalp”] in five volumes. In the first he theorises that baldness is like seborrheic alopecia in that microbacilli constitute the trigger.19

On 6 December 1868, The New York Times, published an editorial “Hair” written by Laura Redden Searing under the pseudonym Howard Glyndon, which proposed a correlation between baldness and genetic transmission, but the scientific community ignored it: “The defect is often hereditary, and runs through generations; and nothing will do any good, except the strictest hygienic treatment, adopted at a very early age and continued while growth lasts”.20

One of the biggest misconceptions in the history of trichology is due to a publication by Dorothy Osborne in 1916 in the Journal of Heredity. In her scientific publication entitled “Inheritance of baldness” it is stated that: “Baldness recognises an autosomal dominant hereditary mechanism in men and recessive in women”. It would then take many years to dispel this assumption which created many misunderstandings in the genetic determination of baldness.21
Milestones in the science of trichology

In 1942, James Hamilton set one of the milestones on the road to understanding the pathogenesis of androgenetic alopecia. His report, “Male hormone stimulation is prerequisite and an incitant in common baldness”, published in the American Journal of Anatomy, states that male hormones are an essential prerequisite to the development of androgenetic alopecia. The story of how Hamilton reached this conclusion is legendary. The appearance of thinning after reaching sexual maturity and the frequent occurrence in males suggested that it could pertain to endocrine factors. So Hamilton, to test the validity of this hypothesis, considered the idea of examining a population of males who could not produce male hormones.22

Hamilton, a medical pathologist at Yale, was serving in a community where a high number of castrated patients lived. One day he noticed the twin of one of the residents who had come to visit his brother. The castrated brother, who lived in the community, had a full head of hair. His twin, with testicles intact, was, however, quite bald. Using his intuition Hamilton administered testosterone to the castrated brother. It is said that the voice of the poor castrated brother deepened, he developed acne, large muscles appeared and, his sexual...
desire. Hamilton reported that he became bald and his hair did not grow back.

That “population” of castrates gave Hamilton a means to demonstrate the relationship between baldness and male hormones, androgens. Testosterone was administered orally to 104 of the castrated men, and they were compared with 312 “normal men”. Once the testosterone had been administered, in the castrated patients hair thinned in cases where a history of baldness was present in the family. There was also a direct connection between the duration of administration and the degree of baldness reached: the longer the treatment the more severe the baldness. Echoing Hippocrates, Hamilton concluded, “Men who do not reach sexual maturity do not become bald”.

The cause of baldness was established. Hamilton’s classification of the degrees of baldness was updated in the ’70s by Norwood, a famous surgeon, who innovated the technique of hair transplantation. The Hamilton-Norwood scale is the reference sample in medical and surgical trichology.

The term “Male pattern baldness”, which is used scientifically to clinically describe baldness, came as a result of the intuition of an English doctor, Agnes Savill, who trained at Sabouraud’s “Saint Louis” school in Paris, and published “The Hair and Scalp” in Baltimore in 1935.23

“The current status of our knowledge on baldness” is the title of a work by Edward Ludwig who, in 1962, coined the scientific term “Androgenetic Alopecia” to refer to common baldness. This name implied the two major pathogenetic factors of the disease, namely: androgens and inheritance. Androgenetic alopecia is induced by the action of androgens on genetically predisposed individuals. This predisposition is transmitted with polygenic characteristics and affects both men and women equally.24

Commercial interests in the field of trichology

Until the ’70s, despite the various texts that had been published dealing with the anatomy and clinical aspects of the most common hair and scalp diseases, the pathogenetic mechanisms underlying baldness still evaded both doctors and researchers. As a result, pharmaceutical research could not produce the desired treatment. Doctors, who felt powerless faced with the pressing demands of trichology patients (who are generally considered among the most apprehensive attendees of doctors’ surgeries), realised that it was not expedient to take charge of alopecia patients. Showing ingratitude to the bald, Western medicine rejected the very same hair which had in fact created it: after all, were not barbers the very first doctors? Trichology patients were unable to find a safe haven in doctors in which they could shelter their hair.

The landing place was found by Lynn Robert Akers, who in 1945 founded the Hair & Scalp Clinic in New Orleans, the largest non-medical trichology organisation. In 1961, he owned 50 clinics around the world employing 1,500 people. A staff of scientists, doctors and researchers worked for him and he continued to invest in this laboratory work. In 1961, Dr. Wallace, funded by Akers, arrived in Rome with 16 pairs of identical twins, who were received by Cioccetti, the Mayor of Rome, and the Pope. The next day, at Rome University, Professor Pende began his initial checks. Prof. Paul Niehans, a Swiss doctor who pioneered cell revitalisation, was hired as a consultant. The strengths from a commercial point of view, of this powerful organization were: free consultation and the ability to demonstrate an empathetic interest in the patient’s problem. The Adventure of Mr Akers ended in Italy and in many other European countries in 1964 with closure by the court for “abuse of the medical profession”. The senior management of the organisation by now disjointed, in just a few years became managers of almost all the non-medical trichology centres to the present day.25

Medicines which were used to counteract the onset of androgenetic alopecia

Finally, in 1979 an American endocrinologist published the scientific article that would reveal the ultimate mystery of androgenetic alopecia. The researcher Julianne Imperato-McGinley, who lead an expedition of anthropologists in the Dominican Republic, sensed that “the enzyme 5α-reductase allows the maturation of sexual characteristics in the male and its presence is a necessary condition for the development of baldness”. In a rural village in the south-west of the island, studies were carried out on the genetic material of a population in which there was a very particular hereditary autosomal recessive trait: the absence of the 5α-reductase enzyme,
capable of converting testosterone into dihydrotestosterone. This deficiency manifests itself as pseudohermaphroditism: in practice males do not develop male sexual traits due to the lack of dihydrotestosterone production. The observation that most interests us is that males in this condition did not develop baldness. With this in mind, the medical team led by Imperato-McGinley would conclude that the conversion of testosterone to dihydrotestosterone, promoted by 5α-reductase, is an essential condition for the development of androgenetic alopecia.26

The discovery of the first FDA-listed drug for hair regrowth, however, was completely by chance, but isn’t observation the first cornerstone of scientific methodology? Anthony Zappacosta, with his curiosity as an attentive observer could not fail to note that when taking minoxidil to combat high blood pressure a particular side effect could be observed: the growth of both head and body hair. Minoxidil is a pyrimidine derivative which has been used as a drug of last resort since the early ’70s as an oral treatment in refractory hypertension. The drug has, in fact, a marked arteriolar vasodilator effect related to its capacity to open intracellular channels to potassium at the level of the smooth muscle cells of peripheral arterioles. One of the side effects of the drug was hypertrichosis so some dermatologists decided to use it as a treatment for hair loss, also motivated by the fact that Zappacosta reported the case of a patient suffering from androgenetic alopecia, who while taking oral minoxidil for hypertension, was greatly improved.27 Since systemic use in healthy subjects was not indicated because of the occurrence of side effects, it was decided to use a topical formulation. The drug was extensively tested until it was approved by the FDA in 1988 and by the Italian Ministry of Health in 1990.28

The fact that the success rate of treatment with both minoxidil and androgenic metabolism modulators is unsatisfactory for some cases led some researchers to propose the possibility of other possibilities in the pathogenesis of androgenetic alopecia, such as follicular inflammation. One of these considered the implication of different inflammation activators in the etiology of androgenetic alopecia. A first study detected an inflammatory infiltrate of mononuclear cells and lymphocytes in about 50% of the scalp samples observed. Subsequently in 1992 Jaworsky et al. observed an inflammatory infiltrate of activated T-lymphocytes and macrophages in the upper third of the hair follicle, associated with a thickening of the connective sheath composed of bundles of collagen (perifollicular fibrosis) precisely in the areas where the androgenetic alopecia was in progression. The significance of these findings is controversial.29 However, a survey by Whiting points out that only 55% of male patients with androgenetic alopecia accompanied by micro-inflammation, had hair regrowth following treatment with minoxidil, which is less than 77% of patients without signs of inflammation, suggesting that, to some extent, the micro-inflammation could explain the cases of male pattern type androgenetic alopecia that do not respond to minoxidil.30

In 1989, the Italian dermatologist and endocrinologist Andrea Marliani in his publication “Common baldness” indicates the usefulness of association of topical hydrocortisone butyrate lotion with minoxidil to counteract the effects of follicular micro-inflammation. At least in Italy this insight was then followed by most trichology doctors.31

At this point, pharmaceutical research made the first substances effective in counteracting baldness available to doctors. Following its registration in 1988, minoxidil became the first drug ever to be approved for the treatment of hair regrowth. Finasteride at a dosage of 1 mg/day was authorised for use in the treatment of androgenetic alopecia in 1997 by the FDA. Doctors finally had effective weapons to combat common baldness and immediately wanted to regain their role in the field of trichology. In the ’90s the major representatives of Italian dermatologists (Sidev, Aida, Adoi) joined forces in an information campaign against non-medical trichology centres accusing them of a lack of professionalism and causing personal injury, especially regarding transplant of artificial fibres.32

**Pioneers of surgical therapy**

Meanwhile, surgeons also brought their contribution to the aesthetic resolution of baldness. The Japanese dermatologist Dr. Shoji Okuda was a pioneer in hair transplants who started to operate as long ago as 1939. The extraction method involved the removal of “hairy” circular zones of the scalp using a “punch”, then placing the graft obtained in small circular incisions on hairless areas.33 Norman Orentreich performed the first hair transplant surgery in North America. His theory, “The
predominance of hair taken from the donor area”, was presented in New York in 1959 at the Academy of Science. Over the next twenty years, surgeons used smaller punches, but the results were questionable, with “plugs” of 4 mm producing an unsightly “doll effect”. In the ’80s Uebel, in Brazil, became popular through the transplant of micrografts isolated from a single strip of scalp taken from the donor area.35

Hair science in the academic world

The Italian Society of Dermatology and Venereology in the early ’90s perceived that different disciplines were escaping from the sphere of control of dermatology, such as cosmetology which, with the development of Aesthetic Medicine, saw the competence of the skin specialist “par excellence” being increasingly eroded. The same for venereal diseases where, with the spread of AIDS and the specific skills of immunologists, dermatologists were losing another slice of their business activities; and this also happened to outpatient dermatological surgery and the use of lasers which day-by-day passed to plastic surgeons. And, incidentally, it was the most profitable market niches which “took flight”. The policy of the Association of Dermatologists, at this point, was to create specific study groups in order to better protect their activities in these “border disciplines.” It was thus, that Gitri-Trichology Group was formed in 1994, but it was to form with only a restricted group of university dermatologists.36

Trichology was being performed, by now, by a large number of dermatologists, but also by endocrinologists and aesthetic doctors, and in any case by licensed doctors who were not being accepted by and not represented by Gitri. These doctors, along with other professionals involved in trichology as surgeons, biologists, pharmacists and cosmetologists felt the need to meet, train each other, and unite in some way. Andrea Marliani, who had already been working in trichology for some time, was at the centre of a network of contacts and colleagues and realised the time had come to stand up and be counted and create a real scientific society: Sitri, the Italian Society of Trichology, was therefore founded in Florence in 1996.37

One of the weak points of trichology, as a medical discipline, was the lack of an academic qualification confirming the title of Trichologist on a person engaging in such activities. Finally, in 2008, the Director of the Interuniversity Centre for Biological and Psychosomatic Dermatology, University of Florence, Prof. Torello Lotti, promoted the establishment of a Master of Science in Trichology. The course was established in the Faculty of Medicine for the academic year 2008/2009 under the name “Master of Science in Medical and Surgical Trichology” with coordination entrusted to Prof. Silvia Moretti.38 A few years later, in 2010, the University of Rome declared the establishment of a university course in trichology named “Master of Science in Skin Appendages”. Lectures started in the academic year 2011/2012 under the direction of Prof. Alfredo Rossi.39

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The rope sign: a case of interstitial granulomatous dermatitis with arthritis

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**Key words:** Synovitis granulomatous with uveitis and cranial neuropathies - Dermatitis - Granuloma annulare - Lupus erythematosus, cutaneous.

Interstitial granulomatous dermatitis with arthritis (IGDA), also known as Ackerman’s syndrome, is a rare cutaneous disease classically characterized by the triad of cutaneous cords, a typical histologic infiltrate mainly constituted by histiocytes and arthritis/connective tissue disease. Here we report the case of IGDA with the typical clinical and histological features in a patient affected by lupus erythematosus. In this article we underline that IGDA may have a variety of different clinical and histological features. The rope sign is typical but infrequent, while histology is usually characteristic and shows a dermal inflammatory infiltrate, with a predominance of histiocytes, localized interstitially and in a palisaded array between collagen fibres, that show signs of degeneration. Clinical and histological differential diagnoses are discussed.

Laboratory investigations showed an increased C reactive protein (16 mg/L), an elevated anti-nuclear antibodies titre (1:640, antilyssosomal pattern), positive antidouble-stranded DNA antibodies (titre >400 KU/L), and Western Blot antihistone antibodies ++.

Antibodies against extractable nuclear antigens, lupus anticoagulant testing, rheumatoid factor test, anti-citrullinated protein antibodies, as well as IgM and IgG antibodies against Borrelia burgdorferi were negative. Further laboratory analyses were unremarkable.

We performed a punch biopsy, and histology showed a cutaneous infiltrate mainly constituted by histiocytes, mixed with some eosinophils and rare neutrophils, in the superficial and deep dermis. The infiltrate separated, but did not destroy, the collagen fibres, which were focally degenerated. The histiocytes, stained with PGM1, were sometimes arranged in short bundles and some non-necrotizing microgranulomas were evident. The epidermis was normal (Figures 2-4).

Clinical, laboratory and histological features allowed a diagnosis of IGDA.

The patient was treated without success with clobetasol oint-
However, the clinical manifestations of IGDA may vary and include erythematous or violaceous papules or plaques, skin-colored papules or plaques, annular patches, macular erythema, and cord-like lesions.\textsuperscript{3-5}

Such lesions mainly occur symmetrically on the trunk and proximal limbs, but other areas such as the abdomen, buttocks or thighs may be involved; the cord-like indurated bands are classically observed close to the axillae. The presence of linear bands is also known as “the rope sign”, which is considered the sign of an underlying autoimmune disease with autoantibodies and is

\textbf{Discussion}

IGDA is classically characterized by the triad of cutaneous cords, a typical histologic infiltrate mainly constituted by histiocytes and arthritis/connective tissue disease, as first reported by Ackerman in 1993.\textsuperscript{1}
typical of IGDA, even though the erythematous papules and plaques form is more frequently observed. The “rope sign” is usually asymptomatic but may also be associated with burning and pain.

Clinical differential diagnoses of IGDA presenting with the rope sign mainly include Mondor’s disease, linear scleroderma and periarteritis nodosa, while the other clinical presentations of IGDA should be differentiated from the inflammatory stage of morphea, eosinophilic fasciitis and cellulitis, granuloma annulare, erythema chronicum migrans, urticarial vasculitis, Lyme disease, leukemia cutis, necrobiosis lipoidica, mycosis fungoides, and Sweet syndrome.

Arthritis associated with IGDA usually involves the small joints of the upper extremities and may occur before, during or after the onset of skin lesions.

Histologically, IGDA is classically characterized by a dermal inflammatory infiltrate, with a predominance of histiocytes, localized interstitially and in a palisaded array between collagen fibres, that show signs of degeneration. Elastic fibers and collagen bundles may show a piecemeal fragmentation. Usually, small amounts of eosinophils and neutrophils may be present, while mucin deposition and vasculitis are not expected. However, histiocyty may vary according to the amount of neutrophils and eosinophils, the presence or absence of leukocytoclasia and vasculitis, and the evidence of palisaded granulomas.

Our case showed the typical features reported by Ackerman in 1993 but we wish to emphasize that IGDA may have a variety of presentations and in the English literature there are cases with the classical rope sign and an atypical histology and, on the contrary, cases with atypical cutaneous lesions and typical histological findings.

The variability of the histologic presentations of interstitial granulomatous dermatitis led some authors to coin the term palisaded neutrophilic and granulomatous dermatitis (PNGD), a new entity including Churg-Strauss granulomas or extravascular necrotizing granulomas, granuloma annulare-like lesions in Churg-Strauss syndrome, rheumatoid papules, superficial ulcerating rheumatoid necrobiosis and IGDA. These authors hypothesized that PNGD has different histopathologic evolutive stages. Initially, PNGD shows leukocytoclastic vasculitis, nuclear debris, dense neutrophilic infiltrate and degenerated collagen fibers. Fully developed lesions show palisaded granulomas surrounding degenerated collagen bundles with a reduced number of neutrophils, while older lesions show signs of dermal fibrosis, scant neutrophils and palisaded granulomas. Linear bands were considered an unusual clinical picture of PNGD.

Recently, however, Peroni et al. have pointed out that interstitial granulomatous dermatitis has peculiar clinical and histological findings that allow a distinction from PNGD. Clinically, PNGD presents with crusted, ulcerated or umbilicated papules, symmetrically located at the elbows and the extensor surfaces of the digits. Histologically, interstitial granulomatous dermatitis do not show a predominance of neutrophils and do not show leucocytoclastic vasculitis, which is a feature of the early stages of PNGD.

IGDA should be primarily differentiated clinically and mainly histologically from granuloma annulare, as reported and discussed by Peroni et al. and Tomasini et al.

Another important clinical and histological differential diagnosis of IGDA is interstitial granulomatous drug reactions (IGDR), which may be recognized because histologically characterized by parakeratosis, basal cell vacuolization with lichenoid changes at the dermo-epidermal junction, presence of eosinophils, granulomatous vasculitis and sparing of the deep dermis. Moreover, from a clinical point of view, discontinuation of the drug leads to complete healing and IGDR is only rarely associated with arthritis.

The inflammatory stages of deep morphea and eosinophilic fasciitis have extremely different histological features that allow an accurate diagnosis. The first disease is in fact characterized by the thickening and homogenization of collagen bundles, with a perivascular and interstitial infiltrate constituted by lymphocytes and plasma cells in the dermis. The second is characterized by an inflammatory infiltrate mainly constituted by eosinophils along the deep fascia and the adjacent subcutaneous tissue.

Finally, granulomatous mycosis fungoides and myelogenous leukemia should also be ruled out, as reported by Tomasini and Pippione in 2002.

Pathogenesis of IGDA is still unknown but the presence of high titre autoantibodies has been thought to be involved. It was speculated that the precipitation of immune complexes into dermal vessels or their diffusion into dermal interstitium is responsible for collagen...
fibre degeneration and granulomatous changes. In this pathogenetic mechanism a TH-1 immune response and an increase in lymphocytes apoptosis may also be involved.\textsuperscript{6, 10}

IGDA has been reported in association with autoimmune diseases such as rheumatoid arthritis, LE, autoimmune thyroiditis, inflammatory bowel disease, vitiligo and hemolytic anemia, but also in association with systemic mycoses, polyfibromatosis and malignancies.\textsuperscript{5}

The course of the disease is frequently chronic or recurrent, especially when IGDA presents with the rope sign, but there are reports of complete healing after different therapies or even spontaneously, especially when IGDA presents with papules and plaques.\textsuperscript{2, 5}

There is no standardized treatment for IGDA. Therapies may be disappointing and include systemic or topical corticosteroids, hydroxychloroquine, dapsone, methotrexate, isotretinone, acitretin, esters of fumaric acid, erythromycin, mycophenolate mofetil, azathioprine, ciclosporine, etanercept, infliximab, and tocilizumab.\textsuperscript{12} It is, however, important to underline that anti-TNF\(\alpha\) drugs may be a cause of IGDR.\textsuperscript{13}

Conclusions

In conclusion, Ackerman’s syndrome is a rare distinct entity characterized by the combination of rheumatoid symptoms and cutaneous lesions. The rope sign at the axillae is the typical clinical feature that can help physicians make an early diagnosis, but it is rare.Histology is usually characteristic and shows a dermal inflammatory infiltrate, with a predominance of histiocytes, localized interstitially and in a palisaded array between collagen fibers, which show signs of degeneration. IGDA may show a variety of different clinical and histological features and dermatologists should be aware of this.
CASE REPORT

Gianotti-Crosti syndrome associated with Ebstein-Barr virus and Parvovirus B-19 coinfection in a male adult: case report and review of the literature

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Gianotti-Crosti syndrome (GCS) is a self-limiting, mostly childhood-appearing, cutaneous eruption with characteristic symmetric areal distribution. The original cases, described by Gianotti in 1955, were associated with hepatitis B virus infection, but other viral and bacterial infections, as well as immunizations, have been implicated in etiology of this condition. Adult cases are rare and have been reported almost exclusively in women. We present the case of a 20-year-old Caucasian man who had typical clinical presentation: monomorphic, pink-to-flesh-colored or erythematous papules and papulovesicles localized symmetrically over the extensor surfaces of the extremities, buttocks and the face; some lesions were detected on knees, elbows and palms, as well. Laboratory tests revealed slight bilirubin and alanine aminotransaminase elevation. Serology tests demonstrated antibodies against Epstein-Barr virus and parvovirus B-19. Histology of skin biopsy specimens revealed a vesicular dermatitis with perivascular lymphocytic infiltrate. Oral and topical corticosteroids and oral antihistamines led to complete resolution of lesions in 3 weeks. GCS is rare in adults, especially men. To the best of our knowledge, this is the fifth male adult case and the first with Parvovirus B-19 and EBV coinfection.


Key words: Acrodermatitis - Epstein-Barr virus infections - Parvovirus B-19, human.

Nevertheless, pathogenesis still remains unclear.1, 3 The assumption is that it may be an immune-mediated process requiring prior stimulation. It has a seasonal predilection,1, 2 often occurring in spring and the early summer,1 and usually resolve in 10-15 days.3 There is no specific therapy,2, 3 and in most cases no treatment is necessary.1 The histopathology is non-specific and variable.2

The GCS has been described in the adults only exceptionally, with just 21 patients reported,5-19 17 women6-15, 17, 19 and 4 men.5, 16, 18

We present the case of male adult patient, Epstein-
GCS ASSOCIATED WITH B-19 AND EBV COINFECTION

Case report

A 20-year-old Caucasian male of Serbian nationality was admitted to our Clinic for sudden bilateral and symmetric papular eruption of two-week duration. The patient was in good general health. He had not received any medication nor did he have any recent vaccination. He denied prodromal symptoms. The rash developed initially on the forearms, later involving the upper arms, shoulders, buttocks and, finally, face and the neck. Eventually, few lesions showed on the trunk (on the chests and on the back), and on the palms and soles (Figure 1). The lesions were small (2 to 5 mm) erythematous papules and papulo-vesicles that developed in several attacks with gradually increasing frequency and the intensity. The eruption was followed by pruritus, and on the left forearm Köebner phenomenon was noticed. The patient had no fever or lymphadenopathy.

Laboratory examination revealed slightly elevated levels of alanine aminotransferase (ALT-46 U/L), total (26.7 U/L) and direct bilirubin.

Figure 1.—A) Clinical presentation of Gianotti-Crosti syndrome: erythematous papular and papulo-vesicular lesions on the face, shoulders, elbows, forearms, hands and trunk. Köebner’s phenomenon on the right forearm; B) erythematous papular and papulo-vesicular lesions on the forearms, hands, wrists and palms.

Figure 2.—A) Vesicle in moderately acanthotic epidermis, and superficial perivascular lymphocytic infiltrates - hematoxylin-eosin stain; B) original magnification x100; CD8 positive cells in superficial perivascular lymphocytic infiltrate - streptavidin-biotin; original magnification x200.
rubin (5 U/L), while complete blood count showed a slight relative neutropenia (42%). Other serum parameters and urinalysis were normal. Serum IgE level was also normal and direct immunofluorescent test of lesional skin revealed no deposition of immunoreactants. On serologic investigation (ELISA) positive IgM and IgG antibodies to EBV, as well as Parvo B19 IgM antibodies were found. Other serologic tests (HBs antigen, hepatitis C virus (HCV), human immunodeficiency virus (HIV), parainfluenza 1 and 3, respiratory syncytial virus, cytomegalovirus (CMV), Mycoplasma pneumoniae, Borrelia Burgdorferi) were all negative. Abdominal echosonography was normal. Lesional histopathology demonstrated hyperkeratosis, moderate irregular acanthosis, and mild spongiosis in the epidermis, with centrally located intraepidermal vesicle filled with proteinaceous fluid and neutrophils under the parakeratotic scale (Figure 2A). Superficial and deep perivascular lymphocytic infiltrates in the dermis were composed of CD4+ and CD8+ T cells (Figure 2B). Immunohistochemical staining of EBV latent membrane antigen (LMP-1) was negative in dermal infiltrate.

Based on clinicopathological features, in correlation with the serologic and laboratory tests, the diagnosis of GCS has been made. Oral prednisolone (0.5 mg per kg with gradually decreasing doses during three weeks) and antihistamines were administered, as well as topical corticosteroids (fluocinonide 0.05%) and emollients. The lesions start to resolve, with slight desquamation, in a following 10 days and complete recovery occurred in 3 weeks. The repeated biochemical test showed normal complete blood count, ALT and bilirubin.

Discussion

GCS is a relatively common disease, seen worldwide, but accurate incidence is difficult to estimate because this entity is often misdiagnosed.

GCS primarily affects children, but there are case reports of GCS in adults, although still a minority compared with those in infants. From the first adult case (32-year-old male), published by Voglino and Papa in 1973, only 21 adult patients with this disease have been reported thus far, 17 women and 4 men (Table I).

GCS is considered a dermatosis with neither gender nor racial predilection in children, although Tilly et al. have reported that it is more frequent in boys. Most of the patients with GCS are between 3 months and 16 years old, with the peak incidence between 1 and 6 years of age. More than 90% of patients are younger than 4 years. According to the published data, in adult patients average age was 30.4 years (range 17-45 years). All women were in childbearing age and one was pregnant, suggesting the possibility that hormonal factors might play a role in the disease development. That could also be an explanation for the striking gender difference in adult patients (female-to-male ratio 3.4:1).

According to current knowledge, key etiological factor of GCS are microbes. Historically, viral infections were the first etiological factors connected with this entity. HBV was established as the first causative viral agent and it was previously thought that hepatitis B virus exclusively induce GCS. Over the time, HBV became less often evidenced in GCS patients, even in developing countries where HBV is quite common, perhaps due to a hepatitis B immunization.

Table I.—Gianotti-Crosti syndrome in adults - Literature review.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Sex</th>
<th>Age</th>
<th>Cause</th>
</tr>
</thead>
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<tr>
<td>Voglino et al.</td>
<td>1</td>
<td>M</td>
<td>32</td>
<td>Unclear</td>
</tr>
<tr>
<td>Maleville et al.</td>
<td>2</td>
<td>F</td>
<td>19/55</td>
<td>Paul-Bunell +/HBV</td>
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<tr>
<td>Claudy et al.</td>
<td>3</td>
<td>F</td>
<td>17/25/27</td>
<td>HBsAg+</td>
</tr>
<tr>
<td>Ramon et al.</td>
<td>1</td>
<td>F</td>
<td>31</td>
<td>HBV</td>
</tr>
<tr>
<td>Giam et al.</td>
<td>1</td>
<td>F</td>
<td>24</td>
<td>Unclear (HBsAg excluded)</td>
</tr>
<tr>
<td>Cambiaghi et al.</td>
<td>1</td>
<td>F</td>
<td>28</td>
<td>Influenza immunization</td>
</tr>
<tr>
<td>Mempel et al.</td>
<td>1</td>
<td>F</td>
<td>26</td>
<td>EBV</td>
</tr>
<tr>
<td>Niitsuma et al.</td>
<td>1</td>
<td>F</td>
<td>20</td>
<td>HBV</td>
</tr>
<tr>
<td>Gibbs et al.</td>
<td>2</td>
<td>F</td>
<td>44/45</td>
<td>Unclear (HBsAg, Enterovirus, Adenovirus, Mycoplasma, Chlamidia excluded)</td>
</tr>
<tr>
<td>Chuh et al.</td>
<td>1</td>
<td>F</td>
<td>23</td>
<td>Unclear (HBsAg, HHV 6, HHV 7 excluded)</td>
</tr>
<tr>
<td>Manoharan et al.</td>
<td>1</td>
<td>F</td>
<td>44</td>
<td>Mycoplasma pneumoniae</td>
</tr>
<tr>
<td>Turhan et al.</td>
<td>1</td>
<td>M</td>
<td>21</td>
<td>HBsAg+</td>
</tr>
<tr>
<td>Ting et al.</td>
<td>2</td>
<td>F</td>
<td>37/21</td>
<td>Unclear (Varicella, EBV, HCV, Parvo B19, Streptococcus pyogenes excluded)</td>
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<tr>
<td>Coccione et al.</td>
<td>2</td>
<td>M</td>
<td>43/43</td>
<td>HIV, HBsAg, HBeAg, HIV, HBsAg, HBeAg, HBeAg</td>
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<tr>
<td>Iorizzo et al.</td>
<td>1</td>
<td>F</td>
<td>20</td>
<td>Unclear (HBsAg excluded)</td>
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<tr>
<td>Present case</td>
<td>1</td>
<td>M</td>
<td>23</td>
<td>EBV, Parvo B19</td>
</tr>
</tbody>
</table>

F: female; M: male; EBV: Epstein-Barr virus; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B core antigen; HBeAg: hepatitis B e antigen; HIV: human herpesvirus; HCV: hepatitis C virus; HIV: human immunodeficiency virus.
EBV is considered the most common etiological factor of GCS in USA, either as an initial infection or as reactivation. In addition to HVB and EBV, many other viruses have been documented as triggers of GCS, and this eruption may also occur following some bacterial infection or vaccinations (Table II).

The majority of GCS in adults, as well as in children, were caused by viral infection. Most of them, seven patients, had HBV, and two patients had EBV. In one report, authors assumed that the patient had an asymptomatic EBV and CMV coinfection, but it was not proved. Coccinolone et al., in 2011, first reported viral co-infection (HHV and HBV) in two male adult patients and that is the only report of GCS eruption in adults with the virus coinfection, prior to the case. So far, our case is the first report of EBV and Parvovirus B-19 coinfection. In eight adult patients (36.4%) the triggering factor was unclear, and in some of them certain possible associations were excluded. This is similar to children, in whom the causative agent remained unknown in about 50% of all patients.

Although more cases are needed to get firmer conclusions, existing data allow us to postulate that the viral associated agents in adults differ from those in children, where EBV is the most common triggering factor. The possible explanation could be the fact that EBV is common in children and rare as a new infection in adults, in whom HBV is still the most common cause. Association of viruses, bacteria and immunization with the occurrence of GCS indicates possible infectious-allergic pathway and mechanism in the developing of this disease, although it is not proved yet. The fact that children with slightly modified immune system, such as those with atopic dermatitis, are more frequently affected, supports such assumption. The genetic factors or immunologic imbalance could be possible explanation why GCS in much more frequent in persons with atopic history or dermatitis, as they might reflect a special reaction pattern to some common stimuli. Until now, direct interaction between immune-competent cells and viral antigen in GCS-skin-lesions has not been proved, neither viral particles or viral antigens have been confirmed in skin lesions. In some children, who developed GCS after receiving vaccinations, the hypothesis of possible immunological modifications by a viral infection was proposed, because most of such patients had clinically apparent or subclinical viral infection at the time of immunization.

There are some differences in clinical presentation between adults and children as well. One of unanswered questions is why the course of the disease is much milder among children than in the adults. Possible etiologic factors in Gianotti-Crosti syndrome.

<table>
<thead>
<tr>
<th>Viruses</th>
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<th>Postimmunization</th>
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<tbody>
<tr>
<td>Hepatitis A virus 1, 2, 3, 20</td>
<td>Bartonella henselae 1, 2, 3, 20</td>
<td>Smallpox vaccination 3</td>
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<tr>
<td>Hepatitis C 1</td>
<td>Mycoplasma pneumoniae 1, 2, 3</td>
<td>Diphtheria pertussis vaccine 2, 3, 20</td>
</tr>
<tr>
<td>Cytomegalovirus 1, 2, 3, 20</td>
<td>Beta-hemolytic streptococci 3, 20</td>
<td>Diphtheria-vaccinia 1</td>
</tr>
<tr>
<td>Human herpes virus 6 1, 2, 3, 20</td>
<td>A group 1</td>
<td>Oral polio vaccine 1, 2, 3</td>
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<td>Coxsackievirus 1, 2, 3, 20</td>
<td>Mycobacterium aviumintracellulare 30</td>
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<td>Naisseria meningitides 22</td>
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<td>Parvovirus B 19 1, 2, 3, 20</td>
<td>Borrelia burgdorferi 1, 2, 3</td>
<td>Measles, measles-mumps-rubella 1, 2, 3, 20</td>
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<td>Molluscum contagiosum 2, 3, 20</td>
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<td>Bacillus-Calmette-Guerin (BCG) 1, 2, 3</td>
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<td>Respiratory syncytial virus 1, 2, 3, 20</td>
<td></td>
<td>Influenza 1, 2, 3</td>
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<td>Mumps virus 1, 2, 3, 20</td>
<td></td>
<td>Hepatitis A vaccine 2, 3</td>
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<tr>
<td>Parainfluenza virus 1 type 1, 2, 3, 20</td>
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<td>Hepatitis B vaccine 1, 2, 3</td>
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<td>Echovirus 1, 2 type 9 3, 20</td>
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<td>Japanese encephalitis 1, 2, 3</td>
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<td>Influenza H1N1 1, 2, 3</td>
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<tr>
<td>Paravaccinia-Orf virus 20</td>
<td></td>
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</table>
sible explanation could be different response to viral infection mediated by immature immune system of infants.11

Morphology of lesions does not differ significantly between adults and children – in adults GCS has been presented mostly as the erythematous papulo-macular or papulo-vesicular eruption, what is, also, the classical presentation in children.1-3 The only unusual presentation in adults, in contrast to classical GCS, has been pale perilesional halo about some erythematous, incompletely blanchable papules, reported in two male patients, HIV-HBV co-infected.13

Lesions on the trunk, as unusual localization, were noted in our case as well as two other male patients18 who also had viral coinfection and another male patient, with HBV.16 Predominantly involved areas in children are acral regions, extensor aspects of the extremities, tights, buttocks, and face.1-4 Rarely, the trunk, knees, elbows, antecubital and popliteal surfaces could be involved.1-3 Palms and soles are usually spread.1 Our patient showed lesions on elbows and knees, antecubital fossae and on palms and the soles. Iorizzo et al.19 also reported patient with lesions on knees and elbows, Manoharan et al.15 presented patient with lesions on the knees and Gibss et al.13 reported patient with lesions on the palms and soles.

The duration of rash in adult patients varied from 1 week15 to 25 months.18 In four adult patients6, 10, 14 the duration was not stated. Mean duration of skin changes in adults was 38 days (5.4 weeks). In children lesions heal over 10 to 60 days, but sometimes process can be very rapid (5 days) or very long (12 months).3 All male adult patients had prolonged skin changes duration,7, 11, 21 except our patient whose changes resolved in five weeks, which is approximately the average duration in adults. In one male patient the cutaneous lesions disappeared in 45 days,10 in another in 61 days.21 In other two male patients the exanthema lasted for 4 months and 25 months,7 which might be due to HIV-associated immunosuppression, although a lengthy duration of skin manifestations was not a feature in HIV positive children with GCS.3

Considering non-cutaneous (systemic) symptoms, in eleven adult patients (52.3%) abnormal liver function tests have been reported,5, 7, 12, 15, 16, 18, 19 including all males, as in our case. Most of the patients with abnormal liver tests had HBV (7 patients),7, 8, 16, 18 two of them having HBV and HIV co-infection;8 one patient had Myco-

plasma pneumonia,15 and in three patients the cause was not identified.5, 12, 19 It is different from children in whom hepatic involvement is uncommon,3 and if it is present, mostly EBV or CMV were detected, whereas HBV is much rarely the cause.3

Hepatomegaly, which is the most frequent clinical finding in children 3 has been reported only in one female 8 and in two male adult patients.5, 16 Two adult patients had icteric hepatitis,5, 18 and in both of them viral infection (HBV) was the cause. That is uncommon clinical presentation in children - if hepatitis is presented, only anicteric form is seen.1-3 Lymphadenopathy has been noted in seven adult patients 5-8 which makes 33.3% of all adult cases and that is similar percentage as in children (25-35%).2 Pruritus was reported in nine patients,13-19 as well as in our case. Considering only male patients, pruritus was present in three of them.16, 18 In children with GCS pruritus is not among the common symptoms.1, 2

Our patient had slight neutropenia that has also been noticed in another adult male patient, where it was more pronounced.18 That patient also had viral coinfection, but it was HIV and HBV combination.18 In children, lymphocytosis or lymphopenia may be found in peripheral blood.1, 3 Sometimes, increased number of monocytes is present, mostly in patients with EBV.1, 3

Considering histology, it is important to notice that the histologic findings of GCS are highly variable and not specific.1-3 The histopathologic picture may include acanthosis, hyperkeratosis, occasional focal parakeratosis, focal spongiosis, and psoriasiform epidermal hyperplasia; lichenoid histology has also been reported.4 There is a slight difference between vesicular and non-vesicular presentation. The vesicular form is characterized by striking epidermal changes with mild acanthosis accompanied by diffuse spongiosis and vesicles. Langhans cells are the dominant cells in the vesicles. In the papillary dermis an intense lymphocytic perivascular infiltrate consisting of T cells and dendritic cells can be seen, similar to many other inflammatory dermatoses.3 In the non-vesicular variant there may be moderate acanthosis and focal parakeratosis in the epidermis as well as the spongiosis. In the dermis superficial or deep infiltrate may be present, composed of lymphocytes and some histiocytes.3 There is a hypothesis that the variety in histopathologic changes reflects the diversity of etiological factors, meaning that different histologic
pictures are created by different agents. Only in three adult patients with pruritic lesions eosinophils have been identified among lymphocytic infiltrate. Other patients, as well as ours who also had significant pruritus, did not show eosinophilic infiltrate. The exact cause of pruritus in these cases remains unclear. Among the adult male patients, vesicular histopathological pattern has been found only in our case. CD4+ and CD8+ T cells represent the majority of the lymphocytes in the perivascular infiltrate. It has been described that cytotoxic T cells seems to be a special feature of EBV-induced GCS. In our case the same immunophenotype of lymphocytic infiltrate has been observed. Immuno-histochemical analysis of EBV antigens has been rarely performed, providing negative staining with both EBV-encoded nuclear antigen (EBNA2) and EBV-latent membrane antigen (LMP-1).

Since the histopathologic picture of GCS is nonspecific, the diagnosis of GCS cannot be based on this finding alone. Although in most children it is established on clinical findings, the diagnosis should be made by the combination of clinical history, common cutaneous findings, general symptoms, along with the histopathological features and laboratory tests, especially in adults in whom this entity is quite rare.

Conclusions

To the best of our knowledge, this is the fifth male adult case of GCS and the first one with Parvovirus B-19 and EBV coinfection. Also, considering histopathologic findings, this is the first male adult case with vesicular changes. As it has been suggested, GCS in adults may not be as uncommon as previously thought, but physicians probably might not consider this disease in adults. In diagnostic terms, the final conclusion should be made according to all the relevant facts (history, clinical features, laboratory, histology and appropriate serology testing).

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Hidradenoma papilliferum: diagnostic challenge

Dear Editor,

A 22 years old woman was referred to our Dermatological Clinic with a 2-month-history of a painless and rapidly growing vulvar lesion. Physical examination revealed a 1x0.7 cm sized, solitary, palpable reddish nodular mass on the left labia minora. The lesion appeared ulcerated with unevenly distributed grayish and whitish areas (Figure 1).

The patient’s past personal history was negative for sexually transmitted diseases, her gynecological history was positive for endometriosis. The lesion was asymptomatic and the patient complained fluctuation bleeding not associated with the menstrual cycle. Dermoscopy showed atrophic area and anomalous vascularity characterized by telangiectasia and branched and convoluted capillaries (Figure 2). A 1.7x1.3 cm sized excisional biopsy was performed.

The histological examination through hematoxylin-eosin procedure showed acanthosis and hyperkeratosis of the epidermis (Figure 3A) with dermal architecture characterized by several glandular structures organized in nests (Figure 3B). Many of them were small and well-delimited; the others were larger with cystic dilatation and pseudopapillar pattern. The lumina were surrounded by a layer of columnar epithelial cells with apocrine differentiation (Figure 3C). In the stroma there were focal fibrous and inflammatory areas with aggregates of plasma cells and lymphocytes (Figure 3D).

On immunohistochemistry, epithelial cells express positivity for low molecular weight keratins (CAM 5.2), epithelial membrane antigen (EMA) and estrogen receptors and negativity for carcinoembryonic antigen (CEA).

The clinical and microscopic features of the lesion allowed us to postulate the diagnosis: acanthosis and hyperkeratosis of the epidermis allowed us to exclude the diagnosis of ameloblastic melanoma, suspected for the dermoscopic features. We excluded endometriosis owing to the CEA negativity, the absence of endometrial stromal cell, the evidence of apocrine secretion and the negative clinical history of catamenial growing or bleeding. Although the stromal lymphoplasmacellular inflammatory component is not as typical as syringocystadenoma papilliferum, the site of the lesion

Figure 1.—A 1x0.7 cm sized, solitary, reddish nodular mass on the left labia minora.

Figure 2.—Dermoscopy shows atrophic area and anomalous vascularity characterized by telangiectasia and branched and convoluted capillaries (original magnification 30x).
Despite the benign nature of the lesion and the rare malignant transformation, surgical excision is the treatment of choice. HP shows a wide variety of clinical and histopathological presentations which makes the diagnosis of this tumor very complex.5, 8, 9 Clinically and dermoscopically, our lesion mimicked amelanotic melanoma: recently Panasiti et al.9 described a case, similar to ours, emphasizing the role of dermoscopy for the diagnosis of adnexal tumors and the necessity of a histological examination to rule out malignancy. The path to reach the diagnosis has been very tortuous: the lesion presented a complex and heterogeneous histology mimicking, both tumors originating from apocrine glands like syringocystadenoma papilliferum, and inflammatory/heterotopic disease like endometriosis.

Figure 3.—Histopathology shows (A) acanthosis and hyperkeratosis of the epidermis; with (B) dermal architecture characterized by several glandular structures organized in nests; C) the lumina were surrounded by a layer of columnar epithelial cells; and (D) in the stroma there were focal fibrous and inflammatory areas with aggregates of plasma cells and lymphocytes (Hematoxylin and eosin stain; original magnification [a] 4x [b] 10x [c] 16x [d] 20x).
Several authors included syringocystadenoma papilliferum in the histological differential diagnosis of HP when stromal focal areas infiltrated by plasma cells and lymphocytes are present, like in our case.5–8

Dermatologists should be aware that, owing to the difficulty to differentiate this lesion from other malignant and benign conditions both clinically and histologically, the diagnosis of HP requires a multidisciplinary approach with collaboration between clinician, dermatologist, and anatomopathologist.

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A. Campanati and K. Giuliodori contributed equally to the paper.

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Annular lichen planus on the mammary areola: an unusual localization

Dear Editor,

A 53-year-old woman presented to our outpatient clinic with a 2-month history of asymptomatic lesion on her left mammary areola. Closer examination revealed a single, well demarcated, reddish-purple annular papular plaque on the edge of the areola (Figure 1). There were no other lesions on her skin or on mucous membrane. The lesion was totally surgically removed. The histopathologic examination showed an interface dermatitis characterized by mild hyperkeratosis, acanthosis with prominent granular layer and vacuolar basal degeneration of the epidermis. A focal band-like lymphocytic infiltrate with scattered melanophages was observed in the superficial dermis (Figure 2A-D). The histopathological findings were consistent with lichen planus in its annular variant. Lichen planus is a chronic, pruriginous inflammatory dermatosis affecting skin, mucous, scalp and nails. Many variants in the clinical presentation have been described and are generally categorized according to the configuration of the lesions, morphology or site of involvement. Annular lichen planus (ALP) is a rare type of lichen planus and the lesions are reported in only 3-7% of patients with lichen planus, mainly black patients.1 The most typical localization of ALP is represented by in-

Figure 1.—Annular lichen on the edge of the areola, near multiple hyperplastic glands.
tertriginous sites and genitalia, especially penis and scrotum. Genital lesions are present in about 25% of patients with lichen planus, however isolated ALP of the genitalia is rarely reported. ALP commonly develops as an arcuate grouping of individual papules that develop rings or peripheral extension of clustered papules with central clearing. Indeed annular lichen lesions grow through two different processes; the first, named “papule-formed ring” is characterized by several lichenoid papules converging in a circinate layout, creating the annular shape; while in the “ring-formed papules” configuration, the annular lesion is due to the central involution of a flat papule, growing peripherally with raised borders. The mechanisms leading to the formation of these particular annular lesions are not yet known. Friedman and Hashimoto proposed a lymphocyte-mediated elastolysis process, responsible for the annular and rarely atrophic appearance of the lesions; while conducting an immunohistochemical analysis, Ohta et al. discovered that the intercellular adhesion molecule 1 (ICAM-1), expressed by the peripheral keratinocytes of the active lesions, could have a key role. We describe the first case of isolated ALP localized on the mammary areola in a 53-year-old woman. We have noticed a particular similarity between the mucosa of the genitalia and the mammary areola, justifying this particular localization of ALP. In fact, if we compare the areola with a part of female genitals, affected by lichen lesions as the labia, we can observe several common features. The histological examination reveals similar aspects with an epidermis and epithelium interdigitating deeply with long papillae on a highly vascularized connective tissue and a rich presence of sebaceous, sweat glands. We present this case because ALP should be considered among the potential diagnosis

Figure 2.—A, B) Mild hyperkeratosis of the stratum corneum, focal thickening of the granular layer. Hematoxylin and eosin, original magnification X 5-X 10. C, D) A band-like lymphocytic infiltrate at the dermal-epidermal junction with hydropic degeneration of the basal layer and melanophages in the papillary dermis. Haematoxylin and eosin, original magnification X 20-X 40.
of the lesions affecting the mammary areola, even in those patients who don’t present any other lichen planus-like lesions on their skin or mucous membrane. We also think that the clinical identification of this type of lesion on the mammary areola is also important to distinguish it from other dermatologic disorders, like granuloma an- numlare, syphilis, porokeratosis and basal cell carcinoma which can appear in this site.

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Figure 1.—Papules with excoriated nodules surrounded by edematous erythema on the trunk. Erosions and scabs could also be seen on the surface of some of the lesions (Figure 1). He had no history of systemic disease. Skin biopsy taken from the back revealed epidermal hyperkeratosis and acanthosis with vertical fibrotic bands in the dermal papilla. Neutrophils were seen around blood vessels and interstitially without eosinophils or bullous formation (Figure 2). The patient was diagnosed with prurigo nodularis according to the clinical and pathological examination. After a two-month treatment regimen of oral thalidomide combined with cetirizine and topical betamethasone, there were no signs of improvement. This led us to suspect PN as an alternative diagnosis. Serological examination was performed on peripheral blood from the patient. Indirect immunofluorescence using 1% NaCl split skin was performed using antihuman IgG antiserum as a secondary antibody. Circulating antibasement membrane zone (BMZ) antibody reacted with the epidermal side of the split (Figure 3). ELISA was used to measure IgG against BP230 and the NC16a domain of BP180. The index values were 18 and 31 IU, respectively (normal <9). Thus, a diagnosis of PN was established. The patient was given methylprednisolone (40 mg/d), tetracycline (0.5g t.i.d.) and nicotinamide (0.3g t.i.d.). After two weeks of treatment the skin lesions began to recover, and methylprednisolone was gradually reduced. During the six-month follow-up there was no recurrence of pruritic lesions and antibody titers of BP180 and

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Diagnosis of pemphigoid nodularis with serological assay

Dear Editor,

Pemphigoid nodularis (PN) is a rare variant of bullous pemphigoid. Patients with pemphigoid nodularis have clinical features of prurigo nodularis in combination with clinical or immunologic characteristics of bullous pemphigoid.1,2 We herein report a case of PN in a patient who presented with clinical and histological features mimicking prurigo nodularis. The diagnosis was established by positive indirect immunofluorescence (IIF) on salt-split skin and enzyme linked immunosorbent assay (ELISA). These results emphasize the importance of conducting serological examination when pruritic nodules occur on elderly patients.

A 63-year-old man with a one-year history of severe, generalized pruritus was referred to our department in February 2013. A year earlier, without any apparent causes, he had developed red papules and nodules on his trunk accompanied by severe pruritus. Two months prior to his visit to our clinic, the pruritic lesions worsened. Dermatological examination showed papules and nodules surrounded by edematous erythema on the trunk. Erosions and scabs could also be seen on the surface of some of the lesions (Figure 1). He had no history of systemic disease. Skin biopsy taken from the back revealed epidermal hyperkeratosis and acanthosis with vertical fibrotic bands in the dermal papilla. Neutrophils were seen around blood vessels and interstitially without eosinophils or bullous formation (Figure 2). The patient was diagnosed with prurigo nodularis according to the clinical and pathological examination. After a two-month treatment regimen of oral thalidomide combined with cetirizine and topical betamethasone, there were no signs of improvement. This led us to suspect PN as an alternative diagnosis. Serological examination was performed on peripheral blood from the patient. Indirect immunofluorescence using 1% NaCl split skin was performed using antihuman IgG antiserum as a secondary antibody. Circulating antibasement membrane zone (BMZ) antibody reacted with the epidermal side of the split (Figure 3). ELISA was used to measure IgG against BP230 and the NC16a domain of BP180. The index values were 18 and 31 IU, respectively (normal <9). Thus, a diagnosis of PN was established. The patient was given methylprednisolone (40 mg/d), tetracycline (0.5g t.i.d.) and nicotinamide (0.3g t.i.d.). After two weeks of treatment the skin lesions began to recover, and methylprednisolone was gradually reduced. During the six-month follow-up there was no recurrence of pruritic lesions and antibody titers of BP180 and...
BP230 gradually declined to normal (4.2 and 5.1 IU, respectively).

PN is a rare subtype of pemphigoid bullous that clinically mimic prurigo nodularis. Accurate diagnosis of PN depends on the identification of antibody deposits on the epidermal side of the 1 M NaCl split skin. Diagnosis of PN can be challenging, especially when the typical clinical signs, such as blisters, are absent. It is important to consider the diagnosis of PN when blister formation or resistance to conventional treatment occurs in a patient with prurigo nodularis. The histological manifestations of PN include hyperkeratosis and acanthosis of the epidermis and inflammatory cell infiltrates in the papilla of the dermis. While eosinophils can be seen in most patients with PN, Powell et al.\(^3\) reported four PN patients in whom eosinophil infiltration was not obvious. In the current case report the clinical and pathological features did not immediately point to a diagnosis of PN, therefore, direct immunofluorescence was not performed during the first visit. The patient was thus mistreated for prurigo nodularis. A diagnosis of PN was subsequently suspected due to resistance to therapy. Serological examination demonstrated antibasement antibodies in the patient’s serum. Once the correct diagnosis of PN was made, the patient responded quickly to systemic steroid therapy.

Lehman et al.\(^4\) reported a case of prurigo nodularis with negative direct immunofluorescence that was diagnosed as PN through positive serological findings. This indicates that a negative direct immunofluorescence (DIF) finding does not rule out PN, and serological examination is necessary to establish the diagnosis.

The pathogenesis of PN may be related to destruction of the basement membrane induced by the itch/scratch cycle of prurigo nodularis. The exposed antigen in the basement membrane triggers the production of antibodies. Both the BP180 and BP230 antibodies were detected in the serum of our patient. The titer of BP180 was low and this may explain the fact that no blister formation was found throughout the course of the disease. BP230 antibody has also been previously reported in patients with PN;\(^5\) however, the exact mechanisms of the BP230 antibody in the development of the disease are still unknown.

In conclusion, we diagnosed a case of PN in a patient with clinical and pathologic features mimicking prurigo nodularis. When multiple pruritic nodules develop in elder patients, a skin biopsy along with DIF would be appropriate initial examinations for excluding PN. If DIF is negative, further investigation with serological assays is necessary to complete the workup.

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Misleading mycosis fungoides: perichondritis

Dear Editor,

Mycosis fungoides (MF), the most common type of cutaneous T-cell lymphoma (CTCL), can manifest in a variety of clinical and histological forms. Nodular lesions - characterizing the stage T3 of the ISCL/EORTC revision to the classification of MF and Sézary syndrome - have a cephalic localization more frequently than plaques lesions. However, only few cases of ear, nose and throat (ENT) localization of MF are described in literature. To the best of our knowledge, this is the first reported case of perichondritis-like MF.

A forty years old woman comes to our attention reporting a 10-years history of recurrent external and media otitis with perichondritis treated by otorhinolaryngologists leading to a persistent deformation of the left ear.

At our first observation, an intense oedema and erythema of the pinna were present; the lobule was spared. The external auditory canal resulted partially obliterated by a swelling vegetation on the floor of the external meatus (Figure 1A).

In the absence of purulent secretions, some small preauricular lymph nodes were palpable.

Antibiotic therapy led to reduction of acute inflammatory manifestations (Figure 1B), whereas infiltration of the pinna persisted.

A complete skin examination allows the detection of diffuse patches and papules on the entire body surface with accentuation in not sun-exposed areas. Slightly erythematous papules were few millimetres in diameters, sometimes confluent, infiltrated and finely scaly (Figure 2A-C).

In order to obtain a histological characterization, a papule of the gluteal region was biopsied. The histological and immunohistochemical scenario was consistent with the diagnosis of MF (Figure 3).

A skin biopsy repeated on the auricular lesion confirmed the clinical suspicion of nodular MF localization. The disease was staged as IIB (EORTC T3, No, Mo, Bo).

Recombinant Interferon alfa-2b (IFN-alfa) was started together with a local radiation therapy of the auricular tumour (30 Gy in 15 fractions) leading to a partial response (radiologically confirmed).

After a 10 months follow-up, patient remains in partial remission. The lesion of the ear markedly reduced its infiltrative component (Figure 2C).

To date no further systemic antibiotics was necessary in the absence of new infective episodes.

Figure 1.—A) Edema and erythema of the left pinna; B) good response of tumours lesion of the ear after RT, with reduction in soft tissue swelling and partial regression of the vegetation on the floor of the external meatus.

Figure 2.—Infiltrated and finely scaly diffuse patches and papules on the entire body surface.
MF, a low-grade lymphoproliferative disorder, is the most common type of CTCL. Diagnosis of MF can be challenging due to highly variable presentations and the sometimes unspecific characteristics of histological findings at initial disease stages. A considerable number of reports since 1996 have documented MF mimicking more than twenty different dermatoses. In every chronic cutaneous disease resistant to treatment, lymphoma has to be considered.

Whole body inspection often allows to reach the correct diagnosis towards the identification of typical MF lesions besides atypical manifestations.

In the natural history of the disease, skin-homing neoplastic T cells produce patches, plaques and then tumours or erythroderma. Tumours usually appear later than plaques lesions and have most frequently a cephalic localization. Nevertheless, cases of “nodular MF d’emblée” account for about 5% of total MF diagnosis. In our case the nodular lesion of the ear, if taken alone, was clinically and histologically misleading and interpreted as a perichondritis. In order to reach the correct diagnosis it was crucial to take all clinical, histological and immunohistochemical information together.

This case underlines the importance of an accurate clinical approach to the patients in order to overcome the diagnostic challenges of atypical MF presentations.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.


Letter to the Editor

Linear basal cell carcinoma: clinical significance and better surgical approach

Dear Editor,

Linear basal cell carcinoma (LBCC) was first reported as a distinct condition in 1985 by Lewis as a rare morphological variant of basal cell carcinoma. This report described a 20 mm linear pigmented BCC on the left cheek of a 73-year-old man. From the histological point of view, this tumor was of the nodular subtype of BCC, but because of the linearity of the tumor, it was classified as a separate condition. Since that time, only 45 cases have been reported in the literature as a distinct morphological entity. Of these 45 cases, 39 are from the review “Linear basal cell carcinoma: a distinct condition?”, by Al-Niaimi and Lyon. More objectively define linear BCC as a lesion that appears to extend preferentially in one direction, resulting in a lesion with relatively straight borders and with a length much greater than the width (with a ratio of at least 3:1). Histologically, it does not have its own peculiarities but it may vary from a predominantly nodular to an aggressive subtype. Having managed 11 cases during our clinical experience and reviewed 45 cases in the literature, we want to study the correlation between clinical characteristics, arrangement and therapeutic outcome.

A total of 11 patients, 5 women and 6 men, mean age 66.2 (male mean age 73.8, female mean age 57.8, range 41-92 years), Fitzpatrick skin types I-IV, mainly II-III, with the clinical diagnosis of LBCC, were surgically treated in our Outpatient Service (Table I). A previous laser resurfacing treatment in association with the site of the linear BCC was described in only one case, while other two cases of LBCC were relapses after previous treatments with photodynamic therapy (PDT). The study design was approved by
the local Institutional Review Board in compliance with the Helsinki Declaration, and the patients were enrolled after obtaining a detailed personal history (skin type, clinical symptoms, health conditions, previous medications, life-style) and informed consent for treatment. A local injection of mepivacaine chlorhydrate 2% (Mepivacaina Angelini®, ACRAF, Rome) was employed before the beginning of the surgical excision. For all the lesions we kept a free surgical edge to 1 mm with the aid of surgical magnifier (Heine C.2.3x) to identify the real extent of lesions. The wound was covered by some strips (Leukosan® Strip, Germany). Photographs were taken with a Nikon Coolpix 990 digital camera connected with Heine Delta20 for dermatoscopy, before the treatment and at the 16-week follow-up. The photos were standardized using the same camera, setting, twin flash, ambient light and chin holder to guarantee the same distance.

The lower eyelid was the most frequently site (N.=6; 55%) followed by the neck (N.=3; 27%) and then by the preauricular area (N.=2; 18%). From the clinical point of view, the most frequently variant was the nodular (N.=6; 55%), of which five cases of nodular- ulcerative BCC. Moreover we reported three cases of morpheic BCC (N.=3; 27%) and two cases of pigmented BCC (N.=18%). Most tumours were histologically nodular (N.=9; 81%), of which one case of nodular-morpheic BCC, two cases of nodular-pigmented BCC and two cases of nodular-ulcerative BCC. The method of definitive treatment used was surgical excision, histologically confirmed. Up to the present, no recurrences were observed. We would like to emphasize the particular relation between the linear shape of the lesions and the Langer’s lines of the face and neck (Figure 1).

Most of the linear tumors reported were aligned along relaxed skin tension lines. BCCs depend on stromal interactions for progression and growth, and Pierard et al.4 found that in the reticular dermis, skin tension lines have an anatomical counterpart consisting of a preferential parallel orientation and a straightening of thin collagen bundles and elastic fibers. These parallel bundles lie perpendicular to the direction of contraction of the underlying muscles. The linearity of the tumor may therefore be due in part to the stromal interactions with relaxed skin tension lines, coupled with muscle contraction constraining growth in one direction. Chopra et al.5 suggested that the linearity can be explained by lateral limitations to the spread of the lesion resulting from reactive dermal fibrosis. This may explain the linearity of the tumors appearing on the background of fibrotic dermis after radiation, trauma and possibly previous scarring. Other authors have speculated on the possibility of a Koebner phenomenon, based on its linear patterns and the fact that these tumors are oriented along the tension lines of the skin. However, there were only 9 patients with a history of trauma among the 56 cases reported.

Our survey and our data confirm the relation between the linear shape and Langer’s lines of the face and neck. These assumptions include limitation of lateral spread of the lesion by dermal fibrosis or interactions of the stroma with Langer’s lines.6 Moreover, this is confirmed by the histological examination of correctly oriented samples, in which tumor cells are arranged in elongated strands parallel to skin surface (Figure 2.2b). This aspect of proliferation of the neoplastic cells according to a linear arrangement makes possible a closer surgical excision and, consequently, a better esthetic outcome. Our position contrasts with what reported by Lim et al., who asserted that LBCC showed a potential increase of the subclinical spreading.7

The practice guidelines of NCCN (National Comprehensive Cancer Network) about the Basal cell skin cancer ranks the BCC in high and low risk based on the chance of recurrence.8 Thus, despite our series of patients presenting various forms of BCC of high risk, both because of the seat, both because of the histological subtype, the clinical morphology and the linear arrangement of these tumors make surgical therapy more effective from the point of view of the radicality. In addition, we emphasize the fact that the arrangement of BCC along the Langer’s lines allows to maintain the lateral margin of excision also only 1mm, ensuring complete excision, besides allowing an optimal esthetic result.

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Figure 2.—2.1) Morpheic linear BCC on the lower eyelid; 2.1a) outcome of surgical treatment; 2.2) morpheic linear partially ulcerated BCC in the periocular area; 2.2a) outcome of surgical treatment; 2.2b) particular histological examination of the lesion 1.2 that showed features of sclerodermiform type, with groups of tumoral cells arranged in elongated strands parallel to cutaneous surface (H&E original magnification 50); 2.3) nodular linear BCC on the lower eyelid; 2.4) nodular linear partially ulcerated BCC on the lower eyelid; 2.5) morpheic linear BCC on the lower eyelid; 2.6) pigmented linear BCC on the left lower eyelid; 2.7) morpheic linear partially ulcerated BCC in the preauricular area; 2.8) three distinct nodular BCCs in the preauricular area aligned along a linear scar outcome of a previous treatment of LBCC with PDT; 2.9) nodular linear ulcerated BCC on the neck; 2.10) pigmented linear BCC on the neck; 2.10a) dermoscopy image of pigmented linear BCC of the neck; 2.11) nodular linear partially ulcerated BCC on the neck.
Table I.—Clinical and histological data about our eleven cases of LBCC.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Anatomical location</th>
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<td>Morphea</td>
<td>Superficial</td>
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<td>2</td>
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<td>Lower eyelid</td>
<td>Morphea</td>
<td>Nodular-morphea</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>Lower eyelid</td>
<td>Nodular</td>
<td>Nodular</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>Lower eyelid</td>
<td>Nodular- ulcerative</td>
<td>Nodular</td>
</tr>
<tr>
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<td>M</td>
<td>Lower eyelid</td>
<td>Morphea- ulcerative</td>
<td>Morphea</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
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</tr>
<tr>
<td>7</td>
<td>M</td>
<td>Preauricular area</td>
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</tr>
<tr>
<td>8</td>
<td>M</td>
<td>Preauricular area</td>
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<tr>
<td>9</td>
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Bullous pemphigoid induced by escitalopram in a patient with depression

Dear Editor,

A 78-year-old woman was referred to our department for examination because of pruritic, tense blisters on an erythematous base located on the trunk and limbs. The patient’s history was significant for major depression, diagnosed in 2012. When the patient presented to our Department she was treated with escitalopram (10 mg/day), started one month before, and the psychiatric disease was under control with this drug. Two days after starting escitalopram treatment (the patient had never used this drug before), she had experienced firstly pruritus, erythema and then, about after ten days, blisters that had spread quickly to cover the entire body (Figure 1). However, the patient and her general practitioner not considered that the assumption of escitalopram could be potentially implicated in the pathogenesis of the disease, so this drug had not been suspended immediately. A skin biopsy was performed: histological examination from a fresh bulla revealed a subepidermal blister with superficial dermal inflammation consisting of lymphocytes, histio-

Figure 1.—Clinical presentation on admission.
cytes, and eosinophils. Results of direct immunofluorescence of a perilesional biopsy sample were positive for linear deposits of IgG and C3 at the basement membrane zone (BMZ). Indirect immunofluorescence (IF) was negative. Immunoblot analysis of epidermal extracts revealed that serum autoantibodies were directed to BP180 and BP230. On the basis of these findings, we made a diagnosis of “drug induced bullous pemphigoid” (DIBP). We started therapy with betamethasone (15 mg/day), which achieved a modest clinical improvement. This therapy was continued for three weeks before evaluating it as ineffective. So, before the remission of the dermatitis, betamethasone was completely discontinued. Challenge-dechallenge test with escitalopram was performed by us and was very helpful for the diagnosis. In fact, definitive resolution of bullous pemphigoid (BP) was evident only after the withdrawal of escitalopram. However, the rechallenge test was not performed, since it is not ethically correct, according to our opinion. The patient was kept in follow-up after the resolution of the lesions for about 5 months.

BP is an autoimmune blistering disease typically affecting the elderly. The onset and course of BP depend on a variable interaction between predisposing and inducing factors. Facilitating factors in genetically predisposed individuals are various (drug intake, physical agents, and viral infections). Among them, drugs have also been reported as exogenous factors capable of inducing BP. DIBP is a term introduced to designate cases of BP presenting clinical, histological, and immunopathological features identical or closely similar to those of the idiopathic disease, induced by systemic ingestion or local use of certain drugs. A recent review on drug-induced pemphigoid suggests that some clinical and histopathological aspects can help in discriminating these forms from the naive ones (for example, the younger age of onset, the marked eosinophilia in serum and skin, the possible presence of necrotic keratinocytes and thrombus formation among histological aspects, the rapid response to treatment with oral corticosteroids and the rare relapses).

Of course, these criteria are not mandatory, but the presence of at least some of these (in our patient only eosinophilia in skin and the absence of relapses) could add more value to the diagnosis.

However, although the occurrence of BP two days after the consumption of escitalopram suggested a correlation between the drug intake and the disease, we tried to provide another evidence. In particular, we used one of the questionnaires for adverse drug reactions (in particular, the Naranjo algorithm).

Both systemic and topical treatments can induce BP. The inducing medications can be grouped according to their chemical structure. The majority of the systemic drugs contains or releases sulfhydryl groups (thiols: penicillamine, captopril, penicillin, furosemide, some cephalosporins). Also drugs containing a phenol ring (phenols: some cephalosporins, aspirin) and non-thiol non-phenol drugs (ACE-inhibitors other than captopril, most NSAIDs, nifedipine, biological modifiers of the immune response such vaccines, escitalopram) can facilitate the onset of BP. Escitalopram is an antidepressant drug of the selective serotonin reuptake inhibitor (SSRI) class. This is, to our knowledge, the first case of BP induced by escitalopram.

In all BP patients it is essential to consider the possibility of drug-induction. Therefore, a careful investigation on drug intake is necessary and useful, since the prompt discontinuation of the “culprit” drug may result in rapid improvement or even resolutive cure.

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Rosacea and abatacept: the first report of a possible correlation

Dear Editor,

A 48-year-old woman with rheumatoid arthritis (RA), treated with etanercept, developed a mild form of rosacea. For this reason,
the drug was replaced with abatacept (10 mg/kg at weeks 0, 2, 4). During the first administration of abatacept, the patient developed mild flushing, nausea and headache, corresponding to an acute infusion reaction, which subsided without infusion related side effects. However, after a few time, she complained of worsening of skin manifestations: persistent facial erythema with development of acne-like papules and pustules. The standardized skin surface brushing showed an increase of Demodex folliculorum on patient’s cheeks. So we made diagnosis of papulopustular rosacea and treated the patient with oral tetracyclines and metronidazole cream. We suggested to stop abatacept treatment.

Abatacept is a modulator of T-lymphocyte activation. In particular, it selectively inhibits costimulatory molecules as CD80 and CD86. Abatacept is used for treatment of RA in combination with methotrexate (MTX) in biologic-naïve patients or in patients failing prior antiTNFα therapy. Skin common side effects of abatacept are rash, alopecia and itch; nothing is reported about rosacea. The mechanisms by which abatacept induces rosacea are not known and they are certainly complex. Normally, interaction of CTLA-4 with its ligands, CD80/CD86, is required for activation of Tregs to mediate their suppressive effects. Probably abatacept, binding to CD80 and CD86, invalidates the suppressive effects of Tregs on T-effectors and, therefore, there is a wrong transfer of T-effectors population in various districts, such as skin. To the best of our knowledge, this is the first report on rosacea caused by abatacept.

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Diagnosis of high risk multisistemic Langerhans cell histiocytosis: the practical use of cytology in dermatology

Dear Editor,

A 5 month-old child presented to our department with heterogeneous cutaneous lesions (pink, erythematous and scaly papules and vesicles) localized on groin, perianal region, armpits, trunk and scalp appeared almost at second month from birth and accompanied with fever for 15 days (Figures 1, 2). Macous membranes, palms and soles were spared. He had normal birth weight,
but an elevated monocytes/eosinophils ratio (8:1; n.v.: 3:1), some istiocytic, an elevated number of metamielocytes, eosinophils and monocytes, and the absence of blast cells.

Cytology smear, taken from a recent lesion by gently scraping it with a straight scalpel (Figure 3), showed atypical Langerhans cells, with a large, hypochromic, and usually amphophilic, microvacuolated or granular cytoplasm, and a hypertrophic, hypochromic and polydimensional nucleus.

Furthermore, a skin lesion biopsy (Figure 4) showed an upper dermal and junctional accumulation of histiocytic cells with pink cytoplasm and confirming LHC diagnosis.

In the next days, we observed a reduction of blood laboratory results (hemoglobin 9.6 g/dL, RBC 3,840,000/mm³, WBC 1,000/mm³). A bone marrow biopsy showed normal cellularity,
confirmed. We started protocol therapy LCH III 2001 Multisystem Risk Patients, initially using vinblastine and prednisone (for a short period of 6 weeks), then 6-mercaptopyrurine (for a total of 12 months). After two months, the skin, pulmonary and bone marrow lesions were resolved.

LCH is a reactive proliferative disease characterized by an infiltration and accumulation of cells of the monocyte-macrophage series in the involved tissues. It is found most commonly in children. The Histiocyte Society has categorized LCH into two major groups, with significantly different prognoses: - single-system LHC, which only involves unifocal lymph node, skin, lung, pituitary or bone, multifocal bone or multiple nodes and has an excellent prognosis; - multi-systemic LHC, which involves two or more organs at diagnosis with/without evidence of organ dysfunction.1,2

In our case, the presence of skin and lung lesions was enough to classify the disease as multi-systemic LCH. Despite the early onset (before 1 year) and multi-systemic disease, prognosis was positively influenced by an early and correct diagnosis, done thanks to cytology and in correlation with radiology.

Cytological examination proves to be a rapid, practical, economic aid in establishing precise clinical diagnosis in a variety of cutaneous and mucosal lesions. Smear taking for cytology is very well tolerated as it causes negligible trauma or discomfort to the patient. Therefore, it can be performed (and, when necessary, repeated) even in the most timorous of individuals, in children, and in sites which prove difficult to biopsy (e.g. eyelids, lips, oral cavity, genitals) or where aesthetic problems may arise (the face). This is especially valuable in a setting where cytopathologist expertise may not be easily available and histopathology services are located only in big cities and are inaccessible to patients in rural areas due to the long distance and high cost involved. Unfortunately, not all dermatologists are able to carry out and interpret the results of this test. The appropriate and careful use of cytdiagnosis gives the dermatologist an operational autonomy which is by no means inferior to other procedures, which are more modern, more sophisticated, certainly more expensive, but possibly less streamlined and efficient than the plain Tzanck Test.3,4 This paper stresses that with this simple test the dermatologists can have an important diagnostic orientation, even though the diagnosis is confirmed with histopathology and immunohistochemistry.

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Classic erythema ab igne: still possible?

Dear Editor,

We present the case of a 13-years old girl admitted to Pediatric Hospital Anna Meyer of Florence for a prolonged history of anorexia nervosa of restrictive type. She was examined at our
pediatric dermatologic service for a hyperpigmentation of the abdomen which extended bilaterally over the proximal inner thighs (Figure 1). The lesions appeared without any type of desquamation and were asymptomatic. On further questioning she revealed the persistent use of heating pads to reduce the frequent episodes of abdominal pain and postprandial fullness with epigastric discomfort. On this basis a diagnosis of erythema ab igne was made. Erythema ab igne is a reticular, macular dermatosis that develops secondary to prolonged and repeated skin exposure to mild heat in the range of 43–47°C, insufficient to produce a burn; it appears generally on the shins and inner thighs after exposure to heat from a space heater, stove or fireplace in close proximity. Some cases are already been reported in the literature and recently only reports of laptop-induced erythema ab igne on the thighs and one case attributed to the automobile seat heater have been described.1,2 To the best of our knowledge only five cases of erythema ab igne are reported in the literature in young patients with eating disorder, anorexia nervosa or bulimia nervosa.3,4 Clinically it presents as a hyperpigmented livedo reticularis-like lesions and the distribution of skin involvement should mirror the heat source in question.5 The precise pathophysiology is not known, but microscopic changes include epidermal atrophy, vasodilation, and dermal deposition of melanin and hemosiderin.6 The pigmentation may persist for several months or also years and the treatment consist in the removal of the source of chronic heat exposure. Treatment of erythema ab igne is obviously aimed at the removal of the heating source. Topical tretinoin may improve the clinical appearance. Recently good results have been described with the use of a Nd:YAG laser 1064 nm.7

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Idiopathic atrophoderma of Pasini-Pierini associated with morphea: the same disease spectrum?

Dear Editor,

A 62-year-old man presented with several reddish atrophic patches on his back for three months and came to our clinic in July 2010. The skin lesions were painless, bean-sized oval, and they had no local edema and sclerosis initially, then progressed slowly. Five months ago, the patient received a treatment in another hospital because his right upper limb had linear sclerosis lesion for one year. Histopathological examination in our hospital of the linear sclerosis lesion demonstrated epidermal atrophy, dermic chronic inflammatory cell infiltration and collagen fibre hyperplasia. The diagnosis of morphea (localized scleroderma) was established. After rubbing testosterone propionate ointment, 0.1% tacrolimus ointment, the linear sclerosis lesion improved. Previously the patient was healthy without any endocrine disease, vascular disease or allergic disease. There was no family history of this disease. The patient developed normally and had no history of trauma or injection. Physical examination showed well-defined multiple fingernail-sized to kids palm-sized oval reddish atrophic patches on the back, whose surface had mild atrophy. Blood vessels under the atrophic lesions were visible (Figure 1). The lesions had no sclerosis or paresthesia either. The right upper limb had red linear sclerosis plaque and part of it was atrophic (Figure 2). No regional lymph node was touched. Laboratory tests showed that blood routine examination, urine routine examination, lupus full inspection, erythrocyte sedimentation rate, Humoral Immunity Test, anti-O and rheumatoid factor were all normal. Histopathological examination of resected patch demonstrated epidermal atrophy, dermic perivascular focal lymphocytic infiltration and unaccompanied significant collagen fibre hyperplasia (Figure 3). Basing on clinical and pathological manifestations, a diagnosis of idiopathic atrophoderma of Pasini-Pierini (IAPP) was established. The curative effect was under observation after
the patient took tripterygium wilfordii, hydroxychloroquine and vitamin E.

IAPP is a rare disease, which was first described in 1923 by Pasini. The disease can be easily misdiagnosed as morphea in clinical. It usually occurs in adults especially young women and the incidence in children is about 10%. IAPP is mostly found on the trunk especially back and often asymmetrically distributed, and it is rarely on the hands and feet, but never on the head.

It usually presents as well-defined round, oval or irregular shape, coin to palm-sized atrophic patch. It gradually increases in size. Partial cases have similar performance like morphea at their later stage. Histopathological examination mainly demonstrates epidermal atrophy, dermic non-specific inflammatory cell infiltration and unaccompanied significant collagen fiber hyperplasia.

Its exact pathogenesis remains obscure. Genetic factors, neurogenic factors, abnormal metabolism of dermatan sulphate, and immunological factors have all been implicated in the pathogenesis of IAPP. Some scholars think it might be caused by infection of borrelia.

Differential diagnosis for IAPP includes morphea (localized scleroderma), patchy atrophy, vascular atrophic poikiloderma and lipoatrophy. Morphea usually presents as a discrete circumscribed, erythematous to sclerotic plaque, often with a white center and characteristic peripheral lilac rim and has partial sclerosis initially. Patchy atrophy presents as slightly elevated flat plaque of pale white or pearl colored. Vascular atrophic poikiloderma presents as obvious inflammation mixing hyperpigmentation, hypopigmentation, telangiectasia and skin atrophy. Lipoatrophy presents as subcutaneous fat atrophy and its epiderm and color are normal.

The relationship between IAPP and scleroderma is still controversial. Some scholars speculated that IAPP was an independent disease which may have pseudo-sclerosis at its later stage, while morphea has sclerosis initially and atrophy as its sequelae. Others deduced that the disease may be the atrophic type of morphea, because sclerosis lesion can appear not only at its later stage but...
also its early stage sometimes and some patients of IAPP also have sclerosis lesions on other parts of their bodies.

It was reported that IAPP was associated with morphea, which is consistent with our case report. Ru-Zhi Z. et al. also reported that a 62-year-old woman presented with morphea-like atrophic lesions on lumbar sacral portion and thought it might be a special IAPP - abortive type or superficial type of morphea. In our case IAPP came up after morphea, so we think that IAPP and scleroderma might be the same disease spectrum. Mayo Clinic Classification identifies 5 main morphea types: plaque, generalized, bullous, linear and deep. On the basis of certain clinical and histopathological features, IAPP might be a variant of Morphea en plaque classified in a subtype of localized scleroderma.

Some scholars believed that IAPP might be a syndrome. Kopeć-Medrek et al. reported that a female patient suffering from IAPP was also diagnosed as papillary thyroid cancer, so they thought that IAPP might be a paraneoplastic syndrome. Kim et al. also reported that a 15-year-old patient suffering from juvenile idiopathic arthritis was also diagnosed as IAPP and thought it might be a Pasini-Pierini-juvenile idiopathic arthritis overlap syndrome.

The disease is benign and may be self-healing after several months or years, but in some cases, the skin lesions may appear forever.

The disease has no effective treatment, topical and systemic glucocorticoid, Vit E, retinoids, niacin, and phototherapy is optional. Hydroxychloroquine is suggested as the treatment of chronic refractory IAPP.

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An unusual manifestation in a patient with Neurofibromatosis type 1

Dear Editor,

Neurofibromatosis type 1 (NF1) (OMIM 162200), also called von Recklinghausen disease, is an autosomal dominant condition with an incidence of 1:3000 and a prevalence of 1:4000 to 1:5000.

Diagnostic criteria include at least two of the following: six or more café-au-lait spots, two neurofibromas or one plexiform neurofibroma, axillary or groin freckling, optic glioma, two Lisch nodules, bone dysplasia and first-degree relative with NF1.1

Patients with NF1 are at increased risk of developing many neoplasms, approximately four times higher than general population matched for age and gender, particularly neoplasia originated from the neural crest derivatives.2 Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia in the Western world, with an incidence of approximately 1 out of 100.000 patients for year, and usually affects individuals older than the age of 65. The majority of cases are diagnosed in asymptomatic patients with an incidental finding of lymphocytosis or lymphadenopathy.3

We report herein the extraordinary occurrence of CLL in an adult patient with NF1.

A 48-year-old man was examined for the presence of axillary freckling, café-au-lait macules and hundreds of cutaneous and subcutaneous neurofibromas spread over the entire body (Figure 1). On the basis of these findings, the diagnosis of NF1 was made. In addition, on physical examination a generalized lymphadenopathy and a marked splenomegaly were present. The patient reported fatigue and weight loss over recent months.

Hematological studies revealed the following: hemoglobin 9.4 g/dL, WBC 97x10³ µL with 93% lymphocytes and platelets 82x10³ µL.

Bone marrow examination showed diffuse infiltration of the marrow with around 82% of the cells being lymphocytes. Flow cytometry performed on the peripheral blood showed the lymphocytes to be positive for CD5, CD19, CD20 and CD23 and negative for CD10 and CD7. Cytogenetic studies did not reveal any chromosomal abnormalities.

Based on CD5/CD19 positive lymphocytosis, lymphadenopathy and thrombocytopenia, a diagnosis of CLL, Rai stage IV was made.

He was elected to undergo chemotherapy with fludarabine, cyclophosphamide and rituximab (FCR), with clinical remission. NF1 is a genetic condition which confers an increased risk of a wide range of cancers.

Although gliomas and neurofibrosarcomas are the most frequent malignant complication of NF1, it is well known that there is also an elevated risk of leukemia, particularly of chronic myeloid leukemia.

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The NF1 gene is located on chromosome 17q11.2 and encodes for a protein called neurofibrin. This protein interacts with the ras p21 protein and may regulate ras activity. Literature also suggests that activating ras mutations may result in increased T- or B-cell malignancies in animals. The association between hematologic malignancies and germline mutations of NF1 gene has been established in the pediatric setting. Children with neurofibromatosis type 1 have a 500-fold increased risk of developing a rare form of leukemia, known as juvenile myelomonocytic leukemia; a higher incidence of non-Hodgkin’s lymphoma and acute lymphoblastic leukemia has also been reported.4

In adults patients affected by NF1 the risk of malignancies is well known and increases with age, though the association between NF1 and malignant blood disorders has rarely been demonstrated.

Typical CLL is often found incidentally, on a routine laboratory evaluation. Common manifestations of the disease can be fatigue, autoimmune hemolytic anemia, frequent infections, splenomegaly, hepatomegaly, lymphadenopathy or extranodal infiltrations.3

Our database (from 1984 to 2013) contains 457 patients with NF1 who undergo regular multidisciplinary follow-up visits and none of them developed CLL so far.

To our knowledge, this is the second case of CLL in an adult patient with NF1.5

Although we cannot exclude that such association is a coincidental finding and therefore further studies are needed, we suggest to collect a thorough anamnesis, to perform an accurate skin examination with palpation of the main lymphnode stations and routine annual blood tests including complete blood count and liver function in all patients with NF1.

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Primary idiopathic anetoderma

Dear Editor,

A 32-year-old Italian woman has come to our clinic with a one-year history of progressive eruption of erythematous patches on the trunk and back.

Dermatologic examination revealed many well-defined pink patches disseminated on the trunk. On the back, older lesions became flattened and changed into wrinkled, atrophic skin. During chest bending, older lesions tended to herniate upward (Figure 1A). There were no cutaneous lesions elsewhere. The patient was otherwise in good health, and her past medical history was unremarkable.

Complete blood cell count, erythrocyte sedimentation rate, C3,
C4, anti-double-stranded-DNA, antiextractable nuclear antibodies, antinuclear antibodies, lupus anticoagulant, anticardiolipin antibody were all negative.

Excisional biopsy of a lesion on the back showed no relevant changes with hematoxyline-eosine, but staining for elastic tissue showed a loss of elastic fibers in the superficial dermis, and an almost complete absence in mid and deep dermis (Figure 1B). On these basis, we concluded for a diagnosis of primary idiopathic anetoderma.

Primary anetoderma, described for the first time by Jadassohn in 1892 1 like a “macular atrophy”, is an uncommon syndrome often idiopathic, characterized by localized areas of loss of substance and elastic tissue with flaccid skin, mainly in women aged 20-40 years, but occasionally in younger and older patients of both sexes.

The term anetoderma (anetos=slack) refers to these areas of slack skin with a loss of dermal substance on palpation and a loss of elastic tissue on histological examination.

At first, primary anetoderma was divided into the Jadassohn-Pellizzari type, where the lesions are preceded by erythema or urticaria, and the Schweninger- Buzzi type, where there are no preceding inflammatory lesions. That is today only of historical interest, because in the same patient some lesions may be preceded by inflammation and the others may not, and the prognosis and histology are the same in the two types. Histologically there is distinction between early erythematous lesions, where there could be a perivascular and less frequently interstitial infiltrate composed predominantly by lymphocytes, occasionally plasma cells and eosinophils, whereas neutrophils could be observed in very early lesions. Established lesions show no marked changes in hematoxylin and eosin-stained sections. With elastic tissue stains, elastic fibers are sparse in the superficial dermis and absent in mid dermis.2

A recent proposal of classification 3 distinguishes primary anetodermas, where the clinical manifestations of the disease are not consequence of a prior cutaneous condition, from secondary anetodermas, that include a list, constantly expanding, of causing antibodies diseases,4 such as antiphospholipid syndrome, systemic lupus erythematosus, HIV (or more generally associated to autoimmune disease) or true idiopathic form.

Up to date there is no satisfactory treatment for anetoderma. Many treatments had been used but with average results. Recently, a single case of secondary anetoderma has been treated satisfactorily with an ablative 10,600-nm fractional laser.5


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