Correspondence

Measurement of epidermal moisture content

Sir, We were interested and somewhat surprised by the results presented recently by Franconi et al., in assessment of a hydration cream by measurement of epidermal moisture content by magnetic resonance imaging (MRI). These authors measured a modification of hydration induced by a moisturiser in living epidermis and even superficial dermis.

Preliminary results by MRI have clearly established that hydration effects induced by external mechanisms are limited to the outer layers of thick stratum corneum (heel or palm). Other methods employed to study hydration phenomena on thin stratum corneum areas, and confocal microscopy, for example, showed no modification of epidermis (thickness or shape of the cells) after 15 min of water immersion of the dorsal aspect of the hand, whereas clear modifications of stratum corneum were observed. We also performed the same experiment by MRI with an improved depth pixel size of 35 μm (unpublished results), and no difference in T1 or T2 values in living epidermis was established. These results are in agreement with the well-known role of the barrier function of the stratum corneum in protection. So, it is surprising that MRI of the skin with a depth pixel size of 86 μm can detect hydration effects at the level of the wrist where stratum corneum is thin.

However, we admit that a moisturiser could have induced such modifications, but we would require consistent results based on a rigorous statistical analysis of the data. This is unfortunately lacking in this paper.

Concerning the short-term study where it is more difficult to imagine immediate modifications of hydration induced in the living epidermis, firstly, a reproducibility of the method of about 5% cannot be assessed by Figure 1 only. We need absolute T2 values and a precise statistical analysis in order to estimate it, as it is well established that the measurement of NMR parameters present important variations in reproducibility.

Second, data presented do not allow a conclusion relating to ‘a correlation between skin dryness and ΔT2 in living epidermis.

Concerning the long-term study, many factors can be involved in the T2 modifications and only by a comparison with a control zone on the same or on the other wrist, and with cautious variance analysis could one evaluate the assumptions of the authors.

In summary, we do not deny that epidermal hydration can be modified by cosmetic products, but we consider that such modifications are not proven by this paper.

References


Reply

Sir, We are grateful to Quereux and Bittoun for their comments on our paper.

They state that hydration of epidermis is known to be limited to stratum corneum (SC), so that they were surprised by our results showing ‘modifications of hydration in living epidermis and even in superficial dermis’. In fact, these authors referred to tests of skin hydration performed on heel and palm, where SC is very thick. No hydration effect could therefore be evidenced on the inner layers of epidermis in these areas in view of the well-known role of barrier of SC. In our study, however, measurements were carried out on the wrist, a cutaneous area where SC is thinner. There it may be assumed that deeper layers of epidermis undergo modification of hydration. Incidentally, it should be mentioned that we never wrote about ‘modification of hydration in superficial dermis’ but rather only about ‘epidermis’.

They say that variations of T2 parameter we observed could not be significant in view of the reproducibility usually obtained in NMR parameter measurements. The authors based their remark on studies performed on brain. However, it is well known that T2 accuracy is specially dependent upon the homogeneity of the radiofrequency field in measurement area. Therefore, because we worked on areas much smaller than brain, homogeneity of the B1 field was very low. This point was commented on studies performed on brain. However, it is well known that T2 accuracy is specially dependent upon the homogeneity of the radiofrequency field in measurement area. Therefore, because we worked on areas much smaller than brain, homogeneity of the B1 field was very low. This point was verified experimentally using one imaging method. Moreover, in one of their studies, the authors themselves indicated having found an in vivo long-term reproducibility of approximately 3%, in experimental conditions similar to those we used.

They challenge the correlation between skin dryness and T2 variations. However, we never mentioned any such correlation but said that ‘Figures 3b, c, d demonstrate a good correlation between the shape of T2 evolution and . . . skin dryness’; subsequently, the correlation was not established with the value of T2.

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Finally, they suggest that, in our long-term study, we should have done measurements on the contralateral wrist as a reference. In fact, we performed these reference measurements to prove the validity of the comparison of $T_2$ values. Please refer to Table 1 (caption) and to the text: ‘$T_2$ was measured... both on the treated wrist and on the contralateral side (untreated)’.

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Faculte´ de me´decine, Tours
Re´sonance magne´tique
to in our medical schools as ‘piodermitis chancriforme de

Chancriform pyoderma

Sir, We read with interest the recent case report by Holmes and
Thomson. These authors erroneously ascribe to Hoffman1 the
honour of first describing chancriform pyoderma. In the
Spanish translation of the sixth and seventh German edition of
Jessner’s Handbook of Skin and Sexual Diseases,2 which
appeared in 1927, Covisa and Bejarano added an Appendix
where they described three children they saw in 1925 at the
Hospital San Juan de Dios in Madrid.4 These boys each had ‘a
lesion in the foreskin with all the characteristics of a syphilitic
chancre... and painless bilateral inguinal lymphadenopathy
was noted.’ Bacteriological studies showed ‘...the presence of
pyogenic cocci, mostly Staphylococcus’. The lesions cleared with
topical antiseptic. Covisa and Bejarano were seeing ‘a syndrome
whose description we have not been able to find, and that we are
permitted to name genital chancriform pyoderma of
children’. Microphotographs of biopsy specimens from two
cases are shown in the text. Covisa and Bejarano also predicted
that identical lesions might appear in adults, and indeed they
described in the same article two adult patients with ‘lesions
clinically very similar to syphilitic chancre, in one case on the
chin and on the upper eyelid in the other’. Excellent clinical
photographs were provided. In both patients, the presence of
Treponema pallidum was excluded, and instead, ‘direct smears from the lesions showed the presence of numerous pyogenic
cocci, mainly Staphylococcus’. Hence, the term chancriform
pyoderma was coined.

In other Spanish standard classical textbooks, Covisa and
Bejarano are recognized as authors of the first description of
chancriform pyoderma5 and this entity is commonly referred
to in our medical schools as ‘piodermitis chancriforme de
Covisa y Bejarano’. However, it is sad that most non-Spanish
standard textbooks of dermatology fail to mention these two
outstanding dermatologists.

Isolated lichen planus of the lip

Sir, In a recent issue Itin et al. reported the first well-
documented case of isolated lichen planus of the lip.1 We
wish to report a further case. A 51-year-old man presented with a 9-month history of irritation and scaliness of the lower lip. He had no previous history of any skin condition and in particular nothing to suggest lichen planus. His general health was excellent. He had not been receiving any oral medication in the months preceding the development of symptoms and had not experienced excessive sun exposure. He was a non-smoker and there were no dental fillings in his front teeth.

Examination revealed irregular white streaks forming a reticular pattern along the entire length of the lower lip (Fig. 1). The upper lip showed no abnormality. No other mucosal site was affected and the skin, hair and nails were normal.

Biopsy from the lower lip showed a dense band-like lymphohistiocytic infiltrate in the papillary dermis with basal cell liquefaction and Civatte bodies. These features are consistent with lichen planus. In the weeks following the biopsy spontaneous improvement of the lesions on the lip was noted. Treatment was commenced with a potent topical steroid (betamethasone valerate 0.1% cream for 2 weeks).

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Computer screening for early detection of melanoma—is there a future?

Sn, I enjoyed the review by Hall et al. with its clear definition of the pre-requisites regarding image analysis of melanocytic lesions. However, some studies investigating the benefits and pre-requisites of this image analysis in detail are missing.

One study, based on the use of colour and texture image analysis in a data set of 350 malignant melanoma and benign melanocytic lesions, demonstrated a classification rate higher than 90%. Most of the requirements for image acquisition, image segmentation, colour analysis, and classification, mentioned by Hall et al., were met in this article. In addition, a subsequent study showed that the combination of conventional and dermatoscopic (skin surface microscopy at 10× magnification) images leads to a further improvement in diagnostic accuracy.

Furthermore, the classification rates obtained by the use of directly digitized lesions in comparison with the use of digitized colour slides were compared. A reliable and efficient method for identifying malignant melanoma was obtained by using both image acquisition techniques.

The use of the dermatoscope, which we developed as a handheld instrument for skin surface microscopy at 10× magnification, enabled us to define the ABCD rule of dermatoscopy, which allows a semi-quantitative analysis of the features: asymmetry, border, colour, and differential structure during the examination of a patient offering a high sensitivity for diagnosing malignant melanoma.

I agree with Hall et al. that an entirely automatic classification of melanocytic lesions is not possible at present. However, digital imaging of dermatoscopic images provides a very useful technique monitoring pigmented skin lesions because the current and previous image can be compared on the screen simultaneously and the clinician can act directly upon this information.

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References


Conjunctival oedema: a side-effect of cyclosporin and a consequence of obesity

Sn, We report a 43-year-old woman with obesity (weight 173 kg) and pyoderma gangrenosum which was resistant to treatment with minocycline, prednisolone (40 mg/day), nicotinamide and azathioprine. She was treated with cyclosporin, 5 mg/kg per day according to her actual body weight (i.e. a daily dose of 850 mg), and 4 weeks later developed bilateral conjunctival oedema. This resolved when the cyclosporin dose was reduced to 5 mg/kg per day according to her lean body mass of 75 kg, based on height–weight tables. The patient’s past history included hidradenitis suppurativa and acanthosis nigricans due to obesity, but she had no history of peripheral oedema, or thyroid disease and her routine blood count, biochemical profile, autoantibody tests, rheumatoid factor and serum/urine electrophoresis were all normal.

During the first 6 weeks of treatment with cyclosporin, the pyoderma gangrenosum healed completely, but a rise in her serum creatinine was noted from the average baseline of 89 to 130 μmol/l at week 5. Her cyclosporin trough level was 367 ng/ml (usual 0–200). Her dose of cyclosporin was adjusted to her lean body mass, which is 75 kg, giving a dose of 355 mg daily at 5 mg/kg per day. The dose of cyclosporin was reduced to 280 mg daily because of a continuing rise in her serum creatinine. At this dose there was an improvement in her conjunctival oedema and a reduction in her serum creatinine, but her hidradenitis suppurativa and pyoderma gangrenosum worsened.
The side-effects of cyclosporin are usually dose dependent and respond to a dose reduction. The most common is an increase in the serum creatinine, which, along with the blood pressure, needs to be monitored. There is wide variation in the absorption, metabolism and elimination of cyclosporin. When used to prevent transplant rejection, cyclosporin is prescribed at a dose dependent on the patient’s weight and adjusted to give a therapeutic trough range of 100–200 ng/ml. The administration of cyclosporin to obese patients, at doses based on actual body weight, frequently results in early and acute nephrotoxicity. It is suggested that there is an inverse correlation between body weight and the incidence of cyclosporin nephrotoxicity. In renal transplant recipients, prescribing cyclosporin on a per kilogram basis is unfounded and carries the risk of underdosing lightweight patients and overdosing heavy ones. It has been proposed that a cyclosporin dose of approximately three times the desired cyclosporin target level (in nanograms per millilitre of parent drug) should provide a reasonable initial estimate for the required dosage.

Obesity can alter drug pharmacokinetics in many ways. Lipophilic drugs, such as cyclosporin, are proportionately distributed into excess fat. There is no significant impact of obesity on cyclosporin absorption and the drug distribution and systemic clearance are similar in non-obese and obese patients when normalized to ideal body weight or body surface area. The distribution of cyclosporin is limited primarily to lean body mass.

Sandoz Pharmaceuticals have no previous report of conjunctival oedema being caused by cyclosporin, although oedema is a recognized side-effect. The mechanism of peripheral oedema is not well understood, although it may be related to fluid retention. In our patient, the conjunctival oedema may be an idiosyncratic reaction. We emphasize that cyclosporin should be given according to ideal body weight, in obese patients, in order to avoid toxicity.

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References

Cervical intraepithelial neoplasia in a patient receiving long-term cyclosporin for the treatment of severe plaque psoriasis

Sir, The efficacy of cyclosporin in treating psoriasis and other chronic skin disorders is well established. The risk factors for the development of cyclosporin-induced toxicity, including renal toxicity and hypertension, have been assessed, and an estimation of the ‘safe’ duration of treatment has been proposed. However, the potential effects of long-term immunosuppression by low dose cyclosporin are not clearly defined. We report a patient who developed cervical intraepithelial neoplasia (CIN III) after 43 months of cyclosporin treatment for chronic plaque psoriasis.

A 49-year-old woman with plaque psoriasis, of 10 years duration, entered into an audit evaluating the efficacy and safety of cyclosporin treatment. The Ethics Committee approved the study and informed written consent was obtained. Physical examination and laboratory assessment revealed no abnormalities. A routine Papanicolaou smear was performed, in November 1990, and showed no evidence of inflammation or dystrophic changes. The patient had no prior history of human papilloma virus (HPV) infection, had never received immunosuppressive agents, and was human immunodeficiency virus (HIV) negative. Cyclosporin was commenced, at a dose of 3 mg/kg per day, in November 1990, with clinical and laboratory examinations performed at regular intervals. No Papanicolaou smears were performed during treatment. After 40 months treatment, the erythrocyte sedimentation rate increased to 45 mm in the first hour, and clinical assessment included a Papanicolaou smear. A large zone of inflammation was present surrounding the cervical orifice, and several biopsies revealed inflammatory and haemorrhagic changes. A cone biopsy was performed. This revealed CIN grade III of the cervix, associated with multinucleated cells with viral inclusions.

An increased incidence of malignancy including non-Hodgkin’s lymphoma, Kaposi’s sarcoma and squamous cell carcinoma, has been demonstrated in transplant recipients receiving immunosuppressive therapy with cyclosporin. High doses, combined immunosuppressive regimens, and prolonged treatment periods, are considered as risk factors. In patients receiving low-dose cyclosporin for psoriasis, only an increased risk of cutaneous squamous cell carcinoma has been demonstrated.

An increased incidence of viral infections, and re-activation of viral infection, has also been demonstrated in patients receiving prolonged immunosuppressive therapy. An increased rate of detection of HPV type 16, accompanied by an increased prevalence of CIN, has been reported in allograft recipients in comparison to a control population. Recent studies have demonstrated the presence of transforming genes encoded by HPV type 16. Several reports have described an association between the duration of immunosuppression and the development of HPV infection. In the transplant population, routine Papanicolaou smears are performed before the commencement of immunosuppression, and thereafter on a regular basis. Routine Papanicolaou smears have not been included in clinical studies of cyclosporin in the treatment of psoriasis and, thus, controlled studies are needed to evaluate the

incidence of HPV infection and squamous cell carcinoma of the cervix in this patient population. These studies are necessary to help define the ‘safe’ duration of immunosuppression by cyclosporin in the non-transplant population.

We suggest that all female patients should undergo a gynaecological examination, with a Papanicolaou smear, before receiving cyclosporin for psoriasis, and the presence of HPV infection should be a relative contraindication to cyclosporin. In those patients in whom cyclosporin is the only viable therapeutic alternative, sequential cervical smears must be performed. Once CIN develops, cyclosporin should be discontinued, and early diagnosis and surgical intervention are important. During the course of treatment with cyclosporin, all female patients should receive a Papanicolaou smear every 6 months.

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References

Splenosis in exit gunshot wound

Sr., A 49-year-old male was admitted for excision of a nodule under an old cutaneous scar. He had suffered a gunshot wound 20 years previously. The missile entered through the upper abdomen, tore the spleen and the upper pole of the left kidney and left the body below the inferior edge of the left scapula. He underwent urgent exploratory laparotomy and splenectomy and left total nephrectomy were performed. The patient was asymptomatic for nearly 17 years until 3 years before his current admission when he noticed a subcutaneous mass in the exit wound scar. The man was otherwise healthy.

On examination the patient had a mid-line abdominal scar and a left subscapular scar. Embedded within the latter was a mobile, soft, non-tender round mass, 5 cm in diameter. The clinical diagnosis of the referring physician was lipoma. Excision was performed. Surgery was uneventful with complete healing.

Macroscopic examination revealed a few oval–round nodules measuring 0.5–0.8 cm, consisting of dark brown soft tissue.

Histological examination revealed fragments of fatty tissue admixed with striated muscle surrounding nodules composed of normal splenic tissue (Fig. 1). Tissue was mainly red pulp with small foci of white pulp (lymphatic tissue) (Fig. 2). There were new and old haemorrhages with deposition of haemosiderin granules especially at the periphery of the splenic nodules.

Splenosis is defined as the heterotopic autotransplantation of splenic tissue, first described by Buchbinder and Lipkof in a case report from 1939.1 The main cause of splenosis is splenic rupture following abdominal trauma, in which fragments of splenic tissue are seeded throughout the peritoneal cavity. The capacity of splenic tissue to differentiate allows the structural elements of the splenosis nodule to form.2 We report a case of splenosis of subcutaneous tissue in a scar of a gunshot wound.

Figure 1. Excisional biopsy specimen. On the right hand side there is an area of splenic tissue (red pulp). Opposite this, fatty and muscular layers are seen (haematoxylin and eosin, ×70).
Although it has been reported in the pelvis, pericardium and thorax, subcutaneous splenosis is an extremely rare event which has previously been reported in only six cases (Table 1). In four of these cases, autografts of splenic tissue were found in old abdominal surgical scars, while one case presented at the site of a gunshot exit wound. Skinner and Hurtelou reported a case of autotransplantation of splenic tissue into the pleural space. The patient sustained a shrapnel injury that ruptured his spleen and caused a tear in his diaphragm. Ten years later splenosis was found at the site of the shrapnel penetration in the thorax. The mechanism of splenosis in that case resembles our case in which the missile carried fragments of splenic tissue that were implanted in the exit wound site. Later, the tissue differentiated, enlarged, and formed an asymptomatic subcutaneous nodule. While the immunological function of splenosis tissue has not been completely elucidated, it probably compensates in part for the asplenic state. Therefore it is recommended that these splenic implants should not be removed. Splenosis is rarely symptomatic. Sometimes it can produce symptoms, usually due to the effect of the mass and pressure on adjacent structures which may cause intestinal obstruction, intra-abdominal and gastrointestinal bleeding. Although subcutaneous splenosis is a rare complication of splenic rupture, it should be considered in the differential diagnosis of tumours in abdominal and thoracic scars with a prior history of splenic rupture.

**Table 1. Reported cases of subcutaneous splenosis**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Sex</th>
<th>Age</th>
<th>Cause of splenic trauma</th>
<th>Site of implantation</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaw and Shafi</td>
<td>1937</td>
<td>M</td>
<td>20</td>
<td>Blunt trauma</td>
<td>Abdominal scar</td>
<td>Found at autopsy</td>
</tr>
<tr>
<td>Gill</td>
<td>1944</td>
<td>M</td>
<td>54</td>
<td>Gunshot wound</td>
<td>Exit gunshot wound</td>
<td>Subcutaneous mass</td>
</tr>
<tr>
<td>Raper</td>
<td>1951</td>
<td>M</td>
<td>30</td>
<td>?</td>
<td>Abdominal scar</td>
<td>Found at autopsy</td>
</tr>
<tr>
<td>Cohen</td>
<td>1954</td>
<td>M</td>
<td>30</td>
<td>Splenectomy for ITP</td>
<td>Abdominal scar</td>
<td>Subcutaneous mass</td>
</tr>
<tr>
<td>Baack et al.</td>
<td>1990</td>
<td>F</td>
<td>38</td>
<td>Blunt trauma (car accident)</td>
<td>Abdominal scar</td>
<td>Incidental finding on CT scan</td>
</tr>
<tr>
<td>Grantham and Clore</td>
<td>1990</td>
<td>M</td>
<td>57</td>
<td>Shrapnel injury</td>
<td>Abdominal scar</td>
<td></td>
</tr>
</tbody>
</table>

CT, computed tomography; ITP, immune thrombocytopenic purpura.

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Interface dermatitis in acute varicella-zoster virus infection: demonstration of varicella-zoster virus DNA in keratinocytes by in situ polymerase chain reaction

Sns, The classical histological findings of acute varicella-zoster (VZV) infection are well known. However, a variety of other histopathological changes have also been described. Molecular diagnostic methods permit the demonstration of DNA and RNA of infectious agents in tissue. Recent technical advances allow amplification of DNA and RNA within a single cell in a tissue section. Amplification product was most intense overlying necrotic keratinocytes. We did not see similar staining in the stratum corneum or in the colour-generating reagents to keratinous material. However, we did not see similar staining in the stratum corneum or in the negative controls. Additionally, hot-start in situ PCR was used to minimize mispriming.

This report demonstrates that VZV infection can be associated with an interface reaction, similar to that of HSV. With this in mind, cases of erythema multiforme that do not contain HSV or VZV DNA, and of unexplained interface dermatitis, might be screened by PCR using a variety of probes to look for DNA or RNA of other infectious agents. These results raise questions regarding the role of infectious agents in the generation of necrotic keratinocytes in interface processes. Perhaps intracellular viral load correlates with the development of individual cell necrosis.

References


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**The significance of chevron nails**

*SIR,* In describing ‘herringbone’ nails, Parry et al. wonder whether mild forms exist (but are) not recognized. They do, as will be confirmed by a generation of Newcastle registrars and students who, although too often bored by their demonstration, will, I hope, continue to prefer my term ‘chevron nails’, because unlike herringbones, they have no central spine. Juvenile chevron nails are very common; they point distally and are usually found as one or two oblique ridges superimposed upon the better known axial ridges. Despite their triviality, I have always found they make a useful pedagogic exercise in working out biological mechanisms and understanding what they tell us, in this case about nail development.

There are only two possible groups of mechanism, one with oblique and the other with axial growth, but whilst the first may be more easily understood mechanistically, the second is more easily achieved biologically.

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**Figure 1.** Prominent amplification product overlies keratinocytes adjacent to a viral vesicle, in varicella-zoster viral infection, after *in situ* polymerase chain reaction (oxidized diaminobenzidine and haematoxylin; ×40).

**Figure 2.** Amplification product, appearing as dark staining overlying nuclei, is present in scattered necrotic keratinocytes removed from the herpetic blister (oxidized diaminobenzidine and haematoxylin; ×400)
(a) by a progressively greater rate of nail growth laterally than centrally, inducing oblique movement;
(b) by oblique positioning of the direction of growth without change of rate.

Both these possibilities can be excluded, however, the first because it implies an inconceivable plasticity in the formed nail plate, the second because it would give a double thickness along a central ridge of nail, and both because they cannot explain the coexistence of oblique and axial ridges.

2 Axial growth producing oblique ridges which could occur in two different ways:
(a) synchronous growth changes: the implication here is that, regardless of the anatomical territory of the juvenile nail root, its functional growing edge corresponds to a chevron, and not the digit-end shape of the adult lunula. Thus, when the whole of the growing edge functions in concert, as in the formation of a Beau’s line, a distally pointing chevron will be produced corresponding to the shape of that functional edge; however, because growth remains axial, axial ridges can also be formed. Presumably with growth, the root edge shapes up to adult life and the obliquity of youth gives way to a rounded maturity;
(b) sequential growth: in this mechanism, a localized variation in nail production rate in the functional edge of the root’s growth zone is ‘propagated’, as a wave, from the centre of the nail to its sides, the rate of propagation controlling the angle of the chevron apex (indeed chevron angle could be used to measure the rate of propagation). As with 2(a), axial ridges can be formed concurrently.

All that is needed to confirm the argument is observation of a linear groove made horizontally across the proximal surface of the juvenile nail, to show it remains horizontal with growth (or one on each side of the nail at 90° to the chevron ridges, to show no medial movement). Sadly, however, I have never managed to persuade my bored listeners to do this simple study, whilst I have left it undone in order that the pedagogic game may continue. So, until the arrogance of logic has its essential testing by experiment, I will maintain the consequences of my axial explanation.

Koebner phenomenon in pemphigus vulgaris

SIR, The Koebner phenomenon is well known to occur in psoriasis, vitiligo and lichen planus, but few cases have been described in pemphigus vulgaris. We describe two patients with pemphigus vulgaris who showed the Koebner phenomenon.

A 45-year-old woman presented with a 3-month history of blisters on the abdomen and upper thigh. Four months previously she had had an appendicectomy with the concurrent excision of a caecal mass, later found to be due to amoebiasis, through a median lower abdominal incision. Examination revealed tense blisters localised to the appendicectomy scar with, on the median abdominal scar, crusting and eczema (Fig. 1). A solitary blister was present on the thigh. She had erosions on the palate. A diagnosis of pemphigus vulgaris as made and she was commenced on oral prednisolone and azathioprine with a good response.

A 19-year-old man who had had pemphigus vulgaris for 18 months, controlled on prednisolone 10 mg daily, suffered a relapse of his condition. His dose of prednisolone was increased to 60 mg daily, with control of the blistering. He sustained a linear injury to the right shin. The wound healed but, after 2 weeks, blisters and crusting developed along its entire length. A biopsy showed the changes of pemphigus vulgaris. The blisters at the site of trauma healed within one month and his pemphigus is currently in remission.

The Koebner phenomenon in pemphigus vulgaris has been described in two patients. In another two, the lesions appeared at sites of trauma, but the authors did not mention the possibility of this being due to the Koebner phenomenon. A possible explanation of the Koebner phenomenon in pemphigus vulgaris can be proposed. The pemphigus antigen is a glycoprotein which makes up part of the desmosomes. The scarring process within a damaged epidermis may have defective or deficient levels of pemphigus antigens so that even low titres of pemphigus autoantibodies can induce blistering lesions within a scar. Similarly, a scarred dermis may fail to promote normal differentiation of keratinocytes, with the effect that the keratinocytes may be more vulnerable to low titres of pemphigus auto-antibodies.

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References

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Bullous pemphigoid induced by vaccination

Sirs, Drs Venning and Wojnarowska reported a patient with bullous pemphigoid that was possibly induced by a routine tetanus booster injection.1 We have observed two cases of bullous pemphigoid developing 24 h after vaccination.

Patient 1. An 84-year-old man suddenly developed a blistering eruption in November 1994. The eruption began the day after an anti-influenza vaccination (Previgrip). He has been on long-term buflomedil and amiodarone for arteriosclerosis and arrhythmia. On examination, there were tense blisters on palms and soles associated with urticarial erythematous skin lesions over sides of trunk. Histology of a skin lesion showed a subepidermal bulla. Direct immunofluorescence (DIF) revealed linear deposition of immunoglobulin G (IgG) and C3 along the basement membrane zone (BMZ). Circulating anti-BMZ antibody was detected. These features were compatible with the diagnosis of bullous pemphigoid. The eruption was initially controlled by local administration of clobetasol propionate.

Patient 2. An 84-year-old woman was referred with a generalized blistering eruption which was preceded by itching for 1 month. Pruritus first appeared 24 h after a routine tetanus vaccine booster injection. She had previously been in good health and was only taking indapamide for hypertension. The clinical diagnosis of bullous pemphigoid was confirmed by histological and immunological results showing subepidermal blister and linear deposition of C3 along the BMZ with circulating anti-BMZ antibody respectively. The patient was successfully treated by application of clobetasol propionate.

A large variety of precipitating factors may induce bullous pemphigoid.2 Recently, two publications have emphasized the possible role of vaccination in inducing or flaring bullous pemphigoid. Venning and Wojnarowska have observed a case similar to our second patient: they described an 83-year-old man who developed generalized pruritus 24 h after a tetanus booster injection followed 3 weeks later by blisters.1 Bodokh et al. reported two cases of exacerbation of bullous pemphigoid following anti-influenza vaccination (Vaxigrip).2 The association of vaccination and appearance or exacerbation of bullous pemphigoid may be coincidental. Nevertheless in our two patients a relationship seems likely since before vaccination they were free of disease and skin manifestations appeared 24 h after the injection. The mechanism of induction of bullous pemphigoid by vaccination is not clear. Vaccination could reveal a subclinical bullous pemphigoid by enhancing the autoimmune response: this may be related to bullous pemphigoid “induced” by infections.1,3

References

Necrobiosis lipoidica of the glans penis

Sir. Necrobiosis lipoidica of the glans penis may manifest as painful recurrent ulcers on an erythematous base. There are two reported cases,\(^1,2\) and here we report a third. A 57-year old man gave a 2-year history of recurrent painful ulceration of the glans. Ulcers healed spontaneously within 2 or 3 weeks, leaving a depressed scar. He was otherwise well and had no history of diabetes. Examination revealed erythema of the glans with two ulcers and some small depressed scars (Fig. 1). The ulcers measured 5 and 2 mm in diameter and had sharply defined raised borders, with a yellowish base. He had no lymphadenopathy. Full blood count, erythrocyte sedimentation rate, and glucose tolerance test were normal. He had normal liver and renal function, and venereal disease research laboratory test was negative. Direct immunofluorescence of a swab for herpes simplex was negative. Skin biopsy showed partial ulceration of the epidermis, with large areas of necrosis of dermal collagen, which was surrounded, in a palisading manner, by histiocytes (Fig. 2). Some blood vessels showed a necrotizing vasculitis, but there was no perivascular lymphocytic infiltrate, and tuberculoid granulomas were not present. Stains for mucin were negative. He was treated with pentoxifylline, 400 mg three times daily. After 2 months, improvement was limited, and dipyridamole, 75 mg twice daily, and aspirin, 50 mg twice daily, were added. The ulcers healed 1 month after this and, no further ulcers have appeared after 6 months' follow-up.

Necrobiosis lipoidica is seen in 0.3–3% of diabetics.\(^3\) Sixty per cent of patients with necrobiosis lipoidica have diabetes, 20% have glucose intolerance or a family history of diabetes, and 20% have no abnormality of carbohydrate metabolism.\(^4\) In 15% of patients with necrobiosis lipoidica, skin lesions may precede the onset of diabetes mellitus, on average by a period of 2 years. Typically, necrobiosis lipoidica appears as erythematous or violaceous plaques with an atrophic yellow centre. Ulceration after minor trauma is seen in 35% of cases. The legs are affected in 85% of cases, but other body sites, including trunk, arms, face and scalp, may be affected.\(^5,7\) Involvement in less typical sites is less commonly associated with diabetes.\(^8\)

Necrobiosis lipoidica of the glans penis is uncommon. All three reported cases showed identical features of recurrent painful ulcers that healed with depressed scars and which, histologically, showed necrotic collagen with palisading granulomas. One case was associated with diabetes and necrobiosis lipoidica on the legs.\(^1\) The differential diagnosis of penile necrobiosis lipoidica includes granuloma annulare, infectious granulomatous disorders including orificial tuberculosis or syphilis, and epithelioid sarcoma. Granuloma annulare histologically shows mucin and a perivascular lymphocytic infiltrate. Orificial tuberculosis occurs in patients with active

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**Figure 1.** Ulceration and depressed scarring of the glans penis.

**Figure 2.** A large area of necrotic collagen surrounded by palisading histiocytes (×200).
tuberculosis elsewhere. The ulcers do not heal spontaneously and biopsy shows tuberculoid granulomas. Syphilis was excluded on clinical and serological grounds. Epithelioid sarcoma may rarely simulate Peyronie’s disease of the penis, and, histologically, is characterized by malignant epithelioid cells surrounding areas of tumour necrosis.

There is as yet no definitive treatment for necrobiosis lipoidica. Pentoxifylline has been reported to be effective, but our patient showed only partial improvement. Aspirin and dipyridamole may also be effective. Necrobiosis lipoidica should be included in the differential diagnosis of recurrent painful penile ulcers.

References


Surgery for pretibial myxoedema

Sirs. We were interested to read the report of successful surgical treatment of a patient with pretibial myxoedema (PTM) by Derrick et al.1 published recently in your journal. We report a similar patient with PTM who also underwent successful surgical therapy.

A 42-year-old male carpenter presented in April 1991 with gradual development of swelling of the lower legs and hands. Graves’s disease was diagnosed in 1989 and treated with subtotal thyroidectomy. Examination revealed bilateral, asymmetrical, firm, non-pitting oedema extending from mid-calves down to all toes typical of PTM, associated with oedema of hands. Initial treatment with multilayer compression bandaging resulted in a reduction in the swelling, but residual PTM was present over calves and feet. He presented again in January 1994 with worsening of the PTM of the legs and toes which caused considerable difficulty in wearing shoes. In May 1994 he underwent soft tissue reduction of the right big toe and second toe with split skin grafting with good results. A further debulking procedure and grafting was performed on the left big toe and second toe and the right third toe in September 1994. Nine months after surgery there was a recurrence of proliferative tissue on the right big toe and second toe and therefore repeat excision and skin grafting was performed on these toes with good results on 2-month follow-up.

Many of the skin and subcutaneous tissue changes seen in PTM are indistinguishable from lymphoedema. Indeed research from our department using lymphoscintigraphy in two patients with PTM (including the patient reported above), demonstrated marked lyphatic insufficiency, as well as an inability to opacify dermal lymphatics in affected sites with fluorescence microlymphangiography.2 These findings we considered supported our hypothesis that the clinical manifestations seen in PTM are due to mucin interfering with interstitial lymphatic transport. We wish to point out that although the patient reported by Derrick et al.1 had no recurrence at 1 year, in view of our patient’s relapse, there should be some caution regarding the success of surgery.

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Sirs. Terbinafine, a synthetic antifungal of the allylamine class, has been proven to be very effective in the oral treatment of dermatophyte onychomycosis. Little is known about the long term outcome, and relapse rate in toenail onychomycosis treated with terbinafine. Between February 1991 and February 1992, our centre participated in a multicentre trial comparing two doses of terbinafine, 250 mg/day (group I) and 500 mg/day.

References


Long-term evaluation of terbinafine 250 and 500mg daily in a 16-week oral treatment for toenail onychomycosis

Sirs. Terbinafine, a synthetic antifungal of the allylamine class, has been proven to be very effective in the oral treatment of dermatophyte onychomycosis. Little is known about the long term outcome, and relapse rate in toenail onychomycosis treated with terbinafine. Between February 1991 and February 1992, our centre participated in a multicentre trial comparing two doses of terbinafine, 250 mg/day (group I) and 500 mg/day.

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(group II), in a 16-week treatment of toenail onychomycosis. The overall results of the study were published previously. We analysed the results in our patients separately and performed a long-term follow-up for more than 2 years after the end of the study. A total of 45 patients were included, of whom 37 completed the study protocol and were evaluated at week 48. In group I, Trichophyton rubrum was isolated in 13 patients and T. mentagrophytes in five; one culture grew T. rubrum and Scopulariopsis brevicaulis. In group II, mycological culture isolated T. rubrum in 15 cases, and T. mentagrophytes in three. There were six drop-outs because of adverse events, and two because of non-compliance.

At week 48, 89% (17/19) in group I were clinically cured (six) or had minimal residual lesions (11) (defined as minimal distal hyperkeratosis and/or minimal distal onycholysis): 84% (16/19) were mycologically negative, two patients had positive microscopy with negative cultures, one culture yielded yeasts (non-Candida albicans). In group II, 94% (17/18) were clinically cured (seven) or had minimal residual lesions (10), 94% (17/18) were mycologically negative, and one culture grew yeast (non-C. albicans) (Table 1).

Thirty-five patients were re-evaluated in 1994. Two patients did not return for long-term follow-up, both were mycologically cured at week 48 and had minimal residual lesions. One was cured, in one patient, 82% (13/17) were clinically cured (seven) or had minimal residual lesions (seven), and 82% (13/17) had negative mycology. In one patient, T. rubrum was isolated, and two had positive microscopy with negative cultures. In group II, 94% (17/18) were clinically cured (eight) or had minimal residual lesions (nine), and 83% (15/18) were mycologically negative. Two cultures grew Scopulariopsis brevicaulis and, in one patient, T. rubrum was isolated. All patients with a positive culture for yeasts (not C. albicans) at week 48, and Scopulariopsis brevicaulis at more than 2 years, had negative microscopy and were considered as clinically cured. These patients had originally grown a dermatophyte. In our opinion these yeasts and moulds are contaminants. The patient who originally grew T. rubrum and Scopulariopsis brevicaulis was scored as a clinical failure. This patient had positive microscopy with negative culture at long term follow-up. Both patients with T. rubrum at more than 2 years presented with minimal improvement at week 48. The lesions deteriorated and were finally considered as a relapse. In one patient, with minimal residual lesions at week 48, a deterioration of the clinical symptoms was observed at long-term follow-up, but the mycology remained negative.

These results indicate that the excellent therapeutic response to terbinafine in toenail onychomycosis is maintained after 2 years. Terbinafine is equally effective at 250 or 500 mg daily for 16 weeks. The low relapse rate of dermatophyte infection (one patient with T. rubrum in each group) can probably be explained by the fungicidal effect of the drug. In our opinion the yeasts and moulds isolated at the end of the study and at follow-up did not contribute to the clinical disease.

Acknowledgment

The multicentre trial was supported by SANDOZ, Brussels, Belgium. The long-term evaluation was performed on a personal basis.

Table 1. Mycological and clinical results at week 48 and at more than 2 years

<table>
<thead>
<tr>
<th>Mycological cure</th>
<th>Clinical cure and MRL*</th>
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<tr>
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<td>48 weeks</td>
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<td>Group I</td>
<td>Terbinafine 250 mg/day</td>
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<td>Group II</td>
<td>Terbinafine 500 mg/day</td>
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MRL, minimal residual lesions.
Fonseca and Leão. It is a typical infection of tropical and subtropical regions.¹–⁵ However, due to worldwide travel, it may also occur sporadically in other regions, even in Europe.⁶–⁷ The infection is characterized by the presence of large black nodules that appear externally on the hair.

A peculiar feature of P. hortae, unique among pathogenic fungi, is the production of sexual spores in the parasitic phase. Natural habitats of P. hortae, other than the hair of primates⁸ including man, are not known. However, it has been suggested that its source could be stagnant water,⁹ soil¹⁰ or vegetables.¹¹ The morphology of the infecting structures has previously been reported using light and electron microscopy,¹² and it has been concluded that fungal activity is confined to the cuticle, without penetration of the hair shaft.¹³–¹⁵

We provide clear evidence of the keratinolytic activity of this fungus at the cuticular and at the cortex level. Hairs with black piedra isolated from Brazilian Indians (Xingu) were investigated studying serial sections for light and transmission electron microscopy. The fungus showed a strong keratinolytic activity being able to destroy both the cuticle and the hair cortex. The sequence of degradation of the histological components of the hair followed a similar pattern to that reported for dermatophytes and other keratinolytic fungi.¹³–¹⁵ In mature nodules the cuticular scales almost completely disappeared while the cortex remained unaltered except in those regions where its normal components were degraded by the fungus or where active boring hyphae penetrated it in several directions (Fig. 1). The activity of the penetrating hyphae does not leave empty spaces. The lytic regions are filled up with electron dense extracellular fibrous material. Something similar occurs with other keratinolytic fungi such as Chrysosporium tropicum¹⁶ and Microsporum canis.¹⁷ Details of the keratinolytic process will be extensively described elsewhere.

It is also worth mentioning that in P. hortae infection the natural self-degeneration of the fungal cells involved in the hair breakdown arising in keratinolytic fungi at the later stages of hair destruction,¹³ does not occur. In P. hortae, the cementing extracellular material that holds together and compacts the pseudoparenchymatous cells of the nodule is probably the main factor responsible for preserving the fungus against desiccation and environmental attack. Furthermore, this compact organization can also impair successful treatment explaining why the untreated disease may have a very chronic course. The classical and most effective therapy has been the cutting or shaving of the hairs.¹⁸ Recently the use of newer antifungal drugs, such as terbinafine, has shown promising results.⁶–⁷

Acknowledgment

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Figure 1. Mature nodule of black piedra. The cuticular scales (cu) have almost completely disappeared. Active boring hyphae (arrows) penetrate the cortex (co) in several directions digesting the cortex keratin (x 410).
Prurigo pigmentosa treated with minocycline

Sir, Prurigo pigmentosa (PP), is a peculiar, reddish, pruritic papular eruption which leaves a marble-like or reticular pigmentation. It was first described in the Japanese.\(^1\)\(^2\) PP is symmetrical and its onset is often sudden.\(^3\) The back, neck, chest, lumbosacral region and antecubital fossae are characteristically involved,\(^1\)\(^4\) sometimes with the limbs and abdomen.\(^5\) To date, only nine non-Japanese patients have been described.\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\) We report two Italian patients with PP: both were mentally retarded.

The first patient, a 17-year-old mentally retarded autistic boy, in poor health but with no history of atopy, presented with a severely pruritic erythematous eruption of sudden onset. There were confluent, symmetrical and hyperpigmented papules, showing a reticulate pattern, mainly on the lumbosacral area and the legs, with a few isolated papules on the forearms (Fig. 1), and abdomen. The lesions were 1–2 mm in diameter. The buttocks and axillae were darkly pigmented, and some pustules were present on the upper back.

The second patient, a 34-year-old female with Crouzon syndrome and behavioural disturbances, developed a pruritic rash, of sudden onset, with erythematous, isolated, symmetrical and hyperpigmented papules on the buttocks and the sacral area. The lesions were 2–3 mm in diameter and a hyperpigmented reticulated pattern was observed between the papules. She had been taking carbamazepine, clomipramine and bromazepam.

Both patients had a normal full blood count. On histology, early papules showed non-specific dermal infiltration by mononuclear cells. Pigmented lesions showed an increase in epidermal melanin, with an increased number of melanocytes. Direct immunofluorescence was negative. Electron microscopy showed acantholysis of the basal and suprabasal keratinocytes with intercellular oedema (Fig. 2). Lymphocytes were observed among the epithelial cells, melanocytes were numerically increased, and melanosomes were abundant. A large number of melanosomes were observed in the keratinocytes. Langerhans cells were activated.

In the first patient, minocycline, 50 mg/day, for 2 months, induced resolution of the papular eruption, the folliculitis, the pruritus, and the pigmentation. In the second patient, minocycline, 100 mg/day, for 2 weeks, resolved the papular eruption and pruritus, and reduced the pigmentation. However, the PP relapsed slightly a month after minocycline was stopped.

The pathogenesis of PP is unknown. An environmental factor is suggested.\(^5\) In a few cases, PP has been related to friction from clothing;\(^7\)\(^8\) or contact with an allergen.\(^7\)\(^11\) In one case, PP was associated with the ingestion of a bismuth compound.\(^4\) We excluded atopic dermatitis, lichen pigmentosus, prurigo melanotica, pigmented contact dermatitis, ashy dermatosis, reticulate papillomatosis, and dermatitis herpetiformis. PP has never been described in mentally retarded or in autistic persons, but it is unlikely that the mental state is relevant.

It may be relevant that our first patient was in poor health and had a low body weight, as did one previous patient,\(^1\)\(^2\) and, he had folliculitis of the back, as did another patient.\(^4\)

Our second patient took carbamazepine, clomipramine and bromazepam, but we do not know if these drugs are relevant. Minocycline is to be preferred to sulphamethoxazole,\(^13\)\(^14\) due to the potential side effects of sulphonamides.\(^15\)

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Figure 1. Isolated papules and reticulate pigmentation are seen over the antecubital fossa (first patient).
Muir–Torré syndrome in a patient with acquired immunodeficiency syndrome

Sna Muir–Torré syndrome (MTS) is defined by the association of sebaceous skin neoplasms and keratoacanthomas with visceral malignancy. Recently, its relation with immunosuppression has been highlighted. We describe a patient with acquired immunodeficiency syndrome (AIDS) who fulfilled the diagnostic criteria for MTS.

A 53-year-old heterosexual man was referred, in September 1993, because of a rapidly growing keratotic tumour on his right forehead. He had been on haemodialysis since December 1992, following bilateral nephrectomy for bilateral urinary tract transitional carcinoma diagnosed in 1990. When entering haemodialysis, human immunodeficiency virus (HIV) infection was detected. He did not have any HIV-related condition, and his CD4 count was 198/mm³.

The forehead tumour was excised and shown, on histology, to be a keratoacanthoma. Over his face, about 10 asymptomatic yellowish papular lesions, 2–10 mm in diameter, were noted (Fig. 1). These had appeared over the previous 2 years. Histology showed well-demarcated dermal nodular tumours, with palisading basaloid cells, and central sebaceous differentiation (Fig. 2), characteristic of sebaceous adenomas. The patient’s sister and niece have colonic adenocarcinoma, but have not been examined for cutaneous lesions. No other relatives are affected.

MTS is defined by the presence of at least one sebaceous tumour (i.e., an adenoma, epithelioma or carcinoma) and one visceral malignancy. Patients usually present with multiple cutaneous lesions, which may include keratoacanthomas. Visceral malignancy is relatively non-aggressive. MTS is inherited in an autosomal dominant pattern, and is regarded as the cutaneous phenotypic expression of the cancer family syndrome. Colonic adenocarcinomas and genitourinary tract tumours are the most frequent internal malignancies. The mean age at diagnosis of the sebaceous tumours and of the visceral cancers is 53 years and 50 years respectively.

Little is known about the role of immunosuppression in
MTS. In some reports there is a high incidence of lymphoproliferative malignancies. Stone et al. describe a 44-year-old man who developed rapidly appearing sebaceous neoplasms and keratoacanthomas during cyclosporin and prednisolone treatment for cardiac transplantation. This patient had no visceral malignancy. Dover et al. reported a 39-year-old patient with AIDS who presented with a rapidly growing sebaceous adenoma but no other feature of the syndrome.

Our patient presented with a keratoacanthoma and multiple sebaceous adenomas when he was 53 years old. His low CD4 count reflected a severe immunodeficient state. While cutaneous lesions appeared, no new visceral neoplasms developed, and his urinary tract neoplasia was apparently controlled. It is possible that HIV infection could have influenced the appearance of cutaneous lesions, but, in spite of severe immunosuppression, aggressive or multiple neoplasms did not develop. Visceral neoplasia in MTS may not be related to defects in immunological surveillance but more experience is needed to define the role of immunosuppression in this condition.

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Figure 1. A 1-cm yellowish papular lesion over the right cheek, corresponding to a sebaceous adenoma.

Figure 2. Photomicrograph of a well-defined dermal nodular tumour, with peripheral palisading, and central sebaceous differentiation (haematoxylin and eosin; ×40).


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**Poem**

**In appreciation**

Thank God for the epidermis  
Our silent body hero  
Sweating sympathetically  
Protecting us from stress  
Repeatedly turning over  
Each and every day.

We grip and touch  
Yet take for granted  
Our lubricated friend.  
Not so the deeper tissue  
Which sustains  
And regularly maintains  
Its superior relation.

Julian Verbov  
Editor