British Journal of Dermatology 1998; **138:** 357–373.

Correspondence

Streptococcal impetigo induces Th1-preponderant activation of T lymphocytes with subsequent anergy to superantigenic exotoxins in patients with atopic dermatitis

SIR, Impetigo is a contagious superficial pyogenic infection of the skin caused by *Staphylococcus aureus (S. aureus)* or *Streptococcus pyogenes (S. pyogenes)*. Streptococcal impetigo, which appears as a non-bullous, crusty eruption, readily occurs in patients with atopic dermatitis (AD).[1] We investigated the changes in peripheral blood eosinophil counts associated with streptococcal impetigo of nine patients with AD (aged 12–25 years; two males and seven females; four patients in addition had poststreptococcal glomerulonephritis and eight had simultaneous secondary infection with *S. aureus*).[2] In all but one of the patients, the total peripheral blood leucocyte count was elevated on presentation with active impetigo. In contrast, the eosinophil count was decreased when the patients presented with active impetigo, began to increase 7–10 days after admission (impetigo subsiding) and rose further in another 7–11-day period with clearance of the impetigo. Contrariwise, there was no tendency for a change in eosinophil count in six AD patients whose impetigo was purely staphylococcal (five males aged 14–44 years and one 23-year-old female). In five patients with streptococcal impetigo, the serum IgE levels fell between admission and 10–46 days later, by 16–75%. However, in patients with staphylococcal impetigo, the changes in IgE were variable (−22% to a 43% elevation). Hence, after impetigo caused by streptococci, the eosinophil count falls quickly, and the IgE level declines slowly.

This observation raised the possibility that *S. pyogenes* modulates the Th2-predominant immunological profile in AD patients.[3] We cultured peripheral blood mononuclear cells (PBMC) from three normal subjects for 72 h in the presence of *S. pyogenes* isolated from one patient and treated with mitomycin C (MMC),[4] and quantified interferon-γ (IFN-γ) and interleukin (IL)-4 levels in the culture supernatant. MMC-treated *S. pyogenes* stimulated PBMC to produce IFN-γ; the IFN-γ concentration of the *S. pyogenes* addition group and that of the control were 558 ± 78 and 11 ± 2 (mean ± SD, units/mL; $P < 0{\cdot}001$), respectively. No detectable IL-4 was present in either supernatant. Similar results were obtained using superantigenic streptococcal pyrogenic exotoxin (SPE) A.[5]

Cutaneous infection with *S. pyogenes* seems to alter systemic immunity in AD patients by releasing superantigens. PBMC taken from three patients (cases 1–3, concomitant infection with both species) on admission (active impetigo) were cultured with staphylococcal enterotoxin B (SEB), toxic shock syndrome (TSS) toxin-1 (TSST-1), SPEA, or SPEC, as described previously.[6] In a representative, healthy subject (Fig. 1, left column), SEB and TSST-1 induced T-cell proliferation at a concentration as low as 0·1 ng/mL, while the mitogenic activities of SPEA and SPEC became apparent at 1 ng/mL. In patients 1 and 2, while PBMC responded normally to SEB and TSST-1, they responded poorly to SPEA and SPEC

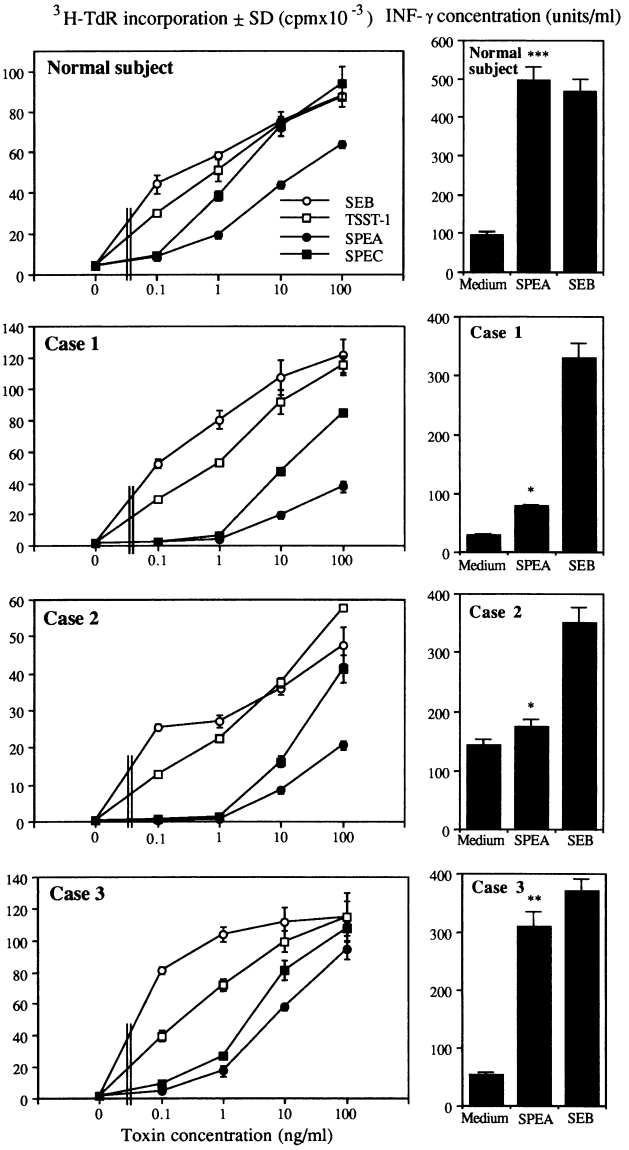

Figure 1. Poor responses of peripheral blood mononuclear cells (PBMC) to streptococcal pyrogenic exotoxin (SPE) A and SPEC and reduced production of IFN-γ by PBMC in response to SPEA at the active stage of impetigo. (Left column) PBMC from cases 1–3 at the time of active impetigo and PBMC from a normal subject were cultured for 72 h in the presence of staphylococcal enterotoxin-B (SEB), toxin shock syndrome toxin-1 (TSST-1), SPEA, or SPEC at the indicated concentration. (Right column) PBMC were cultured for 72 h in the presence or absence of SPEA or SEB (triplicate experiments). IFN-γ in the culture supernatants was quantified by an enzyme-linked immunosorbent assay. Vertical bars represent SD. *$P < 0{\cdot}005$, **$P < 0{\cdot}05$, ***statistically not significant, compared with the corresponding SEB.

(proliferative responses to these toxins were not substantial at 1 ng/mL). Although less apparent, patient 3 exhibited a similar pattern. In addition, SPEA and SEB stimulated PBMC from a normal subject to produce IFN-γ at comparable levels, whereas PBMC from patients 1 and 2 on stimulation with SPEA produced smaller amounts of IFN-γ than with SEB, at the time of active impetigo (Fig. 1, right column). When the SPE-stimulated proliferation and IFN-γ production in case 1 were tested again after the impetigo had healed (11 days after admission), they increased markedly (data not shown). Vβ2 and Vβ8 are the T-cell receptor elements possessed by T-cell populations that are reactive with both SPEA and SPEC.[5] We monitored the percentage of these T cells in patient 1 by flow cytometry. When taken at the time of active impetigo, PBMC contained 5·3% $V\beta2^+$ cells (normal, $4{\cdot}7 \pm 1{\cdot}8$: mean ± SD) and 3·1% $V\beta8^+$ cells (normal, $3{\cdot}4 \pm 1{\cdot}2$). Neither the percentage of $V\beta2^+$ cells (5·7%) nor $V\beta8^+$ cells (2·3%) was substantially increased after clinical improvement. Thus, the degree of T-cell proliferation in response to streptococcal toxins did not correlate with the number of T cells bearing relevant Vβ, suggesting that T-cell clonal anergy, but not clonal deletion, is the mechanism of hyporesponsiveness, as observed in TSS.[7]

These findings suggest that superantigens released from *S. pyogenes* induce a transient burst of Thl-preponderant cytokine production, sufficient to depress eosinophil recruitment and, subsequently, temporary T-cell anergy to these exotoxins. The Th1 skewing effect of the superantigen was also reported with TSST-1.[8] Circulating superantigen was detected in patients with streptococcal TSS.[9] Such diffusion of exotoxins from lesions to the blood may also occur in cutaneous infection with *S. pyogenes*. Given that Th2 cells play an important part in AD,[3] it was to be expected that streptococcal impetigo might improve the clinical condition of AD. However, we did not see any such remarkable improvement of AD skin lesions during the course of impetigo in our patients. Presumably, the unsustained production of IFN-γ is not sufficient to affect the disease process of AD or, alternatively, Th1 cells in addition to Th2 cells may be involved in producing the eruption of AD.[10]

Department of Dermatology, Y.TOKURA
Hamamatsu University School of Medicine, M.ISHII-GINOZA*
3600 Handa-cho, N.SEO
Hamamatsu 431–31, T.ITO
Japan M.SAKURAI†
**Ishii Clinic,* F.FURUKAWA
Haibara, M.TAKIGAWA
Japan
†Section of Dermatology,
Shizuoka General Hospital,
Shizuoka, Japan

References

1 Brook I, Frazier EH, Yeager JK. Microbiology of infected atopic dermatitis. *Int J Dermatol* 1996; **35:** 791–3.
2 Dajani AS, Ferrieri P, Wannamaker LW. Endemic superficial pyoderma in children. *Arch Dermatol* 1973; **108:** 517–22.
3 Leung DYM. Atopic dermatitis: immunobiology and treatment with immune modulators. *Clin Exp Immunol* 1997; **107** (Suppl. 1)**:** 25–30.
4 Tokura Y, Furukawa F, Wakita H *et al.* T-cell proliferation to superantigen-releasing *Staphylococcus aureus* by MHC class 11-bearing keratinocytes under protection from bacterial cytolysin. *J Invest Dermatol* 1997; **108:** 488–94.
5 Fleischer B, Gerlach D, Fuhrmann A *et al.* Superantigens and pseudosuperantigens of gram-positive cocci. *Med Microbial Immunol* 1995; **184:** 1–8.
6 Tokura Y, Yagi H, Ohshima A *et al.* Cutaneous colonization of Staphylococci influences the disease activity of Sèzary syndrome: a potential role for bacterial superantigens. *Br J Dermatol* 1995; **133:** 6–12.
7 Mahlknecht U, Herter M, Hoffmann MK *et al.* The toxic shock syndrome toxin-1 induces anergy in human T cells in vivo. *Hum Immunol* 1996; **45:** 42–5.
8 Lester MR, Hofer MF, Renz H *et al.* Modulatory effects of staphylococcal superantigen TSST-1 on IgE synthesis in atopic dermatitis. *Clin Immunol Immunopathol* 1995; **77:** 332–8.
9 Sriskandan S, Moyes D, Cohen J. Detection of circulating bacterial superantigen and lymphotoxin-α in patients with streptococcal toxic–shock syndrome. *Lancet* 1996; **348:** 1315–6.
10 Werfel T, Morita A, Grewe M *et al.* Allergen specificity of skin-infiltrating T cells is not restricted to a type-2 cytokine pattern in chronic skin lesions of atopic dermatitis. *J Invest Dermatol* 1996; **107:** 871–6.

Two populations of CD1a+ epidermal dendritic cells expressing B7 molecules in human skin

SIR, Langerhans cells (LC) may be defined as epidermal, CD1a expressing, dendritically shaped cells containing Birbeck granules, which are capable of antigen presentation.

Ohki *et al.* recently described a functional CD86 (B7–2/B70) expression on human LC in atopic dermatitis.[1] We want to support the findings of Ohki *et al.* as we have found expression of B7–1 and B7–2 on CD1a positive epidermal dendritic cells in atopic dermatitis lesions and in other inflammatory skin diseases, as well. However, we would like to point out that, in contrast to the normal human skin micromilieu,[2] the CD1a expression is not specific to LC in an inflammatory environment. As shown recently, two immunomorphological and ultrastructural distinct CD1a bearing cell populations are present in the inflammatory epidermis: the 'classical' human LC containing Birbeck granules (CD1a+++, HLA-DR+++, CD11b–) and the inflammatory dendritic epidermal cells (IDEC), which lack Birbeck granules (CD1a+, HLA-DR+++, CD11b+++).[3] In using a highly sensitive, quantitative method for three-colour, flow cytometric dendritic cell phenotyping, we were able to differentiate the expression of B7 molecules in a LC and IDEC population. Thus, the study of Ohki *et al.* as well as many other studies of inflammatory skin has collected data on a mixture of these two cell types, because immunohistochemistry is unable to discriminate between LC and IDEC.

Therefore, it seems crucial to clarify the issue whether LC or IDEC are functionally the most important CD86 expressing CD1a-positive epidermal dendritic cell population in atopic dermatitis as well as in other skin diseases.

Department of Dermatology,
Ludwig-Maximilians-University,
Frauenlobstr. 9–11, 80337 München, Germany
A. WOLLENBERG
T. BIEBER*

**Department of Dermatology,*
Friedrich-Wilhelms-University,
Sigmund-Freud-Str. 25,
53105 Bonn, Germany

References

1 Ohki O, Yokozeki H, Katayama I *et al*. Functional CD86 (B7–2/B70) is predominantly expressed on Langerhans cells in atopic dermatitis. *Br J Dermatol* 1997; **136:** 838–45.
2 Fithian E, Kung P, Goldstein G *et al*. Reactivity of Langerhans cells with hybridoma antibody. *Proc Natl Acad Sci USA* 1981; **78:** 2541–4.
3 Wollenberg A, Kraft S, Hanau D, Bieber T. Immunomorphological and ultrastructural characterization of Langerhans cells and a novel, inflammatory dendritic epidermal cell (IDEC) population in lesional skin of atopic eczema. *J Invest Dermatol* 1996; **106:** 446–53.

Metallothionein expression in tattooed skin

SIR, Tattoo granuloma is a local hypersensitivity reaction to tattoo pigments,[1] and can be a manifestation of a systemic sarcoidal reaction. Our interest has focused on the long latent period of the reaction and its spontaneous resolution. Usually, the period between the tattooing procedure and the onset of the granulomatous response is over 9 years.[2]

Metallothionein (MT)[3] has the capacity selectively to bind essential metals due to its characteristically high cysteine content. In addition to metal homeostasis, MT plays a part in the detoxification of toxic metals. Because most tattoo granules contain metal elements which can readily induce MT in various cells, we postulated that MT might participate in the pathological course of tattoo granuloma formation.

Figure 1. Tattoo of a Japanese 'long-nosed goblin' on the upper right arm. Granulomatous changes are localized to the red areas of the tattoo.

Over a period of 3 months, a 33-year-old male truck driver developed widespread oedematous nodules localized to the red areas of a tattoo (Fig. 1), together with features similar to those of systemic sarcoidosis, including enlargement of axillary lymph nodes, a pulmonary infiltrate evident on chest X-ray, fatigue and fever. Ophthalmoscopic examination showed white spots indicating granulomatous uveitis. He had been extensively tattooed 14 months previously with red, black, yellow and green pigments over the entire trunk and upper arms. We have already reported a similar Japanese case associated with a systemic sarcoidal reaction following tattooing.[4]

Light microscopy demonstrated abundant non-caseating sarcoidal granulomata and tattoo pigment in biopsy specimens obtained from the red areas of the tattoo and from the lung. The metal elements in the pigment particles in the red tattoo were shown by X-ray energy dispersive spectroscopy to be mercury, magnesium and calcium. Histological localization of MT was studied by immunohistochemistry using a rabbit

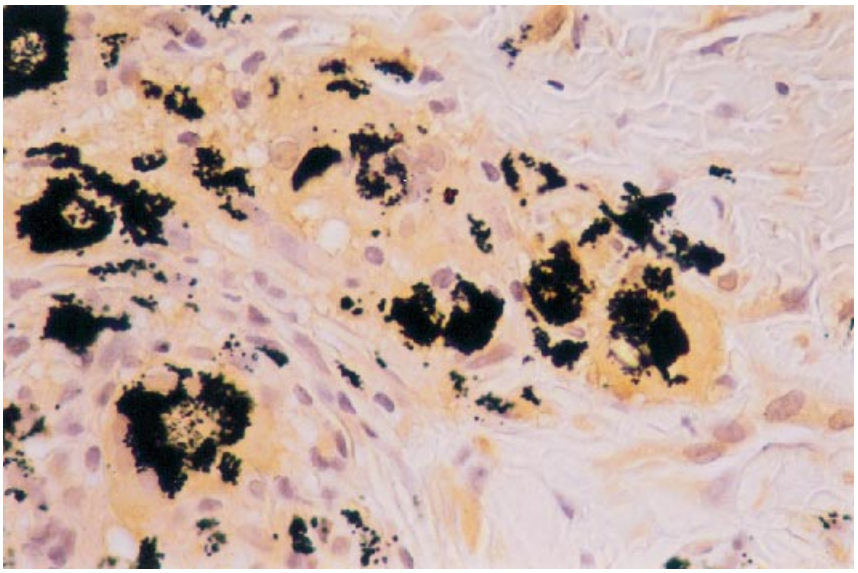

Figure 2. Immunohistochemical localization of metallothionein (MT) in the tattoo granuloma. Strong immunoreactivity for MT is evident in granuloma tissue including pigment granules (haematoxylin and eosin; original magnification ×200).

polyclonal antibody against rat MT-1. In the inflammatory lesions before corticosteroid treatment, strong positivity for MT was observed in the granuloma cells and surrounding fibroblasts (Fig. 2). In contrast, after treatment, the immunopositive area had completely disappeared or showed exclusive localization in cells containing tattoo pigment. MT has been demonstrated in hair follicles and sweat glands of normal skin, and in basal cell epithelioma and other hyperplastic skin lesions.[5] However, its expression in tattoo granuloma suggests that MT may play a significant part in the pathogenesis of the tattoo reaction, as tattoo pigments contain mercury, a potent inducer of MT. Although MT expression does not explain the long time lag until the occurrence of tattoo granuloma, tissue MT may contribute to suppression of the granulomatous reaction caused by the metal in the tattoo pigment, through its metal detoxifying effect.

Department of Dermatology, K.HANADA
Hirosaki University School of Medicine, I.HASHIMOTO
Hirosaki 036,
Japan

References

1 Turk JL. The mononuclear phagocyte system in granulomas. *Br J Dermatol* 1985; **113:** 49–54.
2 Collins P, Evans AT, Gray W, Levison DA. Pulmonary sarcoidosis presenting as a granulomatous tattoo reaction. *Br J Dermatol* 1994; **130:** 658–62.
3 Kaegi JHR, Vallee BL. Metallothionein: a cadmium- and zinc-containing protein from equine renal cortex. *Biol Chem* 1960; **235:** 3460–5.
4 Hanada K, Chiyoya S, Katabira Y. Systemic sarcoidal reaction in tattoo. *Clin Exp Dermatol* 1985; **10:** 479–84.
5 van den Ood JJ, de Ley M. Distribution of metallothionein in normal and pathological human skin. *Arch Dermatol Res* 1994; **286:** 62–8.

Perforating granuloma annulare complicating tattoos

SIR, Tattoos are known to be complicated by several dermatological conditions, including a foreign-body reaction to pigment, keloid, sarcoid granulomas, lichen planus and allergic sensitivity to pigments. We describe a case of perforating granuloma annulare complicating tattoos. As far as we are aware, this is the first reported example of this association.

A 56-year-old man presented with lumps developing over 1 year in the red areas of tattoos on both upper arms and forearms. The tattoos had been present for 37 years. The lumps became scaly and itchy, and bled and discharged on trauma. On examination, there were small papules in the red areas of the tattoos and these were associated with scaling and induration. Histological examination showed that the dermal collagen contained several large necrobiotic areas, some with a rim of histiocytes (Fig. 1a). Some of these areas were immediately subjacent to the epidermis, which was covered by inflammatory exudate, and degenerate collagen could be seen among the epidermal cells, indicating perforating granuloma annulare (Fig. 1b). In the adjacent dermis there was tattoo pigment with an associated heavy lymphoid infiltrate, shown immunohistochemically to be T lymphocytes. Energy-dispersive X-ray spectroscopic microanalysis was performed on unstained deparaffinized sections and the foreign material gave strong signals for mercury and sulphur, consistent with it being mercuric sulphide. The lesions were treated with topical clobetasol propionate (Dermovate®) and they improved, but the patient failed to attend for further follow-up.

Granuloma annulare is a common dermatological condition that is generally considered to be idiopathic, but which has been associated with trauma.[1] Its development in tattoos of 37 years duration is difficult to ascribe to trauma, but as the lesions occurred only in the red areas and the biopsy also

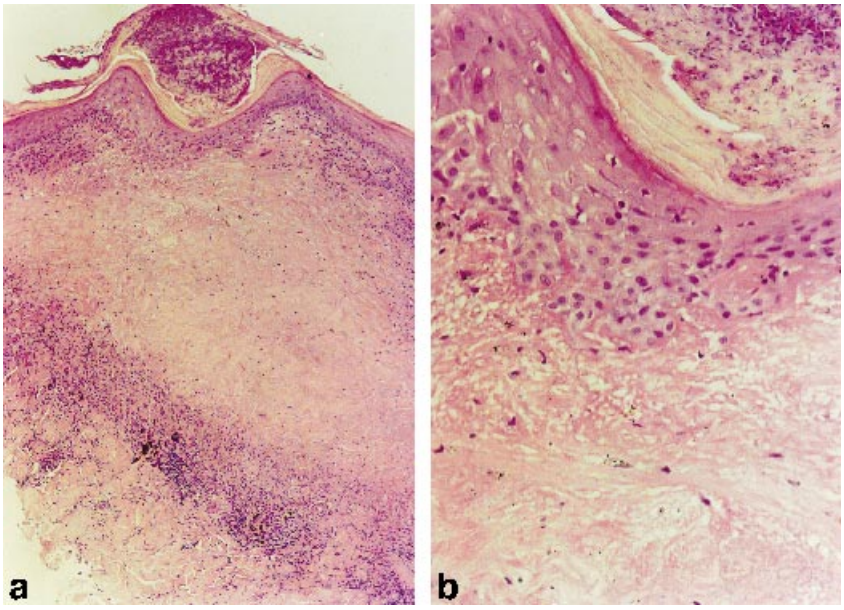

Figure 1. (a) A necrobiotic dermal nodule is seen, with a cellular rim containing pigment (haematoxylin and eosin, original magnification × 100). (b) A high-power view of the necrobiotic nodule showing degenerative collagen in between basal epidermal cells (haematoxylin and eosin, original magnification × 240).

showed a marked lymphoid response, the granuloma might be a manifestation of a delayed hypersensitivity reaction to tattoo pigment. Granuloma annulare and the perforating variety have been described as complicating herpes zoster scars[2,3] and in these cases have been interpreted as a hypersensitivity reaction. Whatever the cause, we consider that perforating granuloma annulare should be added to the list of conditions that can complicate tattoos.

Acknowledgments

We are indebted to Dr C.E.Keen, Consultant Pathologist, Lewisham Hospital, London for performing the energy-dispersive microanalysis.

Whiston Hospital, E.Gradwell
Warrington Road, S.Evans
Prescot,
Merseyside L35 5DR, U.K.

References

1 Mills A, Chetty R. Auricular granuloma annulare: a consequence of trauma? *Am J Dermatopathol* 1992; **14:** 431–3.
2 Wolf R, Brenner S, Ruocco V, Filioli FG. Isotopic response. *Int J Dermatol* 1995; **34:** 341–8.
3 Krahl D, Hartschuh W, Tilgen W. Granuloma annulare perforans in herpes zoster scars. *J Am Acad Dermatol* 1993; **29:** 859–62.

Endothelin-secreting angiosarcoma occurring at the site of an arteriovenous fistula for haemodialysis in a renal transplant recipient

Sir, We read with interest the study by Kibe *et al.*[1] concerning angiosarcomas in renal transplant recipients. We report another case of angiosarcoma arising at the site of an arteriovenous fistula for haemodialysis in a renal transplant recipient. We examined the plasma and intratissular levels of endothelin-1 and discuss its contribution as a tumour marker during the course of this pathology.

In 1987, a 61-year-old man required haemodialysis for end-stage renal failure secondary to polycystic kidney disease. At that time, a right side-to-side anastomosis between the humeral artery and the cephalic vein was performed. In May 1989, he received a cadaver kidney transplant and was treated with azathioprine, cyclosporin and prednisolone. In May 1994, he was hospitalized for a 4-month history of pain, swelling and tenderness at the site of the right-elbow fistula. A diagnosis of thrombosed aneurysm of the fistula was suspected and it was surgically ligated; there was no attenuation of the symptoms. Over the next 6 weeks, three exploratory surgeries with evacuation of 'haematoma', dissection of an 'aneurysm' of the cephalic vein and right humeral artery ligature were carried out but, unfortunately, no samples were sent for histological examination. At the same time, cutaneous lesions developed on his right hand and forearm; a red-violaceous tumefaction of the nail of the thumb with small red-blue nodules on the pads of the third and fourth fingers (Fig. 1a,b) and one 5 × 5 mm nodule on the forearm. Marked inflammatory swelling of the right wrist was also noted, but without lymphoedema of the right arm. Histological examination of one cutaneous lesion revealed an epithelioid angiosarcoma. The superficial and reticular dermis were diffusely infiltrated by cohesive sheets of epithelioid cells and numerous vascular spaces were also lined by epithelioid tumour cells. Immunohistochemical labelling of the tumour cells showed positivity for factor VIII-related antigen, CD31 and CD34 antigens. In addition, most cells with epithelioid morphology were positive for cytokeratin, epithelial membrane antigen and vimentin. Bone X-rays showed total lysis of the cubital extremity. Results of computed tomography scans of the head, chest, abdomen and pelvis were negative. Serological tests for HIV-1 and -2, and HTLV-1 and -2 were negative. Immunosuppressive treatment was decreased for cyclosporin from 225 to 150 mg/day and from 20 to 10 mg/day for prednisolone, while azathioprine was stopped. The patient initially refused amputation of his right arm. Over the next 2 weeks, the initial cutaneous lesions underwent rapid progression with extensive necrosis of the tips of the thumb and third and fourth fingers with marked enlargement of the forearm tumour (Fig. 1c). The right arm was amputated above the elbow in August 1994. Histopathological examination of the amputated limb showed an epithelioid angiosarcoma arising from the cephalic vein at the initial site of the fistula. Seven months after amputation, the patient died from lung metastases; an autopsy was refused by the family.

Plasma and intratissular endothelin-1 concentrations were measured by radioimmunoassay, as described previously.[2] The inter- and intra-assay variations were 14% and 9%, respectively. The plasma endothelin-1 concentration was 1·98 pg/mL on day 0 (before tumour removal), 0·98 pg/mL on day 30 (after removal), 2·75 pg/mL on day 60 (no detected metastasis) and 10·2 pg/mL on day 140 (lung metastases). In normal subjects, endothelin-1 was detectable in plasma at 0·5–2 pg/mL. The endothelin-1 concentration in the tumour homogenate was 29·2 ng/g of wet tissue. Two samples of normal tissue from the patient's right arm contained 0·387 and 0·169 ng/g of wet tissue.

Endothelin-1 is a potent vasoconstrictor peptide produced in endothelial cells but not stored in secretory granules. It has been reported that endothelin-1 stimulates DNA synthesis of fibroblasts, smooth muscle cells and endothelial cells, and may induce proliferation of the latter.[3] In the present case, the endothelin-1 concentration in the tumour homogenate was about 80-fold higher than in the normal tissue. The diagnosis of epithelioid angiosarcoma from undifferentiated metastatic carcinoma, melanoma or epithelioid sarcoma is difficult.[4] The usefulness of immunohistochemical evaluation, with a panel composed of the factor VIII-related antigen, *Ulex europaeus* lectin type 1 and CD31, was reported recently.[5,6] However, immunohistochemical labelling with antiendothelin-1 antibody has been observed in three angiosarcomas and could be a potential sensitive marker of such tumours.[7,8] Yokokawa *et al.*[8] described two elderly patients suffering from angiosarcoma of the scalp whose elevated blood pressures were associated with a sharp increase of the plasma endothelin-1

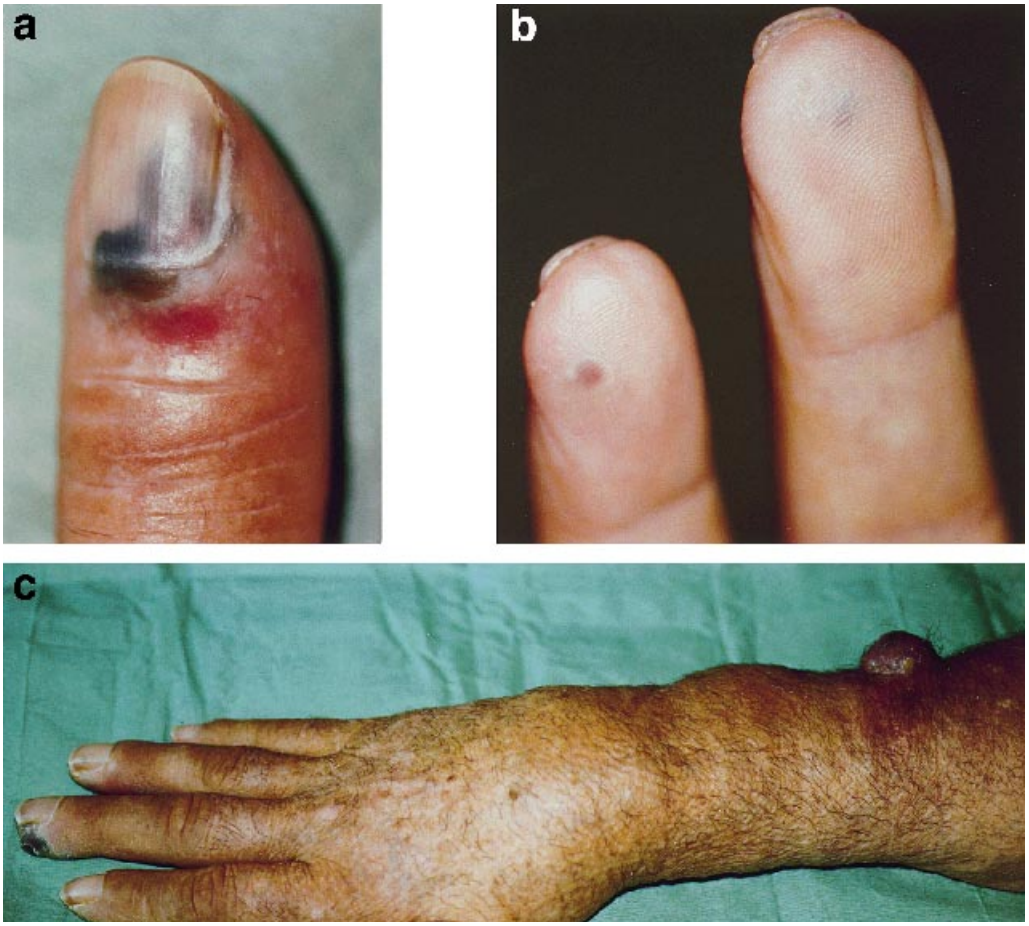

Figure 1. Epithelioid angiosarcoma. Cutaneous metastases of (a) the right thumb and (b) the third and fourth fingers (day 0); (c) Rapid progression of the cutaneous metastasis of the right arm 15 days later.

level. Blood pressure and plasma endothelin-1 levels became normal after tumour excision and increased again when the angiosarcoma recurred in one of the two patients. In the present case, tumour excision resulted in a decrease of the plasma endothelin-1 level, which increased again 60 days after surgery, despite finding no metastases. When pulmonary metastases became detectable on day 140, the plasma endothelin-1 concentration was 10-fold higher than after the removal of the tumour (day 30). Throughout this development, no hypertension was detectable in the patient. These results suggest that the measurement of plasma endothelin-1 could have diagnostic and prognostic value in vascular tumours such as angiosarcoma. Any increase in plasma endothelin-1 level after tumour excision could suggest a recurrence or metastatic proliferation, even in the absence of clinical or radiological signs.

Service de Dermatologie-Phlébologie, D.Bessis
Hôpital Saint-Eloi, A.Sotto*
2, Avenue Bertin Sens, P.Roubert†
34295 Montpellier Cedex 5, France P-E.Chabrier†
**Service de Médecine Interne B,* G.Mourad‡
Hôpital Carémeau, J-J.Guilhou
rue du Professeur Debré,
BP n°26, 30006 Nimes, France
†*Institut Henri-Beaufour,*
Centre de Recherche de Courtaboeuf,
1, avenue des Tropiques,
91952 Les Ulis, France
‡*Service de Néphrologie,*
Hôpital Lapeyronie,
371, avenue du Doyen G. Giraud,
34295 Montpellier Cedex 5, France

References

1 Kibe Y, Kishimoto S, Katoh N *et al.* Angiosarcoma of the scalp associated with renal transplantation. *Br J Dermatol* 1997; **136:** 752–6.
2 Roubert P, Viossat I, Lonchampt MO *et al.* Endothelin receptor control by endothelin synthesis in vascular smooth muscle cells. Effects of dexamethasone and phosphoramidon. *J Vasc Res* 1993; **30:** 139–44.
3 Levin ER. Endothelins. *N Engl J Med* 1995; **333:** 356–63.
4 Fletcher CDM, Beham A, Bekir S *et al.* Epithelioid angiosarcoma of deep soft tissue: a distinctive tumor readily mistaken for an epithelial neoplasm. *Am J Surg Pathol* 1991; **15:** 915–24.
5 Ohsawa M, Naka N, Tomita Y *et al.* Use of immunohistochemical procedures in diagnosing angiosarcoma: evaluation of 98 cases. *Cancer* 1995; **75:** 2867–74.
6 Orchard GE, Zelger B, Wilson Jones E, Russell Jones R. An

immunocytochemical assessment of 19 cases of cutaneous angiosarcoma. *Histopathology* 1996; **28:** 235–40.
7 Watanabe K, Hoshi N, Suzuki T, Suzuki T. Epithelioid angiosarcoma of the intestinal tract with endothelin-1-like immunoreactivity. *Virchows Arch (Pathol Anat)* 1993; **423:** 309–14.
8 Yokokawa K, Tahara H, Kohno M *et al.* Hypertension associated with endothelin-secreting malignant hemangioendothelioma. *Ann Intern Med* 1991; **114:** 213–5.

Does influenza vaccination induce bullous pemphigoid? A report of four cases

Sir, Although the cause of bullous pemphigoid is presently unknown, several associations have been described.[1] Two elderly patients developed bullous pemphigoid 3 weeks after a tetanus toxoid booster,[1,2] and a further two developed it 1 and 10 days after influenza vaccination.[2,3] We present a further four patients, in whom bullous pemphigoid developed approximately 1 month after vaccination for influenza.

An 86-year-old man presented with a 1-week history of an erythematous, pruritic eruption with the subsequent development of generalized blisters. Histology confirmed pemphigoid. He had received a Fluvirin influenza vaccination (Evans Medical Ltd, Surrey, U.K.) 4 weeks prior to the onset of symptoms. A 90-year-old man was seen with a 2-month history of a progressive itchy eruption, shown on histology to be pemphigoid. He had been given Fluvirin 1 month before his symptoms began. A 72-year-old man gave a 4-week history of generalized blistering, which was confirmed as pemphigoid on histology. Five weeks previously, Fluvirin had been given. The fourth patient, an 83-year-old lady, had developed localized bullous pemphigoid, confirmed on biopsy, on the lower legs in two consecutive winters, on each occasion 3 weeks after vaccination with Fluvirin.

Vaccination against influenza is cost-effective, compared with the morbidity and mortality generated by the condition. Thirty-five per cent of vaccinations produce no protective antibody titres in the elderly.[4] The injection is given intramuscularly or by the deep subcutaneous route. Recognized complications include haematomas, ovalbumin allergy and, rarely, a postvaccination demyelination syndrome.

There are two types of influenza vaccine. These are subunit vaccines that consist of neuramidase and haemagglutinin surface antigen proteins in an ovalbumin media, and split virion vaccines that also contain matrix proteins.[5] All our cases had received the subunit vaccine Fluvirin (Evans Medical Ltd).

Influenza vaccinations are common in the elderly, and bullous pemphigoid is a disease of the elderly. Our observation of postvaccination pemphigoid may be no more than coincidence. However, the onset of the disease approximately 1 month postvaccination is appropriate for bullous pemphigoid antibody induction by the vaccination. Vaccination may induce a non-specific immune response that unmasks subclinical bullous pemphigoid. Alternatively, a specific antibody generated by the influenza vaccine may cross-react with bullous pemphigoid antigens.

One of our cases developed a relapse of pemphigoid after having received a further vaccination 1 year later. Exacerbations of pemphigoid have been reported previously in two cases following influenza vaccination.[6] Further influenza vaccinations in all our cases may precipitate a relapse of bullous pemphigoid and should therefore not be recommended. A case-controlled study is needed to differentiate between coincidence and true association, before influenza vaccination is recognized as a potential cause of bullous pemphigoid.

Department of Dermatology, A.M.R.Downs
Bristol Royal Infirmary, J.T.Lear
Bristol BS2 8HW, U.K. C.P.R.Bower
C.T.C.Kennedy

References

1 Venning VA, Wojnarowska F. Induced bullous pemphigoid. *Br J Dermatol* 1995; **132:** 831–2.
2 Fournier B, Descamps V, Bouscarat F *et al.* Bullous pemphigoid induced by vaccination. *Br J Dermatol* 1996; **135:** 153–4.
3 Lear JT, Tan BB, English JSC. Bullous pemphigoid following influenza vaccination (letter). *Clin Exp Dermatol* 1996; **21:** 392.
4 Saririan K, Wali A, Almeida RP, Russo C. Increased serum HLA class I molecule levels in elderly human responders to influenza vaccination. *Tissue Antigens* 1993; **42:** 9–13.
5 Chaloupka I, Schuler A, Marschall M, Meier-Ewart H. Comparative analysis of six European influenza vaccines. *Eur J Clin Microbiol Infect Dis* 1996; **15:** 121–7.
6 Bodokh I, Lacour JP, Boudet JF *et al.* Réactivation de pemphigoide bulleuse après vaccination antigrippale (letter). *Thérapie* 1994; **49:** 154.

Pemphigus vulgaris with involvement of the cervix

Sir, A 44-year-old woman with a 12-year history of pemphigus vulgaris was referred for colposcopy because of persistently abnormal cervical smear cytology. This showed inflammatory changes and abnormal parabasal-type cells with dense cytoplasm, vesicular nuclei and prominent single or multiple eosinophilic nucleoli (Fig. 1). They were coded as borderline. She had had three previous normal pregnancies, was menstruating regularly and had no gynaecological symptoms.

Her pemphigus had been generally limited to the oral mucosa, although there had been some involvement of the conjunctivae on a few occasions, and a single crusted lesion on the back on one occasion. The diagnosis of pemphigus vulgaris had been established from a biopsy of this lesion on the back which showed characteristic suprabasal acantholysis and blister formation with immunoperoxidase staining demonstrating IgG deposition in epidermal desmosomes. Circulating pemphigus antibodies were present. Treatment over the years had been with systemic and topical steroids, azathioprine and dapsone, and currently consisted of oral azathioprine and prednisolone.

Colposcopic examination was abnormal with ectopy of the transformation zone and, in continuity with this, an unusual eccentric eroded area involving about 5% of the ectocervix. The abnormal area was removed with a diathermy loop and sent for histology. This showed features of pemphigus with

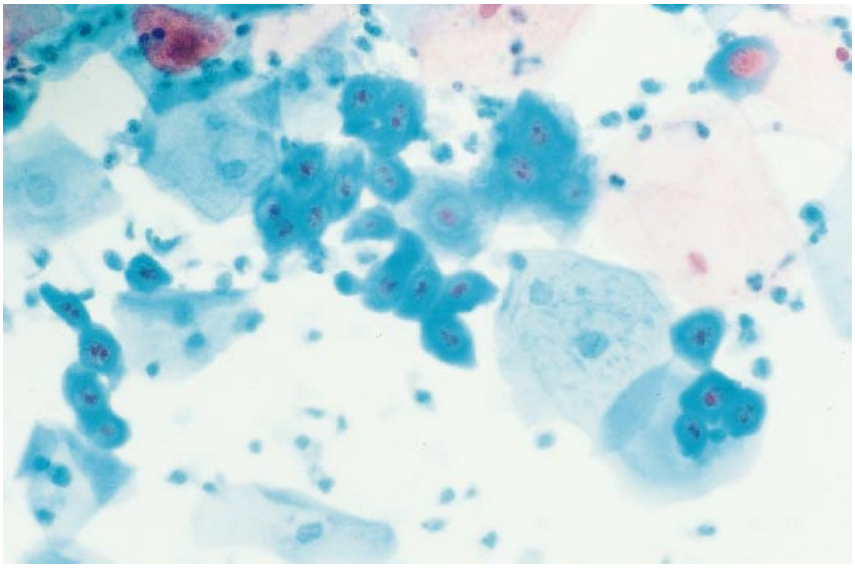

Figure 1. Clusters of parabasal-type squamous cells with dense cytoplasm, prominent nucleoli and coarse chromatin may be seen (Papanicolaou, original magnification × 200).

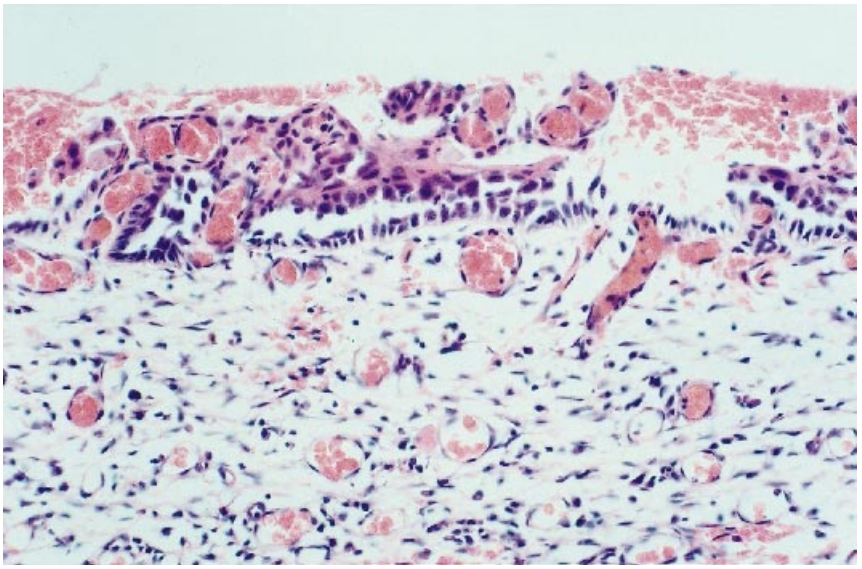

Figure 2. A cone biopsy of the cervix shows suprabasal acantholysis with shedding of all but the basal cells. The haemorrhage is biopsy-related (haematoxylin and eosin, original magnification × 200).

suprabasal clefts and bulla formation, acantholysis and shedding of surface squamous and metaplastic mucosa (Fig. 2). No atypia was identified. She was reassured that the abnormal smears were due to pemphigus of the cervix. However, it was advised that in view of her immunosuppressive treatment, annual cervical smears should be carried out.

There are very few reports of pemphigus involving the cervix,[1–6] but because it is usually asymptomatic, it probably occurs more commonly than the scarcity of case reports would suggest. In one small study,[4] 13 of 16 women with pemphigus were found to have a positive Nikolsky sign on the cervix (i.e. the epithelium could be easily dislodged by moderate sideways pressure with a cotton-tipped applicator). The validity of this physical sign was confirmed histologically and with the use of control subjects who did not have pemphigus.

The involvement of the cervix in pemphigus is not just an academic curiosity but is of practical relevance for three reasons: (i) the acantholytic suprabasal cells that might be obtained from a pemphigus erosion on the cervix during a routine cervical smear may show dyskaryotic changes falsely suggestive of cervical intraepithelial neoplasia (CIN). The person examining the smear microscopically clearly needs to be aware of the diagnosis of pemphigus to be able to interpret the changes seen and not overdiagnose CIN or malignant change. This could avoid unnecessary anxiety for patients, cytologists and doctors alike. (ii) Underdiagnosis of malignant change is also a danger, however, as there is almost certainly an increased risk of malignant change in the cervical epithelium in patients with pemphigus. This is probably due in part to chronic inflammation, erosion and repair, and in part to immunosuppressive treatments which are often used long-term in the treatment of pemphigus. Two cases of micro-invasive squamous cell carcinoma of the cervix associated with pemphigus of the cervix have been described, and in both

cases diagnosis was delayed because of confusion about the cytological changes seen.[6] It may be possible to distinguish between the acantholytic cells of pemphigus and dyskaryotic cells of CIN,[6] but if there is any doubt, biopsy is advisable. (iii) Dermatologists, gynaecologists, practitioners in sexually transmitted diseases and general practitioners need to be aware that pemphigus can involve the genital mucosa and should be prepared to enquire about symptoms such as dyspareunia and postcoital bleeding which are often very distressing, not easily volunteered and may well have a bearing on the management of the disease. Pemphigus may occasionally present with predominantly genital involvement.[5]

Department of Histopathology, R.N.Lonsdale
Norfolk and Norwich Health Care NHS Trust, S.Gibbs*
Norwich NR1 3SR, U.K.
**Dermatology Centre,*
West Norwich Hospital,
Norwich NR2 3TU, U.K.

References

1 Mikhail GR, Drukker BH, Chow C. Pemphigus vulgaris involving the cervix uteri. *Arch Dermatol* 1967; **95:** 496–8.
2 Libcke JH. The cytology of cervical pemphigus. *Acta Cytol* 1970; **14:** 42–4.
3 Friedman D, Haim S, Paldi E. Refractory involvement of cervix uteri in a case of pemphigus vulgaris. *Am J Obstet Gynecol* 1971; **110:** 1023–4.
4 Sagher F, Bercovici B, Romem R. Nikolsky sign on cervix uteri in pemphigus. *Br J Dermatol* 1974; **90:** 407–11.
5 Zosmer A, Kogan S, Frumkin A *et al.* Unsuspected involvement of the female genitalia in pemphigus vulgaris. *Eur J Obstet Gynaecol Reprod Biol* 1992; **47:** 263–6.
6 Dvoretsky PM, Bonfiglio TA, Patten SF, Helmkamp BF. Pemphigus vulgaris and microinvasive squamous cell carcinoma of the uterine cervix. *Acta Cytol* 1985; **3:** 403–10.

The pustular eruption of ulcerative colitis: a variant of Sweet's syndrome?

Sir, We report a patient with a generalized painful eruption of sterile neutrophilic pustules in association with an exacerbation of ulcerative colitis. This may represent a variant of Sweet's syndrome. The patient was a 39-year-old female who had suffered from ulcerative colitis for 10 years. She developed a severe exacerbation of her colitis which failed to respond to immunosuppressive therapy (prednisolone 30 mg and azathioprine 100 mg daily). After 4 weeks, she developed a painful skin eruption and was admitted to hospital. She was pyrexial with exquisitely painful, large (up to 1 cm in diameter) tender pustules in all areas (Fig. 1), a stomatitis and bilateral conjunctivitis. Pus from the lesions was sterile on bacterial and viral culture. Histological examination revealed a heavy infiltrate of neutrophils in the dermis and lower epidermis involving a hair follicle, with a mixed perivascular inflammatory infiltrate but no vasculitis. She had a peripheral blood neutrophilia (leucocytes $14{\cdot}7\times10^9$/L, 90% neutrophils). Circulating antineutrophil antibodies were detected

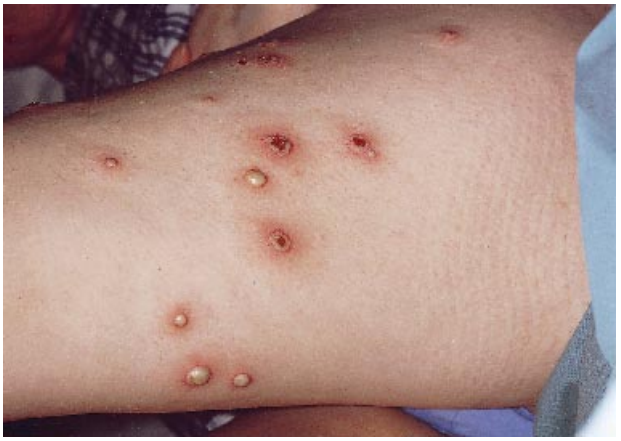

Figure 1. Inflammatory pustules are evident on the thigh.

with the classical staining pattern (c-ANCA), which did not bind to the common ANCA antigens (PR3, MPO and BPI).

The azathioprine was replaced by cyclophosphamide (50 mg daily), because, at this early stage, Wegener's granulomatosis had not yet been excluded as a possible diagnosis: cyclophosphamide can, of course, be used to treat pyoderma gangrenosum.[1] The colitis improved and the eruption resolved over the next week, and circulating ANCA were undetectable by 10 days. Over the following year, her colitis has remained well controlled without systemic immunosuppressant therapy. The eruption has not recurred.

Three similar cases with a sterile neutrophilic pustular eruption, pyrexia, malaise and a peripheral neutrophilia, triggered by an exacerbation of ulcerative colitis, have been reported.[2,3] Two of them had mucous membrane involvement.[3] Their acute illness settled with the colitis. In another patient, the eruption waxed and waned with the colitis over a prolonged period.[4] The authors of these reports suggested that this is a variant of pyoderma gangrenosum[3] (some lesions did develop into classical pyoderma gangrenosum in one case).[5] However, the clinical picture in our case, and in theirs, does fit some of the criteria for the diagnosis of Sweet's syndrome,[6] except that our patient's large pustules with a little surrounding erythema are not typical of Sweet's.[6] Sweet's syndrome has, of course, been observed in ulcerative colitis[7] and other inflammatory bowel diseases.[8] We consider that her disease lies within the spectrum of overlapping clinical entities[7,9] which comprise the neutrophilic dermatoses.

In ulcerative colitis, there is neutrophilic infiltration of the colonic mucosa, and about a third of patients with that disease have circulating ANCA (both c- and p-ANCA).[10] ANCA has also been identified in neutrophilic dermatoses: atypical ANCA in Sweet's syndrome[11] and c-ANCA in a patient with a combination of erythema elevatum diutinum and pyoderma gangrenosum.[9] *In vitro* studies suggest that ANCA may play a pathogenic role in the activation of neutrophils,[12] and abnormalities of circulating neutrophils have been demonstrated in patients with ulcerative colitis.[13] It is therefore tempting to postulate that our patient's ANCA may have contributed to both her eruption and her colitis by their effect

on circulating neutrophils, although there is no direct evidence for this.

Our patient is the fourth described with this pustular eruption of ulcerative colitis, which does appear to be a distinct clinical entity. This disorder lies within the spectrum of the neutrophilic dermatoses and we consider that it is best classified as a variant of Sweet's syndrome.

Departments of Dermatology and R.P.E.SARKANY
**Histopathology,* N.P.BURROWS
Addenbrooke's Hospital, J.W.GRANT*
Cambridge, CB2 2AA, U.K. R.J.PYE
P.G.NORRIS

References

1 Newell LM, Malkinson FD. Pyoderma gangrenosum. Response to cyclophosphamide therapy. *Arch Dermatol* 1983; 1; **19:** 495–7.
2 Bames L, Lucky AW, Bucuvalas JC *et al.* Pustular pyoderma gangrenosum associated with ulcerative colitis in childhood. *J Am Acad Dermatol* 1986; **15:** 608–14.
3 O'Loughlin S, Perry HO. A diffuse pustular eruption associated with ulcerative colitis. *Arch Dermatol* 1978; **114:** 1061–4.
4 Fenske NA, Gem JE, Pierce D *et al.* Vesiculopustular eruption of ulcerative colitis. *Arch Dermatol* 1983; **119:** 664–9.
5 Callen JP, Woo TY. Vesiculopustular eruption in a patient with ulcerative colitis. *Arch Dermatol* 1985; **121:** 399–404.
6 Su WPD, Liu HNH. Diagnostic criteria for Sweet's syndrome. *Cutis* 1986; **37:** 167–74.
7 Benton EC, Rutherford D, Hunter JAA. Sweet's syndrome and pyoderma gangrenosum associated with ulcerative colitis. *Acta Derm Venereol (Stockh)* 1985; **65:** 77–80.
8 Kemmett D, Gawkrodger DJ, Wilson G, Hunter JAA. Sweet's syndrome in Crohn's disease. *Br Med J,* 1988; **297:** 1513–4.
9 Bayle P, Laplanche G, Gorguet B *et al.* Neutrophilic dermatosis: A case of overlapping syndrome with monoclonal antineutrophil cytoplasmic autoantibody activity. *Dermatology* 1994; **189:** 69–71.
10 Schlenker T, Apenberg S, Raedsch R *et al.* Antineutrophile Zytoplasmatische Antikorper Bei Chronisch-Entzundlichen Darmerkrankungendeutsche Medizinische. *Deutsch Med Wochenschr* 1992; **117:** 1463–8.
11 Kemmett D, Harrison DJ, Hunter JAA. Antibodies to neutrophil cytoplasmic antigens: A serologic marker for Sweet's syndrome. *J Am Acad Dermatol* 1991; **24:** 967–9.
12 Falk RJ, Terrell RS, Charles LA *et al.* Antineutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. *Proc Natl Acad Sci USA* 1990; **87:** 4115–9.
13 Stadnicki A, Hrycek A, Mazur W *et al.* The changes in metabolism and function of polymorphonuclear leucocytes in patients with ulcerative colitis. *Arch Gastroenterol* 1994; **13:** 40–3.

Unusual skin ulceration in an HIV-positive patient who had cutaneous syphilis and neurosyphilis

SIR, I read the report by Tucker *et al.*[1] with great interest. It is true that there are an increasing number of reports in the literature highlighting atypical presentations of syphilis in HIV-infected individuals. But in the case by Tucker *et al.* I feel there is not much evidence to say that this patient had neurosyphilis. Their venereal disease reference laboratory (VDRL test) titre was highly reactive (128 units) and cerebrospinal fluid (CSF) VDRL was not available. It is known that the CSF abnormality can occur in secondary syphilis. Moreover, the clinical improvement of the patient's mental state following penicillin treatment could be a coincidence or result from the control of some other infection which was not diagnosed. The authors accept that the lesions did not show clinical, histopathological or bacteriological features of syphilis and did not respond to antiluetic treatment. I feel it is likely that this patient had a secondary or early latent syphilis with some other central nervous system and cutaneous pathology, with a background HIV infection.

Department of Dermatology, Medical College, K.AJITHKUMAR
Kottayam, Kerala, India

References

1 Tucker SC, Yates VM, Thambar IV. Unusual skin ulceration in an HIV-positive patient who had cutaneous syphilis and neurosyphilis. *Br J Dermatol* 1997; **136:** 946–8.

Reply

SIR, Dr Ajithkumar has asserted that he does not feel that the patient we reported[1] had neurosyphilis, rather that he had secondary or early latent syphilis with other, unspecified, central nervous system pathology. While there was insufficient cerebrospinal fluid (CSF) sample for the venereal disease reference laboratory (VDRL) assay, our patient's CSF *Treponema pallidum* haemagglutination assay (TPHA) and fluorescent treponemal antibodies-absorbed (FTA-ABS) tests were both positive. It is noteworthy that there have been reports of patients with HIV and neurosyphilis with a negative CSF VDRL, particularly in the early stages of infection.[2] Moreover, and what may not have been clear from the case report, there was a vast improvement in our patient's mental state following antiluetic treatment. Prior to this treatment, his mental state was severely disturbed with gross disorientation and confabulation. Penicillin treatment brought about a rapid and total reversion of these problems and his mental state became normal. Furthermore, his hair regrew and his widespread ulcers improved considerably with treatment. There was only one area on his right forearm which remained resistant to therapy.

There are no undisputed rules governing the serological diagnosis of neurosyphilis,[3] particularly in patients co-infected with HIV. In such cases, the serological findings can be modified and complicated, and clinical parameters necessarily become diagnostically important. Our belief that our patient was suffering from neurosyphilis stems from a combination of his serum and CSF serological results, together with his striking clinical response to treatment.

Dr Ajithkumar states that 'other infection' could have caused the changes in the mental state of our patient. Cytomegalovirus (CMV) infection is known to be a problem in HIV-infected individuals,[4] and may lead to an encephalitis which could give rise to a similar clinical picture to that seen in our patient. However, his CMV serology was negative, and, had this been a cause for his confusion, his clinical state would not have responded so dramatically to penicillin.

Departments of Dermatology and S.C.Tucker
**Genitourinary Medicine,* V.M.Yates
Burnley General Hospital, I.V.Thambar*
Casterton Ave, Burnley, BB10 2PQ, U.K.

References

1 Tucker SC, Yates VM, Thambar IV. Unusual skin ulceration in an HIV positive patient who had cutaneous syphilis and neurosyphilis. *Br J Dermatol* 1997; **136:** 946–8.
2 Kvinesdal B, Pedersen NS. False positive HIV antibody tests in RPR reactive patients. *JAMA* 1992; **60:** 923–5.
3 Sanchez M, Luger AFH. Syphilis. In: *Dermatology in General Medicine* (Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Frank Austen K, eds), 4th edn, Vol II. New Yory: McGraw-Hill, Inc., 1993; 2703–43.
4 Gallant JE. Incidence and natural history of cytomegalovirus disease in patients with advanced human immunodeficiency virus disease treated with zidovudine. *J Infect Dis* 1992; **166:** 1223–6.

Autoerythrocyte sensitization syndrome with positive anticardiolipin antibodies

Sir, In 1955, Gardner and Diamond[1] described a condition characterized by recurrent crops of painful ecchymotic lesions in four emotionally unstable women in whom no haematological disorder was found. The authors postulated an autoimmune reaction to erythrocytes, as further lesions were reproduced by intracutaneous injections with autologous erythrocytes or erythrocytic stroma. Later, it was shown that the reaction occurs against the stromal erythrocyte phospholipids, particularly phosphatidylserine.[2] Other internal manifestations of the syndrome are described.[3]

A 17-year-old girl was seen in April 1996 for three successive crops of erythematous or ecchymotic lesions, mainly located on the extremities and lower abdomen (Fig. 1). The lesions appeared approximately weekly and were preceded by pain or a burning sensation, occasionally with an erythematous surrounding border. They faded gradually in 7–10 days, leaving slight hyperpigmentation that resolved completely in a few days; they did not undergo the diverse change in colour of common ecchymoses. A full blood count, serum C-reactive protein and coagulation studies were normal. Two skin biopsies showed extensive intradermal haemorrhages and scant perivascular lymphocytic infiltrates. A diagnosis of autoerythrocyte sensitization syndrome was considered. There was no history of emotional problems, psychiatric disease or trauma; psychological tests were not performed. No other symptoms of autoerythrocyte sensitization syndrome were found.

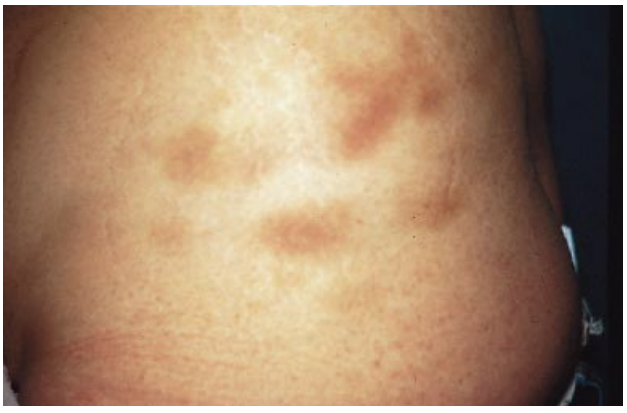

Figure 1. Tender erythematous or violaceous plaques are evident on the flank.

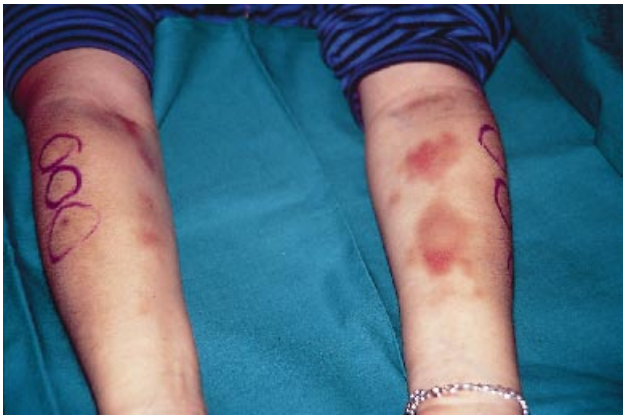

Figure 2. Erythematous or violaceous plaques are seen adjacent to the sites of the intradermal tests with normal saline and autologous plasma.

In June 1996, further laboratory analyses showed a serum gamma globulin level of 239 g/L (normal 147–217), with anticardiolipin antibodies (ELISA, IMMCO), i.e. an IgM of 52 MPL/mL (positive when > 12), and normal IgG. Normal or negative results were obtained with VDRL, serum complement C3 and C4, antinuclear antibodies and the Mantoux test.

In October 1996, serum anticardiolipin antibodies were determined again (ELISA, Chromogenix); the IgG was 28 GPL/mL (positive when > 23), IgM was 18 MPL/mL (positive when > 11). Skin testing to the patient's erythrocytes, autologous plasma and normal saline were performed by intradermal injections with 0·1 mL of each substance in three adjacent areas on the dorsal aspect of her forearms (she was unaware of the injected substances). About 48 h later, she noted induration and slight erythema in the zones where plasma and normal saline were injected, with two adjacent tender erythematous plaques (Fig. 2). We prescribed pentoxifylline 400 mg, twice a day for 4 months. The ecchymotic episodes appeared less frequently (from weekly to monthly intervals), were less severe and were not tender. In December 1996 she had a nose bleed and in January 1997 an ecchymotic lesion that was larger than usual. The dose of pentoxifylline was increased to 400 mg three times a day. The titres of anticardiolipin antibodies have not varied.

There are three theories of pathogenesis; first, it may be a psychiatric condition, based on the high frequency of emotional and psychiatric features in these patients;[4] second, it may be self-inflicted (purpura factitia),[5] although this is unlikely as the lesions in true factitial purpura lack an erythematous border and are not usually preceded by pain; third, it may be an immune disease, as suggested by Gardner and Diamond.[1]

Positive responses to intradermal injection are reported with many agents and at sites distant from the injection of blood.[3] Inflammatory bruises have also been induced after injection with purified protein derivative, attributable to its phospholipid content.[6] For this reason, anticardiolipin antibodies were determined in this patient and found to be positive. Anticardiolipin antibodies are found in $<2\%$ of the normal population[7] and we believe that this finding may be significant.

Unlike the antiphospholipid syndrome, autoerythrocyte sensitization syndrome is not commonly associated with thrombotic phenomena. However, two cases reported by Gardner and Diamond[1] presented with cerebral haemorrhage, and another suffered three attacks of thrombophlebitis. In a review of 71 patients with autoerythrocyte sensitization syndrome[3] only five episodes of thrombophlebitis were detected; there were no descriptions of recurrent abortion or thrombocytopenia.

In patients with positive anticardiolipin antibodies, the risk of a thrombotic complication is related to the presence of high titres of IgG anticardiolipin antibodies.[8] Low titres of circulating anticardiolipin antibodies could explain the varied neurological, ocular and other symptoms of autoerythrocyte sensitization syndrome. All patients with the syndrome should be screened for anticardiolipin antibodies.

Departamento de Dermatologia Occidente and E.SUDY
**Servicio de Medicina, Universidad de Chile,* F.URBINA
Hospital San Juan de Dios, Santiago, Chile. P.VASQUEZ*

References

1 Gardner FH, Diamond LK. Autoerythrocyte sensitization. A form of purpura producing painful bruising following autosensitization to red blood cells in certain women. *Blood* 1955; **10:** 675–90.
2 Groch GS, Finch SC, Rogoway W, Fischer DS. Studies in the pathogenesis of autoerythrocyte sensitization syndrome. *Blood* 1966; **28:** 19–33.
3 Ratnoff OD. Psychogenic purpura (autoerythrocyte sensitization): An unsolved dilemma. *Am J Med* 1989; **87:** 3–16N.
4 Ratnoff OD, Agle DP. Psychogenic purpura: a re-evaluation of the syndrome of autoerythrocyte sensitization. *Medicine* 1968; **47:** 475–500.
5 Stefanini M, Baumgart ET. Purpura factitia. An analysis of criteria for its differentiation from autoerythrocyte sensitization purpura. *Arch Dermatol* 1972; **106:** 238–41.
6 Waldorf DS, Lipkin G. Sensitization to erythrocytes. A distinctive syndrome. *JAMA* 1968; **203:** 597–9.
7 Shapiro SS. The lupus anticoagulant/antiphospholipid syndrome. *Ann Rev Med* 1996; **47:** 533–53.
8 Finazzi G, Brancaccio V, Moia M *et al.* Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies. A four year prospective study from the Italian registry. *Am J Med* 1996; **100:** 530–6.

Pyoderma gangrenosum successfully treated with perilesional granulocyte-macrophage colony stimulating factor

SIR, Pyoderma gangrenosum (PG) is an ulcerative skin disease whose pathogenesis remains obscure, although associated systemic conditions have been identified. About 30% of the cases are related to inflammatory bowel diseases.[1] Systemic and local steroids, dapsone, clofazimine and lately cyclosporin are all used as acceptable treatment regimens for PG.[2] We report a case of PG coexisting with Crohn's disease, which was successfully treated with perilesional granulocyte macrophage-colony stimulating factor (GM-CSF), a proinflammatory cytokine.

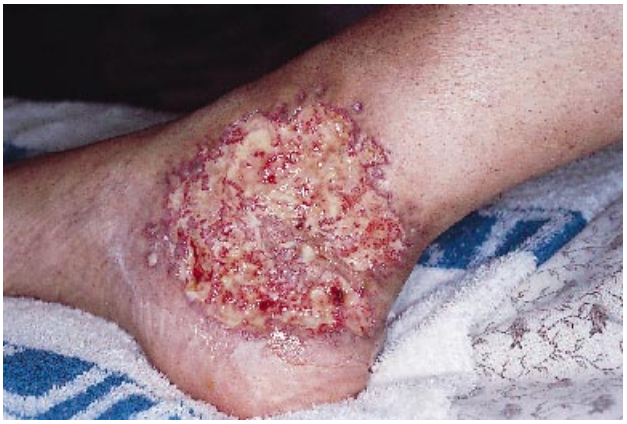

Figure 1. The pyoderma gangrenosum lesion on the right ankle before granulocyte macrophage-colony stimulating factor treatment.

A 45-year-old woman was admitted suffering from three abruptly developing skin lesions, two on her right ankle and one on the abdominal wall. She had previous exacerbations and remissions from Crohn's colitis in the previous 20 years. She was treated accordingly with steroids, azathioprine and salazopyrine. Shortly before admission, she received 5-aminosalicylic acid. During her follow-up in the gastroenterology unit, a few of the intestinal episodes were reported to occur simultaneously with the appearance of the PG lesions; some lesions eventually required skin grafting. One week before admission, she was suffering from weakness, abdominal pain and bloody diarrhoea. Typical skin lesions of PG appeared on her right ankle and on the lower abdomen. Treatment with systemic prednisolone and local (perilesional) steroids was initiated, with additional antibiotics (ofloxacin). When her condition worsened she was admitted to hospital, when a well-defined violaceous plaque on an erythematous background was found on the medial right ankle; it was 15×10 cm and there was epidermal maceration in its centre, with a purulent discharge. A tense bulla was detected on the lateral aspect of the right ankle. On the lower portion of the abdominal wall another erythematous plaque (2×2 cm) was discovered.

Upon admission, the dosage of steroids was increased to 100 mg daily, with cimetidine 400 mg twice daily. When there was no response and the skin lesions extended dramatically, dapsone 100 mg per day was added, but this was discontinued because it was not effective and the patient became anaemic. During this treatment the ulcer on the medial aspect of the ankle continued to progress (Fig. 1). Leucomax (Molgramostim, GM-CSF) 400 mg was then injected perilesionally each week for 4 weeks, producing a prompt and impressive improvement. Because there was an opacity in the left lung, steroids were tapered off and treatment with isoniazid initiated; no adverse reactions were detected. On discharge

from hospital, a wide band of healthy skin covered most of the lesions, whereas the remaining ulcer grounds were covered with granulation tissue.

GM-CSF, first identified as a stimulatory factor for the production of granulocytes and monocytes/macrophages, has since been shown to enhance their immunological function.[3] GM-CSF promotes phagocytosis, the expression of adhesion molecules, primes chemotaxis and enhances migration.[4] All these functions are pivotal in the process of wound healing. It has been shown that previous local treatment with GM-CSF expedites the healing of skin after controlled punch biopsies. Hence, we decided to exploit its pro-inflammatory properties and use GM-CSF for its wound-healing effect.

Boente *et al.*[5] recently reported the clearing of a plantar Kaposi's sarcoma lesion after local injections with recombinant GM-CSF, exerting a purely local effect. Following their publication, A.Sharon (Assaf Haropeh Medical Center, Israel) suggested this approach for PG. To adopt such an approach, the PG ulcer should be seen as a sign of immune incompetence rather than as the outcome of an exaggerated immune or autoimmune response. Indeed, various immunological abnormalities are reported to coexist with PG.[1] Some of the defects might account for the difficulties in healing PG ulcers; reported immunological defects, e.g. inadequate expression of adhesion molecules, might be corrected by the immunoregulatory functions of GM-CSF. Hence, GM-CSF injected locally could express its potential to promote inflammation, with the aim of initiating wound healing. The choice was useful in the present patient; after the first perilesional injection there was an immediate response. The lesions stopped progressing and then rapidly regressed. After the fourth injection there was no need to continue treatment. Recently, Bulvik and Jacobs[6] described the prompt healing of a PG ulcer in response to the concurrent subcutaneous administration of GM-CSF in a patient who was a candidate for bone-marrow transplantation. Before this report, the systemic administration of GM-CSF was anecdotally implied in aggravating PG.[7] Alli *et al.* reported the rapid healing of a large genital ulcer in a patient with Behçet's disease after local intralesional injection with GM-CSF.[8]

Hence, we suggest perilesional injection with GM-CSF as a possible treatment for otherwise refractory PG; inasmuch as its known side-effects should also be considered, its therapeutic effect might improve our understanding of the pathophysiology of PG.

Department of Dermatology, D.Shpiro
Sheba Medical Center D.Gilat
*and *Assaf-Haropeh Medical Center,* L.Fisher-Feld
Tel Hashomer, 52621 Israel A.Shemer
I.Gold*
H.Trau

References

1 Powell FC, Su WPD, Perry HO. Pyoderma gangrenosum: Classification and management. *J Am Acad Dermatol* 1996; **34:** 395–409.
2 Chow RKP, Ho VC. Treatment of pyoderma gangrenosum. *J Am Acad Dermatol* 1996; **34:** 1047–60.
3 Fleischmann J, Glde DW, Weisbart RH *et al.* Granulocyte-macrophage colony-stimulating factor enhances phagocytosis of bacteria by human neutrophils. *Blood* 1986; **68:** 708–11.
4 Lopez AF, Williamson DJ, Gamble JR *et al.* Recombinant human Granulocyte-macrophage colony-stimulating factor stimulates in vitro mature human neutrophil and eosinophil function, surface receptor expression, and survival. *J Clin Invest* 1986; **78:** 1220–8.
5 Boente P, Sampaio C, Bradao MA. Local perilesional therapy with rhGM-CSF for Kaposi's sarcoma. *Lancet* 1993; **341:** 1154.
6 Bulvik S, Jacobs P. Pyoderma gangrenosum in myelodysplasia responding to GM-CSF. *Br J Dermatol* 1997; **136:** 637–8.
7 Perrot JL, Benoit F, Segault D *et al.* Pyoderma gangrenosum aggrave par administration de GM-CSF. *Ann Dermatol Venereol* 1992; **119:** 846–8.
8 Alli N, Karakayali G, Kahraman I *et al.* Local intralesional therapy with rhGM-CSF for a large genital ulcer in Behçet's disease. *Br J Dermatol* 1997; **136:** 639–40.

Cyclosporin for the treatment of granuloma annulare

Sir, Cyclosporin A (CyA) has become an accepted treatment for severe psoriasis and atopic dermatitis. It has also been used in a wide variety of other dermatological disorders, but the results in these two conditions have often been variable. I describe two patients with multiple granuloma annulare (GA) in whom treatment with CyA led to complete resolution.

Two women aged 52 years (patient 1) and 58 years (patient 2) presented with refractory multiple GA of several years' duration. Both patients had an unsatisfactory response to topical corticosteroid therapy. Patient 2 had also been treated unsuccessfully with systemic corticosteroids. All the above therapies had been discontinued for several months. At

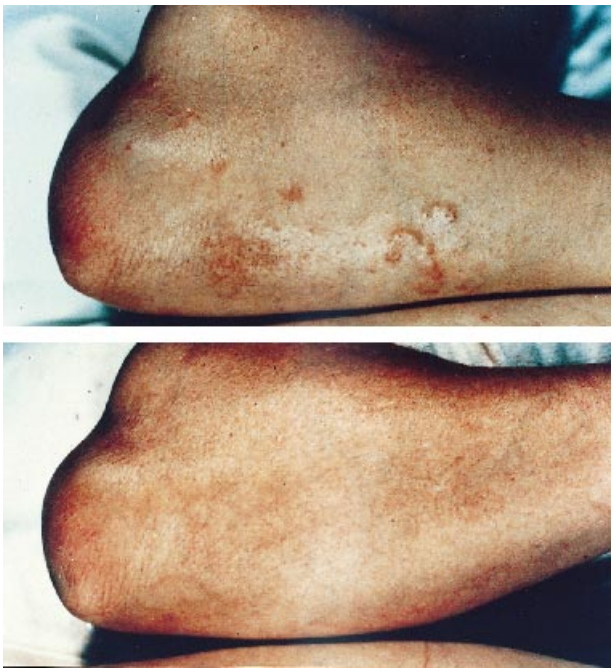

Figure 1. (top) Numerous erythematous papules, some in an annular pattern, on the forearms and (bottom) complete resolution after cyclosporin therapy.

presentation, apart from the skin lesions, the two patients were in good health; there was no history of recent drug therapy. There were numerous, erythematous papules on the skin, some of which showed an annular pattern. The lesions were on the trunk, neck and extensor aspects of the arms and legs (Fig. 1 (top)). The clinical diagnosis of GA was confirmed in both patients by histopathology. Results of laboratory tests were within normal range. CyA, 3 mg/body weight per day, was administered as the sole medication, and blood pressure and serum creatinine level monitored throughout treatment. The skin lesions gradually flattened and disappeared within a month. The dosage was gradually tapered and after 2 additional months, the therapy was stopped. No recurrence occurred during a 1-year follow-up (Fig. 1 (bottom)).

GA is a benign inflammatory skin disease, the cause of which remains obscure. Although a pathogenetic role has been suggested for delayed-type hypersensitivity,[1] the initiating antigens are, as yet, unidentified.

Many treatments for GA, including CyA,[2] have been used, often with unsatisfactory results. The most important action of CyA, a suppressor of cell-mediated immunity, is the inhibition of lymphokine production (primarily interleukin-2) by activated T-helper cells.[3] None the less, granuloma formation may be independent of T cells.[4] In athymic mice the production of monokines, e.g. interleukin-1 and tumour necrosis factor, by tissue macrophages[5] leads to skin granuloma formation. Thus, even if the role of monokines in GA is still unknown, CyA can be postulated to exert its favourable effect in this condition not only by suppressing cell-mediated immunity, but also by inhibiting monokine production.

Interestingly, GA in the present patients responded rapidly to CyA treatment and did not recur during follow-up after discontinuing treatment. This indicates that CyA 'turned off' the inflammatory process. Unlike the previous report on the use of CyA in GA,[2] the present skin lesions resolved completely with a lower dose of CyA and in a shorter time. This could be achieved using the new microemulsion formulation of CyA, which has been shown to have a better bioavailability than the original oral formulation, as reported in transplant recipients.[6] This preparation enhances the safety and effectiveness of CyA treatment and simplifies its clinical application.

There is controversy about the use of CyA in relatively benign conditions. GA is a symptomless skin disorder but may cause mental distress in some patients; treatment should not expose the patient to unnecessary risks. The administration of CyA, 3 mg/kg per day for 3 months is well tolerated, provided the patient has no overt renal failure or severe hypertension. In conclusion, the previous report[2] and the present two cases support the view that CyA is a useful drug in the treatment of GA. Further controlled studies on more patients are required to confirm these encouraging results.

Servizio di Immunopatologia Cutanea, P.Fiallo
Università di Genova,
Viale Benedetto XV,
7, I-16132 Genoa, Italy

References

1 Buechner SA, Winkelmann RK, Banks PM. Identification of T-cell subpopulations in granuloma annulare. *Arch Dermatol* 1983; **119:** 125–8.
2 Filotico R, Vena GA, Coviello C, Angelini G. Cyclosporin in the treatment of generalized granuloma annulare. *J Am Acad Dermatol* 1994; **30:** 487–8.
3 Lafferty KJ, Borel JF, Hodgkin P. Cyclosporin A (CSA); models for the mechanism of action. *Transplant Proc* 1983; **15** (Suppl. 1)**:** 2230–41.
4 Epstein WL, Okamoto M, Suya H, Fukuyama K. T-cell independent transfer of organized granuloma formation. *Immunol Lett 1986/1987; **14:** 59–63.*
5 Suya H, Fujioka A, Pincelli C *et al.* Skin granuloma formation in mice immunosuppressed by cyclosporine. *J Invest Dermatol* 1988; **90:** 430–3.
6 Trull AK, Tan KKC, Uttridge JA *et al.* Cyclosporin absorption from microemulsion formulation in a liver transplant recipient. *Lancet* 1993; **341:** 433.

Intralesional treatment of cutaneous leishmaniasis with meglumine antimoniate

Sir, We report the results of the administration of intralesional meglumine antimoniate in 45 patients from Cagliari (Sardinia) with cutaneous leishmaniasis. From January 1984 to December 1996, 45 cases of cutaneous leishmaniasis (23 male and 22 female, age range 8 months to 63 years, including 13 children < 10 years old) were treated in our dermatology clinic. The mean (range) duration of the lesions, calculated from the appearance of the first clinical symptoms to the time of referral, was 2·5 (1–10) months. Thirty-eight patients had a single 'Oriental sore' with diameters ranging from 0·5 to 4 cm. The remaining seven patients had between two and four skin lesions. In total, 59 lesions were examined, 18 of which were ulcerated (30%), with 34 (58%) lesions on the face, 13 (22%) on the upper extremities, 10 (17%) on the lower, and one each (2%) on the nasal mucous membrane and prepuce. All the lesions were treated by local infiltration with meglumine antimoniate (300 mg/mL) weekly for a maximum of 6 weeks. The solution was infiltrated until the whole lesion had blanched, which required 0·5–3 mL (mean 1·3) depending on the size of the lesion. However, the maximum dose never exceeded 5 mL, corresponding to 1·5 g of meglumine antimoniate. All the patients recovered completely and the microbiological findings at lesional sites became negative after 3–6 weeks of treatment; 20 lesions (34%) cleared after 3 weeks, 33 (56%) after 4 weeks, four (7%) after 5 weeks and two (3·4%) after 6 weeks. Small and non-ulcerated lesions responded better to treatment, and those on the lower limbs responded more slowly than lesions elsewhere.

At the end of the treatment, 18 lesions (31%) showed hyperpigmentation which resolved completely within 5 months. Mild scarring was present in 14 lesions (24%) and was more frequent among ulcerated lesions. None of the patients presented systemic side-effects (electrocardiograms, renal and hepatic function were normal in all patients) or relapse. Local intolerance was observed in five patients (11%) but produced only mild reactions such as erythema or

pruritus, which did not require an interruption to the treatment.

The choice of therapy for treating cutaneous leishmaniasis is undoubtedly justified and influenced by the geographical, clinical and microbiological differences found in this pathology. Previous studies have shown an efficacy of intralesional treatment with pentavalent antimonial salts of 68–100%.[1–5] Recently, Tallab *et al.*[6] reported an overall success rate of 99·2% using sodium stibogluconate in three different treatment schedules, with the best results obtained when local infiltrations were performed weekly.

In the present study, the use of meglumine antimoniate achieved complete recovery in all the lesions, with no relapse or side-effects and with only minimal scarring at 14 lesional sites (24%) at the end of treatment. However, during the follow-up, noticeable scars remained at only six of these sites (10%). We suggest that these results are attributable to correct infiltration procedures, injections at 7-day intervals and adequate infiltration of the drug at each lesional site. Indeed, inadequate drug infiltration is probably responsible for the failure of this treatment.[7] The technique of intralesional injection is important; the whole lesion, including the advanced edges, should be infiltrated until completely blanched, indicating the full infiltration of the nodular element. Adequate doses are also essential, not only in obtaining a quick and complete clinical and microbiological recovery, but also in avoiding the development of resistant organisms. The appearance of parasites resistant to antimonials is a potential risk of inadequate doses.[6,8] We used meglumine antimoniate at doses of 0·5–3 mL in all but two lesions, for which a dose of 5 mL was used, but the maximum dose per visit did not exceed the recommended dose of 60–100 mg/kg for parenteral use.[3]

From our experience and the long follow-up in the present study, we think that intralesional meglumine antimoniate should be considered the first choice in the management of cutaneous leishmaniasis in our region. Although pentavalent antimonials are long-standing drugs in the cure of cutaneous leishmaniasis, their intralesional use has many advantages; they produce a quick therapeutic response with high rates of complete recovery, are tolerated well, have no side-effects and, last but not least, offer therapeutic cycles at a relatively low cost.

Clinica Dermatologica, N.Aste
Ospedale S. Giovanni di Dio, M.Pau
Via Ospedale, C.Ferreli
54 09124 Cagliari, Sardinia, Italy P.Biggio

References

1 Skarquie KE, Al-Talib KK, Chu AC. Intralesional therapy of cutaneous leishmaniasis with sodium stibogluconate antimony. *Br J Dermatol* 1988; **119:** 53–7.
2 Faris RM, Jarallah JS, Khoja TA, Al-Yamani MJ. Intralesional treatment of cutaneous leishmaniasis with sodium stibogluconate antimony. *Int J Dermatol* 1993; **32:** 610–2.
3 Lambert D, Mambre B. Traitement des leishmanioses cutanées. *Ann Dermatol Venereol* 1988; **115:** 641–3.
4 Kellum RE. Treatment of cutaneous leishmaniasis with an intralesional antimonial drug (Pentostam). *J Am Acad Dermatol* 1986; **15:** 620–2.
5 Oliveira-Neto M, Pirmez C, Coutinho S, Grimaldi G. Intralesional pentavalent antimonial therapy in american cutaneous leishmaniasis: a two-year follow-up study. Presented at 17th World Congress of Dermatology. Berlin. 1987; part I: 25 (Abstr.).
6 Tallab TM, Bahamdam KA, Mirdad S *et al.* Cutaneous leishmaniasis: schedules for intralesional treatment with sodium stibogluconate. *Int J Dermatol* 1996; **35:** 594–7.
7 Kellum RE. Intralesional injection of sodium stiboglucanate by dermal pressure-jet instrument. *J Am Acad Dermatol* 1987; **17:** 694.
8 Grogl M, Odoula AM, Corder LD, Kyle DE. *Leishmania* spp: development of pentostam-resistant clones in vitro by discontinuous dry exposure. *Exp Parasitol* 1989; **69:** 78–90.

Erbium:YAG laser-assisted treatment of miliary osteoma cutis

Sir, The term osteoma cutis denotes rare disorders with cutaneous ossification.[1] The therapy of existing osteoma is regarded as extremely difficult and there is no effective treatment to prevent the eruption of new lesions.[2,3] There are 12 case reports of multiple miliary osteoma cutis of the face in women,[4–6] although it has not been recorded previously in men.

A 54-year-old healthy man presented with multiple firm, non-tender, skin-coloured 1–3 mm papules on his forehead and both cheeks, which had developed progressively over 3 years with no symptoms (Fig. 1a). As in the other reported cases, no abnormalities in calcium/phosphate metabolism were detected and no inflammatory condition, e.g. acne, preceded the ossification. Histological examination of the papules showed circumscribed ossification in the mid-corium with multiple osteocytes and few osteoblasts. The laboratory analyses were unremarkable. We also treated a woman with multiple miliary osteoma cutis; her details were published earlier;[4] both patients had requested treatment.

After topical occlusive application of prilocaine/lidocaine cream (EMLA® cream), the tissue layers covering the osteoma were gently removed by erbium:YAG laser passes (SupERB®, Baasel-Lasertechnik, 2940 nm, pulse width 200 μs, 250–300 mJ per pulse, repetition rate 5–8 Hz, spot size 2 mm). Depending on the site, three to five shots per papule were required to ablate the entire epidermis and upper dermis. Once the osteoma was uncovered it could be removed either by simple pressure or a fine curette (Fig. 1b). The lesions re-epithelialized after 7–10 days and after 12 weeks, the cosmetic result was excellent (Fig. 1c).

Osteoma cutis has no potential for malignant transformation but affected patients request treatment either to prevent the occurrence of new lesions or to remove existing ones; the former goal was not previously possible. Preventive trials with etidronate disodium (diphosphonate) were ineffective.[2,7] A variety of surgical techniques has been used for the symptomatic removal of cutaneous osteomas, including simple incision, excision, dermabrasion or punch excision.[3,6] Recently, the removal of digital calcinosis by carbon dioxide laser vaporization was described.[8] Apart from the likelihood of new lesions appearing after removal, all surgical procedures risk unpleasant scarring. We therefore aimed at a precise and

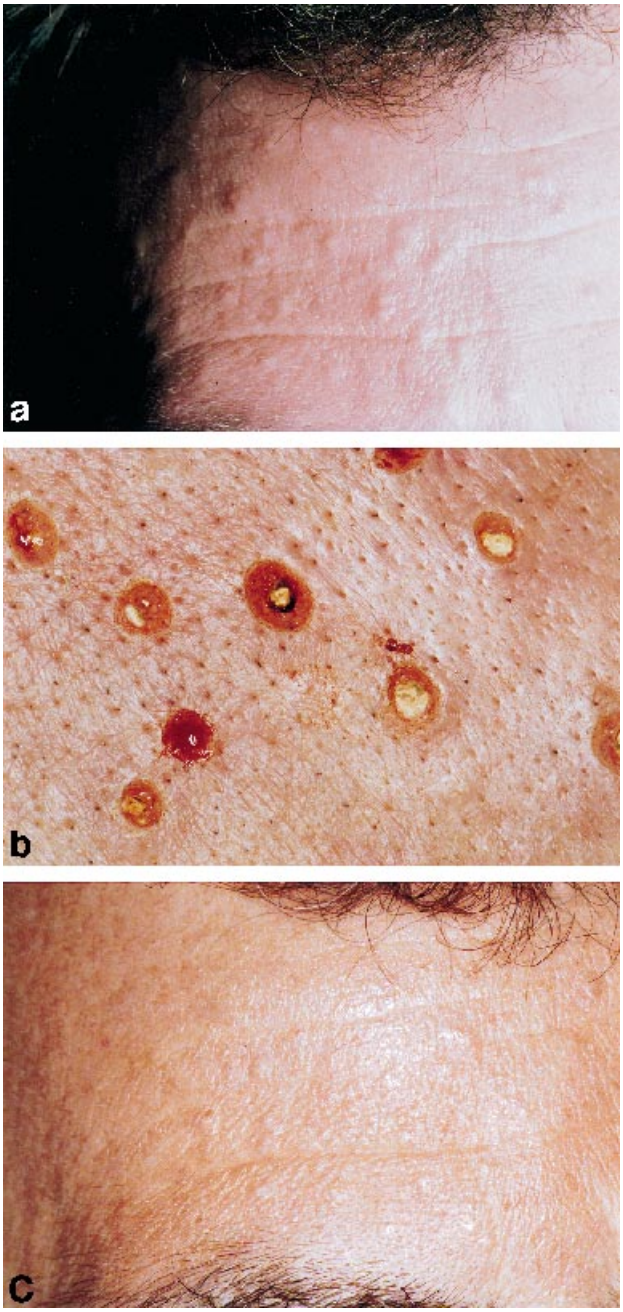

Figure 1. (a) The preoperative appearance of multiple miliary osteoma cutis on the forehead of a 54-year-old man. (b) The intraoperative appearance. (c) A good cosmetic result was evident at follow-up.

controlled removal of the osseous particles, to avoid unnecessary trauma to surrounding tissues. This was achieved using pulsed mid-infrared ablation, capable of removing both skin and bone. Among the various infrared systems which have been investigated by our group[9] and others, the erbium:YAG laser has proved extremely useful because it has unique absorption characteristics in tissue water and collagen.[10] The emission wavelength (2940 nm) of this system exactly matches the absorption peak of tissue water, resulting in a 10-fold higher absorption than for carbon dioxide laser light.[9] Therefore, a precise and clean ablation can be achieved, avoiding unnecessary thermal injury, including tissue shrinkage or residual necrosis. This precise ablation is unique and superior to the ablative properties of the pulsed carbon dioxide laser systems.

In both patients, laser ablation was fast and easy to perform. Although the ablation of bone tissue was possible by additional laser pulses, the exposed bony material was easily removed using small curettes. The procedure can be performed without local anaesthetic after the topical application of EMLA cream and larger areas can be treated at one time, with good patient tolerance. When reviewed after 12 weeks, the cosmetic result was excellent, with no residues of osteoma and no osteomas recurring at the treated sites within a follow-up of 24 months. The erbium:YAG laser is thus the preferred treatment for this rare disorder.

Zentrum Dermatologie und Venerologie, Klinikum d. J.W. Goethe-Universität, Theodor-Stern-Kai 7, 60590 Frankfurt/M, Germany

F.R. Ochsendorf
R. Kaufmann

References

1 Orlow SJ, Kalman KL, Bolognia JL. Skin and bones. II. *J Am Acad Dermatol* 1991; **25:** 447–62.
2 Schuhmachers G, Worret WI. Osteoma cutis. Pathogenese und therapeutische Möglichkeiten. *Hautarzt* 1992; **43:** 422–5.
3 Fulton JE. Dermabrasion-loop-punch-excision technique for the treatment of acne-induced osteoma cutis. *J Dermatol Surg Oncol* 1987; **13:** 655–9.
4 Boehncke WH, Kaufmann R, Weber C, Sterry W. Osteoma cutis. Multiple miliare Osteome des Gesichts. *Hautarzt* 1993; **44:** 245–7.
5 Levell NJ, Lawrence CM. Multiple papules on the face. Multiple miliary osteoma cutis. *Arch Dermatol* 1994; **130:** 370, 373–4.
6 Ratnavel RC, Burrows NP, Pye RJ. Osteoma cutis as a sequela of acne. *J R Soc Med* 1994; **87:** 107–8.
7 Goldminz D, Greenberg RD. Multiple miliary osteoma cutis. *J Am Acad Dermatol* 1991; **24:** 878–81.
8 Bottomley WW, Goodfield MJ, Sheehan-Dare RA. Digital calcification in systemic sclerosis: effective treatment with good tissue preservation using the carbon dioxide laser. *Br J Dermatol* 1996; **135:** 302–4.
9 Kaufmann R, Hartmann A, Hibst R. Cutting and skin-ablative properties of pulsed mid-infrared laser surgery. *J Dermatol Surg Oncol* 1994; **20:** 112–18.
10 Kaufmann R, Hibst R. Clinical evaluation of Er:YAG lasers in cutaneous surgery. *Lasers Surg Med* 1996; **19:** 324–30.

Chronic buccal ulceration induced by nicorandil

Sir, Nicorandil (Ikorel, Rhone-Poulence Rorer Ltd, Kent, U.K.) is a potassium channel activator used in the treatment of angina pectoris in Japan for more than 10 years. It has recently been introduced in some European countries and has been available commercially in France since the end of 1994. Nicorandil has a similar efficacy in angina pectoris to that of the currently available antianginal agents.[1,2] Specific

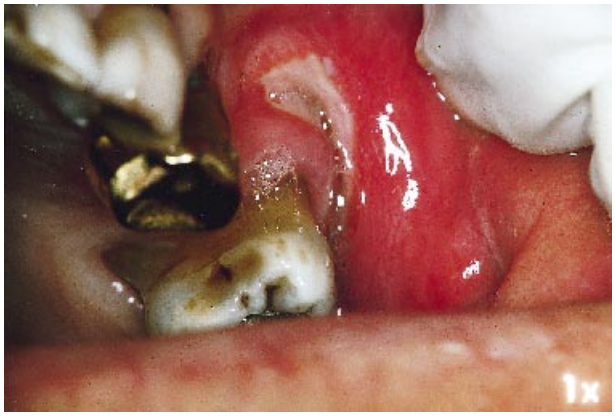

Figure 1. A large gingival ulcer (patient 5).

cutaneous or mucous side-effects of nicorandil were limited to cutaneous erythema.[2] In the past 3 months, we have observed seven patients treated by nicorandil who developed severe and chronic buccal ulcerations. The six first patients included four women and two men aged 65–81 years. All suffered from severe coronaropathy and were treated by nicorandil 2 × 20 mg/day for 5–30 months before developing buccal ulcerations.

The lesions were large irregular and painful ulcerations of 3–4 weeks' duration, located on the tongue, the inside of the cheeks and the gingiva. The total duration of this side-effect was 2–18 months. Severe dysphagia was noted in four patients, three of them having a weight loss of 2–5 kg. Various treatments were administered, including colchicine and systemic steroids, but new lesions appeared continually. Pain was improved in one patient treated with prednisolone 60 mg/day. Because the ulcerations were large (1–2 cm in diameter), biopsies were taken in two patients, showing non-neoplastic mucosal ulcerations and a dense dermal inflammatory infiltrate, rich in eosinophils in one case. In five of the six patients, nicorandil was withdrawn and all lesions healed within a few weeks. There was a dramatic improvement in pain in the first few days after ceasing treatment.

During a follow-up of 2–20 weeks, the patients remained free of lesions; nevertheless, two had a visible scar of the tongue. In one case, the lesions healed although the treatment was maintained, but the patient could not be followed. Three of these six patients had a past history of occasional benign aphthae that were not very painful and that healed spontaneously within 3–4 days. All patients noted that the present ulcerations were much larger and more chronic than their past aphthae.

The last case was a 67-year-old woman who had frequent benign aphthae. Immediately after the onset of treatment with nicorandil, 2 × 20 mg/day, she complained of a severe worsening of her aphthae, with multiple lesions occurring on the lateral parts of the tongue. We examined her 6 weeks later; she had ulcerations inside the cheek of 1 cm and 0·4 cm diameter. Nicorandil was then interrupted but the patient could not be followed.

Mouth ulcerations are not commonly attributed to side-effects of drugs; aphthosis has occasionally been described after treatment with ketorolac, diclofenac, griseofulvin, isoniazide, dideoxycytidine, captopril, barbiturates, alpha interferon, auranofin, levamisole, chlorhexidine, proguanil and tiopronin.[3,4] It is more common with D-penicillamine and interleukin 2.[3] The present patients developed an unusual clinical form of aphthous stomatitis. No other causes of mouth ulcers could be detected. In the present cases, the role of nicorandil is highly probable because: first, the various other drugs taken by these patients were not known to be responsible for mouth ulcers and were maintained after withdrawal of nicorandil; second, all patients had very similar lesions, i.e. large mouth ulcers often located on the tongue, that continually appeared despite various symptomatic treatments; and third, even in cases with a history of aphthae, the ulcerations differed from the previous attacks and after withdrawal of nicorandil, the pain rapidly decreased and the lesions healed spontaneously.

Minor side-effects are known to be associated with the administration of nicorandil, such as nausea, gastralgia or diarrhoea, but this drug is generally well tolerated, as shown in a large series of patients. Although available in Japan for more than 10 years, severe mouth ulcers as a side-effect of nicorandil treatment have not been reported there. In France, several other cases of the mouth attributed to nicorandil in 1996 and 1997 were reported to the Centre de Pharmacovigilance, including four recently published cases;[5,6] all the patients were treated with high doses of nicorandil (20 mg twice a day). Why nicorandil may be associated with mouth ulcers is unknown; metabolites of nicorandil could concentrate in saliva, especially in elderly patients. A past history of aphthae could be a cofactor of this side-effect, as pointed out by Reichert *et al.*[5]

*Clinique Dermatologique des Hopitaux Universitaires and *Centre de Pharmacovigilance Alsace, Strasbourg, France*

B.Cribier
C.Marquart-Elbaz
D.Lipsker*
M.Alt*
E.Grosshans

References

1 Knight C, Purcell H, Fox K. Potassium channel openers; clinical applications in ischemic heart disease—overview of clinical efficacy of nicorandil. *Cardiovasc Drug Ther* 1995; **9** (Suppl. 2)**:** 229–36.
2 Frampton J, Buckley MM, Fitton A. Nicorandil. A review of its pharmacology and therapeutic efficacy in angina pectoris. *Drugs* 1992; **44:** 625–55.
3 Zizrcher K, Krebs A. *Cutaneous drug reactions*. Basel: Karger, 1992; 388–90.
4 Dukes MNG. *Meyler's side effects of drugs*. Amsterdam: Elsevier, 1996; 1295.
5 Reichert S, Antunes A, Trechot P, Barbaud A, Weber M, Schmutz JL. Major aphthous stomatitis induced by nicorandil. *Eur J Dermatol* 1997; **7:** 132–3.
6 Boulinguez S, Bedane C, Bouyssou-Gauthier ML *et al.* Aphtose géante induite par le nicorandil. *Presse Med* 1997; **26:** 558.