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CORRESPONDENCE

Seborrhoeic wart or basal cell papilloma: what's in a name?

SIR, I would like to point out a potential source of confusion that turned up recently in my practice. A 70-year-old woman presented to her general practitioner with a small pigmented lesion on her abdomen which he curetted off and submitted for histology. He was surprised to get the report back of a basal cell carcinoma, but as there was nothing left he agreed to observe it. When the lesion appeared to be recurring at the same site she was referred to me. I found a seborrhoeic wart, which I treated with liquid nitrogen. Further investigation revealed that the lesion had been reported by the consultant pathologist as a basal cell papilloma but that there had been a typographical error.

I have previously encountered this problem of confusion, either on tape recorders or over the telephone, between basal cell papilloma and basal cell carcinoma. In this particular instance no harm was done, but plainly there could be serious consequences to this sort of confusion. We have agreed in future always to use the term seborrhoeic wart, which, although it sounds less scientific than basal cell papilloma, is much less capable of confusion.

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Seborrhoeic wart or basal cell papilloma: what's in a name? Commentary

SIR, Andrew Pembroke raises an extremely important issue and his solution is simplicity at its best.

As well as the example mentioned by Dr Pembroke, I am aware of other instances where basal cell papilloma and carcinoma have been the subject of reporting transposition and, indeed, resulting inappropriate management. Furthermore, this is a not uncommon medicolegal issue in dermatopathology. Fortunately, being somewhat old-fashioned, I firmly believe that all of my dermatopathology reports should have a conclusion. That largely acts as a reporting fail-safe that prevents this error being made. I acknowledge, however, that transposition errors could still occur elsewhere in the system.

I am sure that Dr Pembroke is correct in his belief that histopathologists are slightly resistant to the use of the term seborrhoeic keratosis/wart. Seborrhoeic sounds too clinical and dare I say 'greasy' to be included in a formal dermatopathology report! Likewise, however, the use of the term basal cell papilloma could be construed as pseudoscientific, because definitive proof that the lesion arises from basal cells is to date lacking. There is also the irony that so-called 'irritated' basal cell papilloma looks more squamous than basal! This is always a difficult point to teach to trainees. With interest, I looked up basal cell papilloma in the largest dermatopathology and clinical dermatology textbooks available to me. I noted with interest that all of these preferred the term seborrhoeic keratosis (or seborrhoeic wart) and that basal cell papilloma was poorly represented in preferred choices.

On that basis, to avoid these errors, it would seem highly desirable that terminology in the U.K. becomes standardized towards seborrhoeic keratosis rather than basal cell papilloma. Seborrhoeic wart is clearly also acceptable but some pathologists dislike the term 'wart' in view of its possible implied links to human papillomavirus (HPV). Some seborrhoeic keratoses, however, have been linked to HPV and therefore the term could also be defended. I will convey this simple but important message to the Royal College of Pathologists via its Bulletin publication to all members.

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A case of cutaneous-type adult T-cell leukaemia/lymphoma showing granuloma formation under a parapsoriatic eruption

SIR, Adult T-cell leukaemia/lymphoma (ATLL) is known to be associated with various types of skin lesions, such as hair-loss plaques, erythema multiforme-like changes and pruriginous nodules, as well as erythematous, papular or plaque types of eruption.[1] This suggests the involvement not only of infiltrating tumour cells in the skin, but also of inflammatory processes in the skin lesions of patients with ATLL. We describe a case of cutaneous-type ATLL in which a parapsoriatic eruption was accompanied by multifocal granuloma formation in the lesional dermis.

A 64-year-old Japanese man had a 3-year history of asymptomatic erythematous skin changes with indistinct borders on the abdominal wall, buttocks and proximal thighs. The skin lesions became darker in colour and developed a scaly surface and a thick infiltrative hardness (Fig. 1A). Histology showed a dense infiltrate of mononuclear cells in the dermis with exocytosis to the epidermis and formation of microabscesses, and multifocal granuloma formation by epithelioid cells containing multinucleated giant cells in the dermis (Fig. 1B-D). Laboratory values were almost normal, including peripheral blood cell count, blood chemistry and levels of cytokines [interleukin (IL) 1–5 and interferon-γ]. No abnormal lymphocytes were detected in a peripheral blood smear. No lymph node swellings were seen in computed tomographic scans and uptakes in gallium scintigraphy were absent, but there was a increased titre of antihuman T-cell

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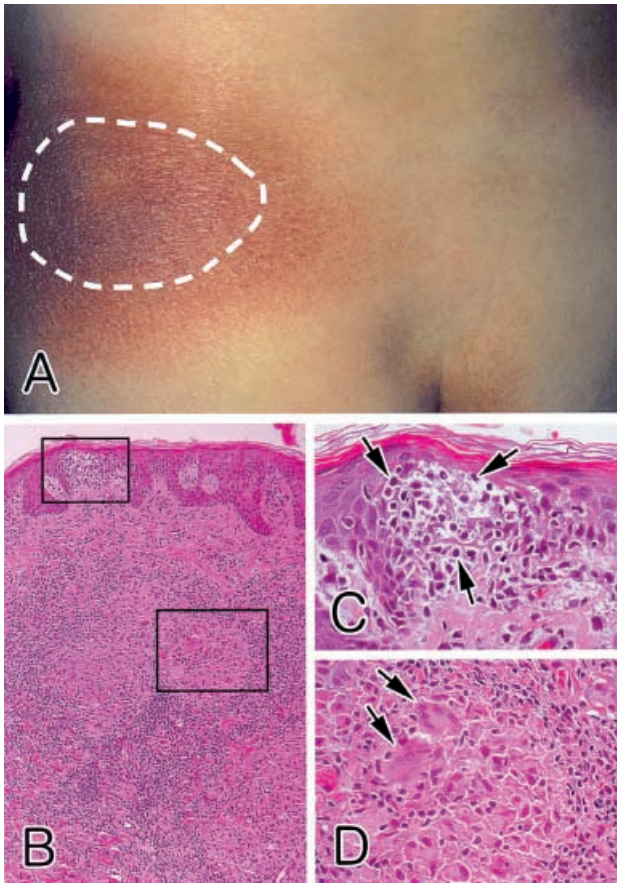

Figure 1. (A) Dark brown erythematous macules with pityriatic scaling on the waist. The circled area showed a dense infiltrate in the dermis. (B) Routine histology of a skin biopsy showed a dense infiltrate of mononuclear cells in the dermis. (C) Enlargement of the upper rectangular area of (B) showing a microabscess in the epidermis disclosed some atypical lymphoid cells (arrows). (D) Enlargement of the lower rectangular area of (B) showing a granuloma focus disclosed epithelioid cells and multinucleated giant cells (arrows) surrounded by mononuclear cells (B–D, haematoxylin and eosin).

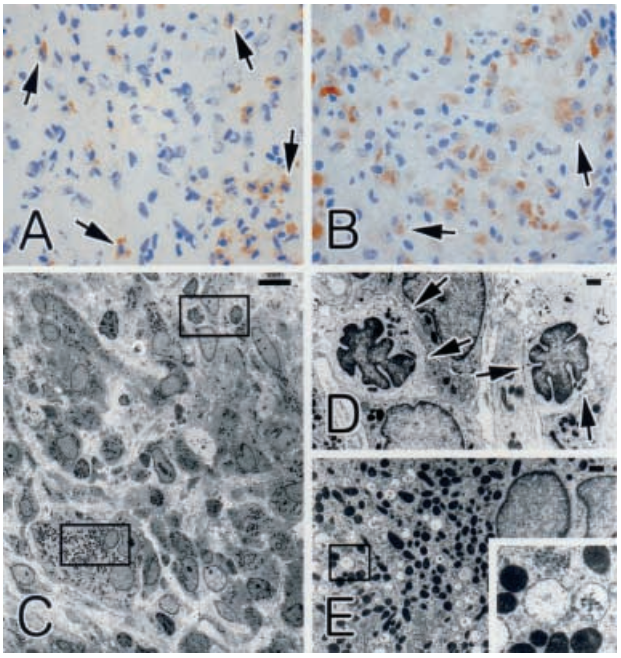

Figure 2. (A) Immunohistochemical staining revealed interleukin-2 receptor-positive cells (arrows) participating in the infiltrates of the upper dermis and in the granuloma. (B) Some of the epithelioid cells in the granuloma were diffusely positive to anti-CD68 antibodies (arrows). (C) A low-powered electron micrograph of the mid-dermis shows numerous dense body-containing epithelioid cells, multinucleated giant cells and lymphoid cells. Scale bar = 10 μm. (D) Enlargement of the upper rectangular area of (C) showing the apposition of epithelioid cells and lymphoid cells. The nuclei of the lymphoid cells are highly indented, and the cytoplasmic processes are in contact with the cytoplasmic membrane of epithelioid cells (arrows). Scale bar = 1 μm. (E) Enlargement of the lower rectangular area of (C) showing cytoplasm of a multinucleated giant cell. Numerous dense bodies and vesicles are found to be degenerated mitochondria under higher magnification. Scale bar = 1 μm. Inset: enlargement of the rectangular area of (E).

lymphotropic virus type 1 (HTLV-1) antibody (×1024). Gene analysis of the skin biopsy showed T-cell receptor gene rearrangement and HTLV-1 provirus. Immunohistochemical staining revealed that most of the infiltrating mononuclear cells were CD4-positive. IL-2 receptor (IL-2R)-positive cells were contained in the infiltrates in the upper dermis and in the granulomas (Fig. 2A). Some of the epithelioid cells were positive to anti-CD68 antibodies, which recognize a membrane protein of lysosomes (Fig. 2B), but most of the granuloma cells were negative to antilysozyme staining. Electron microscopy of the infiltrates disclosed numerous mononuclear cells with indented nuclei, some of which in the granuloma were apposed to the epithelioid cells with cell-to-cell membrane contact. The epithelioid cells and multinucleated giant cells lacked phagosomes (Fig. 2C-E). Mononuclear cells from the patient's peripheral blood and from a normal control individual were stimulated with concanavalin A, according to a previously described method.[2] Supernatants from the cultured mononuclear cells were added to cultured monocytes from the patient and the control. The patient's monocytes showed a relatively low index of transformation to multinucleated giant cells, which was greatly increased by the addition of supernatant from the patient's cultured mononuclear cells. Based on the diagnosis of cutaneous-type ATLL, the patient underwent superficial X-ray therapy (0·8 Gy fractions, 11 fractions per session, 20 sessions in total), and whole-body ultraviolet B irradiation. After 3 months of treatment, the infiltrate in the skin lesions disappeared and the erythematous plaques had decreased.

Our patient presented only a parapsoriatic eruption; no atypical lymphocytes in the peripheral blood, lymph node swelling or hepatosplenomegary were detected, so he was diagnosed as having cutaneous-type ATLL[3] or ATLL-related parapsoriasis en plaque, with granuloma formation in the

lesional dermis. Histological characteristics were the multifocal granuloma formation by epithelioid cells containing abundant multinucleated giant cells and the presence of IL-2R-positive cells in the granulomas as well as in the lesional skin infiltrate.

More than 50 cases of granulomatous mycosis fungoides[4–8] and a few cases of ATLL[9,10] have been reported to show a granulomatous reaction in the skin. The mechanism of granuloma formation in ATLL skin lesions is obscure. LeBoit *et al.*[11] showed the debris of degenerated lymphocytes in the multinucleated giant cells of the granuloma of cutaneous T-cell lymphoma (CTCL), and speculated that the granulomatous reaction was due to phagocytosis of tumour cells by macrophages. However, extensive electron microscopy did not show phagocytic lysosomes in the epithelioid cells or multinucleated giant cells in our patient. The numerous tiny dense granules observed in these cells were degenerative mitochondria and autolysosomes derived from them. In our case, CD68 staining, which detects the membranous protein of the lysosomes, resulted in a fine granular reaction in some of the granuloma cells, and lysozyme staining was negative. These findings supported the absence of phagocytosis of the epithelioid cells in the granuloma in our patient.

The *in vitro* study showed a relatively increased ability for giant cell formation of the culture supernatant of the mononuclear cells in our patient. Although most of the cytokine levels in the peripheral blood were almost within normal limits, and showed no remarkable changes during the course of the disease, it may be possible that undetectable cytokines may have stimulated the monocytes to migrate and form granulomas in our patient. Furthermore, electron microscopy of the granulomatous tissue disclosed a tight apposition between lymphoid cells with indented nuclei and epithelioid cells showing cell-to-cell membrane contact. Such apposition has been observed between lymphocytes and Langerhans cells in mycosis fungoides[12] and lymphomatoid papulosis.[13] The apposition of the lymphocytes and epithelioid cells in our case suggests that ATLL cells, or other T cells accelerated by ATLL cells, may also have affected monocytes to form epithelioid cells and multinucleated giant cells. Although the precise mechanism is obscure, granuloma formation in CTCLs, including ATLL, is at least partly due to the interaction between ATLL cells, or other T cells accelerated by ATLL cells, and monocytes, through cytokines or direct cell-to-cell contact, rather than by phagocytosis by tissue macrophages.

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Linear cutaneous leishmaniasis occurring on a leg affected by tuberculoid leprosy

SIR, We have observed an interesting association of cutaneous leishmaniasis and tuberculoid leprosy that prompted us to examine the similarities between the two diseases. A 32-year-old Indian man presented with a few weeks' history of ulcerated nodules on both legs. Seven lesions were distributed linearly along the medial side of the left leg, and four lesions were scattered on the right leg. In addition, a large, round, scaly, hypopigmented, hypoaesthetic patch, 19 cm in diameter, was seen on the left knee (Fig. 1). A thickened and tender popliteal nerve was palpated on the left leg.

Routine blood and urine tests were within normal limits. Slit-skin smear from a nodule revealed Leishman-Donovan bodies. Culture was not performed due to lack of facilities. The main species causing leishmaniasis in Saudi Arabia have

Figure 1. Leishmanial nodules along the medial side of the left leg, and a patch of leprosy on the knee.

been documented to be *Leishmania major* and *L. tropica*.[1] Biopsy from the knee patch showed a perivascular superficial lymphocytic infiltrate in the papillary dermis and a granulomatous infiltrate with giant cells surrounding nerves in the dermis. No acid-fast bacilli were seen on Fite stain. On the basis of these findings, the patient was diagnosed as having both cutaneous leishmaniasis and tuberculoid leprosy. The leishmanial nodules subsided after intramuscular injections of sodium stibogluconate (Pentostam, GlaxoWellcome, Uxbridge, U.K.) 8 mL (100 mg mL^{-1}) daily for 3 weeks. The patient is currently on treatment for tuberculoid leprosy, rifampicin 600 mg once monthly and dapsone 100 mg daily.

Reports of the concomitant occurrence of leprosy and leishmaniasis are rare.[2,3] The similarities between these two diseases make the association noteworthy. Clinically and pathologically, both leprosy and leishmaniasis exhibit a spectrum of behaviour from localized lesions showing well-formed granulomas with few or no organisms to a lepromatous form with foamy cells and many organisms. Biochemically too, they share many antigenic determinants, although the presence of phenolic glycolipid-1 in *L. donovani* progmastigotes has been questioned.[4] In pathogenesis, the replication of both organisms is affected by an integral protein, Nramp protein, expressed in the lysosomal compartment of the macrophages.[5] The serum tumour necrosis factor level does not correlate with the disease dissemination in either disease,[6] and interferon production has been found to be low in the lepromatous or anergic form of both conditions.[7] The same model has enabled the study of vaccine development against leprosy and leishmaniasis.[8] Rifampicin and dapsone, the main chemotherapeutic agents against leprosy, are also effective against leishmaniasis.[9]

In our patient the lesions were linear on one leg and scattered on the other. This is different from the nodular lymphangitic sporotrichoid form of cutaneous leishmaniasis.[10] Curiously, on the more affected leg the large anaesthetic patch was devoid of leishmanial nodules. This may not be coincidental; the dry and scaly tuberculoid patch may have failed to attract the sandfly vector of leishmaniasis, or there may have been insufficient inoculation of organisms due to loss of efficacy of maxadilan, a vasodilatory peptide, in the sandfly saliva[8] secondary to neural damage of the microvasculature in tuberculoid leprosy. The therapeutic response in our patient was good. In lepromatous leprosy, a poor response to antileishmanial therapy has been documented.[2]

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Recalcitrant ulcers in necrobiosis lipoidica diabeticorum healed by topical granulocyte-macrophage colony-stimulating factor

Sir, Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a haematopoietic growth factor that acts as a potent stimulator of granulocyte and macrophage proliferation and function. The principal clinical use of recombinant GM-CSF is subcutaneous administration to patients who are neutropenic. It has also been shown to promote wound

healing. We report a patient in whom topical application of GM-CSF completely healed recalcitrant ulcers caused by necrobiosis lipoidica diabeticorum.

A 16-year-old girl with well-controlled type I diabetes mellitus had suffered from progressive necrobiosis lipoidica diabeticorum for 4 years. Lesions were present on the shins and thighs, many of which had become ulcerated over the last year (Fig. 1a). She had previously been treated with topical clobetasol propionate (Dermovate®; GlaxoWellcome, Uxbridge, U.K.) under occlusion but without significant improvement. We treated her with GM-CSF (Leucomax®; Novartis, Camberley, U.K./Schering-Plough, Welwyn Garden City, U.K.) 2 mL (75 μg mL^{-1}) on the basis of a previous report by Remes and Ronnemaa.[1] The solution was made up with 0·9% saline solution and was applied topically to the ulcerated lesions. The ulcers were cleaned and excess slough removed prior to application of the solution, which was allowed to sit in the ulcers for 15 min while the patient remained still. Each ulcer was then covered with a dressing (Mepitel®; Mölnlycke, Dunstable, U.K.) for 24 h. The process was repeated twice weekly for 4 weeks. The clinical condition at this stage is shown in Fig. 1(b). Thereafter, any new erosions were treated with GM-CSF applied topically with a small paintbrush. After 3 months of follow-up there has been no recurrence of the ulcers.

The mechanism of wound healing in the skin is well described.[2] Neutrophils are recruited early in the process and destroy invading bacteria both by phagocytosis and by release of oxygen free radicals and proteolytic enzymes. GM-CSF and other cytokines such as tumour necrosis factor-α are thought to stimulate neutrophil function and to increase their lifespan within the wound. As the number of neutrophils declines, so the number of macrophages and monocytes increases. As well as being phagocytic these cells produce a range of cytokines including fibroblast growth factors 1 and 2, and extracellular matrix molecules which contribute to the formation of granulation tissue. Adding GM-CSF topically stimulates the proliferation and function of these cells and promotes wound healing.

Topical GM-CSF has previously been reported in the diabetic literature to heal ulcers in two patients with necrobiosis lipoidica.[1] Topical GM-CSF has also been reported to heal

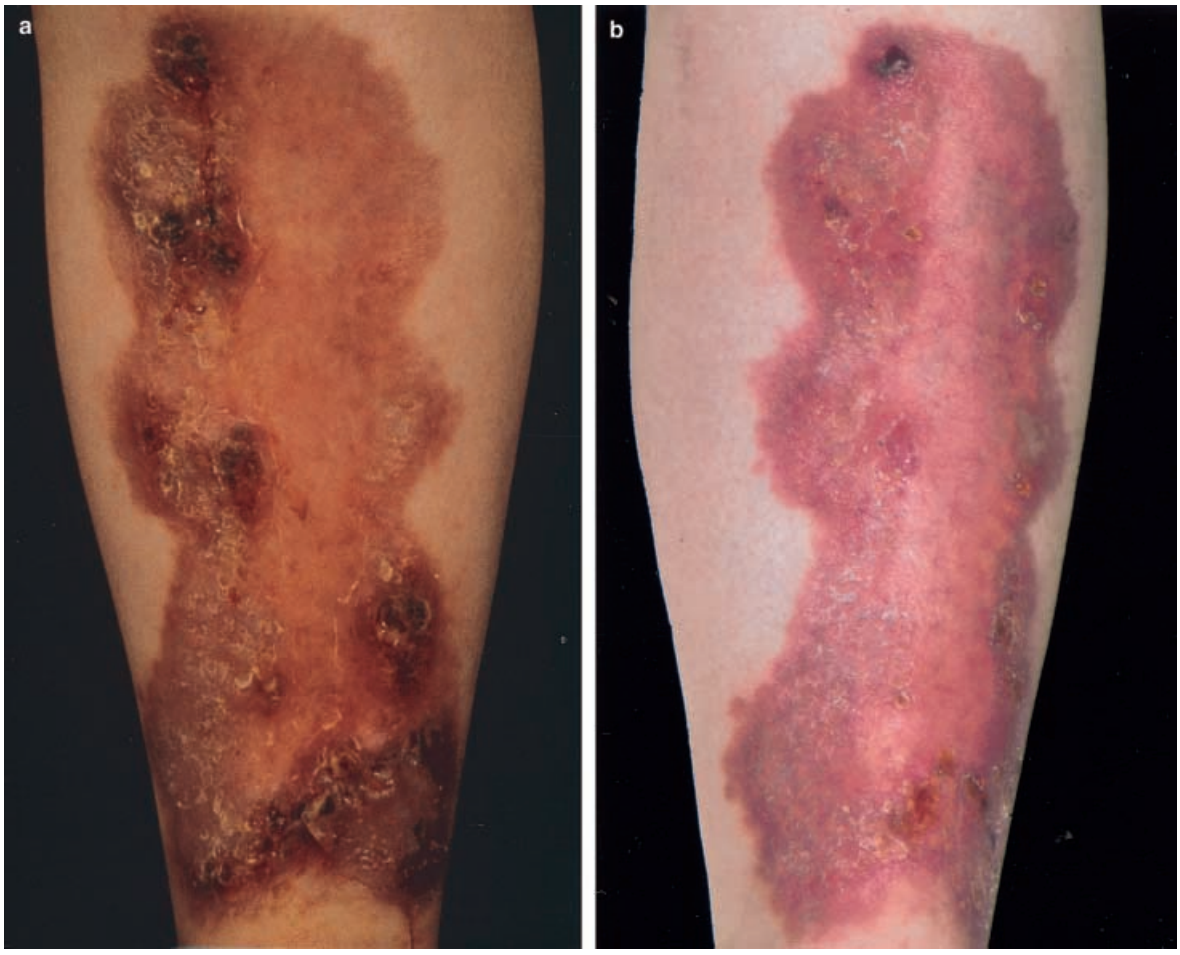

Figure 1. (a) Necrobiosis lipoidica diabeticorum on the left shin. (b) The same patient after 3 weeks of treatment with topical granulocyte-macrophage colony-stimulating factor.

cutaneous ulceration caused by venous disease,[3] aphthous ulceration[4] and hydroxyurea.[5] When injected perilesionally, GM-CSF has been effective in treating ulceration caused by venous disease,[6] pyoderma gangrenosum,[7] haemoglobinopathies[8,9] and cryoglobulinaemia.[10] The optimium route of administration and dosage of GM-CSF remain to be established.

The efficacy of GM-CSF in healing ulcerated lesions in a variety of conditions suggests that its mode of activity is not specific to any one disease process and that it may have many different applications. The cost of treatment compares favourably with the cost of admission for intensive treatment of ulcers, and with the use of drugs such as cyclosporin which have also been used to treat necrobiosis lipoidica.[11]

There are no reports of significant toxicity after topical use of GM-CSF and any systemic absorption is likely to be minimal compared with the doses administered subcutaneously for the treatment of neutropenia. There is one case report of anaphylaxis after subcutaneous injection of GM-CSF[12] and it would seem sensible to try topical application as a first-line treatment.

Topical GM-CSF appears to provide a safe, convenient and efficacious mode of treatment for ulcers in necrobiosis lipoidica and other diseases.

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Multiple fixed drug eruptions due to cetirizine

SIR, Cetirizine is known to be a relatively safe second generation H-1 antihistamine. Chemically it is a carboxylic acid metabolite of hydroxyzine and causes milder sedation than the parent compound,[1] which is the only known important side-effect of this frequently used drug. Recently we saw a patient who had developed multiple fixed drug eruptions (FDEs) due to cetirizine.

A 45-year-old male patient attended our outpatient department with a 2-day history of a few itchy, dusky red lesions over his trunk. On questioning he admitted receiving treatment from a dermatologist for *Tinea corporis*. He had been using topical clotrimazole cream and and taking cetirizine tablets (10 mg) daily for the previous 3 days. On the second day of tablet intake, he sensed a burning pain on a few points on the trunk where the lesions gradually developed. On examination, multiple, slate-coloured, well circumscribed, round lesions were seen on his trunk surrounded by erythema (Fig. 1). One lesion was found over the scaly patch of *T. corporis*. We stopped the drug and with the patient's consent performed an oral challenge test with cetirizine after 15 days. In response to that challenge, the patient developed well-defined erythematous lesions on the previously affected sites.

Cetirizine is a drug very commonly prescribed by dermatologists, ENT specialists, ophthalmologists, and even general

Figure 1. Fixed drug eruption due to cetirizine.

practitioners. Because of its safety profile and easy dosage schedule, it is sold as an over-the-counter drug in many developing countries such as India. Cutaneous adverse drug reactions due to cetirizine, such as urticaria[2] and FDE[3,4] are very rarely reported. Hence, we felt the need to make our colleagues aware of this important side-effect of an apparently innocuous antihistamine drug.

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Perforating granuloma annulare presenting on the ears

Sir, Perforating granuloma annulare (PGA) is a rare variant of granuloma annulare, which usually occurs on the extremities.[1] We describe a patient who presented with nodular lesions on both ears. This is an unusual site for PGA to occur, and has not previously been reported in the literature.

A 27-year-old man presented with a 3-year history of evolving yellow papules on the inner helices of both ears. Some of the lesions had started to discharge serous fluid, and were tender to applied pressure. There was no history of trauma, insect bites or excess solar exposure. There was no history of diabetes mellitus or other illnesses, and he was not on any medication. Rheumatoid factor was negative. Physical examination revealed coalescing papules on the middle inner helices of both ears (Fig. 1). Some papules had a whitish colour embedded within them, others were crusted. Scattered telangiectases and patchy erythema surrounded the lesions. A punch biopsy was performed on one of the lesions. Microscopic examination showed ulceration of the epidermis, through which degenerated collagen was perforating (Fig. 2). In the dermis, degenerated collagen bundles were surrounded by palisading histiocytes. Subsequently, similar lesions appeared on both elbows. He was treated with four 20-s freeze cycles of cryotherapy at 8-weekly intervals, with a satisfactory response.

Figure 1. Patient's left ear. Cluster of pearly papules on the inner helix, with surrounding erythema and telangiectases.

PGA was first described by Owens and Freeman in 1971,[1] as an unusual localized, papular, umbilicated variant of granuloma annulare (GA), showing transepidermal elimination of necrobiotic material. Shimizu *et al.*[2] subsequently divided the eruptions into two types according to their clinical features. One type, called papular perforating type (P-type), is characterized by multiple papular umbilicated lesions, 7–8 mm in diameter, occurring mostly on the extremities, and showing transepithelial elimination. The other type, ulcerative perforating type (U-type), is characterized by 1–4 cm diameter lesions with necrobiotic centres, ulceration and crusting, and a strong association with diabetes mellitus. A particularly high incidence of PGA has been reported in the Hawaiian Islands.[3] Although typical papular and annular lesions of GA may involve the pinna,[4] PGA usually occurs on the extremities[1,2,5] and to our knowledge, this is the first documented case of PGA involving the ears.

The various types of granuloma annulare, including disseminated, papular, subcutaneous and linear, all share the same characteristic histological findings.[6] Foci of mucin-

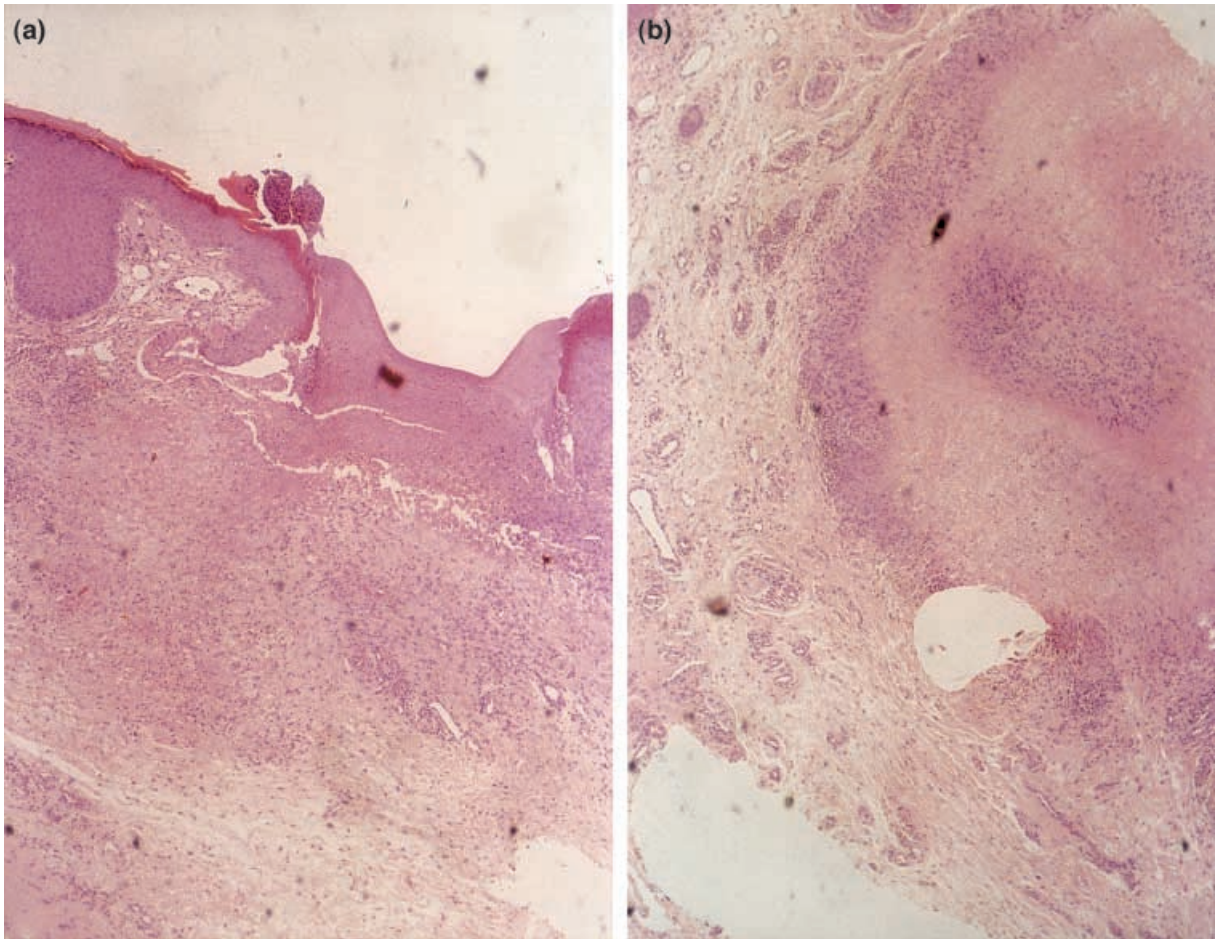

Figure 2. (a) Epidermal ulceration and transepidermal perforation of degenerated collagen; (b) foci of degenerated collagen within the dermis, surrounded by palisading histiocytes (haematoxylin and eosin, original magnification: a, ×40; b, ×100).

ous degenerate collagen are localized in the superficial and mid-dermis, surrounded by a lympho-histiocytic infiltrate and variable numbers of multinucleated giant cells. In PGA, the necrobiotic material perforates through the epidermis. Although the exact aetiology of PGA is unknown, there is some evidence to suggest that a delayed hypersensitivity reaction and vascular injury may be involved in the pathogenesis.[7] The lymphocyte population in GA lesions, which shows a predominance of T helper/inducer cells over cytotoxic/suppressor cells,[8] supports this.

The differential diagnosis of PGA includes other transepithelial elimination disorders such as Kyrle's disease, elastosis perforans serpiginosa, perforating collagenosis, perforating folliculitis and perforating papules of diabetic dialysis patients, molluscum contagiosum, and sarcoidosis. There have been three reports of sarcoidosis with transepithelial elimination.[9]

Treatment of PGA is often difficult. Superpotent topical steroids under occlusion,[3] intralesional triamcinolone and cryotherapy[10] have all been tried, with variable success. One patient was successfully treated with isotretinoin (0·5 mg kg^{-1} day^{-1} for 4 months),[10] but there are no reports of other systemic treatments used in PGA.

In summary, we describe the first patient with PGA occurring on the ears, and suggest that this should be included in the differential diagnosis of papular lesions occurring on the ears. Cryotherapy may be a useful treatment option for limited disease.

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Phakomatosis pigmentovascularis type IIa with generalized vitiligo

SIR, Phakomatosis pigmentovascularis (PPV) is defined as simultaneous occurrence of congenital cutaneous vascular and pigmentary anomalies.[1] There are several associated pigmentary abnormalities in PPV, but vitiligo has not been reported to be associated with the disease. We report a patient with generalized vitiligo, port-wine stain, naevus of Ota and Mongolian spot.

A 27-year-old man presented with depigmented patches over the whole body that had been present for 10 years. Examination revealed generalized vitiligo of the bilateral type involving about 40% of the body surface, a port-wine stain on the left side of the face, and bluish-grey patches on the left side of the face (Fig. 1a) and the back. There was no family history of similar or other skin disorders. No other abnormalities were observed on general physical and neurological examination. There were no autoimmune endocrinopathies such as Hashimoto's thyroiditis, insulin-dependent

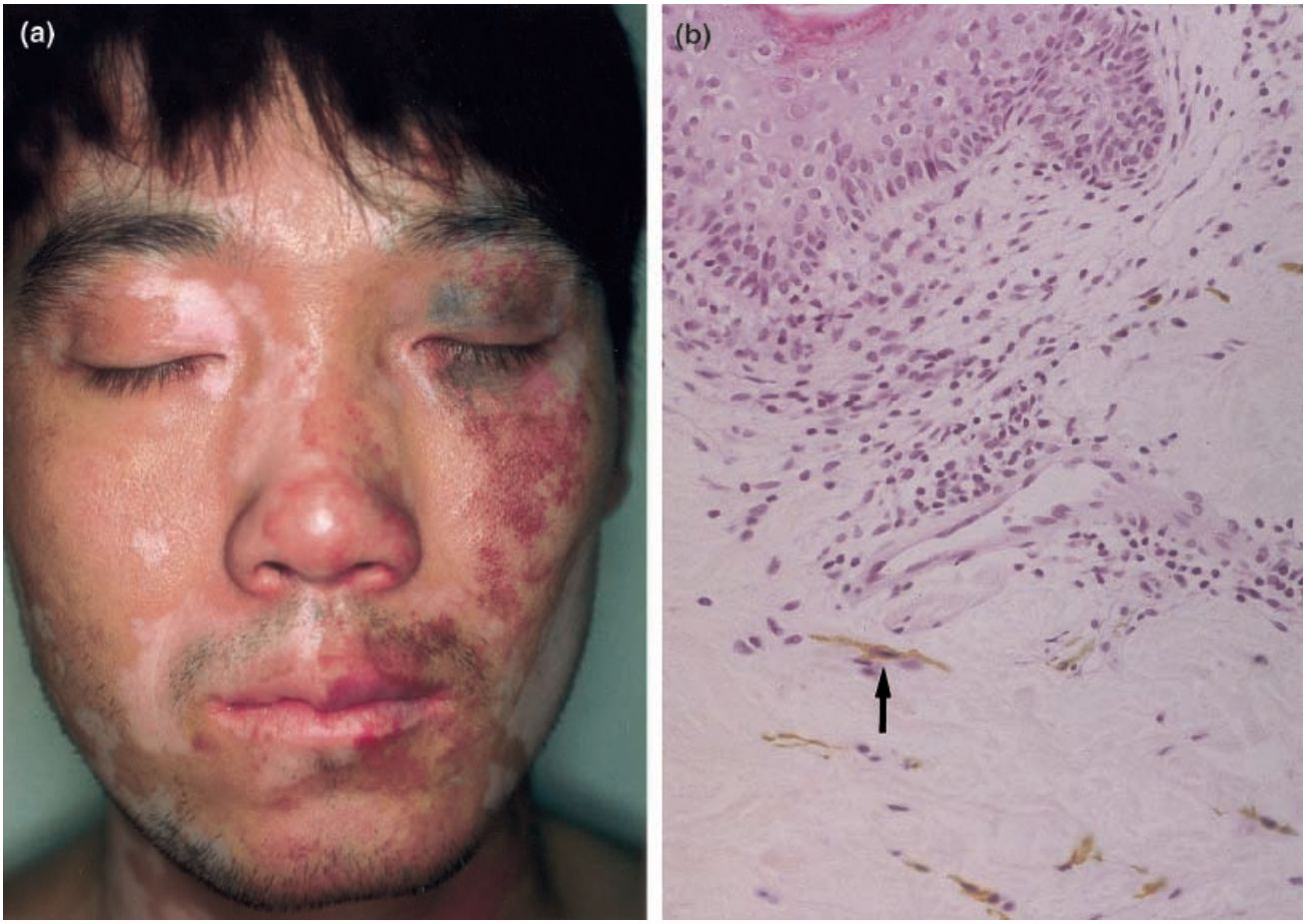

Figure 1. (a) Vitiligo, port-wine stain, and bluish-grey patch on the face. (b) Photomicrograph showing a dilated capillary and a few melanocytes with dendritic processes (arrow) and melanin in the upper dermis (haematoxylin and eosin).

diabetes mellitus, pernicious anaemia or idiopathic adrenal insufficiency. Skin biopsy from the areas of mixed vascular and pigmentary alteration on the face revealed dilated capillaries and a few melanocytes with dendritic processes in the upper dermis (Fig. 1b). Systemic psoralen plus ultraviolet (UV) A therapy was performed to treat the vitiligo. Perifollicular repigmentation began after 15 treatments. The cumulative UVA dose was 21 J cm^{-2}.

PPV, first described by Ota *et al.*[1] in 1947, is characterized by coexistence of cutaneous vascular and pigmentary anomalies in the same individual. This entity is currently classified into four types according to the main pigmented lesion.[2] A constant finding in PPV is the presence of a port-wine stain, which is sometimes associated with a naevus anaemicus. Pigmentary abnormalities include naevus pigmentosus et verrucosus (type I), naevus fuscocaeruleus (type II), naevus spilus (type III), and Mongolian spot and naevus spilus (type IV).[3] The pigmentary abnormalities in type II PPV include four variants: Mongolian spot (naevus fuscocaeruleus sacrococcygealis), naevus of Ito (naevus fuscocaeruleus acromiodeltoides), naevus of Ota (naevus fuscocaeruleus ophthalmomaxillaris) and naevus fuscocaeruleus zygomaticus.[3] Each type has been further classified into two subdivisions: (a) cutaneous involvement only, and (b) cutaneous and systemic involvement. Central nervous system, eye and skeletal abnormalities are the most frequent systemic complications in PPV.[4] Our case is classified as PPV type IIa, i.e. coexistence of port-wine stain, naevus of Ota and Mongolian spot without systemic involvement. Naevus anaemicus is sometimes associated with port-wine stain in types II, III and IV. Clinically, naevus anaemicus is a hypopigmented patch similar to vitiligo. However, it is not a disease of the pigmentary system, but rather a localized physiological state of permanent vasoconstriction.

There is some controversy as to whether PPV is a separate entity or whether it represents a form of Sturge–Weber syndrome. Patients with PPV may have systemic features associated with Sturge–Weber syndrome: facial port-wine stains and ocular and intracranial disorders.[5] However, it has been suggested that PPV differs firstly in the presence of widespread dermal, and usually scleral melanocytosis, secondly in the generally more extensive port-wine staining, and thirdly in the presence of ultrastructural distinctions in the appearance of endothelial cells.[6]

The pathogenesis of PPV is still unknown. Hasegawa and Yasuhara[2] considered the entity to be a developmental abnormality of the vasomotor nerves and melanocytes derived from the neural crest. Several investigators proposed the concept of twin spotting as the genetic basis of PPV.[7–9] De las Heras *et al.*[9] reported a case of PPV with a triangular hypopigmented patch on the upper back, which was first noted in early childhood. They indicated that different gene loci that control either cutaneous vascularization or pigmentation are found close to each other on the same chromosome. The vascular component of PPV may manifest itself as paired patches of port-wine stain and naevus anaemicus, while the pigmentary component may manifest itself as paired patches of hyperpigmented and depigmented naevus, reflecting allelism of the underlying genes situated on neighbouring loci. According to this concept, vitiligo in our case may be a depigmented lesion as one of the paired pigmented anomalies. To clarify the association of vitiligo and PPV, more clinical investigation and molecular research is necessary.

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Merkel cell carcinoma, Kaposi's sarcoma, basal cell carcinoma and keratoacanthoma: multiple association in a patient with chronic lymphatic leukaemia

SIR, The development of multiple primary malignant neoplasms in the same individual has aroused interest due to the hope of discovering factors that may play a role in inducing the neoplastic process. Associations between leukaemia and Merkel cell carcinoma (MCC) and between leukaemia and Kaposi's sarcoma (KS) have been noted and would appear to be more than coincidental.[1,2]

A 71-year-old man presented in March 2000 for evaluation of an enlarged nodule ($\sim 0{\cdot}5 \times 0{\cdot}7$ cm diameter) on the left forearm. Examination showed hepatosplenomegaly and enlarged regional lymph nodes. Chest X-ray showed an enlargement of the mediastinum. The lesion was excised and microscopic examination revealed a circumscribed but not encapsulated dermal and subcutaneous nodule composed of round to oval monomorphous cells with scanty cytoplasm.

The nuclei were large and vesicular, with fine granular chromatin and multiple nucleoli. There were numerous mitotic elements, including atypical ones, and unicellular necrosis (Fig. 1a). Immunohistochemical staining for low molecular weight keratin, chromogranin and synaptophysin was positive, and CD45RO, CD20, CD5 and CD23 were negative. A diagnosis of MCC was made.

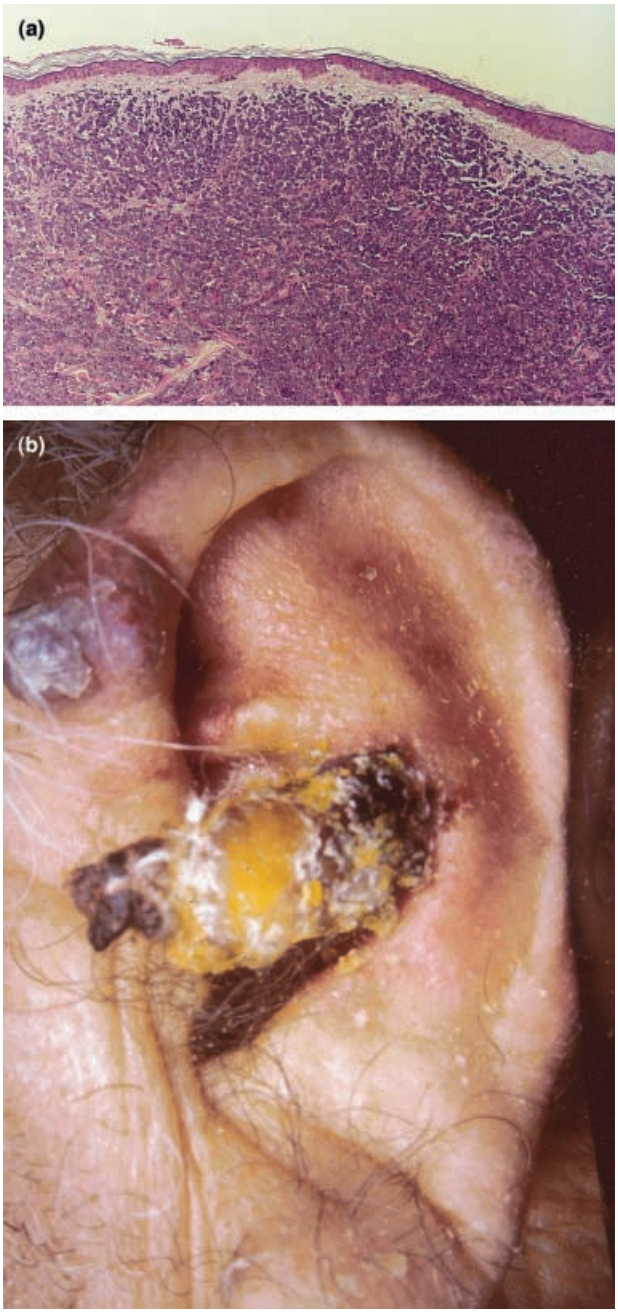

Figure 1. (a) Merkel cell carcinoma. Dermal diffuse infiltrating tumour with a trabecular pattern and no involvement of the overlying epidermis (haematoxylin and eosin; original magnification × 110). (b) Kaposi's sarcoma: a purple nodule and a hyperkeratotic nodule.

The patient had had chronic lymphatic leukaemia (CLL) since 1995; in 1998 he had undergone treatment with chlorambucil (Leukeran®) and prednisone, with good results. In 1999 a basal cell carcinoma (BCC) had been excised from the right shoulder and submitted for histological examination.

In June 2000, the tumour recurred on the left wrist and consisted of a nodule 2 × 3 cm in diameter. A large skin dissection was performed and histological examination confirmed MCC. In October, a keratoacanthoma was excised from the nose; clinical diagnosis was confirmed by microscopic examination. In November, a new plaque lesion was noted on the upper left arm, with lymphoedema. There was lymph node enlargement in the left axilla, and four lymph nodes were excised for examination. Microscopic examination showed a total substitution of lymph node parenchyma by round monomorphous malignant cells with scanty cytoplasm, vesicular nuclei and small nucleoli. Unicellular necrosis was present. Immunohistochemical staining for CAM 5.2, chromogranin, synaptophysin and neurone-specific enolase was positive. A diagnosis of metastatic MCC was made.

In the same period a reddish-purple nodule was observed on the left ear. Histological examination confirmed the clinical diagnosis of KS. Subsequently, a hyperkeratotic lesion appeared (Fig. 1b). Both the KS and MCC specimens were submitted to polymerase chain reaction analysis for human herpesvirus 8. The former was positive, while the latter was negative. At this time laboratory tests showed haemoglobin 6·4 g dL^{-1}, white blood cell count 10·1 × 10^9 L^{-1} (neutrophils 5·8%, lymphocytes 89·5%), platelets 2 × 10^9 L^{-1}, erythrocyte sedimentation rate 59 mm in the first hour, haptoglobin 274 mg dL^{-1}, γ-glutamyltransferase 118 U L^{-1}, alkaline phosphatase 147 U L^{-1}, lactate dehydrogenase 5098 U L^{-1}, and electrophoretic tests showed a reduction in albumin (45·5 g L^{-1}) and an increase in α1, α2 and β globulins. A bone marrow biopsy showed invasion by MCC. The patient died 1 month later and postmortem examination was refused.

The interest of the present case lies in the simultaneous presence of multiple primary tumours in the same patient and in their possible interrelationship. The tendency of patients with CLL to develop a second malignant illness is well documented, as is the increased risk of developing a second neoplasm in MCC and KS.[3,4] In addition, associations between MCC and CLL and between KS and CLL have been reported. The possible role of immune status has often been taken into account to explain this coexistence. Indeed, in the literature, an increased incidence of MCC and KS has been found among immunosuppressed patients.[5,6] In addition, a high incidence of second neoplasms in MCC is reported, including breast, endometrium, colon and prostate cancers, ovarian clear cell carcinoma, bladder transitional cell carcinoma, BCC, squamous cell carcinoma (SCC), Bowen's disease, appendageal tumours with pilar differentiation, benign adn-

exal adenoma, epidermal cysts, sweat gland carcinoma, congenital naevus and melanoma. Recently, a case of MCC, SCC and BCC has been described, suggesting a common epithelial origin for these neoplasms.[7] This observation would give weight to Merkel cells deriving embryologically from the fetal epithelia. However, a Merkel cell origin for MCC has never been definitely confirmed. Other suggested origins for MCC include pluripotent stem cells, adnexal epithelium or dermal neuroendocrine cells. At present, many believe the tumour to arise from a pluripopotent stem cell capable of neuroendocrine differentiation.[8]

There have been several reports regarding KS and its association with other tumours.[4] In addition, the association between KS and other lymphoproliferative disorders, including leukaemia, has been seen by many authors, although with different incidence. Some authors found an increased risk of neoplasms only in patients with AIDS-related KS and excluded this risk in human immunodeficiency virus-negative KS.[9] It is possible that, in our patient, impaired immune function could have been the cause of this multiple association. To the best of our knowledge, this is the first reported case where CLL, BCC, keratoacanthoma, MCC and KS were present in the same patient. Finally, the bone marrow invasion by Merkel cells and their substitution of leukaemic cells is a further point that makes our case of particular note. Indeed, only four cases have been reported in the literature, although none in CLL.[10]

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Is topical tacrolimus effective in alopecia areata universalis?

SIR, tacrolimus (FK506) is a powerful immunomodulatory macrolide and is used in transplantation medicine to prevent graft rejection. Topical tacrolimus is used successfully in the treatment of atopic dermatitis.[1] Similar to cyclosporin, tacrolimus inhibits the activation and maturation of T cells and blocks the transcriptional activation of several lymphokine genes.[2] *In vitro* and *in vivo*, tacrolimus is about 100 times more effective than cyclosporin.[3]

Alopecia areata is an autoimmune disease caused by a T-lymphocytic infiltrate around the bulb of the hair follicle.[4] In rats with alopecia areata, tacrolimus is able to induce a drastic reduction in the follicular inflammatory infiltrate on the site of topical application.[5] In addition, there was regrowth of hair in C3H7HeJ mice with alopecia areata treated with topical tacrolimus.[6] Based on these data, topical tacrolimus might also be effective in humans with alopecia areata. To date, there are few data on this hypothesis.[7] Therefore, we offered topical treatment with 0·1% tacrolimus ointment (Protopic®) to patients with long-standing alopecia areata.

Five patients with alopecia areata universalis were treated with 0·1% tacrolimus topically on a 6 × 6 cm area on the scalp. The ointment was applied once daily in a non-occlusive fashion.

In all patients a weekly diphenylcyclopropenone (DCP) therapy for several months had been ineffective (Table 1). In addition, four of five patients had other unsuccessfull treatments such as corticosteroids (topical and systemic), dapsone, ultraviolet (UV) B irradiation or zinc tablets (Table 1).

Treatment was given on an individual basis. All patients were aware that the treatment with tacrolimus ointment had not been licensed for use in alopecia areata. Each patient was treated once daily for 6 months with 0·1% tacrolimus ointment. To our disappointment not one patient showed regrowth of hair (Table 1).

The treatment failure with topical tacrolimus 0·1% in five patients with alopecia areata universalis may be due to several factors. Firstly, there was an extremely unfavourable patient selection: all patients had extensive and long-standing alopecia areata. Secondly, all previous therapies, including DCP, were unsuccessful. Thirdly, the penetration of tacrolimus is best in inflamed skin.[2] In alopecia areata with intact epidermis, higher concentrations of the tacrolimus ointment, possibly up to 1%, may be necessary because topical tacrolimus acts in a dose-dependent manner.

Rodriguez Rilo *et al.*[7] described rapid hair regrowth in one patient with alopecia areata universalis after liver transplan-

Table 1. Demographic, clinical and treatment data of the five alopecia areata universalis patients*

Patient no. (sex)	Age (years)	Duration of alopecia areata (years)	Previous therapies	Duration of DCP (months)	Duration of topical tacrolimus (months)
1 (male)	54	40	UVB light, oral steroids, zinc	8	7
2 (male)	33	7	None	10	6
3 (female)	61	3	Topical steroids, dapsone, minoxidil	1 (no eczema)	7
4 (female)	38	3	Steroids (oral and topical), dapsone, PUVA	10	6
5 (female)	26	1·8	Steroids (oral and topical), zinc	5	6

DCP, diphenylcyclopropenone; UVB, ultraviolet B; PUVA, psoralen plus UVA. *All the patients failed to respond to any mode of treatment including 0·1% tacrolimus

tation and systemic tacrolimus (FK506) therapy. Using topical tacrolimus, Thiers[8] reported a treatment failure in one patient with alopecia areata.

Although topical immunotherapy with DCP has unpleasent side-effects such as erythema, itching and swelling of the regional lymph nodes, it is still the most effective treatment for extensive alopecia areata.[9] In our experience, tacrolimus ointment 0·1% once daily is not a therapeutic option for patients unresponsive to other treatments of alopecia areata.

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Erythematous actinic lichen planus: a new clinical form associated with oral erosive lichen planus and chronic active hepatitis B

Sir, Actinic lichen planus (LP) or 'LP tropicus' is a rare variant of LP which occurs in dark-complexioned individuals.[1–4] A 41-year-old North African woman, with no relevant medical history, was seen in our unit in October 1989 for a pruriginous erythematous and squamous dermatosis of the face. The lesions had begun after sun exposure a few months previously. No drugs were taken during this period. Examination showed well-delineated squamous erythema of the sun-exposed areas of the face, lichenoid papules on the dorsa of the hands, and white plaques with a lacy pattern on the vermilion of the lips (Fig. 1a). No abnormalities of the oral or genital mucosa or nails were found. Laboratory investigations revealed no inflammatory syndrome, no antinuclear antibodies and no anti-DNA antibodies. A skin biopsy was performed on the right cheek. Histopathological findings revealed orthokeratosis, irregular thickening of the granular layer, hydropic vacuolization of the basal cell layer and a dense band-like dermal lymphocytic infiltrate at the dermoepidermal junction typical of LP. Direct immunofluorescence was negative. We considered that our patient had an atypical form of actinic LP, and different treatments were administered (antimalarials, sun block and topical cortisteroids) without effect.

The patient was seen 8 years later in October 1997 for the same persisting dermatosis. She was referred by a gastroenterologist who discovered a chronic active hepatitis B virus (HBV) infection, treated with interferon therapy for

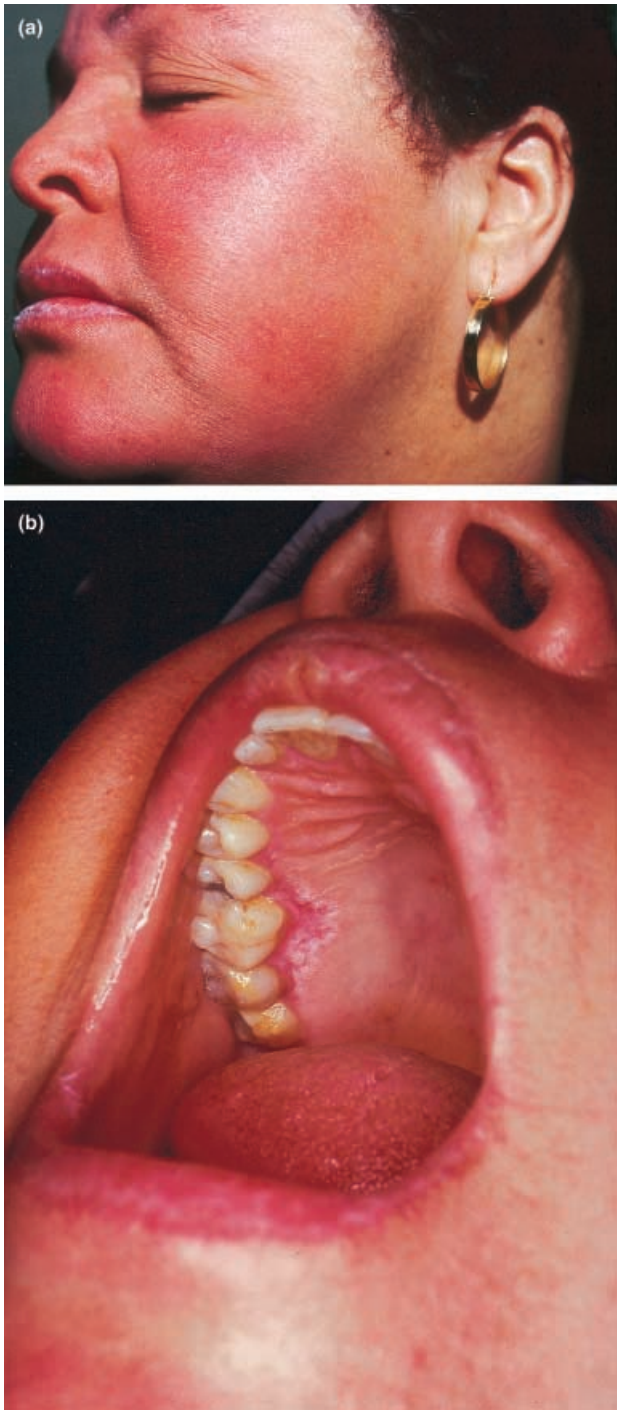

Figure 1. (a) Clinical aspect of the face, with well-delimited lesion-free area corresponding to the area protected from the sun by a headscarf, and white plaques with a lacy pattern on the vermilion of the lip. (b) Oral involvement with dentogingival erosive lesions of lichen planus.

1 year without improvement. The plasma load of HBV was 117 Meq mL^{-1} in bDNA. Routine laboratory tests revealed a hepatic cytolysis. There was no infection by hepatitis C virus. New biopsy specimens of involved skin showed similar alterations as before, and direct immunofluorescence was negative. Photodermatological explorations revealed a normal minimal erythema dose (MED) and repeated phototests (10 MED ultraviolet B) were negative. Polymerase chain reaction of HBV showed no qualitative difference between involved and normal skin.

In April 1998, she was treated with lamivudine for a worsening of her hepatitis. The plasma load of HBV decreased from 328·7 Meq mL^{-1} in bDNA in March 1998 to 9·8 in September 1998. In November 1998, the dermatosis had completely disappeared.

In February 2000, the patient was seen for a relapse of her facial eruption. The hepatitis was still active. In addition to her erythematous and squamous facial dermatosis, examination showed oral mucosal involvement with erosive LP (Fig. 1b).

In our case, we had excluded prior photosensitivity by phototesting. The clinical findings of a white lacy pattern on the vermilion of the lips and lichenoid papules of the dorsa of the hands, which were well-delineated on sun-exposed areas, and the histopathological findings showing typical LP, were strongly consistent with the diagnosis of actinic LP. The classical features of actinic LP were associated with an unusual slightly squamous diffuse erythema of the face, which leads us to call this new clinical form 'erythematosus actinic LP' (EALP).

Seven years after the presenting facial eruption, our patient exhibited an active HBV infection. The decrease in plasma load of HBV with lamivudine therapy induced the healing of the actinic LP, suggesting a strong association between the two pathologies. Two years later, while the HBV infection was active, our patient developed a relapse of facial lesions and, more interestingly, of erosive oral LP. This clinical association suggests that EALP is a photodistributed form of LP. Indeed, erosive LP in Southern Europe, particularly in Italy, Spain and France, is frequently associated with chronic active HBV infection and, more recently, an association between LP and vaccination against HBV was discussed.[5,6]

We suppose that the HBV infection had existed since the first signs of the dermatosis. The HBV infection can be considered as a trigger factor in the occurrence of this photodermatosis, and the unusual erythematous character of actinic LP could be an early sign of HBV infection. To our knowledge, this is the first report of actinic LP associated with HBV infection.

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Chronic erosive herpes simplex virus infection of the penis in a human immunodeficiency virus-positive man, treated with imiquimod and famciclovir

SIR, Herpes simplex virus (HSV) infections are exceedingly common, and are the most common sexually transmitted disease among patients seropositive for human immunodeficiency virus (HIV).[1] The treatment of HSV can be a particular problem in immunodeficient patients as aciclovir resistance is more common in this group.[1] Chronic erosions on the genitalia are very disabling and painful, and increase the risk of transmitting not only HSV but also HIV to sexual partners.

We describe a 28-year-old black man from Africa with a 4-year history of penile erosions. In February 1996 he attended our sexually transmitted diseases clinic in Copenhagen, with a penile erosion measuring 2×2 cm. Biopsy showed an eroded epidermis with an underlying inflammatory infiltrate. HSV-1 was identified by immunofluorescence, and the virus was shown to be sensitive to aciclovir. Treatment with valaciclovir for 1 week healed the erosion, but it recurred within a few weeks. Laboratory tests for syphilis, *Borrelia* and *Haemophilus ducreyi* were negative.

Three months later the patient was diagnosed positive for HIV-1 and HIV-2. Due to a very low CD4 cell count and high viral load, he was initially treated with nucleoside analogues. When highly active antiretroviral therapy became available, the treatment was changed to nucleoside analogues and proteinase inhibitors. This treatment increased the CD4 cell count and suppressed the viral load.

Treatment with aciclovir/valaciclovir/famciclovir was given several times from May 1996 to December 1998, due to recurrence of the herpes erosion. The erosion healed when treatment was given, but always recurred a few weeks afterwards. However, after December 1998 antiviral treatment with aciclovir/valaciclovir/famciclovir had only a minor effect on the erosion. Intravenous foscarnet was therefore administered, and the erosion almost healed, but it recurred within a few weeks. Subsequently, famciclovir and valaciclovir were given repeatedly, with no effect, and intravenous foscarnet was administered again, with no effect. On the basis of the persistent erosion, the patient was diagnosed as having AIDS.

In November 1999 the erosion measured 3×3 cm, and was very painful (Fig. 1a). Treatment with topical imiquimod and systemic famciclovir (500 mg three times daily) was started. The erosion healed slowly, and within 5 weeks measured $0{\cdot}3 \times 0{\cdot}5$ cm (Fig. 1b). Ten weeks after the treatment was started the erosion had completely healed, and imiquimod was discontinued. Famciclovir was still prescribed. Twenty months later there were no signs of the herpes erosion. Treatments are listed in Table 1.

HIV-infected patients often suffer from severe chronic and recurrent mucocutaneous HSV infections that are more severe and longer lasting than corresponding infections in immunocompetent hosts.[1] A sharp rise in the incidence of HSV infections has been shown when CD4 cell counts are below 50 mm^{-3}, and it is known that acute and reactivated HSV infections may stimulate HIV replication, leading to progression of the HIV disease.[1] Most erosions can be treated with systemic aciclovir, valaciclovir or famciclovir also in immunosuppressed patients,[2] but aciclovir-resistant HSV infections have been reported.[1] In HIV-infected patients

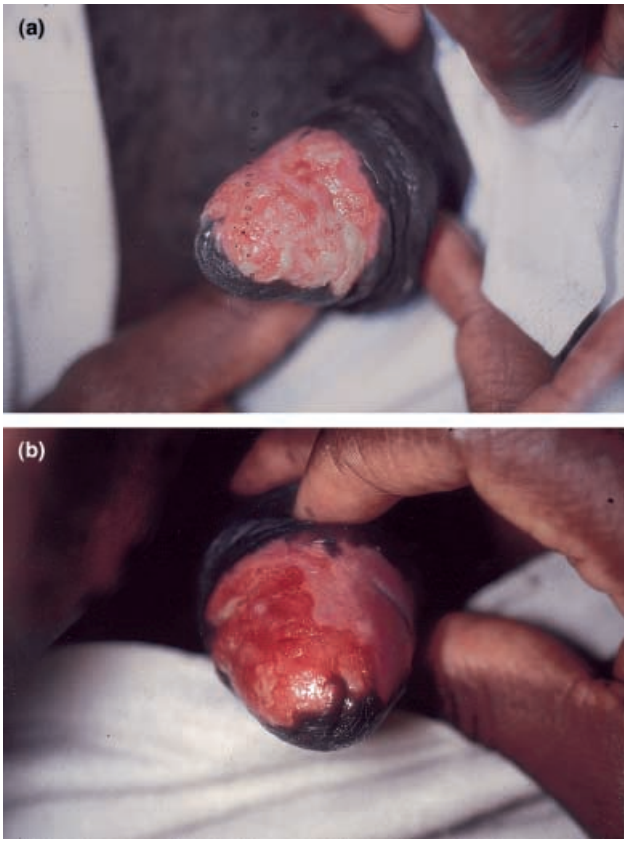

Figure 1. Clinical appearance of the erosion (a) before and (b) after 5 weeks of treatment with imiquimod and famciclovir.

Table 1. Treatments given

Date	CD4 count (mm^{-3})	HIV load	Systemic/local treatment	Size of erosion	Effect of treatment
1999					
Jan	304	< 20	Famciclovir 250 mg × 3	0·3 × 0·3 (cm)	No effect
Jan			Foscarnet 53 mg kg^{-1} i.v. × 2 for 10 days	1·5 × 1·5 (cm)	No effect
Feb			Valaciclovir 1 g × 2 for 10 days	1·5 × 1·5 (cm)	No effect
Feb			Famciclovir 250 mg × 3	2·0 × 1·5 cm	No effect
April			Valaciclovir 500 mg × 2, aciclovir cream		No effect
July	384	< 20	Foscarnet 53 mg kg^{-1} i.v. × 2 for 17 days	2·0 × 1·5 (cm)	Regression
July			Valaciclovir 500 mg × 2, aciclovir cream		No effect
Sept	459	< 20	Valaciclovir 1 g × 3 for 2 weeks		No effect
Oct	288	< 20	Foscarnet 93 mg kg^{-1} i.v. × 2 for 20 days, aciclovir and mupirocin cream	3 × 3 (cm)	No effect
Oct			Famciclovir 500 mg × 3 for 11 days	3 × 3 (cm)	No effect
Nov			Famciclovir 500 mg × 3, imiquimod and flamazine cream	3 × 3 (cm)	Regression
Dec			Famciclovir 500 mg × 3, imiquimod and flamazine cream	0·3 × 0·5 (cm)	Regression
2000					
Jan			Famciclovir 500 mg × 3, imiquimod and flamazine cream, followed by prophylaxis with famciclovir 500 mg × 3		Healed

HIV, human immunodeficiency virus; i.v., intravenously.

treatment with intravenous foscarnet has been shown to be efficient for the treatment of aciclovir-resistant HSV infection.[3] Once the treatment is stopped, however, there is a high frequency of relapse.[3]

We treated our patient with the novel drug imiquimod, which recently became available for the treatment of genital and perianal warts. Imiquimod belongs to the family of imidazoquinolines, that have been shown to have potent antiviral and antiproliferative effects in animal studies.[4] The drug has no direct antiviral or antitumour effects, and its effects might be mediated through activation of monocytes-macrophages to secrete various cytokines, resulting in a T-helper (Th)1-dominant response.[5–7] It has recently been shown that imiquimod induces functional maturation (cytokine-mediated) of human Langerhans cells and induces their migration to the regional lymph nodes.[8,9] The Th1 cytokine switching and the increased antigen presentation might be very helpful in patients with underlying immune deficits, especially those predisposed to a Th2 cytokine switching pattern, such as HIV-infected patients.[4,8]

In the case described here, the therapy-resistant erosion did not respond to famciclovir given alone (see Table 1). Imiquimod induces local interferon-α production (which is known to have direct antiviral activity), which persists beyond the time of an effective concentration of the drug.[4] We speculate that the topical imiquimod reduced virus shedding, causing the erosion to heal. Systemic famciclovir has been continued to prevent recurrence of the erosion. Imiquimod has only recently in a single case been reported to have a possible beneficial effect in the treatment of HSV erosions in humans.[10]

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Hypersensitivity to mosquito bites in association with chronic Epstein–Barr virus infection and natural killer (NK) cell leukaemia/lymphoma with expansion of NK cells expressing a low level of CD56

SIR, Hypersensitivity to mosquito bites (HMB) is a disorder reported mostly in Japanese patients and is characterized by necrotic skin reactions at bite sites and concomitant general symptoms.[1] HMB occurs in association with chronic Epstein–Barr virus (EBV) infection and natural killer (NK) cell leukaemia/lymphoma whose malignant cells are infected with monoclonal (or oligoclonal) EBV.[2–4] This clinical entity had been vaguely called 'mosquito allergy',[5] but is now termed 'Tokura–Ishihara disease'[6] or 'HMB–EBV–NK disease' in a recent article[7] featuring the triad. In a survey of 58 Japanese cases of HMB,[7] the age at onset of HMB ranged from 0 to 18 years. After recovering from each episode, patients are symptomatically free until the next mosquito bite. Between the ages of 10 and 31 years, following repeated episodes of severe symptoms, more than a half of patients died of haemophagocytic syndrome, granular lymphocytic proliferative disorders or malignant lymphoma. The patients' NK leukaemic cells are large granular lymphocytes (LGLs) positive for CD2, CD11b, CD16, CD38, CD56 and HLA-DR.[7] Normal NK cells generally express two types of NK cell inhibitory receptors: lectin-type receptor CD94 and immunoglobulin superfamily type receptors such as NKB1 (CD159) and NKAT2.[8] CD94 is highly expressed on NK cells in HMB-EBV-NK disease, whereas only a few NK cells express CD94 in healthy subjects.[9] NKB1 and NKAT2 are expressed on normal NK cells, but the patients' NK cells do not express them.[9] We report a patient with HMB–EBV–NK disease, whose NK cells expressed a low level of the typical NK cell marker CD56.

A 16-year-old Japanese boy had a 13-year history of intense skin reactions at mosquito bite sites, and systemic symptoms including a high temperature, general malaise and multiple peripheral lymphadenopathies, which occurred several hours after each mosquito bite. Examination revealed an increased level of serum IgE (15 010 IU mL^{-1}, normal < 300). No atypical lymphocytes or LGL were found in peripheral blood smears, but the eosinophil count was elevated (15%). His antibody titre to IgG EBV viral capsid antigen was 1 : 160; titres to nuclear antigen and early antigen IgA were below detection levels. Skin biopsy from a mosquito bite lesion showed a subepidermal bulla beneath the necrotic epidermis and a dense dermal and subcutaneous infiltrate of lymphocytes with angiocentricity and fewer numbers of eosinophils and neutrophils. Most lymphocytes were CD2+, CD3–, CD4–, CD7+, CD8–, CD10–, CD16+, CD19–, CD20–, CD56–, CD57+, HLA-DR+, Ki67– and Mikβ-1–. By *in situ* hybridization, EBV-encoded RNA-1-positive cells were shown to be present in the dermis and subcutis.

A flow cytometric analysis of peripheral blood mononuclear cells (PBMC) showed that CD94 was expressed by 57% of PBMC, some of which also expressed CD56 at low to intermediate levels (Fig. 1A). These cells did not express NKB1 (Fig. 1B) or NKAT2 (Fig. 1C), while they were CD2+, CD3– (Fig. 1D), CD4–, CD7+, CD19–, CD20–, CD94+ and HLA-DR+ (Fig. 1F). Eighteen per cent and 25% of PBMC bore CD16 and CD57, respectively. CD8 was expressed on some of CD94+ cells at a low level (Fig. 1E). Clonal proliferation of EBV was confirmed by Southern blotting using a probe complementary to terminal repeats of EBV in PBMC and skin. No T-cell receptor (TCR) gene rearrangement was found.

The patient's PBMC were cultured for 4 days in the presence or absence of mosquito salivary extracts and pulse-labelled with ^{3}H-thymidine, as described previously.[10] The extracts were prepared from each of the five mosquito species shown in Fig. 2 and were added to the culture. The PBMC proliferated highly in response to *Aedes albopictus* and moderately to *Aedes aegypti* and *Anopheles sinensis* but not to *Culex pipiens pallens* or *Anopheles stephensi*. As PBMC from eight normal subjects did not exhibit such high responses, the

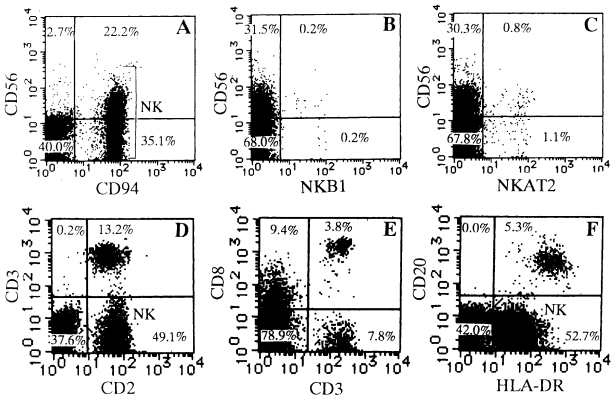

Figure 1. Immunophenotype of peripheral blood mononuclear cells (PBMC) by double-staining flow cytometry. (A) CD94 was expressed by 57% of PBMC, some of which also expressed CD56 at low to intermediate levels. The natural killer (NK) cells did not express NKB1 (B) or NKAT2 (C). (D) The NK cells were positive for CD2 and negative for CD3. (E) Some of the CD94+ cells expressed CD8 at a low level. (F) The NK cells positive for HLA-DR.

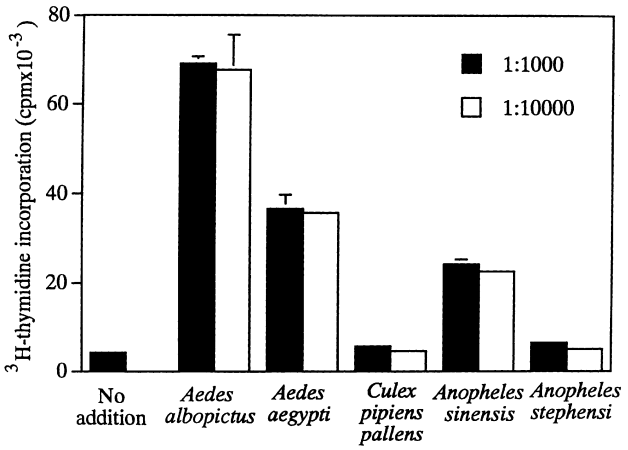

Figure 2. Proliferative responses of the patient's peripheral blood mononuclear cells (PBMC) to mosquito salivary extracts. Salivary extracts were obtained from each of five mosquito species by homogenizing 10 mosquito salivary glands in 10 μL of phosphate-buffered saline. PBMC (3×10^5 cells per well) were cultured in triplicate with each of the extracts at a final dilution of 1 : 1000 or 1 : 10 000 in a final volume of 100 μL of culture medium in 96-well flat-bottomed microtitre plates for 4 days and pulsed with ^{3}H-thymidine (1 μCi per well) 8 h before harvest, as described previously.[10] The cells were collected on glass fibre filters in a cell harvester. Vertical bars represent SD; cpm, counts per min.

results confirmed that the patient had hypersensitivity to mosquito salivary extracts.

In our case, although neither LGL nor atypical cells were found in PBMC, clonal proliferation was confirmed by Southern blotting with a probe to EBV terminal repeats. As seen in typical HMB-EBV-NK disease,[9] approximately 60% of PBMC were CD94+, NKB1− and NKAT2−. Besides NK cells, CD94 is occasionally expressed by CD8+ cells. However, the patient's CD94+ cells expressed CD8 at a very low level and no monoclonal TCR rearrangement was found, indicating that the NK cells but not the T cells were neoplastic. Notably, this patient differs from reported cases in that his NK cells bore CD56 at low to intermediate levels. Although a pathophysiological role for this unique NK cell population remains unelucidated, the NK cells seem to act as effectors/mediators upon mosquito biting as well as reservoirs of EBV. The present patient suggests that cases exhibiting low expression of CD56 exist in HMB-EBV-NK disease and that NK cell inhibitory receptors are useful diagnostic markers in this disease, especially when CD56 is not highly expressed.

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Angiopericytomatosis and subcutaneus thrombophlebitis in multiple myeloma

SIR, In 1992, Le Boit *et al.*[1] reported, under the term 'angiomatosis with luminal cryoprotein deposition' (ALCD), three patients with cryoproteinaemia (one with Waldenström's macroglobulinaemia) presenting with papules and ulcerated plaques, histologically characterized by tufts of capillaries with a periluminal proliferation of pericytes and intraluminal thrombi, and considered it as a variant of reactive angioendotheliomatosis (RAE).

We report an additional case in a woman with myeloma in the absence of cryoproteinaemia, but associated with subcu-

taneous thrombophlebitis, and suggest that this condition is due to vascular occlusion and subsequent recanalization in the setting of a hyperviscosity syndrome. A more appropriate term could be 'angiopericytomatosis'.

A 66-year-old woman, diagnosed 1 month previously as having multiple myeloma, but not treated, had a painful erythematous, infiltrated plaque of 25 cm diameter with overlying haemorrhagic bullae and eschars on the epigastric region (Fig. 1a). There were other similar lesions nearby.

Laboratory tests showed anaemia, leucocytosis, hypergammaglobulinaemia (46·2%, normal 11–20) with elevated creatinine (1·6 mg dL^{-1}, normal < 1) and IgG (> 3000 mg dL^{-1}). Antinuclear antibodies, antiextractable nuclear antigens, antiphospholipid antibodies, antineutrophil cytoplasmic antibodies, cryoglobulins and cryofibrinogen were absent. Protein C and S were normal. Immunoelectrophoresis revealed a monoclonal light chain production (IgG κ chains) and bone marrow examination showed a plasma cell population greater than 10%. Bence–Jones protein was present in the urine.

Histopathology showed clusters of rounded aggregates of capillaries in the papillary and reticular dermis. The capillary lumina were dilated and the endothelial cells lining them were flat. Spindle and epithelioid cells were arranged concentrically around the lumen of the capillary tufts. Endothelial cells lining the lumen of the capillary tufts proved strongly CD31+ and CD34+ (Fig. 1b). The proliferating cells surrounding the capillaries were CD31– and CD34– (Fig. 1b), but most of them reacted with actin (Fig. 1c) and some exressed CD68. No intraluminal cell proliferation was seen but scattered capillaries were partially occluded by fibrin thrombi. The stroma was moderately fibrous with a slight inflammatory lymphocytic and eosinophilic infiltrate. Haemorrhage was present. No periodic acid–Schiff (PAS)-positive material or amyloid was detected in the endothelial cells. Antileucocyte common antigen antibody reacted with the slight inflammatory infiltrate, but not with the perivascular cells. Antibodies to κ and λ light chains were negative in the intravascular spaces. In the subcutaneous septa, a vein with a thickened wall showed a luminal thrombus (Fig. 1d).

Angiomatoses are reactive cutaneous capillary proliferations mostly associated with systemic vascular occlusive diseases. They include different skin conditions such as RAE, diffuse dermal angiomatosis, intravascular histiocytosis, reactive glomeruloid angioendotheliomatosis and angiomatosis with luminal cryoproteins (Table 1).

RAE is a benign process usually associated with systemic infections, cryoglobulinaemia, paraproteinaemia, severe peripheral vascular atherosclerotic disease, iatrogenic arteriovenous fistulas or rheumatoid arthritis, and is characterized by a proliferation of endothelial cells within the lumina of capillaries and, occasionally, by a few pericytes (actin-positive cells).[2–4] In one case, RAE was secondary to amyloid deposits in the vessels due to an associated monoclonal gammopathy.[4] In contrast, our patient exhibited a proliferation of pericytes with scattered histiocytes around the tufts of dermal capillaries in a periluminal arrangement.

Diffuse dermal angiomatosis is associated with peripheral vascular atherosclerotic disease or iatrogenic arteriovenous fistulas and with a diffuse proliferation of endothelial cells arranged interstitially between the collagen bundles of the reticular dermis.,[5,6]

In intravascular histiocytosis, the capillary proliferation is intraluminal and is composed mostly of histiocytes.[7] In our patient, the proliferation was periluminal and consisted mostly of pericytes, with a few histiocytes.

Reactive glomeruloid angioendotheliomatosis is associated with cutaneous necrosis by cold agglutinins in the setting of a non-Hodgkin lymphoma, and is characterized by numerous closely packed 'glomeruloid' capillaries within pre-existing dilated vessels.[8] The glomeruloid pattern is also seen in glomeruloid haemangioma associated with POEMS syndrome (osteosclerotic myeloma), which exhibits multiple purple-red angiomatous papules on the trunk and limbs.[9] In addition, eosinophilic, PAS-positive globules, corresponding to polytypic immunoglobulins and other proteinaceous material, are seen both in the intravascular endothelial cells and within the thrombi.[9]

Our case is, instead, similar to ALCD, in which the capillary proliferations are composed of perivascular pericytes and lumina are thrombosed.[1] It differs from ALCD clinically, being associated with multiple myeloma without cryoglobulins, cryofibrinogen or obvious abnormality of the coagulation system, and histologically, in that it exhibits histiocytes in the tufted perivascular proliferation in addition to the prominent pericytes. In our patient, the high titres of monoclonal IgG with κ light chains could be responsible for the vascular damage, via different immune or non-immune mechanisms.

The underlying subcutaneous thrombophlebitis is another distinctive feature. Although rare, subcutaneous thrombophlebitis has been described in myeloma,[10] but this is the first case in which angiomatosis and subcutaneous thrombophlebitis have been observed simultaneously in the same lesion of a patient with myeloma.

No evidence of vasculitis was observed to confirm that angiomatosis is an unusual sequela of leucocytoclastic vasculitis.[2] Instead, the thrombophlebitis and the pericytes admixed with the CD68+ histiocytes around the dermal capillary tufts both suggest that the luminal occlusion could result in an exaggerated pericyte reaction, with secondary organization and recanalization of the thrombus involving histiocytes as resorbing cells.

In conclusion, angiopericytomatosis is a histological variant of angiomatosis, pathogenetically correlated to other rare angiomatoses (Table 1) that represent reactive cutaneous vascular proliferations due to vascular occlusion and subsequent recanalization. In this setting, 'angiopericytomatosis' is a late stage of angiomatosis in which the pericyte proliferation may represent the last step of reconstitution of normal capillary vessels. In any case, patients with cutaneous angiomatoses should be thoroughly investigated to exclude the possibility of associated systemic diseases with vascular

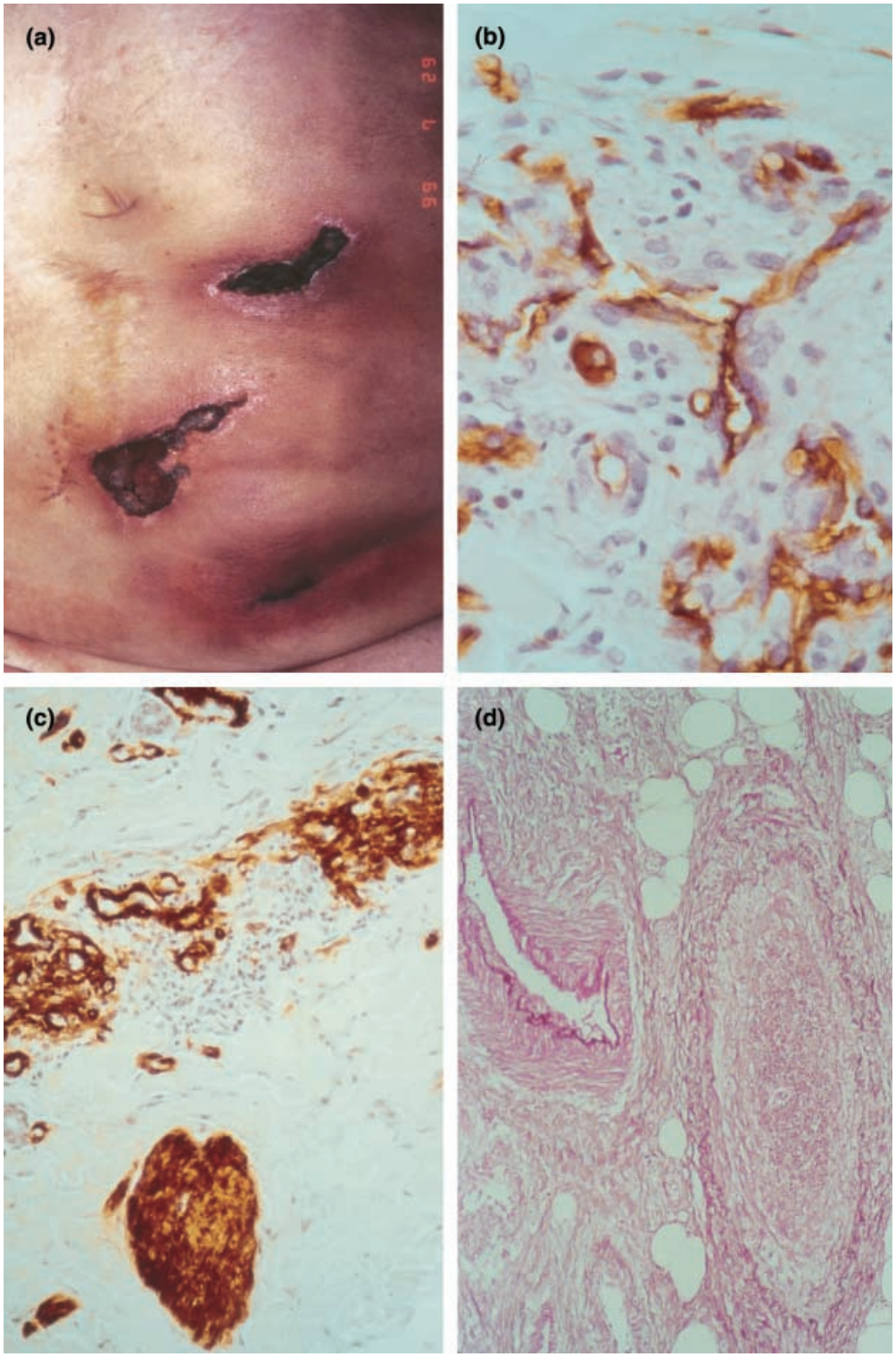

Figure 1. (a) Necrotic lesions on a dusky erythematous plaque are evident on the abdomen. (b) Immunohistochemistry showed positive staining of endothelial cells with CD31 in the capillary tufts. Note that proliferating extraluminal cells compressing the vessels are CD31– (original magnification × 250). (c) Immunohistochemical staining for muscle-specific actin confirms that the proliferating cells surrounding the capillaries are pericytes (original magnification × 100). (d) Elastic tissue staining confirmed that the thrombotic vessel in the septum of the fat was a vein lacking an internal elastic membrane. Note an opened adjacent arteriole with an evident elastic internal membrane.

Table 1. Cutaneous angiomatoses associated with occlusive vasculopathic conditions

Type	Clinical presentation	Histological features	Proliferating cells	Systemic changes
Reactive angioendotheliomatosis	Violaceous papules and plaques	Endoluminal proliferations	Endothelial cells ± pericytes	Infections (endocarditis), hepatitis, cholesterol emboli, arteriovenous shunt, monoclonal gammopathy
Diffuse dermal angiomatosis	Ulcerated violaceous plaques	Interstitial clusters in the reticular dermis	Endothelial cells	Atherosclerosis, arteriovenous shunt
Intravascular histiocytosis	Erythematous patches	Intraluminal proliferations with occlusion	Histiocytes	Monoclonal gammopathy, vascular insufficiency, rheumatoid arthritis
Reactive glomeruloid angioendotheliomatosis	Erythematopurpuric patches and ulcerated necrotic plaques	Intraluminal glomerulus-like tufts of capillaries	Endothelial cells	Cold agglutinins, lymphoma
Angiopericytomatosis (angiomatosis with cryoproteins)	Ulcerated necrotic plaques and erythematous patches and papules	Periluminal proliferation with or without thrombi	Pericytes ± histiocytes	Myeloma, cryoproteinaemia

occlusive involvement, in particular monoclonal gammopathies.

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A case of IgA pemphigus successfully treated with acitretin

SIR, IgA pemphigus is now a well defined entity that includes a group of autoimmune diseases characterized by the presence of pruritic vesiculopustular eruptions, neutrophilic infiltrates, acantholysis and *in vivo* bound and circulating IgA autoantibodies against keratinocyte cell surface components.[1] Such cases have also been reported under various different names, such as intercellular IgA dermatosis[2] or intraepidermal IgA pustulosis.[3] Two subgroups of IgA pem-

phigus have been described: the subcorneal pustular dermatosis (SPD) type and the intraepidermal neutrophilic dermatosis (IEN) type.[4] Dapsone and etretinate have been commonly used for the treatment of IgA pemphigus[1,3–5] but in some cases responses may be either insufficient or only transient.[1,4] We describe the good response to acitretin therapy of a patient with SPD type IgA pemphigus showing autoantibodies against human desmocollin 1 and an IgA gammopathy.

A 67-year-old man presented with a 26-year history of recurrent episodes of generalized and pruritic papulovesiculous and papulopustular lesions that evolved into great areas of erosions and crusts. He had been treated with topical steroids, dapsone and cotrimoxazole with partial remissions. Physical examination revealed erosive and crusted plaques of sizes varying from 0·5 cm to 20 cm on the thorax, back and proximal extremities, predominantly on the intertriginous areas (Fig. 1). Scattered pustules could be observed. The mucous membranes were not involved and Nikolsky's sign was negative. The results of various blood tests and urinalysis, including antinuclear antibodies, serum levels of immunoglobulins and immunoelectrophoresis, were within normal range.

Histological study showed a slightly acanthotic epidermis with subcorneal pustules and acantholytic cells. There were scattered perivascular lymphocytic infiltrates. Direct immunofluorescence of perilesional skin showed cell surface deposits of IgA at the malphigian stratum. Indirect immunofluorescence of normal skin sections with the patient's serum was negative.

Immunoblotting of extracts of ethylenediamine tetraacetic acid-separated normal human epidermis was performed as previously reported,[6] and no particular positive protein band was detected for both IgG and IgA antibodies in the patient's serum. We have recently established a novel enzyme-linked immunosorbent assay for IgA autoantibodies against desmoglein (Dsg)1 and Dsg3, and we found that a few IgA pemphigus sera reacted with either antigen.[7] With this assay, IgA antibodies in the patient's serum did not react with either Dsg 1 or Dsg3. In addition, we also used the cDNA transfection method to detect IgA antibodies to human desmocollins 1, 2 and 3, as reported previously.[8] In this study, IgA antibodies in the patients' serum clearly reacted with desmocollin (Dsc)1 expressed on the cell surfaces of COS-7 cells by immunofluorescence (Fig. 2), while no reactivity with either Dsc 2 or 3 was detected.

Treatment with topical steroids, dapsone (100–200 mg day^{-1}) and colchicine was started achieving only slight improvement. One year later the patient presented with a new generalized flare-up of the lesions and treatment with acitretin 50 mg day^{-1} and topical steroids was started. Three months later only pigmented macules with scattered active lesions were observed and the dosage was reduced to 25 mg per 2 days. Four months later the patient presented with only residual lesions and the tolerance to the medication was excellent. During the disease course an IgA monoclonal gammopathy was detected and he needed treatment with melphalan to control the disease activity.

Different entities have been classically included under the diagnosis of SPD defined by Sneddon and Wilkinson.[9] Increasingly, some conditions have been individualized, such as IgA pemphigus. Our patient represents a case of SPD type of IgA pemphigus. The clinical presentation with irregular, erythematous and vesiculopustular lesions that resemble the clinical features of the Sneddon–Wilkinson SPD is typical of this entity, but the presence of subcorneal pustules with a few acantholytic cells and intercellular IgA deposits in the upper portion of the epidermis are the clue for the diagnosis. The fact that indirect immunofluorescence and immunoblotting showed negative results in our case is not surprising as it has been said that circulating autoantibodies cannot be detected in up to 50% of cases of IgA pemphigus.[1] In such cases, similar to ours, immunofluorescence using cells transfected with cDNA encoding antigenic proteins is a useful method for defining antigens whose epitopes are conformation-dependent and cannot be detected with standard immunoblotting techniques.[1] Using this technique we could demonstrate that the autoantigen in our patient corresponded to the target

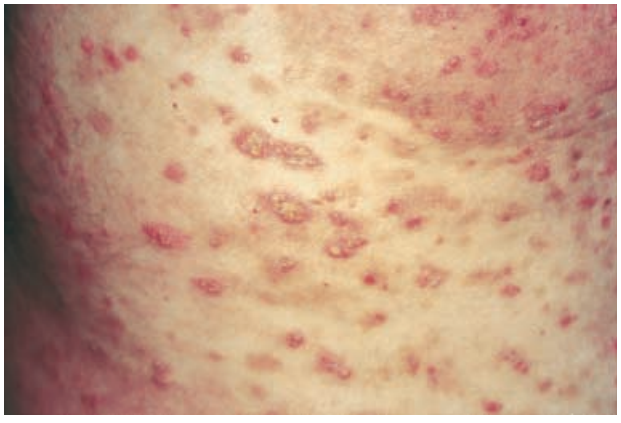

Figure 1. Erosive and crusted plaques.

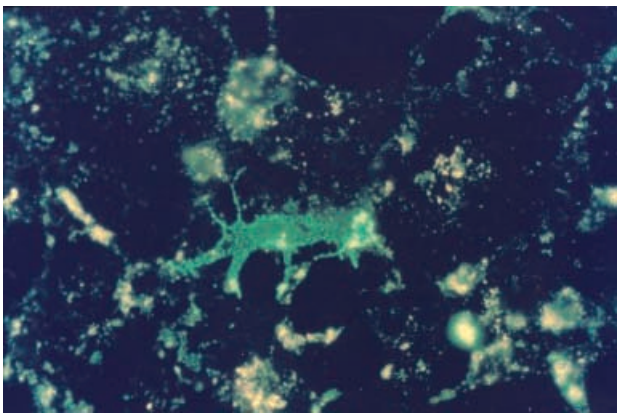

Figure 2. IgA deposit on the surface of desmocollin 1 expressing cells.

antigen for the SPD type of IgA pemphigus, human desmocollin 1,[8] allowing us to make the diagnosis.

The relationship between IgA pemphigus and IgA gammopathy remains uncertain and it has been described only in a few cases that did not present special features in comparison with cases without gammopathy.[4]

Dapsone has been used as the drug of first choice in the treatment of IgA pemphigus,[1] but other therapies such as etretinate,[2–5] psoralen with ultraviolet A[2,3,5] or colchicine[3,10] have been successfully used. Isotretinoin[11] and acitretin[12] have been reported to show an excellent result in one patient. Low dosage acitretin has achieved excellent results in our case. Our patient represents another example of IgA pemphigus that was not responsive to dapsone but showed a dramatic response to retinoids.

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Possible causal role of lisinopril in a case of Kaposi's sarcoma

SIR, Patients receiving immunosuppressive therapy are at increased risk for Kaposi's sarcoma (KS).[1] In addition to immunosuppressive agents and corticosteroids, there were two case reports of KS in whom lesions had begun after captopril [angiotensin-converting enzyme (ACE) inhibitor] treatment and disappeared after it was stopped.[2,3] Here we present a case of KS possibly caused by lisinopril therapy, which is another ACE inhibitor.

A 78-year-old man presented with a 6-month history of erythematous–violaceus plaques and nodular angiomatous lesions on the right shoulder (Fig. 1), left axilla and presternal region and a few nodules in the thighs. In addition, there were haemorrhagic and peduncular tumoral lesions on his left groin and gluteus. Oral mucosa was normal. He had severe lymphoedema of the lower extremities, and multiple, painless and mobile lymphadenopathies on the submandibular, axillary and inguinal areas. He had had diabetes mellitus for 6 years and hypertension for 28 years and had been taking lisinopril for 12 months. In addition, he had used digoxin, dipyridamole, pentaerythritol tetranitrate, ginkgo glicozids, carbamazepine and isophase insulin.

Routine laboratory findings including blood chemistry, urine analysis, erythrocyte sedimentation rate and full blood count were normal except for anaemia (haemoglobin 9·2; haematocrit 27·9). Hidden blood in the stool was positive.

Figure 1. Erythematous–violaceus plaques and nodular angiomatous lesions on the right shoulder.

Results of the enzyme-linked immunosorbent assay for human immunodeficiency virus (HIV)-1, HIV-2, and rapid plasma reagin were negative. Serum iron and ferritin levels were low and iron-binding capacity was high. The histopathological examination of the cutaneous lesions showed dilated capillaries with an intact zone in superficial dermis. Vascular spaces and tumoral formation containing spindle-shaped cells were also seen. Spindle cell tumour showed strong factor VIII immunoreactivity. Thorax computed tomography (CT) examination revealed pathological lymph nodes on the retrocaval and retrosternal areas. Abdominal ultrasonography revealed simple renal cysts. Venous Doppler ultrasonography of the lower extremities revealed bilateral inguinal lymph nodes. Total body scintigraphy findings with normal Tc-99m MIBI and colonoscopic examination findings were normal. Multiple oesophageal haemorrhagic lesions were detected on endoscopic examination. The histopathological features of the oesophageal lesions and one of the submandibular lymph nodes were consistent with KS.

Because the lesions appeared 6 months after the start of lisinopril and there were two case reports in the literature of KS associated with captopril, we decided to stop the lisinopril therapy. Marked improvement of the cutaneous lesions on the upper part of the body was observed 4 months later and complete regression 8 months after the withdrawal of lisinopril (Fig. 2a,b). However, a few lesions on the thighs remained stable and these lesions were treated by cryotherapy and surgery. A complete regression of the previous oesophageal lesions was detected in endoscopic control examination 8 months after the cessation of lisinopril. In control thorax and cervical CT examinations, the lymph nodes on retrocaval and retrosternal areas and jugular chain were seen to be smaller in size and fewer in number.

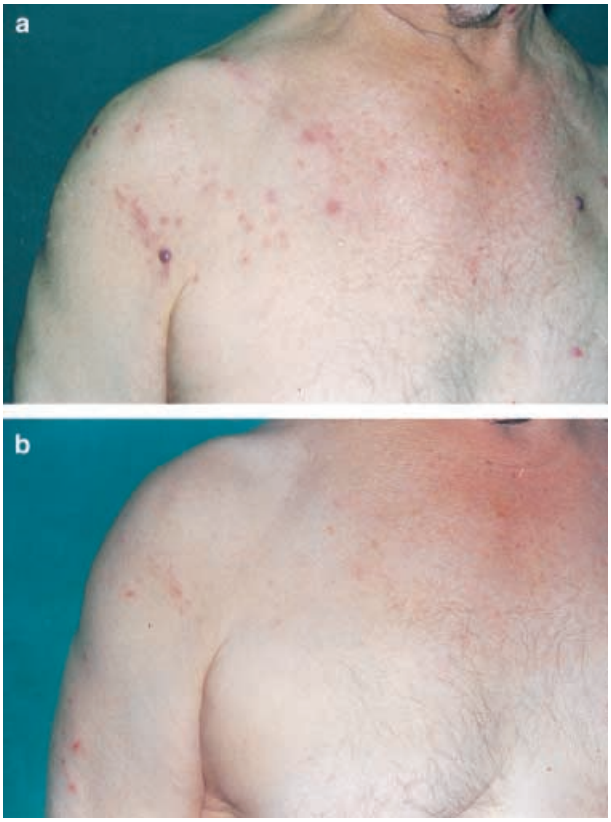

Figure 2. Marked improvement in the cutaneous lesions located on the upper part of the body (a) 4 months after withdrawal of lisinopril and (b) complete regression 8 months after.

As a rule, classic KS is slowly progressive[4] but the lesions in immunosuppressive or transplantation-associated KS tend to be aggressive, involving lymph nodes, mucosa and visceral organs.[1] Widespread and rapid dissemination of the cutaneous lesions, visceral and nodal involvement led us to consider that our case was an immunosuppressive-associated KS.

Captopril leads to the regression of KS[5] and Vogt and Frey[6] prescribed captopril in an immunosuppressive patient who developed KS after kidney transplantation, and during the following weeks there was a marked regression in the cutaneous lesions.

On the other hand, captopril has also been described as a contributing factor to the aetiology of KS. Puppin *et al.*[2] reported an HIV-negative KS patient associated with captopril in whom the lesions disappeared in 3 months after captopril was stopped. Larbre *et al.*[3] reported a case of KS that appeared 8 months after the start of captopril treatment in a patient with rheumatoid arthritis and a marked reduction of cutaneous and gastric lesions occurred when captopril was stopped.

Kallenberg *et al.*[7] reported a 50% reduction of lymphocyte proliferation during captopril treatment in 10 patients. The antihypertensive effects of captopril have been ascribed in part to an increase in the plasma concentration of prostoglandin E2 which has been reported to suppress mitogen-stimulated lymphocytes *in vitro*.[8] Constantinescu *et al.*[9] demonstrated the ability of captopril and lisinopril to suppress interleukin (IL)-12 production, which plays an essential role in cell-mediated immunity. Both ACE inhibitors also suppressed interferon-γ production.[9] Previous studies in mice have shown that chronic administration of recombinant IL-12 hampers the progression of both chemical- and oncogene-dependent carcinogenesis.[10] It was reported that IL-12 induces the enforced secretion of antiangiogenic factors and stimulation of antitumoral immunity.[11] The prevention of this suppression might be the cause of the formation of KS. The appearance of the KS lesions after the initiation of lisinopril therapy and regression after withdrawal of the drug led us to think that lisinopril had a possible causal role in our case. To our knowledge there has been no case of KS associated with lisinopril in the literature. We do not know whether lisinopril alone or an interaction with the other drugs resulted in KS. It may be of interest to evaluate the role of ACE inhibitors in KS, especially in renal transplant patients who need both antihypertensive and immunosuppressive therapy.

This case was presented as a poster at the Third Congress of the Mediterranean Association of Dermatology, Antalya, 23–27 May 2001.

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Absent lentigines in psoriatic plaques

SIR, The development of lentigines within psoriatic plaques is a well-described clinical phenomenon that remains unexplained.[1] We report the inverse phenomenon in two patients with chronic plaque psoriasis in whom lentigines were absent within psoriatic plaques.

Patient 1. A 44-year-old white European woman with psoriasis was seen during an inflammatory flare of her disease that followed a holiday to Egypt. She had a 10-year history of chronic plaque psoriasis and psoriatic oligoarthritis, the former previously treated with dithranol, coal tar, calcipotriol and topical corticosteroids. She was of Fitzpatrick skin type 2 and had received only one course of phototherapy (narrow-band ultraviolet B) 3 years previously but had been on sunny holidays every year. She was noted to have widespread brown macules over the trunk and limbs but there was no actinic damage. These lentigines surrounded the plaques but strikingly spared the psoriatic lesions (Fig. 1). The lentigines had been present for many years and increased in sunny weather. Histology of a lentigo adjacent to a psoriatic plaque revealed an increase in basal melanocytes and basal hyperpigmentation. Her psoriasis cleared with dithranol. When she was reviewed 2 months later the areas where psoriasis had been remained clear of lentigines although they were still slightly erythematous.

Figure 1. Forearm of patient 1 showing an absence of lentigines in the resolved psoriatic plaque.

Patient 2. A 10-year-old white European boy presented with plaque psoriasis affecting the right cheek and both knees, associated with psoriatic nail dystrophy. He was of Fitzpatrick skin type 3 and had not received prior topical or phototherapy for his psoriasis. Since the age of 3 years he had facial lentigines which persisted throughout the winter. Although the lentigines extended to the margin of the plaque they did not involve the lesional psoriatic skin. His psoriatic plaques cleared with topical coal tar. When reviewed 3 months later there was residual erythema at the site of the plaque but it remained free of lentigines.

Melanocytes may be involved in the psoriatic process in several ways. In 1898 Hallopeau and Gasne described postinflammatory hypopigmentation following the resolution of psoriatic plaques.[2] There have been several reports suggesting an association between chronic plaque psoriasis and vitiligo and in some patients they colocalize.[3,4] However, in our patients the plaques did not develop into vitiligo and we presume that the melanocytes within the lentigines were selectively destroyed by the psoriatic process.

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Book Review

Atlas of Cryosurgery (2001). Edited by NIKOLAI N.KORPAN. NewYork: SpringerWien. With over 1200, mostly colour, illustrations. Hardback, 520 pp. Price £131.

'*This is the first time that a book of this kind has ever been published in the history of global medicine and surgery. The Atlas of Cryosurgery is the first fundamental publication to document the modern era of cryosurgery*' – so begins this extraordinary example of 'vanity publishing'. This is a multi-author publication, but most chapters are written, at least in part, by Dr Korpan. Chapter 1 covers definitions and terminology, chapter 2 a history of cryosurgery from 2500BC to the 1980s, when Dr Korpan and colleague developed 'new, highly-efficient universal cryogenic techniques'. Chapter 3 covers theoretical aspects of cryosurgery but starts with a completely pointless 'block schema' of the experimental model. Chapter 4 summarises the experimental foundations for the technique using cryoprobes and a gelatine solution kept at a constant temperature. These experiments are interesting and important but do not justify the subsequent 131 figures rather than a simple table to summarise the findings.

In chapter 5 Dr Korpan introduces his automated 'universal cryosurgical complex' (UCC), which we are told is the subject of 21 national and three world-wide patents. The majority of the remainder of the book illustrates examples of cryosurgery using his equipment. A wide range of body tissues are frozen with Dr Korpan's cryoprobes and sequential photographs illustrate the steps involved. However, the choice of lesions subjected to cryosurgery is rather dubious and includes lymph nodes in metastatic melanoma, a primary breast tumour in a 37-year-old female, benign moles, and massive basal and squamous cell carcinomas of the skin. There is little information about the technical aspects of the freezing procedure for each example and most illustrate only single cases.

This Atlas serves, more than anything, to illustrate the major disadvantages of cryosurgery i.e. the lack of histological evidence of cure and the uncontrolled manner in which this form of treatment can be applied to human tissue. It presents, in a very grandiose manner, an antithesis to the carefully controlled studies undertaken by Dr Rod Dawber and his colleagues, who have defined the standards for cryosurgery in the UK. Dermatologists with an interest in cryosurgery would be much better served by reading one of Dr Dawber's publications on the subject.

RICHARD MOTLEY

News and Notices

5th Annual Lasercare Educational Day
3 December 2002, Birmingham, UK

The 5th Annual Lasercare Educational Day will take place at the Postgraduate Centre, City Hospital, Birmingham, and is open to all interested doctors and nurses. For further information please contact Ann. Tel.: + 121 507 6655; e-mail: Ann@lasercarebirmingham.fsnet.co.uk

Annual Meeting of the British Society for Investigative Dermatology
7–9 April 2003, University of Southampton, U.K.

The annual meeting of the British Society for Investigative Dermatology will be held on Monday 7th – Wednesday 9th April 2003 at the University of Southampton, U.K. Young investigators may apply for a travel bursary to assist attendance at this meeting provided they are presenting or co-presenting a paper. Annually the BSID awards a Young Investigator Fellowship to a promising UK researcher (age limit 35 years) working in an area of dermatological research. Abstract forms, registration forms and details of how to apply for a travel bursary or the Young Investigator's Fellowship are available on-line: http://www.bsid.org.uk or by post from Prof. N.J.Reynolds, Dermatological Sciences, Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, UK. Tel: 0191 222 8936, Fax: 01 91 222 7094, e-mail: bsid@ncl.ac.uk

The deadline for receipt of all abstracts is **7 December, 2002**.

Second Annual Caribbean Dermatology Symposium
14–18 January 2003, Dorado, Puerto Rico

The Second Annual Symposium will be held at the Hyatt Regency Cerromar Beach Resort and Casino. For more

information, tel.: + 1 866 637 3376; e-mail: help@caribederm.org, or visit the symposium's website: http://www.caribederm.org

British Epidermo-Epidemiology (BEES) Annual Course: Getting to Grips with Evidence-based Dermatology
29–31 January 2003, University of Nottingham, UK

This popular course is now in its sixth year. The course aims to: (a) improve your skills of critical appraisal when reading dermatological research and (ii) improve your ability to design and participate in clinical research projects. The course uses the principles of epidemiology and statistics to provide a framework to achieve these aims. The main taught elements of dermato-epidemiology and statistics are part of most specialist trainee curricula. The course may also appeal to consultants who wish to improve their skills at critically appraising published clinical trials. Overseas dermatology trainees are always welcome.

The course is taught by Professor Hywel Williams in collaborations with epidemiologists and statisticians from the Trent Institute for Health Services Research at Nottingham University. Dermatological examples are used to illustrate concepts throughout the course It is a 3-day residential course that is hard work, but good fun. Full CPD approval is usually granted. There is a maximum of 20 places each year. For further details and to reserve a place, please contact Joanne Elliott, Trent Institute for Health Services Research, B Floor, Medical School, Queen's Medical Centre, Nottingham NG7 2UH, U.K. Tel.: + 44 115 970 9765; fax: + 44 115 970 9766; e-mail: Joanne.Elliott@nottingham.ac.uk

83rd Annual Meeting of the British Association of Dermatologists
1–4 July 2003, Brighton, UK

The 83rd Annual Meeting of the British Association of Dermatologists will be held at the Hilton Brighton Metropole, 1–4 July 2003, co-organised by Dr Meg Price (BAD President Elect), under the Presidency of Dr Allan Marsden. Abstracts of papers and posters should be submitted for consideration by the Scientific Committee. Original communications will be allotted 15 minutes, which must include time for discussion. Clinicopathological cases will be allotted 7 minutes for presentation, again allowing time for discussion.

All authors are strongly encouraged to submit papers either by e-mail or on line. An on-line submission facility will be available at http://www.bad.org.uk. Alternatively, forms can be downloaded from the website or obtained by contacting: Emma Clayton, Conference Manager, British Association of Dermatologists, 19 Fitzroy, London, W1T 6EH, UK; email: emmac@bad.org.uk

The closing date for the receipt of abstracts is **Monday, 13 January 2003** and the deadline will be adhered to strictly. Any abstracts received after this date will not be considered. The deadline for any of the special interest group meetings will be **Monday, 10 February 2003**.

Announcement

Invitation to compete for the Paul Gerson Unna Award 2003: Pathophysiology of Skin Ageing

To commemorate the foundation of the Beiersdorf AG, an international dermatological science award, the Paul Gerson Unna prize has been posted every two years since 1982. The prize is awarded for work in the field of fundamental dermatological research and is endowed with prize money of € 25 000, one of the highest in dermatology worldwide.

In view of the undeniable demographic tendencies in the western industrial nations, geriatric research has become a highly visible discipline within life sciences. The subject of skin ageing is therefore also in the focus of dermatological research. The 8th Paul Gerson Unna-Preis 2003 is dedicated to the field of 'Pathophysiology of skin ageing'. Work that is of direct importance for the practice or giving direction to research in diagnostics, therapy and prevention will be awarded. Applicants can submit their work in English or German, and **the deadline is 15 January**. Competitors are asked to submit their best original work only.

The awards ceremony will take place during the 43rd Congress of the German Dermatological Society (Deutsche Dermatologische Gesellschaft DDG) in Berlin, Germany, 6–11 May 2003.

For further information and application forms, contact: Beiersdorf AG, Research and Development cosmed, Dept. 4210, Unnastrasse 48, D-20245 Hamburg, Germany.