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Interleukin 5-inducing activity in the blister fluid of eosinophilic pustular dermatosis

SIR, Eosinophilic pustular dermatosis (EPD) was originally reported in Japan, and is characterized by pruritic follicular papules on the face and trunk; eosinophilia in the peripheral blood is also frequently present.^{1,2} Since the late 1980s, there has been an increasing number of reports of EPD associated with HIV infection,^{3–5} suggesting that EPD is a dermatosis related to immune dysfunction. Although the aetiology of EPD still remains unclear, it has been reported that interleukin (IL)-5 could play a critical part.⁶ IL-5 is one of the Th2 cytokines, and potentially mobilizes, differentiates, activates and aids survival of eosinophils.⁷

A 31-year-old woman noticed pruritic erythematous macules on both cheeks in November 1995; follicular papules and pustules later developed over the pre-existing erythematous lesions. On admission in September 1996, she had circinate erythematous plaques on the cheeks and forehead accompanied by follicular papules, pustules and vesicles, some of which fused to form blisters (Fig. 1a). Histopathological examination of a biopsy of the cheek skin revealed a subepidermal bulla containing eosinophils and mononuclear cells, and dense perivascular and perifollicular infiltration of mononuclear cells and eosinophils (Fig. 1b). Taken together, a diagnosis of EPD was made. Her peripheral blood white cell count was $6.3 \times 10^9/L$ (normal $4\text{--}11 \times 10^9$) with 3.7% eosinophils (normal 0–8%). The serum IgE was elevated to

470 IU/mL (normal < 165). She was negative for HIV antibody. Liver and renal function, serum electrolytes and urinalysis were normal. She was treated with a topical corticosteroid, oral minocycline and indomethacin for 4 weeks without clinical improvement. She was then given prednisolone 35 mg/day and dapsone 75 mg/day, which resulted in a gradual subsidence of the erythematous plaques and papules, pustules and vesicles. The oral prednisolone was tapered as the eruption improved and, after 3 months, it was discontinued.

Before systemic administration of prednisolone, we collected and pooled blister fluid from her cheek to examine immunological activity. Her peripheral blood mononuclear cells (PBMC) were cultured for 72 h *in vitro* in the presence of the blister fluid (1:100, at final concentration). Reverse transcription–polymerase chain reaction revealed that IL-5 mRNA was upregulated in PBMC treated with blister fluid, while no IL-5 mRNA was detected in PBMC treated with her serum. Representative results of two independent experiments are shown in Figure 2. At the same time, enzyme-linked immunosorbent assay detected IL-5 protein in the culture supernatant of PBMC treated with the blister fluid, but not in the serum-treated PBMC culture supernatant. This result suggested that T lymphocytes in the PBMC were activated to produce IL-5 in response to a putative antigen in the blister. However, blister fluid from untreated bullous pemphigoid did not induce IL-5 mRNA in the patient's PBMC, and the patient's blister fluid did not induce IL-5 mRNA in a healthy donor's PBMC. Although HLA typing of the patient was not

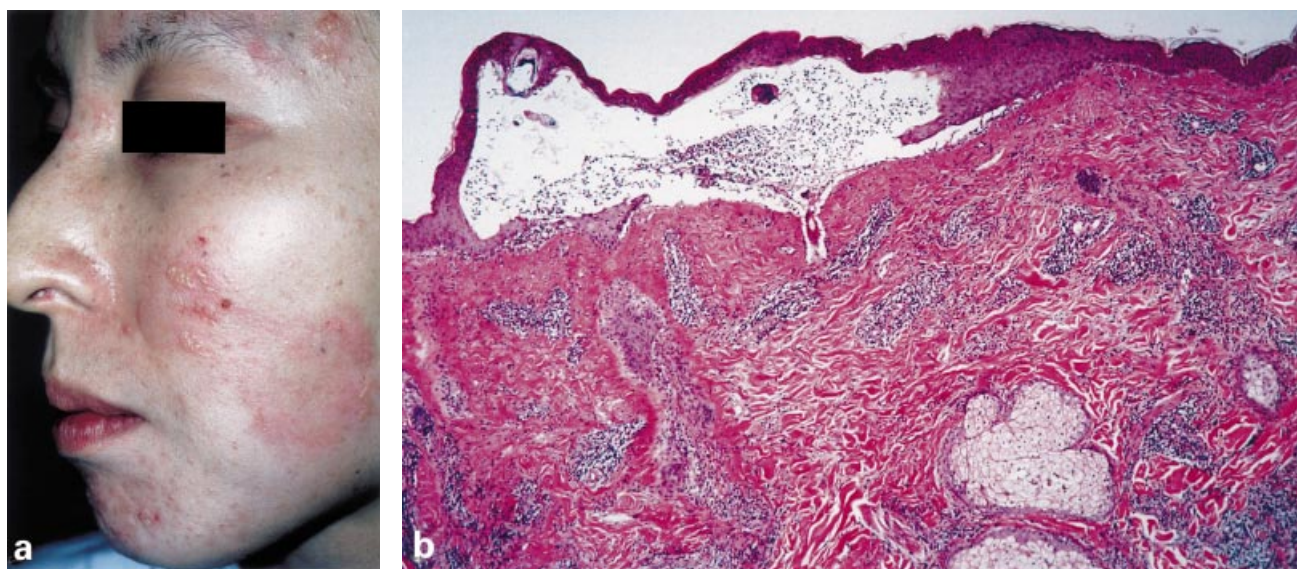


Figure 1. (a) Circinate and annular erythematous patches are evident on the cheeks, forehead and chin, overlaid by papulovesicles, blisters and occasional papulopustules. (b) A photomicrograph of a biopsy taken from the lesional skin of the left cheek shows a subepidermal bulla containing eosinophils and mononuclear cells, underlain by perivascular and perifollicular infiltrates of eosinophils together with mononuclear cells (haematoxylin and eosin; original magnification $\times 100$).

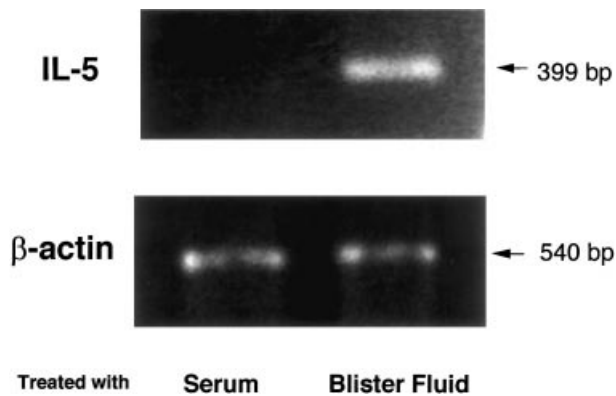


Figure 2. Detection by reverse transcription–polymerase chain reaction of upregulated interleukin (IL)-5 mRNA in the patient's peripheral blood mononuclear cells treated with blister fluid but not serum.

performed, this result suggested that a genetic predisposition such as HLA haplotype is involved in the pathogenesis of EPD. Alternatively, a skewed immune status of T lymphocytes, i.e. Th2 switching, might play a pathogenetic role,⁶ as frequently observed in patients with HIV.⁸ In an *in vitro* experiment, the putative antigen in the blister fluid was presented to T lymphocytes by antigen-presenting cells (APC) such as monocytes. However, it is not known whether APC in the EPD lesions are epidermal Langerhans cells, intrafollicular Langerhans cells or dermal APC. Although the nature of the putative antigen in the blister is also unknown, follicular components may act as an autoantigen because the subepidermal blister space was apparently connected to degraded hair follicles (Fig. 1b). In conclusion, these data imply that a lesion-associated local antigen may be responsible for stimulating the patient's T lymphocytes to produce IL-5, and may play a part in triggering and/or maintaining eosinophilic mobilization and activation, resulting in the development of EPD.

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Bullous pemphigoid associated with chronic B-cell lymphatic leukaemia: the anti-230-kDa autoantibody is not synthesized by leukaemic cells

SIR, The association between bullous pemphigoid (BP) and chronic lymphatic leukaemia (CLL) has been reported,^{1,2} but it is very rare, like the association between paraneoplastic pemphigus and chronic B-cell lymphatic leukaemia (CBLL).^{3,4} It seems quite reasonable to speculate on a possible relationship between BP and CBLL because BP is an autoimmune disease due to autoantibodies produced by B lymphocytes.⁵ While studying a patient who had these two diseases, we speculated whether BP might be induced by the production of antibodies by leukaemic B cells. We tried to demonstrate this through the production of a monoclonal antibody by immortalized leukaemic cells.

An 81-year-old man presented with a CBLL and typical BP. Both disorders were diagnosed simultaneously. The CBLL was characterized⁶ by a persistently raised peripheral blood white cell count of $100 \times 10^9/L$. Most of the cells were typical leukaemic B cells. The bone marrow aspirate showed a lymphocytic infiltration. The BP was confirmed by histological examination and direct and indirect immunofluorescence. An immunoblot assay identified circulating antibodies against a 230-kDa epidermal antigen.

Mononuclear cells were isolated from blood by flotation on Ficoll-Paque[®] (Pharmacia, Uppsala, Sweden). Monocytes were removed by allowing them to adhere to plastic flasks. The non-adherent cell suspension was deprived of T lymphocytes by rosetting with 2-aminoethylisothiuronium bromide-treated sheep red blood cells. Cells were cultured and 10 U/mL of recombinant human interleukin (IL)-2 were added to test cultures but not to control cultures. Superinfection with Epstein–Barr virus (EBV) was realized with a virus preparation kindly provided by C.Desgranges (INSERM U271, Lyon, France) as already described.⁷ The expression of CD1a, CD2, CD3, CD4, CD8, HLA-DR, CD14, CD19, CD21, CD25, CD40, IgA, IgG, IgM, κ chain and λ chain was studied by flow cytometry. After elimination of monocytes and T cells, 82×10^6 cells were isolated from a 12-mL sample of blood. These cells were mainly B cells, as demonstrated by the labelling of up to 95% cells with anti-DR, anti-CD19 or anti- γ chain antibodies. CD25 labelled 98.8% of cells and 94.6% were CD40+; however, no spontaneous lineage could be established. The addition of IL-2 at 10 U/mL increased the cell count transiently but their survival did not exceed 22 days. After EBV infection, the cells proliferated continuously and

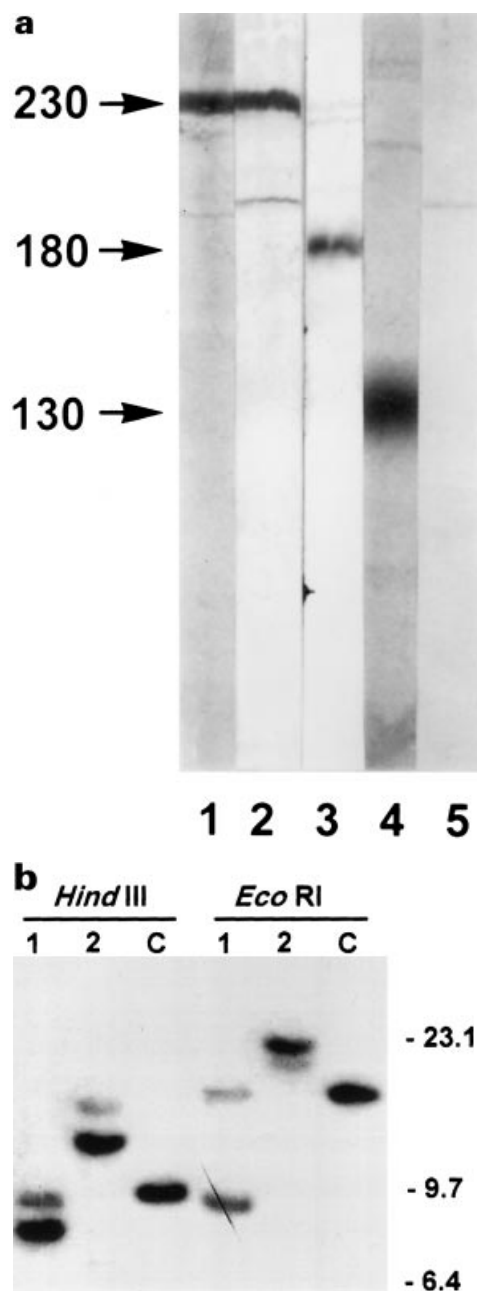


Figure 1. (a) Immunoblot experiments. Lane 1: IgG fraction isolated from the cell line supernatant. Lane 2: serum from the patient. Lane 3: positive control for BPAG2. Lane 4: positive control for a 130-kDa antigen (pemphigus). Lane 5: negative control. (b) Analysis of IgG gene configuration. Ten micrograms of genomic DNA extracted from tumoral cells (1), from a lymphoblastoid cell line (2) and from normal peripheral blood lymphocytes (C) were digested with the indicated enzyme, electrophoresed through a 0.8% agarose gel and blotted on to a nylon membrane. The filter was assayed for hybridization to a heavy chain joining region gene probe. The scale is in kilobases.

grew in aggregated form. After 21 passages, all the cells were CD19 +, CD21 +, CD25 +, CD40 +, HLA-DR + and $\gamma + \lambda$ +.

Cells from the 20th passage were expanded and 23 mg of immunoglobulins were isolated by immunoabsorption from 1 L of collected supernatant. Agarose gel electrophoresis of the isolated immunoglobulin fraction gave a homogeneous band in the slow β region; it was identified as IgG1. The serum from the patient and cell culture supernatants were used on 4 μ m cryostat tissue sections of salt-split skin (SSS) according to previously described methods.⁸ The specific binding was revealed using fluorescein isothiocyanate-conjugated goat antihuman IgG. The dermoepidermal junction and basal keratinocytes were stained with the same pattern with the patient's serum and the IgG fraction obtained from the supernatant of the immortalized cells. Immunoblot experiments were performed as previously described⁸ and allowed the identification of the molecules recognized by the IgG fraction as the 230-kDa epidermal antigen (Fig. 1a). Furthermore, the use of the patient's serum with the same technique led to the same result.

Chromosome preparations were performed on the lymphoblastoid cell line. The karyotype was classified according to the International System for Human Cytogenetic Nomenclature (ISCN 1991) recommendations. Cytogenetic analysis was normal on the lymphoblastoid cell line and was not performed on fresh tumoral cells. Molecular studies were performed on the lymphoblastoid cell line and on peripheral blood tumoral cells. High molecular weight DNA was extracted following standard procedures from the cell line and from the mononuclear cells obtained after isolation by Ficoll-Hypaque centrifugation and containing at least 70% leukaemic cells. Molecular analysis of the sample DNA was performed by Southern blot analysis using the standard technique. Southern blot analysis using an immunoglobulin heavy chain joining region probe (a gift from T.H. Rabbitts, Cambridge, U.K.) detected two rearranged fragments in *Eco*RI and *Hind*III-cleaved DNA from the lymphoblastoid cell line (Fig. 1b). The DNA from tumoral cells showed one rearranged band in addition to the germinal band. These results were confirmed using *Bam*HI and *Xba*I (data not shown).

We have generated a cell line from the B cells isolated from blood of the patient. The cell line was expanded during more than 20 passages and the cell phenotype remained stable; the cytogenetic study indicated a specific gene rearrangement suggesting that the cell line is monoclonal. Moreover, the cell supernatant from passage 4 as from the last passages contained an IgG antibody directed towards a 230-kDa epidermal antigen. The patterns of reactivity (indirect immunofluorescence on SSS and by immunoblot experiments) of the immunoglobulin fraction isolated from cell supernatant and patient's serum were superimposable. Leukaemic cells and the cultured cell line share common membrane markers, in particular γ and λ chains. However, despite the large quantity of leukaemic B cells in the sample treated with EBV, the cell line was probably established from autoreactive B lymphocytes because leukaemic B cells and the B-cell line cells express different gene rearrangements. Accordingly, leukaemic cells probably did not induce BP in our patient but a clone of

autoimmune B cells sufficiently well represented in the patient's blood to be immortalized might do so. None the less, this cell line allowed us to generate a new human monoclonal IgG directed towards a 230-kDa hemidesmosomal protein BPAg1.

Another study, in a patient with CLL and paraneoplastic pemphigus, also excluded the induction of cutaneous lesions by leukaemic cells because the isotypes of the immunoglobulin light chains responsible for pemphigus and those produced by the leukaemic cells were not identical.³ Thus, the reason why bullous autoimmune diseases and CLL are sometimes associated remains unknown. The possibility of a common basic immune disorder inducing the generation of B cells producing autoimmune antibodies and a dysregulation of B cells leading to the CBLL cannot be excluded. We suggest that leukaemia might be responsible for an inhibition of the natural control of autoreactive clones.

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Bullous pemphigoid preceded by recurrent oral lesions: identification of autoantibodies against BP180 by immunoblot using epidermal extracts and BP180 fusion proteins

SIR, It has been reported that mucous membranes are involved in some patients with bullous pemphigoid (BP).^{1–3} We report a patient with BP who had recurrent oral lesions before the onset of skin lesions, and examine the antigenic specificities of the serum from this patient by immunoblotting.

An 80-year-old woman presented in August 1996 with recurrent oral lesions and pruritic bullous skin lesions on the back and face. She had had recurrent oral lesions for 4 years and bullous lesions for 1 year. These had developed mainly on the back. The oral and skin lesions had been treated mainly with a topical corticosteroid for 1 year without improvement. On examination, there were erosions up to 5 mm in diameter on the central region of both sides of the buccal mucosa



Figure 1. Erosive lesions are seen on the buccal mucosa.

(Fig. 1). Blisters and erosions were present on erythematous plaques on the upper back. There was no involvement of other mucosal sites such as the urogenital region and conjunctiva. Pathogenic bacteria and fungi were not detected on culture of specimens from oral and skin lesions. Routine laboratory tests were within normal limits. A skin biopsy was taken from a newly developed pruritic tense blister on the face. Histology showed subepidermal blister formation with infiltration of eosinophils within the blister cavity. Direct immunofluorescence showed a linear band of C3 at the dermoepidermal junction. There was no deposition of IgG, IgA or IgM. Indirect immunofluorescence (IIF) was carried out several times using intact and NaCl-split normal human skin as substrates,⁴ but circulating IgG and IgA antibodies were not detected. No circulating autoantibodies were detected by IIF using monkey oesophagus sections as substrate (Inova Diagnostics, San Diego, CA, U.S.A.).

To detect circulating autoantibodies, we performed immunoblot analysis using normal human epidermal extracts and BP 180-kDa antigen (BP180)-glutathione-S-transferase (GST) fusion proteins. Immunoblot analysis using normal human epidermal extracts was carried out as described previously,⁵ and immunoblot analysis using BP180-GST fusion proteins was carried out as follows. Bacterial strains (DH5 α) expressing

BP180-GST fusion proteins were kindly provided by Dr S.D.Balding (Medical College of Wisconsin, Milwaukee, WI, U.S.A.).⁶ Affinity-purified BP180 fusion proteins S Δ 1, 4575 and recombinant GST were used. S Δ 1 is a GST fusion protein that encodes a 42-amino acid stretch of BP180 beginning with 18 amino acids outside the membrane-spanning domain. GST fusion protein 4575 contains 49 amino acids of the carboxy terminal region of BP180. Immunoblot analysis using normal human epidermal extracts showed that the patient's serum IgG but not IgA recognized a 180-kDa epidermal antigen (Fig. 2a). To confirm this finding we examined the reactivity of the patient's serum IgG and IgA against the BP180-GST fusion proteins. The patient's serum IgG but not IgA reacted only with S Δ 1 fusion protein encoding 42 amino acids of the BP180 NC16A domain (Fig. 2b). Considering these findings, we diagnosed the patient as having BP with circulating IgG autoantibodies against the NC16A domain of BP180.

Initially, the patient was treated with topical betamethasone valerate ointment and hydrocortisone acetate ointment for the skin lesions and oral lesions, respectively. However, there was no improvement, and treatment with oral betamethasone 2 mg/day was started. Both cutaneous and oral lesions responded well to the oral betamethasone, with complete healing in 9 months. There has been no scar formation or recurrence.

On IIF using intact and NaCl-split normal human skin as substrates, circulating autoantibodies were not detected in serum samples taken from the patient at various times. Immunoblot analysis revealed the presence of circulating IgG autoantibodies against the NC16A domain of BP180. The BP180 antigen is a transmembrane glycoprotein,⁷ and is the major antigen in herpes gestationis (pemphigoid gestationis)⁸ and cicatricial pemphigoid.⁶ The NC16A domain of the BP180 antigen was shown to be a pathogenic epitope in a neonatal mouse model.⁹ Concerning the relationship between clinical findings and antigen specificities of autoantibodies in BP patients, Tanaka *et al.*² reported that oral and facial lesions predominantly occurred in patients whose sera detected BP180.² However, the relationship between BP antigen profiles (BP230 and/or BP180) and clinical findings or laboratory data still remains controversial.³ It was also shown that patients with antibodies to BP230 tended to have a high titre of antibasement membrane zone antibodies, and anti-BP180 antibodies may be more related to disease severity than anti-BP230 antibodies. Considering these findings in our case, low-titre anti-BP180 IgG antibodies (below the detection level by IIF) may be responsible for the lesions of the skin and oral mucosa. It has been suggested that immunoblot analysis is a useful tool for detecting autoantibodies which are negative on IIF.¹⁰

More than half of patients with adult linear IgA disease and chronic bullous disease of childhood, other autoimmune subepidermal bullous diseases of IgA class autoantibodies, show bullous lesions on the oral mucosa.^{11,12} In our patient, we excluded the diagnosis of linear IgA bullous dermatosis because we did not detect IgA class autoantibodies either by IIF or by immunoblot analysis using normal human epidermal

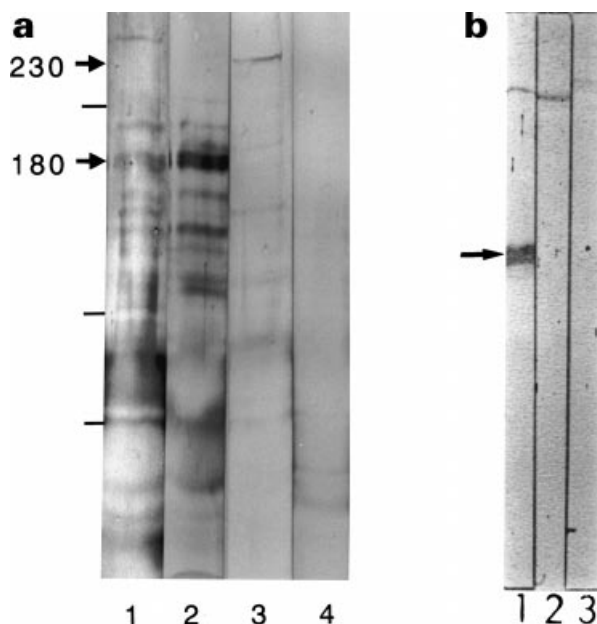


Figure 2. (a) Immunoblot analysis using normal human epidermal extracts. The patient's serum reacted with a 180-kDa epidermal antigen (lane 1). Positive control sera from patients with bullous pemphigoid reacted with 180-kDa (lane 2) and 230-kDa epidermal antigens (lane 3). Normal serum showed no specific band (lane 4). Arrows indicate 180 and 230 kDa. Bars at left indicate the positions of standard molecular weight markers: from top to bottom, 200, 97 and 66 kDa. (b) Immunoblotting using BP180-glutathione-S-transferase (GST) fusion proteins. The patient's serum reacted with S Δ 1 (lane 1), but not with 4575 (lane 2) or recombinant GST (lane 3). The arrow indicates the position of the S Δ 1 fusion protein.

extracts and BP180-GST fusion proteins. We therefore made the diagnosis of BP with circulating anti-BP180 IgG antibodies. Considering the clinical and laboratory findings described above, this case implies that long-term recurrent oral ulceration or erosion could be an early symptom of BP.

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Absence of a link between human herpesvirus 8 and pemphigus

SIR, Memar *et al*. have reported the presence of DNA sequences from human herpesvirus 8 (HHV-8) in both the skin and the peripheral blood mononuclear cells of a patient with pemphigus vulgaris and suggested that HHV-8 could be implicated in the pathogenesis of pemphigus vulgaris.¹ Moreover, the same authors have confirmed their results in other patients.² However, in a study on the prevalence of HHV-8 antibodies in patients with various dermatological diseases we found that only one of 13 patients with pemphigus had antibodies for HHV-8.³ Here we extend our results to another series of patients with pemphigus to illustrate that HHV-8 is not implicated in the pathogenesis of pemphigus.

Twenty-three patients (mean age: 55 years; 10 men and 13 women) were included in this study. The diagnoses were pemphigus vulgaris ($n = 16$) and pemphigus foliaceus ($n = 7$). A control series was formed from 100 healthy subjects (50 men and 50 women). An immunofluorescence assay (IFA) searched for antibodies to HHV-8, using a body-cavity-related B-cell lymphoma cell line (primary effusion lymphoma) latently infected with HHV-8 (BCP-1, kindly provided by Professor P.S. Moore, Columbia, NY, U.S.A.). Briefly, BCP-1 cells were fixed in 4% paraformaldehyde, rendered permeable with 0.2% Triton-X100, incubated with human serum (diluted 1 in 100) for 30 min at room temperature, washed in phosphate-buffered saline/3% fetal calf serum and incubated for 30 min with antihuman IgG-fluorescein isothiocyanate conjugate (Dako, Amersham, U.K.) then washed again and examined by fluorescence microscopy.

Antibodies to HHV-8 were not found in the 23 patients with pemphigus. Antibodies to HHV-8 were found in two of the 100 control subjects (2%). The prevalence of antibodies to HHV-8 in patients with pemphigus was similar to the prevalence of antibodies to HHV-8 in controls. In our serological study, we do not find any significant association between HHV-8 infection and pemphigus. Lack of sensitivity of our IFA is not probable, because using the same assay, we have detected antibodies to HHV-8 in 100% of sera from patients with classical Kaposi's sarcoma.⁴ Our results confirm our previous study which suggests³ that there is no link between HHV-8 and pemphigus.

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Parvovirus B19 infection associated with acute hepatitis and a purpuric exanthem

SIR, Human parvovirus (HPV) B19 infection shows a wide spectrum of cutaneous manifestations and, especially in adults, systemic involvement.^{1–5} Acute hepatitis and hepatic disorders are rare.⁶

A 41-year-old woman developed a skin eruption with pyrexia and constitutional symptoms. She denied any drug intake or exposure to children or adults with exanthematous diseases. The disease started acutely with pyrexia (39.5 °C), fatigue, headache, anorexia, nausea, vomiting, chills, profuse sweating and arthralgia/myalgia. A burning eruption began in the right axilla and spread, 2 days later, to the arms and then to the contralateral axilla, trunk and legs.

Examination showed an erythematous and purpuric eruption localized to the axillae (Fig. 1), trunk and extremities. The lesions were intensely purpuric in the folds. The hands and feet were spared. There was no hepatosplenomegaly nor palpable lymph nodes. Normal tests included full blood count, prothrombin time, muscle enzymes (creatinine phosphokinase and aldolase) and urinalysis.

The peripheral blood monocyte count was raised at $0.09 \times 10^9/L$ (normal $0.02–0.08 \times 10^9$) with $0.028 \times 10^9/L$ reactive lymphocytes. The serum alanine aminotransferase level was 106 U/L (normal 0–40), aspartate aminotransferase 74 U/L (normal 0–37) and lactate dehydrogenase 537 U/L (normal 230–460). Serological tests for cytomegalovirus, Epstein–Barr virus and hepatitis A, B and C viruses were negative or indicative of immunity. Enzyme-linked immunosorbent assay (ELISA) revealed specific anti-HPV B19 IgM (+ + +) and IgG (+ +) antibodies. Using the polymerase chain reaction (PCR), the serum proved negative for HPV B19. Biopsy of axillary lesional skin showed a markedly oedematous papillary dermis with dilated vessels, mononuclear cell perivascular infiltrate and extravasated erythrocytes. Direct immunofluorescence revealed discontinuous granular deposits of IgM and C3 at the dermoepidermal junction. The patient was treated with antipyretics and rest. The skin eruption cleared in 5 days without desquamation while the general symptoms

resolved more slowly with complete remission in about 1 month. Aminotransferase levels became normal within 20 days. Three weeks later, anti-HPV B19 ELISA had changed to IgM (+) and IgG (+ + +).

In children, the most common manifestation of primary HPV B19 infection is erythema infectiosum.¹ In adults, a broad spectrum of manifestations has been described, the eruption often being faint and transient with less specific features, sparing the face.² Most typical is the papular purpuric 'gloves and socks syndrome',³ but atypical exanthems, mostly papulovesicular or purpuric, have been reported.^{4,5} Systemic features are rare in children but may be severe in adults, including arthralgia with synovitis,² and rarer manifestations such as aplastic crisis in patients with chronic haemolytic anaemia,⁷ bone marrow failure in immunocompromised hosts,⁷ a transient febrile myasthenia-like syndrome,⁵ and hepatitis, hepatic dysfunction and fulminant liver failure.⁶ In our patient, the primary HPV B19 infection was suggested by serology. The short period of the viraemic phase, limited to the first days of infection, probably accounts for the negative PCR result on the serum sample.



Figure 1. An atypical erythematous and purpuric eruption is evident at the right axilla.

The purpuric eruption in our patient is of interest. Although this is typical of the 'gloves and socks' pattern of parvovirus skin eruption, it is otherwise unusual in patients without aplastic crisis, thrombocytopenia or coagulopathy due to hepatic dysfunction. The unilateral onset at the right axilla recalls the unilateral laterothoracic exanthem (ULE), also called 'asymmetric periflexural exanthem of childhood',⁸ which has been described in only two adults.^{9,10} This eczematous or scarlatiniform eruption spreads centrifugally all over the body, often retaining a predominant involvement on the half of the body initially affected. An infectious aetiology, particularly viral in nature, has been suspected, but investigations have yielded negative results for HPV B19 or other viruses. In addition to being the third adult patient with ULE, therefore, our patient is the first in whom ULE can be related to a definite viral infection. However, as occurs with other exanthems, e.g. Gianotti-Crosti syndrome, ULE may be a non-specific reaction to one or several infectious agents. It is probably under-diagnosed because of the frequent spread to the contralateral side.

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Does plantar epidermoid cyst with human papillomavirus infection originate from the eccrine dermal duct?

SIR, Plantar epidermoid cyst (PEC) arises on the sole of the foot, and histologically is an epidermal cyst. PEC has long been assumed to be derived from implantation of an epidermal fragment due to a penetrating injury or other cause. It has recently been suggested that human papillomavirus (HPV) (especially HPV 60) infection may be closely related to the occurrence of PEC.¹ The histogenesis of PEC, especially with HPV infection, has not been well established. There have been some reports^{2,3} that PEC may develop from the eccrine duct due to HPV infection, and not from epidermal implantation. The authors proposed two points as evidence of eccrine ductal origin: first, that carcinoembryonic antigen (CEA) recognized by a polyclonal antibody was expressed in the cyst wall of PEC; secondly, that a connection between the cyst wall and the eccrine duct was frequently observed in serial sections.

In order to clarify this hypothesis, the immunophenotypes in five cases of PEC with HPV infection were examined by immunohistochemistry using a panel of cytokeratin (CK) antibodies, and compared with those in normal eccrine gland tissue from various sites.⁴ Immunoreactivities in normal eccrine gland tissue from the sole of the foot in five patients with other diseases such as naevus were also investigated. In the PEC cases examined, vacuolated cells were noted in the inner layers of the cysts or cavities, and stained with anti-HPV antibody. With antibodies against simple epithelial CKs such as 35βH11 (against CK 8; Enzo, New York, NY, U.S.A.), 4.1.18 (against CK 8; Boehringer, Indianapolis, IN, U.S.A.), CAM5.2 (against CKs 8 and 18; Becton-Dickinson, Mountain View, CA, U.S.A.), 170.2.14 (against CK 19; Boehringer), RCK108 (against CK 19; Dakopatts, Glostrup, Denmark) and Ks19.1 (against CK 19; Progen, Heidelberg, Germany), no positive staining was noted. The suprabasal cells in the cyst wall were stained with 34βB4 (against CK 1; Enzo), KL1 (against CKs 1, 2, 5–8, 11, 14 and 16–18; Immunotech, Marseilles, France) and DE-K10 (against CK 10; Dakopatts). The results of immunostaining with other antibodies in the PEC and normal eccrine gland tissue are summarized in Table 1.

There were significant differences in immunoreactivities between PEC and normal eccrine gland tissue at various sites including the sole of the foot. Antibodies against simple epithelial CKs specific to luminal and secretory cells of the eccrine glands⁴ failed to react with any case of PEC. Therefore, on the basis of CK expression, no evidence of eccrine ductal origin in PEC was found. The inconsistency between the hypothesis and our results may be explained as follows: polyclonal antibody against CEA may contain some contamination, and sometimes shows non-specific staining. CEA does not represent a single oncofetal antigen but comprises a group of closely related glycoproteins.⁵ Therefore, there are some differences in immunoreactivities between monoclonal and polyclonal antibodies.^{6,7} With the polyclonal anti-CEA antibody, non-specific staining to necrotic tissue or infiltrating inflammatory cells has also been reported.⁷ In contrast, monoclonal antibodies against CKs do not contain contamination, and are specific, although cross-reactivity

Table 1. Immunohistochemical staining in plantar epidermoid cyst and normal eccrine gland

Antibody	Specificity	Plantar epidermoid cyst		Normal eccrine gland	
		Inner layer	Outer layer	Dermal duct	Secretory cell
34βB4	CK 1	+	± (outermost -)	-	-
AE3	CKs 1-8	+	+	+	+
KL1	CKs 1, 2, 5-8, 11, 14, 16-18	+	-	±	+
34βE12	CKs 1, 5, 10, 14	+	+	+	-
MNF116	CKs 5, 6, 8, 17 and probably 19	±	±	- (basal ±)	+
LP34	CKs 5, 6, 18	±	+	++	±
RCK102	CKs 5, 8	-	+	- (±)	- (±)
35βH11	CK 8	-	-	-	+
4.1.18	CK 8	-	-	- (luminal +)	±
CAM5.2	CKs 8, 18	-	-	-	+
DE-K10	CK 10	+	± (outermost -)	-	-
AE1	CKs 10, 14-16, 19	-	+	+	+
Ks13.1	CK 13	-	-	-	-
E3	CK 17	-	-	-	-
170.2.14	CK 19	-	-	- (luminal +)	+
Ks19.1	CK 19	-	-	- (luminal +)	+
RCK108	CK 19	-	-	-	+

CK, cytokeratin. Staining intensity: ++, strong; +, moderate; ±, weak; -, negative; (outermost -), the outermost layer of the cyst revealed negative staining; - (luminal +), only the luminal layer in the dermal ducts revealed positive staining; - (basal ±), only the basal layer in the dermal ducts revealed weak staining; - (±), focal weak staining was noted.

AE3, AE1 supplied by Boehringer; 34βE12, supplied by Enzo; MNF116, LP34 and E3 supplied by Dakopatts; RCK102 supplied by Sanbio, Udem, The Netherlands; Ks13.1 supplied by Progen.

to other antigens is sometimes observed. Eccrine hidrocystoma, which is thought to be derived from the eccrine duct, revealed similar immunophenotypes of CKs to those in eccrine ducts.⁸ Therefore, immunostaining with monoclonal antibodies against CKs is more reliable than that with polyclonal antibodies against CEA. Furthermore, epidermal implantation may possibly involve pre-existing eccrine dermal ducts, because there are many eccrine sweat glands on the sole.

In PEC with HPV infection, immunoreactivities of CKs, especially differentiation-specific CKs (CK 1 and CK 10), were identical to those of suprabasal layers of epidermis and follicular infundibulum. Therefore, PEC may differentiate towards the normal epidermis or follicular infundibulum. Furthermore, because no follicular structures are recognized in the plantar skin, we speculate that PEC may originate from epidermal implantation or injury rather than from follicular infundibulum.

In conclusion, the notion that PEC is of eccrine ductal origin is not supported by our immunohistochemical observation of CK expression, and we speculate that most cases of PEC with HPV infection originate from epidermal implantation or injury.

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Porokeratosis in patients with hepatitis C virus infection: does hepatitis C virus infection provide a link between porokeratosis and immunosuppression?

SIR, We present three cases of porokeratosis that would otherwise be considered to occur in association with immunosuppression or liver disease. These patients were found to have concomitant hepatitis C virus (HCV) infection. HCV has reportedly been associated with many extrahepatic disorders, including autoimmune diseases and skin diseases of unknown aetiology;¹ such disease association suggested to us that HCV may act as a trigger for the development of porokeratosis in patients with immunosuppression and autoimmune disease. To confirm this association, we have investigated whether cases of immunosuppression-induced porokeratosis reported in the medical literature had increased risk factors for HCV infection. The results, together with our cases, suggest that HCV infection has an important aetiological role in the clinical expression of porokeratosis in an immunosuppressive setting.

Patient 1, an 80-year-old man, was first seen in March 1996 with an eruption that had begun on his trunk and extremities. In 1991, he had been diagnosed as having active chronic HCV infection. He denied intravenous drug abuse and had never received a blood transfusion. On examination, scattered, annular plaques, 0.5–1 cm in diameter, with a palpable, scaling border, were noted on the trunk and extremities, each exclusively affecting a non-sun-exposed area (Fig. 1). Laboratory evaluation revealed liver dysfunction. Histopathological findings of biopsy specimens taken from his back were consistent with the diagnosis of disseminated superficial porokeratosis. In May 1996, he was diagnosed as having hepatocellular carcinoma (HCC).

Patient 2, a 64-year-old man, was seen in 1996 with annular plaques, which had enlarged centrifugally during the previous few years, on his buttock and genitalia. He had suffered from alopecia totalis since the age of 20, and he had a 30-year history of liver dysfunction. Hepatitis C antibody



Figure 1. Discrete, small, round, superficial lesions with a thin, slightly elevated border are seen on the trunk (patient 1).

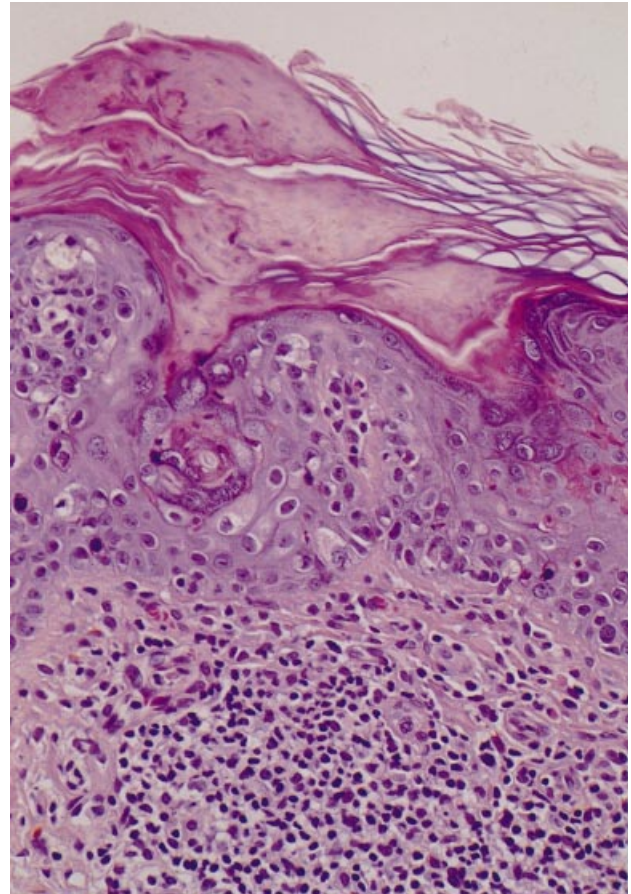


Figure 2. A photomicrograph showing the characteristic cornoid lamella consisting of a tightly packed, thin column of parakeratotic cells at the edges of the lesion with lymphocytic infiltration in the upper dermis (patient 2: haematoxylin and eosin; original magnification $\times 66$).

testing using a second-generation enzyme-linked immunosorbent assay was positive. He had been diagnosed as having active chronic HCV infection. He denied previous blood transfusions, intravenous drug use and other hepatitis risks, but he reported that he had received acupuncture therapy since the age of 10 years. In February 1989, he had suffered from psoriasis and was treated with topical corticosteroids. In June 1992, pruritic erythematous lesions suddenly occurred on his face, neck and forearms after sun exposure. This skin condition was diagnosed as a photosensitive dermatitis, and resolved spontaneously. In 1994, he developed symptoms of liver failure and was eventually found to have HCC. Examination showed a 12 $\times$ 9 mm, brown-red, oval-shaped eruption surrounded by a raised keratotic border on his buttock. Laboratory evaluation revealed liver dysfunction. Histopathological findings from the lesion on his buttock demonstrated a cornoid lamella with apoptosis and liquefaction degeneration (Fig. 2). The diagnosis of porokeratosis of Mibelli was made. The family history was negative for porokeratosis. He died of liver failure in mid-June 1997.

Patient 3, a 41-year-old woman, was seen in 1996, with a

10-year history of an erythematous plaque on her lower left leg, which had gradually enlarged during the previous 5 years. She had suffered from systemic lupus erythematosus from the age of 34 and had taken oral corticosteroids. In 1990, she had been given a blood transfusion after septic shock. Laboratory investigations revealed mild liver dysfunction and a positive antinuclear antibody titre of 1 : 320. Hepatitis C antibody was positive. Histopathological findings were consistent with porokeratosis of Mibelli. The family history was negative for porokeratosis.

The onset of porokeratosis is thought to depend on a variable interaction of genetic factors and exogenous trigger factors, which are not sufficient *per se* for the clinical expression of porokeratosis. Such trigger factors include prolonged irradiation,¹ infective agents and immunosuppression.² Among these, immunosuppression is the most frequently reported condition associated with porokeratosis; in conjunction with this condition, porokeratosis has frequently been reported in patients with autoimmune diseases. Indeed, patient 2 had a history of autoimmune diseases, such as alopecia totalis, and had underlying diseases associated with immune dysfunction, such as psoriasis and a photosensitive dermatitis. In patient 3, porokeratosis developed during treatment of systemic lupus erythematosus with oral corticosteroids. According to traditional paradigms, a straightforward interpretation of our cases would be that the porokeratosis developed in these patients as a result of immunosuppression or immunological dysfunction. Nevertheless, careful consideration should be also given to the alternative possibility that an infectious agent, either a consequence or a cause of immunological dysfunction, could trigger the disease in genetically predisposed patients. Consistent with this possibility, our three patients with porokeratosis were found to have concomitant HCV infection.

To demonstrate further the association between HCV infection and porokeratosis in immunosuppression, we have extensively reviewed the previously reported cases of porokeratosis in association with immunosuppression. Immunosuppressive conditions shown to be associated with porokeratosis include organ transplantation,¹⁻³ liver disease,^{1,4,5} autoimmune diseases treated with systemic corticosteroids and other immunosuppressive agents,^{6,7} leukaemia³ and myelodysplastic syndrome⁸ receiving chemotherapy and blood transfusions, and human immunodeficiency virus infection.⁹ We were surprised to find that most of the patients (35 of 51 cases; 69%) had identifiable risk factors for HCV infection: in particular, most immunosuppressive cases associated with porokeratosis were organ transplant recipients. Recent studies have demonstrated that HCV can be transmitted by organ transplantation and that it causes post-transplantation liver disease.¹⁰ The remainder of the reported cases had a history of the transfusion of blood products, plasmapheresis and intravenous drug use. Blood transfusion was a major source of transmission of HCV until screening of blood donors for HCV was instituted. It is likely that many, if not all, of the reported cases (before 1991-92) with porokeratosis in organ transplant recipients and those receiving blood products may have been positive for HCV had the authors been able to perform

serological studies for HCV. Thus, previous reports of an association between porokeratosis and immunosuppression could now be interpreted as being due to concurrent HCV infection.

In view of our cases and a review of the literature, HCV infection may be of primary importance as a trigger factor for the development of porokeratosis in a setting of immunosuppression. Whatever the mechanisms involved, we propose that porokeratosis be added to the list of HCV-associated diseases.

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Vesiculobullous mycosis fungoides

SIR, Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma. Its annual incidence has more than doubled during the last decades, accounting for about 1% of all lymphomas.¹ MF may occur with a broad variety of clinical features. The classic form evolves through the patch, plaque and tumour stages. The less common forms include granulomatous, hypopigmented, verrucous and pustular MF. However, the presence of bullous lesions is rare. We describe a patient with long-term MF who showed vesiculobullous lesions.

A 36-year-old woman was first seen in April 1989 because of pruritic erythematous plaques over her arms, legs, abdomen and thorax. Skin biopsy findings were consistent with a diagnosis of MF. She was treated with PUVA therapy with improvement but persistence of the cutaneous lesions. From June 1990 to February 1993 she was treated with interferon



Figure 1. (a) Vesiculobullous and ulceronecrotic lesions are evident on the toes. (b) A photomicrograph showing intraepidermal vesicles containing atypical lymphocytes (haematoxylin and eosin; original magnification $\times 25$).

alfa-2a plus etretinate, which produced marked improvement but was poorly tolerated (thrombopenia and leucopenia) and was stopped. Alternating treatments with topical nitrogen mustard and PUVA, according to clinical evolution, were given from February 1993 to April 1997. She occasionally showed tumoral lesions on her legs and buttocks which resolved with local radiotherapy. The persistence of the cutaneous lesions forced a further change of treatment. Since April 1997 to date she has been treated with topical carmustine (BiCNU). In October 1997 she developed vesiculobullous lesions over erythematous and normal-appearing skin on the toes (Fig. 1a) and left heel, and painful necrotic ulcers on the dorsal aspects of the feet. A skin biopsy showed spongiosis and intraepidermal vesicles containing atypical lymphocytes with convoluted hyperchromatic nuclei (Fig. 1b). Routine blood tests were normal. Application of topical carmustine to the feet was stopped and occlusive and systemic steroids were used, resulting in marked improvement and resolution of the lesions. She continues to be treated with topical carmustine plus PUVA, which is well tolerated, but she occasionally develops vesicular lesions on the toes and dorsal aspects of the feet.

Although mild spongiosis is a well-known pathological feature of MF,² it is usually limited to foci of epidermotropism, and a wide spongiosis has been used as a negative criterion against the diagnosis by some authors.³ The development of vesiculobullous clinical lesions in MF is uncommon. In 1887, Kaposi described pemphigus-like skin lesions in a patient with MF.⁴ In 1943, Garb and Wise proposed the term MF bullosa for the occurrence of blisters over infiltrated plaques in a patient previously diagnosed as having MF.⁵ To date, only a few sporadic cases of this clinical variant of MF have been published. In most reported cases, including ours, vesiculobullous lesions developed on both erythematous and

normal-appearing skin, and followed the start of the classic form of MF by several months or years.^{6,7} Pathologically, the blisters may be subcorneal, subepidermal and, less commonly, intraepidermal,⁸ as in our patient. Immunofluorescence studies have always been negative, supporting the view that the bullae are not part of a coexistent immunobullous disease.⁴⁻⁸ Electron microscopic studies show scattered lymphoid cells with convoluted nuclei in the dermis and epidermis or a patchy lichenoid infiltrate containing numerous atypical lymphoid cells.⁴ These atypical cells show marked epidermotropism with formation of intraepidermal collections. The cause of blister formation is unknown. Bacterial and viral cultures, when performed, have been persistently negative. It has been postulated that bullae may appear secondary to a confluence of microabscesses or a release of a cytokine produced by the atypical lymphocytes. The cytokine may act to reduce cohesion between basal keratinocytes and the basal lamina.⁴ Mechanical trauma may also play a part in the development of blisters over damaged skin. In our opinion, the spongiosis and vesiculation observed in our patient are a direct consequence of MF.

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Angiosarcoma of the head and neck associated with xeroderma pigmentosum variant

SIR, Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder with photosensitivity and a greatly increased risk for developing multiple skin neoplasms. XP variants (XPVs) are clinically indistinguishable from classical XP but have a defect in postreplication DNA repair following ultraviolet (UV) exposure, rather than nucleotide excision repair. We describe a patient with XPV who developed cutaneous angiosarcoma of the head and neck (AS). This association does not appear to have been reported previously.

A 43-year-old man had a history of repeated keratoacanthomas. It was noticed that his skin showed marked atrophy, telangiectasia and pigmentary changes on sun-exposed sites (Fig. 1a). There was a family history of XP: two of his sisters had a confirmed diagnosis of XPV and one has since died following unsuccessful treatment of a choroidal melanoma. There was no consanguinity in their parents. Analysis of DNA repair in the patient's fibroblasts following UV irradiation demonstrated impaired postreplication repair using alkaline sucrose gradients to measure the size of newly synthesized DNA¹ (and A.R.Lehmann, personal communication). Cell survival studies showed twice the normal photosensitivity to killing by UV radiation. Phototesting on two occasions was normal. These findings confirmed the diagnosis of XPV. Despite medical advice, he was poorly compliant with sun-protection measures. He subsequently developed multiple actinic keratoses, four basal cell carcinomas, a lentigo maligna melanoma and one squamous cell carcinoma, all of which were treated surgically. At the age of 63 years he developed a 1.5-cm haemorrhagic nodule on the left cheek. There was no local lymphadenopathy. A clinical diagnosis of squamous cell carcinoma was made and the lesion was surgically removed with 5 mm margins and primary closure of the skin.

Microscopically, the lesion showed freely communicating vascular channels lined by atypical endothelial cells dissecting the dermal collagen fibres. The epidermis showed foci of melanocytic dysplasia and pseudoepitheliomatous hyperplasia. Immunohistochemistry showed positive reactivity of the endothelial cells with CD31 (Fig. 1b). Factor-VIII-related

antigen staining was non-specific. HMB45 was negative and cytokeratin staining was non-specific. The dermal lesion was therefore classified as a well-differentiated AS, and was completely excised. Over 18 months later there has been no sign of recurrence of the tumour.

XPV is an autosomal recessive disorder of postreplication DNA repair (daughter strand repair) following UV exposure, with normal nucleotide excision repair, unlike classical XP.¹



Figure 1. (a) The patient's facial appearance: note atrophy and telangiectasia. (b) Photomicrograph of the angiosarcoma, showing positive staining of endothelial cells with CD31 (green) (original magnification $\times 40$).

Traditionally, the diagnosis was made by assaying post-replication repair in cultured fibroblasts together with the clinical findings in affected individuals.¹ However, diagnosis can now be made by the finding of: (i) normal unscheduled DNA synthesis; (ii) normal recovery of RNA synthesis; and (iii) decreased replicative DNA synthesis in patients' fibroblasts which is enhanced in the presence of caffeine.² Because of defective DNA repair, UV-induced damage leads to cell death and somatic mutations. Clinically affected individuals have atrophy, pigmentary changes and telangiectasia on sun-exposed sites. The risk of developing cutaneous malignancy is markedly increased. Benign tumours such as keratoacanthoma and angioma have also been reported.³

AS has not been reported in association with XPV. We are aware of a previous report in a 15-year-old girl with classical XP⁴ who had an aggressive and subsequently fatal tumour of the scalp. Our patient had early excision of a clinically unsuspected AS and so far has had no further recurrence. The most common clinical presentation of AS is of a spreading bruise-like lesion (the 'malignant bruise'), but haemorrhagic nodules, as in our patient, and ulcerated tumours have also been described. AS affects elderly men predominantly, with rapid progression and poor prognosis often due to delayed diagnosis. Holden *et al.* reported an overall 5-year survival of 12% in a series of 72 patients.⁵ Small tumours (<2 cm) have the best outcome; this is independent of the grade of the tumour.⁶ Wide excision together with wide-field radiotherapy may improve the prognosis.⁷ Histologically, AS is an invasive dermal lesion consisting of freely anastomosing vascular channels lined by atypical endothelial cells dissecting the collagen bundles. Immunohistochemistry using a monoclonal antibody to CD31 is highly specific and sensitive for vascular endothelium and is helpful in making the diagnosis, especially in poorly differentiated or undifferentiated tumours. CD34 is a sensitive, but not specific, marker for neoplastic endothelium and AS is often negative for Factor-VIII-related antigen.⁸ The aetiology of AS is unclear. At other sites it has been associated with chronic lymphoedema and has developed many years after radiotherapy. It has been suggested that the development of telangiectasia together with continued UV-induced DNA damage may predispose to the development of AS in XP.⁴ It has also been proposed that UV radiation may be directly involved in its pathogenesis. However, as does occur in the sun-protected hairy scalp and has been seen in skin type V, which would make this theory less likely.

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Eccrine angiomatous hamartoma with verrucous features

SIR, Eccrine angiomatous hamartoma (EAH) is a benign tumour lesion that combines proliferation of multiple eccrine structures and angiomatous channels.¹ It may also contain fatty tissue,² pilar structures³ and epidermal proliferation.¹ We report a unique case of this hamartoma which shows a verrucous figure with epidermal proliferation.

A 73-year-old Japanese woman presented with a keratotic linear nodule, 1.5 × 0.2 × 0.5 cm, on her right buttock close to the sacral region (Fig. 1a). The patient first noticed an asymptomatic erythematous scaly lesion together with occasional local hyperhidrosis about 10 years previously. Although being treated with a topical steroid, the lesion had gradually become enlarged and was painful for the last 2 years. Excisional biopsy was performed. Histological examination of the lesion disclosed that the irregular proliferation of the epidermis extended upward with thick hyperkeratosis and acanthosis, and downward with a serrated configuration and elongation of the rete ridges as well as skin appendages (Fig. 1b,c). There were no foci of vacuolated cells and intracytoplasmic inclusion bodies in the upper portion of the epidermis (Fig. 1c). The reticular dermis contained increased numbers of eccrine structures and numerous vascular channels (Fig. 1b,c). The nests of eccrine structures ran transversely in the deep dermis and appeared larger in the

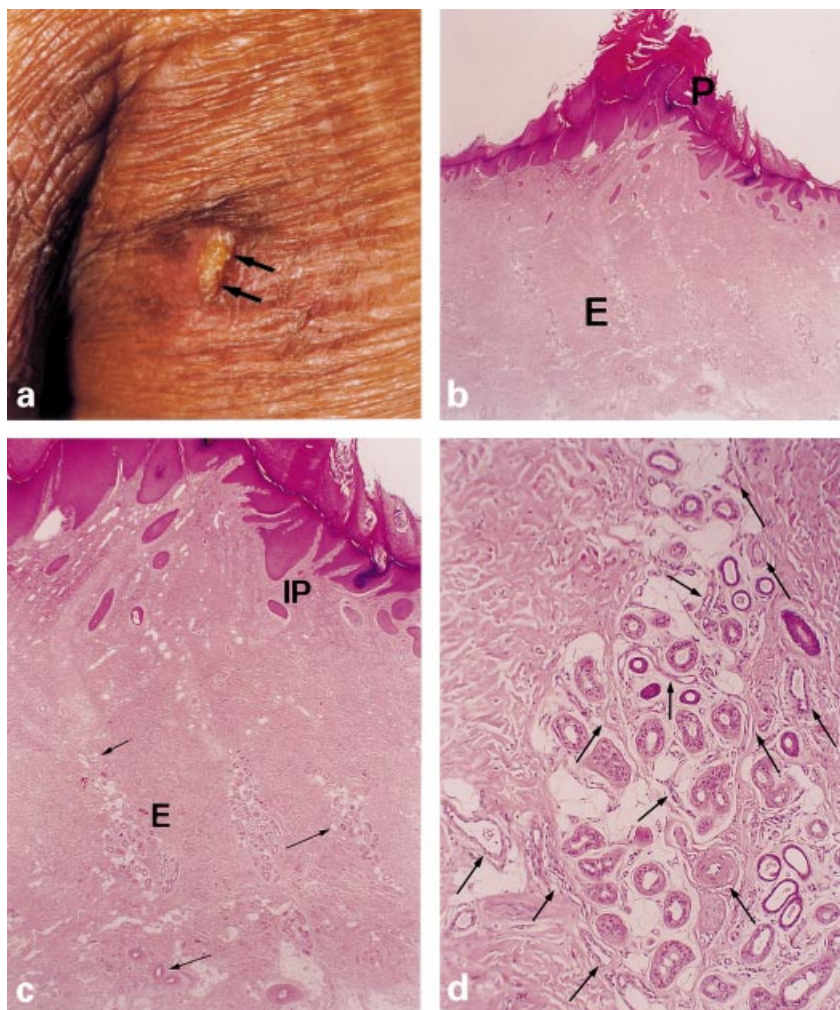


Figure 1. (a) The clinical appearance of the lesion. Arrows indicate the linear verrucous aspect. (b) Low-power photomicrograph showing epidermal proliferation (P) and an increased number of eccrine structures (E) in the deep dermis. (Haematoxylin and eosin (H&E), original magnification $\times 50$.) (c) Irregular proliferation (IP) of epidermis including skin appendages with thick hyperkeratosis and increased numbers of eccrine structures (E) and vascular channels (arrows) in the upper and deep dermis. (H&E, original magnification $\times 100$.) (d) Higher power view of stroma of eccrine structures with intermingled vascular channels (arrows) in (c). (H&E, original magnification $\times 400$.)

centre of the lesion (seen as the peak of the epidermal proliferation) than at the periphery (Fig. 1b). The nests of eccrine structures were composed of eccrine ducts and secretory portions and did not show structural abnormalities (Fig. 1d). A proliferation of dilated vascular channels with walls of various thickness was intimately related to the glandular component (Fig. 1c,d). The vascular component was formed by capillary channels with thin walls in the upper areas. Thick arteriovenous vessels were observed in the deep dermis.

EAH is usually a single, asymptomatic lesion that appears as a nodule or plaque on the extremities at birth.⁴ Hyperhidrosis and/or pain may be present.⁴ In the present case the patient first noticed an erythematous scaly lesion on the buttock close to the sacral region when she was about 60 years old. She also noticed hyperhidrosis and pain in the lesion. The location of EAH on the buttock area is very rare. To our knowledge there is only one report of a lesion on the sacral region.⁵ It is also uncommon to find EAH in elderly persons.^{2,6} Our case was noteworthy because the lesion showed a linear keratotic

change whose histology revealed epidermal proliferation with thick hyperkeratosis and an increased number of eccrine and angiomatous components in the deep dermis. Although epidermal proliferation has been found in cases previously published, only one of these showed an associated thick horn.¹ The reason why the epidermal proliferation with keratotic changes occurred in our case is not clear, but it may be a reaction to the presence of a naevus, or caused by chronic irritation to the sacral region by clothes and local sweating. The finding that the nests of eccrine structures appeared larger in the centre than at the periphery of the lesion may support the former. Papillomavirus infection may be excluded because there were neither vacuolated cells nor intracytoplasmic inclusion bodies in the epidermis. The typical histological features of EAH include lobules of mature eccrine glands and ducts closely associated with thin vascular channels, usually of a capillary nature, but variations in the eccrine and angiomatous elements have also been described.⁷

In addition to the two principal histological components (eccrine structures and vascular channels), the presence in the

tumour of other elements of different histogenetic origin, such as adipose tissue, or follicles, has been described.^{3,4} Several cases of painful EAH have been described in which occasional histological nerve involvement could be demonstrated,⁸ although it was not seen in our case. An abnormal mesenchymal–epithelial induction during the embryonic period has been suggested as a possible causative factor.

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Sweet's syndrome associated with oral squamous cell carcinoma and exhibiting the Koebner phenomenon

SIR, Sweet's syndrome was first described in 1964 by Robert Douglas Sweet.¹ He termed it 'acute febrile neutrophilic dermatosis', but as fever and neutrophilia are not always present the eponym Sweet's syndrome is more commonly used. Sweet's syndrome has been described in association with malignancy, infection, autoimmune disease, vaccination and pregnancy.² We describe a patient with Sweet's syndrome exhibiting the Koebner phenomenon in association with oral carcinoma.

A 64-year-old retired painter and decorator was referred to the Department of Maxillofacial Surgery with a 4-month history of pain and swelling in the area of his left submandibular gland. He was previously healthy and took no medication. He had smoked 20 cigarettes per day from the age of 15 years until 1 year previously, and drank 14–18 units of alcohol per week. Examination revealed a 2.5 × 2 cm ulcer in the floor of his mouth involving the left submandibular duct papilla and the ventral surface of the tongue. There was an enlarged tender submandibular gland on the left and bilateral cervical lymphadenopathy. Histology of an incisional biopsy of the ulcer revealed poorly differentiated squamous cell carcinoma.

The following week the patient had bilateral neck dissections, resection of the floor of mouth carcinoma and reconstruction of the defect using a radial forearm fasciocutaneous free flap. During the operation a sandbag was placed beneath the shoulder blades to assist access for the tracheostomy and to improve access for the neck dissections. A haemostatic pressure cuff was inflated around the upper arm for 75 min to reduce blood loss during harvesting of the forearm flap. He made a good recovery. On the second postoperative day he complained of a burning sensation across his upper back and on his left arm laterally. Examination showed red plaques studded with vesicles at sites corresponding to the position of the sandbag (Fig. 1) and haemostatic cuff used during the operation. He was apyrexial and his peripheral blood neutrophil count was elevated at $11.5 \times 10^9/L$ (normal $2-7.5 \times 10^9$). The appearance of the eruption was characteristic of Sweet's syndrome and this diagnosis was confirmed histologically. The lesions settled spontaneously over the next week.

The annual incidence of Sweet's syndrome in Scotland was estimated to be two to seven cases per million population in 1990.³ The disease is thought to be a hypersensitivity reaction triggered by viral, bacterial or tumour antigens.² The association with solid malignancy was first reported in 1971 and that with haemoproliferative malignancy in 1973. Haemoproliferative malignancy accounts for 85% of malignancy-associated Sweet's syndrome.⁴ Cohen *et al.* reported that the initial appearance of Sweet's syndrome preceded or occurred within 1 month of the detection of a solid malignancy in at least 42% of cases.⁴ In the first reported case of Sweet's syndrome associated with oral carcinoma, the condition occurred during radiotherapy treatment.⁵ In the second case, Sweet's syndrome heralded the diagnosis of oral carcinoma and was a marker for its recurrence.⁶ In both cases, Sweet's syndrome resolved within 2 weeks. In 1975, Gunawardena *et al.* reviewed previously published case reports and observed that Sweet's syndrome may exhibit the Koebner phenomenon.⁷ There have been reports of new lesions of Sweet's syndrome localized to areas of sun exposure,



Figure 1. Erythematous plaques studded with vesicles are evident, corresponding to the position of the sandbag.

chemical irritation and previous skin trauma.⁸ In our patient, the pressure effect during surgery was responsible for the localization of the skin lesions. This substantiates the assertion that the Koebner phenomenon occurs in Sweet's syndrome.

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Nodular prurigo occurring in the same distribution as sciatic pain from a prolapsed intervertebral disc

SIR, Nodular prurigo is a chronic dermatosis characterized by the development of severely pruritic, lichenified and excoriated nodules mainly on the extremities. The cause remains unknown. In most cases, patients are otherwise well and investigations are unhelpful. However, local and systemic causes of pruritus have been associated with nodular prurigo. Of these, atopic eczema has been most strongly implicated as a contributing factor.¹ Others include contact sensitivity, insect bites, anaemia, hepatic dysfunction, uraemia, malignancy, gluten enteropathy and psychological disorders.^{2,3} We describe an unusual case of nodular prurigo occurring in the same distribution as sciatic pain from a prolapsed intervertebral disc.

A 66-year-old woman presented to an orthopaedic surgeon in January 1994 with low back pain radiating to the left buttock, posterior thigh and outer border of the foot. She also experienced numbness and paraesthesiae on the left lateral leg. An magnetic resonance imaging scan confirmed lumbar disc herniation at L5–S1 and a more minor disc bulge

at L4–L5. Excision of the L5–S1 disc was undertaken in March 1994. After initial improvement in her symptoms, the back and left sciatic pain recurred in October 1994. In January 1995, she developed a pruritic eruption localized exclusively to the left leg. There was no personal or family history of atopy. She had no other systemic diseases. Examination revealed lichenified excoriated nodules and eczematous changes strikingly located in the same distribution as her sciatic pain on the left buttock, posterior thigh and lateral lower leg (Fig. 1a). Neurological examination of the legs revealed normal reflexes and sensation and no muscle weakness. Routine blood tests including full blood count, liver and renal function were normal. Biopsy of one of the nodules was histopathologically consistent with nodular prurigo, showing hyperkeratosis and irregular acanthosis. No neural changes were seen (Fig. 1b). The lesions improved with topical clobetasol propionate but have not cleared. They persist 4 years after initial presentation. The sciatic pain also persists but further back surgery is not planned. No nodular prurigo lesions have appeared elsewhere on the body during this time.

Prolapsed intervertebral lumbar discs frequently produce pain radiating from the back into one buttock and leg along its posterior or lateral aspect. The exact mechanism of this pain is not known but it is thought to be due to a combination of radicular pain arising from compression of the nerve roots, commonly L5 and S1, and referred pain that results from stimulation of spinal structures such as the annulus fibrosus, muscles and ligaments.⁴ Our patient experienced chronic pain in this typical distribution on the lateral left leg prior to the onset of nodular prurigo in the same area. This association between pain, itch and nodular prurigo is difficult to explain but it may be that neuropeptides have an aetiological role. Neural changes such as prominent neural hyperplasia have been described in nodular prurigo⁵ but are not considered to be an essential feature for diagnosis.⁶ Immunohistochemical analysis in nodular prurigo has shown proliferation of substance P and nerve fibres containing calcitonin gene-related peptide.⁷ As well as having a role in sensory processing, these neuropeptides are also involved in the inflammatory response. They are potent histamine releasing factors, mediators in neurogenic inflammation and have a significant role in fibroblast and keratinocyte proliferation.⁸ Sensations of itch and pain share common mechanisms. The neuropeptide, substance P, is thought to be important for transmission of pain and itch sensation in unmyelinated C fibres. Neuropeptides such as substance P that are stimulating the nociceptive receptors in the skin may therefore also be causing itch and acting as inflammatory mediators that induce the nodular prurigo lesions. Capsaicin (8-methyl-N-vanillyl-6-nonenamide), a naturally occurring compound found in chilli pepper and other spices, depletes neurotransmitters such as substance P from sensory neurons and has been used topically with success in nodular prurigo.^{9,10}

This rare occurrence of nodular prurigo in an area of pain from a prolapsed lumbar intervertebral disc has not to our knowledge been described previously. It is interesting, however, that previous studies of nodular prurigo have shown neuronal changes and raised sensory neuropeptides in the

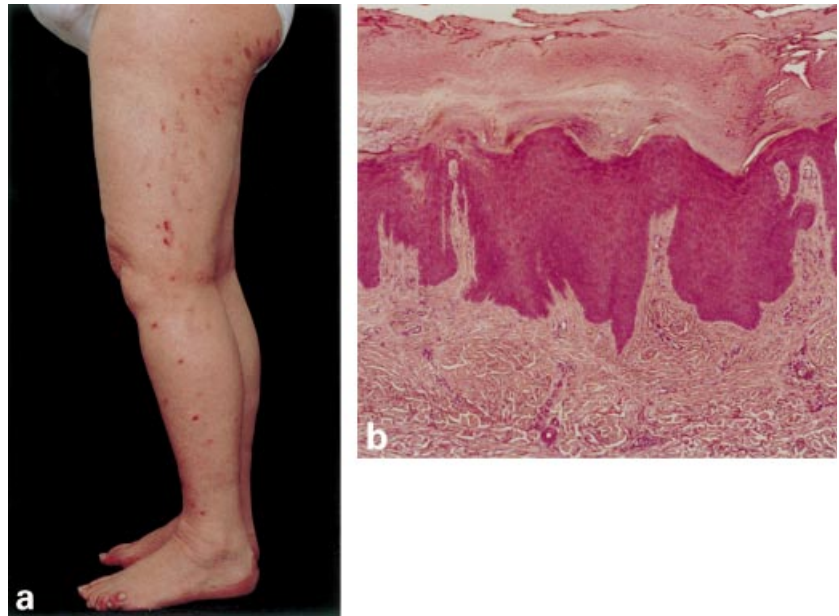


Figure 1. (a) Nodular prurigo and eczematous changes located in the same distribution as the patient's sciatic pain on the left buttock, posterior thigh and lateral lower leg. (b) Nodular prurigo lesion showing hyperkeratosis and irregular acanthosis (haematoxylin and eosin; original magnification $\times 40$).

lesional skin of these patients. Some of these changes have been assumed to be secondary to trauma from scratching. Our case raises the possibility that these changes may also be primary causative factors in the pathogenesis of nodular prurigo.

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Leg ulcers in patients treated with hydroxyurea for myeloproliferative disorders: what is the trigger?

SIR, Wirth *et al.*¹ report a patient with chronic myelogenous leukaemia who developed painful leg ulcers which arose 1 year after institution of treatment with hydroxyurea. When the high platelet count proved refractory to hydroxyurea, this drug was replaced by the megakaryocyte inhibitor anagrelide. The platelets normalized within 2 weeks, and the ulcers healed within the next few months. The authors argue that the ulcers were likely to have been caused by thrombocytosis because they healed when the platelet count returned to normal, and dismiss a possible association with hydroxyurea, because the patient had received this drug for 1 year without side-effects.

Leg ulcers associated with hydroxyurea treatment of chronic myeloproliferative disorders represent a fairly well-defined entity which has been documented over the past 15 years in a series of articles.^{2–7} Approximately 40 patients have been described who all showed remarkable similarities in clinical features and course: the ulcers resembled those of livedoid vasculitis; most were located on the lower legs, were exquisitely painful and developed only after long-term

treatment with hydroxyurea (1–10 years, mean 4). They all were therapy resistant and healed only after discontinuation of hydroxyurea. We feel that the patient reported fits well into this pattern.

Although an aetiological role of thrombocytosis proper in the genesis of the ulcers cannot be ruled out, there is circumstantial evidence that hydroxyurea (or its combination with thrombocytosis) may be the real culprit. There is little support in the literature for thrombocytosis *per se* being a prominent cause of leg ulcers. In most of the patients who were treated with hydroxyurea and developed leg ulcers, no correlation became apparent between leucocyte or platelet counts and ulcer formation.^{3–5} In contrast, in some cases the ulcers arose while the platelet count was low, and in others the ulcers healed after hydroxyurea was withdrawn, although the platelet count was still massively elevated. In several cases, leg ulcers healed following withdrawal of hydroxyurea but rapidly relapsed when the drug was reinstituted.^{2,3} The spontaneous healing of the ulcers of the patient described may thus be due to the withdrawal of hydroxyurea rather than to normalization of the platelet count.

At present, it is unclear by which mechanisms hydroxyurea may lead to the formation of leg ulcers. It has been speculated that it may promote coagulation in the malleolar vessels,³ or cause delayed wound repair^{2,3,5} and/or cutaneous atrophy after minor trauma^{2–5} due to its antimetabolic effects. None of these explanations is totally satisfactory, however. With regard to the occasional finding of fibrinous thrombi in the vicinity of the leg ulcers and the general resemblance to livedoid vasculitis,^{2,3,6} it appears more likely that hydroxyurea may have a direct effect on the vessel endothelia or the platelets, or the interaction of these components.

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Abnormal liver function tests induced by dapsone in a patient with dermatitis herpetiformis and primary sclerosing cholangitis

SIR, A 32-year-old farmer presented with a 1-year history of a widespread pruritic rash which was most pronounced on extensor surfaces. The itch was so severe that he had been unable to sleep for 2 months prior to presentation. Plaques of annular urticated erythema with tense straw-coloured blisters were seen in the suprasternal notch and on the elbows, typical of dermatitis herpetiformis (DH). Both his mother and sister had DH. He drank approximately 20 units of alcohol per week. A full examination was normal and he had no stigmata of chronic liver disease. Histology of an affected area showed suprapapillary abscesses with subepidermal bulla formation and large neutrophilic aggregates. Direct immunofluorescence of normal skin demonstrated a granular deposition of immunoglobulin A along the basement membrane zone. Baseline liver enzymes showed an obstructive picture (Table 1). One week after taking dapsone 100 mg/day there was a fourfold rise (Table 1). This deterioration coincided with darkening of the urine.

Routine investigations were normal. Antiendomysial, α -gliadin antibodies and hepatitis A, B and C titres were negative. An ultrasound of the liver showed a distended gall bladder with a distended biliary tree. An endoscopic retrograde cholecystopancreatogram was unsuccessful and a percutaneous transhepatic cholangiogram showed a long stricture at the lower end of the common bile duct with stricturing and beading of the intrahepatic biliary tree, diagnostic of primary sclerosing cholangitis (PSC). A small bowel biopsy, colonoscopy and colonic biopsies were normal.

The rash proved difficult to control. Re-introduction of dapsone resulted in a further deterioration of the liver function tests. Prednisone 60 mg/day cleared the skin but reduction of the dose below 40 mg resulted in a severe exacerbation of the rash. Sulphapyridine 1 g three times daily in combination with a gluten-free diet allowed the prednisone to be discontinued. The patient's HLA genotype was A1–, B8, B37, Cw6, Cw7, DR3, DR15 and DRw52a.

Abnormal liver function tests have been reported in both coeliac disease and DH.^{1,2} A variety of liver conditions has been reported in association with coeliac disease including PSC.^{2,3} Our patient represents the second reported case of coexistent DH and PSC.⁴ Although our patient had no evidence of active coeliac disease, all patients with DH are considered to have an associated gut abnormality, and in one-third of patients this is mild (Professor L.Fry, St Mary's Hospital, London, personal communication). Both DH and PSC are strongly associated with certain HLA types. The HLA antigen B8 is found in 83% of patients with DH in Ireland and the combination of HLA B8 and A1 is found in 91%, compared with 25–35% of the general population.⁵ HLA B8 has been reported in 60–80% and DR3 in 70% of patients with PSC.

Table 1. Serial liver function tests on and off dapsone

	Off dapsone 16/3/95	On dapsone 20/3/95	Off dapsone 31/3/95	On dapsone 13/4/95	Off dapsone 29/5/95
Alkaline phosphatase (normal 30–130 U/L)	469	1457	467	582	210
Bilirubin (normal < 20 µmol/L)	21	27	14	34	39
Aspartate aminotransferase (normal 5–50 U/L)	167	373	273	344	60
γ-Glutamyltransferase (normal 10–40 U/L)	n/a	n/a	566	1004	511

n/a, not available.

HLA DRw52a is found in 94% of patients with PSC compared with 35% in the general population and is positive in our patient.⁶ These data coupled with reports of familial clusters of PSC and the well-recognized occurrence of familial DH⁵ strongly suggest a genetic predisposition to the development of DH and PSC. Reports of autoantibody abnormalities in PSC and the known association of α-gliadin and antiendomysial antibodies in DH⁷ suggest a possible underlying immune mechanism.

In the previously reported case, abnormal liver function tests developed while on dapsone and subsequent investigation revealed the underlying disease.⁴ It is not stated whether dapsone was discontinued. In our patient the liver function tests deteriorated fourfold on dapsone and with its subsequent re-introduction. Liver function test abnormalities have previously been reported with dapsone, in isolation or as part of the dapsone syndrome.⁸ The most likely explanation is that this was a direct idiosyncratic hepatotoxic effect which is dose-dependent⁸ and that the presence of PSC may have predisposed to the hepatotoxicity. Sulphapyridine, which is metabolized by a similar mechanism, has not resulted in liver function test deterioration.

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Severe erythrodermic reactions to the proton pump inhibitors omeprazole and lansoprazole

SIR, The proton pump inhibitors (PPIs) omeprazole and lansoprazole are used extensively in the treatment of peptic ulcers, for the eradication of *Helicobacter pylori* in combination with antibiotics, and are the drugs of choice for erosive oesophagitis with stricture formation.¹ The frequency of drug eruptions induced by PPIs is unknown, although it is stated that rashes have been reported in fewer than 1% of patients on omeprazole.² We report three patients with severe exfoliative dermatitis, erythema multiforme (EM) and toxic erythema induced by PPIs, in which the patients presented with erythroderma.

The first patient was an 83-year-old man who was admitted as an emergency with exfoliative erythrodermic dermatitis. He had taken lansoprazole 30 mg daily for an oesophageal stricture and gastric ulcer over a 9-week period. He had hypertension, ischaemic heart disease and osteoarthritis and had been on long-term atenolol, azapropazone, dihydrocodeine, amitriptyline and magnesium trisilicate for some years. The whole skin surface was involved by the eruption and he was tachycardic with mild congestive cardiac failure. Lansoprazole was stopped and he was treated with betamethasone valerate 0.025% ointment twice daily. Twenty-four hours later, because of acute gastrointestinal haemorrhage, he underwent emergency truncal vagotomy

and undersewing of a bleeding duodenal ulcer. The skin eruption settled over the next 2 weeks and he was started on omeprazole 20 mg twice daily.

Ten weeks later he was re-admitted with a 3-week history of a generalized eruption. Again, he had an exfoliative erythroderma and was in cardiac failure. Skin biopsy showed a chronic inflammatory infiltrate in the dermis with a prominent eosinophil content. There was focal spongiosis and hyperkeratosis. Omeprazole was stopped and he was treated with betamethasone valerate 0.1% ointment twice daily. The erythroderma resolved but he required oesophageal dilatation for a persistent stricture, and was then started on ranitidine. Five months later, after a further oesophageal dilatation, he was re-started on omeprazole. Within a week, he became erythrodermic. He was re-admitted, the drug was stopped and he was treated with betamethasone valerate 0.1% ointment, whereupon the eruption settled completely.

The second patient also presented with erythroderma but had histological changes consistent with EM. She was a 52-year-old woman with systemic sclerosis who developed oesophageal reflux. Endoscopy showed a dilated oesophagus with oesophagitis, and she was commenced on omeprazole 20 mg twice daily. She was taking no other medication. Within 7 days she developed erythroderma. A skin biopsy showed a focally dense lichenoid inflammatory infiltrate with prominent colloid body formation and liquefaction of the basal cell layer. The omeprazole was changed to ranitidine and she was treated with betamethasone valerate 0.1% ointment twice daily. The erythroderma settled within 2 weeks and has not recurred.

The third patient was a 74-year-old man who was started on omeprazole 20 mg twice daily for reflux oesophagitis and presented 9 days later with a severe toxic erythema which progressed to erythroderma. He was otherwise well and on no other drugs. The eruption consisted of multiple target-like lesions over the palms and abdomen with confluent erythema over the trunk and limbs. There was no other systemic involvement. A skin biopsy showed an extensive inflammatory infiltrate in the epidermis and superficial dermis with a prominent eosinophil and neutrophil content. There were superficial pustules with spongiosis and focal parakeratosis. There was no keratinocyte necrosis, basal cell damage or vasculitis. Direct immunofluorescence was non-specific. Blood film showed a leucoerythroblastic picture, with metamyelocytes and the occasional nucleated red blood cell suggesting severe marrow stress, and a raised eosinophil count of $6.4 \times 10^9/L$ (normal $0-0.4 \times 10^9$). The omeprazole was stopped and he was treated with emollients and an oral antihistamine. The eruption and the blood abnormalities resolved within 8 days.

Skin manifestations account for about 20% of all adverse reactions to PPIs reported to the Committee on Safety of Medicines (CSM) (personal communication). By January 1998, a total of 1296 skin reactions to omeprazole had been reported, 500 to lansoprazole and 44 with pantoprazole. The main categories are 'non-specific' rashes, pruritus, urticaria, 'erythematous' rashes and photosensitive eruptions.²⁻⁴ Erythroderma has been reported only four times with

omeprazole and twice with lansoprazole. There has been one published case report of exfoliative dermatitis associated with omeprazole which occurred 3 weeks after starting the medication.⁵ Exfoliative dermatitis may present several weeks after starting a drug and is thought to be mediated by a type IV hypersensitivity reaction.⁶ This appeared to be the case with our first patient who had taken lansoprazole and who also took some time to develop a reaction to omeprazole. However, on rechallenge with lansoprazole, he developed erythroderma within a week, which is consistent with the criteria for the assessment of a drug reaction.⁶ There have been no studies on cross-sensitivities between the different types of PPIs. Wyeth Laboratories (Maidenhead, U.K.), the manufacturers of lansoprazole, state that on changing to lansoprazole in patients who have had a rash while taking omeprazole, some patients transfer uneventfully, but others have recurrence of the eruption. They advise caution and close patient monitoring if transferring patients between PPIs in such cases (personal communication, Wyeth Laboratories). Our first patient undoubtedly showed cross-sensitivity between omeprazole and lansoprazole.

There have been five reports of toxic epidermal necrolysis with omeprazole and one with lansoprazole, three of which were fatal (personal communication, CSM). EM has been reported 26 times in association with omeprazole and 10 times in association with lansoprazole. Our second patient developed erythroderma with histological changes of EM within 7 days of starting omeprazole. Drugs are a common cause of EM and she was on no other medication. Our third patient showed features of toxic erythema, which usually develops within 2 weeks of starting a drug. Again, the time course was consistent with a drug eruption.

There have been occasional case reports of other types of reactions to PPIs and these include acute generalized exanthematous pustulosis (to lansoprazole), and pityriasis rosea, erythema nodosum and acute disseminated epidermal necrosis (with omeprazole).⁷⁻¹² PPIs may cause potentially severe drug eruptions. The possibility of a class effect with these agents should be considered.

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Intolerance of isotretinoin in a patient with anhidrotic ectodermal dysplasia

SIR, The use of isotretinoin (Roaccutane^R) for acne universally results in a dose-dependent dryness of the skin.¹ This is usually well tolerated and relieved by the use of emollients. We report a patient with anhidrotic ectodermal dysplasia (AED) who was unable to tolerate isotretinoin because of severe dryness and irritation of the skin.

This young man had originally presented as a child with AED and the case has previously been reported.² On examination, he had dry sparse hair and other features of AED including wrinkled dry skin and partial adontia.² As a baby, he initially presented with unexplained hyperpyrexias and dry skin. His maternal aunt who attends our clinic with vitiligo also has AED. He presented again aged 23 years with papulopustular and nodular acne which only partially responded to minocycline 100 mg daily for 3 months. Isotretinoin was commenced at a dose of 60 mg (1 mg/kg) daily. Within 12 h his skin was extremely irritated and itchy with an intolerable sensation of dryness. He discontinued the drug and the reaction settled within 48 h. Three weeks later, isotretinoin was re-introduced at a dose of 10 mg daily. Within hours he suffered a recurrence of the same distressing dryness and, when seen at the clinic, had pronounced cheilitis. The drug was discontinued and his symptoms settled quickly. He was recommenced on minocycline 100 mg daily and his acne has partially responded.

Isotretinoin inhibits lipid synthesis in the sebaceous glands.¹ This alters the surface lipid content markedly, resulting in skin dryness.³ Patients with AED have a reduced number of sweat glands which results in a mild generalized dryness of the skin.⁴ Although isotretinoin does not appear to reduce sweat production,⁵ its alteration of lipid surface content in a patient with AED may produce a severe dryness and cheilitis. We report this case to serve as a warning in other patients with AED and acne in whom isotretinoin is being considered.

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Successful treatment of severe refractory atopic dermatitis with mycophenolate mofetil

SIR, Atopic dermatitis is an intensely pruritic dermatitis with a typical morphology and distribution. Although the cause remains unknown, immunological mechanisms are likely to be important. In most patients, the disease begins in infancy and steadily improves throughout childhood. However, some patients remain severely affected into teenage years and adult life and, in addition to topical therapy, may require treatment with steroids, azathioprine or cyclosporin. As these drugs may lead to a wide range of severe side-effects, new treatments with an improved risk–benefit ratio are of great interest.

Recently, mycophenolate mofetil (MMF), an ester of mycophenolic acid, which is currently used to prevent rejection in renal transplant patients,¹ has also been successfully used in blistering autoimmune diseases and pyoderma gangrenosum.^{2–4} MMF is a non-competitive inhibitor of inosine-monophosphate-dehydrogenase and thus influences the function of lymphocytes via the inhibition of purine synthesis. The drug reversibly and non-competitively blocks the *de novo* synthesis of guanine nucleotides required for DNA and RNA synthesis during T- and B-cell proliferation. Thus, having lymphocyte antiproliferative activity, MMF might be effective in the treatment of autoimmune diseases. As immunological mechanisms are likely to play an important part in the pathogenesis of atopic dermatitis, we hypothesized that MMF might also be of benefit for patients with severe atopic dermatitis.

We report two patients with severe atopic dermatitis, who had not responded to conventional topical treatment nor to systemic treatment with oral steroids, psoralen-ultraviolet A (PUVA) photochemotherapy or cyclosporin. Atopic dermatitis was diagnosed according to the criteria described by Hanifin and Rajka.⁵ The severity of the skin disorder was scored using modified SCORAD scores.⁶ Both patients were given MMF 1 g twice daily as a monotherapy. Efficacy was assessed once a week by two independent investigators. Routine laboratory testing was normal at the beginning of therapy and at weekly intervals.

The first patient, a 55-year-old woman, had suffered from allergic rhinitis for 32 years and, from the age of 6 to 11 years,

had also had allergic asthma. A year prior to presentation she had developed pruritic, scaling erythema involving her neck, shoulders, hands, volar arms and legs (Fig. 1a). She presented with pruritic, scaling erythema and lichenification and excoriation of the skin on the trunk and extremities. Initial treatment for 3 months with topical steroids and oral prednisone (1 mg/kg per day for 6 weeks then tapered off over 6 weeks) had been without success. Subsequent therapy

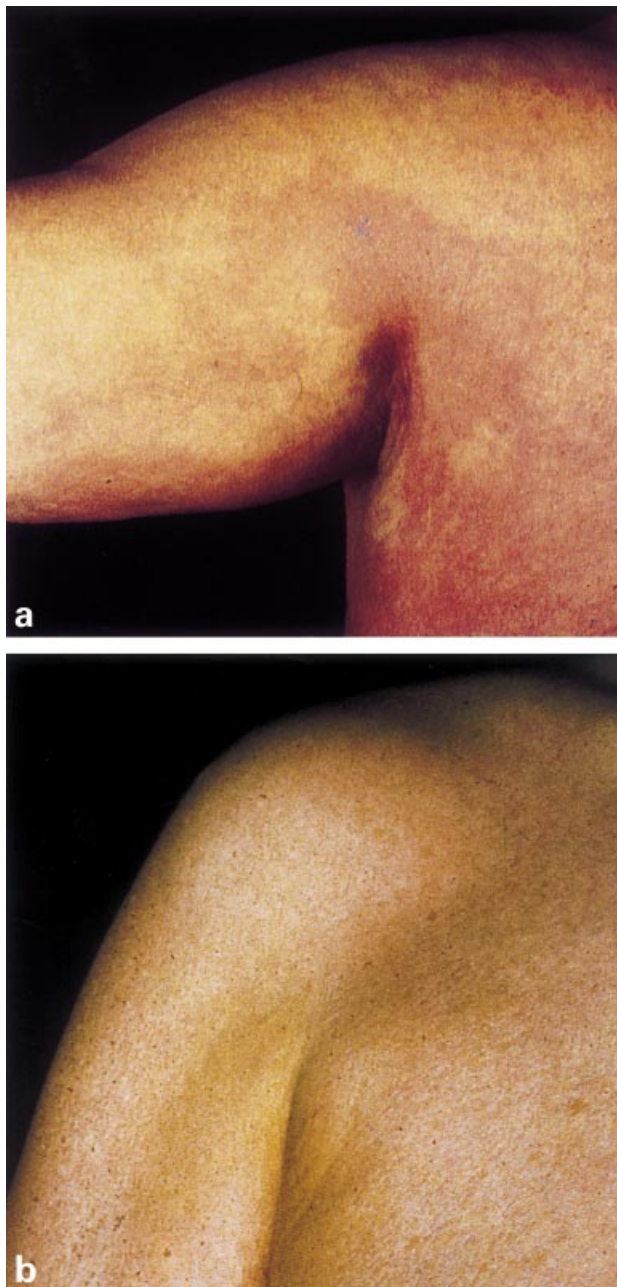


Figure 1. (a) The first patient's dermatitis prior to therapy with mycophenolate mofetil. (b) Complete remission after treatment with mycophenolate mofetil.

with cyclosporin (3 mg/kg per day) had to be discontinued after 3 weeks because she developed severe hypertonia. The patient was given oral MMF 2 g daily as monotherapy. After only 2 weeks of treatment with MMF she was free of symptoms (SCORAD score before treatment: 30.4; SCORAD score after 2 weeks of treatment with MMF: 8.0; Fig. 1b).

The second patient, a 64-year-old man, had had atopic dermatitis for 60 years. In his early childhood he had also suffered from allergic rhinitis. He presented with a pruritic and scaling erythema on the trunk and extremities. Treatment with topical steroids and oral prednisone (1 mg/kg per day) as well as PUVA photochemotherapy (total dose 78 J/cm²) was ineffective. The patient was given oral MMF 2 g daily as a single therapy. The lesions cleared nearly completely after 4 weeks of therapy with MMF (SCORAD score before treatment: 36.8; SCORAD score after 3 weeks: 12.8).

In both patients MMF monotherapy was continued for another 4 weeks and was tolerated without side-effects. During follow-up over 12 weeks no relapse was seen. Adverse effects observed in transplantation patients treated with MMF include gastrointestinal symptoms as well as leucopenia and anaemia.⁷ Thus, in comparison with the unwanted side-effects of systemic glucocorticosteroids, azathioprine or cyclosporin, MMF seems to have an improved risk-benefit ratio for patients with severe atopic eczema. MMF was well tolerated by our patients. Our data suggest that MMF therapy may be beneficial for patients with atopic dermatitis, as both our patients responded well with no signs of recurrence after 3 months of follow-up. These preliminary results suggest that a randomized controlled clinical trial of MMF in atopic dermatitis is warranted.

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Combination treatment of psoriasis with photochemotherapy and tazarotene gel, a receptor-selective topical retinoid

SIR, Psoriasis is a chronic skin disorder affecting approximately 1–3% of the world's population. In the past decades, several treatment regimens combining topical agents with photochemotherapy or photochemotherapy have been successfully used.¹ However, as most commonly used topical therapies have major limitations, a need remains for new topical treatments that have enhanced short- and long-term antipsoriatic effectiveness, an improved side-effect profile and suitability for photocombination therapies. Tazarotene, the first member of a novel generation of acetylenic topical retinoids, normalizes altered keratinocyte differentiation, has antiproliferative effects and decreases expression of inflammatory markers.^{2,3} It is generally well tolerated and overcomes cosmetic problems associated with many other topical antipsoriatic therapies.⁴ Psoralen-ultraviolet (UV) A (PUVA) bath photochemotherapy is very efficacious in severe psoriasis and is an attractive alternative to oral PUVA therapy because of lack of systemic side-effects and reduced cumulative UVA doses.⁵

To assess the efficacy of topical tazarotene in combination with PUVA bath therapy, 12 patients with extensive plaque psoriasis were treated in a left–right study. Psoriatic plaques on one half of the body were treated either with topical tazarotene 0.05% (Zorac®, Allergan, Germany) or vehicle only once daily (assignment of tazarotene to body half was random); in addition, lesions on both halves were treated with PUVA bath therapy four times a week (Monday, Tuesday, Thursday and Friday). Initial UVA doses were approximately 30% of the minimal phototoxic dose and were gradually increased at each third irradiation to maximum single UVA doses of up to 2 J/cm². A mean cumulative UVA dose of 15.8 ± 4.7 J/cm² (mean ± SD) was applied with a mean number of 16 irradiations (range 11–18). The follow-up period was 6 weeks; patients were treated until a sufficient therapeutic success was obtained. Efficacy was assessed using a modified psoriasis area and severity index (PASI) separately for both body halves before therapy and once a week thereafter. The mean ± SD PASI score at baseline was 23.6 ± 7.8 for combination therapy body half and 23.4 ± 7.7 for side assigned to PUVA bath monotherapy.

After 2 weeks, both treatment modalities notably reduced PASI scores, with values in all patients being significantly lower in skin areas treated by photochemotherapy in combination with topical tazarotene as compared with areas treated by photochemotherapy alone. After 3 weeks, the mean PASI reduction was 76% with combination therapy (mean PASI score after 3 weeks 5.7; median PASI reduction 76.5%; range 54–92%; 95% confidence interval (CI) 65–86%), whereas the mean PASI reduction with PUVA bath therapy alone was 58% (mean PASI score after 3 weeks 9.8; median PASI reduction 58.5%; range 45–75%; 95% CI 50–69%). For the body half receiving combination therapy, the PASI score after 4 weeks was 1.0 and after 6 weeks 0.6. For the body half assigned to PUVA bath monotherapy, the PASI score after 4 weeks had decreased to 2.3 and after 6 weeks to 1.1. Within the first 3 weeks of treatment, reduction of scaling and

induration was slightly quicker than reduction of erythema on the tazarotene side.

Both treatment modalities were well tolerated, with no significant PUVA-tazarotene phototoxicity under combination therapy. Phototoxic side-effects such as erythema, pain or blistering did not occur in any of the patients. Adverse effects of tazarotene gel were limited to mild local cutaneous irritation such as transient burning and erythema of the skin. The clinical difference between combination therapy and PUVA bath monotherapy was statistically significant ($P < 0.05$, Wilcoxon matched-pairs test). Our findings support the concept that in patients with psoriasis, combination treatment with photochemotherapy and a topical retinoid may enhance the therapeutic efficacy, with a reduction in mean number of treatment sessions and application of lower cumulative UVA doses. Although long-term results are not yet available, PUVA bath treatment combined with tazarotene seems to be an efficacious new treatment regimen which may develop into an attractive and advantageous photocombination therapy.

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Pruritic folliculitis of pregnancy treated with narrowband (TL-01) ultraviolet B phototherapy

SIR, Pruritic folliculitis of pregnancy is a rare specific dermatosis of pregnancy characterized by a sterile folliculitis of unknown aetiology. There is no standard effective therapy. The duration is reported to be from 1 week to several months.

We report a 30-year-old woman who presented in the tenth week of her second pregnancy with a 1-week history of a pruritic pustular eruption. It had worsened despite treatment with oral flucloxacillin, oral chlorpheniramine and topical hydrocortisone 0.25% and crotamiton 10% cream. Her first pregnancy had had a full-term Ventouse delivery without complication. She had a widespread monomorphic erythematous papulopustular follicular eruption predominantly affecting her arms and legs (Fig. 1a). There was relative sparing of

the head and trunk. The palms and soles were unaffected. She was treated empirically as having staphylococcal folliculitis with oral erythromycin, Fucibet cream (betamethasone valerate 0.1%, fusidic acid 2%) and continued oral chlorpheniramine. She noted some symptomatic improvement but the eruption persisted. A swab was negative on culture. Incisional skin biopsy showed formation of a follicular vesicle with

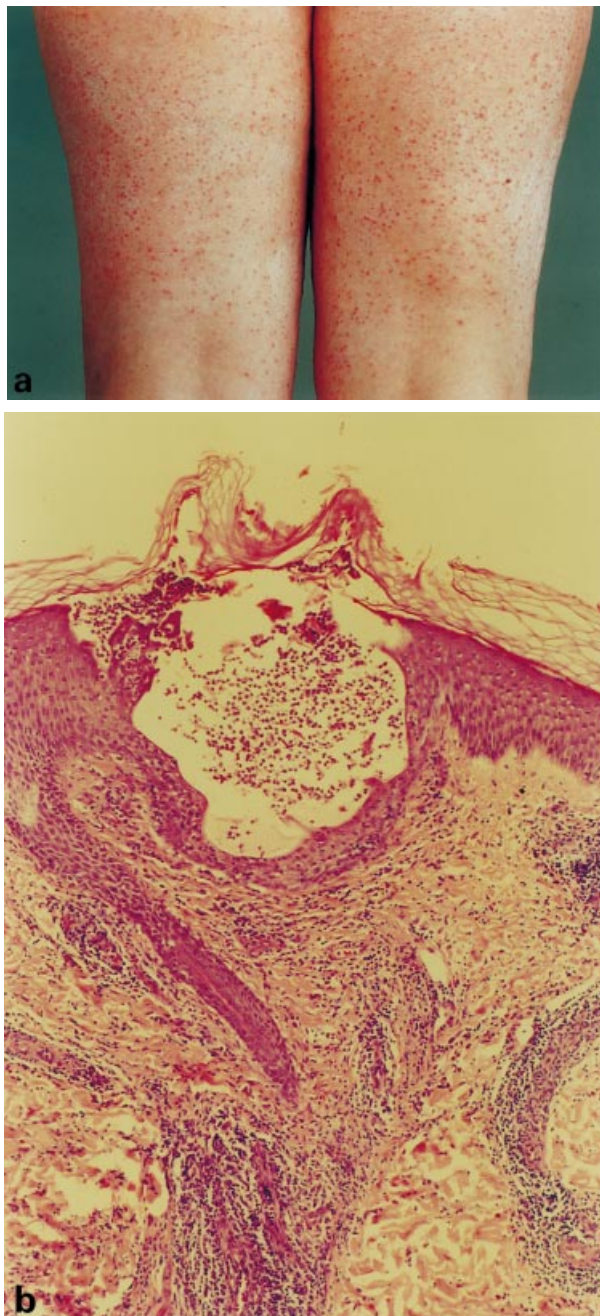


Figure 1. (a) Erythematous papulopustular follicular lesions are evident on the legs. (b) Photomicrograph showing a folliculitis with neutrophils and occasional eosinophils (haematoxylin and eosin; original magnification $\times 20$).

neutrophils and occasional eosinophils. There was mild superficial dermal oedema and a moderate perivascular infiltrate of lymphocytes, macrophages and a few eosinophils. Gram and periodic acid-Schiff stains were negative, excluding *Pityrosporum* folliculitis (Fig. 1b). This was consistent with an acute sterile pustular folliculitis, and a diagnosis of pruritic folliculitis of pregnancy was made.

She was commenced at 11 weeks gestation on narrowband ultraviolet (UV) B phototherapy at 70% of the minimal erythmal dose with 20% increments using a three times per week treatment schedule. Her skin had improved dramatically after 10 treatments and was clear by the end of a course of 20 treatments. She remained clear throughout the remainder of her pregnancy. At 32 weeks she suffered an antepartum haemorrhage due to placental abruption, necessitating an emergency caesarean section delivering a male neonate weighing 1.95 kg. Now aged 7 months, he is well and developing normally.

The specific dermatoses of pregnancy have been classified into four groups: (i) pemphigoid gestationis; (ii) polymorphic eruption of pregnancy; (iii) prurigo of pregnancy; and (iv) pruritic folliculitis of pregnancy.¹

Pruritic folliculitis of pregnancy was first used as a descriptive term in 1981 by Zoberman and Farmer.² They described six patients with a pruritic erythematous papular eruption developing between the fourth and ninth months of pregnancy. Treatment with topical steroids, topical gamma benzene hexachloride and oral antihistamines produced no objective change and only mild relief of pruritus. Resolution of the eruption occurred within 1 month postpartum, except in one patient where spontaneous clearance occurred within 1 week of onset. Two had developed similar rashes in previous pregnancies and in one of these also while on danazol. Histologically, there was a sterile folliculitis with intraluminal pustule formation with neutrophils, lymphocytes and occasional eosinophils. The dermis showed mild oedema and a similar mixed perivascular inflammatory cell infiltrate. Direct immunofluorescence studies were negative. There was no adverse prognostic effect on the mothers or neonates. No therapeutic interventions were recommended.

Holmes and Black¹ reported two further cases in a study of 64 patients with pregnancy-associated dermatoses. They achieved considerable symptomatic relief using a cream containing benzoyl peroxide 10% and hydrocortisone 1%. There are no data on its use or whether it has any effect on the duration of the condition. They suggested that the morphology was similar to corticosteroid-induced acne and speculated that it was a hormonally induced acne. There has been little additional evidence to support this hypothesis.³⁻⁵ Wilkinson *et al.*⁶ described a patient who had raised levels of testosterone and androstenedione, but were unable to determine if this was pathological or secondary to pregnancy. More recently, however, measurement of serum androgen levels in a series of patients with pruritic folliculitis of pregnancy compared with controls found no increase.⁷

Roger *et al.*⁸ reported a further case in a prospective study of 3192 pregnant women. Topical betamethasone dipropionate 0.05% was administered and the symptoms resolved within

2 weeks. There have never previously been any reported complications in mothers or neonates associated with pruritic folliculitis of pregnancy. The complications in our patient developed at least 3 months after the clearance of the rash and completion of phototherapy. It therefore seems unlikely that the condition or treatment had any deleterious effect. UVB therapy is recommended as safe to use in pregnant women.⁹

Narrowband (TL-01) UVB lamps have an emission spectrum within the therapeutic waveband for psoriasis phototherapy. They have been used successfully to treat other inflammatory dermatoses including atopic eczema and idiopathic photodermatoses.⁹ As for many forms of UV phototherapy, the mechanism of action remains speculative. This is the first reported use of narrowband UVB phototherapy in the treatment of pruritic folliculitis of pregnancy. We cannot, however, exclude the possibility of spontaneous resolution. There is no universally accepted treatment for pruritic folliculitis of pregnancy and we suggest the use of narrowband UVB phototherapy as an alternative in cases resistant to topical treatment.

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Anaphylactic reaction after a mouse bite in a 9-year-old girl

SIR, Anaphylactic reactions after animal bites are rare. In the literature, we have found case reports of anaphylactoid reactions occurring after bites by rodents¹ and mosquitoes,² and many studies have demonstrated the importance of anaphylactic reactions after insect bites, such as bees and venom.³ To the best of our knowledge, however, this is the first case report of anaphylaxis occurring after a mouse bite.

A 9-year-old girl was bitten by her pet white house mouse while playing with it, and within 30 min developed an exanthema associated with general pruritus. Thirty minutes later, she experienced shortness of breath. The patient required emergency treatment in hospital with high-dose corticosteroids and antihistamines. After excluding other causes of anaphylactic reactions, she was referred to us for allergy diagnosis. All serum laboratory data were normal. In prick tests inducing seasonal and perennial aeroallergens (Allergopharma, Reinbek, Germany) a type I sensitization was detected to dog hair, cat hair, horse hair and mouse epithelia. Furthermore, specific IgE antibodies against egg (RAST class 2) and mouse epithelia (RAST class 3) were found. Considering the clinical and laboratory data, we diagnosed an anaphylactoid reaction (grade III)^{4,5} after a mouse bite. We recommended that the patient avoids playing with mice and provided an emergency set consisting of corticosteroids, antihistamines and adrenaline for the patient.

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