

CORRESPONDENCE

Irritant dermatitis due to prolonged contact with Oilatum Plus®

SIR, A 7-year-old boy with mild eczema was treated with Oilatum Plus® (Stiefel, High Wycombe, U.K) and intermittent application of mometasone furoate ointment. He developed an unusual eruption on his neck, axillae, popliteal and antecubital fossae and groin. He had three separate episodes of this rash over a 2-year period, each coinciding with the use of Oilatum Plus® bath additive and settling with its withdrawal. The recommended dose of a capful of Oilatum Plus® had been added in a standard size bath and the amounts used were therefore not excessive. However, he had repeated prolonged contact with Oilatum Plus® from soaking in the bath for 20 min daily for 2 weeks.

Examination revealed localized areas of brown-staining skin, severe erythema and extensive desquamation symmetrically involving flexural sites (Fig. 1).

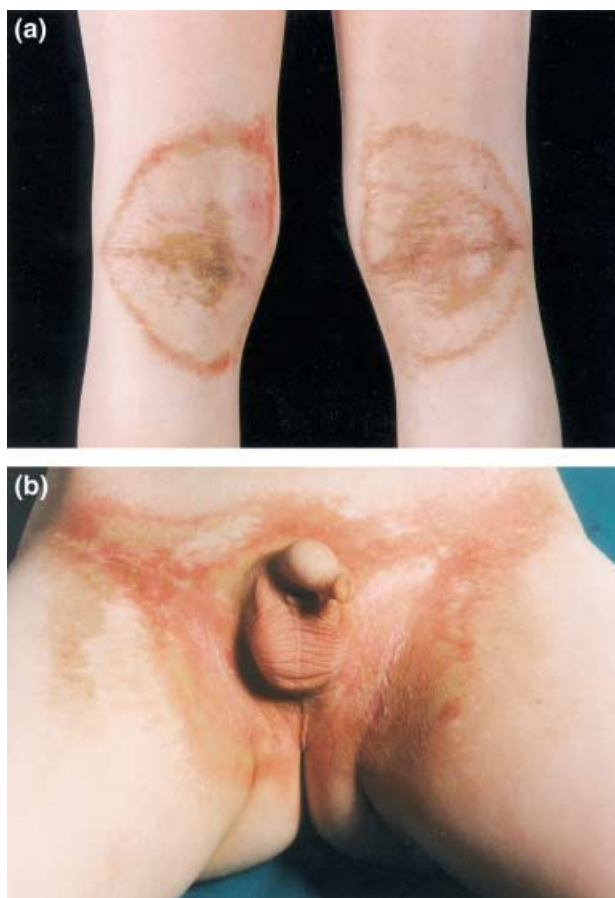


Figure 1. (a) Desquamation and unusual brown discoloration symmetrically involving the popliteal fossae. (b) Superficial erosions on a background of erythema in the groin.

Full blood count, erythrocyte sedimentation rate, C-reactive protein and antistreptolysin-O titres, serum zinc, fungal culture and skin swabs were normal or negative. Patch test to the European standard battery, cream constituents, steroid battery and constituents of Oilatum Plus® showed no reaction. Skin biopsy showed focal spongiosis, a mild perivascular lymphocytic dermal infiltrate and necrotic keratinocytes consistent with an irritant response.

We believe our patient had developed an irritant reaction to Oilatum Plus®. Prolonged immersion in the bath may have increased penetration of Oilatum Plus® into the skin. Our patient had atopic eczema associated with increased skin sensitivity and decreased skin barrier function, and the prolonged contact with Oilatum Plus® resulted in an extensive erythematous reaction and subsequent painful desquamation. In addition, the accentuation in skin folds suggests that local factors such as friction, skin temperature and eccrine gland distribution may have contributed to the development of this rash. Another possible factor may be incomplete mixing of the Oilatum Plus® in the bath.

Irritant reactions to Oilatum Plus® have been reported previously in a case series involving seven patients.¹ Irritant dermatitis can occur even with adherence to the manufacturer's recommendations and not just with prolonged exposure or excessive use of Oilatum Plus®. Oilatum Plus® contains the antiseptics triclosan and benzalkonium chloride, which may be the causative agents. Benzalkonium chloride is a known irritant,^{2,3} and is corrosive at a concentration of 10%.⁴ Oilatum Plus® contains a significantly higher concentration of benzalkonium chloride (6%) than most antiseptic bath emollients; the concentration of this antimicrobial agent is only 0.5% in Emulsiderm® (Dermal, Hitchin, U.K) and Dermol® 600 (Dermal) bath emollients. The acute skin irritation potential and allergenicity of triclosan is very low considering its widespread use in the cosmetic industry.⁵ It therefore seems less likely that the reactions were attributable to triclosan.

Unlike previous cases that were essentially asymptomatic, in our patient the rash was associated with severe pain and discomfort. These symptoms and the distribution of the rash were different from his usual experience of eczema. In addition, patch testing and skin biopsies were not performed in previous cases. In our patient, the clinical diagnosis was supported by patch testing which ruled out an allergic contact dermatitis and a skin biopsy that showed histological features consistent with an irritant dermatitis.

This bath emollient is widely used for the treatment of eczema. Although rare, clinicians should be aware of its potential in causing irritant dermatitis.

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Severe urticaria due to recombinant interferon beta-1a

SIR, Recombinant interferon beta-1a (rIFN- β -1a), which is used in the treatment of relapsing–remitting multiple sclerosis (RRMS), requires continued administration to reduce disease activity.¹ Therapy with IFN- β -1a may be associated with a number of side-effects such as influenza-like symptoms, menstrual disorders, raised liver enzymes and blood disorders; cutaneous reactions to its administration are usually described as injection site complications such as locally painful, irritated and hardened skin lesions.²

In a previous study, an urticarial reaction over the leg that was injected was reported after 9 months of treatment with another form of IFN- β , IFN- β -1b.³ We report the first case of a severe widespread urticarial reaction to IFN- β -1a.

A 30-year-old woman presented in 1998 with paraesthesia, right hemiparesis and weakness. At first she was treated with methylprednisolone; when RRMS was diagnosed, treatment with intramuscular rIFN- β -1a 6×10^6 U once weekly was started.

This treatment was continued for 13 months and was then suspended due to pregnancy. Eighteen months later treatment with rIFN- β -1a was again prescribed but at the second administration she developed severe widespread urticaria within 30 min. She went to the first-aid unit and there received intravenous chlorphenamine maleate 10 mg and betamethasone 4 mg. The urticarial weals disappeared completely only after a 2-week course of treatment with oral deflazacort 30 mg daily and oral cetirizine 10 mg daily. The rIFN- α -1a was discontinued.

Other possible causes of the onset of the reaction were excluded; at the time of the reaction our patient was not taking any other medication and had a negative history for adverse food reactions and allergic respiratory diseases. Cutaneous tests with the most common food and inhalant allergens were negative. Routine laboratory tests and IgE levels were within normal ranges, antinuclear antibody, antidouble-stranded (native) DNA and antismooth muscle antibody were negative, and C3 and C4 serum levels were not significantly modified.

After giving informed consent, our patient underwent prick and intradermal tests with rIFN- β -1a as well as with glatiramer acetate (Copolymer-1) as an alternative drug. The prick

test was considered positive when the weal was 5 mm or more, and the intradermal test was considered positive when the weal was 10 mm or more. If the prick test was negative, intradermal tests with 0.03 mL of the drug diluted in normal saline were carried out, starting with a concentration of 1 : 1000 and, if still negative, continuing with dilutions of 1 : 100, 1 : 10, 1 : 1 and finally undiluted. Histamine 10 mg dL^{-1} and physiological saline were used as positive and negative controls, respectively. The test with rIFN- β -1a was positive at the first concentration of 1 : 1000, but was negative in 10 healthy control subjects. After 24 h the patient underwent prick and intradermal tests with glatiramer acetate (Copolymer-1) which were negative, as was a challenge with subcutaneous injections of increasing doses of the drug, until the therapeutic dose was reached. Our patient has now been undergoing glatiramer acetate treatment for 9 months without developing any adverse drug reaction.

In literature, only one case of severe allergic reaction to rIFN- β -1a has been reported: a woman with RRMS who was treated for 6 months developed anaphylactic shock after a dose of the drug.⁴ The late onset of this reaction, after several months of treatment, as was the case with our patient, emphasizes that this kind of reaction may occur long after institution of therapy with rIFN- β -1a.

The clinical history and the positive skin tests indicate a possible IgE-mediated mechanism even though there is evidence that drug-specific lymphocytes play an important role in the development of drug-induced hypersensitivity reactions.⁵

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Allergic contact dermatitis to broccoli

SIR, A 56-year-old female psychiatric nurse presented with a 3-year history of severe eczema and recurrent blisters of her palms (Fig. 1), with the left being more severely affected than



Figure 1. Vesicular eczema affecting the left hand.

the right. She was a keen gardener and cook but had given up gardening 2 years previously because of the hand eczema. She had never suffered from eczema in the past and had no history of asthma or hay fever although her mother and brother suffered from eczema and hay fever, respectively. We patch tested her to the British Contact Dermatitis Group extended series, nurses and rubber series and with parts of fresh vegetables which she commonly used (carrot, parsnip, potato, broccoli, onion, tomato and bean). There was a 1+ reaction to cobalt, Compositae mix and broccoli at 48 and 96 h.

A usage test with latex gloves, skin prick test to commercial latex solution and skin prick test to broccoli were negative. Patch tests on 22 control subjects with parts of fresh broccoli were negative. Our patient's hand eczema improved remarkably on avoiding direct contact with broccoli and other vegetables although she continues to have mild vesicular eczema over the fingertips.

Our patient suffers from vesicular hand eczema and showed positive patch test reactions to Compositae mix, cobalt and broccoli. The reaction to Compositae mix can be attributed to gardening exposure in the past. We do not think that it is of present relevance as she has no cut flowers or flowering plants in the house. She has been advised about cobalt avoidance although continued exposure to alloys containing cobalt may explain her ongoing fingertip eczema. However, this is debatable as Nielsen *et al.* evaluated the effects of daily repeated exposure to low cobalt or chromate concentrations on the hands of patients with hand eczema and cobalt or chromate allergy. They were unable to elicit a flare of hand eczema even after repeated exposure to cobalt solution on the hands of cobalt-sensitive patients.¹

Contact sensitization to broccoli is of definite importance, as avoiding direct contact improved the hand eczema remarkably. Broccoli belongs to the Brassicaceae family. The genus *Brassica* includes other vegetables such as cabbage, cauliflower, radish, horseradish, turnip and mustard, which contain allergenic isothiocyanates. It has not been possible to test these as our patient has declined further patch test investigations. Allergic contact dermatitis to members of this

family is rare and has previously been reported only as an occupational dermatitis in greengrocers and plant-growers.^{2,3} IgE-mediated anaphylactic reactions to members of this genus have been reported.⁴ Broccoli is unrelated to the Compositae family of plants and there are no reports of cross-reactions between Compositae and other plants in the Brassicaceae family.

We report a case of hand eczema with relevant allergic contact sensitivity to broccoli that emphasizes the importance of patch testing to vegetables in the evaluation of palmar hand eczema.

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Bilateral nail dystrophy associated with vibrating tool use

SIR, We report a 68-year-old man who presented with an 18-month history of paraesthesia affecting the radial three digits of both hands. This was associated with abnormal growth and appearance of the index and middle fingernails. He had no specific past medical history and was not taking any medication. He had worked as a labourer for an electricity company for 30 years using drilling tools to break tarmac to allow the laying of cables. Examination revealed wasting of the thenar eminence of both hands with reduced power of thumb flexion (Fig. 1a). There was decreased light touch sensation affecting the index and middle fingers, and Tinel's sign was positive bilaterally. Nail dystrophy in the corresponding area was evident with subungual hyperkeratosis of the left middle fingernail, and thickening of the right index and middle fingernails (Fig. 1b). Blood investigations were unremarkable and there was no evidence of fungal elements on mycological examination of nail clippings. A diagnosis of carpal tunnel syndrome (CTS) with secondary nail dystrophy was felt to be in keeping with the clinical findings. He is currently awaiting nerve conduction investigations, although it is felt that nerve decompression is unlikely to improve his symptoms due to his late presentation and age.

CTS following the use of vibrating tools is well-described. Some authorities consider it as part of the hand–arm

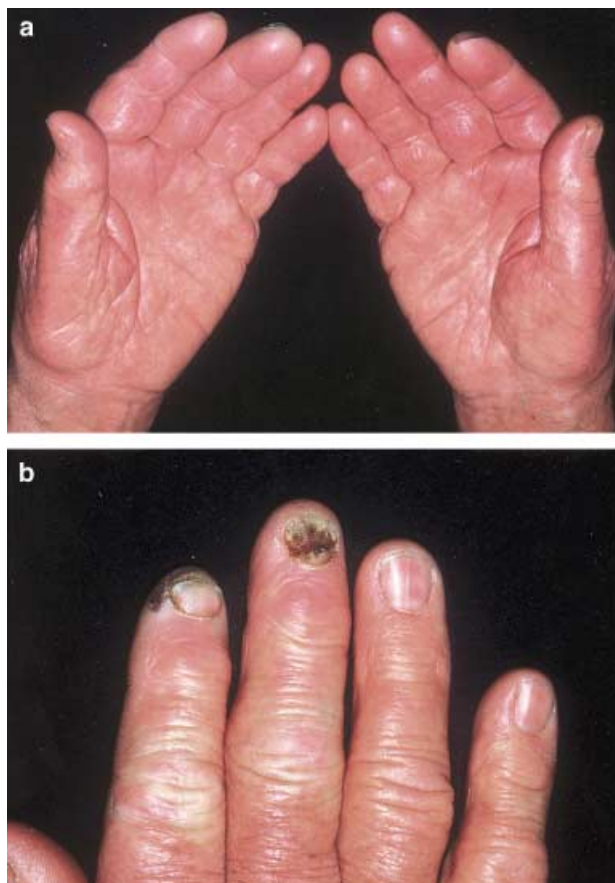


Figure 1. (a) Bilateral wasting of the thenar eminence with reduced power of thumb flexion. (b) Dystrophy of the right index and middle fingernails.

vibration syndrome in which disturbances of sensory, neurological, vascular and musculoskeletal components of the upper limb result from regular use of handheld vibrating tools.^{1,2} Forty-three per cent of forestry workers in one study who used chainsaws had reduced peripheral sensation, with 20% having clinical CTS, in 48% of whom this was bilateral.¹ The incidence of CTS in other workers using vibrating tools such as those in the gas distribution industry may be lower at about 5%,² although studies of other workers have found both Tinel's sign and nocturnal paraesthesia to be present in well over a quarter of individuals.³ The vibration-induced nerve damage in CTS is thought to result from a combination of local vascular insufficiency and intraneural oedema, leading to the clinical symptoms. Skin changes, due to either central or peripheral nerve compression or damage, are also well recognized, and are reported to occur in 20% of cases of CTS.^{4,5} Reported nail changes in peripheral nerve lesions include transverse furrows, pigmented streaks, hyperkeratosis of the eponychium, nail shortening, fragility and yellow discoloration.⁵⁻⁷

Although CTS is usually idiopathic even in males, in our patient it may have been caused by the prolonged use of

vibrating tools. The associated nail dystrophy changes may therefore relate to vibrating tools. In the U.K., CTS following the use of vibrating tools has been described as an industrial disease, and as such is liable to compensation claims.⁸ Therefore, claimants with industrial disease should have documented assessment of their nails, and similarly, patients presenting with nail changes should be questioned about occupations and sensory symptoms.

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Mycetoma caused by *Scytalidium dimidiatum*

SIR, The term 'mycetoma', a tumour-like granulomatous infection of skin and deeper tissues of the foot due to a variety of fungi and actinomycetes, was coined in 1860.¹ The infection is frequently caused by saprophytes traumatically inoculated into the skin, and affects the feet, legs, hands or other parts.¹ The most common form involving the foot is called 'Madura foot', named after Madura, a town in southern India.² The triad of tumefaction, draining sinuses and discharging grains characterizes the clinical features of mycetoma.¹ Mycetomas are of two types: eumycetomas caused by fungi and actinomycetomas caused by actinomycetes (filamentous bacteria). Organisms responsible for eumycetomas include *Acremonium falciforme*, *Madurella*

mycetomatis, *M. grisea*, *Exophiala jeanselmei*, *Leptosphaeria senegalensis* and *L. tompkinsii*, while those causing actinomycetomas include *Nocardia asteroides*, *N. brasiliensis*, *Actinomyces madurae* and *Streptomyces somaliensis*.² Besides these classic agents, dermatophytes can rarely cause this infection.¹ There is a tendency to geographical grouping with regard to aetiological agents.¹ A diagnostic evaluation in each case is therefore important for proper treatment.

Scytalidium dimidiatum, a saprophytic mould, is a pathogen of tropical plants and fruit trees such as banana and citrus.³ The organism usually causes infection of the skin or nails, but has been implicated in a case of mycetoma.⁴ The infection is commonly derived from soil in barefooted persons.³ To the best of our knowledge, only one case of mycetoma secondary to *S. dimidiatum* has been reported. We report the second such case, the first from Pakistan.

A 20-year-old woman, resident of Dera Ghazi Khan in Pakistan, a rice-field worker by occupation, presented to the dermatology outpatient clinic at Mayo Hospital, Lahore, Pakistan, in September 2001, with swelling of the right foot, multiple nodules and discharging sinuses (Fig. 1a). The disease had begun 6 years previously as a single nodular swelling on the plantar surface of the foot after a thorn prick. After a few months, painless multiple nodules developed on both plantar and dorsal surfaces of the foot. Some of the

nodules broke down, forming sinuses discharging yellowish material.

Examination revealed nontender, gross swelling of the right foot with multiple discharging sinuses and crusts. Direct microscopic examination of the exudate showed a few pus cells but no sulphur granules. Bacterial culture exhibited *Staphylococcus aureus* while culture for acid-fast bacilli was negative. Enzyme-linked immunosorbent assay for human immunodeficiency virus types 1 and 2 was negative. Biopsy showed an inflammatory infiltrate in the deep dermis composed of many neutrophils along with lymphohistiocytes. Periodic acid–Schiff and Gram staining was inconclusive. X-ray of the foot was normal.

Direct microscopy using 25% potassium hydroxide solution revealed fungal hyphae. The material was cultured on Sabouraud's dextrose agar containing 0.005% chloramphenicol with and without 0.04% cycloheximide. *Scytalidium dimidiatum* was isolated on more than two occasions on cycloheximide-free Sabouraud's dextrose agar. Positive culture was confirmed by gross colony morphology, initially pale but later becoming greyish-black. Microscopy of teased mounts of a mature colony stained with lactophenol-cotton blue revealed long dark-walled branching hyphae with cylindrical and barrel-shaped arthrospores. *Staphylococcus aureus* isolated from the lesions initially was considered to be a secondary invader as there was no growth on reculture after the use of systemic antibiotics.

Our patient was diagnosed as having mycetoma due to *Scytalidium dimidiatum* and was prescribed ketoconazole 200 mg twice daily. After 6 weeks of therapy, the lesions showed nearly 50% clinical improvement (Fig. 1b). She is currently under observation with continued treatment.

Mycetoma is common in tropical and warm temperate zones.¹ Causative agents are usually transmitted from soil or plants to barefooted outdoor workers.⁵ *S. dimidiatum*, a darkly pigmented mould formerly known as *Hendersonula toruloidea*, was first recognized as a human pathogen in 1970.⁴ It is highly sensitive to cycloheximide and can be isolated only in the absence of this antibiotic.³ There have been several reports of skin and nail infections caused by this organism, mostly in patients from Pakistan, India, the Caribbean and Kenya.^{3,6} To date, subcutaneous infection by this mould has only been reported in two cases, a deep facial lesion and a mycetoma affecting the foot.⁴ We report a further case of mycetoma caused by *S. dimidiatum*, confirmed by fungal culture.



Figure 1. (a) Multiple nodules with discharging sinuses (plantar aspect of foot); (b) clinical improvement after 6 weeks of treatment with ketoconazole.

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An audit of the use of self-administered adrenaline syringes in the east end of Glasgow

SIR, We were interested to read the recent article by Sabroe *et al.*¹ We had become increasingly aware that some patients prescribed self-administered adrenaline syringes (EpiPen[®]; ALK-Abello, Hungerford, U.K.) did not have adequate information about their usage, and an audit of patients' comprehension was therefore undertaken. We identified 32 adults (> 18 years) attending our clinic who had been prescribed EpiPen[®]. An unsupervised questionnaire survey among these patients was carried out, and 20 (62.5%) of the 32 patients completed the questionnaire. There was a female preponderance (60%), as observed by Sabroe *et al.* The median age of our patients was 33.5 years (range 18–51), which was lower than that of the cohort of patients of Sabroe *et al.* (mean 42 years, range 13–67). The greatest number ($n = 8$, 40%) of our patients belonged to the 31–40-year age group. Six of 20 patients (30%) had used EpiPen[®], which was lower than the figure of 50% reported by Sabroe *et al.* Four of the 20 (20%) had to use EpiPen[®] between two and six times a year, and one each (5%) had used it once a year and more than six times a year. Eighteen of the 20 patients (90%) always carried the device with them. Nine patients (45%) were prescribed one EpiPen[®], 10 patients (50%) two, and one patient (5%) had more than two EpiPen[®]s at one time. Most EpiPen[®]s were prescribed by general practitioners ($n = 11$, 55%), followed by allergy specialists ($n = 5$, 25%), dermatologists ($n = 3$, 15%) and a consultant in a dental hospital ($n = 1$, 5%). The indications for EpiPen[®] prescription were anaphylaxis in 10 (50%), latex allergy in three (15%), angio-oedema, urticaria and peanut allergy in two (10%) patients each and a combination of anaphylaxis and angio-oedema in one (5%) patient. Only seven patients (35%) knew to use EpiPen[®] both for severe wheeze and for throat/tongue swelling. Eight patients (40%) thought to use it only in the circumstances of throat/tongue swelling and one patient (5%) felt to use it only for severe wheeze. In addition, two patients (10%) would use it for hives/urticaria and two (10%) in mild wheeze. Fourteen patients (70%) could remember that the use of EpiPen[®] was explained and demonstrated to them either by the doctor or nurse, and a

comparable figure of 71% was obtained by Sabroe *et al.* Six (30%) patients claimed to have received no explanation or demonstration of EpiPen[®]. In this group, three (50%) were prescribed EpiPen[®] by their general practitioners, and one each (17%) by a dermatologist, allergy specialist and dental hospital consultant. Six patients (30%) did not receive any information leaflet on the correct usage of EpiPen[®]. Two (10%) patients claimed to have received no explanation, demonstration of EpiPen[®] or information leaflet but neither patient had had to use the device. It was reassuring that all patients knew to inject EpiPen[®] into the thigh. Eighteen patients (90%) were not aware of any medications they should be cautioned about if using EpiPen[®]. Eight (44%) of them had asthma and two (11%) had raised blood pressure. Eighteen patients (90%) had no idea regarding adverse effects of EpiPen[®]. When they were asked what to do after using an EpiPen[®], 16 patients (80%) stated that they would attend the nearest Accident and Emergency department, while three patients (15%) thought it would be better to take it easy and relax and one patient (5%) felt she ought to see her general practitioner. Fourteen (70%) patients were quite happy with information they had received but 10 of them (71%) were still interested to receive more information about EpiPen[®].

Our study has identified a number of worrying issues regarding self-administered adrenaline syringes use, as pointed out by Sabroe *et al.*¹ We feel strongly that both doctors prescribing EpiPen[®]s and patients prescribed EpiPen[®]s should be more educated in their use than as is the case presently. This can be achieved in a number of ways. Firstly, regarding the indications for its prescription by doctors, it is difficult at times to justify what condition or potential condition should or should not need EpiPen[®] and therefore the use of EpiPen[®] other than in anaphylaxis or severe angio-oedema should be judged on its merit case by case. We found in this study that at least two patients were prescribed EpiPen[®] for urticaria, an indication that we felt was improper for EpiPen[®] use. Secondly, regarding the adequacy of delivering information about its usage, although adrenaline can be life-saving, it has potentially dangerous side-effects. All patients should be given both verbal and written information about EpiPen[®] in addition to a practical demonstration of how to use it, initially with a dummy syringe. We strongly agree with Sabroe *et al.* that a more detailed patient information leaflet is required. Thirdly, patients' understanding of correct usage is of paramount importance. As this was an unsupervised questionnaire study we could not check the demonstration by patients with a dummy syringe. Incorrect use of EpiPen[®] by accidental injection in the thumb has been reported, causing digital ischaemia and resultant amputation.² This unwarranted injury can consequently delay saving the patient's life. Hence, from time to time every patient should be asked to demonstrate the use of EpiPen[®] with a dummy syringe to see whether they can follow all steps correctly. Finally, we have seen in this study that 45% patients had only one EpiPen[®] prescribed. Patients may need to use EpiPen[®] again

in the case of a late-phase reaction and the possession of a second EpiPen[®] should be mandatory, with the importance of replacing EpiPen[®]s before their expiry date emphasized to patients.

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Erythromelalgia in a patient with idiopathic thrombocytopenic purpura

SIR, Erythromelalgia is a rare condition characterized by the triad of red, hot and painful distal extremities.¹ It may be idiopathic or may be related to various diseases. Secondary erythromelalgia is induced most frequently by myeloproliferative syndromes, such as essential thrombocythemia and polycythemia vera.² We report a woman suffering from idiopathic thrombocytopenic purpura (ITP) who developed erythromelalgia during ITP flares.

A 66-year-old woman was diagnosed as having ITP in September 1998 when her platelet count was $40 \times 10^9 \text{ L}^{-1}$, with positive antiplatelet autoantibodies and high megakaryocyte count in bone marrow aspirate. She was treated with intravenous immunoglobulins (IVIg) and prednisolone, with a good response. She had a relapse in April 1999, with a platelet count of $20 \times 10^9 \text{ L}^{-1}$. Concomitantly she noted the occurrence of erythromelalgia with paroxysmal burning pain and redness of the distal extremities, relieved by cooling with ice or cold water. Aspirin treatment did not relieve the pain. Symptoms were such that sleep was disturbed.

Physical examination revealed erythema of the hands and feet. Capillaroscopy was normal. After prednisolone associated with IVIg had been restarted, her platelet count increased to $160 \times 10^9 \text{ L}^{-1}$ and she noted a regression of erythromelalgia. Recurrence of erythromelalgia was observed when the platelet count decreased with tapering of the dose of prednisolone. A splenectomy was performed which resulted in rapid improvement of platelet count and clearance of erythromelalgia, with no recurrence after 18 months' follow-up. Initially, when platelet count was low, plasma serotonin levels were undetectable; these returned to normal levels after remission of thrombocytopenia following splenectomy.

In the literature, erythromelalgia has never been described during ITP. However, the strong association between symptoms of erythromelalgia and ITP flares, as well as the dramatic improvement after control of thrombocytopenia

observed in our patient, suggest a link between ITP and erythromelalgia. The pathological mechanism of erythromelalgia is not yet completely understood but platelet aggregation and serotonin, which may cause vasoconstriction or vasodilatation depending on the vessel involved and the integrity of the endothelium, have been implicated in the pathogenesis.¹ Intravascular platelet activation and aggregation are important especially in secondary forms of erythromelalgia associated with myeloproliferative disorders or thrombotic thrombocytopenic purpura.³ It has been suggested that a pronounced fall in platelet count might produce a rise followed by a reduction in the blood levels of serotonin, leading to an episode of migraine.⁴ The underlying mechanism in our patient may be similar, with abrupt changes in serotonin metabolism related to variation of platelet count, which could induce erythromelalgia.

Our observation suggests a link between erythromelalgia and periods of low platelet count in ITP. However, further cases need to be reported to confirm such an association and to produce a better understanding of the pathological mechanism involved.

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Bupropion and generalized acute urticaria: eight cases

SIR, We wish to emphasize that bupropion (Zyban[®]) may induce generalized acute urticaria.

Bupropion is an antidepressant drug, structurally related to phenylethylamines (amphetamines), used for several years under the trade name Wellbutrin[®]. A slow-release formulation of bupropion was marketed in May 1997 under the trade name Zyban[®] (GlaxoWellcome, Research Triangle Park, NC, U.S.A.), and was uniquely indicated for usage in smoking cessation. Hurt *et al.*¹ demonstrated that a sustained-release form of bupropion was effective in smoking cessation without consequent weight gain and with few side-effects, e.g. headache, insomnia or dry mouth. According to Ascher *et al.*² bupropion is a weak inhibitor of the neuronal reuptake

of noradrenaline and dopamine, with no effect on serotonin, while other authors think that bupropion is a weak blocker of neuronal reuptake of serotonin, noradrenaline and dopamine.³

In France, Zyban® has been marketed since September 2001. In only 5 months, we have observed eight patients who developed acute urticaria during treatment with bupropion prescribed for smoking cessation. In the absence of any other drug intake, all the patients (four men, four women, age range 17–52 years) developed generalized urticaria 8–21 days (mean 14) after the beginning of treatment. Urticaria was associated with facial angio-oedema in three cases, with arthralgias in two other cases and transient liver cytolysis in a sixth case. According to the criteria of Moore *et al.*,⁴ bupropion was the probable or very probable cause in seven cases. In general, the symptoms disappeared 4–6 days after the drug was discontinued, except for liver dysfunction, which remained for 1 month afterwards in one patient.

Allergy investigations performed 6 weeks after the disappearance of the urticaria had negative results: patch tests with Zyban® diluted at 30% in petrolatum and water were negative in five of five cases, and prick tests with undiluted Zyban® gave one doubtful reaction and four negative results. As there is no injectable form of bupropion and no sterile form of the pure product allowed for human use, it was not possible to perform intradermal tests in our patients.

Bupropion is strongly suspected of having induced urticaria in all eight patients. International pharmacovigilance networks have recorded similar cases, but to our knowledge no publication has previously reported this adverse effect.

The mechanism of urticaria induction by Zyban® is unknown, and we have no evidence for an allergic mechanism as results of our skin tests were negative. We propose two hypotheses. First, this phenomenon could be linked to the structure of bupropion, which is unrelated to other classes of antidepressants but is chemically similar to diethylpropion, which stimulates the central nervous system with an indirect sympathomimetic effect exactly like dexamphetamine. Indeed, amphetamines increase the histamine level in rat brains.⁵ The second hypothesis implicates the action of central nervous system stimulants on central serotonin pathways.⁶

We emphasize that it is necessary to determine the benefit-risk ratio before beginning treatment with Zyban®, as it can induce severe adverse effects such as urticaria and liver dysfunction and has also been suspected as being responsible for sudden deaths in the U.K.

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Shiitake dermatitis

SIR, In Asia, shiitake (*Lentinula edodes*) is a well-known savoury mushroom for which healthy effects such as immune modulation and lowering of blood pressure have been reported.¹ However, this mushroom may induce allergic reactions and a dermatological disorder called toxicodermia or shiitake dermatitis.² The latter occurs after eating raw shiitake, whereas allergic reactions such as asthma, contact dermatitis or alveolitis develop after contact with the mushroom or its spores.³ We describe three patients who developed severe skin lesions after ingestion of shiitake and review the relevant literature.

Patient 1. A 45-year-old man presented with conjunctivitis and papules on his face, which developed after preparing and eating cooked shiitake mushrooms.

Patient 2. A 54-year-old woman developed papular lesions mainly on the face and extremities 2 days after eating a raw shiitake mushroom for the first time. Most of these papules were grouped in a linear pattern (Fig. 1a). She had cultivated shiitake mushrooms in her garden for 2 years. Skin biopsy showed the features of an acute dermatitis with spongiosis in the epidermis, oedema in the papillary dermis and a dermal mixed inflammatory cell infiltrate.

Patient 3. A 46-year-old man noticed linear grouped erythematous papules on his face, trunk and extremities after eating raw shiitake mushrooms. He had eaten roasted shiitake mushrooms several times before without any problems.

All patients complained of severe pruritus. The clinical symptoms cleared within 1–2 weeks. Further investigations showed no evidence of an autoimmune disorder or a photodermatosis.

A prick-to-prick test with shiitake mushroom extract (shiitake soaked in physiological saline) was performed.⁴ Five healthy individuals who served as a negative control were also prick tested and showed no reaction. Specific IgE to shiitake mushroom was investigated with allergen extracts prepared from fresh and dried shiitake mushrooms.⁵



Figure 1. (a) Papules developed 2 days after eating raw shiitake mushrooms. (b) Papules and vesicles at the skin test site, 48 h after prick-to-prick test with shiitake extract.

Patient 1 developed a weal of 4 mm diameter after the skin prick test. Papules were seen 24 h later, followed by vesicular eruptions. In the other two patients, skin prick tests with shiitake extracts were negative. After 48–72 h, shiitake induced infiltration, itching papules and vesicles at the prick test site (Fig. 1b). This reaction cleared within a week. Specific IgE to shiitake was negative in all cases.

Shiitake causes allergic reactions mainly by contact with the mushroom or its spores. People who are involved in cultivating or marketing this mushroom may develop an allergic contact dermatitis, with positive patch test results to the mushroom and its spores, or an allergic alveolitis.^{3,6} Contact urticaria related to shiitake mushrooms has also been reported. The course of reaction in this patient resembled that in patient 1, as the prick test reaction was also followed by an oedematous induration.³ To our knowledge, the only report on positive findings of specific IgE to shiitake described a truck driver who transported shiitake and suffered from asthma and rhinoconjunctivitis.⁷

In contrast, shiitake dermatitis is a disease that occurs after ingestion of raw or half-cooked shiitake. The typical

skin lesions develop 1–2 days after eating the mushroom. Patients often show itchy papules in a linear pattern on the trunk and extremities and sometimes on the face.² As skin exposed to sunlight is frequently involved, photosensitizing agents, perhaps a toxin of the mushroom, could be a possible culprit in these cases.⁸ Histological findings, however, show no typical changes. Skin tests such as prick-to-prick tests or patch tests with the mushroom seem to be negative.²

One can speculate that the polysaccharide lentinan, which can be isolated from shiitake mushrooms, may be the responsible agent. Reduced blood pressure, lowered serum cholesterol and immune modulating properties have been attributed to this polysaccharide. Interestingly, some patients taking this substance developed skin lesions resembling shiitake dermatitis.^{9,10}

The history and clinical symptoms of patients 2 and 3 allow the diagnosis of shiitake dermatitis. In contrast to most other previous reports, we observed an eczematous reaction appearing some hours later at the prick test site with shiitake. Only one similar case has been reported before. This patient developed characteristic skin lesions after eating raw shiitake mushrooms. Prick-to-prick tests with the mushroom were negative, but 48 h later a weal and flare occurred at the test site.³

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Malignant proliferating trichilemmal tumour associated with human papillomavirus type 21 in epidermodysplasia verruciformis

SIR, Epidermodysplasia verruciformis (EV) is a rare life-long skin characterized by the development of flat warts, red plaques or pityriasis versicolor-like lesions caused by specific types of human papillomavirus (HPV). About 30% of patients with EV develop nonmelanoma skin cancer on sun-exposed areas in their third or fourth decade. Moreover, DNA of certain types of HPV such as HPV 5, 8, 14, 17, 20 and 47 has been detected in the malignant neoplasms.¹⁻⁴ These observations indicate the close interaction between HPV infection and development of skin cancers in EV patients. We report a Japanese patient with EV, in whom HPV 21 DNA was detected in both malignant proliferating trichilemmal tumour (MPTT) and wart-like lesions.

A 59-year-old Japanese man visited our department in April 1996 with a 1-year history of a growing tumour on his

forehead. He had noted pityriasis versicolor-like lesions and warty papules since the age of 12 years. Physical examination revealed a 40 × 30 mm pale reddish, dome-shaped tumour with a scaly, crusted surface on the forehead (Fig. 1a). Flat wart-like lesions on the dorsa of both hands (Fig. 1b) and forearms, and pityriasis versicolor-like lesions on the trunk and proximal arms were also present. His parents were cousins, and had 10 children. Although a precise family history could not be obtained, he mentioned that his younger brother had similar lesions on his trunk and extremities.

Skin biopsy of the flat wart-like lesions on the dorsa of the hands showed hyperkeratosis and acanthosis. Numerous swollen keratinocytes with pale-staining cytoplasm were present throughout the spinous layer (Fig. 1c). Pityriasis versicolor-like lesions on the breast exhibited similar histological changes, except for hyperkeratosis and acanthosis. Histopathology of the tumour on the forehead revealed lobular structures containing cystic spaces filled with an



Figure 1. (a) Clinical finding of a dome-shaped tumour on the forehead (April 1996). (b) Flat wart-like lesions on the dorsa of the hands. (c) Biopsy of a flat wart-like lesion showing slightly basophilic, swollen cells with pale-staining cytoplasm and a relatively large nucleus throughout the spinous layer (haematoxylin and eosin).

amorphous eosinophilic substance (Fig. 2a). Tumour cells were composed of clear cells and basophilic cells with prominent nuclear atypia. Trichilemmal keratinization was observed in the cyst wall (Fig. 2b). Most of the clear cells contained periodic acid–Schiff-positive granules. Based on these clinical and histological findings, the patient was diagnosed as having EV with skin cancer, MPTT. Although we strongly persuaded him to undergo surgery, he rejected it and did not attend for more than 3 years. When he attended again in July 1999, the tumour on his forehead had expanded over the forehead and frontal scalp. Examination revealed a 150 × 140 × 30 mm reddish cauliflower-like tumour with an ulcerated surface (Fig. 3). Computed tomographic (CT) scan of the head showed intracranial invasion through the frontal bone. Chest CT scan disclosed multiple nodular lesions, suggesting lung metastases. After four cycles of combination chemotherapy (cisplatin 90 mg, methotrexate 750 mg, 5-fluorouracil 1000 mg and levofoinic acid 255 mg) and radiotherapy (Linac X-ray, total dose 60 Gy), a partial remission of the tumour was achieved. However, he died 8 months later.

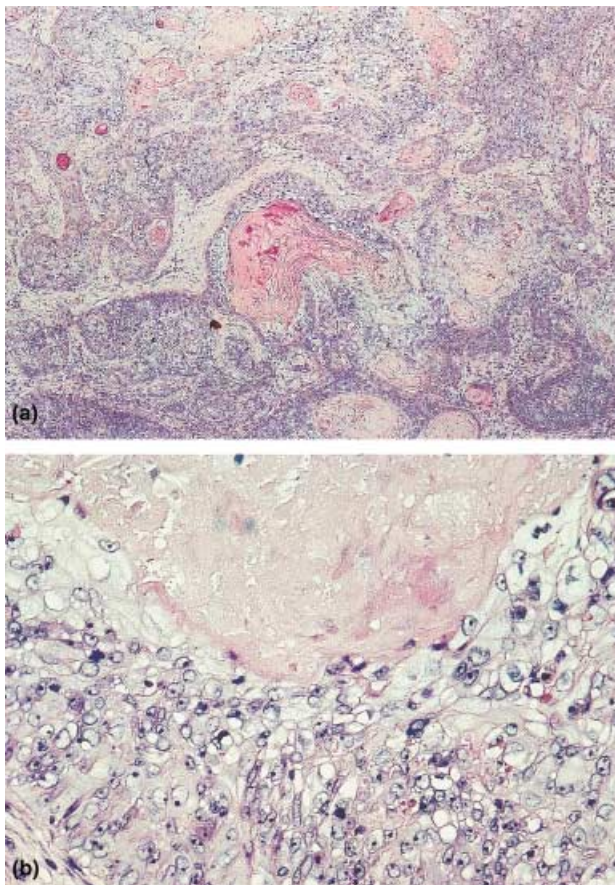


Figure 2. Histology of the tumour. (a) Lobular proliferation of tumour cells with abrupt keratinization. (b) Trichilemmal keratinization and clear cells with atypical nuclei in the lobule (haematoxylin and eosin).

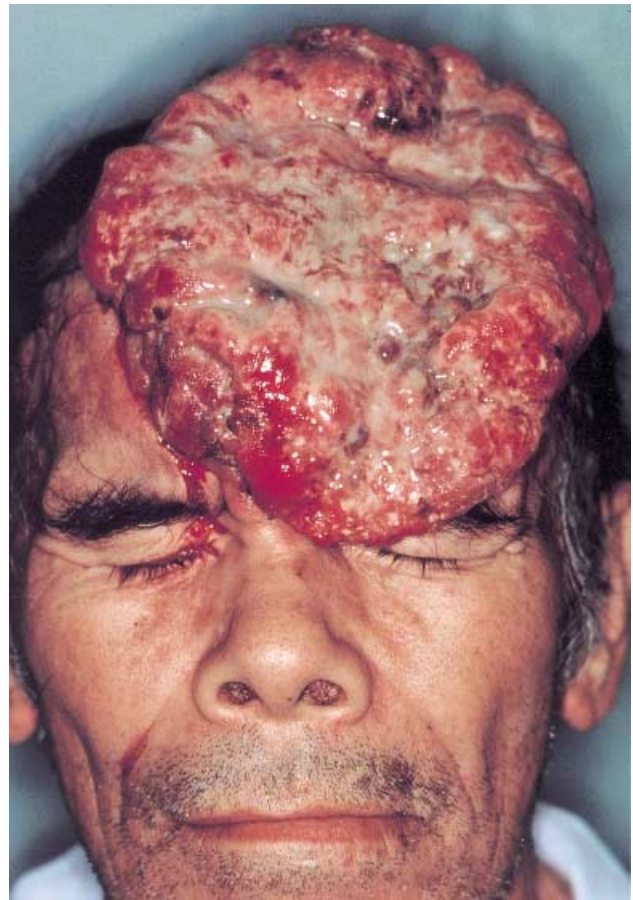


Figure 3. A giant tumour with an ulcerated surface extending from the forehead to the frontal scalp (July 1999).

Specimens from the flat wart-like lesions and the MPTT were analysed for HPV type, using a degenerate polymerase chain reaction (PCR) method. Briefly, total cellular DNA was extracted using standard techniques and screened for EV-associated HPV (EV-HPV) by PCR. The first amplification was performed using a primer set consisting of two degenerate primers (CP65/CP70)⁵ for the complete set of EV-HPV types. These primers located in the open reading frame of L1, which is the most highly conserved region of the papillomavirus genome. The second (nested) PCR amplification was done with two degenerate primers (CP66/CP69).⁵ The fragments were cloned into a plasmid vector and sequenced using the ABI PRISM Dye Terminator, (Applied Biosystems, CA, U.S.A.) according to the manufacturer's instructions. The HPV types detected in the flat wart-like lesions and the MPTT shared 94% and 95% homology, respectively, with the HPV 21 L1 open reading frame.

EV is a rare autosomal recessive disease characterized by the appearance of chronic skin lesions and the evolution of malignant skin tumours near or at the benign lesions in approximately one-third of patients. The type and location of

Table 1. The type and location of 126 malignant skin tumours reported in patients with epidermodysplasia verruciformis (1965–2001)

	No. of tumours
Type	
Squamous cell carcinoma	91
Bowen's disease	25
Basal cell carcinoma	8
Ecrrine carcinoma	2
Location	
Scalp	2
Face	41
Upper arm	2
Forearm	6
Hand	3
Trunk	11
Vulva	3
Leg	4
Unknown	54

126 malignant skin tumours reported between 1965 and 2001 are summarized in Table 1. Squamous cell carcinoma (SCC; 72%) was the most common, followed by Bowen's disease (20%), basal cell carcinoma (6%) and ecrrine carcinoma (2%). Although the possibility that MPTT might have been included in SCC cannot be ruled out, the present case is the first recorded EV patient to develop MPTT. It has been recognized that the metastatic spread of EV-related skin carcinomas is rare.⁶ In our patient, however, multiple lung metastases occurred. The unfavourable prognosis in our patient may be explained by the higher metastatic potential of MPTT than cutaneous SCC,⁷ which is the predominant EV-related skin carcinoma.

A cocarcinogenic role of ultraviolet irradiation has been emphasized in EV patients because of the predilection of sun-exposed areas for development of carcinomas. The incidence at sun-exposed areas (40%) was over twice that at unexposed areas (16%), while the site was not mentioned in 43% of reported cases. However, the occasional occurrence of malignancies in unexposed areas (16%) indicates that HPV infection, along with an immune system defect, may be essentially responsible for carcinogenesis in EV.

A genetic defect of the immune system in EV patients confers an unusual susceptibility to infection with HPV. Many types of HPV have been detected in patients with EV. These EV-HPV types include HPV 5, 8, 9, 12, 14, 15, 17, 19–25, 36–38, 47, 49, 75, 76 and 80.^{8,9} HPV 5, 8, 14, 17, 20 and 47 have been isolated from malignant tumours developing in patients with EV.^{1–4} Of these, HPV 5 has been most frequently detected in skin carcinomas of EV patients, and is therefore generally considered as a high-risk HPV type.² EV-HPV groups can be divided into several subgroups of related genotypes. The subgroup to which HPV 21 belongs includes HPV 14 and 20, which are also associated with carcinogenesis in EV.¹⁰ HPV 21, which has rarely been

detected in malignant tumours in EV patients, may also be related to carcinogenesis.

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Detection of immediate-type reaction to the epitope of β -lactam antibiotics by the quick patch test

SIR, The determination of the chemical structures responsible for drug hypersensitivity and resultant anaphylaxis is crucial. Furthermore, the use of a safe method to identify epitopes rapidly, and to screen drugs for contraindication, is preferred. We attempted to use a quick patch-testing method, and found that in a patient with a history of anaphylaxis, this technique was able to detect the drugs responsible.

A 25-year-old woman was admitted to our department to determine the drugs responsible for her hypersensitivity. She

first experienced anaphylaxis caused by antibiotics at the age of 19 years. At age 24 years, she delivered her second child and was given amoxicillin (AMPC), bromelain, methylergometrine maleate, mefenamic acid and cetraxate hydrochloride. Immediately after taking the medication, she developed generalized urticaria accompanied by mild dyspnoea. She experienced similar anaphylactic reactions when she opened packages of powdered drugs containing cefroxadine (CXD), lysozyme chloride and cyproheptadine hydrochloride prescribed to her child.

Prick tests revealed marked weal and flare reactions to AMPC, CXD and mefenamic acid. In β -lactams, the structures at positions R1 (side-chain) and R2 (substituent attached to dihydrothiazine ring) usually play a major role in defining antigen specificities. To evaluate the antigenic determinant, a series of β -lactam antibiotics was patch tested for 30 min using a Finn chamber (Epitest, Tuusula, Finland)¹ (Fig. 1). She showed positive reactions to ampicillin (ABPC), bacamp-



Figure 1. Quick patch test for β -lactams. The patient showed weal reactions to ampicillin (ABPC), bacampicillin hydrochloride (BAPC), sultamicillin tosilate (SBTPC) and cefaclor (CCL). PCG, benzylpenicillin; CDTR-PI, cefditoren pivoxil; CFDN, cefdinir; CETB, ceftibuten; CFDM-PI, ceftam pivoxil; CPDX-PR, cefpodoxime proxetil; CTM-HE, cefotiam hexetilhydrochloride.

Table 1. Results of quick patch tests

Drug ^a	Reactions ^b
Benzylpenicillin	—
Ampicillin	++
Bacampicillin hydrochloride	+
Sultamicillin tosilate	+
Cefroxadine	++ ^c
Cefaclor	++
Cefdinir	—
Ceftibuten	—
Ceftam pivoxil	—
Cefpodoxime proxetil	—
Cefotiam hexetilhydrochloride	—
Cefditoren pivoxil	—
Mefenamic acid	+ ^c

^aSubstances were prepared at 1% in petrolatum and were applied for 30 min. ^bWeal or erythema. ^cReactions to the scratch test.

icillin hydrochloride, sultamicillin tosilate and cefaclor (CCL) (Table 1).

The drugs that induced a reaction share common structural formulae, i.e. phenylacetamide and benzylacetamide in their R1 positions. Moreover, another drug to which the patient responded, mefenamic acid, contains a benzylamide residue with a similar three-dimensional structure to the R1 position of β -lactams such as ABPC and CCL.

Prick or scratch tests have a small risk of inducing systemic anaphylactic reactions. In contrast, the quick patch test can be used in patients with severe hypersensitivity, as applied substances are absorbed more slowly. The quick patch test is a convenient and specific technique for detecting immediate hypersensitivity and identifying antigenic epitopes.

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Merkel cell carcinoma composed of small, intermediate and squamous cell foci showing mutually exclusive expression of neuroendocrine markers and cytokeratin 20

SIR, Merkel cell carcinoma (MCC) is a malignant epithelial tumour of the skin that shows neuroendocrine differentiation.¹ The tumour is known to be positive for various neuroendocrine markers and epithelial markers.

Cytokeratin 20 (CK20), which is expressed by normal and neoplastic epithelium of the gastrointestinal tract, is considered to be a specific marker that distinguishes MCC from metastatic small cell carcinoma of the lung.² It is also well known that MCCs sometimes show divergent differentiation. We report a case of MCC that showed a diverse pattern of histological and immunohistochemical features.

An 83-year-old woman was admitted to hospital with a tumour that had been noticed about 6 months previously on the left cheek. Macroscopically the tumour was a well-demarcated red nodule measuring 18 mm in diameter with surface ulceration. The tumour was resected with a free margin of 5 mm at the middle of the subcutaneous fat. A systematic search failed to detect metastases in other organs.

The tumour was an invasive multinodular lesion forming an elevated mass, infiltrating the entire depth of the dermis. Each nodule was either separated by desmoplastic stroma or was closely packed with other nodules, and was composed of three types of tumour cells (Fig. 1a). Squamous cells, which were often seen within the nests of intermediate cells, formed the minority. They sometimes showed keratin formation or differentiation towards sweat ducts. Small cells were mostly found to form separate nests with smooth or irregular contours, and were mainly situated at the periphery of the nests of intermediate cells. A focus with squamous cell differentiation was continuous with the epidermis, suggesting a preceding squamous cell carcinoma (SCC) *in situ*. Both intermediate cells and small cells showed frequent rosette formation, but the latter lacked a trabecular structure that was sometimes seen in the former. The dermis showed prominent solar elastosis.

Immunohistochemically, the squamous cells were negative for synaptophysin, CK20 and neurone-specific enolase (NSE), but were focally weakly positive for Bcl-2. Most of the intermediate cells stained positive with CK20. The minority of them stained weakly positive with Bcl-2. They were negative for synaptophysin and NSE. The small cells were negative for CK20, and were invariably positive for Bcl-2, NSE and synaptophysin (Fig. 1b). All of the cell types were negative for chromogranin (CG). p53 was mostly negative.

MCC is a distinctive clinicopathological entity, although its histogenesis is unclear. Despite its name, there is no definitive evidence for the theory of neoplastic transformation of normal Merkel cells. A recent review, focusing on the frequent divergent differentiation in this tumour, suggests epidermal stem cell origin with genetic instability being the attribute of phenotypic diversity.³ In 1985, Gould *et al.* classified MCC into three types: trabecular type, intermediate cell type, and small cell type.⁴ Even though this classification is not frequently used, there appear to be distinct differences in cell morphology. Morphological divergence in MCC may include the coexistence of not only squamous or eccrine differentiation but also the presence of foci composed of cells distinctly different in size, as suggested by our case. Morphological divergence may have corresponding immunophenotypic divergence, namely divergent expression of various markers in the same lesion. Various neuroendocrine markers

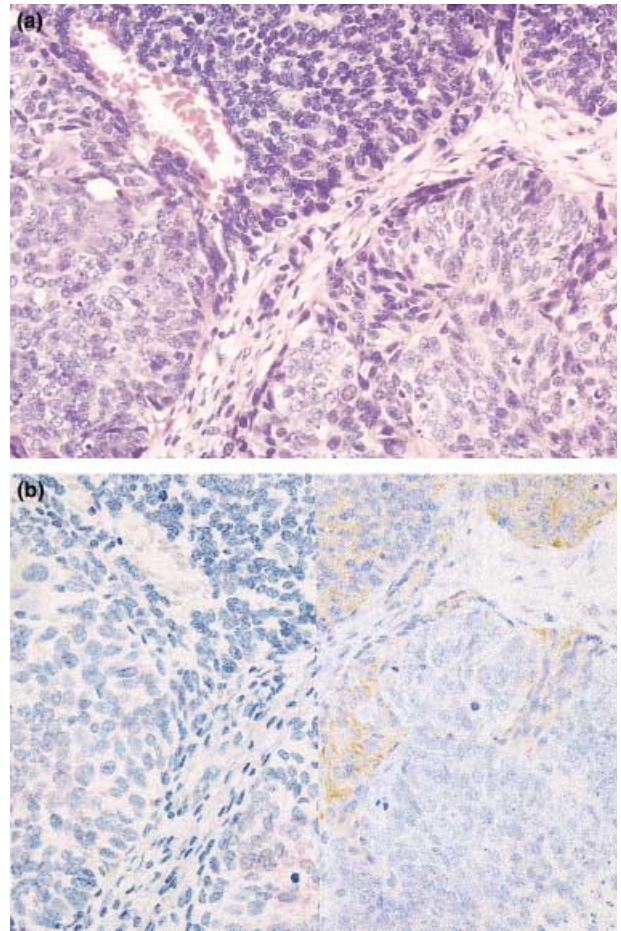


Figure 1. (a) Representative histology of our case. A nest composed of small cells is merged with a nest of intermediate cells, part of which shows squamous differentiation (haematoxylin and eosin). (b) Immunostaining of the same field with cytokeratin 20 (CK20; left, red) and with synaptophysin (right, brown). CK20 is positive only for intermediate cells while synaptophysin shows positivity only for small cells (original magnification: a, b $\times 75$).

as well as CK20 are frequently expressed by MCC, the latter being important in that it can be used to exclude metastatic small cell carcinoma of the lung. In one recent series, two-thirds (18 of 27) of MCCs were positive for CK20.⁵

Perveen *et al.* studied 16 cases of MCC.⁶ Ten cases stained positive with both CK20 and CG, five cases were positive for CK20 but negative for CG and one case was positive for CG but negative for CK20. Our case is unique in that mutually exclusive expression was seen in a single lesion, and that it corresponded to morphological diversity. Iacocca *et al.* have recently reported the immunohistochemical features of four cases of mixed MCC and SCC of the skin.⁷ According to this study, foci with features of MCC showed positivity for both neuroendocrine markers and CK20, whereas areas of SCC were negative for both markers. Their cases seemed to show no mutually exclusive pattern of staining with neuroendocrine markers and CK20 as in our case.

In conclusion, our case suggests that histological divergence in MCC includes the coexistence of separate intermediate and small cell foci of neuroendocrine morphology as well as squamous cell or skin appendage differentiation in a single lesion, and that each type of morphological focus may show a distinctive immunohistochemical profile. Caution should be shown when interpreting small biopsy material from MCC. In particular, CK20 may not be coexpressed with neuroendocrine markers.

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Multiple dermatofibroma-like lesions in a human immunodeficiency virus-positive patient coinfecting with visceral leishmaniasis

SIR, We report the investigation of unusual dermatofibroma-like lesions in a 32-year-old woman with human immunodeficiency virus type 1 (HIV-1) infection. Heterosexually acquired HIV-1 infection was diagnosed 5 years prior to the current illness but there was no history of acquired immune deficiency syndrome-defining illnesses. Due to intolerance of various antiretroviral regimens her peripheral blood CD4⁺ lymphocyte count was only $20 \times 10^9 \text{ L}^{-1}$ at presentation.

The patient was admitted to hospital with a 12-month history of weight loss, night sweats, malaise and nausea, and had developed multiple asymptomatic skin lesions over the

preceding 3 months. Cachexia, axillary lymphadenopathy and hepatosplenomegaly were found on examination. Ten violaceous indurated nodules, each of approximately 5 mm diameter and similar in morphology to dermatofibromas, were also noted disseminated over the limbs (Fig. 1a) and trunk. Analysis of peripheral blood revealed a pancytopenia (haemoglobin 8.6 g dL^{-1} , white cell count $1.5 \times 10^9 \text{ L}^{-1}$ and platelet count $32 \times 10^9 \text{ L}^{-1}$) and a bone marrow trephine showed multiple intracellular amastigotes, indicating a diagnosis of visceral leishmaniasis (VL). It was then noted that she had travelled to the Mediterranean on multiple occasions over the past decade, including Spain, Portugal and Cyprus, which are countries known to have endemic leishmaniasis.

The patient was transferred to the Hospital for Tropical Diseases in London for treatment. Despite their benign appearance, in view of the patient's marked immunosuppression it was felt important to investigate the skin lesions. The differential diagnosis for these lesions included disseminated cutaneous lesions from VL, atypical mycobacterial infection, multiple eruptive dermatofibromas and atypical Kaposi's sarcoma. Biopsies of the lesions revealed granulomas with a diffuse infiltrate of macrophages containing multiple *Leishmania* amastigotes, with positive Giemsa staining (Fig. 1b,c). Ziehl–Neelsen stain was negative for acid-fast bacilli and there was no evidence of mycobacterial or fungal infection on culture. Speciation by the polymerase chain reaction identified *L. donovani* complex.

The patient was treated with liposomal amphotericin B (4 mg kg^{-1}) given intravenously on days 1–10, 17, 24, 31 and 38, and she was also commenced on highly active antiretroviral therapy. After day 38 of treatment the patient's disease status was re-evaluated. Constitutionally, she felt much improved and the splenomegaly and all but three of the skin lesions had resolved. Blood haemoglobin concentration, platelet count, albumin and CD4⁺ lymphocyte count had all increased. No amastigotes were seen in slit-skin smears from two of the skin lesions or from a splenic aspirate, indicating a marked reduction in parasite load. Monthly intravenous pentamidine is being administered as secondary prophylaxis for leishmaniasis. The patient has had no recurrence of the cutaneous lesions after 5 months of follow-up.

Among HIV-infected individuals, VL has emerged as an important opportunistic infection. The clinical features of VL reflect the host immune response as well as the virulence of the parasite, so the presence of HIV coinfection has, not surprisingly, resulted in the development of atypical forms of the disease.¹ Skin lesions are rare in VL but have been reported among HIV-infected male intravenous drug users in Spain.^{2,3} In these patients various morphologies have been described, including xanthoma-like lesions,⁴ linear brown macules⁵ and Kaposi's sarcoma-like lesions.³ Multiple eruptive dermatofibromas of undetermined aetiology have also been reported in immunocompromised individuals, including one HIV-infected individual without VL.⁶ However, this is the first report of multiple disseminated

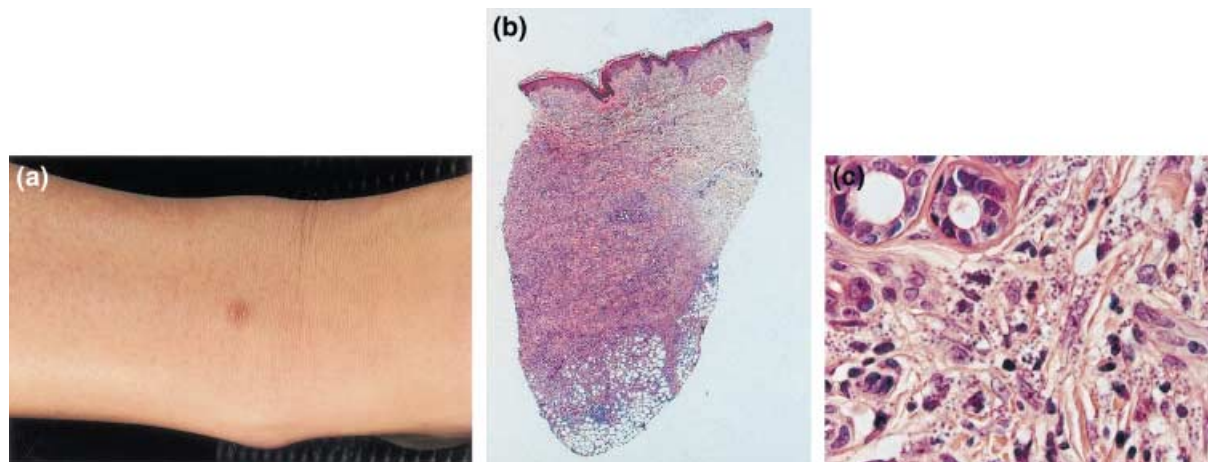


Figure 1. Dermatofibroma-like lesions disseminated over the limbs (a). Granulomas with a diffuse infiltrate of macrophages containing multiple *Leishmania* amastigotes within skin nodule: (b) low-power view and (c) high-power view.

dermatofibroma-like lesions in an HIV-1-infected individual due to leishmaniasis.

The significance of skin lesions in patients with VL has been questioned,³ as the presence of amastigotes has also been reported in healthy skin and incidentally in lesions including Kaposi's sarcoma⁷ and herpes zoster⁸ as well as in single dermatofibroma.^{5,9} There was no evidence of epidermal hyperplasia on histopathological examination and the nodules were therefore presumably due to dermal expansion secondary to large numbers of amastigote-laden macrophages. Most of the skin lesions in our patient cleared with treatment, which suggests that they were a manifestation of VL. Immunosuppression associated with HIV infection is characterized by abrogation of T-helper type 1 cell-mediated immune responses. Thus, *Leishmania* parasites rapidly replicate in HIV-infected individuals and subsequently disseminate to the skin following either primary infection or reactivation of latent infection.¹⁰

This case highlights the fact that even benign-looking skin lesions should not be ignored in a patient with severe, prolonged immunosuppression. The presence of skin lesions in an HIV-positive patient may disclose a diagnosis of VL; such lesions may provide an accessible tissue site for evaluation of VL treatment response and may subsequently alert the physician to relapse of disease. Most previous reports of cutaneous manifestations of VL associated with HIV coinfection have been among individuals living in areas with endemic leishmaniasis, such as southern Spain, where local physicians are familiar with this disease. For physicians in nonendemic areas, this case highlights the importance of taking a travel history and including leishmaniasis in the differential diagnosis of cutaneous lesions occurring in HIV-infected patients who have travelled to the Mediterranean and other areas with endemic leishmaniasis.

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Pigmented wart showing fibrillar intracytoplasmic inclusion bodies

SIR, Pigmented wart is a recently described type of wart associated with human papillomavirus (HPV) types 4, 60 or 65.¹ It is characterized clinically by brown to black nodules and histopathologically by melanin blockade melanocytes and intracytoplasmic inclusion bodies. The inclusion bodies were found as eosinophilic homogeneous intracytoplasmic bodies in keratinocytes.¹ On the other hand, a new type of nonpigmented viral wart with peculiar fibrillar intracytoplasmic inclusion bodies was recently described.² The causal HPV

type was thought to be a new HPV type that had not yet been characterized. We describe a patient with a pigmented wart showing fibrillar intracytoplasmic inclusion bodies.

A 61-year-old woman presented with an asymptomatic brown nodule on her right hand. She had noticed a tiny, dark-brown nodule 2 years previously. The nodule then gradually enlarged with the colour fading into brown. On examination, a brown hyperkeratotic nodule, measuring 4 mm in diameter, was observed on the ulnar lateral aspect of her right hand. The nodule had a rough surface on which dark brown dots were observed (Fig. 1a). The appearance of the nodule was that of a common wart except for its colour.

On histopathology, the nodule showed hyperkeratosis, parakeratosis, hypergranulosis, acanthosis and papillomatosis. Many vacuoles were observed in the horny layer. Keratinocytes with intracytoplasmic inclusion bodies were scattered in the upper spinous to granular layers. These inclusion bodies were eosinophilic and looked like thick, wavy, entangled bundles (Fig. 1b). In the lower spinous to basal layer, melanin blockade melanocytes were observed

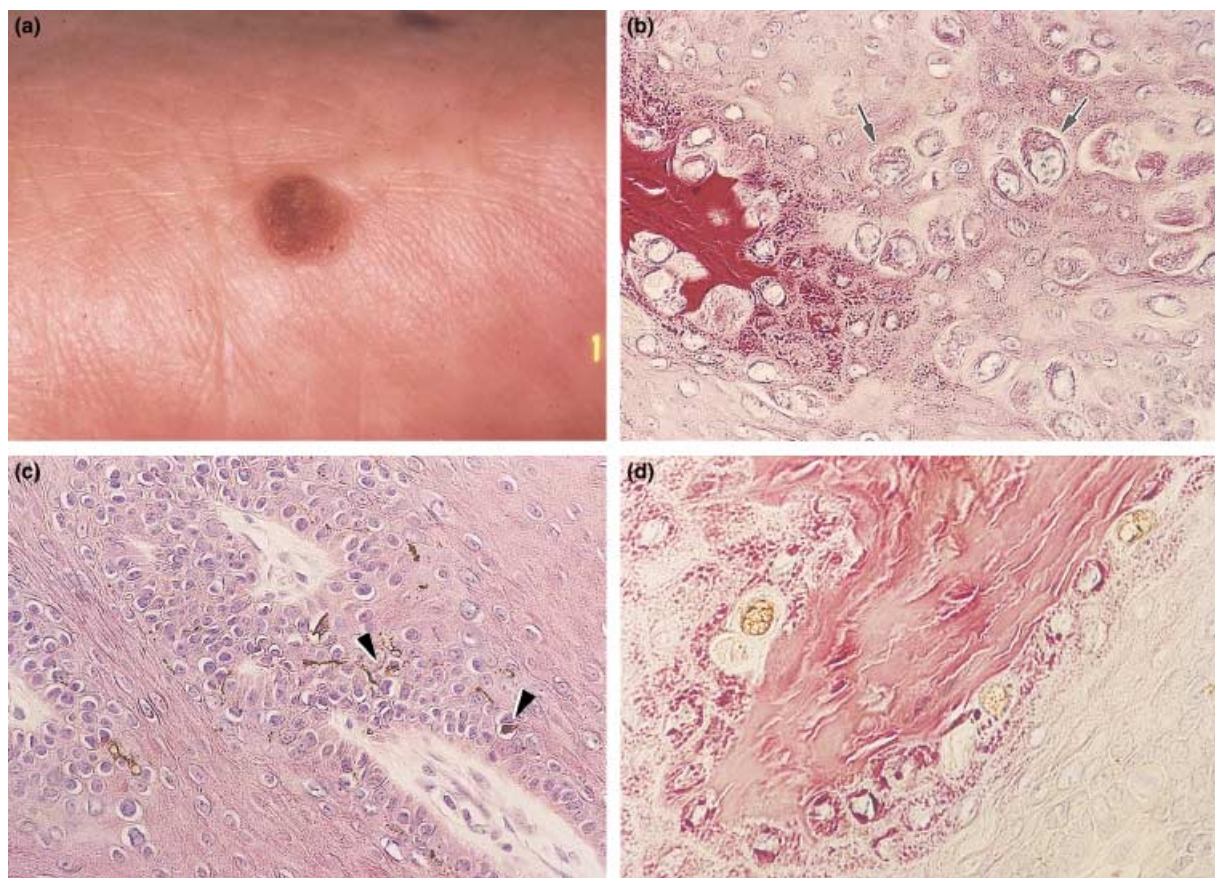


Figure 1. (a) A brown hyperkeratotic nodule is evident on the ulnar lateral aspect of the right hand. The nodule has a rough surface on which dark brown dots are observed. (b) Keratinocytes with intracytoplasmic inclusion bodies are scattered in the upper spinous to granular layers (arrows). These inclusion bodies are eosinophilic and look like thick, wavy, entangled bundles (haematoxylin and eosin; original magnification $\times 240$). (c) In the lower spinous to basal layer, melanin blockade melanocytes are observed (arrowheads; haematoxylin and eosin; original magnification $\times 240$). (d) Immunohistochemistry with genus-specific antipapillomavirus antibody stains the nuclei of keratinocytes with the fibrillar inclusion bodies. Counterstaining was performed briefly with haematoxylin and eosin (original magnification $\times 350$).

(Fig. 1c). Immunohistochemistry with a genus-specific polyclonal antibody against papillomaviruses (Dako Japan, Kyoto, Japan) stained the nuclei of keratinocytes with inclusion bodies (Fig. 1d) and many vacuoles in the horny layer.

Some viral warts are characterized by specific intracytoplasmic inclusion bodies and are designated as inclusion warts. Based on clinical features, types of inclusion bodies and HPV types, they have been classified into three types: myrmecia or deep warts, multiple punctate keratotic warts and pigmented warts.³ This classification seems to be rigid in the former two types of warts, as they are exclusively associated with granular inclusion bodies and HPV-1, and filamentous inclusion bodies and HPV-63, respectively. Although pigmented warts are associated with the related HPV types 4, 60 or 65, the inclusion bodies of these warts have been defined to date as homogeneous.¹

In this report, a nodule resembling a common wart showed fibrillar intracytoplasmic inclusion bodies. These clinical and histopathological characteristics are identical to those of the newly described inclusion wart,² except for its brown hue. The colour of the nodule did not represent the darkening sometimes shown by involuting warts,¹ because it developed as a tiny black nodule from the beginning. Moreover, this nodule showed melanin blockade melanocytes, which are thought to be a major histopathological finding of pigmented warts.¹ This nodule therefore represents a pigmented wart showing fibrillar intracytoplasmic inclusion bodies. The causative HPV type should be identical or closely related to the putative new type described previously.²

It is likely that some HPV types, HPV-60 and probably this putative new type, could cause both pigmented and nonpigmented warts^{2,4-6} and that pigmented warts could be related to inclusion bodies and HPV types other than those described originally.¹ Therefore, the features of pigmented warts do not seem to correlate histopathologically and virologically as closely as those of other inclusion warts. This is because pigmentation of warts can be ascribed to melanocytes that are not usually susceptible to and not directly affected by HPV infection.

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Localization of human β -defensin-2 and human neutrophil peptides in superficial folliculitis

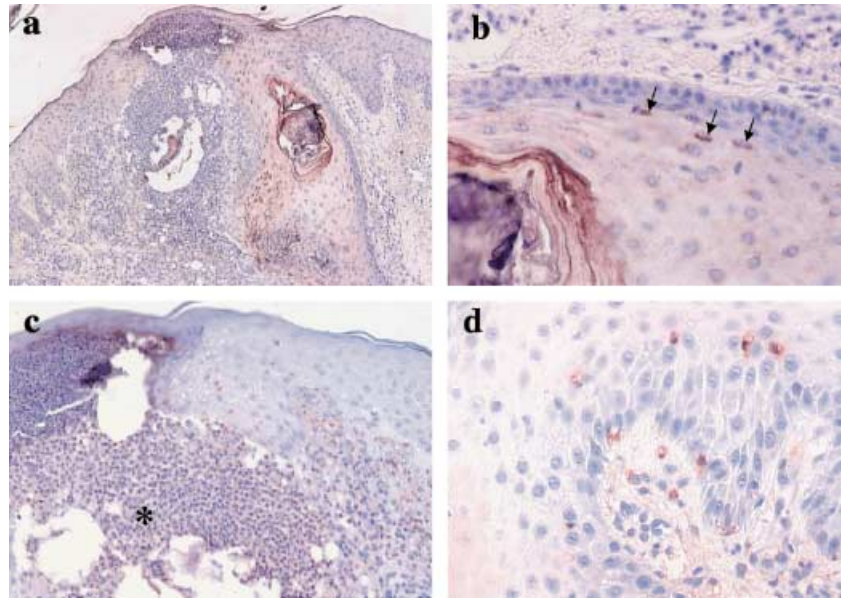
SIR, Folliculitis is a common skin disease with inflammation of the hair follicle, clinically manifested as papules and pustules. Microenvironmental conditions such as maceration and occlusion seem to be the triggers. In superficial folliculitis, *Staphylococcus aureus* and *S. epidermidis* are often cultured from follicular lesions.¹ The basic mechanism of folliculitis remains unclear, although microbial infection may play an important role in the pathogenesis of the disease.

Defensins are cationic, cysteine-rich antimicrobial peptides of the innate mammalian immune system.² These peptides are bactericidal against both Gram-positive and Gram-negative bacteria. Defensins form at least three structural groups: α - β - and θ -defensins. Neutrophils contain α -defensins, human neutrophil peptide (HNP)-1-4 in azurophilic granules; these HNPs account for 50% of the neutrophil granule protein.³ In human epithelial cells, four β -defensins, human β -defensin (hBD)-1-4 are expressed constitutively or upregulated by stimuli from bacterial components and cytokines. In addition to antimicrobial activity, a chemotactic activity of defensins for immature dendritic cells, memory T cells and monocytes has been described.⁴ These reports indicate that defensins have a role in linking innate and adaptive immunity.⁴

A recent report showed that hBD-1 and hBD-2 are expressed in the follicles and lesions of acne vulgaris, indicating the important role of these peptides in disorders of human pilosebaceous units.⁵ The purpose of the present study was to elucidate the role of defensins in common superficial folliculitis.

Skin samples were obtained from nine patients with superficial folliculitis diagnosed by clinical and histological findings. Informed consent was obtained from all patients. Formalin-fixed, paraffin-embedded blocks were cut into 4- μ m sections. The sections were incubated with a 1 : 1600 dilution of rabbit antiserum to hBD-2 (Peptide Institute, Osaka, Japan) for 20 min at room temperature, or with a 1 : 1000 dilution of mouse monoclonal antibody to HNP-1, 2 and 3 (Immunodiagnostika und Biotechnologie GmbH, Berlin, Germany). Specific binding was detected using the LSAB 2 kit against primary rabbit serum (Dako, Carpinteria, CA, U.S.A.) according to the manufacturer's instructions. To confirm the specificity of immunostaining, sections used as negative controls were incubated with an identical concentration of preimmune rabbit serum. These controls always yielded negative results.

Figure 1. Immunohistochemistry of skin biopsies from patients with superficial folliculitis. (a) Immunoreactivity of human β -defensin (hBD)-2 was observed in the suprabasal layer of perilesional and lesional epidermis and in the horny layer (original magnification $\times 100$). (b) hBD-2 expression was observed in the suprabasal layer of lesional epithelium (arrows; original magnification $\times 400$). (c) Immunoreactivity for human neutrophil peptides (HNPs) was seen in the polymorphonuclear (PMN) leucocytes that infiltrated the superficial dermis and pustules (*; original magnification $\times 100$). (d) A few infiltrating PMN leucocytes were positively stained by anti-HNP-1–3 antibody in the epidermis (original magnification $\times 400$).



The following antibodies were used to characterize the infiltrating cells: anti-UCHL1, anti-CD20, anti-S100 (Dako); anticoagulation factor XIII, α -subunit (Calbiochem, Germany); and anti-CD8 (Nichirei, Tokyo, Japan).

Immunoreactivity for hBD-2 was observed in the suprabasal layer of perilesional epidermis and in the horny layer (Fig. 1a). Positive staining was also seen in the suprabasal layer of lesional epithelium (Fig. 1b, arrows). No remarkable staining for hBD-2 was seen on the dermal infiltrating cells. Positive immunostaining for HNPs was observed on polymorphonuclear (PMN) leucocytes infiltrating around the follicles and in follicular pustules (Fig. 1c, asterisk). In the epidermis only the infiltrating PMN leucocytes were positively stained (Fig. 1d). HNP staining was not seen in perilesional and lesional keratinocytes.

CD45RO+ (UCHL1+) memory T cells were predominantly distributed in the dermal lymphoid infiltrate around the affected hair follicle (Fig. 2a). Only a sparse infiltrate was seen in the epidermis. A few CD20+ cells were seen in the dermal lymphoid infiltrate (Fig. 2b). CD8+ T cells were seen in perivascular regions of the dermis around the affected hair follicle (Fig. 2c), and in the epidermis adjacent to the affected follicle (Fig. 2d). Numerous XIIIa+ cells were observed around superficial capillaries and between collagen bundles in the dermis. Around the affected hair follicle, a relatively dense infiltrate of XIIIa+ dermal dendritic cells was observed (Fig. 2e). A few S100+ dendritic cells were seen in the lymphoid cells infiltrating the superficial dermis around the affected hair follicle (Fig. 2f). In the epidermis, several S100+ Langerhans cells and melanocytes were seen.

We have shown by immunohistochemistry that HNPs and hBD-2 are abundantly present in the lesions of superficial folliculitis. Immunoreactivity for HNPs was

observed in infiltrating PMN leucocytes and pustules in the interfollicular spaces. In contrast, immunoreactivity for hBD-2 was observed in the perilesional and lesional epidermis of the affected hair follicle. The distribution pattern of hBD-2 was similar to that in acne vulgaris lesions recently reported by Chronnell *et al.*⁵ Our observations indicate that the expression of hBD is up regulated not only in acne vulgaris lesions but also in other inflammatory follicular conditions. Dorschner *et al.* reported that the antimicrobial peptide LL-37, which belongs to the cathelicidin family, was expressed in both keratinocytes and infiltrating neutrophils during wound healing.⁶ They hypothesized that the role of LL-37 expressed in keratinocytes was rapid delivery of peptide independent of the time required for leucocyte recruitment. We have shown that HNPs and hBD-2 are expressed by restricted cells in superficial folliculitis lesions. The distribution pattern of HNPs and hBD-2 may indicate that HNPs are part of a second defence barrier against intruders that cross the barrier of epidermal defensins such as hBDs.

Recent evidence shows that defensins play a role in linking innate and adaptive immunity.^{4,7} HNP is chemotactic for CD8+ T cells,⁷ and hBD is chemotactic for CD45RO+ (UCHL1+) memory T cells.^{4,7} Both peptides are chemotactic for immature dendritic cells.⁷ To investigate the role of defensins in superficial folliculitis further, we characterized cells that infiltrated around the affected hair follicle. We showed that many UCHL1+ memory T cells and CD8+ T cells were distributed in the dermal lymphoid infiltrate around the affected follicle. The role of T cell immunity in immune defence against extracellular bacterial infection such as folliculitis caused by *S. aureus* has not been well examined. However, HNPs enhanced the acquired host response through T cell proliferative responses and cytokine secretion,

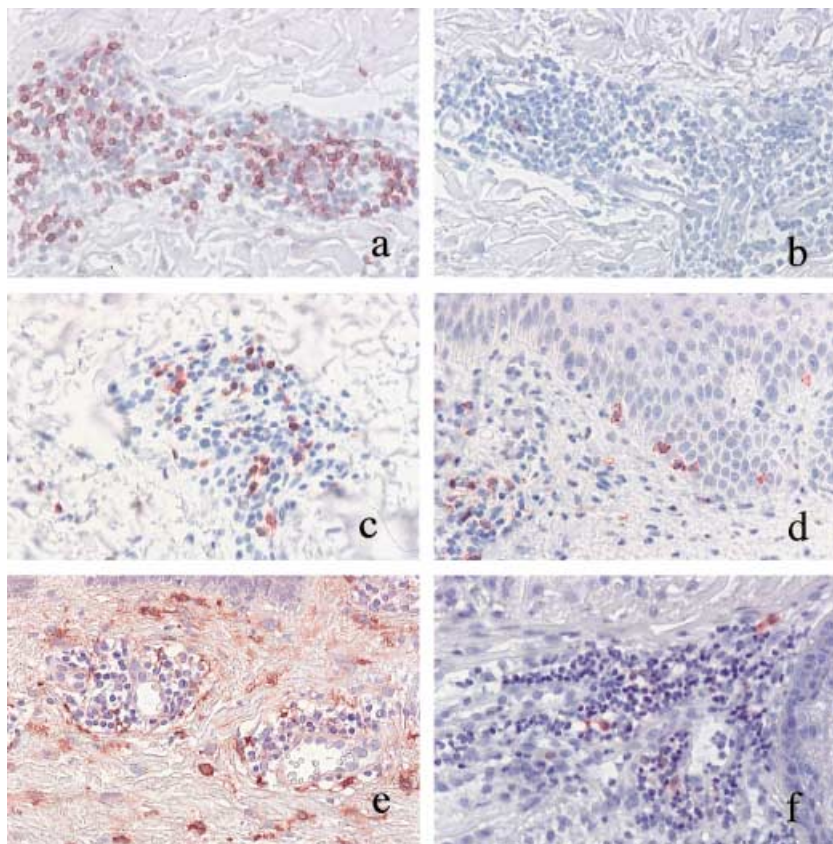


Figure 2. Immunohistochemistry of skin biopsies from patients with superficial folliculitis. (a) CD45RO+ (UCHL1+) T cells infiltrated perivascular lesions in the superficial dermis. (b) A few CD20+ cells were present in the dermal lymphoid infiltrate. (c) Many CD8+ T cells were observed in the perivascular lymphoid infiltrate. (d) CD8+ T cells were also observed in the epidermis. (e) Numerous XIIIa+ dermal dendritic cells were seen in perivascular areas and between collagen bundles. (f) A few S100+ dendritic cells were present in the dermal lymphoid cell infiltrate. Original magnification, a-f, $\times 400$.

indicating an important role for HNPs in cellular immunity.⁸ Adaptive immunity is induced by activation of T lymphocytes by antigen-presenting cells. We showed that factor XIIIa+ dermal dendritic cells and S100+ dendritic cells (possibly Langerhans cells) also infiltrated the superficial dermis around the hair follicle. Whether defensins are chemotactic for these dendritic cells *in vivo* remains to be addressed. Our observations indicate that in addition to antimicrobial activity, these peptides could participate as chemotactic factors in the inflammatory process of superficial folliculitis. Recent reports have shown that cytokine-activated neutrophils express CCR6, which is a chemokine receptor for hBD-2 and CCL20 chemokines.^{9,10} hBD-2 expressed in the epidermis may directly attract neutrophils to the lesions. The role of defensins in innate and adaptive immunity should be further investigated in infectious skin disease.

The expression of HNPs and hBD-2 in superficial folliculitis lesions indicates that these peptides play a role in host defence against bacterial skin infection.

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Book reviews

Controversies and Conversations in Cutaneous Laser Surgery (2002). Edited by KENNETH ARNDT and JEFFREY DOVER. AMA Press. ISBN 1 57947 261 3

The last 10 years have brought an expansion both in the types and complexity of lasers and in their potential applications, which is confusing even to physicians closely connected to the field. Marketing is now so sophisticated and client-led that patients quote media or internet articles relating to technology that may still be unfamiliar to their doctors and unknown to the peer-reviewed medical literature. When scientific data are eventually published, questions often remain unanswered.

One way to make sense of this flood of claim and conjecture is to attend meetings not organized by industry and to take an aggregate view of the data and experience of reputable laser surgeons whose commercial interests have been disclosed. One such symposium 'Controversies and Conversations in Cutaneous Laser Surgery' is directed each year by Drs Ken Arndt and Jeffrey Dover, both of whom are highly regarded in this field.

This book is a transcript of the lectures and panel discussions contained within the 2002 meeting. The lecturers have usually published widely, some of their presentations reflecting previous research work and some recording anecdotal experience. As one might expect, different views are sometimes expressed, and these are questioned and commented upon by discussants, often equally well known, in subsequent panel discussions.

The meeting (and the book) are divided into areas of interest or controversy and opinion is sometimes refreshingly frank. One reads in relation to non-ablative resurfacing, for example, that the results were often 'variable and difficult to quantitate (sic)'. Clinical photographs are frequently suspect and attempts at objective measurement, such as profilometry, are mysteriously abandoned in favour of newer and possibly favourable alternatives.

I have enjoyed reading this book (which is no primer for beginners) and would recommend it to those with knowledge of laser surgery and its problems.

RICHARD J. BARLOW

Primer of Dermatopathology. Philadelphia: Lippincott, Williams & Wilkins (2002). A.F.HOOD, T.D.HORN, T.H.KWAN, M.C.MIHM JR, and B.SMOLLER. ISBN: 0 7817 3236 0. Paperback, 559 pp. Price \$99; £64

Eighteen years in print, plus this new third edition, firmly indicates that this primer textbook has now truly become of age. Martin Mihm Jr remains the senior author and main mentor, but he and his colleagues are now ably joined by Bruce Smoller. The underlying theme for this book remains the original teaching of Wallace Clark, with histological diagnosis being based on a systematic appraisal of patterns of disease. The book is emphasised to be an introductory starter for dermatologists and pathologists and it is hoped that it will act as an inspiration to read fuller texts. Those quoted include Lever, Graham, Helwig and A.B.Ackerman but surprisingly not Weedon, Pinkus, Barnhill or indeed Farmer and Hood! For those unfamiliar with the book, the format is the same throughout. Anatomical location of disease within the skin is then further subdivided and discussed under three vertical columns, headed the reactive process and the disease, histopathology and comments. The histopathology entry incorporates points of importance in bold type and comments incorporate differential diagnoses. With an aim to produce an affordable book, all of the illustrations are in black and white, although this is admirably countered by an accompanying CD with approximately 2000 colour illustrations under similar headings. I thoroughly enjoyed the self-assessment quizzes on the CD but was somewhat disappointed that they were relatively few in number. Features in the book I personally found unfortunate included the frequent presence of blank (but paid for!) page space, and references that could perhaps have been more up-to-date. Whether you find the book easy to use will be based entirely on personal taste. If you like to read the maximum information in a somewhat lecture-note fashion, then this book will be ideal for you. If however, like me, you prefer classic, more leisurely and more extensive prose, then you will probably want to look elsewhere. Be warned, however, as very few good primer textbooks of dermatopathology are now in print and this is one of them! I can certainly recommend it highly as a standard benchbook in the reporting room. Trainees will

benefit greatly by tracking down diagnoses, using the algorithms present, so long as they bear in mind that algorithms are not absolute and vary between books. For readers unaware of the pustulo-ovoid bodies of Milian or

Henderson–Patterson inclusions, you are clearly still at the primer stage and use of this book will give you the answers!

DAVID SLATER

News and Notices

The First International Conference on Cytokine Medicine

27–28 February 2003, Manchester Conference Centre

For further information, visit the conference website: <http://www.cytokines.org.uk> or e-mail: cyto@hamptonmedical.com

Workshop in Advanced Methods in Pharmacokinetics and Pharmacodynamics

6–11 April 2003, San Francisco, CA, U.S.A.

For further details, please contact: Linda Mansouria, Advanced Pharmacokinetics, c/o Make It Happen, 137

Alhambra Stree, San Francisco, CA 94123, U.S.A. Fax: + 1 415 567 8667; e-mail: advancedpkpd@c255.ucsf.edu; web-site: <http://www.plessthan.com/course/>

International Symposium on Vitiligo 16–17 May 2003, Royal College of Physicians, London, U.K.

Topics will include: Clinical Nature of Vitiligo, From Biology to Treatment, Genetic Research, Understanding Melanocytes and the Psychology of Vitiligo.

For further information visit www.vitiligosociety.org.uk or email: vitaligo@hamptonmedical.com