Correspondence

Treatment of severe erythrodermic acute graft-versus-host disease with photochemotherapy

Sir, graft-versus-host disease (GVHD) is a frequent complication occurring after allogenic bone marrow transplantation. Skin changes may be divided into acute and chronic GVHD, both displaying a particular pattern. Acute GVHD may develop into generalized erythroderma and even further into skin necrosis and epidermal blistering. Photochemotherapy (PUVA) is highly effective for the treatment of patients with acute GVHD. However, since the overall prognosis of patients with severe manifestations of GVHD is poor, treatment of these patients with PUVA is still challenging. It is further complicated by severe immunosuppression. We report here on the successful treatment of a patient suffering from overall grade IV GVHD with PUVA therapy.

A 34-year-old male patient had received allogenic bone marrow transplantation due to myeloid leukaemia. Despite GVHD prophylaxis with cyclosporin and methotrexate, the patient developed severe mucositis after several days. After a further 3–4 weeks, GVHD of the liver developed which required additional systemic glucocorticoids (prednisolone 5 mg kg\(^{-1}\) body weight daily). Two weeks later the patient developed a rapidly progressing erythematous rash, which finally led to a generalized erythroderma (Fig. 1). Histopathological examination revealed an acanthotic epidermis with many dyskeratotic cells and scattered inflammatory lymphocytes (Fig. 2). The basal epidermal layer showed extensive vacuolization, and the dermal compartment a marked oedema and a moderate inflammatory infiltrate of lymphocytes accompanied by erythrocyte extravasation. These findings were characteristic of acute cutaneous GVHD. The prednisolone dosage was increased and the immunosuppressive agent mycophenolate mofetil (2 g daily) was added. Because skin lesions did not respond to this treatment regimen, oral PUVA therapy was started. 8-methoxypsoralen (0.6 mg kg\(^{-1}\) body weight) was administered 2 h before UVA exposure. After 3 weeks of treatment the skin lesions had dramatically improved. PUVA therapy was stopped for 2 weeks due to bone marrow re-transplantation. After that, PUVA therapy was continued with local application of 8-methoxypsoralen cream combined with UVA irradiation. Skin lesions cleared completely after a further 3 weeks of treatment and an overall dosage of 12 J cm\(^{-2}\) (Fig. 3). Histopathological evaluation of skin biopsy showed a flattened epidermal layer and slight fibrosis in the dermal compartment, features which might indicate early chronic GVHD.

Although a series of reports on PUVA treatment of acute GVHD have been published, treatment of more severe cases is less common. In the present report the severe skin involvement of an overall grade IV GVHD did not respond to a combination of three different high-dose immunosuppressive agents (prednisolone, cyclosporin and mycophenolate

Figure 1. 34-year-old patient with acute severe graft-versus-host disease (GVHD) before treatment with oral photochemotherapy (PUVA therapy).

Figure 2. Histopathology of a skin biopsy of the patient with acute severe graft-versus-host disease (GVHD) before photochemotherapy (PUVA) treatment. The epidermis shows plenty of dyskeratotic cells and an inflammatory infiltrate mainly composed of lymphocytes. The basal layer shows extensive vacuolization.
mofetil). It might be speculated that our patient would have developed cutaneous necrosis and blistering if the immunosuppressive treatment had been lower or tapered too early. In fact, histopathological examination detected numerous necrotic/apoptotic keratinocytes presenting as dyskeratotic cells within the epidermis and extensive basal cell vacuolization. After a total of 6 weeks of PUVA therapy complete clearing was achieved. At that time only prednisolone was administered for immunosuppression. Thus, PUVA treatment has proven to be highly effective for this patient.

The mechanisms of the response to PUVA treatment are poorly understood. Our report further argues for a direct influence of PUVA therapy on the immune system. It seems likely that PUVA therapy depletes activated lymphocytes directed against antigens present in the skin, which is supported by in vitro findings of Kripke et al. and Ullrich. It had been speculated that PUVA might even induce suppressor T cells acting at local and more distant sites of the deregulated immune response. These suppressor T cells might be active at sites not directly accessible to irradiation, such as the oral mucosa, which might explain the clearing of mucosal lesions under PUVA therapy. As keratinocytes are a major target of acute and chronic GVHD and are highly activated during the disease, it might well be that the direct effect of PUVA on this cell type is of importance. Langerhans cells have been implicated in the mechanisms of the PUVA response. However, the overall contribution of the different cell types still remains to be determined in more detail. Taken together, the present report underlines the potent immunomodulatory effects of PUVA therapy and emphasizes the role of PUVA treatment in severe cases of GVHD.

Figure 3. 34-year-old patient with acute graft-versus-host disease (GVHD) 6 weeks after treatment with oral and local (cream) photochemotherapy (PUVA therapy). Lesions have completely cleared on the whole skin surface after application of a total UVA dosage of 12 J cm\(^{-2}\) in combination with 8-methoxypsoralen.

References

**Differential expression of Fas in tumour-stage mycosis fungoides (MF) and MF-like cutaneous T-cell pseudolymphoma**

Sir, Differentiation between cutaneous pseudolymphoma and cutaneous lymphoma is often a challenging question that goes well beyond mere academic debate because it carries important prognostic and therapeutic implications. Zoï-Toli and colleagues recently reported loss of Fas expression in aggressive types of cutaneous T cell lymphoma, but not in indolent types of lymphoma. Here, we investigated whether this interesting observation could provide a criterion to differentiate mycosis fungoides (MF)-like cutaneous T-cell pseudolymphoma from tumour-stage MF.

Paraffin-embedded tissue sections were obtained from three patients with tumour-stage MF and from eight patients with MF-like cutaneous T-cell pseudolymphoma (lymphomatoid drug eruption, \( n = 2 \); idiopathic, \( n = 6 \)), which were histologically characterized by a band-like infiltrate of mostly T lymphocytes in the papillary dermis. All diagnoses were histologically characterized by a band-like infiltrate of mostly T lymphocytes in the papillary dermis. All diagnoses were based on a combination of clinical, histological and immunophenotypic criteria, as described previously. Immunohistochemistry using anti-Fas rabbit polyclonal antibody (C-20, Santa Cruz Biotechnology, Santa Cruz, CA, U.S.A.) was carried out on 4 µm paraffin-embedded sections. Briefly, the slides were heated on a polymerase chain reaction (PCR) plate at 90 °C for 15 min in a citrate buffer, pH 5–6. The sections were incubated with antihuman Fas (diluted 1 : 50 in TNB) and the signal was detected with a tyramide signal amplification kit (TSA™ Biotin System, NEN Life Science, Boston, MA, U.S.A.). Negative controls were provided by replacing the primary antibody with non-immune serum. The percentages of T cells expressing Fas were scored as follows: −, no or occasional positive cells; +, 10–50% positive cells; + +, > 50% positive cells.

Confirming the results reported by Zoï-Toli et al., we found low level of Fas expression in tumour-stage MF [− in one of three cases (33%) and + in 2 of 3 cases (67%)]. In contrast, in MF-like cutaneous T-cell pseudolymphoma, Fas was expressed by the majority of the T cells [++ in eight of eight cases (100%)].

Differential expression of Fas in tumour-stage MF may be difficult, with no single criterion to differentiate both entities. Here, we found that MF-like cutaneous T-cell pseudolymphoma exhibits a stronger Fas expression than tumour-stage MF. Although these data need to be confirmed by larger studies, they are in line with those recently reported by Zoï-Toli and colleagues, and suggest that immunohistochemical expression of Fas may represent a reliable criterion to differentiate MF-like cutaneous T-cell pseudolymphoma from tumour-stage MF.

**References**


**Primary cutaneous pleomorphic small/medium-sized T-cell lymphoma in a young man**

Sir, Primary cutaneous pleomorphic small/medium-sized T-cell lymphoma (PSMTCL) is a rare, recently recognized type of cutaneous T-cell lymphoma (CTCL), clinicopathologically different from mycosis fungoides (MF)/Sezary syndrome. Only a few cases have been reported in the literature, and the treatment has not been well defined. The prognosis of PSMTCL can be favourable and it tends to occur in an older age group similarly to other types of CTCL. We report an additional case of PSMTCL occurring in a 19-year-old man.

A 19-year-old man presented with a 3-year history of a red-purple, infiltrated plaque on the left side of the face. His past medical history was not contributory, and there was no history of a preceding patch-like lesion of MF. The lesion was asymptomatic and measured about 5 × 7 cm. A skin biopsy showed a dense, dermal interstitial, folliculotrophic, and focally epidermotrophic infiltrate of small to medium-sized, pleomorphic lymphocytes (Fig. 1). Alcian blue stain showed no mucin deposits. Immunophenotyping showed strong expression of CD2 and CD3. CD4 was expressed by 50% of the cells, but CD5, CD7 and CD8 were expressed by < 5% of the cells. CD30 was not expressed, and CD20 was expressed by approximately 20% of the cells.

DNA extracted from the paraffin block showed gamma T-cell receptor gene clonality on polymerase chain reaction analysis. Laboratory examinations including full blood count, peripheral blood smear review, erythrocyte sedimentation rate, liver function tests, antinuclear antibody, serum protein electrophoresis, immunoelectrophoresis, human T-cell lymphoma virus type 1 and type 2, and Epstein–Barr virus serological tests, were within normal limits or negative. Chest X-ray and computed tomography of the abdomen and pelvis showed no abnormalities. The patient was treated with local radiation therapy, which led to a complete remission of the lesion. He has now been free of disease for more than 14 months.

PSMTCL is rare, representing about 3% of all primary CTCLs. CD30-negative pleomorphic CTCLs are usually divided into two types according to tumour cell size: small cell type and medium to large cell type by the updated Kiel classification, and small to medium-sized cell type and
large cell type by the European Organization for Research and Treatment of Cancer classification (Table 1). Beljaards et al. proposed subdivision of medium-sized and large cell pleomorphic lymphomas, which are grouped together in the updated Kiel classification, because pleomorphic small or medium-sized cell types had a significantly better prognosis compared with patients classified as having the pleomorphic large cell type. Differentiating small to medium-sized cell type lymphomas from large cell type lymphomas is based on the presence of more or less than 30% large pleomorphic tumour cells.

PSMTCL is clinicopathologically different from classic MF. At onset, PSMTCL shows lesions consisting of one or more papulonodules, tumours or deeply infiltrated plaques, without the erythematous finely scaling patches suggestive of the initial stage of MF. Pruritus is absent in PSMTCL, while the lesions in MF are usually pruritic. In our patient, a red-purple, asymptomatic, infiltrated plaque occurred on the face without the patches typical of MF. The histopathological findings of PSMTCL consist of tumour cells which are small to medium-sized pleomorphic lymphocytes with irregular, but not cerebriform nuclei that efface the dermis with a tendency to infiltrate the subcutis. Epidermotropism is frequently absent, but may be present. The lesion of our patient showed a dense, dermal interstitial and folliculotropic infiltrate of small to medium-sized, pleomorphic lymphocytes. Focal epidermotropism was present. Folliculotropic MF, a rare variant of MF, shows folliculotropism of atypical lymphocytes without follicular mucinosis, as in our case, but the follicular infiltration is more dense and epidermotropism is absent.

The tumour cells in PSMTCL often express a helper T-cell phenotype with frequent loss of pan-T-cell markers as in most CTCLs. CD4 expression and the loss of pan-T antigens (CD5 and CD7) in our case were consistent with PSMTCL.

In one study, the age at onset of the PSMTCL ranged from 31 to 87 years with a median age of 60 years. In our patient, the age at onset of the tumour was 16 years, which is the youngest age reported. The treatment modalities of this type of lymphoma have not been well defined. Cyclophosphamide as a single-agent therapy and interferon alfa have been reported to be effective in patients with disseminated lesions. Radiation therapy is known to be the preferred mode of treatment for a localized lesion, but relapse may follow complete remission after treatment. Our patient had a lesion without metastasis for 3 years without treatment. Because the lesion was localized to the face, we treated him with local radiation therapy and obtained a complete remission without relapse. However, our clinical follow-up is limited to 14 months. The good prognosis of our patient may be due to the histological small to medium-sized cell subtype of pleomorphic CTCL, and his young age.

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Figure 1. (a) Dense, dermal interstitial, folliculotropic and focal epidermotropic infiltrate; (b) folliculotropic involvement of small to medium-sized pleomorphic lymphocytes; (c) small to medium-sized lymphocytes with irregular and variable nuclear shape (haematoxylin and eosin; original magnification: a, ×40; b, ×100; c, ×400).
Table 1. European Organization for Research and Treatment of Cancer (EORTC)\(^2\) and Kiel\(^{6}\) classification of primary cutaneous T-cell lymphoma

<table>
<thead>
<tr>
<th>EORTC classification</th>
<th>Kiel classification</th>
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<tbody>
<tr>
<td>MF</td>
<td>Small cell, cerebriform</td>
</tr>
<tr>
<td>MF-associated follicular mucinosis</td>
<td>Not listed</td>
</tr>
<tr>
<td>Pagetoid reticulosis</td>
<td>Not listed</td>
</tr>
<tr>
<td>Granulomatous slack skin</td>
<td>Not listed</td>
</tr>
<tr>
<td>SS</td>
<td>Small cell, cerebriform</td>
</tr>
<tr>
<td>Lymphomatoid papulosis</td>
<td>Not listed</td>
</tr>
<tr>
<td>CD30-positive large T-cell lymphoma</td>
<td>Large cell anaplastic (CD30 +)</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>Pleomorphic, medium-sized/large cell</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>T immunoblastic</td>
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<tr>
<td>Immunoblastic</td>
<td>Pleomorphic, medium-sized/large cell</td>
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<td>CD30-negative large T-cell lymphoma</td>
<td>T immunoblastic</td>
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<tr>
<td>Pleomorphic large cell</td>
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<td>Immunoblastic</td>
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<tr>
<td>Pleomorphic, small/medium-sized cell</td>
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<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
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MF, mycosis fungoides; SS, Sézary syndrome.

References


Panniculitis heralding blastic transformation of myelofibrosis

Sir, The term ‘panniculitis’ comprises a group of disorders with chronic inflammation and fibrous thickening of the subcutaneous adipose septa. Paraneoplastic panniculitis has been reported occasionally.\(^1\) We report a unique case of septal panniculitis heralding blastic transformation of myelofibrosis.

An 80-year-old Chinese female patient presented with anaemia and heptosplenomegaly in March 1999. Peripheral blood examination showed a leukoerythroblastic blood picture and teardrop red cells, with haemoglobin level of 7·6 g dL\(^{-1}\), white cell count 9·3 \times 10^3 \text{ L}^{-1} (13% myelocytes, 13% nucleated red cells), and platelet count 245 \times 10^3 \text{ L}^{-1} with circulating bare megakaryocyte nuclei. A bone marrow biopsy showed myelofibrosis. Cytogenetic studies were normal and reverse transcription polymerase reaction for bcr/abl fusion was negative. She was treated with supportive transfusion. Four months afterwards, she complained of recurrent painful calf swellings (Fig. 1a). Each lesion lasted for a few months and tended to coalesce, resolving with pigmented scarring. There was also noticeable progressive skin thickening and stiffness. Examination revealed multiple erythematous tender nodules over both calves, especially pronounced around the ankles. The distal thirds of the calves were affected by circumferential sleeve-like induration compatible with fibroscelerotic change. There were no other new systemic symptoms, and no recent drug exposure. Screening for autoimmune and infective causes, including an intradermal tuberculin reaction and chest radiographs were normal. A biopsy showed paraseptal and septal granulomatous panniculitis (Fig. 1b) with a mixed infiltrate of lymphocytes, plasma cells, eosinophils and epithelioid histiocytes, with no caseation. A medium-sized artery in the dermosubcutis interface showed necrotizing arteritis with fibrinoid necrosis. She was treated with cimetidine, pentoxiphylline, colchicine and ibuprofen with a reduction in pain and number of lesions. Two months afterwards, myeloperoxidase-positive circulating blast cells (15%) were noticed in the peripheral blood, and blastic transformation was confirmed. She was commenced on oral chemotherapy for disease control.

Paraneoplastic causes account for 3–10% of cases of panniculitis.\(^1,2\) Panniculitis has a well-documented association with pancreatic diseases, including occult pancreatic carcinoma.\(^3\) However, the commonest cause of cancer-associated panniculitis is haematological malignancies (60%), mostly lymphomas. Two-thirds of cases occur in...
females. Skin inflammation usually precedes the diagnosis of malignancy, with a median lag time of 12 months. In our case, however, panniculitis heralded the blastic transformation of underlying myelofibrosis. Diagnosis is by clinical history and histological exclusion of other primary and reactive skin conditions. Although inflammatory rheumatological complications, especially vasculitis, may complicate the course of myeloid dysplasia, a panniculitic pattern of involvement is seldom observed. Reported cases showed a predilection for myelomonocytic lineage involvement probably due to tissue infiltration tendency and lysozyme release. The reason for the subcutaneous localization of inflammation in these cases is, however, unclear. Apart from treating the underlying cause, histamine (H2) antagonists (especially cimetidine) have documented efficacy. Only one case of panniculitis complicating myeloproliferative disease has been reported. In elderly patients, or patients with a history of previous cancers or premalignant conditions, unexplained panniculitis should be an indicator for malignancy screening. On the other hand, since blastic transformation may be occult in patients with myelofibrosis, the development of new systemic manifestations should always prompt a careful peripheral film or marrow examination for evidence of disease acceleration.

References


Granulomatous disease associated with HLA class I deficiency

Sir, I read with interest the letter of Mertens et al. with regard to a patient with granulomatous skin disease and HLA class I deficiency. A series of five similar cases with destructive granulomata in skin and respiratory mucosa associated with human leucocyte antigen (HLA) class I deficiency has recently been published. The case described by Mertens et al differs from the previous cases by a decreased number of CD8+ T cells and normal number of CD56+ T cells, suggesting that normal CD8 counts and increased CD56+ natural killer cells are not a constant feature of HLA class I deficiency.
deficiency and destructive granulomatous disease. In the cited series the clinical syndrome was associated with defective expression of the transporter associated with antigen processing (TAP) genes, in two cases with a deleterional mutation of adenosine at codon 326 in TAP-2, causing a premature stop codon. HLA deficiency at the cell surface in these patients is secondary to TAP deficiency. HLA molecules cannot be charged with peptides normally translocated by TAP 'Empty' HLA class I molecules are unstable and rapidly degraded. Mutations in TAP-1 or TAP-2 should be evaluated in patients with unusual patterns of granulomatous disease having some similarities to Wegener's granulomatosis.

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References

Management of ulcerated necrobiosis lipoidica: an innovative approach

Ulceration in necrobiosis lipoidica diabetorum (NLD) is notoriously difficult to heal.1,2 We describe successful use of a bioengineered human dermis preparation in management of ulcerated NLD.

The patient was a 56-year-old female, with type II diabetes for 3–5 years who smoked heavily (30–40 cigarettes per day), was overweight (BMI 32·9) and had chronic hyperglycaemia. Bilateral NLD of 17 months duration was diagnosed in 1996, at which stage there was an ulcerated lesion on the dorsum of the left foot measuring 6 × 5·5 × 0·1 cm depth. A variety of dressings, including hydrogels, hydrocolloid type dressings, sodium sulphate, silver sulphadiazine and 1% steroid creams were used unsuccessfully. In 1998 she was finally admitted suffering from an extremely painful, sloughy ulcerated area on her left foot that required opiate analgesia to control pain and permit sleeping. Vascular examination revealed barely palpable dorsalis pedis pulses, and impalpable posterior tibial pulses. Doppler waveform analysis showed monophasic waveforms and ankle brachial indices were 0·92 in both feet. The patient experienced bilateral calf claudication at <200yds. There was no clinical evidence of neuropathy and the skin of the feet did not appear ischaemic. She was still smoking and diabetes control was still poor (HbA1c 9·6%, NR <5·5). Over the next 3 months she was treated with erythromycin for haemolytic streptococcus and Staphylococcus aureus infection, insulin therapy was started, and the area was managed using a variety of dressings that included hydrogels, hydrocolloid gels and sugar paste. The NLD ulceration had reduced to 2·3 cm × 1·2 cm × 0·1 cm depth (Fig. 1a) but provided a route for infection and was causing intolerable pain, to the extent that the patient was asking us to consider amputation.

We decided to treat the ulcer with Dermagraft (Advanced Tissue Sciences, La Jolla, USA), a bioengineered human dermis preparation. After only the second implant the ulcer had reduced to 2 mm diameter. Following a further tiny implant the ulcer healed (Fig. 1b). This was the first time that the wound had closed in 3 years. The patient’s pain disappeared and analgesia was stopped. Sixteen months later the ulcer remains closed and the patient enjoys a hugely improved quality of life.

Eight months after the lesion on the left foot had healed, the patient attended the diabetic foot clinic as an emergency with a 6-week history of ulceration within NLD on the lateral aspect of her left leg, which had become intensely painful. The ulcer was a circular lesion 3·5 cm in diameter and the entire wound bed was covered with adherent yellow slough. The patient once again described the pain as unbearable. The lesion was dressed on alternate days with hydrogels for 2 months after which the ulcer remained the same size and the pain was undiminished. Although the sloughy area had reduced to 1 cm diameter.

Six-weekly implants of Dermagraft were applied. A persisting area of slough remained on the lateral margin of the wound surface for five of the six implants and a Staphylococcus aureus infection developed which was treated with erythromycin and metronizadole. By the sixth application of Dermagraft the wound base was slough-free and had reduced in size to approximately 2 cm in diameter. Interestingly, from the first implant the patient noted that the pain had eased considerably and by the second implant pain had reduced sufficiently to allow extensive debridement of the remaining slough. One week after the last implant of Dermagraft the ulcer had reduced to 1 cm2 and was described by the patient as painfree. Thereafter alternate daily hydrogel dressings were applied. The ulcer continued to reduce in size until it healed 10 weeks later. The ulcer remains healed.

The overall prevalence of NLD is estimated to be <0·3% and 65% of NLD cases occur in diabetic subjects. The disorder has predisposition for areas that are subject to trauma, most commonly the anterior tibia.3 Up to 35% of NLD lesions spontaneously ulcerate.2 Once ulcerated, such lesions have shown notorious resistance to healing despite use of many forms of therapy.1,4 Methods of management have ranged from conservative approaches, involving moist wound-healing techniques, to bovine collagen implants and intradermal steroids.3,5,6

Systemic treatments which have been used in an attempt to induce healing include prostaglandin, pentoxyffilline and antiplatelet agents and complete exision of the lesion has also been advocated.4,7,8 Failure to heal, however, remains common.
Although ‘necrobiosis’ refers to the degeneration of collagen, the precise aetiology and pathogenesis of NLD are unknown, making the management of this condition a considerable challenge.9

Dermagraft is a bioengineered human dermis preparation consisting of cryopreserved neonatal dermal fibroblasts cultured on a bioabsorbable mesh. In contrast with conventional dressings which provide optimal environmental conditions in which the wound is encouraged to heal, this metabolically active dermal tissue contains and produces a balanced natural cocktail of growth factors and matrix proteins normally present in healthy human dermis during wound healing.10 The functionality of fibroblasts in this dermal replacement have been shown to be unaffected by whatever underlying pathological process is affecting the host tissue.11 This bioengineered tissue provides a structural framework for wound healing which becomes actively involved in the healing process. Implanted fibroblasts can remain detectable and viable in scar tissue many months after healing.

Dermagraft has been used with some success in managing diabetic neuropathic foot ulcers12 but to date there is no reported experience of its use in ulcerated NLD. As NLD is now widely accepted to be associated with collagen degeneration we postulated that the introduction of healthy fibroblasts into the wound bed could play a contributary role in healing an ulcerated NLD lesion. In practice this seems to have been the case with this lady’s NLD ulcers. Matrix proteins, notably collagen, have been found to be abnormal in human diabetic studies.13 It was interesting to note that on both occasions Dermagraft significantly reduced the level of pain even before healing of the ulcer. This, of itself, was a huge benefit in the management of both ulcerations as it allowed effective mechanical debridement. The mechanisms for this pain relief are not clear.

Whatever the mechanism involved in healing, following 3 years of failed management involving continuous community care and 21 days of in-patient care at considerable cost to both patient and NHS, three implants of Dermagraft healed the first chronic ulcer with rapid complete resolution of pain. The second ulcer was more resistant to treatment with Dermagraft, perhaps because of the persistence of adherent slough (a problem acknowledged in the manufacturer’s product data sheet) and intercurrent infection. Again, however, dermal replacement therapy reduced pain rapidly and promoted healing in a resistant ulcer. Such resolution has since enabled the patient to stop all analgesia and return to normal living.

This bioengineered human dermis preparation is therefore another treatment option that can be effective in healing indolent ulcerated lesions of NLD.

Figure 1. (a) Ulcerated NLD before first dermal implant; (b) ulcer healed 3 weeks later.
Mononuclear variant of juvenile xanthogranuloma in the oral cavity of an adult patient

Sir. Juvenile xanthogranuloma (JXG) is a benign proliferation of histiocytes of the macrophage lineage of uncertain histogenesis. It is probably a histiocytic proliferation reaction to an unknown stimulus. Histologically, it consists of a proliferation of roundish cells with an indistinct border and clear, finely vacuolated, cytoplasm. In their centre, cells have a typical crescent-shaped or roundish nucleus; mitoses, although rare, may be present. The hallmark of JXG is the presence of giant foamy cells with numerous mononuclear nuclei arranged in a wreath along the periphery of the cytoplasm: the Touton cells. The presence of these giant cells has been used as a crucial clue in the differential diagnosis with morphologically similar entities. A subtype of JXG was recently described in which giant plurinucleated Touton cells are distinctly absent or very scant. These cases are probably nothing more than an evolving stage or a late form of JXG in which Touton cells are not yet formed or have regressed. This variant can be correctly diagnosed through the immunohistochemical pattern of the mononuclear cells and by anatomoclinical correlation. Immunohistochemically, the cells are CD68 and vimentin positive, S100 and Melan-A negative. Unless clinically suspected, the mononuclear form is frequently misdiagnosed as histiocytosis, melanoma or other forms of neoplasm.

Clinically, JXG is usually a yellow, pink or brownish papule sited on the head and neck; extracutaneous locations are rare, the most frequent being the conjunctiva. The oral form has been used as a crucial clue in the differential diagnosis of necrobiosis lipoidica diabeticorum. A case report. J Dermatol 1985; 12: 449–54.

As the name implies, JXG is usually found in infants or children. The adult form, although rarier, is, however, well known, and is histologically and clinically indistinguishable from the infantile lesions. JXG in the oral cavity in adults is very rare, with only two cases recorded in the literature. The case we present here seems to combine all the rarest aspects of JXG: appearance in an adult, in the oral mucosa, and with a purely monocellular pattern. A 60-year-old man developed within 2 months a yellow, dome-shaped asymptomatic papule in the alveolar mandibular border. This was excised and histology showed a mononuclear variant of JXG was made.

Being such a rare entity, the differential diagnosis must be carefully discussed. The clinical appearance of a small deep yellow papule suggested that this was a lesion with abnormal lipid storage, the most reasonable entities to be considered being JXG, xanthoma, fibrohistiocytoma and foreign body reaction. Other differential diagnoses included verruciform xanthoma, histiocytosis X, melanocytic naevus and malignant melanoma.

A form of xanthoma was ruled out on the basis of a solitary lesion and normal serum lipid measurements. An isolated xanthoma in the oral cavity of a normolipidaemic patient has not yet been described. Moreover, xanthomas are usually flat and not dome-shaped like the lesion we describe here, and cytologically, xanthoma cells are larger than those of our patient’s lesion. Rare forms of xanthomatosis of the oral cavity can be excluded considering the bural clinical picture of the lesion, the lack of a complicated syndromic picture and the normal serum lipids.

A foreign body reaction and a fibrohistiocytoma can be ruled out by the monomorphic pattern of granular or foamy cells, a picture very different from the heterogeneous infiltrate

References
of the above-mentioned entities that is a mixture of histiocytes, giant cells, lymphocytes and granulocytes. Histiocytosis X is easily excluded by the negative S100 stain and also by the distinctively foamy appearance of many cells. Moreover, CD68, a marker for non-X histiocytosis, was positive. S100 negativity also rules out melanoma and balloon cell naevus.

In conclusion, a mononuclear form of JXG seems the only reasonable diagnosis of this very peculiar case which histologically is identical to previously published cases.4–8

Figure 1. (a) Scanning magnification revealed a uniform pattern of growth; (b) cells show a vacuolar, foamy cytoplasm. No giant cells of any type were found (haematoxylin and eosin).

References

Congenital malalignment of the left index fingernail

Sir. Unilateral congenital malalignment of the fingernail is a disorder in which malalignment of the nail matrix results in angular lateral nail plate growth. There have been frequent reports of congenital malalignment of the great toenails but unilateral involvement of a fingernail is rare. The exact aetiology is unknown. Its severity is variable and complications may not be evident until adult life. Treatment depends on the degree of lateral deviation and associated changes.

A 20-year-old woman presented with a history of recurrent paronychial infections secondary to an ingrowing fingernail. She had a life-long history of lateral deviation of the nail plate of her left index finger. There was no other significant past medical history or history of trauma. No previous surgical treatment had been tried. There was no family history of congenital malalignment of any nails or associated nail dysplasia. On examination of the left index finger, the nail plate was deviated laterally with no obvious thickening or discoloration (Fig. 1). No other fingernails or toenails were affected. Due to recurrent episodes of perionychial infections the lateral one-sixth of the nail plate was excised and the lateral one-sixth of the nail matrix was phenolized.

Congenital nail defects of the index finger were first reported by Iso in 1969 and were initially described as having the following five distinct characteristics: the condition (i) is congenital; (ii) is unilateral or bilateral; (iii) exhibits variability in nail appearance; (iv) has possible hereditary involvement; and (v) is frequently associated with bone abnormalities. The condition was later renamed congenital onychodysplasia of the index fingers. Additional features such as nail thickening and nail malalignment now form part of the syndrome.

In patients with congenital onychodysplasia, multiple forms of nail dysplasia are usually evident. Micronychia is the most common clinical manifestation. Solitary malalignment of one index fingernail with no other evidence of nail dysplasia has been reported in only one other case. It is thus difficult to extrapolate a precise cause.

Multiple underlying causes and cofactors of congenital malalignment of the great toenails have been proposed, and it is probable that similar aetiologies play a role in congenital malalignment of fingernails. Previous reports have suggested an inherited disorder, an acquired intrauterine malformation, digital ischaemia during embryonic development or possibly postnatal trauma. Congenital malalignment of the great toenails has been reported in identical twins and familial cases affecting the great toenails over three generations have been reported. Similar findings have been cited in cases of congenital onychodysplasia, but malalignment was not always evident. These reports suggest the possibility of an autosomal dominant mode of inheritance with variable penetrance.

The nail plate in most cases is deviated laterally with respect to the longitudinal axis of the distal phalanx, although medial deviations may occur. Rotation of the nail matrix in relation to the finger tip will result in malalignment, but does not always result in an abnormal nail plate. In cases of toenail malalignment, transverse ridging, thickening of the nail plate and onycholysis are frequently reported. Discoloration may occur secondary to haemorrhage or infection. The toenail is subject to recurrent trauma, a cofactor in causing these dystrophic changes. The fingernail is not subject to this degree of trauma, explaining the lack of concomitant nail malformation.

Spontaneous improvement has been reported in congenital malalignment of great toenails, sometimes with complete resolution. In all the cases reported this occurred before 10 years of age. There are no reports of this occurring with fingernails. As in any case of congenital malalignment, local complications such as painful inflammation of the lateral nail fold, ingrowing toenails or recurrent paronychia may occur. Treatment depends on the degree of malalignment and associated complications. Surgical realignment of the nail matrix before 2 years of age prevents the development of these complications if there is significant malalignment. Current opinion is to recommend conservative treatment unless complications develop. Recurrent episodes of acute paronychia such as in our patient often require surgical intervention ranging from partial nail matrix excision with phenol cauterization to total nail matrix ablation.

Acknowledgements

S.C.M. was supported as the Clinical Research Fellow in Dermatology at The Oxford Radcliffe Hospital by Novartis Australia, the Australasian College of Dermatologists and the Renwick Vickers Fund.
Effect of house dust mite avoidance measures in children with atopic dermatitis

Sir. Most studies of house dust mite (HDM) avoidance in atopic dermatitis (AD) have not measured HDM levels in the homes of subjects, a measure that greatly helps the interpretation of any changes that are detected in the severity of AD. Ricci et al.1 should be commended for doing this, and for following up subjects for a long period (1 year).

The study comprised two stages. For the first 2 months, the intervention group were encouraged to employ HDM avoidance measures and the control group were not. The authors describe the study as a placebo-controlled trial; however, there does not appear to have been a placebo. During the last 10 months, both groups used intervention measures to avoid HDM, and both groups showed reductions in the Severity Scoring of AD (SCORAD) index that were statistically significant at the 5% level. However, the mean age of subjects was only 3–9 years, and therefore spontaneous improvement would have been expected in many subjects. Therefore this part of the trial cannot fulfill the stated objective of the study, which is to verify if HDM avoidance measures can improve AD in children.

During the first 2 months, the mean SCORAD in the intervention group fell from 33 to 26 and in the control group from 27 to 24. The authors state that the fall in the intervention group is statistically significant at the 5% level but that in the control group is not, and conclude that the intervention is effective. However, the purpose of a controlled trial is to compare the change in the intervention group with the change in the control group and the authors have not done this. If they had, their conclusion may not have been supported. In view of the striking differences between groups at baseline, a comparison of SCORAD between groups after two months using baseline measures as a covariate, would also have been appropriate.

To encase mattresses and pillows, the study used ‘mite microfine fibres or the Goretex® bedding system’ but the authors do not state the proportion of subjects that used each. The experience of Tan et al.2 with the Goretex® bedding system was that it reduced the dust load by 98% within the first month to a mean value of 10 mg m\(^{-2}\). In comparison, Ricci et al.1 detected a fall in the intervention group of only 7% (from 214 mg m\(^{-2}\) to 199 mg m\(^{-2}\)), which was less than the fall in the control group (45%; from 371 mg m\(^{-2}\) to 204 mg m\(^{-2}\)). Their failure to reduce dust load in the intervention group may have occurred because they did not encase the duvet, blankets or top covers, unlike Tan et al.2 Furthermore, they may have used a type of microfine fibre cover that has relatively poor filtration efficacy.

One investigator sampled the dust in the beds of the intervention group and another investigator did this for the control group. The large differences in dust load at baseline between the intervention and control groups (214 and 371 mg m\(^{-2}\), respectively) suggests that the investigators were not collecting dust in a similar way, and perhaps also casts doubt on the reliability of subsequent measurements within each group.

On the basis of the study by Tan et al.2 we agree with the authors that the activity of AD can be greatly reduced by effective HDM avoidance.

References


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Effect of house dust mite avoidance measures in children with atopic dermatitis: reply from authors

Sir. We read with interest the letter of Palmer and Friedman. We believe that by providing further details of our study we may be able to clarify certain points including those raised in the letter. First of all the study was divided into two distinct parts and this fact may have led to some misunderstandings. In the first 2 months, and only in this part of the study, the aim was to observe the improvement of atopic dermatitis (AD) following house dust-mite (HDM) avoidance measures. We agree with Palmer and Friedman that this initial part of our study was not planned as a placebo-controlled trial as, unlike the study performed by Tan et al., our control group did not receive any placebo: they were simply instructed to continue to clean their homes as usual. In fact, the term placebo was not used in our paper. We would also like to stress that the main aim of our study was not to compare the SCORAD of the two groups, but rather to compare the relative improvement in the SCORAD index after 2 months, separately for each group (one group without any preventive measures and the other group with HDM avoidance measures). After 2 months the change in SCORAD improvement in the HDM avoidance group was 21% \((P = 0.022)\) while in the control group it was only 11% and this was the sole purpose of our study. While it is true that both of our groups showed a significant improvement after 10 months, how much of this could be attributed to spontaneous improvement is difficult to say. In any case, it is well known that \(\text{AD}\) shows a major improvement in the first 2 years of life, and this tendency then successively diminishes. It was for this reason that we made sure the average age of our study groups was above 2 years (3.9 years). Although the group studied by Tan et al. with preventive measures showed a great reduction in dust load within the first month (98%), it should be remembered that in addition to Goretext\textsuperscript{10} bedding system they also used benzyltammate complex spray on the carpets to obtain an acaricidal and denaturing effect. In our study a much lower reduction (8%) was observed in the first month, but in the second month the reduction was higher (54%); it could be speculated that this lower reduction may have been due to the lack of use of acaricides. We decided not to use any spray on account of possible noncompliance on part of the family, especially if such measures were to be proposed for long periods.

The control group had a bigger dust load concentration at the beginning, with a marked reduction after 1 month (this value was similar to the initial value of the intervention group) but no further reduction in the second month. Tan et al. also reported a notable reduction in the initial phase in the placebo group which did not change significantly after 2 months. With regards to the possible difference between investigators, both investigators used the same vacuum cleaner, and before the start of the study they had obtained similar results in preliminary tests; it is very unlikely that for such simple standardized methods, vacuuming an upper surface of mattresses for 2 min \( \text{m}^{-2} \), that the difference could be due to the differences in the pattern of dust collection by the investigators. The most important point was to observe the changes within each group and it was therefore vital that the same investigator should analyse the same group. Regarding the dust measurement, although various units are reported in our Table 1, the parameters recommended for evaluating dust concentration from either planar or nonplanar surfaces are best expressed as ‘per unit weight of collected dust’. Most data published in relation to specific threshold values for sensitization propose a threshold level of 2 \( \mu \text{g} \cdot \text{g}^{-1}\) of dust, or even lower, but are always expressed as per unit weight of collected dust. Therefore we think that this is the most suitable parameter to use when analysing dust concentration on mattresses, and in fact by referring to this parameter in our work we were able to observe a clear significant reduction in the intervention group in the first 2 months (from 1.84 to 0.73 \( \mu \text{g} \cdot \text{g}^{-1}\) dust) and not in the control group (from 2.04 to 1.40 \( \mu \text{g} \cdot \text{g}^{-1}\) dust). These data would therefore suggest that our HDM avoidance measures were efficient, even though two different forms of encasement were used. In any case the vast majority of our cases used the Goretext\textsuperscript{10} system and the two types of covering were used at the same percentage by the two groups in the second part of the study.

The aim of the second part of the study was to verify if, after one year, the HDM avoidance measures were still being observed on the basis of the persistently low values of \(\text{Der p} \ 1 + \text{Der f} \ 1\) mattress concentrations. The persistently low values at 12 months of \(\text{Der p} \ 1 + \text{Der f} \ 1\) (0.59 and 0.74 \( \mu \text{g} \cdot \text{g}^{-1}\) dust) confirm that the measures had in fact continued to be observed.

Environmental avoidance measures should be simple and efficacious, otherwise it is difficult to apply them for a long period.

Our work would therefore seem to indicate that environmental measures are able to improve AD in children. We hope that the questions raised by Dr Paltrier and Friedman have now been answered.

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Dermatology and the world wide web

Sir, The internet revolution continues to gather pace with over 10 000 new online subscribers in the U.K. every week. Doctors themselves have come to rely on the internet as an online library and valuable source of references. However, it is estimated that 30–40% of all internet use is by patients looking for medical information.¹ Many common skin disorders run a chronic course and this is associated with patient frustration at the lack of a perceived cure. Such patients naturally will seek opinions and advice from different sources and the internet offers a huge supply of potential information.

Dermatologists must therefore expect to be faced with increasing numbers of patients presenting to clinics armed with detailed information on their condition. This may have a significant impact on the nature of the doctor–patient consultation. It is possible that in addition to being the traditional providers of information to patients, dermatologists will increasingly become interpreters of information obtained elsewhere.

With these thoughts in mind we undertook a study to investigate how many patients currently attending our outpatient clinics are accessing the internet in order to gain information on their condition and if this leads to any desired change in their management.

Two hundred and fifty consecutive patients attending the dermatology outpatient clinic at Leeds General Infirmary between October and December 1999 were recruited (115 male, 135 female). Their ages ranged from 3 to 77 (median 33.5) years. Nine children were included. Patients or parents were asked the following questions during a short interview at the end of their consultation:

1. Do you have internet access?
2. Have you ever used your internet access to gain information on your skin condition?
3. Why did you carry out a search on your condition?
4. How long did you spend searching the internet on your condition?
5. How easy was it to find useful information on your condition from the internet?
6. Can you remember any specific internet sites visited?
7. Has any information you have gained from the internet caused you to seek a change in your treatment?
8. Would you ever believe information obtained from the internet in preference to that obtained from your GP or dermatologist?

Table 1 Details of the eight patients who sought information on the internet.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Duration of condition</th>
<th>Length of search</th>
<th>Change in management?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>Androgenetic alopecia</td>
<td>4 years</td>
<td>4 h</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>Acne</td>
<td>8 years</td>
<td>2 h</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Atopic eczema</td>
<td>2.5 years</td>
<td>3 h</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>Atopic eczema</td>
<td>Since childhood</td>
<td>Unknown</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>Atopic eczema</td>
<td>6 years</td>
<td>Unknown</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>DLE</td>
<td>7 years</td>
<td>2 h</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>Yellow–nail syndrome</td>
<td>Since childhood</td>
<td>1 h</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>Scalded skin syndrome</td>
<td>5 weeks previously</td>
<td>30 min</td>
<td>No</td>
</tr>
</tbody>
</table>

Seventy-eight per cent of the patients had chronic skin conditions with eczema and psoriasis accounting for 50% of the diagnoses. There were, however, 44 different diagnoses among the study group. Sixty-nine of the 250 patients had internet access (36%). Only eight patients (3%) reported having searched for their skin condition. Details of these patients are summarized in Table 1.

Only one of the eight patients was able to recall any specific site visited – the Eczema Society site. No patients stated they would believe information from the internet in preference to their dermatologist. All eight patients claimed to be satisfied with their care but had sought more information than had been available from the hospital consultation. All had difficulty in obtaining clear, understandable information from the internet and reported much of what they found to be confusing. Over one-third of the patients had access to the internet but only 3% had sought information about their condition. This was a surprisingly low number but is similar to the findings of a previous study of 56 psoriasis patients which revealed that no patients had sought information from the internet about their condition.²

Perhaps the small numbers using the internet in our study can be explained by patients denying their true level of usage for fear of embarrassing or upsetting their doctor. Although the questions were asked in an informal way this might have been more of a problem in our study than if an anonymous questionnaire asking the same questions had been used.

The internet has the potential to be as useful to patients as it is to doctors. There are already valuable sites for patient support groups.¹,⁴ However, one of the major problems is the lack of quality control on the information available. Anyone can publish on the internet ranging from world experts to enthusiastic amateurs! Internet sites may have some commercial interest in the treatment they are describing. In the
Most patients seeking information from the internet have a genuine desire to understand their disease and its treatment. It is natural for patients with a chronic disease to seek information on any new treatments. An analysis of patients requesting clinical advice from a German dermatological web site revealed patient frustration at the care they were receiving and concern they were not getting appropriate or the most up-to-date treatments. For better or worse, patients will be seeking medical information from the internet in increasingly large numbers and it seems desirable for dermatologists themselves to lead the way in providing clear, easily obtainable information via the world wide web.

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4 Ehlers–Danlos Syndrome http://www.edn.org

Nodular lichen simplex of the scrotum treated by surgical excision

Sir, Prurigo is a debilitating condition characterized by intractable local or generalized pruritus and is often but not always associated with the atopic state. This condition may affect any part of the body and is sometimes seen on the scrotum. We report two patients who were unresponsive to topical and systemic medical treatment but were subsequently successfully treated by careful surgical excision.

Patient 1. A 50-year-old man had a 1-year history of scrotal pruritus following a holiday in Goa. He was taking ramipril for hypertension but there was no other relevant medical or surgical history. Examination revealed a ‘cobblestone’ or ‘pineapple skin’ lichenification of his scrotum (Fig. 1a) extending from the medial raphe to the superior scrotal sac.

Figure 1. (a) ‘Pineapple skin’ or ‘cobblestone’ appearance of the scrotum (patient 1); (b) appearance of the scrotum before surgery (patient 2).
Differential diagnoses included schistosomiasis, verrucous carcinoma and cutaneous lymphoma. A biopsy showed features consistent with lichen simplex. Treatment with topical clobetasol propionate, intraleional triamcinolone and systemic doxepin, doxycycline, cetirizine and prednisolone 40 mg improved neither the symptoms nor the clinical appearance. He was referred to his local plastic surgery unit for excision of the scrotal plaque. Histological examination of the excised area showed hyperkeratosis, hypergranulosis, striking irregular acanthosis, dense dermal scarring and a perivascular lymphohistiocytic infiltrate with cosinophils but no epidermal dysplasia. Some of the follicular structures contained keratin and pus and were partially lined by acutely inflamed granulation tissue. These features were felt to be perpetuating the process. The patient remains symptom-free and without recurrence after 12 months.

Patient 2. A 54-year-old man was referred with intractable scrotal pruritus of 2 years duration. His medical history included type II diabetes mellitus that was poorly controlled with glitazide and metformin, hyperlipidaemia, carcinoma of the larynx treated with radiotherapy, gout and chronic pancreatitis secondary to alcohol excess. Other medications included colchicine for acute gout and non-steroidal anti-inflammatory drugs for cervical spine pain following a road traffic accident in 1960. He also had a history of angio-oedema following aspirin ingestion. Examination revealed a similar clinical picture to patient 1, with perifollicular inflammatory pustules and ‘pineapple skin’ lichenification of the scrotum (Fig. 1b). Differential diagnoses included nodular prurigo, amyloidosis and cutaneous lymphoma. Topical agents (clobetasone butyrate with oxtetracycline and nystatin, clobetasol propionate, doxepin hydrochloride and hydrocolloid dressings) and systemic measures (oral erythromycin, doxycycline, ciprofloxacin, prednisolone 40 mg, doxepin and cetirizine) were unsuccessful and the patient underwent plaque excision to good effect. The histology showed an acute and chronic folliculitis with mild patchy oedema following aspirin ingestion. Examination revealed a similar clinical picture to patient 1, with perifollicular inflammatory pustules and ‘pineapple skin’ lichenification of the scrotum (Fig. 1b). Differential diagnoses included nodular prurigo, amyloidosis and cutaneous lymphoma. Topical agents (clobetasone butyrate with oxtetracycline and nystatin, clobetasol propionate, doxepin hydrochloride and hydrocolloid dressings) and systemic measures (oral erythromycin, doxycycline, ciprofloxacin, prednisolone 40 mg, doxepin and cetirizine) were unsuccessful and the patient underwent plaque excision to good effect. The histology showed an acute and chronic folliculitis with mild patchy stromal fibrosis and similar appearances to those of patient 1. Remission has been maintained during the past 12 months.

Many dermatologists experience difficulties in treating the ‘neurodermatoses’ and the problems associated with trying to break the itch/scratch habit, particularly when genital skin is involved. Very potent topical steroids (including under occlusion), topical doxepin1 and capsaicin,2 occlusive bandaging (including tar paste medicated bandages), intraleosomal triamcinolone, oral thalidomide,3 steroids and sedating antihistamines all have their place but are difficult to adapt to scrotal disease. Furthermore, once a lichenified plaque is established, the inherent pathology may drive the disease process, rendering it more difficult to eradicate. It is believed that peptidergic neural proliferation occurs in lichen simplex chronicus and nodular prurigo which may potentiate the itch/scratch cycle,4 and hence excision may be curative. However, there has been a report of disease recurrence after surgical excision of a plaque of lichen simplex chronicus,5 which suggests that unknown and more profound factors are responsible for the affliction.

Our patients had intractable scrotal pruritus, disfigurement and great distress for which no effective treatment could be found. Surgical excision should be considered under certain clinical situations and when other treatments have failed, with the caveat that recurrence is possible.

References


Synergistic toxicity of 8-aminolaevulinic acid-induced protoporphyrin IX used for photodiagnosis and hypericin extract, a herbal antidepressant

Sir, Photodiagnosis (PD) and photodynamic therapy (PDT) are now diagnostically and therapeutic modalities for cancer. They are based on the selective accumulation of a fluorescent photosensitizer (PS) in neoplastic tissue. Upon exposure to visible light, the PS can (i) emit light (fluorescence), (ii) react with biomolecules producing radicals, or (iii) transfer its energy to triplet molecular oxygen, yielding singlet oxygen. In PD, fluorescence of the PS is used for tumour detection, whereas in PDT, photochemical reactions directly or indirectly destroy the tumour tissue.1

We describe a phototoxic reaction in a patient treated with 8-aminolaevulinic acid (ALA)-induced protoporphyrin IX (PpIX) for PD of breast tumours during a clinical trial. This patient was also found to have been taking Hypericum perforatum extract (Hypericin®), a popular over-the-counter antidepressant. The hypothesized, synergistic toxic effect of photodynamic therapy is the photosensitization and phototransduction of protoporphyrin IX (PpIX) to singlet oxygen, which is a very reactive oxidant, and photosensitization to the photosensitizer (PS) to singlet oxygen, which is a reactive oxidant.

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interaction between the two agents was confirmed by in vitro experiments.

In a clinical trial, ALA was given to 20 patients with palpable breast tumours. ALA itself is not a PS but a prodrug; when added to cells, it induces the formation of PpIX and haem. In some tumours, e.g. breast cancer, PpIX accumulates preferentially in the tumour cells due to enzymatic changes, resulting in higher fluorescence. We used PD intraoperatively to test the specificity of this method to detect tumour margins. Oral ALA 40 mg kg⁻¹ was given 3–6 h prior to surgery. Nineteen of the 20 participants did not report any significant adverse side-effects. However, in 15 patients we observed a perinasal, non-sensitized swelling 12 h after ALA administration, not previously described in the literature. Two patients developed a mild asymptomatic facial erythema. These findings disappeared spontaneously within 72 h following treatment. One patient, a 47-year-old woman, suffered from a pronounced phototoxic reaction 6 h after ALA administration, consisting of a burning erythematous rash and severe swelling of the face, neck and hands. Only light-exposed body parts were affected. The patient was treated with oral corticosteroids for 3 days and had a complete remission after skin desquamation within 10 days. She was dark haired, fairly tanned, and no previous photosensitivity reactions or allergies to known agents were reported. Further inquiries revealed the intake of Hyperiforce, a popular over-the-counter antidepressant which contains the PS hypericin. As the intake of Hyperiforce, a popular over-the-counter antidepressant, we should therefore be aware of their photosensitive effects, especially in combination with other PSSs, as PD and PDT become increasingly used.

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However, the combination of ALA-induced PpIX and hypericin considerably increased photosensitivity in our patient, and application of the two agents together caused decreased colony formation of HaCaT cells. Synergistic and antagonistic effects in combination with H. perforatum have been reported before. H. perforatum significantly enhanced radiosensitivity of glioblastoma cell lines, but caused stimulated growth of Staphylococcus aureus when combined with photofrin II or mesotetrahydroxyphenylchlorin.

Substances containing hypericin, e.g. Hyperiforce or St John’s Wort, are widely used among the general population as over-the-counter antidepressants. We should therefore be aware of their photosensitive effects, especially in combination with other PSSs, as PD and PDT become increasingly used.

References

Everybody’s free (to wear sunscreen): the power of pop

It is widely accepted that teenagers are a difficult group to influence with health education messages, and as discussed by Melia et al., there are few studies of this age group in the U.K. with respect to primary prevention initiatives for skin cancer. Two recent studies in teenagers used educational videos and literature, and showed that education resulted in increased awareness, a positive attitude to sun protection avoidance and increased sunscreen use when evaluated at 4 months after intervention. The pop single Everybody’s free (to wear sunscreen) by Baz Luhrman was in the U.K. charts for 4 weeks in June 1999, and at number one for 1 week. The recording was a parody of a speech to high-school students, offering advice on lifestyle. The opening and closing statements strongly extolled the use of sunscreen, an example being: ‘If I could offer you only one tip for the future, sunscreen would be it. The long-term benefits of sunscreen have been proved by scientists, whereas the rest of my advice has no basis more reliable than my own meandering experience’. To assess the influence of this novel form of health education on teenagers, 381 children aged 11–14 years (185 boys, 196 girls; mean age 13±1 years) were asked to complete a questionnaire during school sessions, 3 months after the song reached number 1. The response rate was 100%. A greater proportion of girls (93±3%) recalled hearing the recording in comparison with boys (68±1%) (95% confidence interval, CI 18±1–33±1; P < 0·001). The differences in regular sunscreen use between the groups who recalled hearing the song and those who did not were not significant. Overall, girls (72%) were more likely to be regular users of sunscreen than boys (43%) (95% CI 3·7–24·8; P < 0·01). As a result of hearing the recording, 42·4% of girls and 38·1% of boys stated that their attitude to sun protection had changed, and that they would be more likely to use sunscreen or use it more frequently as a result of listening to the track (not statistically significant).

Skin cancer is overall the most common malignancy in the U.K. population; studies suggest a continuing rise in incidence. Health education and the promotion of sensible lifestyles are important to reduce individual morbidity and mortality, yet teenagers can be a difficult age group to influence. Pop music accounts for the biggest share of singles sales in the U.K. (44% in 1999), and more individuals in the 12–14-year age group (56%), followed by the 15–19-year group (36%) will buy at least one of these records each year than at any other age. Thus singles are bought most by precisely the age group that is regarded as difficult to influence. Our brief study has confirmed that some teenagers have recognized a health education message from the format of a commercial recording. As a result of this a large minority of both sexes stated that their attitudes to sunscreen usage have changed. It is encouraging to show that teenagers are receptive to such positive health promotion; unfortunately, the significant cost involved in producing and promoting singles, particularly when there is no guarantee the record will be a hit, probably means that this is not a cost-effective method.

We fully appreciate there are a number of weaknesses in this study: actual change in use of sunscreen was not assessed, we did not follow up the children to assess if the changes in attitude were maintained over time, it is not certain that the stated change in attitude was due to the pop record (other health promotions, or simply filling in a questionnaire, might have contributed), and the numbers studied were relatively small. We also did not assess if there was any effect from the only other health-related advice contained in the song – the single directive to ‘floss’.

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Nasolabial follicular sebaceous casts: a novel complication of isotretinoin therapy

Sir. What Drs Agarwal and Charles-Holmes report as nasolabial follicular sebaceous casts: a novel complication of isotretinoin therapy is in our view not new, but is connected with an early observation of isotretinoin effects on acne patients, reported by many authors.

In our book on acne we wrote: ‘Follicular filaments (follicular casts) and microcomedones are likewise eliminated. It is not unusual to observe finger-like protrusions of oil soaked casts from prominent facial pores’. The histopathology and ultrastructure of these sebaceous filaments was also described.

The sebaceous filaments or sebaceous casts are convincingly shown clinically in Figure a and histologically in Figure c of their paper. Figure b shows an artefact on top of the sebaceous filament, namely a part of a sebaceous gland. This is not infrequently seen in facial biopsies and is explained by the pressure exerted by local anaesthesia or the mechanical force used in obtaining the biopsy. So-called ‘floaters’ are also sometimes seen in this pattern.

Anatomically, sebaceous glands and clusters of sebocytes are never present in follicular filaments but only located within the sebaceous lobules. The best way to study the effects of isotretinoin on sebocyte differentiation is by electron microscopy.

Therefore we do not feel that what has been reported is a novel effect, and especially not a complication, of isotretinoin therapy.

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References

Isotretinoin use and reports of sustained dreaming

Sir. The psychotropic effect of isotretinoin has received a significant amount of attention in the dermatological literature, because in isolated instances isotretinoin has been associated with clinically important psychiatric reactions such as acute depression and suicide. Large-scale epidemiological studies utilizing health databases, however, report no evidence of increased risk for depression, suicide or other psychiatric disorders in acne patients using isotretinoin as opposed to antibiotics. It appears therefore that the psychiatric reactions associated with isotretinoin are sporadic and possibly idiosyncratic, and are therefore difficult to predict. Furthermore, the literature on the possible relation between isotretinoin and psychiatric symptoms is confounded by the fact that the impact of acne upon the quality of life can lead to significant psychological morbidity including depression and suicidal ideation. We report two patients who reported a definite change in their dream patterns 2–3 weeks after starting treatment with isotretinoin. The patients did not have a history of medical or psychiatric problems, and were on no other medications. There was no history of alcohol or other substance abuse. This may provide us with some clues about the possible central nervous system (CNS) effects of isotretinoin in the adult brain.

Patient 1. A 21-year-old university student was started on isotretinoin 40 mg daily for the treatment of cystic acne mainly affecting the face. He lived with a room-mate in university housing. He reported no history of significant medical or psychiatric problems and was on no other medications. After 2 weeks of therapy with isotretinoin he reported some increased irritability, and periods lasting 2–3 days when he experienced a depressed mood and cried easily. He did not describe any other major psychiatric symptoms, there was no suicidal ideation and the mood-related symptoms did not meet the criteria for a full major depressive episode or other psychiatric pathology. He reported that he...
had noticed a definite change in his dreaming patterns; he usually very rarely remembered his dreams, but 2 weeks after starting isotretinoin he started remembering long and coherent dreams that were 'like a continuation of what was going on during the day'. The dreams were not vivid or bizarre, but involved events that were directly related to what he had been doing during the day. For example, they involved extensive conversations with his room-mate that were essentially a continuation of the conversations he had had with him during the previous day. He reported dreams about mundane daily activities such as preparing meals, getting dressed and going to classes. While he had usually slept soundly before starting isotretinoin, he reported that his sleep had become more interrupted. He would wake up briefly and go back to sleep and 'go back to the same dream'. Upon waking in the morning he reported feeling unrested, with a feeling that he had been 'dreaming all night'. This pattern of dreaming continued for about 4 weeks. No change was made in the dosage of isotretinoin and he was followed closely and advised to call if he experienced any change in his emotional state. After 4 weeks his emotional symptoms and sustained dreaming patterns both subsided. He completed the full 6-month course of isotretinoin and experienced a significant improvement in his acne.

Patient 2. An 18-year-old university student was started on isotretinoin 40 mg daily for the treatment of cystic acne affecting his face and back. He reported increased self-consciousness in social situations as a result of his acne, but no other significant psychological symptoms. About 3 weeks after initiation of isotretinoin therapy he reported remembering dreams that had a 'soap opera-like script', wherein he recalled dreaming about a series of related events that would typically involve individuals with whom he was acquainted. He reported that he had never experienced such dreams before starting isotretinoin and typically did not remember his dreams prior to starting isotretinoin; he found the dreams to be quite entertaining and 'looked forward to going to bed so that he could continue to watch his dream'. The dreams persisted for about 5 weeks after which they subsided. The patient was followed regularly and was asked to report any psychiatric symptoms. No other symptoms were reported. He continued a 6-month course of isotretinoin 40 mg daily, and experienced a significant improvement in his acne.

Both patients reported recalling long dreams with a story-like script that was first noted 2–3 weeks after the initiation of isotretinoin. Both patients described the dreams as distinctly different from their usual dreaming experience. Both patients reported feeling that they were 'dreaming all night'. There is an over 85% concordance between the subjective experience of dreaming and rapid eye movement (REM) sleep. Neuroanatomically, REM sleep involves the pons, lateral geniculate body and the visual cortex. Increased cholinergic activity in the CNS, and the modulation of noradrenergic and serotonergic activity in the CNS, are associated with increased REM sleep. The patient histories suggest that the CNS adapts to the possible psychotropic effect of isotretinoin that results in the change in dreaming patterns. Changes in REM sleep are also a robust feature of serious psychiatric disorders such as major depressive disorder. A further evaluation of the possible relation between isotretinoin and increased REM sleep, e.g. with overnight polysomnography, may provide further insights into the neurophysiology of the psychotropic effect of isotretinoin.

References


Amlodipine-associated lichen planus

Sir. We report the case of a 56-year-old woman of Nigerian origin who presented to our department with an 8-week history of a widespread intensely pruritic lichen eruption. She had commenced amlodipine (Istin® [Pfizer]) 5 mg daily for hypertension 2 weeks before the onset of the rash. There was a previous history of sickle cell trait, osteoarthritis, and non-insulin-dependent diabetes mellitus. She had been taking metformin 850 mg daily for the previous 2 years.

At presentation there was a widespread violaceous eruption consisting of plaques and pigmented macules over the limbs, anterior and posterior trunk (Fig. 1). Plaques were notably present on the medial aspects of the wrists, and Wickham’s striae were seen in the oral cavity. Oral and genital ulceration were absent, and the nails were unaffected. Histological examination confirmed our clinical diagnosis of lichen planus, showing an upper dermal infiltrate composed of lymphocytes, saw-toothing of the dermo–epidermal
junction and basal layer degeneration. Eosinophils and colloid bodies were present, consistent with a drug-related aetiology.

Amlodipine was discontinued, and in addition she was treated with oral acitretin 30 mg daily for 5 weeks together with potent topical corticosteroids, oral antihistamines and emollients. There was rapid symptomatic and clinical improvement although marked residual postinflammatory hyperpigmentation remains.

The triad of oral lichen planus, hypertension and diabetes mellitus has been described before and is known as Grinspan’s syndrome. However, a causal association remains uncertain as drug treatment for both diabetes and hypertension can cause lichen planus. Lichen planus has been linked to a variety of other drugs, most commonly beta blockers, methyl dopa, penicillamine, quinidine, quinine and non-steroidal anti-inflammatory agents.

In our case, the temporal relationship between starting amlodipine and the onset and offset of the eruption implicates amlodipine, a second-generation calcium-channel blocker used commonly in the treatment of mild to moderate hypertension and angina. The Medicines Control Agency lists 2488 reported reactions to amlodipine since 1989 of which 542 are cutaneous reactions, including pruritus (63 reports), erythematous rash (41 reports), facial oedema (41 reports) ecchymoses and purpura (38 reports) and urticaria (29 reports). One hundred and three are listed as ‘rash not otherwise specified’. Four reactions are listed as lichen planus but this has not been formally reported in the literature to date.

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References
News and Notices

Twentieth World Congress of Dermatology
1–5 July 2002, Palais des Congrès de Paris, France

For further information, please contact: P. Fournier, Congress Secretariat, Colloquium, 12, rue de la Croix St Faubin, 75011 Paris, France. Tel: + 33 1 44 64 15 15; fax: + 33 1 44 64 15 6; e-mail: p.fournier@colloquium.fr; website: www.derm-wcd-2002.com

Announcements

Maison G de Navarre Essay Prize

The IFSCC is pleased to announce the opening of the competition for the Maison G de Navarre Essay Prize. This prize is granted each year to enable a young cosmetic scientist to attend either a Congress or Conference of the IFSCC. This year’s award winner will be invited to attend the WSCC Conference to be held in Taipei, Taiwan in September 2001 with the cost of travel, accommodation and registration fees up to, but not exceeding, 5000 Swiss francs, being paid by the WSCC. Any Class A member of a member society of the IFSCC, normally under 35 years of age, and with less than 5 years’ experience in the cosmetic industry or related academia is eligible. Applicants shall submit an essay of no less than 500 words on one of the following topics: a) The Future Trend of Cosmetics and Cosmetic Science; b) Cosmetics and Quality of Life; c) Cosmetic Science as Interdisciplinary Science; d) The role of IFSCC in the New Century; or e) Cosmetics as Preventive Medicine.

The essays must be accompanied by the official application form, copies of which are available from the local Societies. The essay must be typed in English and four copies, together with the application form should be sent to: Office of the IFSCC Secretariat, GT House, 24/26 Rothesay Road, Luton, Beds LU 1 1 QX, U.K., by no later than 1 June 2001. A copy of the essay must also be sent to the office of the member society. Applicants must be members of good standing in their Society, which in turn must be current in its Federation subscription. Applicants must submit proof that they are actively employed in a technical capacity in the Cosmetic Industry or related Academia and that they meet the requirements for age and experience. The award winner must attend the Conference and accept the award in person. All eligible candidates are urged to apply.

British Skin Foundation 2001 Awards: Call for Grant Applications

The Trustees of the British Skin Foundation wish to announce that funding is again available for skin disease research. This year there are four categories of award as listed below. Applicants are asked to apply for funding from the category that they feel is most appropriate. The closing date is 17th September 2001.

BSF Research Awards: One- or 2-year project grants of up to £50,000 per annum.

The BSF Fellowship: A grant of £40,000 to support a specialist registrar in dermatology through one year of research. Candidates should submit details of their proposed research and a C.V. in the manner described below. Selection will be by interview in late 2001. It is envisaged that the successful candidate will already hold an NTN or will have just completed their training.

BSF Small Grant Awards: One-off payments of up to £10,000. May be used to purchase equipment or for less costly projects.

BSF Studentship: A 3-year package, value £44,000, covering tuition fees, expenses and some consumables.

If you wish to receive an application form for a British Skin Foundation grant, please contact the office, specifying the type of grant you are interested in at: British Skin Foundation, 19 Fitzroy Square, London W1 6EH, U.K. Tel: 20 7383 0266; fax: 7388 5263.

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