



Fig 1. A high-power view of a calcified subcutaneous nodule. This demonstrates fat necrosis with calcification of cell wall remnants, as shown by bright basophilic material surrounding the remains of the adipocyte fat vacuoles (haematoxylin and eosin; original magnification $\times 400$).

localized erythema. These local reactions were transient and were not associated with persistent nodules or with calcification.³ The depth of injection of interferon appears to influence the incidence of local cutaneous reactions and consequently a longer needle has been supplied with the commercial preparation for injection.⁴

The patient described herein developed calcified necrotic subcutaneous nodules 3 years after commencing interferon beta-1a therapy and these remain palpable after 18 months. In the absence of an alternative explanation, we assume that these are a side-effect of treatment and propose that the localization on the lower abdomen reflects the preferred site of injection. Throughout therapy these lesions were asymptomatic and, in view of the previous satisfactory clinical response, subcutaneous interferon beta-1a treatment was recommenced after completion of breastfeeding as it was considered that the benefits of treatment outweighed the risk of developing further nodules. The site of injection is now rotated without preference and although transient erythema occurs at each site there are no further cutaneous adverse effects. To our knowledge this is the first report of calcified nodules as a long-term complication of subcutaneous interferon beta-1a injections.

Departments of Dermatology,
*Neurology and †Pathology,
University Hospitals of Leicester,
Leicester LE1 5WW, U.K.
E-mail: abbymacbeth@hotmail.co.uk

A.E. MACBETH
B.R. KENDALL*
A. SMITH*
G. SALDANHA†
K.E. HARMAN

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Remission of photosensitivity following treatment of psoriasis vulgaris with tumour necrosis factor inhibitors

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SIR, Psoriasis is known to be associated with several environmental triggering factors.¹ On the other hand, some external stimuli are usually beneficial, such as exposure to ultraviolet (UV) radiation.¹ Nevertheless, a subset of patients shows worsening of pre-existing psoriatic lesions and/or onset of psoriasis following exposure to UV radiation, defining a so-called 'photosensitive psoriasis'.² Tumour necrosis factor (TNF)- α has recently been shown to play a central role in the pathophysiology of psoriasis.³ Accordingly, several TNF-blocking agents have recently been developed, with substantial efficacy in psoriasis.⁴ We report the efficacy of TNF inhibitors in a patient with photosensitive psoriasis.

A 42-year-old woman was referred for a severe photosensitive psoriasis (Fig. 1). She had had psoriasis vulgaris since she was 10 years old, and reported a worsening of her skin condition following exposure to UV radiation since the age of 30 years, with onset during psoralen plus UVA therapy. The



Fig 1. Psoriasis inflammatory lesions predominantly involving photoexposed areas.



Fig 2. Small plaque lesions of psoriasis involving the polychromatic ultraviolet (UV) phototesting area (right side of the back), and the area irradiated for determination of minimal erythema dose (left side), 3 weeks after UV irradiation.

patient then received several systemic treatments, which did not lead to any significant clinical benefit. Photobiological testing (Dermolum IIIk[®]; Müller, Moosinning, Germany and Uvasun[®]; Mutzhas, Munich, Germany) was performed, and revealed an important lowering of minimal erythema dose (MED) down to 1500 mJ cm^{-2} (normal lower value = 2500 mJ cm^{-2}). Ninety-six hours after the last exposure, an iterative polychromatic phototest (irradiation on the back with 2 MED for three consecutive days) was negative, but an iterative UVA phototest (irradiation with 10 J cm^{-2} for three consecutive days) showed a positive reaction with a papulovesicular eruption. Altogether, results from these tests were consistent with the diagnosis of polymorphous light eruption (PLE). Three weeks later, psoriatic lesions occurred exclusively on skin areas exposed to polychromatic UV radiation and to UVA during the last phototesting (Fig. 2). Histological analysis of a skin biopsy performed on these latter lesions showed typical features of psoriasis. Serological tests for antinuclear antibodies and immunofluorescence of a skin biopsy were negative. The diagnosis of photosensitive plaque-type psoriasis was established. Because of the lack of efficacy of classical systemic treatments, infliximab was started in May 2004 (5 mg kg^{-1} on weeks 0, 2 and 6, and then every 8 weeks). Clinical improvement was rapidly observed, and no additional skin flare was observed during the following summer period [initial Psoriasis Area and Severity Index (PASI) score 7.2; week 20 PASI score 2.4; week 28 PASI score 0.3]. Photobiological investigations performed again in September 2004 did not show any abnormal reaction, consistent with healing of the photosensitivity. After a 1-year treatment with infliximab, psoriasis skin lesions relapsed on the forearms in May 2005. At that time, phototests showed a lowering of MED to 1900 mJ cm^{-2} . Iterative polychromatic and UVA phototests were negative after 96 h, but a psoriatic eruption occurred on the UVA phototest area 3 weeks later, consistent with a relapse of photosensitivity. Infliximab was replaced by etanercept, leading to clinical remission, as the patient was evaluated as cleared after 3 months of treatment.

The prevalence of photosensitive psoriasis has been estimated to range from 5.5% to 24% in patients with psoriasis, and may be observed in the context of different clinical subtypes.^{1,2,5-7} Inherited photosensitivity is frequently noted and a history of PLE has been reported in nearly half of patients with photosensitive psoriasis, suggesting that, in this case, psoriasis might be related to a Koebner phenomenon secondary to PLE lesions.⁷ So far, the pathogenesis of photosensitive psoriasis has been poorly investigated. Results of phototesting give different results regarding whether or not PLE is associated with photosensitive psoriasis. In all cases analysed, the UVA irradiation threshold was found to be normal, and a lowered erythema threshold has been inconsistently reported for UVB.^{8,9} Provocation tests with high doses of UVA or UVB (up to 75 J cm^{-2} or 3 and 5 multiples of the MED, respectively) may provoke new psoriasis lesions in some patients.⁹ Interestingly, PLE followed by psoriasis is provoked more easily with UVA, while photosensitive psoriasis with no preceding PLE is easier to provoke with UVB than with UVA.⁹

The contribution of TNF to photosensitive skin disorders remains unknown. As a role for TNF has been advocated in the pathogenesis of lupus erythematosus (LE), and as recent studies suggest that LE and PLE share similar physiopathological mechanisms,¹⁰ it is tempting to speculate that TNF might contribute to the pathogenesis of other photosensitive skin diseases. In our case, the recovery of tolerance to UV following infliximab treatment supports a major role for TNF in the pathogenesis of photosensitive psoriasis. Furthermore, the observation of a relapse of both psoriasis and photosensitivity under infliximab treatment is in accordance with previous publications reporting a secondary failure of this latter agent, usually related to the development of neutralizing anti-infliximab antibodies in treated patients.⁴ Although we did not provide evidence of positive detection of these antibodies, the efficacy of etanercept is in accordance with this latter hypothesis.

Our case argues for a key contribution of TNF to the pathogenesis of photosensitive psoriasis. However, additional clinical and biological studies are needed in larger series of patients, in order to confirm this hypothesis.

Department of Dermatology 1,
Hôpital Saint-Louis, AP-HP,
Université Paris 7, 1 avenue Claude-Vellefaux,
75475 Paris cedex 10, France
Correspondence: Hervé Bachelez.
E-mail: herve.bachelez@sls.aphp.fr

M. VIGUIER
M. JEANMOUGIN
E. BEGON
O. VEROLA
L. DUBERTRET
H. BACHELEZ

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Recalcitrant lithium-induced psoriasis in a suicidal patient alleviated by tumour necrosis factor- α inhibition

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SIR, A 45-year-old white-skinned man who concomitantly had severe plaque psoriasis¹ [Psoriasis Area and Severity Index (PASI) score of 52.7; Fig. 1a,b] and a critical bipolar affective disorder² (a huge abdominal scar as a conspicuous remnant of a serious attempt at suicide is depicted in Fig. 1) was admitted to our department.

The patient was first diagnosed with bipolar affective disorder in 2003 after a suicide attempt. Medical history revealed alcohol abuse until 2003; since then, the patient was clean. He was then treated as an inpatient in a psychiatric clinic for more than 12 months. His history of a serious attempt at suicide 2 years previously prompted systemic therapy with mirtazapine, olanzapine and lithium. Lithium, as a first-line mood-stabilizing agent in affective disorders, is approved particularly in patients with a history of suicide attempts.^{3,4} However, this treatment was associated with massive exacerbation of psoriasis which was initially controlled by systemic acitretin (Neotigason[®]) up to 1 mg kg⁻¹. Unfortunately, the patient rapidly developed a dramatic increase of liver enzymes under this therapy. γ -Glutamyltransferase was elevated from 407 U L⁻¹ before therapy to 658 U L⁻¹ (normal 0–66 U L⁻¹), and alanine aminotransferase increased from normal values before therapy to 106 U L⁻¹ (normal < 50 U L⁻¹) under acitretin treatment, necessitating reduction and finally withdrawal of the retinoid which resulted in a rapid and severe rebound of psoriasis. Given the patient's severely

impaired hepatic function, other systemic therapies potentially impacting on liver function, such as methotrexate, fumaric acid esters or ciclosporin, were also precluded. Ultraviolet (UV) therapy was not possible due to the UV-sensitizing effect of olanzapine. Several topical treatment options were tried, including topical corticosteroids, vitamin D₃ derivatives and dithranol, all with very limited success.

Thus, after infectious diseases including tuberculosis were excluded, we initiated a systemic therapy with etanercept (Enbrel[®]) 50 mg subcutaneously twice weekly. Etanercept is a fusion protein that inhibits the effects of endogenous tumour necrosis factor (TNF)- α via competitive inhibition. Emollients containing up to 5% urea were the only topical treatment. Clinical and laboratory examinations (including liver enzymes, renal parameters, C-reactive protein, differential blood count, lactate dehydrogenase and serum electrolytes) were performed prior to initiating the therapy, and at weeks 3, 6, 9 and 12 of therapy. At each visit, the patient's PASI score was determined. The PASI score (which was 52.7 prior to therapy; Fig. 1a,b), was 24.0 after 9 weeks (decrease of 54.5%; Fig. 1c,d) and 9.1 after 12 weeks (decrease of 82.7%; Fig. 1e,f), indicating a dramatic and almost complete clearance of psoriasis lesions. In more than 2 years, this was the first time this patient experienced such good condition. No undesired side-effects of the treatment have been detected thus far, and the patient's mood improved markedly even though the specific antidepressant medication was not changed. At present, the patient has received 12 weeks of treatment with etanercept 50 mg twice weekly. Our plan is to continue the therapy with etanercept 25 mg twice weekly for another 12 weeks.

This is the first reported case in which severe recalcitrant psoriasis in a suicidal patient, whose continued medication with lithium was vital, was dramatically alleviated through inhibition of TNF- α [three TNF- α -blocking compounds are currently approved for treatment of psoriasis and/or psoriatic arthritis: etanercept (Enbrel[®]), infliximab (Remicade[®]) and adalimumab (Humira[®])] after several other treatments had failed. A well-known side-effect of systemic lithium therapy is the exacerbation of psoriasis, one of the most common chronic inflammatory skin disorders.¹ In turn, the drug-induced worsening of psoriasis can be severely distressing to the patients, thus augmenting a vicious circle. Such patients may develop severe and recalcitrant forms of psoriasis and, therefore, represent considerable therapeutic challenges.⁵ Although efforts to discontinue the triggering compound should be made in such cases, this route of action is sometimes not possible due to the vital necessity for the drug in question. This problem is vividly exemplified in the case presented here, where lithium, the only medication for which the evidence consistently shows an antisuicidal effect,^{3,4} was necessary in order to prevent depression-driven suicide. Although TNF- α -mediated immune reactions are presumably upregulated in lithium-triggered psoriasis,¹ other, TNF- α -independent pathways of inflammation may also contribute to the pathogenic cascade in such cases.⁶ TNF- α has been found to be elevated