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### **Bullous Pemphigoid Occurring during Efalizumab Treatment for Psoriasis: A Paradoxical Auto-Immune Reaction?**

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#### *Key Words*

Bullous pemphigoid · Psoriasis · Efalizumab

Efalizumab, a humanized anti-CD11a monoclonal antibody, has recently been introduced in the treatment of moderate-to-severe plaque psoriasis. Auto-immune manifestations occurring during treatment have been rarely reported, affecting mainly haematological cell lines with thrombocytopenia being the most significant consequence [1], few observations of auto-immune anaemia [2] or pancytopenia [3] along with an isolated case of lupus-like syndrome [4]. We report on the first observation of an auto-immune cutaneous bullous disease developing in a patient treated with efalizumab that further raises the question of its ability to elicit auto-immune side effects.

An 82-year-old diabetic patient with a 40-year history of psoriasis had been treated for 6 weeks with efalizumab when he was first referred for evaluation of extensive bullous lesions. Five weeks after the beginning of this treatment, large, tense and serum-filled blisters rapidly developed on his limbs with a peculiar involvement of the palms and soles and later on his trunk, associated with an increasingly intense pruritus and inflammatory plaques disseminated all over his body surface. Blisters and urticaria-like inflammatory lesions were not particularly localized on psoriasis plaques. Mucous membranes were not affected. No other medication had been introduced in the past 3 months, and the patient denied the presence of any skin symptom reminiscent of auto-immune bullous disease prior to efalizumab introduction like unusual pruritus or inflammatory plaques. Physical examination was otherwise unremarkable, and his general status was good. Standard blood tests displayed only marked hypereosinophilia of unknown duration due to lack of previous biological investigation. Morphological investigations were normal. Histological, immunohistological and serological studies led to a diagnosis of typical bullous pemphigoid (BP) with subepidermal blistering, an eosinophil-rich inflammatory infiltrate of the upper dermis, C3 and IgG deposit in the basal membrane zone and anti-BP230 along with anti-BP180 circulating antibodies upon

ELISA test (titer: 99 and 112 units, respectively). A side effect of efalizumab was suspected, and this medication was discontinued. The search for other auto-immune complications proved negative with absence of antinuclear antibodies, rheumatoid factor, other haematological disturbances and a negative Coombs' test. The patient was initially treated with highly potent topical steroids (clobetasol dipropionate 40 g/day) with a poor clinical result on BP lesions and subsequently with systemic steroids with a significant improvement. Steroids were then rapidly tapered and eventually discontinued after 3 weeks, and methotrexate was introduced with an initial dosage of 12.5 mg/week. Psoriasis did not worsen after efalizumab discontinuation, even during systemic steroid treatment.

Auto-immune phenomena represent serious, although infrequent, side effects of efalizumab therapy whereas unusual skin adverse effects have recently been reported [5, 6]. The main targets are the haematological cell lines and more specifically the platelets since immune-mediated thrombocytopenia has been observed in 0.3% of patients [1]. However, other lineages can be affected and auto-immune hemolytic anemia [1, 2] or pancytopenia [3] have also been reported in 5 and 1 patients respectively during efalizumab treatment, whereas direct toxicity was probably the primary mechanism in another case of pancytopenia [7]. A lupus-like syndrome was finally observed in a patient with hepatitis, polyarthralgia, asthenia, pericarditis and presence of circulating antinuclear antibodies, with rapid resolution after discontinuation of the drug [4]. In all those cases, adverse effects appeared between 4 weeks and 6 months of treatment. The occurrence of auto-immunity during an immunomodulating therapy blocking T-cell activation is paradoxical and might be related to the disruption of immune balance rather than a specific drug-induced pathway requiring a simultaneous binding of the drug to the target molecule. It is of interest to underscore that such paradoxical phenomena have already been reported with other biotherapies of psoriasis, the TNF- $\alpha$  blockers that can both treat and induce lupus syndrome and psoriasis.

The coexistence of psoriasis vulgaris and auto-immune bullous diseases has already been described in the literature mainly with BP, and about 40 cases of BP have been reported in patients with psoriasis [8]. Moreover, the prevalence of psoriasis in patients with BP seems significantly higher than expected. However, this association remains relatively rare when compared to the frequency of both affections, and the pathogenic relationship between psoriasis and BP is unclear. It has been postulated that the auto-immune process responsible for BP lesions may be induced by ultraviolet light therapy or topical corticosteroids; the inflammation that occurs in psoriasis may also result in changes in the basement membrane zone possibly triggering the development of an auto-reactive antibody response.

In our patient, BP appeared after an interval of time comparable with the delay observed in other efalizumab-induced auto-

immune side effects. Although a merely coincidental idiopathic auto-immune bullous disease remains a possibility owing to the age of the patient, the timing of events is consistent with either a drug-mediated (efalizumab) auto-immune bullous disease, perhaps favoured by the inflammation created by the underlying psoriasis, or with the unmasking of a prebullous BP already present but inconspicuous at the time efalizumab was introduced even though no clinical or biological clue actually supports this latter hypothesis. Conversely, a direct drug effect is very unlikely since CD11a is not expressed on epithelial cells. Accordingly, a close monitoring of skin condition remains highly advisable in patients receiving biotherapies for psoriasis including efalizumab, and further observation of auto-immune bullous diseases in this setting may provide additional information regarding this hypothesis.

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