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CASE REPORT

INFLIXIMAB IN RECALCITRANT SEVERE ATOPIC ECZEMA ASSOCIATED WITH CONTACT ALLERGY

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Infliximab is an anti-tumour necrosis factor (TNF)-alpha chimeric monoclonal antibody which is effective in diseases associated with a T-helper (Th) 1 response, such as rheumatoid arthritis, Crohn's disease and psoriasis. There are sporadic case reports of atopic dermatitis (AD) induced or precipitated by anti-TNF-alpha therapy, which have been attributed to the switch towards Th2-mediated reactions. We report the case of a 30-year-old man with long-standing severe AD associated with contact allergy and poorly responding to conventional treatments. The use of infliximab resulted in a dramatic amelioration of AD lesions and pruritus, persisting at follow-up examinations over a 3-year period. Probably, the unexpected response to infliximab therapy in this case might be due to some peculiar features of AD in our patient (i.e. chronic-continuous course and concomitant contact allergy) which could have been responsible for a more preponderant recruitment of Th1 cells as compared to "common" forms of AD.

Infliximab is an anti-tumour necrosis factor (TNF)-alpha chimeric monoclonal antibody which is effective in diseases associated with a T-helper (Th) 1 response, such as rheumatoid arthritis, Crohn's disease and psoriasis (1-5). There are sporadic case reports of immune-mediated cutaneous eruptions induced or precipitated by anti-TNF-alpha therapy, including atopic dermatitis (AD) (6-8). Unaware of the possible risk of aggravating AD with anti-TNF- alpha therapy, in January 2003, we used infliximab in a case of severe recalcitrant AD associated with contact allergy.

MATERIALS AND METHODS

A 30-year-old man presented with a 22-year history of AD, which had notably worsened in the last 4 years, being characterized by a continuous course, long-lasting widespread lesions and incoercible pruritus, refractory to topical steroids and H1-receptor antagonists. The patient also experienced two episodes of erythrodermia associated with generalized lymphadenopathy. The deterioration of AD included pronounced impact on quality of life and mood disorders so that after two years the patient received treatment with paroxetine and benzodiazepines. He also presented a concomitant contact sensitisation to nickel sulphate and potassium bichromate but prevention did not cause any substantial benefit on skin manifestations and symptoms. On two separate occasions over the last three years, histopathological analysis of skin samples taken from lesional skin showed the typical findings of an eczematous dermatitis.

Systemic corticosteroids and cyclosporin gave only partial temporary relief of AD and had to be discontinued after a few months because of side effects, whereas leukotriene antagonists and high-dose immunoglobulins did not show any effects. Treatment with 0.1% tacrolimus

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ointment caused a sustained improvement of facial lesions, but an unsatisfactory control of pruritus and only a slight/moderate patient's self-perceived effect on AD located on other sites because body lesions were diffuse and continuously relapsing. For this reason, the patient discontinued tacrolimus ointment after 6 months. Then, immediately prior to the admission to our unit, the patient was treated with topical mometasone furoate and cetirizine.

Relevant medical history also included childhood asthma and rhinitis, and persistent hyperimmunoglobulinemia E (>5,000 kU L^{-1}). Hyper-IgE syndrome was excluded on the basis of the absence of other typical manifestations (facial or skeletal abnormalities, and relapsing infections) (9). Diagnosis of AD was confirmed according to Hanifin and Rajka criteria (10). On clinical examination, AD was characterized by diffuse confluent lesions on the trunk and limbs. SCORAD index (11), used to assess the extent and intensity of AD lesions and the severity of symptoms, had a value of 74. Histological examination of a biopsy specimen disclosed the features of AD in chronic phase, with sparse microvesicular spongiotic aspects and prominent psoriasiform changes. After obtaining a written informed consent, the patient was treated with infliximab.

RESULTS

Infliximab 3 mg/kg was given intravenously, and, within a few hours, the patient noted a marked relief of pruritus. During the post-infusion period, the symptomatic therapy already used by the patient was continued as needed. After a week, AD showed a slight improvement (SCORAD: 58) which became progressively more evident (SCORAD at 4 weeks: 21.3). At 6 weeks, because of pruritus exacerbation, a second infusion of infliximab was administered at the dose of 5 mg/kg and a rapid antipruriginous effect was again obtained. AD notably improved in the subsequent 4 weeks, with a SCORAD value of 13.6. Treatment with mometasone and cetirizine was gradually tapered and completely stopped within 3 months, as was psychotherapy. Since then, regular follow-up evaluations have shown a stable improvement of AD and itch (maximum value of SCORAD 25), with symptom-free periods during summer months and successful control of flares with tacrolimus ointment. An indirect measure of AD improvement is also provided by the consumption of tacrolimus tubes, the number of which had an approximately 3- to 4-fold reduction as compared with the number previously used. Moreover, in the follow-up evaluations, topical tacrolimus was applied on sparse and limited areas, especially on trunk, face, neck, antecubital and popliteal folds. No adverse events possibly related to infliximab were observed.

DISCUSSION

TNF-alpha is a multifunctional cytokine that regulates not only immune response and inflammation, but also tissue remodeling, keratinocyte motility, cell cycle and apoptosis, as well as basement membrane components and matrix metalloproteases (12-13). Some evidence has suggested the relationship between TNF-alpha-308*2 polymorphism, which is associated with the increased secretion and activity of TNF-alpha, and the risk of developing asthma or atopy but there are still controversial data on this topic (14). Increased secretion of TNF-alpha has been detected in the respiratory tract of atopic asthmatics (15-16).

The role of TNF-alpha in AD is still unknown, although it has been implicated in the expression of adhesion molecules on both endothelia and keratinocytes in this disease (17-18). Determination of TNF-alpha plasma levels and production by mononuclear cells in AD patients gave controversial results (19-22). It should also be mentioned that CD30, which is a marker of Th2 cell activation and whose soluble form is significantly elevated in AD, belongs to the TNF-receptor family (23). Recently, it has been found that TNF-alpha is the main inducer of inducible protein-10, belonging to the CXC chemokine subfamily, by skin fibroblasts from patients with atopic dermatitis (24).

To our knowledge, the present case represents the first report of AD successfully treated with infliximab. On the contrary, there are reports of AD or AD-like eruptions being associated with the use of infliximab or etanercept in patients with psoriasis, rheumatoid arthritis or juvenile idiopathic arthritis (6-8). These events have been attributed to the shift towards a predominant Th2 response due to the downregulation of Th1 cytokines caused by anti-TNF-alpha biologicals (8, 25). Therefore, considering these reports, AD could not represent an indication for anti-TNF-alpha therapy, unlike conventional systemic immunomodulating drugs which have proved effective in both psoriasis and AD, such as cyclosporin A (26-28). The results obtained in our case appear to suggest that there can be selected subgroups of AD patients who might benefit from infliximab, although their discriminating characteristics

are unknown. However, awaiting more precise data on the mechanism of action of infliximab, we can hypothesize that the chronic-continuous and recalcitrant course of AD, as confirmed by the psoriasiform pattern on histology, and the concomitant contact dermatitis in our patient might have influenced a more preponderant Th1-mediated response than that expected in "common" forms of AD (29-34). Interestingly, some evidence supports the role of TNF-alpha in the pathogenesis of contact dermatitis (35-37).

*NOTE: After the submission of this paper, a study evaluating treatment with infliximab in atopic dermatitis has been published (**Jacobi A. et al.** 2005. *J. Am. Acad. Dermatol. 52:522*)

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