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Sustained improvement of psoriatic lesions in the course of sublingual immunotherapy for airborne allergens: clinical evidence of cross-tolerance

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Abstract. – BACKGROUND: A patient with psoriasis is presented who was treated with sublingual immunotherapy for airborne allergens for allergic rhinitis. Allergic rhinitis and psoriasis have entirely different cytokine profiles and result from different aberrations of the immune response. Furthermore, T-cell activation in the two diseases uses different presentation systems, psoriasis being a CD8 cytotoxic cell response requiring presentation through the Major Histocompatibility Complex I, while allergic rhinitis and its treatment with sublingual immunotherapy depend on CD4 T-helper cells and presentation by the Major Histocompatibility Complex II. The rapid and impressive improvement of the psoriatic lesions in the presented patient may, along with evidence of subsiding Th1 activity, give rise to the hypothesis that tolerogenic-to-allergen changes induced by sublingual immunotherapy may induce cross-tolerance and the selective emergence of cytotoxic T cell clones with lessened psoriasis-producing activity.

Key Words:
Psoriasis, Allergy, Cross-presentation, Sublingual immunotherapy, MHC complex.

Report

Psoriasis is characterized by a shifted Th1 profile[1]. Treatment of psoriasis can be frustrating as manifestations are persistent, debilitating and may evolve to severe complications. Flare-ups after short-term use of systemic steroids are common and hard to manage, while topical steroids may actually cause psoriasis to become unstable[2]. For these reasons immune modulation, as opposed to pharmacological intervention, has for long been the focus of disease-modifying approaches to psoriasis[3].

The patient, who presented at the age of 5 for management of allergic rhinitis, had severe psoriasis diagnosed by Dermatologist (Figure 1). Lesions were present in scalp, arms, legs, back and chest with affected surface < 30%. The patient also had perennial allergic rhinitis. Family history was significant for psoriatic arthritis in the mother. Skin tests were moderately positive for a number of airborne allergens. Markers for celiac disease were negative. Total IgE was unremarkable at 11.1 kU/L.

Immunotherapy was initiated for allergic rhinitis with regular sublingual administration of allergen extracts in glycerin. No systemic or topical steroids were prescribed and no immune suppressants. Ten days into sublingual immunotherapy obvious involution of skin lesions was taking place (Figure 2). At 4 weeks from initiation of immunotherapy, resolution of lesions with residual hypopigmentation was demonstrated (Figure 3). In regular follow every 6-8 months, improvement was sustained without use of immune suppressants or topical medication. At thirty months from initiation of sublingual immunotherapy, psoriatic lesions were still absent.

Allergic rhinitis improved on immunotherapy and, after the first 14 months of treatment, the patient needed no regular nasal steroids or antihistamines. Interestingly, while allergic rhinitis was improving, skin reactivity to one single allergen, dust mite, kept increasing. Expressed in mm of wheal diameter, the reaction to standardized intradermal injections of *Dermatophagoides Pteronyssimus/Farinae* every 6-8 months changed as follows: 8 mm on presentation in November; 9 mm in May; 10 mm in following January; 9 mm in following July; 14 mm at thirty months of treatment. Total IgE increased to 26 kU/L. Specific IgE for *D. Pteronyssimus* and *D. Farinae* became detectable at 1.56 and 2.61 kU/L respectively.

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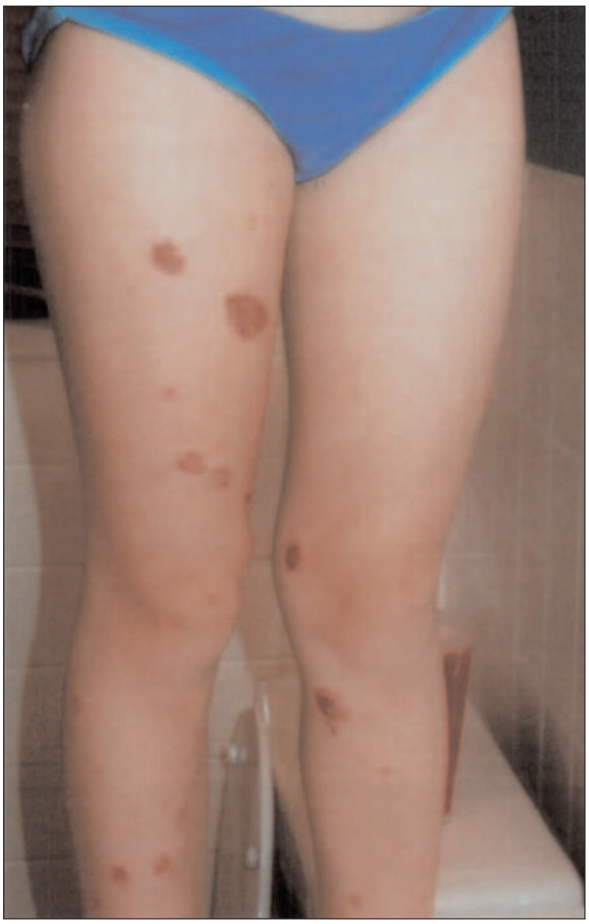

Figure 1. Plaques on presentation.

Both, IgE-mediated allergy and psoriasis, are diseases conditioned by marked Th1/Th2 imbalances. Th1 and Th2 responses often run parallel courses; for example, a shifted Th2 response is an operative condition favoring HIV replication as well as a typical corollary of early HIV infection[4]. New onset AIDS is characterized by loss of Th1 function and emergence of Th2 allergic manifestations in the form of allergic rhinitis, eczema, food and drug allergies. Similarly, a reversal in the balance of Th1/Th2 responses is observed again in late stages of AIDS with the development of unusually severe psoriasis and concurrent loss of previously developed allergies[5].

In our patient, the response of allergic rhinitis to immunotherapy was typical. Improvement of psoriasis with sublingual immunotherapy for airborne and/or food allergens has not been unknown and is anecdotally attributed to regulation of Th2 activity hitherto complicating psoriasis. The rapid resolution, however, of psoriatic lesions was unexpected. The concomitant increase in skin reactivity for one predominant allergen, dust mite, evidences a rearrangement of T cell clonal balances. Unlike the AIDS paradigm, wherein emergence of one Th response is linked to the failure of the other, in this patient with psoriasis and allergic rhinitis, a more dynamic model is proposed whereby downregulation of a Th2 (allergic) cellular response appears to have been followed by downregulation of a Th1 (psoriatic) response. This change probably allowed for previously dust mite-sensitized cell lines to express their activity and lead to (paradoxically) heightened skin reactivity and IgE production while symptoms of allergy were improving.

Sublingual immunotherapy employs dendritic cells for the purpose of tolerogenic antigen presentation in the context of Major Histocompatibility Complex class II (MHC-II)[6]. The process requires endocytosis of allergen-glycerin globules and intracellular processing by lysosomes[6]. Dendritic cells also have the capacity to cross-present exogenous antigens in Major Histocompatibility Complex class I (MHC-I) to induce specific CD8 T-cell responses[7].

It has been shown that CD8 T-cells, activated by cross presentation in a dendritic cell previ-

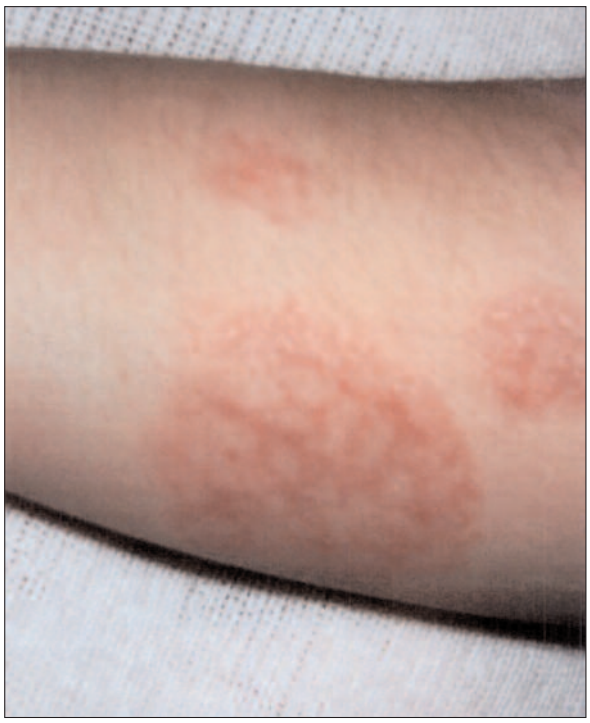

Figure 2. Improvement at ten days of sublingual immunotherapy.

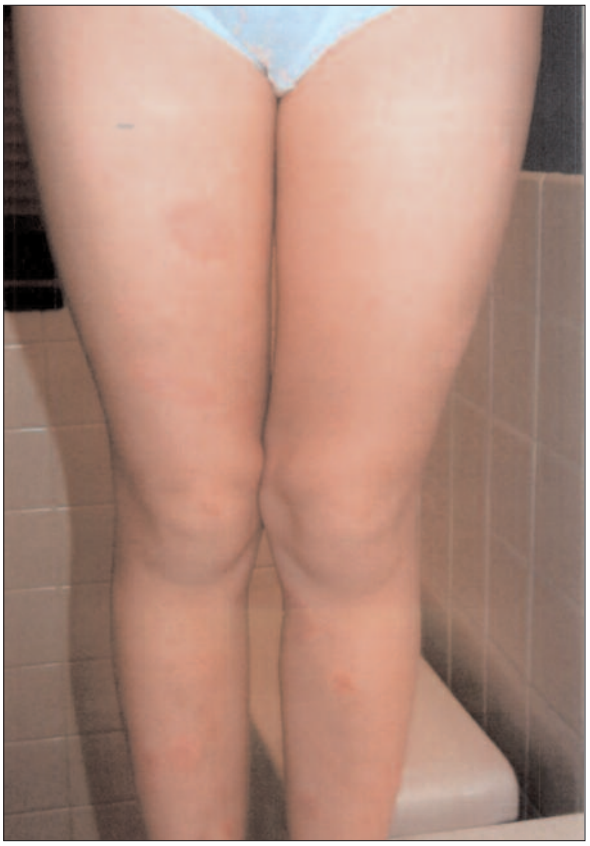

Figure 3. Resolution after 4 weeks of sublingual immunotherapy.

ously committed to tolerogenic responses, are readily deleted from the peripheral pool of recirculating lymphocytes[8]. Sublingual immunotherapy induces such a tolerogenic status of the dendritic cell by its effect on a defined tolerogenic/sensitizing switch mechanism linked to a dual system of well characterized cell surface markers[6,9]. It also induces systemic level cytokine changes as evidenced by the suppression of acute phase reactants[10]. Hereby, it is postulated that the successful induction of dust mite-tolerant CD4 cells also caused the deletion of CD8 psoriasis-producing lines. That the two processes, the one mediated through MHC-I and the other through MHC-II presentation, were related in an interdependent way, is not only supported by their temporal association, psoriasis resolving within weeks from starting sublingual immunotherapy, but also by the gradual restoration of dust mite-specific skin reactivity and IgE production.

The diagnostic and therapeutic implications are manifold:

Skin tests and specific IgE levels for allergens may be affected by psoriasis and may have to be repeated regularly in the course of immunotherapy for allergy.

In psoriatic patients with allergies, manipulation of T cell responses by means of sublingual immunotherapy with a view of generating a tolerogenic-for-allergen dendritic cell switch, may also induce tolerogenic responses from CD8 cell lines previously committed to self-antigen recognition and responsible for psoriasis. Whether cross-presentation takes place at dendritic cell level, or other mechanisms account for the development of cross-tolerance between the two distinct arms of the immune response, remains to be determined. In fact, the eventual cross-tolerance effect presented here may have originated outside the dendritic cell as it has been shown that the dendritic cell-T cell interaction in the course of antigen presentation is bidirectional: dendritic cells promote the activation of specific T cell lines and, in turn, T cells regulate the survival of their respective dendritic cell subsets[10].

The pathophysiology of psoriasis is a very complex one. As has already been demonstrated, psoriasis inflammation is subject to such a fine cytokine balance that entirely paradoxical responses to targeted anti-cytokine treatment are often observed[11,12]. Manipulation of cytokine orientation at the dendritic cell level is, therefore, highly desirable. Furthermore, inflammatory changes in psoriasis are not an isolated aberration of the immune system but are closely associated with a wide range of underlying hormonal and metabolic abnormalities[12,13]. Such changes have been assessed in the context of the metabolic syndrome but are likely to emerge in other conditions which may impact on immune function[14,15]. A comprehensive multi-specialty approach involving allergists-immunologists, endocrinologists, nutritionists and other specialists, and the need to promote patient awareness of the complex nature and the manifold clinical associations of psoriasis is strongly supported by this study[16].

Conclusions

Based on the present case, it is hypothesized that the nurturing of tolerogenic CD4 T cells by means of immunotherapy may, through reciprocal dendritic cell proliferative changes, also induce the development of tolerogenic CD8 lines.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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