

EDITORIAL

The association of hypersensitivity diseases with Dermatophyte infections

Natural exposure to foreign antigens induces immune responses, which may be protective or may give rise to hypersensitivity disease. In general, the distinctions are clear, and it is relatively easy to classify immune responses in this way. Thus, Diphtheria toxoid/toxin produces protective IgG antibodies; pollen antigens induce immediate hypersensitivity; a delayed hypersensitivity response induced by BCG was considered to be protective and poison ivy induces contact sensitivity. However, there are antigens where the line between protective and allergic responses becomes blurred. A good example of these is the Dermatophyte fungi of the genus *Trichophyton*. It is well known that delayed hypersensitivity skin tests and *in vitro* T cell responses to *Trichophyton* are common among adults [1]. Indeed, *Trichophyton* extract is included as part of the battery of skin tests used to evaluate delayed hypersensitivity. However, it has been repeatedly reported that some patients with chronic intertrigo or fungal nail infections have weal and flare skin responses to *Trichophyton* extracts [2-5]. More recently, it has been confirmed that these weal responses correlate with serum IgE antibodies to *Trichophyton* [4,5]. Thus, athlete's foot infections can give rise to either immediate or delayed hypersensitivity. We have also reported the purification of an allergen *Tri t I* from *T. tonsurans*, which binds IgE antibodies but does not give delayed responses [6]. This suggests that the two forms of immune responses are directed against different proteins. The difference in immune response may be relevant to both protective immunity and associated allergic responses. Both Hay, and Honbo and Jones, separately suggested that patients who develop immediate hypersensitivity tend to have more severe fungal infection of the skin [3,4]. However, this is more difficult to evaluate today because of the availability of potent topical antifungals. On the other hand there have been persistent reports associating urticaria, rhinitis and asthma with the combination of fungal infection and specific IgE antibodies [2,5,7,8,9]. The first reports were from Sultzberger and his colleagues in the 1930s, who recommended that *Trichophyton* skin tests should be part of the routine evaluation of allergic patients [2].

In the current issue comes a report from Israel confirming that there are patients presenting with perennial rhinitis who have both immediate hypersensitivity skin tests and chronic *Trichophyton* infections [10]. They also report that some of the patients responded to treatment with systemic antifungals. There are several

interesting features of this report, in particular the diagnosis was made with prick tests (i.e. the diagnosis did not require intradermal skin tests); in addition, they report that their patients did not have chronic sinusitis. Our experience is that many of the *Trichophyton* sensitive patients who present with asthma have chronic sinusitis with or without nasal polyps. Some of these cases had presented to ENT surgeons with sinusitis several years before they developed asthma [9,11]. In agreement with Dr Kivity and his colleagues, we find that these patients will give positive nasal provocation to *Trichophyton* [9,10]. However, it is important to distinguish this from patients with fungal sinusitis. *Trichophyton* is *not* a nasal pathogen or saprophyte, and repeated attempts to grow this dermatophyte from nasal passages, sinuses or the lungs have been negative [9,11]. Thus, if dermatophyte antigens are contributing to the respiratory tract disease the antigen must either be absorbed or become airborne. It is obviously possible that some patients with severe fungal infection shed sufficient skin scales to create an airborne challenge, and it is known that podiatrists can be sensitized by exposure to *Trichophyton* antigens presumably while grinding infected toenails [12]. However, we agree with Dr Kivity that this is unlikely to be the primary route of exposure. It is very unusual to induce delayed hypersensitivity by the inhaled route (i.e. with pollens, or mite antigens), thus absorption of antigen is likely to be occurring in some individuals. Similarly, hives is not commonly associated in inhaled allergen but can occur with *Trichophyton* again suggesting systemic absorption. Finally, our own experience with an immunoassay for *Trichophyton* allergen (*Tri t I*) suggests that this allergen is not measurable in dust samples, suggesting again that the airborne route is not important [6].

Trichophyton infection is universal but is probably more common and more severe in hotter climates (e.g. Virginia and Tel Aviv). Indeed, the allergic complications of *Trichophyton* are widely accepted by allergists practicing in Alabama and Arizona, but are apparently not common in Wisconsin, Maine or the U.K. The real issue is whether the associated allergic disease responds to antifungal treatment. Our own anecdotal experience continues to be good, but it is clearly necessary to carry out double blind placebo controlled trials of antifungal treatment. Controlled trials should be possible using oral Fluconazole, which is very effective against even severe onychomycosis. We certainly continue to see patients with chronic allergic disease whose sole positive skin test

is to *Trichophyton* and who respond to treatment with anti-fungals within weeks. The case of a 29-year-old physician who developed both severe athlete's foot and asthma while spending a year in Argentina was particularly clear. While in rural Argentina he was unable to find treatment for his feet, which became very sore and extensively inflamed. During that period he started coughing and wheezing. Despite intermittent local treatment sufficient to control the worst of his fungal infection, he continued to wheeze and required daily inhaled treatment. In the spring of 1991 he had a positive skin test 10 mm $\times$ 10 mm weal to 1:200 w/v *Trichophyton* mix (i.e. the same extract that Dr Kivity and his colleagues used as a prick test at 1:10 w/v). He had no other positive skin tests and was advised to use Ciclopirox olamine 1% (Loprox) cream to his feet daily. Over 6 weeks his respiratory symptoms stopped and he has required no inhaled treatment over the last 6 months.

Recognizing and understanding the role of dermatophyte infections in hypersensitivity diseases is important because: (i) many of these patients have severe or moderately severe disease, which is very difficult to treat unless their fungal infection is adequately treated; (ii) this form of sensitization to a local infection is potentially a very important model of an 'intrinsic' allergen. As such, these patients offer the possibility of studying the inflammatory response, including T cells, to an intrinsic allergen and offer a model for considering other possible allergens which are 'intrinsic', i.e. growing on the patient.

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