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THE ATOPIC-CHRONIC-DERMATOPHYTOSIS SYNDROME

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Abstract. This article reviews the clinical and laboratory aspects of the relationship between atopy and dermatophytosis. This newly appreciated relationship; chronic, stabilized dermatophytosis and bronchial asthma and/or allergic rhinitis, constitutes a clinical syndrome of importance and interest. The relevant host defense; correlate, cell mediated immunity, is subject to the modulating effects of the mediators of Immunoglobulin-E mediated hypersensitivity in the atopic. Evidence suggests that IgE, the mast cell and histamine act locally within the loose connective tissue of the skin to inhibit T effector cell function and inflammation. The final common pathway for histamine as an immune modulator is unknown but may involve binding to H-2 receptors on the plasma membrane of lymphocytes or endothelial cells. The consequent reduction in intensity of inflammation within the lesion permits establishment of a chronic stabilized dermatophyte infection. Recognition of the atopic-chronic-dermatophytosis syndrome draws attention to the underlying immune mechanism which may have broader implications in biology.

Key words: Atopy; Dermatophyte; Immunoglobulin E; Mast cell; Trichophytin; Immune modulation; Histamine

Because atopy and fungal infection are each common, one would expect occasional coexistence of these diseases in the same patient. In recent years, a relationship has been noted between atopy and chronic, extensive dermatophyte infection which appears to be more than coincidental (5, 7–10, 14).

First, Lobitz et al. (14) described a severe atopic dermatitis patient who had generalized *Trichophyton rubrum* infection. Second, Jones et al. (7), in a 1973 study of dermatophytosis in prison inmates observed that 40% of the inmates who harbored chronic and extensive dermatophyte infection were atopic. Their atopic manifestations were almost exclusively hay fever and/or asthma. Chronic dermatophytosis was 3 times more frequent in those inmates having atopic manifestations.

Subsequently, Hanifin et al. (5) reported that approximately 50% of 49 patients with chronic *Trichophyton rubrum* infection had a personal or family history of atopy. Sorensen & Jones (21) found 9 of 17 chronic dermatophytosis patients to have a personal or family history of hay fever, asthma, or atopic dermatitis. These studies establish a relationship between dermatophytosis and atopy which suggests that atopy is associated with a predisposition to acquire chronic infection (see Table I).

Factors which predispose to dermatophytosis. To place the relationship between dermatophytosis and atopy in proper perspective it is necessary to review what is known to affect an individual's susceptibility to dermatophyte infection (see Table II). Early case reports suggested that individuals with lymphoma and Cushing's disease were more susceptible to dermatophytosis (13, 15). Immunosuppression from systemic medications and topical steroids may be observed to heighten susceptibility to fungal infection including dermatophytosis (12), although how common this occurs is not well documented. In addition, some believe diabetes mellitus predisposes to dermatophyte infection (6), although convincing evidence is lacking.

A new syndrome. Thus atopy, chiefly mild hay fever and/or asthma appears to be the only identifiable condition consistently and frequently associated with chronic and extensive dermatophytosis. To draw attention to the association between these two conditions perhaps we should denote the relationship as the atopic-chronic-dermatophytosis syndrome.

Clinical and laboratory characteristics of atopic individuals who have chronic and extensive dermatophytosis

Clinical characteristics. Typically, the atopic-chronic-dermatophytosis patient is a male who contracts his initial infection in the second decade of life. The personal atopic history typically consists of childhood asthma and/or hay fever; in many the respiratory problems will have resolved spontaneously before dermatophytosis begins. At the time of evaluation, *Trichophyton rubrum* is commonly found to be the infecting fungus. Most patients claim that the

Table I. *Reports which establish relationship between atopy and chronic dermatophytosis*

Authors	Year	No. with chronic infection	No. atopic
Lobitz et al.	1972	1	1
Jones et al.	1973	34	14
Hanifin et al.[a]	1974	49[a]	24[a]
Sorensen/Jones	1976	17	9
Totals		101	48

[a] Hanifin et al. stated that approximately 50% were atopic.

initial manifestation of infection was an intensely inflammed lesion, but with time although never actually resolving, the lesion became less intensely inflammed and spread. The infection will frequently have been present for more than 20 years.

The chronically infected lesion is characterized by pruritus, erythema, scaling and hyperkeratosis. Inflammation is not intense, in fact is minimal. Typically the feet are involved in an erythrodermic, hyperkeratotic moccasin-type pattern. The palmar and plantar skin may develop painful fissures. The crural region, buttocks, thighs, finger and toe nails are commonly affected. When the condition is generalized the picture may be that of an exfoliative erythroderma.

Laboratory findings. The significant laboratory findings are related to the immune system (see Table III). There is enhanced IgE synthesis and decreased cellular immunity. The finding of normal levels of immunoglobulins G, M and A are contrasted with a mild or moderate elevation of serum IgE which again reminds one of the relationship to atopy. In keeping with their personal and family history of atopy, the atopic-chronic-dermatophytosis patient has multiple positive immediate scratch and intradermal tests to common environmental allergens. Intradermal injection of trichophytin, a soluble dermatophyte glycopeptide, typically elicits a large immediate wheal and flare reaction. RAST studies have confirmed that serum from such individuals contains IgE reactive with trichophytin (R. D. King et al., unpublished data).

Table II. *Conditions which may herald a predisposition to chronic, extensive dermatophytosis*

Condition	Frequency found
1. Atopy, especially hay fever and asthma	Commonly
2. Diabetes mellitus	? ? ?
3. Immunosuppression due to medications	Less commonly
4. Lymphoma/thymoma	Uncommonly
5. Cushing's syndrome	Rarely
6. Primary immunodeficiency diseases	Rarely

Table III. *Anticipated immunological findings in the atopic-chronic-dermatophytosis syndrome*

1. Mild-moderate increase serum IgE
2. Multiple positive scratch and intradermal tests to common environmental allergens
3. Immediate hypersensitivity reaction to trichophytin antigen
4. Trichophytin specific IgE by RAST
5. Weak or absent delayed hypersensitivity to trichophytin
6. Weak or absent *in vitro* lymphocyte response to trichophytin
7. Otherwise normal immune function

In contrast to the presence of IgE reactive to trichophytin, cell-mediated immunity to trichophytin is decreased. Intradermal injection of trichophytin typically reveals weak or absent delayed-type hypersensitivity (DTH) to that antigen (10). Lobitz et al. (14) found their atopic-chronic-dermatophytosis patient who had absent DTH to trichophytin to have a severe, general depression of cellular immune reactivity which was reflected both *in vivo* and *in vitro*. It should be noted that this patient had severe atopic dermatitis. Hanifin et al. (5) and Sorensen & Jones (21) could not confirm the presence of a general depression of CMI function in their atopic-chronic-dermatophytosis patients, most of whom had mild respiratory atopy. In fact their patients reacted normally to a battery of delayed-type hypersensitivity skin tests with the exception of one antigen, trichophytin. Hanifin et al. (5) used lymphocyte transformation to confirm *in vitro* the decreased cellular immune response to trichophytin. These reports suggest that the respiratory atopic with chronic dermatophytosis has a minimal and possible antigen specific decrease in cellular immunity. In atopic dermatitis patients the defect in cellular immunity may be more severe.

Characteristic pattern of immune reactivity to trichophytin. Thus the immune responsiveness of the atopic-chronic-dermatophytosis patient is characterized by: (1) enhanced synthesis of IgE to trichophytin and several other antigens, and (2) a relative specific failure to express cell-mediated immunity to trichophytin both *in vivo* and *in vitro*. This distinctive pattern of immune response to trichophytin is intriguing.

Basis of the atopics susceptibility to dermatophytosis

An immunologic predisposition. The immunologic predisposition of the atopic may play an important role in the host parasite struggle, leading to weakened host defenses and chronic dermatophytosis.

Background. Before addressing the question of which host defense mechanism fails in the atopic-

Table IV. *Host defense value of the various immune responses to dermatophyte infection*

Response	Value
Immunoglobulin	
G	Not defined
M	Not defined
E	Negative
Cell mediated immunity	Positive

chronic-dermatophytosis patient we must first review the immune response to these fungi and evaluate the role of each response in host defense (see Table IV). The principle antigens involved are complex glycopeptides referred to as trichophytin. The frequency and titer of IgG and IgM antibody are low. The IgE response to trichophytin is stronger and more frequent. Investigators have not been able to show that any class of antibody plays a positive role in host defense against dermatophytes. In fact, the occurrence and highest titer of antitrichophytin antibody, especially IgE, is most closely correlated with severe infection.

In contrast, studies of cellular immunity to dermatophytes, both in animals and humans, have shown a positive correlation with intact host defense. Also the expected corollary, that compromised cellular immunity to trichophytin would be associated with susceptibility to infection, has been documented. Just how intact cellular immunity to trichophytin provides host defense against dermatophyte fungi is not known. In this regard it may be important that dermatophyte fungi survive poorly in intensely inflammed skin.

It is not widely known that the cellular immune response to trichophytin produces essentially all the inflammation at a dermatophyte infected site (9). The fungal parasite, even though proliferating rapidly, has little capacity to incite intense inflammation. When, however, an immunized host expresses cell-mediated immunity to dermatophyte antigen at the site of infection the involved skin becomes acutely and intensely inflammed. Development of intense inflammation heralds the disappearance of the dermatophyte and subsequent resolution of the infection.

Furthermore, acquisition of cell-mediated immunity to trichophytin via a primary infection is associated with relative resistance to reinfection (9). The exact mechanism mediating host resistance to dermatophytes has not been determined. It has been suggested that intense inflammation may impeed fungal invasion by damaging the epidermis and permitting inhibitory plasma factors access to the pathogen. Inflammation also accelerates epidermal turnover (shedding) (2). In any event, intact cell-mediated immunity to trichophytin and the intense cutaneous inflammation produced within infected skin appears to be the bulwark of host defense against dermatophytes.

How is host defense compromised in the atopic? Now, with the necessary background we may address the question of which host defense mechanism fails in the atopic-chronic-dermatophytosis patient. Atopic patients with chronic dermatophyte infection frequently claim that for a short time their infection was intensely inflammed. Since the host CMI response, and not the parasite, determines the degree of inflammation the change in intensity of inflammation suggests something has altered the host immunity or the inflammation it produces. Experimental dermatophyte infection in an atopic with a past history of asthma and hay fever permitted Jones et al. (10) to document the decrease in inflammation and study the changes occurring in the immune-inflammatory mechanism. The change from an intensely to a minimally inflammed infection occurred 4 weeks into the subjects primary infection and was associated with a dramatic emergence of immediate hypersensitivity to trichophytin. Beginning at that point in the host-parasite interaction delayed-type hypersensitivity to trichophytin was demonstrated to decrease and most importantly the infected lesions became less inflammatory. Spread by continguous extension as well as development of new areas followed. These observations of natural and experimental dermatophyte infection strongly suggest that the synthesis of IgE to dermatophyte antigen is central to the defect in host resistance which predisposes to the atopic-chronic-dermatophytosis syndrome.

The role of IgE in immune modulation of T effector cells

Jones et al. (7–11) suggested that IgE was critically involved via the mast cell and its complement of pharmacoactive mediators in modulation of T-effector cell function in chronic dermatophytosis. They hypothesized that trichophytin, which is water soluble, diffuses into the dermis from the fungus

which parasitizes only the stratum corneum. In the dermis trichophytin would bind specifically to sensitized T-cells or specific antibody. Thus mast cell fixed antitrichophytin IgE would become a trigger that when pulled by trichophytin would activate mast cell secretion of pharmacologic mediators. In this scheme locally released histamine would act on antigen activated T-effector cells within the area temporarily prohibiting further activation and release of lymphokine or other mediators of inflammation. Thus, histamine would inhibit T-effector cell function and suppress delayed-type hypersentitivity mediated inflammation.

Jones et al. (10) presented evidence to support this hypothesis. First, Prausnitz-Küstner (PK) transfer of trichophytin-specific IgE into the skin of a subject exhibiting only trichophytin-delayed hypersensitivity (DH) produced, with antigen challenge a typical immediate hypersensitivity reaction followed in 48/72 hours by a 50% reduction in DH. In a similar manner, local intracutaneous injection of histamine or agents causing release of histamine produced a muting of the delayed hypersensitivity reaction. This strongly suggests that histamine can suppress the delayed hypersensitivity reaction to trichophytin.

Subsequently, evidence accumulating from several laboratories has suggested that histamine exerts this effect via specific receptors (H-2 receptors) located on the T-effector cell membrane (1, 3, 16, 18). The changes in T-effector cell function are thought implemented internally through adenyl cyclase and intracellular cyclic nucleotide regulation of cell function. More recent evidence suggests that histamine may be an intermediate and not the final mediator in this pathway. Rocklin (19) has reported that histamine causes lymphocytes to release a protein of approximately 23,000 to 42,000 molecular weight referred to as Histamine Suppressor Factor (HSF) which inhibits sensitized lymphocytes from proliferating and producing MIF. Furthermore, Schwartz et al. (20) have reported that in mice, serotonin may modulate cutaneous delayed hypersensitivity (DH). Schwartz's group proposed that serotonin does not act directly on the T-cell but on cells of the vascular endothelium, altering the permeability of specialized venules to bone marrow derived mononuclear cells critical to the cutaneous DH reaction.

Plausability of IgE-mast cell-mediator modulation theory. Whichever final common pathway is operative remains to be clarified. Nevertheless, it seems that the IgE-mast cell mediator system is an important mechanism for in-situ immune modulation. The IgE-mast cell mediator modulation theory completely explains several puzzling findings characteristic of the atopic-chronic-dermatophytosis syndrome namely (1) basis of the atopics susceptibility to dermatophyte infection; (2) decrease in inflammation concomitant with appearance of trichophytin specific IgE and (3) antigen specific nature of CMI defect.

An alternative sequence of events capable of leading to chronic dermaphytosis

It is not known if all atopics who contract chronic dermatophytosis do so through the sequence of events discussed above. It is theoretically possible for the atopic to acquire an identical immunological profile (enhanced IgE and depressed CMI to trichophytin) plus a chronic infection through an entirely different process.

The alternative scenario which requires years to be fully expressed is based on immunization through the respiratory passages by non-pathogenic but antigenetically cross reactive fungi. This results in an IgE response that later in life thwarts CMI to antigen from pathogenic dermatophyte fungi which penetrates through the skin. This is a plausible alternative supported by several findings. First, the non-pathogenic molds have been shown to contain antigens which are cross reactive with trichophytin (17). Second, some individuals with asthma and hay fever synthesize IgE very early in life in response to inhalation of airborne molds or fungi. Such individuals when examined at 10–12 years of age don't express CMI to trichophytin or antigens of the airborne molds, yet they exhibit strong immediate type hypersensitivity to airborne mold antigens and to trichophytin (8). Thus, although never infected with dermatophytes these children exhibit the immune profile of the atopic-chronic-dermatophytosis syndrome patient. Should the skin of such an individual subsequently become infected with a dermatophyte what would transpire is unknown. It would seem that even if CMI to trichophytin developed the presence of cross reactive IgE would, via the aforementioned modulation mechanism, inhibit T-effector cells. Thus, chronic dermatophytosis could develop without the individual having ever expressed CMI to the infecting organism.

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DISCUSSION

Rorsman (Lund). Q: I would like to have your opinion on the possibility that the decreased delayed reactions to trichophytin that you observed could be due to a change of vascular reaction only. Could it be due to the edema you have created by your immediate response so that the antigen was transported away?

A: I don't think one can exclude that at all. There is, however, some data from intracutaneous tuberculin testing with a radio-labelled tuberculin that leads one to believe that a fair amount of the antigen remains at the sites.

Strannegård (Göteborg). Q: Is the primary thing that T lymphocytes are more sensitive to histamine in these cases than in normal individuals, or would you imply that there is a modulation course of increased IgE levels?

A: I don't know. Maybe both.

Vickers (Liverpool). Q: I found cases with fungal infections between the toes but widespread fungal infections are rare in Britain.

A: I have never observed a patient with atopic dermatitis who also had an extensive dermatophyte infection as well.

Saurat (Paris). We have seen patients coming from North Africa, many with numerous atopic features, and having granulomas in the scalp.

Zachariae (Aarhus). A: We have a group of about 50 patients who have the same immunological pattern as described by Jones. We have noted the same laboratory findings. Almost all of these patients have an atopic disposition but none have atopic dermatitis. They usually have the clinical picture of trichophyton rubrum infection affecting one hand and a sole, now and then the soles alone.

Aas (Oslo): The reactions to trichophytin depend very much on the preparation, which may vary from batch to batch. Some mould extracts, for example, contain both high and low molecular irritant and endotoxins, so that one can have no allergic irritant reactions in the skin without significance. So it is very important to have defined materials and standardized methods.

A: I agree with that completely. The glycopeptide which we used was prepared by ourselves over a 3-year period and was irritant-free and toxin-free.

Saurat (Paris). Q: When you give patients with trichophytoses griseofulvin for a long time, they improve. Have you observed any modification in the immune responses?

A: If one's therapy is effective and the infection is eliminated, the cellular immune response may come back. In some it will, in some it won't.