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Chronic dermatophytosis in lamellar ichthyosis: relevance of a T-helper 2-type immune response to *Trichophyton rubrum*

R.J. Ludwig J.A. Woodfolk* M. Grundmann-Kollmann R. Enzensberger† U. Runne T.A.E. Platts-Mills* R. Kaufmann T.M. Zollner

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- ☐ R.J. Ludwig
 - ☐ J.A. Woodfolk
 - ☐ M. Grundmann-Kollmann
 - ☐ R. Enzensberger
 - ☐ U. Runne
 - ☐ T.A.E. Platts-Mills

Sir, *Trichophyton rubrum* is a common pathogen causing dermatophyte infections. Causes for high prevalence of *Trichophyton* infection are its ubiquitous occurrence and its ability to escape the host's immune response. Besides pathogen-associated virulence factors, several host conditions are associated with increased prevalence of dermatophytosis. Among these are conditions such as atopy and epidermal barrier defects such as lamellar ichthyosis (LI). As immune responses to dermatophytes in ichthyoses have not been thoroughly investigated, we examined the immune response to *T. rubrum* in a patient suffering from LI complicated by chronic dermatophytosis.

A 2-year-old girl had had generalized scaling and dry, itchy skin since birth. At age 8 months, scaling increased and *T. rubrum* was isolated from scales. Local treatment with econazole and ciclopirox was ineffective. After systemic therapy with griseofulvin, dermatophyte culture was negative and scaling was diminished. Several episodes of scaling and positive dermatophyte culture occurred subsequently and the patient was admitted to our department. Family history revealed that her uncle on her father's side also suffered from an ichthyosis complicated by chronic dermatophytosis.

Examination showed large thick pigmented scales predominantly localized on the trunk (Fig. 1a). Additionally, multiple annular, scaling areas of erythema with hyperkeratotic borders were observed predominantly on the upper legs (Fig. 1b). She had subacute eczema on the large flexures. Besides eczema, pruritus and dry skin, further clinical signs for atopic dermatitis were white dermographism, chronic dermatitis, keratosis pilaris and hyperlinear palms. Biopsy revealed a compact orthohyperkeratosis with increased thickness of the granular layer (Fig. 2a). Periodic acid–Schiff-positive fungi were detected (Fig. 2b). *T. rubrum* was detected from the scales by polymerase chain reaction (PCR) with subsequent sequencing of the amplification product and confirmed by culture.

Laboratory findings revealed elevated total serum IgE (167 kU L^{-1}), specific IgE against birch pollen (0.8 kU L^{-1}) and house dust mite (1.1 kU L^{-1}), and elevated eosinophil cationic protein ($65 \mu\text{g L}^{-1}$); other findings including routine lymphocyte phenotyping, immunoglobulin subclasses, immunoglobulin responses to previous immunizations, complement factors and leucocyte chemotaxis towards C5a were normal or negative. Antibodies to Epstein–Barr virus, cytomegalovirus, human immunodeficiency virus I and II, hepatitis A–C and human parvovirus, and screening tests for infection with bacteria (including mycobacteria), other fungi and parasites, were negative.

Lymphocyte proliferation in response to phytohaemagglutinin (PHA), pokeweed mitogen (PWM) and a recombinant 29-kDa subtilase homologue, *T. rubrum* 2 protein (Tri r2), was compared with that in healthy controls. The T-cell proliferative response to PHA and PWM was higher in the patient than in controls, whereas antigen-specific proliferation in cultures stimulated with Tri r2 was undetectable in the patient (Fig. 3).

Cell lines generated from the patient's peripheral blood mononuclear cells were stimulated with Tri r2 ($10 \mu\text{g mL}^{-1}$) for 6 days followed by stimulation with recombinant human interleukin (IL)-2 (10 U mL^{-1}) for 8 days. After restimulation with Tri r2 for 4 days, supernatants were assayed in triplicate by enzyme-linked immunosorbent assay (R & D Systems, Wiesbaden, Germany). Mean $\pm$ SD levels of IL-4, IL-5 and interferon- γ were $0.31 \pm 0.04 \text{ ng mL}^{-1}$, $1.83 \pm 0.15 \text{ ng mL}^{-1}$ and $1.97 \pm 0.25 \text{ ng mL}^{-1}$, respectively. The same culture conditions were used for determination of expression of cutaneous lymphocyte-associated antigen (CLA) by CD3+ lymphocytes. Mean $\pm$ SD CLA expression on lymphocytes in the starting population at day 1 was $8.2 \pm 1.3\%$ and was markedly suppressed in Tri r2-stimulated cultures ($2.6 \pm 0.6\%$). CLA expression on T cells stimulated with tetanus toxoid ($5 \mu\text{g mL}^{-1}$) as control antigen showed a slight increase in CLA expression ($11.4 \pm 1.8\%$). High titres of anti-Tri r2 IgG and IgE antibodies were measured in patient serum ($> 5000 \text{ U mL}^{-1}$ and $4266 \text{ counts min}^{-1}$, respectively) using methods described previously.¹

We diagnosed LI in our atopic patient, complicated by chronic dermatophytosis by *T. rubrum*. She was treated with oral fluconazole 1 mg kg^{-1} daily for 8 weeks. During therapy, the skin condition improved and *T. rubrum* could not be detected by PCR or by culture. However, 6 months after discontinuation of systemic antimycotic therapy, dermatophytosis recurred (positive culture and PCR for *T. rubrum*).

The aetiopathology of chronic dermatophytosis is still not completely understood. Chronic dermatophyte infection can be caused by pathogen-derived factors (superficial location of infection and virulence factors that suppress the host's immune response). Additionally, host-derived factors (atopy and barrier defects such as in ichthyoses) are known risk factors. It is thought that due to excessive keratin production, ichthyotic skin

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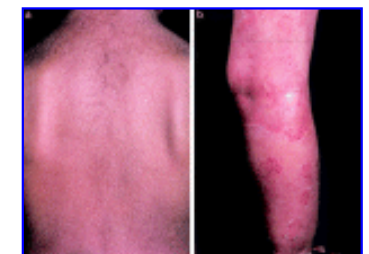
Affiliations

Departments of Dermatology and
†Microbiology,
Johann Wolfgang Goethe-
University,
Theodor-Stern-Kai 7,
60590 Frankfurt am Main,
Germany*Astma and Allergic
Diseases Center, University of
Virginia,
Charlottesville,
VA, U.S.A.

Correspondence: Thomas M.
Zollner.

E-mail: Zollner@em.uni-frankfurt.de

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Figure 1. Clinical presentation. Large brown scales are seen on the back (a) and multiple annular, sc...

provides a habitat for fungi that is more favourable than normal skin.² However, the incidence of tinea corporis is not increased in other disorders with increased keratinization (e.g. psoriasis). One possible explanation for the increased incidence of chronic dermatophyte infections in ichthyotic patients is that the most frequent ichthyosis is ichthyosis vulgaris which is associated with atopy.^{2,3} In contrast to the association between ichthyosis and chronic dermatophytosis, the association between atopy and chronic infection by dermatophytes is well documented down to the molecular level. Certain antigens derived from *T. tonsurans* and *T. rubrum* elicit both immediate hypersensitivity (IH) and delayed-type hypersensitivity (DTH) responses. While acute, spontaneously resolving dermatophytosis is associated with DTH reactions, chronic recurrent infection is associated with IH reactions. Therefore, it has been proposed that cell-mediated responses to dermatophytes play a role in the eradication of infection, while type I reactions are non-protective.⁴

Increased incidence and chronicity of dermatophyte infections in atopy could be attributed to a shift towards a T-helper (Th) 2 response. Indeed, it has been shown for several infectious agents that a Th2 response causes susceptibility whereas a Th1 response is associated with resistance, and a Th2 to Th1 shift can be therapeutically effective against infections.^{5,6} Antigen-specific T-cell lines established from individuals with IH to *Trichophyton* have been shown to have a Th2 or Th0 phenotype.⁷ These findings, coupled with our present findings, i.e. serum anti-Tri r2 IgE antibodies and production of IL-5 by Tri r2-responsive T-cell lines, suggest a Th2 immune response to *Trichophyton rubrum* in LI.

A prerequisite of resistance to infection is the migration of immunocompetent cells to the site of infection. It is therefore of interest that expression of the skin-specific T-cell homing molecule CLA is induced by Th1 and suppressed by Th2 cytokines⁸ and that reduced CLA expression was observed following Tri r2 stimulation in our patient. We therefore speculate that a defect may exist in the recirculation in distinct, antigen-specific T cells. The defect could be limited to those antigens that are known to induce an IH or a DTH response in different individuals depending on the genetic background of the individual. In our atopic patient, we observed a Th2 response to *T. rubrum* that was associated with an antigen-specific decrease in lymphocyte proliferation. Additionally, reduced expression of skin-homing molecules on T cells after stimulation with Tri r2 was demonstrated. We suggest that chronic dermatophytosis in this patient suffering from LI was at least partially aggravated by an antigen-specific T-cell defect.

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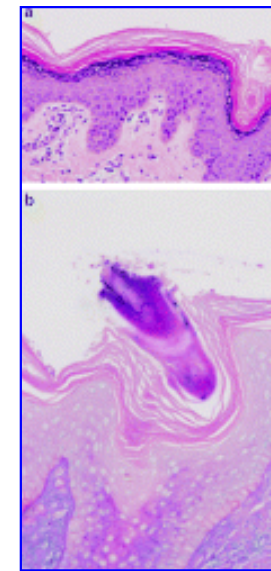
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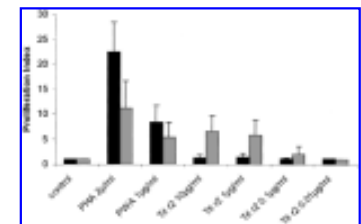
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Figure 2. Photomicrographs showing (a) lamellar ichthyosis with hyperkeratosis and hypergranulosis (h...



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Figure 3. Lymphocyte proliferation in response to *Trichophyton rubrum* 2 protein (Tri r2) is reduced in...

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