

The clinical spectrum of atopic dermatitis

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Updating our clinical concept of atopic dermatitis (AD) evolves from the better understanding of all the immunologic aberrations expressed by the polygenic combinations and permutations associated with the atopic diathesis. Recognizing the immunopathologic features of AD readily underscores that AD without "atopy" is an oxymoron. Appreciating "pruritus" as the impetus to scratch, which isomorphically gives rise to the "eczema," shifts the goal of management from suppressing inflammation to avoiding the triggers of pruritus. Recognizing the full spectrum of dermatologic findings in AD endorses the preferred label as a *dermatitis*, rather than the inferred restrictive label, *atopic eczema*. As our knowledge of immunology evolves, our criteria for the diagnosis and management of the atopic diathesis are sure to change. (*J Allergy Clin Immunol* 1999;104:S87-98.)

Key words: Atopy, allergy, immunologic aberrations, T_H1/T_H2 , IgE antibodies, mast cells, eosinophils, pruritus, allokinesis, eczema, isomorphic response, xerosis.

In 1980 Hanifin and Rajka¹ published diagnostic criteria for atopic dermatitis (AD) that have become universally accepted as the standard for the diagnosis of that clinical entity. Since then, significant progress in our understanding of AD, both on the clinical level and immunopathogenetic level compels us to consider a reexamination of those original criteria.^{2,3} Whether clinicians are aware of the diagnostic criteria or not, few have difficulty in identifying the patient with typical AD, although prescribing the appropriate management for these patients can be a perplexing challenge. The quandary is partially the result of the implication that AD, being part of the atopic triad, must be an allergic disease. Yet, its obvious cutaneous manifestations place it in the realm of dermatology. Thus, depending on one's personal bias, AD is usually regarded to be predominantly allergic or dermatologic, and only casually are both factors fully evaluated.

The discordance is often eloquently supported by the clinical observations of well-reputed "proallergic"⁴⁻⁷ investigators and skeptics.⁸ However, most of the controversy seems to be the result of one's interpretation of the indistinctive designation "allergy," which is defined as

Abbreviations used

AD: Atopic dermatitis
FcεRI: High-affinity IgE receptor

"an altered state of immune reactivity"; but the term is still, almost exclusively, associated with what most physicians recognize as "immediate" or type I (IgE/mast cell) hypersensitivity instead of the full gamut of immunologic phenomena. Thus the interpretations seem to be dependent on the intellectual naivete of the full scope of the immunologic and nonimmunologic mechanisms that partake in the atopic diathesis.

It seems that a (partial) solution to resolving the existing dilemma would be to expunge the term *allergy* from our medical vernacular and to replace it with the more specific, more accurate term *immunologic*. As Leung⁹ so clearly reports "an understanding of the immunologic basis of AD is likely to have important clinical implications in our approach to the (*diagnosis and*) management of AD."

DIAGNOSIS OF AD

The diagnosis of AD can only be made by the presence of 3 essential criteria (each of which are included in the Hanifin and Rajka¹ major and minor features of AD): personal or (first-degree) family history of atopy, pruritus, and eczema.

Atopy

Atopy is universally recognized as a complex genotypic diathesis that manifests a syndrome of immunologic aberrations.¹⁰ The expression of those aberrations is determined by the varied expression of at least 20 genes, interacting with a world of environmental factors (phenotypic). Thus it is not surprising that, as a result of all the possible genetic combinations and permutations, each atopic individual possesses a unique "allergic fingerprint" and that not all atopic individuals have identical findings. To add to the complexity of the clinical manifestations, atopic patients are also seen with another plethora of combinations and permutations of commonly associated genotypic findings, such as xerosis and vascular abnormalities, which are referred to as "non-essential" or "associated" criteria (or "minor" features by Hanifin and Rajka¹).

It would indeed be an oxymoron to make the diagnosis of AD without establishing atopy in the personal or family history and examination. A history of atopy is best

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obtained by specifically asking for the recognized clinical signs and symptoms of the atopic triad and not by the confusing question: "Are you allergic?"

The clinically significant immunologic aberrations of the genotypes include (1) an increased allergen-specific IgE antibody response to common antigens,^{11,12} (2) hyper-releasable basophils and mast cells,¹³ (3) eosinophilia,¹⁴ (4)(antigen-driven) T_{H1}/T_{H2} biphasic reversal,¹⁵ and (5) high-affinity IgE receptors of Langerhans cells, mast cells,¹⁶ eosinophils,¹⁷ and T_{H2} cells.¹⁸

Increased allergen-specific IgE antibody response to common antigens. Atopic individuals are best recognized by their propensity to produce large amounts of specific IgE antibodies to common substances (ie, dust mites, pollens, molds, and foods) and drugs. Skin and/or RAST testing can detect these antibodies. Approximately 85% of patients with AD have some positive skin and/or RAST results for inhalant and food allergens.^{19,20} However, a direct relationship between the positive skin test reactivity to implicated allergens and the course of AD has been difficult to establish consistently. In fact, most (but not all), positive skin tests, especially for foods, must be regarded as false positives. Positive skin and/or RAST tests, however, remain reliable indicators of atopy; if atopy cannot be confirmed from the history, it would be helpful to perform skin tests or to obtain an IgE level. Thus neither skin and/or RAST testing nor IgE levels need to be part of a routine AD work-up!²¹

The complex genetics of elevated serum IgE levels gives the determination value only when it is significantly elevated; it has been reported to be elevated in 43% to 82% of patients with AD.^{22,23} The highest levels are noted when AD coexists with respiratory atopic disease²⁴ and when the level does not fluctuate in close association with clinical flares and remissions.²⁵

Hyperreleasable basophils and mast cells. Dermal mast cells (of the tryptase-chymase type) are found to be closely associated with blood vessels and nerves. Mast cells in different anatomic sites, and even in a single site, can differ substantially in mediator content, in sensitivity to agents that induce activation and mediator release, and in responses to pharmacologic agents.¹⁶ The hyperreleasability of basophils and mast cells can be elicited by both immunologic (ie, IgE, substance P) secretagogues, and nonimmunologic (ie, opiates, aspirin, NSAIDs) secretagogues. The release of vasoactive mediators, chemotactic factors, and cytokines initiate the "allergic cascade."

The case for a mast-cell role in the pathogenesis of AD was essentially rooted on its association with allergic rhinitis and asthma and on the assumption that histamine (a predominant proinflammatory mediator released with mast-cell activation) was the sole pruritogenic agent. Recently, it was noted that mast cells do not appear to be required in some animal models of allergic disease.²⁶ In contrast, helper T_{H2} lymphocytes (with their cytokinal profile of IL-4, IL-13, and IL-5) are essential to elicit the late-phase response.²⁷ Although earlier studies detected elevated skin histamine in AD skin,^{28,29} recent, more

sensitive and specific radioenzyme assay found elevated histamine content in only 3 of 22 patients with AD.³⁰ Elevated plasma histamine levels have also been noted in some patients with AD, but its significance is obscure, because elevated histamine levels have been noted in a variety of inflammatory skin diseases. Hagermark and Wahlgren³¹ convincingly refute the role of histamine in AD (on the basis of the negligible relief of itch) and the beneficial effect on the eczema of AD from antihistamines. The elevated IgE responses and eosinophilia observed in some patients with AD reflects the increased expression of T_{H2} cytokines (ie, increased IL-4, IL-5, and IL-13 with a concomitant decrease in IFN- γ).

Eosinophilia. Eosinophilia occurs in a variety of disorders, but the most common cause in industrialized nations is atopic disease. Diseases involving eosinophilia are the result of stem-cell activation by IL-5, which in allergic diseases is predominantly a product of T_{H2} cells.³² Tissue eosinophilia is a hallmark of atopic diseases, and they are believed to be a major effector cell in the late-phase response of patients with repeated exposure to an allergen (eg, house dust mite). Leiferman et al³³ have found that eosinophil-derived extracellular major basic protein is extensively deposited in the skin of patients with AD. Although the role of eosinophils in the pathogenesis of AD is not completely understood and because major basic protein (an eosinophil product) correlates with disease activity, they are thought to contribute to tissue injury in AD.³⁴ Therapeutically, the beneficial effects of glucocorticoids are associated with reducing eosinophilia and the production and action of their products. The 5-lipo-oxygenase inhibitors (eg, zileuton) have been shown to inhibit the generation of the eosinophil chemoattractant leukotriene B₄.³⁵ Several studies have evaluated the effect of montelukast, (an antileukotriene medication) on peripheral blood eosinophils; when it was compared with placebo, the drug significantly decreased eosinophils by approximately 15%. Whether this amount of decrease can significantly reduce any inflammation in AD deserves double-blind studies.³⁶

*T_{H1}/T_{H2} (biphasic) response.*⁹ The clinical significance of T cells can be noted by their capacity to modulate immune responses by help or suppression or to effect cytotoxic immune responses. This response is dependent on the profile of cytokines they produce.³⁷ T cells that produce predominantly IL-2, IFN- γ , and TNF- β are referred to as T_{H1} cells; T cells that produce predominantly IL-4, IL-5, and IL-13 are referred to as T_{H2} cells. The consequence of these reciprocal cytokine patterns is the generation of cell-mediated immune responses (eg, delayed-type hypersensitivity) by T_{H1} cells and of humoral allergic immune responses by T_{H2} cells.³⁸

The immunologic hallmark of AD is a T_{H1}/T_{H2} dysbalance.³⁹ The eczematous lesions of AD have more similarities to delayed hypersensitivity (eg, allergic contact dermatitis) than to the urticarial lesions of immediate hypersensitivity.⁴⁰ In the early stages of both involved and uninvolved skin of patients with AD, allergen-

induced activation of T_{H2} cells predominate over (IL-12 driven) T_{H1} cells. The T_{H2} -cytokine profile of IL-4 and IL-5 favors IgE production and eosinophilia, respectively, which are essential to the atopic diathesis.⁴¹⁻⁴³ The decreased T_{H1} population noted in the early stages of AD results in an increased susceptibility to viral (eg, warts, molluscum, and herpes) and dermatophytic (eg, tinea pedis, tinea cruris) infections, plus the relative anergy for the elicitation of allergic contact dermatitis. However, in the late and chronic phases of AD, the situation reverses and IFN- γ production by T_{H1} cells predominate.⁴⁴ This observed biphasic response explains many of the previously considered controversial issues (ie, their ability to become sensitized to topical allergens) regarding AD.

High-affinity IgE receptors (Fc ϵ RI). The best studied pathway of mast cell and basophil activation is transduced through Fc ϵ RI that is expressed on the surface of those cells. When adjacent Fc ϵ RI are bridged, the cells are rapidly activated for the release of stored and newly generated mediators. The cells can be sensitized simultaneously with IgE antibodies of much different specificity and therefore can react to stimulation by many different antigens. IgE- and antigen-dependent activation is the basis for the immunologically specific expression of mast and basophil function in IgE-dependent immune responses and allergic disorders (eg, allergic rhinitis, extrinsic asthma).

Epidermal Langerhans' cells have also been recognized to express variable amounts of Fc ϵ RI (and other immunoglobulin receptors),⁴⁵ and the strongest expression is characteristic of the involved skin of AD. The receptor is believed to take part in the pathophysiologic features of this disease by acting as a link between aeroallergens and Ag-specific T cells in an IgE-mediated, delayed-type hypersensitivity reaction.⁴⁶ Expression of the Fc ϵ RI receptor on eosinophils⁴⁷ and T cells infiltrating lesions of AD have recently been reported. Chronic inflammation may be sustained through local antigen processing and presentation to allergen-specific eosinophils and T cells.

The clinical significance of the Fc ϵ RI receptors of Langerhans' cells in AD is supported by the reduction of the number of dermal Langerhans' cells and mast cells with significant clinical improvement after treatment with high-dose ultraviolet-1 light therapy.⁴⁸

Pruritus

The diagnosis of active AD cannot be made if there is no history of itching. Because a primary cutaneous lesion has never been firmly established, it may be that all the cutaneous changes are secondary to itch-induced scratching, as suggested by Jacquet at the beginning of this century. Little could be added to this observation of Hanifin and Rajka¹ when they established the criteria for the diagnosis of AD.

Pruritus must be considered a quintessential feature of AD; pruritus is variable, fluctuating from mild to extremely intense. The itch of AD should be regarded as more than merely the result of a "lowered threshold."

Wahlgren et al⁴⁹ have described it more appropriately as a result of the atopic patient's innate perception of mild mechanical stimulation as "itch" and not as "touch." They also suggest applying the term *allokinesis* to patients with AD, which implies that, once an itch has started, it increases the liability of the surrounding skin to react to light stimuli with itch (a phenomenon noted in the pruritus of some other itchy dermatoses). Feeling "itchy," without a rash, was a common complaint reported by 52% of atopic patients with a history of AD and by 14% of atopic patients without a history of AD, but only 6% of (matched) nonatopic patients, in my survey of 250 patients.

That common dermatologic dictum that "AD is an itch that erupts, rather than an eruption that itches" is not accurate! AD is an itch that *when scratched* erupts. If the atopic patient's itch is not rubbed or scratched, the skin (when provoked) may get red (vasodilate), but no eczema appears until it is traumatized. This can be described as an isomorphic response, or Koebner phenomenon, commonly noted in psoriasis and other skin conditions.

Nassif et al⁵⁰ noted that patients with active AD demonstrated significantly greater irritant skin responses than nonatopic patients. In fact they also reported that even patients with inactive AD and/or respiratory allergies have an increased irritation response compared with nonatopic patients. Thus, just as we consider asthma as a "twitchy lung" syndrome, we can conceive of atopic skin as part of a "twitchy skin" syndrome. With this information, we should infer that the eczema could be prevented if whatever provokes the itch, of the atopic patient, is identified and averted.⁵¹ The most common provokers of itch in patients with AD are heat and perspiration (96%), wool (91%), emotional stress (81%), certain (vasodilatory > allergy) foods (49%), alcohol (44%), common cold (upper respiratory infections; 36%), and dust mites ($\geq 35\%$).^{52,53} The full spectrum of recognized "triggers" of itch in AD are listed in Table I. Not all patients with AD will be triggered by these stimuli. Instead it must be appreciated that there are subsets of patients with AD who will experience exacerbations by some triggers and not by others. Yet each patient with AD should be made aware of all the potential triggers for exacerbations.

An erythema caused by certain histamine-releasing or vasodilatory foods (ie, alcohol, spices) is a more common trigger of pruritus than the IgE-mediated reaction.⁵⁴ Because the former is nonimmunologic, it is dose-related and is not dependent on prior sensitization. Many patients with AD benefit from avoiding the flushing foods that trigger rosacea (ie, hot and spicy foods; hot drinks [including hot cider, hot chocolate, coffee, or tea]; soy and vinegars).

The clinical implication of recognizing the many triggers of itch suggests that the pharmacologic mediator causing the pruritus may be different for each trigger. Despite the fact that histamine is the most abundant pruritogenic mediator in our body, its role as the major causation of itch in the patient with atopy remains questionable. Proteases, kinins, prostaglandins, neuropeptides, acetyl-

TABLE I. The full spectrum of triggers of itch in AD⁵⁵

Xerosis	
All irritants ⁵⁶	Lipid solvents (ie, soaps, detergents) Disinfectants (eg, chlorine in swimming pools) Occupational irritants Household fluids (eg, juices from fresh fruits, meats)
Contact and aero ⁴ allergens	Dust mites, ^{57,58} contact > aero Furry animals ⁵⁹ (cat > dog) Pollens (seasonal) Molds ⁶⁰ Human dander ⁶¹ (dandruff)
Microbial agents ⁶²	Viral infections (especially upper respiratory infections) <i>Staphylococcus aureus</i> ⁶³ (either as a superantigen or pathogen) <i>Pityrosporon yeast</i> ⁶⁴ <i>Candida</i> ⁶⁵ (rarely) <i>Dermatophytes</i> ⁶⁶ (rarely)
Others	Foods ⁶⁷ (as contact irritants>vasodilators>allergens) Psyche ⁶⁸⁻⁷⁰ Climate ⁷¹ Hormones ⁷² (eg, menstrual cycle)

Not all patients with AD will be triggered by every stimulus. There are subsets of patients with AD who will experience exacerbations by some triggers and not by others.

choline,⁷³ cytokines,⁷⁴ and opioids each can induce itch or potentiate histamine release when injected into atopic skin.^{75,76} Therapeutically, the most effective and consistent antipruritics remain the systemic immunomodulators (ie, glucocorticoids, cyclosporin A,⁷⁷ tacrolimus,⁷⁸ and ultraviolet light therapy⁷⁹). Antihistamines, antileucotrienes,⁸⁰ opioid antagonists,⁸¹ topical cromolyn,⁸² Chinese herbal therapy⁸³ and NSAIDs have all been reported to be helpful in some patients with AD.

Pruritus is the basic bane of atopic individuals. Although immunomodulators may offer symptomatic relief for some patients with AD, the ultimate goal of management for the patient with AD is the identification and avoidance of all the triggers of the pruritus.

Eczema

Eczema is a nonspecific term often confounding the clinical and histopathologic description of various unrelated inflammatory diseases. The eczemas include such disparate diseases as allergic contact dermatitis, AD (which may include nummular eczema, dyshidrotic eczema, and eyelid dermatitis), pityriasis rosea, lichen simplex chronicus, and seborrheic dermatitis. These eczemas do not all have clinical and histologic features in common. What is more, the clinical morphologic condition of each entity can undergo evolutionary changes, proceeding through 3 distinct stages, namely acute, subacute, and chronic. Ackerman⁸⁴ (a dermatopathologist) suggests a "more accurate" definition of eczema as a papular or papulovesicular disease characterized histopathologically by (various stages of) spongiosis. The eczematous (spongiotic) eruptions all manifest T-cell proinflammatory mediators involvement, yet may be quite differently clinically. The bulla and vesiculobullous lesions, which can be pathognomonic for the T_{H1}-driven

acute allergic contact dermatitis, are never seen in the T_{H2}-driven acute lesions of AD.

The eczema of AD, we must remember, is the isomorphic response of scratching the itchy, atopic skin; and the clinical morphologic condition (oozy and/or vesicular and/or scaly and/or crusted and/or lichenified) is inherently never stationary and is constantly undergoing an evolutionary process (ie, acute, subacute, and chronic).

The characteristic clinical features of the eczema of AD

1. Distribution can be highly variable but is generally age-related⁸⁵ with facial and extensor involvement during infancy and childhood, flexural and linear, by adolescence (Fig 1). "Hot and sweaty" fossa and folds (Figs 2 and 3) are almost always involved, although the nose and surrounding skin is frequently spared (referred to as the "head-light" sign; Figs 4 and 5). Diaper area is usually spared.
2. Excoriation is a secondary sign of intense scratching (Fig 6).
3. The evolution stages of eczema are acute (oozy and/or crusted microvesicles and erosions of plaques of papular erythema; Fig 7), subacute (thicker, paler, scaly, erythematous excoriated plaques), and chronic (thickened [lichenified], dry, scaly, papular plaques, with "scarred" excoriations; absence of hairs, if hairy areas are scratched or rubbed; Fig 8).
4. Chronicity or chronically signifies a relapsing pattern. Typically, AD is noted at an early age (usually between 2-6 months of age); however, if any of the essential criteria for the diagnosis of AD are missing, the eczema must be differentiated from other childhood eczematous diseases (ie, seborrheic dermatitis, Wiskott Aldrich syndrome, hyper-IgE syndrome, Bruton's X-

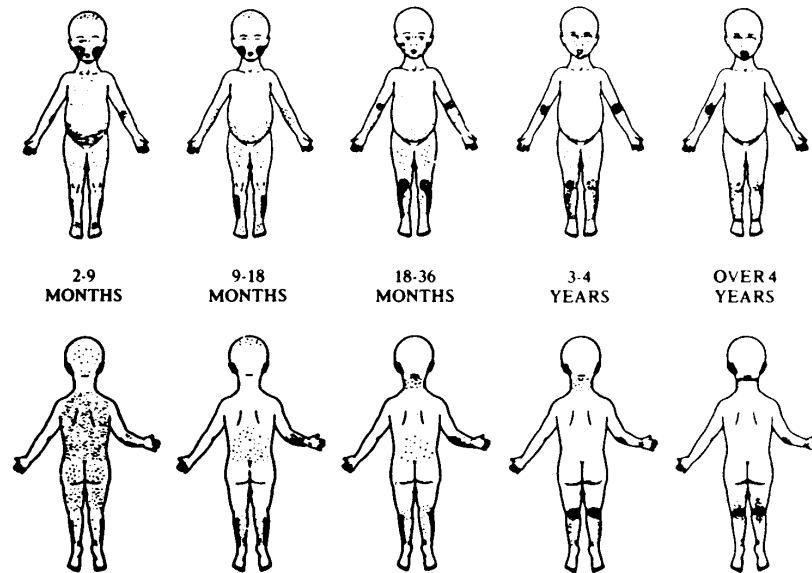


FIG 1. Distribution of eczema in relation to age. From Sedlis, E. Natural history of infantile eczema: its incidence and course. In *Conference on Infantile Eczema* (L. Emmett Holt, circa 1950).



FIG 2. Subacute eczema in antecubital fossa of a young lady with eczema since childhood. Note some lichenification, scaliness, and fine vesicles scattered throughout the erythematous papular plaque.



FIG 3. Acute/subacute eczema in popliteal fossa of a 12-year-old child. Note eroded and excoriated vesiculopapular plaques.



FIG 4. Acute facial eczema in a 4-month-old infant. Note complete sparing of nasal skin, known as the "headlight sign," considered pathognomonic for AD.



FIG 5. Acute facial flare-up of chronic eczema in a 19-year-old girl. Note "headlight sign." (From Beltrani VS. The clinical aspects of atopic dermatitis. In: Leung DYM, ed. *Atopic Dermatitis: From Pathogenesis to Treatment*. Austin, TX: R G Landes Publishers; 1996.)

linked agammaglobulinemia). When AD is suspected for the first time after childhood, contact dermatitis or cutaneous T-cell lymphoma must be ruled out. However, localized eczema can be seen in many atopic adults,⁸⁶ some of whom had only mild AD in the past. This eczema is often localized to the fingers, eyelids, nipples, lips, scalp, and chest. Hanifin and Rajka's¹ original criteria for the diagnosis of AD listed the localized eczematous conditions as minor factors; because we now are more cognizant of the immunopathologic features of AD, it seems more appropriate to list all eczematous lesions as an essential feature of this polymorphic disorder.

Generalized, symmetric involvement of AD is seen most often with acute exacerbations of AD. Typically, in the subacute or chronic stages the lesions tend to be more localized to areas of the body that are accessible to scratching. In the later stages, it is common to identify all the stages of eczema including postinflammatory hypopigmentation and/or hyperpigmentation. (Most common is the generalized xerosis.) A greater incidence of atopy has been noted with many "other eczematous" diseases (Fig 9). Conceptually, when an atopic patient has a chronic or relapsing pruritic "eczematous" eruption restricted almost exclusively to a single area of the body, labeling this as AD may be difficult; however, if the

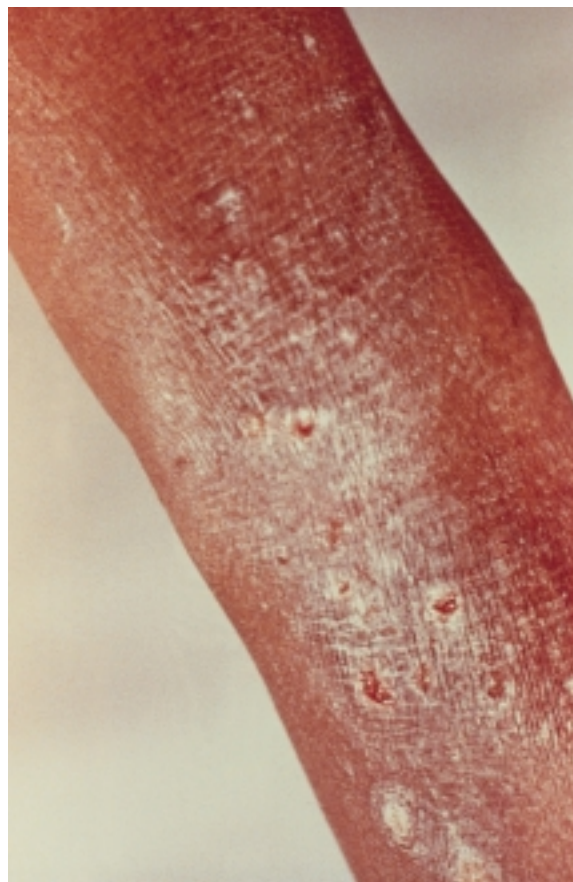


FIG 6. Excoriated lichenified eczema of antecubital fossa.

patient is examined closely (both on history and physical), one will find other signs of the atopic diathesis, including AD.

The localized areas of involvement of AD include palmar/plantar dermatitis, eyelid dermatitis, nipple dermatitis, cheilitis, and pityriasis alba.

Palmar/plantar dermatitis. Palmar/plantar dermatitis has been reported to occur in as many as 70% of children with AD.⁸⁷ The incidence of atopy in patients with chronic hand eczema, including dyshidrosis (or pompholyx) has been reported to be 47% to 64%.⁸⁸ More importantly, atopic hand dermatitis is the major cause of work-related disability caused by skin disease⁸⁹; in fact, a history of childhood AD is most indicative of a risk factor for work-related skin lesions.⁹⁰ The "twitchy" skin of atopic patients is most susceptible to all irritants (ie, cleansers, solvents, juices from foods), especially "wet work" exposure.

The easy accessibility for rubbing of the palms results in thickened, dry, leathery palmar skin. The lack of exaggerated dermatoglyphics differentiates these findings from lichenification. The thickened skin may appear slightly erythematous and scaly, and the fingertips can appear fissured and have the feel of a ping pong ball. When the erythema is the result of papulovesiculation, it



FIG 7. Acute oozing AD on the face of a 6-month-old infant. Within 48 hours of the facial rash, the eczema generalized. This is often the clinical presentation of *Staphylococcus aureus* superantigenicity, requiring both systemic corticosteroids and antibiotics for control. (From Beltrani VS. The clinical aspects of atopic dermatitis. In: Leung DYM, ed. *Atopic Dermatitis: From Pathogenesis to Treatment*. Austin, TX: R G Landes Publishers; 1996.)

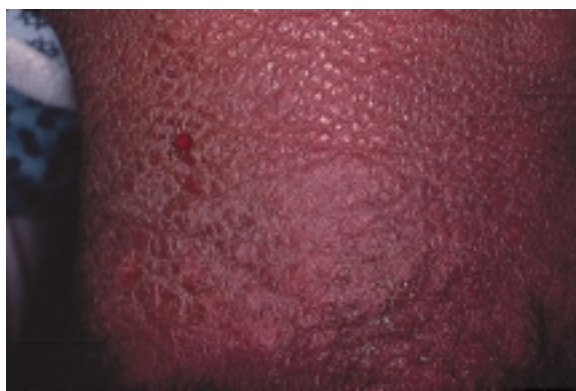


FIG 8. Chronic lichenified AD of the nape of the neck of a 30-year-old woman, who admitted to scratching the area "for years."

can be labeled dyshidrosis. The dorsum of the hand may or may not be similarly involved, but if eczema is present, allergic or irritant contact dermatitis must be considered.

"Sweaty sock dermatitis" or juvenile plantar dermatosis, which frequently is misdiagnosed and treated as athlete's foot, has been reported to occur in up to 57% of atopic patients.⁹¹ Sparing of the interdigital spaces between the toes should negate consideration of a possible dermatophytic infection (Fig 10).

Eyelid dermatitis. Almost all patients whose AD involves the face will have some degree of eyelid involvement. Clinically the spectrum of involvement can be seen as a faint scaly erythema to a hyperpigmented lichenification with visible excoriations, symmetrically localized to the upper and lower eyelids. The vulnerability of the thin skin of the eyelids, which is constantly exposed to contact irritants and allergens, combined with its easy accessibility to being rubbed provokes its chronicity. Eyelid dermatitis becomes a greater challenge

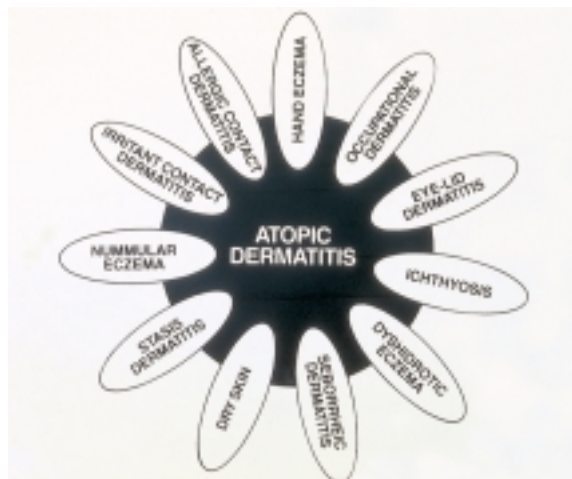


FIG 9. Atopy/other eczemas cartoon. (From All About Atopic Dermatitis [brochure]. Portland, Ore: National Eczema Association for Science and Education.)



FIG 10. Juvenile plantar dermatitis (plantar AD) of an 8-year-old girl. Atopic prepubertal youngsters with the absence of interdigital-space involvement are frequently unsuccessfully treated as "athlete's foot." (From Beltrani VS. The clinical aspects of atopic dermatitis. In: Leung DYM, ed. *Atopic Dermatitis: From Pathogenesis to Treatment*. Austin, TX: R G Landes Publishers; 1996.)

when it is the only dermatologic finding. Svensson's⁹² review of the literature and personal experience reported its incidence varying from 8% to 23% of atopic patients with predominantly eyelid involvement. He reports that the incidence of positive patch test results (to the standard allergens) was less common in atopic patients with eyelid dermatitis.⁹¹ Yet, contact irritant and allergic dermatitis must be differentiated from atopic eyelid dermatitis in these patients. However, the most likely contactant may be the house dust mite, which is not included in the standard patch tray allergens. I have recently noted (whole body) dust mite contact allergy, proved by patch testing to whole body *Dermatophagoides farinae* as part of the standard patch testing, in 6 of 12 atopic patients.⁹³ These patients each had "chronic" eyelid dermatitis of many years duration; in 9 of the patch-tested patients, the eyelid dermatitis cleared completely when a mite-free bedroom was created (ie, encased pillows and mattress). This supports reports that the dust mite may act both as a contact allergen and a contact irritant in



FIG 11. Nipple dermatitis in an adult atopic woman. Despite having minimal eczema over the rest of her body, her chronic nipple dermatitis would often flare acutely. Her bilateral nipple involvement negates the need to rule out Paget's disease. (From Beltrani VS. The clinical aspects of atopic dermatitis. In: Leung DYM, ed. *Atopic Dermatitis: From Pathogenesis to Treatment*. Austin, TX: R G Landes Publishers; 1996.)

atopic patients.⁹⁴ The other common allergens or irritants that cause periorbital dermatitis are cosmetics, the environment, medicaments (especially the topical steroids used on the face), and ophthalmic preparations. Rarely, secondary infections, such as impetigo, can occur around the eyes.

Nipple dermatitis. The very sensitive areola skin is easily koebnerized, in atopic patients, with the slightest rubbing. The symmetric, oozing, papulovesicular erythema may involve just the nipple but more often extends onto the surrounding breast skin (Fig 11). Nipple dermatitis has been reported to occur in 3% to 20% of patients with AD.⁹¹ When it occurs unilaterally, the pruritus and intermittent course in an atopic patient should lessen the suspicion of Paget's disease.

Cheilitis. Atopic patients may have almost confluent eczematization of both their upper and lower lips. The erythema may extend beyond the vermilion border. Besides the habitual lip-licking to relieve the parched sensation, the lips are often in contact with many noxious fluids from foods and drinks. Angular cheilitis is more often the result of hypersalivation than a yeast infection. Rarely are contactants (ie, lipstick) a factor.

Pityriasis alba. Diffusely marginated hypopigmented patches on the face, arms, and trunk occur in areas of previous mild eczema, in 30% to 40% of atopic patients. It represents postinflammatory hypopigmentation. The earlier, fleeting, mildly eczematous stage may occur subclinically, yet spongiosis is noted histologically. Both tinea infections and vitiligo, for which this condition is often mistaken, are rare in children when compared with pityriasis alba.

THE COMPLETE SPECTRUM OF AD

Were eczema the only skin manifestation of AD, the label atopic eczema (preferred in Europe) would be appropriate. However, eczema is but 1 of several other types of skin findings seen in patients with AD. Those

noneczematous manifestations are often associated with many patients with the atopic diathesis. Thus the term *dermatitis*, which infers any inflammation of the skin and is often used to describe any abnormality of the skin, is more relevant. These associated genotypic, noneczematous, dermatitic findings have been assigned as "minor" or nonessential factors for the diagnosis of AD, because they are not attributed to the immunoregulatory abnormalities of atopy and are also seen (less often) in patients without any evidence of atopy; the associated genotype is believed to contain genes that may coincidentally be part of the multiple gene pool of the atopic diathesis.

The associated genotype is expressed in the skin as xerosis (dry skin), keratosis pilaris (chicken skin), palmar and/or plantar hyperlinearity, and anterior neck fold; in the eye as allergic shiners, Denny-Morgan lines, periocular milia, anterior capsular cataracts, keratoconus, and atopic keratoconjunctivitis; and in atypical vascular responses as facial pallor, white dermatographism, abnormal thermal sweating ("heat stroke" susceptible), and paradoxical response to acetylcholine (and Trafuril, a trade name product available only in Europe).

The "associated" findings of the atopic diathesis, when present in groups of 3, were originally allowed to substitute for 1 of a missing major or essential factors for diagnosis. I do not recommend such an arbitrary consideration, because our present-day knowledge of the immunologic features of atopy assures the presence of the essential factors for the diagnosis! Thus these associated findings should remain coincidental findings and not be substituted for a requirement for the diagnosis.

Xerosis. There is no exact definition of xerosis, but it is recognized as finely scaling, clinically noninflamed skin involving large areas of the body. It is considered to be the most common skin finding of atopic individuals, and it persists throughout their life independent of the activity of other atopic symptoms, but a history of seasonal variations is reported by 75% of patients with AD. The variation generally consists of improvement in the spring and deterioration in the winter.⁹⁵ Atopic skin not only appears but also feels dry and is the result of a genetic decreased ability for the atopic keratinocytes to bind water, and it demonstrates a markedly increased transepidermal water loss.^{96,97} Because atopic skin is not the result of abnormal keratinization, it does not appear ichthyotic (ie, large fish-scale plaques). In fact, atopic facial skin usually appears fine and smooth with almost no visible pores. These findings, combined with decreased sebum production,⁹⁸ oftentimes reassures atopic teenagers that they will have little acne.⁹⁹ However, a normal pubertal androgen inundation can activate the sebaceous glands, which can make adolescents have oilier skin, giving them a sebaceous phenotypic appearance. Most importantly is the appearance of the lipophilic organism (ie, *Pityrosporon acne*) during and after puberty. Its presence has been suspected to trigger pruritus and to exacerbate eczema on the scalp and face (the seborrheic areas). Reports of improvement from antiseborrheic therapy in these patients support their pos-

sible causal role in some patients with AD. Pityrosporon IgE antibodies have been noted in some of these atopic patients.

The xerotic epidermis characteristic of atopy not only acts as a trigger of pruritus but also results in an abnormal protective barrier layer, which predisposes them to a higher risk of adverse reactions to both irritant and contact allergens. The clinical implications of this susceptibility are exemplified by the observation of a greater prevalence of occupational skin problems amongst atopic workers.¹⁰⁰ When the thicker, xerotic, acral skin fissures, not only can it be painful, but it can also act as a portal of entry for infectious agents (ie, bacteria and viruses). Atopic axillary and fetid foot odor is often characterized as “sharp” and “acid.” Methanetioli, which is produced by corynebacteria (from the “normal” skin flora growing in atopic “wet” keratin), is 1 of the chief components of that odor.¹⁰¹

Awareness of the significance of xerosis in atopic patients emphasizes the importance of lubrication and hydration in the management of the condition.

Keratosis Pilaris. Keratosis pilaris has been reported to occur in up to 55% of atopic patients either with or without AD and in 15% of nonatopic patients. It may occur as an isolated abnormality or may be seen in several inflammatory dermatoses. It is most often noted on the extensor aspects of the upper arms, thighs, and buttocks but can be generalized, including the face. Keratosis pilaris is regarded as a defect of keratinization of the (xerotic) hair follicles, in which the follicular openings are filled with horny plugs, making the skin feel rough (like “chicken skin”) and dry. It appears in childhood, reaches its peak incidence in adolescence, and becomes less apparent during adulthood.¹⁰² Keratosis pilaris is essentially asymptomatic but may be cosmetically unacceptable (especially to teenagers). Perifollicular accentuation has been described, especially in pigmented individuals.

Palmar and/or plantar hyperlinearity. Palmar and/or plantar hyperlinearity are recognized as exaggerated palmar and/or plantar creases and lines (dermatoglyphics). Although these markings become more apparent when the skin is dry, it is not merely the result of xerosis. It has been noted more often in atopic patients than in nonatopic patients.

Anterior neck fold. Anterior neck fold is described in the literature as a prominent visible, horizontal fold, running across the middle of the anterior neck of some atopic patients. Like the Denny-Morgan line, it has little clinical significance.

Eye findings. The associated eye findings are described as allergic shiners; symmetric, asymptomatic, blue-gray darkening of the orbital skin has been reported to occur in up to 60% of atopic patients (with or without AD) and in 38% of nonatopic patients. Although there is a tendency for orbital darkening to fade with age, it is often seen in other atopic family members. It seems to be more apparent in atopic patients who also have chronic nasal congestion.¹⁰³ Except for its being cosmetically unacceptable for some, it does not require treatment.

Dennie-Morgan lines. Dennie-Morgan lines are sym-

metric, prominent folds below the margin of the lower eyelids (similar to that seen in patients with Down syndrome). Originally it was described as occurring in 100% of atopic patients and subsequently noted in 60% to 80% of atopic patients, with a possible ethnic variation. Morgan¹⁰⁴ noted that it was present usually at birth, or shortly thereafter, and that it persisted for life.

Periorbital milia. Periorbital milia are tiny, 1- to 2-mm dome-shaped white or yellowish papulonodules, occurring individually or in clusters periorbitally. These intraepidermal inclusion cysts form when the disrupted, dry epidermis of atopic patients obstruct the duct of the sebaceous glands. The white milium body is composed of lamellated keratin. It can also occur as a result of chronic corticosteroid-induced atrophy. Incision and drainage with a small needle effectively removes this cosmetic nuisance.

Anterior capsular cataracts. Anterior capsular cataracts tend to develop during adolescence or early adult life, with the peak incidence between 15 and 25 years of age. The incidence of these cataracts has been reported to be from 3% to 10% of patients with AD.¹⁰⁵ The anterior location and shield-shaped cataracts are typical for patients with AD. They almost always occur bilaterally.

Keratoconus. Keratoconus is a conical deformity of the cornea, reported to occur 10 times more frequently in patients with AD than in control subjects, and is thought to result from the increased, constant rubbing of the eyes in patients with eczema and allergic rhinitis.

Atopic keratoconjunctivitis. Atopic keratoconjunctivitis is an inflammatory process that can involve any ocular surface and is almost always associated with AD. It is always bilateral, can be very pruritic, with burning and tearing and a heavy mucoid discharge. It is frequently associated with eyelid dermatitis.¹⁰⁶ The incidence of ocular involvement in AD, reported in the ophthalmologic literature, is from 25% to 42%.¹⁰⁷ This statistic should alert the allergist and dermatologist to carefully evaluate the eyes of all patients with AD.

Vascular abnormalities

The vascular abnormalities seen in atopy include pallor of the skin, white dermatographism, pronounced vasoconstriction on exposure to cold, low finger temperature, paradoxical skin reactions to histamine, nicotinic acid esters, and acetylcholine.

Facial pallor. Atopic persons have been noted to have a peculiar pallor that gives their skin a grayish hue; it is noted in patients of any race and is believed to be due to the atopic patient's vascular tone.

White dermatographism. Lightly stroking the skin of atopic patients results in white dermatographism (a white line, without whealing, which rapidly replaces the initial erythematous reaction).¹⁰⁸ Its incidence does not exceed 80% of atopic patients¹⁰⁹; however, it has been noted to be age dependent and to increase from 11% in patients 1 to 2 months of age to 85% in patients older than 7 months. There was no correlation between the demonstrability of white dermatographism in early infancy and the progno-

sis of AD.¹¹⁰ A similar "white" reaction has been noted after intradermal injections of acetylcholine or methacholine and the topical application of nicotinic acid (available in Europe as Trafuryl), rather than the erythema seen in nonatopic patients.¹¹¹ This has been labeled the paradoxical skin reactions to certain drugs.

Thermal sweating abnormalities. Heat stroke and exercise-induced cholinergic urticaria is thought to occur almost exclusively in atopic patients.¹¹² Sulzberger and Hermann¹¹³ noted a vicious cycle of sweat retention and dermatitis in patients with AD. They suspected that the retention of sweat may cause an itching crisis, irritation, and inflammation through the direct effect of distention of the ducts (seepage or forcing or injection of sweat into the surrounding tissues). Many patients are aware that sweating aggravates their AD.

NATURAL HISTORY OF AD

There is a correlation between the age of onset of AD and its severity. The earlier the onset, the more severe the course.¹¹⁴ Approximately 60% of patients experience the development of signs of AD before their first birthday, and another 30% experience the development by age 5 years.¹¹⁵ Although the natural course of AD is highly variable, many cases resolve before age 2 years, and in the remaining patients improvement at puberty is common. Ominous signs of a more persistent course are (1) early flexural involvement, (2) early extensive involvement, (3) "egg sensitive" patients, and (4) accompaniment by respiratory symptoms. It is rare to see AD after mid-life (50 years of age).¹¹⁵ However, despite the resolution of the eczematous component in atopic patients, many of the nonessential (or minor) findings (ie, xerosis, keratosis pilaris) persist for the rest of the patients' life.

Wuthrich¹¹⁶ recently reported his epidemiologic survey of more than 200 patients with AD. In that study, only 11.3% of the patients were considered cured, and a persistence rate of 63.1% was noted. Twenty-six percent of patients experienced healing during puberty, but in 20% of patients the eczema reappeared. He noted that up to 60% of the patients with AD also manifested respiratory allergies by age 23 years. He also noted that there was an inverse relationship between the AD and those patients with asthma (ie, when asthma worsened, the AD tended to improve, and vice versa). Hay fever, by contrast, appeared to be independent of the skin condition.

Predicting the course of AD is generally quite difficult. Seasonal variations are reported by many atopic patients, usually improving in the summer (ultraviolet light exposure and more relative humidity), worsening in the winter. Exacerbations of eczema may occur in any patient, usually after an encounter with any 1 of the "triggers" of itch. Remissions are noted by many patients, some of which may last for more than 10 years.

CONCLUSIONS

The increasing evidence that the incidence of all atopic diseases has increased worldwide over the last

few decades compels us to re-evaluate our data regarding its immunopathologic features, diagnostic criteria, and management. The recent knowledge explosion regarding the immunologic aberrations of atopy has given us better insight to the clinical manifestations and management of AD.

It seems obvious that the universal requirements for the diagnosis of AD must be atopy, pruritus and eczema. The unique inherent atopic skin findings are amply discussed in other papers of this supplement. The pruritus, which can be considered the "primary lesion" of AD, must be appreciated, because no therapeutic modality can be fully appreciated without the avoidance of all recognizable pruritogenic stimuli. The eczematous response of the atopic scratching can be seen in localized areas (eg, eyelids, nipples) or in hot sweaty areas (eg, the fossae and folds) or at times can be generalized. Its polymorphic (eg, acute, subacute, and/or chronic) presentation can be a diagnostic challenge for the most astute clinician. Fortunately, the common course and natural history of AD facilitates its recognition. Atypical presentations and lack of response to appropriate therapy should suggest an alternative diagnosis.

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