

11. Allergic and immunologic diseases of the skin

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Many skin diseases have an inflammatory or immune component, and anti-inflammatory drugs comprise a major portion of a dermatologist's therapeutic armamentarium. Although causes of most of these diseases remain obscure, mechanisms of lesion formation and explanations for symptoms are increasingly well documented. These developments, coupled with the expected availability of novel selective immunomodulatory agents, herald a new era for immunodermatology. Patients with psoriasis, allergic contact dermatitis, atopic dermatitis, urticaria, and autoantibody-mediated blistering diseases are among those who are likely to benefit from advances in the understanding of disease pathogenesis and the emergence of immunotherapeutics. (*J Allergy Clin Immunol* 2003;111:S560-70.)

Key words: Psoriasis, allergic contact dermatitis, atopic dermatitis, urticaria, pemphigus, chemokines, immunopathogenesis, autoantibodies, immunotherapeutics

Skin represents the body's largest immune organ. Components of both innate and adaptive immune systems are well represented in this tissue. The importance of skin's dendritic cells, resident mast cells, and infiltrating lymphocytes in skin immune reactions is firmly established. The roles that keratinocytes and endothelial cells play in the immunopathogenesis of skin disease are also well recognized. Recently, there has been remarkable progress in understanding innate immune responses in skin, in appreciating the importance of dendritic cells in shaping T-cell responses, and in delineating the roles of leukocyte-chemokine-endothelial interactions in leukocyte trafficking into skin. Many of these novel basic scientific discoveries have important therapeutic implications for patients with cutaneous disease.

Herein, we discuss several skin diseases that illustrate a number of emerging concepts in immune-mediated disease pathogenesis. The importance of T cells, including CD8 cells, as causal elements of skin disease, and the potential utility of T-cell-targeted therapeutics are emphasized in the sections on psoriasis and allergic contact dermatitis. Immunoglobulin (Ig) E-mediated inflammation and anomalous helper T cell development are addressed in the discussion on atopic dermatitis and urticaria. The pathogenic role that IgG autoantibodies play in blister formation in pemphigus is reviewed in the final section.

Abbreviations used

ACD:	Allergic contact dermatitis
ACE:	Angiotensin-converting enzyme
AchE:	Acetylcholinesterase
AD:	Atopic dermatitis
APC:	Antigen-presenting cells
CCR:	Chemokine class with two linked cysteine residues
CLA:	Cutaneous lymphocyte antigen
CTLA4Ig:	(CD152, molecular T-cells that terminate responses)
CTS:	Contact sensitivity
CXCR:	Chemokine class with one amino acid residue separating cysteine residues
Dsg:	Desmoglein
DTH:	Delayed type hypersensitivity
ELISA:	Enzyme-linked immunoadsorbent assay
FcεRI-γ:	High affinity receptor for IgE
HLA:	Human leukocyte antigen
HIV:	Human immunodeficiency virus
ICAM:	Intercellular adhesion molecule
IFN:	Interferon
IG:	Immunoglobulin
IL:	Interleukin
IVIG:	Intravenous immunoglobulin
LFA-3 TIP:	Alefacept
MHC:	Major histocompatibility complex
PDE:	Phosphodiesterase
PF:	Pemphigus foliaceus
PGE ₂ :	Prostaglandin E ₂
PNP:	Paraneoplastic pemphigus
PUVA:	Combination treatment of psoralin (photosensitizer) and ultraviolet light A
PV:	Pemphigus vulgaris
S:	Staphylococcal exotoxin
SSS:	Scalded skin syndrome
TARC:	Thymus and activation-regulated chemokine
Th:	T helper cells
TNF:	Tumor necrosis factor
TSST:	Toxic shock syndrome toxin
VCAM:	Vascular cell adhesion molecule
UV:	Ultraviolet

PSORIASIS

Clinical manifestations

Psoriasis is a relatively common chronic skin disease that affects 2%-3% of the US population. The most common clinical subset of psoriasis is chronic plaque psoriasis. Skin lesions usually appear as well-demarcated erythematous plaques with overlying thick silvery-gray scales. The skin of the scalp and extensor surfaces (eg,

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elbows and knees), as well as nails, are the most common areas affected, although lesions can occur anywhere on the body. Nail lesions appear as pits, onycholysis, or onychodystrophy. Skin disease severity ranges from a limited number of lesions to complete body surface involvement. Guttate psoriasis is a disease subtype that generally affects children and young adults, often developing after infections with β -hemolytic streptococcus. Lesions are small and coin-shaped (ie, guttate) in morphology and may herald the development of chronic plaque psoriasis. Pustular psoriasis and erythrodermic psoriasis are two rare, severe clinical variants of psoriasis. Lesions appear as pustules and diffuse erythema, respectively. Although pustular and erythrodermic psoriasis may develop as initial manifestations of disease, they usually affect individuals with pre-existing chronic plaque psoriasis. In particular, psoriasis patients who have been receiving systemic corticosteroids or cyclosporine may develop acute erythrodermic or pustular flares if they abruptly stop these medications. Additional systemic factors that may trigger or exacerbate psoriasis include infections (eg, HIV and streptococcus), injury to the skin, stress, medications (eg, lithium and beta-blockers), smoking, and alcohol intake.

An inflammatory seronegative spondyloarthropathy, called *psoriatic arthritis*, may coexist in up to 25% of individuals with psoriatic skin lesions. Psoriatic arthritis occurs in five major clinical disease patterns, including asymmetric oligoarthritis (the most common type of psoriatic arthritis), symmetric distal “osteoarthritis-like” joint disease, symmetric proximal “rheumatoid arthritis-like” joint disease, HLA-B27+ “ankylosing spondylitis-like” disease, and a severely deforming, destructive form, termed arthritis mutilans. Inflammatory bowel disease, both ulcerative colitis and Crohn’s disease, also occurs more commonly in patients with psoriasis.

Genetics

The age of onset for psoriasis is biphasic, with one peak in early life (mean age 16 in females, mean age 22 in males) and the other peak occurring later (mean age 60 in females, mean age 57 in males).¹ Overall, psoriasis has a familial basis in approximately one third of cases. First-degree relatives of patients with juvenile-onset psoriasis have a 10-fold higher risk of developing disease compared to the general population.¹ In addition, disease concordance in monozygotic twins occurs at a statistically significant higher rate compared to concordance in dizygotic twins.² No simple Mendelian pattern of dominant or recessive inheritance, however, is observed in familial cases of psoriasis.

Collectively, genetics data suggest that multiple genes at several loci are necessary for the development of disease. There is general agreement that one of the psoriasis genes is located within the MHC region (in the short arm of chromosome 6, termed *PSORS1*), and that several other susceptibility genes are scattered throughout the genome.³ While *HLA-Cw6* is tightly linked to *PSORS1*, it is not believed to be the causal gene. More specifically, the *PSORS1* locus has been localized to a chromosomal

region that is telomeric to *HLA-C*.³ Linkage disequilibrium studies have been helpful in identifying a number of other candidate psoriasis susceptibility genes. *PSORS2* is located on distal chromosome 17q. In addition, less well-established loci on chromosome 4q (*PSORS3*), 1q21 (*PSORS4*), 3q21 (*PSORS5*), 19p (*PSORS6*), and 1p (*PSORS7*), as well as loci on chromosomes 16q and 20, have been proposed as candidate disease genes for psoriasis and are under active investigation.

Pathophysiology

Histologically, psoriasis is characterized by marked keratinocyte hyperproliferation, a dense inflammatory infiltrate consisting of T cells and neutrophils, and vascular dilatation and proliferation. Historically, the primary “defect” in psoriasis patients was believed to be abnormal keratinocyte proliferation. Indeed, expression of many genes associated with keratinocyte proliferation, including epidermal growth factor receptor, are upregulated in psoriasis lesions.⁴ In the past 15 years, however, psoriasis has been re-categorized as a primary T-cell-mediated inflammatory disease. Keratinocyte hyperproliferation is now believed to be a secondary biologic phenomenon, driven mainly by pro-inflammatory and type 1 cytokines produced locally by infiltrating T cells. T cells that demonstrate activated memory (CD45RO+) CD4+ and CD8+ phenotypes are present within the dermis and epidermis, respectively, of active psoriatic skin lesions.⁵

Activated T cells within psoriatic lesions elaborate many type 1 and pro-inflammatory cytokines, including IFN- γ , TNF- α , IL-1, and IL-2.⁶⁻⁸ By contrast, cells within lesions express relatively low levels of type 2 cytokines, such as IL-4 and IL-10.⁹ It is hypothesized that the activated memory T cells within psoriasis lesions are responding to an “autoantigen” within skin, although the nature and location (epidermis versus dermis) of such an antigen is unknown at this time. Recent studies also suggest that T cell trafficking, mediated by coordinated expression of chemokines within skin and corresponding chemokine receptors on inflammatory cells, plays an important role in the pathogenesis of psoriasis.¹⁰

Treatment

For relatively mild or limited disease, patients are often treated with mid-to-high potency topical corticosteroids. Calcipotriene (a vitamin D₃ analogue) and tazarotene (a retinoid) are newer topical agents used for chronic plaque psoriasis that are also effective for these types of patients. Traditional therapies used for more severe psoriasis, believed for years to work by interfering with keratinocyte proliferation, include orally administered methotrexate and acitretin (a retinoid), as well as ultraviolet light B phototherapy and PUVA (a combination approach using the photosensitizing drug psoralen before exposure to ultraviolet light A phototherapy). Findings from newer studies suggest that these traditional approaches to psoriasis may be having direct effects on lesional T cells, instead of or in addition to inhibiting keratinocyte growth.

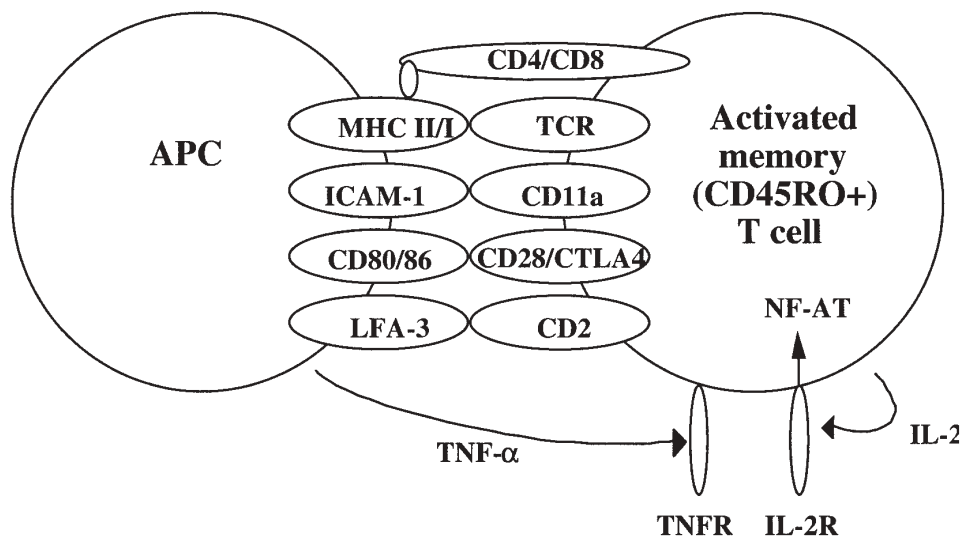


FIG 1. Schematic of potential cell surface interactions between APC (antigen presenting cells) and memory CD4⁺ or CD8⁺ T cells within lesions of psoriasis. Each of these interactions could be targeted for therapeutic purposes to kill T cells or block their full activation and biologic activity.

Notably, recent exciting advances in understanding psoriasis as a T-cell-mediated inflammatory disease have led to the testing and development of drugs that specifically target activated T cells in some way (Fig 1). This revolution began when cyclosporine, which acts by blocking NF-AT-mediated signal transduction in activated T cells, was shown to be effective for patients with psoriasis.¹¹ A key role for T cells in psoriasis pathogenesis was strengthened by the report that psoriasis patients benefited from receiving IL-2 toxin, a treatment that directly killed activated T cells.¹² These seminal studies led the way for additional novel immunotherapeutic approaches to psoriasis. For example, CTLA4Ig, a molecule that binds to CD80 (B7-1) and CD86 (B7-2) on antigen-presenting cells (APC), can interfere with T cell activation and improve psoriasis.¹³ Like IL-2 toxin, treatment with anti-IL-2 receptor antibodies,¹⁴ anti-CD4 antibodies,¹⁵ and LFA-3 TIP (ie, alefacept)¹⁶ are recently described drugs that directly kill activated memory T cells and lead to clearing of psoriasis lesions. Pro-inflammatory and type 1 cytokines produced by activated T cells within psoriasis lesions can also be targeted. In this regard, anti-TNF- α antibodies (ie, infliximab)¹⁷ and soluble TNF- α receptor (ie, etanercept)¹⁸ have recently been shown to have significant anti-psoriatic activity. Alternatively, treating psoriasis patients by supplying supra-physiologic doses of type 2 anti-inflammatory cytokines (eg, IL-10 or IL-11) has also been explored.^{9,19,20} Lastly, T-cell trafficking into skin can be blocked; this is the basis for anti-CD11a antibody therapy, which interferes with T-cell binding to microvascular endothelial cells.^{21,22} Other than cyclosporine, the psoriasis treatments mentioned above that block the biologic effects of T-cell activation are all relatively new. Thus, many confirmatory clinical studies need to be performed with these agents to establish optimal dosing regimens

that maximize efficacy and minimize potential immunosuppressive side effects.

ALLERGIC CONTACT DERMATITIS

Contact dermatitis is a common inflammatory dermatosis affecting primarily adults that, when chronic, is a cause of considerable morbidity.²³ If contact dermatitis occurs in association with occupational exposure, the financial impact on both patients and employers can be considerable. As the name implies, the disease allergic contact dermatitis (ACD) results from an antigen-specific, lymphocyte-mediated hypersensitivity reaction. Irritant contact dermatitis is more common than ACD and reflects antigen-nonspecific toxicity. ACD is of interest because it represents a significant health problem, and also because results of studies of experimentally induced contact sensitivity (CTS) reactions in humans and mice form the basis for our understanding of many aspects of cutaneous immunology.

Clinical manifestations

Lesions of ACD may be difficult to distinguish from those of other forms of eczema such as atopic dermatitis (AD). Acute ACD is characterized by pruritic vesicles on a background of erythema at sites of exposure. A vesicular component may persist in more chronic (subacute) lesions, but erythema and scaling are more usual. Long-standing lesions are typified by skin thickening with increased prominence of skin markings (lichenification) and scaling. Vesiculation is not a feature of chronic eczema, and erythema may not be marked.

Pathophysiology

Although CTS and delayed-type hypersensitivity (DTH) reactions are both T-cell-mediated, recent data

generated from studies in mice (and corroborative studies in humans) suggest that the mechanisms that are responsible for generation and evolution of these inflammatory processes are very different.^{24,25} Effectors in DTH reactions are MHC class II antigen-restricted CD4⁺ T cells, whereas CTS effectors are CD8⁺ T cells. In CTS reactions, CD4 T cells function as regulatory cells that attenuate responses rather than cells that incite inflammation. Antigens that cause DTH reactions are also distinct from those that elicit ACD. The former are typically soluble, relatively large proteins, while the latter are small, reactive lipophilic electrophiles (haptens) or metal ions such as nickel or cobalt that are not allergenic alone, but become immunostimulatory after binding to proteins or peptides. It has been suggested that “complete antigens” in ACD may represent haptens (or metal ions) that are bound to keratinocyte-derived proteins, MHC molecules that are expressed on the surfaces of APC or already processed MHC-binding peptides.

It is generally accepted that CTS reactions are initiated when epidermal Langerhans cells (and perhaps dermal dendritic cells) become activated and migrate to draining lymph nodes where they stimulate naïve T cells that react with antigen in the context of MHC class I (and class II) antigens.²⁴ Mobilization of dendritic cells occurs in response to local generation of proinflammatory cytokines such as IL-1 and TNF- α . Most contact allergens are also irritants to some degree, and it is likely that irritancy plays an important role in dendritic cell activation. Activated dendritic cells express high levels of CCR7, MHC antigens, and costimulatory molecules (eg, CD40, CD80, CD86), and translocate through dermis to lymphatics by means of a mechanism that is dependent on secondary lymphoid-tissue chemokine produced by lymphatics. This latter process also involves expression of metalloproteases by dendritic cells. The eventual outcome of interactions between dendritic cells and T cells in lymph nodes draining antigen-exposed skin is generation of antigen-reactive memory CD8⁺ T cells (as well as CD4⁺ regulatory T cells).

Clinically evident ACD ensues when, after initial sensitization, individuals with prior exposure are rechallenged.^{24,25} Memory CD8 T cells circulate in peripheral blood, home to contact allergen-exposed skin utilizing cell surface adhesion molecules (eg, CLA) that bind to counter receptors on endothelial cells (E-selectin) in venules in inflamed skin, and chemokine receptors (including CXCR3). Although IL-12 does not appear to play an important role in the generation of ACD, CD8 T-cell effectors produce large amounts of IFN- γ . The cytotoxic potential of ACD effectors is also important, since mice that lack perforin and have a disabled Fas-FasL pathway exhibit severely blunted CTS responses.

Clinical evaluation and treatment

Because avoidance is the best (and perhaps the only truly effective) treatment for ACD, accurate diagnosis and successful identification of the inciting agent is crit-

ically important. The diagnosis and treatment of patients with chronic contact dermatitis can be very challenging. Thus, referral to a dermatologist with special expertise in ACD may be advantageous, especially if employment-related compensation or disability issues are involved.

The diagnosis of ACD is facilitated by the combination of careful history taking, a meticulous physical examination, and (if necessary) patch testing.²³ Skin biopsies will reveal features of spongiotic dermatitis, but may not suggest ACD as a specific diagnosis. Elicitation of a history of a recent hike in the woods, followed several days later by development of intensely pruritic vesicles in linear arrays on exposed surfaces of the extremities, suggests acute ACD due to urushiol in “poison ivy” plants, for example. An erythematous scaling plaque in areas where metal in jewelry apposes skin is suggestive of ACD to nickel. Diffuse erythema and swelling involving the eyelids is consistent with allergy to a component of fingernail polish. More challenging is the patient with a long history of eczematous lesions, where a history of discrete exposure cannot be elicited and the distribution of lesions does not suggest an obvious cause.

In these patients, or in patients where the history or physical examination is only suggestive of ACD, patch testing may be very helpful.^{23,26} Patch testing is a procedure in which well-characterized, known contact allergens that have been suspended at standard concentrations in white petrolatum are applied, under occlusion, to small areas of uninvolved skin with a standardized approach. After 48 hours, the chemical patches are removed and the underlying skin is evaluated for erythema, induration, and vesiculation. The vigor of the reactions is quantified with an accepted and validated scoring system. Delayed reactions are assessed at later time points (3-7 days). Although the battery of antigens that is routinely utilized is predicted to include chemicals that will cause most cases of ACD, more extensive testing may be required. This might involve incorporation of additional chemicals into a closed patch testing procedure under carefully monitored circumstances, or testing of potential offending agents or products under conditions of normal use. Interpretation of patch testing results, combined with clues obtained from the history and physical examination, may allow accurate diagnosis. However, false or uninformative positive reactions are frequent.

Identification of the cause of ACD should prompt avoidance of the offending agent. Although exposure of patients to low levels of sensitizing chemicals may be permissible,²⁷ strict avoidance is preferable. Physical barriers (including gloves) may provide protection; barrier creams are not generally useful. Antihistamines may provide some symptomatic relief and high-potency topical corticosteroids may hasten lesion resolution. Cases of severe, acute ACD (such as those associated with rhus dermatitis) may require systemic steroid treatment at relatively high doses for a week or more. Adjunctive phototherapy with ultraviolet B light or PUVA may be indicated for patients with severe chronic ACD. The future availability of topical formulations of anti-inflammatory agents that specifically target cells or signal transduction pathways relevant to ACD is anticipated.

TABLE I. Immunodysregulation in atopic dermatitis

Increased compared to normals (acute disease)
IL-13 (by lesional skin T cells and mast cells)
IL-4 and IL-5-producing T _H 2 cells (in peripheral blood and skin)
Serum IgE
Eosinophils (in blood)
Spontaneous histamine release from basophils
IL-10, GM-CSF, PGE2 from macrophages
Eosinophil-derived protein products
Chemokines (TARC, RANTES, eotaxin) (by skin keratinocytes and endothelial cells)
Increased compared to normals (chronic disease)
IL-5 (by lesional T cells)
IL-12 (by lesional dendritic cells or macrophages)
GM-CSF (by keratinocytes and possibly other cells)
IFN- γ (by lesional T cells)
Macrophages and T _H 1 cells in skin
Eosinophils in skin
Decreased compared to normals
IFN- γ -producing T _H 1 cells (in acute disease)
CD8 suppressor/cytotoxic T cells
IL-15 (by keratinocytes and dendritic cells)

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic, relapsing skin disorder that often begins in childhood, improves with age, but often manifests itself in adulthood with a relapsing course. Commonly associated with allergic rhinitis and asthma, AD reflects an allergic (T_H2) bias in response to a variety of environmental and bacterial stimuli. Although the majority of individuals have mild or moderate disease that can be controlled by topical medications, the increasing prevalence (> 10% of children) of this dysregulation of the immune system increases the need to understand its pathogenesis and improve treatment.

Clinical manifestations

The diagnosis of AD is based on a constellation of clinical features that are variably present. These features include pruritus at typical sites, a chronic/relapsing clinical course, and a personal or family history of the atopic triad: asthma, allergic rhinitis/conjunctivitis, and AD. Acute lesions may present initially with intensely pruritic, erythematous macules or papules. With scratching of primary lesions, secondary lesions may appear as excoriated papules with crust and serum exudates. In young children, lesions tend to occur on the face, scalp, and extensor surfaces of the arms and legs. In older children, lesions tend to localize within flexural areas of the extremities, although intense periorbital pruritus and rubbing may lead to infraorbital folds (Morgan's folds). In both children and adults, AD skin tends to be dry, a well-known trait that may reflect loss of cutaneous barrier function. AD skin is also associated with increased permeability to allergens and microbes. Chronic AD lesions are characterized by lichenification (thickening and accentuation of skin lines) of skin. With intense rubbing, marked hypertrophy of the epidermis resulting in prurigo nodules may occur. In subacute disease, lesions may

appear as erythematous, scaling patches and papules often with crusting that may suggest bacterial superinfection. Intense pruritus is often the most problematic aspect of the disease. Indeed, the trauma related to rubbing and scratching of the skin may lead to additional skin inflammation by means of the release of keratinocyte-derived proinflammatory mediators.

The diagnosis of AD is usually based on clinical history and a physical examination, since biopsies usually reveal only scant lymphocytic infiltrate in the dermis and epidermis. In acute disease, cells such as eosinophils, basophils, and mast cells are not present in large numbers. The lymphocytic infiltrate in early AD consists primarily of CD4⁺ memory T cells. The epidermis may show mild edema but is usually rather unremarkable. In chronic lesions, the epidermis shows moderate to extensive hyperplasia, while the dermis shows increased numbers of eosinophils and mononuclear cells. Because of the relatively non-specific histologic appearance of AD, biopsies are rarely performed when the clinical picture is compatible with AD. Skin biopsies, however, may be indicated in cases of unusual presentations of AD in children or the first presentation of eczematous symptoms in an adult. In these cases, potentially serious systemic diseases with AD-like features must be ruled out. These diseases include Wiskott-Aldrich syndrome, immunodeficiency syndromes, nutritional deficiencies, cutaneous T-cell lymphoma, and pemphigus foliaceus.

Pathophysiology

AD likely results from dysregulated, T_H2-biased immune responses to environmental stimuli.²⁸ A summary of the immunologic features of AD is shown in Table I. In AD, elevated IgE levels, as well as increased numbers of eosinophils, are found in the blood. Allergen-specific T cells that produce IL-4, IL-5, and IL-13 also appear to be increased in number in the peripheral blood of patients with AD. In addition to promoting antibody responses, IL-4 and IL-13 also inhibit the ability of the T cells to generate T_H1 cytokines such as IFN- γ . Indeed, blood mononuclear cells from patients with AD have a reduced capacity to generate this critical T_H1 cytokine. The finding that AD patients respond well to treatment with IFN- γ suggests that the loss of IFN- γ may be a critical pathophysiologic mechanism in atopic disease.²⁹

IL-15, a T_H1-supportive cytokine that up-regulates IFN- γ , is also down-regulated in individuals with AD.³⁰ Professional APC (ie, dendritic cells) in AD skin show surface-bound IgE, which may enable dendritic cells to more efficiently present allergens to T cells. In acute lesions, T cells expressing IL-4, IL-5, and IL-13 are abundant, while IFN- γ ⁺ cells are rare. Interestingly, IFN- γ ⁺ cells become more abundant as the disease progresses, suggesting a switch from a T_H2 to a T_H1 predominant response. Whether this represents further progression of the disease or compensation of the host in an attempt to down-modulate inflammation is not known.

There is emerging evidence that chemokines, a large family of small chemoattractant cytokines, and their G-

protein-coupled, seven-transmembrane-spanning receptors play an important role in the recruitment of specific immune cell populations into skin in AD, as well as other inflammatory skin conditions.³¹ The chemokines thought to stimulate migration of inflammatory cells to the skin are expressed primarily by keratinocytes and endothelial cells, although other cells (eg, dendritic cells) may contribute to the chemokine milieu that attract specific subsets of leukocytes. Based on the spacing of critical cysteine residues, chemokines are grouped into 4 classes, 2 of which (the CC and CXC families) contain the vast majority of known chemokines. The presence of IL-4 and IL-13 in the skin stimulates the expression of chemokines, some of which (eotaxin, monocyte chemoattractant protein-4, and thymus and activation-regulated chemokine [TARC]) appear to be expressed at high levels in atopic skin.³² TARC, a chemokine that engages CC chemokine receptor 4 (CCR4), is expressed to a higher degree by keratinocytes of patients with AD compared to psoriasis. Because inflamed endothelial cells also express TARC, it could potentially act as a pro-adhesive signal that stimulates CCR4⁺ lymphocytes to adhere to dermal vessels in atopic skin. Several reports have demonstrated that chemokine receptor engagement triggers enhanced binding of lymphocyte integrins to their respective ligands (eg, ICAM-1 and VCAM-1). Serum levels of TARC were markedly elevated in the blood of patients with AD, but not in normal controls or in patients with psoriasis.³³ Notably, TARC's receptor (CCR4) appeared to be preferentially expressed by T_H2 cells that express the cutaneous lymphocyte-associated antigen (CLA), a marker for skin-homing T cells.

Other chemokines may be involved in AD, as well. Some of these chemokines (ie, eotaxin and RANTES) appear more specifically to attract T_H2 T cells, as well as eosinophils and basophils to the skin. Interestingly, mutations in the promoter region of the chemokine RANTES that increase its expression by up to 8-fold (vs normals) were found in some children with AD.³⁴ However, this finding has been tempered by other reports that show no association of this mutation with an increased atopic tendency. IL-16, a cytokine produced by a variety of immune cells as well as epithelial cells, is a potent chemoattractant for CD4⁺ T cells and appears to be up-regulated in the skin of both acute and chronic AD. Other biochemical defects in patients with AD include increased expression of cAMP-phosphodiesterase (PDE) in immune cells leading to the increased production of PDE₂ and IL-10 by monocytes and eventual interference with the production of IFN- γ .

Role of allergens in AD

Potential allergens in AD include food, and it is clear that certain subsets of AD patients have well-documented skin eruptions after the ingestion of certain foods, including peanuts, eggs, soy, and wheat. Skin-prick tests have high sensitivity for identification of food-allergic individuals, and the combined use of this screening test with serum testing for food-specific IgE may help in the

identification (and subsequent elimination) of the allergenic food item(s).³⁵ Although limited data suggest that breast-feeding and strict avoidance diets may help infants with AD, the benefits of these regimens with older children and adults are controversial. Inhaled allergens such as ragweed pollen, dust mites, timothy grass, and horse dander may also play a significant pathogenic role in AD. Indeed, 27 of 30 children with AD also had positive patch testing with a mixture of common aeroallergens that resulted in the development of eczematous skin lesions.³⁶

Microbes, particularly *Staphylococcus aureus*, may play a significant role in the pathogenesis of AD.³⁷ The skin of AD patients is frequently colonized by *S aureus*. This may result because *S aureus* bacteria express a fibronectin binding protein that may allow these organisms to attach to fibronectin, which is abnormally expressed in stratum corneum of AD patients.³⁸ The *Staphylococcal* exotoxins (SE-A, SE-B, and TSST-1) represent a family of superantigens that facilitate the binding MHC class II to the T-cell receptor without using the classical peptide groove. SE may activate skin Langerhans cells and macrophages, leading to the production of keratinocyte inflammatory mediators such as IL-1 and TNF- α . These cytokines greatly up-regulate a variety of endothelial cell adhesion receptors and chemokines that, in turn, recruit T cells from the blood. One such adhesion receptor that is relatively specific for skin endothelial cells is E-selection, the molecule that binds to the carbohydrate epitopes displayed by CLA⁺, skin-homing memory T cells. CLA⁺ antigen-specific T cells from patients with AD have an enhanced capacity to produce T_H2 cytokines compared with CLA-negative T cells from the same patients. AD patients often have IgE antibodies against an SE antigen. When bound to basophils, SE-specific antibodies mediate histamine production and can potentially induce itching in patients. IgE antibodies directed against commonly found skin yeast (*P ovale*) and dermatophytes (*T rubrum*) may potentially play analogous roles in triggering humoral immune responses.

Treatment

Successful treatment of atopic dermatitis requires relief of pruritus, restoration of the barrier function of skin, elimination of environmental factors that exacerbate AD, and amelioration of the inflammation.³⁹ For severe pruritus, doxepin hydrochloride blocks both H₁- and H₂- histamine receptors and has sedating activity (for insomnia secondary to intense pruritus). The dry skin associated with AD can be reversed by a number of simple measures (avoidance of hot showers and strong soaps, generous use of emollients, and occlusive dressings on traumatized skin) that will help restore the barrier function of skin. Topical corticosteroids are still a mainstay of treatment for AD. For moderate-to-severe disease, ointment-based corticosteroids (eg, 0.1% triamcinolone acetonide ointment) and higher potency agents (eg, 0.05% fluocinonide ointment) should be used to control disease quickly, rather than using lower strength agents that are unlikely to be effective. Tacrolimus⁴⁰ and pimecrolimus bind FK506-binding protein and block T-cell

function via inhibition of calcineurin-dependent transcription of genes such as IL-2. These agents are expensive, but they appear to be effective for AD and do not have the same risk profile as the corticosteroids. Finally, reduction of bacterial (eg, *S aureus*) colonization with topical antibiotics or brief courses of oral antibiotics is especially useful in AD patients with crusted or exudative disease.

In severe AD patients, a variety of other modalities may be useful. Ultraviolet (UV) light therapy, including recently-developed narrow-band UVB (311 nm) devices⁴¹ and psoralen plus UVA (PUVA), has immunosuppressive effects secondary to its ability to induce apoptosis of APC in the skin and its tendency to stimulate keratinocyte production of immunosuppressive cytokines such as IL-10. Systemic immunosuppressive agents, such as methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, and high-dose intravenous immunoglobulin (IVIG),⁴² have also been used, although these drugs should be reserved for recalcitrant disease in light of their potential for serious adverse effects.

Understanding the molecular pathogenesis of AD has led to the development of agents that may ultimately be of benefit to patients. PDE inhibitors,⁴³ such as Ro 20-1724, could reduce expression of IL-10 and thus help tip the balance toward a T_H1 -type response. Already, topical formulations of PDE inhibitors have shown some clinical benefit in AD. The T_H1 cytokine, IFN- γ , has been shown to be safe and efficacious with long-term (up to 2 years) daily treatment of AD patients and may help reduce other atopic symptoms, as well.²⁹ Perhaps most exciting are agents that specifically target components of the T_H2 immune response such as IL-4, IL-5, and IgE. These agents are already in development and have shown activity in preclinical models. In the future, therapeutics that target AD-specific chemokines that attract eosinophils and T_H2 cells may also be of benefit in this disease.

URTICARIA

Clinical manifestations

Urticaria represent transient localized areas of edema within skin or mucous membrane tissue. Lesions that affect the superficial dermis are called wheals. Wheals are usually oval in shape and pruritic. Initially, wheals have pale centers surrounded by rings of erythema, whereas slightly older lesions are more uniformly pink in color. Individual wheals resolve completely within 24 hours of onset; lesions lasting longer should raise suspicion for the diagnosis of vasculitis presenting as urticarial lesions (ie, urticarial vasculitis). Transient localized edema within deeper areas of skin or mucous membrane tissue are referred to as angioedema and are typically painful, rather than pruritic. The term chronic urticaria, as opposed to acute urticaria, refers to urticaria that has recurred at least twice a week for a total of at least 6 weeks.

Clinical evaluation and pathogenesis

Urticaria occurs following mast cell degranulation with-

in skin. Many factors can trigger mast cell degranulation and the onset of urticaria, including physical factors (eg, heat, cold, sunlight, pressure, stress), medications (eg, aspirin, non-steroidal anti-inflammatory agents, codeine, morphine, radiocontrast media, progesterone, penicillin, ACE inhibitors), infections (sinusitis, *Helicobacter pylori*, parasites, candidiasis), foods (eg, peanuts, shellfish, food additives), and chronic inflammatory, autoimmune, or systemic diseases (eg, gastritis, thyroid disease, C1 esterase inhibitor deficiency).⁴² Thus, evaluation of patients with urticaria begins with a thorough history, focusing the questions on potential triggering factors. In general, patients with acute urticaria require no laboratory evaluation. For patients with chronic urticaria, laboratory testing for causative agents/triggers should be limited and focused on findings uncovered by means of a thorough history and physical examination (eg, thyroid profile testing or sinus x-rays films only if suspected).

Investigators have detected autoantibodies directed against the α subunit of the high-affinity IgE receptor (Fc ϵ RI α) in a third to one half of all patients with chronic urticaria of uncertain cause.⁴⁵⁻⁴⁸ These autoantibodies are of the IgG₁ or IgG₃ subclass and effectively fix complement and induce histamine release from basophils and mast cells that express Fc ϵ RI α . Anti-IgE receptor autoantibodies are also found in patients with other diseases, such as pemphigus vulgaris, dermatomyositis, and lupus erythematosus. The autoantibodies found in these patients, however, are of the IgG₂ or IgG₄ subclass and neither fix complement nor induce histamine release from basophils and mast cells in vitro.⁴⁸ An in vivo assay to detect anti-IgE receptor autoantibodies is called the autologous serum skin test. In this test, a wheal develops at the site of injection within 30 minutes following intradermal injection of autologous serum containing "functional" anti-Fc ϵ RI α autoantibodies.^{45,46} The sensitivity and specificity of this assay are 70% and 80%, respectively. In other words, only 70% of patients that have anti-Fc ϵ RI α autoantibodies (by Western blot or enzyme-linked immunosorbent assay [ELISA]) will have a positive autologous serum skin test, whereas 20% of individuals without detectable anti-Fc ϵ RI α autoantibodies will have a positive test in this assay. Although patients with anti-Fc ϵ RI α autoantibodies tend to have more severe urticaria, there is no other particular clinical correlation that identifies these patients as having "unique" urticarial disease caused by a specific pathogen or trigger.

Regardless of cause, urticaria shows similar features histologically. There is edema in the epidermis and mid-to-upper dermis, with dilation of postcapillary venules and lymphatics. Depending on the age of the lesion, there also is a mixed inflammatory infiltrate of varying intensity consisting of neutrophils, eosinophils, macrophages, T cells, and mast cells. Whether absolute numbers of mast cells are increased in wheals, or whether they are simply more sensitive to degranulation, is still debated. Histamine is the most important pre-formed mediator that is released by mast cells, and many of the early tissue effects observed in urticarial lesions can be attributed to histamine release.

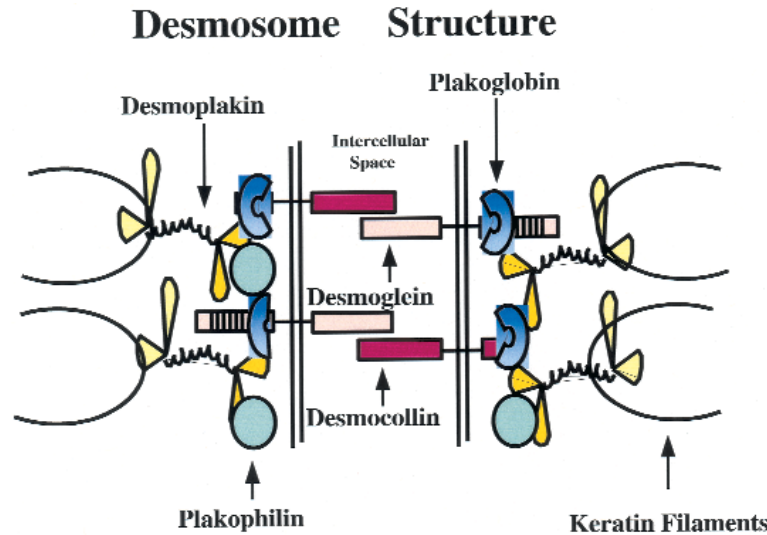


FIG 2. Desmosome structure. Adapted from a figure provided by Dr. Kathleen Green (Northwestern University Medical School) with permission.

Newly synthesized mast-cell products, such as leukotrienes, prostaglandins, platelet-activating factor, and TNF- α , may contribute to later events in the life cycle of a wheal.

Treatment

The cause or triggering events that lead to urticaria must be fully explored through a thorough history and physical examination (as mentioned above). For example, physical factors known or suspected to cause urticaria should be identified and avoided, medications and foods known or suspected to trigger urticaria should be eliminated from the diet, and known or suspected chronic infections should be treated. If disease persists despite these efforts, the first choice of medical therapy for all patients with urticaria is regular use of non-sedating anti-histamines.⁴⁴ Currently, these include cetirizine, fexofenadine, loratadine, and desloratadine. If still unsuccessful, the next step in medical therapy is to add sedating anti-histamines in the evening hours or to add an H₂ antagonist. Potent immunosuppressives, such as systemic corticosteroids and cyclosporine, should be reserved for only the most severe cases of urticaria and should not be used on a chronic basis. Lastly, plasmapheresis and IVIG therapy have been successfully used for patients with anti-Fc ϵ RI α autoantibodies, although experience with both of these modalities is limited.

INTRAEPIDERMAL BLISTERING DISEASES (PEMPHIGUS)

Bullous skin diseases are much less common than the cutaneous disorders discussed thus far, but are important because they cause significant morbidity and, in some cases, mortality. They are of additional interest because results of studies of acquired and inherited blistering skin diseases have provided complementary information that has defined the molecular bases of cell-cell and cell-

matrix adhesion in skin.^{49,50} Almost without exception, proteins targeted by antibodies in patients with blistering diseases represent adhesion molecules. In a number of instances, mutations in genes encoding the same proteins result in identical kinds of skin defects.

Intraepidermal separations reflect a loss of desmosome-mediated keratinocyte-keratinocyte adhesion (acantholysis) and result in clinically apparent blisters that typify patients with pemphigus.^{51,52} Desmosome dysfunction is caused, at least in part, by circulating autoantibodies that target desmosomal cadherins termed desmogleins (Fig 2). Three major types of pemphigus merit discussion.

Pemphigus vulgaris

Pemphigus vulgaris (PV) can occur at any age, but is most commonly diagnosed in middle-aged individuals.⁵¹ Persistent painful oral erosions are an almost invariant feature, and they are usually the presenting complaint. Thus, the diagnosis of PV should be considered in patients with chronic oral ulcerations. Erosions may also occur in other stratified squamous epithelia (eg, nasopharyngeal including laryngeal, esophageal, vaginal, and rectal epithelia) as well, and may cause significant morbidity. Skin lesions of PV are classically flaccid bullae without surrounding erythema. Scalp lesions are frequent and truncal lesions are common. Erosions develop as lesions evolve. Vegetative lesions that do not have an obvious bullous component may develop in intertriginous areas.

Patients with PV have circulating autoantibodies that bind to the surfaces of keratinocytes, and these immunoreactants are also present in situ. PV autoantibodies are pathogenic. In individual patients, disease activity roughly correlates with antibody titer. In addition, lesions of PV are sometimes present transiently in neonates born to mothers with active disease secondary to maternal-fetal transfer of IgG. Finally, injection of IgG fractions of PV sera into neonatal mice causes typical PV lesions.

Desmoglein 3 (Dsg3), a 130 kDa desmosomal cadherin, is a major target of antibodies in patients with PV, and the pathogenicity of anti-Dsg3 antibodies is well established. It has been suggested that autoantibodies that react with non-desmoglein keratinocyte surface proteins are also relevant.⁵³ The identity of these proteins and the extent to which antibodies directed against them contribute to disease pathogenesis is under active investigation. Antibodies reactive with another desmosomal cadherin, desmoglein 1 (Dsg1), however, do clearly contribute to lesion formation (see below).

Early in the course of disease and at a time when lesions are mucosal-predominant, PV patients have circulating antibodies that react exclusively with Dsg3. Non-cross-reactive anti-Dsg1 antibodies develop later, in conjunction with the appearance of skin lesions. Development of skin lesions in association with this classic example of epitope spreading reflects the differential representation of Dsg1 and Dsg3 in keratinocytes, at different levels of stratified squamous epithelia in different tissues, and has been termed the "desmoglein compensation hypothesis."⁵⁴

Current evidence indicates that Dsg3 is the dominant initial autoantigen in PV and that anti-Dsg3 antibodies induce lesion formation by blocking Dsg3 function or by down-modulating Dsg3 expression. In the passive transfer mouse model, complement is not required, and Fab fragments can induce lesions. In addition, the Dsg3 knockout mouse has a mucosal predominant phenotype that is virtually indistinguishable from early PV.⁵⁵

Although much is known about the mechanism of lesion formation, the cause of PV remains unknown. The disease is over-represented in Jews and people of Mediterranean heritage. Several unusual HLA DR alleles (DRB1*0402 and DQB1*0503) are common in subgroups of PV patients. Interestingly, Dsg3 peptides that are predicted to bind to the protein products of DRB1*0402 stimulate T cells from PV patients that carry this allele. This suggests that PV, like other antibody-mediated autoimmune diseases, is likely to result from a T cell, as well as perhaps a B cell, abnormality. The recent development of an active immunization mouse model of PV may facilitate a better understanding of disease etiology.⁵⁶

Diagnosis of PV is usually straightforward. Routine histology reveals suprabasal clefting and acantholysis. An inflammatory infiltrate is usually present, and eosinophils may be prominent. Antibodies that are bound to the surfaces of keratinocytes are demonstrable in biopsies of perilesional skin. Circulating autoantibodies can be detected and quantified by indirect immunofluorescence using monkey esophagus as the substrate or via ELISA.⁵⁷

PV was invariably fatal prior to the advent of corticosteroid therapy. Intractable, progressive mucosal erosions compromised oral intake and widespread skin lesions predisposed to bacterial infections. Today, it is more likely that patients will experience a life-threatening event as a result of treatment, rather than as a result of uncontrollable blistering disease. Corticosteroids remain the mainstay of treatment. High doses may be required for initial control, and improvement generally occurs before antibody titers

decrease. Most clinicians agree that steroid-sparing agents have a role in the long-term treatment of PV patients. Azathioprine and cyclophosphamide have been widely used. Plasmapheresis, used in conjunction with these agents, has been employed in severely affected patients. Recently, the use of mycophenolate mofetil has been popularized. The utility of pulse corticosteroids, pulse cyclophosphamide, intramuscular gold, and dapsone has also been reported. Most recently, IVIG therapy has been advocated. In the absence of controlled trials that define optimal regimens for PV patients, therapy is individualized, aiming for minimal (or acceptable) disease activity with the lowest possible toxicity.

Pemphigus foliaceus

Pemphigus foliaceus (PF) is another blistering skin disease caused by anti-desmoglein antibodies, but in this instance, the 160 kDa desmosomal cadherin Dsg1 is the target antigen.^{49,50} Patients with PF do not have mucosal involvement, and skin lesions are usually easy to differentiate from those of PV. PF skin lesions are characteristically erythematous, scaling plaques, or very superficial erosions found on the trunk and the central face. Intact bullae are rarely seen. When extensive, PF can cause an exfoliative erythroderma that may be difficult to distinguish from erythroderma caused by extensive papulosquamous diseases. The morbidity associated with PF is considerably less than that due to PV, although elderly patients with other medical problems and extensive PF may be at risk.

Anti-Dsg1 antibodies cause lesions of PF. By analogy to anti-Dsg3 antibodies in PV, anti-Dsg1 antibodies may cause PF lesions by blocking Dsg1 function or by reducing levels of Dsg1 surface expression. Recent advances in the understanding of the pathogenesis of staphylococcal scaled skin syndrome (SSSS) and bullous impetigo support this conclusion. Incubation of purified exfoliatins A or B with recombinant desmogleins revealed that these toxins are proteases, and that Dsg1 (but not Dsg3) is degraded by the toxins.^{58,59} Interestingly, routine histologic sections from lesional biopsies of PF and SSS/bullous impetigo both show subcorneal separations and cannot be distinguished from each other. In addition to bolstering support for the concept that Dsg1 is the relevant autoantibody target in PF, these observations provide a potential explanation for the empiric observation that antibiotics are often beneficial in pemphigus patients.

The cause of sporadic PF is unknown. In the United States and Europe, most patients are middle aged at the time of presentation. Jewish patients are not over represented, but several HLA susceptibility genes have been identified (DRB1 0404, 1402, and 1406). An interesting endemic form of PF is found in Brazil. Children and adults are susceptible, and there is no obvious genetic predisposition. Endemic PF (fogo selvagem) and sporadic PF are indistinguishable by means of clinical, histologic, and immunochemical criteria. In Brazil, the disease is most common in rural river valleys that include the range of a particular black fly, *Simulium nigritanum*. Epidemiologic studies suggest that this fly may be a relevant vector.⁶⁰

A fly-borne agent may initiate an infection that, in susceptible individuals, triggers development of PF. Improved understanding of the cause of endemic PF may allow determination of the etiology of the sporadic form.

Like PV, PF can be readily diagnosed with clinical, histologic and immunochemical criteria. Routine histology reveals a separation immediately below the stratum corneum, such that this superficial layer may be lost from biopsy specimens. Inflammation is variable, but may be scant. PV and PF sera also give identical direct and indirect immunofluorescence results. Immunoreactivities in PF and PV sera can be differentiated only by immunoprecipitation studies or by means of commercially available ELISA kits that employ recombinant Dsg1 and Dsg3 antigens.⁵⁷

PF patients with limited disease may be able to be treated with fluorinated topical steroid preparations alone. More extensive disease necessitates systemic therapy with the same agents that are used in PV. Dapsone may be more useful in PF than PV, and antibiotics that eradicate *S aureus* may be useful adjuncts. The level of enthusiasm for multi-drug immunosuppressive regimens with their attendant toxicities should be tempered by the relatively benign course of the disease.

Paraneoplastic pemphigus

Paraneoplastic pemphigus (PNP) is a rare disease that is frequently devastating.^{51,60} Patients with known or suspected neoplasia (usually lymphoreticular) present with erosions involving several mucosal surfaces and polymorphic skin lesions. Notoriously resistant to therapy, patients usually succumb to their malignancy or bronchiolitis obliterans that results from involvement of respiratory epithelium with PNP. The diagnosis of PNP in a child should prompt a search for a tumor. Selected children with PNP in association with solitary Castleman's disease have experienced remission after complete resection of the tumor.

The constellation of clinical findings in PNP patients may be striking. Routine histology of PNP lesions typically reveals an intense band-like lymphocytic infiltrate. Direct immunofluorescence studies demonstrate antibodies bound to the surfaces of keratinocytes, and C3 associated with the basement membrane zone. Antibodies that bind to both keratinocytes and to desmosomes in tissues other than skin can also be detected in the circulation of PNP patients. Immunochemical characterization of antibodies in PNP sera reveals the presence of anti-Dsg3 antibodies, as well as antibodies reactive with members of a family of intracellular desmosomal plaque proteins termed "plakins" (Fig 2).⁶² Anti-Dsg3 antibodies from patients cause blisters in neonatal mice in passive transfer studies.⁶³ The contribution of anti-plakin antibodies to lesion formation has yet to be defined. Antibodies that bind to respiratory epithelia have been detected in sera from PNP patients and may be involved in the pathogenesis of bronchiolitis obliterans.

The cause of PNP is unknown and the mechanisms that are responsible for generation of non-crossreactive antibodies that bind to related proteins (plakins) that are sequestered in a single structure in keratinocytes (desmo-

some) remain to be elucidated.⁶⁴ The apparent relationship between eradication of Castleman's disease and PNP remission in selected patients suggests that one or more tumor-derived (soluble) factors are involved in disease initiation and/or persistence.

PNP is treated with the same spectrum of immunosuppressive agents that are used in patients with PV. PNP patients typically do not respond well to therapy.

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