

# Images in Allergy and Immunology

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## Immunopathology of atopic dermatitis

**Editor's note:** This feature, Images in allergy and immunology, is designed to highlight current concepts of the immunopathology of allergic diseases and other common immunologically mediated diseases. The presentation will appear as sets of images that involve cross-pathology, histopathology, and molecular pathology and will cover a range of topics of interest to allergists and immunologists.

Atopic dermatitis (AD) is a chronic inflammatory disease involving cutaneous inflammatory hypersensitivity to environmental triggers. AD is immunologically complex, involving multiple cell types and inflammatory pathways in its development, progression, and pathology (Fig 1). Although a full understanding of the immunopathology of AD is still lacking, much ground has been covered by analysis of the main cell types and inflammatory proteins in AD skin lesions.

Acute atopic AD skin lesions are associated with increased numbers of CD4<sup>+</sup> cells (Fig 2) that infiltrate the epithelium and an increased number of T<sub>H</sub>2 cells expressing mRNA for IL-4 and IL-13 compared with IFN- $\gamma$  mRNA- and IL-12 mRNA-expressing cells (Fig 3).<sup>1,2</sup> The T<sub>H</sub>2 cells are memory cells that also express cutaneous lymphocyte-associated antigen, a homing receptor to direct the cells to the skin. T<sub>H</sub>2-associated cytokines are thought to promote IgE production and thus sensitization to allergen. In contrast, in chronic lichenified AD skin lesions, fewer IL-4

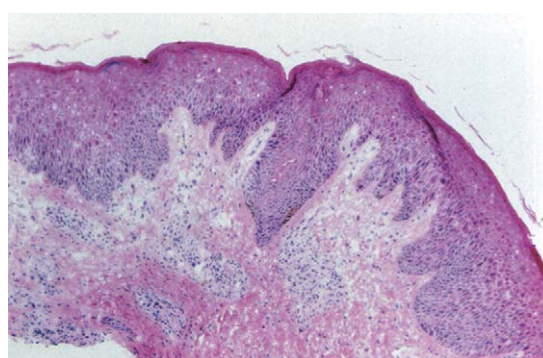


**FIG 1.** Hematoxylin and eosin stain of skin lesions in patients with AD. Note the large numbers of small mononuclear cells infiltrating the tissue.

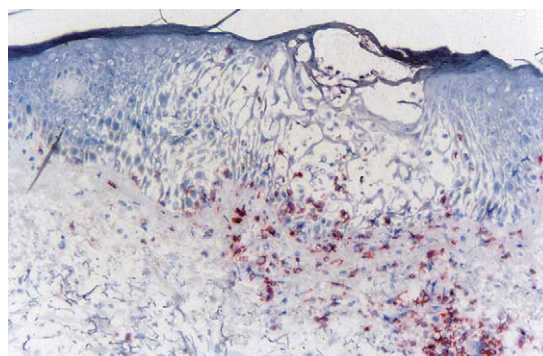


**FIG 2.** Immunohistochemistry demonstrates large numbers of infiltrating CD4<sup>+</sup> cells stained with fast red by using the alkaline phosphatase method in skin lesions of patients with acute AD.

and IL-13 mRNA-expressing cells are present, but greater numbers of IL-5, GM-CSF, (Fig 4), IL-12, and IFN- $\gamma$  mRNA-expressing cells are detected. These cytokines support the growth of eosinophils and macrophages and promote the T<sub>H</sub>1-type inflammation more characteristic of chronic AD. IgE-bearing Fc $\epsilon$ RI<sup>+</sup> inflammatory dendritic epidermal cells also become more prominent in chronic AD lesions and are thought to be involved in cell recruitment and IgE-mediated antigen presentation to T cells and promote T<sub>H</sub>1 cytokine production from T cells.<sup>3</sup>

Many chemokines are upregulated in AD to help recruit cells to sites of injury or irritation and promote the development of lesions. CCL5 (RANTES), CCL13 (monocyte chemoattractant protein 4), and CCL11 (eotaxin) are all increased in AD skin lesions and possibly help in the recruitment of T cells, macrophages, and eosinophils into the skin (Fig 5).<sup>4</sup> IL-16 produced by Langerhans cells might also help in recruitment of T cells and has been reported in AD lesions (Fig 6).<sup>5,6</sup> Microarray analysis of lesions from patients with AD has revealed an increase in other chemokines, such as CCL-18 (pulmonary and activation-regulated chemokine; PARC) and CCL27 (cutaneous T cell-attracting

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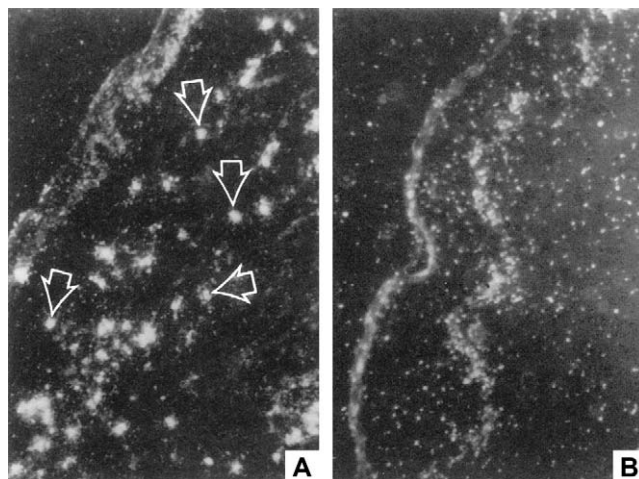


**FIG 3.** Radio *in situ* hybridization, as visualized by means of darkfield illumination, of IL-4 mRNA<sup>+</sup> cells (**A**) and IFN- $\gamma$  mRNA<sup>+</sup> cells (**B**). Arrows point to representative cells positive for accumulation of the IL-4 probe.

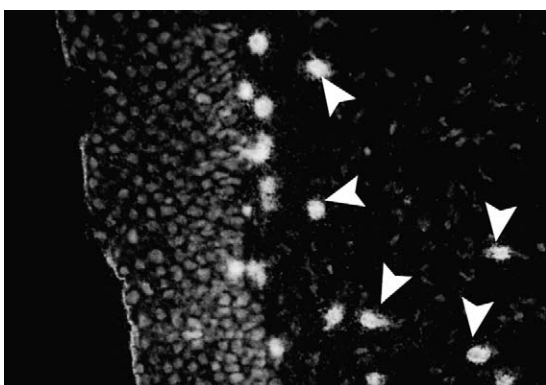


**FIG 4.** Radio *in situ* hybridization, as visualized by means of darkfield illumination, of GM-CSF mRNA<sup>+</sup> cells.

chemokine; CTACK), both of which are T-lymphocyte chemoattractants.<sup>7</sup> Better characterization of key chemokines involved in AD and their function will lead to better elucidation of the disease process and timing of events.

Studies have shown that skin lesions in chronic AD are associated with remodeling, much like other chronic atopic diseases, such as asthma. Levels of profibrotic cytokines, including TGF- $\beta$ 1, IL-11, and IL-17, are all significantly increased in acute and chronic skin lesions from patients with AD compared with uninvolved skin from patients with AD and healthy skin from control patients.<sup>8</sup> In addition, IL-11 is also correlated with collagen I deposition and numbers of eosinophils, a cell type capable of producing significant amounts of profibrotic cytokines (Fig 7).

Comparisons of AD with psoriasis, another chronic skin disease, have yielded interesting insights into the development of AD. Patients with AD, but not with psoriasis, frequently have skin infections. Microarray analysis comparisons of the 2 afflictions have shown decreases in innate immune genes, such as human  $\beta$ -

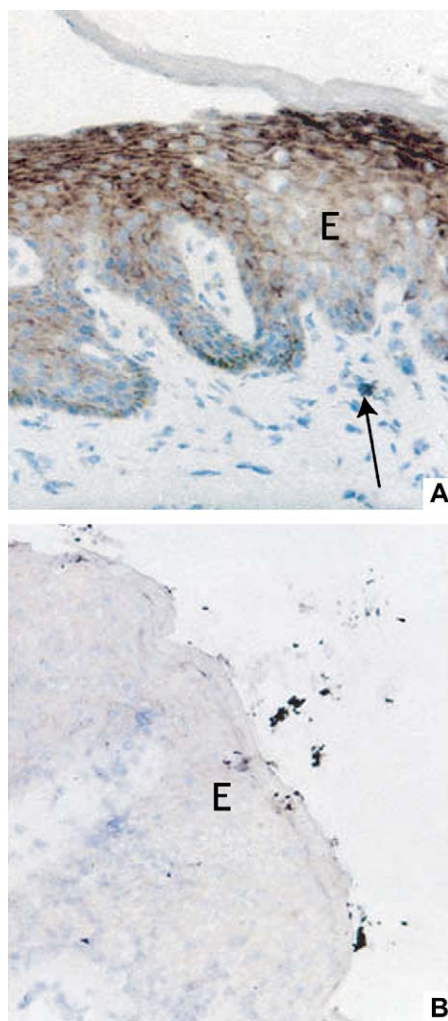


**FIG 5.** **A**, *In situ* hybridization with digoxigenin-labeled anti-sense probe of eotaxin mRNA<sup>+</sup> cells stained in red in the epidermal layer of the skin obtained from subjects with chronic AD. Note the presence of some positive cells within the subepithelial layer (arrow). **B**, Negative control from subjects with chronic AD with use of digoxigenin-labeled sense probe.

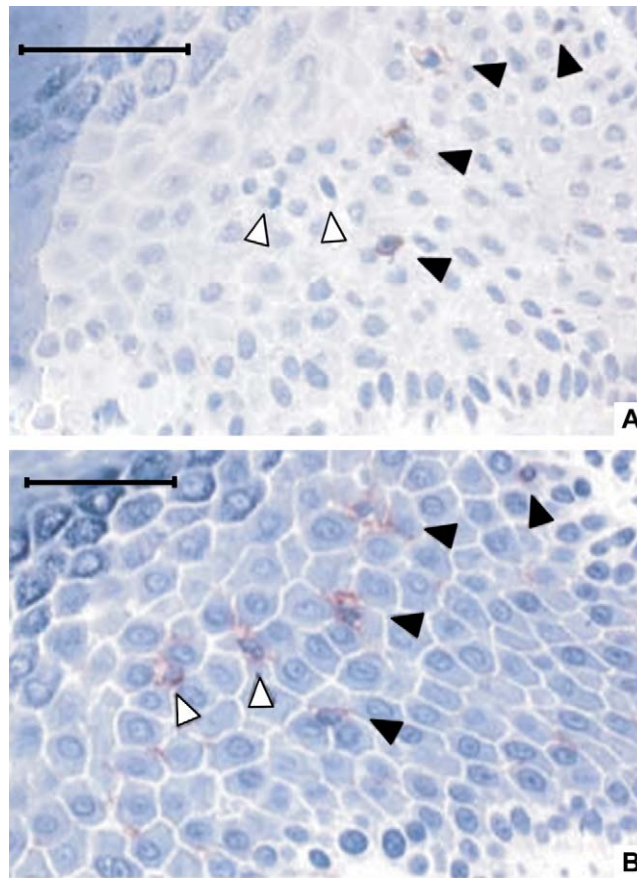


**FIG 6.** Mirror sections of lesions from active AD. **A**, Lesions were stained for IL-16 protein–positive cells by means of the indirect immunoperoxidase method. **B**, Lesions were stained for CD1a by using the alkaline phosphatase–antialkaline phosphatase method. *Solid arrowheads* and *open arrowheads* indicate CD1a<sup>+</sup> cells also positive for IL-16 and negative for IL-16, respectively.

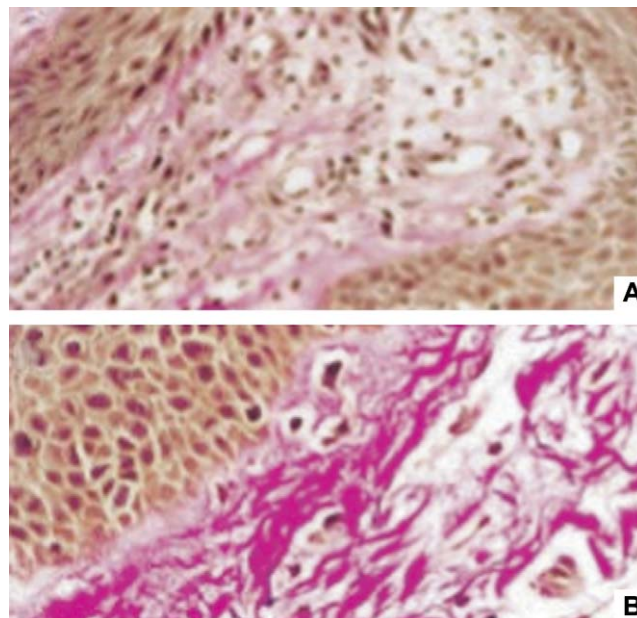


**FIG 7.** Representative examples of total collagen deposition, as detected by using van Gieson staining in skin from patients with chronic (**A**) and acute (**B**) AD.

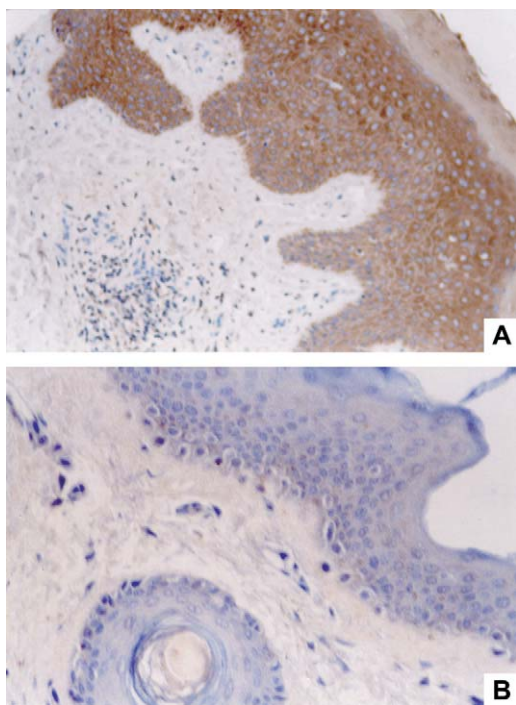


**FIG 8.** Immunohistochemistry, by means of the indirect immunoperoxidase method, was used to detect human  $\beta$ -defensin 3 in psoriasis skin lesions (A) and in AD skin lesions (B).

defensin 2, IL-8, and inducible nitric oxide synthase.<sup>9</sup> In addition, investigation of human  $\beta$ -defensin 3 revealed marked downregulation of this gene in keratinocytes of patients with AD compared with that seen in patients with psoriasis (Fig 8).<sup>9</sup> Decreases in these antimicrobial peptides are not a primary defect of resident cells, such as keratinocytes, but might be

mediated by cytokines produced by infiltrating immune cells. Anticytokine therapies would not only decrease acute inflammation in AD but might also remedy innate immune defects. These therapies could also afford an alternative approach to immunosuppression of the inflammatory response in AD.

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