20 Histopathologic and Ultrastructural Aspects of Atopic Eczema

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20.1 Eczematous Skin in Atopic Eczema

The clinical phenotype that characterizes atopic eczema (AE) is the product of an interaction between susceptibility genes, the environment, defective skin barrier function, and immunologic responses [23]. From the clinical point of view, the atopic skin lesions are characterized as acute, subacute, and chronic, each showing different morphologic features.

Acute eczematous skin lesions present clinically as erythema, vesicles, intensely pruritic papules, and scaling. Histologically, they are characterized by epidermal spongiotic microvesicles (intercellular edema) with oozing and acanthosis, and the stratum corneum (SC) may be parakeratotic and contain aggregates of coagulated plasma, the substrate of crusts. Ultrastructural studies of the SC show dilatation of the intercellular spaces of the SC, which depict an irregular distribution of lipid structures with disturbance of the normally lamellar-arranged epidermal lipid bilayers [12, 18, 27]. These seem to be intermingled with exudates (M. Fartasch, unpublished observations). Additionally, there is an increase in parakeratotic corneocytes. Alterations of the chemically bound lipid envelope of the corneocyte and its relation to the lamellar intercellular lipid bilayers [41] in acute and chronic phases of the disease have not been studied yet. The dermis of acute lesions shows a superficial, perivascular, predominantly lymphohistiocytic infiltrate – with varying amounts of eosinophils present – and a marked infiltration of CD4+ activated memory T cells. When compared to normal skin or uninvolved skin of AE patients, acute skin lesions are believed to have a significantly greater number of IL-4-, IL-5-, and IL-13-mRNA-expressing cells, but few IFN-γ- or IL-12-mRNA-expressing cells. Additionally, epidermal keratinocytes produce chemokines and proinflammatory cytokines following mechanical stimulation, e.g., scratching.

Chronic lichenified skin lesions have undergone tissue remodeling to chronic inflammation and are characterized by thickened plaques with increased markings (lichenification) and dry, fibrotic papules. Spongiosis is usually absent, but when present, the diagnostic consideration is subacute eczema. There is a moderate dense lymphohistiocytic infiltrate around the vessels, varying thickness of the papillary dermis, sometimes epidermal hyperplasia (acanthosis), and focal parakeratosis above hypergranulosis, alternating with orthokeratosis or hyper-para keratosis.

Macrophages dominate the dermal mononuclear cell infiltrate. Eosinophils also contribute to the inflammatory response, and T cells remain present, although in smaller numbers than seen in acute AE. Chronic AE skin lesions have significantly fewer IL-4- and IL-13-mRNA-expressing cells, but greater numbers of IL-5-, GM-CSF-, IL-12-, and IFN-γ-mRNA-expressing cells than in acute AE.

Antigen-presenting cells (APC) (e.g., Langerhans cells [LC], inflammatory dendritic epidermal cells [IDEC], and macrophages) in lesional and, to a lesser extent, in nonlesional skin bear IgE molecules [33], and there seems to be a relation between the amount of surface expression of FcεRI on LC and disease activity [40]. Macrophage numbers are found significantly increased in acutely and chronically inflamed AE skin, compared with nonlesional and healthy skin. The macrophages are found to migrate up to the dermal–epidermal junction where they stop, but their cell protrusions protrude into the epidermis [22].

IL-16, an LC-derived chemoattractant cytokine for CD4+ T cells, is increased in acute AE skin lesions. C-C chemokine ligand 27 is highly upregulated in AE and preferentially attracts CLA+ T cells into the skin. As
compared to psoriasis, the C-C chemokines, RANTES, monocyte chemotactic protein-4, and eotaxin are increased in AE skin lesions and likely contribute to the chemotaxis of C-C chemokine receptor 3-expressing (CCR3-expressing) eosinophils, macrophages, and Th2 lymphocytes into AE skin. Selective recruitment of CCR4-expressing Th2 cells into AE skin may also be mediated by macrophage-derived chemokine and thymus and activation-regulated cytokine, which are increased in AE [23].

Studies by confocal laser scanning microscopy showed increased dermal contacts between mast cells and nerves in lesional atopic eczema. Dermal contacts between mast cells and nerves were increased in number in lesional samples of AE and other forms of eczema such as nummular eczema (NE). Fibres containing the neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP) were more frequent in lesional than in nonlesional papillary dermis of both AE and NE. Since mast cells are also increased in number in AE and NE lesions, it is speculated that they might maintain neurogenic inflammation through activation by SP and CGRP. The increased SP/CGRP nerves in the epidermis of AE and NE lesions may stimulate keratinocytes to release cytokines, which affect various cell types, enhancing inflammation [20].

20.2 Noneczematous Skin in Atopics

Clinically unaffected skin in AE is not normal. It frequently manifests a greater irritant skin response/susceptibility than healthy controls and an increased antigen absorption. This might be due to a disturbance of barrier function, sometimes demonstrated by an enhanced transepidermal water loss (TEWL) (for a review, see [10]), which might initiate and contribute to the immunological reactions and the cutaneous hyper-reactivity characteristic to AE.

Unaffected AE skin seems to contain a sparse perivascular T cell infiltrate not seen in normal healthy skin. Analyses of biopsies from clinically unaffected skin of AE patients, as compared with normal nonatopic skin, demonstrate an increased number of Th2 cells expressing IL-4- and IL-13-, but not IFN-γ-mRNA [16].

A common finding in patients with AE is the high incidence of dry skin (DS) with a scaly, nonerythematous, noninflamed skin surface that feels rough to the touch, often with a perifollicular accentuation. Some morphological studies have reported that atopic DS shows increased intercorneocytic cohesion [3, 14, 43, 44], increased epidermal thickness with focal parakeratosis, and, in places, slight hypergranulosis or hypogranulosis – it was suggested that the atopic DS reflects a subclinical eczema. Other studies could not confirm the previously proposed thesis that the persistent DS of atopics is the result of subclinical eczema. In some cases, the epidermis of nonaffected atopic skin shows signs of suppressed synthesis of keratohyalin with a histological reduction of granular layer thickness [12, 21]. This feature, when clinically accompanied by hyperlinear palms ("ichthyotic" palms) and keratosis pilaris, was believed to be evidence for the coexistence of AE with autosomal dominant ichthyosis (ADI) and was suggested as the cause of DS in as many as 30%–40% of atopics [42]. However, ultrastructurally, it has been shown that only few atopics have concomitant ADI (4%–6%) and that the dry condition in AE is structurally distinguishable from DS in dominant ichthyosis [12].

Several lines of evidence indicate that the process of lipid translocation and transformation might be disturbed in DS [19, 30, 39, 45]. Biochemical, morphological, and functional findings support the view that impaired biosynthesis of ceramides and acylceramides, probably due to immunologically induced alterations of epidermal differentiation with increased epidermopoiesis [21, 37], may be the cause of the atopic DS and the impaired barrier function. There are several studies that postulate abnormalities in the total amount of ceramides [5, 6, 19]. In addition, some studies have found a different composition regarding the seven ceramides that partially form the intercellular lipids of the horny layer in noninvolved skin of atopics [5]. Others postulate a disturbance of lipid metabolism by dysfunction of enzymes [32, 34] or specific, newly found enzymes [17]. From the morphologic point of view, ultrastructurally there seems to be some evidence of disturbed maturation of the water permeability barrier in atopic noneczematous DS. This is induced by a delayed and probably incomplete extrusion of lamellar bodies [7, 10], resulting in a diminished delivery of their “probARRIER” polar lipids in the SC intercellular spaces [11] and thereby causing a disturbed reorganization of the lamellar body lipids into lamellar lipids of the SC [36]. The delayed lamellar body exocytosis may additionally impair the formation of the water perme-