5 Histological, Immunohistochemical and Ultrastructural Aspects of Contact Dermatitis

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5.1 Allergic Contact Dermatitis

The histologic patterns of allergic contact dermatitis are extremely heterogeneous [1]. Moreover, many factors that may alter the typical morphology must be taken in account: the clinical phase (acute, subacute and chronic) and the clinical variability. Most studies are based on the histological evaluation of biopsies obtained from patch test performed to make a differential diagnosis between allergic and irritant contact dermatitis [2]. As for the typical lesions, the finding that best characterize the allergic contact dermatitis is the spongiosis [2] (Fig. 5.1). It is particularly evident in the acute phase (at 48 h in a positive patch test reaction) and occurs as intercellular oedema that separates the keratinocytes. Spongiosis can be focal or involves the whole epidermis and in most cases extends to the hair follicles, sparing the sweat duct units. The intercellular oedema can lead to the intercellular prickles rupture and to the formation of vesicles that, in turn, induce the occurrence of bullae, due to their confluence, localized in the stratum spinosum and rarely in the stratum corneum. Erosions covered by sero-fibrinous exudate are the result of rupture of vesicles and bullae. Occasional intraepidermal leukocytes are detected in the spongiotic vesicles (exocytosis), mostly represented by lymphocytes and sporadic eosinophils and neutrophils that tend to accumulate in the vesicles. In papillary dermis, capillaries are dilated and congested with accentuated interstitial oedema. The inflammatory infiltrate, if present, is perivascular or, rarely, diffuse and sometimes extends to the deep dermis and subcutaneous tissue. It is formed by mononuclear cells, namely lymphocytes and hystiocytes. Occasional neutrophils can be present and progressively increasing is the amount of eosinophils that migrate from the upper dermis to the epidermis. Unclear still remains the role played by mastcells. Histological evidence of mast cells degranulation would suggest an early activation of these cells in allergic contact dermatitis [3]. The prolonged exposure to the antigenic agents induces a progressive hyperkeratosis (orthoparakeratosis) of the epidermis and a decrease of the intercellular oedema and of the inflammatory infiltrate. In case of erosion, the exudate is infiltrated by neutrophils with increasing risk of infection.

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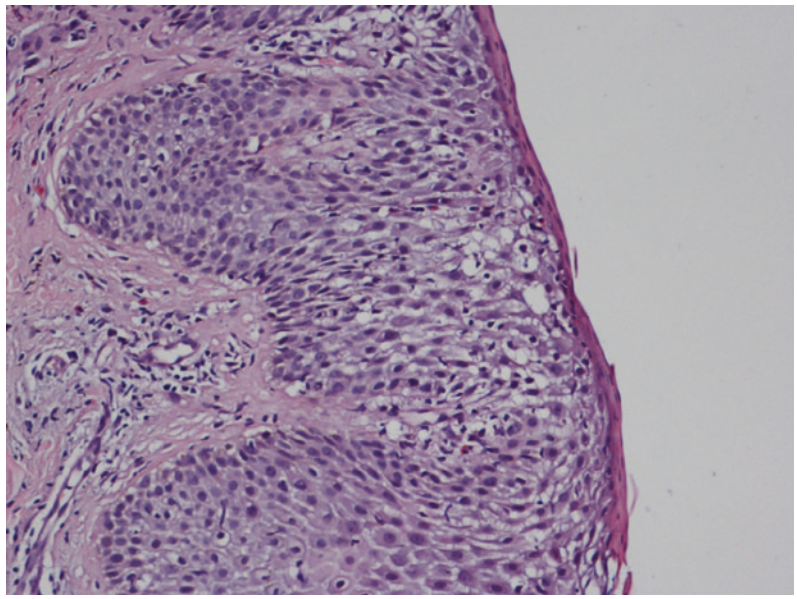

Fig. 5.1 Subacute allergic contact dermatitis. Epidermal spongiosis with exocytosis of mononuclear cells, dermal oedema and a mild perivascular infiltrate of mononuclear cells. Hematoxylin-Eosin stain (×200)

In chronic forms, epidermis shows acanthosis and hyper-parakeratosis. In the dermis, fibrosis predominates with scant inflammation. Other variants of allergic contact dermatitis exist: photo-induced, lymphomatoid, lichenoid, erithema multiforme like, pustulous, orticarioid, purpuric, all of them characterized by the occurrence of lesions that need a differential diagnosis with other dermatosis on both a clinical and histological level. In lymphomatous forms, there is a strong predominance of the inflammatory infiltrate made of lymphocytes, monocytes, macrophages, plasma cells, and eosinophils with a perivascular and periannexial distribution or occasionally as a sub epidermal band. Rarely the inflammatory infiltrate can assume the shape of intraepidermal micro-abscesses to be differentiated from micro-abscesses of Pautrier of mycosis fungoides by the presence of an accentuated cell polymorphism and the absence of the typical cells provided with a convoluted nucleus. The immuhistochemical profile of the lymphocytes involved in allergic contact dermatitis is typically that of T helper lymphocytes with expression of CD3 (Fig. 5.2), CD4 (Fig. 5.3) and CD45RO [4]. Sometimes in the pseudo-lymphomatous variant, the infiltrate is formed by T and B-lymphocytes with possible formation of true lymphatic follicles and in other cases it can predominates a granulomatous appearance with epithelioid sarcoid-like granulomas or foreign-body granulomas. In presence of both spongiosis and a subepidermal band of T lymphocytic infiltrate, a differential diagnosis must be made with lichen planus. However, the diffuse spongiosis and occurrence of a significant eosinophilic component, together with the patch test positivity are strongly suggestive for an allergic contact dermatitis. Similarly, other forms that can mimic amicrobic pustulosis, erythema multiforme-like or orticarioid papulosis still retain spongiosis and eosinophilic infiltrate. Electron microscopy confirms histological features of chronic dermatitis: acanthosis, spongiosis and hyperkeratosis with a mild chronic inflammatory cell infiltrate in the upper dermis [5]. Ultrastructural findings in the epidermis demonstrates separation of the basal cell, a decreased number of desmosomes with marked intercellular oedema

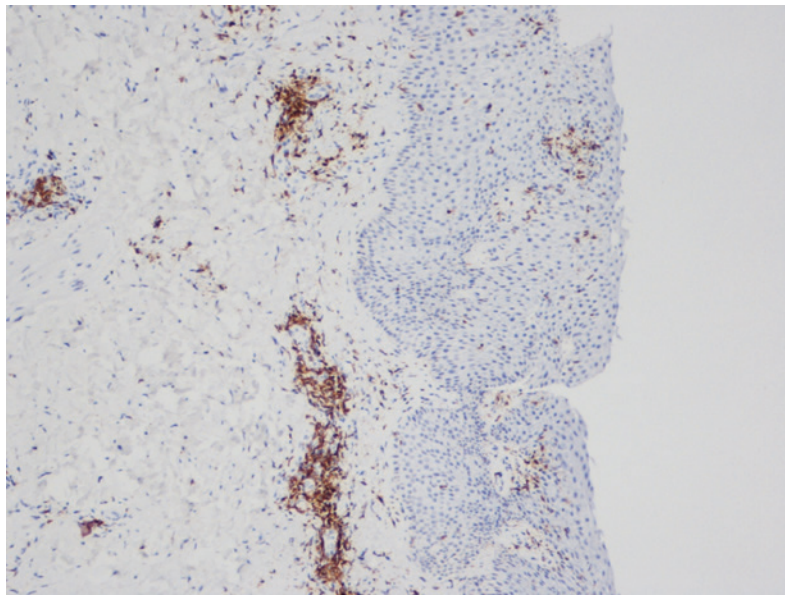

Fig. 5.2 Allergic contact dermatitis. Dense perivascular dermal infiltrate of CD3+T-cells; occasional T-cell in epidermis. Immunostaining for CD3 (×100)

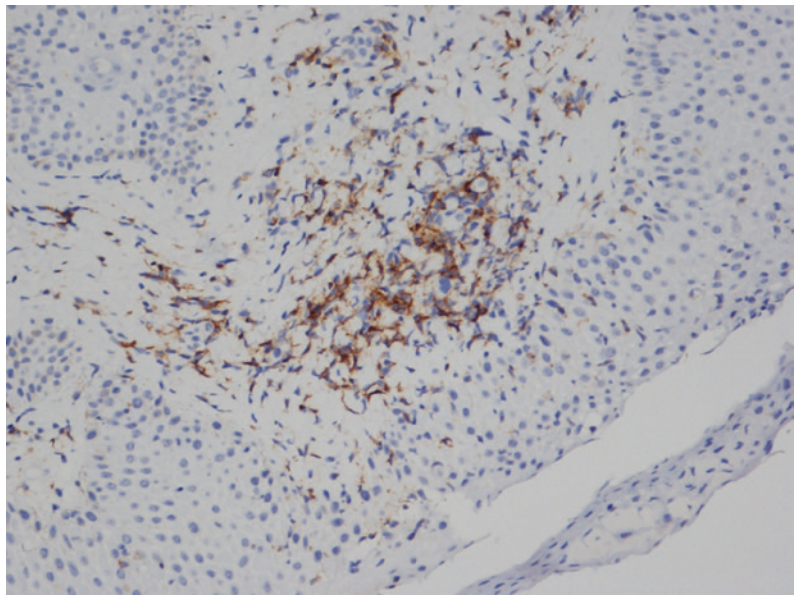

Fig. 5.3 Allergic contact dermatitis. A focal subepidermal infiltrate of CD4+T-cells. Immunostaining for CD4 (×200)

of the lower epidermal keratinocyte (Fig. 5.4), formation of cytoplasmic vacuoles and aggregation of intermediate filaments around the periphery of the cell. Enlarged upper epidermal cells with cytoplasm containing finely dispersed filaments and ribosomes are evident (Fig. 5.5). Apoptotic changes were identified in the basal and suprabasal layers. Hyperplasia of sebaceous

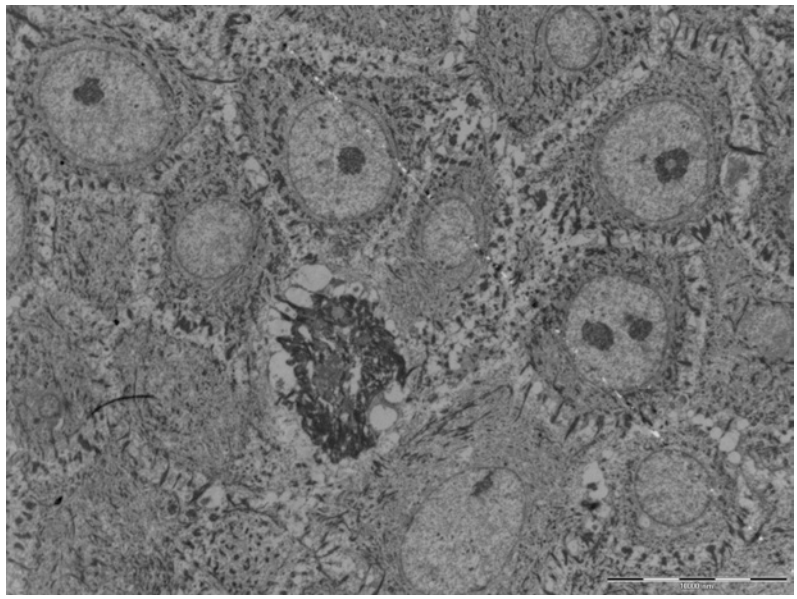

Fig. 5.4 Allergic contact dermatitis. Intercellular oedema in epidermis and isolated apoptotic keratinocyte. Electron Microscopy (×2200)

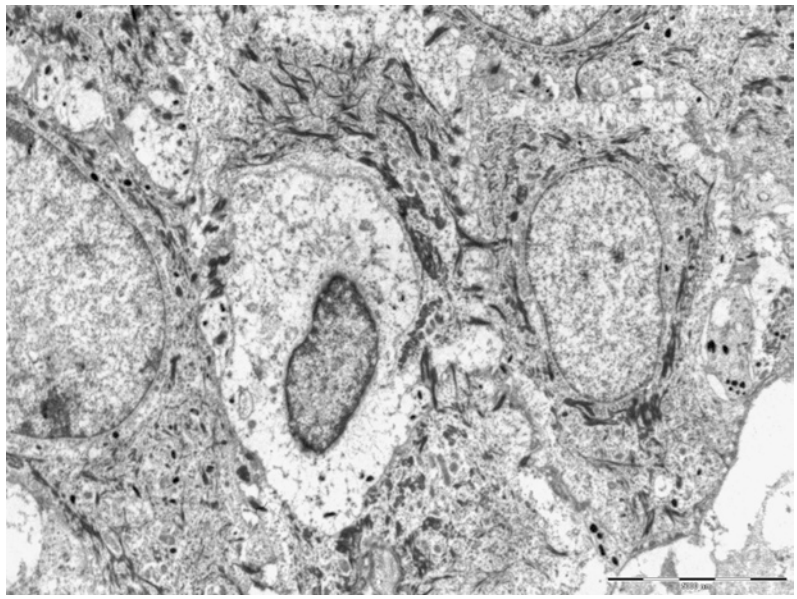

Fig. 5.5 Allergic contact dermatitis. Intracellular oedema, cytoplasmic vacuoles and aggregation of intermediate filaments around the periphery of the cell. (×4400)

glands, with basal cells displaying morphological signs of enhanced metabolic activity such as increased rough endoplasmic reticulum and sebum droplets. The inflammatory infiltrate is low and localized in the perivascular area. Langerhans cells play an important role in the diagnosis of allergic contact dermatitis. As reported in a recent study by Rosa et al. [6],

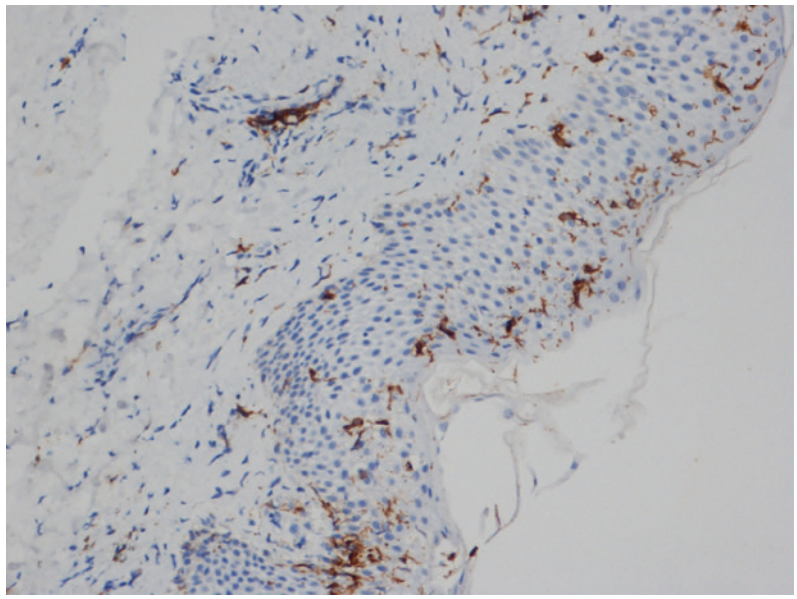

Fig. 5.6 Allergic contact dermatitis. Increased CD1a positive Langerhans cells in epidermis. Immunostaining for CD1a (×200)

the only histopathologic feature associated with patch test-confirmed allergic contact dermatitis was the presence of Langerhans cell collections supporting the concept that the presence of Langerhans cells could be a clue to the diagnosis of the disease (Fig. 5.6). The sensitivity of this finding is relatively low (48%), but the positive predictive value was relatively strong (78%), as was the specificity (75%). In the same study, there was no difference in the patch test positive and patch test negative cases in terms of dermal eosinophilic counts and eosinophilic spongiosis (Fig. 5.7). The explanation of this finding would be that allergic contact dermatitis is a type IV hypersensitivity reaction lymphocyte-driven not dependent on eosinophils.

5.2 Irritant Contact Dermatitis

In irritant contact dermatitis the morphologic pattern depends on the clinical phase and time of sampling (acute, subacute and chronic) but it is also the combined effect of nature of the irritant agent, its concentration, physical state, duration of exposure and finally of subject reactivity [7]. As for allergic forms, also in this case our information derive from experimental models and results of patch tests. In the typical lesions, one of the following aspects can predominate: hyper-parakeratosis, spongiosis, acantholysis with the consequent formation of intraepidermal vesicles or bullae or in most severe cases, due to strong alkali or acid exposure, necrosis of keratinocytes and erosion or ulcerative lesions. In the less aggressive forms, lesions of the upper epidermis predominate as the so-called Bandmann's achromasia that can be circumscribed to the superficial epidermal layer or extends to the upper part of the stratum spinosum; in more severe forms, the whole epidermis is involved. The exposure to strong irritant agents can lead to formation of intra-epidermal pustule with accumulation of polymorphonucleates (Fig. 5.8). Rarely, follicular pustules can be found, especially in atopics or after exposure to particular irritant as metal salts and croton oil. The vast majority of cases show exclusively spongiotic lesions not necessarily associated with vesicles. Spongiosis, in typical cases, seems to be less intense than that observed in allergic reactions. In chronic forms

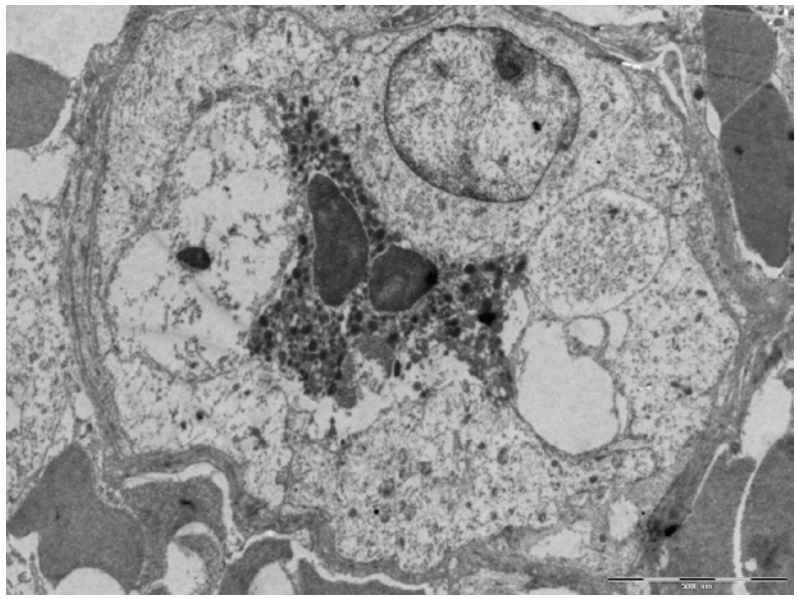

Fig. 5.7 Allergic contact dermatitis. An intraluminal eosinophil in a dermal capillary with evident enlargement and vacuolization of endothelial cells (×2800)

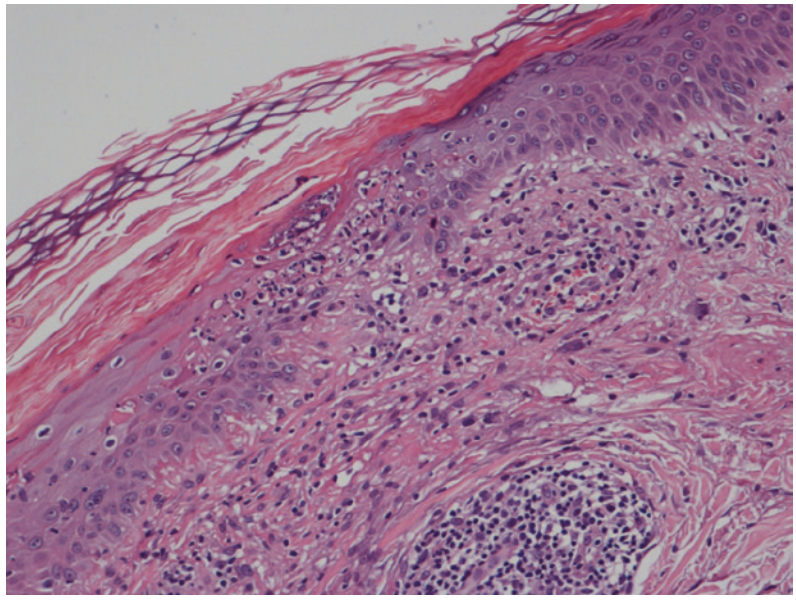

Fig. 5.8 Subacute irritant contact dermatitis. Hyper-parakeratosis of epidermis, neutrophilic exocytosis and dermal perivascular infiltrate of mononuclear cells. Ematoxylin-Eosin (×200)

hyperkeratosis, parakeratosis and elongation of rete ridges can predominate. In all cases, mild oedema and a lymphocytic perivascular and periannexial infiltrate coexist. Eosinophils are virtually absent. As for the infiltrate, in mild to moderate reaction mononuclear cells predominate, namely T lymphocytes CD4 positive with a minor component of suppressor/cytotoxic T

lymphocytes (CD8+), macrophages, Langerhans cells CD1 positive and occasional B lymphocytes, natural killer (NK) cells and follicular dendritic cells. Ultrastructural changes are irritant-dependant and include cytolysis of epidermal keratinocytes, condensation of chromatin and cytoplasm, tonofilament clumping and loss of membrane-bound cell fragments [3].

5.3 Irritant Versus Allergic Contact Dermatitis

The histological differential diagnosis between allergic and irritant contact dermatitis is extremely difficult, if possible, and it can be made only in typical cases as response to pure allergic or irritant agents. In fact, the lesions found at patch tests are virtually similar and the predominance of an aspect cannot be considered as specific [8]. Moreover, many allergens possess also irritant properties even at low concentrations. It is the reason why the skin biopsy is discouraged. Lachapelle et al. [2] sustained that although the conventional histology of positive patch test can provide some useful information, it is of little help to make a differential diagnosis between allergic, irritant and mixed forms. However, some studies based on patch tests underlined the possibility to make a histological distinction between early allergic and irritant reaction; in particular, in strong patch test reactions, the occurrence of follicular spongiosis, lymphocytic exocytosis of the follicular infundibulum would best characterize the allergic forms, especially in early phase [9]. The timing of the biopsy would be critical since these differences are more appreciable in the early phase of reaction. Other histologic findings detected in previous studies [10] included a less intense ("focal") intra-epidermal inflammation in allergic reaction and the presence of epidermal necrosis and dermal infiltration of neutrophils in the more severe forms of irritant dermatitis. A tendency to develop intraepidermal oedema, increased number of epidermal lymphocytes and spongiosis, even though with high variability due to the different technical procedures adopted for processing samples, was already noted in these studies. The presence of dermal and epidermal neutrophils was in favour of a diagnosis of irritant contact dermatitis at patch test. In case of spongiotic dermatitis, Tzank smears showed more than 10 tadpole cells and numerous lymphocytes in the 80.5% of allergic contact dermatitis and more than 10 tadpole cells and numerous neutrophils in most (15/18) irritant contact dermatitis. A tadpole cell is a cell of round shape with a single nucleus and a clearly defined cytoplasm, which was drawn out into one or occasionally two tapered pointed processes. This shape is retained long enough to allow the cell scraped from the blisters to dry on the slides with their "tails" intact. The presence of more than 10 tadpole cell is considered a diagnostic indicator for spongiotic vesicular dermatitis with a sensitivity of 81.5% and specificity of 99.3% [11]; in a previous study Parisier [12] reported similar results. Recently [4], immunohistochemistry has given the possibility to better characterize the lymphocytic subpopulations and clarify the role of Langerhans cells. For example, it has been demonstrated a decrease of CD1a positive Langerhans cells from 48 to 72 hours after the exposure to irritant agents; on the other hand, in allergic forms there would be a mild and transient increase of such cells in the same range of time. However, these findings would lack of specificity and of utility in differentiating irritant from allergic reactions. Analogously the lymphocytic population in both cases is similar and consists of T lymphocytes of helper/inducer type; their number results unaltered in early and late biopsies; on the opposite it has been noted an increase of expression of proliferative (Ki 67 labelling index, transferrin receptor) and activation markers (interleukin 2 receptor) in both allergic and irritant forms.

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