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ORIGINAL ARTICLE

Histopathological study of allergic contact dermatitis

Estudo histopatológico da dermite de contacto alérgica

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Abstract

Introduction: Allergic contact dermatitis (ACD) has a wide spectrum of clinical presentations, which mimic diverse dermatological conditions. When patch tests do not identify that the relevant allergens or treatment is not effective, a skin biopsy is warranted. However, there are few descriptive series on the histopathology of ACD. The purpose of this study was to characterize microscopic changes in ACD and to identify features that may help in the differential diagnosis. **Methods:** We retrospectively included 20 skin biopsies of ACD cases. Slides were reviewed, and microscopic changes analyzed. **Results:** We reported a clinicopathologic concordance of 80%. The main histological differential diagnosis was drug eruption (DE). Common epidermal findings included acanthosis (95%), parakeratosis (85%), and spongiosis (80%). Necrotic keratinocytes were observed in only three cases. The most common dermal change was the presence of a superficial perivascular inflammatory infiltrate. Lymphocytes were present in all cases and eosinophils in 80% of the biopsies, although in much smaller number. Neutrophils and atypical lymphocytes were absent. **Conclusion:** In ACD, isolated pathological findings are nonspecific and clinicopathological correlation is essential. Eosinophilic spongiosis is the typical pattern, but findings depend on the stage of evolution. Several histological features (including parakeratosis and epidermal hyperplasia with signs of spongiosis, superficial dermal infiltrate, absence of both apoptotic keratinocytes, and vacuolar degeneration), may aid in the differential diagnosis with DE.

Keywords: Biopsy. Dermatitis. Allergic contact/diagnosis. Allergic contact/pathology.

Resumo

Introdução: A dermite de contacto alérgica (DCA) possui um amplo espectro de apresentações clínicas, que podem mimetizar outras patologias. Quando as provas de contato não identificam os alergénios relevantes ou o tratamento se releva ineficaz, deve ser realizada uma biópsia cutânea. No entanto, há poucos estudos descritivos sobre a histopatologia da DCA. **Objetivo:** Caracterizar as alterações microscópicas da DCA e identificar características que ajudem no diagnóstico diferencial. **Métodos:** Realizámos um estudo retrospetivo que englobou 20 biópsias cutâneas de casos de DCA. As lâminas foram revistas e as alterações microscópicas analisadas. **Resultados:** Nas lâminas estudadas, verificou-se uma concordância clínico-patológica de 80% sendo o principal diagnóstico diferencial histológico, toxidermia. Na epiderme, as alterações mais comuns incluíram acantose (95%), paraqueratose (85%) e espongiose (80%). Apenas em 3 casos se identificou necrose de queratinócitos. Na derme, a presença de um infiltrado inflamatório perivascular superficial foi o achado mais frequente. Em todos os casos se observaram

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linfócitos e, em 80%, eosinófilos. Em nenhuma das lâminas se identificou a presença de neutrófilos ou de linfócitos atípicos. **Conclusão:** Na DCA, as alterações histopatológicas são inespecíficas e a correlação com a clínica é essencial. O padrão típico é a espongiose com eosinófilos, mas os achados dependem do tempo de evolução das lesões. Várias características histológicas (incluindo paraqueratose e hiperplasia da epiderme com evidências, ainda que subtis, de espongiose; infiltrado dérmico superficial; ausência de queratinócitos apoptóticos e de degeneração vacuolar) podem auxiliar no diagnóstico diferencial com toxidermias.

Palavras chave: Biopsia. Dermatite alérgica de contato/diagnóstico. Dermatite alérgica de contato/patologia.

Introduction

Contact dermatitis is a common inflammatory skin condition induced by exposure to an external irritant (irritant contact dermatitis) or allergen (allergic contact dermatitis [ACD])[1-3]. During the acute phase, it is clinically characterized by erythema, pruritus, vesicles, and scaling. With chronic disease, lichenification and fissuring may develop[1,4]. ACD accounts for approximately 20% of the cases of contact dermatitis[1]. It is a type IV delayed-type hypersensitivity reaction that develops after an initial sensitization phase and results from the activation of allergen-specific T cells when the chemical contacts and penetrates the skin[1-3]. The chemical hapten binds with a protein and form a complex that is presented by dendritic cells T cells and leads to the expansion of an allergen-specific T cell population. Re-exposure to the allergen results in antigen-specific T cells homing to the skin that leads to the development of dermatitis[2,3].

Although the exact prevalence of ACD is not known, it affects a considerable part of the population[5] and it is one of the most common work-related conditions[4], few studies have been published on its histopathology[6]. This is because histopathological examination is not usually involved in the diagnosis which is essentially based on anamnestic data and clinical presentation and confirmed by patch testing. The clinical presentations encompass acute, subacute, or chronic lesions that can imitate a wide spectrum of other cutaneous diseases[5]. Besides, clinical history taking is not always straightforward. When the diagnosis is in doubt, skin biopsy for histopathologic examination may be helpful[4,6].

The general histological hint of eczematous dermatitis, regardless of its origin (allergic, irritant, or endogenous) is the presence of a spongiotic pattern[6]. This pattern is then influenced by many factors including disease duration, secondary changes such as scratching, infection, and lichenification.

The objective of our study was to characterize the microscopic changes of 20 proven cases of ACD. We will discuss criteria that may help in the diagnosis of ACD and in the histopathological differential diagnosis with drug eruptions (DE).

Methods

We conducted a retrospective study of the ACD cases with at least one skin biopsy in the inward Dermatology Department of our institution (Centro Hospitalar e Universitário Lisboa Norte, in Lisbon) during a 4-year period (between July 1, 2016, and July 1, 2020).

Inclusion/exclusion criteria

We included 20 patients with ACD who had at least one skin biopsy during the active phase of the disease. We included only cases with a proven diagnosis confirmed by patch testing or patients with a suggestive clinical picture, suspected allergen with relevant chronology, and clearance of the eruption upon allergen eviction. We excluded cases with doubtful diagnosis (n = 7), including patients who had started a new drug on the previous 2 months (n = 3), without precise clinical information (n = 3), and without a clear ACD history and no patch testing (n = 1).

Clinical data

We retrieved the following data from medical records for each case: age, gender, medication and clinical history, clinical evolution, skin biopsy, and patch test results.

Histopathological examination

Slides were reviewed by two of the authors (MAL and PEL), without knowledge of the clinical data or outcome. A standardized form was used to collect data on abnormalities in the epidermis (parakeratosis, hyperkeratosis, hypergranulosis, acanthosis, pustulosis, exocytosis, spongiosis, exocytosis, necrotic and atypical keratinocytes, presence of Langerhans cells collections, and vacuolar degeneration in the dermo-epidermal junction) and dermis (edema; signs of vasculitis, including fibrinoid necrosis, leukocytoclasia, and the presence of an inflammatory infiltrate in the wall of dermal vessels; and pigment incontinence and dermal infiltrate). The degree of

hyperkeratosis, hypergranulosis, acanthosis, lymphocytic exocytosis, pigment incontinence, and edema was semi-quantified (+, ++, or +++) as well as the number of the different cell types in the dermal infiltrate whose arrangement was also characterized (superficial versus deep and perivascular versus interstitial). The presence of Langerhans cells was evaluated only on routine hematoxylin and eosin (H&E)-stained sections.

The results were then analyzed and compared to those in the literature.

Results

Study population

We obtained biopsy slides from 20 patients from our Dermatopathology Department (mean age of 58 years [± 22.3], 75% of male and 25% of female). The discharge diagnosis was ACD in all patients. Patch tests performed in 11 (55%) patients confirmed the diagnosis. In the remaining nine patients, clinical diagnosis was straightforward. Of the 20 biopsies, seven were done on the upper limbs, six on the lower limbs, four on the trunk, and three on the face. Considering the clinical evolution of the eruption, biopsies were obtained between 1 week and 6 months since the beginning of the lesions (nine biopsies were performed within the first 3 weeks and 11 afterwards; and only one biopsy was done within the 1st week).

Histological features

On histological evaluation, 16 out of 20 had clinico-histologically concordant outcomes. Three cases were pathologically consistent with DE and one case with psoriasis. The case consistent with psoriasis was the one with the longest evolution period (6 months).

Histopathological features analyzed in our study are summarized in Table 1.

Table 1. Histopathologic findings in 20 cases with the clinical diagnosis of allergic contact dermatitis

	N (≤ 3S) NT ≤ 3S = 9	% (NT ≤ 3S)	N (> 3S) NT > 3S = 11	% (NT > 3S)	N (T)	% (T)
Epidermis						
Parakeratosis	7	78	10	91	17	85
Focal	5		6		10	
Continuous	2		5		7	
Hyperkeratosis	7	78	8	73	15	75
+	6		4		10	
++	1		4		5	
Hypergranulosis	2	22	5	45	7	35
+	2		2		4	
++	0		3		3	
Acanthosis	8	89	11	100	19	95
+	4		5		9	
++	4		4		8	
+++	0		2		2	
Intra/subcorneal pustules	1	11	2	22	3	15
Spongiosis	8	89	8	72	16	80
Spongiotic vesicles	2	22	1	9	3	15
Lymphocytic exocytosis	4	44	4	44	8	40
+	2		4		6	
++	2		0		2	
Necrotic keratinocytes	1	11	2	22	3	15
Atypical keratinocytes	0	0	0	0	0	0
Vacuolar degeneration	0	0	0	0	0	0
Langerhans cells	3	33	2	22	5	25

(Continued)

Table 1. Histopathologic findings in 20 cases with the clinical diagnosis of allergic contact dermatitis *(Continued)*

	N (≤ 3S) NT ≤ 3S = 9	% (NT ≤ 3S)	N (> 3S) NT > 3S = 11	% (NT > 3S)	N (T)	% (T)
Dermis						
Signs of vasculitis	0	0	0	0	0	0
Pigment incontinence	1	11	7	64	8	40
+	1		5		6	
++	0		2		2	
Edema	3	33	3	27	6	30
+	3		3		6	
Infiltrate						
Level						
Superficial	9	100	7	64	16	80
Superficial and deep	0	0	4	36	4	20
Perivascular	6	67	8	73	14	70
Interstitial	3	33	3	27	6	30
Cell types						
Eosinophils	6	67	10	91	16	80
+	3		5		8	
++	3		5		8	
Lymphocytes	9	100	11	100	20	100
++	2		4		6	
+++	7		7		14	
Histiocytes	4	44	4	36	8	40
+	4		4		8	
Neutrophils	0	0	0	0	0	0
Atypical T cells	0	0	0	0	0	0

N: number of cases; NT ≤ 3S: total number of cases biopsied within the first 3 weeks of clinical evolution; NT > 3S: total number of cases biopsied after 3 weeks of clinical evolution.

Considering the epidermis, acanthosis was a major feature found in all but one biopsy specimen. Other common epidermal features were parakeratosis (85%) and spongiosis (80%). Langerhans cell microabscesses were noted in five biopsy specimens (25%). Necrotic keratinocytes were observed in only three cases (15%). The most common dermal change was the presence of a superficial and perivascular inflammatory infiltrate. Lymphocytes were the most numerous cells and were present in all cases. Eosinophils were also common and were observed in 80% of the biopsies, although in much smaller number. Neutrophils and atypical lymphocytes were not present in any of the studied cases.

Spongiosis was present in 89% of the biopsies of skin lesions with < 3 weeks of clinical evolution. On the other hand, parakeratosis, hyperkeratosis, and hypergranulosis were consistent features in older lesions. Pigment incontinence was almost exclusively observed in older lesions. The dermal infiltrate was similar at all stages.

Discussion

Epidermal changes were present in all our biopsy specimens. Different epidermal features were observed in relation to the evolution of the skin lesions. In the early stages of ACD, histopathology is characterized by spongiosis, that is., most marked in the lower epidermis[5] (Figure 1). Later, spongiotic vesicles may form at various levels in the epidermis. Spongiosis may be absent in chronic lesions that show progressive psoriasiform hyperplasia of the epidermis which is, in part, a response to rubbing and scratching[5,7,8] (Figure 2). In our study, most biopsies corresponded to lesions in the subacute or chronic stage. Even though, marked acanthosis,

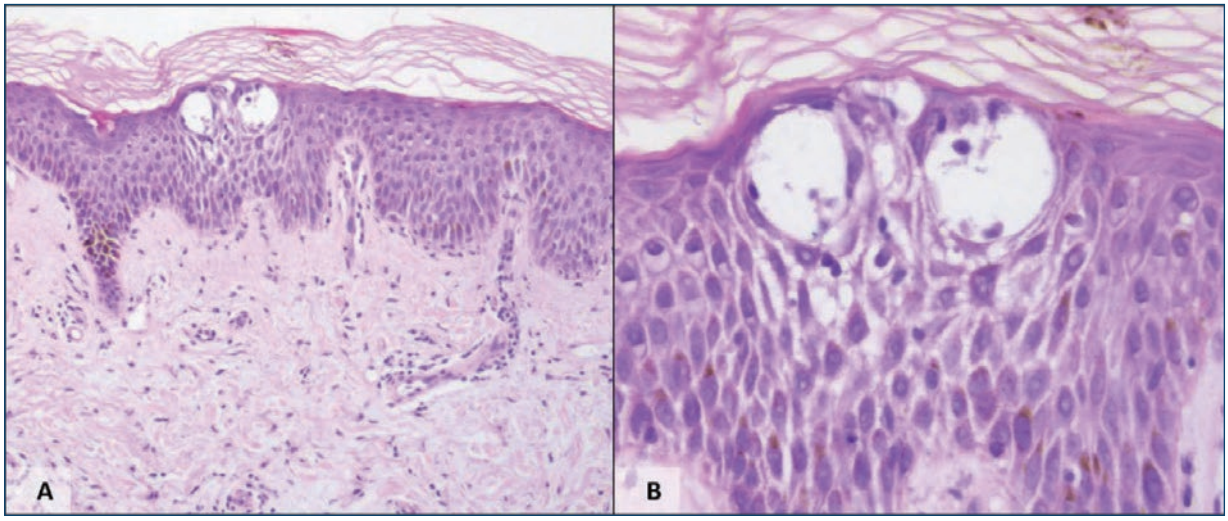

Figure 1. Acute allergic contact dermatitis and histopathological picture. **A:** marked spongiosis with perivascular lymphocytic infiltrates in upper dermis also containing some eosinophils (H&E ×100). **B:** intraepidermal vesicles (H&E ×400).

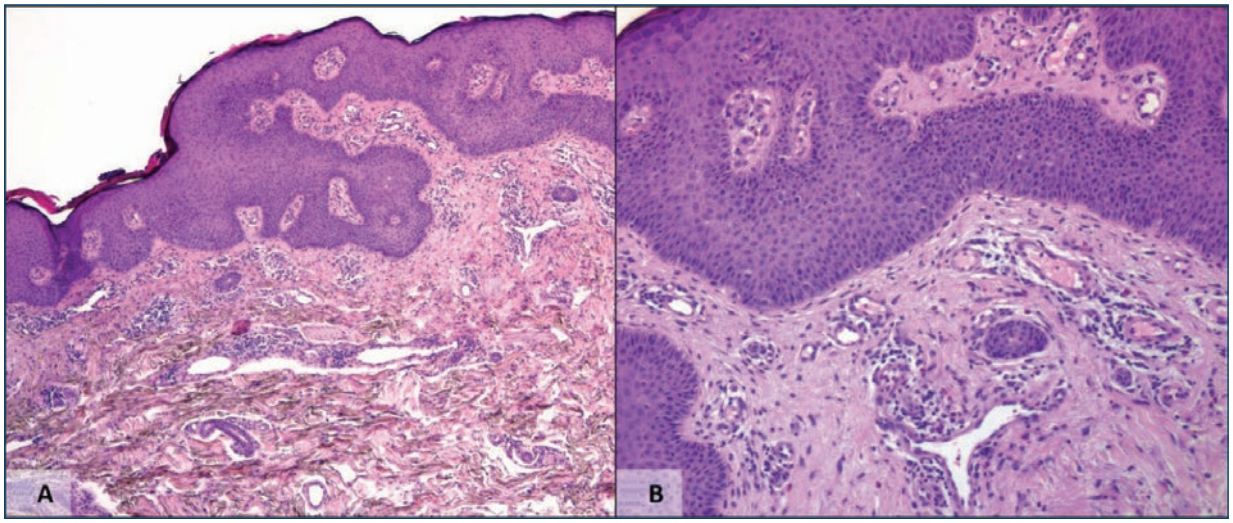

Figure 2. Subacute allergic contact dermatitis and histopathological picture. **A:** hyperkeratosis, hypergranulosis, and acanthosis (H&E ×40). **B:** eosinophils and lymphocytes within the dermal infiltrate (H&E ×100).

hyperkeratosis, hypergranulosis and, to a lesser degree pigment incontinence, were main features of the older lesions. At all stages of the disease, a perivascular superficial dermal infiltrate consisting mainly of lymphocytes and other mononuclear cells was seen. The type and distribution of the inflammatory cells may help in making a specific diagnosis. In ACD, eosinophils are frequently present (Figure 2B), but their absence does not exclude it.

Results regarding the diagnostic value of Langerhans cell collections are somewhat contradictory. While some studies suggest that their presence may play no diagnostic role, other authors have argued that it is a potentially helpful clue[9]. We found Langerhans cell collections in only five cases. However, we did not perform CD1a-staining and we did not examine additional histopathological sections.

Subcorneal pustules were present in three of our cases. This finding has been described as a variant of ACD (pustular contact dermatitis). Other special clinical and histological variants of ACD exist (such as the lymphomatoid contact dermatitis, granulomatous contact dermatitis, purpuric contact dermatitis, and among others) that are beyond the scope of this article.

Atypical keratinocytes, vacuolar degeneration of the basal layer, vasculitis, and neutrophils within the dermal inflammatory infiltrate were not observed in any of our cases. These features may be helpful in the differential diagnosis with other clinical entities.

We reported a clinico-histopathological concordance of 80%. The main histological differential diagnosis was DE (three cases). The case with longer clinical evolution (6 months) was pathologically consistent with psoriasis. In subacute and chronic stages of ACD, epidermal hyperplasia may become a major feature. In subacute lesions, spongiosis is usually still observed and it allows a correct diagnosis. However, in chronic lesions, such as in our case, spongiosis may be discrete or even absent. Our study showed continuum parakeratosis with significant (++) hyperkeratosis, hypergranulosis, and acanthosis without spongiosis. A dermal superficial and perivascular infiltrate with lymphocytes (+++), eosinophils (++), and histiocytes (+) was observed. Although nondiagnostic, the presence of eosinophils in the superficial dermis, hypergranulosis, and epidermal hyperplasia that is not as regular as the one in psoriasis may help in the differential diagnosis. Pathologically differentiation features between ACD and DE are discussed below.

ACD versus DE

DEs have a broad and heterogenous spectrum of histological patterns[8,10]. Spongiotic DE is the most confused with ACD (Figure 3). Parakeratosis, found in 85% of the cases of our series, is uncommon in DE where the cornified layer is mostly basket-woven[10]. The same is true for epidermal hyperplasia, a common feature in long-standing lesions of ACD but uncommon in spongiotic DE. Besides, in DE, there is more exocytosis than would be likely considering the amount of spongiosis in the region. Apoptotic cells are almost invariably present, but a careful examination is needed. In ACD, the dermal infiltrate is usually superficial while, in DE, it tends to extend to the mid and deep dermis. The presence of eosinophils is common in both conditions, although in higher number in DE, where they may be present in the epidermis[11]. In our series of ACD, eosinophils in the epidermis were absent. This feature may be helpful in the differential diagnosis. Red cell extravasation is occasionally present in the upper dermis of DE while pigment incontinence is uncommon[11,12]. Besides, in our study, neutrophils were not found within the dermal infiltrate. In fact, the combined presence of neutrophils and eosinophils has been linked to DE[10,11]. Vacuolar degeneration is also more common in DE, and this feature was not observed in any of our cases. In fact, Weyers et al. state that a perivascular and interstitial infiltrate of neutrophils and eosinophils together with subtle vacuolar degeneration is virtually diagnostic of DE[10]. Atypical keratinocytes although not sensitive nor specific are more common in DE than in other inflammatory diseases[10]. Mixed histological patterns in the same biopsy are also a clue to a possible DE[8,10,13].

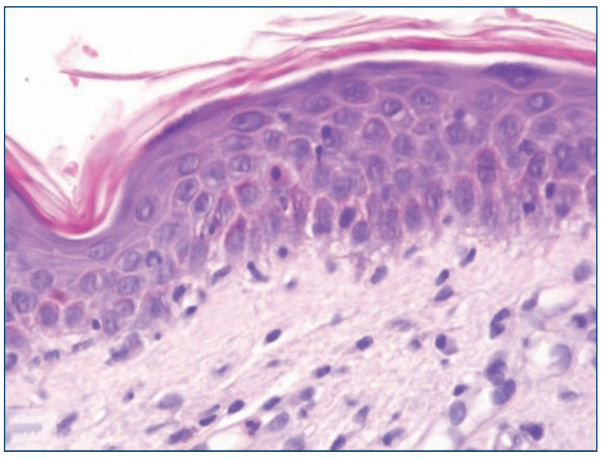

Figure 3. Drug eruption and histopathological picture: Mild spongiosis in the lower half of the epidermis; subtle vacuolar interface dermatitis and scattered apoptotic keratinocytes were clues to the diagnosis of drug eruption (H&E ×400).

Histopathology is a useful tool in difficult to diagnose ACD-cases. Findings that support the diagnosis of ACD may be found and it has an important role in the exclusion of other conditions. However, there is no single histological diagnostic feature, and all the histological findings are nonspecific and insufficient for making a diagnosis.

Our study has several limitations. Although we have only included cases with a highly probably diagnosis of ACD; ideally, all the included cases should have gone through patch test confirmation. However, that would decrease the already small size of our sample. ACD cases are not usually biopsied unless there is doubt about the diagnosis. Therefore, cases submitted for histological examination are in somewhat peculiar and with longer clinical evolution, which may also be a possible limitation. Nevertheless, we may consider it as an advantage because these are the "real world" cases that are actually biopsied and the ones that the dermatopathologist will encounter.

Authors' contributions

All the authors have made substantive intellectual contributions to this work and take public responsibility for it. RBM, MAL, PEL, and LSA have all contributed to the design and implementation of the research and to the analysis of the results. RBM has drafted the manuscript and MAL, PEL, and LSA have revised it critically

for important intellectual content. The final version has been approved by all the authors.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical disclosures

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant Clinical Research Ethics Committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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