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A Traditional Review

Differentiating Allergic and Irritant Contact Dermatitis based on histopathology: Overview

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Keywords: irritant contact dermatitis; allergic contact dermatitis; diagnosis; histology; histopathology; biopsy findings; light microscopy.

Abstract

Differentiating Allergic Contact Dermatitis(ACD) from Irritant Contact Dermatitis (ICD) has posed a significant challenge for dermatologists, allergists, and histopathologists. Over the years, many studies have been conducted to determine whether ACD can be differentiated from ICD based on histopathology findings. A clear-cut distinction based on histopathology will facilitate the diagnosis and appropriate management of both conditions.

Abbreviations: CD, Contact Dermatitis; ACD, allergic contact dermatitis; ICD, irritant contact dermatitis

Objective: This review summarizes the existing literature on whether and how ACD can be differentiated from ICD based on histopathology findings.

Methods: Pubmed, Embase, Web of Science, Scopus, Cochrane Library, and Google Scholar were searched from inception to August 23, 2024, for primary literature reporting on histopathology findings in ACD and ICD. We used the search words: contact dermatitis, allergic contact dermatitis, irritant contact dermatitis, histopathology, histology, biopsy, light microscopy, diagnosis.

Conclusions: Although the difference between ACD and ICD has been extensively studied over the past years, the research still needs to be more conclusive in categorically differentiating the two. Further research on the comparative histopathology of ACD vs ICD will enhance our understanding and ability to accurately distinguish. In addition, many chemicals possess both irritant and allergic properties, which might be the reason for the overlap. Moreover, the studies conducted up till now have only tested patients with one dosage of chemicals. Using a range of low, medium, and high doses might aid in eliciting better and more conclusive findings.

Introduction:

The differentiation of Allergic Contact Dermatitis (ACD) from Irritant Contact Dermatitis (ICD) has been a subject of interest for histopathologists over many decades. Numerous studies have established the biopsy differences between the two, while others consider these findings to be equivocal. This review aims to summarize the existing literature on this subject and investigate the utility of biopsy results in differentiating these two conditions.

Results & Discussion:

Differentiating Contact Dermatitis (CD) types based on clinical features poses a significant challenge. Many studies have been conducted to describe the histopathology findings of ACD and ICD and whether the two can be accurately differentiated based on biopsy results. The chronic forms of the two conditions have significant overlap in clinical findings, with erythema, lichenification, excoriation, scaling, and hyperkeratosis being common to both. Thus, a detailed clinical history along with patch testing proves crucial to accurate diagnosis. (Ale & Maibach, 2006). Histopathology remains a promising avenue to aid in clear-cut differentiation. Therefore, many studies have been conducted to explore its utility. We review the literature on this subject to summarize and integrate the established results and suggest areas for further research.

Two experiments on human volunteers found that ACD and ICD findings are histologically distinct and thus reliable for diagnosing the two. Vestergaad et al (1999) established follicular spongiosis as a defining feature of ACD, while Ferguson (1985) distinguished between the two based on quantitative differences in the cellular infiltrate.

Although the use of animal study results for humans is limited, and extrapolating these results requires a leap of faith, animal studies still benefit our understanding of the differences between the two conditions. Experiments on dogs (Krawiec & Gaafar, 1975) and guinea pigs (Medenica & Rostenberg, 1971) have also demonstrated histological differences between ACD and ICD in animals. These reiterate the presence of spongiosis and mononuclear infiltrate in ACD and necrosis, dermal-epidermal separation, and dermal edema in ICD.

Three studies on human volunteers solely investigated the findings of ACD biopsies. Carr et al, 1967 and Rantuccio et al 1978 described epidermal intercellular edema and inflammatory mononuclear cells as being

associated with ACD. On the other hand, Wildermore et al, 2003 stated that biopsy findings are merely suggestive rather than diagnostic of ACD. A similar study described characteristic findings of hyperkeratosis, parakeratosis, and acanthosis as being associated with ICD (Le et al.,1998)
Two literature reviews propose that a categorical differentiation can be made between ACD and ICD based on biopsy findings. (Lachapelle, 1973 and Taylor, 1986). Taylor described ICD as predominantly demonstrating epidermal cell injury and ACD as revealing spongiosis, edema, and a range of cellular infiltrates at various times.

In contrast, other researchers hold the view that ICD and ACD cannot be differentiated histologically. Among these are Nater and Hoedemaker (1976), who studied the allergic and irritant effects of the compound DNCB. They concluded that ICD and ACD histopathology differences are primarily quantitative and cannot be utilized to differentiate the two.

Jovanovic et Al (2003) state that the presence of eosinophils in the dermal inflammatory infiltrate, edema of the papillary dermis, and the presence of microvesicles can be used to distinguish ACD in doubtful cases. However, they concur that there are no clear-cut histopathological differences between ACD and ICD. They conclude that biopsies should not be routinely used for differentiation between the two.

Numerous reference books have delved into the differentiation of ACD from ICD. Ackerman et al. (1997) categorically distinguish ICD from ACD based on three histological features: necrosis, ballooning of keratinocytes, and neutrophilic infiltrate. In contrast, ACD exhibits spongiosis with perivascular lymphocytic infiltrate and eosinophils instead of the aforementioned histological features.

Ale (2006) further corroborates that histological distinctions can be made based on the type of spongiosis(the presence of intercellular edema between epidermal keratinocytes), the spread of infiltrate, and the presence of pustulation. Vestergaard et al. (1999) concluded from their patch testing of patients with known contact allergy that follicular spongiosis may be a specific feature of early ACD.

While some researchers consider spongiosis to be the hallmark of ACD, still others allude that spongiosis along with acanthosis (diffuse epidermal hyperplasia), multinucleate dermal Dendritic fibro histiocytic cells, acanthosis, lymphocytic infiltrate, dermal eosinophils, and hyperkeratosis are merely suggestive of ACD and are not solely reliable for diagnosis. Hence, there is a need for a correlation between clinical characteristics and patch testing. (Wildermore, 2003) Frings et al. (2017) also found histomorphology to be of little utility in differentiating ACD from ICD. They describe the main value of skin biopsies as their ability to rule out skin conditions in eczematous lesions such as psoriasis, tinea, or cutaneous T Lymphoma. They further describe the differentiation of ACD from ICD as the role of the clinician and allergologist, not the histopathologist.

Lachapelle (2001) establishes the utility of 3 diagnostic modalities for ACD and ICD differentiation. Skin biopsies show promise of aiding in differential diagnosis, but he recommends that patch test biopsies are less valuable and should be limited to scientific studies. Moreover, immunocytopathological techniques provide little assistance in differentiation as the cytokines released do not show major variation.

The range of histopathology findings in various studies is inherently due to the nature of ACD and ICD reactions. The lesions vary based on irritant concentration, type, duration of exposure, and skin reactivity. Thus, it is difficult to equivocally set a histopathological criterion to distinguish the two. (Ale & Maibach 2006). This necessitates further research on light and electron microscopy and molecular and cytokine profiles to aid clinicians in accurately distinguishing the two and solving this long-drawn puzzle. Moreover, histopathology for routine differentiation of the two conditions provides limited benefit. The utility of biopsies is much more in cases where the two are difficult to distinguish clinically.

TABLE 1: Articles included in the study.

First author, year, country	Method	Main findings described	ACD	ICD
Carr, (1968). United States	Poison Ivy(Oleoresin) was applied to the skin of a human volunteer with a known allergy to Poison Ivy. Skin biopsies were observed for the earliest skin changes utilizing light and electron microscopy.	Described ACD histopathological findings.	Intercellular edema of the epidermis, Dermal and epidermal invasion by inflammatory mononuclear cells No intracellular edema or damage to desmosomes or tonofibrils.	Not Studied
Medenica, 1971, United States	Biopsy specimens from the skin of 2 guinea pigs induced with ACD and ICD chemicals.	Light and electron microscopy differences in ACD and ICD were described.	Spongiosis, secondary lysosomes, basophils in the dermis, monocytes, lymphocytes, and macrophages later.	Epidermo-dermal separation, necrosis of the epidermal cells, and dermal polymorphonuclear leukocyte infiltration.
Lachapelle, 1973, Belgium	Review based on biopsies obtained 48 hours after chemical application to the skin.	Allergic and irritant patch test reaction in humans compared.	Spongiosis more frequent, frequent eosinophils, edema, dilation of capillaries and lymphatics	Pustules, necrosis, acantholysis more frequent
Krawiec, 1975, United States	2, 4 nitro-chlorobenzene intradermal injections were used to introduce ACD (14 sensitized and 7 non-sensitized) and ICD in young beagle dogs (6 pups)	Skin biopsy specimens were analyzed histologically for ACD and ICD findings.	Mononuclear predominant infiltrate, Less prominent dermal edema	Epidermal cell Necrosis Dermo-epidermal separation Dermal edema Massive infiltration of PMN Cells

Nater, 1976, Netherlands	Histological characteristics of primary allergic and irritant contact dermatitis studied. Used the same compound DNCB on a group of volunteers through patch testing and histological examination.	Histological changes appeared similar in both ACD and ICD cases.	Spongiosis Degenerative changes Mononuclear infiltrate	Spongiosis Degenerative changes Mononuclear infiltrate
Rantuccio, 1978, Italy	Patch testing of 20 subjects was carried out with known allergens. Skin biopsies examined for specific histological findings	A mixed cellular infiltrate was discovered histologically in ACD.	80-82% Lymphomonocytes 5% Mast Cells 0.2 % Basophils Eosinophils (6/20 Cases)	Not Studied
Ferguson, 1985, United Kingdom	The upper backs of 11 and 9 patients were evoked for ACD and ICD Patch test reactions, respectively, using 5% Nickel sulfate (allergen) and sodium lauryl sulfate (irritant).	Semi-quantitative histological methods were used to differentiate allergic and irritant reactions to patch tests. Dermal infiltrate distribution and cell content are similar in both; quantitative differences present.	Perivascular chronic inflammatory infiltrate: Large and variable	Perivascular chronic inflammatory infiltrate: Small and consistent
Willis, 1986, United Kingdom	Histopathological Features of ACD vs. ICD were compared using patch tests on 17 human patients with known ACD using standardized allergens and irritants.	There were no differences in ACD vs ICD in responding cell types/cellular events.	Predominantly T lymphocytes infiltrate with no polymorphonuclear leukocyte involvement. Apposition of Langerhans cells to lymphocytes in the epidermis	Predominantly T lymphocytes infiltrate with no polymorphonuclear leukocyte involvement. Apposition of Langerhans cells to lymphocytes in the epidermis
Taylor, 1986, USA	Literature Review	Certain general features can distinguish ACD from ICD.	Different inflammatory cell types at different time intervals Dermal-epidermal edema Epidermal spongiotic vesicle formation	Epidermal cell injury Cellular edema and necrosis Dermal-epidermal separation PMN infiltrate
Willis, 1989, United Kingdom	10 healthy human volunteers patch tested with various known irritants. Biopsy specimens were observed with light and electron microscopy.	Specificity and diversity of histopathological findings in ICD observed.	Not Studied	Spongiosis Epidermal infiltration of predominantly mononuclear cells keratinocyte damage (dyskeratosis and parakeratosis)
Ackerman, 1997, United States	Reference Book	Histological diagnosis of various inflammatory skin disorders discussed along with differential diagnosis	No Ballooning No Keratinocytes No Neutrophils Superficial perivascular infiltrate of *lymphocytes*,	*Necrotic and ballooned* Keratinocytes *Neutrophilic* Infiltrate
			sometimes eosinophils *spongiosis*	
Le, 1998, United States	Punch biopsy of 11 human patients with chronic irritant contact dermatitis studied for histology and immunohistochemistry.	Chronic irritant contact dermatitis is histologically characterized by inflammatory changes, epidermal hyperproliferation, and altered differentiation.	Not Studied	hyperkeratosis, parakeratosis, spongiosis, exocytosis, acanthosis, and mononuclear perivascular infiltrates
Vestergaard, 1999, Denmark	Allergic and irritant patch tests were applied to 8 patients with known contact allergy to colophony or quaternium 15. Punch biopsies studied histologically.	Follicular spongiosis is a characteristic finding of ACD that can differentiate early ACD from ICD.	Early spongiosis Lymphocytic exocytosis of the follicular infundibulum	Hardly any changes
Jovanovic, 2003, Yugoslavia	Palmoplantar skin lesion biopsies of 24 patients with Chronic ACD and 24 patients with Chronic ICD were studied to distinguish Chronic ACD from Chronic ICD.	Despite some slight differences, light microscopy cannot differentiate Chronic ACD from Chronic ICD.	Hyperkeratosis, parakeratosis subcorneal vesicle moderate spongiosis acanthosis elongation of dermal papillae Pronounced Inflammatory infiltrate composed of lymphocytes and some eosinophils moderate elongation of epidermal papillae.	Hyperkeratosis, acanthosis moderate inflammatory infiltrate, composed of lymphocytes
Wildermore, 2003, United States	Skin biopsies of 39 cases of ACD were studied to establish specific histopathological findings of CD.	Histological criteria are insufficient for the diagnosis of ACD. Needs integration with clinical findings and patch testing.	Eosinophilic spongiosis, multinucleate dermal Dendritic fibro histiocytic cells, acanthosis, lymphocytic infiltrate, dermal eosinophils, and hyperkeratosis.	Not Studied
Ale, 2006, Germany	Reference Book	ACD and ICD were compared based on clinical, histological, and histochemical differences, as well as their cytokine profiles.	Microvesicle predominant spongiosis Focal cellular infiltrate Rare pustulation	Spongiosis, intracellular edema, exocytosis Diffuse cellular infiltrate Pustulation and necrosis The findings were not uniform.
Ziemer, 2012, Germany	Reference Book	Pathophysiological mechanisms must be used to distinguish ACD from ICD	*Spongiosis* Associated with *eosinophils* but not neutrophils	*Ballooning* of keratinocytes Epidermal *Necrosis* Associated *neutrophils* with but not eosinophils
Cockerel, 2012, United Kingdom	Reference Book	The clinical presentation of ACD and ICD is similar. Diagnosis is made based on clinical findings, patch testing, and supportive histology.	Epidermal spongiosis, *intraepidermal vesicles,* superficial perivascular lymphohistiocytic infiltrate, scattered eosinophils	Epidermal spongiosis, Variable *mild acanthosis,* superficial perivascular lymphohistiocytic infiltrate, scattered eosinophils *Necrotic Keratinocytes*
So, 2015, United States	Reference Book	The differential diagnosis of ACD through clinical characteristics, mechanism, and histology is discussed.	Acute: spongiosis, acanthosis,variable parakeratosis, superficial perivascular lymphohistiocytic infiltrate, eosinophils Langerhans Cell microabscesses Chronic:acanthosis, hyperkeratosis, hypergranulosis, Eosinophils	Spongiosis, neutrophilic infiltrate; may have necrotic keratinocytes

Frings, 2018, Germany	35 Skin biopsies of 28 patients with ACD or atopic dermatitis were histopathologically examined.	Difficult to distinguish ACD from ICD solely based on histomorphology.	Focal parakeratosis	Necrotic epidermal keratinocytes
Lachapelle, 2021, Belgium	Reference Book	Differential diagnosis can be aided by skin biopsy. Patch test biopsies have utility only for scientific purposes. Immunohistopathology is not very helpful due to negligible cytokine differences.	Typical of spongiotic dermatitis: Upper dermis dense lymphocytic infiltrate Epidermal exocytosis of lymphocytes	Varied according to nature/concentration of chemical and individual skin reactivity Epidermal necrosis Epidermal/ adnexal alterations
Marzullo, 2021, Italy	Reference Book	ACD and ICD can be very hard to distinguish histologically. This is due to nonspecific findings and the overlap of allergic and irritant properties between chemicals.	Follicular spongiosis, Lymphocytic exocytosis of the follicular Infundibulum Less intense ("focal") intra-epidermal inflammation	Epidermal necrosis Dermal and epidermal neutrophils

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Munira Malik: Conceptualization; investigation; writing – original draft; methodology; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT:

The authors declare no conflicts of interest.

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