International Journal of Medical and Health Research
ISSN: 2454-9142
Impact Factor: RJIF 5.54
www.medicalsciencejournal.com
Volume 4; Issue 3; March 2018; Page No. 210-212

Study of histopathological patterns of interface dermatitis in skin biopsies of various skin diseases

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Abstract
There are some problems in classifications relating to interface dermatitis/ lichenoid tissue reaction. All these classifications in literature are broader and according to infiltrate pattern and type, which fails to come to the conclusion of individual skin diagnosis. Further the term LTR and IFD are overlapping and not clearly separated by present system of classification. These classifications are not able to explain the actual differentiation of LTR/ lichenoid dermatitis from other dermatosis like MF, histiocytosis, etc. To add to confusion disease showing epidermotropism like MF has been included in the classification as a cell poor IFD. These classifications are not involving the other interface changes seen in skin biopsies of Hansen's disease etc. Lichenoid infiltrate changes seen in skin malignancies like bowen's disease, basal cell carcinoma, paget's disease, etc. are also included under the terminology of "IFD". This study will redefine the true features of IFD and put a new classification by combining the older classifications as well as will try to put sub classification. Further this study will separate the true IFD from lichenoid tissue reaction and secondary interface changes seen in other skin conditions.

Keywords: histopathological, ifd/ltr, dermatitis, skin diseases

Introduction
Pinkus, (1973) stated LTR as one exhibiting epidermal basal cell damage and the chain of histobiological events resulting from such damage. It is not essential whether damage to the basal cells is primary or is itself due to a preceding event in the dermis [1]. Modern workers defined IFD as finding in a skin biopsy of an inflammatory infiltrate that abuts or obscures the dermo - epidermal junction [2]. Crowson defined IFD as an inflammatory infiltrate along dermo – epidermal junction that is of sufficient intensity that it obscures, at least focally, the basilar keratinocytes. When this process is band like it is characterised by the term "lichenoid". [2] Many authors have classified IFD/ LTR. According to Lever's histopathology of the skin [3]

A. Superficial dermatitis with lichenoid infiltrates (lichenoid dermatitis) and further sub classified according to infiltrate type. Such as a. Lymphocytes exclusive - lichen planus, etc, b. Lymphocytes predominant – paraneoplastic pemphigus, etc. c. Others - lichenoid drug eruption etc [4]

B. Superficial dermatitis with interface vacuoles – according to amount of apoptosis - e.g a. Apoptotic cells prominent - erythema multiforme, etc, b. Apoptotic cells usually absent – dermatomyositis, etc, c. Variable apoptosis – induced drug lupus, etc, d. Basement membrane thickened – lupus erythematosus, etc [5]

There are some problems in above classifications IFD/LTR. All these classifications in literature are broader and according to infiltrate pattern and type, which fails to come to the conclusion of individual skin diagnosis. Further the term LTR and IFD are overlapping and not clearly separated by present system of classification. These classifications are not able to explain the actual differentiation of LTR/ lichenoid dermatitis from other dermatosis like MF, histiocytosis, etc. To add to confusion disease showing epidermotropism like MF has been included in the classification as a cell poor IFD. These classifications are not involving the other interface changes seen in skin biopsies of Hansen's disease etc. Lichenoid infiltrate changes seen in skin malignancies like bowen's disease, basal cell carcinoma, paget's disease, etc. are also included under the terminology of "IFD".

This study will redefine the true features of IFD and put a new classification by combining the older classifications as well as will try to put sub classification. Further this study will separate the true IFD from lichenoid tissue reaction and secondary interface changes seen in other skin conditions.

Objective
To study the histopathological findings associated with interface dermatitis in skin biopsies

Material and Methods
All skin biopsies fulfilling the inclusion criteria during the course of the study (May 2010–May 2013) from dermatology department of Krishna hospital, Karad, were enrolled in this study. This was a hospital based observational clinico – histomorphological study. All skin biopsies fulfilling the inclusion criteria during the course of the study (May 2011 – May 2013).

Inclusion criteria
To enrol the biopsies should show any one features mentioned below-

A. Inflammatory infiltrate at the dermo-epidermal junction leading to (IFD)

1. Vacuolar changes at basal layer
2. Variable apoptosis
3. Obscuration of dermo-epidermal junction

B. Inflammatory infiltrate at the dermo-epidermal junction that encroaches to epidermis and passively migrates through the dermo-epidermal junction (epidermotropism)
1. With epidermal changes
2. Without epidermal changes

Result and Discussion

In the current study, we have attempted to involve the diseases showing classical IFD along with some other diseases where IFD is not a classical finding, but there are alterations at the interface which mimic IFD. We have also tried to redefine the true features of IFD and put a new classification by combining the older classifications.

DEJ is the interface between epidermis and dermis, which is affected by various inflammatory dermatoses, and the changes occurring at this junction constitute the IFD. True IFD is defined as inflammatory infiltrate leading to either vacuolar dermatitis with or without variable apoptosis or obscuration with variable apoptosis. According to Leboit *et al* mere obscuration of DEJ is also IFD [6] But according to our understanding there should be damage to basal cell layer leading to vacuolar i.e. hydropic degeneration of basal layer keratinocyte leading to changes in epidermis like necrosis and apoptotic keratinocytes and melanin incontinence, colloid bodies and civatte bodies in the dermis. There should be vacuolisation where apoptosis may or may not be present but if there is obscuration, there should be apoptosis to label it as true IFD.

Pattern 1a i.e. cell poor vacuolisation without apoptosis is seen mainly in diseases like follicular LP, oral LP, LPP, LSEA etc., hence these variants of LP show no necrosis or obscuration, however vacuolisation was seen, though focal is characteristic of LP. Pattern 1b i.e. cell poor vacuolisation with apoptosis is mainly seen in LE, viral exanthema etc. which represents acute necrotic reaction of epidermis secondary to basal cell vacuolisation without any obscuration and mild inflammatory infiltrate. Pattern 1c i.e. cell poor obscuration with apoptosis is not seen individually in any of the diseases; hence this pattern coming individually is really very uncommon. Pattern 1d i.e. cell poor obscuration without apoptosis is mainly shows secondary LTR and interface dermatopathy. In secondary LTR mainly LPP, viral exanthema, BCC, BTHD, acute perforating folliculitis were seen respectively. In interface dermatopathy mainly BTHD, vitiligo, reactive perforating collagenosis, parapsoriasis, porokeratosis etc. were seen.

Pattern 2a i.e. cell rich vacuolisation without apoptosis is mainly seen in EM, DLE, porokeratosis, BTHD, oral LP respectively. Even in the presence of vacuolisation some cases do not show necrosis even in diseases like EM. Pattern 2b i.e. cell rich vacuolisation with apoptosis is mainly seen in DLE, PLC respectively. Pattern 2c i.e. cell rich obscuration with apoptosis is mainly seen in lichen striatus, LP, LE, EM etc. Necrosis could be observed even in absence of vacuolisation, only when obscuration is of cell rich type. Pattern 2d i.e. cell rich obscuration without apoptosis is mainly seen in interface dermatopathy and secondary LTR. Interface dermatopathy was mainly seen in BTHD, BLHD, MF/parapsoriasis, lupus vulgaris, LLHD, PNT, polymorphous light eruption, insect bite reaction etc.

In combination patterns, like pattern 1a and 1d mainly diseases like PLC, LP, drug rash, LSEA, actinic cheilitis, etc were seen. Here, there is absence of necrosis, but both obscuration and vacuolisation can be seen. In pattern 1b and 1c mainly diseases like PLC, EM, LE etc. are mainly seen which is consistent with findings of Lever at al. In pattern 2a and 2d diseases like LP, Hansen's disease, LE, insect bite reaction, lichen nitidus, LDR, LSEA, polymorphous light eruption, photodermatitis etc. were mainly seen where necrosis was absent even in presence of cell rich inflammatory infiltrate. Pattern 2b and 2c is mainly seen in LP, EM, LE, LDR, PLEVA, PLC, parapsoriasis, lichen striatus etc. LP and EM were most commonly seen, thus correlating with other authors like Lever *et al*, that these diseases show true IFD in form of obscuration, vacuolisation and necrosis.

Patterns 1a, 1b, 2a, 2b & 2c individually and combination patterns (1a+1d), (1b+1c), (2a+2d) & (2b+2c) were seen in IFD/LTR, whereas patterns 1d & 2d were seen in interface dermatopathy and secondary LTR. No combination patterns were seen in them.

In our study, IFD was seen mainly with combination of patterns, although they were seen with individual patterns also albeit in lesser frequency. And maximum IFD were seen with combination pattern of 2b and 2c and never seen with pattern 1d and 2d. Pattern 1c was never seen individually. Of all the slides seen, maximum PLC showed IFD changes followed by DLE and EM.

We observed many new diseases showing true IFD changes which were not seen by previous authors for, e.g. Hansen's disease of both BTHD and BLHD type, actinic cheilitis, insect bite reaction, polymorphous light eruption, photoallergic dermatitis, porokeratosis etc. Although necrosis/apoptosis of keratinocytes was not a prominent feature, vacuolisation alone or vacuolisation with obscuration were frequently observed. So disease like Hansen's disease can lead to true IFD changes which were never mentioned previously by any authors. All kind of patterns were seen with IFD except 1c, 1d and 2d. Pattern 1c i.e. cell poor obscuration with apoptosis was never seen individually, so cell poor obscuration with only apoptosis and no vacuolisation is very rare pattern to be seen. Most of the time in IFD, combination of patterns is more common compared to individual pattern, so that means presence of vacuolisation with obscuration with or without apoptosis is more common compared to presence of only vacuolisation or obscuration individually with or without apoptosis. In epidermal changes, spongiosis and psoriasiform hyperplasia was the commonest finding correlating well to Leboit *et al* pattern i.e. IFD with psoriasiform hyperplasia was commonly seen with IFD in our study. Necrosis may or may not be seen and if present we could see occasional necrosis commonly. Obscuration and vacuolisation was most commonly seen and is mainly of focal type respectively. Infiltrate was mainly of lymphocyte predominant type and moderate in density. Melanophages were prominently seen in dermal findings correlating with basal cell damage.

According to Lever's histopathology of the skin, IFD pattern's seen by us fit into IFD with vacuolar dermatitis. While

according to Crowson *et al* [3] they were cell poor IFD. While it was the combination of Le boit's pattern 1 and 2 i.e. acute cytotoxic IFD and IFD with psoriasiform hyperplasia respectively both seen in IFD. LTR is defined as a type of cell rich IFD having dense band like inflammatory infiltrate with true IFD changes i.e. there should be basal cell damage leading to vacuolar degeneration with or without necrotic keratinocytes and melanin incontinence and band like inflammatory infiltrate obscuring the DEJ. So according to previous author the term IFD and LTR are overlapping and not clearly separated. So we propose that LTR is truly a part of IFD and should not be considered as a separate entity. Any cell rich IFD is LTR.

In LTR maximum diseases seen were LP followed by LDR. Among LP variants, LP hypertropicus was the commonest. Diseases like Hansen's disease i.e. BTHD and TTHD, lichenoid photodermatitis previously not included by other authors also showed LTR in our study. Diseases like EM, drug rash, viral exanthema which is considered by Lever histopathology of the skin as main prototype of vacuolar dermatitis with interface vacuoles also showed LTR in few slides in our study, it means that though these diseases mainly show vacuolar changes and never show band like inflammatory infiltrate, there can be rare possibility as few slides showed LTR changes. According to other authors, Levers histopathology of the skin [3], LTR was seen maximum with pattern A i.e. superficial dermatitis with interface vacuoles. According to Crowson *et al* [2]. it was seen with pattern 1 lymphocyte rich type and according to Leboit *et al* it was seen with pattern 2 i.e. IFD with psoriasiform epidermal hyperplasia. Mainly band like infiltrate was seen followed by superficial perivascular. This coincides with other author‟s studies like Lever *et al*. It is not necessary that should be always necrosis in LTR as there were good amount of slides which showed either absence of necrosis or scattered necrosis. Obscuration and vacuolisation were commonly seen mainly of partial and moderate type respectively. Infiltrate type was mainly moderate lymphocyte predominant which coincides with findings of Crowson *et al* [2]. Changes secondary to basal cell damage like melanin incontinence and colloid bodies was also seen in our study in dermal finding.

Pinkus *et al* [1], (1973) stated LTR as one exhibiting epidermal basal cell damage and the chain of histobiological events resulting from such damage, which means that apoptosis/ necrosis of keratinocytes or other epidermal changes are secondary to basal cell damage, but in secondary LTR, the inflammatory infiltrate appearing at the DEJ is not responsible for epidermal changes. So we have included tumours like BCC, BD, keratoacanthoma, malignant melanoma, and mastocytosis which showed only accumulation of tumour cells around DEJ with no vacuolisation or necrosis. The changes occurring in epidermis like epidermal hyperplasia were primary and unrelated to infiltrate at DEJ. One slide of viral exanthema was also showing secondary LTR changes.

Conclusion

True IFD is defined as inflammatory infiltrate leading to either vacuolar dermatitis with or without variable apoptosis or obscuration with variable apoptosis. Mere obscuration is not the IFD and either of vacuolar change and apoptosis/necrosis seen in epidermis are true features of IFD. LTR is truly a part of IFD and should not be considered as a separate entity. Any cell rich IFD is LTR. LTR is defined as a type of cell rich IFD having dense band like inflammatory infiltrate with true IFD changes i.e. there should be vacuolisation with or without necrosis and melanin incontinence and band like inflammatory infiltrate obscuring the DEJ. Diseases where skin biopsy shows only band like inflammatory infiltrate or accumulation of tumor cells in the superficial dermis obscuring DEJ appearing as LTR but not showing true IFD or epidermal changes are known as secondary LTR. It actually mimics LTR but here there are no true IFD changes like apoptosis/ necrosis or vacuolisation. Interface dermatopathy is defined as mild to moderate inflammatory infiltrate appearing at dermo - epidermal junction without epidermal damage seen in IFD but other epidermal changes are possible. Here, there is an inflammatory infiltrate at the DEJ which is either obscuring or migrating the passive epidermis without epidermal damage like apoptosis/ necrosis or vacuolisation. Post vacuolar dermatitis is changes seen after vacuolisation, here we can appreciate only melanin dipping into dermis but true vacuolar changes and necrosis are absent. Every slide showing interface changes should be viewed properly by a dermatopathologist to see whether there is true IFD changes or they are just mimicking IFD changes to come to a specific diagnosis.

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