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Original Research Article

Role of Histopathology in Diagnosis of Cutaneous Lupus Erythematosus: A Cross Sectional Observational Study

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ABSTRACT

Lupus erythematosus (LE) is a multisystem disease with a broad range of clinical manifestations ranging from an isolated cutaneous eruption at one end to a fatal systemic illness at the other. Cutaneous lupus erythematosus may be subdivided into acute, subacute, or chronic based upon the constellation of clinical, histologic, and immunofluorescence findings. Definitive diagnosis prior to treatment initiation is essential as it is a chronic relapsing disease requiring regular-follow-up.

Aims: The objectives of this study are to define and characterize the spectrum of histopathological changes in cutaneous lupus erythematosus and to correlate the clinical findings such as lesion size, site and morphology with its histology and to differentiate from other simulating lesions.

Methods: It is a cross-sectional observational study at post graduate medical college done for the period of eighteen months. Prior ethical approval was taken from institutional ethical committee. Cases were referred from Dermatology OPD of clinically diagnosed cutaneous LE. Detailed history and physical findings were noted. Each case was diagnosed by histopathological examination and confirmed by Lupus band test in selected cases. Descriptive statistics was done using Microsoft excel.

Results: A total of 48 cases were clinically diagnosed as cutaneous lupus erythematosus, 13 male and 35 female. Age of presentation ranged from 5 years to 67 years. Among various subtypes; chronic cutaneous LE (CCLE) was the most frequent subtype most of which presented as discoid lesions. The comparative distribution of histopathological features of the CLE cases, on the basis of which, the lesions are sub classified into ACLE, SCLE and CCLE, along with clinical correlation, were tabulated.

Conclusion: Histopathological examination is indispensable in the diagnosis of LE. The commonest histological feature clinching the diagnosis in our study was interface dermatitis with vacuolar degeneration of the basal keratinocytes and perivascular and periadnexal lymphocytic infiltrate.

Key words: Cutaneous, lupus erythematosus, discoid, lupus tumidus, lupus panniculitis, histopathology

Key message: Histopathological examination plays a significant role in the diagnosis of diverse variants of cutaneous lupus and also in the exclusion of other clinical differentials.

INTRODUCTION

Lupus erythematosus (LE) is a chronic autoimmune disease that affects

multiple organ systems with up to 85% of patients having cutaneous manifestations. [1] Cutaneous lupus erythematosus (CLE) may be subdivided according to the morphology of the clinical lesion and its duration into acute (ACLE), subacute (SCLE), or chronic (CCLE). There are several clinical mimics of CLE such as Jessner's lymphocytic infiltration of the skin, polymorphous light eruption, lichen planus and sarcoidosis.[2] Chronic cutaneous lupus includes discoid LE (DLE), LE profundus (LEP), chilblain LE (CHLE), and LE tumidus (LET). Histopathology is indispensible for distinguishing between these cases. Diagnosis of these diseases requires proper classification of the subtype, through a combination of physical exam, laboratory studies, histology, antibody serology, and occasionally direct immunofluorescence, while ensuring to exclude systemic disease.[3] The objectives of this study were to characterize the spectrum of histopathological changes in cutaneous lupus erythematosus, and to correlate clinical findings such as lesion morphology, location and extent of lesion with the histology of the lesion.

METHODS

This institution based cross-sectional observational study was commenced after approval from institutional ethics committee. Patients attending the Dermatology outpatient department, between January 2014 and June 2015 with skin lesions suggestive of cutaneous lupus were included. Their clinical history was obtained and detailed physical examination performed. Complete blood counts, serum biochemistry panel and appropriate serological markers for SLE were tested to corroborate clinical suspicion. Patients who do not provide informed consent were excluded. The cases with a clinical diagnosis of CLE were subjected to punch biopsy. Sections were stained with hematoxylin and eosin stain and examined.

Histologic features were studied in details. The spectrum of histologic changes, their frequency and characteristic features were noted and correlated with clinical presentation. DIF was performed in selected doubtful cases. The results were tabulated.

RESULTS

Seventy cases of clinically suspicious lesions were biopsied, of which 48 were finally diagnosed as cutaneous LE. The remaining 22 cases were diagnosed as polymorphous light eruption (8), Jessner's lymphocytic infiltrate (6), sarcoidosis (6) and lymphocytoma cutis (2).The 48 cases of cutaneous LE were further evaluated. Thirteen (27%) patients were males, and 35 (73%) cases were females, with male to female ratio being 1:2.7.

Most of the patients (20, 42%) were in the age group of 31-40 years. The youngest patient was a 5 year old female and the oldest was a 67 year old male. The patients had varied occupations with female housewives forming the majority.

Of the 48 cases of CLE, the commonest subtype was CCLE (32 cases, 67%). 11 (23%) cases were of ACLE, and 5(10%) cases were of SCLE.

Of the 32 CCLE cases, most were of discoid lupus type (25 cases, 52.1%).

The LE non-specific lesions included photosensitivity, alopecia, vasculitis and oral ulcers. Table 1 demonstrates the frequency of LE non-specific lesions in the 48 patients.

Table 1. Frequency of LE-nonspecific lesions.(Total 48)

Sl no	LE-NONSPECIFIC LESION	NUMBER OF CASES	PERCENTAGE
1.	Photosensitivity	40	83.33
2.	Oral ulcer	9	18.75
3.	Alopecia	16	33.33
4.	Malar rash	8	16.66
5.	Vasculitis	10	20.83
6.	Joint pain & swelling	5	10.41
7.	Erythema multiforme	1	2.08

The site-wise distributions of lesions showed that the majority of lesions were present in multiple sites throughout the body, specifically the head-neck, trunk and upper extremities (31 cases, 65%). 9 cases (18%) had oral mucosal involvement, of which 8 cases were that of ACLE (89%). No patients had nasal or genital mucosal involvement. In the upper extremities, the arms and hands were mostly involved. The lower extremities were not affected. In head and neck, the sites commonly affected were the scalp, pre and post-auricular area, malar area and lips.

Most common site involved in ACLE was oral mucosa, (8 out of 11 cases, 72%). While SCLE (4 out of 5 cases, 80%) and CCLE affected multiple sites, (24 out of 32 cases, and 80%).

The comparative distribution of histopathological features of the CLE cases, on the basis of which, the lesions are sub classified into ACLE, SCLE and CCLE, along with clinical correlation, were tabulated. (Table 2)

Table 2: Comparative distribution of histologic features of acute, subacute and chronic LE (n=48)

Sl No	HISTOLOGIC FEATURES	ACUTE LE(N=11)	SUBACUTE LE(N=5)	CHRONIC LE(N=32)
1	Interface dermatitis	8	5	27
2	Vacuolar degeneration of basal keratinocytes	10	4	27
3	Lymphocytic infiltrate	11	5	31
4	Mucin deposition	4	4	4
5	Follicular plugging	8	2	15
6	Basement membrane tortuosity	6	2	8
7	Hyperkeratosis	7	4	20
8	Lymphocytic infiltrate in subcutis	0	0	5

The three histological changes, common to all three types of CLE, were interface dermatitis(83%) defined as a dermatosis in which the infiltrate usually composed mostly of lymphocytes appears to obscure the junction when sections are observed at scanning magnification.[4] vacuolar degeneration of basal keratinocytes(85%) and perivascular and periadnexal lymphocytic infiltrate. (98%) (Fig 1)

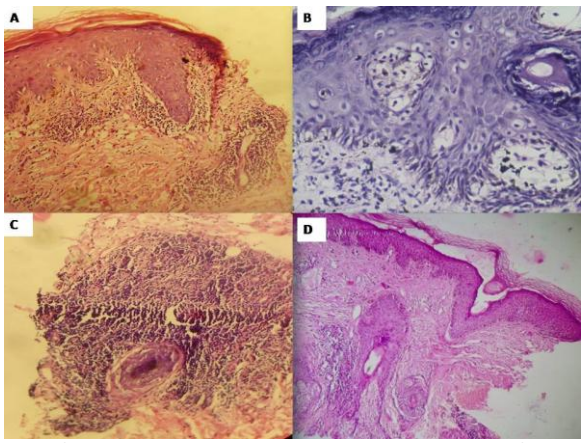

Fig 1-Photomicrograph showing A)Interface dermatitis(HEx40)B)Vacuolar degeneration of basal keratinocytes(HEx400) C) Perifollicular lymphoid infiltrate(HEx100) D)Follicular plugging(HEx40).

Comparative distribution of histopathological features of the three subtypes of CCLE namely discoid LE (DLE), lupus tumidus (LET) and lupus panniculitis/lupus profundus (LEP) is shown in Table 3

Table 3 Comparative distribution of histologic features of subtypes of CCLE (n=32)

Sl No	Histologic features	Discoid LE(n=25)	Lupus tumidus (n=2)	Lupus panniculitis (n=5)
1	Interface dermatitis	20	2	5
2	Vacuolar degeneration of basal keratinocytes	22	1	4
3	Lymphocytic infiltrate	25	1	5
4	Mucin deposition	2	2	0
5	Follicular plugging	15	0	0
6	Basement membrane tortuosity	8	0	0
7	Hyperkeratosis	20	0	0
8	Lymphocytic infiltrate in subcutis	0	0	5

Fig 2.1A and 2.IB shows clinical and histological feature of Subacute CLE.
Fig 2.2A and 2.2B shows clinical and histological feature of DLE. Discoid LE showed epidermal atrophy, hyperkeratosis, interface dermatitis, periappendegeal lymphocytic infiltrate.

whereas Fig 2.3A and 2.3B show clinical and histological features of lupus panniculitis.
It was characterized by lymphocytic infiltrate in the subcutis in 100% cases. LET was characterized by dermal mucin deposition (100%),

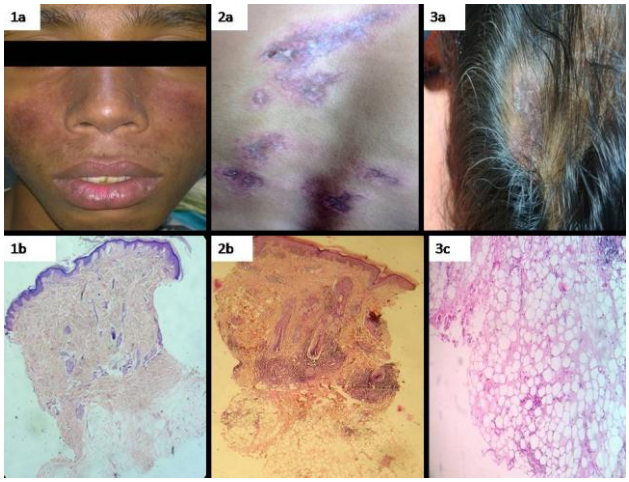

Fig 2-
1a) Clinical picture of patient of subacute CLE.1b)Subacute CLE showing epidermal atrophy, sparse lymphocytic infiltrate. (H&Ex40).
2a) Clinical picture of patient of discoid LE.2b) Photomicrograph of discoid LE showing epidermal atrophy, hyperkeratosis, interface dermatitis, periappendegeal lymphocytic infiltrate.(HE x40).
3a) Clinical picture of lupus panniculitis. 3b) Photomicrograph of lymphocytic infiltrate in the subcutis. (H&E x100)

There was no predilection of CLE with occupational sun-exposure, as only 8 cases, all male, were subjected to sun-exposure during the course of their daily work. However, patients did complain of exacerbation of symptoms on sun-exposure.

Lupus band test (LBT) was done in 8 cases. LBT is deposition of immunoglobulins and complement components in the skin of patients with lupus erythematosus (LE), demonstrable as a linear band at the basement membrane zone (BMZ) by direct immunofluorescence.[5] The results of LBT were positive in 5 cases (62%), negative in 1 case (13%) and had nonspecific patterns in 2 cases (25%).

DISCUSSION

CLE is a disfiguring, chronic skin disease, with a significant impact on the patients' everyday life.[6] Lupus may be seen as a spectrum with CCLE at one end and systemic lupus (affecting other organs and systems) on the other end. Skin lesions in patients with lupus maybe LE-specific or LE non-specific, based on histological criteria (Gillam classification).[7]
LE- nonspecific changes are photosensitivity, urticaria, Raynaud's phenomenon or vasculitis, livedo racemosa, thrombophlebitis, and acral occlusive vasculopathy. Papular mucinosis, calcinosis cutis, nonscarring alopecia, and erythema multiforme are also found defined as LE-non-specific manifestations.[8]
LE-specific lesions are categorized into chronic (CCLE), subacute (SCLE) and acute (ACLE).[9]
The diagnosis of these diseases requires proper classification of the sub-type, through a combination of physical examination, laboratory studies, histology, antibody serology and occasionally direct immunofluorescence, while ensuring to exclude systemic disease.[3]
In our study, the age of presentation ranged from 5 years to 67 years. The majority of

patients were in the 31-40 years age group (20 out of 48 cases, 42%).

There was female predominance (35 of the 48 cases, 73%) with male to female ratio being 1:2.7. Similar findings have been recorded by various studies conducted over the years both in India and abroad. Mahfoudah et al.[10] studied 104 Tunisian cases in 2010 and found chronic lupus erythematosus represented 0.1 % of all the dermatitis seen over 11 years with F/M ratio of 1,9.7 and an average age of 42 years. The discoid form was the most frequent clinical shape, observed in 73 % of cases (76 patients).

Biazar et al in 2013 observed the mean age at onset of disease was 43.0±15.7 years and differed significantly between the CLE subtypes.[11]

In our study, the patients of cutaneous lupus have been classified under the broad categories of acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), and chronic cutaneous LE (CCLE). CCLE has been further classified into discoid LE (DLE), LE panniculitis/profundus (LEP), and LE tumidus (LET).

The rarer forms of cutaneous lupus such as chilblain lupus, neonatal lupus, bullous lupus, lupus verrucous/hypertrophic were not encountered in our study of eighteen months duration.

In our study, the number of cases diagnosed as ACLE were 11 (23%), SCLE were 5 (10%), and CCLE 32 (67%).Of the CCLE cases, 25 were that of DLE (52.1 %), 2 of LET (4.4%) and 5(10.5%) of lupus panniculitis. The majority of CCLE are in the age group of 31 to 40 years, with 14 cases (29.2%). According to gender-wise distribution of cases, the majority of CCLE are females with 24 cases (50%).

George et al. conducted a study on the histopathological and immunofluorescence profile of LE patients in India and found a predominance of discoid LE (28 amongst 65 patients), followed by 5 cases of SCLE.[12]

In our study, ACLE presented in localized and generalized forms. The generalized form presented as a photosensitive, pruritic, symmetric macules and papules. Patients with localized form were found to have associated mucosal ulcerations/apthae (8 out of 11 cases). Szczech et al published that among 64 analyzed subjects of cutaneous LE, 15 (23.4%) patients were diagnosed as having an acute CLE (ACLE) (8 patients with localized and 7 with generalized form).[13]

Histologically, ACLE lesions showed vacuolar degeneration of basal keratinocytes, edema of the upper dermis, and a scattered interface, perivascular, and periadnexal lymphocytic infiltrate. Tebbe et al.[14] conducting a study on 296 patients found that all the histological features of ACLE is generally less pronounced as compared to other CLE subtypes.

Five SCLE cases found in our study were characteristically highly photosensitive lesions, occurring mostly in sun-exposed areas, none seen below the waist. The lesions were non-indurated and non-scarring. The points of difference of SCLE with the other types were: more basal vacuolar change, dermal edema and superficial mucin than in DLE, but less hyperkeratosis, pilosebaceous atrophy, follicular plugging, basement membrane thickening and cellular infiltrate. Also, the infiltrate was found confined more to the upper dermis than in discoid lupus.

CCLE was the most frequent subtype (n=32) in the present study. Discoid lesions were the most common lesions among CCLE. Patients with DLE generally have a more benign disease course as compared to patients with other CLE subtypes, with only a reported 5-10% developing systemic lupus throughout their disease course.[15]

In present study, localized DLE commonly involved the head and neck, and particularly the scalp and ears. Generalized DLE occurred both above and below the neck. Mucosal surfaces were involved in 1 case; on lips and oral mucosa. The lesions appeared as well-demarcated, scaly, erythematous macules or papules that gradually developed into indurated discoid (coin-shaped) plaques with adherent scales.

Plaques tended to extend into the hair follicle, resulting in scarring alopecia. DLE on histology was showed lichenoid reaction pattern and both superficial and deep dermal infiltrate of inflammatory cells which also accumulate around the pilosebaceous follicles.

LET typically presents with juicy papules and plaques that heal without scarring, whereas LEP (lupus panniculitis) involves subcutaneous tissue, leading to painful subcutaneous nodules that heal with depression and atrophy. Biopsy is critical in these latter cases, as lesions have frequently been shown to closely resemble subcutaneous lymphoma.[16]

In lupus tumidus (n=2), there was increased dermal mucin in all cases, accompanied by a sparse inflammatory cell infiltrate. Unlike classic DLE lesions, follicular plugging was not observed. In lupus panniculitis, lymphocytic infiltrate was seen extending up to the subcutaneous fat.

Lupus band test is done upon skin biopsy, with direct immunofluorescence staining, in which, if positive IgM and complement depositions are found at the dermo-epidermal junction.[17] This test can be helpful in distinguishing systemic lupus erythematosus (SLE) from cutaneous lupus, because in SLE the lupus band test will be positive in both involved and uninvolved skin, whereas with cutaneous lupus only the involved skin will be positive.[18] The results of lupus band test done in 8 cases in our study revealed positive in 5 cases (62%), negative in 1 case (13%) and had nonspecific patterns in 2 cases (25%) in lesional skin. George et al have shown that in DLE, the sensitivity of the LE band test was 58% and the specificity 87%.[19]

Thus, we can sum up that histopathologic examination revealed some common findings which can be used to characterize a case as cutaneous LE. These were interface dermatitis with vacuolization of the basal cells, periadnexal and perivascular lymphocytic infiltrate, interstitial mucin deposition, and thickening and tortuosity of basement membrane.

There are quite a few lupus imitators which pose serious differential diagnostic challenge.

Discoid lesions are very distinct in appearance from other entities; however the early indurated erythematous plaques of DLE can resemble those of psoriasis, lymphocytoma cutis, cutaneous T-cell lymphoma, granuloma faciale, polymorphous light eruption, and sarcoidosis.[20] Buccal mucosal DLE may mimic lichen planus; however the former has a radial brush-like appearance originating from a central area of erythema.[21] An uncommon variant of DLE, hypertrophic or verrucous DLE refers to extremely thickened lesions occurring on the arms, hands, and face. These lesions have features in common with kerato-acanthomas and hypertrophic lichen planus. These mimics were excluded by absence of their characteristic histopathological findings.

In lymphocytoma cutis, the infiltrate usually is heavier than in lupus erythematosus, may have an interstitial component, shows no tendency to arrange itself around pilosebaceous structures, and often contains admixture of larger, paler lymphocytes arranged in lymphoid follicles, mimicking germinal centre formation.[22]

The plaque type of polymorphous light eruption is characterized by prominent papillary dermal edema. There is intense superficial infiltrate, with occasional neutrophils.[23]

The dermal infiltrate of Jessner's lymphocytic infiltrate of skin may be indistinguishable from that seen in early, nonscarring or purely dermal lesions of lupus erythematosus. The presence of increased numbers of B-lymphocytes in the infiltrate may help distinguish this from LE.[24]

Under the microscope, hyperkeratotic lesion of lupus erythematosus may closely resemble hypertrophic lichen planus (LP) or keratoacanthomas. Both diseases may show hydropic degeneration of the basal cell layer. In lichen planus, there is wedge-

shaped hypergranulosis and "saw-toothing" of rete ridges, not seen in DLE; in DLE, the epidermis frequently appears flattened. Also, in LP the infiltrate is only superficial and stromal mucin deposition is not seen.[2]
Differentials of ACLE include drug-induced photosensitivity, pemphigus erythematosus, atopic dermatitis, contact dermatitis, and photocontact dermatitis.[3]
The differential diagnosis for SCLE also includes dermatomyositis, cutaneous T-cell lymphoma, tinea corporis, erythema annulare centrifugum, erythema gyratum repens, photolichenoid drug eruption, granuloma annulare, and pemphigus foliaceus. Many of these lesions have similar appearances, and histologic examination is often necessary for differentiation.[3]

CONCLUSION

Lesional biopsy is necessary adjunct to clinical findings for diagnosis of cutaneous lupus. Characteristics histologic findings include interface dermatitis, vacuolar degeneration of basal keratinocytes, lymphocytic infiltrates, interstitial mucin deposition, and thickening and tortuosity of basement membrane. Direct immunofluorescence; though less sensitive may be helpful in non-definitive histologic findings.

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