APPLICABILITY OF THE CUTANEOUS LUPUS ERYTHEMATOUS DISEASE AREA AND SEVERITY INDEX (CLASI) IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

A

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CERTIFICATE

This is to certify that the dissertation entitled **"**Applicability of the Cutaneous Lupus Erythematous disease area and severity index (CLASI) in patients with Systemic Lupus Erythematosus (SLE)**"** is the bonafide original work done by **Dr. Pankaj Sharad Salphale.** This study was undertaken at the **Christian Medical College Hospital, Vellore** from the year 2007 under my direct guidance and supervision, in partial fulfillment of the requirement for the award of the **M.D. degree in Dermatology, Venereology and Leprosy of the Tamilnadu Dr.M.G.R. Medical University.**

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Contents

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune connective tissue disorder with a wide range of clinical features. Dermatological manifestations are among the most frequent presenting signs and remain a major source of disease flares throughout the course of the illness .[1] Assessment of activity of and damage caused by cutaneous disease is essential from research as well as practice point of view. Most of the indices for systemic activity assessment include cutaneous manifestations as one of the components. In 2005, an exclusive index for the cutaneous disease named CLASI (Cutaneous lupus area and severity index) was formulated and applied to research .[2] CLASI assesses the activity of and damage caused by cutaneous lupus erythematosus and has so far been applied to only LE specific lesions.[3] Any given LE patient may manifest more than one type of LE-specific skin lesion, but, in most patients one form of LE-specific skin involvement predominates.[1]

The uniqueness of CLASI lies in its ability to separate damage and activity as such a distinction is essential in any disease that can cause severe persistent organ damage.

Systemic activity of lupus can be assessed by numerous indices of which SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) is the simplest tool to use .[4] It grades the activity of the disease from “no activity” to “very high activity”. Patients with LE-nonspecific skin manifestations have significantly increased disease activity compared to those with only LE-specific lesions.[5]

AIMS & OBJECTIVES

1. To study the applicability of Cutaneous Lupus Erythematosus Disease Area and Severity index (CLASI) in specific lesions of cutaneous lupus erythematosus occurring in SLE patients in our population.

2. To assess the disease activity of patients with Systemic Lupus Erythematosus (SLE) and skin lesions using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

3. To correlate SLEDAI with CLASI activity score in SLE patients with Lupus Erythematosus (LE) specific skin lesions.

REVIEW OF LITERATURE

Cutaneous lupus erythematosus (CLE) is a chronic autoimmune disease with specific and non-specific clinical manifestations. While there are indices like SLEDAI (Systemic lupus erythematosus disease activity index) [4], BILAG (British Isles Lupus Assessment Group) [6] and SLAM (Systemic lupus activity measure) [7] to measure activity of systemic disease in SLE, there was, till recently, no exclusive index to measure cutaneous activity.

CLASI came into existence in 2005 after it was validated in a Philadelphia Hospital, USA.[2] This index scores damage and activity of the cutaneous disease separately. The activity measurement attempts to quantify the level of active inflammation in the skin, scalp and oral mucosa. The damage measurement attempts to quantify the "footprint" of destruction left behind by the previous inflammation.[8] When used in routine practice for patient follow up it can provide useful information on the response to therapy and for planning new or alteration of existing therapy.

EPIDEMIOLOGY

SLE has worldwide distribution, with an estimated prevalence of 12–64/100,000 population. In most patients, SLE develops between the age of 15 and 45 years. The female to male ratio is at least 9:1. In childhood disease, the ratio of girls to boys is 3:1.[9] A review of 32 studies summarized the incidence and prevalence of systemic lupus erythematosus in several countries and documented the increased disease burden, especially in non-white populations .[10]

A prevalence study in India carried out in a rural population near Delhi found a point prevalence of 3 per 100, 000.[11] Malaviya et al reported that the median age of onset of SLE was 24.5 years and the sex ratio (F:M) was 11:1.[12] In a study done from CMC, Vellore that described the clinical profile of 65 patients with LE, the mean ages of onset were 31.3 years in DLE, 33 years in SCLE and 26.8 years in SLE.[13] Though the age differences were not significant, the male to female ratios of 1.3:1 and 1:7 in DLE and SLE respectively were statistically significant.

CLINICAL CLASSIFICATION OF CUTANEOUS LUPUS ERYTHEMATOSUS (CLE)

Skin lesions are common in SLE and were found in up to 90% of a studied cohort.[1]

The vast majority of patients will have LE-related skin disease sometime during the course of their illness. Discoid lesions, malar rash, oral ulcers and photosensitivity constitute 4 of the 11 criteria for the diagnosis of SLE devised by the American College of Rheumatology (ACR) in 1982 and modified in 1997.[14] There are many patients with LE-specific skin disease that do not have, or may never develop SLE.[15]

The cutaneous manifestations of lupus are categorized according to the Gilliam classification (Appendix A).[3] This divides cutaneous lupus erythematosus into LE-specific and LE-nonspecific skin disease. Specific skin lesions show the distinctive histologic change of LE: the interface dermatitis. LE nonspecific skin lesions are not histologically distinct for CLE and may be seen as a feature of another disease process. Nonspecific lesions are frequently seen in patients with SLE, usually in the active phase of the disease.[3]

LE-SPECIFIC SKIN LESIONS

*Discoid LE (*DLE)

It presents as photo- distributed erythematous papules and / or plaques with adherent scaling extending into patulous follicular orifices. Lesions can be localized or disseminated. Localized DLE is confined to the head and neck. Scalp involvement occurs in 60% of DLE patients, and is the only area involved in approximately 10%.[16] Of patients presenting with DLE lesions, 5% to 10% will subsequently develop clear-cut evidence of systemic disease.[16] A study describing the clinical profile of 65 patients of LE in CMC, Vellore had 32 SLE patients of which 7 patients (21.8%) had DLE lesions.[13]

Sub acute cutaneous LE (SCLE)

SCLE was first defined by Sontheimer et al. It presents as non-scarring, erythematous, papulosquamous and/or annular skin lesions, occurring in a symmetrical, photo distributed pattern.[17, 18] Patients presenting with SCLE have accounted for 5–30% of variously reported LE populations.[19] In the CMC study, 5 out of 65 patients (7.7%) had SCLE.[13]

Many patients with SCLE fulfill more than four criteria of the American College of Rheumatology for SLE.[20]

***Acute cutaneous LE* (ACLE)**

ACLE can occur as localized or generalized disease. Localized ACLE is often referred to as the 'malar rash' or 'butterfly rash' of SLE.[21] There is a tendency to spare the nasolabial folds. Generalized ACLE presents as a widespread morbilliform or exanthematous eruption in a photo distribution sparing the knuckles and bullous or toxic epidermal necrolysis- like acute cutaneous LE skin lesions.[3] Usually, the generalized form of ACLE is associated with increased disease activity of SLE and is often accompanied by mucosal changes affecting the mouth (hard palate, buccal mucosa, gingiva, and uvula), nose, pharynx, and vagina.

Bullous LE

Bullous LE typically affects young adults in the second, third, or fourth decade of life. The criteria utilized for making the diagnosis include the diagnosis of SLE based on the ACR criteria, vesicles and bullae arising on, but not limited to, sun-exposed skin and routine histopathologic findings compatible with dermatitis herpetiformis.[22]

Tumid lupus erythematosus

It is a distinct entity within the spectrum of chronic CLE. Patients with TLE are usually young women who present with nonscarring, photo distributed, indurated, violaceous papules and plaques.[23] In a study of 15 tumid LE cases, association with systemic disease was found to be low and the autoantibody profile was negative in 50% of the cases, whereas remaining cases had a low titer (<1:160) ANA.[23]

Lupus panniculitis

Lupus panniculitis occurs frequently in adults between the ages of 20 and 60 years (female: male ratio 2:1).[24] It usually presents as painful (later asymptomatic) or tender, indurated, subcutaneous nodules on the face, proximal extremities and the buttocks. The overlying skin may be normal or ulcerated. The nodules may resolve with deeply indented scars.[21]

Chilblain lupus

Chilblain or perniotic LE presents as purple red papules, nodules or plaques on the toes, fingers and face and is precipitated by cold, damp climates. It is usually seen in females.[25]

Mucosal LE

Cardinali C et al reported a 5.1% prevalence of mucous membrane lesions among the 186 SLE patients who were studied for specific skin lesions.[27]A wide spectrum of oral mucosal lesions is found in cutaneous and systemic forms of lupus erythematosus such as cheilitis, erythematous patches, discoid lesions, “honeycomb patches”, lichen planus like lesions and discrete ulcers.[28]

LE-NON-SPECIFIC LESIONS

The nonspecific lesions are broadly grouped into cutaneous vascular disease, nonscarring alopecia and an assortment of other conditions. They are seen only in patients with SLE and usually in the active phase of the disease .[27] The patients with these lesions

have an increased disease activity when compared to those with specific lesions and to those with both kinds of lesions. Cardinali C et al[5] found LE non –specific skin lesions in 31% of the 186 studied patients. The most common non-specific manifestation was Raynaud's phenomenon that was seen in 39.6% followed by nonscarring alopecia seen in 31% patients.[27]

Cutaneous vascular disease

This includes vasculitis, vasculopathy, periungual telangiectasia, livedo reticularis, thrombophlebitis, Raynaud's phenomenon, and erythromelalgia.

Vasculitis: About 10-20% of SLE patients have some form of vasculitis.[3] Cutaneous vasculitis often correlates with active SLE .[29] In the CMC study, purpuric lesions were encountered in 20% of SCLE and in 15.6% of SLE patients .[13]

Vasculopathy: This may present as atrophie blanche, leg ulcers or Degos disease like lesions. It is frequently associated with the presence of antiphospholipid antibodies.[3] The latter may be associated with livedo reticularis .

Digital lesions are polymorphous, and often considered clinically as vasculitis. These may present as ulceration or gangrene, pitting scars, micro infarcts, urticarial lesions, petechiae or purpura, erythematous non tender lesions and nodules .[30]

Nonscarring alopecia: Hair loss in SLE is common and may be due to telogen effluvium, alopecia areata or lupus hair. Fifty four percent of the patients in one study had hair loss .[31]A positive correlation between diffuse non scarring alopecia and other cutaneous features such as malar rash, discoid lesions, photosensitivity and cutaneous

vasculitis was found by Wysenbeek AJ et al who studied alopecia in a cohort of 74 SLE patients.[32] It correlated with exacerbation of disease activity as assessed by disease activity index.

The incidence of alopecia areata was studied in 39 patients by Werth VP et al and was found to be 10%.[33] It was concluded that alopecia areata may have an association with LE.

Lupus hair is a form of transient alopecia in chronically active SLE patients. Thin, weakened hairs are found at the periphery of the scalp especially the frontal area. These hairs easily fragment above the surface of the scalp .[3, 16]

The other non-specific findings include sclerodactyly, rheumatoid nodules, calcinosis cutis, urticaria, LE-nonspecific bullous lesions, lichen planus, erythema multiforme and cutis laxa or anetoderma .[3]

Antiphospholipid syndrome: It is defined as the occurrence of venous thrombosis, arterial thrombosis, recurrent pregnancy loss and /or thrombocytopenia in the setting of moderate to high titer lupus anticoagulant or anticardiolipin antibody.[1] It may accompany LE or may occur as a primary disease. The cutaneous manifestations include cutaneous necrosis, livedo reticularis, superficial thrombophlebitis, digital gangrene, porcelain white scars, splinter hemorrhages and ulcerations of the legs.[1, 34]

Calcinosis cutis*:* Though less common, it has been reported in patients with SLE in the setting of normal calcium metabolism and renal function. The calcifications are usually on the extremities and the overlying skin is prone to ulcerate and extrude calcified material.[15]

Cutaneous lupus mucinosis

It presents as indurated erythematous papules and plaques typically on the arms and trunk. The histology shows diffuse dermal mucin deposits but lacks the classic vacuolar changes classically seen in LE-specific skin lesions.[15]

Pigmented LE

Cutaneous lupus erythematosus may present as primary pigmented lesions and the histopathology of this reveals the picture of DLE. In the CMC study, 7 patients were described who presented with asymptomatic hyperpigmented macules. [13] Biopsy of these lesions revealed features of DLE. A retrospective review of cutaneous biopsies in elderly patients presenting clinically with single, hyper pigmented macular lesions showed a histopathologic correlation .[35]

CUTANEOUS LUPUS ERYTHEMATOSUS IN CHILDREN

The most common clinical features in childhood DLE are discoid plaques and photosensitivity. Cutaneous lesions are usually on the sun-exposed areas .[36]

Discoid lupus erythematosus is uncommon in childhood. [36-44] The clinical features are similar to those of adults in presentation and chronic course .[36] The range of histological and immunofluorescence features in children with DLE is similar to that in adults .[45]

Subacute lupus erythematosus (SCLE) is extremely rare in childhood though a few cases have been reported .[46-49]

HISTOPATHOLOGY

DLE: The lesions of DLE show hyperkeratosis with keratotic follicular plugging, variable acanthosis and epidermal atrophy. There is basement membrane thickening and an interface dermatitis involving the follicles and the epidermis accompanied by a moderate to heavy superficial and deep perivascular and periappendageal lymphocytic infiltrate.[50,51] Basal epithelial layer destruction and pigmentary incontinence are characteristic. Pronounced dermal mucin deposition is usually present in lesions of DLE .[52]

SCLE: The lesions show a mild hyperkeratosis and mild to moderate epidermal atrophy. Liquefaction degeneration is usually seen at dermo-epidermal interface and occasionally in follicles. Colloid bodies, pigment incontinence, dermal edema and dermal mucinous degeneration are occasional. There is suprabasilar exocytosis of lymphocytes showing satellitosis to necrotic keratinocytes. The interface change exhibits a hybrid pattern comprising cell poor vacuolar foci alternating with zones of lichenoid dermatitis. [52] Bangert et al reported that epidermal atrophy was more common in SCLE in comparison to DLE. They concluded that both DLE and SCLE differ quantitatively in the degrees of certain changes.[53] The results of this study were confirmed by Mooney E et al.[54]

ACLE: The histological changes seen in usually show only discrete interface dermatitis with minimal vacuolar alteration of the basal cell layer, upper dermal edema and a sparse perivascular mononuclear cell infiltrate .[55] Varying mosaics of histological features are seen in the 3 major categories of LE-specific disease: acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), and chronic cutaneous LE (CCLE) .[56] Lesions of generalized acute cutaneous LE can display histological features of erythema multiforme.[57]

In a series of 15 cases of tumid LE that was studied by Alexiades-Armenakas et al[23] dermo- epidermal junction involvement was absent in 80% of the cases and was focal in 20% cases. The hallmark finding present in the study was abundance of mucin in the dermis.

Histology of lupus panniculitis shows lobular panniculitis with a dense inflammatory infiltrate of lymphocytes and plasma cells as well as mucin deposits between fat cells.[21]

Histology of cutaneous lupus mucinosis reveals dermal mucin deposits and moderate to severe mononuclear infiltrate around the blood vessels and hair follicles. The epidermal and junctional changes of SLE can manifest over a period of time .[58]

DIRECT IMMUNOFLUORESCENCE TEST IN CUTANEOUS LUPUS ERYTHERMATOSUS

The test is a valuable adjunct in the diagnosis of SLE when clinical features and laboratory investigations are inconclusive .[34]

The lupus band test (LBT) describes the presence of immunoglobulins and complement components along the dermo-epidermal junction of lesional skin biopsies from LE patients.[52] IgG, IgM and IGA as well as complement components including constituents of membrane attack complex may be deposited. Non-lesional LBT correlates with a more aggressive course of systemic disease including the development of lupus nephritis. It has its greatest utility as a diagnostic test in those with atypical clinical and laboratory manifestations of SLE .[59]

In a study in Indian patients, the lupus band test was found to be highly sensitive. It was positive for lesional skin of all untreated patients with subacute cutaneous LE and systemic LE but was not found useful on nonlesional skin.[13]

CUTANEOUS DISEASE ACTIVITY IN SLE

Appropriate categorization of cutaneous lupus is important for limiting adverse outcomes such as scarring as well as in assessing risks for systemic disease .[26] A minority of patients with DLE will have associated systemic findings, whereas most patients with ACLE have aggressive visceral involvement. Patients with SCLE rarely have life-threatening systemic involvement. Nonspecific skin lesions frequently are seen in patients with active disease. They are histopathologically indistinct for LE and may be an indicator of disease activity.[26]

Therapeutic decisions in cutaneous LE should be based on evaluation of disease activity and severity. Severity denotes the gravity of the manifestation while activity implies a continuous phenomenon ranging from no activity to maximal activity.[7]

The existing outcome measures available for SLE are not sensitive enough to measure the activity of CLE. The cutaneous manifestations of SLE are the least systematically studied aspects of this illness. General scores like Dermatology index of disease severity (DIDS) are too crude in the body surface area assessment in diseases which affect relatively small areas of the skin like CLE.[60]

A standardized, validated instrument to quantify the level of disease burden or improvement in CLE was lacking till 2005 when an index named cutaneous lupus erythematosus disease area and severity index (CLASI) came into existence.[2] It was

designed and validated as an instrument to be used in therapeutic trials in patients with CLE.

CUTANEOUS LUPUS ERTHEMATOSUS DISEASE AREA AND SEVERITY INDEX (CLASI)

This scoring system was developed by investigators at the Veterans Affairs Hospital, Philadelphia and the dermatology departments at the University of Pennsylvania school of Medicine, Philadelphia and Jefferson Medical College, Philadelphia, USA. The design of the CLASI and its characteristics was based on a review of the literature on LE and outcome instruments used in dermatology.[2] It was assessed for its content validity by a group of seven American dermato-rheumatologists and the ACR (American College of Rheumatology) Response Criteria Committee on SLE.

The CLASI has two separate scoring systems for assessing activity of and damage caused by cutaneous lupus. This is necessary in any disease that can cause severe persistent damage. It facilitates the use of activity in short-term studies whereas damage is an important consideration in long term studies where prevention of damage is an important factor. [2] This distinct scoring is well established for scores of SLE where activity and damage are commonly separated .[61] The importance of assigning separate activity and damage scores is explained by the fact that a single score that summarizes damage and activity cannot provide an exact clinical picture of the disease. In scarring forms, as the disease activity decreases and subsequent damage becomes apparent, a combined score would remain paradoxically stable despite the change of clinical picture. This separation makes both aspects easily quantifiable and assures that CLASI is more reactive to therapy induced changes of activity over time. As current activity or damage

may have a significant impact on the quality of patient's life and self-esteem separate damage and activity scores are designed.[2]

The area of skin involved by CLE often reflects disease activity and extent of the disease .[62] The CLASI describes the extent of the disease in terms of the intensity of involvement of anatomical areas. The lesions of CLE are variable in size and may be confluent. Disease improvement may lead to division of larger confluent lesions into greater number of smaller lesions leading to a paradoxically higher score .[2] The area involved by CLE is also difficult to calculate as it involves only small areas of the skin in contrast to psoriasis and atopic dermatitis where body surface area assessment is used in the scores PASI [63] and SCORAD [64,65]respectively. Area measurements are often hard to reproduce due to inconsistencies in assessment of body surface areas and involved areas between investigators.

The indices that assess skin disease depend primarily on erythema as an indicator of skin activity. Erythema is a prominent and easily recognizable sign even in darkly pigmented skin. It is a direct reflection of the hyperemia that accompanies inflammation. Though erythema may be under-appreciated in black skin, in the experience of Bonilla—Martinez Z et al this was not a problem as they applied CLASI in African -American patients.[66] A trained clinician can readily make out erythema except in the darkest skin tones. The absolute value of erythema due to skin tone is not considered relevant as long as the difference in erythema that is attributed to therapy is appreciated.

CLE affects primarily the visible photosensitive areas. In CLASI, scalp and the face (ears, malar areas and nose, rest of the face) are assigned scores that carry more weight through their detailed descriptions. This reflects patient's concerns through their

detailed documentation. DLE often affects only the head, but it can be disfiguring and more serious than the widespread SCLE which usually resolves without scarring. The involvement of visible areas causes greater psychological morbidity to patients and needs greater therapeutic attention by the physician than that of hidden areas. The disease specific shift is taken into account by the weight placed on visible areas in CLASI.[62]

STRUCTURE OF CLASI [2] (Appendix-B)

CLASI is designed as a table with rows denoting anatomic areas and columns include scores for major clinical symptoms. Separate scores for activity and damage are calculated. The activity is assessed by erythema, scale or hypertrophy, mucous membrane involvement, acute hair loss and nonscarring alopecia.

The damage is scored in terms of dyspigmentation, scarring of lesions and/or panniculitis and scarring of the scalp. The dyspigmentation score is doubled if it has remained visible for more than 12 months and is taken to be permanent.

The scores are calculated by simple addition based on the extent of symptoms. The severity of involvement for each symptom is calculated according to the worst affected lesion within that area for each symptom .[2] The maximum possible scores for activity and damage are 70 and 56, respectively.[8]

The CLASI has been designed as one single instrument for at least three clinical entities that constitute CLE i.e. DLE, SCLE and SLE. The CLASI is not meant to document the whole clinical spectrum of CLE. There are some CLE cases that may share characteristics of two or even all three groups of CLE. Future trials in lupus profundus, tumid lupus erythematosus or bullous LE may find it necessary to add and evaluate

additional subscales to measure the subgroup's particular characteristics like such as bullae and induration.[66]

The studies on the applicability of CLASI are limited. Kreuter A et al recently applied the CLASI to a clinical study of 10 patients of SCLE who responded to monotherapy with mycophenolate mofetil. The improvement was assessed by CLASI over a 3 month follow up, the mean scores falling by statistically significant levels. [19]

Krathen M S et al evaluated the validity CLASI for use by rheumatologists via reliability testing.[8] They studied 14 subjects of which 10 had cutaneous lupus erythematosus, one had a mimicker skin disease only (a cutaneous lesion that may appear clinically similar to CLE) and three had both types of lesions. They were rated with the CLASI by academic-based dermatologists and rheumatologists. Reliability testing confirmed its use by both dermatologists and rheumatologists.

Associated subjective symptoms such as pain, pruritus and fatigue as reported by the patients are recorded separately on visual 0-10 analog scales. These symptoms are important for the assessment of therapeutic success as they are more sensitive indicators of disease activity than visual inspection. The relationship of these symptoms to the physician assessed symptoms is unclear and hence they are not integrated with the CLASI score .[2] Bonilla-Martinez Z et al showed that the CLASI activity correlated well with the physicians' and patients' global assessment of the disease activity on a 0 to 10 visual analogue scale. [66]

DISEASE ACTIVITY INDICES IN SLE

Disease activity is defined as a reversible manifestation of an underlying inflammatory process. It reflects the type and severity of organ involvement at each point in time. Assessment of disease activity is very important as many treatment decisions depend on the accuracy of the physician's clinical judgment of disease activity.[4] In clinical practice, concepts of both activity and severity are used to evaluate patients. Activity implies a continuous phenomenon (an interval scale) ranging from no activity to maximal activity. Severity implies gravity of the manifestation.[67]

About 60 consensual systems were developed and applied by rheumatologists to quantify systemic disease activity in their patients with SLE. Of these the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) [4] BILAG (The British Isles Lupus Assessment Group)[6] and the SLAM (Systemic Lupus Activity Measure)[7] designed to assess systemic activity of LE appeared useful for dermatological needs. Goodfield M et al pointed that these indices are more in favour of systemic manifestations.[61] Hence there was need to establish criteria that are more suitable to characterize the disease specific parameters of cutaneous LE.

The indices have been shown to be valid when used by physicians from different countries. The reproducibility, validity and sensitivity to change of these commonly used indices have been confirmed.[68]

SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX (SLEDAI) (Appendix C)[4]

SLEDAI was developed by Bombardier C et al at the University of Toronto.[4] It is a global index containing 24 weighted objective clinical and laboratory variables and

measures disease activity within the last 10 days. The advantage of SLEDAI is the relatively small number of items and the ease of scoring.

It is designed as a one page weighted form consisting of 24 items. An item is noted when present in a patient. The score is calculated by summing the predetermined weights for the items that are present. Life threatening items are assigned higher weights. The maximum possible score is 105. It includes immunology results in the form of positive scoring for an abnormal level of anti-dsDNA antibodies or complement (C3 or C4). The mucocutaneous manifestations that are scored are a new onset inflammatory rash, mucosal ulcers, alopecia and vasculitis. The latter includes ulceration, gangrene, tender finger nodules, periungual infarction and a biopsy proof of vasculitis.

Systemic disease activity categories have been defined on the basis of SLEDAI scores: no activity (SLEDAI = 0), mild activity (SLEDAI = 1-5), moderate activity (SLEDAI = 6-10), high activity (SLEDAI = 11-19), and very high activity (SLEDAI 20 and above).[69] Fitzgerald J D applied SLEDAI in a retrospective chart study and showed that disease activity can be reliably reproduced through such study.[70]

A study from Spain by Formiga et al applied SLEDAI at the moment of diagnosis of SLE and during the first year of the disease in 100 patients. It was found that lupus in the older age group is a distinct clinical entity with a severe course at presentation and during the first year of the disease.[71] Zecevic RD et al applied SLEDAI in a correlation study between specific and nonspecific lesions. They found that patients with LE non-specific skin lesions had significantly high SLEDAI scores.[5]

PATIENTS AND METHODS

The study was conducted from 1st May 2007 to 30th August 2008 (16 months). It was a prospective, cross sectional study done in the Department of Dermatology, Venereology and Leprosy. The subjects were those attending the outpatient department and inpatients referred to us from the Medical, Pediatrics and rheumatology units.

Inclusion Criteria:

1. All patients with systemic lupus erythematosus having lupus specific and non-specific lesions.[3]

Exclusion Criteria:

1. Patients without a cutaneous manifestation of LE.

2. Patients not willing to be included.

3. Neonatal lupus.

Ninety-three patients with a diagnosis of SLE according to the 1997 modification of ARA criteria [14] (Appendix D) were included in the study. Three patients were excluded as they were subsequently diagnosed to have mixed connective tissue disease.

Patients were examined by the principal investigator. A detailed proforma was filled (Appendix E). The demographic data included age, address, gender and occupation.

The presenting mucocutaneous complaints and their respective durations were noted. The body sites affected by lupus specific and non-specific manifestations were recorded. A history of drug intake (corticosteroids, immunosuppressants and hydroxychloroquine) and the topical applications used by the patient in the three months prior to their presentation was noted. Subjects were informed about the purpose of the study (Appendix F) and informed consent (Appendix G) was obtained. Separate child and adolescent assent forms (Appendices H1 & H2) were used for patients in the age groups of 7- 12 years and 13-17 years respectively. Clinical photographs of lesions were taken after patient consent or parenteral consent in case of children.

Clinical Examination

Each patient was examined by the principal investigator for skin lesions. They were classified as specific or non-specific according to the Gilliam classification (Appendix A) [3] for skin lesions of LE. The diagnosis of CLE was based on clinical features and confirmed by skin biopsy, whenever necessary. The lupus specific lesions of acute, subacute and chronic cutaneous lupus erythematosus were recorded. Cutaneous vascular lesions such as palpable purpura, urticarial vasculitis, Raynaud's phenomenon as well as other non-specific manifestations were recorded in the proforma.

Laboratory investigations

These included a hemogram, urine microscopy, urine albumin, 24 hour urine protein, antinuclear antibody (ANA), serum complement, C3 and C4 estimation, and anti-double stranded DNA (anti dsDNA).

Skin biopsy and Direct immunofluorescence (DIF) test

Biopsy of the lesional skin for histopathology was done whenever necessary. The histological features were classified as specific, non-specific and equivocal. It was reported as specific if it showed characteristic features of LE as reported by Lever.[50] If the histological features were highly suggestive, but not characteristic, they were classified as equivocal. The term nonspecific was used when features were not suggestive of LE.

For direct immunofluorescence (DIF) the skin biopsy samples were freshly frozen. Cryostat sections were immunostained by the DIF method using antibodies to IgG, IgA, IgM and C3. It was considered positive if it showed multiple immunoreactants (inclusive of IgG) at the basement membrane zone in a granular or linear pattern.

Scoring of the CLASI (Appendix B)

The activity and the damage scores of specific lesions of CLE were calculated using the physician rating. The maximum possible CLASI activity and damage scores are 70 and 56 respectively.

Thirteen anatomical sites were examined for the most severely affected cutaneous lupus-associated lesion.

Scoring of activity

Activity was assessed by examination of erythema, scale/hypertrophy, mucous membrane disease, acute hair loss, or no scarring alopecia. Erythema was graded on a scale of 0-3 from its absence to dark red/purple/violaceous/crusted/hemorrhagic lesions. Scaling was graded on a 0-2 scale, from absent scaling to verrucous or hypertrophic

lesions. Mucous membrane involvement was recorded as present or absent. Acute hair loss was defined as occurring within the last 30 days or as reported by the patient. Scalp alopecia was graded on a scale of 0-3 from absent alopecia to alopecia that was focal or patchy in more than one scalp quadrant.

For the purpose of defining a scalp quadrant, the scalp was divided by two intersecting lines-one connecting the highest points of both ear lobes and an imaginary line running through the midline of the scalp dividing it into right and left halves. If there was a lesion within the quadrant, the same was considered as involved.

The total activity score was calculated by summation of the scores of erythema, scale, mucosal involvement and alopecia.

Scoring of damage

Damage was assessed by noting dyspigmentation, scarring/atrophy, and scarring alopecia. These parameters were assessed in similar body locations as in the activity assessment.

Dyspigmentation was noted as present or absent. If the dyspigmentation lasted at least 12 months, the score of the same was doubled. Scarring and/or atrophy were graded from absent to severely atrophic scarring or panniculitis on a 0 to 2 scale. Scalp scarring was graded on a 0 to 6 scale from absent scarring to involvement of the whole skull.

If a particular scalp lesion had both scarring and non-scarring alopecia, both were scored independently.

The total damage score was calculated by the summation of the score for dyspigmentation, scarring of skin and scarring alopecia.

Systemic lupus erythematosus disease activity index (SLEDAI) (Appendix C)[4]

SLEDAI was used to assess the systemic disease activity. Apart from the central nervous system manifestations of the disease(seizures, psychosis, cranial nerve disorder, lupus headache and cerebrovascular accident), patients were examined for leg and digital ulcers, gangrene, tender finger nodules, joint swelling or tenderness and questioned about proximal muscle ache or weakness. Biopsy proof of vasculitis was recorded. Urine analysis findings of hematuria, proteinuria, pyuria and casts were noted. Cutaneous manifestations scored for the purpose of SLEDAI were: new onset inflammatory rash, new onset or recurrence of oral or nasal mucosal ulcers and new onset or recurrence of diffuse or patchy hair loss. Laboratory findings noted were total leukocyte counts, platelet counts, total complement and C3, C4 levels and estimation of double stranded DNA antibodies.

Each of the 24 items on the SLEDAI scoring system was recorded according to their presence or absence at the first patient visit or in the previous ten days. These items were given the pre-assigned scores. The individual scores were added to give the total SLEDAI score. Activity categories were defined on the basis of SLEDAI scores from no activity (SLEDAI = 0) to a high activity (SLEDAI 20 and higher).[69]

The maximum SLEDAI score possible is 105.

Statistical analysis

The variables analyzed were the CLASI activity score, CLASI damage score, SLEDAI score, duration of SLE and the duration of the skin lesions. Nonparametric correlation (Spearman correlation coefficient) was done to study the correlation between CLASI activity scores and the SLEDAI scores as well as the correlation of the CLASI damage score with the duration of the disease and the duration of skin lesions. Linear regression analysis was done to quantify the relationship between duration of the disease and of the skin lesions and the CLASI damage score.

The study was approved by the Ethics committee of the Institutional Review Board.

RESULTS

TABLE 1- AGE AND GENDER OF THE PATIENTS

Age (years)	Males (n=6)	Females (n=87)	Total Number (n=93)	Percentage (%)
5-9	0	1	1	1.07
10-19	1	14	15	16.12
20-29	2	34	36	38.70
30-39	2	17	19	20.43
40-49	1	12	13	13.97
50-59	0	6	6	6.45
>60	0	3	3	3.22

Demographic profile

Ninety- three patients met the inclusion criteria of the study. Three patients were excluded as they were subsequently diagnosed to have mixed connective tissue disease. The majority of patients were from West Bengal (40.9%), the southern states of Tamilnadu, Andhra Pradesh and Kerala (29%) and Jharkhand (10.75%). The remaining patients (19.3%) were mostly from the North Eastern and other Indian states and Bangladesh.

Age and gender **(Table 1)**

There were 87 adults (>15 years) and 6 children (≤ 15 years). The mean age of the patients was 29.8±12.73 years (range 5-65). There were 87 females and 6 males. The mean age of males was 28.5±10.46 years (range 13-40) and that of females was 29.9 ±10.46 years (range 5 -65). The male to female ratio was 1:14.5 and 1:5 among adults and children respectively.

Clinical profile

TABLE 2-PRESENTING COMPLAINTS

Presenting complaints	Number of patients (n=93)	Percentage (%)	Mean duration (Months)
Alopecia	67	72%	12.17
Photosensitivity	64	68%	14.3
Oral ulcers	57	61%	9.73
Skin lesions	31	33.3%	10.58

Presenting complaints **(Table 2)**

The most common presenting complaint was alopecia (67 patients; 72%) followed by photosensitivity (64 patients; 68%) and oral ulcers (57 patients; 61%). Skin lesions were the first manifestation in 31 patients (33.3%).

The most common site for skin lesions was the face (85%) followed by involvement of the trunk (75%) and the upper limbs (70%).

The mean duration of SLE at presentation was 31.9 months (range 2-228 months; SD 42.11) and the mean duration of skin lesions was 12 months (range 0.25 -84 months; SD 16.20)

TABLE 3-TYPES OF SKIN LESIONS ON GILLIAM'S CRITERIA[3]

Type of skin lesions in patients	Number of patients (n=93)	Percentage (%)
Specific skin lesions	19	20.43
Non-specific skin lesions	17	18.28
Specific and non-specific skin lesions	56	60.21

Classification of skin lesions based on Gilliam's criteria (Table 3)

More than half the patients (60.21%) presented with a combination of specific and non-specific lesions while 19 (20.43%) had only specific and 17 (18.28%) had only non-specific lesions. Specific lesions of LE alone or in combination with non-specific lesion of LE were observed in 75 (80.65%) patients.

TABLE 4-TYPES OF SPECIFIC LESIONS

Type of specific lesion	Number of patients (n=93)	Percentage (%)
Discoid lesions	51	54.83
Malar rash	29	31.19
Generalised acute cutaneous LE	26	27.96
Papulosquamous rash(SCLE)	7	7.53
Tumid lesions	4	4.31
Panniculitus	1	1.08

LE-specific skin lesions (Table 4)

The most common specific cutaneous lesions were discoid lesions that were seen in 51(54.83%) patients followed by malar rash in 29 patients (31.19%) and generalised acute cutaneous LE in 26 patients (27.9%). Papulosquamous lesions of subacute lupus erythematosus (SCLE) were seen in 7.53% patients.

TABLE 5-TYPES OF NON-SPECIFIC LESIONS

Non-specific lesions	Number of patients	Percentage
Alopecia±Lupus hair	59	63.44
Mucosal ulcers	39	41.93
Palpable purpura	18	19.36
Targetoid lesions	9	9.68
Livedo reticularis	7	7.53
Raynaud's phenomenon	4	4.31
Leg ulcers	3	3.23
Digital ulcers	3	3.23
Urticaria	2	2.15
Alopecia areata	1	1.08
Sclerodactyly	1	1.08
Bullous lesions	1	1.08
Finger nodules	1	1.08
Urticarial vasculitis	1	1.08

LE non-specific skin lesions (Table 5)

Among the non-specific lesions, alopecia (63.44%) was the most common followed by mucosal ulcers (41.93%) and palpable purpura (19.36 %).

TABLE 6 - HISTOPATHOLOGY AND DIRECT IMMUNOFLUORESCENCE FEATURES OF SPECIFIC AND NON-SPECIFIC LESIONS

S.No.	Clinical	HPE	DIF
1	Ulcer/purpura	Stasis dermatitis/LCV	Perivascular IgA and C3
2	GACLE	Erythema multiforme like	Negative
3	DLE	Specific	-----
4	GACLE	Equivocal	IgM only
5	Tumid lesion	Non-specific	-----
6	GACLE	Non-specific	Positivity of BM for IgG,M and C3
7	Purpura	LCV	--------
8	DLE	Equivocal	Positivity of BM for IgG, A, M and C3
9	Papulosquam lesions SCLE	Specific	--------
10	Leg ulcer	Inadequate	---------
11	Purpura	LCV	--------
12	Ulcer	Non-specific	-------
13	GACLE	Non-specific	Positivity of BM for IgG, IgA, IgM and C3
14	GACLE	Non-specific	Positivity of BM for IgG, IgA, IgM and C3
15	Malar rash	Equivocal	C3 only
16	DLE	Non-specific	-------
17	DLE	Equivocal	-------
18	Targetoid	Non-specific	--------
19	GACLE	Equivocal	---------
20	Discoid	Specific	--------
21	Purpura	LCV	Negative
22	Discoid	Perifollicualr and perivasular inflammation	--------
23	Nodules	Panniculitis	----------
24	Discoid	Specific	Positivity of BM for IgG, IgA, IgM and C3
25	Hypopigmented macules	Non-specific	----
26	DLE	Non-specific	C3 only

(Contd…)

S.No.	Clinical	HPE	DIF
27	DLE	Specific	Positivity of BM for IgG, IgA,IgM and C3
28	Malar rash	Specific	----------
29	Cutaneous vasculitis	LCV	----------
30	GACLE	Erythema multiforme like	Fine granular staining for IgG, IgM and C3
31	Purpura	LCV	---------
32	GACLE	ACLE	Fine gran discon stainfor IgG,,IgM , IgA and C3
33	GACLE	Erythema multiforme like	Coarse gran positivity of BM for IgG, IgM and C3
34	Lupus mucinosis	ACLE	Fine gran positivity of BM for IgG, IgA, IgM and C3
35	DLE	DLE	---------
36	Purpura	LCV	----------
37	Ecchymosis	Non-specific	----------
38	GACLE	Specific	Fishnet fluorescence for IgG
39	Malar rash	Non-specific	---------
40	Malar/GACLE	Non-specific	---------
41	Purpura	LCV	Thick linear deposits of IgG,M and A in BMZ and IgG on vessel wall
42	Discoid	Non-specific	IgM only
43	Malar rash	Equivocal	IgM only
44	Discoid	Specific	---------
45	Discoid	Specific	Specific IgA,IgG and C3
46	GACLE	Erythema multiforme like	Negative
47	Malar rash	Non-specific	-------
48	GACLE	Specific	
49	GACLE	ACLE	Negative

DLE-Discoid lupus erythematosus, LCV-leucocytoclastic vasculitis, GACLE-Generalise acute cutaneous LE, ACLE-Acute cutaneous lupus erythematosus, papulosquam-papulosquamous lesions, SCLE-Sub acute cutaneous lupus erythematosus,BM-Basement membrane

Results of histopathology and DIF (Table 6)

Skin biopsy of the representative skin lesion was done in 49 out of 93 (52.68%) patients. Biopsies were done from 35/49 patients with LE specific lesions. Twenty -four out of the 35 (68.5%) patients showed histological features of LE and 11/35 (31.42%) patients showed non- specific features.

DIF was done in 23 (24.73%) patients, 19 of whom had clinically specific and 4 had clinically non-specific lesions. Of the 19 patients, 14 patients had histologic features of LE and 5 patients had non-specific histology. DIF was positive in 10 patients (7 with specific and 3 with non-specific histology).

TABLE 7-PHYSICIAN RATED CUTANEOUS LUPUS ACTIVITY SCORE IN 74 PATIENTS WITH SPECIFIC SKIN LESIONS OF SLE AND THEIR RESPECTIVE SLEDAI SCORES

S.No	Age / Sex	Type of LE Specific Lesion	Mucosal Involvement	Patient reported Alopecia	Non Scaring Alopecia (Grade)	No. Of sites scored (Skin)	CLASA Activity store (Max=70)	SLEDAI Store (Max=105)
1	42/ F	Discoid	N	Y	Y(1)	3	7	7
2	21/ F	Discoid	N	Y	Y(1)	7	12	29
3	21/ F	Discoid	N	Y	Y(3)	10	19	15
4	65/ F	Discoid	Y	Y	Y(1)	10	22	19
5	13/ F	Discoid /GACLE	Y	Y	Y(1)	9	14	17
6	35/ F	PLR/(Tumid lesions)	Y	N	Y(1)	7	11	20
7	22/ F	Discoid /GACLE	Y	Y	Y(3)	11	24	20
8	17/ F	Discoid /GACLE	Y	Y	Y(3)	13	29	28
9	33/ F	Discoid/malar	N	Y	N(0)	4	10	17
10	26/ F	Discoid GACLE/papsquam	Y	Y	Y(1)	6	15	15
11	52/ F	Discoid	N	N	Y(1)	1	2	4
12	54/ F	Discoid /papsquam	N	Y	Y(1)	4	8	12
13	18/ F	Malar rash/GACLE	Y	Y	Y(1)	7	17	24
14	17/ F	Discoid /GACLE	Y	Y	Y(1)	6	11	19
15	32/ F	GACLE	N	N	Y(1)	8	10	15
16	55/ F	Discoid	N	Y	Y(1)	4	9	6
17	18/ F	Discoid	N	Y	Y(1)	1	4	2

(Contd…)

S.No	Age / Sex	Type of LE Specific Lesion	Mucosal Involvement	Patient reported Alopecia	Non Scaring Alopecia (Grade)	No. Of sites scored (Skin)	CLASA Activity store (Max=70)	SLEDAI Store (Max=105)
18	57/ F	Malar	N	Y	Y(1)	2	3	20
19	31/ F	Papsquam	N	Y	Y(1)	10	26	8
20	20/ F	Discoid	N	Y	Y(3)	3	9	6
21	24/ F	Malar /GACLE	Y	Y	Y(1)	4	10	19
22	18/ F	Discoid /Malar /papsquam	Y	Y	Y(1)	11	28	23
23	34/ F	Malar /GACLE	Y	Y	Y(1)	6	22	23
24	27/ F	Discoid	N	Y	Y(1)	6	14	2
25	30/ F	Malar /Papsquam	Y	Y	Y(1)	7	20	16
26	25/ F	Discoid	Y	Y	Y(1)	7	15	13
27	24/ F	Discoid /Malar	N	Y	Y(1)	3	7	6
28	22/ F	Discoid	N	N	N(0)	6	6	14
29	20/ F	Discoid	N	N	N(0)	2	4	2
30	34/ F	Discoid /Malar	Y	Y	Y(1)	8	20	8
31	16/ F	Discoid l/Malar	N	Y	Y(1)	8	21	8
32	23/ F	Discoid	Y	Y	Y(1)	12	37	10
33	46/ F	Discoid	N	Y	Y(1)	4	11	12
34	16/ F	Malar rash/GACLE	Y	N	N(0)	11	22	4
35	32/ F	Discoid lesions	Y	Y	Y(1)	9	27	10
36	23/ F	Discoid lesions	N	Y	Y(3)	9	27	10
37	12/ F	Malar rash/Discoid lesions	N	Y	Y(1)	3	8	4

(Contd…)

S.No	Age / Sex	Type of LE Specific Lesion	Mucosal Involvement	Patient reported Alopecia	Non Scaring Alopecia (Grade)	No. Of sites scored (Skin)	CLASA Activity store (Max=70)	SLEDAI Store (Max=105)
38	20/ F	Malar rash/GACLE	Y	Y	Y(1)	11	28	12
39	30/ F	GACLE	Y	Y	Y(1)	8	17	30
40	19/ F	Discoid/GACLE	N	Y	Y(1)	5	11	12
41	27/ F	Malar/GACLE	Y	Y	Y(1)	9	22	17
42	20/ F	Malar/GACLE	N	Y	Y(1)	9	15	6
43	20/ F	Discoid	Y	Y	Y(1)	5	13	4
44	38/ M	Malar/GACLE	Y	N	N(0)	13	30	22
45	30/ F	Malar/GACLE	Y	Y	Y(1)	10	22	12
46	20/ F	Discoid	Y	Y	Y(1)	1	4	28
47	26/ F	Malar/Discoid	Y	Y	Y(1)	3	10	22
48	61/ F	Discoid/GACLE	Y	Y	Y(1)	11	29	20
49	28/ F	Discoid	N	Y	Y(3)	2	5	4
50	46/ F	Papsquam	Y	Y	Y(1)	7	20	10
51	36/ F	Discoid	N	Y	Y(1)	1	4	10
52	12/ F	GACLE	Y	Y	Y(1)	12	15	15
53	44/ F	Discoid lesions	Y	N	N(0)	9	25	12
54	15/ F	Malar rash	N	Y	Y(1)	2	5	32
55	22/ F	Malar/GACLE	N	Y	Y(1)	6	13	18
56	13/ F	Discoid	N	Y	Y(1)	1	4	6
57	63/ F	Discoid	N	Y	Y(1)	11	28	9
58	47/ F	Malar/Discoid	Y	Y	Y(1)	3	6	16

(Contd…)

S.No	Age / Sex	Type of LE Specific Lesion	Mucosal Involvement	Patient reported Alopecia	Non Scaring Alopecia (Grade)	No. Of sites scored (Skin)	CLASA Activity store (Max=70)	SLEDAI Store (Max=105)
59	21/ F	Malar/GACLE /Discoid	Y	Y	Y(1)	13	36	8
60	20/ M	Malar/discoid	N	N	N(0)	5	10	6
61	40/ F	Discoid	Y	Y	Y(3)	5	12	4
62	40/ F	Papsquam/disc oid	N	N	Y(1)	9	16	6
63	37/ F	Malar/(Tumid)	N	Y	Y(1)	2	10	6
64	32/ M	Discoid	N	N	N(0)	3	4	17
65	26/ F	Discoid	N	Y	N(0)	10	26	8
66	28/ M	Malar	N	Y	N(0)	1	3	25
67	28/ F	Malar/GACLE	Y	Y	Y(1)	11	26	10
68	42/ F	Discoid	Y	Y	Y(1)	3	10	15
69	31/ F	Discoid	Y	Y	Y(1)	9	23	19
70	22/ F	Malar	N	N	N(0)	1	2	6
71	52/ F	Discoid/GAC LE	Y	Y	Y(1)	8	19	10
72	23/ F	Malar/GACLE /Discoid	Y	Y	Y(1)	9	24	20
73	38/ F	Malar/GACLE /Discoid	Y	Y	Y(1)	13	39	14
74	25/ F	Discoid	Y	N	N(0)	4	8	17

GACLE---Generalised acute cutaneous lupus erythematosus, Discoid-Discoid lesions, Malar-Malar Rash, Papsquam- Papulosquamous lesions,Y-Yes, N-No

Grades of clinical nonscarring alopecia: Grade 0-Absent, Grade 1-diffuse,non-inflammatory, 2-focal or patchy in one quadrant, 3-focal or patchy in more than one quadrant

Physician rated CLASI activity score (Table 7)

CLASI activity was scored for the 74/93 (79.56%) patients with specific lesions. Mean CLASI activity score was 15.6±9.28 (range 2-39; maximum score =70)

The average number of sites scored was 6.58 (range 1 to 13). The CLASI activity score was ≥20 in 27 patients of whom 15 (55.5%) patients had 10 or more sites of involvement. There was a trend towards increasing activity scores in patients with higher number of involved sites.

Fifty- one patients (68.9%) had discoid lesions, 41(55.4%) patients had lesions of acute cutaneous LE and 7 (9.45%) patients had papulosquamous lesions of subacute cutaneous LE. Twenty- three (31.08%) patients had more than one type of LE specific skin lesions.

Mucosal involvement was seen in 39 (52.7%) patients. Sixty-one (82.43%) patients had self reported alopecia. Nonscarring alopecia was clinically seen in 62 (83.78%) patients.

Most of the patients had an associated alopecia or oral mucosal involvement. Specific cutaneous lesions without alopecia or oral mucosal involvement were exclusively seen in 5 (6.75%) patients.

Grade 1 erythema (pink, faint erythema) was seen in 56.59% of the patients. Grade 2 (red) and grade 3 (dark red, crusted, hemorrhagic) erythema was seen in 34.54% and 8.86% patients respectively. Erythema was most commonly observed in lesions of the face and the ears. On the face, 46.67% had grade 1 erythema, 40% had Grade 2

erythema and 13.33% had a grade 3 erythema. Erythema was less frequent on the covered areas (legs, feet, and abdomen).

Grade I scaling was most commonly observed on the ear and facial lesions (100%) followed by those on the scalp (97.5%). Grade II scaling was observed in 5 (6.75%) patients.

TABLE 8- MORPHOLOGY OF THE LESIONS AND THE CLASI ACTIVITY SCORES

Types of lesions(n=74)	**Mean CLASI activity score**
SCLE(n=2)	23
ACLE/DLE/SCLE(n=2)	21.5
ACLE/SCLE(n=1)	20
ACLE/DLE(n=18)	18.22
ACLE(n=20)	15.15
DLE(n=29)	13.48
DLE/SCLE(n=2)	12

Morphology of the skin lesions and CLASI activity scores (Table 8)

There was a relationship between the morphology of the lesions and mean CLASI activity scores. Patients with SCLE, and ACLE occurring with other types of LE specific lesions had higher activity scores than those with only discoid lesions or ACLE.

The mean activity score for patients who had only specific skin lesions without mucosal involvement or alopecia was 5.2 and the average number of sites affected was 3.4.

TABLE 9: CLASI damage score, duration of SLE and the duration of skin lesions

Serial Number	Age/sex	Duration of disease(months)	Duration of skin lesions (months)	Number o f sites for damage(skin /scalp)	Dyspigmentation Y/N(sites)	Scarring skin Y/N (number of sites)	Scarring scalp Y/N (Grade)	Number of sites for damage	CLASI damage score (MAX=56)
1	42/F	36	36	12/0	Y(12)	Y(1)	N(0)	12	13
2	21/F	4	4	5/1	Y(6)	N(0)	N(0)	6	6
3	21/F	36	5	0/1	Y(1)	N(0)	Y(6)	1	7
4	65/F	30	30	1/0	Y(1)	N(0)	N(0)	1	1
5	13/F	6	6	3/0	Y(2)	Y(1)	N(0)	3	3
6	35/F	8	1.5	2/1	Y(3)	N(0)	N(0)	3	3
7	22/F	24	3	6/1	Y(7)	Y(1)	Y(4)	7	11
8	17/F	60	60	7/1	Y(8)	Y(3)	Y(5)	8	27
9	33/F	24	1	3/0	Y(3)	Y(1)	N(0)	3	8
10	26/F	4	1	1/0	Y(1)	N(0)	N(0)	1	1
11	52/F	36	36	8/1	Y(9)	N(0)	N(0)	9	18
12	54/F	12	8	9/1	Y(10)	N(0)	N(0)	10	10
13	17/F	6	24	5/0	Y(5)	Y(3)	N(0)	5	8
14	55/F	48	12	3/0	Y(3)	N(0)	N(0)	3	3
15	31/F	24	12	3/1	Y(4)	N(0)	Y(6)	4	14
16	20/F	24	24	2/1	Y(3)	N(0)	Y(5)	3	11
17	24/F	3	3	2/0	Y(2)	N(0)	N(0)	2	2
18	18/F	8	10	8/1	Y(9)	N(0)	N(0)	9	9
19	27/F	36	36	8/1	Y(9)	Y(1)	Y(5)	9	25
20	30/F	12	12	4/0	Y(4)	N(0)	N(0)	4	8
21	24/F	6	6	1/0	Y(1)	N(0)	N(0)	1	1
22	32/F	6	4	4/0	N(0)	Y(4)	N(0)	4	8

(Contd…)

Serial Number	Age/sex	Duration of disease(months)	Duration of skin lesions (months)	Number o f sites for damage(skin /scalp)	Dyspigmentation Y/N(sites)	Scarring skin Y/N (number of sites)	Scarring scalp Y/N (Grade)	Number of sites for damage	CLASI damage score (MAX=56)
23	22/F	3	0.75	6/0	Y(5)	Y(1)	N(0)	6	10
24	20/F	24	1	2/0	Y(2)	Y(2)	N(0)	2	8
25	34/F	60	60	11/1	Y(12)	N(0)	N(0)	12	24
26	16/F	24	24	2/0	Y(2)	N(0)	N(0)	2	4
27	23/F	48	48	3/1	Y(4)	N(0)	Y(5)	4	13
28	46/F	120	36	2/1	Y(3)	N(0)	Y(4)	3	10
29	16/F	3	0.5	1/0	Y(1)	N(0)	N(0)	1	1
30	32/F	6	6	7/0	Y(7)	N(0)	N(0)	7	7
31	23/F	18	18	6/1	Y(7)	N(0)	Y(6)	7	30
32	20/F	6	6	2/0	Y(2)	N(0)	N(0)	2	2
33	30/F	10	1	1/0	Y(1)	N(0)	N(0)	1	1
34	19/F	6	0.5	1/0	Y(1)	N(0)	N(0)	1	1
35	27/F	36	1	1/0	Y(1)	N(0)	N(0)	1	1
36	20/F	6	1	9/1	Y(5)	Y(7)	Y(6)	10	18
37	38/ M	3	3	1/0	Y(1)	N(0)	N(0)	1	1
38	20/F	6	2	1/0	Y(1)	N(0)	N(0)	1	1
39	26/F	6	1	4/0	Y(3)	Y(1)	N(0)	4	4
40	61/F	60	0.5	3/1	Y(4)	Y(2)	Y(4)	4	14
41	28/F	2	1.5	11/1	Y(12)	N(0)	Y(4)	12	16
42	46/F	6	6	2/1	Y(3)	N(0)	Y(6)	3	9
43	36/F	132	3	1/0	Y(1)	Y(1)	N(0)	1	2
44	44/F	120	9	8/1	Y(6)	Y(5)	Y(6)	9	28
45	22/F	3	0.75	1/0	Y(1)	N(0)	N(0)	1	1

(Contd…)

Serial Number	Age/sex	Duration of disease(months)	Duration of skin lesions (months)	Number o f sites for damage(skin /scalp)	Dyspigmentation Y/N(sites)	Scarring skin Y/N (number of sites)	Scarring scalp Y/N (Grade)	Number of sites for damage	CLASI damage score (MAX=56)
46	13/F	24	24	1/0	Y(1)	N(0)	N(0)	1	1
47	63/F	24	12	3/1	Y(3)	Y(2)	N(0)	4	5
48	47/F	36	36	8/1	Y(9)	N(0)	N(0)	9	18
49	21/F	12	12	1/1	Y(2)	N(0)	N(0)	2	4
50	40/F	84	84	2/1	Y(3)	Y(3)	Y(6)	3	13
51	32/M	2	2	2/0	Y(2)	N(0)	N(0)	2	2
52	26/F	42	42	4/0	Y(4)	Y(2)	N(0)	4	10
53	28/F	2	1	1/0	Y(1)	N(0)	N(0)	1	1
54	42/F	6	6	1/0	Y(1)	N(0)	N(0)	1	1
55	31/F	6	6	8/1	Y(9)	N(0)	N(0)	9	9
56	52/F	2	2	7/0	Y(7)	N(0)	N(0)	7	7
57	23/F	8	1	5/0	Y(5)	N(0)	N(0)	5	5
58	38/F	6	0.5	5/0	Y(5)	N(0)	N(0)	5	5
59	25/F	2	2	1/1	Y(2)	N(0)	N(0)	2	2

CLASI damage score **(Table 9)**

The CLASI damage score was done on 59/75(78.6%) patients who had specific lesions of LE. The mean CLASI damage score was 8.24 ± 7.55 (range1 to 30) out of the maximum score of 56. The mean number of sites scored for damage was 4.4 (range 1 to 12).

98.3% patients showed dyspigmentation. It was of less than 12 months duration in 37 (63.79%). The mean number of sites scored for dyspigmentation was 3.22 (range 1 to 12). Scarring of the skin was seen in 18(24%) patients. The mean number of sites scored for scarring were 2.27 (range 1 to 7).

TABLE 10-SCARRING OF THE SCALP

Scarring alopecia	Grade 3	Grade 4	Grade 5	Grade 6
Number of patients (n=15)	0	4(26.6%)	4(26.6%)	7(46.6%)

Scarring scalp: Grade 3-in one scalp quadrant, Grade 4- in two scalp quadrants, 5- in three scalp quadrants, 6-scarring alopecia affecting the whole skull.

Scarring of the scalp **(Table10*)***

Scarring of the scalp was seen in 15 patients. 7 (46.6%) had scarring alopecia affecting all four quadrants of the scalp.

14 patients (16.66%) were scored for both scarring and non scarring alopecia as the two types of alopecia co-existed in some lesions.

CLASI activity and damage score was also done in 9 patients who had only alopecia and mucosal ulcers without cutaneous involvement. Their CLASI activity score ranged from 1 to 3 and the mean was 1.77. It was noted that 5 of these patients had moderate to high SLEDAI scores. The mean SLEDAI scores in these patients were 11.33± 8.62 (range 2 to 26).

TABLE 11-SLEDAI PARAMETERS AND THE NUMBER OF PATIENTS

SLEDAI VARIABLES	NUMBER OF PATIENTS (n=93)	PERCENTAGE (%)
Seizures	1	1.07
Psychosis	0	0
Organic brain syndrome	4	4.3
Visual disturbances	0	0
Cranial nerve disorder	0	0
Lupus headache	0	0
Cerebrovascular accident	0	0
Vasculitis	13	13.97
Arthritis	18	19.35
Myositis	5	5.37
Urinary casts	22	23.65
Hematuria	25	26.88
Proteinuria	22	23.65
Pyuria	22	23.65
New Rash	55	59.14
Alopecia	74	79.57
Mucosal ulcers	39	41.93
Pleurisy	4	4.3
Pericarditis	2	2.15
Low total complement	37	39.78
Elevated dS DNA	57	61.29
Leukopenia	13	13.97
Thrombocytopenia	10	10.75
Fever	19	20.43

Systemic lupus erythematosus disease activity index **(SLEDAI) (Table 11)**

The overall mean SLEDAI score of 93 patients was 13.59 ±7.65 and ranged from 1 to 32 out of a maximum possible score of 105. The mean SLEDAI score for the 75 patients with specific lesions of SLE was 13.48 ±7.39 (range 2 to 32) and for the patients

in whom CLASI activity score was used was 13.45± 7.43(range 2 to 32). Low (1-5), moderate (6-10), high (11-19) and very high (≥20) activity scores were seen in 9 (12.16%), 23 (31.08%), 26 (35.13%) and 16 (21.62%) patients respectively

The most commonly scored cutaneous parameter in SLEDAI was alopecia that was observed in 79.57% patients. This was followed by an inflammatory type rash (specific as well as non-specific LE related) and mucosal ulcers observed in 55 (59.14%) and 39 (41.93%) patients respectively.

Among the systemic manifestations, arthritis was seen in 18 patients (19.35%) followed by vasculitis (gangrene, tender finger nodules or biopsy proven vasculitis) in 13 patients (13.97%).

Elevation of Anti-ds DNA beyond the reference range of the testing laboratory was the most common laboratory parameter seen in 57 patients (61.29%)

None of the patients had psychoses, visual disturbances, cranial nerve disorders, lupus headache or a cerebrovascular accident.

Figure 1 - Distribution of SLEDAI scores

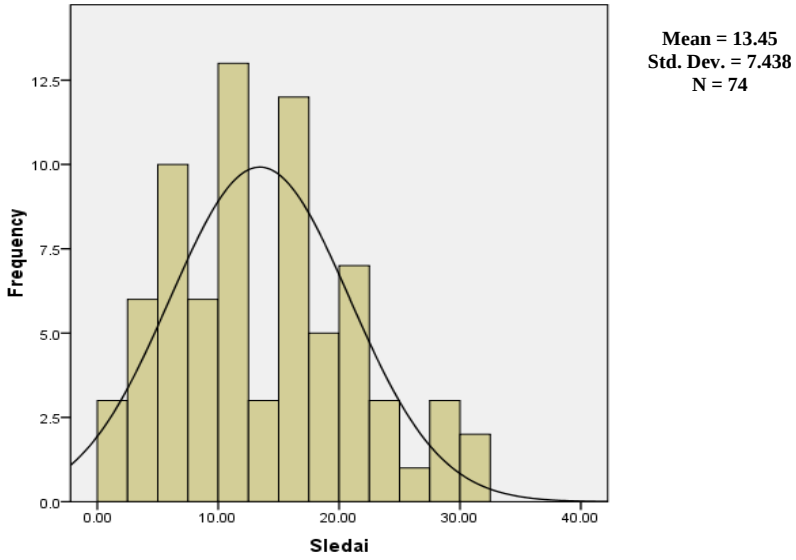
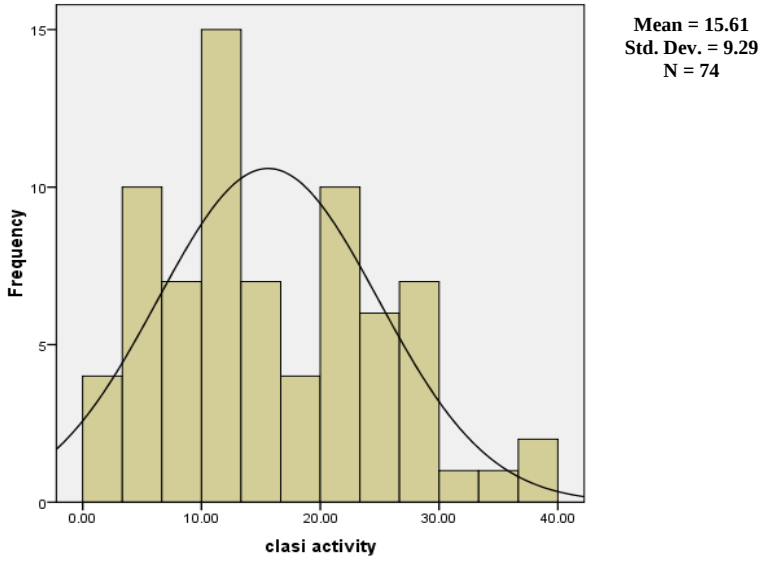
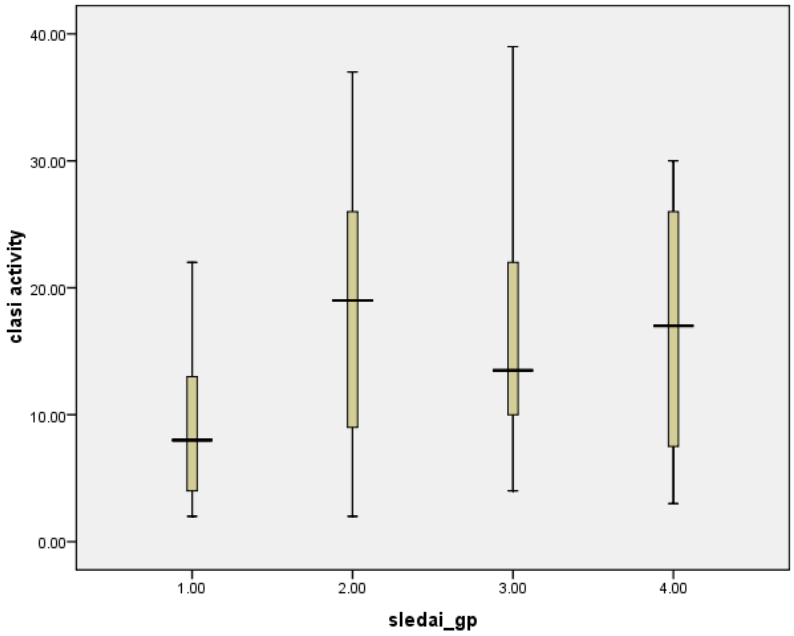


Figure 2 - Distribution of CLASI activity scores



The CLASI and SLEDAI scores with their mean values less than twice the standard distribution have a positively skewed distribution.

Figure 3-Correlation between CLASI activity score and SLEDAI score



The box and whisker diagram (Figure 3) shows the four groups (1=low, 2=moderate, 3=high and 4=very high activity) of the SLEDAI severity score represented as **sledai_gp** against the CLASI activity score represented as **clasi activity**. The band at the middle of the box represents median (50^{th} centile). The bottom and top of the box are the 25^{th} and 75^{th} percentile. The ends of the whiskers represent the maximum and minimum values of the data. The distribution of the variables is asymmetric as seen by the unequal length of the whiskers and the off centre positions of the median values. With increasing SLEDAI severity scores there is no corresponding increase in CLASI activity score.

The correlation between CLASI activity scores and SLEDAI scores did not approach statistical significance. (Spearman correlation coefficient r=0.165, p=0.16).

Figure 4- Correlation between CLASI damage score (clasi_damage) and duration of disease (dur_disease)

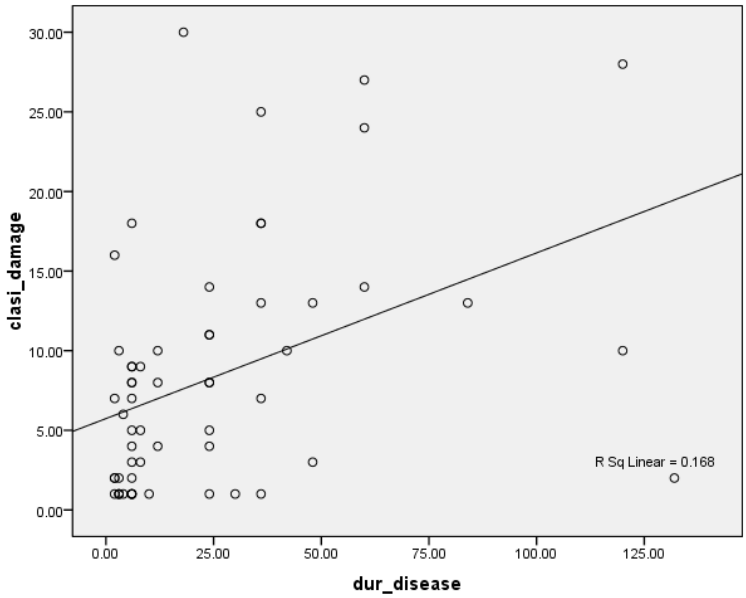
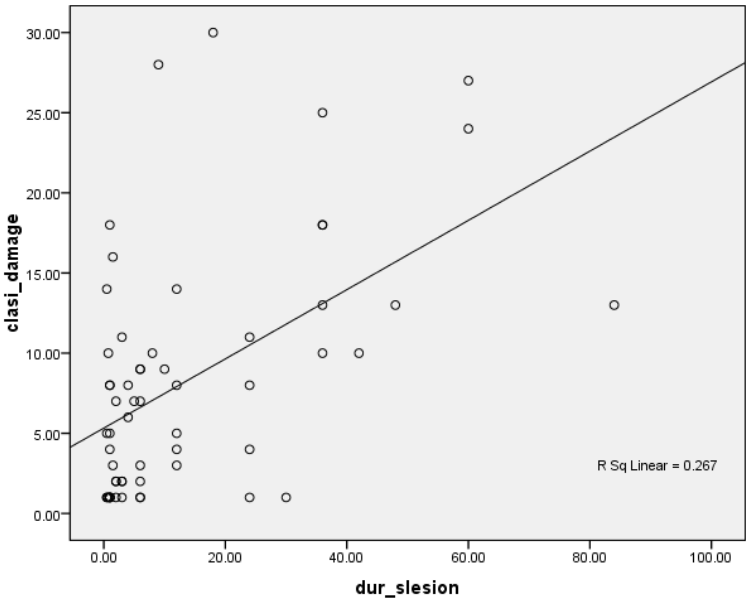


Figure 5-Correlation between CLASI damage score (clasi_damage) and duration of skin lesions (dur_slesion)



The scatter plots (Figures 4,5) display values for CLASI damage score that is the dependent variable and the duration of the disease and the duration of skin lesions. The data is displayed as a collection of points, each having the value of one variable determining the position on the horizontal axis and the value of the other variable determining the position on the vertical axis. The pattern of dots slopes from lower left to upper right, it suggests a positive correlation between the variables being studied.

Correlation done between the duration of disease (**dur_disease**) and CLASI damage score (Spearman's correlation coefficient=0.477) and between the duration of skin lesions (**dur_slesion**) and CLASI damage (Spearman's correlation coefficient=0.472) was statistically significant ($p<0.01$)

Linear regression analysis done to quantify the relationship of damage score with duration of SLE showed that for a unit increase in the duration of disease there is a 0.104 units increase in damage score which was significant at $p<0.01$. It was also seen that for a unit increase in the duration of skin lesion there is a 0.216 units increase in the damage score that was also significant at $p<0.01$.

DISCUSSION

Cutaneous lupus erythematosus disease area and severity index (CLASI) is a relatively new tool formulated in 2005 by American dermatologists at the Veterans Affairs Hospital, Philadelphia, USA.[2] The CLASI consists of physician rated activity and damage scores. There have been only a few studies done worldwide on the application of CLASI in patients with specific lesions of LE in patients with and without systemic involvement. Similarly, studies on its applicability in patients of pigmented skin are also limited.[2,8,19,66] Our aim was to study the applicability of CLASI in specific lesions of cutaneous lupus in patients with SLE. We also studied the correlation of the CLASI activity score with clinical activity of SLE using the SLEDAI (Systemic lupus erythematosus disease activity index), an index used for assessing systemic disease activity.[4]

This study was done in the Department of Dermatology, Venereology and Leprosy. There were 93 patients recruited in this study which comprised 87 adults and 6 children. Among the adults, 5 were males and 82 were females. The male to female ratio of 1:14.5 was similar to a study by Yell J A et al[31] and was much higher than earlier studies done in this centre and from Europe where it was 1:7[13] and 1:5.6 [70] respectively.

Gilliam has classified cutaneous lesions in LE into specific and non-specific lesions.[3] The prevalence of specific and non-specific cutaneous lesions vary. A study of 66 patients by Zecevic R D et al[5] showed that more than half the patients with SLE had specific lesions. In our study a combination of specific and non-specific lesions was seen in 60.21% patients. The most common specific cutaneous lesions in this study were discoid lesions that were seen in 51(54.83%) patients followed by malar rash in 29

patients (31.19%) and generalised acute cutaneous LE in 26 patients (27.9%). Cardinali C et al [27] in their retrospective study on 58 Italian patients with SLE found that discoid lesions, ACLE lesions and SCLE were seen in 32.75%, 39.65% and 13.79% of cases respectively. In the Hopkins Lupus cohort of 570 patients, the most common specific cutaneous manifestation was malar rash seen in 64% of the patients.[1] In a study done on 32 patients of SLE from this centre, discoid lesions were seen in 21.8%, maculopapular rash in 46.8% and malar erythema in 34.3% patients.[13]

The most prevalent non-specific lesion in our study was alopecia (63.44%) followed by oral ulcers (41.93%) and palpable purpura (19.36%). The prevalence of LE non-specific lesions in a study by Cardinali C et al was 31% and the most common lesion in their patient series was Raynaud's phenomenon.[27] In a review of cutaneous disease among 73 SLE patients by Yell JA et al [31] the prevalence of alopecia was lower (54%) than in our series. Oral ulcers were seen in 41.93% of our patients that was comparable to the frequency in the Hopkins cohort.[1]

CLASI is reportedly an excellent scoring tool to assess the activity of cutaneous lupus. The most severely affected lesions within each anatomical area of the body is scored. Serial assessment of the activity and damage using CLASI is useful in studying the outcome of therapy as has been shown in a study by Kreuter A et al.[19] In this cross sectional study, the physician rated CLASI activity and damage score was done on 75 patients. Previous studies have been done on limited number of patients ranging from 8-14 patients.[2, 8, 19, 66]

We applied CLASI activity scoring to 74 SLE patients who had specific lesions. Five (6.75%) out of 74 patients had only skin involvement. The mean CLASI activity

scores in our patients was 15.6 (range 2-39). This score was comparable to that seen in other studies.[19,72] The range of CLASI activity score done in a recent pilot study analysing the impact of therapy on the CLE disease severity and the quality of life at time of entry in the study was 8-49[72] while Kreuter A et al [19] reported the activity scores ranging from 5-25 in a study done on patients with SCLE.

The parameters that are used to assess the activity of CLE are erythema, scale/hypertrophy, mucous membrane involvement, acute hair loss, or non-scarring alopecia.[62] CLASI activity score is largely based on the extent of the erythema. The latter is prominent, easily recognised and can be reliably assessed even in black skin .[62] Erythema was an easily recognizable feature in our patients too. 56.6% patients had grade I (pink, faint) and 34.54% patients had grade II (red) erythema. Only 8.86% patients had a grade III erythema (dark red, violaceous, crusted or hemorrhagic). Erythema was best appreciated on the face including the malar area.

Grade I scaling was appreciated in 100% patients whereas hypertrophic scaling was seen only in 5 (6.75%) patients. The latter was seen on lesions over the scalp, nose, arms and legs. Scaling was a common feature of lesions on the ears .

Among the other parameters scored to assess activity, mucosal ulcers were seen in more than 50% patients, sixty-one (82.43%) patients had self reported alopecia and non-scarring alopecia was present in 62 (83.78%) patients.

The factors affecting the CLASI activity score in our patients were studied.

In SLE it has been reported that the number of different types of skin lesions is highly indicative of disease activity so that the severity of disease increases with the

number of lesions.[5] A similar observation was made in our study in relation to specific skin lesions of LE. It was found that the activity score increased proportionately with the number of anatomical areas involved. In our study, higher CLASI activity scores were also seen in patients with SCLE and ACLE occurring in combination with other specific lesions as compared to those with only discoid lesions. The five patients who had only specific skin lesions without alopecia or mucosal involvement had lower mean CLASI activity score compared to those who in addition had the latter two parameters.

The CLASI damage score was done on 59 out of the 75 patients. The parameters in the CLASI damage score are: dyspigmentation, cutaneous scarring /atrophy/ panniculitis and scarring of the scalp. The damage score in our patients ranged from 1 to 30. The CLASI damage score was studied for its correlation with the duration of SLE and the duration of the skin lesions. A statistically significant correlation was seen with the duration of SLE and the duration of skin lesions ($p<0.01$). It was also found that for a unit increase in the duration of the disease and of skin lesions there was a proportionate increase in the damage score.

SLEDAI was developed by Bombardier C et al at the University of Toronto.[4] It is a global index containing 24 weighted objective clinical and laboratory variables and measures disease activity within the last 10 days. The maximum possible score is 105. The advantage of SLEDAI is the relative small number of items and the ease of scoring. Systemic disease activity categories have been defined on the basis of SLEDAI scores: no activity (SLEDAI = 0), mild activity (SLEDAI = 1-5), moderate activity (SLEDAI = 6-10), high activity (SLEDAI = 11-19), and very high activity (SLEDAI 20 and above).[69]

We chose SLEDAI to assess the systemic disease activity in view of the simplicity

of use. The SLEDAI activity score of our patients varied from 2 to 32. Low (1-5), moderate (6-10), high (11-19) and very high (≥20) activity scores were seen in 9 (12.16%), 23 (31.08%), 26 (35.13%) and 16 (21.62%) patients respectively. 16 (21.62%) patients had a SLEDAI score of greater than 20 that indicated very high disease activity. Majority of patients had high disease activity with the SLEDAI scores between 12 to 19.

Correlation between SLEDAI and CLASI activity scores

The indices such as BILAG,[6] SLAM[7] and SLEDAI[4] developed to assess systemic disease activity in SLE have mucocutaneous manifestations as one of the scoring parameters. The mean SLEDAI score of our patients with only specific lesions (11.42) was lower than those with only non-specific lesions (14.65) and those with combined lesions. However this did not reach statistical significance. When the CLASI activity scores were correlated with SLEDAI, it was found that there was no upward trend in CLASI activity score with increasing SLEDAI scores. This may be in part because the cutaneous parameters in the SLEDAI scoring comprise alopecia, mucosal ulcers and a new rash. While the former two parameters are a part of activity assessment in CLASI, the new rash in SLEDAI score does not specify the type of lesions. It signifies any new onset or recurrence of inflammatory rash. The inflammatory rash could signify the specific lesions of LE, purpura or urticaria. Secondly, the SLEDAI parameters that have been present at the first patient visit or in the preceding 10 days are scored. Hence an inflammatory rash that persisted beyond this duration would not be scored. The mucosal involvement in CLASI is scored irrespective of duration while there is a limited time frame of 10 days in the SLEDAI scoring. Similarly, the alopecia in CLASI is defined as recent hair loss occurring within the last 30 days or as reported by patient, in contrast to new onset or recurrence of hair loss in the past 10 days that defines alopecia in SLEDAI.

This study was performed on patients with SLE as this group is associated with significant morbidity. The skin lesions of SLE may be a pointer to systemic involvement and increased disease activity.[5] To the best of our knowledge, no study of a similar nature has been done in India. The present study shows that CLASI is applicable in our patients. All parameters of the activity and damage scores could be assessed in our patients. The patients with ACLE and SCLE in combination with other specific lesions and those with diffuse involvement had greater CLASI activity scores**.** We also found that there was a positive linear correlation between the CLASI damage score and the duration of SLE and of skin lesions ($p<0.01$). Although CLASI and SLEDAI are reportedly good scoring systems to assess activity of cutaneous and systemic activity respectively we were unable to establish a positive correlation between the two in this study ($p=0.16$).

CONCLUSIONS

1. This study has shown that CLASI is an effective tool to assess cutaneous activity and damage of specific lesions of LE. The mean CLASI activity score was 15.6 (range 2 to 39) and the mean damage score was 8.24 (range 1 to 30). The scores seen in our patients were comparable to other studies.

2. The mean CLASI activity scores were higher in those who had higher number of anatomical sites affected and those with SCLE, and ACLE occurring in combination with other specific lesions.

3. The CLASI damage scores correlated with the duration of SLE ($p<0.01$) and also with the duration of skin lesions ($p<0.01$).

4. The correlation of CLASI activity score and the SLEDAI score was poor

(p=0.16).

5. The mean SLEDAI scores of patients with non-specific lesions were higher than those with specific lesions.

SUMMARY

The study was a prospective, cross sectional study done in the Department of Dermatology Venereology and Leprosy from 1st May 2007 to 30th August 2008 (16 months). Ninety-three patients satisfied the inclusion criteria. The mean age of the patients was 29.8 ± 12.73 years (range 5-65 years). The male to female ratio was 1:14.5. LE specific lesions were seen in 80.65% and LE non-specific lesions were seen in 78.5% patients. Discoid lesions were seen in 51(54.83%) patients followed by malar rash in 29 patients (31.19%) and generalised acute cutaneous LE in 26 patients (27.9%). The common LE non-specific lesions seen in this study were alopecia (63.4%), mucosal ulcers (41.9%) and palpable purpura (19.3%). CLASI was applied to 75 patients with LE specific lesions. The activity and damage scoring was done in 74 and 59 patients respectively. The mean CLASI activity score was 15.6 ± 9.28. (range 2 – 39) and the damage score was 8.24 ± 7.55 (range 1 – 30). Patients with diffuse cutaneous involvement had higher activity scores. Higher mean CLASI activity scores were also seen in patients with SCLE, and ACLE occurring in combination with other specific lesions. The patients with long standing disease and skin lesions had higher damage scores ($p<0.01$). SLEDAI scores ranging from low (1-5), moderate (6-10), high (11-19) and very high (≥20) were seen in 9 (12.16%), 23 (31.08%), 26 (35.13%) and 16 (21.62%) patients respectively. The mean SLEDAI score for the 75 patients with specific lesions of SLE was 13.48 ± 7.43 (range 2 – 32). The correlation between CLASI activity and SLEDAI did not reach statistical significance ($p=0.16$).

LIMITATIONS

1. All patients included in this study had prior disease modifying treatment. CLASI activity scores may have been higher if patients were not on prior treatment.

2. As CLASI scoring is designed for specific lesions, it could not be applied to co-existing non-specific lesions and to LE-specific lesions like tumid lesions.

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