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Cutaneous Lupus and the CLASI Instrument

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Abstract

This article provides an overview of cutaneous lupus erythematosus (CLE), including classification schemes, disease subtypes, and therapy. It also describes a novel clinical outcome instrument called the Cutaneous Lupus Erythematosus Disease Area and Severity Index, which quantifies cutaneous activity and damage in CLE.

Keywords

Cutaneous lupus erythematosus; disease classification; Rowell's syndrome; CLASI; clinical outcome instrument

OVERVIEW OF CUTANEOUS LUPUS ERYTHEMATOSUS

Disease Classification

Cutaneous LE skin lesions have been divided into two categories based on histopathology, LE-specific (histopathology shows interface dermatitis, which is specific for LE) and LE-nonspecific (no interface dermatitis, histopathology is not specific for LE) [1,2]. The diagnosis of cutaneous LE can be confirmed by the presence of LE-specific lesions, whereas LE-nonspecific lesions may be seen in several diseases and thus are not sufficient for establishing a diagnosis of cutaneous LE. LE-specific skin lesions can be further subdivided based on clinical characteristics into acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), and chronic cutaneous LE (CCLE) [2]. Table 1 [2-4] summarizes the classification of skin lesions seen in LE patients.

The risk of systemic LE (SLE) is highest in ACLE and lowest in CCLE, with SCLE falling in between. In one study of 191 patients with LE-specific skin lesions, the prevalence of underlying SLE was 72% in all patients with ACLE lesions, 58% in all patients with SCLE lesions, 28% in all patients with DLE lesions (the most common type of CCLE), and 6% in all patients with localized DLE lesions (limited to the head and neck) [5]. Notably, many patients from this study had lesions from more than one clinical category (ACLE, SCLE, or CCLE), and some had lesions from all three categories. In patients with DLE lesions but no ACLE or SCLE lesions, the underlying prevalence of SLE was 15%.

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Chronic cutaneous lupus erythematosus and the lupus erythematosus tumidus controversy—Chronic cutaneous LE is a photosensitive dermatosis characterized by chronic lesions that may last for many months and produce scarring and atrophy. SLE and lupus-associated antibodies are uncommon in DLE [5,6]. Classic discoid LE (DLE), which can be either localized (confined to head and neck) or generalized (above and below the neck), is the most frequent presentation of CCLE [5]. Systemic symptoms and laboratory abnormalities occur more frequently in patients with generalized than localized DLE [5,7]. DLE lesions are typically erythematous indurated plaques with keratotic scale. Follicular plugging (dilated follicles plugged with keratin) is also characteristic. When lesions heal, they classically leave behind atrophic scars (scarring alopecia on the scalp) and dyspigmentation. Variants of DLE include hypertropic DLE (thick hyperkeratotic plaques which may be confused with squamous cell carcinoma clinically and histologically [8]), mucosal DLE (oral, conjunctival, nasal, and genital lesions [9]), and lichenoid DLE (DLE and lichen planus overlap [10]).

Other types of CCLE lesions include lupus panniculitis (lupus profundus) and chilblain (acral) LE. Lupus panniculitis manifests clinically as deep, tender subcutaneous nodules which heal with lipoatrophy [11]. DLE lesions or ulceration may overly the subcutaneous nodules. A biopsy is needed to exclude subcutaneous panniculitis-like T-cell lymphoma from the clinical differential diagnosis [12]. As with DLE, the risk of SLE in lupus panniculitis patients is low; in one case series of 40 lupus panniculitis patients, 10% fulfilled the criteria for SLE [13]. Chilblain LE, a rare type of CCLE induced by cold temperatures, presents as erythematous papules localized to acral areas [14]. In a series of 15 patients with chilblain LE, 20% had underlying SLE [15].

Most dermatologists also include LE tumidus (papulomucinous LE) in the CCLE category, but this is controversial. LE tumidus lesions are erythematous plaques with an urticaria-like morphology and no clinically visible epidermal changes [16]. Like the other subtypes of CCLE, LE tumidus is a photosensitive dermatosis characterized by chronic or recurrent lesions and a low prevalence of lupus-associated autoantibodies and SLE. One study of 40 LE tumidus patients demonstrated a 10% prevalence of positive antinuclear antibody (ANA) testing and a 0% prevalence of SLE [16]. However, unlike other CCLE lesions, LE tumidus lesions heal without scarring and atrophy, and LE tumidus lesions are more photosensitive than other forms of CCLE [17]. Furthermore, LE tumidus lesions lack the interface dermatitis that characterizes other LE-specific skin lesions. In a study of 91 LE tumidus biopsy specimens from 80 patients, vacuolar degeneration of the dermoepidermal junction was either absent or was slight and focal [18]. The most frequent histopathologic findings were mucin deposition and a superficial lymphocytic perivascular and periadnexal infiltrate. Some suggest that LE tumidus should be classified as intermittent cutaneous LE to reflect the idea that LE tumidus is a distinct clinicopathologic entity with an intermittent, relapsing clinical course and a favorable prognosis [19]. Furthermore, because LE tumidus lacks the characteristic interface dermatitis of LE-specific lesions and the association with SLE that defines LE-nonspecific lesions, others argue that LE tumidus should not be classified among the LE spectrum of skin diseases at all [20]. LE tumidus patients share some clinical and histologic features with non-LE photosensitive skin diseases, such as polymorphous light eruption, lymphocytic infiltrate of Jessner, and reticular erythematous mucinosis [18], and it may be reasonable to classify LE tumidus within this clinical continuum. As new data enter the literature, the ideal classification of LE tumidus will become more apparent.

Subacute cutaneous lupus erythematosus—Subacute cutaneous LE was named to reflect the observation that SCLE lesions last longer than the transient malar rash of acute cutaneous LE but do not produce the chronic, destructive scarring and atrophy seen in chronic cutaneous LE [21]. SCLE typically presents as photosensitive papulosquamous and/

or annular-polycyclic plaques on the back, shoulders, extensor arms, and V-neck. The lesions lack the scale and follicular plugging that characterize DLE lesions. Vesiculobullous lesions can occur, especially around the annular plaques (vesiculobullous annular SCLE [4]). Very rarely, a toxic epidermal necrolysis (TEN)-like bullous eruption can evolve from otherwise typical SCLE lesions [22]. Patients with SCLE often have the human histocompatibility antigen HLA-DR3 and high titers of antibodies to SSA and SSB [23]. Approximately 50% of SCLE patients fulfill the criteria for SLE [5], but SLE patients with SCLE appear to have fewer organ systems involved than SLE patients without SCLE. One study that compared inpatients with both SLE and SCLE to inpatients with only SLE found an increased prevalence of central nervous system disease, renal disease, arthritis, anemia, and pleuritis in the SLE-only group [24]. Another study that compared outpatients with SCLE (some also had SLE) to outpatients with SLE alone found an increased frequency of serositis (pleuritis or pericarditis) and hematologic abnormalities (hemolytic anemia, thrombocytopenia, or leukopenia) in the SLE-only group [25].

Although drug-induced DLE is very rare, numerous drugs have been reported to induce SCLE. Drug-induced SCLE resembles idiopathic SCLE both clinically (papulosquamous or annular-polycyclic photodistributed lesions) and serologically (high prevalence of positive anti-SSA and SSB) [26,27]. The medication classes that have been implicated most frequently in drug-induced SCLE are antifungals, calcium channel blockers, diuretics, antihistamines, beta blockers, and chemotherapeutics [27]. Previous reports have documented drug-induced SCLE occurring anywhere from weeks to years following initiation of the culprit drug, and the skin disease may persist for several months after stopping the offending medication.

Acute cutaneous lupus erythematosus—Of the LE-specific lesions, acute cutaneous LE is most frequently associated with SLE [5]. The usual clinical presentation of ACLE is a transient (hours to days) erythematous photosensitive rash on the malar area (butterfly rash). Less commonly, ACLE patients may have a generalized photosensitive morbilliform rash [28]. ACLE rashes typically spare the nasolabial folds and knuckles, which helps distinguish ACLE from dermatomyositis [3]. Rarely, patients present with a widespread subepidermal bullous eruption resembling TEN, which evolves from otherwise typical photodistributed ACLE lesions [4].

Debate over the existence of Rowell's syndrome—Rowell's syndrome is a clinical entity that has been a source of confusion in the dermatology literature. In 1963, Rowell et al defined a new syndrome based on four patients who had erythema multiforme (EM)-like lesions occurring in association with LE as well as the following immunological serum abnormalities: speckled pattern of ANA, anti-SjT antibody, and rheumatoid factor [29]. Over the next four decades, several other authors reported new cases of Rowell's syndrome, but these cases did not meet the same immunological serum criteria as Rowell's initial patients, possibly because testing for SjT antibody became obsolete. In 2000, Zeitouni proposed new major and minor criteria for Rowell's syndrome (diagnosis requires three major criteria and one minor criteria) [30]. The new major criteria were LE (systemic, discoid, or subacute), EM-like lesions, and speckled ANA; and the minor criteria were chilblains, anti-SSA or anti-SSB antibody, and positive rheumatoid factor.

Although dermatologists continue to publish reports of Rowell's syndrome in the literature, some doubt that Rowell's syndrome is a unique clinical syndrome. These authors suggest that Rowell's syndrome is merely EM and LE coexisting in the same patient and that any common serologic abnormalities are likely coincidental [31]. The lack of conservation of Rowell's original serologic criteria in subsequent cases supports this contention. In addition, later reports of Rowell's syndrome failed to fit the clinical and demographic profile

described in Rowell's original case series [31]. Rowell's patients were females in the third to seventh decade of life who suffered from DLE years before the onset of EM lesions and rarely had mucosal EM lesions. Later cases deviated from all of these commonalities. Furthermore, the authors of a recent report of two patients who presented with clinical features of combined LE and EM but were found to have LE-specific histopathology when the EM-like lesions were biopsied suggest that prior reports of Rowell's syndrome may actually represent LE masquerading as EM [32]. Further studies will help to clarify the significance of EM-like lesions in patients with LE.

Lupus erythematosus nonspecific skin lesions—The wide variety of lesions seen in patients with SLE which lack LE-specific histopathology have been previously divided into the following categories: cutaneous vascular disease, nonscarring alopecia, and miscellaneous other dermatoses [3]. Cutaneous vascular diseases seen in SLE patients include vasculitis, vasculopathy, livedo reticularis, erythromelalgia, periungual telangiectasia, thrombophlebitis, and Raynaud's phenomenon [2]. In a recent study of 670 SLE patients, 11% had vasculitis [33]. Of those with vasculitis, 89% had cutaneous manifestations. The most common vasculitis in SLE patients is a small vessel leukocytoclastic vasculitis, which frequently presents with palpable purpura or erythematous punctuate lesions on the hands (which may rarely enlarge and ulcerate). The small vessel vasculitis may be associated with urticarial lesions lasting longer than 24 hours (urticarial vasculitis). Livedo reticularis is a nonspecific finding with an increased prevalence in several vascular diseases associated with SLE, including vasculitis, vasculopathy, and antiphospholipid antibody syndrome [34].

Nonscarring alopecia in SLE patients may have several causes, including lupus hairs (thinning at the frontal hairline, found during SLE flares [35]), alopecia areata (patches of hair loss, has an increased incidence in lupus patients [36]), and telogen effluvium (diffuse hair thinning). Other nonspecific skin lesions that may be observed in SLE patients include: sclerodactyly, rheumatoid nodules, calcinosis cutis, urticaria, papulonodular mucinosis, cutis laxa, acanthosis nigricans, leg ulcers, lichen planus, and erythema multiforme [2].

Subclassification of bullous SLE (LE-nonspecific bullous lesions)—Bullous SLE (BSLE) is an autoantibody-mediated subepidermal vesiculobullous skin disease which is LE-nonspecific (does not occur as an extension of the skin lesions showing the interface dermatitis that is characteristic of LE). BSLE typically presents as a nonscarring generalized bullous eruption which can be responsive to dapsone treatment [37,38]. A diagnosis of BSLE requires the following criteria [39,40]: (1) SLE, (2) vesiculobullous eruption, (3) histology showing subepidermal blister and neutrophilic upper dermal infiltrate, and (4) immunoglobulin and complement deposition at the basement membrane zone on direct immunofluorescence (immune reactants on or beneath the lamina densa ultrastructurally). Immunoblotting and indirect immunofluorescence on sodium chloride-split skin show that some BSLE patients have serum antibodies to type VII collagen and that their serum may react with a dermal epitope, an epidermal epitope, or both [39-41]. The clinical, histopathological, and immunological patterns seen in BSLE can resemble epidermolysis bullosa aquisita (EBA), dermatitis herpetiformis (DH), and bullous pemphigoid (BP), but BSLE patients have features that are not consistent with any single primary bullous disease.

A recent report argues that BSLE is a vague term which includes a heterogeneous group of vesiculobullous lesions and recommends using immunologic and histologic characteristics to divide BSLE into the following categories: DH-like vesiculobullous LE, EBA-like vesiculobullous LE, and BP-like vesiculobullous LE [4]. Patients with DH-like vesiculobullous LE have histology showing neutrophilic microabscesses in dermal papillae, granular deposition of IgA and/or IgG at the basement membrane zone on direct

immunofluorescence, and no evidence of serum basement membrane zone antibodies on indirect immunofluorescence [42-44]. These findings are immunohistologically similar to idiopathic DH. In EBA-like vesiculobullous LE, there are serum antibodies to basement membrane zone type VII collagen (the EBA antigen), and serum binds a dermal epitope on sodium chloride-split skin (the same indirect immunofluorescence pattern seen in idiopathic EBA) [45,46]. BP-like vesiculobullous LE is characterized by the linear deposition of IgG and C3 at the dermoepidermal junction that is found in idiopathic BP [47]. However, immunoelectron microscopy demonstrates that IgG deposits are largely below the basal lamina, and indirect immunofluorescence is negative for serum basement membrane zone antibodies. In contrast, idiopathic BP patients have IgG deposits which are localized to the lamina lucida area, and their serum frequently shows positive indirect immunofluorescence (binds to the epidermal portion of sodium chloride-split skin) [48]. Of note, BP-like, EBA-like, and DH-like vesiculobullous LE should be distinguished from the rare cases of otherwise typical primary idiopathic BP, EBA, and DH that have been reported in patients with SLE [4].

Cutaneous lesions and systemic lupus erythematosus criteria—The current American College of Rheumatology (ACR) classification criteria for SLE include four cutaneous findings: malar rash, discoid rash, photosensitivity, and oral ulcers [49]. Using these criteria, some patients with disease limited to the skin can be classified as having SLE [50]. Other limitations of these criteria include the associations between the malar rash and photosensitivity and between the discoid rash and oral ulcers, the difficulty of definitively diagnosing the malar rash or discoid lupus without a biopsy, and the lack of specificity of oral ulcers for LE [51]. Integrating dermatologic input into the next revision of the ACR criteria for SLE would help to rectify the current limitations.

Therapy

For all patients, management of cutaneous lupus erythematosus (CLE) begins with prevention of disease exacerbation though avoidance of sunlight and vigilant use of sunscreen. First-line therapeutic agents for CLE include topical corticosteroids, topical calcineurin inhibitors [52], and intralesional corticosteroids (for scalp lesions). Patients who are refractory to topical therapy or who have widespread or scarring skin disease are generally treated systemically with the antimalarials hydroxychloroquine (<6.5 mg/kg/day) or chloroquine (<3.5 mg/kg/day) [3]. Hydroxychloroquine is usually used prior to chloroquine because of the lower eye toxicity associated with hydroxychloroquine use. Quinacrine (100 mg/day) may be added for non-responders. Other systemic medications that can be useful in certain subsets of CLE patients include dapsone, retinoids, azathioprine, methotrexate, thalidomide, and occasionally systemic corticosteroids.

The ability to perform clinical trials evaluating CLE treatments has been hampered by the lack of validated outcome measures for cutaneous lupus. Thus, clinical practices are predominantly based on expert opinion, case reports, and case series. However, the recently developed and validated Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) provides a useful tool to facilitate future systematic research [53,54]. Several recent studies using the CLASI have already provided valuable data to help optimize clinical therapy [55-59].

In a recent retrospective study of 36 patients with LE tumidus, 61% showed complete or almost complete resolution of skin lesions following treatment with hydroxychloroquine or chloroquine [55]. Compared to nonsmokers, smokers had a higher initial CLASI score and a lower CLASI score reduction with antimalarial use. Another retrospective study of 34 SLE and CLE patients with skin lesions which were unresponsive to hydroxychloroquine therapy

demonstrated that combination therapy with hydroxychloroquine and quinacrine was effective in reducing CLASI activity scores in patients with DLE, ACLE, and chilblain lesions, but not in those with SCLE or lupus profundus [56].

Several small studies have used the CLASI activity score to assess newer treatments for refractory CLE. In one prospective study of 10 SCLE patients who had failed at least one standard therapy, treatment with mycophenolate sodium was both effective and safe [57]. Another open prospective study showed promising results in 12 DLE patients refractory to at least one standard therapy who were treated with pulsed dye laser [58]. In addition, a preliminary study describing use of lenalidomide to treat two patients with severe, generalized DLE refractory to multiple treatments demonstrated partial improvement and no serious adverse events attributable to the study medication in one patient [59]. Future trials using validated measures of CLE are needed to further evaluate the treatments used in these small studies and to assess other new treatments for CLE. Such studies will help clinicians to practice evidence-based medicine and will ultimately improve patient care.

THE CLASI

Rationale

One of the greatest challenges in managing patients with CLE is the development of novel therapeutic agents. One reason for this is the difficulty in designing clinical trials for a disease that is so heterogeneous in nature; lupus can affect nearly every organ system and manifests differently in every patient. To address this problem, the Food and Drug Administration (FDA) has recommended focusing on organ-specific therapies, which may be easier to approve than medications that target multiple organ systems [60].

In order to demonstrate efficacy in one organ system, it is important to have an organ-specific index of disease activity. Despite the fact that cutaneous findings are so prevalent in patients with lupus [61], until recently, no such clinical tool was available. There are at least sixty different indices that measure disease activity in SLE, including the SLE Disease Activity Index (SLEDAI) and the Systemic Lupus Activity Measure (SLAM). However, only three of these tools have some utility in measuring cutaneous activity, and even these have limitations [62,63]. In this light, the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) was developed in 2005 as a means of specifically tracking cutaneous activity and damage in patients with CLE [64,65].

The CLASI provides a quantitative measure of the skin-specific burden of disease, which allows for standardized assessments of disease progression. Such a standardized approach facilitates the organization of clinical trials, analysis of results, and comparisons between studies. Similarly, in an outpatient setting, it allows for more objective monitoring of patients undergoing a change in therapy.

General overview

The CLASI is a simple, single-page tool that separately quantifies disease activity and damage (Figure 1). Each part of the body is listed separately, from the scalp to the feet, in addition to sections focusing on mucous membrane involvement and alopecia. For the activity score, points are given for the presence of erythema, scale, mucous membrane lesions, recent hair loss, and inflammatory alopecia. For the damage score, points are given for the presence of dyspigmentation, scarring, and scarring alopecia. For both activity and damage, higher scores are awarded for more severe manifestations. Thus, for example, faint erythema receives one point, whereas violaceous erythema receives three. Similarly, scarring receives one point, whereas severely atrophic scarring receives two. In addition, total dyspigmentation scores are doubled when most of the dyspigmentation has been

present for more than one year. Scores for each area are assigned based on the most severe lesion within the area of interest. Of note, affected body parts are weighted equally regardless of surface area and number of lesions present. Separate composite scores for activity and damage are calculated by simply summing the individual component scores [64].

Development

General Principles—The design of the CLASI was based on guidelines established by Finlay for the development of an outcome instrument for atopic dermatitis [66]. Each criterion is discussed in greater detail below. They include:

1. Ease of administration
2. Clear separation of scores assigned by the clinician versus the patient
3. The signs that are graded should be unambiguous and amenable to change. If there is a high correlation between the presence of two different signs, only one need be recorded
4. Determining the area of involvement should be based on assessments of the sites that are involved rather than estimation of total surface area involvement
5. Validity testing should demonstrate good intra- and inter-rater reliability [66]

Ease of administration—The CLASI can be used even in a busy clinical practice. The layout is easy to follow, and the scoring is self-explanatory. It can be completed in real-time without the use of invasive tests. The average time needed to complete the CLASI is 5.25 minutes, ranging from 1 to 11 minutes [53].

Separation of patient and physician scores—The CLASI includes only those scores that are determined by the clinician, all of which are based on clinical signs. Patient-derived scores are recorded on separate visual analogue scales that measure subjective symptoms including pain, itch, and fatigue.

Clinical Signs: activity and damage—As discussed earlier, the clinical signs that comprise the activity score include erythema, scale, mucous membrane lesions, and inflammatory alopecia. The clinical signs that comprise the damage score include dyspigmentation, scarring, and scarring alopecia. The erythema score is considered a particularly reliable reflection of disease activity because it is easily identified in most skin types [64,65]. Physiologically, it mirrors disease activity well because it results directly from the hyperemia associated with inflammation [65]. The physician's visual estimation of erythema is considered an accurate measurement of activity because several studies have demonstrated a good correlation between subjective visual assessments of erythema and objective laser Doppler assessments of blood flow [67,68].

Following a common trend in rheumatology, the CLASI clearly differentiates between activity and damage, providing two independent summary scores. This distinction is seen in other outcomes measures for SLE; the SLEDAI and SLAM-R, for example, specifically measure activity, whereas the SLICC/ACR Damage Index specifically measures damage [69]. This separation is critical because activity and damage embody two different aspects of the disease. The activity score reflects ongoing inflammation, which has the potential to decrease with treatment. The damage score represents the aftermath of inflammation, which cannot itself be treated, only prevented. As such, the activity score is most appropriate for short-term drug studies, whereas the damage score is helpful in long-term preventative studies [65].

There is little clinical utility in combining scores because of the potential for deceptively stable scores despite significant clinical changes. Clinical experience has shown that patients who respond to therapy can have a simultaneous decrease in the activity score and increase in the damage score, reflecting the alleviation of active inflammation amidst organ damage caused by previous inflammation [54]. Thus, it is most appropriate to treat each score as a separate indicator of disease burden.

Area of involvement—An important decision in the development of any outcome measurement for cutaneous diseases is how best to capture the extent of the disease. One method considered was lesion counting, as is commonly used in acne. This system was rejected for two reasons. First, the inter-rater reproducibility is poor [70]. Second, the lesions in CLE tend to range in size, and improvement can lead to a paradoxical increase in the number of lesions, as large confluent lesions fragment into smaller lesions [65].

Another popular method is the estimation of surface area involvement, as has been used in the PASI (Psoriasis Area and Severity Index) and the SCORAD (Severity Scoring of Atopic Dermatitis) [71-73]. This method was rejected for two reasons. First, studies have shown that area assessments are difficult to perform, resulting in poor inter-rater reproducibility and a high incidence of errors [74,75]. Second, this method fails to account for the fact that patients are most concerned about noticeable lesions, regardless of the total surface area involved.

Cutaneous lupus tends to affect photo-exposed areas, such as the face, V-neck area, scalp, and extensor surfaces of the arms— in other words, the areas that are most visible to the naked eye. Studies in psoriasis have shown that patients with visible lesions who feel stigmatized by their disease suffer from impaired quality of life [76]. Furthermore, it has also been shown that patients with visible skin lesions suffer from more psychiatric symptoms than patients with lesions in unexposed areas [77]. As such, these areas require special attention and aggressive treatment, even if the area of involved skin is relatively small. To account for this, the CLASI separates exposed areas into a number of distinct categories, thereby effectively weighing those areas more heavily in the total score. The head, for example, is divided into the scalp, ears, nose, and rest of face. Each of these individually carries the same weight as much larger areas of the body, such as the back/buttocks and abdomen.

Inter- and Intra-rater reliability—This will be discussed in detail in the following “Validation” section.

Validation

Content Validity—Content validity refers to the inclusion of essential features of the disease in the outcome instrument. This was accomplished by collaborating with a group of seven dermato-rheumatologists with expertise in CLE during the development of the CLASI. The instrument was further assessed by a group of dermatologists and rheumatologists at the American College of Rheumatology Response Criteria Committee on SLE at a meeting in Germany in 2004. Finally, during the initial testing of the CLASI, the raters were interviewed extensively, and their feedback was used to make several improvements on the instrument [64].

Inter-rater reliability—Inter-rater reliability refers to the similarity between measurements made by two different observers on the same subject. For both activity and damage scores, the inter-rater reliability was high; eleven physicians scored nine different patients and achieved intra-class Pearson’s correlation coefficients of 0.86 (95% confidence

interval 0.73-0.99) and 0.92 (95% confidence interval 0.85-1.00) for the activity and damage scales, respectively [64].

Intra-rater reliability—Intra-rater reliability refers to agreement of multiple measurements made by one observer on a single subject. For this assessment, eight physicians scored four patients, one of whom was evaluated twice. The intra-rater reliability was also found to be quite high; for the activity score, the Spearman's correlation coefficient was 0.96 (95% confidence interval 0.89-1.00), with a mean difference between scores of two points. For the damage score, the Spearman's correlation coefficient was 0.99 (95% confidence interval 0.97-1.00) with a mean difference between scores of zero points [64].

Clinical responsiveness—In order to assess clinical responsiveness, changes in the CLASI were monitored for two months (56 days) following initiation of a new therapy. These scores were correlated with changes in other clinical outcome instruments, including the physician's global skin assessment, the patient's global skin assessment, and the patient's assessment of pain and itch. Eight subjects with CLE (4 DLE, 2 SCLE, and 2 DLE/SLE) were included. The results indicated a high correlation between changes in the CLASI activity score and in the physician's global skin assessment (r_p=0.97, p=0.003, n=7), the patient's global skin assessment (r_p=0.85, p=0.007, n=8), and the pain score (r_p=0.98, p=0.004, n=5) [54]. These early findings suggested that the CLASI is responsive to changes in disease activity.

Recent studies performed by other groups have further validated the clinical responsiveness of the CLASI. Kreuter et al has shown that CLASI activity scores in patients with tumid LE decrease significantly after three months of therapy with an antimalarial medication [55]. In another study, Kreuter et al illustrated that CLASI activity scores decrease significantly after three months of therapy with mycophenolate sodium, which correlated with improvements on ultrasound and colorimetry [57]. A third study by Erceg demonstrated that CLASI activity scores in patients with DLE decrease significantly after 6-18 weeks of pulsed dye laser therapy [78].

Extension to rheumatology—As rheumatologists frequently encounter patients with CLE, further validation studies were performed to assess the CLASI when used by rheumatologists rather than dermatologists. Internal structure reliability (inter- and intra-rater reliability) and diagnostic skill were evaluated. Diagnostic skill was assessed in order to ensure that the CLASI is used for CLE to the exclusion of mimicker skin diseases. Fourteen subjects were enrolled, including ten with CLE, three with CLE plus a mimicker disease, and one with a mimicker disease only. The subjects were evaluated by five rheumatologists and five dermatologists [79].

The results indicated that the CLASI has high reliability when used by rheumatologists. The inter-rater reliability correlation coefficients were 0.83 (95% confidence interval 0.70-0.96) for activity and 0.86 (95% confidence interval 0.75-0.97) for damage. The intra-rater reliability correlation coefficients were 0.91 (95% confidence interval 0.71-1.00) for activity and 0.99 (95% confidence interval 0.94-1.00) for damage. The diagnostic skill assessment, however, suggested that rheumatologists may not have the training to reliably distinguish between CLE and mimicker diseases; several mimicker lesions were misdiagnosed as CLE, resulting in poor specificity compared to dermatologists (0.46 vs. 0.74, respectively) [79]. These results indicated that it may be prudent for rheumatologists to consult with dermatologists when recruiting patients for studies utilizing the CLASI.

Practical Applications

With the design and validation of the CLASI complete, more recent work has focused on practical applications of the CLASI, particularly for use in clinical trials. The quantified scores allow for an objective measure of disease burden, which can be utilized to standardize patient assessments.

Severity—Many clinical trials only enroll patients with moderate or severe disease. It is therefore important to have a standardized method of assessing disease severity in order to ensure that that the patient populations included in different trials are comparable. This was accomplished by categorizing 37 patients (45 visits) as “mild”, “moderate”, or “severe” based on the principal investigator’s subjective assessment. Corresponding CLASI activity scores were also calculated and analyzed with crosstab row percents and receiver operating characteristic (ROC) curves. The results indicated that mild, moderate, and severe disease corresponded with CLASI activity score ranges of 0-9 (sensitivity 93%, specificity 78%), 10-20, and 21-70 (sensitivity 80%, specificity 95%), respectively (Table 2) [80].

Future directions—There are a number of potential applications for which the CLASI can be utilized. The CLASI activity score can be used for assessments of disease progression, including response to therapy, flare, stability, and remission. The CLASI damage score can evaluate residual changes in skin after the activity has resolved. Finally, changes in either score can be correlated with changes in quality of life to better understand the tangible ramifications of disease progression.

Summary

Overview of CLE—Cutaneous lupus lesions are classified as lupus erythematous (LE)-specific or LE-nonspecific based on histology. LE-specific lesions are subclassified as acute, subacute, or chronic based on clinical information. Outstanding issues in the classification of cutaneous lupus include the categorization of LE tumidus and bullous systemic LE and the significance of Rowell’s syndrome. There are few controlled studies of cutaneous LE treatments, and therapy is largely based on expert opinion. Future trials using validated outcome measures to document skin disease activity are needed to help guide clinical practice.

The CLASI—The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) is a clinical tool that quantifies activity and damage in CLE. It was designed to be easy to use, completed by physicians, and inclusive of the most significant signs of disease burden (erythema, scale, dyspigmentation, and scarring). The CLASI measures disease extent based on the number of involved areas, giving more weight to those that are most visible. Total surface area of affected skin is not estimated. Validation studies have demonstrated good content validity, inter- and intra-rater reliability, and clinical responsiveness. The CLASI is reliable when used by both dermatologists and rheumatologists. Some practical applications of the CLASI include standardized assessments of disease severity and responsiveness to new therapies.

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Figure 1.
The CLASI

Table 1

Skin lesions seen in lupus erythematosus, based on the Gilliam classification [2], the modified Gilliam classification [61], and the vesiculobullous classification [4]

- **I.** LE-specific skin disease (characterized by interface dermatitis)
  - **A.** Chronic cutaneous LE (CCLE)
    - **1.** Classic discoid LE (DLE)
      - **i.** Localized DLE
      - **ii.** Generalized DLE
    - **2.** Hypertrophic/verrucous DLE
    - **3.** Lupus panniculitis/lupus profundus
    - **4.** Mucosal DLE
      - **i.** Oral DLE
      - **ii.** Conjunctival DLE
      - **iii.** Nasal DLE
      - **iv.** Genital DLE
    - **5.** LE tumidus/papulomucinous LE*
    - **6.** Chilblain LE
    - **7.** Lichenoid DLE (LE/lichen planus overlap)
  - **B.** Subacute cutaneous LE (SCLE)
    - **1.** Annular SCLE
    - **2.** Papulosquamous/psoriasiform
    - **3.** Vesiculobullous annular SCLE
    - **4.** TEN-like SCLE
  - **C.** Acute cutaneous LE (ACLE)
    - **1.** Localized ACLE (malar rash)
    - **2.** Generalized ACLE (morbiliform)
    - **3.** TEN-like ACLE
- **II.** LE-nonspecific skin disease (no interface dermatitis)
  - **A.** Cutaneous vascular disease
    - **1.** Small vessel cutaneous leukocytoclastic vasculitis secondary to LE
      - **i.** Dependent palpable purpura
      - **ii.** Urticarial vasculitis
    - **2.** Vasculopathy
      - **i.** Degos' disease like lesions
      - **ii.** Secondary atrophie blanche
    - **3.** Periungual telangiectasia
    - **4.** Livedo reticularis
    - **5.** Thrombophlebitis
    - **6.** Raynaud's phenomenon
    - **7.** Erythromelalgia
  - **B.** Nonscarring alopecia
    - **1.** Lupus hair
    - **2.** Telogen effluvium

3. Alopecia areata

C. Sclerodactyly

D. Rheumatoid nodules

E. Calcinosis cutis

F. LE-nonspecific bullous lesions (bullous SLE)**

G. Urticaria

H. Papulonodular mucinosis

I. Cutis laxa/anetoderma

J. Acanthosis nigricans

K. Erythema multiforme

L. Leg ulcers

M. Lichen planus

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* LE tumidus lesions do not show interface dermatitis on histopathology. Some propose that LE-tumidus should be classified as intermittent cutaneous LE or should not be classified among the LE-spectrum of skin disease.

** Includes dermatitis herpetiformis-like, epidermolysis bullosa acquisita-like, and bulllous pemphigoid-like vesiculobullous LE

Table 2

Disease severity based on the CLASI activity score

	CLASI activity score range	Sensitivity (%)	Specificity (%)
Mild	0-9	93	78
Moderate	10-20	-	-
Severe	21-70	80	95