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Classifying discoid lupus erythematosus: background, gaps, and difficulties☆,☆☆,★

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ABSTRACT

To inform our ongoing efforts to develop defining features to be incorporated into a novel set of classification criteria for discoid lupus erythematosus (DLE), we conducted a literature review using the Ovid MEDLINE database. A search was performed to identify studies reporting criteria used to distinguish DLE from other cutaneous lupus erythematosus subtypes. We examined which clinical, histopathologic, and serologic features have data to support their use as effective features in distinguishing DLE from other potential disease mimickers and cutaneous lupus subsets. Through our search, we were also able to identify gaps that exist in the literature which can inform future directions for research endeavors. We found that localization of lesions, characteristic features of damage, and the absence of high titer Ro/SSA antibody seem most effective in differentiating DLE from other cutaneous lupus erythematosus subtypes. Histopathologic features and class of immunoreactant deposition appear to be less helpful.

Introduction

The grouping schema for the set of disorders known as cutaneous lupus erythematosus (CLE) has undergone various iterations throughout the years. Its complicated history has been described in detail elsewhere, but there is no agreement on how best to define and classify CLE (Sontheimer, 1997). Consensus on the current state of CLE definition and classification was expressed in 2013 at the 3rd International Conference on Cutaneous Lupus Erythematosus, where an international group of lupus experts mutually agreed upon the need for better definitions, grouping schema, and classification criteria for CLE variants (Merola et al., 2015).

The results of one study demonstrate the uncertainty that exists over the classification of CLE subtypes. 43% of patients with subacute cutaneous lupus erythematosus (SCLE) were classified with discoid rash, whereas 32% of generalized discoid lupus erythematosus (DLE) patients were classified with psoriasiform and/or polycyclic type lesions (Table 1) (Beutner et al., 1991). Either these patients have overlap between two CLE subtypes or there is some confusion over what a discoid rash really is.

Based upon the results of an initial Delphi questionnaire, a decision was made to begin by developing classification criteria for DLE for use in research endeavors. Since this subtype of chronic CLE is considered one of the most prevalent and readily recognizable forms of CLE because of its resultant scarring, chronic CLE was determined to be a good starting point for the classification of the larger disease state. To inform a consensus on the particular features that serve to best characterize DLE, it is useful to examine the literature for the features that have proven effective in differentiating DLE from other CLE subtypes in prior studies. Although there have been studies investigating the characteristics that distinguish DLE from other CLE subtypes, there is still much-needed research to be done.

This review highlights gaps that exist in the literature to describe future directions for research that might help physicians to better classify this disease. It is our hope that classification criteria will provide investigators with a foundation upon which to base observational and interventional clinical trials, and a common language with which to communicate effectively about this patient population.

Methods

An extensive literature search using the Ovid MEDLINE database was conducted from January 1, 1946, to April 14, 2015. Search terms

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included "discoid lupus erythematosus", "diagnosis", and "classification". Articles in English and pertaining to humans were included. A search of "discoid lupus erythematosus" and "classification" returned 39 articles, of which one was relevant. A search of "discoid lupus erythematosus" and "diagnosis" returned 436 articles, of which nine were relevant (Table 2). Studies included in the review were those that reported on the role of clinical, histologic, or serologic features in the diagnosis or classification of patients with DLE.

Table 2
Summary of literature search results

Terms used	Number of relevant results	Relevant articles
Discoid lupus erythematosus and diagnosis	9	Al-Refu and Goodfield (2010) Walling and Sontheimer (2009) Kontos et al. (2005) Fabbri et al. (2003) Lee et al. (1994) David-Bajar et al. (1992) Jerden et al. (1990) Bangert et al. (1984) Nieboer et al. (1987)
Discoid lupus erythematosus and classification	1	Beutner et al. (1993)

Historical context

Few authors have proposed criteria for the diagnosis of DLE. Fabbri et al. (2003) and Walling and Sontheimer (2009) authored the only two papers to describe characteristics that, if present, might allow physicians to make a diagnosis of DLE (Table 3). The criteria were created as diagnostic criteria derived from the authors' clinical expertise and were not validated. Neither set of authors comment on the number of criteria that must be fulfilled in order to reach a diagnosis of DLE. However, the criteria proposed by these authors serve as a good framework by which to examine the different clinical, histologic, and serologic features that might go into a classification criteria of DLE and to discuss the literature that supports or disproves the incorporation of these features. Although these authors proposed diagnostic criteria, the purpose of the Delphi initiative is to create classification criteria for research purposes. Although we use the diagnostic criteria by these two sets of authors as a framework for our discussion, it is important to recognize that their goals were targeted and may be useful for a different purpose.

Clinical characteristics of DLE activity

Fabbri et al. (2003) and Walling and Sontheimer (2009) describe active DLE as being round, affecting sun-exposed areas, and involving follicular plugging. Walling and Sontheimer (2009) elaborate further on the appearance of the active lesion as being indurated with peripheral scale. David-Bajar et al. (1992) performed a study in 1992 to define features that could help distinguish patients with DLE from those with SCLE. They examined the features of 27 patients—11 with DLE and seven with SCLE—and found localization of lesions on the scalp/face was more prevalent in DLE than in SCLE (David-Bajar et al., 1992). However, a different study found a significantly higher incidence of malar rash in SCLE patients than in those with both localized and generalized DLE (Beutner et al., 1991) (Table 1). Precipitation by sun exposure was less helpful in distinguishing DLE and was more common in patients with SCLE (David-Bajar et al., 1992).

Beutner et al. (1991) presented their results utilizing new criteria developed by the European Academy of Dermatology and Venerology to classify CLE relative to other photodistributed skin eruptions. The new criteria comprised the 11 American College of Rheumatology criteria plus an additional 13 new criteria. Four out of these 24 new European Academy of Dermatology and Venerology criteria were dermatologic in nature: malar rash, discoid lesions, nonscarring diffuse alopecia, and psoriasiform and/or annular polycyclic type lesions. Alopecia, defined as nonscarring and diffuse, was more common in patients with SCLE than localized DLE (Table 1). As mentioned previously, 43% of patients with SCLE were classified with discoid rash, whereas 32% of generalized DLE patients were classified with psoriasiform and/or polycyclic type lesions, highlighting the uncertainty that exists when making a clinical diagnosis of CLE subtype.

Walling and Sontheimer (2009) described active DLE lesions as being indurated. David-Bajar et al. (1992) also investigated whether induration could distinguish between DLE and SCLE lesions. These authors found that 100% of DLE lesions (n = 11) had induration compared with 0% of SCLE lesions (n = 7). They concluded that induration is useful in differentiating early active DLE lesions from SCLE.

However, unpublished data from a study one of our authors (V.P.W.) is currently undertaking calls into question the utility of induration as a distinguishing feature of DLE lesions. In this study, two raters, one dermatologist (V.P.W.) and one pre- or postdoctoral autoimmune skin disease research fellow, independently assessed CLE lesions for different features including induration. Preliminary data include 20 lesions evaluated in eight subjects (seven DLE, one SCLE). Of the 20 lesions, 18 were DLE and two were SCLE, with a clinical diagnosis given by the dermatologist (V.P.W.). Of the lesions evaluated, 17% to 22% of DLE lesions had induration, compared with 0% of SCLE lesions, and all induration was classified as mild. Additionally, when raters were asked to report their level of confidence in assessing induration, both raters reported moderate levels of confidence with average confidence scores of 5.6 and 6.6 (out of 10) for rater 1 and rater 2, respectively.

The fact that neither rater had a high level of confidence in assessing induration calls into question the feasibility of determining the presence or absence of this feature. If it is difficult for dermatologists to determine whether a lesion has induration, it might be challenging for

Table 1
Comparison of 4 EADV criteria between CLE subtypes (Beutner et al., 1991)

Criteria	Localized DLE	Generalized DLE	SCLE
Malar rash	27%	20%	94%
Discoid rash	100%	100%	43%
Alopecia (nonscarring diffuse)	0%	0%*	49%
Psoriasiform and/or annular polycyclic type lesions	16%*	32%	100%

* $p < 0.0001$; no statistically significant difference between SCLE and other CLE subtypes.

Table 3
Potential diagnostic criteria proposed by two sets of authors (Walling and Sontheimer, 2009; Fabbri et al., 2003)

Walling and Sontheimer (2009)	Fabbri et al. (2003)
- Indurated coin-shaped plaque affecting the scalp, face, ears, anterior neck, extensor arm - Peripheral scale with central hypopigmentation - Adherent scale extending hair follicles leading to follicular plugging - Center of lesion hypopigmented and atrophic leading to a depressed scar - More than half of patients will develop destructive scarring - Histopathology qualitatively similar in each CLE subtype and not useful in determining clinical skin type	- Well-demarcated disk-shaped lesion associated with follicular plugging - Lesions most often located on exposed surfaces (face, ears, scalp) - Characteristic histologic alterations (ortho-hyperkeratosis of the epidermis, dilated follicular orifices filled with compact keratin, vacuolar degeneration of the basal keratinocytes, perivascular and perifollicular mononuclear cell infiltrate of the dermis) - Evolution of lesions with atrophy, scar formation, and pigmentary changes - Positive lupus band test on lesional sun exposed skin

nondermatologists as well. Additionally, it may be difficult to determine whether hardening of a lesion is a result of epidermal hypertrophy or dermal involvement. Therefore, including induration as criterion for DLE may be problematic.

Clinical characteristics of DLE damage

Both Walling and Sontheimer (2009) and Fabbri et al. (2003) describe progression of an active DLE lesion to dyspigmented, atrophic scar. David-Bajar et al. (1992) also found scarring to be helpful in distinguishing DLE lesions. One study demonstrated a different pattern in the Cutaneous Lupus Erythematosus Disease Area and Severity Index activity and damage scores of patients with SCLE and DLE (Bonilla-Martinez et al., 2008). In patients with DLE, damage scores can continue to rise while activity scores decrease. This pattern of activity and damage reflects the characteristic course of the lesions, which can have coexisting features of activity and damage simultaneously. In contrast, damage in SCLE tends to be minimal and, when present, roughly follows the trajectory of activity. Although features of damage may not be useful in distinguishing early DLE lesions, they would be helpful in classifying patients with DLE for clinical trials, which can include patients with a long-standing history of disease.

Histopathologic characteristics of DLE

Walling and Sontheimer (2009) and Fabbri et al. (2003) treat histopathology differently in their criteria for the diagnosis of DLE. Walling and Sontheimer (2009) comment that histopathology is similar among CLE subtypes and is overall not useful in differentiating one subtype from another. Fabbri et al. (2003) list a number of features that can be found on histology in cases of DLE, but also note that DLE shares similar histologic features with SCLE.

There have been three major studies to determine whether DLE can be distinguished from SCLE histologically and to identify the features that favor diagnosis of a specific CLE subtype (Table 4). Bangert et al. (1984) identified five histologic features—hyperkeratosis, basement membrane thickening, follicular damage, leukocytic infiltration, and involvement of the deep dermis—to favor the diagnosis of DLE, a finding not duplicated by a second study (Jerden et al., 1990). Two of the five features proposed by Bangert et al. (1984), degree of dermal inflammation and hyperkeratosis, favored the correct diagnosis of CLE subtype in 84% of cases in a third study (David-Bajar et al., 1992). They did not report the sensitivity or specificity of using these criteria for DLE histopathologic diagnosis.

Existing research suggests that histopathology may be helpful, but not definitive, in the diagnosis of CLE subtype. Two of these studies showed that CLE subtype could be predicted in a majority of cases (David-Bajar et al., 1992; Bangert et al., 1984); however, the study with the largest cohort of patients demonstrated that CLE subtype could not be predicted on the basis of histopathologic features alone (Table 4) (Jerden et al., 1990). It is reasonable to conclude that although histology may be helpful in some cases, there is a strong need for clinicopathologic correlation in the diagnosis of DLE. Therefore, histopathologic features have a limited role in the classification criteria for this disease.

Immunopathologic characteristics of DLE

Fabbri et al. (2003) state that a positive direct immunofluorescence (DIF) on lesional sun-exposed skin suggests DLE. Positive DIF on lesional skin was among the 13 additional criteria investigated by Beutner et al. (1991), and the DIF was positive in 95% of localized DLE cases compared with 40% of SCLE and 37% of generalized DLE. In this study, a test was positive with the presence of coarse granular deposits of immunoglobulin (Ig) G, IgM, and/or IgA at the dermal–epidermal junction (DEJ).

The presence of a positive DIF in 20% of normal sun-exposed skin of nonlupus patients might explain the increased incidence of positive DIF in localized DLE lesions, which are frequently located in sun-exposed areas (Fabré et al., 1991). A follow-up study was not able to reproduce these findings (Leibold et al., 1994). Although it is possible that a continuous granular band of IgG at the DEJ in lesional skin could be specific for CLE, further studies would need to be performed to determine whether this finding is indicative of DLE specifically.

Researchers have also looked at the differences in class of immunoreactant deposited along the DEJ in different subtypes of CLE (Table 4). One study found a higher percentage of SCLE specimens containing IgG than DLE specimens (Table 4). Elsewhere, IgG has been reported to be the most commonly deposited immunoreactant in DLE (Kulthanan et al., 1996; Weigand, 1989). A more recent study looked at immunoreactant deposition in a larger cohort of 63 CLE patients (50 DLE, 13 SCLE) and found no clear difference in types of immunoglobulin present between CLE subtypes (Table 5) (Kontos et al., 2005). The only significant pattern observed in this study was the presence of a staining combination pair IgG/fibrinogen in DLE (Kontos et al., 2005).

However, there was a difference in the pattern of immunofluorescence in DLE and SCLE samples (David-Bajar et al., 1992). DLE specimens had particulate staining of both IgG and IgM that was localized to the DEJ. However, SCLE specimens exhibited a particulate staining of IgG through the epidermis exclusively and an extensive particulate staining pattern of IgM that extended through the lower epidermis and upper dermis (David-Bajar et al., 1992). The pattern of immunofluorescence with IgM has also been observed with IgG in SCLE specimens (Nieboer et al., 1988). However, other studies have found this pattern to be infrequent and not exclusively expressed in SCLE specimens (Lipsker et al., 1998).

Immunofluorescence may be useful when trying to differentiate DLE from other mimickers, such as lichen planus or lichen planopilaris. One study found a specificity of 0.97 in the diagnosis of DLE by immunofluorescence alone using presence of a sharply demarcated band of IgG or IgM at the basement membrane zone (BMZ) in combination with C3c and C3d granular or homogenous band-like pattern as a positive test result (Nieboer, 1987). This specificity of diagnosis by IF was higher than histopathology alone (0.84) and the combined methods (0.87), but this difference was not statistically significant (Nieboer, 1987). This suggests that IF might be helpful in differentiating DLE from other lichenoid processes.

A more recent study into the immunopathology of lupus has the potential to help with the classification of CLE subtype in the future. Active and chronic DLE lesions have a greater expression of laminin-332 than SCLE lesions or normal skin (Al-Refu and Goodfield, 2010). In addition, BMZ components laminin-332 and types IV and VII collagen extend into the papillary dermis in active DLE lesions (Al-Refu and Goodfield, 2010). In chronic DLE, SCLE, and normal skin these components are restricted to the BMZ (Al-Refu and Goodfield, 2010). Pattern of expression of laminin-332 and types IV and VII collagen would be particularly helpful in differentiating early DLE lesions without scarring from those of SCLE.

Overall, DIF has a limited role in the diagnosis of CLE subtype. The type of immunoreactant deposited at DEJ in DIF samples is not helpful in differentiating one subtype from another if these observations are validated. The differences in staining pattern found by David-Bajar et al. (1992) are interesting but found in a small sample. Differences in expression and pattern of BMZ components may be useful in the diagnosis of DLE, although the process is costly and not readily available and validated in all practices.

Serological characteristics of DLE

Neither Walling and Sontheimer (2009) nor Fabbri et al. (2003) comment on the role of serology in the diagnosis of DLE. Ro/SSA positivity is a feature that has been associated with SCLE and thought to be

Table 4
Ability to differentiate CLE subtype by histological examination (Bangert et al., 1984; Jerden et al., 1990; David-Bajar et al., 1992)

Study	No. of specimens	Study findings	Accuracy DLE	Accuracy for CLE subtype
Bangert et al. (1984)	38 (12 SCLE, 26 DLE)	Hyperkeratosis, basement membrane thickening, follicular damage, leukocytic infiltration, involvement of the deep dermis favored diagnosis of DLE	77%	82%
Jerden et al. (1990)	77 (36 SCLE, 40 DLE, 1 ACLE)	Could not successfully differentiate CLE subtype based on histologic features	55%	49%
David-Bajar et al. (1992)	17 (7 SCLE, 10 DLE)	Increased intensity of dermal inflammation and degree of hyperkeratosis correlated with clinical diagnosis of DLE	Not reported	84%

ACLE = acute cutaneous lupus erythematosus; CLE = cutaneous lupus erythematosus; DLE = discoid lupus erythematosus; SCLE = subacute cutaneous lupus erythematosus.

Table 5
Differences in immunoreactant class deposition in CLE subtypes (David-Bajar et al., 1992; Kontos et al., 2005)

Study	CLE subtype	IgM	IgG	IgA	C3	Fibrinogen
David-Bajar et al. (1992)	DLE (n = 10)	73%	18%	36%	100%	Not measured
	SCLE (n = 7)	100%	100%	0%	71%	Not measured
Kontos et al. (2005)	DLE (n = 50)	78%	58%	38%	72%	66%
	SCLE (n = 13)	62%	46%	23%	62%	23%

DLE = discoid lupus erythematosus; SCLE = subacute cutaneous lupus erythematosus.

unusual in DLE, making absence of Ro/SSA a potentially good criterion for the classification of DLE.

One study done looked the results of serologic analysis of 32 patients (17 SCLE, 15 DLE) using different assays and isoforms of Ro/SSA antibody and found that all SCLE patients were positive for Ro/SSA-60kd on immunodiffusion compared with 7% (1/15) of DLE patients (Lee et al., 1994). Only 71% (12/17) of SCLE patients were positive for Ro/SSA-60kd on immunoblotting, which the authors attributed to loss of epitope binding site after protein denaturing (Lee et al., 1994). High titers of anti-SSA antibody on enzyme-linked immunosorbent assay were found in 100% of SCLE patients in the study. High titers of anti-SSA antibody were only found in one DLE patient, and low titers of anti-SSA antibody were found in one-third of DLE patients (Lee et al., 1994). Enzyme-linked immunosorbent assay is a useful method of serologic sampling because titer levels are important in distinguishing DLE from SCLE.

Evaluating patients for anti-Ro/SSA antibodies could be useful in making a diagnosis of CLE subtype when titer level of antibodies can be determined. High titer Ro/SSA antibodies suggest SCLE, whereas the absence of high titer SSA antibodies suggests another subtype of CLE. High titer Ro/SSA does not exclude DLE because one DLE patient in the prior study did have high titer Ro/SSA antibody. However, absence of high titer Ro/SSA antibody might serve as a good metric to steer away from a diagnosis of SCLE.

Conclusions and future directions

Prior research has proven localization of lesions to the head and neck and characteristic features of damage such as dyspigmentation and scarring to be helpful clinically in distinguishing DLE lesions from those of SCLE. Histopathologic and immunopathologic evaluation have been shown to be an unreliable means of determining CLE subtype. Clinicopathologic correlation remains necessary to make a diagnosis. Lack of high titer Ro/SSA antibodies is more suggestive of DLE, whereas presence of high titer Ro/SSA antibodies is more suggestive of SCLE.

Early active lesions of DLE are the most difficult to distinguish from other subtypes of CLE. Induration was discussed as a potential distinguishing feature of DLE lesions; however, it is variable and difficult to assess. There is a need for further research on methods to characterize CLE subtype to enable development of reliable ways to differentiate DLE from other subtypes. This is important to manage patient expectations, predict prognosis, and classify patients for clinical trials. However, it is also important to keep classification criteria separate from diagnostic criteria and their respective potential utilities. We have focused on classification and research to begin this effort. Since there is a strong need for better treatments for CLE, it is important that we are able to classify our patients in order to launch clinical trials with novel medications. Classification of DLE is part of a larger process that can serve to advance treatment of and knowledge about this disease so that we can take better care of our patients in the future.

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