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Advances in Cutaneous Lupus Erythematosus and Dermatomyositis: A report from the 4th International Conference on Cutaneous Lupus Erythematosus An ongoing need for international consensus and collaborations

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Conflicts of interest

• **François Chasset**
Advisory Board for GSK and Celgene

• **Benjamin Chong**
Primary investigator for Pfizer Incorporated, Biogen Incorporated, and Daavlin Corporation; received an honorarium for Celgene Corporation as a consultant.

• **Anthony P. Fernandez**
Principal investigator for dermatomyositis clinical trials and received research funding from Mallinckrodt and Pfizer; participated in advisory board meetings for Celgene concerning lupus erythematosus.

• **Steven A. Greenberg**
Inventor of intellectual property related to myositis diagnostics and therapeutics, owned and managed by Brigham and Women's hospital; received sponsored research from Pfizer, Inc.; and founder of Abcuro, Inc.

• **Johann E. Gudjonsson**
Research Support: SunPharma, Amgen, Pfizer
Advisory Board: Novartis, MiRagen

• **Joseph Merola**
Consultant for: Merck Research Laboratories; Abbvie, Eli Lilly and
Company, Novartis, Janssen, UCB, Samumed, Celgene, Sanofi Regeneron, GSK,
Speaker's Bureau: Abbvie
Investigator: Biogen, Pfizer, Sanofi Regeneron, Incyte, Aclaris, Novartis
Financial Consulting: Cowen Healthcare
Editorial Board: Wellspring Health, Inc

• **Ruth Ann Vleugels**
Consultant for Pfizer

• **Victoria Werth**
Consulting: Celgene, Medimmune, Resolve, Neovcs, Genetech, Idera, Octapharma, BSL Behring, Janssen, Lilly, Pfizer, Biogen, BMS, Gilead, Amgen, Medscape, Nektar, Incyte, EMD Sorona, CSL Behring
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The 4th International Conference on Cutaneous Lupus Erythematosus (ICCLE) was held from May 20 to 21 in Orlando, Florida in conjunction with the International Investigative Dermatology Meeting. Members of the steering committee were David Fiorentino, Manabu Fujimoto, Joerg Wenzel and the overall meeting organizer, Victoria P. Werth.

The overall goal was to continue to expand the international scope of the meeting, to include dermatomyositis, to present new developments in translational and clinical studies, to develop approaches that might allow the entire international community to reach consensus using the Delphi process and, to develop mechanisms for ongoing international interactions that strengthen the field of rheumatologic dermatology.

Cutaneous Lupus Erythematosus (CLE)

Towards a new classification of CLE

The first steps towards the acceptance of universal standards for a definition and classification system for CLE were taken during the 3rd ICCLE in Edinburgh, Scotland, five years ago (Schultz et al., 2015).

Dr. Lela A. Lee (Departments of Dermatology and Medicine, University of Colorado, Denver, CO) began with a historical perspective on the CLE classification. Dr. Lee's talk was an introduction to a group discussion about the value of developing a standard lexicon as a basis for uniform grouping and classification criteria for CLE. She noted that, since the Gilliam classification (1975), CLE classification schemes have been based on clinical presentation (lupus specific vs. lupus nonspecific), chronicity, or histology and how to group lupus subsets still lacks a consensus. Dr. Lee endorsed that the term "chronic" can be confusing because one does not know whether it is referring to Discoid Lupus Erythematosus (DLE) only, or to all entities within the "chronic" designation. Investigators have various interpretations of what constitutes Subacute Cutaneous Lupus Erythematosus (SCLE), DLE, and other CLE subtypes. The development of targeted therapies highlights the importance of defining clinical populations as accurately and precisely as possible.

Dr. Scott Elman and Dr. Joseph Merola (Brigham and Women's Hospital, Harvard University, Boston, MA) presented the results of the Delphi exercise on the development of classification criteria for DLE (Elman et al., 2017). A list of 12 potential items has been identified at this key step (Figure 1[1]). This item list is currently being validated through an international multi-center prospective case-control study.

Current Understanding of the pathogenesis of CLE

Dr. Joerg Wenzel (Department of Dermatology and Allergy, University Hospital Bonn, Bonn, Germany) delivered new data on the interaction of both innate and adaptive immune systems in the pathogenesis of lupus erythematosus. In particular, Dr. Wenzel provided substantial evidence for the pathogenic role of endogenous nucleic acids (eNA) in CLE. CLE skin lesions are characterized by excessive activation of innate immune response pathways with strong expression of interferon (IFN)-regulated cytokines. Keratinocytes produce large amounts of these cytokines in response to stimulation of cytosolic nucleic acid receptors. Ultraviolet light stimulation causes translocation of eNA-motifs and enhances the immunostimulatory capacity of eNAs (Scholtissek et al., 2017).

[1]Reprinted from the Journal of the American Academy of Dermatology, Volume 77, Issue 2, Elman et al., Development of classification criteria for discoid lupus erythematosus: Results of a Delphi exercise, p. 266, August 2017, with permission from Elsevier

Dr. Ann Marshak-Rothstein (Department of Medicine/Rheumatology, University of Massachusetts School of Medicine, Worcester, MA) highlighted the regulatory role of Toll-like Receptor (TLR) 9 in the pathophysiology of CLE. Both TLR7 and TLR9 have been implicated in the activation of autoreactive B cells, plasmacytoid dendritic cells (pDCs) and other cell types associated with Systemic Lupus Erythematosus (SLE) pathogenesis. Dr. Rothstein and her team developed an inducible, rapid onset murine model of systemic autoimmunity that depends on T cell detection of a membrane-bound ovalbumin (OVA) pseudo-autoantigen on MHC class II^+ cells. TLR9 deficient mice exhibit more extensive B cell activation than TLR9-sufficient littermates and are also distinguished by high numbers of OVA-specific Tbet (T-box, expressed in T cells)$^+$, IFN-γ^+, FasL (Fas Ligand)-expressing T_H1 cells. Remarkably, contrary to most models of SLE, the DO11 TLR9 deficient mice also develop skin lesions that are very similar to human CLE (Mande et al., 2018).

Little is known about the role of neutrophils in CLE and UVB-induced skin inflammation despite the abundance of neutrophils at the site of photodamage after UVB exposure. Neutrophils release neutrophil extracellular traps (NETs) which are essential in autoimmune inflammation. Microvesicles (MV) are micron-scale bilayer membrane vesicles released from all cell types under activation or apoptosis and are thought to play an important role in autoimmune inflammation through induction of various proinflammatory cytokines (Liu et al., 2016). Dr. Ming-Lin Liu (University of Pennsylvania and Corporal Michael J. Crescenz VAMC, Philadelphia, PA) presented preliminary data which show increased levels of total and cathelicidin antimicrobial peptide LL-37-positive MVs both in blood and skin from CLE patients as compared to healthy controls (Liu et al., 2014). The MVs with LL-37 from neutrophils exposed to tobacco smoke extract and the MVs isolated from smoker CLE patients can amplify the pro-inflammatory responses through induction of TNFα from peripheral blood mononuclear cells (PBMCs). In addition, his team also found that Rho kinase is important in the regulation of nuclear envelope integrity, neutrophil NET release, and cutaneous inflammatory responses to UVB irradiation which may provide insight into new therapeutic targets in CLE (Liu et al., 2017).

Dr. Animesh A. Sinha (Jacobs School of Medicine and Biomedical Sciences, University of Buffalo, NY) discussed the investigational strategies being applied to understand the genetic basis of CLE. Dr. Sinha and his team identified overlapping and non-overlapping CLE skin and blood transcriptional “hot spots” located on the genome that include several differentially expressed genes previously associated with SLE as well as those not previously associated with SLE (Dey-Rao and Sinha, 2015, Dey-Rao et al., 2014). The genes included in the hot spots with no SLE associations can potentially be targeted in future studies aimed at identifying risk genes related specifically to cutaneous disease.

Translational insights into CLE pathogenesis

Dr. Ali Jabbari (Department of Dermatology, University of Iowa, Iowa City, IA), underlined the need for a better understanding of the cytokine signaling circuits that are required to maintain disease activity in CLE. This knowledge has the potential to enhance the development of novel or repurposed therapeutics and reduce the use of non-targeted immunosuppressants of limited efficacy that require frequent lab monitoring and can have

substantial adverse effects. Dr. Jabbari presented data on JAK (Janus kinase) inhibition in a mouse model of CLE and supported that JAK inhibitors are worth exploring in CLE for treatment purposes (Chan et al., 2015, Furumoto et al., 2017, Jabbari et al., 2014).

Dr. Johann Gudjonsson (University of Michigan, Ann Arbor, MI) presented data supporting IFN-κ as a central regulator of apoptotic responses to UVB and identifying IFN-κ as an potential target to regulate photosensitivity in patients whose skin chronically overexpresses it (Stannard et al., 2017). Following the data on tofacitinib presented by Dr. Jabbari, Dr. Gudjonsson reported that treatment of SLE and healthy control non-lesional keratinocytes with baricitinib may block IFN signaling and also significantly diminish UVB-mediated apoptosis.

Although significant advances in the understanding of the molecular basis of innate and adaptive immunity have led to the identification of type I IFN and BLyS/APRIL (B-lymphocyte stimulator/a proliferation-inducing ligand) system as central mediators in the pathogenesis of SLE, there is an unmet medical need to identify biomarkers of SLE activity or predictors of response to new drugs. Dr. François Chasset (Sorbonne Université, Service de Dermatologie, Hôpital Tenon, Paris, France) discussed that translational studies are fundamental to identifying biomarkers of flare and the correlation of B cell-related genes and IFN gene signature with treatment response in order to allow selection of the most relevant therapeutic strategy at the individual level (Hoffman et al., 2017).

Looking into the epidemiology of CLE

Dr. Paul Jarrett (The University of Auckland, Auckland, New Zealand) reported that the overall relative risk of CLE is higher in Māori/Pacific population compared to Europeans, and that Māori and Pacific people have a notably higher relative risk of DLE compared to the European population (Jarrett et al., 2016).

Quality of life and CLE

CLE has a significant impact on the daily lives of patients who make significant lifestyle modifications to avoid flares and to mask the chronic skin lesions. Dr. Benjamin Chong (University of Texas Southwestern Medical Center, Dallas, TX) presented the results of a study using the SKINDEX-29 questionnaire to capture multiple aspects of the quality of life (QoL) of patients with CLE. His group focused on patients with DLE to see what risk factors were associated with worse QoL based on higher SKINDEX-29 scores. Multivariable analyses showed that female gender, current smokers, having an annual income of less than $10,000, and high Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity scores were risk factors associated with poor QoL (Teske et al., 2017). Additionally, Dr. Chong and his group, as well as Dr. Victoria Werth's group at the University of Pennsylvania, showed that using SF-36 scores, QoL in patients with CLE was worse than those having hypertension, diabetes, and myocardial infarction (Vasquez et al., 2013). Dr. Chong also illustrated a modified SKINDEX questionnaire encompassing major themes from patients' interviews that covered photosensitivity, alopecia, and dyspigmentation. QoL scores may be used as endpoints in clinical trials, may aid in

insurance coverage of medications, and may raise the awareness of the impact of CLE and the need for increased public education and grant funding.

Pediatric cutaneous lupus erythematosus is not just CLE in children. Dr. Lisa Arkin (University of Wisconsin School of Medicine and Public Health, Madison, WI) emphasized that there are important differences in CLE subtypes between adults and kids in terms of their association with SLE. Children often present with cutaneous findings before the onset of systemic disease and long-term follow up is a crucial issue (Arkin et al., 2015). Dr. Arkin also presented the results from the CLASI validation study in the pediatric population. This validated tool can now be used in clinical trials for pediatric CLE to standardize the evaluation of treatment effects. Dr. Arkin highlighted the collaborative insights from dermatology and rheumatology for children with DLE and the need for multicenter studies in pediatric patients.

Treatment of CLE: guidelines and new drugs on the horizon

Dr. Anthony P. Fernandez (Cleveland Clinic, Cleveland, OH) reviewed the pharmacodynamics of antimalarials, their mechanism of action, and clinical uses. Dr. Fernandez presented data suggesting that quinacrine is a stronger anti-inflammatory agent than hydroxychloroquine (HCQ) and its mechanism involves down-regulation of TLR-3, −4, and −8 responses (Alves et al., 2017). Regarding the retinal toxicity of antimalarials, Dr. Fernandez stated that ocular toxicity appears to have a cumulative dose risk that is very low during the first five years of use, but increases sharply after about 5–7 years (Melles and Marmor, 2014). He concluded that antimalarials are effective in about 50% of CLE patients and optimal strategies for using them in real world practice have yet to be defined.

Dr. Marzia Caproni (University of Florence, Florence, Italy) presented the treatment guidelines that were guided by the European Dermatology Forum (EDF) and supported by the European Academy of Dermatology and Venereology (EADV) (Kuhn et al., 2017). Topical corticosteroids (CS) are the mainstay for all different subtypes of the disease, but given the well-known side-effects of topical CS, calcineurin inhibitors such as tacrolimus and pimecrolimus are a safe and effective alternative topical treatment for CLE. HCQ or chloroquine is considered the first-line systemic treatment for disfiguring and widespread skin manifestations and for the prevention of systemic disease. In refractory cases, quinacrine may be added. Systemic corticosteroids can be used very rarely as a bridge drug in patients with acute and severe skin disease. Second line treatment options include methotrexate, retinoids and dapsone. Mycophenolate mofetil and mycophenolic acid are considered the third-line treatment options. Belimumab is the only new drug approved for SLE in over 50 years. Several promising new therapeutic options are currently being studied, but their efficacy and safety in the treatment of patients with CLE still needs to be evaluated in clinical trials.

Dr. Victoria Werth (University of Pennsylvania and Corporal Michael J. Crescenz VAMC, Philadelphia, PA) reported new medications on the horizon and illustrated the role of dermatology in CLE drug development. Dr. Werth stated that it is critical to evaluate CLE patients for SLE on an ongoing basis. Lenalidomide seems to work for refractory CLE, and new treatments such as anti-IFNAR (interferon- α/β receptor), inhibition of Ikaros and

Aiolos (CC-220) and ustekinumab are all showing efficacy in the skin in phase 2 studies (Furie et al., 2017a, Furie et al., 2017b, Van Vollenhoven et al., 2017). CLE remains a fertile area for continued clinical and translational studies, as there is still an enormous number of targets to be evaluated. According to Dr. Werth, the challenge is to understand the differences in pathways accounting for the heterogeneity of response to treatments to be able to anticipate those most likely to respond to a given agent.

CLASI as a tool in measuring skin disease in CLE

A discussion about appropriate endpoints for trials in CLE occurred. A vote was taken on which outcome measure should be used to evaluate skin disease severity in CLE. There was 100% agreement from the dermatologists and rheumatologists who were present at the conference that the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) should be utilized in evaluating the skin in CLE patients. The CLASI has already been validated by numerous studies (Albrecht et al., 2005, Bonilla-Martinez et al., 2008, Jolly et al., 2013, Krathen et al., 2008, Kushner et al., 2018) and has been used in numerous phase 2 clinical trials (Cortés-Hernández et al., 2012, Furieet al., 2017a, Van Vollenhovenet al., 2017).

Dermatomyositis (DM)

Pathogenesis and triggers of DM

Dr. Steven Greenberg (Brigham and Women's Hospital) presented evidence that shows a high specificity of type I IFN-signature in DM muscle tissue compared with non-DM myopathies and normal muscle (Salajegheh et al., 2010). On the other hand, DM skin undergoes type I IFN signaling far in excess (20-fold) to that of other skin diseases such as psoriasis (2.8-fold) and eczema (<1.7-fold) (Wong et al., 2012). Interestingly, only the IFN-β transcript correlates well with the skin IFN signature and not IFN-α, IFN-κ and IFN-ω subtypes (Wong et al., 2012). He proposed that the source of type I IFN in DM is mostly from tissue since the gene signature magnitude in tissue cells is much higher than in blood, and that injury to tissue is due to the chronic sustained inappropriate intracellular production of type1 IFN-inducible proteins such as MxA (myxovirus resistance A) and ISG (Interferon-Stimulated Gene) −15 in DM muscle and skin (Wenzel et al., 2005). His studies have shown a strong correlation between the blood and skin tissue gene signature for IFN-β with the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) skin activity score (Huard et al., 2017).

Pruritus is a significant deterrent to the quality of life of DM patients, with 50% of them having moderate to severe itch (Kim et al., 2018). Dr. Hee Joo Kim (Gachon University College of Medicine) has worked with the research team from the Autoimmune Skin Diseases Unit at the University of Pennsylvania to show that IL-31 in the skin may play a role in DM-associated itch (Kim et al., 2018). She demonstrated that in DM patients experiencing itch, gene expression of IL-31 and IL-31RA (Receptor A) in their lesional skin was upregulated in comparison with non-lesional skin and skin from healthy controls. IL-31 mRNA expression also correlated with the VAS itch score. Flow cytometry showed that CD4+ cells were the most common cell type to produce IL-31, although other cell types that

express CD8, CD68, CD11b, or CD11c also secrete the protein. Overall, the severity of itch correlated with the disease activity in DM.

Dr. David Pearson (University of Pennsylvania) reviewed the available literature on exogenous agents that might contribute to the induction and/or exacerbation of DM. He concluded that being definitive about causality is challenging, although there are data that show that specific environmental triggers such as ultraviolet light, urban pollution, small particulate exposure, and infectious agents such as parvovirus B19 and paramyxovirus (especially in juvenile DM) may play a role. He also highlighted the findings of a recent study on the effects of a certain herb-based weight loss supplement on the induction of TNF-α, IFN-α, and IFN-β from immune cells of DM patients *in-vitro* (Zeidi et al., 2017). This investigation was initiated after a series of patients clinically presented with DM shortly after ingesting the said weight loss powder.

Clinical insights into DM

Several DM classification criteria already exist (Lundberg et al., 2018). The latest European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria for the idiopathic inflammatory myopathies (Lundberg et al., 2017), which are the only validated criteria to date, are more inclusive/sensitive than the Bohan and Peter criteria which did not recognize amyopathic DM as dermatomyositis (Bohan and Peter, 1975a, 1975b). However, these new criteria still could be improved, as 25% of the clinically amyopathic DM patients in a recent single center retrospective chart review could not be classified with the new criteria (Patel et al., 2017). Dr. Victoria Werth presented the status of the ongoing process to create a separate set of criteria to classify amyopathic DM from mimickers to create uniform cohorts for research. The candidate items for criteria generation have emerged following two Delphi rounds, and a total of 25 items will be used in a case-control prospective validation study.

Histopathology of DM skin lesions may be one of the potential criteria used to classify DM. Dr. David Fiorentino (Stanford University) presented data from 191 skin biopsies obtained from 122 adult patients in his cohort and showed that in 81% of patients, either interface dermatitis or dyskeratotic keratinocytes is present. In the remaining samples that do not show these findings, the majority show dermal mucin deposition, vascular dilatation or perivascular inflammation. Although no single pathologic finding was disease specific nor greater than 80% sensitive, he postulates that interface dermatitis and mucin deposition are most helpful in the clinicopathologic classification of cutaneous DM.

Dr. Manabu Fujimoto (University of Tsukuba) discussed the recently identified myositis-specific antibodies (MSAs) in DM. He concludes that although certain MSAs are associated with classic clinical manifestation in muscle, skin, and lung, ethnicity/region and age may contribute to certain differences in the frequency and phenotype. For example, in the US and Europe, the overall frequency of anti-MDA (melanoma differentiation-associated protein) 5 antibody positivity appears to be slightly lower, and also rapidly-progressive interstitial lung disease (ILD) appears less frequent (Bodoki et al., 2014, Ceribelli et al., 2014, Fiorentino et al., 2011, Hall et al., 2013, Hamaguchi et al., 2011, Labrador-Horrillo et al., 2014, Moghadam-Kia et al., 2014). Among DM patients without ILD, anti-TIF1 (transcription

intermediary factor-1) and anti-NXP2 (nuclear matrix protein 2) antibodies, which are major MSAs in juvenile DM, have a strong association with cancer in adult DM (Fujimoto et al., 2016). Anti-SAE (small ubiquitin-like modifier activating enzyme) antibody presents similarly to anti-TIF1, but is associated with both cancer and ILD and presents clinically as erythroderma with sparing of the upper back (Fujimotoet al., 2016).

CDASI as a tool in measuring skin disease in DM

The audience, the majority of whom were dermatologists with interest in rheumatologic diseases, unanimously agreed that the Cutaneous Dermatomyosits Disease Area and Severity Index (CDASI) should be consistently used as the tool to measure disease severity in cutaneous disease and monitor improvement/worsening in DM skin activity. The CDASI activity score has recently been shown to correlate well with a type 1 IFN pathway signature biomarker in the blood of DM patients (Huard et al., 2017), correlate with changes in QoL (Robinson et al., 2015), and distinguish responders from non-responders in blinded clinical trials (Werth et al., 2018a).

Updates on treatment in DM

Dr. Alisa Femia (NYU Langone Medical Center) and Dr. Ruth Ann Vleugels (Brigham and Women's Hospital) presented several therapeutic options for recalcitrant DM patients. For DM patients failing the standard antimalarial/cytotoxic regimen, intravenous immunoglobulin (IVIg) may be a next step in the therapeutic ladder. Response to IVIg has been shown to be rapid, corticosteroid-sparing, and well-tolerated in a cohort of refractory amyopathic DM patients (Femia et al., 2013). If IVIg is contraindicated due to a history of intolerable headaches, aseptic meningitis, clotting, and prohibition by religion, tofacitinib may be considered as another option. This JAK-inhibitor and a known blocker of interferon signaling have been shown to induce a mean decrease in CDASI activity of 12 and to reduce pruritus in a series of patients with cutaneous DM failing all standard therapy (Kurtzman et al., 2016). The discovery of the high specificity of the type I IFN signature in DM has led to a multicenter clinical trial using a novel IFN-β blocking agent in skin-predominant DM.

Dr. Josef Symon S. Concha (University of Pennsylvania) presented data on a novel oral non-psychoactive cannabinoid that targets explicitly the cannabinoid receptor-2. Lenabasum has been shown in an NIH-funded double-blind, randomized placebo-controlled single-center trial to significantly reduce CDASI activity scores and improve several quality of life measures of DM patients with skin-predominant refractory disease (Werthet al., 2018a). Twenty of the 22 patients in this trial have entered a one-year, long-term extension study and continue to show clinical improvement overall (Werth et al., 2018b). The only adverse events deemed related to Lenabasum were dizziness and dry mouth (Werthet al., 2018a). In terms of biomarker data, Lenabasum has been shown to downregulate IL-31, a mediator of itch, and IL-4 from CpG stimulated PBMCs (Kim et al., 2018). Improvement of itch after treatment also correlated with a significant reduction in IL-31 intensity in lesional skin (Kim et al., 2018). Lenabasum also significantly reduced IFN-β protein and mRNA in skin compared to placebo, as well as reduced IFN-β in PBMCs compared to placebo (unpublished). The investigation of Lenabasum in DM is led by Dr. Victoria Werth at the University of Pennsylvania.

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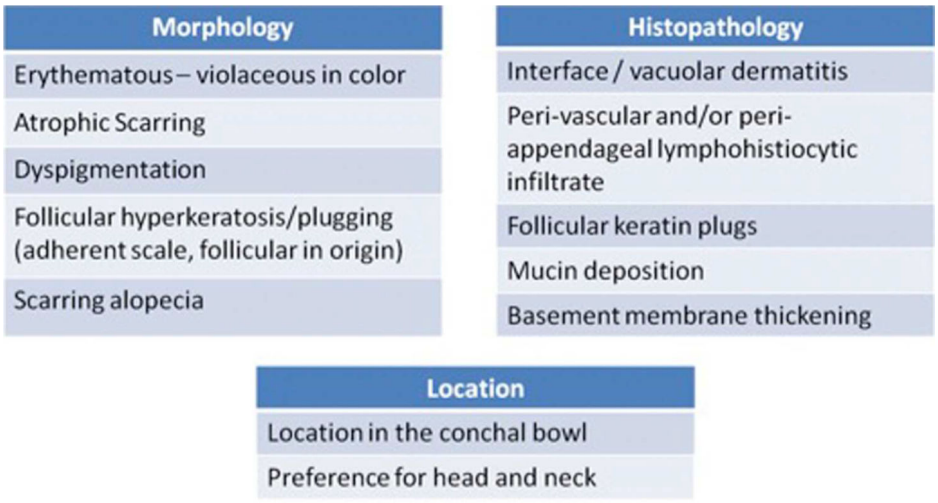

Figure 1. Twelve potential classification criteria for Discoid Lupus Erythematosus (DLE).
This list, resulting from the Delphi exercise on the development of classification criteria for DLE, is currently being validated through an international multi-center prospective case-control study. Reprinted from the Journal of the American Academy of Dermatology, Volume 77, Issue 2, Elman et al., Development of classification criteria for discoid lupus erythematosus: Results of a Delphi exercise, p. 266, August 2017, with permission from Elsevier