Role of biomarkers in the diagnosis and prognosis of patients with cutaneous lupus erythematosus

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Abstract: Cutaneous lupus erythematosus (CLE) is a connective tissue disease with varying presentations, and clinical sequelae including itching, dyspigmentation, and scarring. CLE can occur as its own entity or in conjunction with systemic disease, known as systemic lupus erythematosus (SLE). Because CLE is clinically diverse, identification of a biomarker may help not only facilitate early diagnosis and management but also identify individuals at risk for poor prognosis and development of SLE. While potential biomarkers in SLE have been extensively studied, few biomarkers for CLE have been identified and incorporated into clinical practice. Anti-SS-A antibody is a commonly used biomarker for diagnosis of subacute CLE patients. Type I interferon-related proteins such as MxA and guanylate binding protein-1 (GBP-1) and chemokines such as CXCR3, CXCL9, and CXCL10 have been identified as biomarkers that may support diagnosis and track disease activity. First-line oral treatment for CLE currently consists of anti-malarials such as hydroxychloroquine (HCQ), chloroquine (CQ), and quinacrine (QC). Studies have found that an increased myeloid dendritic cell population with higher TNF-α expression may be predictive of poor treatment response to HCQ in CLE patients. Autoantibodies against nuclear antigens (e.g., anti-double-stranded DNA and anti-Smith antibodies) and elevated erythrocyte sedimentation rate have been more commonly found in CLE patients progressing to SLE than those who have not. This review aims to summarize previous and emerging biomarkers for CLE patients.

Keywords: Biomarkers; cutaneous lupus erythematosus (CLE); systemic lupus erythematosus

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Introduction

A biomarker is a biological entity that contributes to disease pathogenesis and reflects disease activity. Nonetheless, there are many biomarkers that can be difficult to measure and thus challenging to incorporate into clinical practice. As such, in order for a biomarker to have clinical utility, it must not only be able to accurately and sensitively respond to changes in disease activity but also be simple enough to incorporate to routine clinical practice.

Cutaneous lupus erythematosus (CLE) is an autoimmune condition with a wide range of clinical presentations. While some patients have skin-limited disease, others develop systemic symptoms and subsequently progress to systemic lupus erythematosus (SLE). CLE is clinically divided into

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three main subtypes—acute, subacute, and chronic CLE (CCLE). Chronic cutaneous lupus can be further subdivided into discoid lupus erythematosus (DLE), lupus panniculitis, and lupus erythematosus tumidus (LET). Because CLE is a heterogenous and complex disease, clinical diagnosis and management of CLE remain a challenge. Identification of a biomarker may help not only facilitate early diagnosis but also identify individuals at risk for poor prognosis and/or development of SLE. Given the heterogenous nature of CLE, it is unlikely that a single biomarker may be used universally for diagnosis and management. As such, there may be several relevant biomarkers. For example, some may be potentially used to facilitate accurate and early diagnosis of CLE while others may help identify individuals at risk for severe disease and poor prognosis. Finally, other biomarkers may have utility in evaluating treatment efficacy.

The utility of biomarkers in SLE has been extensively studied, as several biomarker candidates have been identified. Autoantibodies including antinuclear autoantibodies (ANA), anti-Smith (Sm) antibodies, and anti-double stranded DNA (dsDNA) antibodies have traditionally been used to diagnose SLE (1,2). More recently, studies have identified that SLE patients have abnormal levels of erythrocyte-bound complement activation product C4d (E-C4d) and complement receptor 1 (E-CR-1) compared to healthy patients (3). As such, E-C4d and E-CR-1 may be potential diagnostic biomarkers for SLE. Other biomarkers such as mannose binding lectin, IL-6, IL-10, and interferon-inducible chemokines (i.e., CXCL10, CCL2, and CCL19) have been found to correlate with SLE disease activity (4-6).

Despite the numerous advances that have been made in understanding CLE pathogenesis, few biomarkers for CLE have been validated and widely incorporated into clinical practice. In this review, we aim to summarize previous and more recent developments of candidate biomarkers for CLE (*Table 1*).

Biomarkers associated with CLE and its subtypes

Biomarkers including type I interferon-related proteins, annexin-1, and IL-18 help distinguish CLE from normal skin and other mimics of the disease. Recent studies have demonstrated that type I interferon plays an important role in driving CLE disease pathology. An immunohistochemistry study found that CLE lesions were characterized by strong expression of MxA, a protein specifically induced by type I interferons (9,28,29), and CXCR3, whose chemokine ligands are type I interferon-inducible (9,30,31), compared to healthy skin. Furthermore, large numbers of infiltrating CXCR3 positive lymphocytes were detected in lesional skin suggesting a Th1-based cellular immune response. CXCL10, one of the chemokine ligands for CXCR3, was found in both DLE and subacute cutaneous lupus erythematosus (SCLE) lesions and was predominantly expressed between inflammatory cells and basal layer keratinocytes and around hair follicles (9). Another study analyzed the mRNA expression of type 1 interferon-related genes from microarray data of CLE lesions (n=90) and healthy controls. CLE lesional skin was found to have significantly elevated expression of two type I interferon-related genes—IFNα10 and IFNκ compared to healthy controls regardless of CLE subtype (8). Guanylate binding protein-1 (GBP-1) is one of the most abundantly induced proteins by type I interferons and endothelial cells are known to express GBP-1 when exposed to IFN-α and γ, IL-1α and 1β, and TNF-α (32-34). GBP-1 expression was determined to be upregulated in lesional skin of all CLE subtypes but not in atopic dermatitis or healthy controls (11). Finally, CLE skin lesions can histologically appear similar to dermatomyositis skin lesions, making it difficult to distinguish the two. It has recently been reported that IL-18 is uniquely elevated in dermatomyositis lesions. This cytokine in combination with *LCE2D*, *LCE1B*, *KRT80*, and *TPM4* expression successfully distinguished dermatomyositis from CLE lesions (22). While these results are promising, additional studies are warranted to investigate the negative predictive value of this gene signature for CLE.

Different autoantibodies and protein biomarkers are associated with specific subtypes of CLE. SCLE is a subtype of CLE characterized by non-scarring photosensitive lesions that are most often found in upper trunk and arms. Anti-SS-A antibodies are present in approximately 63% of SCLE patients and is often used as a distinguishing feature for this subtype (26). Other CLE subtypes, particularly DLE, have not been as strongly associated with specific biomarkers as SCLE. Antibodies against annexin, an anti-inflammatory molecule that is externalized during apoptosis, have been found to be in significantly higher concentrations in the sera of 78 CLE patients *vs.* 51 healthy controls. Specifically, 32% of patients with DLE were positive for anti-annexin 1 antibodies compared with 9.7% of patients with SCLE. However, antibody levels did not correlate with disease activity (35). We previously employed

Table 1 Candidate biomarkers for the diagnosis, management, assessment of disease activity, and prognosis of CLE

Biomarker of Interest	Supportive findings
Gene/Protein	
Type I Interferon-related genes	RNA higher in SCLE and DLE peripheral blood (7), expression correlates with disease activity in SCLE and DLE patients (7)
IFN-α10, IFN-κ	mRNA higher in lesional CLE skin (8)
MxA	Increased protein expression in CLE lesional skin (9), increased expression in CLE PBMCs (9), protein expression in CLE lesional skin decreases with disease activity (10)
GBP-1	Increased protein expression in lesional skin of all CLE subtypes (11)
CXCR3	Increased CXCR3-expressing lymphocytes in CLE lesional skin (9)
CXCL10	Increased protein expression in CLE lesional skin (9), protein expression in CLE lesional skin decreases with disease activity (12)
HERC5, ISG-15	Increased protein expression in lesional CLE skin (12), protein expression in CLE lesional skin decreases with disease activity (12)
TNF-α	Increased protein expression in DLE PBMCs (13), positive correlation of disease activity and protein, expression in DLE (13), increased lesional expression predicts poor response to hydroxychloroquine (14)
BAFF	mRNA higher in DLE skin (15), mRNA higher in DLE patients with concomitant SLE (15)
VEGF, CD34	Decreased expression after treatment with chloroquine in CLE (16)
ESR	Associated with concomitant diagnosis of SCLE and SLE (17), associated with concomitant diagnosis of CCLE and SLE (17-19), associated with progression of DLE to SLE (20)
Low complement, Rheumatoid factor	Associated with concomitant diagnosis of SCLE and SLE (17), associated with concomitant diagnosis of CCLE and SLE (17-19)
Low CH50	Associated with concomitant diagnosis of SCLE and SLE (17), associated with concomitant diagnosis of CCLE and SLE (17-19,21)
IL-18, LCE2D, LCE1B, KRT80, TPM4	Increased protein expression in lesional DM skin that distinguish it from CLE lesional skin (22)
Autoantibody	
ANA	Associated with concomitant diagnosis of SCLE and SLE (17), associated with concomitant diagnosis of CCLE and SLE (17-19,23), associated with progression of CLE to SLE (20,24,25)
Anti-dsDNA antibody	Associated with concomitant diagnosis of SCLE and SLE (17), associated with concomitant diagnosis of CCLE and SLE (17-19,23), associated with progression of CLE to SLE (24)
Anti-annexin antibody	Increased in sera of CLE patients (26)
Anti-SS-A antibody	Increased in sera of SCLE patients (22), associated with concomitant diagnosis of SCLE and SLE (17), associated with concomitant diagnosis of CCLE and SLE (17,18)
Anti-U1 RNP antibody, Anti-smith antibody	Associated with concomitant diagnosis of SCLE and SLE (17), associated with concomitant diagnosis of CCLE and SLE (17-19), associated with progression of CLE to SLE (27)

ANA, anti-nuclear antibody; BAFF, B-cell activating factor; CH50, CH50, total hemolytic complement ; CLE, cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; DM, dermatomyositis; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; GBP-1, guanylate binding protein-1; HERC-5, hect domain and RCC1-like domain 5; IFN, interferon; ISG-15, interferon-induced protein 15; RNP, ribonucleoprotein, SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; VEGF, vascular endothelial growth factor.

autoantigen arrays to examine autoantibody profiles of healthy controls, DLE patients without SLE (DLE+SLE-) patients, SLE patients without DLE (DLE-SLE+ patients), and DLE patients with SLE (DLE+SLE+ patients) (36). Although no autoantibodies were distinctively elevated in DLE patients, increased IgG:IgM ratios of autoantibodies against nuclear antigens progressively increased from healthy controls, DLE+SLE- patients, DLE+SLE+ patients, and finally DLE-SLE+ patients. These autoantibodies seemed to correlate with disease severity in these groups of lupus patients. BAFF (B-cell activating factor) aids in B cell survival and homeostasis and has been shown to be elevated in SLE patients, driving abnormal B cell development (15,37-40). Its mRNA levels have been found to be significantly higher in DLE lesional skin compared to psoriasis and healthy controls suggesting that BAFF may be a potential biomarker that can be used to distinguish DLE from other diseases (13). TNF-α has previously been reported to be substantially increased in the sera of SLE and CLE patients. In one study, TNF-α was found to be significantly elevated in PBMCs from DLE patients compared to healthy controls, but not in PBMCs from SCLE patients or LET patients (7).

Biomarkers associated with CLE disease activity and treatment response

Biomarkers such as type I interferon-inducible proteins have been shown to reflect disease activity in CLE. A previous study found that patients with SCLE and DLE had increased type I interferon-regulated gene expression compared to healthy controls regardless of concomitant SLE. Interestingly, LET patients did not have an elevated interferon signature compared to controls. Patients were assigned an interferon score based on blood expression level of five type I interferon-regulated genes previously shown to correlate with disease activity in SLE patients. This study determined that interferon scores correlated with cutaneous disease activity, suggesting its potential role as a biomarker for CLE activity (10). In a clinical trial investigating the efficacy of BIIB059, a monoclonal antibody targeting blood DC antigen 2 (BDCA2) in SLE patients, MxA skin expression was used as a marker of disease response. Skin biopsies from active lesions from SLE patients were evaluated at baseline and week 4 for IFN-regulated proteins MxA and IFITM3 using immunohistochemistry. Four weeks after receiving BIIB059 administration, 6 of 7 patients had a marked reduction in MxA percentage area immunoreactivity (12). Another clinical trial investigated the utility of anti-IFN-α monoclonal antibody in treating SLE patients. A panel comprised of 21 IFN-α/β-inducible genes was used as a pharmacodynamic biomarker in this study. Skin lesions from 16 SLE patients were collected prior to treatment and compared to biopsies collected 14 days post-treatment. Baseline lesions were found to have overexpression of IFN-α/β-inducible genes. Immunostaining for 3 IFNα/β-inducible proteins, hect domain and RCC1-like domain 5 (HERC-5), interferon-induced protein 15 (ISG-15), and CXCL10 was performed and revealed decreased expression of proteins in lesional skin post-treatment compared to pre-treatment (41). In DLE patients, a positive correlation has been observed between disease activity as measured by Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), and peripheral blood mononuclear cell TNF-α protein levels and sera anti-ribonucleoprotein (RNP) IgG antibody levels (7,16).

CLE skin biomarkers have altered levels correlating with anti-malarial response and non-response. First-line oral treatment for CLE consists of anti-malarials, including hydroxychloroquine (HCQ), chloroquine (CQ), and quinacrine (QC). A study of 10 patients with DLE had lesional skin biopsies at baseline and after 3 months of treatment with oral CQ. Skin expression of vascular endothelial growth factor (VEGF), a cytokine involved in angiogenesis, and CD34, an antigen expressed on endothelial cells of blood vessels, were measured by skin biopsy immunohistochemistry. After 3 months of CQ treatment, DLE skin showed reduced erythema, number of surrounding telangiectasias, and lesion size while scarring and skin atrophy persisted. Compared to baseline skin biopsies, VEGF expression was significantly reduced post-treatment and CD34+ blood vessels were smaller and less prevalent, suggesting that VEGF and CD34 may potentially be markers of successful CQ treatment in patients with DLE (42).

Approximately 50% of CLE patients are not responsive to HCQ monotherapy (14,43,44). Those who do not respond to HCQ often are treated with a combination of HCQ and QC. A study comparing 22 CLE patients who responded to HCQ and 27 CLE patients requiring HCQ and QC (HCQ-QC) found that patients in the HCQ-QC group had significantly increased number of myeloid dendritic cells and higher expression of TNF-α in their skin lesions compared to the HCQ group. As such, increased myeloid dendritic cell population with higher TNF-α

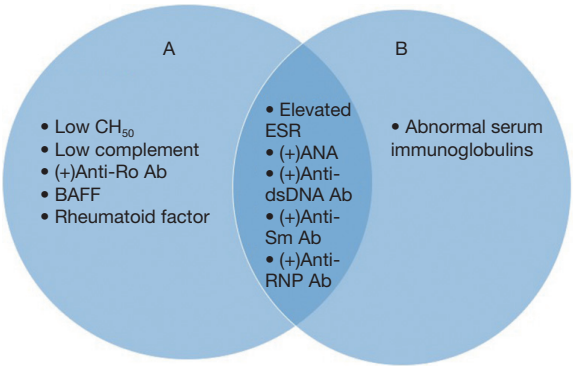

Figure 1 Biomarkers associated with systemic involvement in patients with CLE. Laboratory tests associated with SLE development from studies comparing SLE patients with CLE and CLE-only patients (A), and those comparing CLE patients who develop SLE and DLE-only patients (B). Signs commonly identified from both types of studies are listed in the Venn diagram overlap. Ab, antibody; ANA, antinuclear antibody; BAFF, B-cell activating factor; CH50, total hemolytic complement; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; RNP, ribonucleotide protein; CLE, cutaneous lupus erythematosus; SLE, systemic lupus erythematosus. Adapted from Chong *et al.* 2011 (46).

expression may be predictive of poor treatment response to HCQ in CLE patients (23).

Biomarkers associated with SLE and the progression of CLE to SLE

Anti-dsDNA antibody, anti-SS-A antibody, ANA, low complement, and BAFF are associated with SCLE and CCLE and a concomitant diagnosis of SLE. Multiple studies have examined CCLE or SCLE patients with and without SLE and identified key serum differences between them. In a retrospective study of 62 DLE patients, six had concomitant diagnoses of DLE and SLE. A positive ANA and dsDNA antibody were found to be associated with DLE and SLE diagnosis as compared to DLE alone (17). Retrospective studies investigating CCLE patients have found that ANA, anti-dsDNA antibody, anti-SS-A antibody, anti-RNP antibody, anti-Sm antibody, rheumatoid factor, elevated erythrocyte sedimentation rate (ESR), and low complement are associated with a concomitant SLE diagnosis (18,45). A retrospective study involving 73 DLE patients found that 10 fulfilled SLE diagnosis, with 8 at baseline and 2 subsequently after 4 and 6 months of initial presentation. A positive ANA was found to correlate with diagnosis of SLE. Additionally, this study noted that in patients with both DLE and SLE, SLE diagnostic criteria was primarily satisfied through mucocutaneous and serological criteria. Serious organ involvement was less frequent and only seen in 20% of patients with DLE and SLE (21). In another retrospective study, 80 CCLE patients (Group 1) were compared to 15 CCLE patients with at least one systemic lupus manifestation (Group 2) and 13 SLE patients with biopsy-proven nephritis (Group 3). This study identified low CH50 complement to be associated with SLE, as 4% of CCLE only patients had low CH50 versus 47% of patients in group 2 and 3 (19). In a 10-year retrospective study of patients with CLE in Korea, 44 patients with CCLE only and 91 patients with both CCLE and SLE were evaluated. Among this group, patients who had SLE diagnosis were more likely to have positive ANA, anti-dsDNA, anti-Sm, and anti-RNP antibodies. Additionally, they more frequently had an elevated ESR and reduced levels of C3, C4, and CH50. This study suggests that CCLE patients with presence of these biomarkers have a worse prognosis than those without (24). In DLE, serum BAFF mRNA and protein levels have been found to be higher in DLE patients with concomitant SLE compared to DLE patients without SLE and healthy controls (13). Finally, in a retrospective cohort study involving 112 Caucasian SCLE patients, 46 (41%) had SLE at the time of SCLE diagnosis. This study found that patients with SCLE and concomitant SLE had elevated ESR, positive ANA, anti-dsDNA antibody, anti-SS-A antibody, anti-RNP antibody, anti-Sm antibody, rheumatoid factor, and low C3 and CH50 (18).

ANA, anti-dsDNA antibody, anti-Sm antibody, anti-U1 RNP antibody, and elevated ESR may reflect CLE patients who are predisposed to developing SLE. While there are fewer studies comparing CLE patients who did and did not progress to SLE, they have identified similar sera biomarkers, such as autoantibodies against nuclear antigens, and elevated ESR, as studies comparing CLE patients without and with SLE (*Figure 1*). Positive ANA and anti-dsDNA antibody have been demonstrated to be associated with DLE progression to SLE in a retrospective study of 130 DLE patients (20). Another retrospective study of a cohort of DLE patients determined that patients that developed SLE persistently had elevated ESR, positive ANA, and abnormal serum immunoglobulins (25). A prospective, longitudinal study of 77 CLE patients found that 13.5% of patients went on to meet criteria for SLE

primarily by meeting mucocutaneous ACR criteria. At baseline, patients that developed SLE (SLE_C group) were more likely to have a positive ANA and a greater number of ACR criteria compared to patients that remained CLE (CLE group) (47). We recently conducted a retrospective cohort study aimed to identify risk factors that predispose CLE patients to develop SLE. 57 patients remained CLE (CLE-only) while 12 CLE patients progressed to SLE (CLE to SLE). CLE to SLE patients had more likely to have immunologic disorder than CLE-only patients; however, individual autoantibodies and laboratory abnormalities were not significantly higher in these patients (27). In a retrospective study of 40 children with DLE, six had SLE concurrently with their DLE diagnosis while nine progressed from DLE to SLE. Twenty-five patients remained DLE only. Patients with SLE, either concurrently or after progression to SLE, were more likely to present with certain immunologic findings including positive anti-Sm antibody and anti-U1 RNP antibody (48).

Conclusions

In summary, the clinical heterogeneity of CLE makes the identification and development of specific biomarkers for CLE challenging. Nonetheless, studies have identified several promising biomarkers such as type I interferon-related proteins, and anti-SSA-autoantibody that may be informative for the diagnosis of CLE and its subtypes. Type I interferon-inducible proteins can potentially be measured in the sera and skin of CLE patients to assess disease activity. Lastly, autoantibodies against various nuclear antigens, elevated ESR and low complement in CLE patients may reflect poorer prognosis and an increased risk of developing systemic disease. Further larger observational and mechanistic studies are needed to confirm roles of these various candidate biomarkers and their potential role in CLE pathogenesis and heterogeneity.

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