



Cutaneous lupus erythematosus: insights from molecular pathogenesis to targeted therapies

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Abstract

Cutaneous lupus erythematosus (CLE) is the most common organ manifestation in individuals diagnosed with systemic lupus erythematosus (SLE). CLE can occur either alone or in association with SLE; in the latter case, it substantially increases the occurrence of disease flares and can cause disfigurement. The clinical pathogenesis of CLE is well established, as exposure to ultraviolet (UV) light and/or other environmental triggers, such as smoking or drug use, can lead to keratinocyte death in genetically susceptible individuals. This in turn activates cytotoxic T cells, plasmacytoid dendritic cells (pDCs), and B cells, creating a continuous interaction between the innate and adaptive immune systems. This interaction plays a pivotal role in CLE development, driving the formation of skin lesions. However, the molecular mechanisms underlying these cutaneous manifestations are not yet fully understood. While significant advances have been made in SLE treatment over the past few decades, U.S. Food and Drug Administration (FDA)-approved therapies remain limited to hydroxychloroquine, glucocorticoids, belimumab, and anifrolumab. Although new therapies for CLE have emerged, given the highly heterogeneous nature of the condition, personalized medicine is essential to prevent disfigurement and systemic disease flares. Understanding the molecular pathogenesis of CLE is crucial for developing targeted therapies and improving patient outcomes. This review presents current insights into CLE pathogenesis, highlighting key mechanisms driving the disease and exploring recent advances in treatments that have shown promise in clinical practice.



Keywords

systemic lupus erythematosus, cutaneous lupus, keratinocytes

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease driven by autoantibodies (autoAbs), autoreactive B and T cells, and cytokine dysregulation, leading to systemic inflammation and organ damage [1–4]. The estimated prevalence of SLE in the United States ranges from 20 to 150 cases per 100,000 individuals [5–8]. Cutaneous lupus erythematosus (CLE) is a prevalent manifestation of SLE that affects up to 85% of patients and can present as the sole clinical feature in some cases [9]. CLE often leads to significant disfigurement, impacting mental health, occupational productivity, and overall quality of life. Although the precise mechanisms underlying CLE remain incompletely understood, multiple factors, including genetic predisposition, sex, ethnicity, and environmental exposures, are believed to contribute to its pathogenesis.

CLE can be classified into three subtypes on the basis of its clinical presentation, disease course, and histological findings: acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE) (Table 1). These subtypes exhibit distinct patterns of systemic involvement, with ACLE showing the highest likelihood of progression to SLE and chronic discoid lupus erythematosus (CDLE) being the least likely to develop into systemic disease [10]. The progression of CLE to SLE occurs at varying frequencies across subtypes, i.e., in over 90% of ACLE cases, 50% of SCLE cases, and 28% of generalized DLE cases, and approximately 10% of lupus profundus and localized DLE cases evolve into SLE. Notably, lupus erythematosus tumidus is rarely associated with SLE [11–15]. Disease onset, disease progression, and treatment responses are influenced by socioeconomic determinants, including ethnicity, sex, income, and education, all of which impact the severity of CLE manifestations [16].

Table 1. Clinical subtypes of specific cutaneous manifestations of lupus erythematosus.

Subtypes of cutaneous lupus erythematosus (CLE)	Description	Histopathologic findings*
Acute cutaneous lupus erythematosus (ACLE)		
- Localized (i.e., malar rash, butterfly rash) - Generalized/Disseminated (morbilliform)	82% photosensitivity[†] - Transient (lasting from hours to weeks) and often occurs after sun exposure - Resolves without scarring - Localized: mild erythematous to intense edema extending across the midface region and nasal bridge and sparing the nasolabial fold - Generalized: maculopapular rash	- Vacuolar interface dermatitis with keratinocyte necrosis - Superficial lymphohistiocytic infiltrate at the dermal-epidermal junction - Dermal mucin deposition [17]
Toxic epidermal necrolysis (TEN)-like ACLE	Erythema multiforme or TEN appearing eruption in pre-existing ACLE or SCLE lesions. With erythema multiforme (EM)-like presentation (also known as Rowell syndrome), lesions have a targetoid appearance, and with TEN presentation (also referred to as acute syndrome of apoptotic pan-epidermolysis or ASAP), there is diffuse erythema and Nikolsky sign (sloughing of the skin upon lateral pressure)	Full-thickness epidermal necrosis; otherwise, histologic features are similar to those above [18]
Subacute cutaneous lupus erythematosus (SCLE)		
- Annular - Psoriasiform/Papulosquamous - Drug-induced (DI)-SCLE	76% photosensitivity[†] - Resolves without scarring - Annular: polycyclic plaques configuration with raised red border and central clearing - Psoriasiform: hyperkeratotic plaques potentially imitating psoriasis vulgaris	- Similar histologic features to discoid lupus (see below), but often shows i. A greater degree of epidermal atrophy and necrotic keratinocytes ii. Less prominent hyperkeratosis,

Table 1. Clinical subtypes of specific cutaneous manifestations of lupus erythematosus. (continued)

Subtypes of cutaneous lupus erythematosus (CLE)	Description	Histopathologic findings*
	- Localized: affects sun-exposed areas and shows a pattern of photodistribution - Sides of the face affected, and the central facial skin is usually unaffected - V of the neck - Extensors of the upper extremity - The drug-induced form may have a strong association with Ro/SS-A autoantibodies	- follicular plugging, and minimal to absent basement membrane zone thickening [17, 19] - DI-SCLE histologic features are similar to those observed in other forms of SCLE [20, 21] - DI-SCLE may be histologically indistinguishable from idiopathic SCLE, requiring strong clinicopathologic correlation for accurate diagnosis. The presence of leukocytoclastic vasculitis, however, may favor DI-SCLE
• Vesiculobullous annular	Vesiculobullous annular (also called bullous lupus): bullous or vesicular lesions corresponding to intense inflammation along the basement membrane; sometimes anti-basement membrane antibodies are found, which may represent a concurrent presentation of bullous pemphigoid or epidermolysis bullosa acquisita in systemic lupus erythematosus (SLE).	- Distinguishing features include a subepidermal blister with neutrophils in the papillary dermis and perivascular chronic inflammatory infiltrate - Analysis of dermal mucin deposition, direct IF studies, and clinicopathologic correlation analysis may help to differentiate this form of LE from other subepidermal blistering conditions [22, 23]
• Neonatal LE	Polycyclic papulosquamous lesions in neonates driven by transplacental transfer of maternal antibodies	Histologic features are similar to those observed in other forms of SCLE [24]
- Less common variants: - Erythrodermic - Poikilodermatous - EM-like (Rowell syndrome) - Vesiculobullous annular SCLE	Rowell syndrome: target-like erythematous plaques imitating erythema exsudativum multiforme	Histologic features are similar to those observed in other forms of SCLE [18, 25, 26]
Chronic cutaneous lupus erythematosus (CCLE)		
- Discoid LE (DLE) - Localized DLE - Generalized DLE - Hypertrophic/Verrucous DLE - Mucosal DLE	46% photosensitivity[†] - Lesions begin as flat or slightly elevated, sharply demarcated, red macules or papules with a scaly surface - Later, hyperkeratotic, central scarring plaques appear, with hyperpigmentation, alopecia in scalp lesions - Common locations: - Face, scalp, ears, and conchal bowl	- Vacuolar interface dermatitis with dense pandermal perivascular and peri-appendageal lymphocytic inflammation - Follicular hyperkeratosis/plugging - Variable epidermal atrophy or epidermal hyperplasia, and scarring - Dermal mucin deposition - Thickening of the basement membrane zone [27, 28]
• LE tumidus	63% photosensitivity[†] - Violaceous or erythematous edematous papules and plaques in sun-exposed areas - Lesions have erythema and induration but lack scaling and follicular plugging - Common locations of lesions: - Face, upper trunk/upper chest, and upper arms - Single or multiple lesions	- Dense perivascular and peri-adnexal lymphocytic inflammatory infiltrate with abundant dermal mucin deposition - Distinguishing features include a lack of significant vacuolar interface dermatitis and follicular plugging. - Does not show prominent basement membrane zone thickening [29] - May appear histologically identical to Jessner lymphocytic infiltration of the skin

Table 1. Clinical subtypes of specific cutaneous manifestations of lupus erythematosus. (continued)

Subtypes of cutaneous lupus erythematosus (CLE)	Description	Histopathologic findings*
Lupus profundus (also known as lupus panniculitis)	0% photosensitivity[†] - Intense inflammation in the fat leads to indurated plaques that can evolve into disfiguring, depressed areas - Retracted atrophic lesions mainly over proximal extremities and with a distinctive distribution predominantly on the face, upper arms, upper trunk, breasts, buttocks, and thighs	- Lobular panniculitis with lymphoid follicles containing reactive germinal centers, clusters of B lymphocytes and plasmacytoid dendritic cells, mixed cell infiltrate with plasma cells, and polyclonal T-cell receptor γ gene rearrangements - Dermal mucin deposition, +/- vacuolar interface dermatitis [30–32]
Chilblain LE/Perniosis LE	0% photosensitivity[†] - Tender erythematous lumps in acral areas - Acral, dusky to purple plaques that worsen in cold temperatures	- Dense dermal perivascular lymphocytic infiltrate, erythrocyte extravasation, and variable fibrin deposits within vessels (lymphocytic vasculitis) - Papillary dermal edema - May show vacuolar interface dermatitis [33, 34]
- LE/Lichen planus overlap - Lichenoid CLE-lichen planus overlap syndrome (LE-LP overlap syndrome)	- Overlap syndrome, in which one or more of the clinical, histological, and immunopathological features of both LE and LP are present [35] - Mainly painful, bluish-red plaques with atrophy and scaling, and hyperkeratotic papules and nodules predominantly on the extremities - Erythematous/Violaceous plaques and papules with scaling, overlapping histological features of CLE and LP, with or without serological markers - Red or dusky purple papules and plaques on the following: - Toes, fingers, and sometimes the nose, elbows, knees, and lower legs - Lesions are brought on or exacerbated by cold temperatures and moisture	It may be difficult to distinguish by light microscopy alone; however, some authors have reported a double-layer indirect IF technique using patient serum and autologous lesional skin as substrates to establish the correct diagnosis [36]
Comedogenic LE	Comedogenic LE: a rare variant of chronic cutaneous lupus with comedones and inflammatory papules, and plaques resembling acne vulgaris, and also leading to scarring. Notably, discoid lupus lesions can also present with comedonal lesions, particularly in the ears	Histologic features are not well documented in the literature; however, this subtype is reported to feature dilated follicles with prominent follicular plugging [37]

†: Photosensitivity (%) indicates the proportion of patients with each subtype that exhibit an increased skin reaction to sunlight, as quantified in clinical studies. *: Overlapping pathological features in several types of CLE include apoptosis, epidermal vacuolization, pervasive (including papillary and reticular dermis) inflammation, dermal mucin, basement membrane thickening, follicular plugging, and interface dermatitis [19]. IF: immunofluorescence.

CLE is diagnosed primarily through clinical evaluations, supported by histopathological examinations showing features such as apoptosis, interface dermatitis, and dermal inflammation [19]. In CLE, skin damage arises from a complex interaction between innate and adaptive immune responses, with keratinocytes playing a central role in disease initiation. UV radiation exposure can trigger keratinocyte apoptosis in susceptible individuals, leading to the release of intracellular debris. This, in turn, attracts inflammatory cells and promotes the secretion of cytokines and chemokines, ultimately driving an inflammatory cascade. A key consequence of this process is the overexpression of type I interferons (IFNs), which further amplify the immune response [29]. As the immune response intensifies, autoreactive T cells, plasmacytoid dendritic cells (pDCs), and B cells drive tissue damage, ultimately leading to lesion formation. These immune responses culminate in the deposition of autoAbs and immune complexes (ICs) at the dermal-epidermal junction, which manifests as interface dermatitis on hematoxylin and eosin (H&E) staining [19]. Immunofluorescence (IF) staining is used to detect immunoglobulin deposition at the dermoepidermal junction, which is an indicator of IC deposition and represents a positive result in the lupus band test [38].

Despite advances in our understanding of the clinical and immunopathological features of CLE, the molecular mechanisms driving disease pathogenesis remain poorly defined. Thus far, the U.S. Food and Drug Administration (FDA) has approved a limited number of therapeutic agents, including hydroxychloroquine, glucocorticoids, belimumab, and anifrolumab, which have shown varying degrees of efficacy. The heterogeneity of CLE underscores the necessity for more personalized treatment strategies, and a deeper understanding of the molecular underpinnings of CLE is critical for developing targeted therapeutic approaches that could improve clinical outcomes. This review explores the genetic, epigenetic, and cellular factors involved in CLE pathogenesis, as well as the available topical treatment options. Additionally, this study provides a framework for future research efforts aimed at elucidating the complex mechanisms driving this disease.

Genetic factors and epigenetic modifications in CLE

The genetic landscape of CLE is complex and shaped by both monogenic mutations and polymorphic variations that influence disease susceptibility (Table 2). A subset of lupus patients inherit monogenic mutations, such as those in the *TREX1* gene, which encodes an enzyme crucial for breaking down cytosolic DNA [39]. When this process is disrupted, unprocessed DNA triggers an immune response, leading to familial chilblain LE, a condition characterized by painful, pernio-like nodules and recurrent swelling in the extremities [39].

Table 2. Genes associated with cutaneous lupus erythematosus (CLE).

Gene	Associated subtype	Gene function (expression/activity)	Reference(s)
HLA			
HLA-DRB1*04	DLE	High	[40]
HLA-B8	DLE, SCLE (annular)	High	[41–43]
HLA-DR3	SCLE (annular)	High	[42, 43]
HLA-DR2	SCLE	High	[43]
HLA-DR5	SCLE (annular)	Low	[42]
HLA-DQA1	NLE (with an allele with glutamine at position 34 of the first domain); CCLE (with the OI02 allele)	High	[44, 45]
HLA-DRw6	CLE	High	[41]
Non-HLA genes			
Genetic polymorphisms			
TREX1	CLE, SLE, FCL	Low activity	[39, 46–50]
MICA/B	CLE, SLE	High	
IZKF	CLE, SLE	High	
SAMHD1	CLE, FCL	Low activity	[51–53]
STING	FCL	High activity	
Perforin	SCLE	Low	
ITGAM	DLE (with loci encoding integrin α_M , also known as CD11b)	High	[54]
FCGRA	Malar rash (with loci encoding low-affinity IgG Fc region receptor IIa)	High	[55]
IFN- κ	CLE (with a gene encoding IFN- κ)	High	[56]
Complement factors			
Complement factor C1qA	SCLE	Low	[57]
Complement factor C2	SCLE, DLE	Low	[51, 58, 59]
C4	DLE (with the null C4 allele B*Q0)	Low	[60]

DLE: discoid lupus erythematosus; SCLE: subacute CLE; NLE: neonatal LE; FCL: familial chilblain lupus erythematosus; CCLE: chronic CLE; SLE: systemic lupus erythematosus; IFN: interferon.

In addition to monogenic mutations, gene polymorphisms play a pivotal role in CLE by affecting key cellular processes, such as apoptosis, ubiquitination, debris clearance, and immune regulation [51]. Variants in genes such as SAMHD1 and those encoding complement factors (C1q and C2) further increase the likelihood of developing CLE lesions [51, 61]. Additionally, polymorphisms in human leukocyte antigen (HLA) genes have been linked to both CLE and neonatal lupus erythematosus (NLE), a rare condition affecting newborns that manifests as skin lesions, congenital heart block, and hematologic abnormalities [40, 44].

A genome-wide analysis of CLE patients revealed striking similarities to SLE patients, particularly regarding the overexpression of genes associated with IFN signaling and apoptosis, two central pathways driving CLE pathology [62–65]. IFN-1 pathway genes (OAS1/2/L, IFIT1, and PLSCR1) and the chemokine C-X-C motif chemokine ligand 1 (CXCL1) are notably upregulated in CLE lesions [65, 66], supporting their role in disease progression. Moreover, genes involved in complement activation (C1R, C2, C1QB, C3AR1, CFB, CFD, and C4A/C4B) and leukocyte chemotaxis (FCGR3A, ITGAL, ITGB2, and NCF4) are dysregulated, further contributing to immune dysfunction.

While genetic changes lay the foundation for CLE development, epigenetic modifications add another layer of complexity to CLE pathogenesis. DNA hypomethylation in CD4⁺ T cells has been implicated in SCLE, as it alters the immune balance through the demethylation of key immune genes, including those at the perforin locus [67, 68]. Similarly, in CD4⁺ T cells in SLE, genes regulating inflammation, apoptosis, and cell migration are hypomethylated, promoting disease activity [69]. Notably, CXCL13 and TLR7 (Toll-like receptor 7) hypomethylation have been directly linked to skin damage in CLE [63, 69]. However, tumor necrosis factor (TNF) and TNF receptor family genes are epigenetically upregulated, amplifying the inflammatory responses characteristic of lupus [69].

Together, these genetic and epigenetic alterations underlie the complexity of CLE pathogenesis, with immune dysregulation, impaired debris clearance, and chronic inflammation converging to drive disease progression. Understanding these mechanisms not only improves our understanding of CLE pathogenesis but also paves the way for the development of targeted therapies aimed at modulating these underlying pathways.

Nonimmune cells

Keratinocytes

Keratinocytes, the primary cells of the epidermis, play a crucial role in the pathogenesis of CLE. In genetically susceptible individuals, exposure to UV radiation and other environmental factors induces keratinocyte death, leading to the release of damage-associated molecular patterns (DAMPs), including endogenous nucleic acids, high-mobility group box 1 (HMGB1) protein, and autoantigens such as Ro52 [70, 71]. DAMPs are recognized by pattern recognition receptors (PRRs), such as melanoma differentiation-associated protein 5 (MDA5), on keratinocytes, triggering the transcription of IFN-regulated genes via a TLR-independent pathway [10, 72]. This inflammatory response amplifies the autoimmune cascade in CLE [72]. Additionally, HMGB1 functions as a proinflammatory cytokine and an autoantigen, further contributing to tissue damage in CLE [73].

Additionally, keratinocytes secrete IFN- κ and IFN- λ (type I and type III IFNs), which, via self-signaling mechanisms, amplify the expression of IFN-responsive proinflammatory cytokines, such as IL-6, and chemokines, such as CXCL9-11, which bind to C-X-C motif chemokine receptor 3 (CXCR3) ligands to recruit more immune cells [72, 74, 75]. Consequently, cytotoxic T cells induce additional keratinocyte death through CXCR3-mediated mechanisms [70, 71]. This ongoing damage activates antigen-presenting cells (APCs), particularly DCs, which stimulate T- and B-cell responses. The autoAbs produced as a result of this process further target keratinocytes, perpetuating tissue damage and inflammation in CLE.

IFNs are activated via Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling [74]. Nucleic acid motifs also activate the inflammasome via absent in melanoma 2 (AIM2) [76]. Interestingly, IFN- κ expression is upregulated, and basal phospho-STAT (pSTAT) activity is greater in the

healthy-appearing skin of CLE patients than in the skin of patients with other chronic inflammatory skin diseases, such as psoriasis [74].

UVB radiation upregulates the expression of Ro52 in keratinocytes and promotes its interactions with TNF-like weak inducer of apoptosis (TWEAK), which binds to its receptor, fibroblast growth factor-inducible 14 (Fn14) [77, 78]. This interaction activates the NF- κ B and PI3K/Akt pathways, leading to increased expression of Ro52 and activation of proinflammatory pathways, resulting in increased levels of proinflammatory cytokines [77, 78]. This sequential chemokine production sustains inflammation in the epidermal layer [62]. In established CLE lesions, keratinocyte apoptosis and proinflammatory chemokine production are limited to the dermal-epidermal junction, resulting in interface dermatitis [79]. On the other hand, keratinocytes from the healthy-appearing skin of CLE patients are more sensitive to UV radiation-induced cytotoxicity than keratinocytes from healthy donors are [80, 81].

UV radiation also alters keratinocyte DNA, generating immunostimulatory motifs such as 8-hydroxyguanosine [72]. Interestingly, compared with healthy individuals, CLE and SLE patients exhibit a larger number of dying keratinocytes and impaired clearance [81]. In CLE, autoAbs further amplify this response [82]. However, autoAbs targeting ribonucleoproteins may directly drive the formation of lupus lesions in mice [83].

Innate immune cells

pDCs and DCs

pDCs and DCs are APCs that play important roles in regulating inflammation in CLE and contribute to lesions. pDCs are specialized type I IFN-producing cells that express TLR7 and TLR9 and thus recognize nucleic acids, especially in the form of ICs [63]. pDCs are observed in skin biopsy samples from CLE patients, both with and without lesions, and are involved in the pathogenesis of both SLE and CLE [84–86]. The majority of pDCs are located within perivascular inflammatory areas in the dermis, whereas others are situated along the dermal-epithelial junction [85]. However, not all skin lesions contain pDCs [87]. Recently, single-cell RNA and spatial RNA sequencing revealed that the skin of CLE patients, both with and without lesions, harbors a type I IFN-rich environment attributed to CD16⁺ DCs, leading to proinflammatory subtypes [88].

Both DCs and pDCs are recruited to skin lesions through CXCL-chemokine interactions with CXCR3 by sensing nucleic acids released following keratinocyte death [62]. pDCs are further stimulated via TLRs, particularly TLR7 and TLR9 [89]. TLR9 and CD32 are activated upon the uptake of nucleic acids and ICs via endocytosis [90]. Once activated, pDCs produce large amounts of type I and type III IFNs, cytokines, and interleukins (ILs), further perpetuating the autoimmune response [91]. Additionally, the presence of type I IFN is essential for pDC maturation and migration [92]. Moreover, pDCs secrete large amounts of TNF and IL-6 in response to IFN- α , which further increases apoptosis [93], and contribute to the regulation and recruitment of T, B, and natural killer (NK) cells. The number of peripheral circulating pDCs is reduced in patients with LE, as pDCs preferentially migrate to affected tissues, including the skin [63]. While pDCs are most abundant in active lesions, low-level infiltration in non-lesional skin is a key subclinical feature that distinguishes the skin of CLE patients from that of healthy controls and may prime the skin for future flares [88, 94–96], with infiltration noted after skin injury [63] or UV exposure [97]. In a lupus-prone murine model, transient depletion of pDCs before disease initiation was found to ameliorate autoimmunity [86]. In human studies, anti-BDCA2 monoclonal antibodies, which specifically target the BDCA2 receptor on pDCs, have been shown to suppress type I IFN production and inflammatory mediators, thereby alleviating lupus-associated cutaneous manifestations [98, 99].

NK cells

NK cells are abundant and proliferate in CLE skin lesions, and the number of these cells in the peripheral blood decreases due to their trafficking from blood to tissue [100–103]. In SLE, peripheral blood NK cell counts are inversely correlated with disease activity [104]. Compared with those of healthy controls, the NK cells of lupus patients secrete more IFN, and their cytotoxic functions are impaired [101, 105]. However, the

precise role of NK cells in CLE pathophysiology is unclear, although it is known that NK cells colocalize with CD8⁺ T cells at the dermal-epidermal junction, releasing granzyme B to induce keratinocyte apoptosis [100]. Type I IFNs provide negative feedback, reducing the amount of granzyme B released and limiting tissue damage. Invariant NK cells secrete IFN- γ , influencing both inflammatory and anti-inflammatory responses to tissue damage [100].

Neutrophils and monocytes

Neutrophils, as early responders in the innate immune system, are present in the skin before lesion onset in murine models of CLE [106]. UV radiation and other stimuli induce keratinocyte death, inducing the release of DAMPs that activate neutrophils. These neutrophils secrete antimicrobial peptides (AMPs), such as LL-37, and reactive oxygen species (ROS) and form neutrophil extracellular traps (NETs) composed of chromatin, histones, and other intracellular contents [107, 108]. Elevated levels of LL-37 and other AMPs have been observed in CLE lesions compared with healthy skin [109, 110]. The increases in NETosis and IL-17 externalization by neutrophils in SLE-affected skin suggest that NETs and IL-17 play a role in tissue damage and that the number of NETs and IL-17 levels are correlated with disease activity [104, 106]. In patients with various CLE subtypes, including tumid lupus, panniculitis, ACLE, and DLE, NETs are present in lesions, with higher NET numbers in tumid lupus, ACLE, and DLE lesions than in SCLE lesions, indicating distinct roles for neutrophils depending on the disease subtype [111, 112]. NETs also impact pDCs by complexing with double-stranded DNA (dsDNA) and LL-37, which are internalized through TLR9 and subsequently produce type I IFN in SLE [113, 114]. Additionally, LL-37/dsDNA complexes can function as autoantigens [115]. Notably, UV light exposure leads to the recruitment of neutrophils to the skin, which may further lead to temporary damage and upregulation of type I IFN gene expression in other organs, such as the kidneys [112]. However, the precise pathophysiological role of neutrophils and AMPs in CLE remains to be elucidated.

Furthermore, monocytes act as APCs and are recruited and activated by colony-stimulating factor 1 (CSF-1) produced by keratinocytes upon UV exposure, leading to increased keratinocyte apoptosis [116]. Moreover, monocyte-derived DCs, the numbers of which are elevated in both the lesional and healthy skin of SLE patients, may contribute to CLE pathology because of their strong activation signature [88].

Macrophages

Macrophages act as APCs and play roles in processes such as phagocytosis and cytokine production [117]. An increased number of macrophages in CLE lesions predicts a poor response to hydroxychloroquine [118, 119]. CD68-positive macrophages expressing FasL are found around hair follicles and contribute to hair follicle destruction through Fas-FasL interactions in CLE [120]. UVB irradiation increases the expression of CSF-1 in keratinocytes, thereby attracting macrophages that trigger keratinocyte apoptosis in lupus-prone mice with CLE but not in lupus-resistant mice with CLE [116]. Interestingly, macrophage infiltration after UV exposure may cause systemic symptoms such as arthralgia, weakness, fatigue, and headache [118].

Adaptive immune cells

T cell

T cells, including CD4⁺, CD8⁺, memory, and $\gamma\delta$ T cells, regulatory T (Treg) cells, and T helper 17 (Th17) cells, play crucial roles in the pathogenesis of CLE [79]. CD4⁺ T follicular helper and T peripheral helper cells promote B-cell activation and autoAb production [121–124]. The role of Treg cells in CLE remains unclear, as studies have reported both increased and decreased numbers of these cells in SLE skin samples [125–128]. In lupus-prone mice, UV exposure enhances CD4⁺ and CD8⁺ T-cell activation in draining lymph nodes while suppressing Treg cells, an effect that is amplified in a type I IFN-dependent manner [129]. However, whether this mechanism occurs in the skin and its impact on CLE inflammation remains unknown. Th1 cells are considered key drivers of CLE pathogenesis, with a notable shift toward Th1-associated chemokines across all CLE subtypes [130, 131]. Th17 cells, which are prevalent in individuals with IL-2-deficient SLE, exacerbate inflammation by skewing naive T-cell differentiation toward Th17 cells rather than Treg cells [132, 133].

Upon UV exposure, keratinocytes release chemokines such as CXCL9, CXCL10, and CXCL11, which bind to the CXCR3 receptor on T cells. This interaction results in the recruitment of autoreactive cytotoxic T cells, triggering keratinocyte death [70–72, 74, 75]. Among these chemokines, CXCL10 plays a key role in directing CXCR3-expressing T cells to skin lesions. Consequently, T-cell activation occurs through interactions between the T-cell receptor (TCR) and major histocompatibility complex (MHC) class II, initiating downstream signaling [134]. This cascade involves increased phosphorylation of signaling molecules and increased calcium influx, which is mediated by the association of spleen tyrosine kinase (SYK) with the Fc receptor γ -chain (FcR γ), further amplifying TCR signaling [135].

Upon recruitment, cytotoxic CD8⁺ T cells target basal keratinocytes, contributing to interface dermatitis, as observed via H&E staining [136]. These cells express granzyme B, which is elevated in CDLE scarring lesions compared with SCLE lesions, suggesting a role for the cells in scarring pathophysiology [137]. While Th2 cells may initiate inflammation, Th1 cells dominate established lesions, promoting type I IFN production by cytotoxic T cells and macrophages [136, 138]. Transcriptomic analysis of skin T cells revealed an IFN-rich signature, with reduced numbers of cytotoxic and effector T cells compared with those in lupus nephritis biopsy samples [139]. T cells induce keratinocyte apoptosis via FAS/FASL interactions [120], whereas IL-21 from Th cells increases granzyme B levels in pDCs and NK cell-mediated keratinocyte damage [140, 141]. However, type I IFNs suppress granzyme B production in pDCs [140]. Moreover, Th cells respond to nucleosomes, driving anti-DNA antibody production in B cells in SLE [142–144]; Th clones produce IL-2, IFN- γ , and IL-4; and lupus CD4⁺ T cells overexpress perforin through epigenetic regulation via DNA methylation [68, 145].

Interestingly, CLE patients present significantly lower numbers of CD4⁺, CD8⁺, Tregs, and $\gamma\delta$ -T cells than individuals with other inflammatory skin diseases and healthy controls do, contributing to autoimmunity via impaired immunosuppressive function [125, 134, 146]. The proportions of CD4⁺ T cells and FOXP3⁺ T cells and the CD4/CD8 ratio are significantly lower in SCLE lesions than in CDLE lesions [126]. Additionally, a proteomic study revealed a unique increase in IL-16 expression in CLE lesions [147].

When upregulated, CD40L on T cells interacts with B cells to promote maturation and antibody secretion [134] and engages APCs to amplify the TCR signal [148]. Signaling pathways, such as the cyclic adenosine monophosphate (cAMP)-dependent phosphorylation and protein kinase C (PKC) pathways, are either inhibited or activated, similar to the PI3K pathway [134].

B cells and plasma cells

B cells play a pivotal role in the pathogenesis of CLE through multiple mechanisms, primarily via autoAb production and interactions with T cells [149–152]. Following keratinocyte death induced by UV exposure or other triggers, naive B cells become activated, differentiate into plasma cells, and begin secreting autoAbs, a process further amplified by IFN signaling [153, 154].

Plasma cell differentiation, survival, and sustained autoAb production are supported by survival signals mediated through B-cell-activating factor, also known as B-lymphocyte stimulator (BAFF/BLyS) and IL-6 from surrounding cells [149, 155]. Additionally, Th cells support plasma cell differentiation [156], as somatic hypermutation and isotype switching depend on CD40 and IL-21 [149]. IL-21 and TLR7/9 facilitate B-cell recruitment to inflammation sites in CLE lesions and localized autoAb production in mouse models [157], whereas IL-17 recruits immune cells and increases B-cell autoAb production in SLE [133]. Plasma cells can accumulate at the site of inflammation [158], whereas B cells form clusters in the skin and arrange in lymphoid-like structures, called tertiary lymphoid organs/structures (TLOs) [87, 159].

B cells interact with keratinocytes via BAFF and its receptor (BAFF-r) in both SLE and CLE; BAFF is expressed by lesional keratinocytes, and associated receptors [BAFF-r, transmembrane activator and CAML (calcium-modulating cyclophilin ligand interactor) interactor (TACI), and B-cell maturation antigen (BCMA)] are expressed by B cells [87, 160–162]. BAFF is essential for B-cell maturation [163], and its expression in keratinocytes can be induced by immunostimulatory DNA motifs, highlighting its importance in CLE [161].

Patients with ACLE and SCLE commonly have detectable circulating autoAbs, including anti-Ro (Ro60/Ro52), anti-La, and anti-galectin-3, which are rarely present at measurable levels in CDLE [104, 164, 165]. These autoAbs are associated with HLA-DR3 in SLE [165] and with disease severity [166]. AutoAbs form ICs at the dermal-epidermal junction, resulting in the characteristic “lupus band” visible via IF, which aids in CLE diagnosis [167–169]. In SLE, B-cell deposition in nonlesional skin is correlated with a worse prognosis [170], and the extent of B-cell infiltration in lesional skin varies by LE subtype [87, 171], with DLE patients showing a stronger B-cell signature and greater enrichment of B cells than ACLE and SCLE patients [172]. Compared with similar SLE lesions, isolated CLE lesions exhibit a more pronounced B-cell signature, linking cutaneous and systemic disease activity [171]. Despite these differences, circulating B-cell populations largely overlap between SLE and isolated CLE.

Circulating anti-Ro and anti-La autoAbs are strongly associated with photosensitivity, with Ro proteins detected in CLE lesions [170, 173–176]. These findings are supported by the observation that UV exposure induces keratinocyte apoptosis and promotes Ro antigen translocation to the cell surface, where anti-Ro autoAbs can bind [177–181]. Additionally, UVB upregulates Ro/SSA and La/SSB expression on apoptotic keratinocytes, enhancing autoAb interactions [178, 179]. These findings highlight the role of autoantigen redistribution in the aberrant UV response observed in lupus.

The presence of anti-Ro autoAbs in the serum correlates with increased IL-17A⁺ lymphocytes in lesional skin in SCLE, and Ro52 deletion in mice triggers Th17-driven inflammation [182, 183]. Ro52 negatively regulates IFN production, reducing inflammatory cytokine levels, while its deficiency leads to the development of CLE-like lesions [182, 184–186]. Moreover, Ro60, an RNA-binding protein, may mediate UV responses, and Ro60 deficiency in mice results in lupus-like features, including autoAb production, glomerulonephritis, and photosensitivity [187–189]. Nonetheless, the functional link between Ro52/Ro60 autoAbs and their targets remains unclear.

B cells drive skin damage in addition to autoAb production through IFN-dependent processes, including antigen presentation, receptor engagement, and cytokine signaling [153]. Additionally, IL-6 production by B cells sustains the survival of these cells [149, 190]. Notably, B-cell signatures and infiltrates in autoAb-negative CLE highlight the role of B cells in fueling autoimmune reactions through antigen presentation and T-cell activation [87, 172].

Overall, cutaneous lupus exemplifies how environmental triggers, such as UV light, initiate a cascade of immune crosstalk between innate and adaptive immune cells that drives chronic skin inflammation in cutaneous SLE. Keratinocyte injury leads to the release of cytokines, chemokines, and nucleic acids that activate pDCs, which subsequently secrete type I IFNs to orchestrate T- and B-cell activation. CD4⁺ and CD8⁺ T cells amplify local inflammation through IFN- γ secretion and cytotoxic activity, while B cells produce autoAbs that form ICs, further engaging innate immune pathways. This tightly orchestrated network of keratinocytes, pDCs, and adaptive immune cells sustains a self-perpetuating inflammatory loop that underlies the chronicity of cutaneous SLE.

Personalized therapy

CLE can be treated with systemic or topical therapies. In cases where disease activity is limited to the skin with no internal organ involvement, topical therapy is preferred. However, systemic treatment is indicated where the area of the body surface involved is large or where the disease is recalcitrant to topical therapies. Systemic therapies for CLE overlap with therapies for SLE. Systemic therapies include antimalarials, systemic glucocorticosteroids, noncorticosteroid immunosuppressants, and some biologics and have been reviewed elsewhere [191]. Systemic retinoids can be used to treat CCLE or SCLE [192–196], and isotretinoin can be administered at the same dose as that used to treat acne vulgaris (0.5–1 mg/kg body weight). Although the mechanism of action is unclear, retinoids may act by regulating the immune system, clearing inciting antigens or factors, or regulating epidermal differentiation in CLE lesions with otherwise abnormal keratinization [192]. Lesions may recur upon cessation of treatment. In the United States, the use of isotretinoin in patients with child-bearing potential is restricted by the mandatory participation of both

prescribers and patients in iPledge, a Risk Evaluation and Mitigation Strategy program. CLE can also be treated with acitretin at 50 mg daily [197]; however, esterification of acitretin with ethanol converts the drug to etretinate, which has a half-life of 120 days and is a teratogen, thus requiring the use of contraception for 2–3 years after cessation of the drug [198].

Aberrant type I IFN (particularly IFN- α) expression has been observed in the skin, as mentioned above, and drives SLE by activating DCs, enhancing autoAb production, and upregulating interferon-stimulated genes (ISGs), which correlate with disease activity [29]. Anifrolumab blocks IFNAR1, thereby disrupting this inflammatory loop. Its efficacy in cutaneous and musculoskeletal SLE, as demonstrated in TULIP-1 and TULIP-2, supports this mechanism [199, 200]. Anifrolumab is also emerging as a treatment for cutaneous lupus [201–204]. In cases where the disease is recalcitrant to existing systemic therapies, anifrolumab at 300 mg IV every 4 weeks was found to lead to a clinically meaningful reduction in inflammation or clearance of skin lesions after just 1 month. In cases of cutaneous disease resulting in alopecia, some recovery of hair growth was also observed. In patients with lupus limited to the skin, topical therapies alone can be sufficient. In patients with both systemic manifestations of lupus and skin involvement while on systemic therapies, topical therapies can help clear the skin without further escalation of the systemic regimen. Topical therapies targeting inflammatory pathways include corticosteroids, calcineurin inhibitors, and JAK inhibitors. Topical retinoids help control CLE by regulating keratinocyte maturation.

Topical corticosteroids have long been used to treat inflammatory skin disorders, including CLE. They have pleiotropic pharmacologic effects and can therefore modulate the inflammatory response by vasoconstriction, inhibiting the release of phospholipase A2 and the transcription of inflammatory mediators [199]. Specifically, corticosteroids pass through the cell membrane of inflammatory cells and bind glucocorticoid receptors in the nucleus to alter the gene expression of inflammatory transcription factors. However, prolonged use of topical steroids can lead to tachyphylaxis, i.e., loss of efficacy, as demonstrated by loss of the vasoconstrictive effect of the steroid [200]. The long-term use of topical steroids can also increase the risk of atrophy of the skin resulting from loss of collagen in the dermis [205]. Thus, topical regimens should involve steroid-sparing strategies, such as alternating the use of a topical steroid with a calcineurin inhibitor or avoiding the use of topical steroids in areas that have higher rates of absorption due to thinner skin (the face) or where there is occlusion (intertriginous areas) that may increase the potency as well as the risk of adverse effects. Despite this, both topical steroids and calcineurin inhibitors remain the first-line topical therapies to manage CLE flares [206].

In areas of thinner skin such as the face and neck or intertriginous areas such as the axilla, inguinal areas, and inframammary or infraabdominal pannus areas, lower-potency topical steroids such as hydrocortisone 2.5%, alclometasone 0.05%, or desonide 0.05% can be used, whereas medium-potency topical steroids such as triamcinolone acetonide 0.1% or even high-potency topical steroids such as betamethasone dipropionate 0.05% or ultrahigh potency topical steroids such as clobetasol 0.05% can be used on the scalp, trunk, and extremities.

If chronic use of a topical agent is anticipated or if the anatomical site is at high risk of adverse events, such as the face, use of a topical calcineurin inhibitor is advisable. Calcineurin inhibitors such as tacrolimus ointment or pimecrolimus cream work by binding to the cytoplasmic protein macrophilin-12 to form complexes that inhibit calcineurin, blocking calcium-dependent signaling and thus the transcription of many cytokines [207]. Tacrolimus is considered more potent than pimecrolimus but may also cause more irritation during initial application [208]. Tacrolimus 0.1% ointment is considered as potent as mid-potency topical steroids such as betamethasone valerate 0.12% [209].

Although the FDA has approved ruxolitinib for only atopic dermatitis and vitiligo, ruxolitinib 1.5% cream can be used to treat CLE as a steroid-sparing agent. Ruxolitinib is a JAK1/2 inhibitor and thus inhibits the JAK-STAT pathway, which is involved in the autocrine elaboration of type I IFNs in CLE [210]. A systematic review of the literature revealed that other JAK inhibitors targeting JAK1 or TYK2 also demonstrated efficacy in treating CLE [211].

Topical retinoids, such as tretinoin [212], tocoretinate [213], and tazarotene [214], have been reported to treat CLE and are particularly appropriate for lesions with comedonal features. A clinical feature of SCLLE is photosensitivity, and this is also the case for CLE. Sun protection and avoidance remain paramount strategies to reduce flares of both types of CLE and to avoid the exacerbation of internal disease. Indeed, a recent study revealed that lupus nephritis triggered by sun exposure may be mediated by neutrophils [112]. However, many patients do not realize that SLE can be triggered by sun exposure [215]. Furthermore, dark-skinned individuals with CLE practice less photoprotection than light-skinned individuals do [216]. In a trial, among 25 patients treated with SPF 60 sunscreen containing a mix of organic filter and organic and mineral pigments, none developed lesions in treated areas; however, 14 patients developed lesions in vehicle cream-treated areas exposed to UVA and UVB [217].

Conclusions

The pathogenesis of CLE is highly complex, posing significant challenges to the development of personalized therapies. This review highlights mechanisms involving both immune and nonimmune cells, emphasizing disease heterogeneity. CLE can manifest as a distinct entity or in association with SLE, with variable pathogenetic pathways. Notably, serum autoAbs and proinflammatory cytokines are often detected months to years before an SLE diagnosis, indicating that their emergence precedes clinical onset. Similarly, subclinical inflammation is detected in the apparently clinically normal skin of CLE/SLE patients, reflecting disease processes that occur prior to lesion onset. However, the timing of this skin inflammation and the potential effectiveness of early interventions remain unknown. Keratinocytes, in addition to immune cells, play critical roles in tissue injury, suggesting their promise as therapeutic targets. Strategies targeting both immune and nonimmune cells are essential for improving CLE outcomes and potentially mitigating SLE progression.

Abbreviations

ACLE: acute cutaneous lupus erythematosus

AMPs: antimicrobial peptides

APCs: antigen-presenting cells

autoAbs: autoantibodies

BAFF: B-cell-activating factor

BAFF-r: B-cell-activating factor receptor

CLE: chronic cutaneous lupus erythematosus

CDLE: chronic discoid lupus erythematosus

CLE: cutaneous lupus erythematosus

CSF-1: colony-stimulating factor 1

CXCL1: C-X-C motif chemokine ligand 1

CXCR3: C-X-C motif chemokine receptor 3

DAMPs: damage-associated molecular patterns

dsDNA: double-stranded DNA

FDA: Food and Drug Administration

HLA: human leukocyte antigen

HMGB1: high-mobility group box 1

ICs: immune complexes

IF: immunofluorescence

IFNs: interferons

ILs: interleukins
JAK: Janus kinase
NETs: neutrophil extracellular traps
NK: natural killer
pDCs: plasmacytoid dendritic cells
SCLE: subacute cutaneous lupus erythematosus
SLE: systemic lupus erythematosus
STAT: signal transducer and activator of transcription
TCR: T-cell receptor
Th17: T helper 17
TLR: Toll-like receptor
TNF: tumor necrosis factor
Treg: regulatory T
UV: ultraviolet

Declarations

Author contributions

FKA: Conceptualization, Writing—original draft, Validation, Writing—review & editing, Supervision. JG: Conceptualization, Writing—original draft, Writing—review & editing. PCC: Conceptualization, Writing—original draft, Writing—review & editing. All the authors read and approved the submitted version.

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