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Cutaneous Lupus Erythematosus as a Proposed Sentinel Model of Systemic Autoimmunity: Immunobiological Convergence between the Skin and Systemic Disease

Gustavo Alberto Gutiérrez-Barros[1], María Victoria Morales-Morales[2], Gabriela María Morales-Donado[3], Sharon Nicole Rueda-Cogollo[3], Daniela Valentina Fontalvo-Bustamante[3], Isabella María Mercado Athias[3], Katheryn Coronel Ortiz[3], Jafet David Rios Pérez[3], Eva Esther Hinestrosa Flórez[3], Edilma Rosa Quintero Gámez[3], Eliannys Paola Quintero Gámez[3], Ricardo José Boneth Pérez[3], Jair Jose Daza Redondo[3], Leonel David Mendoza Daza[3], Valery Paola Jiménez López[3]

[1]Internal Medicine, Universidad Libre, Barranquilla, Colombia
[2]Internal Medicine, Universidad Simón Bolívar, Barranquilla, Colombia
[3]General Medicine, Barranquilla, Colombia
Email: gustavogutierr8@gmail.com, Vicky.mvmm@gmail.com, gabrielam-moralesd@unilibre.edu.co, sharonn-ruedac@unilibre.edu.co, danielav-fontalvob@unilibre.edu.co, Isabellamercado06@gmail.com, Katheryncoronelo20@gmail.com, jafetriosperez@gmail.com, eva.hinestrosa@hotmail.com, edilmar-quinterog@unilibre.edu.co, eliannys-quinterog@unilibre.edu.co, ricardoj-bonethp@unilibre.edu.co, jotajdaza@gmail.com, leoneldavidmendozad@hotmail.com, Valeryjimenezloplez08@gmail.com

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Abstract

Cutaneous lupus erythematosus (CLE) has traditionally been considered a dermatologic manifestation within the lupus spectrum; however, recent clinical, immunologic, and transcriptomic evidence suggests that the skin may constitute an immunologically active and accessible compartment for studying early stages of lupus autoimmunity. In this review, the concept of a "sentinel model" is used as a proposed integrative hypothesis, and not as an established pathogenic mechanism or as evidence that the skin is the demonstrated causal origin of systemic disease. We synthesize the available evidence on local cutaneous immune activation, highlighting the role of the keratinocyte as an immunologically active cell capable of producing type I interferons, particularly interferon-kappa (IFN-κ), and of participating in nucleic acid-sensing pathways such as cGAS-STING. These mechanisms support the existence of an interferon-dominated cutaneous inflammatory signature; nevertheless, their direct contribution to systemic propagation remains incompletely defined. Ad-

ditionally, transcriptomic studies have identified shared inflammatory programs between the skin and target organs such as the kidney in lupus nephritis, especially those related to interferon-stimulated genes, chemokines, and infiltrating immune populations. These similarities support immunobiological convergence between tissue compartments, but do not by themselves demonstrate direct cellular migration or skin-organ causality. Finally, we discuss the role of phenotypic, serologic, and molecular stratification in identifying patients with CLE at risk of systemic progression. Hydroxychloroquine retains an established role in cutaneous disease control, whereas its potential disease-modifying effect on progression to systemic lupus erythematosus should be interpreted as emerging and non-definitive evidence. Similarly, therapies targeting the interferon pathway have shown benefit in populations with established SLE and cutaneous involvement, but their ability to prevent systemic progression in isolated CLE has not yet been demonstrated.

Keywords

Cutaneous Lupus Erythematosus, Sentinel Organ, Type I Interferon

1. Introduction

Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease characterized by marked clinical heterogeneity and multiorgan involvement, which complicates both early diagnosis and prognostic stratification. Globally, it is estimated that more than five million people live with SLE, with an approximate incidence of 5 per 100,000 person-years, although these figures vary considerably according to geographic region and the ethnic composition of the population [1] [2].

Epidemiologic studies have consistently shown a higher disease burden among women of reproductive age, as well as higher prevalence and severity among individuals of African ancestry and Hispanic populations. In these groups, SLE is not only more frequent, but is also associated with faster progression toward organ damage, including renal and cardiovascular involvement [3] [4].

These differences reflect the interaction among genetic, environmental, hormonal, and immunologic factors that shape the clinical expression of lupus. Within this spectrum, cutaneous lupus erythematosus (CLE) has traditionally been considered a predominantly dermatologic manifestation; however, a subgroup of patients develops systemic disease during follow-up, with progression rates that vary according to cutaneous phenotype, inflammatory burden, and serologic profile [5].

Because cutaneous manifestations may constitute one of the earliest clinical expressions of lupus, dermatologists occupy a critical position in the early identification of patients at risk of systemic involvement. To reduce diagnostic delay, practical tools such as the mnemonic "LABS FOR SLE"—low complement lev-

els, ANA, blood count, serology, fatigue/fever, organ function, and renal assessment—have been proposed to identify warning signs and facilitate early coordination with rheumatology before the development of irreversible organ damage [6].

In addition, the clinical relevance of distinguishing between isolated CLE and CLE with subclinical systemic criteria or "laboratory SLE" has been increasingly recognized. The latter category includes patients whose clinical presentation is predominantly cutaneous, but who already have hematologic, immunologic, or serologic abnormalities sufficient to increase suspicion of systemic evolution. Factors such as younger age at diagnosis, darker skin phototypes, and high ANA titers have been identified as predictors of progression in recent cohorts [7].

The transition from CLE to SLE should not be interpreted as a uniform or inevitable process. Longitudinal studies show that the probability of progression varies widely across cohorts and depends on clinical subtype, extent of cutaneous disease, presence of autoantibodies, and coexistence of hematologic or complement abnormalities. In general terms, acute and subacute phenotypes show a closer association with systemic activity, whereas some chronic variants, such as tumid lupus, tend to remain confined to the cutaneous compartment [5] [8].

These observations have generated interest in understanding the skin not only as a target organ, but also as an immunologically active compartment capable of reflecting, amplifying, or anticipating relevant immune signals in patient subgroups. The skin has a complex immunologic architecture in which keratinocytes can act as effector cells, producing proinflammatory cytokines and type I interferons, even in the absence of viral infection. Likewise, environmental stimuli such as ultraviolet radiation can induce keratinocyte apoptosis, release of nuclear autoantigens, and activation of innate immune pathways [9].

In this context, we propose interpreting the skin as a "sentinel model" of systemic autoimmunity, understood as a conceptual framework that integrates clinical, serologic, and immunopathologic observations. This model does not imply that the skin is the demonstrated causal origin of SLE, nor is there direct evidence of cellular propagation from the skin to internal organs. Rather, it suggests that studying the skin may provide an accessible window to analyze shared immune mechanisms, identify higher-risk patients, and generate hypotheses regarding the transition between localized and systemic autoimmunity [10].

The objective of this review is to critically analyze the immunobiological convergence between skin and systemic disease in lupus, evaluating the available evidence on the cellular and molecular mechanisms involved, their level of experimental or clinical support, and their potential utility for risk stratification and the design of early intervention strategies.

2. Immunopathological Basis: Mechanisms of Cutaneous Activation and Systemic Signaling

The pathogenesis of cutaneous lupus erythematosus (CLE) involves a complex in-

teraction among innate immunity, adaptive immunity, skin-resident cells, and environmental stimuli. Within the framework of this review, these mechanisms are interpreted as evidence of local cutaneous immune activation and convergence with systemic lupus pathways, but not as a direct demonstration that the skin causally originates or propagates multiorgan disease.

2.1. Keratinocytes and Type I Interferon Signaling

Keratinocytes represent a central component of the cutaneous immune response. Experimental studies have shown that these cells can produce type I interferons, particularly interferon-kappa (IFN-κ), even in the absence of viral infection, thereby generating a basal state of immunologic activation [11] [12].

In this context, the keratinocyte is no longer considered a simple physical barrier, but rather an immunologically active cell, or "cytokinocyte," capable of expressing pattern-recognition receptors, responding to cellular damage signals, and secreting cytokines and chemokines such as IL-1, IL-6, TNF, CXCL9, and CXCL10. This functional capacity allows the epidermis to act as a local amplifier of inflammatory signals, modulating immune-cell recruitment and contributing to the persistence of cutaneous lesions [13].

The skin of patients with lupus may exhibit a state of immunologic priming even in clinically unaffected areas. In this scenario, overexpression of IFN-κ and activation of pathways such as JAK-STAT may lower the response threshold to environmental stimuli, particularly ultraviolet radiation [14]. The latter may induce keratinocyte apoptosis, redistribution of nuclear autoantigens, and release of nucleic acids, favoring activation of innate immunity and recruitment of inflammatory cells to the dermoepidermal junction [15].

Overall, this evidence derives primarily from studies in human biopsies, cellular models, and experimental analyses of keratinocytes; it supports local interferon-dominated cutaneous immune activation but does not by itself demonstrate systemic propagation from the skin.

2.2. Nucleic Acid Sensing and the cGAS-STING Pathway

The accumulation of nucleic acids derived from apoptotic cells constitutes a key stimulus for activation of innate immunity. The cGAS-STING pathway detects cytosolic DNA and promotes type I interferon production through activation of transcription factors such as IRF3 [16] [17].

In CLE, ultraviolet radiation, keratinocyte apoptosis, and deficient clearance of cellular debris may increase the availability of nucleosomes and other autoantigens. These stimuli can activate dendritic cells, keratinocytes, and other resident immune cells, generating an inflammatory microenvironment rich in type I and type III interferons [18] [19].

These mechanisms provide a plausible framework to explain local amplification of cutaneous inflammation; however, their role as a direct driver of progression from isolated CLE to SLE remains inferred and has not been demonstrated longi-

tudinally.

2.3. Neutrophils and Neutrophil Extracellular Trap Formation

Neutrophils contribute to lupus pathogenesis through the formation of neutrophil extracellular traps (NETs), structures composed of DNA, histones, and antimicrobial peptides with immunostimulatory capacity [20]. These components can activate plasmacytoid dendritic cells through Toll-like receptors, favor type I interferon production, and contribute to immune-complex formation [21].

In the skin, NETs may amplify local inflammation by increasing the availability of nuclear autoantigens and promoting nucleic acid-dependent innate signals. Nevertheless, the magnitude of their specific contribution to the transition from localized CLE to systemic disease remains uncertain.

The clinical heterogeneity of CLE is accompanied by immunologic heterogeneity. Molecular profiling and single-cell transcriptomic studies have identified variable cellular populations and inflammatory programs in cutaneous lesions, including activated keratinocytes, T cells, B cells, plasma cells with an interferon-stimulated gene signature, plasmacytoid dendritic cells, and NK cells [15] [22]. These findings support the existence of cutaneous endophenotypes, but their utility as a routine clinical stratification tool still requires validation.

The evidence on NETs is robust in SLE and systemic vascular damage, but their specific contribution to progression from isolated CLE to multiorgan involvement derives mainly from mechanistic extrapolations and indirect inferences.

2.4. Plasmacytoid Dendritic Cells and Interferon Production

Plasmacytoid dendritic cells (pDCs) constitute an important source of type I interferon in lupus. In cutaneous lesions, their presence has been associated with activation of interferon-dominated inflammatory programs and amplification of local immune responses [22].

The functional relevance of pDCs in the skin has been supported by early therapeutic studies. pDC depletion has been associated with reduced local type I interferon activity and improvement in cutaneous disease activity in patients with cutaneous lupus [23]. Likewise, BDCA2 blockade with litifilimab has shown efficacy in reducing cutaneous disease activity in patients with histologically confirmed CLE, with or without concomitant SLE [24].

This evidence derives from human studies in cutaneous tissue and clinical trials targeting pDC/BDCA2; it supports the role of these cells in local cutaneous inflammation but does not demonstrate that their modulation prevents systemic progression or that causal cellular trafficking exists from the skin to internal organs.

2.5. B-Cell Responses and Cutaneous Immune Organization

Affected cutaneous tissue in CLE may harbor populations of activated B cells, memory B cells, and plasma cells. Transcriptomic studies have identified signa-

tures associated with B-cell activation, plasmablast-like differentiation, and systemic activity in subgroups of patients with CLE [25].

These findings suggest that the skin may contain locally organized immunologic microenvironments capable of sustaining adaptive responses within the tissue. However, the presence of B cells or plasma cells in cutaneous lesions does not necessarily imply that the skin is the primary source of systemic autoantibodies. It may also reflect the local imprint of an already established systemic immune response.

The available evidence derives primarily from human transcriptomic studies in CLE biopsies; it supports a local cutaneous adaptive response but does not allow the conclusion that the skin directly originates systemic autoantibody production.

3. Molecular Convergence between the Skin and Target Organs

Recent transcriptomic analyses have identified shared inflammatory programs between lupus skin and target organs such as the kidney in lupus nephritis. These programs include interferon-stimulated genes, chemotaxis mediators, and signals associated with activation of infiltrating immune cells.

Nevertheless, these findings require cautious interpretation. Single-cell transcriptomic studies have shown that lupus skin and the kidney in lupus nephritis may share an interferon signature, but they also show important differences in cellular composition and in the effector profiles of infiltrating cells. Complementarily, integrative skin-kidney analyses suggest shared immunologic signatures and possible cross-tissue biomarkers, but their results should be understood as hypothesis-generating and not as definitive evidence of a skin-kidney causal pathway [26] [27]. In this sense, the skin may function as an accessible window for studying immune programs relevant to lupus, particularly those related to type I interferon, chemokines, and adaptive activation. However, molecular similarity between tissues does not amount to demonstration of a common origin, direct cellular migration, or causal propagation from the skin to internal organs.

The evidence in this subsection derives from human transcriptomic studies, including single-cell and integrative cross-tissue analyses; it supports immunobiological convergence between the skin and target organs, but does not demonstrate direct cellular trafficking or causality between compartments.

4. Cutaneous Phenotypes and Serologic Correlation

The clinical expression of cutaneous lupus erythematosus (CLE) reflects an underlying biological heterogeneity that can be partially captured through the integration of clinical, histopathologic, serologic, and molecular characteristics. In this context, the traditional classification based on the Gilliam-Sontheimer model remains a useful clinical framework, distinguishing between lupus-specific and lupus-nonspecific cutaneous lesions, as well as between acute, subacute, and chronic forms of cutaneous disease [28].

The Gilliam classification distinguishes lupus-specific cutaneous lesions by the presence of interface dermatitis. Among these, chronic cutaneous lupus erythematosus (CCLE), particularly its discoid variant, usually follows a predominantly localized course; however, patients with extensive or disseminated disease, or coexistence of multiple cutaneous subtypes, may have a higher probability of systemic manifestations during follow-up [5] [29]. In contrast, subacute cutaneous lupus erythematosus (SCLE) and acute cutaneous lupus erythematosus (ACLE) show a closer association with systemic activity. ACLE, which typically presents as malar erythema, usually correlates with systemic inflammatory activity and classic biomarkers such as anti-double-stranded DNA antibodies and complement consumption [30].

The association between cutaneous phenotype and serologic profile is particularly evident in SCLE, in which a high proportion of patients have anti-Ro/SSA antibodies. Ultraviolet radiation may favor redistribution of these autoantigens to the keratinocyte surface, facilitating immune recognition and contributing to cutaneous inflammation. In addition, anti-Ro/SSA antibodies have been associated with specific clinical manifestations, including secondary Sjögren syndrome and neonatal lupus. However, the presence of isolated autoantibodies should not be interpreted as a sufficient predictor of systemic progression. Risk stratification requires integration of the cutaneous phenotype, disease extent, coexistence of hematologic or immunologic abnormalities, ANA titers, complement consumption, and the appearance of extracutaneous clinical manifestations [5] [7] [31].

From a molecular perspective, transcriptomic and single-cell studies have shown that lupus cutaneous lesions are not immunologically homogeneous. Subpopulations of activated keratinocytes, T cells, B cells, plasma cells with interferon-stimulated gene signatures, plasmacytoid dendritic cells, and NK cells have been identified, with variations across cutaneous subtypes and between patients with or without systemic activity [22] [25]. These findings suggest that molecular characterization of the skin could complement clinical stratification in the future, although it does not yet constitute a validated tool for predicting systemic progression in routine practice.

The 2019 EULAR/ACR classification criteria incorporate cutaneous manifestations as relevant components within the diagnostic algorithm for SLE, in the context of antinuclear antibody positivity as an entry criterion. Lupus-specific cutaneous lesions contribute significantly to the total score, highlighting their clinical relevance in the comprehensive evaluation of patients with suspected lupus [32]. Nevertheless, there is a subgroup of patients with CLE and negative serology in whom the disease may remain confined to the skin, and progression to SLE is less frequent. This observation reinforces that cutaneous immune activation, although relevant, is not sufficient by itself to drive systemic disease, and that the transition toward a multiorgan phenotype depends on additional clinical, serologic, genetic, and immunologic factors [33].

From a risk-stratification perspective, factors associated with progression from

CLE to SLE can be grouped into three domains. In the clinical domain, risk appears to be higher in patients with ACLE, SCLE, extensive or generalized cutaneous disease, and coexistence of multiple CLE subtypes, findings consistent with reviews and cohorts on progression from CLE to systemic disease [5] [28]-[30]. In the serologic domain, ANA positivity, high ANA titers, hematologic abnormalities, complement consumption, and systemic autoantibodies, such as anti-double-stranded DNA, increase suspicion of systemic evolution [5] [7] [31]. In the demographic domain, younger age at diagnosis and certain skin phototypes have been associated with higher risk in recent cohorts [7]. These factors should not be interpreted in isolation, but rather integrated into a longitudinal assessment aimed at identifying patients with CLE who require close rheumatologic surveillance.

5. Therapeutic Implications

The management of cutaneous lupus erythematosus (CLE) should distinguish between interventions with established efficacy for controlling cutaneous disease activity and interventions whose potential to modify systemic progression remains hypothetical or supported by emerging evidence. In clinical practice, the primary therapeutic goals are to control cutaneous inflammation, prevent scarring, dyspigmentation, and irreversible damage, reduce recurrences, and minimize prolonged exposure to glucocorticoids. Clinical guidelines recommend strict photoprotection, smoking cessation, and the use of topical corticosteroids or calcineurin inhibitors as first-line therapy in localized disease; in patients with persistent, extensive, scarring, or topical treatment-refractory disease, systemic therapy is indicated [34]. In this context, hydroxychloroquine represents the cornerstone of systemic treatment for CLE. Accumulated evidence supports its efficacy in controlling cutaneous disease activity, with a favorable safety profile when used at weight-adjusted doses and with appropriate monitoring [35]. For this reason, it should be considered standard treatment in patients with clinically significant CLE, extensive disease, frequent recurrences, or insufficient response to topical therapy.

More recently, interest has emerged in its possible effect on progression from isolated CLE to systemic lupus erythematosus (SLE). In a longitudinal cohort of patients with isolated CLE, early initiation of hydroxychloroquine was associated with a lower risk of progression to SLE and a lower frequency of severe forms with organ involvement during follow-up [36]. However, this finding should be interpreted with caution, because this was an observational study, and indication bias, residual confounding, and baseline differences between patients treated early and those with delayed initiation cannot be excluded.

In contrast, the randomized trial of hydroxychloroquine in incomplete lupus did not definitively demonstrate that the intervention prevents the accumulation of classification criteria or transition to established SLE across all preclinical disease states [37]. Taken together, these data support a balanced interpretation: hydroxychloroquine has established support for cutaneous disease control, whereas

its possible role as a modifier of the systemic disease trajectory should be considered a promising clinical hypothesis, but not a demonstrated preventive intervention. The use of hydroxychloroquine should remain within a well-defined safety framework. Dose adjustment according to actual body weight, avoidance of unnecessary cumulative exposure, and periodic ophthalmologic monitoring are recommended, in accordance with current recommendations to reduce the risk of retinal toxicity and other adverse events associated with chronic treatment [38].

In patients with refractory CLE, therapeutic escalation should be directed toward controlling cutaneous inflammatory activity and reducing prolonged glucocorticoid use. Options include methotrexate, mycophenolate mofetil, dapsone, retinoids, and thalidomide, selected according to clinical subtype, disease extent, presence of scarring, comorbidities, teratogenic potential, and the individual safety profile [39]. These therapies should be interpreted primarily as strategies for cutaneous disease control; there is insufficient evidence to consider them preventive interventions for systemic progression.

The development of targeted therapies has reinforced the relevance of the type I interferon pathway and plasmacytoid dendritic cells in lupus. Anifrolumab, a monoclonal antibody directed against the type I interferon receptor, has demonstrated efficacy in patients with active SLE [40]. Nevertheless, this evidence comes from populations with established SLE, frequently with concomitant cutaneous manifestations, and not from cohorts with isolated CLE or studies designed to prevent systemic progression. Therefore, anifrolumab should be presented as a targeted therapy for active SLE with potential benefit on cutaneous manifestations, but not as a validated strategy to modify the course of isolated CLE.

In parallel, the pDC/BDCA2 pathway constitutes an emerging therapeutic axis. Litifilimab has shown efficacy in reducing cutaneous disease activity in patients with histologically confirmed CLE, with or without concomitant SLE [24]. Recent reviews on targeted therapies in CLE highlight that these advances open opportunities for more precise medicine, although longitudinal studies are still required to demonstrate an impact on systemic outcomes, organ damage, or modification of the natural history of the disease [41]. In addition, another trial of litifilimab in established SLE evaluated its effect in patients with active systemic disease, supporting the relevance of this pathway in lupus, but not allowing inference of prevention of progression from isolated CLE [42].

In summary, current therapeutic evidence is robust for cutaneous disease control in CLE, especially with general measures, topical treatment, and hydroxychloroquine; in contrast, modification of systemic progression remains an investigational objective. Patient selection for early interventions should be based on clinical and serologic stratification, longitudinal surveillance, and coordination between dermatology and rheumatology.

6. Conclusions

Cutaneous lupus erythematosus should be understood as a heterogeneous mani-

festation within the lupus spectrum, capable of reflecting local immune activation and, in specific subgroups, coexisting with clinical or serologic signals of systemic disease. The skin may be considered a proposed sentinel model, useful for organizing risk stratification, but not as the demonstrated origin of systemic autoimmunity.

The interpretation of this model requires caution. CLE phenotypes are diverse and do not necessarily share the same risk of progression; longitudinal evidence on transition to SLE remains limited and heterogeneous; and, although shared inflammatory signatures exist between the skin and target organs, causal cellular trafficking from the skin to internal organs has not been demonstrated.

From a clinical perspective, the identification of patients at higher risk should be based on the integration of cutaneous phenotype, disease extent, serologic profile, hematologic abnormalities, complement, demographic variables, and longitudinal follow-up. Hydroxychloroquine remains the cornerstone of systemic treatment for CLE because of its cutaneous efficacy, whereas its possible role in modifying systemic progression remains a non-definitive clinical hypothesis.

Overall, the study of the skin offers an accessible pathway to improve early stratification and guide interdisciplinary management. Validation of the proposed sentinel model will require well-phenotyped prospective cohorts and studies designed to determine whether early intervention modifies systemic outcomes, organ damage, or disease trajectory.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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