PATHOGENESIS OF SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS

REVIEW ARTICLE

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ABSTRACT

Subacute Cutaneous Lupus Erythematosus (SCLE) is a photosensitive form of lupus specific skin lesion which is strongly associated with the presence of anti-Ro/SSA autoantibody. The pathogenesis of SCLE includes genetic, environmental and immunologic factors. Recent studies provide strong evidences for the involvement of innate and cell mediated immunity, underlying the important role of plasmacytoid dendritic cells (pDC), IFNα and antibody depended cell cytotoxicity (ADCC). In addition, a variety of cytokines, chemokines and adhesion molecules have been found to participate in the expansion phase of the autoimmune effector mechanisms. This article summarizes the recent immunological findings and reviews the current mechanisms which are implied in the development of the disease.

INTRODUCTION

Subacute Cutaneous Lupus Erythematosus (SCLE) represents a distinct lupus-specific cutaneous lesion, intermediate between the acute lesion of malar rash and the chronic lesions such as discoid lupus or lupus profundus which usually cause scarring. SCLE is a photosensitive, non-fixed, non-scarring, exacerbating and remitting skin disease which commonly occurs in sun-exposed areas and may be generalized. It may present as a papulosquamous eruption that resembles psoriasis or as an annular lesion that resembles erythema multiforme. The most commonly affected areas are the shoulders, the upper back, the extensor arms and the V-area of the upper chest.
while the face and the neck are less commonly affected. SCLE presents in the third or fourth decade of life and women are 3-4 times more likely to be affected than men. Half of the patients who exhibit SCLE meet the diagnostic criteria for SLE and develop a less severe systemic disease although the skin lesions may be more refractory.

Sometimes, SCLE needs to be differentiated from other clinical subtypes of chronic cutaneous lupus erythematosus (LE) such as chronic discoid LE (CDLE), LE tumidus (LET) and LE profundus (LEP). Interestingly, 20% of patients with SCLE have concomitant CDLE. However, CDLE presents as one or more erythematous papules and/or plaques which are more likely to appear on the face, the external ears, the scalp, the extensor aspects of the forearms and the trunk and have a tendency for scarring and atrophy. LET corresponds to discoid, urticaria-like single or multiple plaques with a bright reddish or violaceous smooth surface on sun exposed areas. The eruption is remarkable photosensitive and persistent without a tendency for scarring. Histopathologically, is characterized by dermal inflammation and the absence of epidermal involvement. Finally, LEP is an inflammatory condition involving the subcutaneous adipose tissue (lupus panniculitis) and clinically presents as deep cutaneous nodules which are not painful and are symmetrically distributed on the upper arms and the face.

The pathogenesis of SCLE is multifactorial and although the exact cause remains unknown genetic, environmental and immunologic factors seem to contribute to the development of the disease. Recent genetic data has elucidated potential candidate genes for SCLE. Among the environmental factors, ultraviolet light (UVL) and drugs appear to play the most important role in the pathogenesis of SCLE and cutaneous lupus in general. Many studies have led to the postulate that innate
and cell mediated immunity participates in the development of the cutaneous skin lesions 12-15. Finally, a complex network of cutaneous cytokines, chemokines and adhesion molecules orchestrate and promote tissue injury observed in skin lesions of SCLE 16, 17. In summary, the etiopathogenesis of SCLE is considered to result from three distinct stages in genetic susceptible patients: initiation, amplification and maintenance of autoimmune response and finally induction of tissue injury.

**IMMUNOPATHOLOGY-HISTOPATHOLOGY**

Histological, LE-specific lesions share many common features but SCLE can be distinguished from the other forms 18. The major characteristics are moderate hyperkeratosis with focal disorientation and liquefactive degeneration of the basal layer, mild to prominent atrophy and periappendageal mononuclear cell infiltrate confined to the superficial dermis. A dermal edema can be also observed but basement membrane thickening and follicular plugging is minimal or absent 19. The inflammatory infiltrate of the characteristic interface dermatitis observed in SCLE lesions, consists mainly of activated T cells and macrophages. These inflammatory cells appear to be in close apposition to epidermal basal keratinocytes which undergo apoptosis and cytotoxic injury 18. **The interface dermatitis is characterized by a hybrid pattern comprising cell-poor vacuolar foci alternating with zones of lichenoid dermatitis** 20. Immunohistochemical studies including staining for the cytotoxic molecule granzyme B, revealed a significant lower expression in lesional lymphocytes of patients with SCLE compared to patients with CDLE 21. Furthermore, when analyzing the expression of both granzyme B and Tia1 in skin biopsies of patients with CDLE, LET, LEP and SCLE, it was found that
granzyme B and Tia1 positive cells were present in all subsets but their number was lower in patients with SCLE \(^15\). The above data suggest that the number of CD8 lymphocytes is lower in SCLE lesions compared to other clinical subtypes of cutaneous LE. Immunofluorescence studies demonstrate deposition of IgG immunoglobulin and/or complement components in a granular pattern at the dermal-epidermal junction, in about 60% of patients with SCLE. A dust like pattern of IgG deposition overlying epidermal basal cells and cells below the dermal-epidermal junction is considered by some investigators, a specific immunopathological feature of SCLE \(^22\).

Anti-SS-A/Ro and anti-SS-B/La autoantibodies have been strongly associated with cutaneous lupus and SCLE \(^23, 24\). Approximately 90% of SCLE patients have positive anti-Ro/SS-A antibodies \(^25\) while a smaller percentage is being positive for anti-La/SS-B \(^23\). Other autoantibodies such as antinuclear antibodies (ANA), anti-dsDNA and anti-Sm, have also been found in SCLE patients but less commonly than anti-Ro/SS-A \(^2, 25\). Previous studies have focused on the close association of antibodies against the Ro/SS-A antigen with the development of clinical symptoms \(^23, 26\). Deposition of immunoglobulins and complement at the dermoepidermal junction suggests a direct participation of anti-Ro/SS-A antibodies in the pathogenesis of SCLE. Several mechanisms though have been implicated in the pathophysiology of the disease including direct autoantibody effects, immunoglobulin deposits and cell-mediated immunity \(^27\).

Independently of the underlying immunological mechanisms that mediate the tissue damage, epidermal keratinocytes and especially the basal cells seem to be the major target of the immune system. Dermal-epidermal localization of immunoglobulins and complement possibly results from nuclear material deriving from apoptotic keratinocytes \(^28\). These nuclear autoantigens can react with circulating
autoantibodies and form immune complexes which precipitate and initiate tissue injury. Besides this model which is also observed in SLE and drug induced lupus, a direct effect of autoantibody has been also proposed as a possible mechanism for the pathogenesis of cutaneous lupus and SCLE. It has been previously shown that the binding of anti-Ro/SS-A antibodies to the surface of epidermal cells, is an important inducer of antibody-dependent keratinocyte damage in photosensitive cutaneous LE. In addition, these autoantibodies have been found to bind to UVB-irradiated human keratinocytes both in vivo and in vitro. It has also been shown that binding is dependent on UVB dose and glycation.

Antibody-dependent cell–mediated cytotoxicity (ADCC) and CD8+ cytotoxicity may also be involved in tissue damage. Keratinocytes can be killed both by complement-mediated cytotoxicity lysis and ADCC. Gershwin et al demonstrated a destruction of DNA-coated targets by lupus antisera and lymphocyte effectors. In a recent study Furukawa et al supported that keratinocytes from patients with SLE and SCLE showed enhanced cytotoxicity to UV radiation and to antibody-mediated cytotoxicity. More specifically, keratinocytes from SCLE patients have been found to be more susceptible to ultraviolet radiation-induced cytotoxicity and binding of anti-Ro/SS-A and showed significant ADCC after irradiation, incubation in their own patients’ sera and exposure to mononuclear cells from normal individuals. Furthermore, antiRo/SS-A IgG fractions induce enhanced cytotoxicity of irradiated keratinocytes from SCLE patients. Taking into consideration that basal keratinocytes are relative resistant to ultraviolet radiation-induced apoptosis while suprabasal keratinocytes undergo apoptosis in vivo after irradiation, it seems possible that suprabasal keratinocytes are the major targets of ADCC in SCLE lesions.
Tissue injury in SLE is mainly attributed to immune complex formation and deposition. This concept is also confirmed in SCLE skin lesions, since immunoglobulin and complement have been identified at the dermal-epidermal junction, leading to complement activation, membrane attack complex formation and cellular injury. Moreover, the presence of immunoglobulin at the dermal-epidermal junction is not always accompanied by tissue damage. Besides, the presence of a lymphocytic infiltrate implies a cell-mediated immunity. Recent findings suggest ADCC and CD8+ cytotoxicity as underlying immunological mechanisms responsible for the injury phase and the development of clinical symptoms. Taking together, we can speculate that immune complexes and a direct autoantibody effect possibly characterize the early phase of tissue damage. ADCC and direct T cell-mediated cytotoxicity probably occur later enhancing the inflammatory response. It appears that the injury phase of SCLE is a complex phenomenon, attributed to distinct autoimmune effectors mechanisms which include both humoral and cell-mediated immunity. The initial hypothesis of immune complex deposition has been enriched by new findings which point out the role of cell mediated immunity and provide new insights in our understanding the pathophysiology of the disease.

In another recent study, a quantitative immunohistochemical analysis of CD4+ T cells from patients with cutaneous lupus erythematosus including SCLE, revealed that the number of Foxp3+ Treg (CD4+ CD25+) was significantly reduced compared to that in lesions from patients with other inflammatory diseases. There was no correlation between disease subtypes and the frequency of Foxp3+ Treg in the skin of patients with cutaneous lupus erythematosus. Referring to the phenotype and number of Treg as well as to their sensitivity of apoptosis, no differences were observed in peripheral blood between SCLE patients and normal donors. The fact that Treg are reduced in skin lesions but not in peripheral blood of patients with CLE, reflects a
limitation of the disease to the skin while a systemic decrease could explain an involvement of multiple organs in patients with SLE. The relative lack of Treg could amplify the autoimmune process and enhance the inflammatory response in skin lesions of SCLE patients. However, a more careful interpretation is needed since this reduction could be the result of the disease process rather than a causative factor.

GENETIC CONSIDERATIONS

Multiple genes have been involved in the development of CLE and especially SCLE. It is well established that polymorphisms of genes encoding HLA, TNFa and complements molecules, have the strongest genetic association with SCLE. Specific combinations of these genes may determine individual susceptibility to SCLE. It is currently believed that a specific genetic background is necessary for peculiar environmental factors to act and lead the immune system to autoimmunity and SCLE lesions.

Firstly, the HLA1, B8, DR3 haplotype has been found in 25% of a cohort of SCLE patients and since then it has been widely extended. Subsequently, the HLA1, B8, DR3, DQ2, DRw52 and C4 null ancestral haplotype has been proposed as a susceptibility haplotype for SCLE, especially for patients with positive anti-Ro autoantibodies. In addition, HLA-DR3 women have been associated with SCLE, SLE and Sjögren syndrome as well as with the presence of anti-Ro autoantibodies suggesting a crucial immunogenetic role for the antibody production. In a past study, the presence of HLA DQ1 and DQ2 has been found to enhance the production of autoantibodies in patients with Sjögren syndrome. The mechanisms, by which the HLA genes are involved in the pathogenesis of the disease, have not been elucidated.
yet. It is well documented though that MHC loci influence many autoimmune diseases and many models have been proposed. It is generally accepted that HLA molecules are possibly involved in T cell repertoire selection and antigen presentation leading to abnormal autoimmune responses.

In addition, deficiencies of C2 and C4 components of complement have been associated with both SLE and SCLE. The majority of patients with C2 or C4 homozygous deficiency have anti-Ro autoantibodies implying a possible role for this antibody in the development of SCLE. In a recent study a homozygous single nucleotide polymorphism of the complement C1qA gene which encodes the A chain of the C1q complement component, has been associated with decreased levels of C1q and a SCLE phenotype. Similarly, patients with a complete deficiency of C1q, C1r or C1s are prone to develop SLE and present with photosensitive cutaneous lesions.

More specifically, Pickering et al supported that C1q component of complement is very important in the physiological clearance of apoptotic cells. Furthermore, complement deficiency states may lead to impaired clearance of immune complexes allowing subsequent deposition in tissues and injury via ligation of Fcγ receptors on leukocytes. Thus, another physiological activity of complement is processing and clearance of immune complexes and apoptotic cells. In this context, complement system contributes in the resolution of immune response and prevention of autoimmune phenomena.

Finally, a polymorphism of the TNFα gene promoter (-308A) has been found to encode increased expression of TNFα by UV-B irradiated keratinocytes and has been associated with SLCE lesions. However, the TNFα gene is located within the HLA region and thus shares the same extended haplotype with DR3, implying a possible linkage equilibrium. Evidence in SLE patients though, supports that each is likely to contribute independently to disease susceptibility.
THE EFFECT OF ULTRAVIOLET LIGHT

There is a clear relationship between ultraviolet light (UV) and photosensitivity in patients with SLE and SCLE. Photosensitivity is included in the diagnostic criteria of SLE while SCLE is considered to be the most photosensitive lesion of cutaneous lupus. The UV spectrum is divided into two major segments: UVB which represents the wavelengths between 290-320nm and UVA which consists of wavelengths between 320-400nm. Epidermis is a major absorbent of UVB and less than 10% penetrates to dermis. On the contrary, UVA penetrates to the dermis and contribute in altering structural and matrix proteins. Although solar light includes both UVB and UVA, UVB is more efficient in evoking photosensitive responses and has been markedly involved in forms of CLE \(^{10,51-53}\). However, UVA has been also found to induce lupus skin lesions \(^{11,27,54}\).

DNA damage and apoptosis

UV light is capable of DNA damage. More specifically, UVB can cause excitation of DNA molecules leading to formation of pyrimidine dimmers acting on a direct way \(^{55,56}\). On the contrary UVA seems to damage DNA indirectly via a photosensitized reaction by modifying singlet oxygen generating purine bases \(^{55,56}\). Altered DNA molecules with specific modifications might possess immunogenic properties and in combination with a possible insufficiency of repairing mechanisms could lead the immune system to autoimmunity. Consistent with this speculation is
the observation that SLE patients can develop immune responses to UV altered DNA molecules.\(^5^7\)

Apoptosis is considered a programmed cell death which is characterized by specific steps such as DNA cleavage and fragmentation, nuclear condensation, surface blebbing, cytoplasmic contraction and finally packaging of cellular components within membranes and formation of apoptotic bodies. During this process toxic agents such as cytolytic enzymes are released and many self antigens can be redistributed and presented to the immune system. In addition, enzymatic degradation can cause alterations in these autoantigens and thereby increase their immunogenicity.\(^5^8\) Normally, apoptotic debris is eliminated by phagocytes and overexposure of autoantigens to immune system is prevented. Therefore, an increase rate of apoptosis or a decreased rate of clearance of apoptotic cells predisposes to autoimmunity.

UV exposure is known to induce apoptosis in keratinocytes although basal keratinocytes are more resistant than suprabasal cells.\(^3^7, 5^9\) UVB is considered to be a strong inducer of apoptosis and in that way enhances the exposure of autoantigens at the surface of apoptotic cells. Carrichio et al supported that UVB dose plays a crucial role in inflammation and autoantigens redistribution and determines the rate of apoptosis.\(^6^0\) Low and intermediate doses induce non-inflammatory apoptotic procedures while high doses result to proinflammatory necrosis. More specifically, UVB can cause an upregulation of both Fas and FasL leading to apoptotic death via the activation of this particular pathway.\(^6^1\) In cutaneous lupus lesions, the increased rate of apoptosis results to translocation and display of autoantigens such as Ro/SSA and La/SSB to keratinocytes cell surface. In a past study, it was demonstrated that UVB irradiated keratinocytes from SLE patients, underwent apoptosis and formed apoptotic blebs rich in lupus autoantigens including both Ro/SSA and La/SSB.\(^6^2\) This finding has led to the suggestion that these autoantigens can be phagocytozed,
processed and presented to lymphocytes and thus contributing to the beak of immune tolerance and generation of primary immune responses to self-antigens. Furthermore, Golan et al demonstrated enhanced membrane binding of antibodies to Ro/SSA and La/SSB to cultured keratinocytes of SLE patients after UV irradiation implying a possible translocation of these antigens to the cell surface.

Several studies supported a disturbed clearance of apoptotic cells in SLE. More specifically, macrophages have been proposed to exhibit impaired clearance capacity of apoptotic cells. Furthermore, apoptotic neutrophils from SLE patients have been found incapable of binding the C1q component of complement, leading to accumulation of apoptotic debris. Similarly, C1q appears to bind directly to surface blebs of apoptotic human keratinocytes. It has been mentioned previously that decreased C1q levels have been also associated with the SCLE phenotype. The decreased rate of clearance and the subsequent accumulation of apoptotic debris predisposes to self antigen presentation and processing which may result to autoimmune responses.

**Apoptosis, inflammation and type I INFs**

Besides, apoptosis has been also associated with the development of inflammatory skin lesions in SLE. Macrophages that have ingested apoptotic cells seem to release anti-inflammatory cytokines such as TGFβ and thus a decreased clearance rate enhances an inflammatory profile which can induce autoimmune procedures. It has been supported that apoptotic cells can interact with Fcγ receptors on phagocytes and thereby activate the latter cells and promote the inflammatory response in SLE. In the skin of patients with SLE, it has been shown that DNA and RNA particles released from apoptotic cells can induce the production of IFNα by plasmacytoid dendritic cells. In a past study, Farkas et al found that pDC were
present at skin lesions of patients with SLE and DLE suggesting that pDC are an important source of IFNα/β in cutaneous LE lesions. Activation of pDC leads to production of INFα which induces the secretion of specific chemokines such as CXCL9, CXCL10 and CXCL11. These chemokines are the major ligands of the CXCR3 which is expressed by skin homing lymphocytes and premature pDC and therefore contribute to the recruitment of inflammatory cells at skin lesions. Furthermore, in a recent study it has been shown that the expression pattern of interferon–inducible proteins including CXCL9 and CXCL10, reflects the characteristic histological distribution of infiltrating immune cells in different CLE subsets, including SCLE. More specifically, in SCLE lesions it was demonstrated an association between these specific chemokines and the distribution of CXCR3+CD3+ focused in epidermis and upper dermis. In another study, it has been shown that in patients with active CLE lesions, IFN-inducible chemokines such as IP10 and CXCL10 can lead to the recruitment of CXCR3 expressing T cells into the skin lesions, suggesting that type I INFs can induce a Th1-bias inflammatory immune response. These findings have revealed the important role of innate immunity and IFNα and open up options for novel therapeutic approaches in CLE.

**Cytokines and adhesion molecules**

UV light is also involved in cytokine expression, vascular activation and induction of adhesion molecules, chemokines and selectins which mediate the migration of inflammatory cells and lymphocytes to skin lesions of CLE. UVB can promote the release of proinflammatory cytokines such as TNFα and IL-1 by keratinocytes. These cytokines can cause upregulation of ICAM on keratinocytes and therefore account for the increased homing of leukocytes to the skin. Additionally,
TNFα is capable of inducing translocation of Ro/SSA and La/SSB autoantigens to the surface of keratinocytes and apoptosis via the TNFR1. Immunohistochemical studies in skin biopsies of SCLE patients who were receiving treatment, demonstrated that refractory lesional skin tissue displayed a strongly positive distribution of TNFα particularly in epidermis while no prominent staining was seen in non lesional skin from the same group or the control group. These findings suggest a potential role of TNFα in the pathogenesis of SCLE as well as a possible therapeutic target. UVA exposure can also promote IL-12 and IFN-γ production in the skin leading to a Th1 inflammatory response. Blood vessels and endothelium are also involved in SCLE lesions. Activated endothelium expresses a variety of adhesion molecules which mediate the recruitment and transmigration of leukocytes through vascular wall, at the sites of skin lesions. TNFα and INF-γ are potent inducers of ICAM-1 by the endothelium after UVB exposure while VCAM-1 has been found to be highly expressed by endothelial cells in skin lesions of lupus. Finally, E-selectin has also been found to be increased in lupus photosensitive lesions and after UVB exposure.

Although the data mentioned above are referring to SLE and cutaneous lupus, similar alterations in vascular endothelium and cytokines are implied in SCLE. It is obvious that the overproduction of proinflammatory cytokines affect both the inflammatory procedures observed in skin lesions and cutaneous endothelium. Keratinocytes are induced to express ICAM-1 which facilitates T-cell migration to the skin. The endothelium of cutaneous lesions is activated and expresses associated adhesion molecules such as ICAM-1, VCAM-1 and E-selectins which contribute to recruitment of leukocytes from the circulation to the inflammatory sites. Probably, LFA-1 is also upregulated on the surface of leukocytes and type I INFs promote the release of specific chemokines which further attract the inflammatory cells. This
complex network of cytokines and chemokines plays an important role in perpetuating and amplification of inflammation and therefore contribute to propagation and maintenance of the autoimmune procedures.

**OVERVIEW**

SCLE is the most photosensitive form of cutaneous lupus erythematosus and it has been associated with the presence of anti-Ro/SSA autoantibodies. Data over the past years support that the etiopathogenesis of SCLE share common features with SLE and the other forms of CLE, although it is considered a distinct skin lesion. It is well documented that specific genetic background is an important factor for the development of SCLE and many candidate genes have been identified. The ancestral haplotype HLA1, B8, DR3, DQ2, DRw52 and C4 null, deficiencies of C1q, C2 and C4 components of complement and the TNFα -308 polymorphism have been found to predispose to the SCLE phenotype. Although the exact mechanisms have not been established yet, it seems possible that this genetic susceptibility interferes with T cell repertoire selection and autoantigen presentation. The effect of UVL and especially UVB appears to play an important role at the initiation and maintenance of autoimmunity. UVL increases the rate of apoptosis of keratinocytes and causes redistribution of autoantigens such as Ro/SSA and La/SSB. The apoptotic blebs arise form the nuclear structures and harbor a variety of self antigens which are processed by phagocytes and presented to lymphocytes, leading to primary autoimmune responses. Impaired clearance of apoptotic cells results in accumulation of apoptotic debris and further enhancement of autoantigen presentation to the immune system. UVL also causes damage and alteration in DNA molecules which become more
immunogenic. These mechanisms participate in the induction phase and the loss of immune tolerance. In addition, persistent apoptosis activates phagocytes via the Fcγ receptors and contributes to the development of an inflammatory environment at the skin lesions. UVL induces the overproduction of proinflammatory cytokines including IL-1 and TNFα by the skin and the expression of adhesion molecules (ICAM-1, VCAM-1, E-selectins) by both keratinocytes and endothelial cells. Plasmacytoid cells produce high levels of IFNα which causes secretion of specific chemokines such as CXCL9, 10, 11 by keratinocytes and fibroblasts. This complex network of cytokines, adhesion molecules and chemokines participate in leukocyte recruitment at the skin and is responsible for the expansion phase through perpetuation and maintenance of inflammation. Finally, the injury phase is mediated by immune complexes deposition, direct autoantibody effect, direct T cell cytotoxicity and ADDC. Recent studies provide strong evidence for the dynamic role of the latter mechanisms and suggest further therapeutic approaches. The current immunological concepts in the pathogenesis of SCLE are summarized in Figure 1.

These new findings have improved our understanding of the genetic, environmental and immunologic mechanisms which are involved in the pathogenesis of SCLE. The variety of potent molecules and cytokines implies molecular orientated therapeutic strategies which include cytokine inhibition, direct T cell therapies and disruption of T cell interactions with adhesion molecules. The role of innate and cell mediated immunity has now become apparent and directs our insights into new researching fields.
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Figure 1. Current immunological concepts in the pathogenesis of SCLE.