Role of soluble and cell surface molecules in the pathogenesis of autoimmune skin diseases

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ABSTRACT

The skin is one of the most commonly involved tissue in rheumatic autoimmune diseases. Different mechanisms are thought to be implicated in the pathogenesis of skin lesions. In genetically predisposed individuals, ultraviolet (UV) light can contribute to the induction of skin lesions via an inflammatory process. UV light promotes the release of cytokines by keratinocytes and the induction of adhesion molecules on the surface of epidermal cells initiating a cascade of inflammatory events and recruiting immunoinflammatory cells into the skin.

In this review data regarding the expression of TNF-α in lesional skin tissue from subacute cutaneous lupus erythematosus patients and the role of interferons in the pathogenesis of skin manifestations of rheumatic autoimmune diseases are reported. In addition, an overview on the expression of cellular adhesion molecules in these diseases is provided.

UV light can also induce apoptosis in keratinocytes. During this cell death several enzymes became activated. Among them, desoxyribonuclease (DNase) is an enzyme involved in degrading DNA during apoptosis. Data regarding the activity of DNAse in patients with cutaneous lupus erythematosus as a possible risk factor for the development of systemic disease are here reported.

Introduction

Several soluble and cell membrane molecules are thought to play an important role in the induction and progression of skin tissue damage in rheumatic autoimmune diseases. Skin lesions are consequent to an inflammatory process in which cytokines and other soluble and cell surface mediators are involved. Tumor necrosis factor (TNF), transforming growth factor, interferons (INFs), and interleukins control and regulate the local immunoinflammatory response that leads to the characteristic skin tissue damage mediating the differentiation, maturation and activation of several cell types.

There is a documented relationship between exposure to sunlight and development of cutaneous manifestations in rheumatic autoimmune disease. In genetically predisposed individuals, the exposition to ultraviolet light acts as an inflammatory stimulus inducing the release of pro-inflammatory mediators and cytokines by epidermal cells in the exposed skin tissue. In particular, UV light triggers TNF-α release from epidermal cells, specifically keratinocytes. This pro-inflammatory cytokine in turn induces the release of other pro-inflammatory cytokines leading to a cascade of inflammatory events. In addition, TNF-α induces the activation of the Langerhans cells, a special type of antigen presenting cells, resident in the epidermis, via binding to the TNF receptor (TNFR) II present on the surface of those cells (1) suggesting a direct contribution of TNF-α to the pathogenesis of skin disease.

UV exposure induces also the release of IFNs, in particular IFN-γ. It has been shown that this cytokine is able to induce the expression of cellular adhesion molecules on endothelial cells. The enhanced expression of these molecules is an important step for promoting the leukocytes inflammatory cell recruitment to the skin. Adhesion molecules and their ligands can be targeted with pharmacological agents to block the inflammatory cascade leading to tissue destruction.

In addition, IFN-γ and UV light can induce apoptosis in keratinocytes and endothelial cells. During apoptosis several intracellular enzymes became activated and numeorus antigens are modi-

fied by the activated enzymes. In particular, deoxyribonuclease (DNase) is an enzyme involved in degrading DNA during this cell death. Several studies have suggested that the increased liberation or disturbed clearance of nuclear DNA-protein complexes after cell death may play a role in the induction of disease.

Apoptotically modified molecules can be relased by keratinocytes and/or endothelial cells from the cutaneous lesions into the circulation. Therefore, abnormal levels of these molecules (IFN-induced or UV-induced) can be identified as a systemic expression of a primarily localized skin tissue damage.

TNF expression in subacute cutaneous lupus

TNF-α is a proinflammatory cytokine with a wide variety of immunoregulatory functions in systemic lupus erythematosus (SLE).

High serum levels of this cytokines have been detected in SLE patients in correlation with disease activity (3). Even soluble TNFR (sTNFR) serum levels are increased in SLE compared to normal subjects and the levels of both receptors (sTNFRI and sTNFRII) seem to correlate with disease activity (3).

The increased TNF-α found in SLE sera is bioactive because it stimulates the surface expression of intracellular adhesion molecules (ICAM) on fibroblasts *in vitro* (4).

Moreover, TNF-α has been specifically immunolocalized in kidney sections from SLE patients with glomerulonephritis in correlation with histological activity (reviewed in 5). In particular, this cytokine is expressed in glomeruli mainly by infiltrating macrophages. Moreover, *in situ* hybridization studies have demonstrated that TNF mRNA is predominantly detected in macrophages and rarely in glomerular cells, suggesting that in the kidney TNF-α is mainly produced by non resident invading immune cells.

Subacute cutaneous lupus erythematosus (SCLE) consists of non-scarring, non-indurated papulosquamous or annular skin lesions that occur in characteristic photodistribution (6). SCLE lesions are associated with the polymorphism of -308A promoter of TNF-α linked to HLA-DR3 and with the presence in the patients sera of anti-Ro/SSA autoantibodies.

It thought that the etiopathogenesis of SCLE skin results from different factors (reviewed in 7) which may triggered the disease acting sequentially: 1) genetic predisposition (HLA-DR3 and TNF-α -308A polymorphism, complement components deficiency); 2) loss of immune tolerance induced by environmental factors (drugs/chemicals, UV, infections); 3) expansion and maturation of the autoimmune response (anti-Ro/SSA and anti-La/SSB autoantibodies, circulating immune complexes, autoreactive T cells); 4) clinical manifestations of the disease resulting from different mechanisms of tissue injury (autoantibody-mediated, immune complexes-mediated, autoreactive T cell-mediated).

The majority of SCLE patients can be treated with conventional topical and systemic therapy, but in approximately 25% of these patients skin lesions can be particularly severe and refractory to conventional therapy. There is strong evidence that thalidomide, a TNF-α blocking agent, can be very effective in the treatment of some refractory SCLE. However, the relevant side effects of this drug have to be carefully considered. In fact, thalidomide is highly teratogenic and can induce irreversible peripheral neuropathy in treated patients without any correlation with cumulative dosage (8).

Recently, data on TNF-α immunolocalization on excisional biopsies from lesional and non lesional sun-protected skin of SLE patients with specific and diagnostic cutaneous manifestations of SCLE has also been reported (9).

TNF-α serum levels were measured in SCLE patients and the tissue immunolocalization was investigated on frozen sections from 4 samples of active lesions of SCLE, 4 of normal human skin from sun-protected areas of the same patients, 3 samples of mycosis fungoides, 3 of cutaneous T-cell pseudolymphoma, and 2 of parapsoriasis as controls.

Positive staining was observed on keratinocytes of all layers of the epidermal compartment in lesional skin of SCLE samples, suggesting that keratinocytes are the major source of this cytokine during the cutaneous inflammatory process.

No correlation between TNF-α tissue localization and duration of skin lesions or systemic therapy has been observed in all patients. Samples of both the sun-protected normal skin from SCLE patients and the pathological skin conditions investigated were negative for TNF-α immunostaining.

TNF-α serum levels were found to be associated with diseases activity (ECLAM score), but no relation between the level of TNF-α in the sera and the intensity of the immunostaining on skin tissue was observed. These findings support the hypothesis that TNF-α is locally produced by keratinocytes and could have not leaked from the patient's circulation into inflammatory lesions, binding to TNF receptors locally. Similar findings of TNF-α skin immunolocalization have been reported in children affected with cutaneous neonatal lupus, a type of skin lesions which resembles SCLE (10). These data support the hypothesis of a pathogenetic role of this proinflammatory cytokine in the pathogenesis of cutaneous neonatal lupus and SCLE.

The direct involvement of TNF-α in the pathogenesis of cutaneous lupus erythematosus can explain the successful treatment of these manifestations with Thalidomide.

Recently, an open label study on SLE patients treated with anti-TNF-α antibody in addition to conventional therapy showed a clinical improvement in the inflammatory manifestation of the disease, although the development of ANA and anti-dsDNA autoantibodies in those patients has been reported (11). Moreover, the possible side-effect of anti-TNF-α therapy to induce cutaneous lupus erythematosus (CLE) in treated patients has also to be considered.

Successful treatment with TNF-α blockers in a patient suffering from SCLE (12) and TNF-α immunolocalization in the skin from SCLE patients suggest that anti-TNF-α therapy could be useful in the treatment of selected cases of refractory SCLE.

The INF-inducible IFI16 protein: a target of antinuclear antibodies in patients with SSc

Systemic sclerosis (SSc) is an autoimmune disorder of unknown aetiology characterized by severe and progressive cutaneous and visceral fibrosis, pronounced alterations in the microvasculature, and several cellular and humoral immunological abnormalities. Patients with SSc express a variety of autoantibodies that have their own clinical associations. Disease heterogeneity and difficulties in separating SSc from SSc-like conditions make a classification an important issue. Limited cutaneous (lc) and diffuse cutaneous (dc) SSc, with different severity and survival, have been recognized for several years as distinct subsets. This issue remains unsettled, but transition from one to the other is seldom seen, which could favour the former interpretation. Importantly, the two classical SSc-selective autoantibodies segregate clearly between the subsets, lcSSc being associated with anti-centromere and dcSSc with anti-topoisomerase antibodies. The lcSSc/dcSSc classification has now been widely accepted and used in numerous clinical studies and therapeutic trials.

Several lines of evidence link the IFNs to autoimmune disorders, in particular to SLE. Serum levels of IFN-γ are elevated in active SLE, and therapeutic IFN-γ has occasionally been noted to induce lupus autoantibodies and even clinical SLE. The prominent role of IFNs in the hierarchy of immune system mediators involved in SLE has been demonstrated recently by data from large-scale analyses of gene expression in peripheral blood mononuclear cells (PBMCs) from patients with active SLE and healthy control subjects (13). Expression of a spectrum of genes that constitutes an "IFN signature" is the most significant result from these studies and indicates that either type I or type II IFNs may be dominant among the pathogenic mediators involved in lupus. In contrast to SLE, the link between IFNs and SSc pathogenesis is much less defined, and so far is only supported by observations of SSc developing in association with the use of IFN-γ therapy in a case of myeloproliferative disorder or chronic viral hepatitis (14).

One family of IFN-inducible genes is designated HIN200 in the human and IFI200 in the murine species, and encodes evolutionarily related human (IFI16, IFIX, MNDA, and AIM2) and murine proteins (p202, p203, p204, p205/D3). The IFI16, p202, and p204 nuclear phosphoproteins are relatively well characterized with respect to their role in IFN action: these proteins are demonstrated to participate in the inhibition of cell cycle progression, modulation of differentiation, and cell survival (15). Generally, IFI200 proteins are thought to act as scaffolds to assemble large protein complexes involved in the regulation of transcription. The HIN200 proteins contain a 200-amino acid repeated that constitute the HIN domain, which is always near the C-terminus. The common domain architecture PYD-HIN of these protein family basically consists of one or two copies of the HIN domain and an N-terminal PYD domain, also named PAAD, DAPIN, or PYRIN domain after the protein Pyrin/Marenostrin, the product of the familial Mediterranean fever gene. The PYD domain is frequently found in regulators of inflammatory immune responses and apoptosis. Generation of mice congenic for the Nba2 locus (derived from the NZB strain of mice) interval on C57BL/6 background, coupled with gene expression analyses, has identified p202 as a candidate for lupus susceptibility (16). Studies also showed that increased expression of p202 in splenic cells (both B- and T-cells) correlated with splenomegaly and autoantibody production in female mice. Moreover, 29% of SLE patients were found to contain anti-IFI16 antibodies as shown by Western blot analysis, always accompanied by positive findings on indirect immunofluorescence for ANA, but were no further characterized in terms of antigen reactivity (17). Finally, serological analysis of antigens by recombinant cDNA expression cloning using sera from patients with Sjögren's syndrome (SS) identified IFI16 and two kelch-like proteins, KLHL12 and KLHL7, as novel autoantigens in SS (18).

The presence of autoantibodies against IFI16 protein in sera from both SSc as well as in SLE patients, but not from other autoimmune diseases such as rheumathoid arthritis (RA) and idiopathic autoimmune urticaria (IAU), or from healthy individuals has been demonstrated.

Anti-IFI16 antibodies were investigated by a "home made" ELISA, using purified recombinant proteins, which were produced in *E. coli* as His-tagged fusion proteins. Anti-IFI16 antibodies were detected in 26% (n = 100) of SLE, 21% (n = 82) of SSc, 4% (n = 50) of RA, 5% (n = 38) of IAU, and in 5% of healthy controls (n = 90). Antibody titers and prevalence were significantly higher in SSc and SLE than in sera from other patients or healthy individuals. Moreover a strict association with the limited cutaneous form of SSc was demonstrated, with a prevalence of 28% in patients with this phenotype compared to the 4% in sera from dcSSc patients. No association was found with other clinicopathological parameters, such as disease severity scale (measured by the procedure used by Medsger *et al*., 19), disability index (by Health Assessment Questionnaire, HAQ) or organ involvement. Interestingly, anti-IFI16 antibodies do not segregate with anticentromere or antitopoisomerase I antibodies, thus providing a novel tool in the differential diagnosis of lcSSc from dcSSc.

Vasculitis in autoimmune connective tissue diseases is not an uncommon complication. SSc is associated with reactive angiogenesis, but in spite of this the disease finally leads to irreversible loss of capillaries (20). The reduction in the number of capillaries is associated with endothelial swelling, basement membrane thickening, and hyperplasia of the intima with infiltration of inflammatory cells in the skin.

Prominent IFI16 expression is seen in vascular endothelial cells from blood and lymph vessels and in stratified squamous epithelia (21), suggesting its possible link to inflammation in addition to hematopoiesis. Consistent with this hypothesis, transduction of IFI16 into

human umbilical vein endothelial cells (HUVEC) with a herpes simplex virus (HSV)-derived replication-defective vector efficiently suppressed formation of capillary-like structures *in vitro* and cell-cycle progression, associated to cell death (22). It is therefore conceivable to hypothesize that the release of nuclear proteins by endothelial cells from the cutaneous lesions, undergoing apoptosis and necrosis, triggers the immune system leading to the production of autoimmune antibodies among which anti-IFI16 antibodies appear to play a prominent role.

Plasmacytoid monocytes/interferon producing cells in SLE

SLE represents a prototype of autoimmune diseases, where both T cells and B cells are believed to be involved in the pathogenesis of the disease. Recently, several observations have suggested a role of plasmacytoid monocytes/interferon producing cells (PM/IPC) in SLE. For example, serum IFN-γ levels coincide with disease exacerbations and SLE and SLE-like conditions may develop in patients treated long-term with IFN-γ (23). By global gene expression profiling of PBMCs, it has been demonstrated that dysregulated expression of genes in the IFN-γ pathway distinguishes most SLE patients from healthy controls. This IFN "signature" identifies a subgroup of patients with more severe disease and can be shut down upon treatment with high-dose glucocorticoids (24).

Since the number of circulating plasmacytoid monocytes/interferon producing cells (PM/IPC) is decreased in patients with SLE, persuasive evidence for a role of PM/IPC and IFN-γ in lupus pathogenesis is provided by the recruitment of PM to sites of tissue damage, such as skin (25) and lymph nodes (personal observation). It is also of interest that Jessner's benign lymphocytic infiltrate of the skin, in which clusters of PM/IPC are commonly observed (26), is considered by several Authors to be a variant of lupus erythematosus (*Lupus tumidus*).

Necrotic or apoptotic cells released material combined with autoantibodies induce IFN-γ production by PM/IPC (27), supporting the hypothesis that tissue damage occurring in SLE would lead to on-going hyperproduction of IFN-γ. Furthermore, this hyperproduction would in turn activate myeloid dendritic cells to stimulate auto-reactive T-cell clones and support B-cell proliferation and differentiation with generation of a high number of plasma cells producing autoantibodies. Evidence that PM/IPC actively produce IFN-γ in tissues has been provided by the demonstration of high levels of the an IFNγ-inducible protein MxA (28). Furthermore, a direct role of PM/IPC in tissue damage is suggested by their close relationship with epithelial structures (such as epidermis and hair follicles) typically damaged in SLE.

In analogy with lupus erythematous, PM/IPC are also recruited in lichen planus (LP) (29), a mucosal and skin autoimmune disease in which T cells eliciting a Th1 immune reaction occur. Active production of IFN-γ in LP biopsies was indicated by the demonstration of high expression of MxA (31), as well as IFI27, another IFNγ-inducible protein (30).

It should be noted that in both SLE and LP, PM/IPC might facilitate and amplify the cytotoxicity of surrounding cytotoxic lymphoid and NK cells by secreting Granzyme-B (31, 32).

The evidence that PM/IPC and IFN-γ produced by these cells are directly involved in SLE and LP may help to select patients who can benefit from therapies targeting the IFN-γ pathway. It is essential to understand how a physiologically protective molecule is rendered harmful in these diseases and then it would be of interest to investigate the regulation of mechanisms that normally inhibit INF-γ production (e.g., via BDCA2 and its ligand).

Adhesion molecules in autoimmune skin diseases

Cellular adhesion molecules (CAMs) and their ligands are necessary for cell-cell and cell-matrix contact in inflammatory responses, including activation, emigration and homing of lymphocytes, platelet activation and phagocytosis (33). CAMs are thought to participate in the pathogenesis of inflammatory diseases such as atherosclerosis, rheumatoid arthritis, SLE, psoriasis and other disorders. There are several lines of evidence for important roles for CAMs in autoimmune diseases, such as studies showing upregulated expression in tissues from patients with the studied disease, *in vitro* and animal model systems and clinical trials with anti-adhesion molecule/ligand.

CAMs in the skin

Intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1), are members of the immunoglobulin gene superfamily and are upregulated and/or induced on several cell types in the skin during inflammation (34). ICAM-1 is an 85-110 kD transmembrane glycoprotein, mapped to human chromosome 19 and constitutively expressed by a variety of cells but normally not by keratinocytes. Binding of ICAM-1 to its ligand, lymphocyte function associated antigen 1 (LFA-1), is the major pathway for activated keratinocytes and Langerhans' cells to interact with leukocytes, and mediates both antigen independent and antigen-dependent adhesion. ICAM-1 is induced or up-regulated by cytokines such as TNF-α, TNF-β , IL-1, and IFN-γ. The responsiveness to cytokines that induce ICAM-1 transcription differs between tissues, thus IL-1 induces ICAM-1 on endothelial cells but probably not on keratinocytes. ICAM-1 expression is maximal in basal, undifferentiated keratinocytes, induced by TNF-α and IFN-γ from dermal inflammatory cells as well as histamine from mast cells.

VCAM-1 is minimally expressed on resting endothelial cells, but is expressed by various cell types upon activation. IL-1 and TNF-α induce VCAM-1 on endothelial cells. The receptor for VCAM-1 is VLA-4 on monocytes and lymphocytes.

E-selectin (115 kD) is one of three proteins in the selectin family, encoded on the long arm of human chromosome 1. E-selectin is only expressed by activated post-capillary venules and shows specificity for skin homing lymphocytes. E-selectin recognizes the carbohydrate ligand Sialyl-Lewis X and is

upregulated by cytokines such as TNF-α, with a maximum expression after 3 to 4 hours after stimulation while P-selectin is induced on endothelial cells by inflammatory signals such as histamine within minutes.
Circulating forms of ICAM-1 and E-selectin are probably proteolytically cleaved at the cell membrane, and are biologically active in that they retain their binding function. Possible physiological roles for soluble CAMs are inhibition of binding by competition, or that the shedding of surface molecules is a process that serves to downregulate the adhesion of the relevant ligand.

Effects of UV radiation on CAMs
The effect of UV radiation (UVR) on CAMs expression has possible clinical implications for photosensitive disorders such as CLE (35).
Ultraviolet B (UVB) activates the NFκB, potential transcriptional activator for ICAM-1, in the cystosol of epidermal cells. A direct effect of UVA on transcription of the ICAM-1 gene has been shown via a singlet-oxygen-dependent mechanism. After UVB irradiation of cultured keratinocytes, a biphasic effect is seen on ICAM-1 expression with suppression in the first 24 hours and then upregulation. UVB irradiation of cultured human dermal endothelial cells has induced ICAM-1 but not VCAM-1 or E-selectin.
In vivo a dose- and time-dependent upregulation of ICAM-1, VCAM-1 and E-selectin have been shown in PPD reaction and polymorphous light eruption (PLE) as well as by UVA and UVB.

CAMs in autoimmune diseases in the skin
SCLE, erythema multiforme and lichen planus showed different epidermal expression patterns of ICAM-1 (36), and different patterns of ICAM-1 expression in the epidermis have been documented in CLE versus other cutaneous inflammation, and also between subsets of CLE. Endothelial VCAM-1 staining in CLE lesions and in non-lesional skin in SLE patients has been shown.
VLA-4 and LFA-1 have been reported to be overexpressed on lymphocytes from patients with SLE, VLA-4 only in patients with vasculitis. Different expression patterns of ICAM-1, VCAM-1 and E-selectin in SLE and SCLE patients compared to DLE and PLE patients were found in serial biopsies from evolving, experimentally UV-induced reactions, the differences were correlated to duration of lesion (37). More recently, the upregulation of ICAM-1 and HLA-DR showed similar expression patterns in LE tumidus (LET), discoid LE (DLE) and SCLE both in spontaneous and experimentally induced lesions, and dermal endothelium expressed ICAM-1, VCAM-1, E-selectin and P-selectin with no differences between these LE subtypes (38, 39).

Soluble CAMs
Elevated levels of soluble (s-)E-selectin was found in sera of photosensitive patients with widespread CLE lesions and increased levels of sICAM-1 and sVCAM-1 was found in SLE and SCLE patients (40, 41). Increased levels of VCAM-1 in SLE serum have been reported by several authors and correlated to disease activity and also in DLE patients, although to a lesser extent than in SLE (42). Increased levels of s-CAMs were found in sera from patients with bullous pemphigoid (BP) as well as upregulation of CAMs in their skin, while sE-selectin and the tissue expression of CAMs faded during metothrexate therapy (43, 44).

Possible new treatments
Treatment with anti-ICAM-1 antibody decreased the rejection of skin grafts in experimental animal models (45) and prevented neurological symptoms and vasculitic skin lesions in SLE-prone mice (46). Psoriasis can be treated with anti-CD11-a (LFA-1) efaluzimab, but there are currently no reports on treatment of CLE. Soluble E-selectin might be useful clinically as an activity marker but selectin deficient knock-out mice develop accelerated joint and kidney inflammation while loss of ICAM-1 significantly inhibits the development of arthritis and glomerulonephritis (47). Statins downregulate ICAM-1 and LFA-1 and have recently been proposed as possible new treatment for autoimmune diseases in the skin (48).

DNase activity in lupus erythematosus with cutaneous manifestations
Lupus erythematosus (LE) is a systemic autoimmune disease associated with a variety of autoantibodies directed to native or double stranded (ds) DNA, nucleosomes and ribonucleoproteins. In SLE the amount of circulating anti ds-DNA antibodies parallels the disease activity. The immune complexes accumulate in vessel walls, glomeruli, joints and cause the organ damage.
The etiology of LE is unknown, but several studies suggest that increased liberation or disturbed clearance of nuclear DNA-protein complexes, after cell death, may initiate and propagate the disease. The clearance of nuclear DNA-protein complexes, after apoptotic cell death, is normally guaranteed by DNase 1, which is the major nuclease present in the serum, urine and secreta. Serum DNase 1 guarantees a fast and effective breakdown of chromatin during cell death by the combined cleavage of DNA and DNA binding proteins as well. The DNase activity in serum and urine of SLE-prone NZB/NZW mice is lower than in control mice (49). In DNase 1 deficient mice, a SLE-like syndrome develops with immune-complex deposition in glomeruli and high titres of anti ds-DNA antibodies. This strongly supports the pathogenetic role of DNase 1 in SLE (50). As for humans, two SLE patients with a heterozygous mutation in 2 exons of DNase 1, were shown to have a low DNase activity and very high serum titres of anti ds-DNA antibodies.
Furthermore, the presence of anti-DNase antibodies is another factor involved in decreasing serum DNase activity (51). About 62% of SLE patients sera are positive for anti DNase antibodies compared to only 8% of normal controls (51).
DNase activity in the serum of 59 patients (4 males and 55 females, mean age 52 years) with LE and prevalent cutaneous lesions were studied using an ELISA method (ELISA Orgentec Diagnostika GmbH, Mainz, Germany). The wells of the strips were coated with

a specific DNase substrate, in order to evaluate the degradation activity of the sera against DNase. Thirty-two patients had localized discoid LE, 7 patients had disseminated discoid LE, 8 patients had subacute cutaneous LE and 9 patients had other cutaneous lesions. Nine patients could be classified as having SLE according to ARA criteria (they had 4 or more ARA criteria) from a cutaneous point of view: 2 had a disseminated LE, 4 had a localised LE and 3 had a butterfly rash. In 11 patients the DNase activity was evaluated at least twice in 1 year.

DNase activity was also studied in the serum of 12 patients (control patients) with other autoimmune connective tissue diseases (scleroderma and mixed connective tissue disease). Four patients (7%) had reduced serum DNase activity (about 25%). Among them: 3 patients had localised LE and 1 patient had subacute cutaneous LE. Among the 4 patients with a decreased DNase activity, 3 had 4 or more ARA criteria (systemic disease) and 1 had 3 ARA criteria. The patient with subacute cutaneous LE and reduced DNase activity was controlled twice in a year and the DNase activity was found reduced in the two occasions. The other 10 patients, with a normal serum DNase activity, controlled twice a year showed normal values in both occasions.

All the patients with reduced serum DNase activity had positive antinuclear antibodies, 1 was also anti Ro/SSA antibody-positive and 1 was anti-Ro/SSA and anti-La/SSB positive. All the patients with reduced serum DNase activity had positive antinuclear antibodies, 1 was also anti-Ro/SSA antibody positive and 1 was anti-Ro/SSA and anti-La/SSB positive. All the controls had a normal serum DNase activity.

Genetic studies to evaluate if the patients with a decreased DNase serum activity had a DNase mutation were not performed and the possible presence of anti-DNase antibodies was not studied.

In conclusions, 7% of patients with LE and prevalent cutaneous lesions had a low DNase serum activity and the decrease of serum DNase activity is prevalent in patients with a systemic disease (3 out of 9 SLE patients). One patient without any sign of SLE, had low serum DNase activity.

These findings suggest that the patients with a decreased serum DNase activity should be controlled closely to prevent organ damages.

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