SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS
- A DECADE'S PERSPECTIVE -

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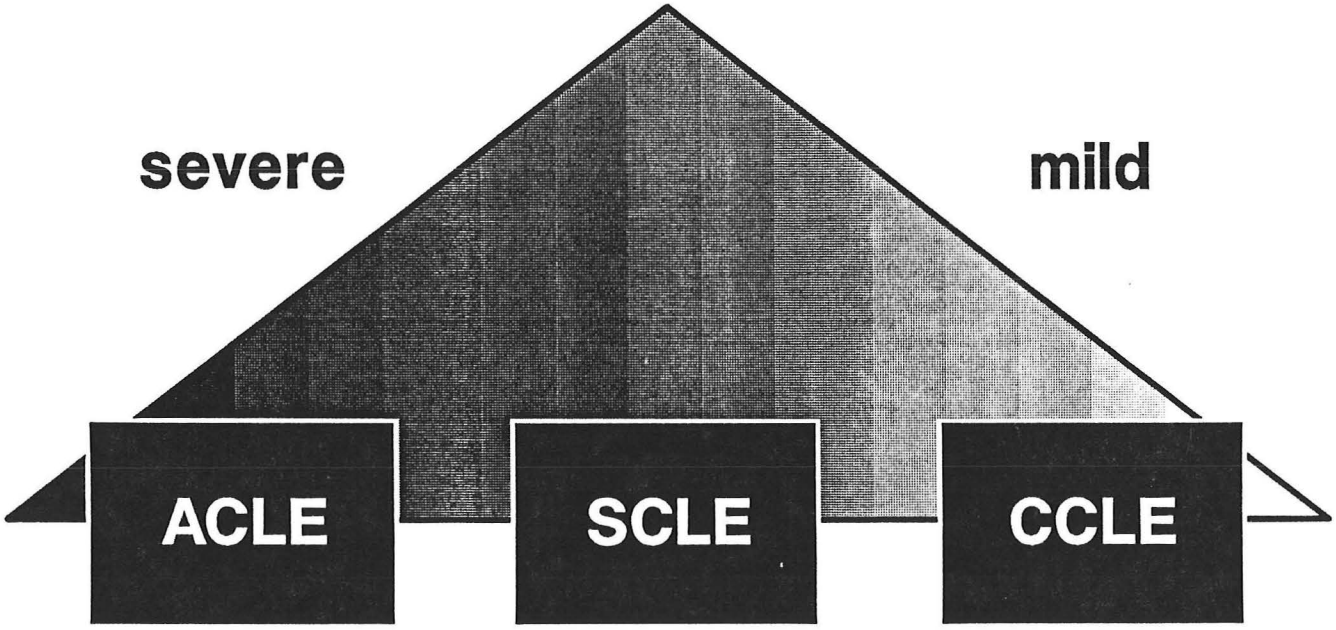
THE SPECTRUM OF LUPUS ERYTHEMATOSUS



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CLINICAL CONSIDERATIONS

The idea that patients who develop subacute cutaneous lupus erythematosus (SCLE) lesions might represent a clinically and immunologically distinct LE subset was initially suggested by Dr James N. Gilliam in 1977 (19) and formally presented by our laboratory in 1979 (59). In the ensuing ten years, this notion has received a considerable degree of attention within both the dermatology and rheumatology communities. Data have been formally presented on at least 200 SCLE patients in clinical series and more than 30 patients in case reports by labs other than our own. While this disease concept as originally presented has been accepted by most workers around the world, some have raised questions about the clinical, serological and genetic homogeneity of this LE subset. In addition, this disease concept continues to evolve because of recent observations documenting overlapp with immunologically related disorders such as Sjogren's syndrome and rheumatoid arthritis as well as the realization that drugs such as hydrochlorothiazide appear to be capable of triggering the clinical and immunological manifestations of this disorder. For these reasons it would appear justified to reassess the clinical concept of SCLE on this occassion of its tenth anniversary. To accomplish this goal, I will compare and contrast the results of our published and unpublished experience with over one hundred SCLE patients with that of a number of other workers around the world who have more recently presented a considerable degree of experience with such patients.

DISEASE MANIFESTATIONS

Our original concept of the unifying features of SCLE was based upon observations made during a point-prevelance, retrospective analysis of 27 patients whose mean disease duration had been 4.5 years. (57,59). The findings in a subsequent follow-up study involving a group of 47 of our patients whose mean disease duration had been 10 years (16,51,52) was not substantially different from the results of our original observations. We have now identified and personally examined at least 115 SCLE patients in our department over the past 15 years. While a number of interesting clinical features and disease associations have been observed while examining this larger group of patients, our view of the overall significance of this LE subset has not changed substantially from that presented in our original reports 10 years ago.

It should be emphasized at this point that our definition of SCLE has never required features other than nonscarring papulosquamous and/or annular skin lesions occurring in a characteristic, photoexposed distribution that have a LE-specific histopathology upon biopsy (1). It appears that some individuals have come to equate SCLE with the production of precipitating anti-Ro/SS-A (anti-Ro/SS-A) autoantibodies. It has never been our intention to imply that this diagnosis should be limited only to those patients who produce anti-Ro/SS-A antibodies, even though our studies have suggested that a considerable majority of SCLE patients do produce this autoantibody specificity at some point in the course of their disease.

Epidemiology

Most data suggest that SCLE lesions occur in 5-10% of total LE patient populations in the USA as well as a number of other nations around the world (Figure 1). We have found the proportional rate of SCLE to be 9% of all LE

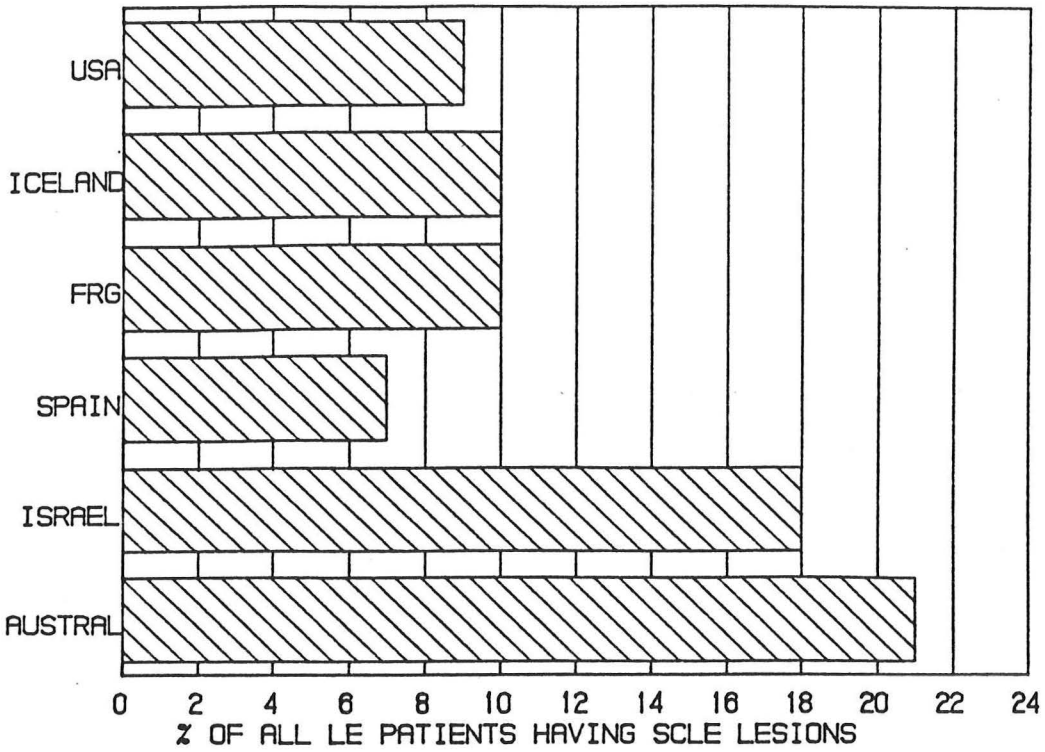

Figure 1 - Proportional rates of SCLE worldwide.

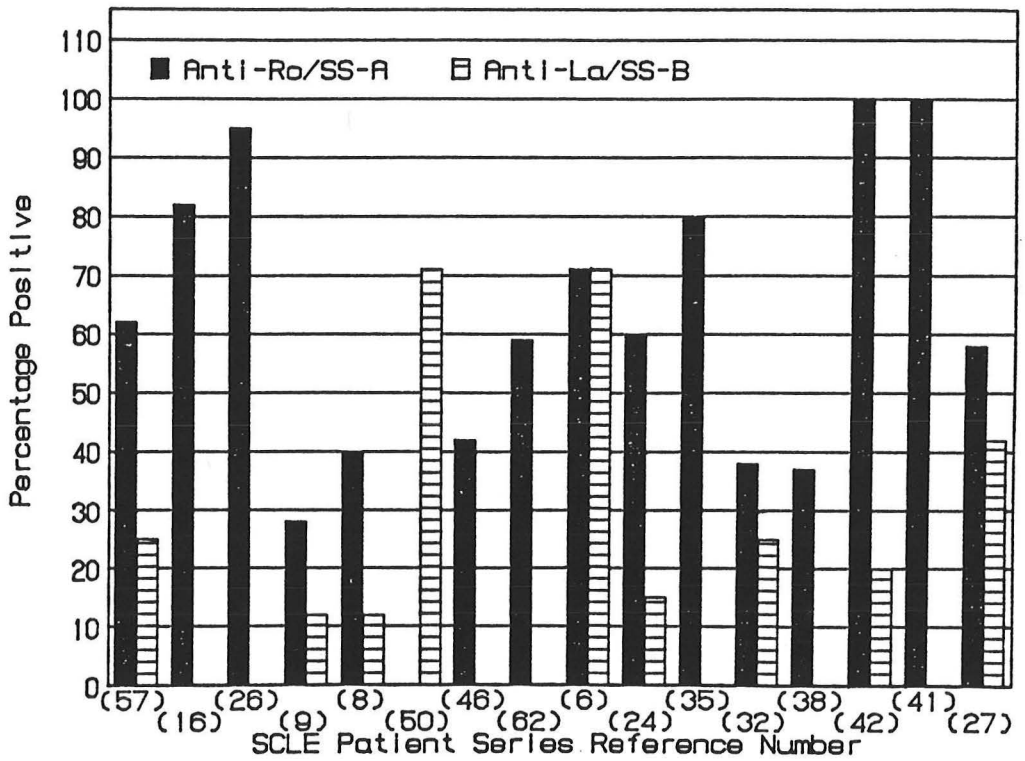

Figure 2 - Frequency of anti-Ro/SS-A and anti-La/SS-B autoantibodies in SCLE. A percentage of "zero" means that data were not reported for this variable in the indicated publication.

patients seen at our institution (59). Mooney and Wade have reported a 10% SCLE proportional rate in Iceland (35) while Kind and Goetz reported the same SCLE rate in West Germany (28). Herrero et al (24) have found that 7% of Spanish LE patients develop SCLE skin lesions. However, somewhat higher proportional rates have been reported in the Israeli (18%) and Australian (21%) LE populations (34,62). The proportional rate of SCLE in the Japanese population appears to be much lower than that for caucasoid populations.

Most of our cases of SCLE have occurred in young to middle-aged Caucasian females. Only 30% of our patients have been male. While at least one-half the entire patient population seen at our institution is black or hispanic, only 15% of our SCLE cases have occurred in these two racial groups. Similar demographic features have been noted in other SCLE patient series in this country (8) as well as Israel (34), Spain (24), China (50), and Sweeden (27).

Cutaneous Features

Virtually all our SCLE patients have had primary papulosquamous lesions that soon evolve into a psoriasiform or annular/polycyclic array predominately within a photoexposed distribution (see ref. #51,52,56,57,59 for detailed clinical descriptions and photographic documentation of SCLE lesions). While a few patients have had a combination of both psorisiform and annular lesions, the large majority have predominately had either one or the other lesional subtype. This has been the experience of others as well (9).

About one-half of our patients have had the psoriasiform array of lesions while the other half have had the annular/polycyclic configuration. Some investigators have noted a predominance of the annular pattern (75%-85%) (24,50) while others have seen a preponderance of the papulosquamous/psorisiform pattern (89%) (34). Callen and Klein's large clinical series was also enriched (67%) for patients having the papulosquamous array (8). Other than possible enrichment for anti-Ro/SS-A autoantibody production and the HLA-DR3 phenotype in SCLE patients with the annular type lesions (24,57), there have been no statistically significant clinical or laboratory associations with either of these two lesional patterns of SCLE skin involvement (9,16,57).

Several of our patients, each of whom has been positive for anti-Ro/SS-A antibodies, have had a more widespread array of confluent, pityriasiform lesions. Such patients have also been commented upon by others (26). On occassion, the early lesions of annular SCLE can closely simulate the appearance of erythema multiforme (56). In two of our patients the active borders of the annular SCLE lesions have undergone vesiculobullous degeneration both histopathologically and clinically. Such changes have also been reported by others (22,60) and have, in at least one such case, evolved into a picture simulating toxic epidermal necrolysis (4). The absence of follicular plugging, adherent scale with the carpet tack sign, and dermal atrophy distinguishes SCLE lesions clinically from those of chronic cutaneous (discoid) LE (DLE).

After the active inflammatory component of SCLE has subsided, a long lasting and occassionally permanent vitiligo-like leukoderma can remain. Whether this represents merely persistent, post-inflammatory hypopigmentation or an autoimmune state of melanocyte destruction as seen in true vitiligo has not yet be formally examined. Persistent telangiectasia can also be observed

within these leukodermatous areas, a clinical finding which can distinguish this from true vitiligo.

One unusual case of SCLE presented with the appearance of exfoliative erythroderma (17). We have also observed a patient whose annular lesions of SCLE were slowly replaced over a 8 year period by plaque-type morphea lesions (43).

It is now quite clear that other types of LE-specific as well as LE non-specific skin lesions can also be seen in SCLE patients (see Table 1). We noted during our initial observations that approximately 15-20% of our SCLE patients have also had DLE lesions at some point in their disease course (16,52,59). Other workers have noted somewhat lower frequencies of DLE in their SCLE cases (0%) (34), (10%) (50) while some have noted even higher rates (29%) (8). In most of our cases the DLE lesions have been localized to the scalp or face and have often predated the development of SCLE lesions. More recently, it has also become clear that some SCLE patients also develop classic malar (butterfly) erythema reactions (acute cutaneous LE) (20). In our patients this has usually occurred well after the appearance of SCLE lesions. Fifteen percent of our cases have taken this course, and as might be predicted, this subgroup of SCLE patients has had a higher frequency of severe systemic manifestations of LE including SLE nephritis. Interestingly, while all nine SCLE patients reported by Molad et al (34) were described as having acute cutaneous LE as well, none appears to have developed renal disease.

Our original study reported a 52% incidence of photosensitivity based upon rather rigid criteria (59). Our subsequent observations as well as the results of studies by others suggest that we initially underestimated the frequency of photosensitivity expressed by this patient group by a considerable degree. Photosensitivity has been noted in 100% of 21 patients by Hymes et al (26), 90% of 72 patients by Callen et al (8) and 70% of 13 patients by Herrero et al (24). In a more recent analysis of our data, sun sensitivity was noted in 85% of our cases (16). Curiously, Shi Shou-yi et al felt that only 27% of their 30 Chinese SCLE cases experienced a photosensitive component to their disease (50).

The other cutaneous findings which have been reported in SCLE patients are outlined in Table 1. As can be seen, subsequent reports have also suggested that we may have initially overestimated the frequency of non-scarring alopecia suffered by these patients. Mucus membrane lesions, periungual telangiectasia and livedo reticularis, found in one-third to one-fourth of our original patients, have been reported with similar to lesser frequencies by others. Raynaud's phenomenon, a relatively rare finding in our initial group of patients, has been seen to occur in 20-25% of SCLE patient in other series. Cutaneous vasculitis and sclerosis have been relatively rare findings in all studies to date.

Histopathology/Immunopathology

While most studies including our own have failed to identify discrete histological differences between papulosquamous/psoriasiform SCLE lesions and annular/polycyclic SCLE lesions, we have observed significant qualitative disparities between the pathologies of SCLE and DLE lesions. The lesser degrees of hyperkeratosis, perifollicular and deep perivascular inflammation

Table 1

CUTANEOUS FINDINGS IN SCLE PATIENTS

Cutaneous Feature	SCLE Patient Series						
	(n=27)[a]	(n=47)[b]	(n=49)[c]	(n=72)[d]	(n=30)[e]	(n=9)[f]	(n=13)[g]
Alopecia	59%	nr[h]	2%	4%	3%	78%	33%
Photosensitivity	52%	85%	86%	90%	27%	nr	70%
Mucus membrane lesions	37%	40%	2%	1%	nr	44%	38%
Livedo reticularis	22%	20%	nr	1%	nr	nr	0%
Periungual telangiectasia	22%	20%	51%	47%	7%	nr	38%
Discoid LE	19%	15%	35%	29%	10%	nr	0%
Acute cutaneous LE	nr	15%	nr	nr	7%	100%	nr
Vasculitis	11%	rare	12%	8%	7%	nr	nr
Raynaud's phenomenon	7%	rare	6%	rare	20%	22%	23%
Sclerosis	7%	rare	nr	nr	nr	nr	nr

[a] Sontheimer et al, 1979 (59)
[b] David et al, 1984 (16); Sontheimer, 1985 (51)
[c] Callen et al, 1986 (9)
[d] Callen and Klein, 1988 (8)
[e] Shou-yi et al, 1987 (50)
[f] Molad et al, 1987 (34)
[g] Herrero et al, 1988 (24)
[h] not reported

Table 2

SYSTEMIC FINDINGS IN SCLE PATIENTS

Systemic Manifestation	SCLE Patient Series						
	(n=27)[a]	(n=47)[b]	(n=49)[c]	(n=72)[d]	(n=30)[e]	(n=9)[f]	(n=13)[g]
Arthritis/arthralgia	74%	80%	43%	42%	67%	100%	46%
Fever/malaise	37%	nr[h]	4%	rare	17%	22%	nr
Myalgia	22%	nr	0%	rare	20%	nr	nr
CNS disease	19%	13%	6%	6%	0%	11%	8%
Renal disease	11%	8%	19%	14%	10%	0%	8%
Serositis	7%	10%	12%	nr	0%	0%	8%
4 or more ARA SLE Criteria	48%	62%	51%	50%	nr	nr	46%

[a] Sontheimer et al, 1979 (59)
[b] David et al, 1984 (16); Sontheimer, 1985 (51)
[c] Callen et al, 1986 (9)
[d] Callen and Klein, 1988 (8)
[e] Shou-yi et al, 1987 (50)
[f] Molad et al, 1987 (34)
[g] Herrero et al, 1988 (24)
[h] not reported

which we have found in SCLE lesions (1) does correlate with the lesser degrees of adherent hyperkeratosis, follicular plugging and dermal atrophy seen clinically in SCLE compared to DLE lesions. While others have made similar observations (35,117), some have not noted the same degree of difference in this regard (25).

Wechsler and Stavrides initially pointed out that the active edge of annular SCLE lesions can undergo a vesiculobullous change due to intense liquefaction degeneration of the epidermal basal cell layer (60). A similar case has been reported by Grant (22) and we too have seen two such cases. Herrero et al have more recently again emphasized this point (24), suggesting that such patients are more frequently positive for anti-Ro/SS-A antibody and the HLA-DR3 phenotype.

A granular, band-like array of immunoglobulin and complement deposits at the dermal-epidermal junction of lesional skin detected by direct immunofluorescence (the lupus band) was noted in 60% of our original SCLE patients (59). Similar findings were seen in only 46% and 26% of nonlesional deltoid and flexor skin forearm biopsies respectively (i.e., positive lupus band test). Subsequent studies by others have yielded similar results (24,26,50,62). Molad et al, however, reported a somewhat higher frequency of the lesional lupus band in a group of 5 SCLE patients (34).

Nieboer et al recently reported a "dust-like particle" pattern of intercellular and intracellular IgG deposition scattered throughout the basal layers of the epidermis and the subepidermal regions in 30% of SCLE lesional skin biopsies (38). They have suggested that this pattern, which is different than the lupus band, is specific for SCLE; however, others have disputed the specificity of this finding (118). This finding is strikingly similar to the array of human IgG deposition which has been reported to develop in human skin explants grafted onto nude mice following passive intravenous infusion of anti-Ro/SS-A antibody-containing human patient serum (30). In addition, we have recently observed a very similar pattern of human IgG and IgM deposition in guinea pig epidermis after intradermal injection of human anti-Ro/SS-A antibody-containing SCLE patient serum (personal unpublished observation). Neiboer et al, however, were unable to demonstrate a positive correlation between the presence of this dust-like particulate array of cutaneous IgG and circulating anti-Ro/SS-A antibody (38).

Systemic features

The frequencies with which the various systemic features have been observed in SCLE patient series consisting of 5 or more patients is presented in Table 2. Space limitations do not allow a more detailed analysis of the numerous individual SCLE case reports which have been published over the past 10 years. As can be seen, the more recently published data from clinical series have for the most part agreed with our initial impression that, overall, this is a relatively mildly affected subgroup of LE patients when compared to unselected systemic LE cases. However, from the perspective of the dermatologist who deals predominately with individuals who have DLE, this would appear to be a more severely affected subgroup of LE patients.

While approximately one-half of SCLE patients can be classified as having SLE by virtue of their having four or more of the American Rheumatism

Association's criteria for SLE, when systemic disease is present, it is most commonly manifested as inflammation of the musculoskeletal system. When central nervous system (CNS) involvement has been present, it has for the most part been relatively mild (i.e., otherwise unexplained seizure disorders, transient neuropsychiatric symptoms). Most workers have observed that renal disease occurs in no more than 10% of SCLE patients. Callen and coworkers have found a somewhat higher incidence of renal involvement in their patients and have suggested that SCLE patients overall represent a less distinct LE subset than we originally reported (8,9). They have suggested that differences in patterns of patient ascertainment might account for these results, with SCLE patients who are identified in a private practice setting being somewhat different from those who are seen at tertiary referral centers such as ours. I have formally presented elsewhere my views of the possible reasons for our difference of opinion on this point (54).

However, it is quite clear now that some SCLE patients do on occassion develop the more severe manifestations of SLE. During our follow-up study of 47 patients whose mean disease duration had been 9.9 years and whom we had personally observed for a mean period of 4.9 years, we found that 5 (10.6%) had died. However, only 1 of these 5 patients, a young white male with pancreatic vasculitis, had succumbed from LE-related complications. In addition, one of the surviving patients was found to have experienced several severe episodes of neuropsychiatric LE. Several of the SCLE/Sjogren's syndrome overlapp patients reported by Provost et al have also had similar complications (42). Weinstein et al have also reported two SCLE patients who developed severe renal and CNS LE respectively (61). In at least one of these two patients the SCLE lesions were accompanied by a "characteristic malar rash of SLE," (acute cutaneous LE). Callen and Klein also have also described several SCLE patients who have suffered functionally significant renal and CNS disease (8). Several of the originally designated "ANA-Negative SLE" cases had SCLE lesions as well as rather severe SLE (Dr. T.T. Provost, personal communication, 1988). In addition, one of Herrero et al's 13 SCLE patients developed CNS and renal SLE (24).

A great challenge for the future in this area of clinical research will be to identify prognostic factors that might more reliably predict the development of a severe systemic disease outcome in this LE subset. This was a major goal in our interim follow-up study in 1984 (16). Renal disease was identified in five patients (11%) in that cohort of 47 individuals. Each of these five cases shared the following features: papulosquamous SCLE lesional morphology, leukopenia, high titer ANA's (> 1:640) and circulating anti-double stranded DNA antibodies. Interestingly, each of these 5 patients had also developed acute cutaneous LE lesions at some point in their disease course and all had been refractory to antimalarial treatment alone. While it is not appropriate to draw conclusions from such a small subgroup of patients, I think that it is reasonable to suggest that the prognostic significance of these clinical and laboratory findings, which are summatized in Table 3, should be more carefully assessed in future studies. I should reiterate at this point that other workers have not found statistically significant clinical associations with the SCLE lesional subtype when entire patient populations have been analyzed (9). However, it is curious that the clinical series which has reported the highest incidence of accompanying renal disease has also been enriched for patients who had the papulosquamous/psoriasiform lesional subtype (9).

Table 3

Table 3

POSSIBLE POOR PROGNOSTIC FACTORS IN SCLE

CUTANEOUS FEATURES
Papulosquamous/psorisiform lesional morphology
Acute cutaneous lupus erythematosus
LABORATORY FEATURES
Leukopenia
High-titer ANA (> 1:640)
Anti-double stranded DNA antibodies

Laboratory Features

An overview of the different laboratory values which have been reported in SCLE patient series can be found in Table 4. The more recent analyses have not addressed the elevations of erythrocyte sedimentation rate (59%) and gamma globulin levels (30%) which we initially reported (59) often enough to determine the true frequency that these reflections of systemic inflammation are present in SCLE patients. There is general agreement that depressed complement levels and leukopenia occur in approximately 20% of SCLE patients. Molad et al's report that 100% of their patients had depressed C3 or C4 levels suggests the possibility that they might be dealing with SCLE patients who are genetically defficient in a complement component (34). Genetic defficiency of C-2 and C-4 has been documented to be asscoiated with SCLE (39,40). Anemia and thrombocytopenia appear to be unusual findings in SCLE patients.

Antinuclear antibodies (ANA) have been observed in a large majority of SCLE patients in most reports in which a human ANA substrate has been employed. Mouse or rat liver or kidney tissue sections (ANA substrates which are known to be relatively defficient in the Ro/SS-A antigenic epitopes recognized by human anti-Ro/SS-A autoantibody), were used in the three clinical series which have reported the lowest incidence of ANA (approximately 50%) (9,24,34). Precipitating antibodies to the nRNP (U1RNP) or Sm saline-extractible nuclear antigens have been seen only rarely. Antibodies to native or double-stranded DNA have been present in 10-20% in most studies. One report has indicated that single-stranded DNA antibodies can be seen in one-fifth of SCLE cases (9). Sporadic reports have suggested that approximately 20-60% of SCLE patients make anti-lymphocyte and anti-thyroid autoantibodies as well as circulating immune complexes. Rheumatoid factor production also appears to be a component of the autoimmune response exhibited by these patients and on occassion this has been associated with the development of full blown, erosive rheumatoid arthritis.

Biological false positive VDRL reactions, indicative of anti-phospholipid autoantibody production (53) have been reported in 7%-33% of SCLE cases. In a limited analysis of 10 unselected SCLE sera, we have found that only one (10%) had significantly elevated anti-cardiolipin antibody levels by enzyme-linked immunosorbent assay (personal communication, Dr. R.A. Asherson, 1987). Another of our patients who has had three episodes of deep vein thrombosis and theraputically refractory SCLE skin lesions was found to have high levels of IgG and IgM anti-cardiolipin antibody. Thus, while the anti-cardiolipin syndrome (53) can occur in SCLE patients, based upon these limited data, this does not appear to happen very commonly.

Immunogenetic Associations

In 1981 (58) and 1982 (57), we initially reported that SCLE patients have the rather homogeneous immunogenetic phenotype of anti-Ro/SS-A autoantibody production on a background of the HLA-DR3 tissue type. Callen and coworkers subsequently challenged the validity of our conclusions in this area (9). The basis for our differences of opinion was the subject of an in-depth discussion published elsewhere in 1987 (54). Since that time, additional data has been published which bear upon this point. This more recent information has been combined with the results of the earlier studies in this area and presented in Figure 2. Of the 15 published or in-press reports of which I am aware that

have presented data on anti-Ro/SS-A autoantibody production in 5 or more patients, 10 have found this autoantibody specificity in more than 50% of the SCLE cases examined. In all except one (9) of the remaining five reports, 37%-42% of the patients were anti-Ro/SS-A positive, a frequency well above the population average for unselected SLE cases (25%). Callen et al have suggested that SCLE cases which are seen in a private dermatology practice setting are less homogenous serologically than those ascertained in a tertiary referral setting (9). As might be expected from earlier work pointing out the "paired" nature of anti-Ro/SS-A and and anti-La/SS-B (La) autoantibody responses (12), anti-La antibodies are also seen in some SCLE patients. However, it is distinctly unusual to find patients who are producing anti-La but not anti-Ro/SS-A.

Unfortunately, fewer reports have presented HLA typing data on SCLE patients. Again, four of the six studies which have reported such data (Figure 3) have found that at least one-half of their patients possessed the HLA-DR3 phenotype. Again, Callen et al's two sets of data represent the exceptions (8,9). Provost has more recently suggested that SCLE/Sjogren's syndrome overlapp patients have the following extended HLA haplotype: HLA-B8, DR3, DRW6, DQ2 and DRW52 (41). It has been recognized for some time now that this is the particular genetic background upon which the highest levels of anti-Ro/SS-A autoantibodies are produced (2,23,119).

Genetic defficiency of complement, particularly C2 and C4, also appears to be a predisposing factor for the development of SCLE (39-40). In a patient who has heterozygous or partial defficiency of a single complement component, it can be quite difficult to determine whether low values for the routine clinical complement assays represent complement consumption secondary to systemic LE disease activity or genetic defficiency. However, in patients who have a complete (homozygous) component defficiency, the total hemolytic complement activity will be zero, a level which is difficult to achieve by consumption alone.

Figures 4 and 5 compare the frequencies of the various clinical and laboratory features which we observed in our original cohort of SCLE patients in 1979 to the average frequencies derived from a compilation of over 200 SCLE patients reported by other investigators during the ensuing decade. As can be seen, the subsequent reports have for the most part confirmed our initial impressions concerning these patients.

Treatment

The management plan for any patient with SCLE must always include provisions for the contingency that severe manifestations of SLE (i.e., nephritis, CNS disease) will occassionally supplant what otherwise is a relatively mild disease course. A more detailed discussion than is possible here of this issue as well as a review of the psychosocial aspects of this disorder and the specifics of cutaneous disease treatment have been presented elsewhere (55).

Local treatment of the SCLE lesions is usually not practical or effective. Topical corticosteroids alone usually fail to completely control skin disease activity. However, we have encountered several patients with rather limited cutaneous disease who have responded completely to the newer agent, clobetasol

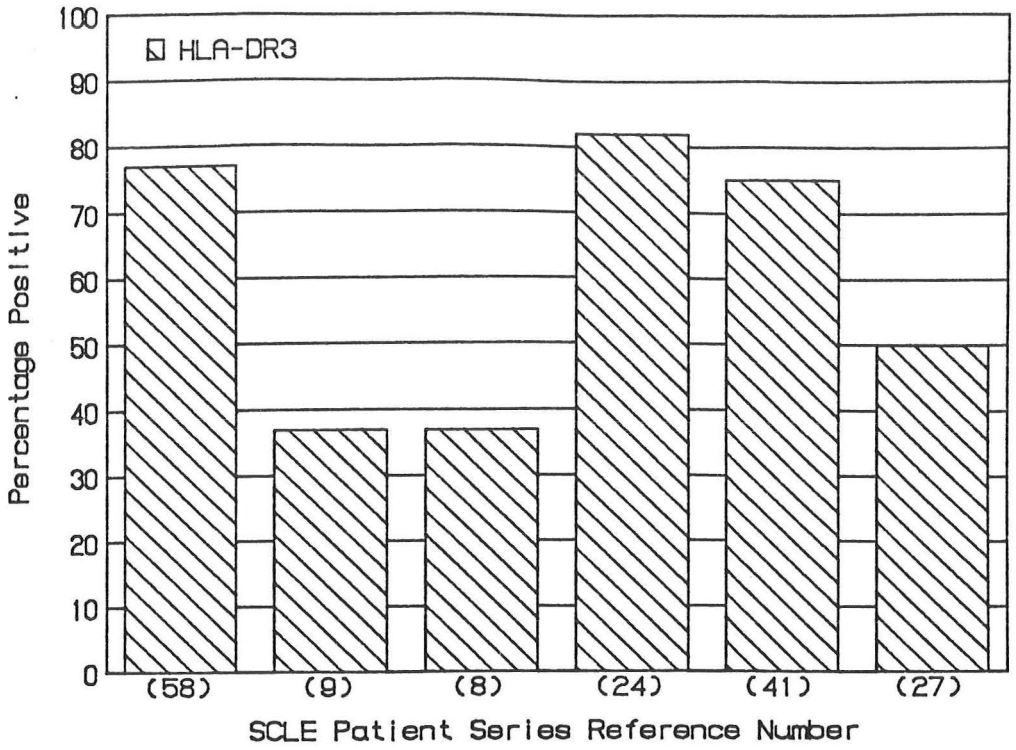

Figure 3 - HLA associations of SCLE

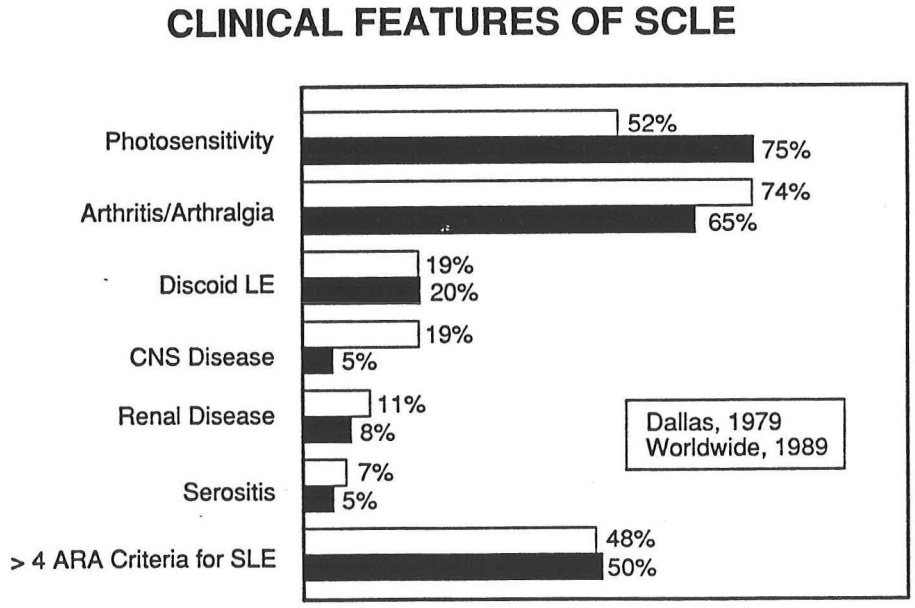

Figure 4 - Comparison of the frequencies of various clinical features observed in our original cohort of SCLE patients in 1979 to the averge frequencies of the same clinical findings in a compilation of 200 SCLE patients reported by other investigators around the world during the ensuing decade.

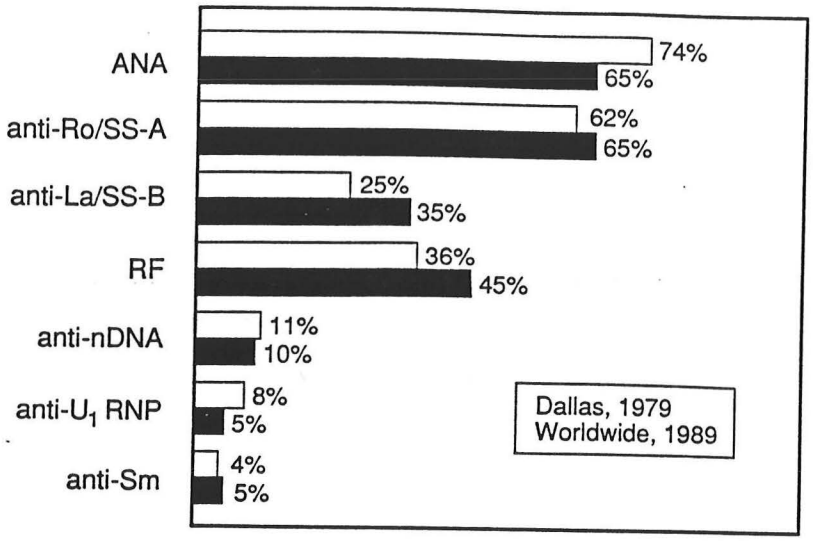

Figure 5 - Comparison of the frequencies of various laboratory features observed in our original cohort of SCLE patients in 1979 to the averge frequencies of the same laboratory findings in a compilation of 200 SCLE patients reported by other investigators around the world during the ensuing decade.

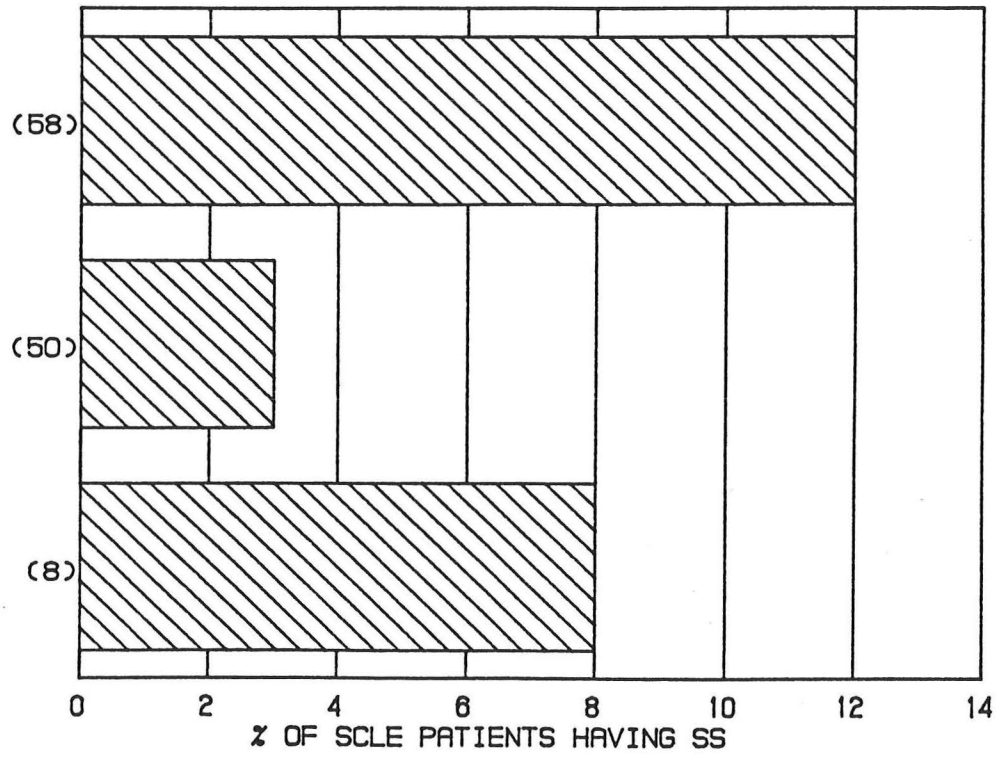

Figure 6 - Incidence of Sjogren's syndrome observed in three SCLE patient populations. The numbers in parenthesis on the vertical axis represent the SCLE patient series reference numbers. SS - Sjogrens syndrome.

propionate (Temovate). Others have also had good luck on occassion with topical corticosteroids (8). The SCLE lesions are usually too numerous and widespread for intralesional corticosteroid therapy to be feasible.

Every effort should be made to avoid the use of long term systemic corticosteroids to control skin lesions alone in these patients. While a brief course of these drugs can be used intially to more quickly gain control of the cutaneous and mild systemic disease manifestations than is possible with the aminoquinoline antimalarials, it should be remembered that with support and encouragement most patients can be successfully managed with these latter drugs alone. Some physicians fail to appreciate the fact that anitimalarials alone can have a steroid-sparing effect on the inflammatory musculoskeletal manifestations of this disorder, even though the saluatory effects might take 4-6 weeks to become fully manifestated. Thus, for those patients who will occassionally experience a flair of joint and muscle pain during periods of skin disease quiscence, a trial of antimalarial therapy alone should be considered. The complications of long-term, high-dose systemic corticosteroids in patients who have pedominately SCLE skin lesions, particulary skeletal effects such as avascular necrosis, can greatly overshadow the overall threat presented by the disease itself.

Hydroxychloroquine sulfate (Plaquenil: 200-400 mg/day) alone, or a combination of this drug with quinacrine hydrochloride (Atabrine; 100 mg/day) has successfully controlled 80-90% of our patients. A common error is to prematurely abandon these agents. It can take 4-6 weeks after starting or changing the dosage of one of these agents to see the potential of its full clinical effect. Patients should have ophthalmological exams every 6 months while taking hydroxychloroquine in order to detect the early, reversible manifestations of antimalarial retinopathy. However, this risk is very low when daily doses greater than 400 mg/day are avoided. A number of other agents have been used by ourselves and others for patients who do not respond adequately to antimalarials alone: dapsone (31), retinoids (47), oral gold (14), thalidomide (36), clofazamine (13) and occassionally immunosuppressive agents such as azathioprine, cyclophosphamide and methotrexate. The wisdom of casually using these latter agents in patients whose disease is limited predominately to the skin must be seriously questioned.

SCLE OVERLAPPING WITH OTHER RHEUMATIC DISORDERS

It is now clear that SCLE lesions can preceed or follow the development of other rheumatic disease (Table 5). We and others have followed SCLE patients who have later developed erosive, seropositive rheumatoid arthritis (RA) as well as RA patients who have subsequently manifested SCLE (7,11). This was not completely unexpected in view of the fact that as many as one-third of SCLE patients produce rheumatoid factor. At least one of our SCLE-RA patients has also developed Sjogren's syndrome.

Provost and coworkers have recently reported ten patients who have had both SCLE and Sjogren's syndrome (41,42). As with the SCLE-RA patients, there was no consistent relationship between the onset of the SCLE lesions and Sjogren's syndrome symptoms: some patients developed Sjogren's symptoms first while others had SCLE skin lesions as their initial disease manifestation. In 3 of these patients, clinically significant extraglandular manifestations of

Table 4

LABORATORY FINDINGS IN SCLE PATIENTS

Laboratory Measurement	SCLE Patient Series							
	(n=27)[a]	(n=47)[b]	(n=21)[c]	(n=49)[d]	(n=72)[e]	(n=30)[f]	(n=9)[g]	(n=13)[h]
↑ ESR	59%	nr[i]	nr	nr	nr	13%	nr	nr
↑ gamma globulin	30%	nr	nr	nr	nr	47%	nr	nr
↓ C3, C4, CH-50	22%	nr	19%	nr	26%	13%	100%	23%
Leucopenia	19%	nr	nr	24%	19%	50%	nr	23%
Anemia	15%	nr	nr	2%	4%	3%	nr	nr
Thrombocytopenia	nr	nr	nr	nr	nr	40%	nr	nr
ANA	74%	81%	81%	49%	60%	78%	55%	54%
anti-nRNP (U1RNP)	8%	nr	nr	2%	nr	19%	nr	0%
anti-Sm	4%	nr	nr	0%	nr	12%	nr	0%
anti-dsDNA	11%	21%	nr	2%	nr	10%	14%	15%
anti-ssDNA	nd	nr	nr	20%	nr	nr	nr	nr
anti-Lymphocyte antibody	33%	nr	nr	nr	nr	nr	nr	nr
anti-Thyroid antibody	nr	nr	nr	18%	nr	nr	nr	nr
Rheumatoid factor	36%	nr	48%	nr	nr	nr	nr	nr
Serum immune complexes	59%	nr	nr	nr	nr	40%	nr	nr
LE cell prep	55%	nr	nr	nr	nr	10%	75%	nr

[a] Sontheimer et al, 1979 (59); 1981 (58); 1982 (57)
[b] David et al, 1984 (16); Sontheimer, 1985 (51)
[c] Hymes et al, 1986 (26)
[d] Callen et al, 1986 (9)
[e] Callen and Klein, 1988 (8)
[f] Shou-yi et al, 1987 (50)
[g] Molad et al, 1987 (34)
[h] Herrero et al, 1988 (24)
[i] not reported

Table 5

DISORDERS WHICH HAVE BEEN REPORTED IN SCLE PATIENTS

RHEUMATIC DISEASES
- Sjogren's syndrome
- Rheumatoid arthritis

OTHER DISORDERS
- Carcinoma
  - breast, lung, gastric
- Sweet's syndrome
- Porphyria cutanea tarda
- Malabsorption
- Gluten sensitive enteropathy

Sjogren's syndrome, such as central or peripheral nervous system disease, has also been present.

Seventeen of our initial cohort of SCLE patients were analyzed for evidence of Sjogren's syndrome during a study of their HLA phenotypes (58). While none initially complained of dry eyes or dry mouth, a history of one or the other of these symptoms was found in 4 of 17 (24%) patients who completed a questionaire. However, only two of these four patients (12%) had objective evidence of xerophthalmia or xerostomia upon Shirmer's testing and minor salivary gland biopsy. We therefore concluded that the preponderance of the HLA-DR3 phenotype which we had observed in our SCLE patients was not due to underlying subclinical Sjogren's syndrome. Callen and Klein have noted an 8% incidence of Sjogren's syndrome in their analysis of 72 SCLE patients (8) while Shou-yi et al have observed this in only 1 of their 30 patients (3%) (50). While it is still not clear how often SCLE does overlap with Sjogren's syndrome, these data, which are summmarized in Figure 6, would argue that this is not a very common occurrence. However, since the clinical features of Sjogren's syndrome can be quite subtle, it will take a prospective analysis of a large group of SCLE patients to determine the true frequency with which these two disorders overlap will develop in the same individudal.

Annular SCLE is quite uncommon in Japan, however annular cutaneous erythema reactions are frequently seen in anti-Ro/SS-A autoantibody positive Sjogren's syndrome patients (120). These Sjogren's syndrome-associated annular erythema lesions generally lack the epidermal components of SCLE (i.e., liquefactive degeneration of the epidermal basal cell layer with associated scaling clinically, pigment incontinence with associated depigmentation clinically, and dermal-epidermal junction immunoglobulin/complement deposition). More recent data (121) has suggested that these findings are present occassionally in these annular erythema lesions, suggesting that possibility that such lesions could represent the incomplete expression of annular SCLE lesions perhaps due to immunogenetic differences in the Japanese population.

The development of Sjogren's syndrome in a SCLE patient raises at least one important clinical question: Are such patients at increased risk for developing B-cell lymphomas, especially following cytotoxic immunosuppressive therapy, as are Sjogren's syndrome patients in general?

OTHER POSSIBLE DISEASE ASSOCIATIONS

Some workers have suggested that SCLE can represent a paraneoplastic syndrome (29). Several case reports have suggested an association between SCLE and breast (37,48), lung (5) as well as gastric cancer (29). We have not personally seen SCLE related to malignancy. In addition, individual case reports have suggested an association with Sweet's syndrome (21), porphyria cutanea tarda (10), and gluten sensitive enteropathy/malabsorption (33,45). We have also seen two SCLE patients who have also had chronic active hepatitis (personal unpublished observation).

DRUG-INDUCED SCLE

In 1985, Reed and coworkers reported 5 patients who developed skin lesions with the clinical and histological features of SCLE as well as circulating anti-Ro/SS-A antibodies while taking hydrochlorothiazide (44). All patients

enjoyed resolution of their skin lesions with discontinuation of the drug. The one patient who was followed up was observed to have ceased producing anti-Ro/SS-A antibody after drug withdrawal. Other such thiazide-induced SCLE cases have subsequently been reported (3,15). In addition, cases with somewhat similar skin lesions have been reported to follow treatment with griseofulvin (122), procainamide (49) and oxprenolol (18). Unfortunately, the results of anti-Ro/SS-A antibody assays were not included in these latter two reports. We have also observed several hydrochlorothiazide-induced, anti-Ro/SS-A antibody positiive SCLE cases. In addition, we have seen single cases of penicillamine and sulfonylurea (glyburide)-associated SCLE. In at least one of these patients, the anti-Ro/SS-A antibody response appears to be directed toward Ro/SS-A epitopes other than those which are the usual targets of the anti-Ro/SS-A autoimmune responses that occur in SCLE cases which are not triggered by drugs (132). The HLA tissue types of these drug-induced SCLE patients have yet to be reported. In addition, the frequency with which drug-induced SCLE occurs in large populations of hydrochlorothiazide treated patients has not yet been determined.

SUMMARY AND CONCLUSIONS CONCERNING CLINICAL MANIFESTATIONS OF SCLE

Based upon the rather large worldwide experience which has been published recently, it would appear that the concept of SCLE as presented in our original reports starting ten years ago is still a viable one. However, now we must also consider the possibility that these patients will occassionally develop other types of autoimmune disorders such as rheumatoid arthritis and Sjogren's syndrome and on occassion have their skin disease triggered by drugs such as hydrochlorothiazide. Whether SCLE patients are at significantly increased risk for the development of internal malignancy has yet to be determined. Still, the majority of these patients will have recurrent skin disease activity and musculoskeletal symptoms as the major manifestations of their illness. Thus, patients with SCLE lesions do appear to occupy an intermediate position on the spectrum of lupus erythematosus. These patients fall somewhere between the polar extremes of the more mildly affected chronic cutaneous LE (discoid LE) patient group and the more severely affected acute cutaneous LE (facial butterfly erythema reactions) patient group (see Figure on cover of protocol).

While most of these patients do have a relatively mild disease course, a small percentage do seem to be at risk for developing potentially life threatening complications of systemic LE. The future challenge in this area will be to identify prognostic features which might correlate with this more aggressive disease course so that this subgroup of patients can be more effeciently managed. Our preliminary studies in this area have suggested several candidates for further study: the papulosquamous/psoriasiform SCLE lesional subtype, development of acute cutaneous LE, resistence to the theraputic effect of antimalarials alone, leukopenia, high titer ANA and the presence of circulating double-stranded DNA antibodies. Other possibilities might include the rate of systemic disease onset. Discoid LE patients who have not developed clinically significant systemic LE manifestations within the first two years of the appearance of their skin lesions have a very low risk for suffering from severe systemic LE complications later in their disease course. The same question might be asked of SCLE. In addition, some SCLE patients have a single episode of disease activity followed by long-term if not permanent remission. More needs to be learned about this more benign pattern of illness in the hope of identifying favorable prognostic signs. Most of our

impressions regarding SCLE disease outcome have come from retrospective or point-prevalence types of clinical analyses. More prospective examinations of large groups of patients will be required to better address the issue of prognosis in SCLE.

PATHOGENETIC CONSIDERATIONS

The skin is a major target organ in patients with lupus erythematosus (LE). In LE population studies, skin disease is second only to joint involvement in frequency of initial symptom presentation and cumulative percentage of involvement overall. Symptomatic or disfiguring cutaneous LE accounts for a considerable degree of the physical and psychological disability which results from this systemic autoimmune disorder. The immunopathogenetic mechanisms which are responsible for the characteristic pattern of lichenoid tissue injury that is seen in LE-specific skin lesions such as subacute cutaneous lupus erythematosus (SCLE), neonatal LE and discoid LE have not been fully elucidated. For the past 15 years, our laboratory has been devoted to the premise that a better understanding of the clinical and pathogenetic aspects of the different forms of LE-specific skin disease could yield important new insight into the pathogenesis of LE overall, and thereby provide improved management strategies for the systemic as well as cutaneous manifestations of this important human disorder.

An overview of our current understanding of the pathogenesis of lupus erythematosus (LE)-specific skin disease is presented as a framework for considering the specific immunopathogenetic mechanisms which might be responsible for the elicitation of anti-Ro/SS-A autoantibody associated skin disease subsets such as subacute cutaneous LE and immunologically related conditions like neonatal LE and congenital heart block.

OVERVIEW OF PATHOGENESIS OF CUTANEOUS LE

The characteristic histopathologic changes of LE-specific skin lesions include a perivascular and periappendageal mononuclear cell infiltrate rich in macrophages and activated T lymphocytes (113). These same inflammatory cells are also found to be intimately associated with a liquefactive or hydropic pattern of epidermal basal cell degeneration. An overview of the pathogenesis of these LE-specific histologic changes and LE-related photosensitivity is presented graphically in Figure 7.

The proposed mechanisms by which ultraviolet light exposure initiates or exacerbates cutaneous LE can be organized into three broad categories: 1) augmentation of release of epidermal and/or dermal inflammatory mediators, 2) induction of local and/or systemic immunoregulatory disorders, 3) induction of new antigens (neoantigens) within the epidermis or at the dermal-epidermal junction or the redistribution of autoantigens that are normally sequestered within epidermal cells.

Ultraviolet light exposure is known to enhance the production and/or release within different compartments of the skin of T lymphocyte activating cytokines such as ETAF (IL-1) and IL-6 as well as other inflammatory mediators like prostaglandins and histamine (63,73,74,78,108,111). Whether LE patients are genetically predisposed to abnormally enhanced responses of this sort has not yet been examined. Some of these substances such as IL-1 have T cell

chemoattractant activity and can promote T cell binding to microvascular endothelial cell surfaces. Such substances could promote the accumulation of neoantigen or autoantigen-specific T cells as well as antibody-dependent cell mediated cytotoxicity (ADCC) effector cells within the epidermis and dermis. It is also possible that UVL exposure might either directly or indirectly

Fig 7

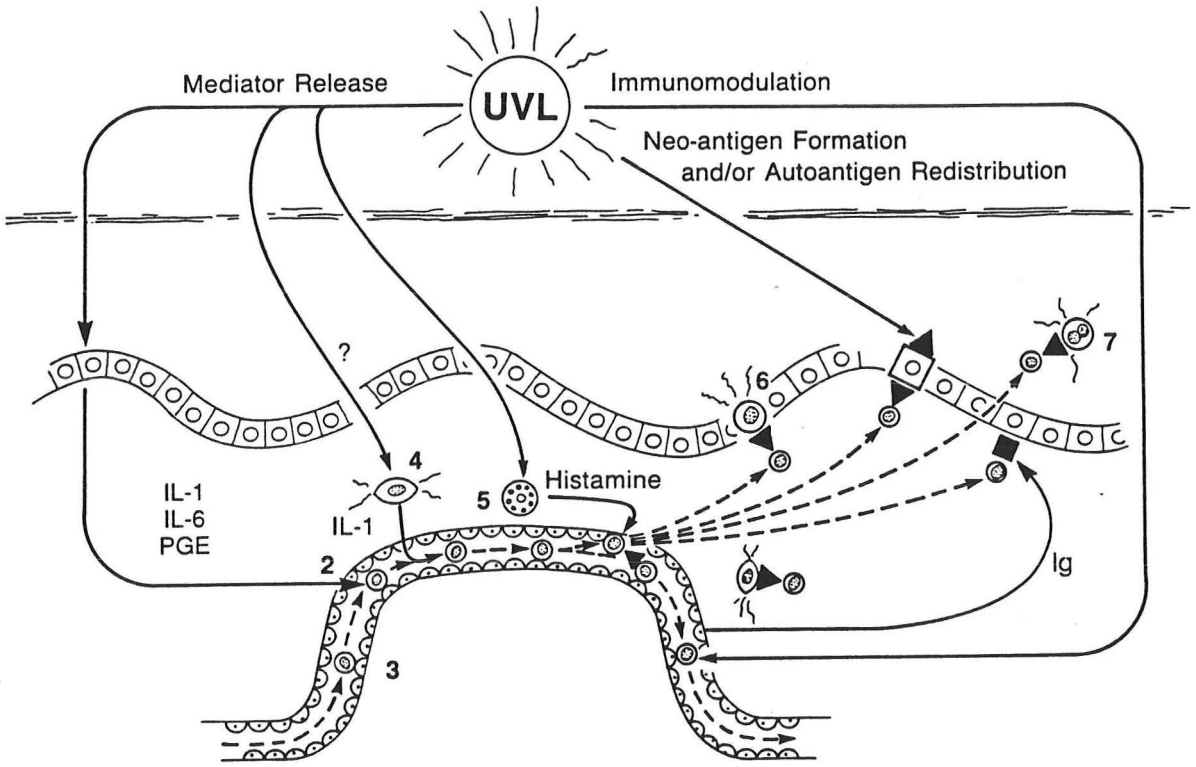

Figure 7 - Pathogenesis of LE-specific skin disease. The proposed mechanisms by which ultraviolet light exposure initiates or exacerbates cutaneous LE can be organized into three broad categories: (1) augmentation of release of epidermal and/or dermal inflammatory mediators (i.e., cytokines, growth factors), (2) induction of local and/or systemic immunoregulatory disorders, (3) induction of new antigens or the redistribution of autoantigens that are normally present within the epidermis or at the dermal-epidermal junction. Key to figure symbols: 1 - epidermal keratinocytes, 2 - circulating T lymphocytes, 3 - dermal microvascular endothelial cells, 4 - dermal perivascular dendritic cells, 5 - dermal mast cells, 6 - epidermal melanocytes, 7 - epidermal Langerhans cells, ▲ - neoantigens induced in epidermis by ultraviolet light exposure , ■ - autaontigen redistributed to surface of a keratinocyte by ultraviolet light exposure.

Table 6

TABLE 6

EVIDENCE FAVORING AND OPPOSING A DIRECT ROLE FOR ANTI-RO AUTOANTIBODIES IN THE PATHOGENESIS OF SCLE AND NEONATAL LE *

FAVORING:

1. Circulating anti-Ro antibodies are seen in 70-80% of SCLE and virtually 100% of neonatal LE patients.
2. Ro antigen is expressed in human adult, neonatal and fetal cutaneous and cardiac tissue.
3. In neonatal LE patients, the duration of cutaneous inflammation closely parallels the presence of placentally passaged maternal IgG anti-Ro in the newborn's circulation.
4. When human Ro antibodies are infused into nude mice bearing explants of normal human skin, preferential binding of the human anti-Ro to the human epidermal cells has been observed and UV-B light exposure appears to potentiate this pattern of anti-Ro antibody binding.
5. Ultraviolet (UV)-B light and estrogen pretreatment, perturbations which are relevant to the clinical manifestations of LE, have been shown to perturb the intracellular distribution of Ro antigens in human keratinocytes, inducing translocation of this antigen to the cell surface where it could be bound by anti-Ro antibodies present in the interstitial fluid.

OPPOSING:

1. Studies have failed to demonstrate a positive correlation between circulating anti-Ro levels and SCLE skin disease activity.
2. Primary Sjogren's syndrome patients have serum levels of anti-Ro that are equal to those of SCLE patients but only infrequently develop photosensitive cutaneous LE lesions.
3. Only a very small percentage of infants who are exposed to Ro antibody from their mother's circulation during fetal development actually develop NLE or CHB.
4. While the anti-Ro antibody that was passively infused into nude mice bearing grafts of normal human skin did bind preferentially to the human epidermal cells, no pathological injury could be detected as a result of this binding.
5. Whereas human IgG could be demonstrated in the cutaneous and cardiac tissue of newborn guinea pigs whose mothers had been injected with anti-Ro containing serum, neither skin nor heart pathology was found.

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enhance the expression of integrins such as ICAM-1 on dermal endothelial cells or epidermal keratinocytes (personal communication, Dr. David N. Norris). Preliminary findings also indicate that ETAF (IL-1) might enhance the expression in keratinocytes of cutaneous LE related autoantigens such as Ro/SS-A (personal observation, D. Sauder, M.D.).

Most of the earlier work which has examined the effects of UVL on immune regulation have been carried out in experimental animals. In such systems short term exposure with low doses of UV-B have generally resulted in decreased class II antigen expression and the generation of antigen-specific T suppressor cells. Since LE patients frequently have deficient suppressor cell function to begin with, it is conceivable that UVL exposure in an LE patient generates less down regulation in response to UVL induced antigens than would be seen in normal individuals. Recent studies have also shown that in vivo UVL exposure results initially in a decrement of class II antigen expression within the epidermis, however, 72 hours after exposure there was an increase in HLA-DR antigen-bearing, alloantigen-presenting cells (67). This UVL-induced influx of antigen presenting cells into the epidermis might facilitate T cell recognition of UVL-induced auto/neo antigens.

Earlier studies have documented that UVL exposure can produce at least one highly immunogenic neoantigen (i.e. thymine dimers) within the nucleic acids present in epidermal keratinocytes (98). In addition, it has been suggested that some LE patients are unable to repair such UVL damaged nucleic acid at normal rates (data reviewed in reference #68). It is therefore conceivable that the actived immune response of LE patients is regularly being challenged by potent immunogens created in the skin by UVL. There are a number of resident, class II antigen-expressing skin cells (epidermal Langerhans cells, dermal dendritic cells) that would be capable of presenting such UVL-induced antigens to CD4 positive T cells. In addition, a number of other resident skin cells (i.e., keratinocytes, dermal endothelial cells) express class I histocompatibility antigens which might endow them with the ability to present UVL induced antigens to CD8 positive cytotoxic T lymphocytes.

It is also possible that UVL might physically alter or disturb the cellular distribution of cutaneous autoantigens such as the Ro/SS-A ribonucleoprotein, thereby making this normally intracellular antigen more accessible to either Ro/SS-A autoantibody or Ro/SS-A antigen-specific T cells. The remainder of this discussion will focus upon this latter possibility.

Ro AUTOANTIBODY AS A DIRECT PATHOGENETIC FACTOR IN CUTANEOUS LE

A unifying feature of SCLE as well as neonatal LE and congenital heart block patients is the extraordinarily high frequency with which they are found to have circulating antibodies to the Ro/SS-A small cellular ribonucleoprotein (RNP) particle (54,57,80,86,102,106,107,112,115). An hypothesis which states that the characteristic patterns of cutaneous and cardiac tissue damage which are seen in these disorders might result directly from cellular injury that is triggered by anti-Ro/SS-A antibody binding to perturbed cellular Ro/SS-A antigen has been proposed by Norris et al (99) based upon data from several lines of investigation (Figure 8).

Observations which support a direct pathogenetic link between anti-Ro/SS-A antibody and cutaneous LE

Among these studies (summarized in Table 6) includes the observation that circulating Ro/SS-A autoantibody has been found in virtually all mother-neonate pairs affected with neonatal LE and congenital heart block (86,115) and in a large majority of SCLE patients (54,57,112). While La/SS-B antibodies are also frequently seen in this setting, Ro/SS-A autoantibody specificity represents by

Figs 8-9

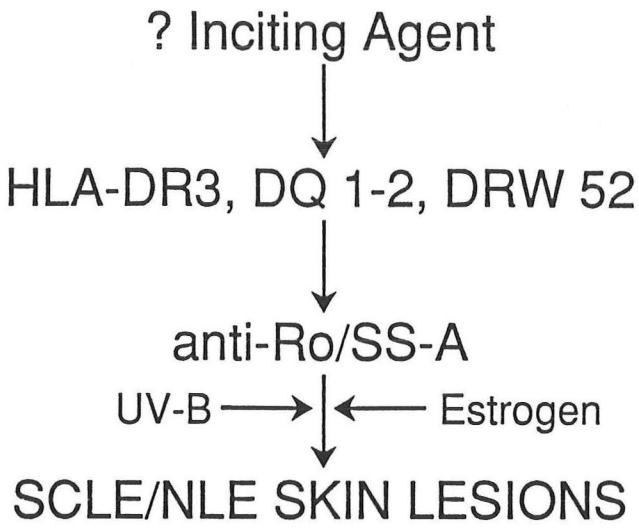

Figure 8 - Hypothetical pathogenesis of anti-Ro/SS-A autoantibody associated LE skin lesions such as subacute cutaneous LE and neonatal LE.

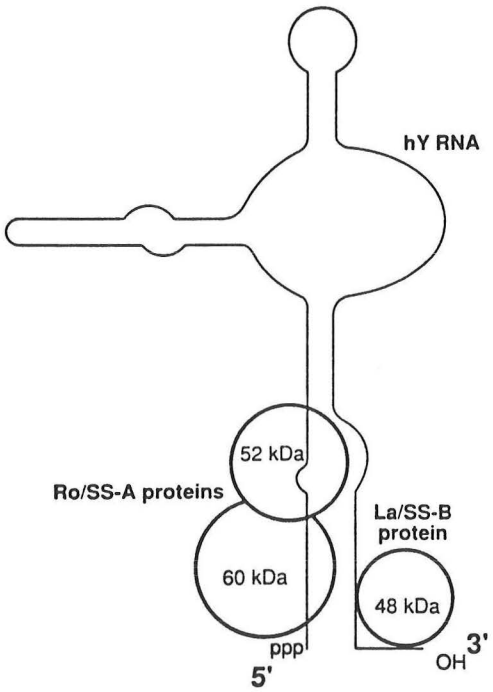

Figure 9 - Current model of the Ro/SS-A ribonucleoprotein particle.

far the strongest serological correlate of these clinical disorders. Ro/SS-A antigenic activity is expressed in human adult, neonatal and fetal cutaneous and cardiac tissue (69,81,85,114). Passively infused human anti-Ro/SS-A autoantibody has been shown to preferentially bind to the epidermal basal cell layer of normal human skin explants on nude mice (87) and ultraviolet B (UVB) light exposure appears to potentiate this pattern of antibody binding. In preliminary studies, passive transfer of human anti-Ro/SS-A serum to pregnant guinea pigs has resulted in anti-Ro/SS-A binding to newborn guinea pig cardiac tissue (82). Clinically relevant manipulations such as UVB light exposure or estrogen pretreatment appear to be capable of redistributing cellular Ro/SS-A antigenic activity to a position in the plasma membrane of human epidermal keratinocytes that is more accessible to binding by Ro/SS-A antibody (72,89). A direct immunofluorescence pattern of in vivo epidermal IgG binding that is associated with anti-Ro/SS-A (38,84) is suggestive of the array of Ro/SS-A antigen expressed in vitro at the epidermal keratinocyte plasma membrane following UVB exposure (89). The immunoglobulin class and subclass profiles of circulating Ro/SS-A autoantibodies found in SCLE patients are compatible with potentially pathogenic autoimmune responses such as complement mediated cytolysis or antibody dependent cell mediated cytotoxicity (ADCC) (93). Antigen-bound anti-Ro/SS-A is capable of triggering ADCC in vitro, a possible immunopathogenetic mechanism of cutaneous injury in non-scarring forms of LE-specific skin disease (100). The cell-poor lichenoid pattern of histopathologic injury seen in SCLE and NLE is compatible with an in vivo ADCC pathogenic reaction.

Observations which do not support a direct pathogenetic link between anti-Ro/SS-A autoantibody and cutaneous LE

Several clinical and experimental observations, however, are not consistent with the idea that anti-Ro/SS-A antibody alone can elicit cutaneous LE lesions (Table 6). Our studies have failed to demonstrate a positive correlation between circulating anti-Ro/SS-A levels and SCLE skin disease activity (103). Many Sjogren's syndrome patients have equally high serum levels of anti-Ro/SS-A but only infrequently develop photosensitive cutaneous LE. In addition, only a relatively small percentage of infants who are exposed to Ro/SS-A antibody from their mother's circulation during fetal development actually develop neonatal LE or congenital heart block (94,105). While the mononuclear cell infiltrate which is seen in the pathology of SCLE and neonatal LE lesions is consistent with an ADCC immune effector mechanism, the experimental models which have most closely simulated the lichenoid histopathology of LE-specific skin disease are antibody independent systems in which activated T cells are reacting to allogeneic or syngeneic histocompatibility antigens within the skin, [e.g., graft-versus-host disease (65) and experimental lichen planus (110)]. While the anti-Ro/SS-A that was passively infused into nude mice bearing grafts of normal human skin did bind to the human epidermal cells, no pathological injury could be detected as a result of this binding (87). Furthermore, while human IgG could be demonstrated in the cutaneous and cardiac tissue of newborn guinea pigs whose mothers had been injected with anti-Ro/SS-A containing serum (82), neither skin nor heart pathology was found (personal communication, Dr. Lela A. Lee). It is quite possible that the design of these animal models was insufficient to allow the full development of anti-Ro/SS-A mediated tissue injury to occur. The heterologous mix of human IgG and rodent effector mechanisms (e.g. complement, Fc receptor-bearing mononuclear cells) and/or host immune defects (e.g., absence of mature T cells in nude mice) might have

prevented a pathological immune reaction from being fully expressed. An immunocompetent experimental model which incorporates autologous antibody triggers and immune effector mechanisms, such as might be constructed in a human Ro/SS-A transgenic mouse model, could be better suited for this purpose.

THE POSSIBLE ROLE OF Ro/SS-A ANTIGEN-SPECIFIC T CELLS IN THE PATHOGENESIS OF CUTANEOUS LE

It is possible that the prominent anti-Ro/SS-A autoantibody response which is seen in SCLE patients is not in itself pathogenic but rather serves only as a marker for a pathogenetic Ro/SS-A antigen-specific T cell mediated response. There is increasing evidence to suggest that antigen-specific T cells might be involved in the paired autoimmune responses which occur to physically linked autoantigens such as Ro/SS-A and La/SS-B (12,101,104). This raises the interesting possibility that Ro/SS-A specific T cells might exist in SCLE patients and have the capacity to directly participate in the cutaneous injury pattern which is seen in their skin lesions. This possibility is supported by the predominance of activated T lymphocytes and macrophages in the cellular infiltrate of LE-specific skin lesions and the fact that the closest histopathological models of the LE-specific histopathological pattern which have been developed to date [e.g., graft-versus-host disease (65) and experimental lichen planus (110)] are T cell mediated. In addition, there is now considerable evidence to indicate that autoantigen-specific T cells, often apparently triggered through mechanisms of molecular mimicry, are the immunological mediators of tissue injury in experimental models of other human disorders such as multiple sclerosis [experimental autoimmune encephalomyelitis (116)], rheumatoid arthritis [adjuvant arthritis (66)] and autoimmune thyroiditis (95). The recent cloning of several human Ro/SS-A genes (71,96,97) will now provide a ready source of large amounts of pure, non-toxic antigen in the form of immunodominant synthetic peptide epitopes or full-length recombinant antigenic protein which can be used to probe for such Ro/SS-A specific T cells in the skin lesions and circulation of SCLE patients. If such Ro/SS-A specific T cells can be identified, there are ways in which they might be used to develop an experimental in vitro model of the LE-specific lesional histopathology.

MOLECULAR CHARACTERISTICS OF THE Ro/SS-A RIBONUCLEOPROTEIN

Whether the basic immunopathological mechanism is mediated by antibodies or autoantigen-specific T cells, a better appreciation of the molecular configuration of the Ro/SS-A RNP and factors which relate to its modulation in epidermal cells should lead to an improved understanding of the pathogenesis of SCLE and neonatal skin disease.

Until recently, the Ro/SS-A autoimmune response appeared to be rather straightforward. This family of autoantibodies was felt to be directed toward determinants on the peptide component of a small cellular RNP particle which consisted of a single 60 kD protein that was associated, on a 1:1 molar basis, with one of four unique small RNA molecules known collectively as the hY RNAs (h-human) (Y-cytoplasmic) (76). The La/SS-B 48 kD polypeptide, a RNA polymerase III transcription termination factor, was also known to be at least transiently associated with the Ro/SS-A RNP. These RNP particles, whose normal cellular function is still not known, were initially felt to be restricted to the cytoplasm, however it is now quite clear that a component of Ro/SS-A

antigenicity can be found in the nucleus as well. Earlier studies have indicated that species differences in the structure and quantity of the Ro/SS-A RNP do exist (75). In addition, other studies have suggested that this RNP is variably expressed quantitatively in different organs within the same species (88). However, it has been only within the past two years that work by several groups has suggested that different isoforms of this RNP particle might exist within the same individudal and that qualitative differences in the autoimmune response to this family of autoantigens might be possible. At this time it appears that there might be as many as 4 immunologically distinct polypeptides ranging in molecular weight from 52-60 kD as determined by SDS-polyacrylamide gel electrophoresis that have human anti-Ro/SS-A autoantibody binding activity (64,71,92,96,97,104) (Figure-9). The genes for a 60 kD Ro/SS-A protein (71) and another highly acidic 46 kD Ro/SS-A protein, which because of its negatively charged carboxyl terminal migrates abberently between 52-60 kD in SDS-polyacrylamide gels (92,96,97), have now been cloned and sequenced. In addition, it appears that clinically relevant differences might exist in the autoimmune response which develops against different epitopes on the same Ro/SS-A protein (90). It therefore appears that this a much more complex pattern of autoimmune response than was originally appreciated.

We have recently found that the acidic 46 kD human Wil-2 cell Ro/SS-A autoantigen that migrates aberrantly at 52-60 kD in SDS-PAGE has some very interesting characteristics (123). Its first 24 amino-terminal amino acid residues are identical with two exceptions to the first 24 amino terminal amino acids of a 60 kD canine brain, high affinity calcium binding protein (124). This canine brain calcium binding protein is very similar to calreticulin (syn. calregulin), a high affinity calcium binding protein present in the endoplasmic reticulum of rabbit and mouse cells (125-127). A rabbit antiserum against a Ro/SS-A synthetic amino terminal epitope (amino acids 6-19) reacted strongly in Western blot analysis with the canine brain calcium binding protein but not with calsequestrin, another calcium binding protein present in skeletal muscle sarcoplasmic reticulum. The full amino acid sequence of our 46 (52-60) kD human Ro/SS-A was found to be 92% homologous to that of rabbit liver calreticulin as deduced from their cDNA sequences. Goat anti-rabbit calreticulin antiserum bound strongly to our Ro/SS-A protein in Western blot. The anti-rabbit calreticulin antiserum also bound in enzyme-linked immunosorbent assay (ELISA) to our native human Ro/SS-A protein as well as to 2 of its epitopes in the form of synthetic peptides. In addition, several Ro/SS-A antibody containing patient sera also had abnormally elevated ELISA IgG binding levels against purified rabbit uterus calreticulin. Finally, our native 46(52-60) kD Ro/SS-A protein and the 60 kD calcium binding protein were found to have similar calcium binding properties in a radiolabeled calcium ligand overlay assay. Thus, a 46(52-60) kD human Ro/SS-A autoantigen is a calcium binding protein which has remarkably homology to the highly conserved calreticulin family of high affinity endoplasmic reticulum calcium binding proteins.

Synthetic oligonucleotides corresponding to this 46(52-60) kD human Ro/SS-A sequence were next used to amplify the homologous gene from a murine B-cell cDNA library utilizing the polymerase chain reaction. The mouse cDNA encoded amino acid sequence was found to be 94% homologous to the human Ro/SS-A sequence and is 100% homologous to murine calreticulin (128). Human Ro/SS-A antisera were originally reported to produce cytoplasmic immunofluorescence, a pattern similar to that seen with calreticulin antisera and with a rabbit

antiserum directed against the amino terminal end of our Ro/SS-A protein. The RAL-1 antigen of Onchocerca volvulus, (129) a human filarial parasite, was also found to be 63% homologous to the 46(52-60) kD human Ro/SS-A. In addition, the human Ro/SS-A protein has a similar molecular weight, isoelectric point and significant amino acid sequence homology to the Aplysia californica snail neuronal protein 407 which is upregulated by behaviorial conditioning (130). These homologies suggest that this human Ro/SS-A protein is highly conserved across species and has a very basic cellular function(s) which in part may involve calcium binding. The high degree of homology with a conserved parasitic antigen suggests that a foreign Ro/SS-A protein homologue could possibly trigger an autoimmune response in humans. We have recently determined that onchocerciasis patients from West Africa have antibodies present in their serum which bind by ELISA and Western blot analysis with our 46(52-60) kD human Ro/SS-A autoantigen and which will immunoprecipitate the hYRNAs that are associated with Ro antigens (131).

While it is clear that Ro/SS-A antigens, including a 60 kD Ro/SS-A polypeptide identified by SDS-PAGE, are expressed in normal adult and fetal human epidermal cells (77), at this time it is not clear which of the various Ro/SS-A gene products are expressed by human keratinocytes, a major target cell of autoimmune injury in LE-specific skin diseases such as SCLE. In preliminary studies, we have observed that messenger RNA for the 46(52-60) kD acidic Ro/SS-A polypeptide is expressed in normal human epidermal keratinocytes in vivo.

In addition, the exact molecular determinants (epitopes) to which the anti-Ro/SS-A autoantibodies produced by SCLE patients are directed have not been fully characterized. Once these and related questions have been answered, we should have a clearer view of the molecular basis of Ro/SS-A antibody response and the role which it plays in the elicitation of SCLE and neonatal LE.

SUMMARY AND CONCLUSIONS CONCERNING THE PATHOGENESIS OF SCLE

Patients with several clinically distinctive types of cutaneous LE (SCLE, neonatal LE) frequently are found to have autoantibodies to the Ro/SS-A ribonucleoprotein particle present in their circulation. Some studies have suggested that these antibodies might be capable of directly triggering the type of histopathologic changes seen in SCLE/neonatal LE through immunological effector mechanisms such as antibody-dependent cell mediated cytotoxicity. Other investigative results, however, are not compatible with this hypothesis. A better understanding of the molecular configuration of the Ro/SS-A small cellular ribonucleoprotein particle, the factors which regulate the expression of this complex autoantigen system in epidermal keratinocytes, and the overall potential of the Ro/SS-A autoimmune response should provide some insight into this seeming paradox.

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