

## CLINICAL REPORT

# Clinical Follow-up of 102 Anti-Ro/SSA-positive Patients with Dermatological Manifestations

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**Patients with Ro/SSA autoantibodies can develop cutaneous lupus erythematosus and photosensitivity. The aim of this study was to evaluate disease progression and clinical outcome in Ro/SSA-positive patients after 2 years in a prospectively followed cohort. A total of 102 previously clinically and serologically characterized Ro/SSA-positive patients received a questionnaire 2 years after the baseline investigation. Evaluation of 98 questionnaire responses was performed and clinical examination was offered to patients with cutaneous lupus erythematosus established at baseline, or skin symptoms developed over the 2 year period since baseline. Skin symptoms (42%) and arthralgia (31%) were common self-reported health-related answers. Twenty of the 98 patients (20%) showed disease progression with development of new diagnoses such as drug-induced subacute cutaneous lupus erythematosus. This prospective study reveals that new autoimmune diseases and skin disease progress are common in Ro/SSA-positive patients also in the short-term perspective, and stresses the importance of regular follow-up of these patients. Key words: follow-up; subacute cutaneous lupus erythematosus; Sjögren's syndrome; SLE; Ro/SSA autoantibodies.**

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Lupus erythematosus (LE) is a disease with clinical manifestations ranging from limited cutaneous lesions in chronic cutaneous lupus erythematosus (CCLE), to a systemic disease that may affect a multitude of internal organs in systemic lupus erythematosus (SLE). Subacute cutaneous lupus erythematosus (SCLE) is a distinct subset of LE characterized by photosensitivity, typical non-scarring papulosquamous and/or annular cutaneous lesions and Ro/SSA autoantibodies (1). The pathogenesis is not fully understood, but a combination of genetic and exogenous factors contributes to the development of clinical manifestations in this disease. An environmental factor influencing the disease is ultraviolet (UV) radia-

tion, which can aggravate or even induce skin lesions in all subtypes of CLE. SCLE may also be induced or exacerbated by drugs, including anti-hypertensives and anti-fungal agents (2).

Autoantibodies against Ro/SSA are also a feature of Sjögren's syndrome (SS), SLE and neonatal LE, including congenital heart block (3, 4). These autoantibodies are also found in 0.2–0.44% (5, 6) of healthy blood donors. The diseases related to Ro/SSA autoantibodies are chronic or recurrent, and a long observation time is needed to predict prognosis. A 10-year follow-up study showed that anti-Ro/SSA-positive patients with diverse clinical presentation at baseline have a dynamic disease process over time, and that the disease progresses in the majority of Ro/SSA-carrying patients (7). Less is known about disease development in a shorter-term perspective, and the life-time risk for developing clinical manifestations connected to Ro/SSA antibodies from the detection of seropositivity is not known. Patients with SCLE and SLE in whom disease has evolved later in life have a less aggressive form of lupus than those whose disease evolved earlier (8). Furthermore, in patients with undifferentiated connective tissue disease (UCTD) the risk of developing a defined connective tissue disease (CTD) is higher during the first few years and decreases over time (9). Predictive markers at the time of diagnosis would aid the clinician in planning follow-up and counselling to the patients. In relation to this, we have observed that higher levels of Ro/SSA autoantibodies to the Ro52 antigen in patients with CLE correlate with systemic manifestations (10).

Few prospective studies of the clinical outcome in patients with Ro/SSA autoantibodies have been reported. We therefore performed a 2-year follow-up of 102 previously identified Ro/SSA-positive patients. Specifically, we aimed to evaluate disease progression and activity and to identify cases of drug-induced SCLE.

## MATERIALS AND METHODS

### Study population

This study included 102 patients (89 females and 13 males) ranging in age from 17 to 85 years (mean 59 years). All the included patients participated in a previous study on anti-Ro/SSA-positive patients, recruited in 2003 on the basis of having a positive test for Ro/SSA autoantibodies between 1996 and

2002, self-reported photosensitivity and skin symptoms (11). The first testing of the patients had been initiated by many different physicians from different specialities in Stockholm County, and it was therefore not possible to determine which symptoms or clinical features led to testing in each individual case. However, in clinical practise these autoantibodies are tested when suspicion of autoimmune disease is present. The Ro/SSA autoantibodies had been investigated by enzyme-linked immunosorbent assay (ELISA) and/or immunodiffusion as a confirmatory test (11). The antibody levels to the different epitopes of Ro/SSA, namely Ro52 and Ro60, and to La/SSB have also been analysed (10). The patients were diagnosed at baseline 2003 as SCLE (with or without SLE and SS), CCLE, SLE, primary Sjögren's syndrome (pSS) and "other" (UCTD, secondary Sjögren's syndrome (sSS), polymyositis or polymorphous light eruption). Diagnoses were based on the currently accepted criteria for diagnoses of SCLE, SLE, SS, UCTD, rheumatoid arthritis (RA) and polymyositis (1, 12–16). Polymorphous light eruption was defined as a history of non-scarring itchy papules and/or vesicles appearing on sun-exposed parts of the skin 12–48 h after UV light exposure with spontaneous regression within one to two weeks. In this study 75 of the 102 patients reported a history of polymorphous light eruption at baseline. Patients with discoid lupus erythematosus (DLE) who did not fulfil criteria for any other systemic inflammatory disease were classified as CCLE (17).

#### Study design

A detailed questionnaire inquiring about health and medication in 2003 to 2005, specifying new symptoms and diseases or changes in their health since their last visit in 2003, was sent to the 102 patients. Ninety-eight of the 102 patients completed the questionnaire. All questionnaires were evaluated. Patients diagnosed with CLE already at baseline (SCLE  $n = 10$  or CCLE  $n = 5$ ) were called for a clinical examination. In addition, patients for whom the questionnaire response indicated new skin disease, were also called for a clinical examination ( $n = 34$ ). Patients who were unable to visit the clinic were interviewed by telephone. Patients who neither had a diagnosis of CLE at baseline 2003 nor an indication of new skin disease in the questionnaire ( $n = 49$ ) were not called for clinical investigation. If new symptoms indicating rheumatic disease were reported in the questionnaire, medical records were reviewed for confirmation. Forty-nine patients were called for examination, and of these patients 31 were examined clinically. Eight additional

patients were interviewed by telephone while the remaining 10 patients could not be reached either by post or by telephone. The clinical examination of the patients occurred 2 years after the initial examination (14–38 months between the visits, mean 25 months) and was performed by KP and FN at the Department of Dermatology at Danderyd Hospital, Stockholm. All skin diagnoses diagnosed at the clinic were histologically confirmed.

#### Ethics approval

The study was approved by the human ethics committee at the Karolinska University Hospital. Written informed consent was obtained from all patients.

#### Statistical analysis

Comparisons between groups were made with the Mann-Whitney  $U$  test.  $p$ -values less than 0.05 were considered statistically significant. Calculations were performed by the Statistica® software, version 7.0.

## RESULTS

### Diagnoses and demographic data in 98 questionnaire-responders

Ninety-eight of the 102 identified patients (96%, 86 women and 12 men) completed the questionnaire. One patient with SCLE had deceased due to myocardial infarction and metastasis from pulmonary carcinoma Table I. Three patients were lost to follow-up (one patient with SCLE refused to participate in the follow-up study, one patient with pSS and one patient with RA could not be reached). The clinical diagnoses at baseline in the 98 questionnaire respondents were: SCLE ( $n = 10$ ), CCLE ( $n = 5$ ), SLE ( $n = 28$ ), pSS ( $n = 18$ ) and "other" ( $n = 37$ ).

### Self-reported findings in 98 anti-Ro/SSA-positive patients

The most common self-reported subjective feature was cutaneous manifestations ( $n = 41$ ), closely followed by

Table I. Diagnoses in the 98 patients at follow-up in 2005. Distribution of sex, mean age, mean age at onset of disease and mean disease duration in respective diagnostic group at follow-up in 2005

Diagnosis	Patients at follow-up 2005		Sex, F/M	Age mean (range)	Age at onset mean (range)	Disease duration mean (range)
	Patients at baseline ( $n$ )	Patients at follow-up ( $n$ )				
SCLE	12	10 <sup>a,d</sup>	9/1	61 (20–83)	49 (16–79)	12 (4–40)
CCLE	5	5	5/0	62 (51–68)	51 (26–65)	11 (3–25)
SLE	28	28 <sup>b</sup>	23/5	53 (17–83)	38 (13–80)	15 (2–50)
pSS	19	18 <sup>e</sup>	17/1	61 (33–84)	50 (23–76)	10 (3–45)
Other	38	37 <sup>c,e</sup>	32/5	62 (40–85)	–	–
Total	102	98	86/12	59 (17–85)	–	–

<sup>a</sup>3 SCLE, 5 SCLE-SLE, 2 SCLE-SS.

<sup>b</sup>8 SLE-SS.

<sup>c</sup>24 UCTD, 7 PLE, 5 RA-SS, 1 RA.

<sup>d</sup>One patient deceased due to myocardial infarction and metastasis from pulmonary carcinoma, one patient refused to participate in the follow-up study.

<sup>e</sup>One patient could not be reached.

SCLE: subacute cutaneous lupus erythematosus; CCLE: chronic cutaneous lupus erythematosus; SLE: systemic lupus erythematosus; pSS: primary Sjögren's syndrome; UCTD: undifferentiated connective tissue disease; PLE: polymorphous light eruption; RA: rheumatoid arthritis.

arthralgia ( $n=30$ ). The 41 patients with skin manifestations reported new skin symptoms since the last visit in 2003. Eight patients self-reported a new diagnosis of a rheumatic disease during the time from baseline to follow-up: SLE ( $n=2$ ), RA ( $n=1$ ), vasculitis ( $n=2$ ), SS ( $n=3$ ), psoriasis arthritis ( $n=1$ ). These diagnoses were confirmed by review of medical records from the rheumatology departments attended by the patients.

#### Clinical features at follow-up in 31 clinically examined and 8 telephone interviewed Ro/SSA-positive patients

Patients with SCLE ( $n=10$ ) or CCLE ( $n=5$ ) at baseline and patients in whom the questionnaire response indicated new skin disease ( $n=34$ ) were called for a clinical examination. Of the 15 patients with CLE at baseline, 9 had cleared skin and 6 had CCLE with relapses. One patient with SCLE developed SLE and another patient with SCLE developed SS. We found 4 patients with new CLE diagnosis. Two of these 4 patients developed drug-induced SCLE and will be discussed later. One patient with pSS at baseline was diagnosed with DLE at follow-up and one patient with SLE developed chilblains and DLE during the observation time. One patient with pSS developed SLE during the observation time.

Apart from CLE, other new skin diagnoses were squamous cell carcinoma on the lip in the area of DLE lesions ( $n=1$ ), and cutaneous vasculitis consistent with cutaneous polyarteritis nodosa (PAN) ( $n=1$ ). The most common extracutaneous feature was arthralgia.

#### Occurrence of drug-induced subacute cutaneous lupus erythematosus

As many as 51% of the 98 questionnaire respondents reported new medication since their last visit. The novel drugs are listed in Table II. The most commonly prescribed new drug was an anti-hypertensive ( $n=16$ ). Glucocorticoids ( $n=9$ ), antimalarials ( $n=8$ ) and immunosuppressants ( $n=8$ ) were also prescribed frequently.

Table II. Novel medication prescribed to the 98 patients during the 2-year follow-up period

Drugs	Number of patients prescribed the new drug
Anti-hypertensives <sup>a</sup>	16
Glucocorticoids	9
Antimalarials	8
Immunosuppressants <sup>b</sup>	8 <sup>f</sup>
Gastrointestinal acid inhibitors <sup>c</sup>	6 <sup>f</sup>
Biological agents <sup>d</sup>	3
Other <sup>e</sup>	42

<sup>a</sup>Beta-blockers ( $n=7$ ), thiazides ( $n=3$ ), calcium antagonists ( $n=3$ ), furosemide ( $n=2$ ), angiotensin-converting enzyme inhibitors ( $n=1$ ).

<sup>b</sup>Methotrexate ( $n=2$ ), mycophenolate mofetil ( $n=1$ ), azathioprine ( $n=3$ ), chlorambucil ( $n=1$ ), natriumaurothiomalate ( $n=1$ ).

<sup>c</sup>Omeprazole ( $n=4$ ), lansoprazole ( $n=1$ ), ranitidine ( $n=1$ ).

<sup>d</sup>Rituximab ( $n=2$ ), infliximab ( $n=1$ ).

<sup>e</sup>Anti-thrombotics, analgesics, non-steroidal anti-inflammatory drugs, anti-hyperlipidaemics, allopurinol, amphotericin B, leuporelin, vitamins, minerals, calcium phosphates, anti-histamines.

<sup>f</sup>Drug-induced subacute cutaneous lupus erythematosus ( $n=2$ ).

Two Ro/SSA-positive SLE patients with no signs of CLE at baseline developed SCLE within one month after treatment with new drugs. One of the patients was treated with omeprazole due to gastroesophageal reflux and developed SCLE after one month of treatment (Fig. 1A and B), while the second patient developed SCLE after 2 weeks of methotrexate treatment (Fig. 1C). In both patients resolution of SCLE lesions occurred after the drug was discontinued. The patient treated with methotrexate was treated a second time with methotrexate, but once again developed SCLE lesions.

#### Two-year outcome in relation to Ro52 autoantibody levels

In the previous investigation patients with CLE and no systemic manifestations had significantly lower mean levels of Ro52 ( $p<0.05$ ) than patients with systemic disease such as SLE, SS and RA (10). Patients with low levels of Ro52 autoantibodies at baseline still had a condition limited to the skin ( $p<0.05$ ) at follow-up.



Fig. 1. (A, B) A 39-year-old Ro/SSA-positive woman with systemic lupus erythematosus (SLE) diagnosis and vitiligo, clinically and histologically subacute cutaneous lupus erythematosus (SCLE) lesions which appeared early autumn one month after first intake of proton pump inhibitor and cleared after approximately 3 months. (C) A 63-year-old Ro/SSA-positive woman with SLE diagnosis, previously without skin disease, clinically and histologically SCLE lesions, which appeared early autumn 2 weeks after first intake of methotrexate and cleared after approximately 4 months.

Only one patient diagnosed with CLE and with low levels of Ro52 autoantibodies at baseline was diagnosed with SLE on the basis of fulfilling 4 of the ACR criteria. However, her systemic manifestations were mild. There was no difference in disease progression among patients with regard to Ro52 antibody levels at baseline.

## DISCUSSION

Ro/SSA autoantibodies are recognized as characteristic markers helpful in the diagnostics of clinically different rheumatic diseases, including SCLE, SLE and SS, commonly seen at rheumatology or dermatology departments, which limits the physician's possibility for overview of the clinical spectrum. Ro/SSA autoantibodies are not known to commonly associate with other forms of CLE such as CCLE. We conducted a prospective study with a 2-year follow-up of 98 patients with Ro/SSA autoantibodies to investigate the short-term risk for developing CLE. In particular, we wanted to explore the risk of developing CLE in a group of Ro/SSA-positive patients.

In a previous study by Simmons O'Brien et al. (7) 100 Ro/SSA-positive patients, originally seen at medical institutions, were followed over a 10-year period, while our patients were evaluated in detail for dermatological symptoms. The study by Simmons O'Brien et al. (7) revealed that 65% of anti-Ro/SSA-positive patients had a chronic progressive disease process, and that at least 25% developed SS and/or progressive "rheumatoid-like arthritis". Our results confirm the observation that anti-Ro/SSA-positive patients have a dynamic disease process, also evident during a short observation period of only 2 years, as in this study. Among the clinically examined SCLE and CCLE patients, one patient with SCLE and DLE developed SLE marked by arthralgia. The other patients with CLE (86%), showed no systemic transition and the prognosis was thus more favourable during the observation period.

A 10-year follow-up study of SCLE patients by Sontheimer (18) showed a relatively stable clinical course with little progression or mortality. However, since 50% of SCLE patients fulfil four or more ACR criteria for SLE, and 5–10% of DLE patients develop SLE (19–21), the physician should regularly evaluate CLE patients for the presence of other autoimmune diseases that may develop. Previous studies have shown that CLE patients with signs of nephropathy (proteinuria, haematuria), arthralgia and presence of high titres of ANA are at risk of developing SLE (22). However, we are not aware of any prospective studies covering different diagnostic groups all connected to Ro/SSA autoantibodies. Our short observation time makes it difficult to evaluate the true figure of transition into systemic disease in this patient group. We unexpectedly identified a few cases

of CCLE in our patient group. The diagnosis was stable at follow-up, with no SLE features after an observation time of 2 years, suggesting a stable course for the different subgroups of CLE.

Apart from skin manifestations, the onset or worsening of arthralgia was a commonly reported symptom, and appeared in 31% of the patients. This self-reported symptom has been found to affect quality of life in psoriatic patients (23), and may also affect quality of life in the patients in this study.

Certain drugs can induce a clinical picture of SCLE (2). It is not clear if Ro/SSA autoantibodies are present before the drug-induced skin reaction occurs, thus making the patient more susceptible to drug-induced SCLE, or if the autoantibody develops as a consequence of the drug treatment. In a previous study we found only one possibly drug-induced SCLE among 20 clinically examined photosensitive anti-Ro/SSA-positive SCLE patients (11), although other studies have indicated a more prevalent occurrence of drug-induced lupus (2). We hypothesized that this may have been due to the retrospective approach of the study, and that patients may not be aware of the connection with new prescriptions and disease onset (11). Also, because of the transient nature of drug-induced SCLE, patients may not have been diagnosed correctly and thus may not be able to self-report the incidence. Two of our patients both fulfilling four or more ACR criteria at baseline developed drug-induced SCLE after treatment with the drugs omeprazole and methotrexate, respectively. These two patients were known to possess Ro/SSA autoantibodies years prior to the occurrence of the SCLE. It is unclear if this was also the case among the drug-induced anti-Ro/SSA-positive CLE patients in the study of Srivastava et al. (2), or if the autoantibodies appeared together with the drug-induced lesions. Proton pump inhibitors can be photosensitizing (24, 25), and one of the patients in our study had received omeprazole before the suspected, drug-induced SCLE appeared. Methotrexate, on the other hand, is a drug less well known to induce photosensitization, but a case of reactivation of photodermatitis has been described previously (26). Our data indicate the importance of providing specific information to anti-Ro/SSA-positive patients of a possible cutaneous adverse drug reaction. Since methotrexate has documented efficacy in the treatment of CLE (27) and our patients with documented Ro/SSA autoantibodies, were also prescribed a number of other, potentially photosensitizing drugs, awareness of the risk and counselling about sun avoidance is mandatory.

There are no diagnostic tools for predicting disease process and prognosis and the Ro/SSA autoantibodies have been reported to be stable and persist for years (28–29). Serial measurements of Ro/SSA autoantibodies in sera over a 2-year time period of patients with SLE and SS showed fluctuations during the course of the illness, but were found to have only limited clinical value in

predicting activity or exacerbations of the diseases (28). The fine specificity of Ro/SSA autoantibodies was also found to remain stable during the 2-year time period (29). We recently found that high levels of anti-Ro/SSA and anti-La/SSB correlate with systemic inflammatory disease (10). These findings were confirmed since only one patient with low anti-Ro52 developed mild SLE. Quantitative ELISA testing of fine specificities of Ro/SSA and La/SSB autoantibodies may thus be of value as a prognostic tool (10).

In summary, our study shows a highly dynamic disease process in Ro/SSA-positive patients during an observation time of 2 years. The development of new diagnoses such as CLE, RA, SS, SLE, vasculitis and psoriasis arthritis within 2 years, emphasizes the importance of clinical follow-up and co-operation between rheumatologists and dermatologists in these patients. Transition between different manifestations of CLE was less common, underscoring the value of a thorough examination of the skin including histopathology when the patient first presents. Although patients with SCLE and CCLE usually have a benign prognosis, with disease confined to the skin or mild systemic disease, they should be evaluated not only for the possibility of developing systemic disease but also because early treatment of CLE may minimize deforming scars, atrophy or dyspigmentation. Patients with Ro/SSA antibodies are also at risk of developing drug-induced SCLE and care should be taken when prescribing photosensitizing drugs to these patients. Further clinical follow-up of our CLE patients with Ro/SSA autoantibodies is ongoing.

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