

Five-year follow-up of 665 Hungarian patients with undifferentiated connective tissue disease (UCTD)

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Abstract

Objective

To determine the clinical symptoms and the panel of autoantibodies of patients with early undifferentiated connective tissue disease (UCTD) followed for at least 1 year.

Methods

716 UCTD patients with manifestations suggestive but not diagnostic of specific connective tissue disease (CTD) were recruited and followed up between 1994-1999. The patients with early UCTD were subdivided into those with isolated Raynaud's phenomenon (RP) (50 patients), unexplained polyarthritis (31 patients) and "true" UCTD (665 patients). UCTD was diagnosed on the basis of clinical manifestations suggestive of a connective tissue disease and the presence of at least one non-organ specific autoantibody. The patients' sera were tested for anti-nuclear (ANA), as well as for nine different specific autoantibodies (anti-dsDNA, -Sm, -RNP, -SSA, -SSB, -Scl-70, -centromere, -Jo1 and -PM-Scl).

Results

The most common clinical manifestations of UCTD included RP, arthritis/arthralgias, pleuritis/pericarditis, sicca symptoms, cutaneous involvement (photosensitivity, rash), central nervous symptoms, peripheral neuropathy, fever, vasculitis, less pulmonary involvement and myositis. 230 of the 665 true UCTD patients (34.5%) developed a defined CTD (28 systemic lupus erythematosus [SLE], 26 mixed connective tissue disease [MCTD], 19 progressive systemic sclerosis [PSS], 45 Sjögren's syndrome, 3 polymyositis/dermatomyositis [PM/DM], 87 rheumatoid arthritis [RA], and 22 systemic vasculitis). 435 of 665 patients (65.4%) remained in the UCTD state, and 82 of 665 patients (12.3%) achieved complete remission with symptoms not reappearing within the 5-year period. The highest probability of evolution to a defined CTD was during the first 2 years after onset: of 230 UCTD patients 183 (79.5%) developed major organ symptoms and signs. In particular skin and cardiac complications seemed to spread during the follow-up period in those patients who progressed to SLE. The condition of 18/50 patients with isolated RP evolved to UCTD and 3 of 31 patients with unexplained polyarthritis progressed to definite CTD (2 patients RA and one MCTD).

Conclusion

In our study most of the UCTD patients did not develop a definite CTD, but during the follow-up period we found new clinical and serological manifestations. One-third of the UCTD patients showed progress into different types of specific CTD.

Key words

Undifferentiated connective tissue disease (UCTD), connective tissue disease (CTD), prognosis, treatment.

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Introduction

Connective tissue diseases (CTDs) such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), mixed connective tissue disease (MCTD), polymyositis/dermatomyositis (PM/DM), Sjögren's syndrome (SS), rheumatoid arthritis (RA) and systemic vasculitides are chronic autoimmune/inflammatory disorders involving several internal organs. CTDs have characteristic signs and symptoms. The well established CTDs have universally accepted diagnostic criteria (1-5)

In contrast to established CTDs, a number of patients show some clinical signs and laboratory abnormalities characteristic of CTDs, but these do not completely meet the criteria for established CTDs. Therefore, this clinical entity is generally referred to as unclassified or undifferentiated connective tissue disease (UCTD) (6-8).

The term UCTD is used to describe patients with unclassifiable CTD. In these patients progression to a well-established autoimmune disease was likely on the basis of their symptoms, as described using the term "non-differentiated collagen disease" in the early 1960's by Petrányi (9). The term UCTD gained wide acceptance in the 1980s (10-13). Today UCTD represents a disease state where the clinical symptoms and serological abnormalities are suggestive of an autoimmune disease, but are not sufficient to fulfil the diagnostic criteria of any well-established CTD.

In the present study we analyzed the symptoms and disease course of 746 patients diagnosed with early UCTD. We investigated the onset of new symptoms and signs during a five-year follow-up period after the onset of UCTD and tried to determine clinical and laboratory indicators with predictive value for evolution to established CTDs.

Patients and methods

Patients

Between January 1994 and December 1999, 991 new patients were admitted to the special clinics of our institution with suspected CTD. These patients manifested some signs or symptoms of CTDs, but did not fulfil the specific cri-

teria for any established CTD.

Patients with early UCTD were subdivided into three subgroups with isolated Raynaud's phenomenon (RP), unexplained (undifferentiated) polyarthritis (UDP) and "true" UCTD. Isolated RP was diagnosed when RP occurred alone, in the absence of any associated clinical symptoms resembling established CTDs. Similarly, UDP patients had polyarthritis without any signs or symptoms of known CTDs. The diagnosis of "true" UCTD was established using criteria similar to what was earlier described by Mosca *et al.* (14). UCTD was diagnosed when the clinical manifestations suggestive of any CTD were present accompanied by the existence of at least one non-organ specific autoantibody, such as antinuclear antibodies (ANA) or anti-extractable nuclear antigen antibodies (ENA). Patients with the diagnosis of early UCTD undergoing follow-ups for at least one year were included in this study.

Out of the 991 patients described above, 194 were excluded within one year, as they were diagnosed with specific CTDs during this follow-up period. Out of these 194 patients, 22 were diagnosed as SLE, 8 as MCTD, 10 as SSc, 49 as SS, 6 with PM, 85 with RA, and 14 with systemic vasculitis within the first year (Fig. 1).

Thus, 797 patients were included in the study: 50 patients had isolated RP, 31 had UDP, and 716 patients had "true" UCTD. Among the 716 UCTD patients 51 were lost to follow-up during the first year, resulting in 665 UCTD patients followed for five years. By the end of this 5-year follow-up period, 230 out of 665 UCTD patients developed an established CTD, while 435 patients still had UCTD. Patients still having UCTD after 5 years were termed as "stable" UCTD" (Table I). The diagnosis of specific CTDs including SLE, MCTD, SSc, SS, PM/DM, RA and systemic vasculitides were determined by the established classification criteria (15-21).

Clinical and laboratory diagnosis of UCTD

The clinical symptoms characteristic for UCTD were systemic symptoms

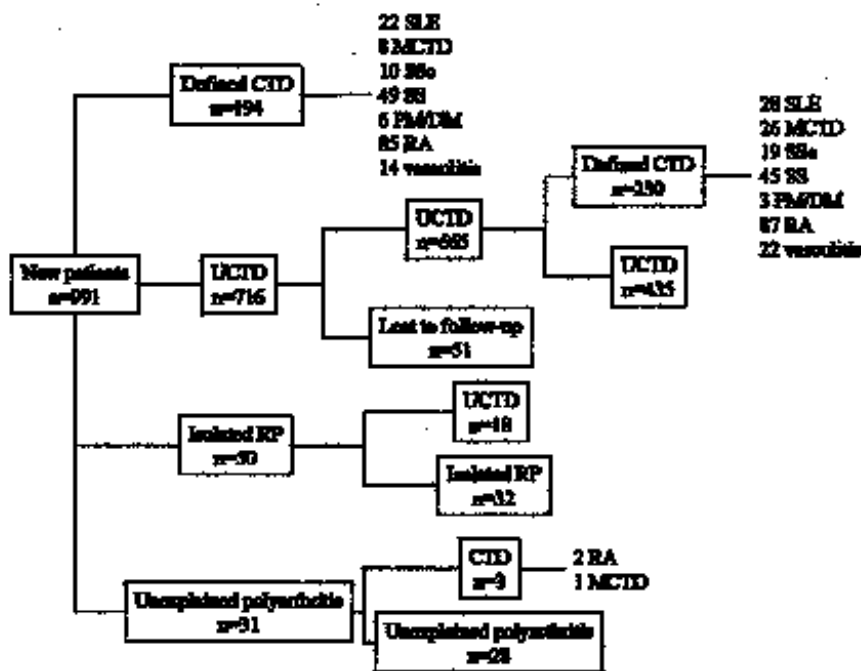


Fig. 1. Five-year outcome among patients with undifferentiated connective tissue disorder.

Table I. Diagnosis of patients at entry and during follow-up.

Disease category	No. of patients
Total entered	797
Isolated Raynaud's phenomenon (at entry)	50
Unexplained polyarthritides (at entry)	31
"True" UCTD (at entry)	665
"Stable" UCTD (during 5 years)	435
Established CTD (during 5 years)	230
Lost to follow-up (within 5 years)	51

including weight loss and unexplained fever; RP; arthritis/arthralgia; skin involvement including rash, photosensitivity or cutaneous vasculitis; pleuritis or pericarditis; sicca syndrome including xerophthalmia and/or xerostomia; central nervous system involvement including convulsions, headache, migraine or trigeminal neuralgia; pulmonary involvement; peripheral neuropathy and myositis as described by others (8, 14).

ANA were determined by indirect immunofluorescence on rat liver sections and on HEp2 cell lines. On liver sections and Hep2 cells, ANA positivity was determined on the basis of titers above 1:64 and 1:80, respectively. Specific autoantibodies including anti-dsDNA, anti-Sm, anti-RNP, anti-SSA,

anti-SSB, anti-Jo1, anti-Scl-70, and anti-PM-Scl were determined by ELISA (Cogent Diagnostics, UK). The diagnosis of UCTD was established when the patients exerted at least two clinical symptoms accompanied by at least one detectable autoantibody in their sera.

As described above, some patients developed established CTD during the follow-up. Diagnostic procedures for SLE, SSc, MCTD, SS, RA and vasculitides included X-ray, CT and MRI imaging, lung function tests, electromyography and electroneurography, Schirmer's test, Rose-Bengal staining, sialometry, parotis ultrasound and salivary gland biopsy. RP was assessed by a cold provocation test, nailfold capillary microscopy (Nikon, Vienna, Aus-

tria) and hand perfusion scintigraphy (22). Cutaneous vasculitis was diagnosed by a dermatologist and skin biopsy was performed in all vasculitis patients. Laboratory follow-up performed at each visit included the erythrocyte sedimentation rate (ESR), full blood count, kidney and liver function tests, creatine phosphokinase (CPK) and urinalysis. In addition, immunolaboratory screening was performed at each visit in order to confirm the onset of established CTDs. These tests included serum concentrations of rheumatoid factor, C reactive protein (CRP), total immunoglobulin G (IgG), IgA, IgM, complement factors 3 (C3) and C4, total complement activity (CH50), as well as immunocomplexes using standard assays.

Data analysis

Statistical analysis was carried out using Fisher's exact test and Student's t test. P values < 0.05 were considered statistically significant. Individual relative risk (RR) and 95% confidence intervals (CI) were calculated using separate logistic regression for variables found to be significant or approaching significance in the former analyses.

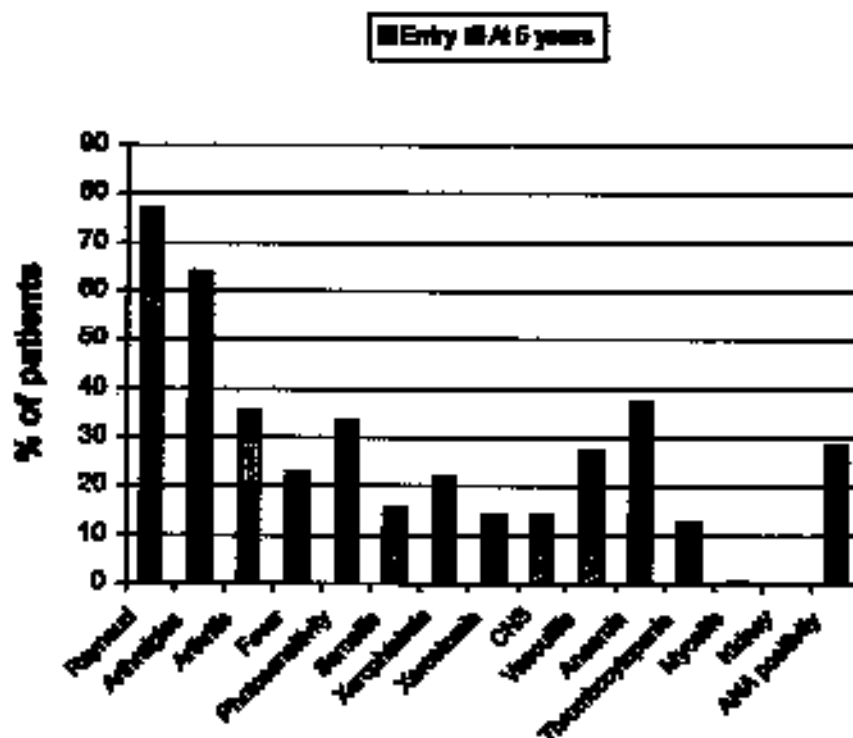
Results

Clinical data of 435 patients with "stable" UCTD

As described above, 435 patients still had UCTD after the 5-year follow-up period, thus the term "stable UCTD" was used. Clinical data on these 435 patients are shown in Table II. In addition, the symptoms of the 435 true UCTD patients at the first visit and at the end of the 5-year follow-up period are shown in Figure 2. The most frequent symptoms at the onset of UCTD were RP (58.8%), arthralgia (49.0%), arthritis (29.9%), fever (15.1%), cutaneous symptoms (photosensitivity, malar rash, alopecia) (23.4%), xerophthalmia (11.7%), xerostomia (13.1%), serositis (9.8%), central nervous system involvements (8.5%), anemia (30.3%) and thrombocytopenia (11.3%). The frequency of cutaneous vasculitis (erythema nodosum, panniculitis, leukocytoclastic vasculitis) increased during

Table II. Basic characteristics of 435 patients with “stable” UCTD.

Number of patients	435
Male/female ratio	26/409
Mean age (years \pm SD)	44.3 \pm 10.9 (range: 17-76)

**Fig. 2.** Clinical and laboratory manifestations of 435 patients with “stable” UCTD.

the follow-up (7.3% vs 20.2%; $p < 0.01$). Muscular disease was rare and kidney involvement was absent in the “stable” MCTD patients. ANA could be detected in 25% of the patients. Out of 435 UCTD patients, 82 (18.9%) achieved full remission with disappearance of symptoms during the five-year follow-up period.

Evolution of established CTD in 230 UCTD patients

During the five-year follow-up period, 230 out of 665 patients (34.5%) developed an established CTD (Fig. 1).

Among these patients, 87 (37.8%) developed RA, 45 (19.5%) SS, 28 (12.1%) SLE, 26 (11.3%) MCTD, 19 (8.3%) SSc, 3 (2.1%) PM/DM, and 22 (15.4%) systemic vasculitis. The highest probability of CTD evolution was observed within the first 2 years after onset (183 out of 230 patients, 79.5%).

Univariate analysis and identification of risk factors

We evaluated the symptoms and immunoserological characteristics present at the onset of UCTD in order to determine their protective value against

a given outcome. Univariate analysis and identification of the relative risk (RR) allowed us to select those characteristics that correlated with and thus had predictive value for the development of SSc, SS, MCTD, RA and SLE (Tables III-VII).

The development of RP, sclerodactyly and ANA positivity with a nucleolar immunofluorescent pattern highly predicted evolution to SS. RP was found in 89% of the UCTD patients who eventually developed SSc versus 60% of “stable” UCTD patients [$p = 0.0085$; RR: 5.3 (1.2-23.1)]. Similar observations were made regarding sclerodactyly [36.8% vs 5.8%; $p = 0.0012$; RR: 4.28, (1.14-19.32)] and ANA positivity with a nucleolar pattern [57% vs 1%; $p = 0.0001$; RR: 40.1 (17.9-89.9)] (Table III).

Xerostomia, xerophthalmia, as well as anti-SSA and anti-SSB autoantibodies showed good correlation with the development of SS (xerophthalmia: 80% vs 19%; $p = 0.0001$; RR 12.9 (6.3-26.2), xerostomia: 75% vs 9%; $p = 0.0001$; RR: 18.5 (9.7-35.3); anti-SSA: 60% vs 6%; $p = 0.0001$; RR: 12.9 (7.5-22.2); anti-SSB: 62% vs 2%; $p = 0.0001$; RR: 22.6 (13.4-38.2) (Table IV).

Polyarthritides in the hand joints and the presence of anti-U1RNP autoantibodies had predictive value for the evolution of MCTD (polyarthritides: 80.7 vs 36%; $p = 0.0001$; RR: 6.7 (2.5-17.6); anti-U1RNP: 69% vs 9%; $p = 0.0001$; RR: 16.6 (7.5-37.1) (Table V).

Polyarthritides, high serum levels of RF, and an elevated erythrocyte sedimentation rate correlated with the development of RA (polyarthritides: 67% vs 33%; $p = 0.0001$; RR: 3.3 (2.2-5.1); RF: 72% vs 9%; $p = 0.0001$; RR: 12.4 (8.1-19.0); ESR: 77% vs 48%; $p = 0.0001$; and RR: 3.0 (1.8-4.8) (Table VI).

SLE patients who developed this disease from UCTD were significantly younger than those with “stable” UCTD (36.2 ± 12.4 years vs 44.3 ± 10.9 years; $p < 0.001$) (data not shown). Symptoms with predictive value for the development of SLE included fever (60 vs 20%; $p = 0.0001$), serositis (53 vs 11%; $p = 0.0001$), and photosensitivity

Table III. Correlation of clinical and laboratory parameters with evolution into scleroderma (SSc).

Parameters	Univariate analysis	RR (CI)
Raynaud's phenomenon	$p = 0.0085$	5.39 (1.26-23.14)
Sclerodactyly	$p = 0.0012$	4.28 (1.14-19.32)
ANA (nucleolar pattern)	$p = 0.0001$	40.19 (17.96-89.95)

Table IV. Correlation of clinical and laboratory parameters with evolution into Sjögren's syndrome (SS).

Parameters	Univariate analysis	RR (CI)
Sicca syndrome ^a	p = 0.0001	18.54 (9.74-35.33)
Anti-SSA	p = 0.0001	12.96 (7.54-22.28)
Anti-SSB	p = 0.0001	22.69 (13.47-38.22)
ANA	n.s.	1.65 (0.92-2.94)

^aSicca syndrome: xerostomia and xerophthalmia; ANA: anti-nuclear antibodies; n.s.: not significant.

Table V. Correlation of clinical and laboratory parameters with evolution into MCTD.

Parameters	Univariate analysis	RR (CI)
Polyarthrititis	p = 0.0001	6.75 (2.58-17.69)
Raynaud's phenomenon	n.s.	0.63 (0.30-1.35)
ANA granular pattern	p = 0.0078	2.98 (1.37-6.35)
Anti-U1RNP	p = 0.0001	16.69 (7.50-37.12)

n.s.: not significant

Table VI. Correlation of clinical and laboratory parameters with evolution into RA.

Parameters	Univariate analysis	RR (CI)
Polyarthrititis	p = 0.0001	3.39 (2.22-5.17)
RF positivity	p = 0.0001	12.42 (8.12-19.01)
Bone erosions (MRI)	p = 0.0001	3.033 (1.88-4.88)

Table VII. Correlation of clinical and laboratory parameters with evolution into SLE.

Parameters	Univariate analysis	RR (CI)
Fever	p = 0.0001	5.49 (2.63-11.47)
Serositis	p = 0.0001	7.46 (3.68-15.17)
Photosensitivity	p = 0.0011	3.49 (1.70-7.20)
ANA (homogenous pattern)	p = 0.0001	17.28 (9.11-32.79)
Anti-DNS	p = 0.0001	64.74 (33.34-125.71)

Table VIII. Comparison of the clinical and laboratory characteristics of SLE patients with and without previous UCTD phase.

Attributes	SLE patients without UCTD (n = 22)	SLE patients with UCTD (n = 28)	Significance	RR (CI)
Age at onset	29.9 ± 7.1	36.2 ± 12.4	0.0001	
Fever	20 (90.9%)	23 (82.1%)	n.s.	0.444 (0.48-5.48)
Serositis	14 (63.6%)	26 (92.8%)	0.0145	0.437 (0.25-0.73)
Skin rash	16 (72.7%)	9 (32.1%)	0.0096	2.667 (1.25-5.68)
Renal involvement	17 (72.3%)	8 (28.5%)	0.0014	3.400 (1.48-7.79)
Arthritis	5 (22.7%)	5 (17.8%)	n.s.	1.176 (0.57-2.41)
Hemolytic anaemia	15 (68.2%)	9 (32.1%)	0.022	2.321 (1.14-4.69)
ANA (homogenous)	20 (90.9%)	26 (92.8%)	n.s.	0.870 (0.30-2.44)
Anti-DNS	19 (86.4%)	24 (85.7%)	n.s.	1.031 (0.41-2.58)

(53 vs 23%; p = 0.0011). The corresponding RR (CI) values were 5.49 (2.6-11.4), 7.4 (3.6-15.1), 5.6 (2.1-14.7), and 3.4 (1.7-7.2), respectively. The presence of ANA with a homogenous pattern and anti-ds DNA autoantibodies were also associated with the evolution of SLE (ANA: 39% vs 2.0%; p = 0.0001; RR: 17.2 (9.1-32.7); anti-ds DNA: 67% vs 0.3%; p = 0.0001; RR: 64.7 (33.1-125.7) (Table VII).

We compared the clinical symptoms and laboratory and immunological markers of patients who had SLE without and with UCTD stage (Table VIII). Twenty-two SLE patients who did not pass through a previous UCTD stage were younger than the 28 SLE patients who developed this disease from UCTD (29.9 ± 7.1 years vs 36.2 ± 12.4 years; p < 0.0001). Skin rashes, kidney involvement (proteinuria) and hemolytic anemia with a positive Coombs test were significantly more common in SLE patients without a UCTD stage compared to those with previous UCTD. In contrast, recurrent serositis was more frequent in SLE patients with a previous UCTD stage. (SLE patients without and with UCTD stage: rash: 72% vs 32%; p = 0.0096; RR: 2.6 (1.2-5.6); renal disease: 72% vs 28%; p = 0.0014; RR: 3.4 (1.4-7.7); hemolytic anemia: 68% vs 32%; p = 0.022; RR: 2.3 (1.1-4.6), serositis: 63% vs 92%; p = 0.0145; RR: 0.4 (0.2-0.7). There was no significant difference in the frequency of ANA positivity or the presence of anti-dsDNA autoantibodies between SLE patients without and with a previous UCTD stage. Regarding mortality, two SLE patients without previous UCTD died during the 5-year follow-up period due to renal and cardiac disease. In contrast, there were no deaths among patients who developed SLE after having UCTD (data not shown).

In addition to patients with "true" UCTD, 50 patients with isolated RP were also followed. During the five-year follow-up period, new symptoms developed in 18 out of 50 patients (36%) including polyarthrititis, serositis, digital vasculitis, and swollen hands and fingers. ANA was detected in 12 cases, anti-U1RNP autoantibodies in 6 cases, and anti-SSA antibodies in 2 patients.

Isolated RP progressed into UCTD in 18 out of 50 patients (36%). None of the patients with isolated RP at entry developed any established CTD during the follow-up period (Fig. 1). Among the 31 patients who had UDP at entry, 3 developed an established CTD: 2 patients had RA and one had MCTD (Fig. 1).

Regarding therapy, patients with UCTD were treated with corticosteroids when non-steroidal anti-inflammatory drugs (NSAID) were ineffective. Among these patients, 238 (48 with recurrent serositis, 59 with skin vasculitis and 131 with synovitis) received low-dose (< 20 mg/day) corticosteroid treatment for 2 to 4 months. In the symptom-free periods the daily dose of corticosteroids was reduced or discontinued. Antimalarials were administered in more severe cases of rash or photosensitivity (data not shown).

Discussion

The diagnosis of CTDs is established following specific classification criteria based on characteristic clinical symptoms and laboratory markers. However, in a number of cases, clinical and laboratory markers are suggestive of a certain CTD, but the classification criteria are not yet completely fulfilled. These cases have been defined as undifferentiated connective tissue disease (UCTD) (23-25). There are a number of debates ongoing in the literature regarding the diagnostics and differential diagnostics of UCTD. In addition, the question as to whether UCTD in the majority of cases is a "stable" disease or if it instead progresses to an established CTD is still not fully answered. There are at least two accepted classification systems for UCTD. Williams *et al.* suggest that the diagnosis should be made in the presence of at least 3 of 11 specific clinical and laboratory markers of CTDs (26). According to Mosca *et al.*, the development of only one characteristic clinical symptom accompanied by the presence of one non-organ specific autoantibody in the sera of patients would be sufficient for the diagnosis of UCTD (14).

A number of investigators have studied UCTD patients in order to determine their possible outcomes. Some cases of

UCTD remain "stable" for years while others may progress to an established CTD. Mosca *et al.* suggest that UCTD is a stable disease in most cases. This group evaluated 91 patients with UCTD and found that 79 still had UCTD after a follow-up period of at least one year (1-22 years). Only 12 patients developed an established UCTD: all SLE. These authors did not find differences in clinical symptoms or the presence of specific autoantibodies when comparing patients who had SLE from the outset and patients who developed SLE after having UCTD (14). Williams *et al.* and Danieli *et al.* also reported that UCTD progressed to SLE more frequently than to other CTDs. However, these groups also reported evolution to RA, SSc, SS and MCTD after the stage of UCTD (26, 27).

In the present study we analyzed the clinical and laboratory features of 665 patients with "true" UCTD patients, in addition to 50 patients with isolated RP and 31 patients with UDP, in order to assess the disease course and the development of established CTDs. We diagnosed UCTD based on the presence of at least two clinical symptoms characteristic of CTDs accompanied by at least one detectable non-organ specific autoantibody in the sera of patients. Only patients followed for at least one year were included in the assessment and all patients were regularly evaluated for 5 years. Arthralgia/arthritis, RP, skin manifestations, xerostomia/ xerophthalmia, skin vasculitis and serositis were the most frequently observed clinical features in our patients. Renal or muscular disease was less common in UCTD than in other established CTDs. Major organ involvement such as of the kidney or muscles were found to be less frequently implicated than in other CTDs. Comparing our patients to other UCTD patient populations, the frequencies of arthritis/arthralgia, xerophthalmia/ xerostomia, photosensitivity, and anemia were similar to what has been found in American and Italian populations, with the exception of RP, which was more frequent in our study than in the reports by Mosca *et al.* and Alarcon-Segovia *et al.* (8, 14). Geo-

graphic differences may explain the clinical profiles of the various UCTD patient populations.

After the 5-year follow-up period, 65.4% of "true" UCTD patients remained in the UCTD stage, hence the terminology "stable" UCTD. Among these patients, disease remission was observed in 82 cases (18.8%). Evolution into a specific established CTD was found in 34.5% of patients with "true" UCTD at entry. The highest probability of CTD development was observed within the first 2 years after the onset of UCTD (79.5% of patients). UCTD most frequently progressed into RA (87 patients) and SS (45 patients). In addition, the development of SLE (28 patients), MCTD (26 patients), systemic vasculitis (22 patients), SSc (19 patients) and PM/DM (3 patients) was also observed. Univariate analysis showed that a number of different variables had significant predictive value for the development of established CTDs. Sicca symptoms, as well as anti-SSA and anti-SSB autoantibodies, were strongly associated with a progression to SS. Polyarthritis and anti-U1RNP autoantibody positivity had predictive value for the evolution of MCTD, while RP and ANA positivity with a nucleolar immunofluorescent pattern were associated with the development of SSc. Patients with polyarthritis, high serum levels of RF, and elevated ESR had a high relative risk for RA. Fever, serositis, ANA positivity with a homogenous pattern and the presence of anti-dsDNA autoantibodies had high predictive value for progression into SLE, as similarly described by others (28).

We compared the clinical manifestations of SLE patients without or with a previous UCTD stage. Patients who had SLE from the beginning were younger than those with previous UCTD. Organ involvement, including renal or skin manifestations and hemolytic anemia, were more common and mortality was more frequent among patients who were diagnosed with SLE within one year. Our results correspond with data reported by Swaak *et al.* This group found that skin and kidney involvement is less com-

mon and the overall prognosis is better in the incomplete forms of SLE, also termed "latent lupus" (29, 30).

Regarding the 50 patients who had isolated RP at entry, 36% progressed to UCTD during the 5-year follow-up period. Previous studies suggest that RP patients with ANA positivity are more likely to develop established CTD or progress to UCTD (31).

Two out of our 31 patients with UDP evolved to RA and one MCTD. Our data regarding the evolution of RA from UCTD is consistent with the report of Wolfe *et al.* (32). In contrast, differentiation of UDP into MCTD has not yet been previously reported.

In summary our study, as well as data reported by other investigators, suggest that the greater portion of patients with "true" UCTD remain stable during years of follow-up. In about one-third of UCTD patients practically any established CTD including RA, SS, SLE, SSc, MCTD, systemic vasculitis or PM/DM may develop. Some specific clinical symptoms, ANA positivity, the immunofluorescent pattern of ANA, as well as specific autoantibodies may have variable predictive values for the evolution of well-defined CTDs. SLE patients undergoing transition from UCTD may have a better prognosis than those with SLE diagnosed within one year after the onset of disease. Most UCTD patients can be treated with NSAIDs. Sometimes the onset of certain organ manifestations (serositis, synovitis, vasculitis) may require corticosteroid treatment, but aggressive immunosuppressive therapy is not justified. Further large-scale, population based, possibly international studies may be needed in order to exclude possible geographic variations and to obtain more detailed information on the diagnosis, optimal therapy and outcome of UCTD.

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