Undifferentiated Connective Tissue Disease: Analysis of 83 Patients with a Minimum Followup of 5 Years

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ABSTRACT. ***Objective.*** Undifferentiated connective tissue disease (UCTD) refers to a cluster of systemic disorders characterized by a simple clinical and autoantibody profile. Previously, we had described a series of 91 patients with UCTD who were followed at our unit for a minimum period of one year; here we report the extended followup of these patients.

Methods. Of the original 91 patients, 8 were lost to followup; the remaining 83, with a minimum followup of 5 years, were included in our analysis.

Results. During the followup 18 patients developed systemic lupus erythematosus (SLE) and one developed Sjögren's syndrome within a mean period of 54 months after the onset of the disease (range 17–96 mo). On analysis the 18 patients with SLE showed a clinical profile similar to cohorts reported in the literature. In one patient the evolution to SLE occurred during puerperium, but no other triggering factors were observed in our series. The presence of anticardiolipin antibodies and of multiple antibody specificities was significantly correlated with the development of SLE ($p < 0.05$).

Conclusion. This analysis confirms the findings of our one year followup study that UCTD comprises a distinct group of mild diseases and that the rate of evolution to defined connective tissue diseases is higher during the first years after its onset. Patients who maintain an undifferentiated profile during the followup seem to run a decreasing risk of developing a defined CTD. (J Rheumatol 2002;29:2345–9)

Key Indexing Terms:
UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE CONNECTIVE TISSUE DISEASE
SYSTEMIC LUPUS ERYTHEMATOSUS CLASSIFICATION CRITERIA

The terms undifferentiated connective tissue syndrome, latent lupus, incomplete lupus, and undifferentiated connective tissue disease (UCTD) have all been used to refer to a group of systemic autoimmune disorders with signs and symptoms that are not sufficiently evolved to fulfil the accepted classification criteria for the defined connective tissue diseases. There is now considerable data on the clinical and serological characteristics of UCTD, and many authors agree that only a small percentage of patients with undifferentiated disease will develop a defined CTD, while in the majority the condition will remain basically unchanged[1-13].

As awareness of this condition increases, new questions have arisen with regard to the dynamics of its evolution to defined CTD, the existence of triggering factors for this evolution, and the clinical picture of defined CTD that began as UCTD.

This study presents the results of an extended followup of a series of 91 patients with UCTD described previously[6], the aim being to reassess the rate of evolution to a defined CTD in these patients after a minimum followup of 5 years and to search for predictors and triggering factors for this disease evolution. Further, the clinical and serological features of those patients who developed a CTD during the followup were analyzed.

MATERIALS AND METHODS

From a total of 145 patients (138 women, 7 men) followed at our units between 1974 and 1995 and initially diagnosed with a UCTD, 91 with a followup of at least one year were selected for a previous study[6]. All patients were diagnosed as having UCTD on the basis of the following criteria: (1) signs and symptoms suggestive of a CTD, but which did not fulfil the criteria for any of the defined CTD; and (2) the presence of at least one non-organ-specific autoantibody. Only patients with a disease duration of at least one year were included in the study cohort. Between 1995 and May 2001 we continued to see these patients, who thus had a minimum followup of 5 years. Clinical and serological data on these patients were prospectively collected and the diagnosis was reevaluated yearly. In patients whose disease subsequently evolved to an overt CTD, the second diagnosis was made on the basis of published criteria[14-22], and clinical and serological data from the onset of the CTD to the end of the study period were collected and analyzed.

Environmental factors (i.e., hormones, ultraviolet light, drugs, infections) believed to play a role in the etiopathogenesis of systemic lupus erythematosus (SLE)[23] were taken into consideration as possible triggering factors, and their presence/absence in the history of the patients who evolved to SLE was examined.

Patients who developed a CTD were divided into groups based on the timing of their evolution to the defined disease, arbitrarily taking 5 years as the cutoff value.

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Submitted October 26, 2001; revision accepted May 7, 2002.

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Standard, validated techniques were used for the laboratory analyses. Indirect immunofluorescence (IIF) was employed to detect antinuclear (ANA) and anti-dsDNA antibodies, with HEp-2 cells and rat liver cells as antigen sources for ANA and *Crithidia luciliae* for anti-dsDNA. Counterimmunoelectrophoresis was used to detect anti-extractable nuclear antigens (anti-SSA/Ro, anti-SSB/La, anti-RNP, anti-Sm, anti-Scl70, anti-Jo1, anti-Ku). ELISA was used to detect anticardiolipin antibodies.

Statistical analysis. All variables were analyzed independently using the chi-squared test or Fisher's exact test for contingency tables, as appropriate. Multivariate linear analysis was then applied to identify those variables that could independently contribute to predict evolution to SLE. Survival analysis was used to evaluate the disease progression towards SLE in groups with different laboratory variables.

RESULTS

Of the original cohort of 91 patients with UCTD, 76 were still being followed at our unit in May 2001. One patient had died after 18 months of followup due to unknown causes. Seven were lost after followup of less than 5 years (minimum 36, maximum 48; mean 39 mo) and were excluded from this study, while 7 were lost after followup of more than 5 years (minimum 90, maximum 284; mean 132 mo) and were included in our analysis (all 14 still had undifferentiated disease at the time of their last observation). Thus a total of 83 patients with a minimum followup of 5 years were included in the study.

During the course of the followup, 64 patients (61 women, 3 men) with a mean followup of 120 months (minimum 60, maximum 228; median 108 mo) still had UCTD at their last observation, while 18 patients developed SLE and one developed primary Sjögren's syndrome (23%). The clinical and serological manifestations of these patients at onset are reported in Table 1. Since patients who had been diagnosed as early as 1974 were included in the analysis, the data on anticardiolipin antibodies at baseline are not complete (61/83 patients tested at baseline). However, testing for anticardiolipin antibodies was carried out in all patients during the followup.

The single case of Sjögren's syndrome was observed after 66 months of followup. Full-blown SLE appeared after a mean period of 54 months (range 17–96). Survival analysis revealed a reduction in the rate of evolution to SLE over time, with a survival rate of 83% at 5 years and 76% at 10 years (Figure 1). Univariate analysis showed anticardiolipin antibodies to be associated with the development of SLE (38% vs 10% in patients with evolved and stable UCTD, respectively; $p < 0.05$). The coexistence of multiple antibody specificities was also correlated with an evolution to SLE (57% vs 30% in evolved and stable UCTD, respectively; $p < 0.05$).

One patient developed SLE during puerperium, with a clinical picture marked by fever, pericarditis, pleurisy, and renal involvement (type IV glomerulonephritis and nephrotic syndrome). No other triggering events for the evolution to SLE emerged from our analysis.

Clinical profile of 64 patients with UCTD whose condition did not change after minimum followup of 5 years. The most frequent clinical manifestations presented during the followup by the 64 patients with stable UCTD were arthralgias (81%), Raynaud's phenomenon (48%), arthritis (45%), leukopenia (42%), sicca symptoms (xerostomia and/or xerophthalmia) (42%), and photosensitivity (28%). An associated autoimmune thyroid disease was observed in 13% of the patients. During the followup all patients underwent a complete ANA evaluation (anti-extractable nuclear antigens and anti-dsDNA) using validated techniques. Forty-three (67%) had a definite ANA specificity, while the remaining 21 (33%) had undefined ANA positivity; 10 patients presented anticardiolipin antibodies in association with ANA. Twenty-eight patients (44%) were found to have a simple autoantibody profile characterized by the presence of

Table 1. Clinical manifestations at onset in patients who still had undifferentiated disease at the end of the followup compared with patients who developed SLE during the course of their disease.

	Undifferentiated Patients, %	Evolved Patients, %
Arthralgias	69	67
Arthritis	33	44
Alopecia	19	28
Fever	11	28
Malar rash	3	11
Photosensitivity	17	0
Serositis	6	11
Sicca symptoms	22	6
Anemia	6	0
Leukopenia	25	22
Thrombocytopenia	12	6
Anticardiolipin antibodies *	13	50
Anti-dsDNA	10	27

* Anticardiolipin antibodies $p < 0.01$.

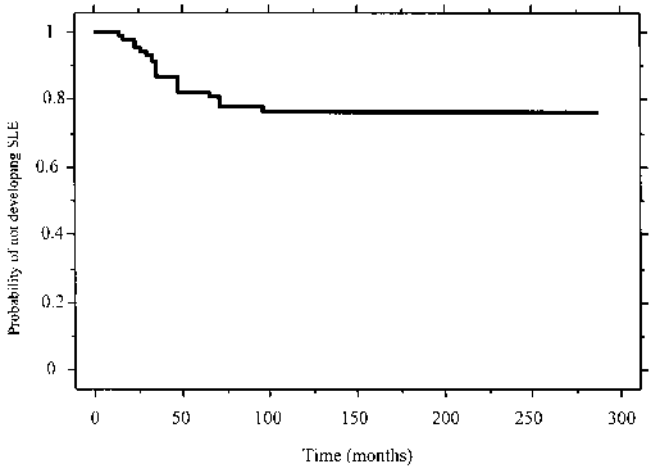

Figure 1. Probability of not developing SLE. At 5 years the survival rate was 83% (66 patients at risk), while at 10 years the survival rate was 76% (25 patients at risk).

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a single specificity: 13 (46%) exhibited anti-Ro/SSA antibodies alone, 10 (43%) anti-RNP antibodies alone, and 5 anti-dsDNA antibodies alone (11%). Twenty patients (31%) presented multiple antibody specificities (multiple ANA or ANA and anticardiolipin antibodies). In 16 patients (25%) the ANA specificity was undefined.

Our analysis of the clinico-serological correlations showed that anti-RNP antibodies were significantly correlated with Raynaud's phenomenon ($p < 0.001$).

Clinical profile of the 18 patients with UCTD who developed SLE. Sixteen of the 18 patients whose condition evolved to SLE were still being followed at our unit in May 2001; the other 2 were lost to followup shortly after the diagnosis of SLE. The American College of Rheumatology criteria[14] most frequently present in these 18 patients were renal involvement (44%), immunologic abnormalities (39%), arthritis (33%), malar rash (28%), hematologic abnormalities (28%), and serositis (24%).

The clinical manifestations presented by the 16 patients with SLE who completed the study (mean 101 mo, minimum 10, maximum 240, median 102) are reported in Table 2. The most serious organ involvement was renal (44% of the patients), consisting of type IV glomerulonephritis in 63%, type III glomerulonephritis in 25%, and type II glomerulonephritis in 12% of the patients. When patients were analyzed based on the timing of the disease evolution, it was found that those whose SLE had appeared within the 5th year of followup had a higher incidence of renal involvement (55% vs 28%) and type IV glomerulonephritis (observed only in this group).

New autoantibody specificities were observed in 7 patients, with the appearance of anti-dsDNA antibodies in 6 patients and anticardiolipin IgG in one patient.

Table 2. Cumulative clinical and laboratory manifestations in patients with UCTD who evolved to SLE compared with our SLE cohort and with the data on SLE patients reported in the literature.

Manifestation	UCTD Patients Who Evolved to SLE, %	Our SLE Cohort (n = 350), %	Literature Data, %[23,30]
Arthralgias	94	82	53–95
Alopecia	89	63	3–45
Arthritis	72	69	53–95
Photosensitivity	78	60	11–45
Malar rash	72	55	39–61
Leukopenia	50	42	41–66
Raynaud's phenomenon	44	49	18–58
Renal involvement	44	53	31–60
Fever	44	26	41–86
Skin vasculitis	33	35	21–37
Lymphoadenopathy	33	12	10–59
Serositis	33	29	31–63
Thrombocytopenia	28	23	7–45
Anemia	39	58	30–78
Thyroiditis	17	10	2–32

DISCUSSION

The following conclusions can be drawn from our extended followup of 83 patients with UCTD: (1) the evolution of UCTD to a defined CTD (usually SLE) is not frequent, although it did occur in 23% of our patients; (2) the rate of evolution to a defined CTD is high in the first years of followup and decreases over time; (3) the presence of anticardiolipin antibodies and multiple autoantibody specificities are prognostic factors for the evolution to SLE; (4) no specific triggering factors for the evolution could be identified in our patient series, but the presence of factors known to influence autoimmune activity (such as pregnancy) are an indication for careful monitoring; (5) the clinical profile of patients who develop SLE from UCTD is comparable to the profile reported for other SLE cohorts, although patients whose SLE evolves later apparently have a less aggressive form of lupus than those whose disease evolves earlier.

Following the first report on undifferentiated autoimmune diseases (undifferentiated connective tissue syndromes) published in 1980 by LeRoy and colleagues, many authors have studied these conditions and a large amount of data is now available regarding their clinical and laboratory features[1-13,24-29]. It is generally agreed that UCTD is a mild autoimmune disease with a limited clinical and autoantibody repertoire that will evolve to a defined CTD in only a small percentage of cases. Therefore UCTD should be considered a distinct clinical entity rather than as the early phase of a defined CTD.

Important questions remain. Does the risk of evolution to a defined CTD change over time, and to what extent? Are certain conditions likely to trigger the evolution of UCTD to defined CTD? What is the clinical and laboratory profile of the evolved disease?

In this study of a cohort of 83 patients with UCTD, 18 developed SLE and one developed Sjögren's syndrome. These results are in agreement with our findings based on a one year followup of the same cohort[6], and are also consistent with most of the data in the literature. Indeed, although some papers have reported an evolution rate as high as 68%, when similar selection criteria were adopted — i.e., patients with an undefined disease who had been followed for at least one year — the percentage who actually developed a defined CTD decreased to values ranging between 6% and 37%[7,8,11].

In contrast with our initial hypothesis[6] and others' results[7,10,29], the presence of anti-dsDNA antibodies was not significantly correlated with an evolution to SLE. This finding, however, could be attributed to the fact that power calculation for this variable was only 0.45. In contrast with our previous findings but in accord with data reported by others[8], the presence of both anticardiolipin antibodies and multiple autoantibody specificities were significantly correlated with the evolution of UCTD to SLE.

In view of the recent modifications in the classification

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criteria for SLE[15], the predictive role of anticardiolipin antibodies deserves discussion, since in this longterm study the 1982 criteria were used. With the new criteria, some UCTD patients might be reclassified as SLE solely on the basis of a positive antiphospholipid antibodies test. In our cohort, patients with positive anticardiolipin and/or anti-dsDNA antibodies at their first observation were diagnosed as UCTD since their clinical profile was very mild and clinically not yet suggestive of SLE. Therefore, the evolution from UCTD to SLE was diagnosed based on the appearance of both clinical and serological manifestations of the disease.

However, given the role of antiphospholipid antibodies as a classification criterion, the presence of anticardiolipin alone (without ANA antibodies) deserves further evaluation as an additional criterion for the definition of UCTD. In this case, a thorough evaluation to exclude the possibility of antiphospholipid syndrome would be essential.

We were unable to correlate the evolution to SLE with specific triggering factors, except in the case of one patient who developed SLE during puerperium after a disease duration of 27 months, who presented with serositis, renal involvement (type IV glomerulonephritis and nephrotic syndrome), and anti-dsDNA antibodies. This observation suggests that any event that could alter the natural history of the patient's autoimmune condition (such as pregnancy, infection, or other environmental factors) may also cause a disease flare in UCTD and in some cases trigger the evolution to a defined CTD; therefore, patients experiencing such an event should be carefully monitored.

In our cohort the risk of evolution to a defined CTD decreased over time, although some cases developed very late in the followup. It is generally agreed that at least one year may be necessary for a full-blown CTD to manifest itself[6] and since cases evolving from UCTD develop even more slowly, one could hypothesize that the subsequent CTD may retain this characteristic and represent a distinct, less aggressive or more slowly evolving form of SLE. The patients in our cohort who developed SLE do not seem to support this hypothesis, however, since they were comparable to the classic SLE cases reported in the literature. It is nevertheless interesting that those whose SLE developed late during their followup seemed to have milder disease with a lower incidence of serious adverse events, although the relatively small number of patients studied limits the conclusions that may be drawn from this observation. Further studies are clearly needed.

In conclusion, our study of 83 patients with UCTD for a minimum followup period of 5 years confirms the hypothesis that UCTD make up a spectrum of distinct conditions that will evolve to defined CTD (usually SLE) in only a small percentage of cases, and generally early in the clinical course of the disease. Although it is clear that the clinician must base treatment and followup of a patient on the specific signs and symptoms shown by that patient and not on "classification" criteria, we feel that a correct diagnosis of UCTD is important for at least 2 reasons. First, it allows the clinician to reassure patients with regard to their prognosis, in view of the limited risk of major organ involvement, whereas a mistaken diagnosis of latent or incomplete SLE would involve unnecessary psychological and, in some cases, economic costs. Second, UCTD is a simple autoimmune condition that could offer a model for the study of different autoantibody specificities, the effects of various factors (such as pregnancy) on the disease course, and the general pathogenesis of autoimmune conditions.

ACKNOWLEDGMENT

We gratefully acknowledge the assistance of Daniela Totti in the day-to-day care and followup of the patients, and Lisa Chien for correcting the English in this manuscript.

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