# Undifferentiated connective tissue disease: predictors of evolution into definite disease

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## Abstract

### Objective

*The natural evolution of undifferentiated connective tissue diseases (UCTD) has not yet been established. The aim of our study was to analyse the clinical outcomes of a cohort of UCTD patients followed in a routine outpatient setting and to establish which clinical, serological or capillaroscopy features are associated with an increased risk of evolution to definite connective tissue disease (CTD).*

### Methods

*Data for this study were collected by a retrospective review of 758 patients referred to our hospital, between 1999 and 2008, with suspected CTD. After selection criteria, 98 patients were considered eligible and their records, laboratory findings and nailfold-capillaroscopy pattern (NCP) were analysed until clinical outcome. Three groups of patient outcomes were established: remission, UCTD, and definite CTD. Logistic regression analysis was performed to study the association of baseline clinical features, including NCP progression during monitoring, with clinical outcomes.*

### Results

*After a mean follow-up of 11±3 years, 62% of the patients continued to suffer from UCTD, 24% regressed to a remission state and 14% developed definite CTD. Cytopenias (p=0.030), positivity for antibody specificities (ENA) (p=0.008), anti-Ro (p=0.036) and antiphospholipid antibodies (p=0.032), and the presence of an altered NCP (p=0.026) at baseline proved different between groups and were more frequently encountered in the group that evolved to definite CTD when compared with the others two groups. Specifically, cytopenias (odds ratio -OR- 4.20 [1.30–13.56] p=0.016), the presence of an antinuclear antibody (ANA) titre ≥1/640 (OR 7.00 [1.99–24.66], p=0.002) and anti-centromere positivity (OR 3.77 [1.03–13.79], p=0.045) at baseline and NCP progression (OR 6.63 [1.70–25.87], p=0.007) were associated with the future presence of definite CTD.*

### Conclusion

*Most patients with UCTD remain in an undifferentiated state after routine outpatient clinic follow-up. High ANA titres or the presence of cytopenias at baseline, as well as progression of NCP during follow-up, are the leading factors associated with evolution to definite CTD.*

**Key words**

undifferentiated connective tissue disease, connective tissue disease

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## Introduction

Since the widespread acceptance of the term undifferentiated connective tissue disease (UCTD) in the 80s, this entity has been variably defined using heterogeneous clinical, serological and temporal criteria. It generally applies to a clinical situation in which there are isolated features of connective tissue diseases (CTD) without fulfilling the classification criteria of any specific condition. It is estimated that up to 25% of the patients seen by rheumatologists in tertiary centres fall into this category (1). Although evolution to definite CTD after 5 years has been described in up to 30% of such individuals, most reportedly continue to suffer from UCTD (2).

Some authors have identified certain clinical, serological and capillaroscopy features as predictive factors for evolution (3-12). However, the great heterogeneity in the inclusion criteria chosen by each author has hampered not only comparisons between studies, but also to characterise, in clinical and prognostic terms, UCTD. The classification criteria proposed by Mosca *et al*. (13) require an observation time of three years, rendering them inapplicable at the time of disease onset. For this reason, and in order to distinguish between "true" UCTD and incomplete CTD forms, this group has proposed some exclusion criteria based on clinical and serological features considered specific to definite CTD (14).

Since currently an accurate diagnosis of UCTD is only possible retrospectively, the ability to properly identify predictive factors of its evolution to definite CTD will allow clinicians to individually tailor patients' follow-up and improve their diagnosis and therapeutic management. In this sense, the aim of our study was to analyse the clinical outcome of a cohort of UCTD patients followed in our hospital and to establish which clinical, serological and capillaroscopy features are associated with an increased risk of evolution to definite CTD.

## Materials and methods

### *Study design*

Patients with suspected CTD under care of the Division of Rheumatology outpatient clinic at Hospital Universitario de Canarias between 1999 and 2008 who remained in an undifferentiated state after the first year of follow-up were selected. As previously described, these patients were characterised by the presence of isolated clinical features suggestive of CTD and at least one non-organ specific autoantibody (6, 15) or an altered nailfold-capillaroscopy pattern (NCP) (10). Patients presenting definite CTD or pre-scleroderma (according to the LeRoy and Medsger classification system (16)) at baseline were excluded. Since evolution to a definite connective tissue disease occurs in the first 5 years of follow-up in the vast majority of the reported cases (2), patients followed up for a shorter period were excluded.

Three groups of patients were established based on their clinical outcomes: definite CTD, UCTD, and remission. Patients who presented typical clinical and serological features consistent with definite CTD and/or met classification criteria (17-23) during follow-up were considered as such, while those whose features were insufficiently distinctive to establish a diagnosis at the end of the follow-up period were considered as UCTD. Patients who experienced stable regression and remained in any of the following situations at the end of follow-up were considered in remission: 1) presence of a single clinical feature (excluding those considered specific to definite CTD (14)) without autoimmune markers and with a normal NCP; 2) asymptomatic patients with antinuclear antibodies (ANA) ≤1/160 as the only autoimmune marker and a normal NCP (24, 25); 3) non-specific NCP persistently stable in asymptomatic patients without autoimmune markers (26, 27).

In this regard, 758 patients were initially selected for our study. One hundred and forty one lacked sufficient data for classification in the study, and 394 did not meet the inclusion criteria. Of the 223 patients who fulfilled the inclusion criteria, 97 were classified as definite CTD after initial screening, and 28 were followed for less than 5 years, and so were excluded. Accordingly, 98 patients were included in the present study.

### *Data collection*

The following baseline variables recorded during routine clinical practice

were retrospectively collected from the patients' medical records: i) clinical features suggestive of CTD reported by patients and/or identified by a rheumatologist: Raynaud's phenomenon, cutaneous manifestations (puffy fingers, sclerodactily, scleroderma, telangiectasia, livedo reticularis, photosensitivity, malar rash, discoid lupus, recurrent aphthosis), musculoskeletal manifestations (muscle weakness, myalgias, artrhralgias, arthritis), oesophageal dysfunction (dysphagia, gastroesophageal reflux, hypotonia), *sicca* syndrome (xerostomia, xerophthalmia), ocular manifestations (episcleritis, scleritis, uveitis) and serositis; ii) laboratory features suggestive of CTD: normochromic normocytic anaemia, leukopenia, lymphopenia, neutropenia, thrombocytopenia, ANA titres and patterns, antibody specificities (ENA), anti-ds-DNA antibodies, lupus anticoagulant, anticardiolipin and anti-beta 2 glycoprotein antibodies, rheumatoid factor, anti-citrullinated peptides antibodies, hypocomplementaemia and dysgammaglobulinaemia. All results stem from the same laboratory. ANA were determined by indirect immunofluorescence (IIF) on HEp-2 cell lines, ENA by Western blotting and anti ds-DNA antibodies by ELISA and IIF on *Crithidia lucilliae*.

*Nailfold-capillaroscopy study*

Patients' NCP at baseline and 5 years later were obtained from the capillaroscopy registry of the Division of Rheumatology. All the nailfold capillaroscopies were performed by the same observer using a Leica stereomicroscope 10447123 10x23 who examined the fingers of both hands (excluding thumbs) and made qualitative assessments on the basis of widefield findings. Scleroderma and normal NCP were defined according to Maricq descriptions (28). The existence of minor changes in a single capillaroscopy parameter was considered a variant of the normal NCP; when these changes occurred very frequently, in moderate intensity or were accompanied by changes in other capillaroscopy parameters, they were regarded as non-specific NCP (27). The evolution from normal or non-specific NCP to scleroderma pattern, or from normal NCP to non-specific NCP were considered as evidence of NCP progression. Both non-specific and scleroderma NCP were considered altered NCP.

*Statistical analysis*

Demographic characteristics at baseline are shown in Table I; continuous variables are expressed as the mean ± standard deviation (SD); for non-continuous variables, data are expressed as a median (interquartile range-IQR). The baseline characteristics between outcome groups displayed in Table II, and the relation between NCP and clinical outcomes presented in Table III, were compared using chi-square tests for categorical variables or an ANOVA test for continuous variables (data expressed as the mean ± standard deviation). For non-continuous variables, a Kruskal-Wallis test was performed. Differences between ANA titre medians were analysed using a Mann-Whitney U-test; this involved comparing outcome groups in pairs: remission *versus* UCTD, remission *versus* definite CTD, and UCTD *versus* definite CTD. Variables with a *p*-value lower than 0.20 in Table III were selected in order to analyse their relation with definite CTD using logistic regression, as shown in Table IV. All the analyses used a 5% two-sided significance level and were performed using SPSS software, v. 21 (IBM, Chicago, IL, USA). A *p*-value <0.05 was considered statistically significant.

## Results

*Participant characteristics*

A total of 98 patients with a mean ± SD age of 42±16 years were included in this study. A summary of the main demographic and CTD-related characteristics of the participants are shown in Table I. Ninety-seven (99%) of the patients were female. The principal clinical features included Raynaud's phenomenon (89 patients, 91%), cutaneous (41, 42%) and musculoskeletal manifestations (53, 54%), and *sicca* syndrome (27, 28%). Laboratory data disclosed cytopenias in 28 (29%) patients, and positivity for ANA (87, 89%) and ENA (39, 40%) were the most frequent features. Similarly, 55 (56%) patients had, at baseline, a normal NCP, while 36 (37%) and 7 (7%) patients were categorised as having, respectively, a non-specific and a scleroderma NCP.

**Table I.** Patient characteristics at baseline.

| | Total of patients (n=98) |
|---|---|
| Age, years | 42 ± 16 |
| Female, n (%) | 97 (99) |
| *Clinical features* | |
| Raynaud's phenomenon, n (%) | 89 (91) |
| Cutaneous manifestations, n (%) | 41 (42) |
| Musculoskeletal manifestations, n (%) | 53 (54) |
| Oesophageal dysfunction, n (%) | 13 (13) |
| Sicca syndrome, n (%) | 27 (28) |
| Ocular manifestations, n (%) | 0 (0) |
| Serositis, n (%) | 0 (0) |
| Cytopenias, n (%) | 28 (29) |
| *Serological features* | |
| ANA (+), n (%) | 87 (89) |
| ENA (+), n (%) | 39 (40) |
| dsDNA (+), n (%) | 5 (5) |
| APL (+), n (%) | 11 (11) |
| RF (+), n (%) | 8 (8) |
| ACPA (+), n (%) | 0 (0) |
| Low seric complement, n (%) | 7 (7) |
| Immunoglobulins disorders, n (%) | 24 (25) |
| *Nail-fold capillaroscopy pattern* | |
| Normal, n (%) | 55 (56) |
| Non-specific, n (%) | 36 (37) |
| Scleroderma, n (%) | 7 (7) |

ANA (+): positive anti-nuclear antibodies.
ENA (+): positive antibody specificities.
dsDNA (+): positive anti double stranded DNA antibodies.
APL (+): positive anti-phospholipid antibodies.
RF (+): positive rheumatoid factor.
ACPA (+): positive anti-citrullinated peptide antibodies.

*Clinical outcomes and relation of baseline characteristics with clinical outcomes*

After an average follow-up of 11±3 years, 61 (62%) patients remained categorised as UCTD, 23 (24%) regressed to a remission state and 14 (14%) were diagnosed with definite CTD (9 systemic lupus erythematosus, 2 prescleroderma, 1 mixed connective tissue disease, 1 diffuse systemic sclerosis and 1 scleroderma-Sjögren syndrome overlap). Median time to evolution was 4 years (IQR 3-8); among patients with systemic lupus erythematosus this time was shorter than that of patients with a scleroderma-spectrum disease: 4 years (IQR 1-6) *versus* 7 years (IQR 4–9), re-

spectively. In the subset of 12 patients with Raynaud's phenomenon and anticentromere positivity at baseline, we observed a higher frequency of evolution to a definite CTD (25% *vs*. 14%), with progression only to diseases of the scleroderma-spectrum.

The distribution of baseline characteristics between outcome groups is presented in Table II. Age at UCTD onset and median follow-up until outcome did not differ between groups. Cytopenias ($p$=0.030), positivity for ENA ($p$=0.008) and for anti-Ro ($p$=0.036), the presence of antiphospholipid antibodies ($p$=0.032) and the occurrence of an altered NCP ($p$=0.026) were more frequent in the group in which definite CTD was reached at the end of the follow-up.

The ANA titre median was higher in the definite CTD group (1/640 *vs*. respectively, 1/320 and 1/160 in the UCTD and remission groups). The differences were statistically significant between remission *versus* UCTD groups ($p$=0.045) and remission *versus* definite CTD groups ($p$=0.028), but not between UCTD *versus* definite CTD groups ($p$=0.95). The remaining clinical and laboratory data between groups did not reach statistical significance, although a trend for the presence of lymphopenia in the definite CTD group was observed ($p$=0.100).

### *Nailfold-capillaroscopy pattern progression and clinical outcomes*

As previously mentioned, the presence of a baseline altered NCP was more frequent in the group where the patients were categorised, after follow-up, as having definite CTD (64% *vs*. 47% and 22% in the UCTD and remission groups, respectively; $p$=0.026).

Twenty-one patients showed NCP progression (Table III). Those in the definite CTD group showed a higher tendency to do so (64% *vs*. 20% and 21% in the remission and UCTD groups, respectively; $p$=0.012). The type of progression was also different, with more cases evolving from a non-specific to a scleroderma pattern in the definite CTD group (71% *vs*. 60% and 0% in the UCTD and remission groups, respectively).

**Table II.** Clinical and serological characteristics vis-à-vis clinical outcomes.

| | Remission (n=23) | UCTD (n=61) | Definite CTD (n=14) | *p* |
|---|---|---|---|---|
| Age, years | 39 ± 16 | 44 ± 16 | 41 ± 17 | 0.223 |
| Follow-up , years | 12 ± 3 | 11 ± 3 | 10 ± 3 | 0.221 |
| *Clinical features* | | | | |
| Raynaud's phenomenon, n (%) | 22 (96) | 55 (90) | 12 (86) | 0.573 |
| Cutaneous manifestations, n (%) | 7 (30) | 27 (44) | 7 (50) | 0.415 |
| Musculoskeletal manifestations, n (%) | 13 (57) | 33 (54) | 7 (50) | 0.928 |
| Arthritis | 0 (0) | 6 (10) | 1 (7) | 0.260 |
| Oesophageal dysfunction, n (%) | 3 (13) | 10 (16) | 0 (0) | 0.264 |
| Sicca symptoms, n (%) | 6 (26) | 17 (28) | 4 (29) | 0.983 |
| Dry mouth | 4 (17) | 15 (25) | 3 (21) | 0.473 |
| Dry eyes | 3 (13) | 10 (16) | 4 (29) | 0.233 |
| Both | 1 (4) | 8 (13) | 3 (21) | 0.180 |
| Cytopenias, n (%) | 7 (30) | 13 (21) | 8 (57) | **0.030** |
| Red cells | 0 (0) | 3 (5) | 0 (0) | – |
| Platelets | 4 (17) | 2 (3) | 2 (14) | 0.138 |
| White cells | 5 (22) | 11 (18) | 7 (50) | 0.684 |
| Neutropenia | 2 (9) | 3 (5) | 2 (14) | 0.870 |
| Lymphopenia | 0 (0) | 3 (5) | 4 (29) | 0.100 |
| Several series | 2 (9) | 3 (5) | 1 (7) | 0.736 |
| *Serological features* | | | | |
| ANA (+), n (%) | 19 (83) | 54 (89) | 14 (100) | 0.197 |
| *Titre* | | | | |
| 1/80, n (%) | 5 (22) | 11 (18) | 2 (14) | 0.640 |
| 1/160, n (%) | 7 (30) | 14 (23) | 3 (21) | 0.478 |
| 1/320, n (%) | 5 (22) | 8 (13) | 2 (14) | 0.429 |
| 1/640, n (%) | 1 (4) | 8 (13) | 7 (50) | **0.003** |
| ≥ 1/1280, n (%) | 0 (0) | 13 (21) | 0 (0) | – |
| *Indirect Immunofluorescence pattern* | | | | |
| Homogeneous, n (%) | 3 (13) | 11 (18) | 4 (29) | 0.747 |
| Coarse speckled, n (%) | 7 (30) | 16 (26) | 3 (21) | 0.487 |
| Fine speckled, n (%) | 3 (13) | 12 (20) | 2 (14) | 0.753 |
| Centromere, n (%) | 1 (4) | 8 (13) | 5 (36) | 0.075 |
| Others, n (%) | 3 (13) | 6 (10) | 0 (0) | 0.279 |
| ENA (+), n (%) | 3 (13) | 27 (44) | 9 (64) | **0.008** |
| Anti Centromere | 0 (0) | 8 (13) | 5 (36) | 0.160 |
| Anti Scl-70 | 0 (0) | 3 (5) | 0 (0) | – |
| Anti RNP | 0 (0) | 7 (12) | 4 (29) | 0.298 |
| Anti Sm | 0 (0) | 5 (8) | 3 (21) | 0.417 |
| Anti Hystone | 0 (0) | 1 (2) | 2 (14) | 0.171 |
| Anti Ro | 3 (13) | 7 (12) | 3 (21) | **0.036** |
| Anti La | 1 (4) | 3 (5) | 0 (0) | 0.248 |
| Several ENA (+) | 1 (4) | 7 (12) | 5 (36) | 0.264 |
| Anti dsDNA (+), n (%) | 0 (0) | 4 (7) | 1 (7) | 0.469 |
| APL (+), n (%) | 0 (0) | 7 (12) | 4 (29) | **0.032** |
| RF (+), n (%) | 1 (4) | 5 (8) | 2 (14) | 0.574 |
| Low seric complement, n (%) | 0 (0) | 5 (8) | 2 (14) | 0.254 |
| Dysgammaglobulinaemia, n (%) | 4 (17) | 16 (26) | 4 (29) | 0.712 |
| High immunoglobulins levels | 3 (13) | 10 (16) | 3 (21) | 0.829 |
| Low immunoglobulins levels | 1 (4) | 6 (10) | 1 (7) | 0.829 |

UCTD: undifferentiated connective tissue disease; ANA (+): positive anti-nuclear antibodies; ENA (+): positive antibody specificities; dsDNA (+): positive anti-double stranded DNA antibodies; APL (+): positive anti-phospholipid antibodies; RF (+): positive rheumatoid factor.

### *Clinical and analytical features associated with definite CTD*

Those features with a $p$-value lower than 0.20 in Table II were selected for logistic regression analysis of their evolution to definite CTD (Table IV). In this sense, cytopenias (odds ratio -OR- 4.20 [1.30–13.56] $p$=0.016), the presence of an ANA titre ≥1/640 (OR 7.00 [1.99–24.66], $p$=0.002) and anticentromere positivity (OR 3.77 [1.03–13.79], $p$=0.045) at baseline, and a NCP progression (OR 6.63 [1.70–25.87], $p$=0.007) were associated with future onset of definite CTD.

Lymphopenia (OR 5.78 [0.82–40.76],

**Table III.** Capillaroscopy pattern vis-à-vis clinical outcomes.

| | n | Remission (n=23) | UCTD (n=61) | Definite CTD (n=14) | *p* |
|---|---|---|---|---|---|
| Baseline NCP | | | | | |
| Normal, n (%) | 55 | 18 (78) | 32 (53) | 5 (36) | **0.026*** |
| Altered, n (%) | 43 | 5 (22) | 29 (47) | 9 (64) | |
| Non-specific | 36 | 5 (22) | 24 (39) | 7 (50) | |
| Scleroderma | 7 | - | 5 (8) | 2 (14) | |
| NCP progression, n (%) | 21 | 4 (20) | 10 (21) | 7 (64) | **0.012**† |
| Normal → Non-specific | 9 | 4 (100) | 3 (30) | 2 (29) | |
| Normal →Scleroderma | 1 | - | 1 (10) | - | |
| Non-specific → Scleroderma | 11 | - | 6 (60) | 5 (71) | |

UCTD: undifferentiated connective tissue disease; NCP: nail-fold capillaroscopy pattern.
*Pearson Chi-square (Altered NCP by Clinical outcome): $p$=0.026.
†Pearson Chi-square (NCP progression by Clinical outcome): $p$=0.012.

**Table IV.** Logistic regression analysis of the relation of clinical and analytical features with definite connective tissue disease.

| | OR (95% CI) | *p* |
|---|---|---|
| Sicca symptoms | 1.23 (0.75-2.01) | 0.41 |
| Cytopenias | 4.20 (1.30-13.56) | **0.016** |
| Thrombopenia | 0.78 (0.12-5.02) | 0.79 |
| Lymphopenia | 5.78 (0.82-40.76) | 0.078 |
| ANA ≥ 1/640 | 7.00 (1.99-24.66) | **0.002** |
| ENA (+) | 2.70 (0.82-8.85) | 0.101 |
| Anti-Centromere | 3.77 (1.03-13.79) | **0.045** |
| Anti-Ro | 1.00 (0.21-4.86) | 0.99 |
| APL (+) | 4.19 (0.94-18.70) | 0.060 |
| Altered NCP | 2.65 (0.82-8.59) | 0.105 |
| NCP progression | 6.63 (1.70-25.87) | **0.007** |

ANA: anti-nuclear antibodies; ENA (+): positive antibody specificities; APL (+): positive antiphospholipid antibodies; NCP: nail-fold capillaroscopy pattern.

$p$=0.078), positivity for ENA (OR 2.70 [0.82–8.85], $p$=0.101), positivity for antiphospholipid antibodies (OR 4.19 [0.94–18.70], $p$=0.060), and the presence of an altered NCP at baseline (OR 2.65 [0.82–8.59] $p$=0.105) trended to be associated with a higher risk of evolution to definite CTD, although statistical significance was not reached.

## Discussion

Nearly four decades after its recognition as an entity, in the absence of features that distinguish it from transient systemic processes and emerging forms of definite CTD, the diagnosis of UCTD is still based on its behaviour over the passage of time. The central finding of our study is that after a mean follow-up of 11 years, most of the patients initially classified as UCTD remain in the same situation. In those patients who experienced an evolution to definite CTD, we demonstrate the significance of several serological and capillaroscopy features as potential predictors of outcome.

Interestingly, in our study, 14% of patients evolved to definite CTD after an average follow-up of approximately 11 years. Our findings are similar to those reported previously. Guerrero *et al*. (7) recently published a study in which a total of 94 patients with UCTD were followed an average of 51±36 months. In this study only 13 patients (13.8%) evolved to definite CTD. More classical studies have reported higher frequencies of evolution, probably due to the inclusion of early UCTD forms (less than one year of follow-up after symptom onset). In this sense, Williams *et al*. (29, 30) have reported a 62% rate of evolution to definite CTD after 10 years of study survival in 68 patients from an initial cohort of 155 patients. Analogously, Calvo-Alén *et al*. (3) have reported a 29% evolution rate in 143 patients with ascertainable clinical status after 5 years of follow-up from an initial cohort of 213 patients followed at 11 tertiary centers. Regarding time to evolution, our results are also consistent with what has been previously published, with systemic lupus erythematosus patients evolving faster than patients with other definite CTD (31). Contrary, the percentage of remission in our study was higher than that of previous studies; this fact may be due to the less restrictive definition of remission we used. As we only included patients who remained in an undifferentiated state after at least one year of follow-up, inclusion of transient and self-limiting conditions mimicking connective tissue diseases (32) does not seem likely. It would have been interesting to study if therapy could influence the evolution of patients with early stages of definite CTD (33). According to our clinical practice basis, none of our patients should have received immunosuppressive treatment while they remained in an undifferentiated state. Only those who presented cutaneous lupus erythematosus (5 patients) and/or arthritis (7 patients) could have received short courses of low-medium doses of oral glucocorticoids and/or hydroxychloroquine. Regrettably, as patients' therapy was not included as a variable in our study protocol we did not further analyse this issue.

The ability of ANA to identify patients at increased risk of evolution to definite CTD, as evident in our own study, is consistent with several other studies, especially in terms of its positivity or specific IIF pattern (3, 4, 6). In our cohort, we noted a trend to an increased risk in patients with centromere-pattern. Similarly, while the ANA titre at baseline did not permit any distinction between UCTD and definite CTD groups, it did so between them and the remission group. On the other hand, we observed an association between the presence of ENA in general, and of anti-centromere and anti-Ro antibodies in particular, and the evolution to definite CTD. Additionally, in line with previous reports, in our study most patients who developed definite CTD exhibited several positivities for ENA at baseline (34, 35). However the limited number of patients who developed definite CTD and the lack of an anti-Ro assessment, in terms of 52 kDa *versus* 60 kDa specificities (36), prevented us from form-

ing any clear conclusions. Although anti-centromere positivity clearly points to a scleroderma-spectrum disease (37), the only set of criteria for early systemic sclerosis which has demonstrated its validity in a prospective design (38) is the one proposed by LeRoy, which requires apart from the presence of specific autoantibodies, Raynaud's phenomenon and specific-capillaroscopy changes. The EUSTAR group proposal also requires these three major criteria when other features are absent (39), rendering the anti-centromere positivity as a necessary but not sufficient criterium.

In the present study, NCP and pattern progression were also assessed in terms of their associations with clinical outcomes. Similarly to what was described by Pavlov *et al*. (12), the most common NCP at baseline in our cohort was the normal one, with the scleroderma pattern limited to 8% of the cases. This contrasts with the report by Lambova *et al*. (40), in which the most frequent pattern was the non-specific one, with the scleroderma pattern accounting for 39% of cases. These differences could reflect the exclusion of patients with early forms of systemic sclerosis (termed pre-scleroderma in our study and as a suspected secondary Raynaud's phenomenon in Pavlov's study), a possibility not considered in Lambova's study (40). Previous reports have pointed out some capillaroscopy parameters as potential predictors of evolution to definite CTD (10, 11); we have observed that NCP as a simple variable (without considering each of its parameters individually) is also relevant, with increased risk of developing definite CTD in patients with an altered NCP at baseline and in those with NCP progression during follow-up.

The two main limitations of our study are its retrospective design and the limited number of patients who developed definite CTD. The second is similar to what has previously been reported in the literature, and has not allowed us to perform multivariate Cox regression analysis. Although the generalisation of our results should be confirmed in future prospective study, our findings are consistent with previous reports and with current knowledge about the behaviour of UCTD in particular, and CTD in general.

In conclusion, the main finding of our study is that patients with suspected UCTD who present high ANA titres, ENA positivity, presence of cytopenias and an altered NCP at baseline, as well as those with NCP progression during follow-up, are at a higher risk for the development of definite CTD. The presence of these features should prompt physicians to frequently and closely monitor these patients because of their greater risk for developing definite CTD.

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