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Impact of the new 2019 EULAR/ACR classification criteria for Systemic Lupus Erythematosus in a multicenter cohort study of 133 women with undifferentiated connective tissue disease

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Abstract

Objective

We aimed to investigate the impact of applying the 2019 EULAR/ACR classification criteria for systemic lupus erythematosus (SLE) in a previously described cohort of women with undifferentiated connective tissue disease (UCTD).

Methods

This study included 133 women with UCTD. At the time of inclusion into the study, none of the patients meet any classification criteria for other defined systemic connective tissue disease.

Results

When applying the 2019 EULAR/ACR classification criteria to the cohort, 22 patients (17%) fulfilled the classification criteria of SLE. Patients classified as SLE had significantly higher frequency of mucocutaneous manifestations (23%vs.5%;p=0.007), arthritis (59%vs.17%; p<0.001), isolated urine abnormalities (18%vs.1%;p<0.001) and highly specific antibodies (50%vs.15%;p<0.001). At follow-up, these patients were statistically significantly more likely to fit also the ACR 1997 and SLICC criteria (18.2%vs. 1.8%;p<0.001).

Patients who were diagnosed as SLE per the ACR 1997 and SLICC criteria during the follow-up scored significantly more points in the new 2019 EULAR/ACR classification criteria when compared to the other UCTD patients (mean score 8.3±3.7 vs. 4.5±4;p<0.05).

Conclusion

When applying the 2019 EULAR/ACR criteria for SLE in a cohort of patient with UCTD, we observed that in up to 17% of cases the original classification could be challenged. New implementation will help to early identify patients at higher risk of developing more severe CTD manifestations.

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Significance and Innovations

- When applying the new 2019 EULAR/ACR classification criteria, up to 17% of UCTD patients of our cohort of 133 patients meet the classification criteria for SLE
- Patients meeting the 2019 EULAR/ACR classification criteriafor SLE had higher frequency of mucocutaneous manifestations, arthritis, isolated urine abnormalities and highly specific antibodies to SLE.
- This study supports the need of classification criteria for UCTD, especially to identify patients at higher risk of developing more severe CTD manifestations.

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1.0 Introduction

Classification criteria for any given disease may provide some framework to help in diagnosis and are frequently used this way for teaching purposes. They traditionally have a high specificity, which generally is counterbalanced by a lower sensitivity. Consequently, few individuals are incorrectly labeled as having a disease (false positives), but a proportion of those with the disease diagnosis may be "missed," i.e., labeled as not having the disease based on the classification criteria (false negatives). This may make classification criteria inappropriate for use in routine clinical care (1).

The case of undifferentiated connective tissue disease (UCTD) is emblematic. UCTD is an umbrella term describing a condition characterized by clinical and laboratory findings suggestive for connective tissue disease (CTD) butnot fulfilling the current classification criteria for any definite CTD (2–4). In September 2019 a new set of classification criteria for systemic lupus erythematosus (SLE) have been proposed (5). As a main difference from previous SLE classification criteria the presence of antinuclear antibodies(ANA) are required as entry criterion, showing a sensitivity of 96.1% and specificity of 93.4%. Several studies applied the new 2019 EULAR/ACR classification criteria for SLE to different cohorts and compared them with the previous classification criteria (6,7). However, it is unknown if the new classifications criteria for SLE might impact on the categorization of patients previously diagnosed with UCTD. Far from being only an academic question, being classified or not as having SLE may pose clinical and logisticconsequences, as patients with a diagnosis of 'SLE' might be followed-up according to a specific local protocol and have in-label access to certain medications (such as biologics) or may be eligible for the participation in clinical trials.

Herein, we applied the 2019 EULAR/ACR classification criteria for SLE (5) in a previously described cohort of 133 women with UCTD and ANA positivity (8).

2.0 Methods

2.1 Patients

The multicenter retrospective study (8)described the foetal/perinatal and maternal outcomes of a cohort of UCTD patients ever pregnantfrom 2010 to 2019.

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All patients were diagnosed with UCTD according to the established consensus (4,9,10)and were ANA positive. ANA positivity was confirmed and tested as previously described (8).

At the time of pregnancy none of the patients fulfilled the ACR 1997 criteria (11), the SLICC criteria (12)for SLE or other any other defined systemic CTD.

2.2 Statistics:

Categorical variables are presented as number (%) and continuous variables are presented as mean (S.D.). The significance of baseline differences was determined by the chi-squared test, Fisher's exact test or the unpaired t-test, as appropriate. A two-sided P-value <0.05 was statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

3.0 Results

3.1 Patients characteristics of our multicenter cohort

The analysis included 133 women (mean age at data collection 38.3±6.8 years old; mean disease duration at data collection 10.2±5.1 years; mean follow-up at data collection 9.2±4.7 years).

Clinical and laboratory characteristics of the cohort have been previously described elsewhere (8).Briefly, the most common clinical manifestations were joint involvement (57.9%), followed by Raynaud's phenomenon (40.6%), photosensitivity (32.3%) and haematological manifestations (27.1%). Thirty-three patients (24.8%) tested persistently positive for aPL (13)andforty-eight patients (36.1%) were also found to be positive for anti-ENA, being anti-Ro/SSA positivity the most common (45 patients; 33.8%).

3.2 Disease Evolution at Follow-up

Patients had a mean follow-up at data collection of 9.2±4.7 years and during the follow-up, 16 patients (12%) developed novel clinical and/or laboratory features, and their diagnosis was changed in definite CTD. Mean time of follow-up before the diagnosis of definite CTD was achieved was 5.3±2.8 years. Seven patients (5.3%) were later classified according to ACR 1997 criteria (11) and SLICC criteria (12) as SLE, seven

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patients (5.3%) as mixed CTD, one patient (0.75%) as systemic sclerosis and one patient as Sjögren's syndrome.

3.3 Application of the 2019 EULAR/ACR classification criteria for SLE

When applying the 2019 EULAR/ACR classification criteria to the cohort, 22 patients (17%) at the time of their first pregnancy scored ≥10 points and meet the classification criteria of SLE (5).

Table 1 and Figure 1 summarize the positive clinical and immunological domains when considering all the UCTD patients and the patients that meet the 2019 EULAR/ACR classification criteria for SLE at study entry.

When considering the most frequent positive domains, patients that scored ≥10 points, and were therefore classifiable at study entry as SLE by 2019 EULAR/ACR classification criteria, had significantly higher frequency of mucocutaneous manifestations (23% vs. 5%; p=0.007), arthritis (59% vs. 17%; p<0.001), isolated urine abnormalities [isolated proteinuria ≥0.5 g/24h (defined as presence of proteinuria without other urine abnormalities); 18% vs. 1%; p<0.001] and highly specific antibodies (50% vs. 15%; p<0.001)when compared to patients with UCTD who scored <10 points.

When considering patients who met the 2019 EULAR/ACR SLE criteria, those patients at follow-up were statistically significantly more likely to be classified as having SLE according to the ACR 1997 (11)and SLICC criteria (12)compared to the other UCTD patients(18.2% vs. 1.8%; p<0.001), had also fewer years of disease duration (8.23 vs. 10.7; p<0.05) and were more likely to develop pre-eclampsia in pregnancy (18% vs. 0%; p<0.001).

Patients who were diagnosed as SLE according to the ACR 1997 and SLICC criteria scored significantly higher when applying the 2019 EULAR/ACR classification criteria when compared to the other UCTD patients (mean score 8.3 ±3.7 vs. 4.5±4; p<0.05).

Table 2 summarize the clinical and immunological characteristic of the patients that at the follow-up fulfilled the ACR 1997 and SLICC criteria for SLE.

4.0 Discussion

UCTD is a heterogeneous nosologic entity which includes various clinical scenarios, encompassing from mild symptoms, such as arthralgia, to more severe manifestations

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including severe organ involvement such as non-specific interstitial pneumonia. Since the 1980s many studies were carried out to analyze all the aspects of UCTD, from incidence, prevalence, clinical and serological profile to possible evolution over time to a defined CTD. It is now fully accepted that UCTD represents a separate clinical entity and that only up to 30% of UCTD patients will develop a defined CTD in a five years period time (9,10).

To date, UCTD has been reported as one of the most common rheumatic diseases (14), however, there are no validated classification criteria for UCTD patients.

In our previous experience (8), we demonstrated that at follow-up, up to 12% of patients evolved from UCTD to definite CTD(5.3% towards SLE), rates in line with previous experiences reported in the current literature (15). When applying the new 2019 EULAR/ACR classification criteria (5), up to 17% of patients would have been classified as SLE patients before their pregnancy. This has some important implications, as, to date, there are no well-defined recommendations for the diagnosis and, more importantly, the management UCTD patients.

These patients, with higher scores, according to the new 2019 EULAR/ACR classification criteria (5), had higher rates of pre-eclampsia during pregnancy, which suggests that were at higher risk of pregnancy complications.

Taken the above together, this study carries some important messages. One could speculate that an early identification as SLE of patients with a previous diagnosis of UCTD might impact of their clinical management, leading for instance to a closer follow-up. Similarly, it might lead to an in-label access to specific treatment (e.g. belimumab), eligibly to enter a clinical trial or the patients may be eligible to different forms of monetary reimbursement.

Finally, the lack of tailored classification criteria in UCTD might result in underestimating or neglecting patients that fall under the umbrella term UCTD. For the patient this may result in lack of timely follow up, lack of ‘awareness’/education of their underlying condition (as they are not classified as having a disease *per se*) with an exhaustive list of possible consequences related to their non-classification.

Some limitations should be acknowledged. First the retrospective nature of the study could potentially affect the reproducibility of the results. Second, since this study carries

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an intrinsic gender bias, results might not be consistent when applied to a male population.

In conclusion, when applying the 2019 EULAR/ACR criteria for SLE in a cohort of women with UCTD, we observed that in up to 17% of cases the original classification could be challenged, advocating the need of updated classification criteria for UCTD. This study further supports the concept that in selected cases classification and diagnostic criteria represent a continuum. When discriminating between conditions with a marked overlap, such as SLE and UCTD, the proposal of new classification criteria should balance specificity and sensitivity. When developing new classification criteria, one approach is to select patients and the control groups as representative as possible of the settings (the medical practices) in which these criteria will be used.

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Legends of Figures and Tables

Table 1. Positive Domains in All patients and in patients with Systemic Lupus Erythematosus

Table 2. Clinical and immunological characteristic of the patients that at the follow-up fulfilled the ACR 1997 and SLICC criteria for Systemic Lupus Erythematosus

Figure 1. Clinical and Immunological Domains Positive in All patients and Systemic Lupus Erythematosus

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	ALL (n=133)	UCTD (n=111)	SLE* (n=22)	p
Mucocutaneous	11	6	5	**.007**
Arthritis	32	19	13	**<.001**
Serositis	7	4	3	.054
Hematologic	25	21	4	.94
Renal**	5	1	4	**<.001**
Antiphospholipid Antibodies	28	26	2	.131
Complement	21	16	5	.954
Highly Specific Antibodies***	28	17	11	**<.001**

*Table 1. Positive Domains in All patients and in patients with Systemic Lupus Erythematosus**

All the reported number are percentage; SLE – Systemic Lupus Erythematosus; UCTD – Undifferentiated Connective Tissue Disease;

*As per new classification criteria (5)

** Isolated proteinuria ≥0.5g/24h without other urinary anomalies

*** Highly specific antibodies stand for anti-dsDNA and/or anti-Sm antibodies

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	Clinical manifestations at study inclusion, prior SLE Diagnosis (ACR1997, SLICC)	**Clinical manifestations at follow-up and subsequent SLE Diagnosis (ACR1997, SLICC)**
Patient 1	Thrombocytopenia and Arthritis	After 1 year: LN class IV and acute cutaneous lupus
Patient 2	Acute Cutaneous Lupus and Arthritis	After 9 years: LN class IV
Patient 3	Hypo C3 and Hypo C4 and Arthritis	After 8 years: Discoid Lupus and anti-dsDNA positivity
Patient 4	Thrombocytopenia and anti-dsDNA positivity	After 5 years: Arthritis and leucopenia
Patient 5	Antiphospholipid antibody positivity	After 3 years: LN class IV and anti-dsDNA positivity
Patient 6	Isolated proteinuria(>0.5g/24h) and anti-dsDNA positivity	After 3 years: LN class IV and anti-dsDNA positivity
Patient 7	Arthritis	After 1 year: Acute cutaneous lupus and HypoC3 and HypoC4

Table 2. Clinical and immunological characteristic of the patients that at the follow-up presented new clinical manifestations and/or laboratory features, fulfilling the ACR 1997 and SLICC criteria for Systemic Lupus Erythematosus.

Patients that evolved towards a diagnosis of SLE, after a mean follow-up of 4.3 years (S.D. ±3.2), they met the ACR 1997 and SLICC criteria on follow up.

SLE – Systemic Lupus Erythematosus; LN – Lupus Nephritis

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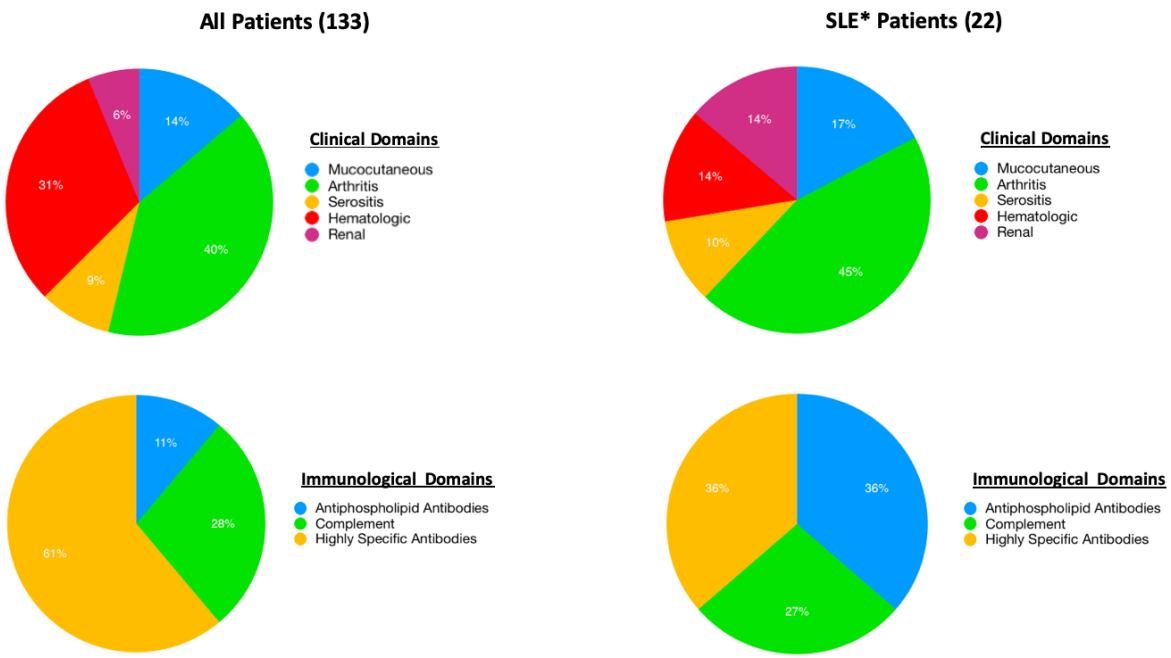

*Figure 1. Clinical and Immunological Domains Positive in All patients and Systemic Lupus Erythematosus**

*As per new classification criteria (5)

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