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The diagnosis and classification of undifferentiated connective tissue diseases

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ABSTRACT

The term undifferentiated connective tissue disease (UCTD) refers to unclassifiable systemic autoimmune diseases which share clinical and serological manifestations with definite connective tissue diseases (CTDs) but not fulfilling any of the existing classification criteria. In this review we will go through the more recent evidence on UCTD and we will discuss in what extent the availability of new criteria for the CTDs could interfere with the “UCTD concept”. The development of criteria able to identify early phases of defined CTD, may help in the differentiation of stable UCTD from their early stages and may offer a valuable guide to the treating physician to set up appropriate follow up schedules as well as therapeutic protocols. This simplified subset of CTD could offer a model to study clinic pathological correlations as well as the role of possible environmental factors in the development of autoimmunity.

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1. Introduction

It is a common clinical condition for a rheumatologist to face patients with clinical and serological manifestations strongly suggesting a connective tissue disease but without the possibility to diagnose or classify them as having a specific CTD [1–8].

It is estimated that up to 50% of patients with CTDs have an unclassifiable profile at disease onset [3]; however, other than merely a classification exercise, the reliable identification of these conditions is a critical clinical point with therapeutic and prognostic impact.

In addition, this situation may arise many questions and doubts in the patient which have to deal with an undefined disease.

It is widely accepted that, with respect to diagnostic criteria, classification criteria primarily serve as a tool to identify homogeneous groups of patients with comparable features so that data obtained by different researchers in different places can be compared and the recruitment into clinical studies standardized; however, the diagnostic support of such instruments is reasonable, leading to a similar use for both classification and diagnostic criteria.

In recent years, growing efforts have been made toward early diagnosis and classification; the introduction of new biomarkers and the availability of advanced imaging diagnostic techniques

significantly contributed to this objective. The development of new classification and diagnostic criteria for RA, SSc and SLE are well representative of such an effort.

On the other hand, it can be hypothesized that with the availability of new and more sensitive diagnostic and classification tools, the shape of the UCTD could be drawn more efficiently.

In this review we will go through the more recent evidence on UCTD and we will discuss in what extent the availability of new criteria for the CTDs could interfere with the “UCTD concept”.

2. UCTD: still a matter of debate?

The term undifferentiated connective tissue disease (UCTD) refers to unclassifiable systemic autoimmune diseases which share clinical and serological manifestations with definite connective tissue diseases (CTDs) such as Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SSc), Sjögren Syndrome (SS), dermatomyositis/polymyositis (DM/PM), Mixed Connective Tissue diseases (MCTD) and Rheumatoid Arthritis (RA) but not fulfilling any of the existing classification criteria [9].

Over the last decades, however, the better understanding of the natural course of these unclassifiable conditions highlighted the importance of the “UCTD concept” which overcomes the lack of a classification label.

To date, among the nebulous field of the unclassifiable systemic autoimmune diseases, we are becoming much more able to distinguish at least two different conditions with variable disease course and prognosis.

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3. “Stable UCTD”

The first case is represented by the so called “stable UCTD” (sUCTD). After a long scientific debate, it is now widely accepted that these conditions represent a distinct clinical entity with peculiar clinical findings; the proposed preliminary classification criteria for UCTD include at least one clinical manifestation of CTDs, positive ANA results, and disease duration of at least three years [9].

Several long-term observational cohorts are actually available elucidating the clinical course of these conditions. Despite differences in case definitions and observational periods among the cohorts, Raynaud’s phenomenon, arthralgias/arthritis, skin rash and mild cytopenias are the most frequent disease manifestations while the serological profile is frequently monospecific [10–12]. (For a complete list of clinical and serological manifestations derived from a systematic literature review see Table 1).

Life threatening conditions and severe organ involvements (such as renal or neurological manifestations) are only occasionally reported [10–12], but a moderate to severe interstitial lung involvement (ILD) can be also observed and up to 88% of patients with idiopathic nonspecific interstitial pneumonia meet the criteria for UCTD [13,14].

These conditions are clinically stable over time and usually necessitate mild therapeutic intervention [7,15].

However, a recent study by Iudici M et al. [16] showed that UCTD patients perceive an impaired quality of life in both physical and mental domains, similarly to SSc patients. Moreover, these conditions deserve careful clinical monitoring especially in conditions such as pregnancy which might driver disease exacerbation or evolution [17,18].

4. Early or evolving “UCTD”

The second group of undifferentiated diseases refers to patients with recent onset of symptoms and unclassifiable clinical picture; in this group of patients, the undifferentiated condition better refers to a “incomplete”, “atypical” or “mild” disease presentation which is very likely to progress into a definite CTD in the short time or, sometimes, even years after symptoms onset.

Several prognostic factors for evolution into CTDs have been identified and contrasting results have been reported among the different cohorts; among these, the presence of multiple autoantibodies specificities and their accrual over time as well as symptoms or laboratory abnormalities strongly suggestive of a specific CTD (i.e. puffy fingers, Gottron’s papules, anti-centromere autoantibodies) are widely considered reliable exclusion criteria for UCTD [3,4,6,10,19].

Among the UCTD patients who evolved to CTDs, SLE is the most frequently reported diagnosis (20–60%); the evolution is likely to occur during the first 1–5 years after the symptoms appearance but some late evolutions are also described.

Taking into account these data, this group of undifferentiated conditions represents the “early phase” of a CTD and their effective

recognition has a crucial clinical importance in term of treatment decision making and disease monitoring.

5. Can new classification/diagnostic criteria redefine UCTD?

It is well recognized that early diagnosis, identification of prognostic factors for disease severity as well as targeted and timely therapy are the common basis in the management of CTDs in order to prevent late organ damage. However, a delayed identification of the disease, especially in the presence of less defined clinical pictures, can still occur and it can be related with the lack of disease specific assessment and biomarkers.

In RA the development of adequate referral and monitoring strategies as well as the availability of new imaging techniques and biomarkers significantly contributed toward an early identification of RA patients among all patients with early unclassified arthritis [20–22].

In 2010, a new set of criteria have been derived by a joined ACR/EULAR initiative; with the major aim to obtain criteria fulfilled at an early stage of RA [23,24]. In a recent study Huizinga et al. observed that, with the introduction of new criteria, undifferentiated arthritis is less prevalent compared with when the 1987 ACR criteria are applied [25].

Other than RA, the very early diagnosis of SSc is considered as one of the greatest challenges in the management of rheumatic diseases with significant clinical impact on disease outcomes and patients prognosis. Very early stages of SSc are clinically characterized by the onset of Raynaud’s phenomenon (RP), sclerodactily, and often by the presence of SSc-specific autoantibodies [26,27]. However, the lack of early diagnostic criteria and valid predictors of disease evolution are significant limiting factors for identification and treatment in the earliest phase of the disease. The SSc classification criteria have been recently revised and puffy fingers (PuFi) were also included; even in the updated version, they are frequently used to identify patients with established disease but do not identify early SSc cases [28–32].

In order to conquer this limitation, the EULAR (European League Against Rheumatism) Scleroderma Trials and Research Group (EUSTAR) has identified the presence of RP, PuFi and antinuclear antibody (ANA) positivity as the three key features (‘red flags’) that should raise suspicion of very early SSc. The SSc pattern on NC and the presence of some specific auto-antibodies (ACA and TOPO-I) were considered to be necessary for the diagnosis of very early SSc [33].

Over the past years, the importance of a better classification and diagnostic accuracy has emerged also for SLE. In 2012, a new set of classification criteria has been developed and validated by the SLICC group. After validation in a separate cohort, the SLICC classification criteria demonstrated superior performances than the revised ACR 1997 criteria in terms of sensitivity and they performed equally for specificity [34]. However, the SLICC criteria are intended to be clinically more relevant, allowing the inclusion of more patients with clinically defined SLE than are included using the current ACR criteria. Far to providing a diagnostic tool, the project was aimed to improve the clinical relevance of the existing classification

Table 1
Main clinical features in “stable UCTD” as reported in the recent literature.

Author, year,	N	Disease duration (mean, years)	Arthralgias/ arthritis	Hematological	Skin	RP	Serositis
Vila LM, 2000	79	4.4	–/15.2%	10% leukopenia, 30.4% anemia, 5.1% TCP	40.5% PS, 25.3% malar rash	6.3%	1.3%
Vaz CC, 2009	184	3.04	66%/32%	19% leukopenia, 15% anemia	17% PS	30%	2%
Bodolay E, 2003	435	5	49%/29.9%	30.3% anemia, 11.3% TCP	23.4%	58.8%	9.8%
Mosca M, 2002	83	10	69%/33%	25% leukopenia, 12% anemia, 6% TCP	17% PS, 3% malar rash	48%	6%
Danieli MG, 1999	165	5	37%/22%	19%	52%	50%	6%

RP = Raynaud’s phenomenon; PS = photosensitivity; TCP = thrombocytopenia.

criteria by taking into consideration the advanced disease knowledge and a rigorous scientific methodology.

We have applied these 3 sets of criteria to our historical cohort of 91 UCTD patients (ref), with the aim to assess whether the introduction of new classification criteria could be able to separate evolving UCTD from stable UCTD since disease onset.

Of the initial cohort of 91 patients diagnosed as UCTD (ref) based on previously published criteria (disease duration of at least one year and not fulfilling existing classification criteria for CTD), 12 could be classified as SLE and 3 as very early systemic sclerosis based on the new revised criteria. Of the 76 patients maintaining a diagnosis of UCTD, 20 developed a CTD during the follow up, while 56 remained undifferentiated.

6. Conclusions

Undifferentiated connective tissue diseases (UCTDs) are conditions characterized by a simplified clinical and serological profile and the absence of severe organ involvement. The development of criteria able to identify early phases of defined CTD, may help in the differentiation of stable UCTD from their early stages and may offer a valuable guide to the treating physician to set up appropriate follow up schedules as well as therapeutic protocols.

This simplified subset of CTD could offer a model to study clinic pathological correlations as well as the role of possible environmental factors in the development of autoimmunity.

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