Defining Unclassifiable Connective Tissue Diseases: Incomplete, Undifferentiated, or Both?

The term connective tissue disease (CTD) refers to a group of autoimmune disorders that are classified among the systemic rheumatic diseases and include systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis-dermatomyositis (PM-DM), primary Sjögren's syndrome (pSS), primary antiphospholipid syndrome (APS), mixed connective tissue disease (MCTD), and rheumatoid arthritis (RA).

CTD share a number of epidemiological and immunological features that suggest a common pathogenetic pathway[1]. Experimental data indicate that genetic susceptibility to develop an autoimmune disease is multigenic and that some genetic defects can predispose patients to more than one autoimmune disease[1]. The sharing of immunogenetic features may to some extent lead to the development of common clinical features. Among these, the most frequent are Raynaud's phenomenon and arthralgia/arthritis, often associated with antinuclear antibodies (ANA) and/or rheumatoid factor; taken together these features constitute a clinical syndrome that can often represent the onset of a CTD. It is, however, common knowledge that patients presenting with this syndrome cannot be diagnosed as having a definite CTD. The classification of these pauci-symptomatic conditions remains a matter of debate.

To be diagnosed with one of the CTD, a patient must develop some disease-specific manifestations, or alternatively a cluster of nonspecific, but characteristic findings.

Since the majority of CTD-specific features are neither frequent nor pathognomonic for a single disease, the most common way to identify CTD is to look at a combination of clinical and laboratory findings. This is also the major reason why classification criteria have been developed for CTD[2].

The first aim of classification criteria is to improve communication within the scientific community by allowing data from different sources to be compared. It is important to note that they are referred to as classification rather than diagnostic criteria, in order to emphasize that meeting or not meeting classification criteria does not provide the basis for a diagnosis since misclassification may occur[2,3].

With this caveat, classification and diagnostic criteria certainly share a similar aim: to separate subjects with a definite CTD from those without such CTD, including both patients with difficult to distinguish conditions and healthy individuals[2]. The difference between diagnostic and classification criteria is that the former should theoretically have 100% sensitivity and specificity, while the latter may have less than 100% sensitivity and specificity. Therefore, diagnostic criteria can be applied to every individual case, whereas classification criteria cannot[2].

Nevertheless, classification criteria are selected by means of statistical methods to cluster the combination of features to improve sensitivity and specificity. It is worth noting that the higher the sensitivity and specificity of a classification criteria set, the smaller the difference will be between diagnostic and classification criteria.

High sensitivity and specificity of CTD criteria have been shown in many clinical studies[4,5], and it has been suggested that they may have a role in guiding diagnosis in clinical practice as well as indicating major disease features to students or physicians in training[3].

Patients with clinical manifestations suggestive of CTD who do not fulfill existing classification criteria are generally considered to have an unclassifiable CTD. For these conditions classification criteria are adopted, even in clinical practice, in order to distinguish definite from unclassifiable CTD.

However, despite their high sensitivity and specificity and widespread use, classification criteria have some limitations[2,3]. In defining unclassifiable conditions, the most important limitation seems to be the rate of false-negative diagnoses. A variable proportion of patients diagnosed with a definite CTD in clinical practice do not meet the classification criteria: they may be considered false-negative patients when such criteria are applied. In other words, they are patients with less than the required number of criteria but with one or more features that are so specific that they allow a definite diagnosis. These have to be differentiated from patients with unclassifiable CTD (Table 1).

In more recent publications patients with unclassifiable CTD have been alternatively defined as having incomplete (or latent) lupus[6,7] or undifferentiated connective tissue diseases (UCTD)[8-18]. These distinctions suggest that within the group of patients with unclassifiable CTD different populations may exist: patients with incomplete SLE are those who

Table 1. Patients who do not fulfill CTD classification criteria.

Patients with unclassifiable CTD
  A. False-negative based on the CTD classification criteria
  B. True unclassifiable CTD
    a. Incomplete CTD
    b. UCTD

Table 3. Clinical manifestations (A) and autoantibody reactivities (B) that may be considered specific for a definite CTD.

Clinical Manifestations	Autoantibody Reactivities
Malar rash	Anti-dsDNA
Subacute CLE	Anti-Sm
Chronic CLE	Anti-P protein
Skin sclerosis	Anti-Scl-70
Heliotrope rash	Anticentromere
Gottron's plaques	Anti-La/SSB
Erosive arthritis	Anti-Jo1
	Anti-Mi-2

CTD: connective tissue disease, CLE: cutaneous lupus erythematosus.

will develop definite SLE, and therefore incomplete SLE could be considered as an early stage of SLE, whereas the UCTD represent truly undifferentiated conditions that could potentially evolve into different CTD. It has also been proposed to group both incomplete SLE and UCTD in the category UCTD[19].

In an attempt to distinguish true undifferentiated disease from an early stage of a definite CTD we have suggested a preliminary classification criteria set[20], according to which a patient may be defined as having a UCTD when he (1) shows signs and symptoms suggestive of a CTD without fulfilling the criteria of any defined CTD; (2) is ANA positive; and (3) has a disease duration of at least 3 years. Indeed, an evolution to CTD is observed in the majority of patients within the first year of disease and thus a longer followup could permit correct classification of at least some false-negative patients.

However, it has been observed that UCTD may evolve into a wide variety of CTD (Table 2)[10,12-18]. The primary reason for this variability is that populations in studies on UCTD are heterogeneous. We cannot grasp the differences between patients merely by looking at the prevalence of prominent clinical and laboratory features, which are very similar in all the studies. Some studies clearly took into consideration patients who had CTD-specific features (either clinical or serological) at presentation[8,9,11-13,18], such as those reported in Table 3A and 3B. It is very rare to observe a patient with an isolated CTD-specific clinical feature (Table 3A) such as, for example, a patient presenting only with malar rash. It is more frequent that he/she has some

other clinical or serological abnormalities. If this patient does not fulfil SLE classification criteria, we should consider him/her as false-negative based upon those criteria and not as having unclassifiable CTD.

In clinical practice it is more common to encounter a patient with specific ANA reactivities (Table 3B), but without any significant manifestation on which to base a diagnosis of a definite CTD. Arbuckle, *et al*[21] clearly show that ANA can appear before the onset of symptoms. Moreover, some specific ANA including anti-dsDNA, anti-Sm, anti-P proteins, anti-Scl-70, anticentromere, anti-La/SSB, anti-Mi-2, and anti-Jo1 are highly specific for definite CTD, and some of them have been found to be highly predictive for the development of definite CTD in patients with UCTD[9,12,16,18].

Taken together these data suggest that patients with true unclassifiable CTD (UCTD and incomplete CTD), excluding patients false-negative to CTD classification criteria, may evolve into a definite CTD less frequently and more slowly than has been previously reported. Moreover, patients with UCTD or incomplete SLE could represent distinct clinical entities with specific clinical and serological profiles.

Table 2. Evolution of undifferentiated connective tissue diseases (UCTD) to definite diseases according to different studies with approximately 5-year followup.

Study	Patients, n	Evolved Patients, n (%)	Patients Who Developed a Definite CTD, %						
			SLE	RA	pSS	SSc	OS	PM-DM	Others
Williams[10]	81	22 (27)	55	18	—	—	18	5	5
Danieli[12]	84	33 (40)	21	9	21	40	9	—	—
Danieli[13]	165	10 (6)	50	—	40	—	10	10	—
Dijkstra[14]	65	38 (58)	15	45	31	3	—	—	18
Cavazzana[16]	148	36 (24)	30	5	50	5	3	3	3
Mosca[17]	83	19 (23)	95	0	5	0	0	0	0
Bodolay[18]	665	230 (34)	12	38	19	8	11	2	15

CTD: connective tissue disease, SLE: systemic lupus erythematosus, RA: rheumatoid arthritis, pSS: primary Sjögren's syndrome, SSc: systemic sclerosis, OS: overlap syndromes, PM-DM: polymyositis-dermatomyositis.

Therefore, a review of the preliminary classification criteria for the UCTD[20] is necessary to distinguish patients who are false-negative based on CTD classification criteria from those with a true unclassifiable CTD, as well as patients with a UCTD from those with an incomplete CTD.

We propose that exclusion criteria be introduced and applied before patients are categorized in the group of unclassifiable diseases. Therefore, patients with specific clinical manifestations that indicate a definite CTD (Table 3A) should not be considered as unclassifiable even though they do not fulfill classification criteria for a definite CTD.

Moreover, the unclassifiable CTD should be split into 2 different subsets (Table 1): incomplete CTD and true UCTD based on the presence/absence of those specific autoantibodies that are clearly associated with a unique definite CTD (Table 3B).

More exact and correct classification could improve the clinical and therapeutic approach to these patients and lead to a better definition of their prognosis. Further multicenter analysis is necessary to better define both clinical and serological exclusion criteria.

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