Undifferentiated connective tissue diseases in 2004

M. Mosca, C. Baldini, S. Bombardieri

Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy

Please address correspondence to:
Marta Mosca, MD, Rheumatology Unit, Department of Internal Medicine, Via Roma no. 67, 56126 Pisa, Italy.
E-mail: marta.mosca@int.med.unipi.it

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ABSTRACT

The existence of patients with signs and symptoms suggestive of a systemic autoimmune disease but not fulfilling the classification criteria for defined diseases is a common experience in clinical practice. The first description of these diseases dates back to 1980, when LeRoy proposed the term "Undifferentiated Connective Tissue Syndromes" (UCTS) to define the early phases of connective tissue diseases that at their onset are undefined, as opposed to mixed or overlapping syndromes in which the disease appears well defined. LeRoy also raised the fundamental question as to whether a proportion of patients with an undifferentiated profile may see their condition remain undifferentiated or even experience a remission of all pathologic features, rather than evolving to a definite connective tissue disease (CTD).

Many studies conducted on undifferentiated diseases have shown that up to 75% of patients will not develop a defined CTD and that these conditions exhibit typical clinical and serological manifestations and a good prognosis. We and others have defined these conditions as Undifferentiated Connective Tissue Diseases (UCTD) and it is our opinion that the UCTD represent distinct clinical entites. UCTD could offer an ideal clinical model for the study of single autoantibody specificities, the effects of various factors (such as pregnancy) on the disease course, and the general pathogenesis of autoimmune conditions. Before they can be so used, more must be discovered about their nature and characteristics, and studies will be necessary to improve the sensitivity and specificity of the existing preliminary classification criteria.

Introduction

The existence of patients with signs and symptoms suggestive of a systemic autoimmune disease, but not fulfilling the classification criteria for defined diseases is a common experience in clinical practice. The first description of these diseases dates back to 1980, when LeRoy proposed the use of the term "Undifferentiated Connective Tissue Syndromes" (UCTS) to define the early phases of connective tissue diseases that at the onset appear undefined, as opposed to the concept of mixed or overlapping syndromes, two conditions in which the disease appears to be well defined (1). Overlapping diseases exhibit the features of two or more defined connective tissue diseases (CTDs) and fulfil their classification criteria. Classification criteria for mixed connective tissue disease were proposed by Sharp in 1972 (2).

In the same paper LeRoy raised the fundamental question as to whether the UCTS in a proportion of patients may remain undifferentiated rather than evolving to a definite CTD, or show a remission of all pathologic features.

Since 1980 undifferentiated diseases have been extensively studied; however, a major obstacle in the analysis of the literature resides in the different definitions used to select patients (3-22). Indeed undifferentiated diseases have been variably named by many authors (Table I), and different criteria have been applied for their definition. In 1991 Alarcon *et al.* defined as Early Undifferentiated Connective Tissue Diseases those patients presenting with an undefined clinical profile at their first visit (5). Clearly, this definition included different types of patients: (i) those with a transitory clinical manifestation; (ii) patients in the very early phases of a defined disease which will develop within a few weeks/months, and finally (iii) patients who will maintain an undifferentiated profile during follow-up. We and other authors have defined as undifferentiated connective tissue disease (UCTD) those conditions characterized by the presence of signs and symptoms suggestive of a connective tissue disease, positive antinuclear anti-

Table I. Names and definitions used to indicate undifferentiated diseases.

Author	Term	Definition
LeRoy (1980)	Undifferentiated connective tissue syndromes	Early phases of connective tissue diseases indefinite at their onset
Greer (1989)	Incomplete lupus erythematosus	Patients with fewer than 4 but not less than 2 of the classification criteria for SLE
Ganczarczyk (1989)	Latent lupus	Patients with features suggestive of SLE (one or two ARA criteria) but not fulfilling the classification criteria
Alarcon (1991)	Early undifferentiated connective tissue diseases	Patients with RP*, isolated KCS*, UPA* other manifestations suggestive of connective tissue diseases and disease duration of less than 12 months
Mosca (1998)	Undifferentiated connective tissue diseases	Patients with signs and symptoms suggestive of a CTD* and at least one non-organ specific autoantibody, not fulfilling criteria for any defined CTD, and disease duration of at least 12 months
Danieli (1998)	Undifferentiated connective tissue diseases	Patients with signs and symptoms suggestive of CTD, lasting for at least 12 months.
Danieli (1999)	Undifferentiated connective tissue diseases	Patients with signs and symptoms of suspected autoimmune origin not fulfilling criteria for any defined CTD
Dijkstra (1999)	Undifferentiated connective tissue diseases	Patients with ANA and features of CTD but insufficient to fulfill criteria for any established CTD
Mosca (1999, 2002)	Undifferentiated connective tissue diseases	Systemic autoimmune disorders with signs and symptoms not sufficiently evolved to fulfill any of the accepted classification criteria for the defined CTD
Swaak (2001)	Incomplete lupus erythematosus	Patients with ANA and disease symptoms related to one organ system
Cavazzana (2001)	Undifferentiated connective tissue diseases	Patients with anti-Ro-SSA antibody positivity and addditional clinical or serologic abnormalities not sufficient for a diagnosis of defined CTD
Bodolay (2003)	Undifferentiated connective tissue diseases	Presence of clinical symptoms and serological abnormalities suggestive of an autoimmune disease, but are not sufficient to fulfil the diagnostic criteria of defined CTD

RP: Raynaud's phenomenon; KCS: keratoconjunctivitis sicca; UPA unexplained polyarthritis; CTD: connective tissue disease; ANA: antinuclear antibodies.

Table II. Percentage and timing of evolution of undifferentiated diseases to defined CTDs.

Year	Author (ref.)	% of evolved patients	Timing of evolution (months)
1989	Ganczarczyk (22)	32	n.r.
1989	Greer (38)	5	17.5
1996	Calvo-Alèn (143)	29	60
1998	Mosca (91)	13	36
1998	Danieli (84)	37	48
1999	Danieli (165)	6	n.r.
1999	Dijkstra (65)	51	24
2001	Swaak (122)	20	60
2001	Cavazzana (148)	24	57
2002	Mosca (83)	23	90
2003	Bodolay (665)	34	60

bodies and a disease duration of at least one year, in the attempt to exclude the very early phases of CTDs or transitory conditions and select "true" undifferentiated conditions (9, 11, 13, 15, 17, 20, 21).

It is with these observations in mind that, in this paper, we will review the existing literature on undifferentiated connective tissue diseases with particular attention to future perspectives in this field of clinical research.

Undifferentiated connective diseases: distinct entities or early phases of defined CTDs?

As previously mentioned, the first question with regard to undifferentiated patients relates to their future evolution: will they develop at some point in time a defined CTD or will their condition remain indefinitely undifferentiated? From an analysis of the literature it appears that an average of 25% (range 5-51%) of patients with undifferentiated diseases will evolve to a defined CTD during the follow up (Table II) (3-4, 7, 9-14, 16, 19-22).

One of the main explanation for the discrepancies observed in the literature resides in the different selection criteria adopted, since the evolution rate is higher in those cohorts that include patients from their disease onset, while it appears to be lower when patients with a disease duration of at least one year are included. The differential work-up in the diagnosis of patients at disease onset may also impact on the calculated evolution rates, since a more thorough work-up may help to exclude slowly developing CTDs (9, 15, 20).

Agreement exists on the timing of the evolution, which is to be expected earlier rather than later during the course of the follow-up (13, 21). Recently we evaluated the rate and timing of the

Table III. Evolution of undifferentiated diseases to defined CTDs in different cohorts.

Author	SLE	RA	SS	SSc	MCTD	PM/DM	Vasculitis
Lom Orta (31 pts.)	68%	-	-	-	-	-	-
Ganczarczyk (22 pts.)	32%	-	-	-	-	-	-
Greer (38 pts.)	5%	-	-	-	-	-	-
Calvo-Alén (143 pts.)	13%	10%	-	4%	-	2%	-
Danieli (84 pts.)	8%	3%	8%	15%	3%	-	-
Mosca (91 pts.)	13%	-	-	-	-	-	-
Danieli (165 pts.)	3%	-	2%	-	0.6%	0.6%	-
Dijkstra (65 pts.)	6%	26%	18%	1%	-	-	-
Belfiore (57 pts.)	9%	-	12%	-	-	-	-
Swaak (122 pts.)	20%	-	-	-	-	-	-
Cavazzana (148 pts.)	7%	1%	12%	1%	0,6%	0,6%	0,6%
Mosca (83 pts.)	21%	-	1%	-	-	-	-
Bodolay (665 pts.)	4%	13%	7%	3%	4%	0,4%	3%

SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SS: Sjögren's syndrome; SSc:systemic sclerosis; MCTD: mixed connective tissue diseases.

evolution of undifferentiated diseases to defined CTDs in our patient cohort and observed that the majority of patients will develop a definite disease within the first 5 years, while a later evolution is more rare (21).

As reported in Table III, undifferentiated patients may evolve different defined conditions such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), systemic sclerosis (SSc), rheumatoid arthritis (RA) or a myopathy. In some cohorts a rather homogeneous evolution to SLE is observed while in others the evolution is more variable. Different patient workups and selection criteria could again be the explanation for these differences.

In conclusion, some patients with undifferentiated disease will evolve to defined CTDs; however, a relatively high percentage of these patients will maintain an undifferentiated profile during the follow-up.

How can we predict which patients will develop a defined CTD?

Although some authors have failed to find any feature at disease onset that could be indicative of an eventual progression to SLE (3,9), considerable data regarding predictive factors are available in the literature and are summarized in Table IV (7,11,13,14,19-23).

Agreement exists on the predictive role of the autoantibody profile. Indeed the type of antinuclear antibody pattern on immunofluorescence, anti-dsDNA antibodies, anti-Sm antibodies and anticardiolipin antibodies, as well as the presence of multiple antibodies specificities have been significantly correlated with the evolution to SLE in many studies. Less homogeneous data were obtained relative to the clinical manifestations, with fever, discoid lupus, alopecia, serositis and photosensitivity being correlated with the development of SLE in single studies.

Less data are available on the predictive factors for the evolution to other CTDs, since this phenomenon is less frequently observed. Sicca symptoms, Raynaud's phenomenon, sclerodactyly, oesophageal dysfunction and ANA with a nucleolar pattern were found to be significantly predictive of the development of SSc (13,22). Raynaud's phenomenon, xerostomia, and anti-SSA

Table IV. Predictive factors for the evolution to defined connective tissue diseases.

Author	(year)	Variables
Ganczarczyk	(1989)	Not found
Mosca	(1998)	Not found
Swaak	(2001)	Not found
Swaak	(1985)	High avidity anti-dsDNA
Calvo-Alèn	(1996)	Age, African-American ethnicity, alopecia, serositis, discoid lupus, positive Coombs' test, positive anti-dsDNA and anti-Sm antibodies, positive ANA (homogeneous pattern), false positive test for syphilis
Danieli	(1998)	Sclerodactyly and oesophageal dysfunction (SSc) Xerostomia and anti-nuclear antibodies (SS-A pattern) (SS) Fever and anti-DNA antibodies (SLE)
Cavazzana	(2001)	Leukopenia, anti-ds-DNA
Mosca	(2002)	Anticardiolipin antibodies and multiple antibody specificities (SLE)
Bodolay	(2003)	Raynaud phenomenon, sclerodactyly and ANA positivity with a nucleolar pattern (SSc) Xerostomia, xerophtalmia, anti-SSA and anti-SSB (SS) Polyarthritis (hand joints) and anti U1-RNP (MCTD) Polyarthritis, high serum levels of RF and elevated ESR (RA) Age, fever, serositis, photosensitivity, ANA (homogenous pattern) and anti-dsDNA (SLE)

SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SS: Sjögren's syndrome; SSc:systemic sclerosis; MCTD: mixed connective tissue disease.

Table V. Clinical manifestations of undifferentiated diseases.

	Ganczarczyk (22 pts.)	Greer (38 pts.)	Alarçon (213 pts.)	Mosca (91 pts.)	Danieli (84 pts.)	Dijkstra (22 pts.)	Danieli (165 pts.)	Swaak (122 pts.)	Cavazzana (148 pts.)*	Bodolay (665 pts.)
Arthralgias	n.r.*	n.r.*	n.r.*	80%	59%	77%	37%	n.r	86%	49%
Raynaud's	33%	n.r.*	46%	46%	56%	45%	56%	n.r	33%	58,8%
Arthritis	40%	47%	86%	37%	23%	14%	22%	15%	31%	29,9%
Leukopenia	20%	n.r.*	11%	41%	n.r.*	n.r.*	n.r.*	29%	28%	n.r
Xerophthalmia	n.r.*	n.r.*	7%	41%	12%	18%	22%	n.r	30%	11,7%
Xerostomia	n.r.*	n.r.*	7%	36%	12%	18%	22%	n.r	28%	13,1%
Photosensitivity	13%	24%	10%	30%	n.r.*	n.r.*	n.r.*	n.r	34%	23,4%
Anemia	n.r.*	n.r.*	23%	16%	n.r.*	n.r.*	n.r.*	9%	24%	30,3%
Serositis	13%	16%	10%	5%	n.r.*	n.r.*	13%	n.r	n.r	9,8%
Malar rash	n.r.*	13%	11%	6%	n.r.*	n.r.*	n.r.*	4%	n.r	23,4
Oral aphtosis	27%	3%	12%	4%	n.r.*	n.r.*	n.r.*	n.r	n.r	n.r
Thrombocytopenia	33%	n.r.*	2%	13%	n.r.*	n.r.*	n.r.*	6%	10%	11,3%
ANA positivity	73%	82%	55%	97%	63%	100%	58%	100	94%	30%

Table VI. Autoantibody specificities in undifferentiated patients.

	Clegg	Mosca	Danieli	Cavazzana
ANA	83%	97%	58%	94%
Anti-dsDNA	4%	19%	5%	21%
Anti-SSA	8%	30%	14%	64%
Anti-SSB	1%	5%	n.r.*	32%
Anti-Sm	1%	1%	n.r.*	n.r.
Anti-RNP	12%	28%	n.r.*	2%

and anti-SSB antibodies have been correlated with the development of Sjögren's syndrome (20, 22). In one study polyarthritis and anti-RNP antibodies were predictive for the development of mixed connective tissue disease and polyarthritis, rheumatoid factor and an elevated ESR for the development of rheumatoid arthritis (22).

No triggering events for the evolution of undifferentiated diseases to definite CTDs have been observed. In a recent paper we looked for triggering factors in our patient cohort, but no associations were observed. It is certainly important to monitor these patients carefully in the early phases of their disease and also under particular conditions, such as pregnancy which is known to have an impact on the natural history of systemic autoimmune diseases (21).

Clinical and laboratory features of stable UCTDs

Given that an average of 75% of patients with an undifferentiated profile at onset will remain so during their follow-up, it is certainly of interest to evaluate their clinical and serological profile. From an analysis of the above mentioned studies, it appears that undifferentiated diseases exhibit a mild clinical profile characterized by the absence of major organ involvement (particularly renal and neurological). The most frequent manifestations presented by these patients appear to be arthralgias, arthritis, Raynaud's phenomenon, mucocutaneus manifestations and sicca symptoms (Table V) (3-5, 8-22).

In accordance with this simplified clinical profile, undifferentiated patients generally require only symptomatic therapy or no treatment at all (4, 9, 19). For example, in our cohort undifferentiated patients were treated with low dose corticosterois (53%) and/or antimalarial drugs (11%).

With respect to the autoantibody profile of these patients, ANA positivity is generally high, ranging from 58% up to 90%. However, apart from ANA positivity, less data have been reported on the other autoantibodies in the majority of the papers (Table V) (9).

In 2001 Cavazzana *et al*. examined in detail the autoantibody profile of 147 patients with antibodies to Ro/SSA. Analysis of the fine specificity of anti-Ro/SSA antibodies showed that most sera were reactive with Ro 52 kD, alone or in combination with Ro 60 kD (34% and 55% respectively), while only 4% of the sera were reactive to isolated Ro 60 kD (20).

We have reported that a high percentage of patients with UCTD (82% of the patients analyzed) show a simple autoantibody profile characterized by the presence of a single specificity. In particular 30% of patients exhibited anti-Ro/SSA antibodies alone, and 28% anti-RNP alone (9). In their analysis Cavazzana *et al*. observed antibodies to isolated Ro/SSA in 64% of the patients. This difference may be attributed to the study's patient selection criteria, since the authors recruited only anti-Ro/SSA-positive patients.

Conclusions

From the reported data it appears that the majority of patients presenting with undifferentiated diseases will not develop a defined CTD and that these condition indeed show typical clinical and serological manifestations and a

good prognosis.

We call these conditions as Undifferentiated Connective Tissue Diseases (UCTD) and it is our opinion that the UCTD represent distinct clinical entites. Therefore we have proposed preliminary classification criteria to identify UCTD patients: (i) signs and symptoms suggestive of a connective tissue disease, but not fulfilling the criteria for any defined CTDs, (ii) positive antinuclear antibodies, and (ii) a disease duration of at least 3 years. Patients with a shorter follow up should be defined having as early UCTD and include patients who will develop a defined CTD and those with transitory manifestations (15).

UCTD could represent an ideal clinical model for the study of single autoantibody specificities, the effects of various factors (such as pregnancy) on the disease course, and the general pathogenesis of autoimmune conditions. In this light their definition appears to be of paramount importance, and therefore further analysis is warranted to improve the sensitivity and specificity of the proposed classification criteria.

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