Undifferentiated connective tissue disease

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Conflicts of interest

- **Consultant**: Actelion, CSL Behring, LFB Biotechnologies, Lilly, Pfizer, Octapharma
  - Financial support to ARMIIC
- **Investigator**: Actelion, CSL Behring, Pfizer
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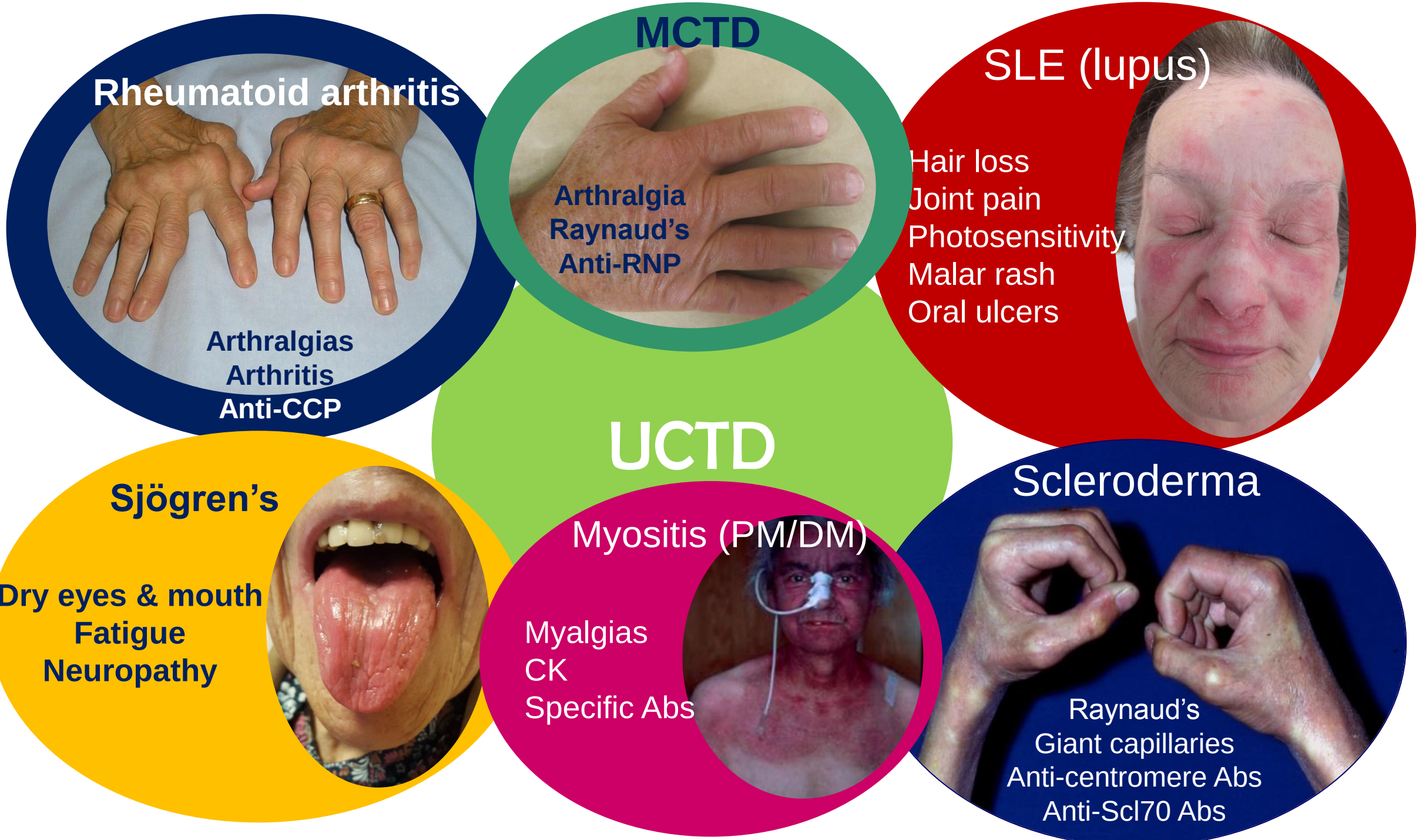
- **Invited conference**: SOBI, Roche, Actelion, CSL Behring, Octapharma, GSK, LFB Biotechnologies, Pfizer, Lilly, UCB pharma

- Since March 2016, I am « Godfather » of the Lebanese Society of Internal Medicine


Rheumatoid arthritis
Arthralgias
Arthritis
Anti-CCP
MCTD
Arthralgia
Raynaud's
Anti-RNP
SLE (lupus)
Hair loss
Joint pain
Photosensitivity
Malar rash
Oral ulcers
UCTD
Sjögren's
Dry eyes & mouth
Fatigue
Neuropathy
Myositis (PM/DM)
Myalgias
CK
Specific Abs
Scleroderma
Raynaud's
Giant capillaries
Anti-centromere Abs
Anti-Scl70 Abs

Undifferentiated connective tissue diseases

The first description was made in 1969 by Sabo who described two illustrative cases of ‘undifferentiated or lanthanic collagen diseases’ and suggested three possible evolutions

- the development of defined CTDs,
- the persistence as undifferentiated conditions (“stable” UCTD)
- an intermittent undifferentiation.

Interestingly, the cases described by Sabo were characterized by severe organ involvement and one patient died from the disease itself

Sabo I. Hiroshima J Med Sci 1969;18:259–64.

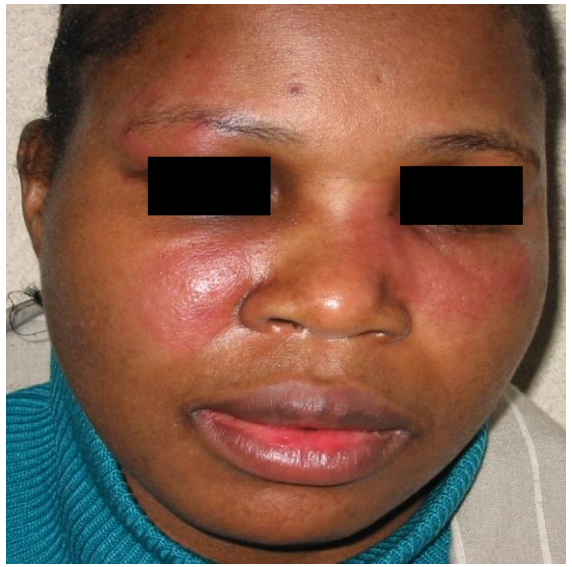
Undifferentiated connective tissue disease (UCTD): classification criteria

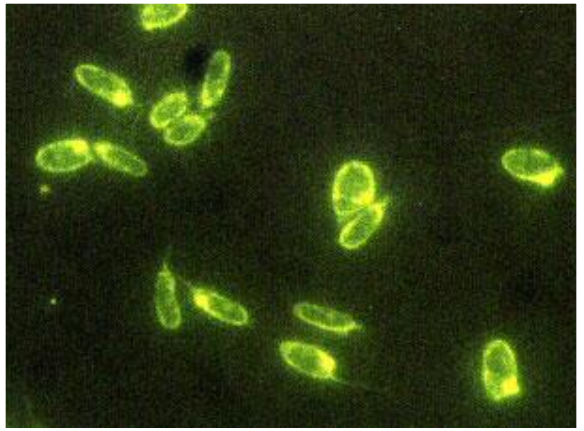
- Undifferentiated connective tissue disease (UCTD) refers to:
- unclassifiable systemic autoimmune diseases which share clinical and serological manifestations with definite connective tissue diseases (CTDs)
  - Systemic Lupus Erythematosus (SLE)
  - Systemic Sclerosis (SSc)
  - Sjögren Syndrome (SS)
  - dermatomyositis/ polymyositis (DM/PM)
  - Mixed Connective Tissue diseases (MCTD)
  - Rheumatoid Arthritis (RA)
- **But not fulfilling any of the existing classification criteria.**

Mosca M et al. Clin Exp Rheumatol 1999;17:615e20.

Systemic Lupus International Collaborating Clinics Classification Criteria for SLE*

Malar rash/photosensitive rash/acute cutaneous lupus
Discoid rash
Oral ulcers
Nonscarring alopecia
Arthritis
Serositis
Renal
Neurologic
Hemolytic anemia
Leukopenia
Lymphopenia, 1,500/mm3
Lymphopenia, l,000/mm3
Thrombocytopenia
Antinuclear antibody
Anti–double-stranded DNA
Anti-Sm
Antiphospholipid antibody
Low complement

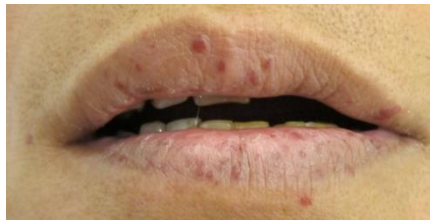


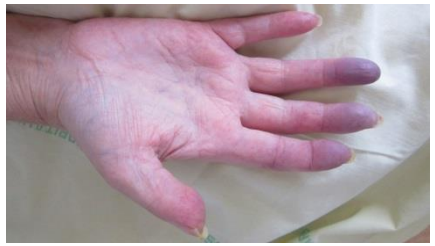


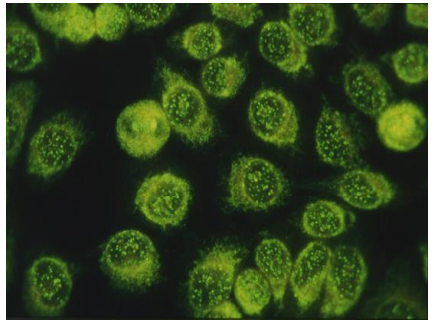
***classify a patient as having SLE if he or she satisfies 4 of the clinical and immunologic criteria used in the SLICC classification criteria, including at least one clinical criterion and one immunologic criterion, OR if he or she has biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies.*

Petri M et al. Arthritis Rheum 2012;64:2677e86.

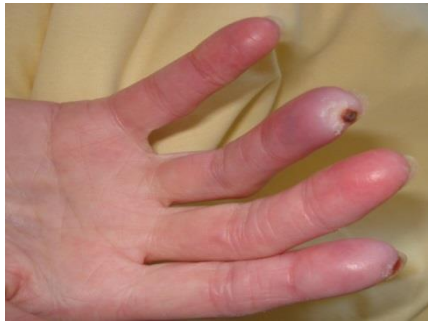
2013 classification criteria for SSc: an ACR/EULAR collaborative initiative (I)

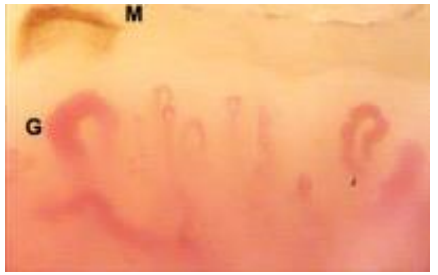


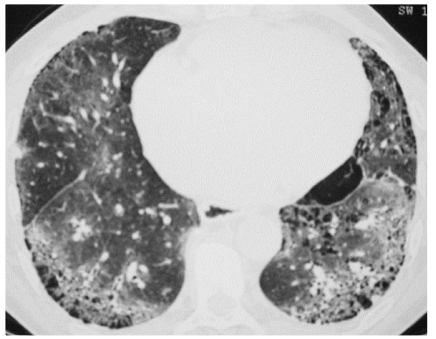




- Skin thickening of the fingers extending proximal to the metacarpophalangeal joints: SSc;
- If that is not present, 7 additive items apply:
  - skin thickening of the fingers,
  - fingertip lesions,
  - telangiectasia,
  - abnormal nailfold capillaries,
  - interstitial lung disease or pulmonary arterial hypertension,
  - Raynaud's phenomenon,
  - SSc-related autoantibodies.



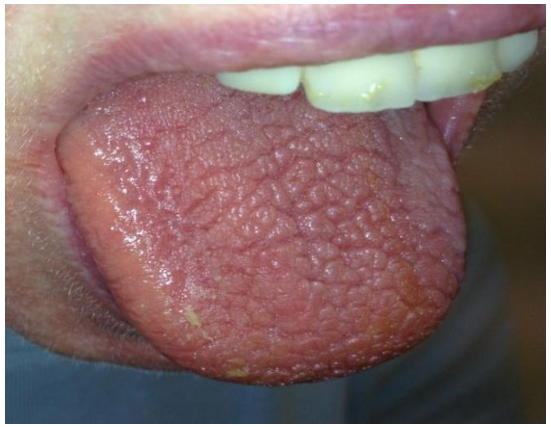


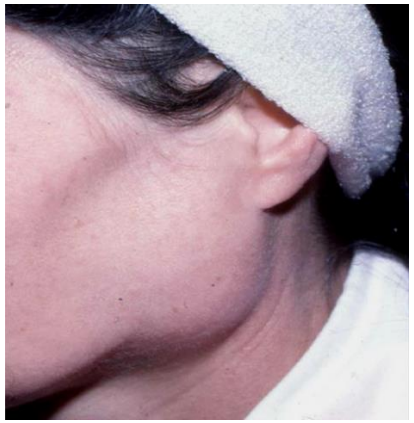


van den Hoogen F et al. Ann Rheum Dis 2013

Syndrome de Sjögren : les critères américano-européens

1. **Symptômes oculaires**
   - yeux secs depuis plus de 3 mois
   - sable dans les yeux
   - Larmes artificielles plus de 3 fois par jour
2. **Symptômes buccaux**
   - bouche sèche depuis plus de 3 mois
   - gonflement parotidien
   - liquides pour avaler les aliments secs
3. **S. objectifs d'atteinte oculaire**
   - Test de Schirmer < 5mm/5 minutes
   - Score Rose Bengale > 4
4. **S. objectifs d'atteinte salivaire**
   - Scintigraphie salivaire
   - Sialographie parotidienne
   - Flux salivaire < 1,5ml/ 15 minutes





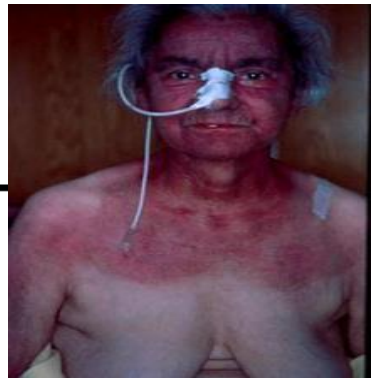
5. **Signes histologiques** sialadénite lymphocytaire focale
   (Focus score ≥ 1)
6. **Auto-anticorps**
   Présence d'anticorps anti-SSA ou anti-SSB

SS primitif : 4 critères/6 avec n°5 ou n°6
ou 3/4 critères objectifs

Vitali, Ann Rheum Dis, 2002, 61 (554-8)

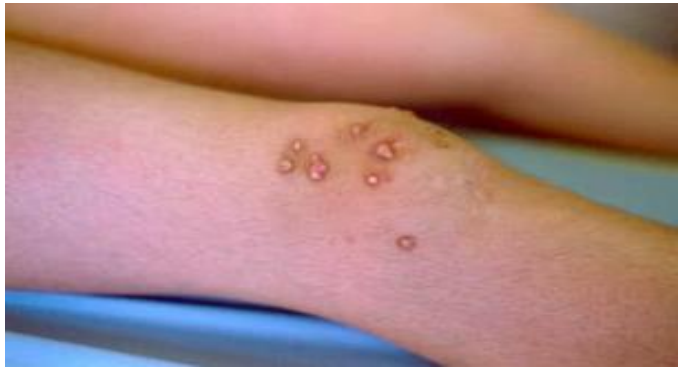
Bohan and Peter Criteria for PM and DM

Bohan and Peter Criteria for Polymyositis and Dermatomyositis *



First rule out all other forms of myopathy!

- Symmetrical weakness, usually progressive, of the limb-girdle muscles
- Muscle biopsy evidence of myositis
  - Necrosis of type I and type II muscle fibers, phagocytosis, degeneration and regeneration of myofibers with variation in myofiber size, endomysial, perimysial, perivascular or interstitial mononuclear cells
- Elevation of serum levels of muscle-associated enzymes
  - CK, Aldolase, LD, Transaminases (ALT/SGPT and AST/SGOT)
- Electromyographic triad of myopathy
  - Short, small, low-amplitude polyphasic motor unit potentials
  - Fibrillation potentials, even at rest
  - Bizarre high-frequency repetitive discharges
- Characteristic rashes of dermatomyositis



Definite PM = all first 4, probable PM = 3 of first 4, possible PM = 2 of 4; Definite DM = rash + 3 others; probable DM = rash + 2 others; possible DM = rash + 1 other

* Modified from (16)

ALT/SGPT, alanine transaminase/serum glutamic pyruvate transaminase; AST/SGOT, aspartate transaminase/serum glutamic oxaloacetic transaminase; CK, creatine kinase; LD, lactate dehydrogenase

NEJM 1975

119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis,

I. Critères cliniques
II. Elévation des CPK
III. Autres critères paracliniques
IV. Critères histologiques

Polymyosite: définie
probable

Dermatomyosite: définie
probable
amyopathique

Possible dermatomyosite sine dermatitis

Myosite non spécifique

Myopathie nécrosante autoimmune

Myosite: Isolée
Associée à une connectivite
Associée à un cancer

Hoogendijk JE, et al. Neuromuscul Disord 2004

Proposed diagnostic criteria for MCTD (IV)

	Serological criteria	Clinical criteria
Alarcon-Segovia (1987)	Anti-RNP Ab titer > 1:1000	1. Edema in hands 2. Synovitis 3. Myositis, 4. Raynaud's phenomenon 5. Acrosclerosis
Diagnosis	Serological criteria plus at least 3 clinical criteria included either synovitis or myositis	

	Serological criteria	Clinical criteria
Kahn (1991)	Presence of high titer anti-RNP Ab corresponding to speckled ANA at titer ≥ 1:2000	1. Raynaud's phenomenon 2. Synovitis 3. Myositis 4. Swollen fingers
Diagnosis	Serological criteria plus Raynaud's phenomenon and at least two of the three following signs (synovitis, myositis and swollen fingers)	

No mention of pulmonary involvement

The American College of Rheumatology criteria for RA

***at least 4 criteria must be met for classification as RA**

- Morning stiffness of >1 hour most mornings for at least 6 weeks.
- Arthritis and soft-tissue swelling of >3 of 14 joints/joint groups, present for at least 6 weeks
- Arthritis of hand joints, present for at least 6 weeks
- Symmetric arthritis, present for at least 6 weeks
- Subcutaneous nodules
- Rheumatoid factor at a level above the 95th percentile
- Radiological changes suggestive of joint erosion

Defining undifferentiated connective tissue diseases: exclusion criteria

Table 1 Proposed exclusion criteria for undifferentiated connective tissue diseases

Clinical criteria	*Laboratory criteria*
Malar rash	Anti-dsDNA
Subacute cutaneous lupus	Anti-Sm
Discoid lupus	Anti-protein P
Cutaneous sclerosis	Anti-Scl70
Heliotrope rash	Anticentromere
Gottron plaques	Anti-La/SSB
Erosive arthritis	Anti-Jo1
	Anti-Mi2

Mosca M Lupus 2008

Most common symptoms of UCTD

- Arthralgia
- Arthritis
- Rashes, usually on the face
- Alopecia
- Raynaud's phenomenon
- Oral ulcers
- Xerophthalmia
- Xerostomia
- Low-grade fever
- Photosensitivity

Mosca M et al. Best Practice & Research Clinical Rheumatology 26 (2012) 73–77

Other symptoms of UCTD

- neuropathy
- pleuritis or pericarditis
- leukopenia
- anemia
- thrombocytopenia

Mosca M et al. Best Practice & Research Clinical Rheumatology 26 (2012) 73–77

Main clinical features in “stable UCTD”

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.

- Arthralgias/arthritis
- Raynaud’s phenomenon
- Photosensitivity

Mosca M et al. J Autoimmunity 2014

UCTD: Evolution

- Less than 20% of patients with UCTD go on to develop a definite connective tissue disease.
- As many as one-third will experience a remission of their symptoms.
- The rest continue with generally mild disease in the undifferentiated form (“stable UCTD).

Stable UCTD

- At least one clinical manifestation of CTDs
- Positive ANA
- Disease duration of at least three years.

Mosca M et al. Clin Exp Rheumatol 1999;17:615e20.

- Up to 50% of patients with CTDs have an unclassifiable profile at disease onset
- However, the reliable identification of these conditions is a critical clinical point with therapeutic and prognostic impact.

Alarcón Segovia G et al. J Rheumatol 1991;18:1332e9.

Stable UCTD: treatment

- Low-dose corticosteroids (CS)
- and/or antimalarial drugs
- 20–40% not requiring any treatment during follow-up.

Mosca,M et al. Lupus 1998; 7: 95–100.
Swaak, AJ et al. Rheumatology 2001; 40: 89–94.
Mosca,M et al. J Rheumatol 2002; 29: 2345–2349.

Stable UCTD: long term treatment

In a cohort of 152 stable UCTD patients who have been followed for more
than 10 years

- 16% were not on any therapy at their last check-up;
- of the remainder
  - 36% were being treated with hydroxychloroquine (HCQ)
  - 26% with HCQ and CS
  - 10% with CS alone
  - no patient was receiving immunosuppressive (IS) drugs

Mosca M Lupus 2008

Early or evolving “UCTD”

- Patients with recent onset of symptoms and unclassifiable clinical picture
- Undifferentiated = incomplete / atypical / mild disease presentation
- Very likely to progress into a definite CTD in the short time or, sometimes, even years after symptoms onset.

A certain proportion of UCTD patients will eventually develop defined CTD:

- Systemic lupus erythematosus (SLE),
- Systemic sclerosis (SSc)
- Sjögren's syndrome
- Mixed connective tissue diseases
- Rheumatoid arthritis (RA)
- Systemic vasculitis
- Myositis (polymyositis, dermatomyositis)

Mosca M Lupus 2008

UCTD: prognostic factors

Several prognostic factors for evolution into CTDs have been Identified:

- the presence of multiple autoantibodies specificities and their accrual over time
- symptoms or laboratory abnormalities strongly suggestive of a specific CTD = reliable exclusion criteria for UCTD
    - puffy fingers
    - Gottron’s papules
    - anti-centromere Abs

Alarcón Segovia G et al. J Rheumatol 1991;18:1332e9.
Danieli MG et al. Clin Rheumatol 1998;17:195e201.
Mosca M et al. J Rheumatol 2002;29:2345e9.
Bodolay E et al. Clin Exp Rheumatol 2003;21:313e20.
Vila LM et al. Lupus 2000;9:110e5.

UCTD: consequences of improvement of CTD diagnosis criteria

Aim : to assess whether the introduction of new classification criteria could be able to separate evolving UCTD from stable UCTD since disease onset.
3 sets of criteria applied to a historical cohort of 91 UCTD patients

- disease duration of at least one year
- not fulfilling existing classification criteria for CTD

Out of 91 patients diagnosed as UCTD based on previously published criteria

- 12 classified as SLE
- 3 classified as very early systemic sclerosis

76 patients with a confirmed diagnosis of UCTD

- 20 developed a CTD during the follow up
- 56 remained undifferentiated.

Mosca M et al. Journal of Autoimmunity 48-49 (2014) 50e5

Case report……

Lady
29 years old
Maurice Iland
Shortness of breath….. PAH
Raynaud's (for years)
Normal capillaroscopy
Positive ANA without specificity
Limited response to specific PAH treatments

Photosensitivity
Intermittent malar rash
Joint pain….

Decision

- CYC
- Glucocorticoids

UCTD: shoehorn diagnosis….

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 form their early stages**
- **Less than 20% of patients with UCTD go on to develop a definite connective tissue disease.**
- **As many as one-third will experience a remission of their symptoms.**
- **The rest continue with generally mild disease in the undifferentiated form (“stable UCTD).**
- **Treatment: glucocorticoids and/or hydroxychloroquine**

French Vasculitis Study Group

GFRS Groupe Francophone de Recherche sur la Sclérodermie

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