Sharp syndrome / Mixed connective tissue diseases

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

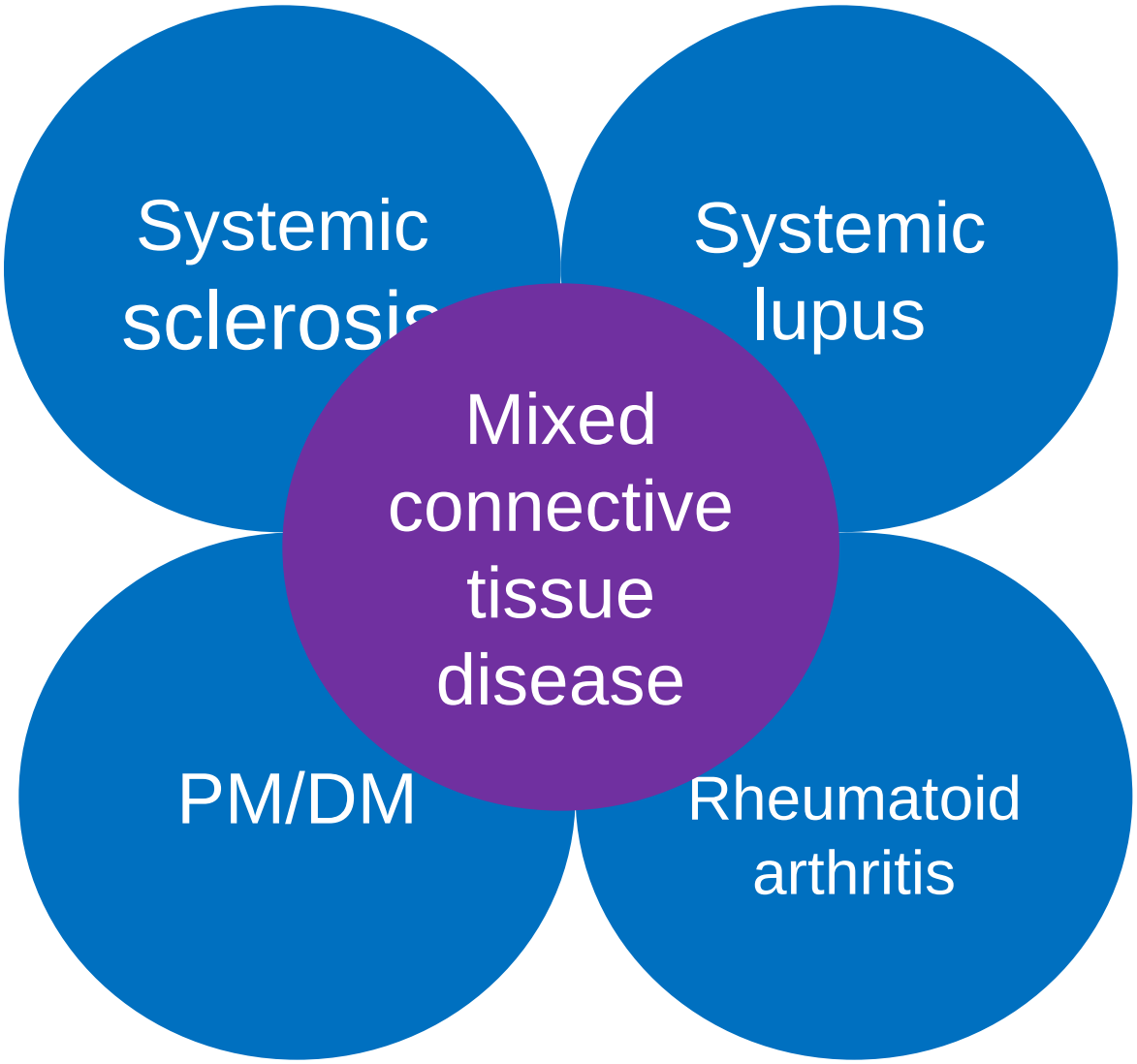
- Since March 2016, I am « Godfather » of the Lebanese Society of Internal Medicine

MCTD: Introduction (I)

- In 1972, Dr Sharp and colleagues described a new connective tissue disease, characterized by overlapping features of:
  - ✓ systemic lupus erythematosus (SLE)
  - ✓ systemic sclerosis (SSc),
  - ✓ polymyositis/dermatomyositis (PM/DM)
  - ✓ and antibodies against the U1 small nuclear ribonucleoprotein autoantigen (U1 snRNP).
- This condition was termed mixed connective tissue disease (MCTD).

Sharp GC et al. Am J Med 1972;52:148-59.
Sharp GC. Kasukawa R, Sharp GC, editors. Amsterdam: Elsevier; 1987. p. 23-32.

Mixed connective tissue disease



MCTD: Introduction (II)

In the original publication, describing MCTD, Sharp made the 4 following claims:

- syndrome clinically identifiable by a particular group of features
- presence of high titers of antibodies to U1 snRNP: unique (and hence diagnostic) serological feature;
- no brain, pulmonary, renal involvement or vasculitis;
- benign prognosis and response to small doses of corticosteroids.

Sharp GC et al. Am J Med 1972;52:148-59.
Sharp GC. Kasukawa R, Sharp GC, editors. Amsterdam: Elsevier; 1987. p. 23-32.

MCTD: Introduction (III)

Later, after observing the clinical evolution of MCTD patients, Sharp himself agreed that the original concept of MCTD had to be modified and that

(1) internal organs were at risk for serious complications;

(2) patients were not always steroid responsive;

(3) prognosis was not always benign.

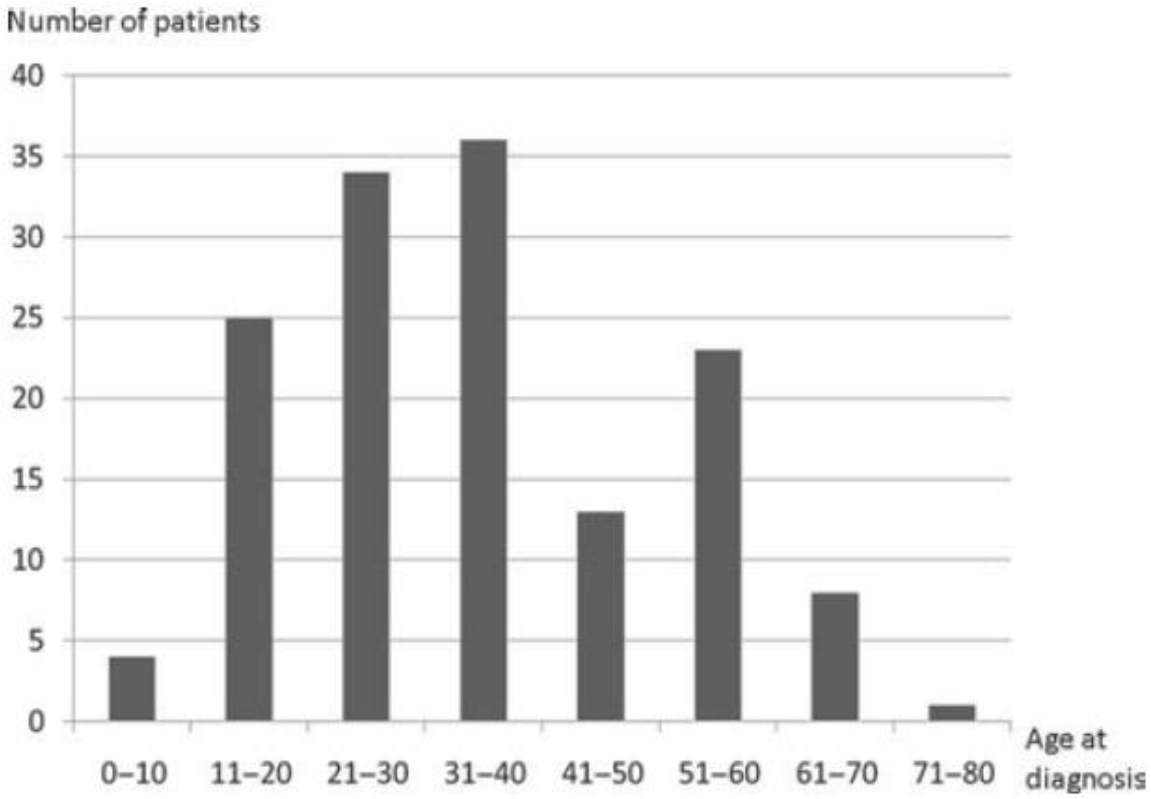
Sharp GC, Anderson PC. J Am Acad Deramtol 1980;2:269-74.
Maddison PJ. Baillières Best Pract Res Clin Rheumatol 2000;14: 111-24.
Bellando Randone S, et al. Curr Rheumatol Rev 2009;5:133-40.

MCTD: epidemiology

- Female to male ratio = 3.3
- Mean age at diagnosis of adult-onset MCTD : 37.9 years (95% CI 35.3 to 40.4 years).
- Point prevalence of living adult MCTD patients in Norway was 3.8 (95% CI 3.2 to 4.4) per 100 000 adults.
- Incidence of adult-onset MCTD in Norway during the period from 1996 to 2005 was 2.1 (95% CI 1.7 to 2.5) per million per year.

Gunnarson R et al. Ann Rheum Dis 2011

The age distribution of the MCTD patients at time of diagnosis.



Gunnarson R et al. Ann Rheum Dis 2011

Proposed diagnostic criteria for MCTD (I)

	Major criteria	Minor criteria
Sharp (1987)	1. Myositis 2. Pulmonary involvement: a. Diffuse capacity < 70% of normal values b. Pulmonary hypertension c. Proliferative vascular lesions on lung biopsy 3. Raynaud's phenomenon or esophageal hypomotility 4. Swollen hands 5. Anti-ENA Ab > 1:10,000 and anti-U1 RNP Ab positive and anti-Sm negative	1. Alopecia 2. Leukopenia 3. Anemia 4. Pleuritis 5. Pericarditis 6. Arthritis 7. Trigeminal neuropathy 8. Malar rash 9. Thrombocytopenia 10. Mild myositis 11. History of swollen hands

Diagnosis
At least 4 major criteria plus anti-U1-RNP Ab titer of at least 1:4000 or two major criteria from among criteria 1, 2 and 3 plus 2 minor criteria plus anti-U1-RNP Ab titer of at least 1:1000 Exclusion criteria: positivity for anti-Sm Ab

Proposed diagnostic criteria for MCTD (II)

	Common symptoms	Mixed symptoms
Kasukawa (1987)	1. Raynaud's phenomenon 2. Swollen fingers or hands Anti-RNP Ab positive	1. SLE-like symptoms: a. Polyarthritis b. Lymphadenopathy c. Facial erythema d. Pericarditis or pleuritis e. Leukopenia or thrombocytopenia. 2. SSc-like findings: a. Sclerodactyly b. Pulmonary fibrosis, restrictive changes of lung, or reduced diffusion capacity c. Hypomotility or dilatation of esophagus. 3. PM-like findings: a. Muscle weakness b. Elevated serum levels of muscle enzymes (CPK) c. Myogenic pattern on EMG

Diagnosis

At least one of common symptoms plus positivity for anti-RNP Ab plus one sign/symptom of the mixed symptoms in at least two of the three diseases

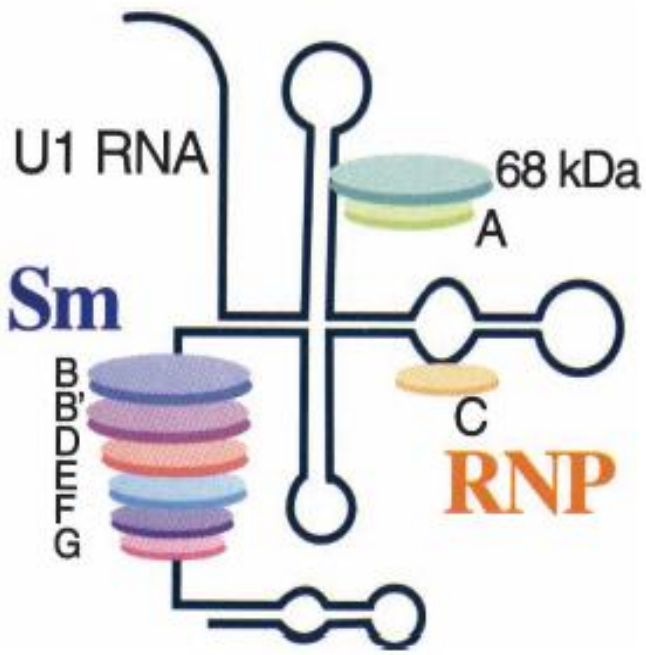
Proposed diagnostic criteria for MCTD (IV)

	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

Structure of U1 sn RNP/ pathogenicity of anti-U1 RNP



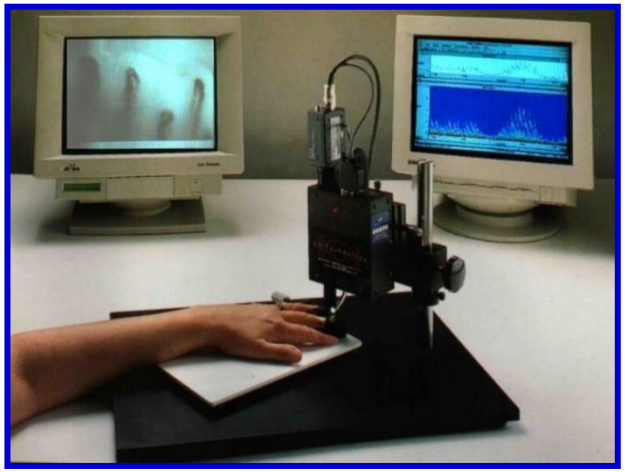
- U1-RNP Abs increase the production of inflammatory cytokines by mononuclear cells.
- Abs to U1-RNP upregulate adhesion molecules and serve as anti-endothelial cell Abs and contribute to the development of tissue injury
- Modified U1-RNP proteins are antigenically distinct and generate specific Ab responses associated with features of CTD
- The TLR mediates disease phenotype in an animal model of MCTD based on U1-70kDa immunity in the presence of U1-RNA.
- Contribution of U1-RNP immunity in the pathogenesis of human CTD is still debated

Migliorini P et al. Autoimmunity 205

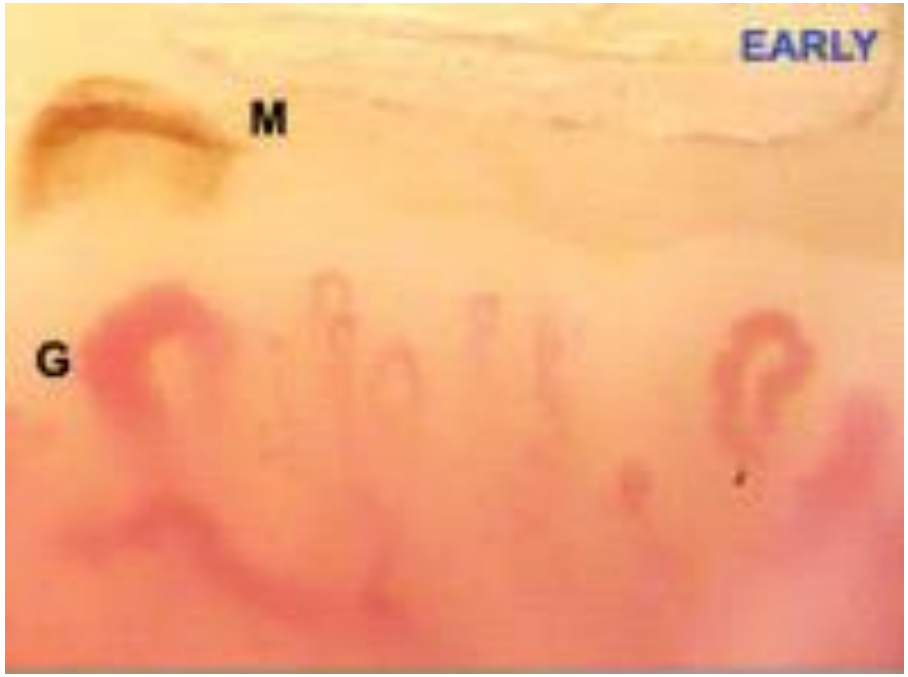
Keith MP et al. Autoimmunity Rev 2007

Giant capillaries

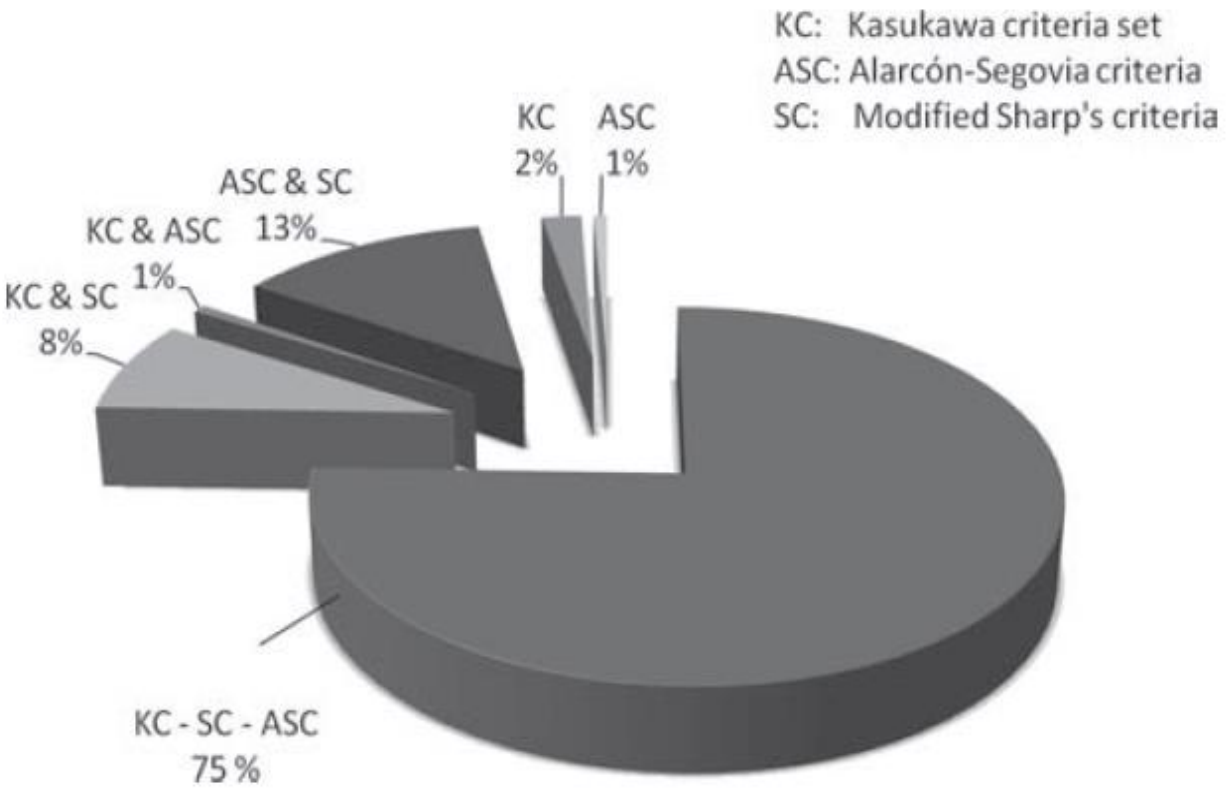
- Systemic sclerosis
- MCTD
- Dermatomyositis



- None of the proposed diagnostic criteria for MCTD took into account detection of giant capillaries



The mixed connective tissue disease population fulfilling various combinations of criteria sets.



Gunnarson R et al. Ann Rheum Dis 2011

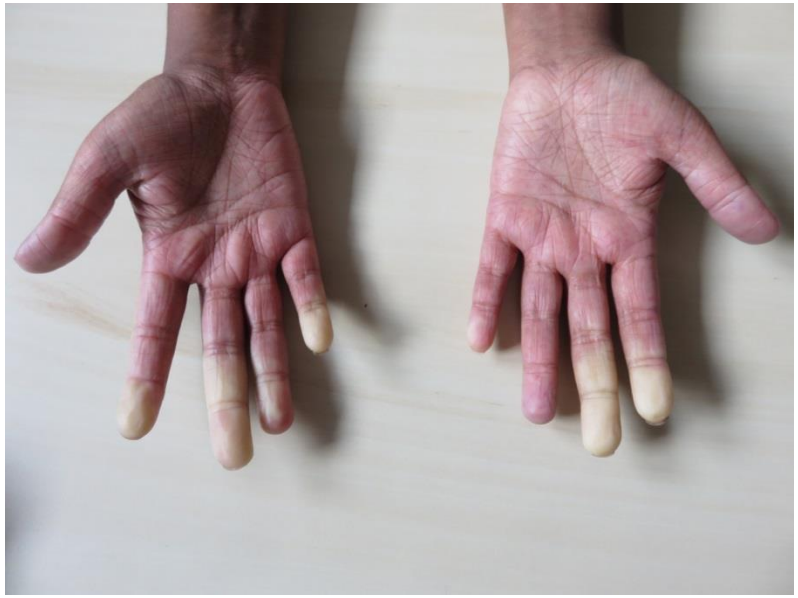
Clinical and serological features at first visit

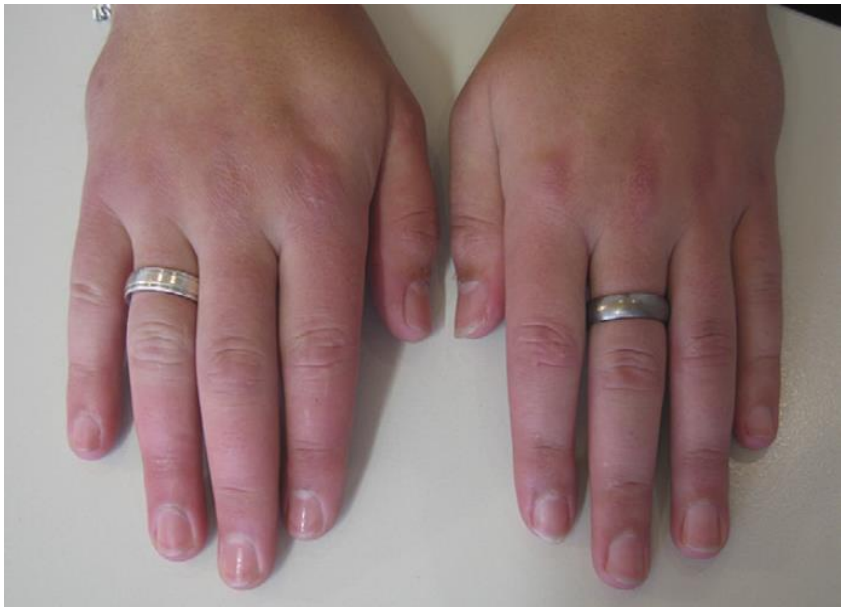
Clinical and Serologic Features	First Visit, No. of Patients/%		2008,[a] No. of Patients/%
Raynaud's phenomenon	150 (93.2%)		137 (85.1%)
Arthritis/arthralgia	119 (73.9%)		80 (49.7%)
Edema of the hands	117 (72.7%)		74 (46%)
Sclerodactyly	47 (29.2%)	SSc features	69 (43%)
Hypomotility or dilatation of esophagus[b]	56 (34.8%)		73 (45.3%)
Pulmonary involvement[c]	46 (28.6%)		71 (44.1%)
Pleuritis/pericarditis	35 (21.7%)		30 (18.6%)
Facial erythema	32 (19.9%)		27 (16.8%)
Lymphadenopathy	29 (18%)	SLE features	22 (13.7%)
Neurological involvement	9 (5.6%)		18 (11.2%)
Renal involvement (nephritis)	11 (6.8%)		16 (9.9%)
Leukopenia/thrombocytopenia	39 (24.2%)		43 (26.7%)
Elevated CPK	45 (27.9%)		31 (19.2%)
ANA	156 (96.9%)		151 (93.8%)
Anti-DNA[d]	27/135 (20%)		25/135 (18.5%)
Anti-RNP[d]	139/139 (100%)		126/139 (90.6%)
Anti-Sm[d]	22/134 (16.4%)		23/134 (17.2%)
Anti-Scl70[d]	15/116 (12.9%)		19/116 (16.4%)
ACA[d]	4/113 (3.5%)		5/113 (4.4%)
Anti-SSA/Ro[d]	31/116 (26.7%)		31/116 (26.7%)
Anti-CCP[d]	Not done		19/114 (16.7%)

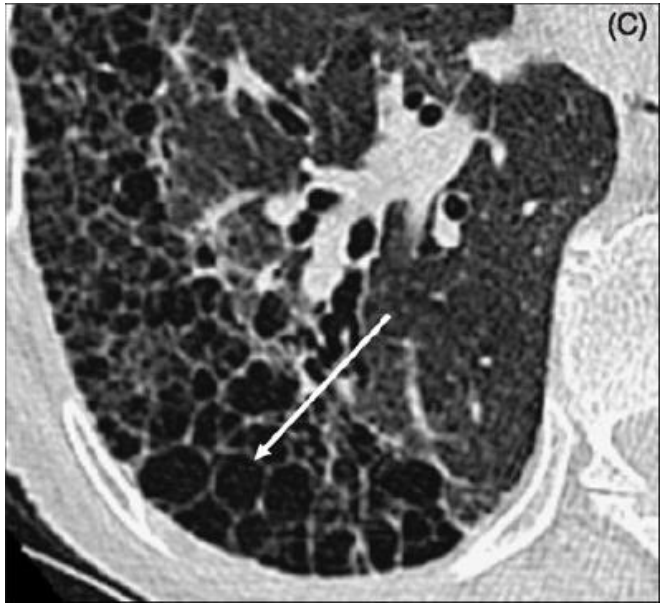
[a]For patients who died before 2008, clinical and serological features were collected at the last visit.
[b]Patients with hypomotility or dilatation of esophagus showed by manometry and/or esophageal barium radiograph.
[c]Patients with evidence of interstitial lung disease (ILD) on chest radiograph (CXR) or tomography (CT) scan and/or restrictive pattern on spirometry and/or reduced diffusion capacity.
[d]These data were not provided for all the 161 patients included in the study.

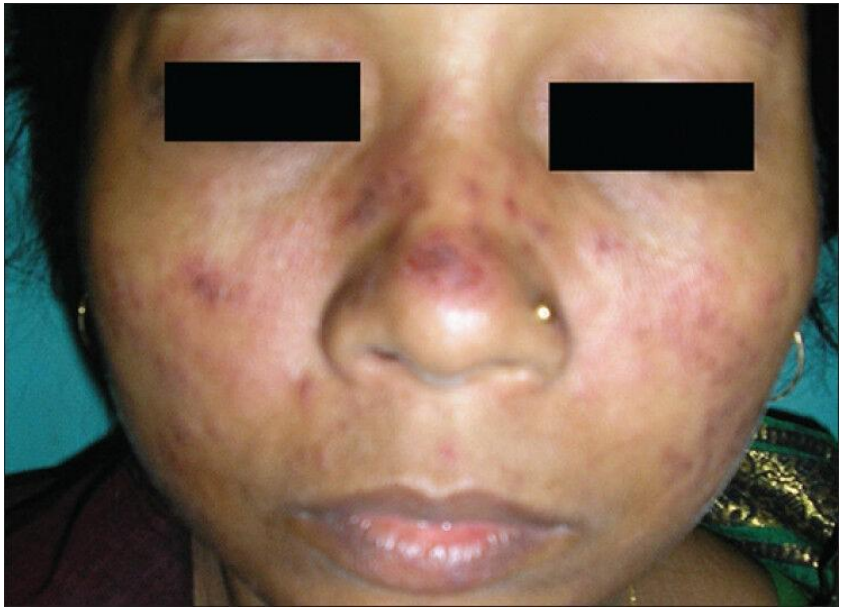
Cappelli S et al. Sem Arthritis Rheum 2012

Connectivite mixte









Ragnar Gunnarsson et al. Ann Rheum Dis doi:10.1136/annrheumdis-2011-201253

Aringer M. Best Practice & Research Clinical Rheumatology 200

Overview of HRCT lung findings in the patients with MCTD

HRCT findings (n=126)	Patients (n)	%
Normal HRCT	61	48
Abnormal HRCT findings	65	52
Specified HRCT abnormalities		
Reticular pattern type 1*	27	21
Reticular pattern type 2*	20	16
Reticular pattern type 3*	7	6
Ground-glass attenuation	2	2
Interlobular septal thickening	10	8
Nodules	7	6
Bronchiectasis/broncholectasis	11	9
Air trapping	1	1
Emphysema	8	6
Pleural effusion	0	0
Pleural thickenings	3	2

*Reticular pattern type 1, fine intralobular fibrosis without evident cysts; reticular pattern type 2, predominantly microcystic reticular pattern involving air spaces ≤4 mm in diameter; and reticular pattern type 3, a predominantly macrocystic reticular pattern with air spaces >4 mm in diameter. When ground-glass opacification was superimposed a reticular pattern, the abnormality was recorded as being reticular. When fine intralobular fibrosis was superimposed microcystic reticular pattern, the abnormality was recorded as being microcystic reticular pattern.
HRCT, high-resolution CT.

Gunnarsson R et al. Ann Rheum Dis 2012;71:1966–1972.

Combined Pulmonary Fibrosis and Emphysema Syndrome in Connective Tissue Disease

Table 1. Classification of connective tissue diseases in the 34 study patients*

Rheumatoid arthritis	18 (53)
Systemic sclerosis	10 (29)
Diffuse cutaneous	3 (9)
Limited cutaneous	7 (20)
Mixed connective tissue disease	2 (6)
Overlapping connective tissue disease	2 (6)
Sjögren's syndrome	1 (3)
Polymyositis	1 (3)

* Values are the number (%) of patients.

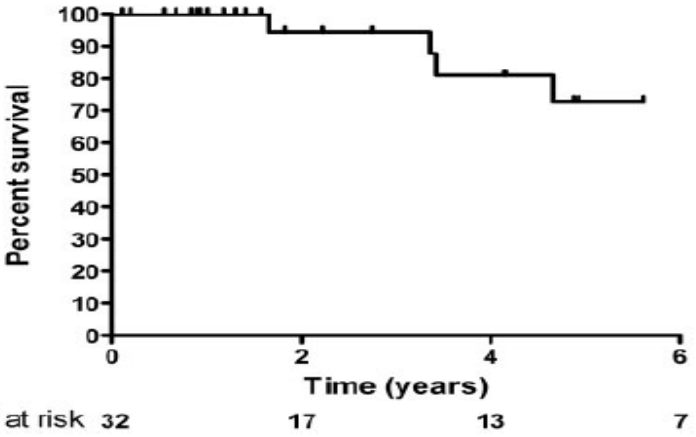
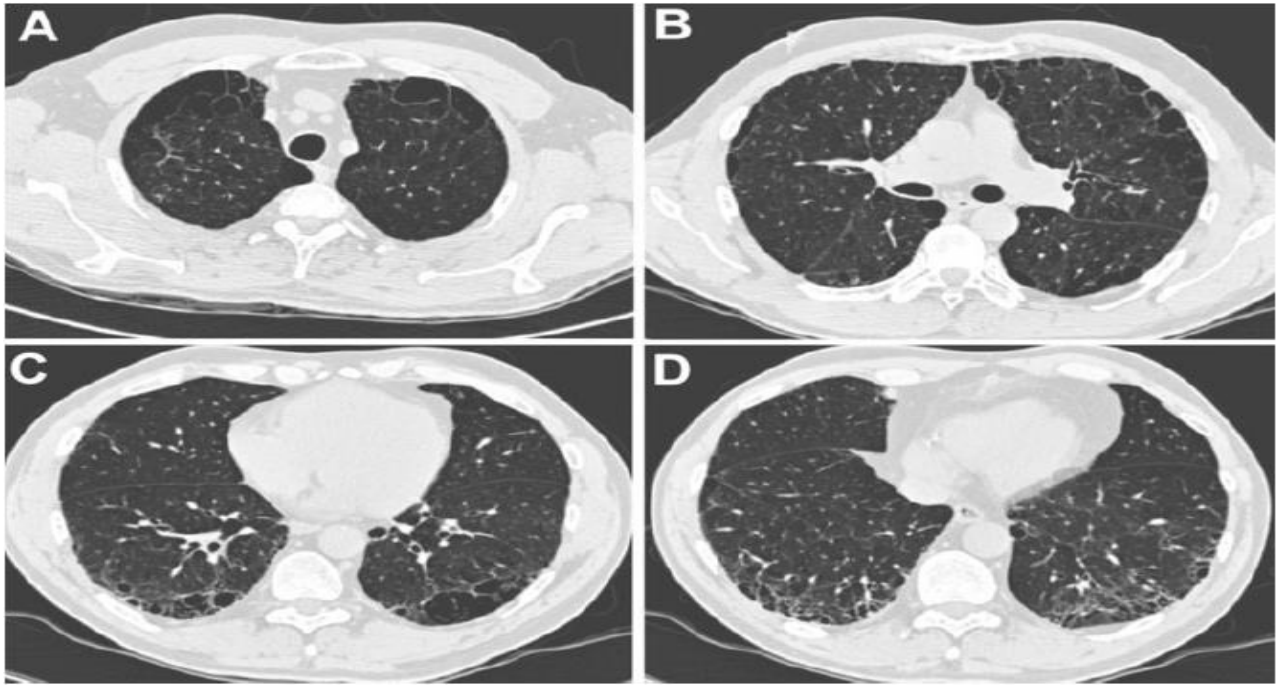


Figure 2. Kaplan-Meier estimates of survival in patients with combined pulmonary fibrosis and emphysema syndrome and connective tissue disease.



Cottin et al Arthritis Rheum 2010

Pulmonary function tests, classification of dyspnoea and functional testing, in 105 patients with MCTD disease with normal HRCT and fibrotic HRCT changes

	Normal HRCT findings (n=61)	Minor and moderate lung fibrosis (n=20)	Severe lung fibrosis (n=24)
Pulmonary function tests			
FVC (litre)	**3.6** (3.4 to 3.8)	**3.4** (3.0 to 3.9)	**2.8** (2.5 to 3.1)
FVC (% of predicted)	**94** (90 to 98)	**89** (83 to 95)	**83** (74 to 92)
FEV1 (litre)	**2.9** (2.7 to 3.1)	**2.7** (2.2 to 3.1)	**2.3** (2.0 to 2.5)
FEV1 (% of predicted)	**90** (86 to 94)	**82** (76 to 89)	**82** (75 to 88)
TLCO (mmol/kPa min)	**7.7** (7.1 to 8.2)	**6.4** (5.4 to 7.3)	**5.2** (4.4 to 6.0)
TLCO (% of predicted)	**80** (77 to 85)	**69** (61 to 77)	**59** (51 to 66)
TLCO/AV (mmol/kPa min/l)	**1.7** (1.5 to 1.9)	**2.2** (1.4 to 3.0)	**1.3** (1.1 to 1.5)
TLCO/AV% (% of predicted)	**91** (87 to 95)	**89** (79 to 100)	**78** (70 to 86)
Dyspnoea classification			
NYHA functional classification*	**1.2** (1.1 to 1.4)	**1.5** (1.2 to 1.7)	**2.0** (1.7 to 2.4)
Functional testing			
6 Min walk test (meters)	**561** (532 to 589)	**534** (462 to 605)	**434** (381 to 491)

Results are shown as mean (95% CI).

*New York Heart Association functional classification was calculated by mean of total NYHA scores (from 1 to 4).[34]
AV, alveolar volume; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution CT; NYHA, New York heart Association; TLCO, carbon monoxide transfer factor.

Gunnarsson R et al. Ann Rheum Dis 2012;71:1966–1972.

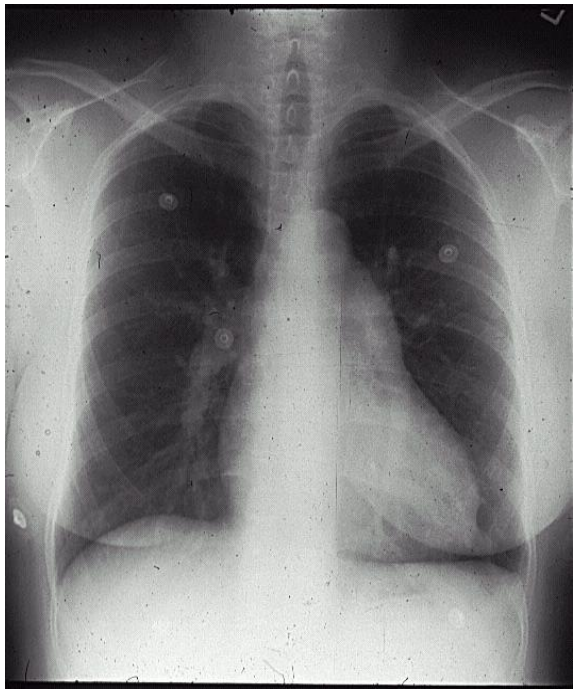
ILD in MCTD

- Severe lung fibrosis is common in MCTD, has an impact on pulmonary function and overall physical capacity and is associated with increased mortality.
- HR CT scan and PFTs with DLCO must be performed at the time of diagnosis of MCTD
- PFTs with DLCO must be performed annually during follow up

Pulmonary hypertension

Definition

Mean pulmonary artery pressure of ≥ 25 mmHg associated with a normal pulmonary artery wedge pressure ≤ of 15 mmHg

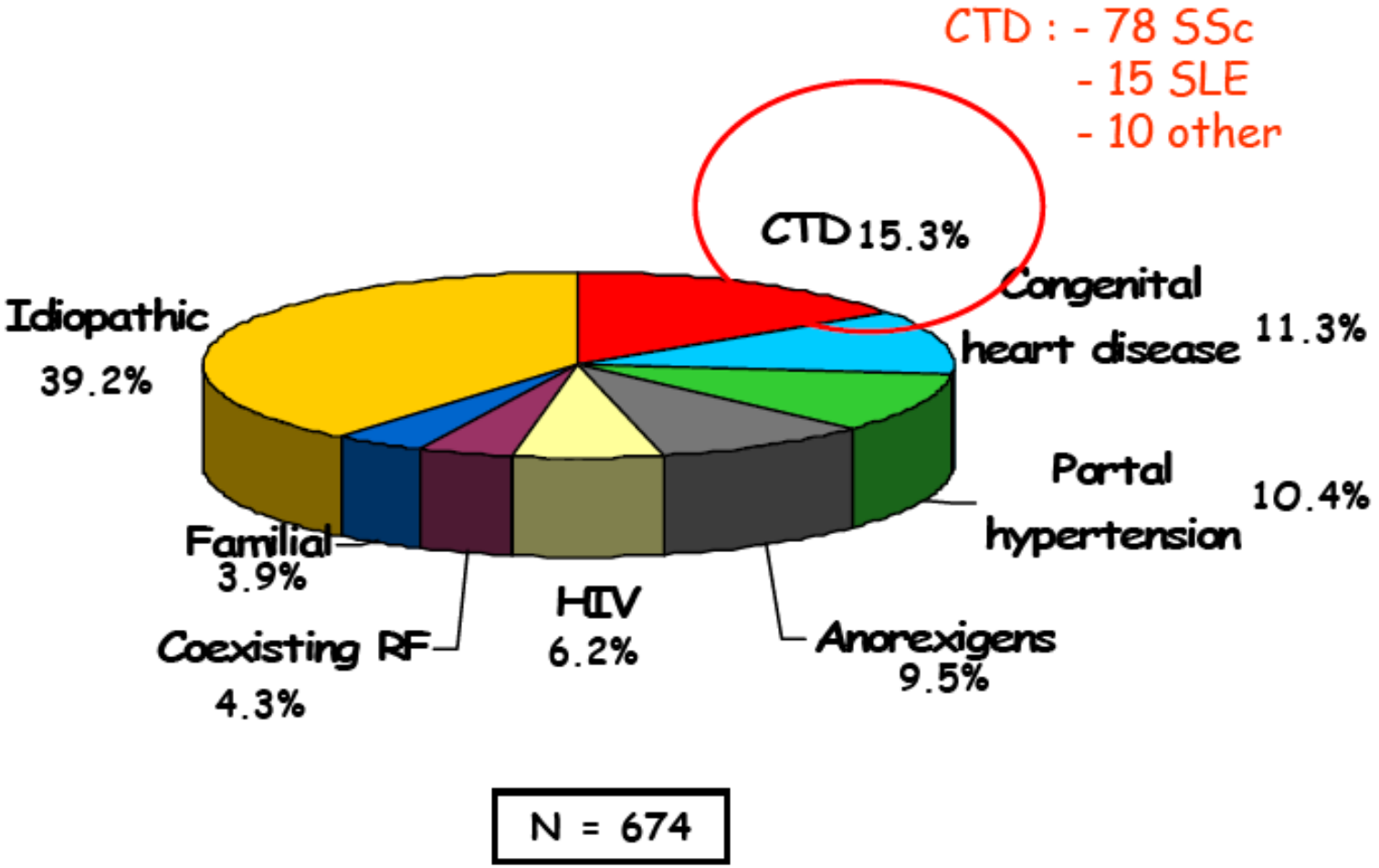


Simonneau, G., N. Galiè, et al. (2004). "Clinical classification of pulmonary hypertension." J Am Coll Cardiol 43(12 Suppl S): 5S-12S

Rubin, L. J. (1997). "Primary pulmonary hypertension." N Engl J Med 336(2): 111-117.

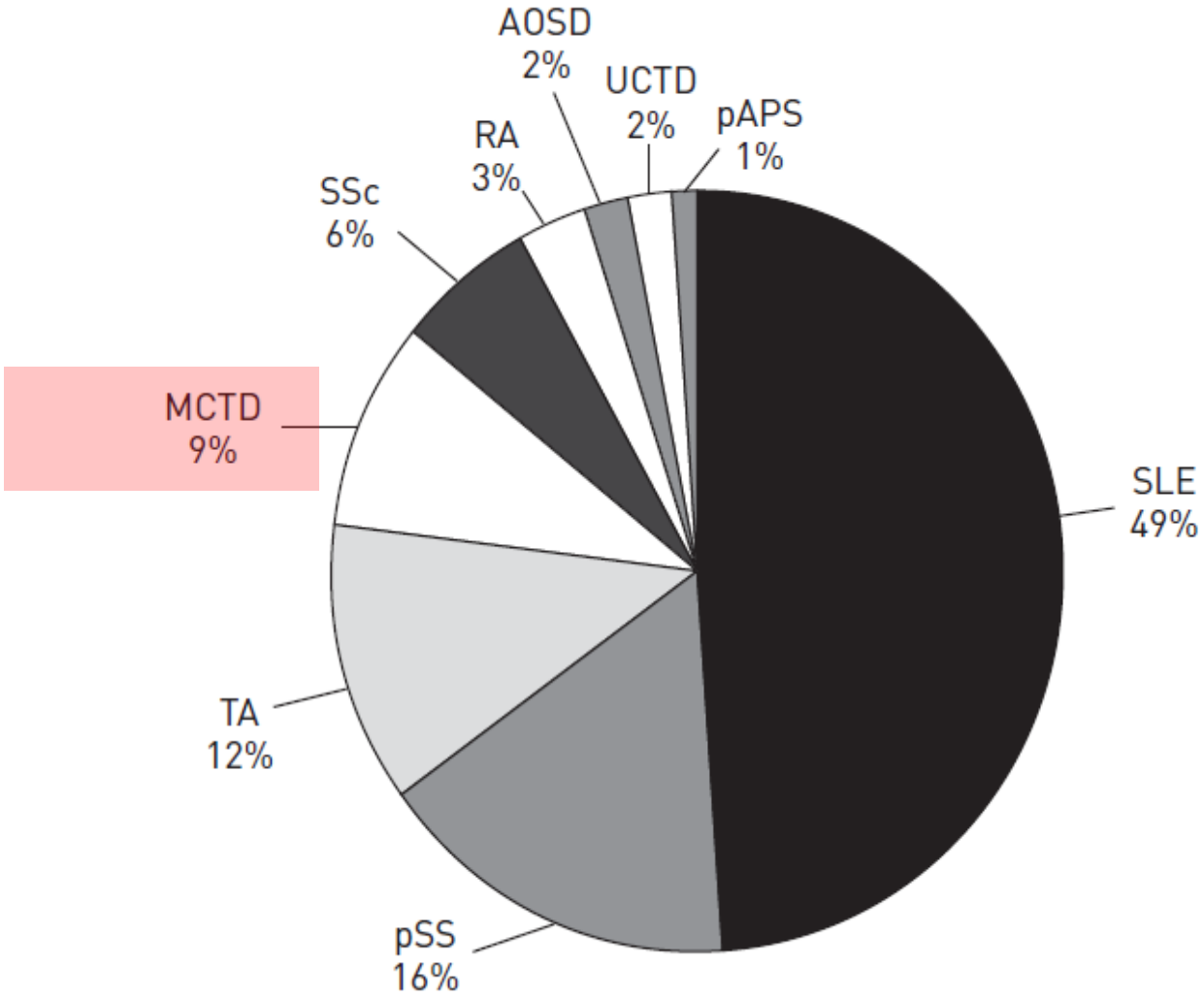
Pulmonary arterial hypertension in France : results from a national registry

Humbert M et al. AJRCCM 2006, Feb 2; [Epub ahead of print]



Humbert M et al. Am J Respir Crit Care Med 2006;173:1023

Proportions of different underlying CTDs in 129 patients with CTD-associated PAH



HAO YJ et al. Eur Resp J 2014

Prevalence of PH in MCTD

	Alpert *et al.* [14]	Sullivan *et al.* [2]	Burdt *et al.* [3]	Wigley *et al.* [15]
Year published	1983	1984	1999	2005
Country	USA	USA	USA	USA and Canada
MCTD population	Hospital cohort	Hospital cohort	Hospital cohort	Screening, rheumatology practices
Location	University of Missouri	University of Missouri	University of Missouri	50 rheumatology practices
Study design	Cohort follow-up	Cohort follow-up	Cohort follow-up	Cross-sectional
Mean disease duration at inclusion (years)	–	4.5	–	–
Mean follow-up time (years)	–	6.3	15	–
MCTD disease criteria	–	–	Kasukawa	Alarcón-Segovia
Number of patients	38	34	47	94 [11 + 83]
Sex	92% females	91% females	91% females	–
Ethnicity	N/A	82% Caucasians	81% Caucasians	–
Method of screening for PH	32 Echo and 17 RHC	15 RHC	–	Echo
PH verified by RHC, *n* (%)	9 (24)	8 (24)	8 (17)	–[a]
Prevalence of PH, %	24	24	17	19[a]
Prognosis of PH	4 deaths	3 deaths	6 deaths	–

Echo: Doppler echocardiography. [a]The diagnosis of PH was based on Doppler echocardiography with estimated right ventricular systolic pressure (ERVSP) ⩾40 mmHg defined as PH in 18 patients with MCTD.

Unselected MCTD cohort : Total PH frequency in the cohort of 3.4% (5/147).

Gunnarsson R et al. Rheumatology 2013

Prevalence of PH in MCTD

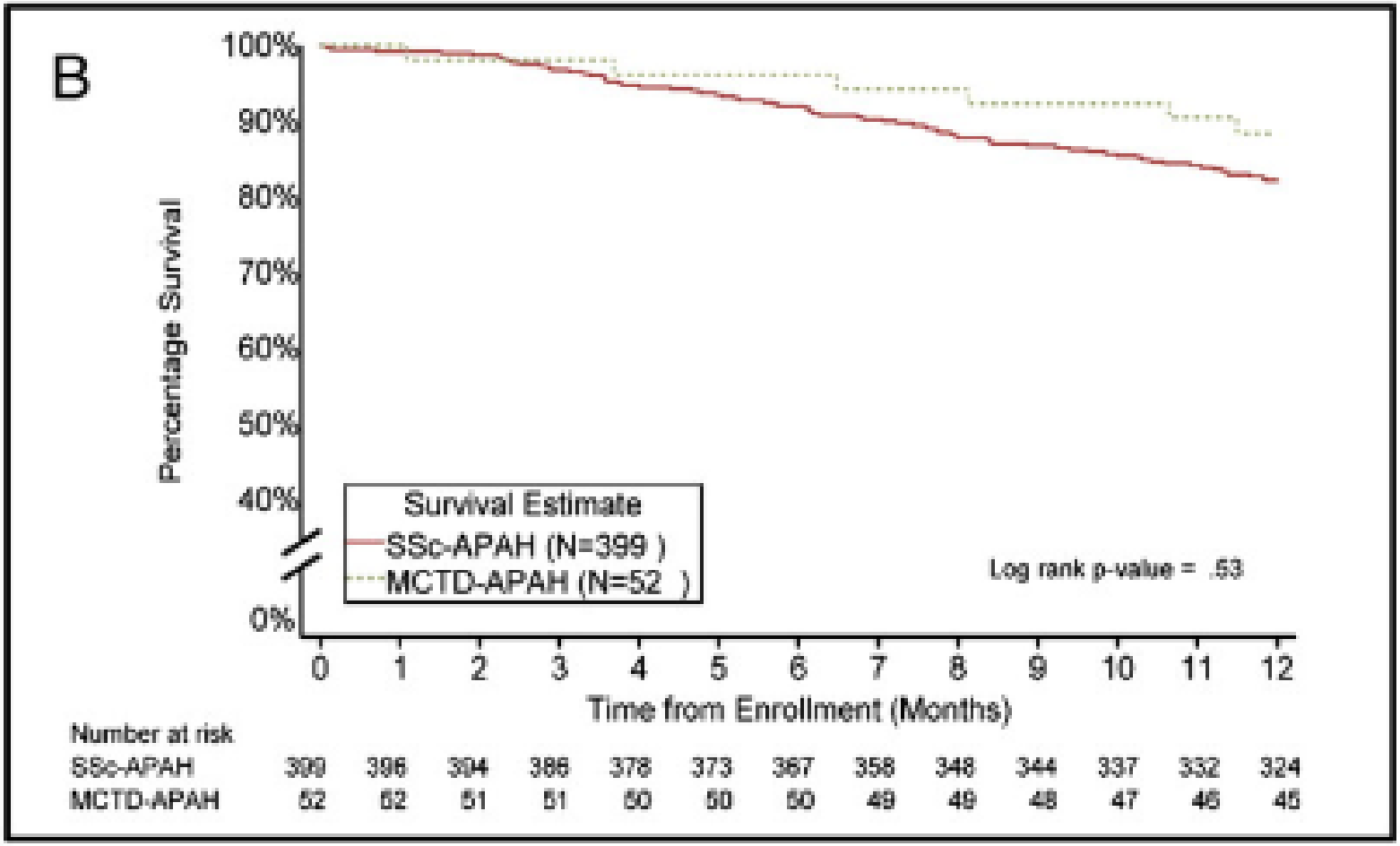
- At inclusion, 2.0% (3/147) had established PH. Two additional PH patients were identified during follow-up, giving a total PH frequency in the cohort of 3.4% (5/147).
- Two had isolated pulmonary arterial hypertension (PAH) and three PH associated with interstitial lung disease (PH-ILD).
- Three PH patients died during follow-up.
- Conclusion: the data from the current unselected MCTD cohort suggest that the prevalence of PH is much lower than expected from previous studies but confirm the seriousness of the disease complication.

Gunnarsson R et al. Rheumatology 2013

PAH - MCTD

- Detection: echocardiography
- Confirmation: right heart catheterism
- Perform regularly:
  - NT pro-BNP
  - PFTS (DLCO)
  - Echocardiography

MCTD-PAH: survival

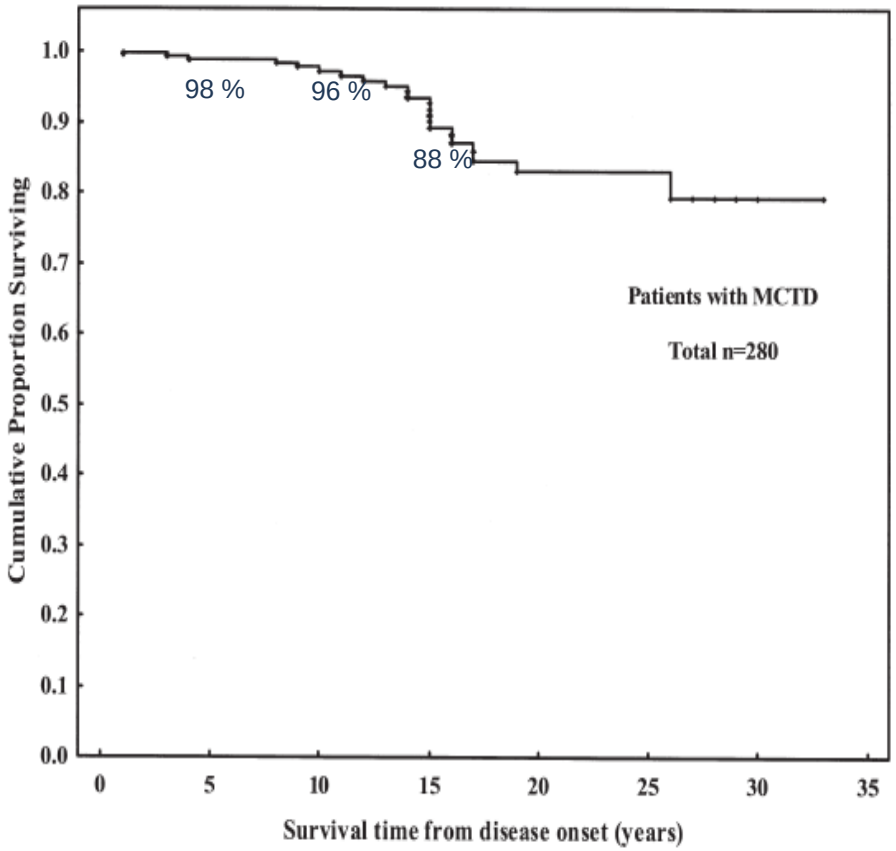


Characterization of Connective Tissue Disease-Associated Pulmonary Arterial Hypertension From REVEAL: Identifying Systemic Sclerosis as a Unique Phenotype

Chest. 2010;138(6):1383-1394

Connectivite mixte : pronostic

- Cohorte hongroise 1979-2011
- n = 280 patients
- 22 décès :
  - 9 liés à l'HTAP
  - 3 purpuras thrombopéniques
  - 3 infections
  - 7 évènements cardiovasculaires
- Facteurs pronostiques :
  - Age jeune au diagnostic de connectivite mixte
  - Évènements cardiovasculaires
  - Hypomobilité œsophagienne
  - Sérite
  - Syndrome des anti-phospholipides secondaires
  - Cancer



" L'HTAP est la première cause de décès chez les patients atteints de connectivite mixte"

Hajas et al J rheumatol 2013

MCTD: Evolution in another CTD

Criteria Fulfilled at the Diagnosis	Patients (%) Evolved into Another CTD		
	Disease, yr		
	0 to 5	5 to 10	>10
Kasukawa	15.2%	39.2%	41.7%
Alarcón	20.4%	34.9%	50%
Sharp	20.6%	43.5%	30%

Cappelli S et al. Sem Arthritis Rheum 2012

MCTD: Evolution of MCTD

Author (yr)	Evolution	Disease Duration
Nimelstein et al (1980) (24)	59% SSc, 5.9% SLE, 5.9% RA	8 yr (follow-up)
Van den Hoogen et al (1994) (21)	46% MCTD, 21% SSc, 15% SLE, 9% RA, 9% Overlap syndrome	5 yr (follow-up)
Gendi et al (1995) (19)	36% MCTD, 34% SSc, 25% SLE, 5% RA	20 yr (mean disease duration)
Burdt et al (1999) (20)	21% SSc, 13% SLE	15 yr (mean duration of follow-up)
Cappelli et al (present 2011)	57.9% MCTD, 17.3% SSc, 9.1% SLE, 2.5% RA, 1.6% Overlap Syndrome, 11.6% UCTD (Kasukawa) 49.9% MCTD, 16.9% SSc, 9%SLE, 1.6% RA, 4.1% Overlap syndrome, 18.5% UCTD (Alarcón) MCTD 52.2%, 13.4% SSc, 6% SLE, 0% RA, 10.5% Overlap syndrome, 17.9% UCTD (Sharp)	7.8 yr (mean disease duration)

Cappelli S et al. Sem Arthritis Rheum 2012

MCTD: autoantibodies as predictors of organ involvement

	Renal Involvement		Neurological Involvement		Pulmonary Involvement	
	OR (95%CI)	*P*	OR (95%CI)		OR (95%CI)	*P*
Anti-DNA	1.1 (0.9 to 1.3)	NS	1.0 (0.9 to 1.2)	NS	0.9 (0.7 to 1.2)	NS
Anti-Sm	1.3 (1.1 to 1.5)	0.004	1.0 (0.8 to 1.2)	NS	1.1 (0.8 to 1.4)	NS
Anti-SSA/ro	1.0 (0.9 to 1.1)	NS	1.2 (1.0 to 1.4)	0.014	1.4 (1.1 to 1.7)	0.010
Anti-Scl70	1.0 (0.8 to 1.2)	NS	0.9 (0.7 to 1.1)	NS	1.3 (0.9 to 1.7)	NS
ACA	0.9 (0.6 to 1.2)	NS	1.2 (0.8 to 1.7)	NS	0.9 (0.5 to 1.5)	NS

OR, odds ratio; CI, confidence interval; NS: not significant; *P*, multivariate analysis.

	Hypomotility or Dilatation of Esophagus		Sclerodactyly		Pleuritis/Pericarditis	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Anti-DNA	0.9 (0.7 to 1.2)	NS	0.9 (0.7 to 1.1)	NS	1.3 (1.1 to 1.5)	0.009
Anti-Sm	1.0 (0.7 to 1.3)	NS	0.9 (0.7 to 1.2)	NS	1.2 (0.9 to 1.4)	NS
Anti-SSA/ro	1.2 (0.9 to 1.5)	NS	1.0 (0.8 to 1.3)	NS	1.3 (1.1 to 1.6)	0.001
Anti-Scl70	1.4 (1.0 to 1.8)	0.048	1.0 (0.7 to 1.3)	NS	1.1 (0.9 to 1.3)	NS
ACA	1.3 (0.7 to 2)	NS	1.9 (1.1 to 3.1)	0.019	1.2 (0.9 to 1.7)	NS

Cappelli S et al. Sem Arthritis Rheum 2012

MCTD: prognosis

- 280 patients with MCTD
- 22/280 patients died: causes of death were PAH (n=9), TTP (n=3), infections (n=3), and cardiovascular events (n=7).
- 5, 10, and 15-year survival rates were 98%, 96%, and 88%, respectively.
- Deceased patients: younger at the diagnosis of MCTD compared to patients who survived (35.5 ± 10.4 vs 41.8 ± 10.7 yrs; $p < 0.03$)
- Cardiovascular events ($p < 0.0001$), esophageal hypomotility ($p = 0.04$), serositis ($p < 0.001$), secondary APLS ($p = 0.039$), and malignancy ($p < 0.001$) significantly higher in the deceased patients.
- anticardiolipin ($p = 0.019$), anti-β2-glycoprotein I ($p = 0.002$), and antiendothelial cell Abs ($p = 0.002$) increased the risk of mortality.
- PAH remained the leading cause of death in patients with MCTD.

Haias A et al. J Rheumatol 2013

MCTD: Adapt treatment to disease severity

- **Skin and joint involvement**
  - hydroxychloroquine
  - NSAID
  - topical corticosteroids
  - low dose oral GC
  - Never use immunosuppressants
- **Pleuritis, pericarditis**
  - hydroxychloroquine
  - NSAID
  - GC 0.5 mg/kg
  - No immunosuppressants
- **Visceral involvement (except PAH)**
  - hydroxychloroquine (prevention of relapses)
  - High dose GC (1 mg/kg)
  - Eventually pulse MP
  - Immunosuppressants
  - anti-CD20, plasma exchanges…
- **PAH**
  - Symptomatic measures
  - GC (1 mg/kg) + IS
  - Specific PAH treatments

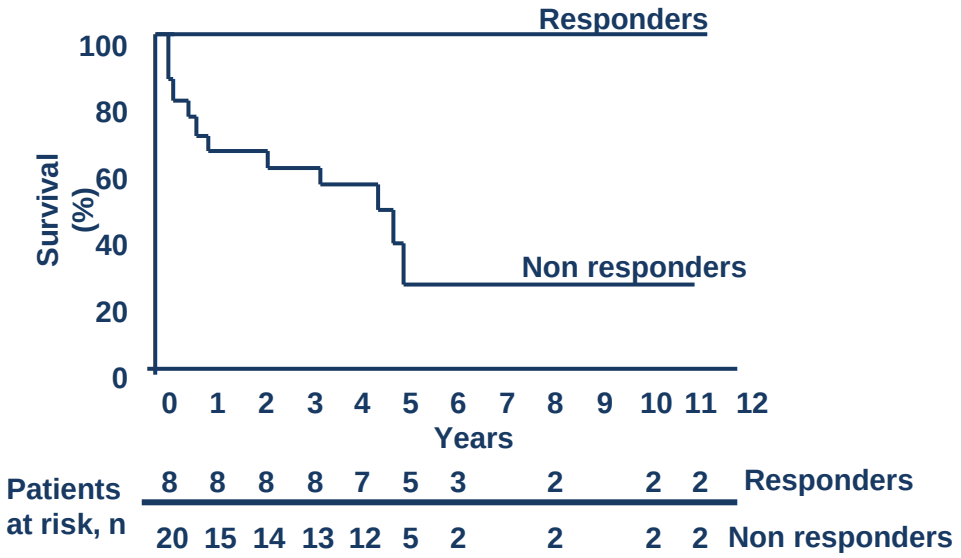
Treatment of MCTD-ILD: similar to SSc-ILD

- **PPI**
- **Cyclophosphamide**
- **Mycophenolate mofetil**
- **Low dose glucocorticoids (10 mg/d)**
- **Oxygen**
- **Lung transplantation**

- **Rehabilitation**

IMMUNOSUPPRESSIVE THERAPY IN CTD-PAH

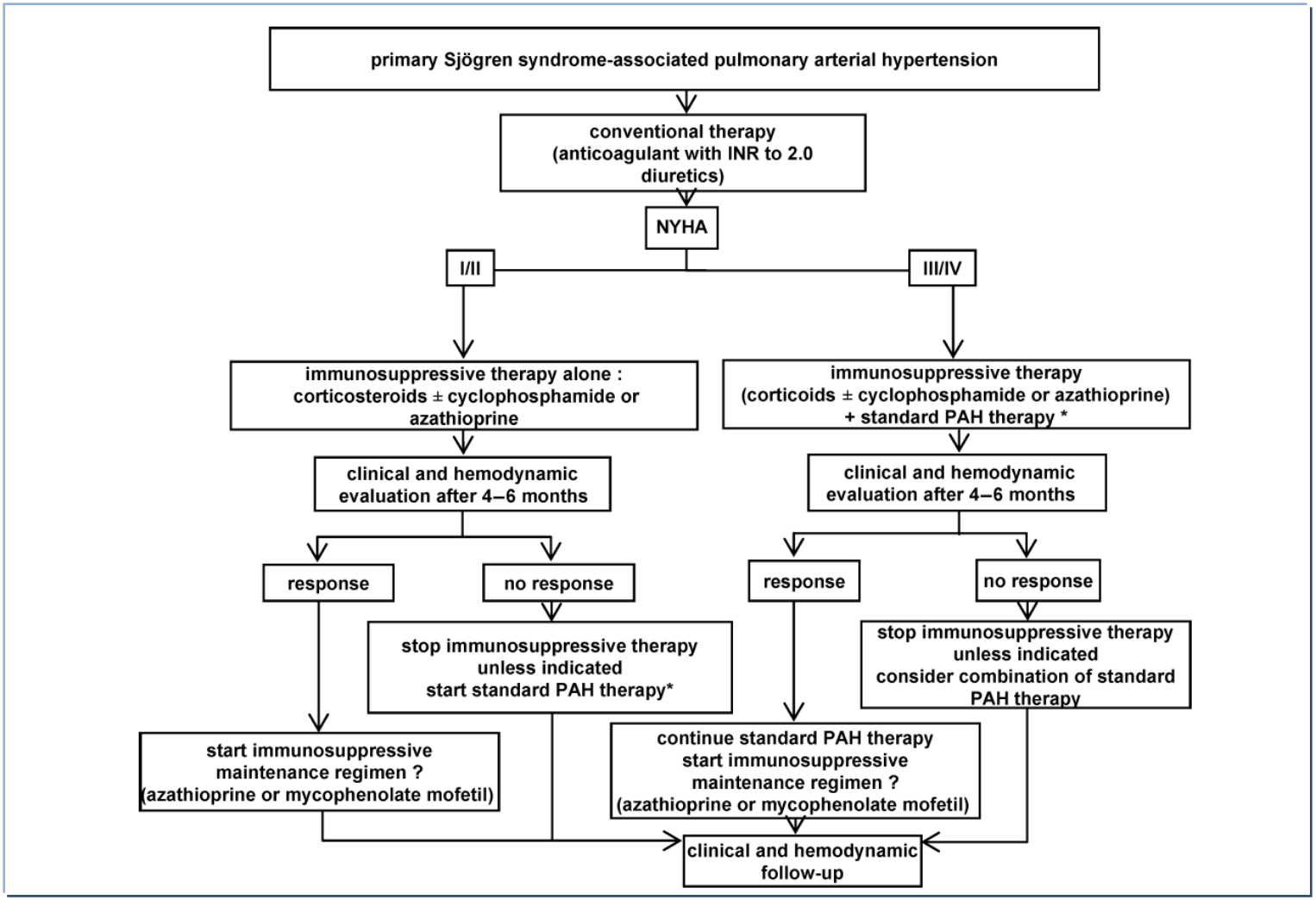
- First line immunosuppressive therapy
  - Monthly IV cyclophosphamide pulses (600 mg/m^2)
  - Steroids (prednisone 0.5 - 1 mg/kg/j)
- Eight out of 28 patients (32%) were “responders” (NYHA I-II after 1 yr)
- No patient with systemic sclerosis responded
- 38% of SLE and MCTD patients responded after 7 ± 6 CYC pulses
  - SLE n = 5 / 13
  - MCTD n = 3 / 8
  - SSc n = 0 / 6



Sanchez O, *et al*. *CHEST* 2006;130;182-9.

Proposed treatment algorithm of pSS-associated PAH.

This algorithm has not been validated by clinical studies.



Launay D et al. Medicine 2007;86:299–315

Conclusion

- Sharp/MCTD defined by overlapping features of SLE, SSc, PM/DM and high titer anti-U1 snRNP Abs.
- Four sets of diagnostic criteria/2 only including lung involvement
- Rare disease: prevalence 3.8 per 100 000
- Evolution in another CTD in about 50% of the cases
- Prognosis is good, although internal organs ar at risk for serious complications; patients do not always improve with steroids.
- Survival rates at 10 years: 96%
- Most of the patients respond to HC and low dose GC
- PAH remained the leading cause of death in patients with MCTD

French Vasculitis Study Group

GFRS Groupe Francophone de Recherche sur la Sclérodermie

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