USZ Universitäts Spital Zürich

Rheuma-Workshop

Mixed Connective Tissue Disease Abklärung und Therapie

Dr. med. Rucsandra Dobrota, Oberärztin

Klinik für Rheumatologie, USZ

USZ Universitäts Spital Zürich

Mischkollagenose

Mixed connective tissue disease (MCTD)

Am J Med. 1972 Feb;52(2):148-59. doi: 10.1016/0002-9343(72)90064-2.

Mixed connective tissue disease--an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antige (ENA)

G C Sharp, W S Irvin, E M Tan, R G Gould, H R Holman

MCTD: a concept which stood the test of time

GC Sharp[1]*
University of Missouri, Columbia, USA

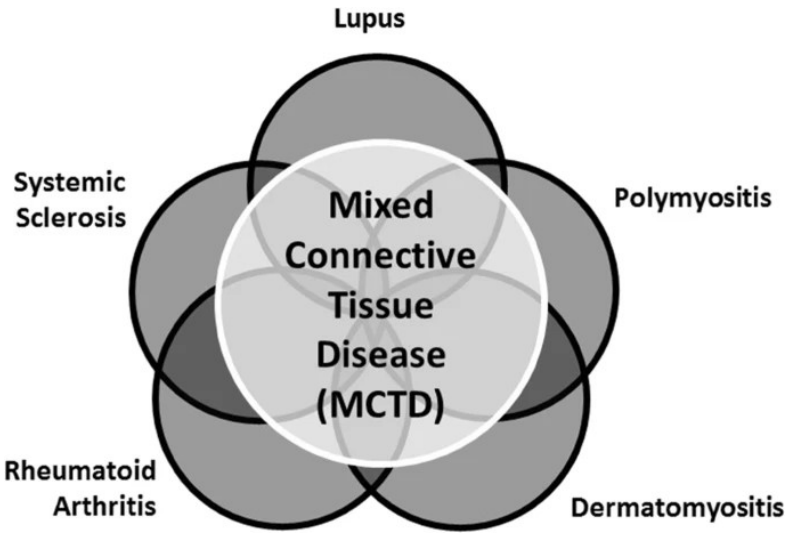
Lupus (2002) 11, 333-339
www.lupus-journal.com

June 7, 2010

(rechts) **Gordon C. Sharp**, MD, MU Emeritus Professor of Immunology & Rheumatology, founder and director of the ANA laboratory at the University of Missouri, since 2010 called the Gordon C. Sharp ANA Laboratory
Pepmueller, 2016

Mischkollagenose
Mixed connective tissue disease (MCTD)

- seltene Krankheit (orphan disease)
- Prävalenz 3.8/100,000 (Norwegen)
- Frauen > Männer (3–5:1)
- EM in jedem Alter, max. 40j
- Oft multiple Organsysteme betroffen
- Outcome sehr unterschiedlich, von mildem bis zu sehr ungünstigem Verlauf



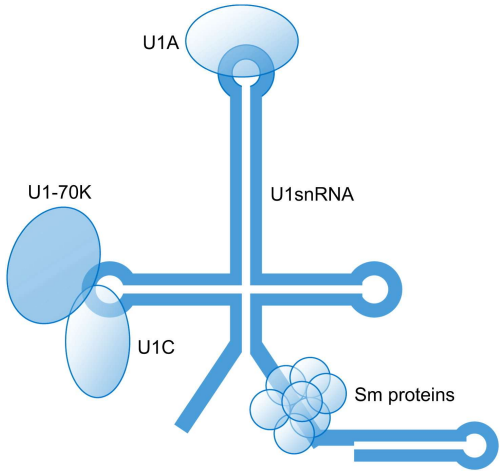
https://bmcrheumatol.biomedcentral.com/articles/10.1186/s41927-021-00179-2

Pathogenese

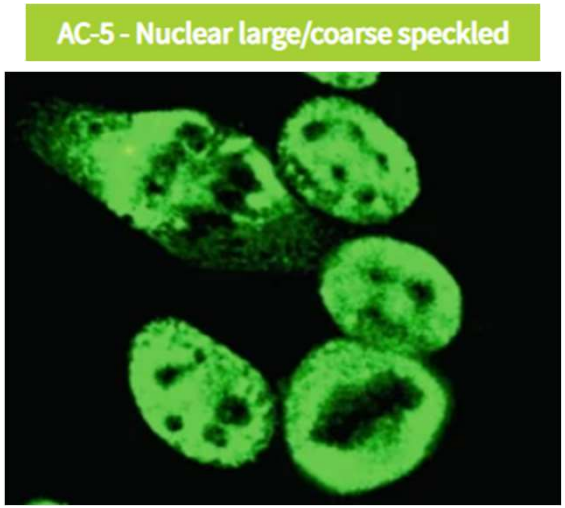
HLA-Assoziation: HLA-DR4 (HLA DRB1*04:01), HLA-B*08

Anti-U1-RNP Ak.:

- Uridin-1 small nuclear ribonucleoprotein particle (U1 snRNP)
- umstritten: Zusammenhang mit Krankheitsaktivität / Prognose ?
- pathogenische Role vermutet



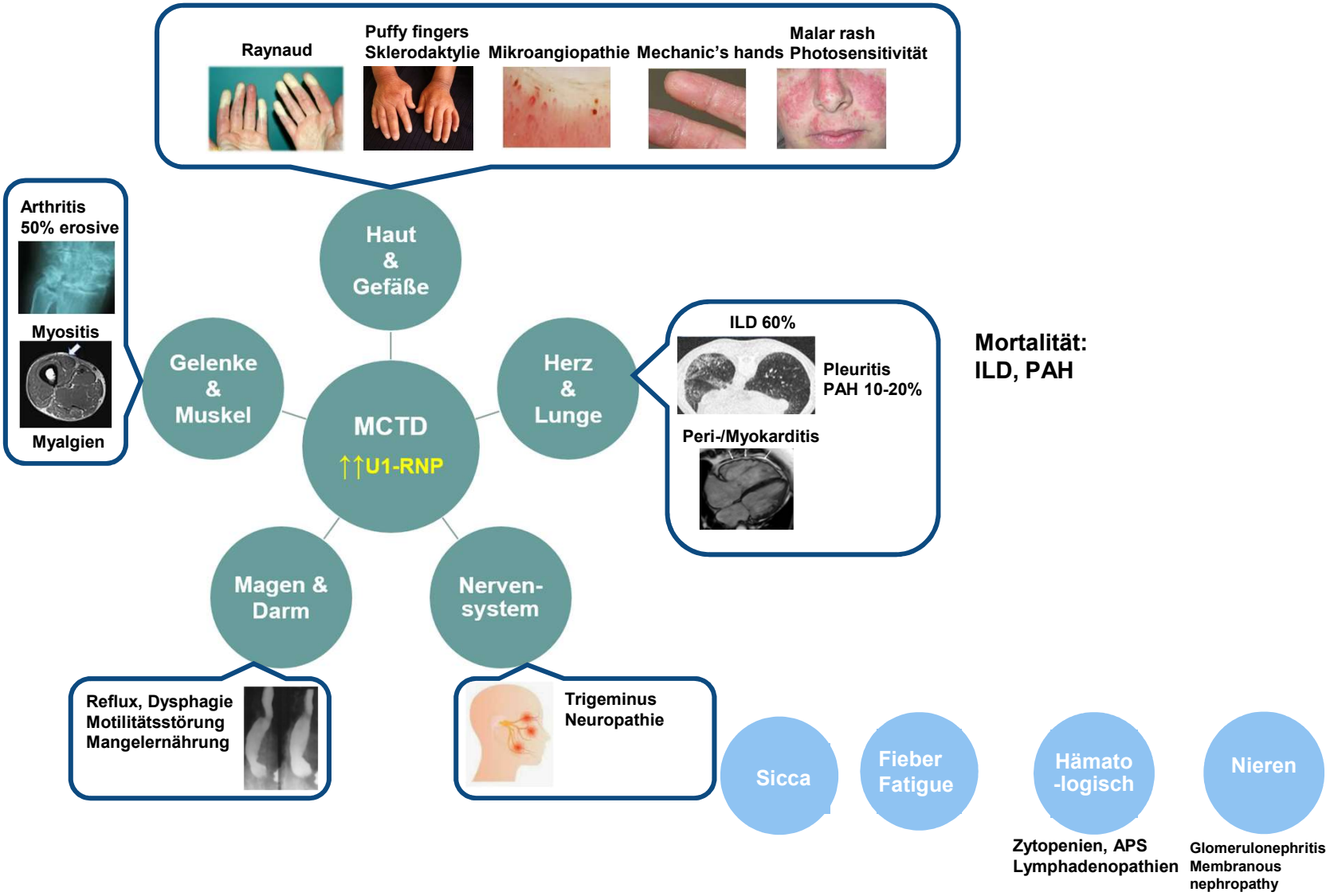
https://pdf.sciencedirectassets.com/

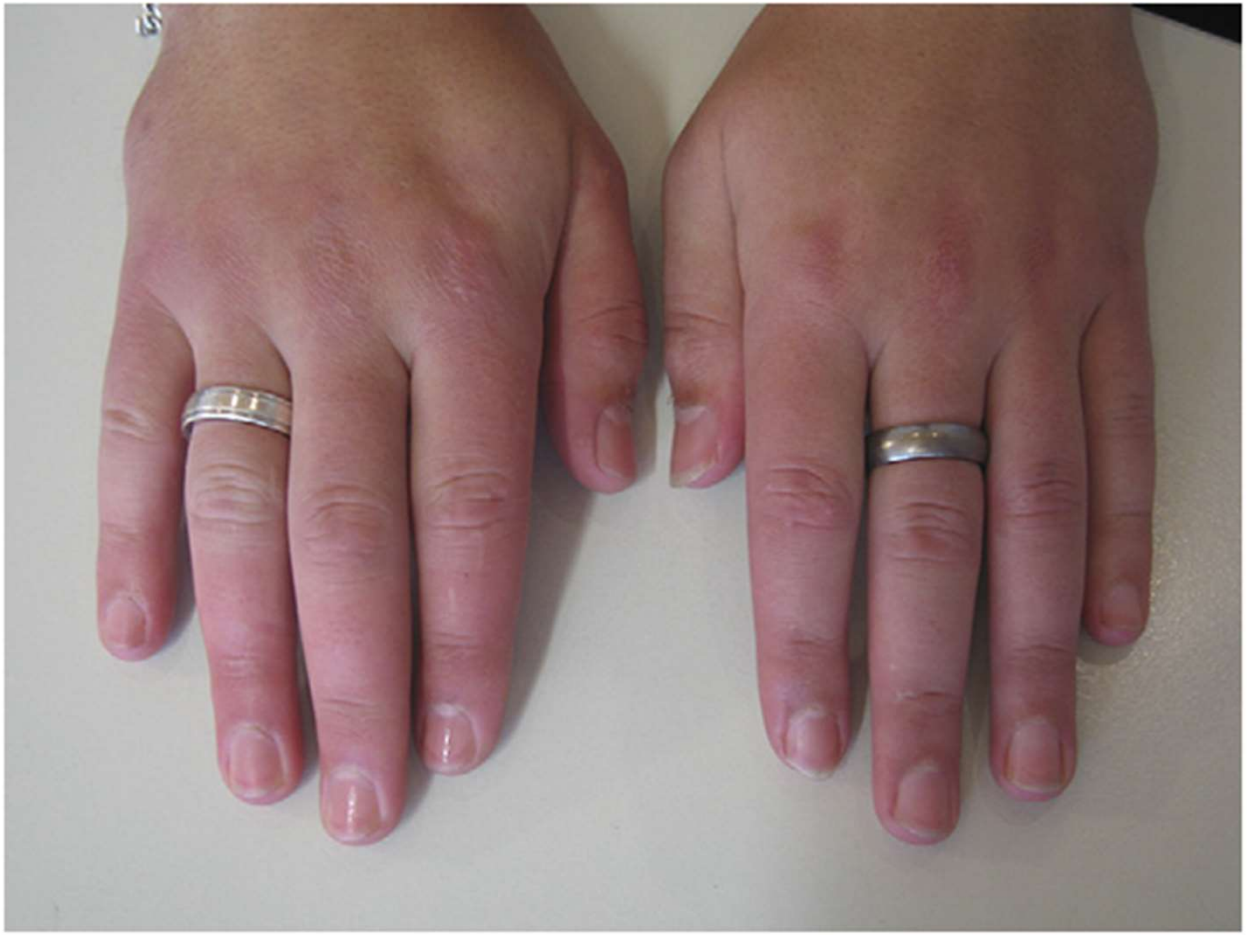


https://link.springer.com/chapter/10.1007/978-3-662-48986-4_459

Indirekte Immunfluoreszenz mit HEp-2-Zellen: grobgranuläre Fluoreszenz, über den gesamten Zellkern, Nukleoli ausgespart

MCTD - Klinik


Raynaud
Puffy fingers
Sklerodaktylie
Mikroangiopathie
Mechanic's hands
Malar rash
Photosensitivität
Arthritis
50% erosive
Myositis
Myalgien
Haut & Gefäße
Gelenke & Muskel
MCTD
↑↑U1-RNP
Herz & Lunge
ILD 60%
Pleuritis
PAH 10-20%
Peri-/Myokarditis
Mortalität:
ILD, PAH
Magen & Darm
Nerven-system
Reflux, Dysphagie
Motilitätsstörung
Mangelernährung
Trigeminus
Neuropathie
Sicca
Fieber
Fatigue
Hämato -logisch
Zytopenien, APS
Lymphadenopathien
Nieren
Glomerulonephritis
Membranous nephropathy

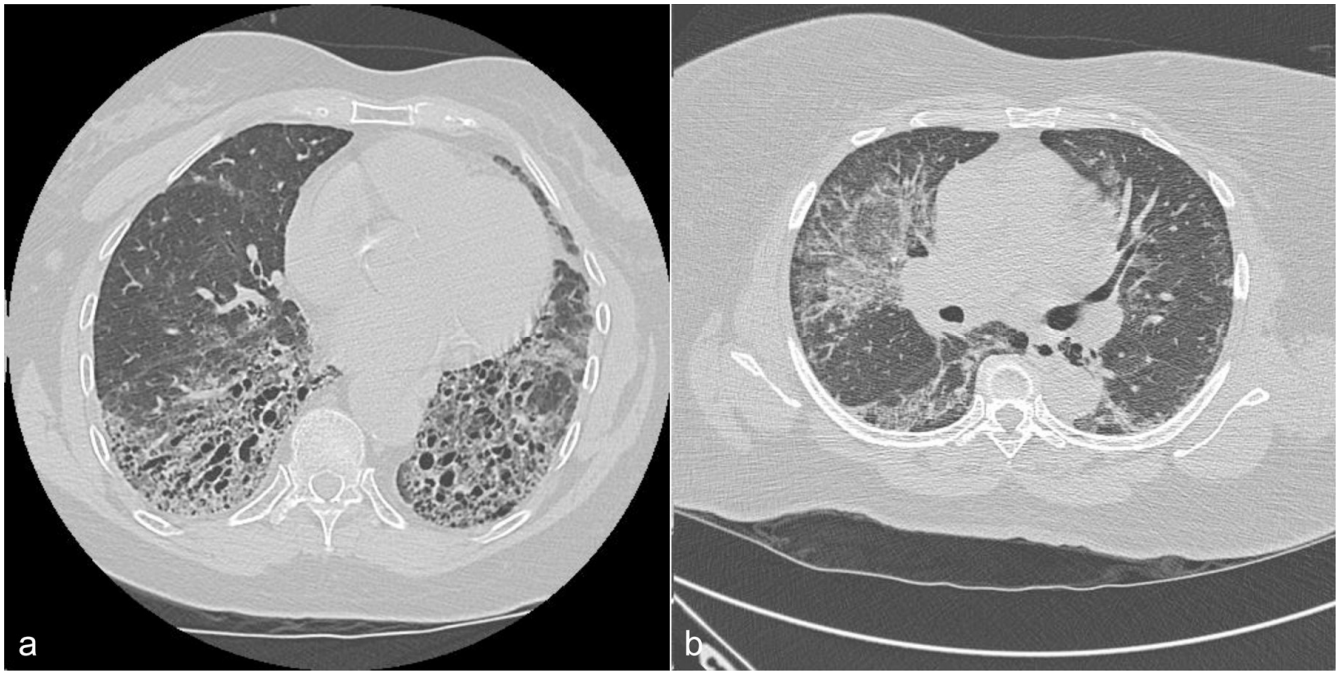


https://pdf.sciencedirectassets.com/

Puffy fingers

MCTD - ILD

- ILD:
  - 50% to 70%
  - Risikofaktoren: Alter, lange Krankheitsdauer, männliches Geschlecht, Anti-Ro52 Ak., ausgeprägter Lungenbefall
  - NSIP, seltener UIP



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8373683/

Falvignette - 1

Frau D., 28j.

- Raynaud-Syndrom
- verlangsamte Wundheilung
- Arthralgien, Myalgien
- Fatigue

- PA: Depression, arterielle Hypotonie

Falvignette - 2

Herr B., 43j.

- Raynaud-Syndrom
- Geschwollene Finger
- Zunehmende Spannung der Haut mit Faustschluss Einschränkung
- Zunehmende Gelenkschmerzen
- Dyspnoe NYHA II-III

- ED MCTD m/b Arthritis vor 3 Jahren
- St.n. Therapie mit Methotrexat und Actemra (selbständig abgesetzt)
- PA: Nikotinkonsum, arterielle Hypertonie

Klinisch:

- Puffy hands
- Polyarthritis
- Periphere Hautfibrose, mRSS 6/51
- Pulmonal: grobblasige RGs, keine Beinödeme

Diagnostische Kriterien für MCTD

*Anti-U1-snRNP Titer angepasst auf USZ-Labor Methode (s. Wanzenried, 2022)
**Originalversion: anti-RNP hemagglutination titres of > 1:1600 in Alarcón-Segovia's criteria, > 1:2000, in Kahn's criteria and instead of the anti-ENA titre, of > 1:10,000 in Sharp's criteria.

Diagnostische Kriterien für MCTD

Table 1. Diagnostic criteria for mixed connective tissue disease 2019, from the Japan research committee of the ministry of health, labor, and welfare for systemic autoimmune diseases.

★ I. Common manifestations
- 1. Raynaud's phenomenon
- 2. Puffy fingers and/or swollen hands

★ II. Immunological manifestation
- Positivity for anti-U1 ribonucleoprotein antibody

☆ III. Characteristic organ involvement
- 1. Pulmonary arterial hypertension
- 2. Aseptic meningitis
- 3. Trigeminal neuropathy

IV. Overlapping manifestations

A. Systemic lupus erythematosus-like manifestations
- 1. Polyarthritis
- 2. Lymphadenopathy
- 3. Malar rash
- ☆ 4. Pericarditis or pleuritis
- ☆ 5. Leukopenia (4,000/μL or less) or thrombocytopenia (100,000/μL or less)

B. Systemic sclerosis-like manifestations
- 1. Sclerodactyly
- 2. Interstitial lung disease
- 3. Esophageal dysmotility or dilatation

C. Polymyositis/Dermatomyositis-like manifestations
- 1. Muscle weakness
- 2. Elevated levels of myogenic enzymes
- 3. Myogenic abnormalities on electromyogram

Diagnosis: Mixed connective tissue disease is diagnosed when a patient meets all the following: at least one common manifestation, immunological manifestation, and at least one characteristic organ involvement; or when a patient meets all the following: at least one common manifestation, immunological manifestation, and at least one feature each in 2 or more from items A, B, and C in overlapping manifestations.

When a patient is positive for one of the following disease marker anti bodies relatively specific to other connective tissue diseases, the diagnosis of mixed connective tissue disease should be carefully made.

1. Anti-double-stranded DNA antibody or anti-Sm antibody
2. Anti-topoisomerase I antibody (anti-Scl-70 antibody)
3. Anti-RNA polymerase III antibody. Anti-aminoacyl-transfer RNA synthetase antibody
4. Anti-melanoma differentiation-associated gene 5 antibodies.

sensitivity 90.6%
specificity of 98.4%

Tanaka Y et al., 2019

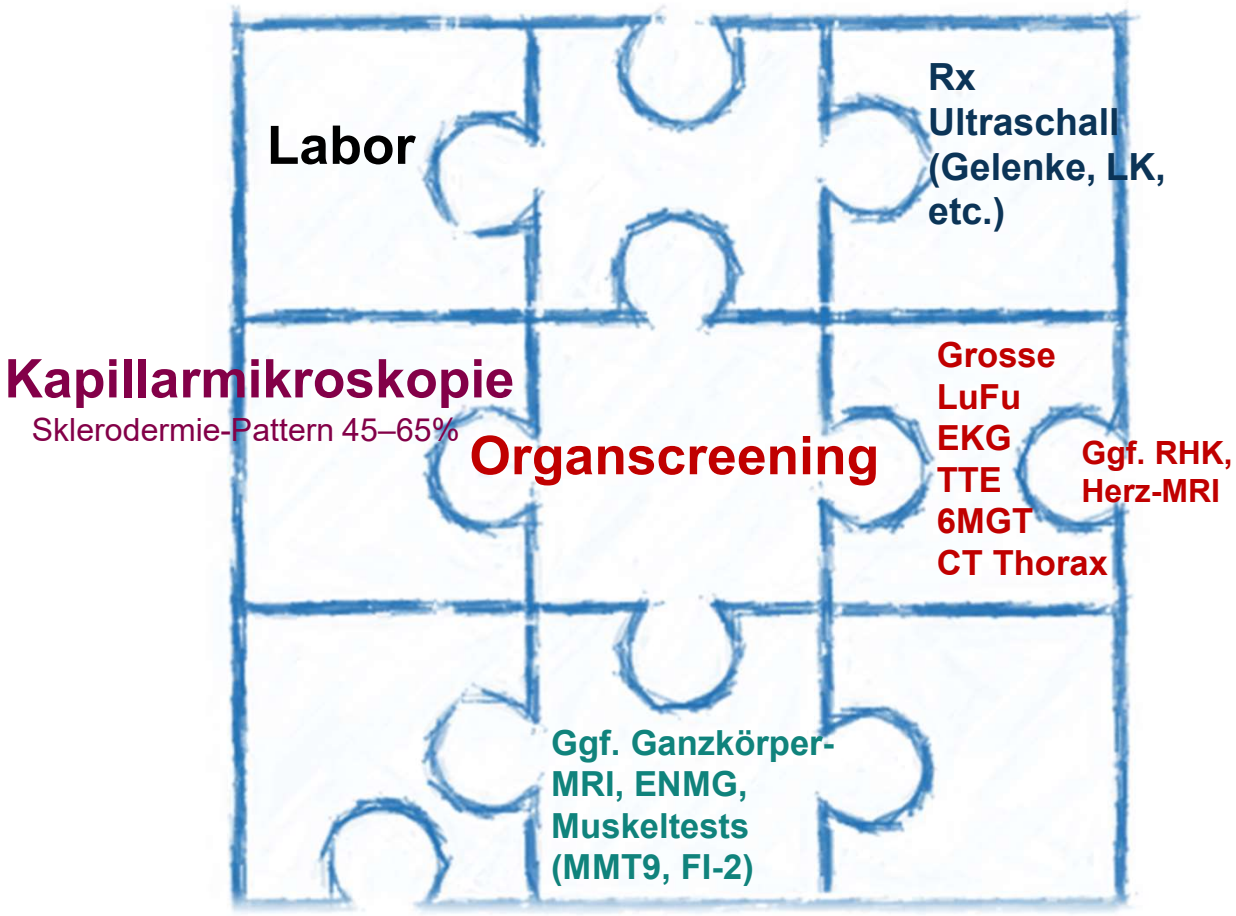
Kriterien Overlap

Table 2 Patients fulfilling classification criteria of MCTD and other CTDs (total $n = 33$)

Diagnostic/classification criteria	Frequency
Sharp MCTD criteria [10]	25 (76%)
Kasukawa et al. MCTD criteria [11]	31 (94%)
Alarcón-Segovia and Villareal MCTD criteria [12]	30 (91%)
Kahn and Appelboom MCTD criteria [13]	28 (85%)
ACR/EULAR systemic sclerosis criteria [17]	16 (48%)
SLICC systemic lupus erythematosus criteria [16]	13 (39%)
ACR/EULAR rheumatoid arthritis criteria [19]	6 (18%)
ACR/EULAR primary myositis criteria [18]	3 (9%)

USZ Kohorte, Wanzenried, 2022

Abklärung


Labor
Rx
Ultraschall
(Gelenke, LK,
etc.)
Kapillarmikroskopie
Sklerodermie-Pattern 45–65%
Organscreening
Grosse
LuFu
EKG
TTE
6MGT
CT Thorax
Ggf. RHK,
Herz-MRI
Ggf. Ganzkörper-
MRI, ENMG,
Muskeltests
(MMT9, FI-2)

Überblick – Labor

Positive Anti-U1 RNP (hochtitrig)

CAVE Anti-Sm, Anti-dsDNS oder andere spezifische Ak. (DDx SLE, SSc, DM, RA) prinzipiell negativ, falls positiv im klinischen Kontext zu interpretieren

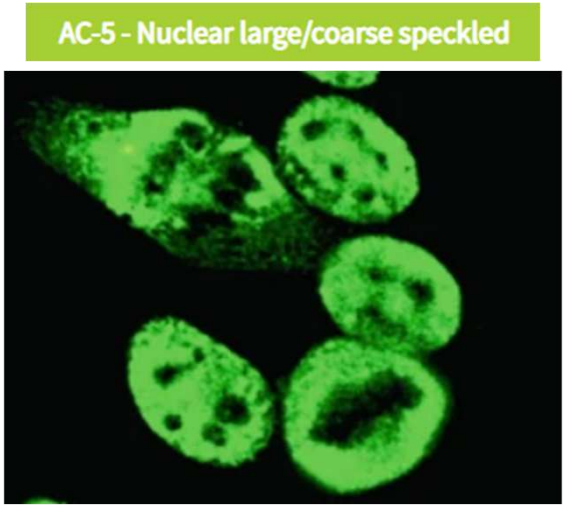
+/- anti-Ro60kDa, anti-Ro52kDa, anti-La (10%)

+/- Rheumafaktor, Anti-CCP

+/- Komplementverbrauch

APS (10%)

Polyklonale Hypergammaglobulinämie (75%)



https://link.springer.com/chapter/10.1007/978-3-662-48986-4_459

- BSR, CRP Erhöhung
- Blutbild (Zytopenien?)
- Direkter Coombs-Test (50%)
- CK, Myoglobin (Rhabdomyolyse?)
- NTproBNP, TropThs
- Leber-, Nierenwerte, Urinsediment

Therapie

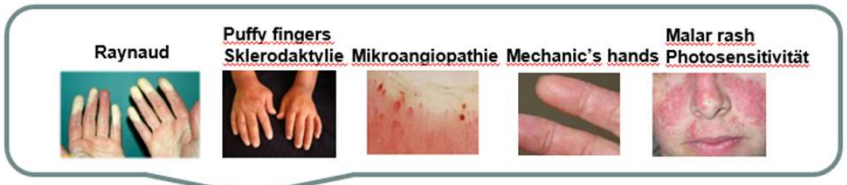
Keine spezifischen Guidelines für MCTD

Gemäss Evidenz aus anderen entzündlichen Erkankungen, je nach vorwiegendem klinischen Muster – SSc / SLE / RA / PM / DM /SjS

Gezielte Behandlung der vorhandenen Organmanifestation(en)

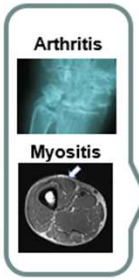
MCTD - Therapie

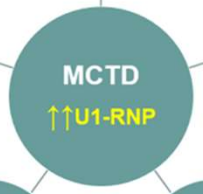
Topisch/Systemisch (s. SLE)
Lymphdrainage (puffy fingers)
Kälteschutz, Rauchstopp

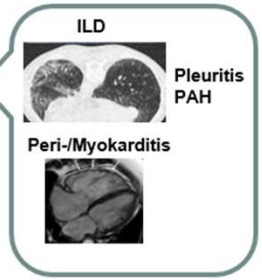


NSAR, GC, cs/bDMARD
CAVE lupus-like NW TNF-Hemmer

GC, MTX, IVIG, AZA, MMF, RTX





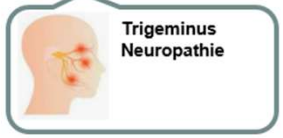


ILD: MMF, RTX, Actemra, Ofev, CYC, GC, Lungentransplant

PAH: ETRA, PDE5h, Prostacycline

Serositis: NSAR, GC, refraktär: DMARD

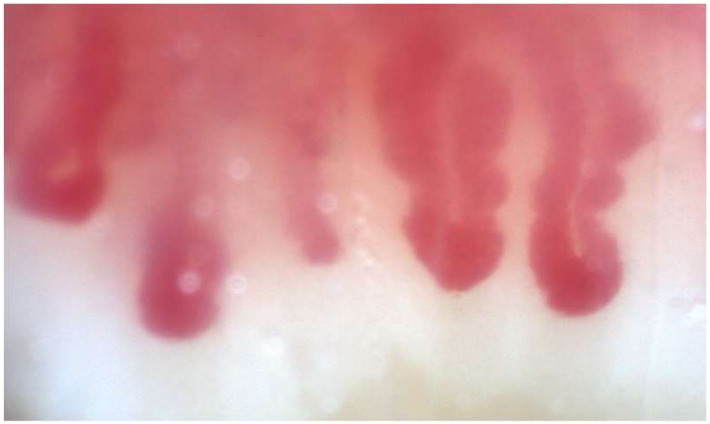
PPI, Antiazida, Prokinetika
Ernährungsberatung



Analgesie, Schmerzdistanzierende Medikam.
GC
schwerer Befall: DMARD

Falvignette Frau D.

- **ANA 1:10’240 (nukleär grob granulär)**
- **Anti-U1RNP-Ak. 262 U/ml (N<10)**
  - Rheumafaktor, Anti-CCP negativ
  - Anti-SSA, -SSB negativ
  - IgG normwertig, Immunfixation unauffällig
- **Kapillarmikroskopie mit Riesenkapillaren (Sklerodermie-Muster)**



- **Polyarthritis (PIP, Handgelenke bds.)**
- Keine Organbeteiligung

(normale CT Thorax, Echokardiographie, 6MGT, Lungenfunktion, Nierenfunktion, Ganzkörper-MRI)

Therapie:

- Methotrexat
- Fluctine
- Ergotherapie (Energiemanagement und Kälteschutzberatung)

Falvignette Herr B.

- **ANA >1:10’240 (AC-5, nukleär granulär)**
- **Anti-U1RNP-Ak. >240 U/ml (N<10)**
- **Anti-Sm >330 U/ml (N<10)**
- **Rheumafaktor 50 IU/ml (N<10)**
- **Komplementverbrauch**
  - Anti-SSA, -SSB, -C1q, -Chromatin, -Histon, -dsDNS, -CCP negativ
  - **IgG 41 g/l (N 7-16**), Immunfixation unauffällig, Kryoglobuline negativ

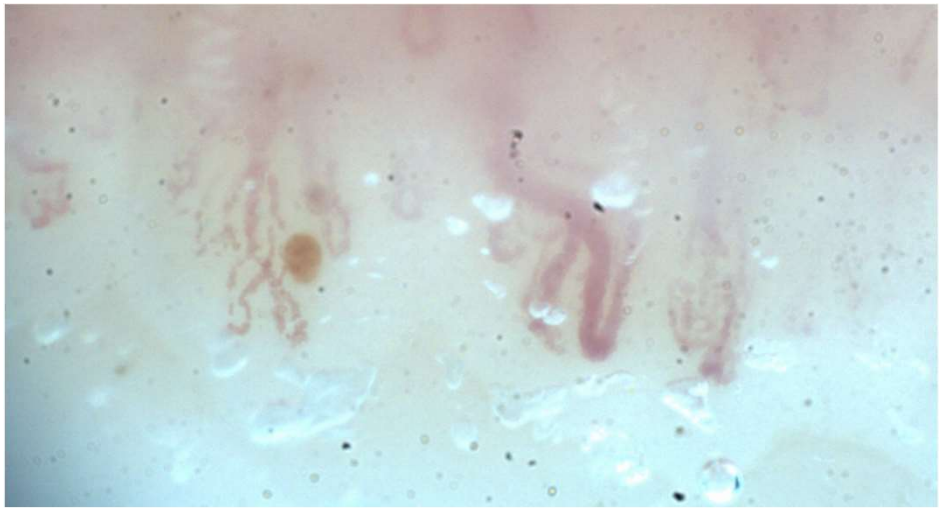
CK, total	< 190	U/l	97
Myoglobin	28 - 72	µg/l	
Troponin T, High Sensitive	< 14	ng/l	36 *
NT-proBNP (Roche)	< 85.8	ng/l	4271 *

Kapillarmikroskopie:

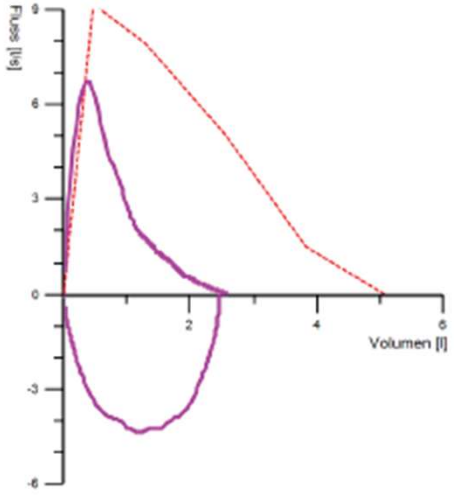
Rarefizierung und

Dysangiogenese

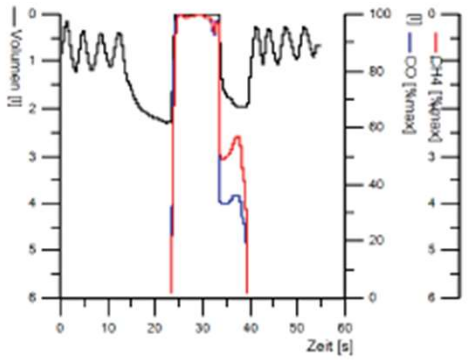
(Sklerodermie-Muster)



Falvignette Herr B.



	Einheit	Soll	LLN	Vor	%Soll	Z-Score
FVCEx	l	5.10	4.05	2.57	51%	-4.00
IVC	l	5.42	4.35	2.34	43%	-4.88
FEV1	l	4.09	3.24	2.00	49%	-3.88
FEV1/FVC	%	81	70	78	96%	-0.50
PEF	l/s	9.19	7.20	6.74	73%	-2.03
MEF75	l/s	7.95	5.14	4.91	62%	-1.78
MEF50	l/s	5.05	2.88	1.78	35%	-2.48
MEF25	l/s	1.49	0.72	0.58	39%	-2.10
MEF25-75	l/s	3.98	2.30	1.53	39%	-2.60
MEF50/MIF50				0.41		
IVC	l	5.42	4.50	2.34	43%	-5.51
FEV1/VC	%	80	68	78	97%	-0.30
ERV	l	1.52	0.68	1.34	88%	-0.31
IC	l	3.79	2.71	1.23	33%	-3.72
FIV1	l			2.46		



	Einheit	Soll	LLN	Vor	%Soll
TLco (Hb)	mmol/kPa/min	10.8	8.5	4.1	38%
Kco (Hb)	mmol/kPa/min	1.6	1.1	1.0	66%
VI	l	5.42	4.35	2.39	44%
ERV	l	1.52	0.68	1.10	72%
FRC	l	3.24	2.21	2.88	89%
RV	l	1.59	0.88	1.78	112%
TLC	l	7.01	5.67	4.17	60%
RV/TLC	%	23	14	43	189%
Tdiff	s			10.05	
Hb	g/dl			9.70	

USZ Universitäts Spital Zürich

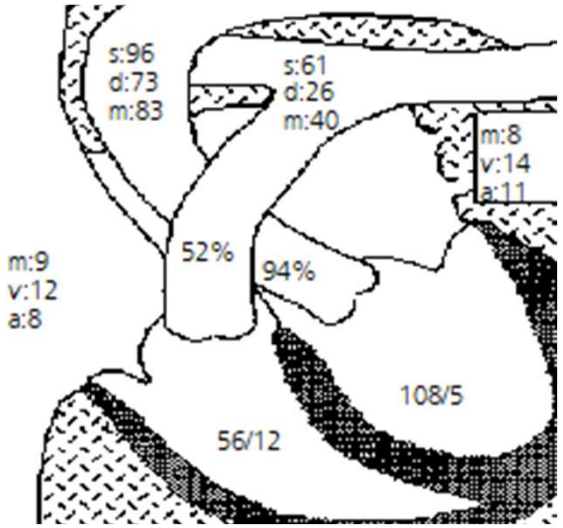
Falvignette Herr B.

6MGT: SpO2 95% -> 89%, 415m, Borg 2

TTE: Cor pulmonale, LVEF 45%, diffuse Hypokinesie, sysPAP geschätzt 43mmHg

RHK: **Präkapilläre pulmonale Drucksteigerung**

- mPAP 40 mmHg, dTPGP 15 mmHg
- CI 2.68 l/min/m2
- erhöhte pulmonale Widerstände

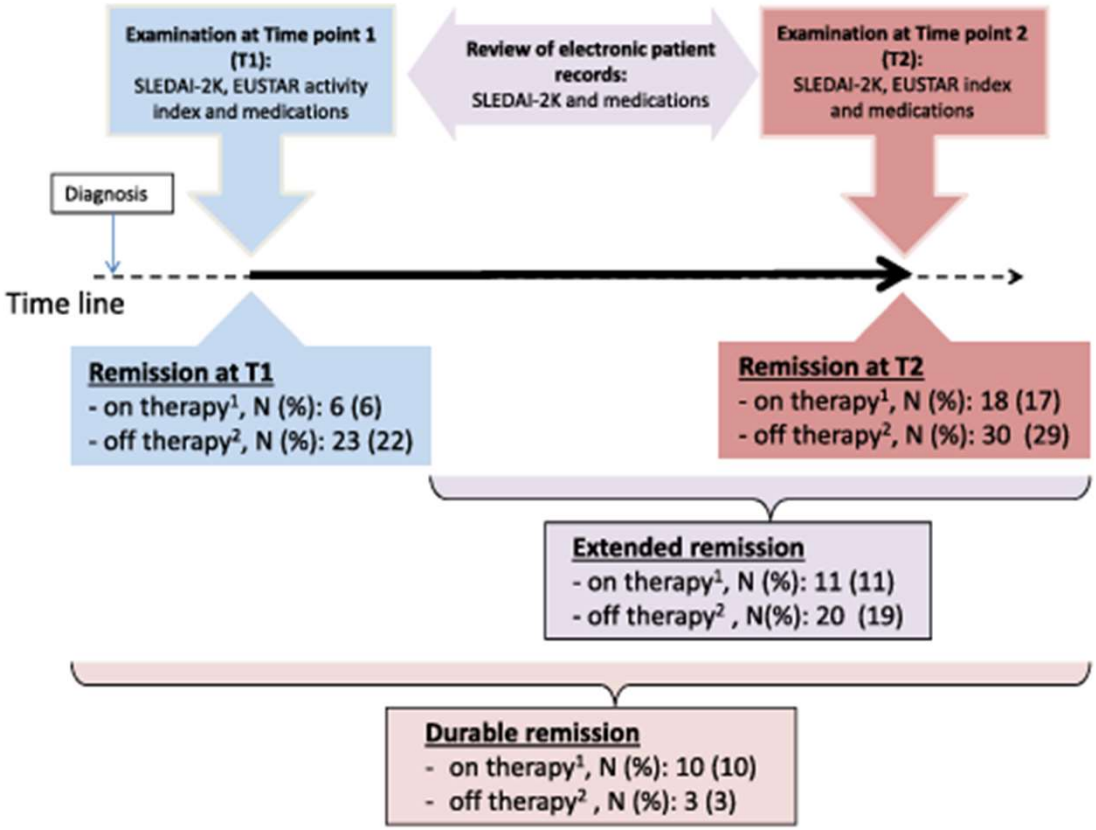


Therapie:

- Spiricort 20mg/d, Plaquenil, RTX (Arthritis)
- Tadalafil 20mg/d (PAH)
- Forxiga 10mg und Lisinopril 2.5mg (HI)

Follow-up

- Regelmässige rheumatologische Anbindung
- Frequenz der VK und Abklärungen je nach Klinik
- Komplexer Verlauf, sowohl schubartige sowie chronische Beschwerden
- NB: Herz/Lungenbeteiligung potentiell schwergradig



Reiseter et al. Arthritis Research & Therapy (2017) 19:284

Follow-up

Prognostische Faktoren für Remission ?

Table 3 Predicting models of remission at time point 2, extended remission and durable remission by multivariable logistic regression analyses ($N = 104$ patients)

Clinical features present at T1	Model 1: remission[a] at T2 ($N = 48$)			Model 2: extended remission[a] (N = 31)			Model 3: durable remission[a] ($N = 13$)		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Increased CK[b]	-	-	-	3.18	1.17–8.67	.024*	-	-	-
Facial erythema[b]	-	-	-	-	-	-	0.11	0.01–0.81	.030*
Digital ulcers[b]	-	-	-	0.25	0.08–0.77	.015*	-	-	-
Trombocytophenia[b, c]	0.05	0.01–-0.44	.006**	-	-	-	-	-	-
FVC % pred (pr 10%)	1.37	1.04–1.79	.026*	1.56	1.13–2.16	.007**	1.71	1.04–2.80	.033*
NSAID medication	-	-	-	-	-	-	0.05	0.00–0.73	.028*
Negative anti-RNP	-	-	-	-	-	-	15.0	1.97–113.59	.009**

Reiseter et al. Arthritis Research & Therapy (2017) 19:284

Follow-up

Übergang in eine andere Kollagenose?

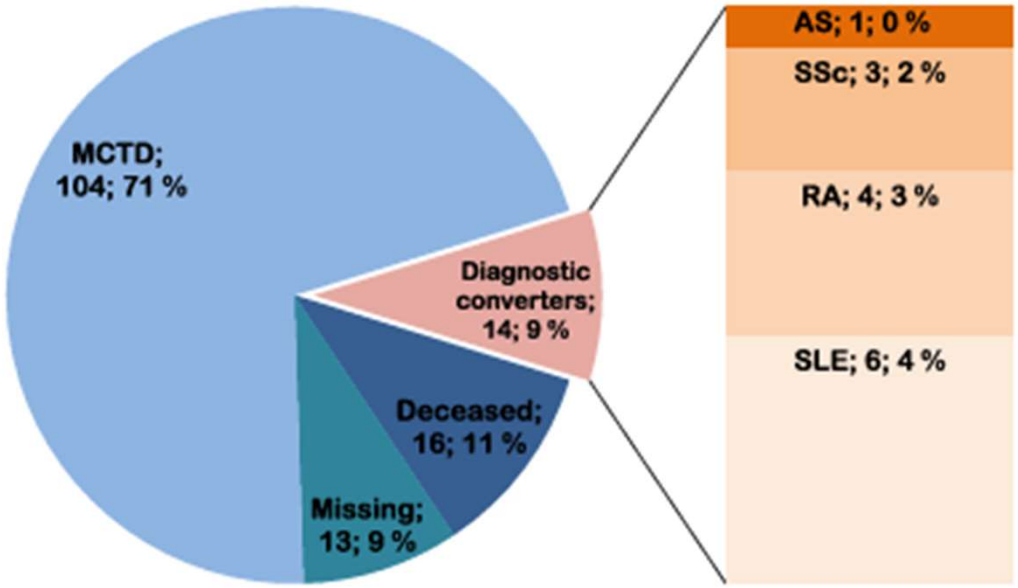


Fig. 1 Overview of long-term disease evaluation in the population-based Norwegian mixed connective tissue disease (MCTD) cohort ($N = 147$). ASA, anti-Jo1 positive anti-synthetase syndrome; SSc, systemic sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

Reiseteretal.ArthritisResearch&Therapy (2017) 19:284

Follow-up

Übergang in eine andere Kollagenose?

Name of study	*n*	Follow-up time—mean (SD)	Classification criteria at diagnosis				Treatment	Outcome		
			Sharp [10]	Kasukawa [12]	Alarcón-Segovia [11] (%)	Kahn [13]		"MCTD" stable	Converters	Deceased and other observations (*n*, %)
Cappelli et al. [25]	161	7.9 (5.9)	41.6%	75.2%	73.3	Not used	58%[a] immunosuppressant 82%[b] steroids 45% antimalarial drug	57.9%[c] (14.4% MCTD alone; 40.5% MCTD + other ARD)	42.1%	Deaths in the MCTD group ($n = 161$) 5/161 = 3.1%
Reiseter et al. [26]	118	17 (9)	96.6%	85.6%	91.6	Not used	Not reported	88.1%	11.9%	Loss of follow = 13 Deaths in the MCTD group ($n = 134$) 16/134 = 11.9%
Hajas et al. [27]	280	13.1 (7.5)	Not used	Not used	100	Not used	78.2% high-dose steroid[d] 74,6% cytotoxic agent[e] 15% anti-TNF	100%	0	Deaths in the MCTD group ($n = 280$) 22/280 = 7.9%
Ungprasert et al. [4][f]	264 (50)[g]	8.3 (3.4; 14.1)[h]	28%	72%	72	54%	Not reported	90%	10%	Deaths in the MCTD group ($n = 50$) 5/50 = 10%

Clinical and Experimental Medicine (2020) 20:159–166

MCTD- challenges

Diagnose	Therapie	Forschung
• Seltene Krankheit • Verschiedene Kriterien • Oft Kriterien für andere Kollagenosen gleichzeitig erfüllt (v.a. SSc/SLE, RA, PM/DM) • Kein Konsensus • 61% andere Erstdiagnose	• Keine Studien, insb. keine RCT • Meistens basiert auf Studien von anderen Kollagenosen	• Heterogene Definition • Seltene Erkrankung • Wenige etablierten Kohorten

USZ Universitäts Spital Zürich

Vielen Dank !

USZ Universitäts Spital Zürich

Ausgewählte Referenzen

- Wanzenried A, Garaiman A, Jordan S, Distler O, Maurer B. The enigma of mixed connective tissue disease-challenges in routine care. Clin Rheumatol. 2022 Nov;41(11):3503-3511.
- Pepmueller PH. Undifferentiated Connective Tissue Disease, Mixed Connective Tissue Disease, and Overlap Syndromes in Rheumatology. Missouri Medicine. 2016 Mar-Apr;113(2):136-140.
- Aringer M, Smolen JS. Mixed connective tissue disease: what is behind the curtain? Best Pract Res Clin Rheumatol. 2007 Dec;21(6):1037-49.
- Tanaka Y et al., 2019 Diagnostic criteria for mixed connective tissue disease (MCTD): From the Japan research committee of the ministry of health, labor, and welfare for systemic autoimmune diseases, Modern Rheumatology, Volume 31, Issue 1, 2 January 2021, Pages 29–33.
- Ferrara CA, La Rocca G, Ielo G, Libra A, Sambataro G. Towards Early Diagnosis of Mixed Connective Tissue Disease: Updated Perspectives. Immunotargets Ther. 2023 Jul 26;12:79-89.