Overlap syndromes

Structure of the presentation

- Definition of overlap syndromes
- Concept of diseases with overlapping features
- Short description of diseases overlapping with myositis
- Specific overlap syndromes with myositis
- Mixed connective tissue disease
- Treatment
- Questions, discussion

Overlap syndromes (with PM/DM)

- Syndromes where clinical or laboratory signs and symptoms of another defined connective tissue disease occur.

- Such as
  - systemic lupus erythematosus (SLE),
  - scleroderma (SSc),
  - rheumatoid arthritis (RA),
  - Sjögren´s syndrome (SjS)
  - Churg–Strauss arteritis, thrombotic thrombocytopenic purpura, antiphospholipid antibody syndrome and autoimmune thyroid disease.

Idiopathic inflammatory myopathies

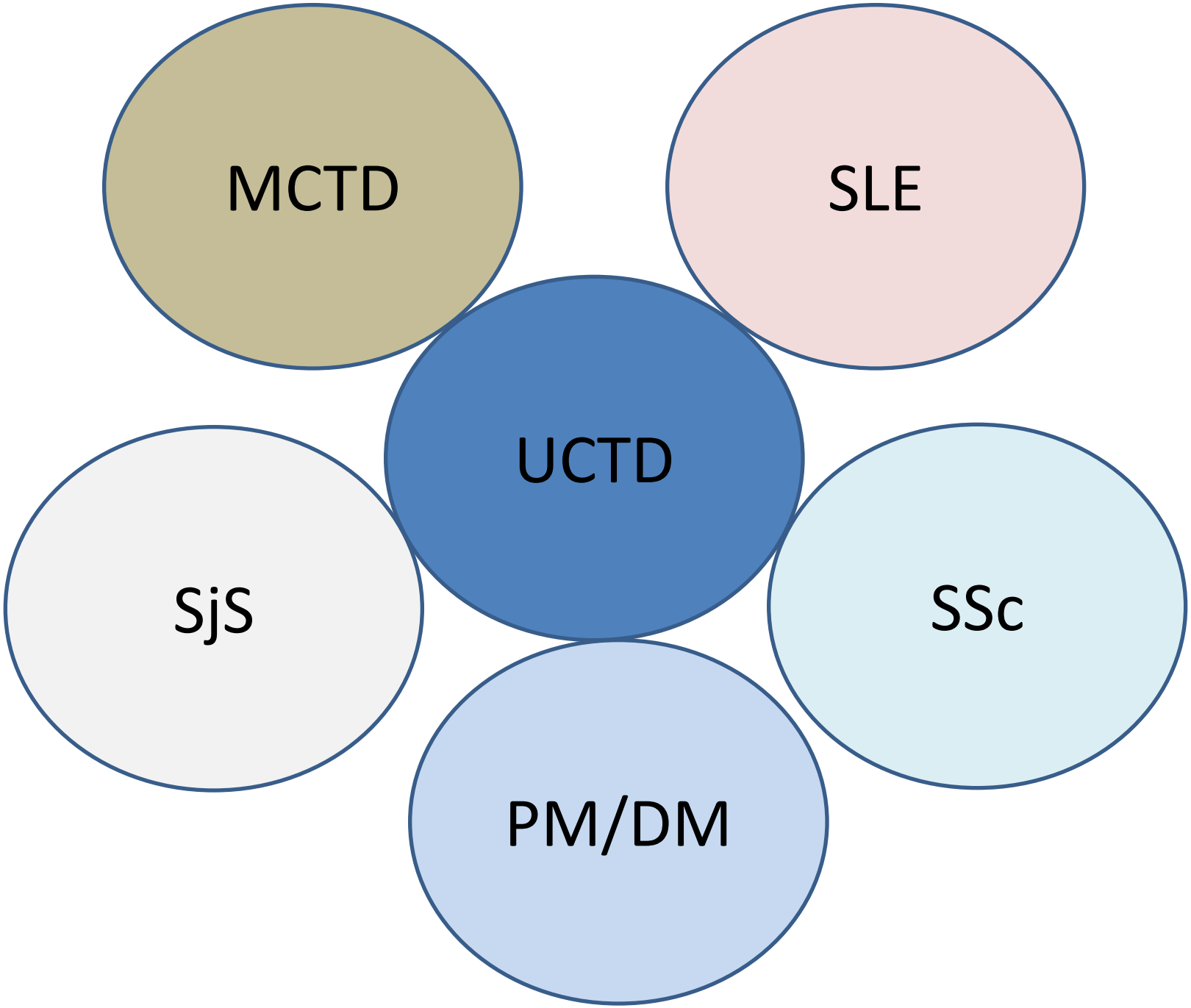
- Primary idiopathic polymyositis
- Primary idiopathic dermatomyositis
- Juvenile poly/dermatomyositis
- Myositis associated with another CTD (10-60%)
- Myositis associated with malignancy

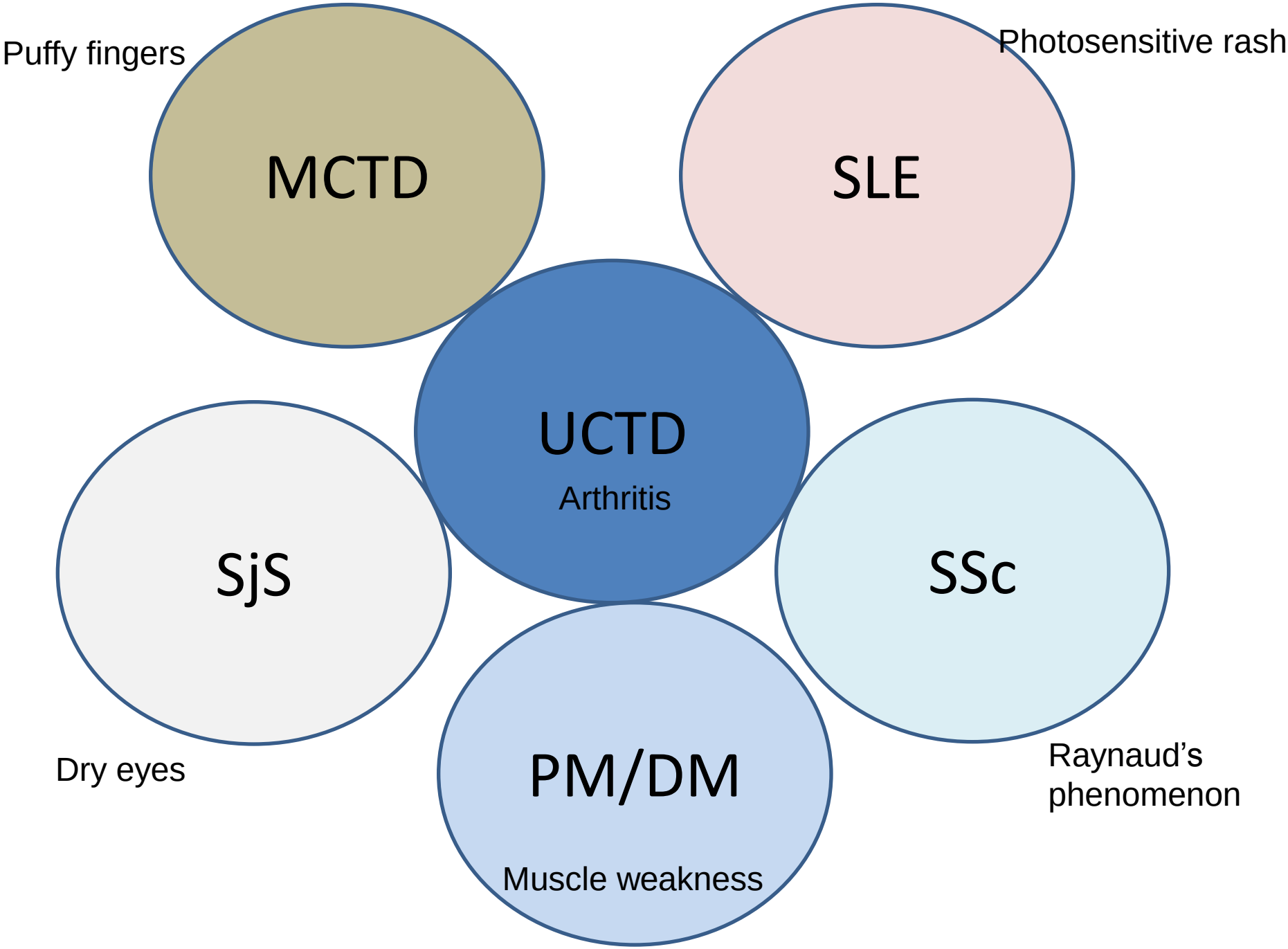
- Inclusion body myositis

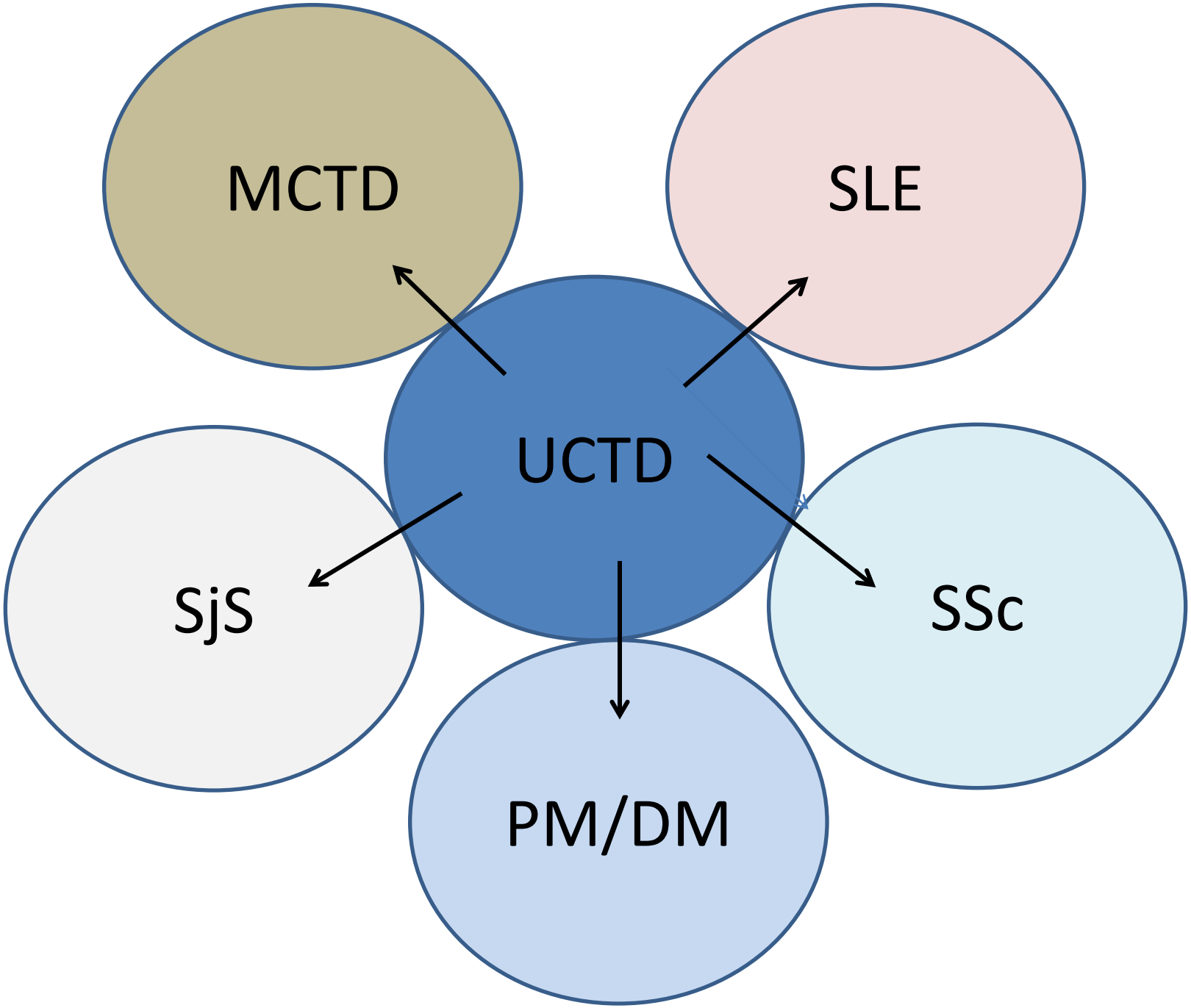
Bohan A, Peter JB et al. N Engl J Med 1975; 292: 344–7, Medicine (Baltimore) 1977; 56: 255–86.

Concept of diseases with overlapping features

- Overlap syndromes
- Undifferentiated connective tissue disease (UCTD)
- Mixed connective tissue disease (MCTD)


MCTD
SLE
UCTD
SjS
SSc
PM/DM

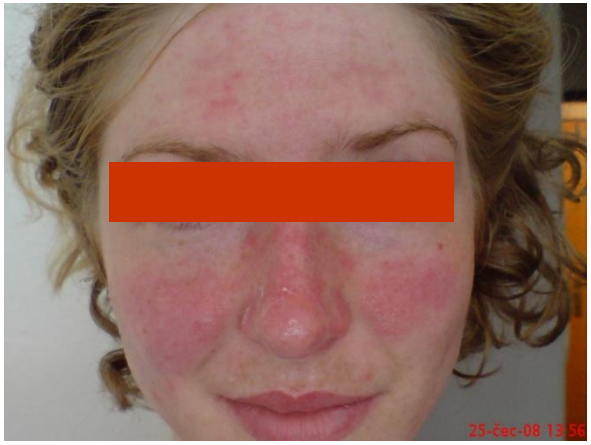

Puffy fingers
MCTD
Photosensitive rash
SLE
UCTD
Arthritis
SjS
SSc
Dry eyes
PM/DM
Muscle weakness
Raynaud's phenomenon


MCTD
SLE
UCTD
SjS
SSc
PM/DM

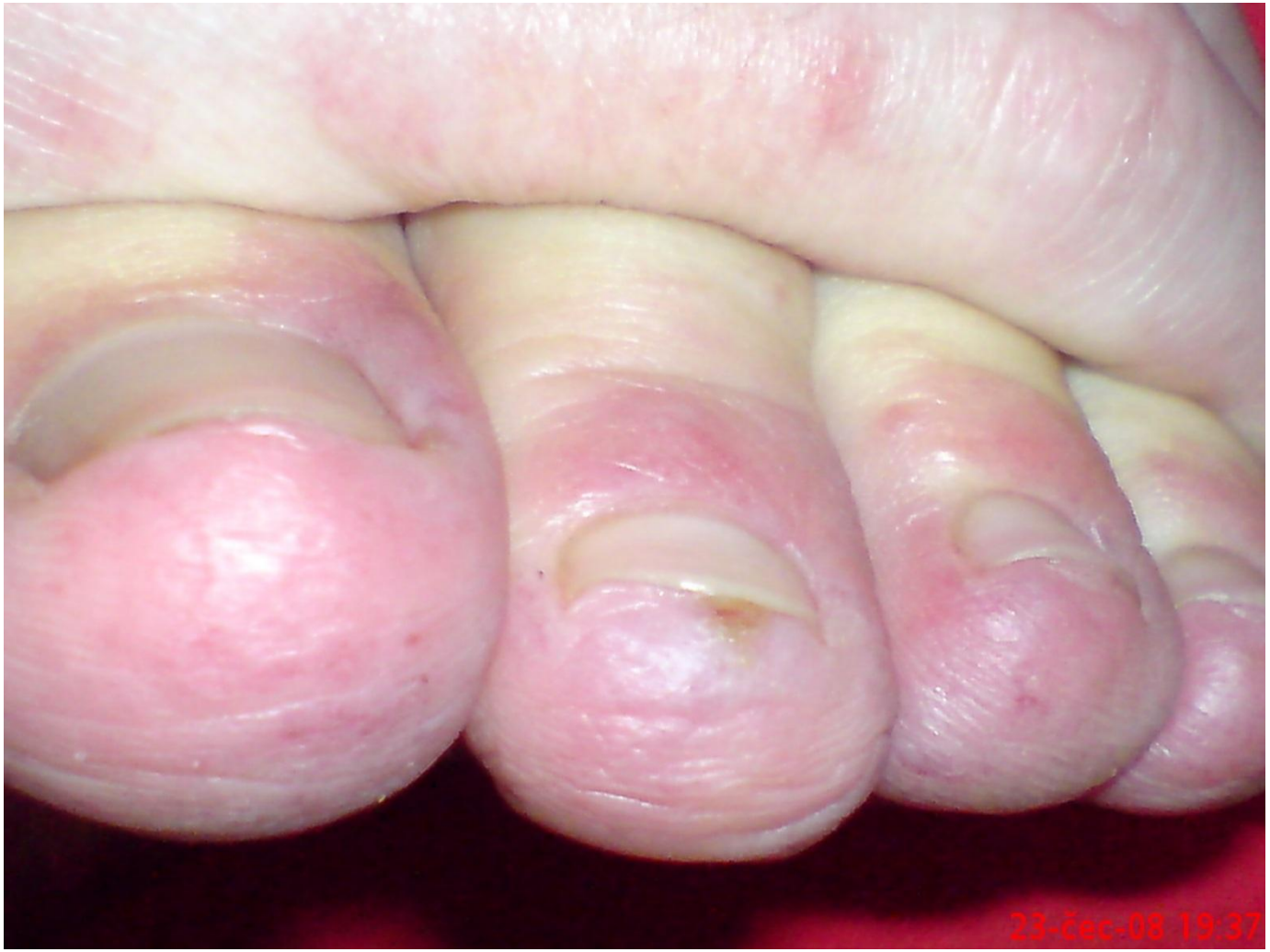
Systemic lupus erythematosus (SLE)

- An autoimmune multisystem disease characterized by heterogeneous clinical and laboratory features and a variable course and prognosis
- Immunological abnormalities lead to B cell hyperactivity, autoantibody production and immune complex deposition in vital organs
- Clinical manifestations encompass constitutional symptoms as well as any combination of organ involvement such as skin, mucous membranes, joints, kidney, brain, serous membranes, lung, heart and gastrointestinal tract

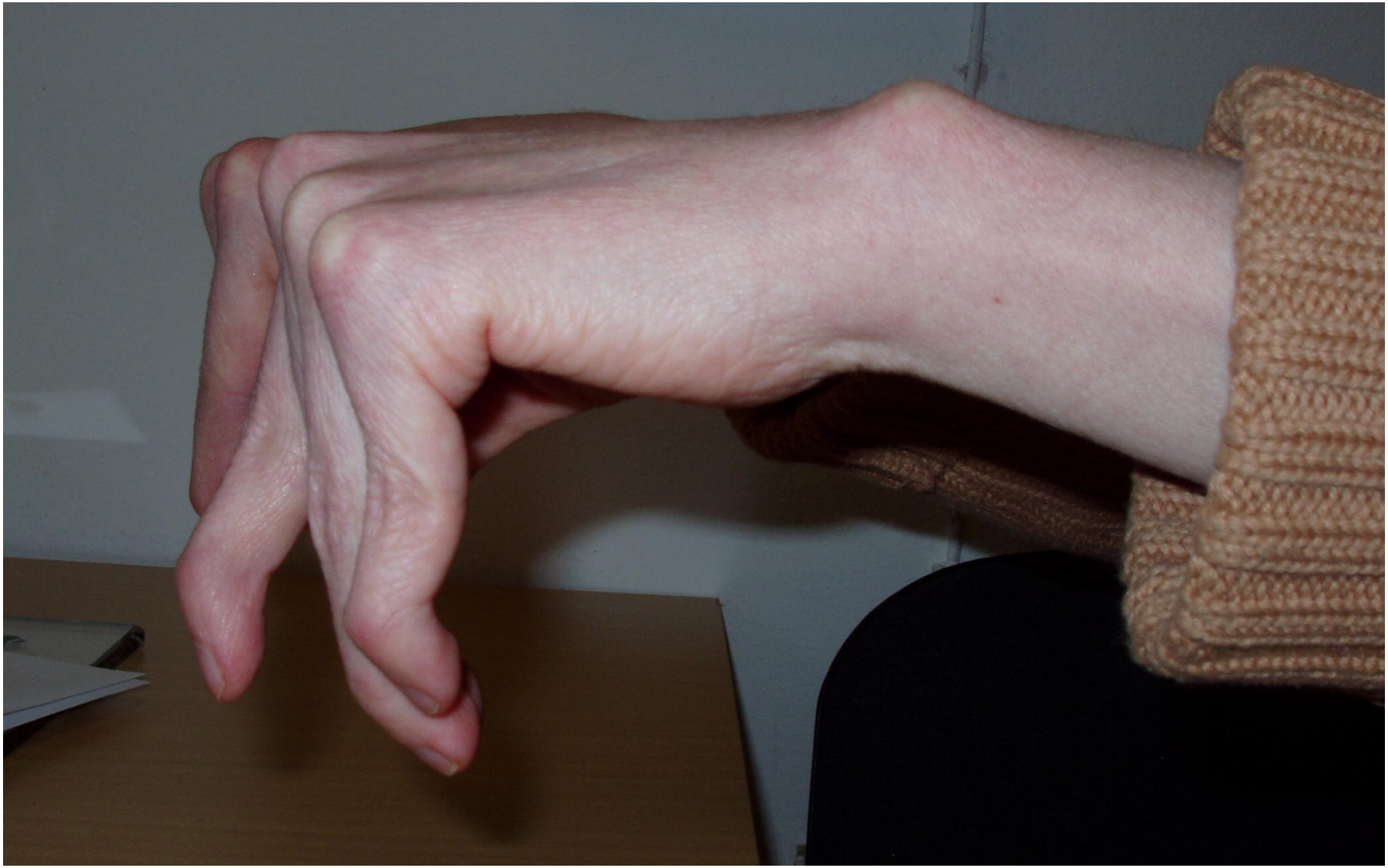
Classification criteria for SLE



- Erythema in the face
- Discoid erythema
- Photosensitivity
- Mouth ulcers
- Arthritis
- Serositis (pleuritis, pericarditis)
- Renal (proteinuria, casts)
- Neurological involv. (seizures, psychosis)
- Hematology (anemia, leuko-, trombocytopenia)
- immunology (anti-dsDNA, anti-Sm, APL – aCL, LA, FP BWR)
- Antinuclear antibodies


23-Dec-08 19:37

Hand deformities in SLE

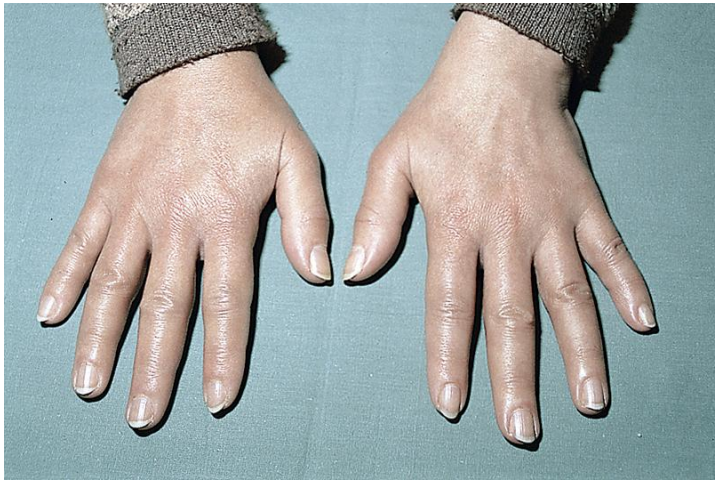


Systemic sclerosis (SSc)

Progressive disease that affects the skin and connective tissue (including cartilage, bone, fat, and the tissue that supports the nerves and blood vessels throughout the body).

- increased deposition collagen in interstitium of small arteries and connective tissue
- sclerotic changes in skin and internal organs

SSc - presentation



- general and skin
  - Raynaud's phenomenon
  - edema fingers and hands
  - skin thickening
- visceral manifestations
  - GI tract, lung, hear, kidneys, thyroid
- arthralgias and muscle weakness

CLASSIFICATION OF SYSTEMIC SCLEROSIS

(adapted according to J.R. Seibold, 1994)

I. diffuse – skin thickening - trunk, face and limbs

II. limited - skin thickening localized distally of elbows and knees, with face involvement, CREST

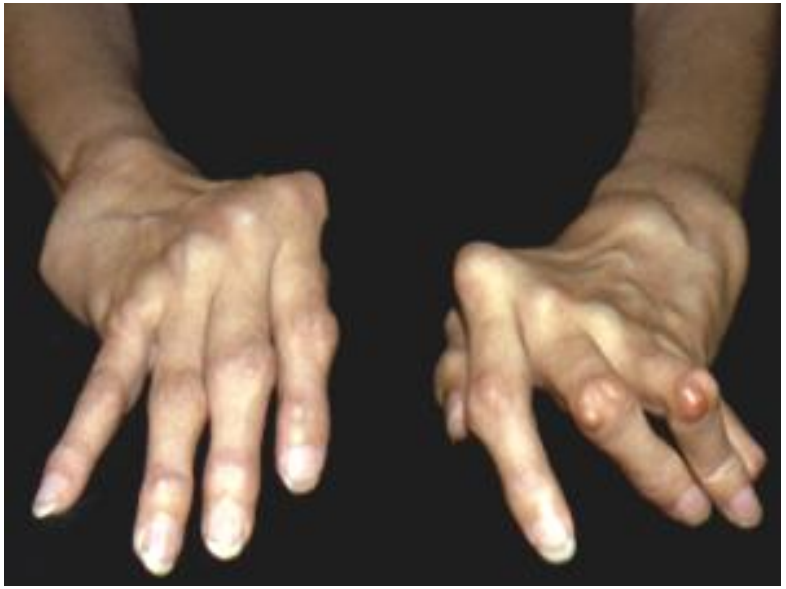
III. sine scleroderma – without skin involvement (except of face), fibrotic changes of visceral organs, vascular and serological findings.

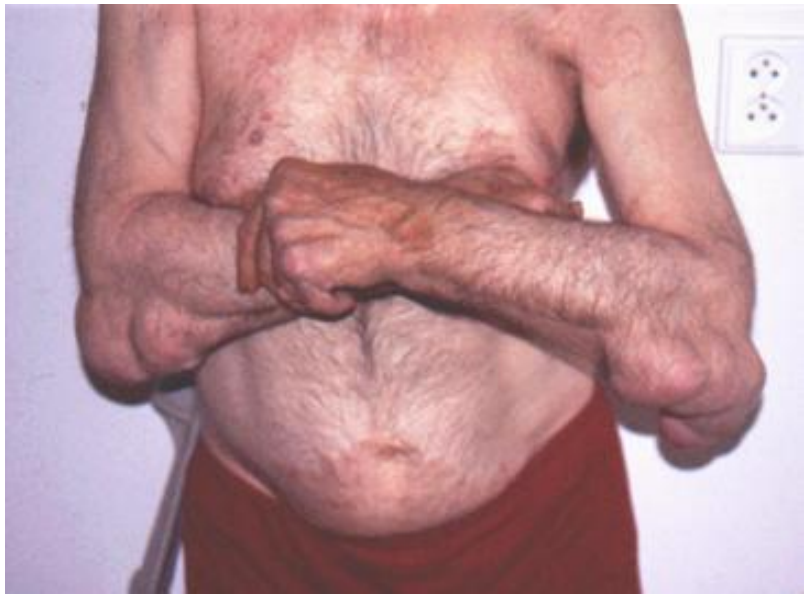
IV. overlap syndrome - fulfilled criteria of SSc and of SLE, RA or polymyositis

V. undifferentiated connective tissue disease - Raynaud's phenomenon with clinical and/or laboratory abnormalities - anticentromere antibodies, skin vascular trophic changes

Rheumatoid arthritis (RA)

- **RA** is a chronic, systemic inflammatory disorder.
- Principally affects joints - synovitis, pannus.
- Leads to destruction of articular cartilage and bones.
- May target also other tissues and organs (lungs, pericardium, pleura, sclera).
- Nodular lesions





IIMs associated with anti-TNFα therapy for RA

Reference	Anti-TNFα	Interval	IIM	Treatment	Outcome	Antibodies
Musial 2003	IFX	13 m	PM/IP	GC	Improved	RF, dsDNA, Jo-1
Urata 2006	IFX	9 m	PM/IP	GC	Improved	RF, ANA, Jo-1
Hall 2006	ETN	6 m	DM	GC, AZA, MTX	Improved	ANA, Jo-1
Liozon 2007	ADA	8 m	PM	GC, MTX	Improved	RF, CCP, ANA, dsDNA, Pm-Scl
Vordenbäumen 2010	ADA/ETN	3 m	IBM	GC/RTX	Unchanged	RF
Brunasso 2010	ADA	48 m	DM	GC, MTX	Improved	RF, ANA
Klein 2010	ETN ETN ADA ADA	Days 24 m 3 m 2 m	DM/IP DM DM DM/IP	GC, MYP, HCQ GC, RTX GC, MTX, HCQ, AZA GC, HCQ, CYP	Improved Improved Improved, not skin Improved	RF RF, ANA ANA RF, CCP
Ishikawa 2010	ETN	2 m	PM/IP	GC, CIS	Improved	CCP, Jo-1

Modified from: Stubgen J-P. J Neurol 2011, on line.

Sjögren's syndrome

Immune mediated destruction of exocrine glands

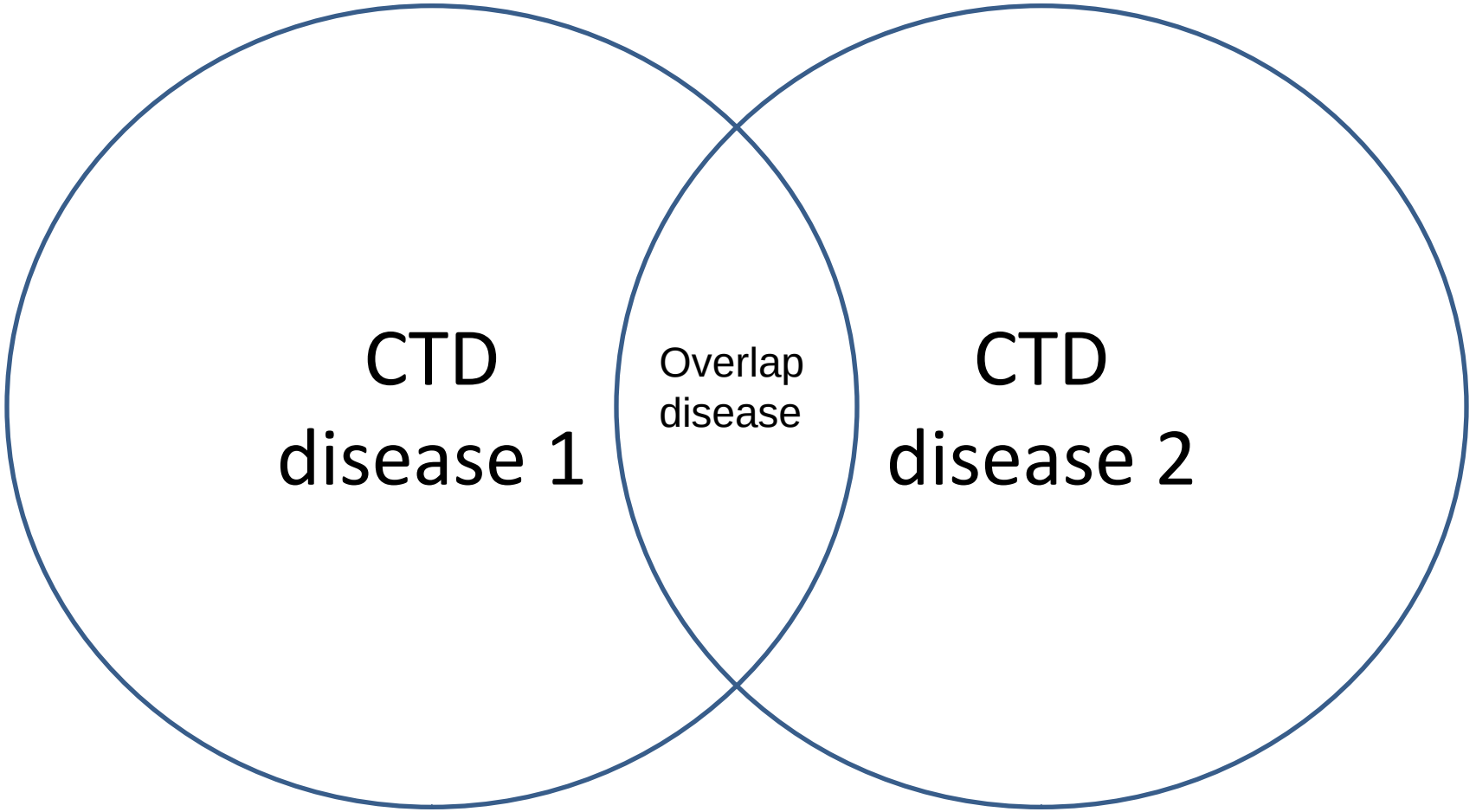
Primary

- inflammation and destruction of lacrimal and salivary glands leading to dry mouth and dry eyes (xerophthalmia, keratoconjunctivitis, xerostomia
other areas - skin, vagina, chronic bronchitis, GI tract, renal tubules)
- extraglandular manifestations (vasculitis, Raynaud's phenomenon, neuropathy, arthritis, nephropathy,).

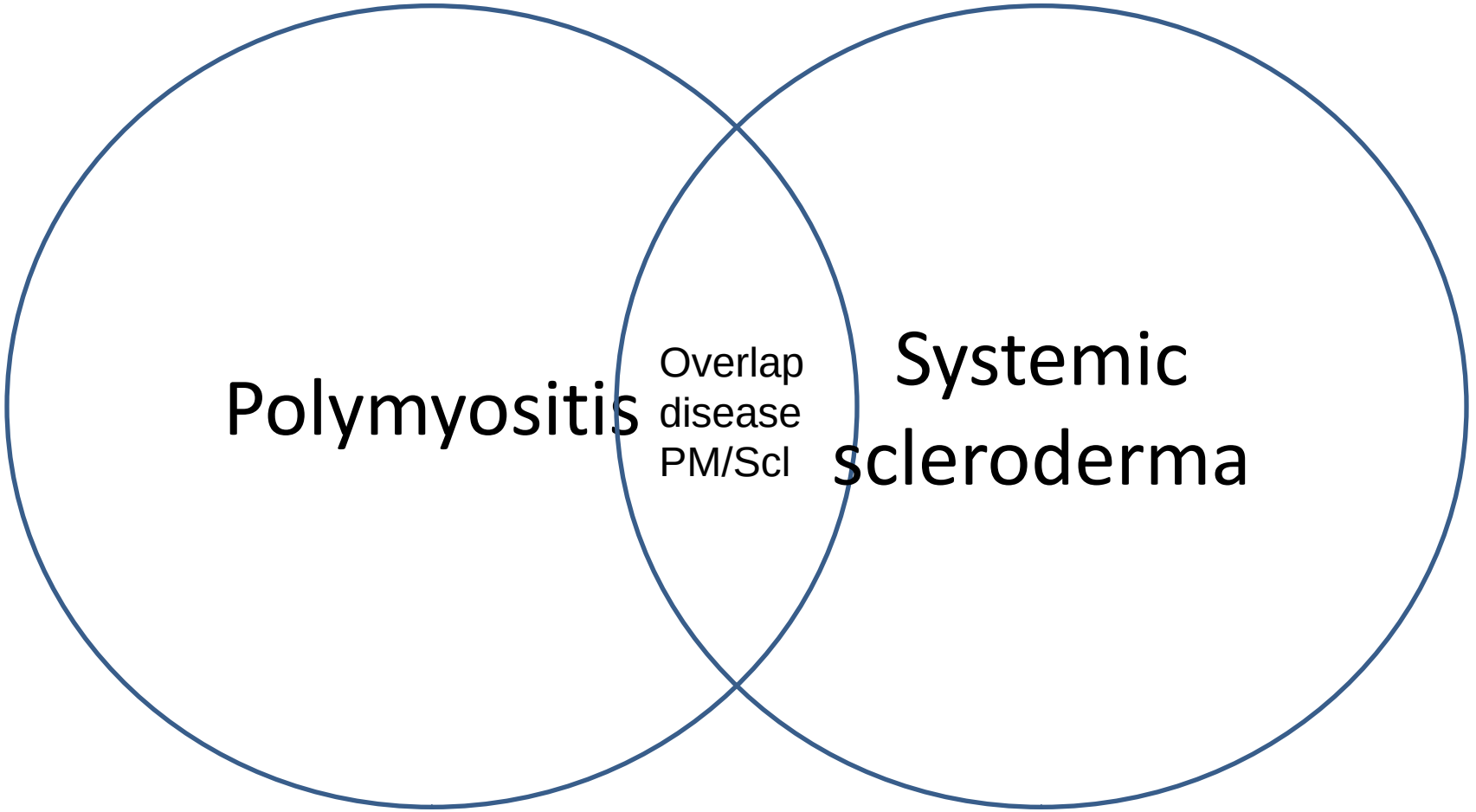
Secondary

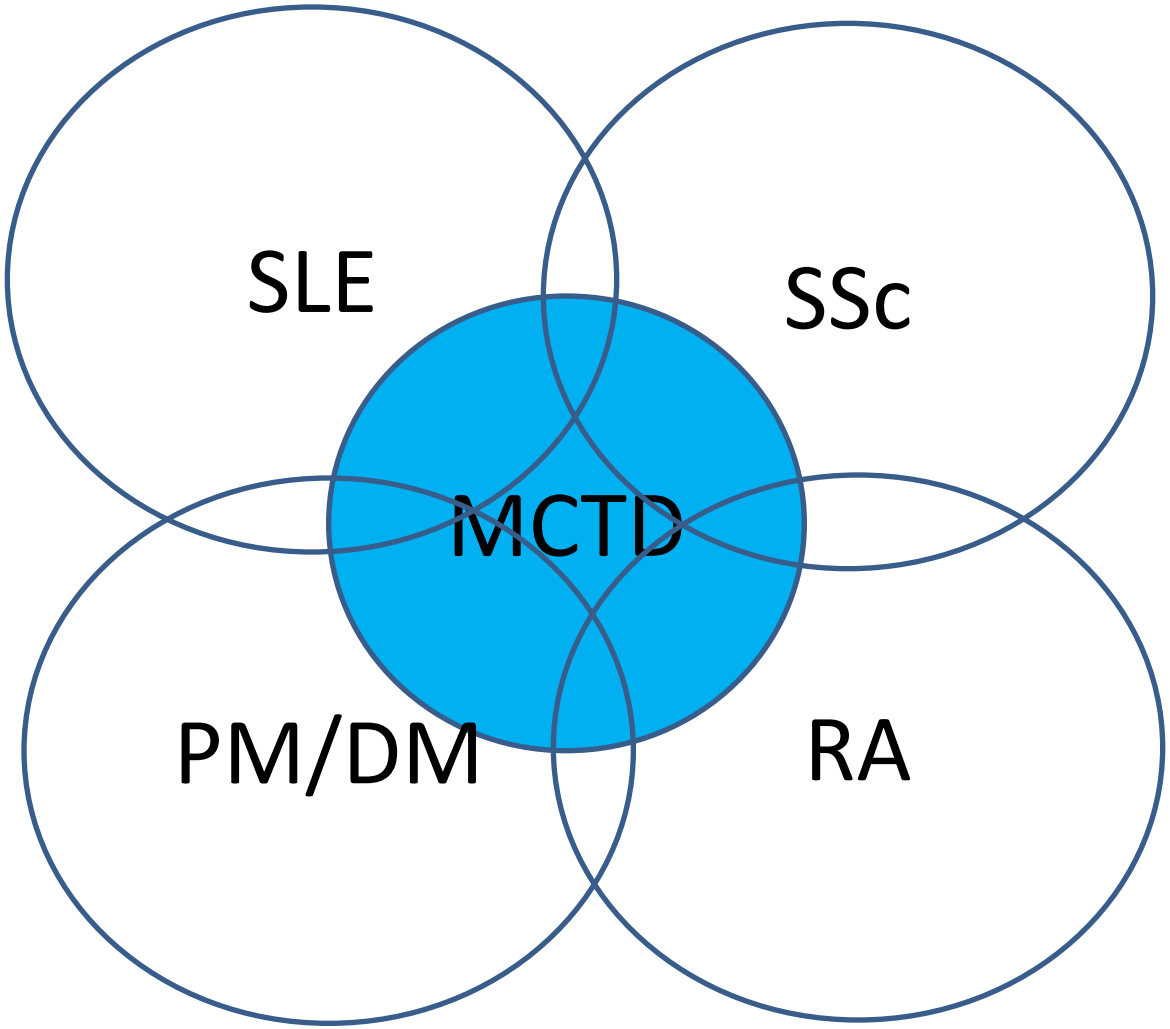
- sicca complex - associated with other CTD

Overlap syndrome



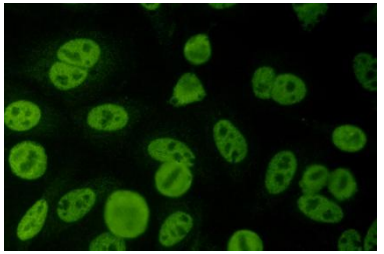
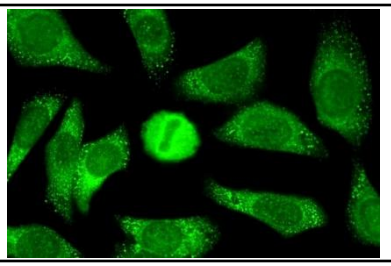
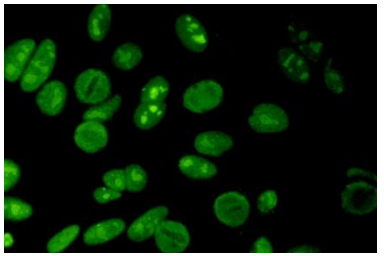
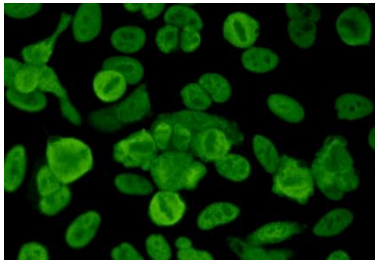
Overlap syndrome




SLE
SSc
MCTD
PM/DM
RA

Overlap syndromes

- Classification into overlap syndromes is facilitated by detection of autoantibodies
- Mixed connective tissue disease (MCTD, Sharp's syndrome) (anti-nRNP autoantibodies, or anti-p70),
- Antisynthetase syndrome (ASS) (anti-Jo-1, anti-PL-7, 12 etc.)
- Polymyositis/scleroderma overlap (PM/Scl) (anti-PM/Scl antibodies)
- Scleroderma/polymyositis (anti-Ku antibody)

autoantibody	immunofluorescence on HEp-2 cells	
U1-RNP	speckled, or coarse granular; no staining of nucleoli and metaphase chromosomes; high titer	
Jo-1	granular cytoplasmic; no nuclear staining (unless other ANA are simultaneously present)	
PM-Scl	nucleolar, plus fine granular staining of nucleoplasm, no staining of metaphase chromosomes; often low titer	
Ku	fine granular, no staining of metaphase chromosomes; mostly high titer	

Prevalence

- MCTD it is probably around 10/100 000
- ASS constitutes 30% of PM and DM cases.
- In MCTD the female:male ratio is about 9:1,
- In ASS 2.7:1.

Diagnostic criteria for MCTD

Clinical criteria
• Oedema of the hands
• Synovitis
• Myositis
• Raynaud's phenomenon
• Acrosclerosis
Laboratory criteria
• Positive anti-nRNP at a high concentration

Requirements for the diagnosis: Serologic criterion + at least 3 clinical
(In the case that oedema, Raynaud's phenomenon and acrosclerosis are combined, then 4 clinical criteria are required).

Alarcon-Segovia D, et al. J Rheumatol 16:328-334.

Mixed connective tissue disease

Clinical features	% of patients
Arthritis/arthralgia	95
Raynaud's phenomenon	85
Decreased oesophageal motility	67
Impaired pulmonary diffusing capacity	67
Swollen hands	66
Myositis	63
Lymphadenopathy	39
Skin rash	38
Sclerodermatous changes	33
Fever	33
Serositis	27
Splenomegaly	19
Hepatomegaly	15
Neurologic abnormalities	10
Renal disease	10

Dysphagia, heartburn

Pericarditis, pleurisy

Trigeminal neuralgia

MCTD (signs appear sequentially)

Clinical features	% of patients
Arthritis/arthralgia	95
Raynaud's phenomenon	85
Decreased oesophageal motility	67
Impaired pulmonary diffusing capacity	67
Swollen hands	66
Myositis	63
Lymphadenopathy	39
Skin rash	38
Sclerodermatous changes	33
Fever	33
Serositis	27
Splenomegaly	19
Hepatomegaly	15
Neurologic abnormalities	10
Renal disease	10

MCTD – most important features

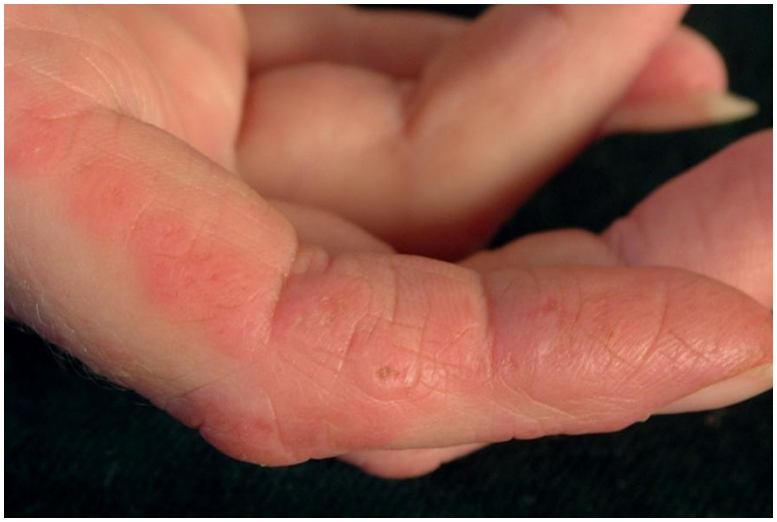
- Myositis
- Fibrosing alveolitis
- Pulmonary hypertension

MCTD – laboratory

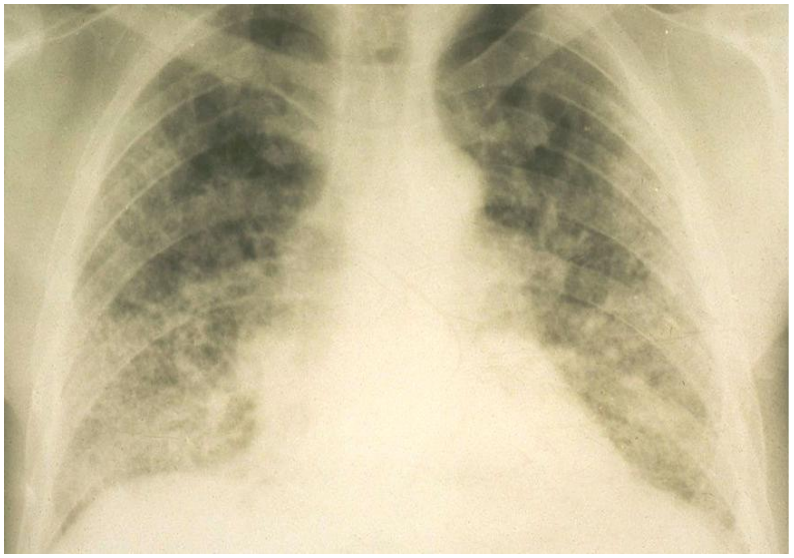
- High anti-U1 RNP
- Absence of anti-dsDNA, anti-Sm
- High immunoglobulins (IgG, gammaglobulins)
- High erythrocyte sedimentation rate
- Often rheumatoid factors
- (Positive anti-RA33)

Antisynthetase syndrome

- Myositis
- Interstitial lung disease (89%)
- Arthritis (94%)
- Raynaud‘s phenomenon (67%)
- Fevers (87%)
- Mechanic‘s hands (71%)

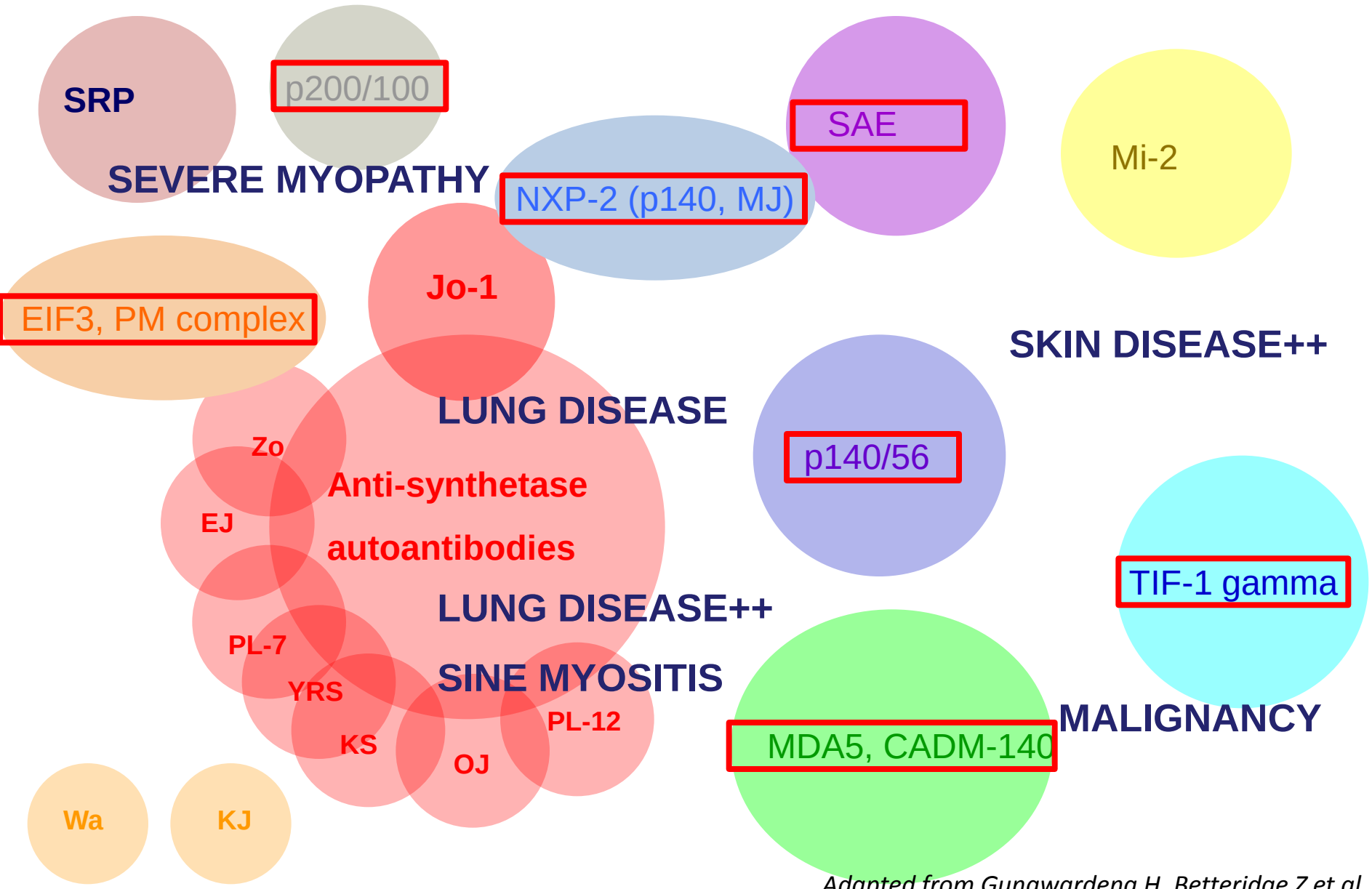


- Anti-Jo-1 – similar pathology
  - Perimysial fragmentation
  - Macrophage predominance
  - Perifascicular changes (atrophy, regeneration, some necrosis)
  - Normal capillary density



Love LA et al. Medicine 1991;70:360-74, Mozaffar T, Pestronk A. J Neurol Psychiatry 2000;68:472-8.

Serological classification



Adapted from Gunawardena H, Betteridge Z et al.

Possibilities in the treatment of myositis

(Probably) efficacious

Glucocorticoids

Methotrexate
Azathioprine (8+8)
Combination AZA+MTX
IVIg (8+7)
Cyklosporine A
Cyclophosphamide
Tacrolimus
Mycophenolate mofetil

Hydroxychloroquine

Probably inefficacious

Plasmapheresis and leukapheresis (13+13+13)
Interferon-beta

Experimental

Anti-TNF
Rituximab
IL-1 blockade
Leflunomide
ASCT

Treatment for Raynaud's phenomenon:
- Often unresponsive to glucocorticoids

Treatment of pulmonary hypertension:
endothelin receptor antagonists bosentan or sitaxentan .
Phosphodiesterase-5 inhibitor sildenafil.
Long-term anticoagulation.
Tyrosine kinase inhibitor imatinib mesylate improved pulmonary fibrosis in MCTD.