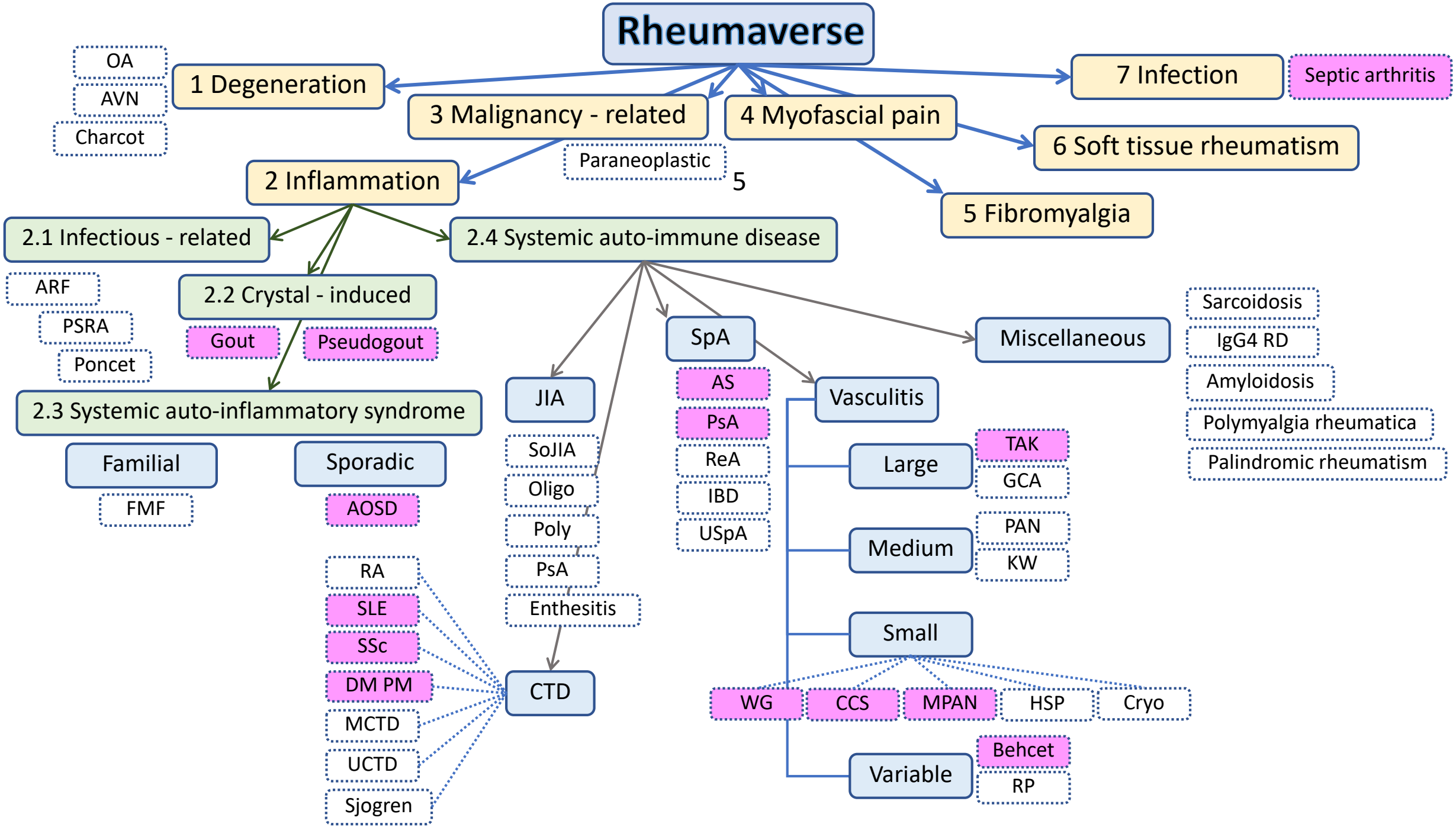
Connective Tissue Diseases
Primary Systemic Vasculitis

23 Nov 2024 08.00 – 09.15 AM

Chayawee Muangchan MD.

Division of Rheumatology, Department of Internal Medicine
Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand


Rheumaverse
1 Degeneration
OA
AVN
Charcot
2 Inflammation
2.1 Infectious - related
ARF
PSRA
Poncet
2.2 Crystal - induced
Gout
Pseudogout
2.3 Systemic auto-inflammatory syndrome
Familial
FMF
Sporadic
AOSD
2.4 Systemic auto-immune disease
JIA
SoJIA
Oligo
Poly
PsA
Enthesitis
RA
SLE
SSc
DM PM
MCTD
UCTD
Sjogren
CTD
SpA
AS
PsA
ReA
IBD
USpA
Vasculitis
Large
TAK
GCA
Medium
PAN
KW
Small
WG
CCS
MPAN
HSP
Cryo
Variable
Behcet
RP
Miscellaneous
Sarcoidosis
IgG4 RD
Amyloidosis
Polymyalgia rheumatica
Palindromic rheumatism
3 Malignancy - related
Paraneoplastic
4 Myofascial pain
5 Fibromyalgia
6 Soft tissue rheumatism
7 Infection
Septic arthritis

Approach to systemic vasculitis

Clinical presentations of vasculitis

	Large vessel	Medium vessel	Small vessel
	Constitutional symptoms (ไข้ เบื่ออาหาร น.น.ลด อ่อนเพลีย), Symmetrical polyarthritis		
	Renovascular HT ○ Refractory HT ○ HT in the young **Limb claudication** **Central retinal a. occlusion** ○ Painless visual loss **Stroke in the young** **Aortic regurgitation** (aortitis)	**Mononeuritis multiplex** Cutaneous ulcer Palpable purpura with ulceration Digital(s)/ Toe(s) gangrene	**Petechial rashes** Palpable purpura (leukocytoclastic vasculitis, LCV) Glomerulonephritis Diffuse alveolar hemorrhage (Nodules, Cavitation) Uveitis, Retinitis
	Could it be vasculitis mimics? (apply Virchow triads)		
1. Vessel wall	Atherosclerotic stenosis/ emboli Thrombotic emboli Thromboangiitis obliterans	Vasospasm (Cafe got) Raynaud disease Embolism	Livedo reticularis
2. Cellular		**RBC** (PV), **WBC** (CML, CLL, ALL), **Platelets** (ET or ↓platelets)	
3. Plasma		APS, DIC, coumadin-induced skin necrosis, calciphylaxis	

Approach to systemic vasculitis

Clinical presentations of vasculitis

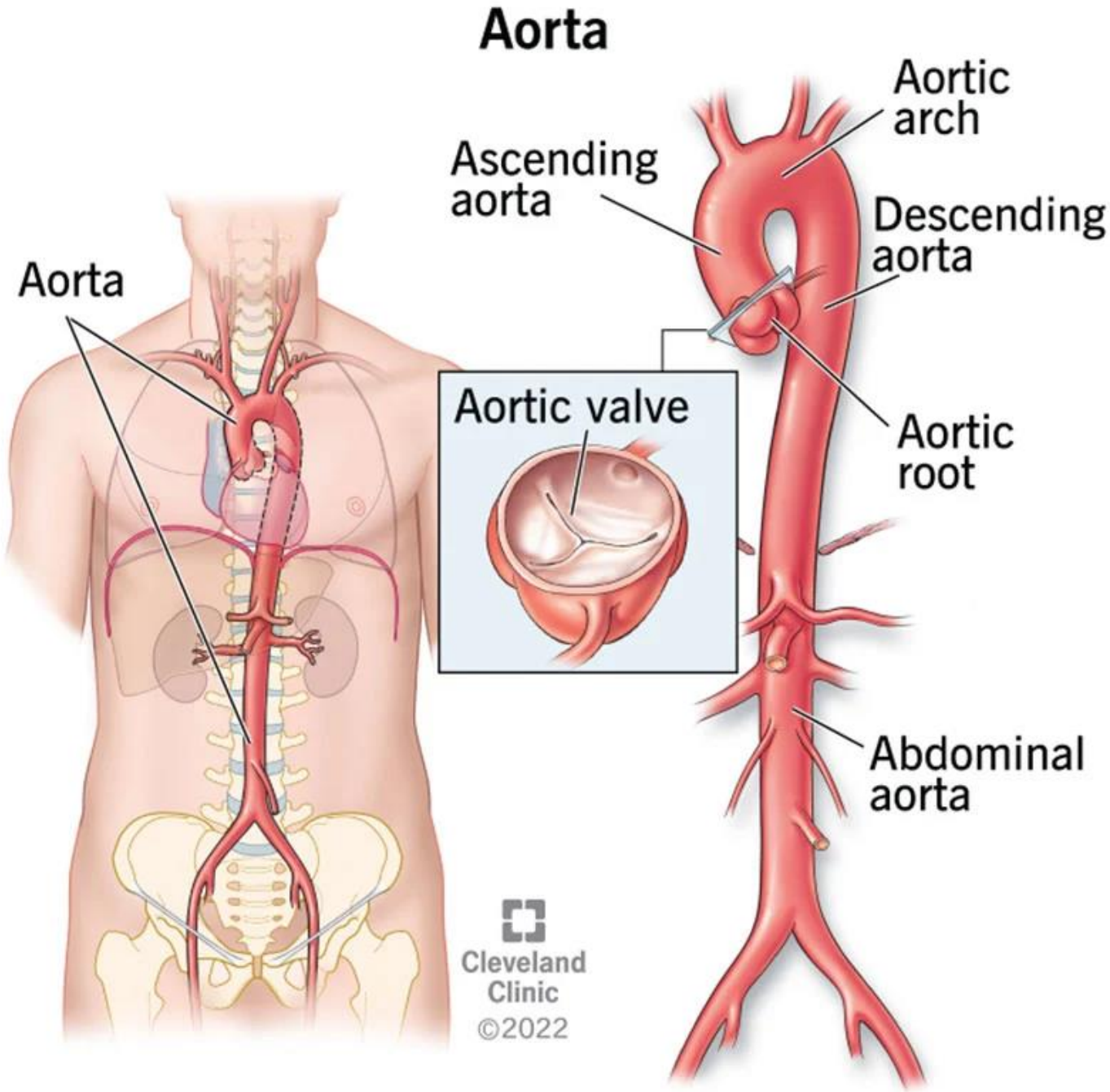
	Large vessel	Medium vessel	Small vessel
	Could it result from other secondary causes?		
1. Infection	Staphylococcus spp. Streptococcus spp. Salmonella spp. Tertiary syphilis Mycobacterium Tuberculosis Pythium insidiosum		Streptococcus group A Coxiella Parvovirus B19 Rubeola Mumps Hepatitis B/C, HIV
2. Inflammation	Behcet aortitis Ankylosing spondylitis aortitis IgG4 related disease	Behcet, Relapsing polychondritis CTD (RA, SLE, Dermatomyositis, Polymyositis, MCTD, Sjogren)	
			Henoch-Schoenlein Purpura Cryoglobulinemic vasculitis
3. Tumor		Paraneoplastic systemic vasculitis	
4. Drugs		Drug-induced hypersensitivity vasculitis	
Primary	Takayasu arteritis Giant cells arteritis	ANCA-associated vasculitis (AAV): GCA, MPA, EGPA	
		Polyarteritis nodosa Kawasaki vasculitis	

Takayasu arteritis

- Noncaseous granulomatous arteritis of extra-cranial branches of the aorta (whole aorta, Subclavian a., Common Carotid a., Superior mesenteric a., Renal a., Iliac a., Pulmonary a.)
- F:M = 1.2-13:1 ; 20-30 years
- **Clinical presentations**
  1. 10-20% asymptomatic, accidentally P.E.
  2. 80-90%
     1. Systemic: fever, ↓wt., carotidynia (30%) EN, pyoderma gangrenosum
     2. Vascular: stenotic symptoms (60%), AR, CRAO, Claudication, **Renovascular HT**

Aortitis caused by SARD

- **Root**
  - Ankylosing spondylitis, IBD, PsA, uSpA
  - Behcet
  - Relapsing polychondritis
- **Aorta – Root**
  - TAK
  - GCA
  - RA



2022 ACR/EULAR classification criteria for TAK

Situation: medium – large vessel vasculitis excluding mimickers

Absolute requirement: age ≤60 years + vasculitis on imaging (CT, MRI, US, PET)

≥5

Additional criteria	**Female sex**	**+1**
	Angina or ischemic cardiac pain	+2
	Arm or Leg claudication	+2
	Vascular bruit	+2
	Reduce pulse in upper extremity	+2
	Carotid artery abnormality	+2
	Systolic BP difference in arms ≥20 mmHg	+1
Additional imaging criteria	**Number of affected arterial territories (select one)**	
	1 arterial territory	+1
	2 arterial territories	+2
	≥3 arterial territories	+3
	Symmetric involvement of paired arteries	+1
	Abdominal aorta involvement with renal or mesenteric involvement	+3

Grayson PC, et al. Ann Rheum Dis 2022;81:1654–1660.

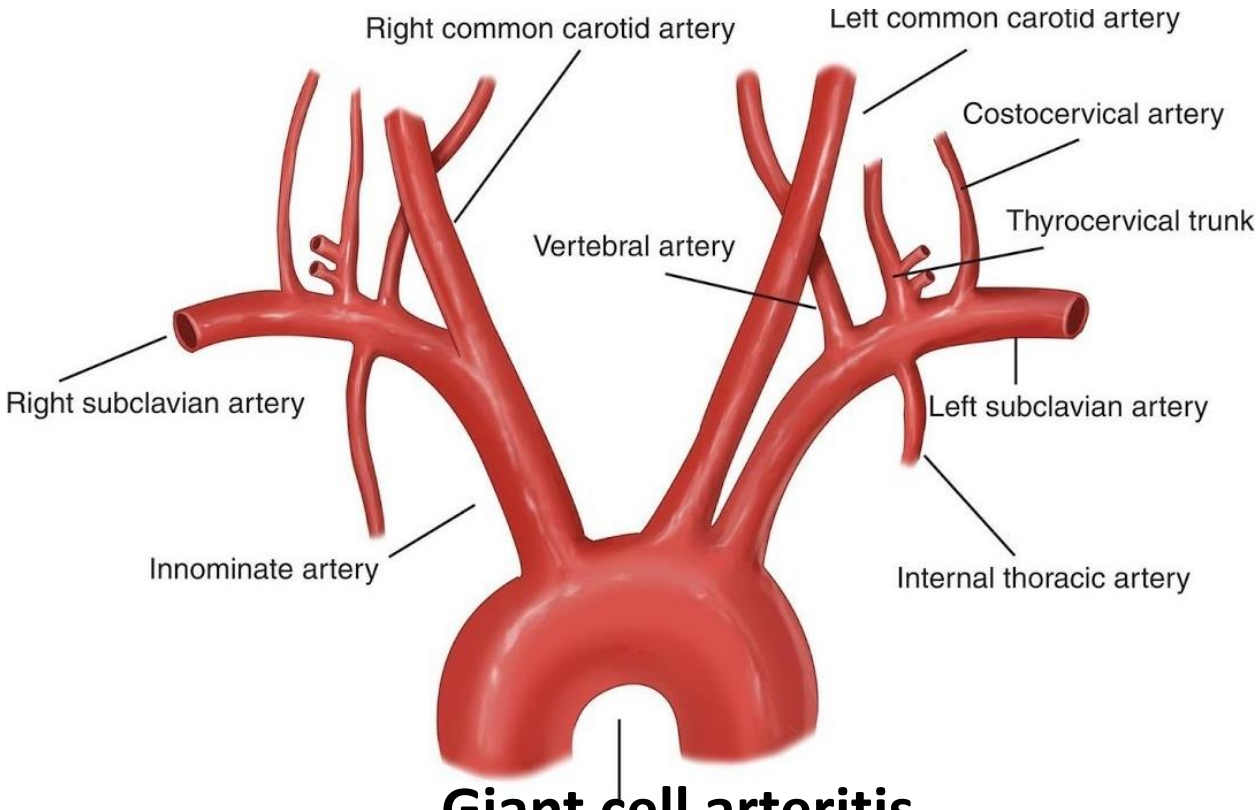
2021 ACR management for TAK

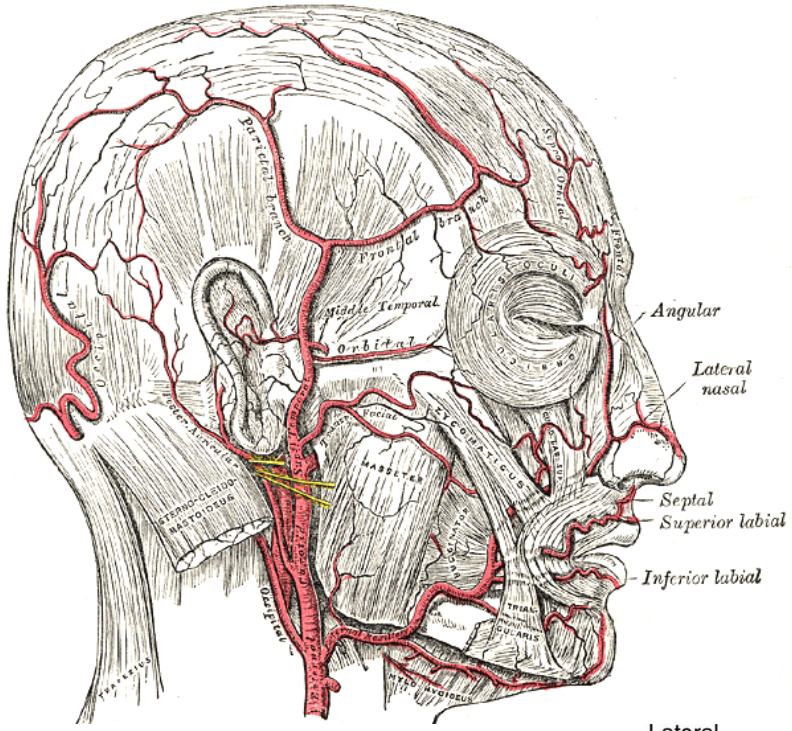
Active TAK vasculitis

Prednisolone (1 MKD) at least 4 wks. plus
Methotrexate 2.5 – 15 mg/wk. OR
Azathioprine 1 – 2 MKD

- Active TAK – cranial or vertebrobasilar involvement → ASA
- F/U ESR, CRP + regularly scheduled noninvasive vascular imaging
- Px of renovascular HT: ACEI/ARB (F/U Cr., electrolyte), CCB
- Vascular intervention during the remission period

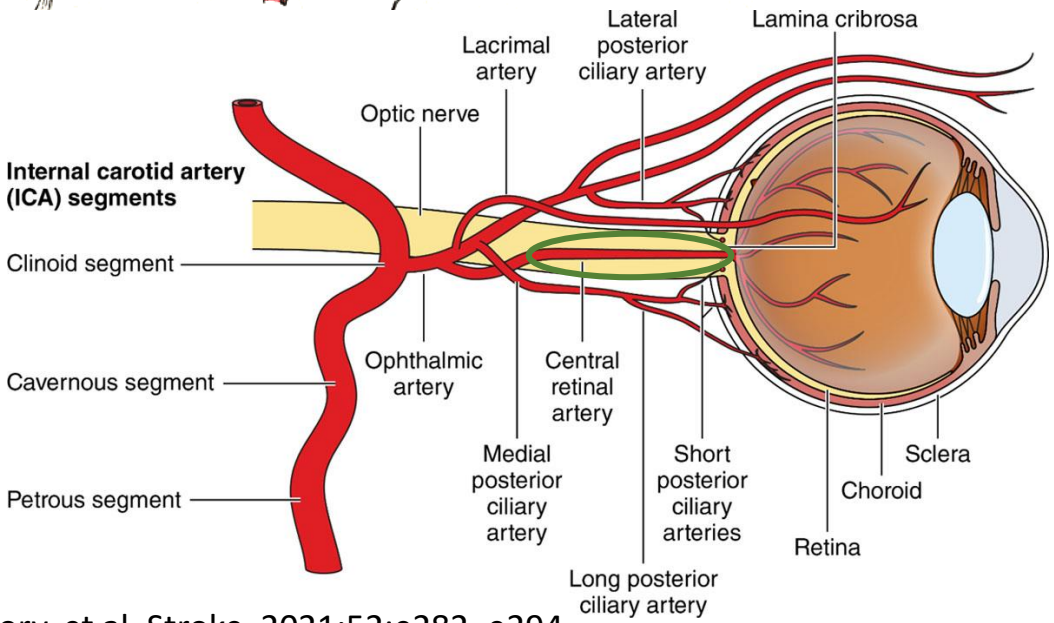
Maz M, et al. Arthritis Rheumatol. 2021 Aug;73(8):1349-1365.





Giant cell arteritis

- Noncaseous granulomatous arteritis of extra-cranial 3rd-5th branches of the aorta
- >50 YO, F: M 2.5:1, 50% fever (FUO) & wasting symptoms
- New (60%) Temporal headache, 50% Jaw/ UE claudication
- 30% anterior optic ischemic neuropathy (AION)
- 50% Polymyalgia rheumatica (shoulder/neck/pelvic girdle)
- Aorta/Arch, Carotid, Vertebral, Subclavian a. Axillary a.
- ↑ESR, ↑CRP



Brian Mac Grory, et al. Stroke. 2021;52:e282–e294
Ninan J et al. Giant cell arteritis. Best Pract Res Clin Rheumatol. 2016 Feb;30(1):169-88.

2022 ACR/EULAR classification criteria for GCA

Situation: medium – large vessel vasculitis excluding mimickers

Absolute requirement: age ≥50 years

≥6

Additional criteria

Morning stiffness in shoulder/neck	**+2**
Sudden visual loss	+3
Jaw or tongue claudication	+2
New temporal headache	+2
Scalp tenderness	+2
Abnormal P.E. of temporal a. (↓pulse, tender, cord-like appearance)	+2

Laboratory, Imaging, Biopsy

Max ESR 50 mm/hr. or CRP 10 mg/L	**+3**
Positive temporal a. biopsy (giant cell) or halo sign on U/S	+5
Bilat. Axillary involvement (stenosis, occlusion, aneurysm)	+2
FDG-PET activity throughout aorta	+2

Ponte C, et al. Ann Rheum Dis. 2022 Dec;81(12):1647-1653.

2021 ACR management for GCA

Very major: 1. visual loss 2. critical cranial ischemia

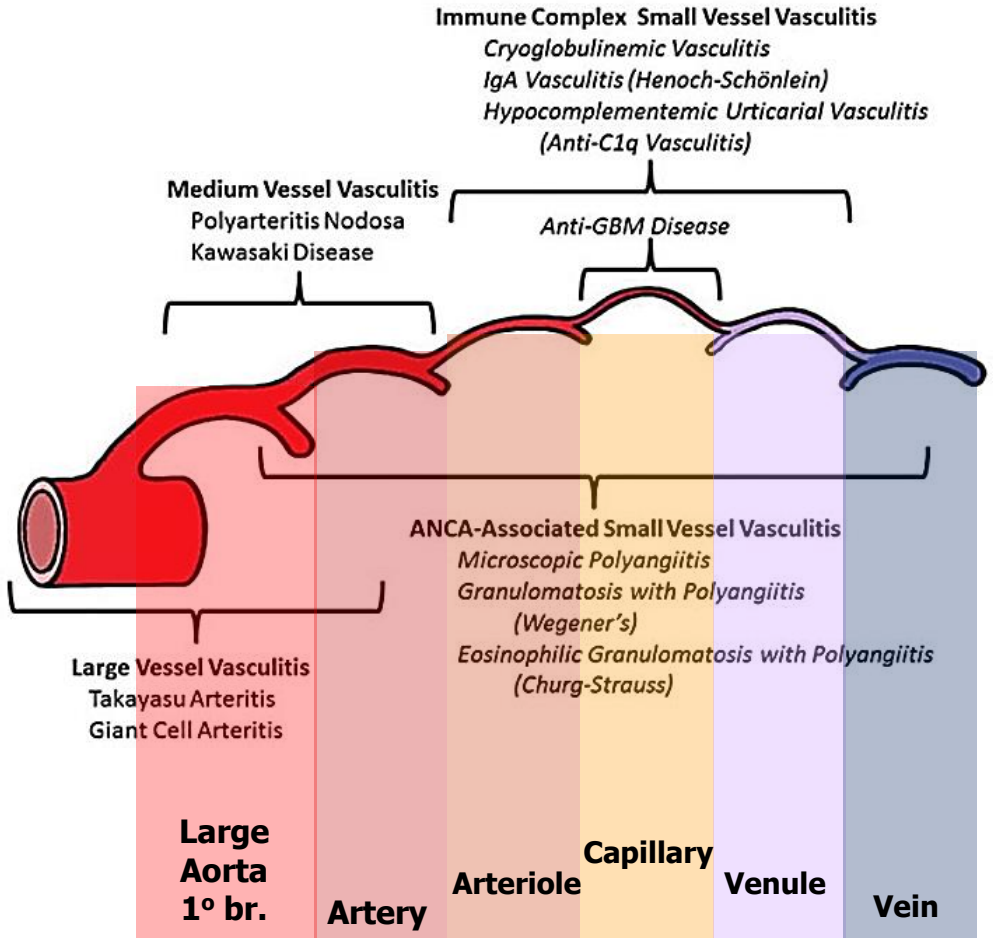
Methyl prednisolone 1 g in NSS 100 ml IV drip in 1 hr. x 3 – 5 days then
Prednisolone (or equivalent 0.5 – 1 MKD) (at least 4 wks.) plus
+ Tocilizumab 8 mg/kg (or 162 mg/wk.) IV or SC q 4 wk. (x 18 wks. then taper) OR
+ Methotrexate 2.5 – 15 mg/wk.

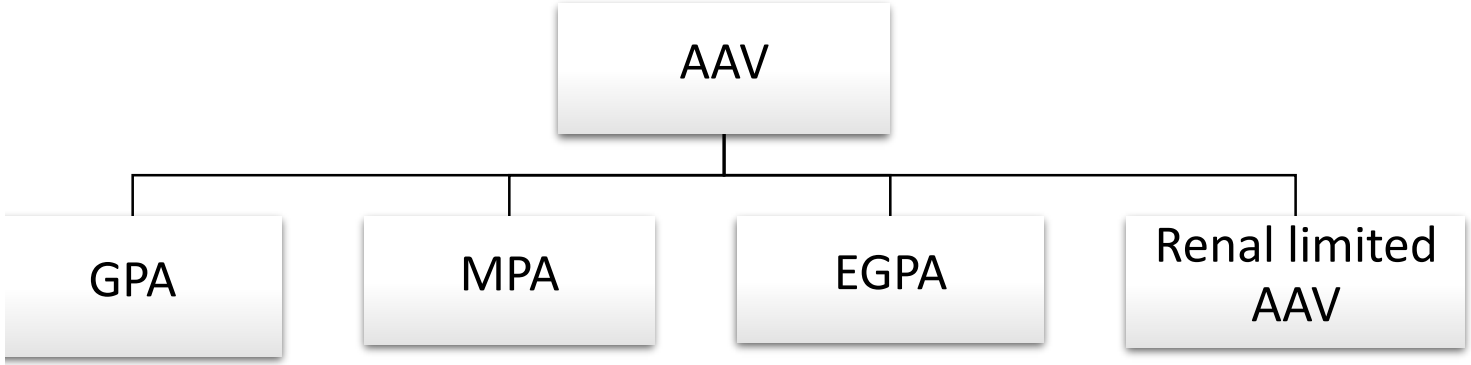
Major: extracranial large vessel involvement

Prednisolone (or equivalent 1 MKD) (at least 4 wks.) plus
+ Tocilizumab 8 mg/kg (or 162 mg/wk.) IV or SC q 4 wk. (x 18 wks. then taper) OR
+ Methotrexate 2.5 – 15 mg/wk.

Maz M, et al. Arthritis Rheumatol. 2021 Aug;73(8):1349-1365.

ANCA associated vasculitis





- Medium (artery) to Small (capillary) to venule/vein 1° vasculitis
- F : M = 1 : 1; 40-60 years; EGPA tend to be younger
- Prevalence: GPA ≥ MPA > EGPA
- Low inherited rate
- Key: Pulmonary + Renal + Neuro + Cutaneous
  (alveolitis) (GN) (MN) (purpura)
- GPA; granulomatosis with polyangiitis; Wegener granulomatosis
- MPA; microscopic polyangiitis; micro-PAN
- EGPA; eosinophilic granulomatosis with polyangiitis; Churg-Strauss syndrome
- Renal limited AAV: pauci-immune crescentic glomerulonephritis usually MPO-ANVA +ve 70-80%

ANCA–associated vasculitis (medium-small arterioles to venues)

Feature	WG	MPAN	CSS
ANCA	80 - 90%	70%	40-50%
Antigen	PR3 (80%) > MPO (15%)	MPO (70%) > PR3 (20%)	MPO (35%) > PR3 (5%)
Histology	LCV (Necrotizing granuloma)	LCV (no granuloma)	LCV (Eosinophilic infiltration)
ENT	Sinusitis, Septal perforation, Conductive/ Sensorineural HL, subglottic stenosis	Absent	Nasal polyps, Allergic rhinitis, Conductive HL
Eye	Scleritis, Episcleritis, Uveitis (50%), Orbital pseudotumor, Dacryocystitis	Scleritis, Episcleritis, Uveitis (occasional)	
Lung	Consolidation, Cavitation, Diffuse Alveolar Hemorrhage (DAH)		
Kidney	70%	90%	27%
Heart	Peri-myo-endo-carditis, Coronary vasculitis	Rare	Peri-myo-endo-carditis
Nerve: MN	10%	58%	78%
Skin	Purpura (40%)	Purpura, ulcer (60%)	Purpura (40-70%), nodule (30%)
GI vasculitis	10%	30%	30%
Eosinophil	Occasionally	None	All

Anti-neutrophilic cytoplasmic antibody

Ethanol dissolves the lipid barrier of cytoplasmic granules, enables +ve charged Ag (MPO) to arrange around the -ve charged nucleus

Not dissolve the lipid barrier of cytoplasmic granules

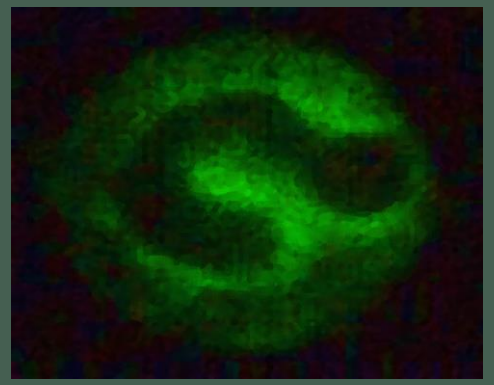
Ethanol fixed → Not dissolve ANA

ANA → false positive ANCA

ANCA can be positive in other conditions those have positive ANA

Formalin fixed → dissolve ANA

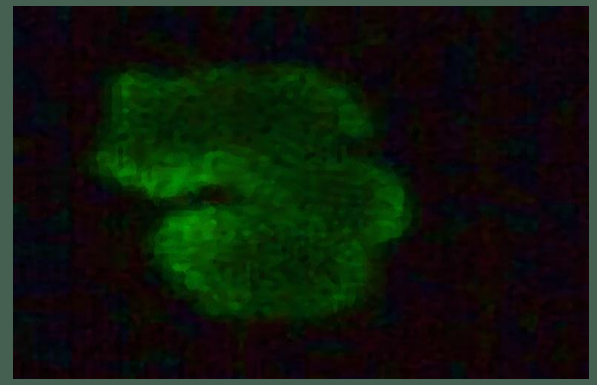
If positive formalin-fixed ANCA → true positive



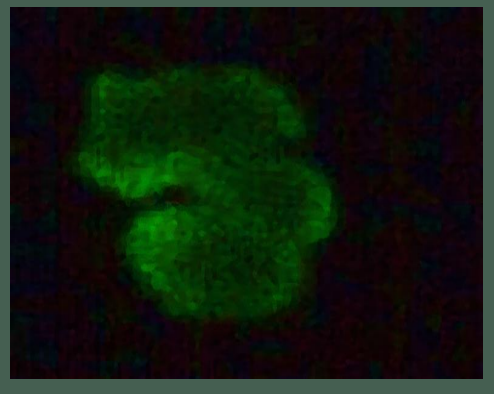
Cytoplasmic pattern

Recognized Ag = PR3, β glucuronidase, Azurocidin, Bactericidal permeability-increasing protein

} Minor ANCA (Low pathogenicity)



Perinuclear pattern



Perinuclear pattern

Recognized Ag = MPO, Elastase, Cathepsin G, Lactoferrin, Lysozyme

} Minor ANCA (Low pathogenicity)

Both PR3-ANCA & MPO-ANCA by IFA have to be confirmed by ELISA!

Anti-neutrophilic cytoplasmic antibody

ANCA staining pattern	Target Ag	Ab	Associated Diseases
C-ANCA	PR3	Anti-PR3	GPA > MPA > EGPA Renal limited AAGN Infective endocarditis ±embolic phenomenon Amoeba infection Healthy individuals
P-ANCA	MPO	Anti-MPO	MPA > EGPA > GPA Renal limited AAGN Inflammatory bowel disease Cystic fibrosis Primary sclerosing cholangitis Healthy individuals
Atypical ANCA	Multiple Ag	ANCA	Inflammatory bowel disease Drug-induced vasculitis Primary sclerosing cholangitis Autoimmune hepatitis Cocaine abuse Hydralazine

2022 ACR/EULAR classification criteria for GPA

Situation: small – medium vessel vasculitis excluding mimickers

≥5

Clinical criteria

Nasal involvement: bloody D/C, ulcers, crusting, congestion, septal defect/perforation	+3
Cartilaginous involvement: ear, nose, trachea, bronchus	+2
Conductive or Sensorineural hearing loss	+1

Laboratory, Imaging, Biopsy criteria

+ cANCA or anti-PR3	+5
Pulmonary nodules, mass, cavitation on CXR	+2
Granuloma, extravascular granulomatous inflammation or giant cell on Bx	+2
Inflammation, consolidation, effusion of nasal/ paranasal sinuses, mastoiditis on imaging	+1
Pauci-immune glomerulonephritis on Bx	+1
+pANCA or anti-MPO	-1
Blood eosinophilia count $\geq 1 \times 10^9/L$	-4

Robson JC, et al. Arthritis Rheum. 2022;74(3):393-399.

2022 ACR/EULAR classification criteria for MPA

Situation: small – medium vessel vasculitis excluding mimickers

≥5

Clinical criteria

Nasal involvement: bloody D/C, ulcers, crusting, congestion, septal defect/perforation	-3

Laboratory, Imaging, Biopsy criteria

+ pANCA or anti-MPO	+6
Fibrosis or Interstitial lung disease on CXR	+3
Pauci-immune glomerulonephritis on Bx	+3
+cANCA or anti-PR3	-1
Blood eosinophilia count ≥1 x 10^9/L	-4

Suppiah R, et al. Arthritis Rheum. 2022;74(3):400-406.

2022 ACR/EULAR classification criteria for EGPA

Situation: small – medium vessel vasculitis excluding mimickers

≥6

Clinical criteria

Obstructive airway disease	+3
Nasal polyps	+3
Mononeuritis multiplex	+1

Laboratory, Imaging, Biopsy criteria

Blood eosinophilia ≥1 x 10^9/L	+5
Extravascular eosinophilic-predominant inflammation on biopsy	+2
+cANCA or anti-PR3	-3
Hematuria	-1

Grayson PC, et al. Arthritis Rheum. 2022;74(3):386-392.

2021 ACR management for GPA/MPA

Active severe GPA/MPA (DAH, RPGN, MN, digital ischemia)

Induction

BW 50-75 kg

MP 1 g NSS 100 ml IV 1 hr. x 3D

Prednisolone 60 mg/D x 1 wk.

Prednisolone 30 mg/D x 1 wk.

Prednisolone 25 mg/D x 2 wk.

Prednisolone 20 mg/D x 2 wk.

Prednisolone 15 mg/D x 2 wk.

Prednisolone 12.5 mg/D x 2 wk.

Prednisolone 10.0 mg/D x 2 wk.

Prednisolone 7.5 mg/D x 2 wk.

Prednisolone 5.0 mg/D x 10 wk.

Rituximab

375 mg/m^2 IV q 4 wk. OR

1 g IV on D1, D15

OR

Cyclophosphamide

1-2 MKD 3-6 mo. OR

15 mg/kg IV q 2 wk. x 3 doses

then q 3 wk. x 3 doses

← No need of plasma exchange!

← Reduced dose GC regimen

Maintenance

Rituximab 500 mg IV q 6 mo. OR 1 g IV q 4 mo.

Methotrexate 2.5-25 mg/wk. OR

Azathioprine 1-2 MKD OR

Leflunomide 20 mg/D

Chung SA, et al. Arthritis Rheumatol. 2021 Aug;73(8):1366-1383.

2021 ACR management for GPA/MPA

Active nonsevere GPA/MPA (mild constitutional symp., LCV, arthritis)

Induction

Prednisolone 1 MKD 2-4 wk.

Methotrexate 2.5-25 mg/wk. OR
Rituximab 375 mg/m^2 IV q 4 wk. OR 1 g IV on D1, D15 OR
Cyclophosphamide 1-2 MKD 3-6 mo. OR 15 mg/kg IV q 2 wk. x 3 then q 3 wk. x 3 OR
Azathioprine 1-2 MKD or
Mycophenolate mofetil 2-3 g/D

Maintenance

Methotrexate 2.5-25 mg/wk. OR
Azathioprine 1-2 MKD OR
Mycophenolate mofetil 2-3 g/D
Rituximab 500 mg IV q 6 mo. OR 1 g IV q 4 mo.

Chung SA, et al. Arthritis Rheumatol. 2021 Aug;73(8):1366-1383.

2021 ACR management for EGPA

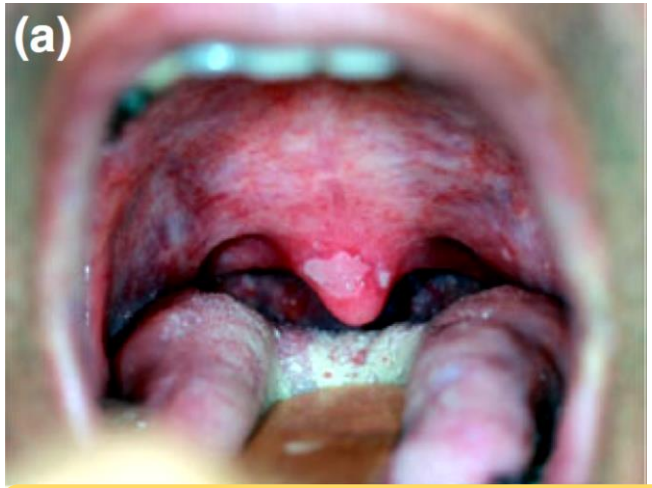
	Active severe	Active nonsevere
Induction	IV MP 1 g IV x 3 days OR Prednisolone 1 MKD	Prednisolone 1 MKD
	Rituximab 375 mg/m^2 IV q 4 wk. OR 1 g IV on D1, D15 OR **Cyclophosphamide** 1-2 MKD 3-6 mo. OR 15 mg/kg IV q 2 wk. x 3 then 15 mg/kg IV q 3 wk. x 3	**Methotrexate** 2.5-25 mg/wk. OR **Azathioprine** 1-2 MKD or **Mycophenolate mofetil** 2-3 g/D **Rituximab** 375 mg/m^2 IV q 4 wk. OR 1 g IV on D1, D15
Maintenance	**Methotrexate** 2.5-25 mg/wk. OR **Azathioprine** 1-2 MKD or **Mycophenolate mofetil** 2-3 g/D **Rituximab** 500 mg IV q 6 mo. OR 1 g IV q 4 mo.	

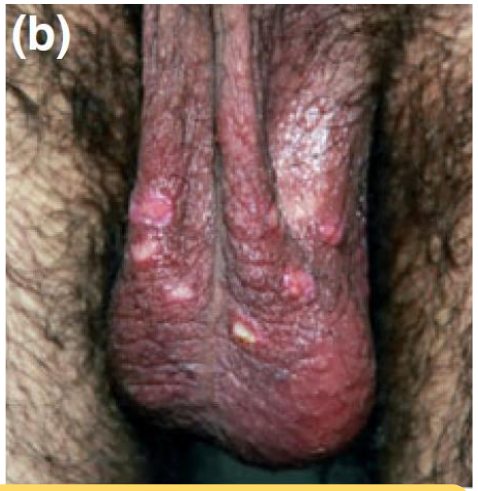
Chung SA, et al. Arthritis Rheumatol. 2021 Aug;73(8):1366-1383.

Identifying Behçet disease

A disease phenotyping for classification

High Sensitivity
Less Specificity
(pathognomic pattern)

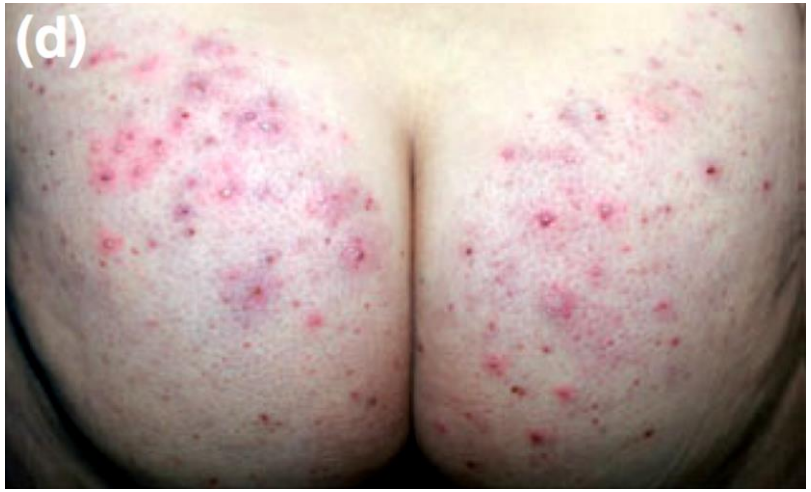




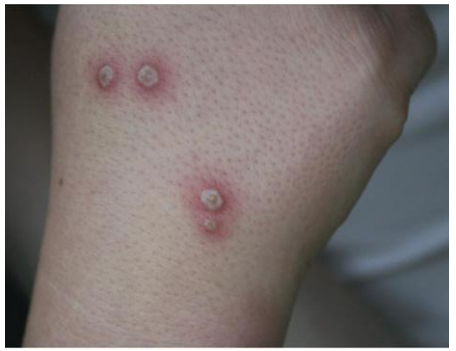
"Disease Hallmark"

- **Oral ulcer (obligatory feature)**
- >80% at initial presentation
- 99% at cumulative presentation
- Well-defined, painful with erythematous halo aphthous
- Minor (<1cm); Major (>1cm)
- >1 (>6 lesions → So suspicious!)
- >1wk – 4wk durations
- ≥5 attacks/yr. (mean 10 attacks)
- (Thai 100%)

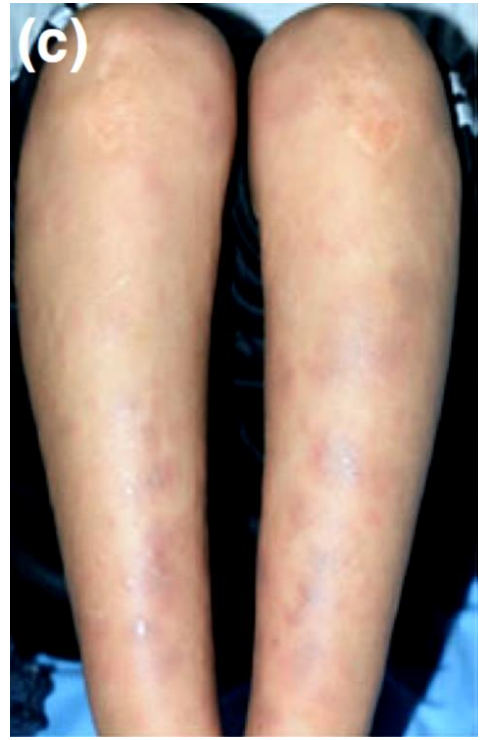
- **Genital ulcer**
- 85% at cumulative presentation
- Recurrence
- Deeper ulcer
- >1wk – 4wk durations
- Tendency to scar
- (Thai 70%)



- **Papulopustular lesions**
- Sterile (pseudo-folliculitis)
- 85% at cumulative presentation
- Trunk, Buttock, Lower limbs



(Thai 64%)



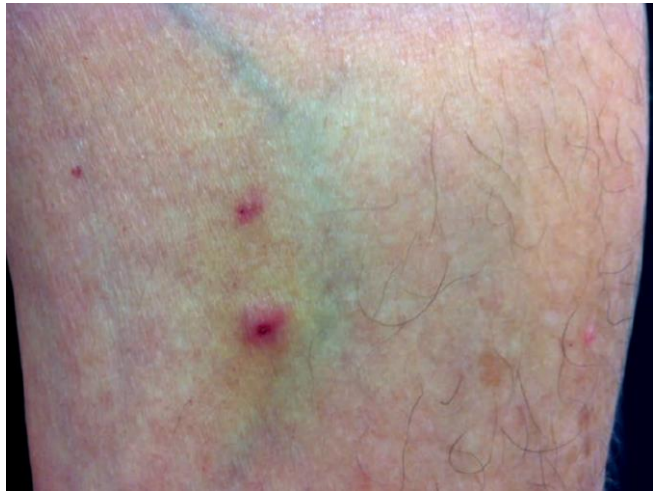
- **Erythema nodosum**
- 50% at cumulative presentation
- Last for 2-3 wk.

Arromdee E, et al. J Med Assoc Thai.2006;89:S182-6.
Scherrer MAR, et al. An Bras Dermatol. 2017 Jul-Aug;92(4):452-464.
Alpsoy E. J Dermatol. 2016 Jun;43(6):620-32.

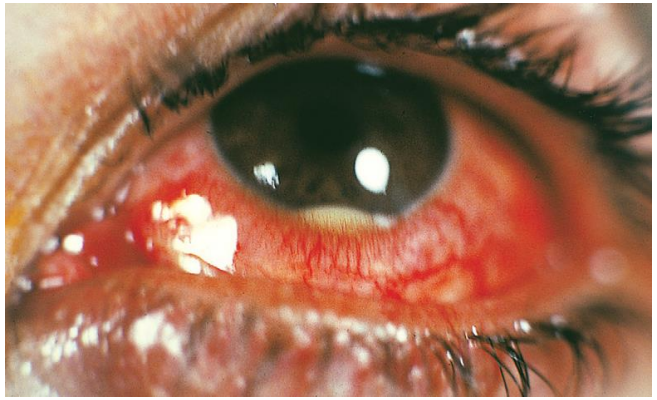
Identifying Behçet disease

A disease phenotyping for classification

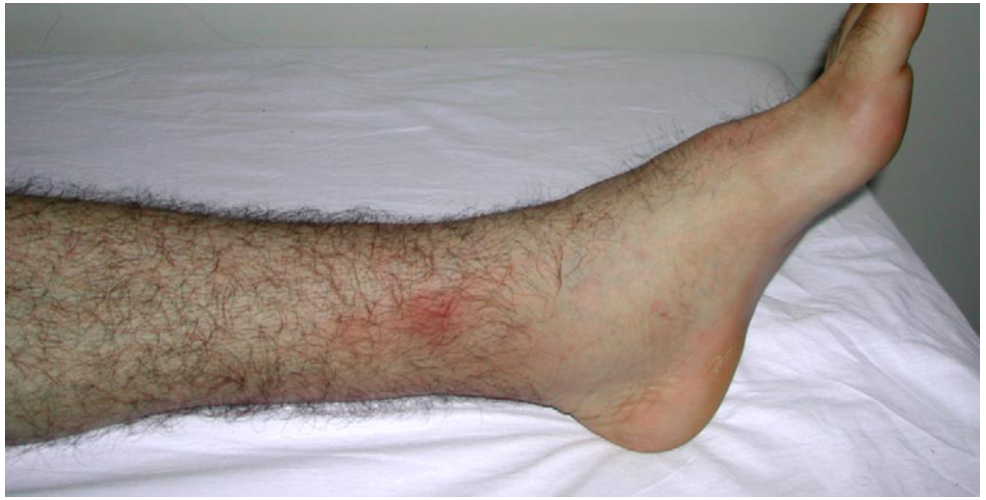
Less Sensitivity
Less Specificity
(Many D/DX)



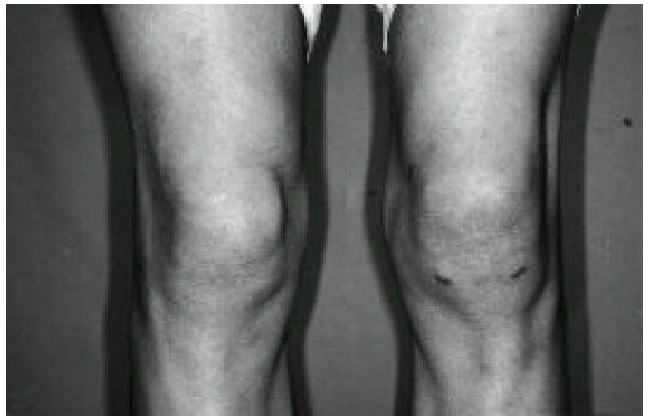
- **Pathergy reaction** (60%; 30%) (Mediterranean Japan; Thai)
- 45º 20-26 G Needle-prick
- 24-48 hr. → ≥2mm pustule



- **Anterior (Pan) uveitis**
- 10-20% initial presentation
- 50% cumulative presentation
- Recurrent/ Bilateral
- (Thai 50%)



- Especially male!
- **Superficial thrombophlebitis** (25%)
- Associated with **DVT** (10%) – Legs, Major Veins, SVC (tight adherence of thrombi → rare embolism)
- **Epididymitis** (10%) (Thai 4%)
- **Ulcerative of ileum** (<30%) (Thai 9%)



- **Arthritis**
- 50% cumulative presentation
- Non-deforming, Non-erosive Oligoarthritis (LE > UE) last ≤ 2-3 wk.

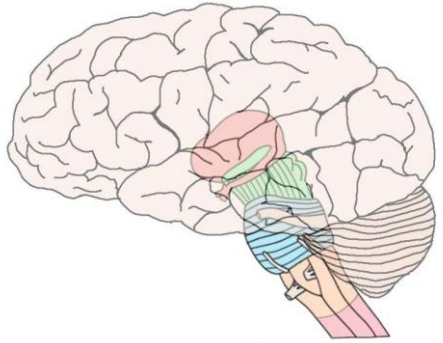
Arromdee E, et al. J Med Assoc Thai.2006;89:S182-6.
Scherrer MAR, et al. An Bras Dermatol. 2017 Jul-Aug;92(4):452-464.
Alpsoy E. J Dermatol. 2016 Jun;43(6):620-32.

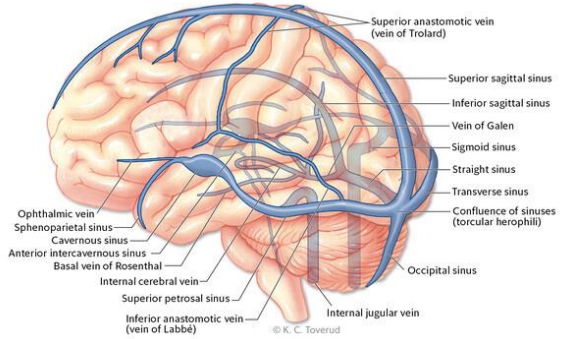
Identifying Behçet disease

A disease phenotyping for classification

Neuro (CNS) Behçet Disease (10%) (Thai 9%)

- Parenchymal
- Non-Parenchymal





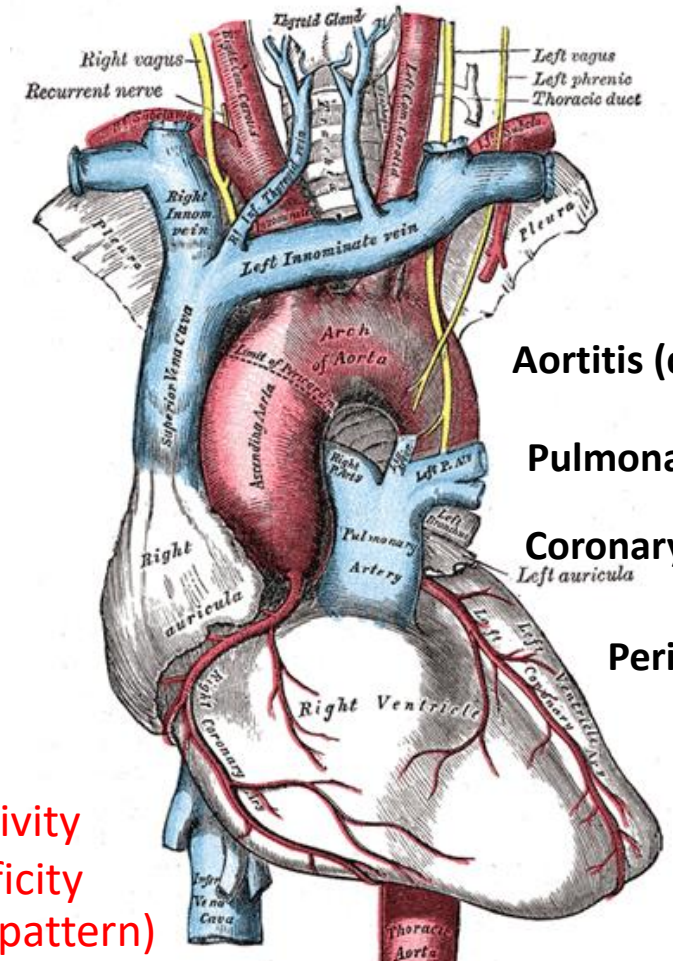
- **Brain stem**
- Typical predilection site!
- Pons, midbrain, BG, diencephalon
- Including ophthalmoparesis, cranial neuropathy, cerebella/ pyramidal dysfunction
- Multifocal or Diffuse
- Brain stem atrophy → powerful discriminator
- Relapsing – Remitting pattern

- **Cerebral venous thrombosis**
- **Pseudotumor cerebri**
- Monophasic pattern

Less Sensitivity
High Specificity
(pathognomic pattern)

Arterial Occlusion/Aneurysm (4%) (Thai 9%)

- Involvement of entire arterial tree (**D/Dx TAK, GCA**)
- The only vasculitis syndrome that causes pulmonary artery aneurysm! → Recurrent hemoptysis



Aortitis (dilatation)

Pulmonary arteritis/aneurysm

Coronary vasculitis

Peripheral arteritis/aneurysm

Arromdee E, et al. J Med Assoc Thai.2006;89:S182-6.

Kalra S, et al. J Neurol. 2014 Sep;261(9):1662-76.

Hatemi G, et al. Clin Exp Rheumatol. 2020 Sep-Oct;38 Suppl 127(5):3-10.

2014 International criteria for Behcet disease

≥4

Sign and Symptom	Point
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	1
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathergy test (optional)	1

International Team for the Revision of the International Criteria for Behçet's Disease [ITR-ICBD]. The international criteria for Behçet's disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol. (2014) 28:338–47

2018 EULAR management for Behcet

Minor lesions

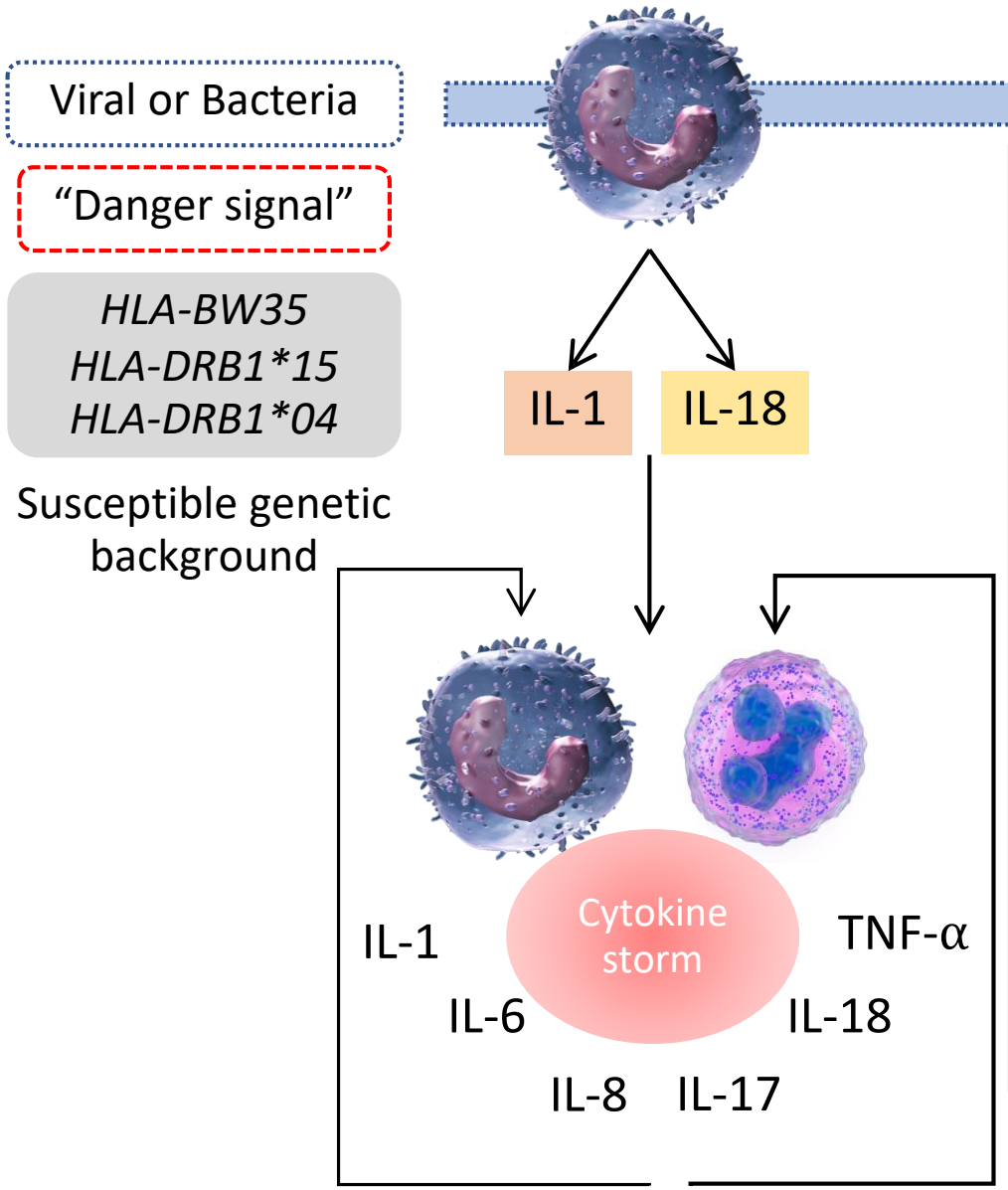
Papulopustular lesion (acne-like lesion): 0.1% TA cream bid.
Genital/ Oral ulcer, Erythema nodosum, arthritis: colchicine (0.6) 1 x 2

Major lesions: uveitis, deep vein vasculitis (DVT), pulmonary vasculitis, CVST

Prednisolone (or equivalent 1 MKD) (at least 4 wks.) plus
+ Azathioprine 1 – 2 MKD (uveitis, DVT, IBD, CNS)
+ Cyclosporine A (uveitis, DVT)
+ Cyclophosphamide (DVT, pulmonary arteritis, aortitis, arteritis)

Hatemi G, Christensen R, Bang D, et al. Ann Rheum Dis 2018;77:808–818.

Adult-onset Still disease



AOSD

- Almost balanced sex ratio
- Adult (16 – 35) & >35 YO
- 4 cardinal symptoms
  - High-grade intermittent
  - RA – like (2/3 non-erosive, 1/3 isolated bilateral carpal ankylosis)
  - Macular/ maculopapular rash during fever spike – proximal limbs/trunk (rarely involve palm/soles/face); nonpruritic
  - ↑WC >10K, ↑N >80%
- ↑ESR/CRP/Fibrinogen/Globulin
- **MAS-related AOSD**
  - Relatively low ESR (↓fibrinogen)
  - ↑CRP
  - Cytopenias, hepatitis, ↑Triglyceride

Yamaguchi

- **Major**
  1. Fever ≥39°C; ≥1 wk.
  2. Arthralgia/arthritis ≥2 wk.
  3. Typical rash during fever spike
  4. WBC ≥10K; PMN ≥80%
- **Minor**
  1. Pharyngitis or Sore throat
  2. Lymphadenopathy/Splenomegaly
  3. Hepatitis
  4. Negative RF or ANA
- **Exclusion**
  1. Infection esp. sepsis & EBV
  2. Malignancy esp. lymphoma
  3. Inflammation e.g. CTD, vasculitis

5 criteria (2 major)

- Sn 96.3%; Sp 98.2%
- Ferritin > ULN Sn 100%; Sp 97.1%

Feist E, et al. Nat Rev Rheumatol. 2018 Oct;14(10):603-618.

AOSD Treatment

1. **Minor organ involvement**: fever, arthritis, rash, pleuritis, pericarditis
   - Indomethacin (25) 1 x 3
2. **Major organ involvement**: hepatitis, MAS, DIC, MAHA, DAH, meningitis
   - Prednisolone 1 MKD equivalent 4-6 wk. then taper
   - Steroid dependence (45%) Risk:
     1. Young age at onset
     2. Splenomegaly
     3. Low glycosylated ferritin levels (<20%)*
     4. Elevated ESR

     → Adding CQ 3 MKD or MTX 7.5 – 17.5 mg/wk. or Cyclosporine A

*The GF level normally exceeds >50% of total ferritin. Glycosylation cannot follow very highly raised ferritin.

Giacomelli R, et al. J Autoimmun. 2018 Sep;93:24-36.

Clinical scenario suspected RA

- Female aged ~ 50 years
  - At the age < 50 years F : M = 4-5 : 1*
  - At the age 60 – 70 years F : M = 2 : 1*
- Symmetrical polyarthritis of hand (± feet) joints
- Likely to has chronic progression (≥ 6 weeks)

* Kvien TK, et al. Ann N Y Acad Sci. 2006 Jun;1069:212-22.

Rheumatoid arthritis (RA)

Investigation

- CBC: ↓Hb, ↑WBC, ↑Plts
- ESR: ↑ (>20 mm/hr.)
- CRP: ↑ (>5 mg/L)
- UA: normal (no proteinuria/sediments)
- Rheumatoid factor (RF)

Sensitivity	0.69	Specificity	0.85
PPV	4.86	NPV	0.38

- Anti-citrullinated peptide antibody (ACPA)

Sensitivity	0.67	Specificity	0.95
PPV	12.46	NPV	0.36

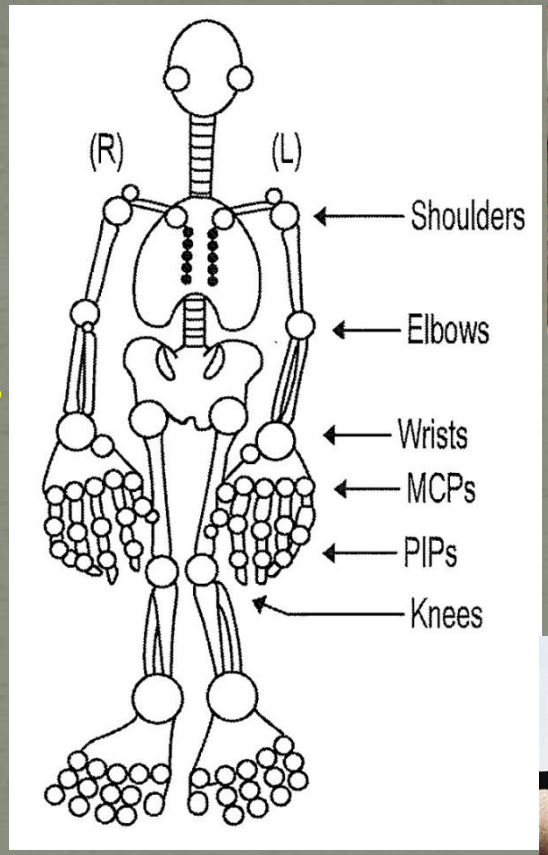
- HBs Ag, Anti-HBs, Anti-HBc, Anti-HCV
- CXR (rule out pulmonary TB)
- **Plain film: Both hands AP**

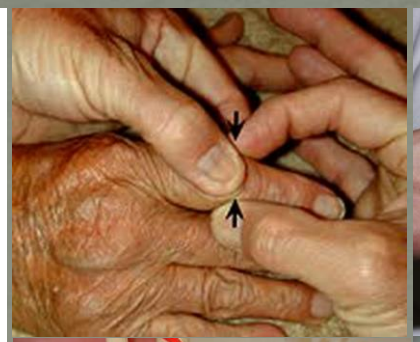
Disease that has positive RF	
Autoimmune	RA, SLE, SjS, SSc, DM, PM, sarcoidosis
Infection	IE, TB, Leprosy, Syphilis, Lyme, parasite
Virus	HIV, EBV, CMV, HBV, HCV, Influenza, Rubella
Lung disease	Chronic bronchitis, ILD, Silicosis
Liver disease	PBC, AIH
Vasculitis	Cryoglobulinemia

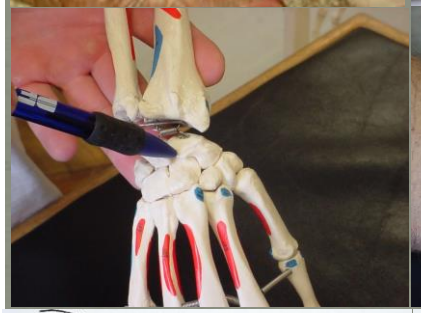
The disease that has RA – liked arthritis	
Virus	HIV, HBC, HCV, EBV, CMV, Influenza, COVID, Chikungunya, Dengue
Bacteria	Salmonella
Reaction	ARF, PSRA, Poncet disease
CTD & SpA	AOSD, SLE, MCTD, SSc, PsA, AS
Vasculitis	AAV, Cryoglobulinemia, HSP
Malignancy	Leukemia, Lymphoma

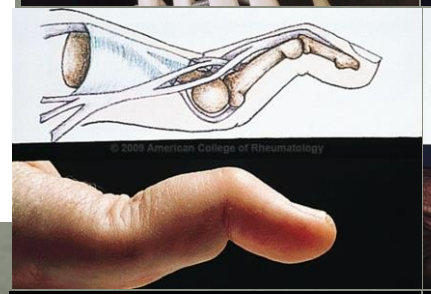
Rheumatoid arthritis & peripheral joint PE

- (TMJ)
- **PIP: 10**
- **MCP: 10**
- **Wrist: 2**
- **Elbow: 2**
- **Shoulder: 2**
- (Hip)
- **Knee: 2**
- Ankle
- (Subtalar)
- MTP
- IP

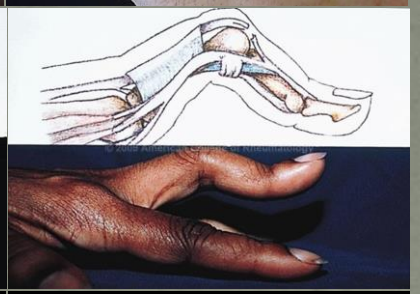








Swan neck deformity



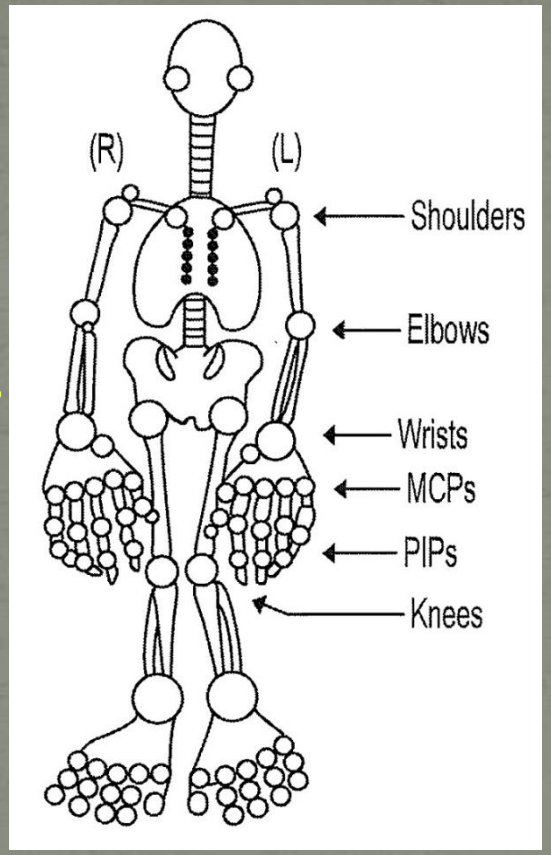
Boutonniere (buttonhole)

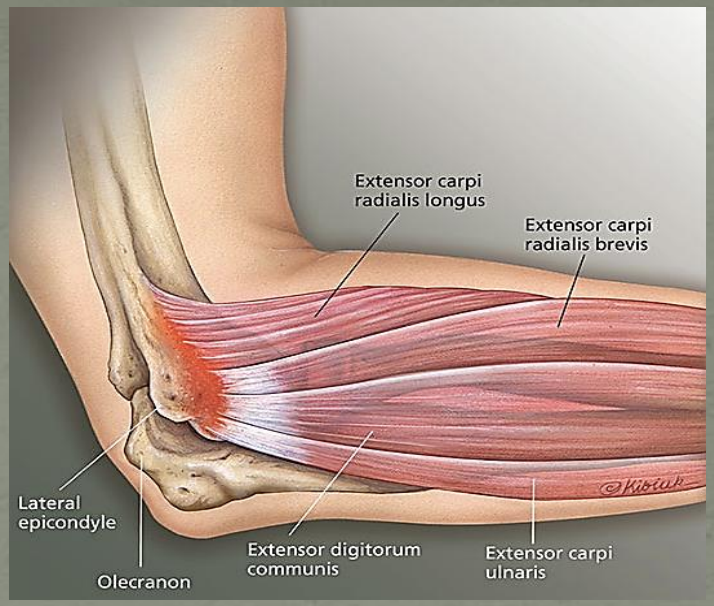
- Yellow indicates DAS28 system
- PE: swollen joint; tender joint
- Shoulder & Hip → tender joint only
- MTP joint → squeeze test

http://at.uwa.edu/currhome/ah321/PalBWristHand.asp

Rheumatoid arthritis & peripheral joint PE

- (TMJ)
- **PIP: 10**
- **MCP: 10**
- **Wrist: 2**
- **Elbow: 2**
- **Shoulder: 2**
- (Hip)
- **Knee: 2**
- Ankle
- (Subtalar)
- MTP
- IP





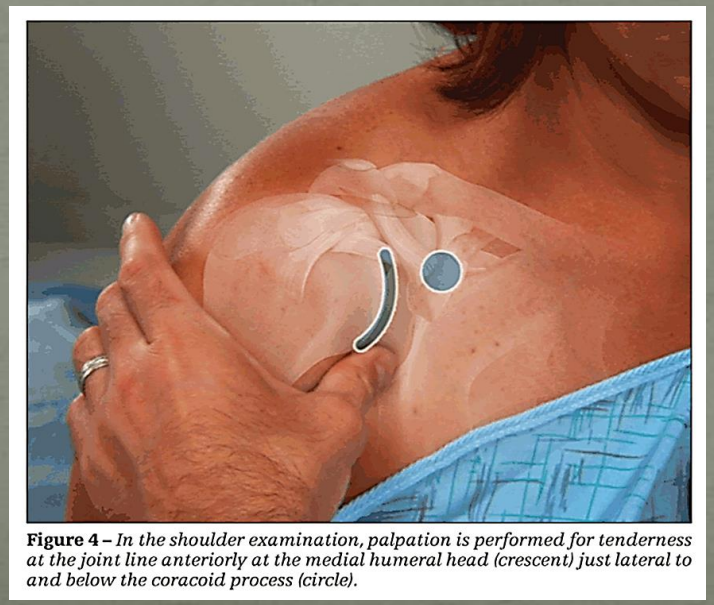
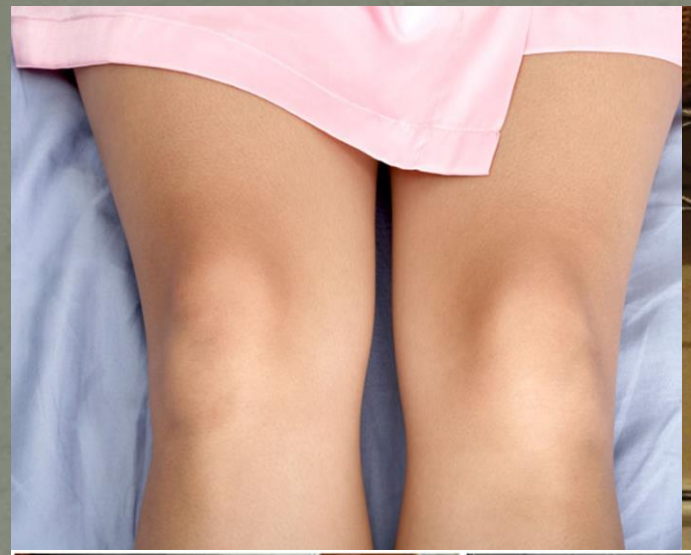


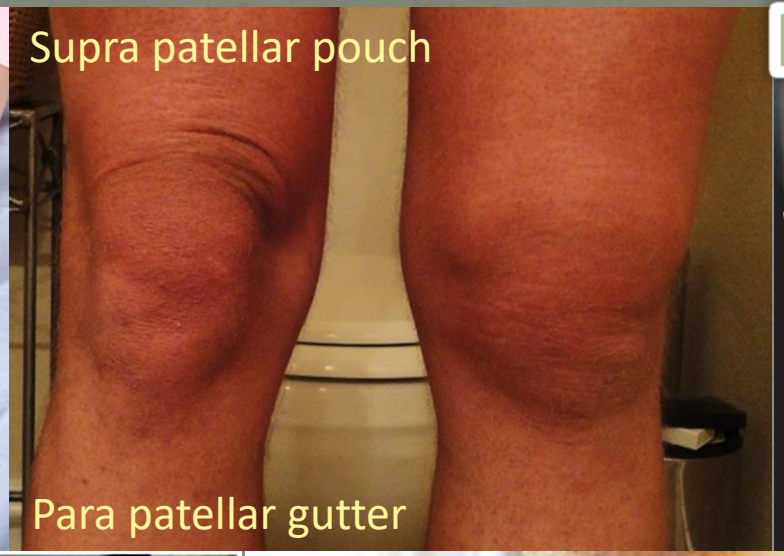
Figure 4 – *In the shoulder examination, palpation is performed for tenderness at the joint line anteriorly at the medial humeral head (crescent) just lateral to and below the coracoid process (circle).*

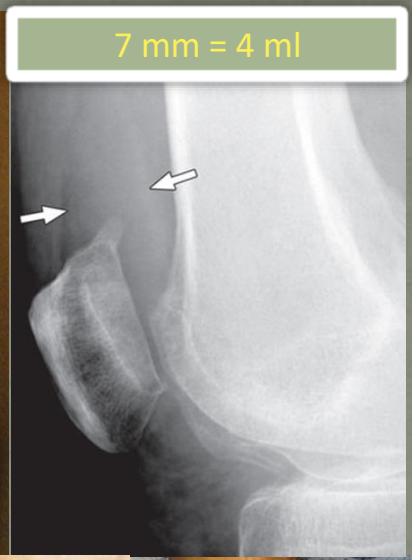
- Yellow indicates DAS28 system
- PE: swollen joint; tender joint
- Shoulder & Hip → tender joint only
- MTP joint → squeeze test

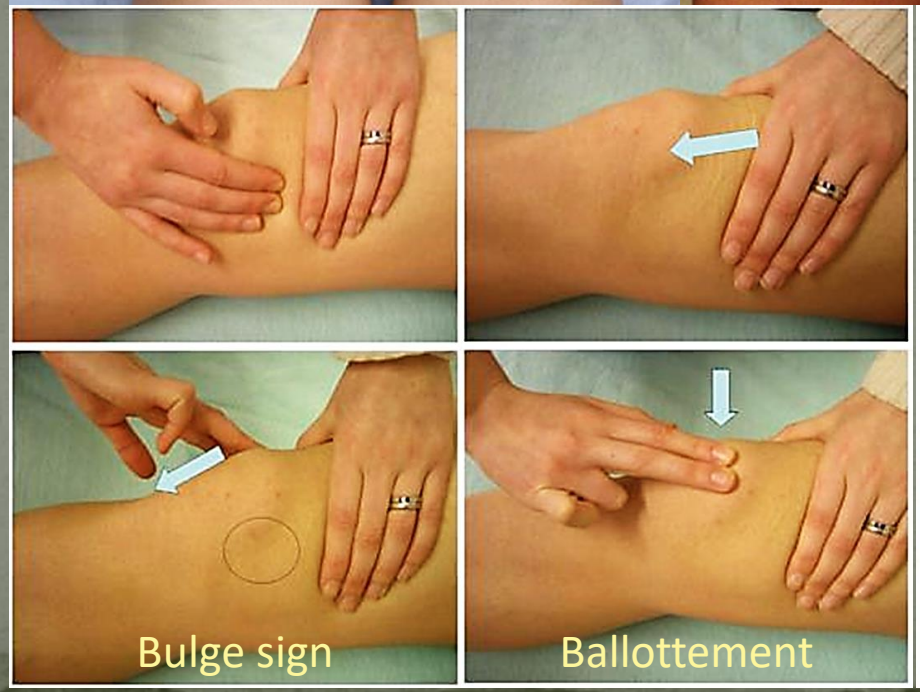
http://catstcmnotes.com/
http://www.rheumatologynetwork.com/

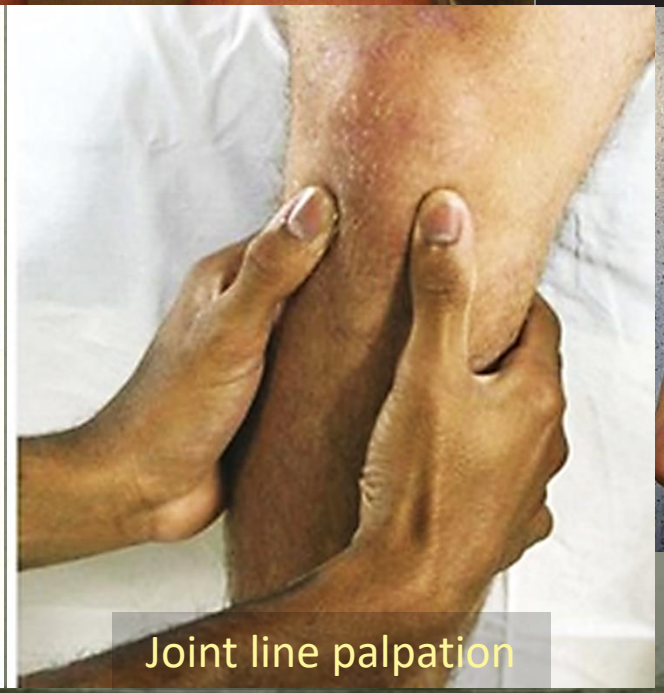
Rheumatoid arthritis & peripheral joint PE

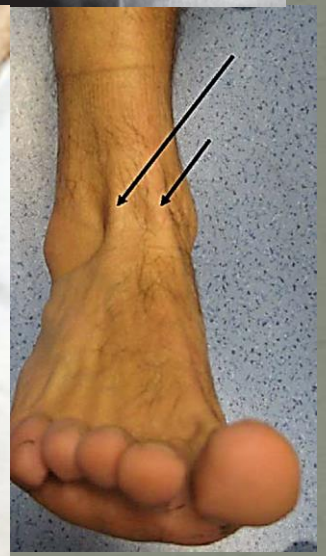




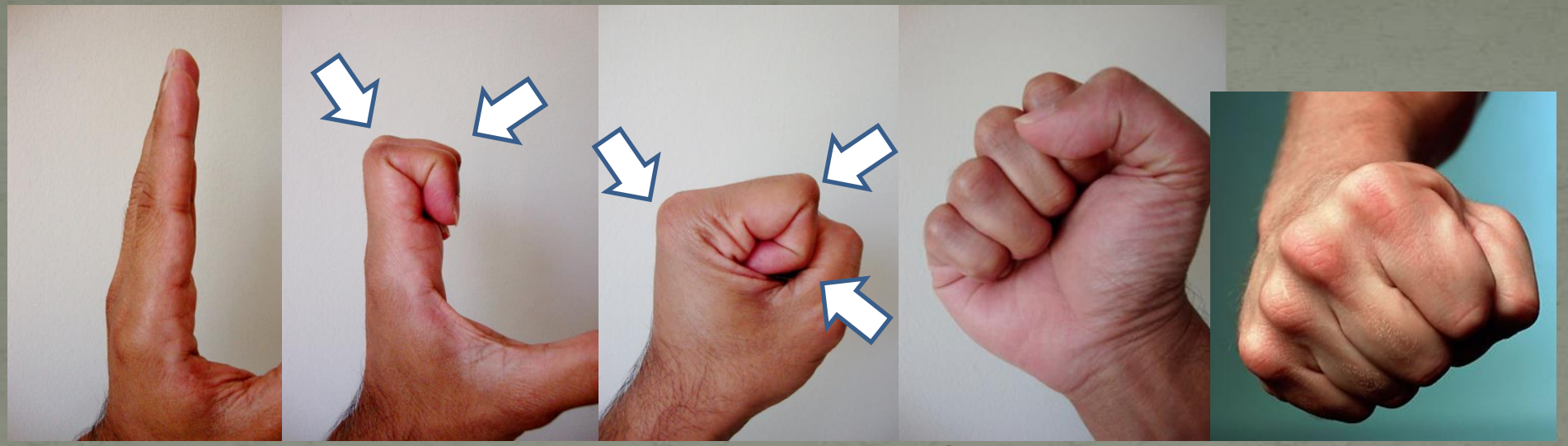








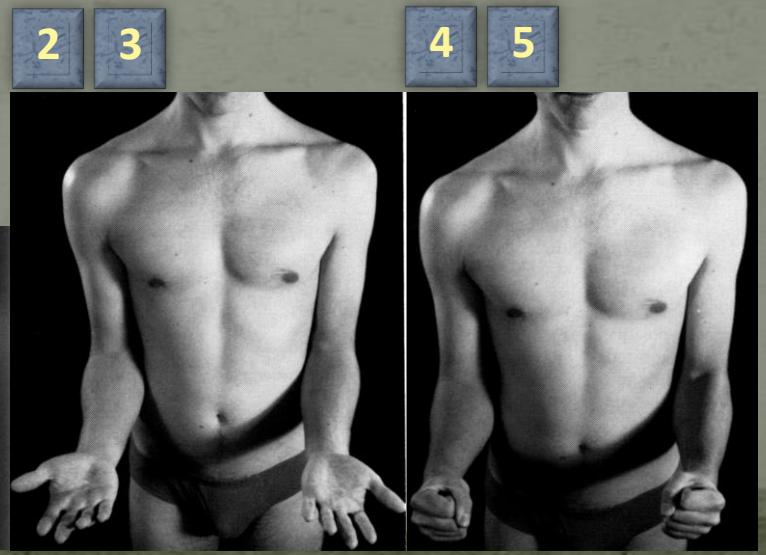
RA: Peripheral joint: Range of Motion



UE Screening: Range of Motion

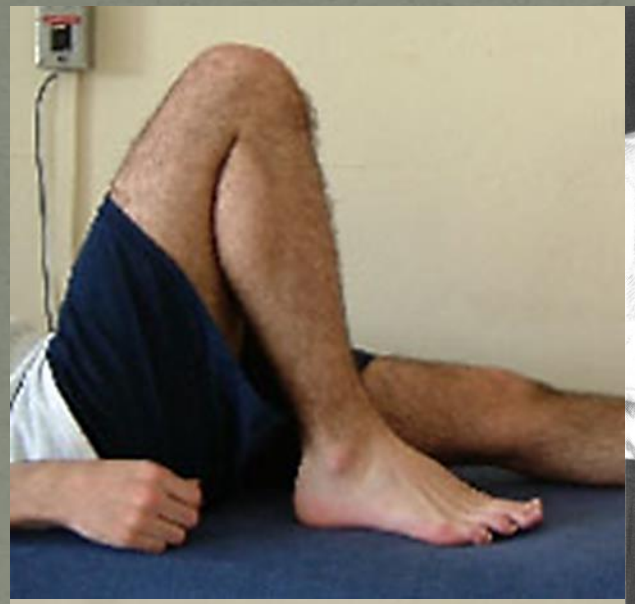
1. Arms behind head: normal glenohumeral, SC & AC joint
2. Arm straight: full elbow extension
3. Hand in front: full finger extension
4. Hand turn over: full supination/pronation
5. Make a fist : full flexion of MCP/PIP/DIP joint
6. Fingers on thumb: full opposition

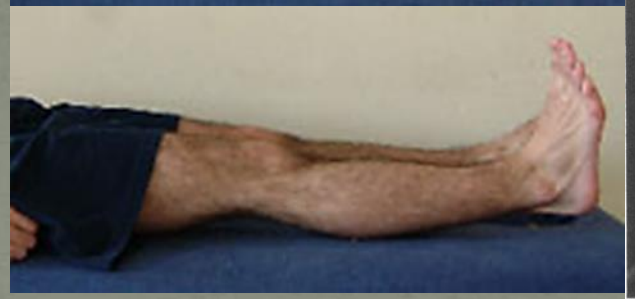
Ann Rheum Dis. 1992 Oct;51(10):1165-9.

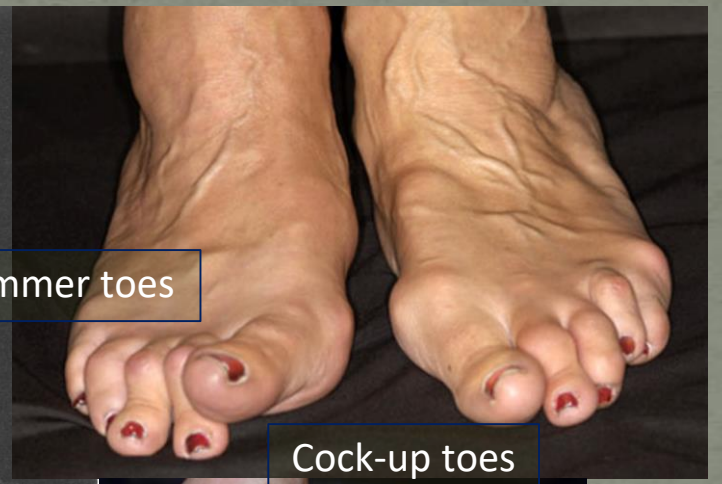


RA: Peripheral joint: Range of Motion

LE Screening: Range of Motion

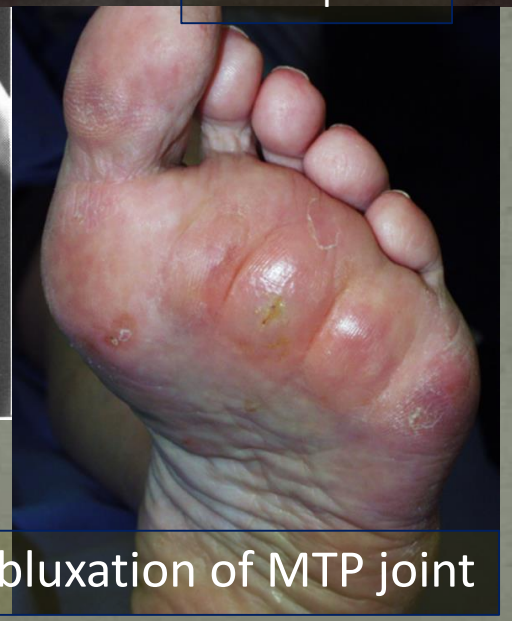






Hammer toes

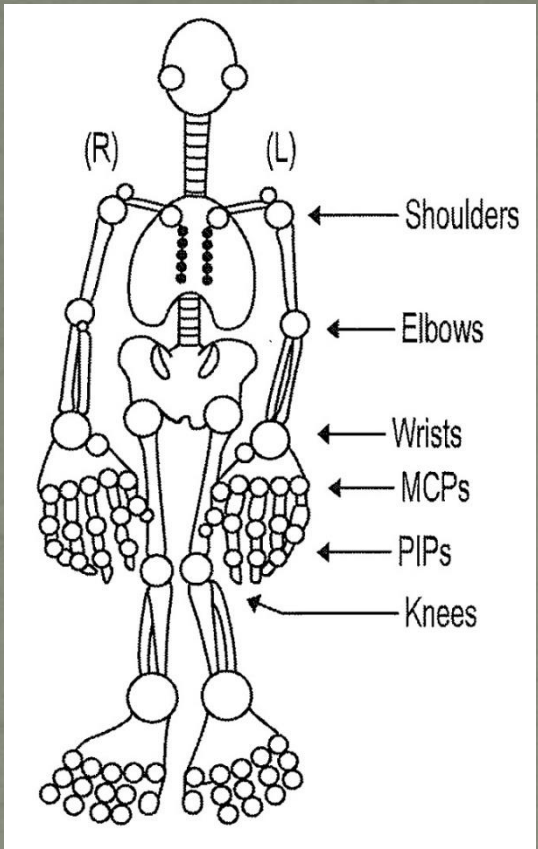
Cock-up toes



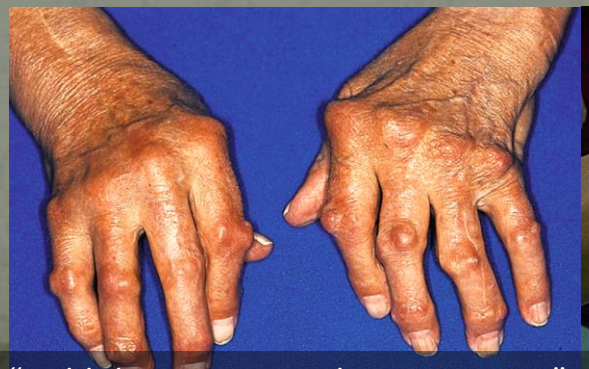
Plantar subluxation of MTP joint

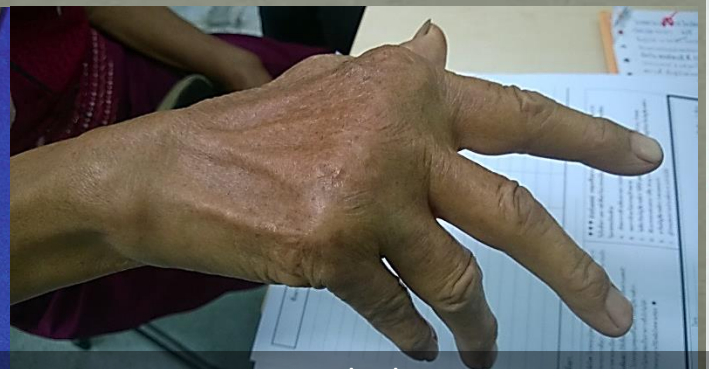
Ann Rheum Dis. 1992 Oct;51(10):1165-9.

Rheumatoid arthritis: Extra-articular PE

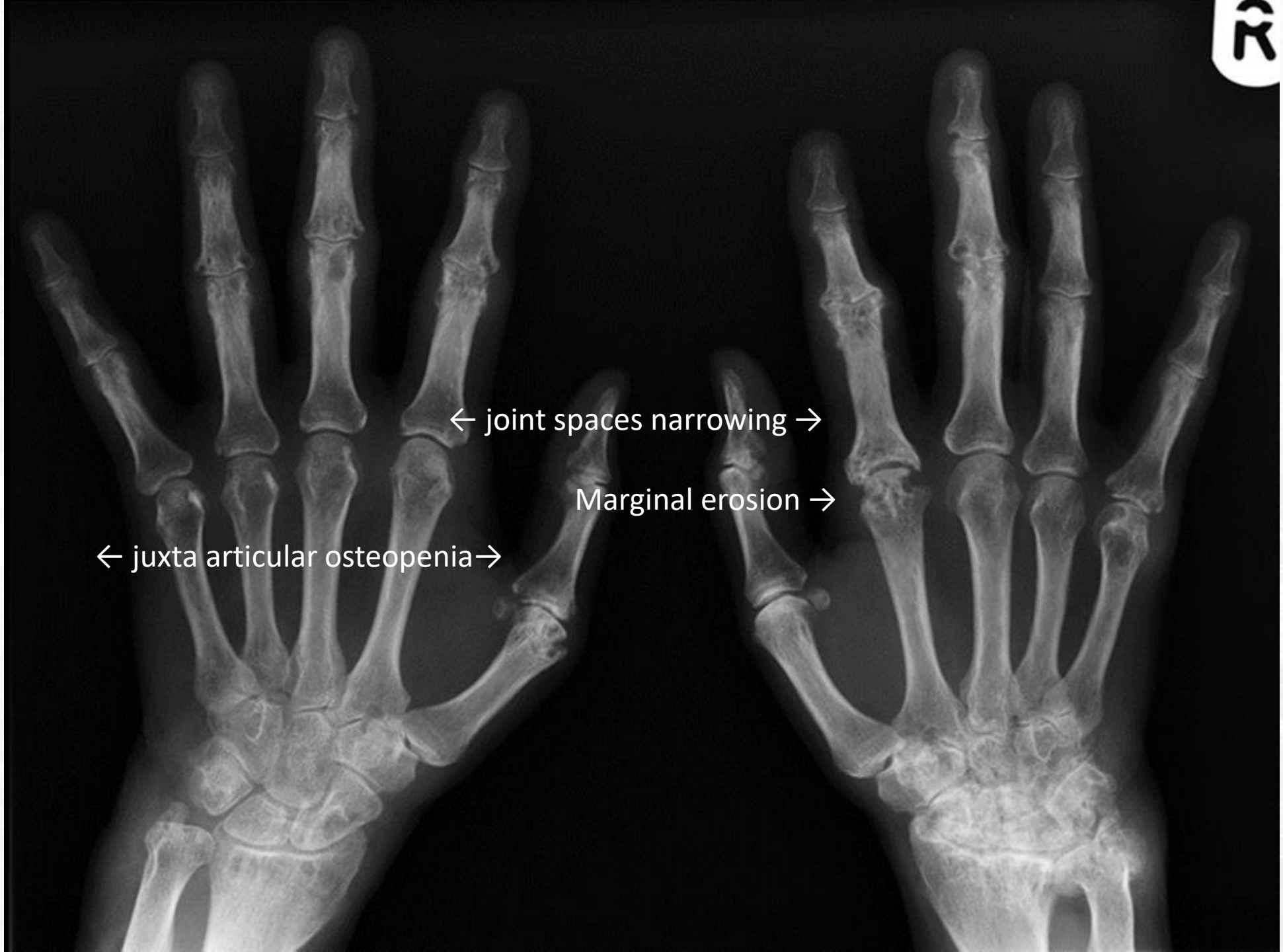


- Eyes: kerato-conjunctivitis (2º Sjogren – 17%), scleritis (1%), episcleritis (0.8%), scleromalacia, anemia (ACD)
- ENT: parotid gland enlargement, ↓salivary pool, hoarseness of voice (crico-arythenoiditis)
- CVS: aortitis (AR murmur), pericarditis (10.9%)
- RS: crackles for ILD/PF (9.4%), pleuritis (9.4%)
- Abdomen: Felty's syndrome (2.7% Triads = RA + ↓WC + Splenomegaly)
- Skin: subcutaneous (rheumatoid) nodule (39.4%)
- Extremity: Bilateral CTS**, MN (RA vasculitis), Teared Extensor tendon**
- C1-2 subluxation





"Hold this position at least a minute" positive test is attained when patient reports numbness in distribution of median n.


← joint spaces narrowing →
Marginal erosion →
← juxta articular osteopenia→

Clinical scenario suspected SLE.

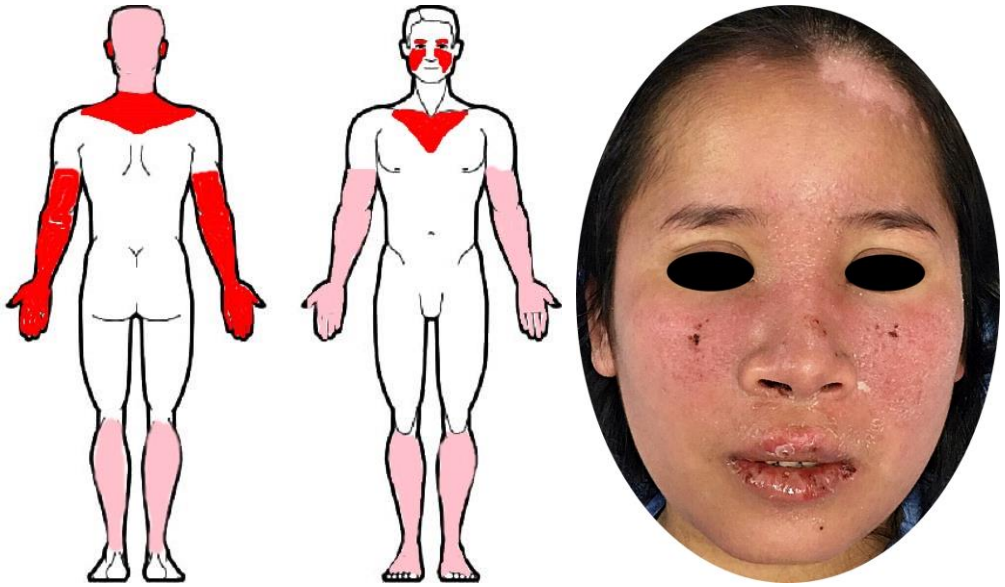
A young female presents with

Constitutional symptoms

RA-liked arthritis

Sun exposure area skin lesions

AIHA, leucopenia, ITP



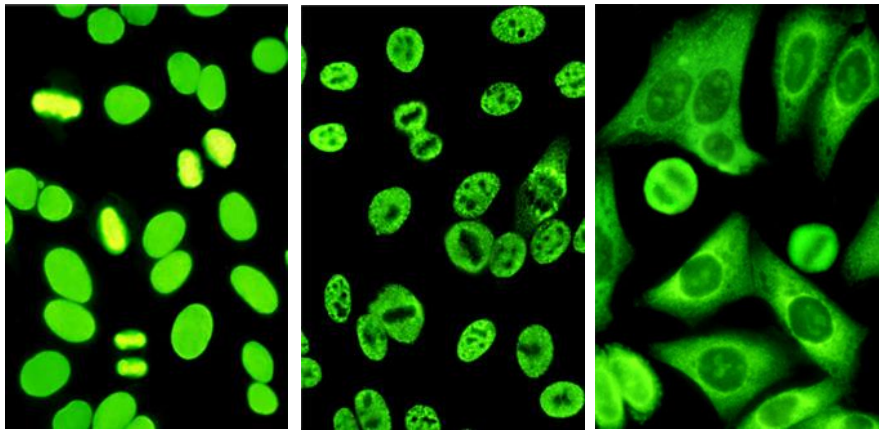
IC: Nephrito – Nephrotic/ RPGN/ TMA

Podocytopathy: MCD, MN, FSGS

ANA (Hep2 cell IFA)

Titer ≥1:80 (>1:1,000)

Homogeneous, coarse speckled, cytoplasmic pattern



Anti-dsDNA, anti-Sm, ±APS panels

C3, C4, CH50 assay

The EULAR/ACR 2019

Entry Criterion	Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)	⦿ Yes ○ No

If absent, do not classify as SLE
If present, apply additive criteria

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.

Occurrence of a criterion on at least one occasion is sufficient.

SLE classification requires at least one clinical criterion and ≥10 points.

Criteria need not occur simultaneously.

Within each domain, only the highest weighted criterion is counted toward the total score

Aringer M, et al. Arthritis Rheumatology 2019. 71:1400-1412.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scaring alopecia	2
Oral ulcers	2
SCLE or DLE	4
ALE	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6

Clinical domains and criteria	Weight
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5 g /24 hr.	4
Renal biopsy class II or V LN	8
Renal biopsy class III or IV LN	10

Immunology domains and criteria	Weight
Antiphospholipid antibody	
Anti cardiolipin OR	
Anti β2GP1 OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA OR	
Anti-Smith	6

Aringer M, et al. Arthritis Rheumatology 2019. 71:1400-1412.

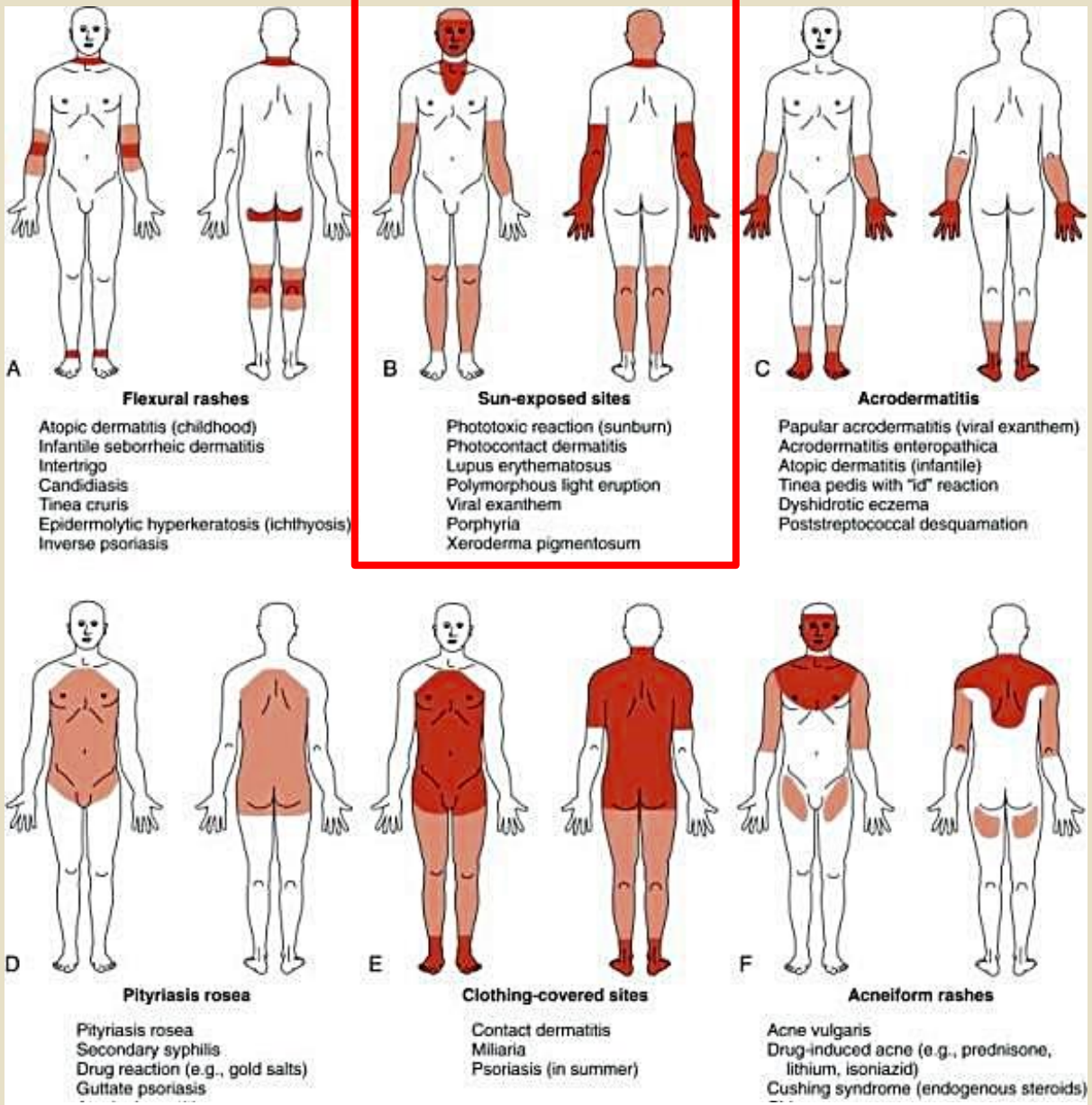
Systemic lupus erythematosus heterogeneity and subphenotypes

1) Anti-dsDNA/ Glomerulonephritis = ไข้ ข้อ skin ไต เลือด
   - *Severe SLE with glomerulonephritis*
2) Anti-Ro antibodies/ SCLE & Sjögren syndrome
   - *Photosensitivity, SCLE rashes, 2nd Sjögren syndrome, less visceral involvement*
3) Antiphospholipid antibody syndrome
   - *Occlusive vasculopathy = CTEPH, Stroke, DVT, CVST*
   - *Livedo reticularis, strokes, miscarriages*
4) SLE/mixed connective tissue disease overlap
   - *Puffy hands, arthritis, which can be erosive; Raynaud phenomenon, pulmonary hypertension, less renal involvement*

SLE: mucocutaneous

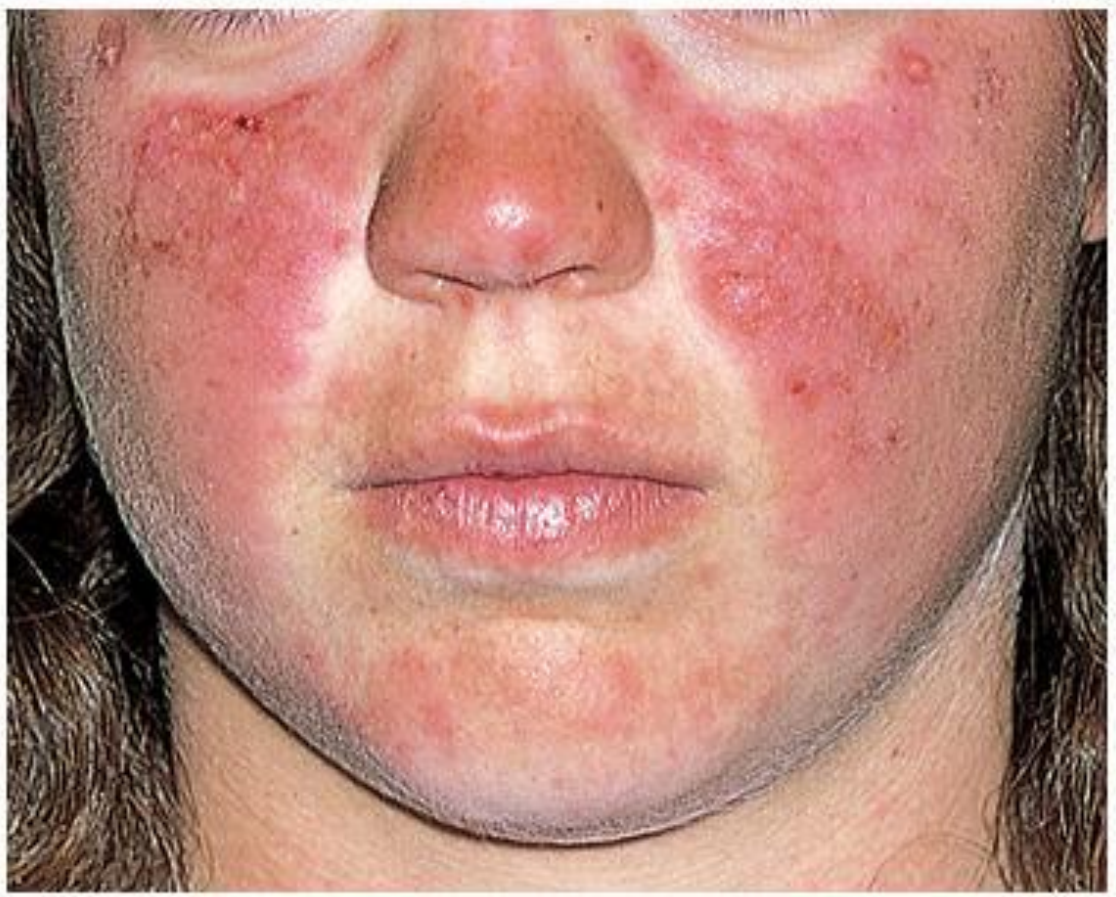
Gilliam classification of Skin Lesions Associated with Lupus

	LE specific rash	LE non-specific rash	
ACLE	Malar rash/Photosensitivity	Leukocytoclastic vasculitis Palpable purpura Urticarial vasculitis Periungual telangiectasia Livedo reticularis Thrombophlebitis Raynaud phenomenon Erythromelalgia Telogen effluvium Alopecia areata Sclerodactyly Rheumatoid nodules Calcinosis cutis	Epidermolysis bullosa Dermatitis herpetiformis Pemphigus erythematosus Bullous pemphigoid Porphyria cutanea tarda Urticaria Papulonodular mucinosis Anetoderma/cutis laxa Acanthosis nigricans Erythema multiforme Leg ulcers Lichen planus
SCLE	Annular/polycyclic Papulosquamous/ psoriasiform		
CCLE	DLE Hypertrophic DLE Lupus profundus Mucosal LE Lupus tumidus Chilblains lupus		



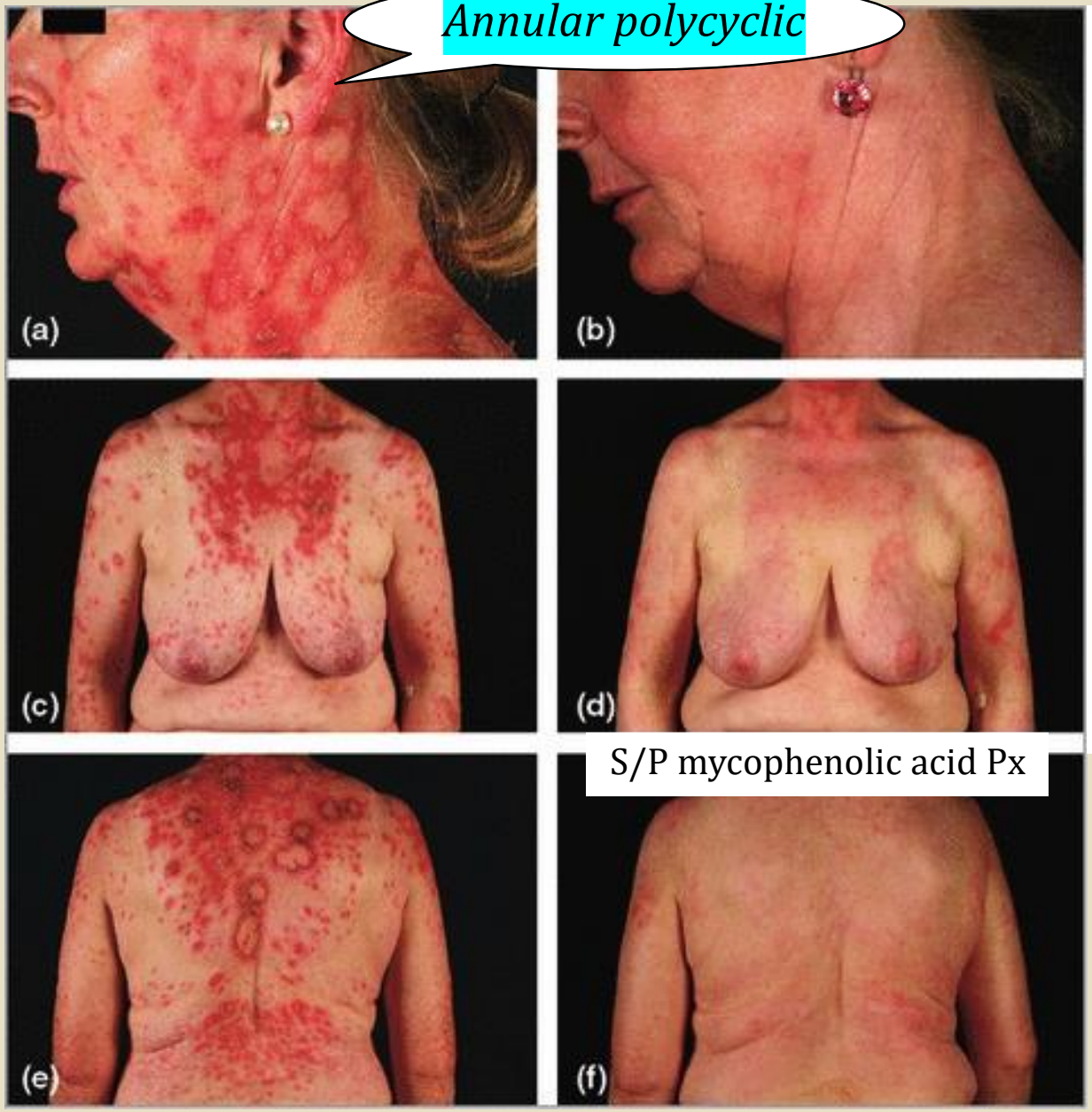
Source: malar rash – dermaamin.com/
skin sites – Oxfordmedicaleducation.com

Wing	*Nasal bridge*	*Wing*



Mala – Latin “cheek-bone”/ Spared nasolabial folds

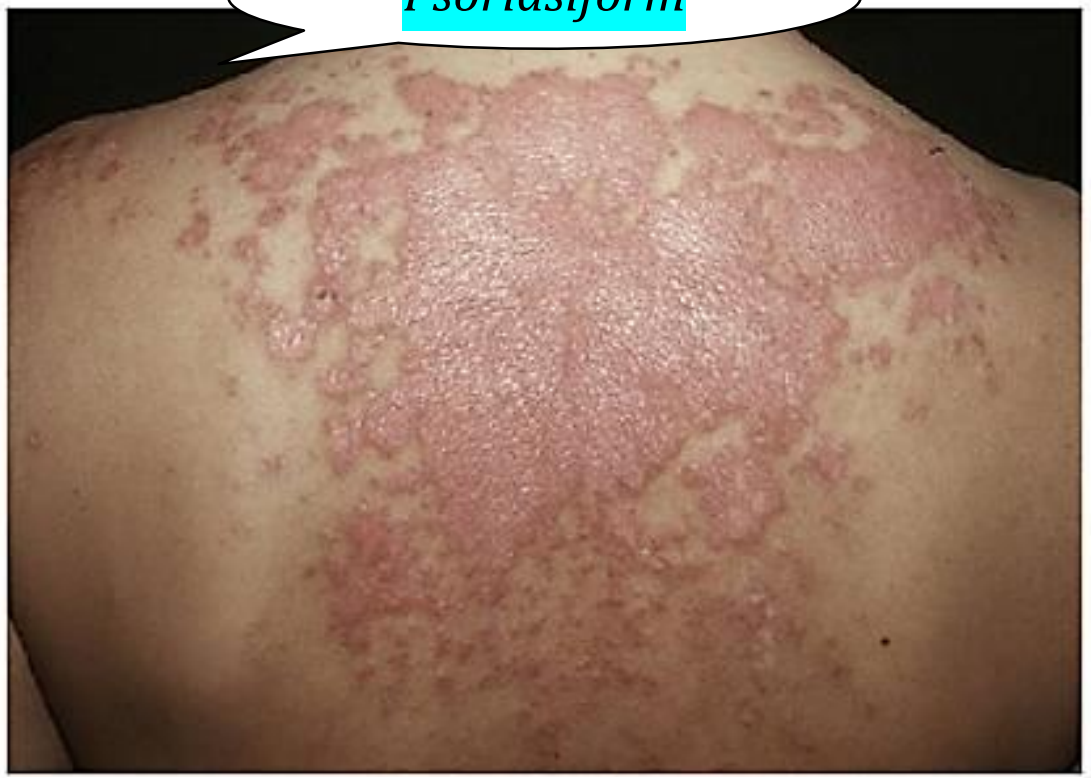
Annular polycyclic



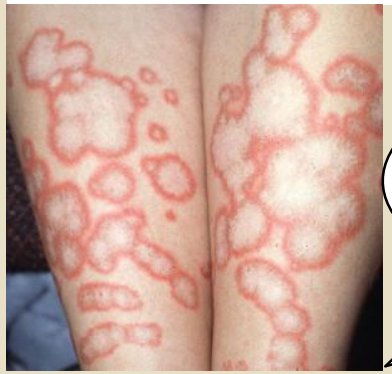
S/P mycophenolic acid Px

British Journal of Dermatology 2007;156(6):1321-7

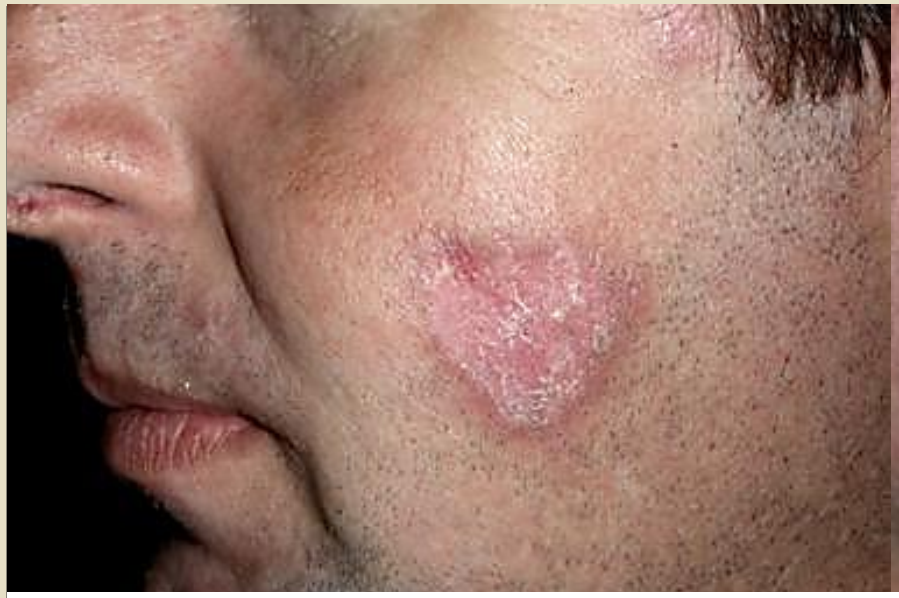
Psoriasiform



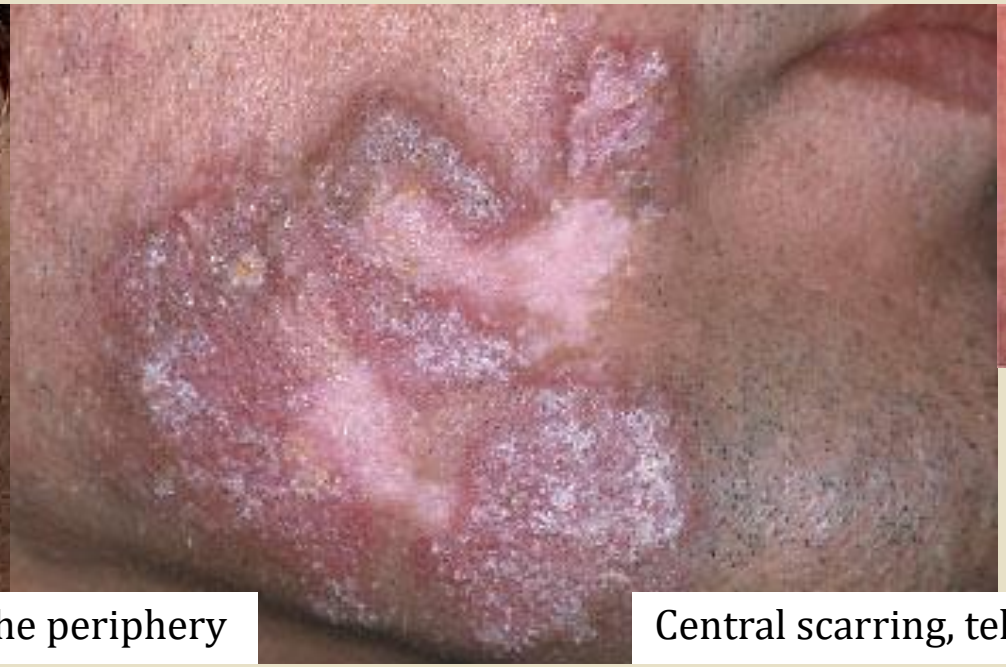
Autoimmune Diseases 2012, doi:10.1155/2012/834291



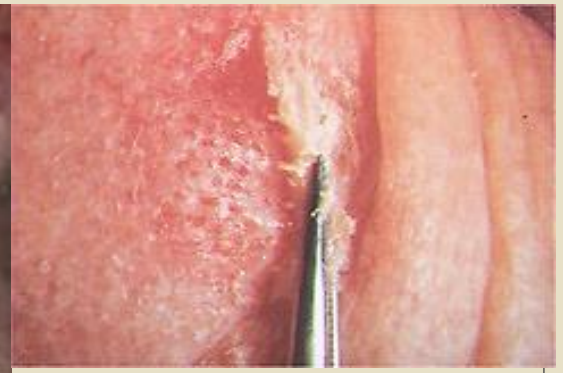
Resembled
"Erythema Marginatum"
in ARF



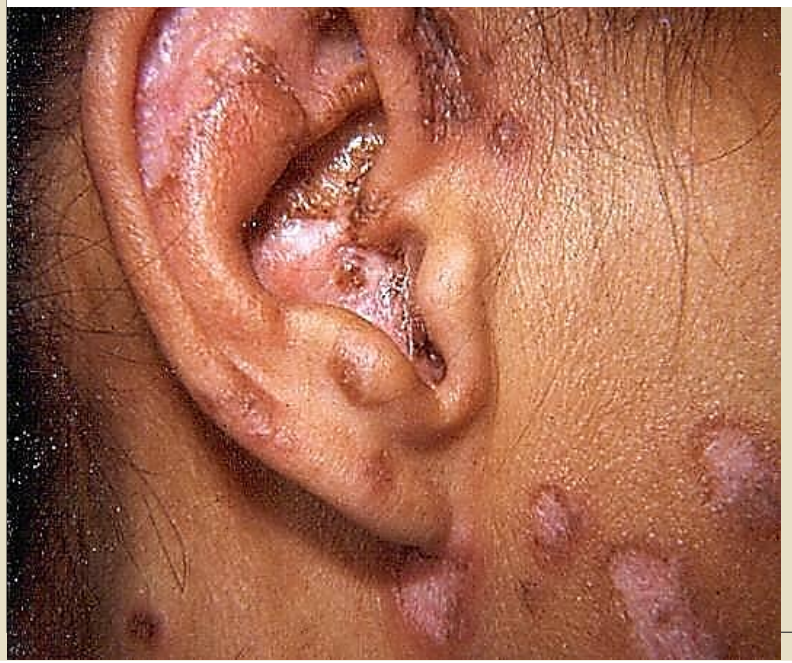
Active inflammation & hyperpigmentation at the periphery



Central scarring, telangiectasia, & depigmentation

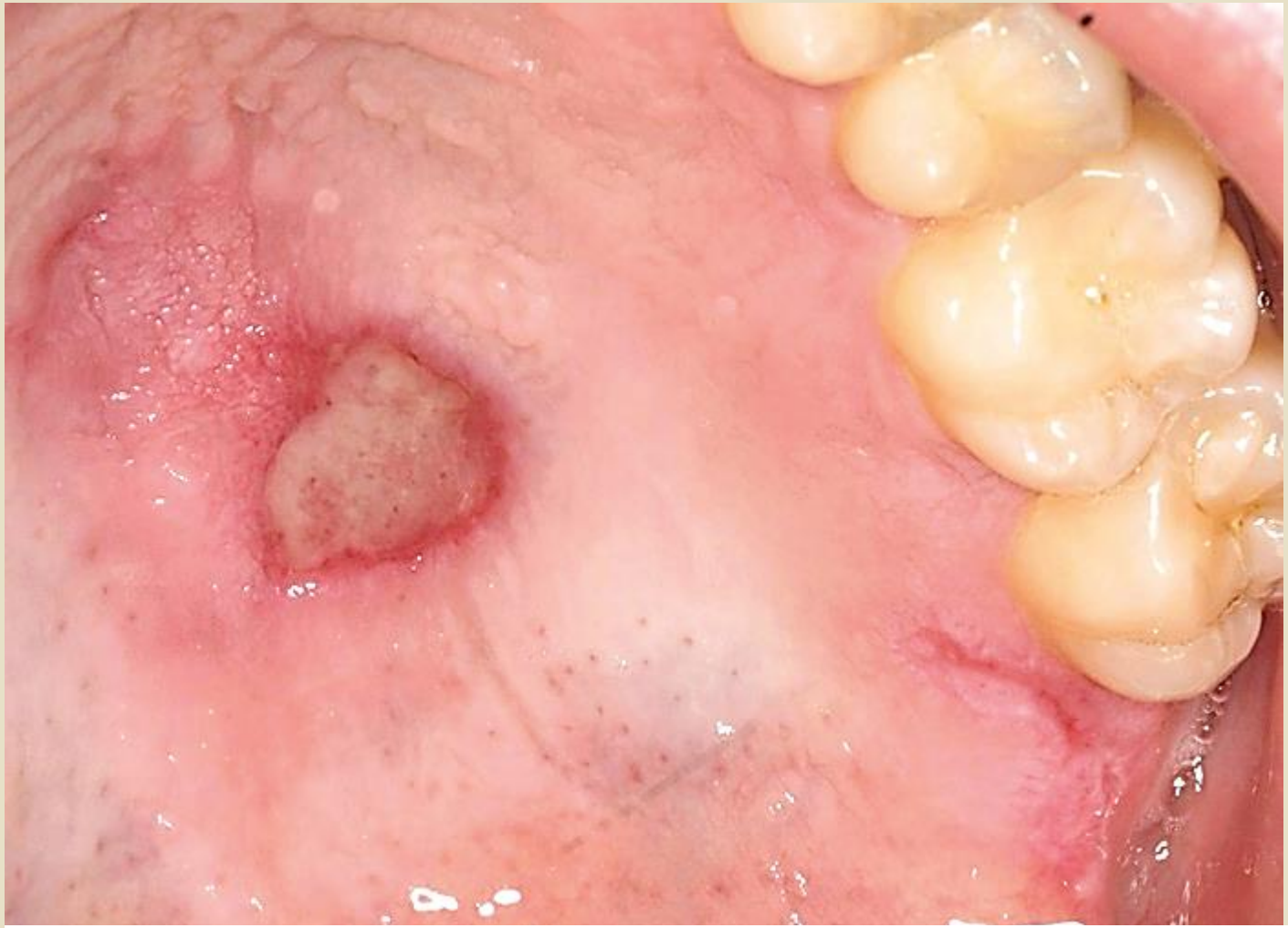


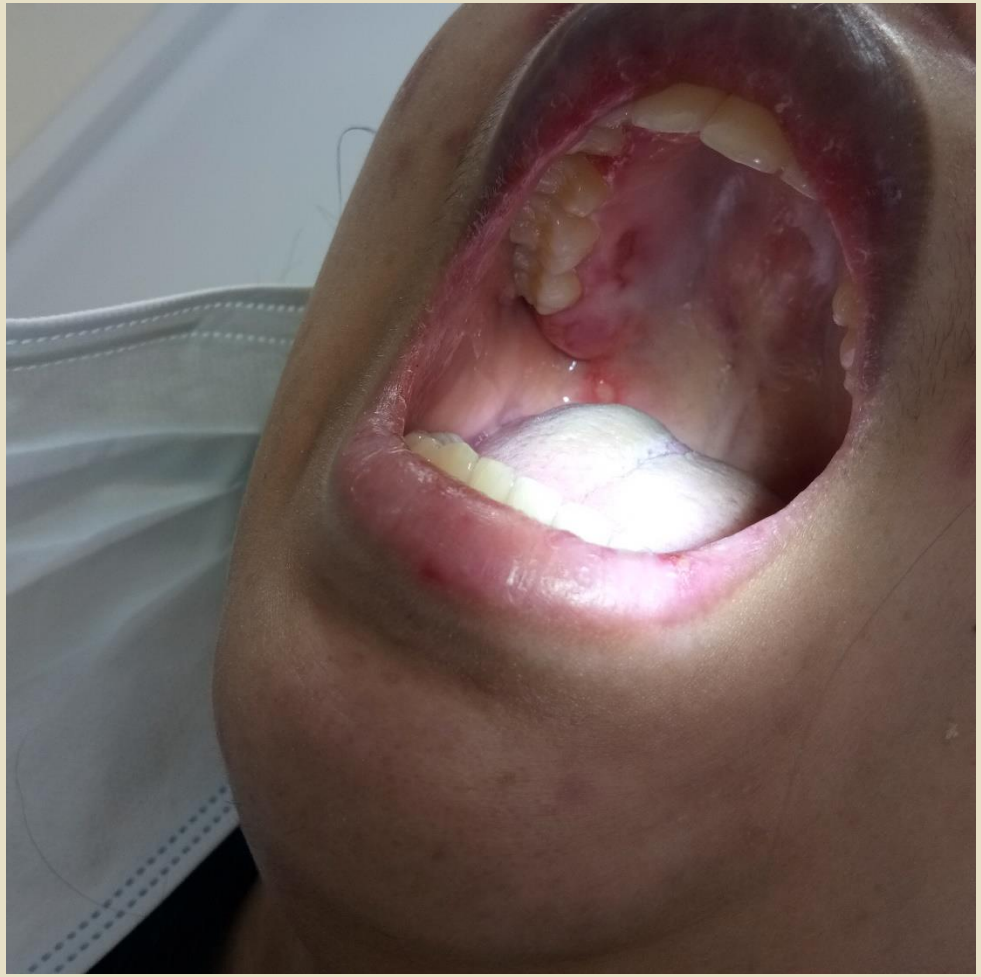
"carpet tacks sign"



DLE lesions

- Flat or slightly elevated, well-demarcated, red-purple macules or papules with a scaly surface
- Commonly evolve into larger, coin-shaped erythematous plaques *covered by* **a** prominent adherent scale that extend into dilated hair follicles
- Scales accumulate in dilated hair follicle openings





Mucosal DLE lesions = “oral ulcers”

- @beginning = painless, erythematous patch
- @chronic = chronic plaque/sharply marginated, irregular scalloped white border with radiating white striae & telangiectasias

Lupus Nephritis: clinicopathology

		BP	Cr	Anti-dsDNA +	albumin	Hb
LN 1	Asymptomatic					
LN 2	Proteinuria ~1±0.5 g/ no NS Hematuria ~57%	↔	↔	43%	↔	↔
LN 3	Proteinuria 3.4±2.4 g/ NS 18% Hematuria 63%	↔	↔	87%	↔	↔
LN 4	Proteinuria 4.7±3.3 g/ NS 33% Hematuria 74%	↑	↑	81%	↓	↓
LN 5	Proteinuria 5.1±3.8 g/ NS 42% Hematuria 33%	↔	↔	70%	↓	↔
LN 6	CKD					

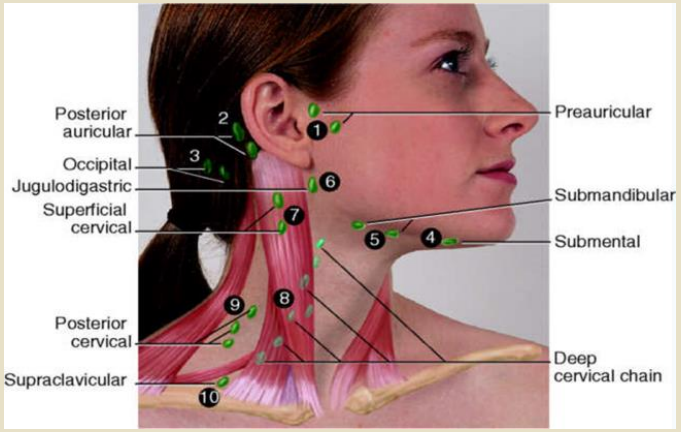
When should a renal Bx be performed?

1. Confirmation of Dx in equivocal cases
2. Determination in advanced case, whether Px is indicated

NS = nephrotic syndrome (alb <2.8 g/dL + ≥3.5g/24h proteinuria)

Bancha Satirapoj. Int J Nephrol. 2015;2015:857316.

SLE : Hematology & Lymphoid



- **LN** – 30-78%
- Regional or generalized
- Cervical or axillary
- Rubbery soft, no tenderness
- Necrotizing lymphadenitis
- ~ Kikuchi Fujimoto

- ↑ESR in SLE
- Muted CRP response in SLE by ↑expression of type I IFN

- 70% ACD, 20% AIHA/IgG
- PRCA (rare)
- HPS (rare – 2.4%) @onset/flare/infection-induced

- AIHA: anti-erythrocyte IgG: RBC
  - Phagocytoses by splenic macrophages
- Coombs Test:
  - antierythrocyte IgG=RBC=Anti-IgG
  - → RBC precipitation
  - + 20-66% of SLE
- 20% SLE has AIHA/ 6% AIHA has SLE

- **WBC**: ↓WC (50%); 2,000 < X < 4,500; lymphopenia (75%)/neutropenia
- **Platelets**: <100K: ITP (7-30%), TTP – anti ADAMTs13 (1-4%)

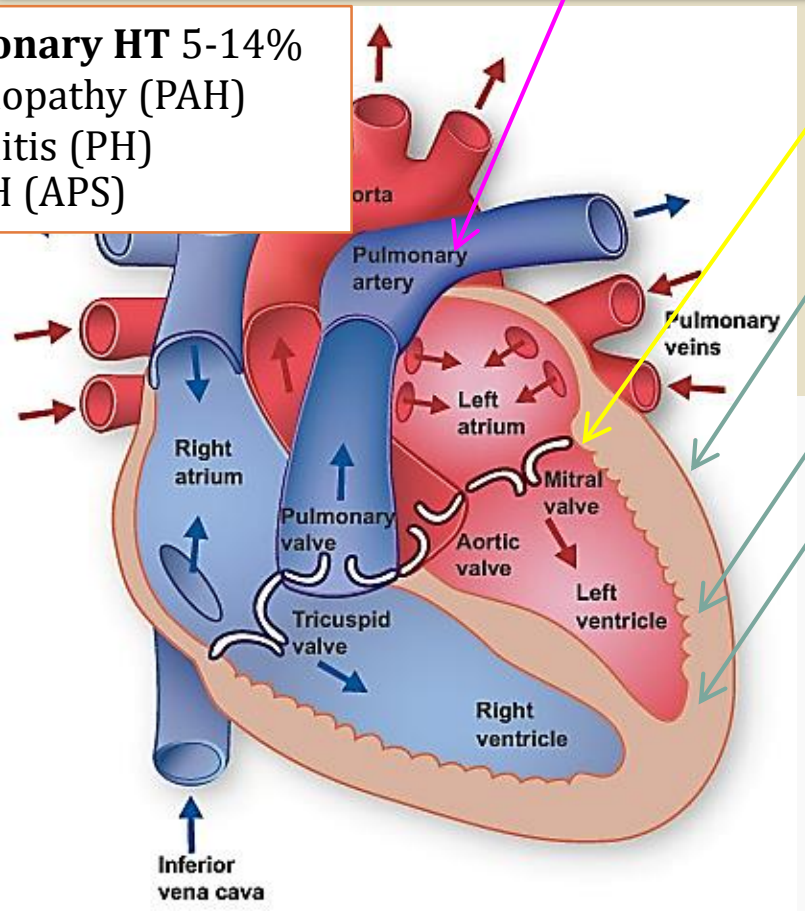
1st 5-yr: Pleuro-pericarditis
acute/chronic ILD
PH-vasculitis
>5-yr: PAH (vasculopathy)
All course: CTEPH

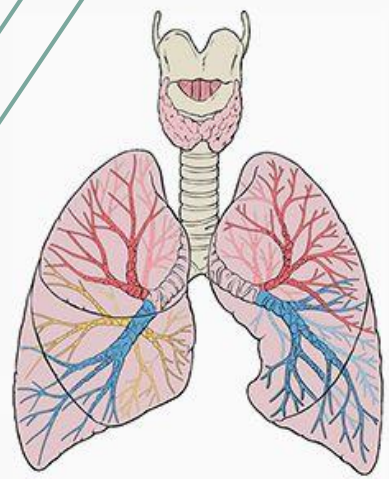
SLE : CV & RS

5 PE (APS)

1st 5 years

6 **Pulmonary HT** 5-14%
Vasculopathy (PAH)
Vasculitis (PH)
CTEPH (APS)





4 asymptomatic Libman-Sacks ~50%
MV; histopatho. Indistinguishable from IE

1 Symptomatic pericarditis 25%
Cardiac tamponade 1-3%
Effusion +ANA, +anti-dsDNA, LE cell

2 Symptomatic myocarditis <10%

3 Conduction defect (1st -2nd AVB)

- Pleuritis – small 400-1000 ml
  exudate>transudate; PMN >50%
  glucose >60 mg/dL/ >0.5 ratio
  pH >7.33; (+)LE cell, ANA ratio >1
- *Lupus pneumonitis (1-7%) 1st 5 years*
- *DAH (1.6-3.7%) 1st 5 years*
- *SLE-ILD →NSIP/UIP (chronic)*
- *Reversible hypoxemia*
- *Shrinking lung syndrome - diaphragm↓*
- *BO & OP*
- *Laryngitis/VC paralysis/epiglotitis*

SLE : nervous system

Within 3 – 5 years

Organic

CNS

7-20%
GTC 67-88%

Seizure

non Seizure

Aseptic meningitis <1%
Cerebrovascular disease 5-18%
Demyelinating syndrome <1% (MS/ Devic)
Headache 24-72% (migraine/tension)
(pseudo tumor cerebri <1%)
Movement disorder <1% (unilateral chorea)
Myelopathy 1%
Acute confusional state 4-7%
Cognitive dysfunction 11-54%

PNS

Guilain-Barre syndrome <1%
Autonomic neuropathy <1%
Myasthenia gravis <1%
Cranial neuropathy 1%
(CN3,CN6,CN5,CN7, CN2)
Mononeuropathy <1%
Polyneuropathy 2-21% (distal symmetrical sensorimotor axonopathy)
Plexonopathy <1%

Psychiatric

Anxiety 4-8%
Mood disorder 24-57%
Psychosis 2-11%

- Aseptic meningitis CSF: WC <200, predominately Lymphocyte, normal glucose, protein <100 mg/dL
- CVD usually ischemic (80%) occur within 1st 5 years of the onset od SLE, small to large vessel involvement, vasculitis/thrombosis/embolic/APS
- Myelitis CSF: ↑WC, ↑protein, ↓Glucose 50% to serum

% = cumulative prevalence

SLE : GI & Hepatic manifestations (1)

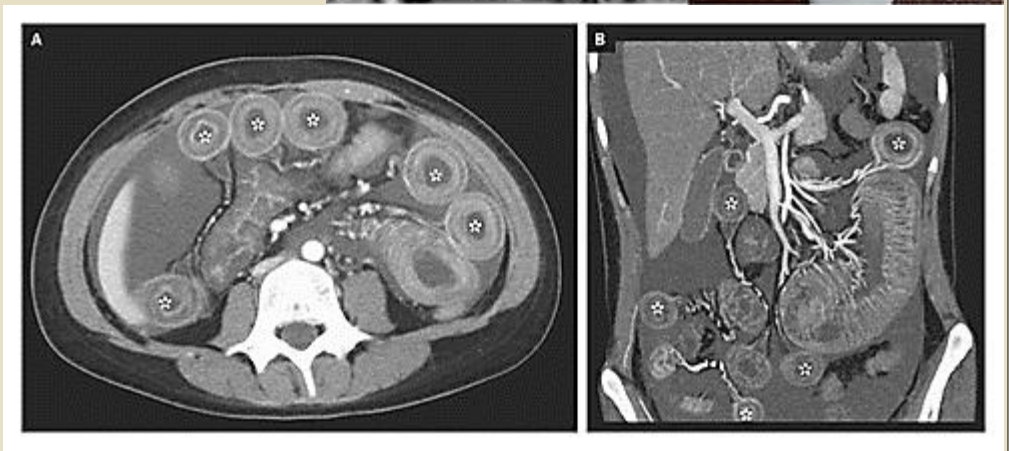
Exclude non-lupus cause

1. **Protein-losing enteropathy**
   - Abdominal pain ±diarrhea, hypoalbuminemia, no proteinuria
   - Tc-99 albumin scintigraphy
   - Double-contrast SBFT enteritis vs.. enteropathy
     - *Lupus enteritis*: irregular spiculation & thickening, thumbprinting mucosa → ischemia
     - *Protein-losing enteropathy*: thickened folds with nodules (lymphangiectasia on Bx)
2. **Ascites (8-12%)**
   - Acute ← lupus peritonitis, pancreatitis, mesenteric vasculitis
   - Chronic ← lupus peritonitis, serositis, NS, Budd-Chiari (APS), protein-losing enteropathy
3. **Pancreatitis (4%)**
   - Abdominal pain, N/V, fever

SLE : GI & Hepatic manifestations (2)

Exclude non-lupus cause

5. **Mesenteric vasculitis (2.2-9.7%)**
   - Abdominal angina, N/V, fever, GIH
   - Contrast CT abdomen: palisade & **comb like** pattern of vessels
   - Diffuse circumferential wall thickening with submucosal edema of the entire small bowel, showing the "**double halo**," or "**target**," sign
6. **Intestinal pseudo gut obstruction (1.96%)**
   - Acute vs. chronic
   - 65 – 75% concomitant bilateral *ureterohydronephrosis*
   - 1 – 10% hepatobiliary dilatation – *megacholedochus*
   - Myositis of intestinal muscularis propria
7. **APS associated hepatopathy**
   1. Budd-Chiari syndrome
   2. Hepatic venoocclusive disease
   3. Nodular regenerative hyperplasia
   4. Liver infarction
   5. Transient elevation of hepatic enzymes resulting from multiple fibrin thrombi



SLE : GI & Hepatic manifestations (3)

1st 5-yr: occurs along w/ other organs

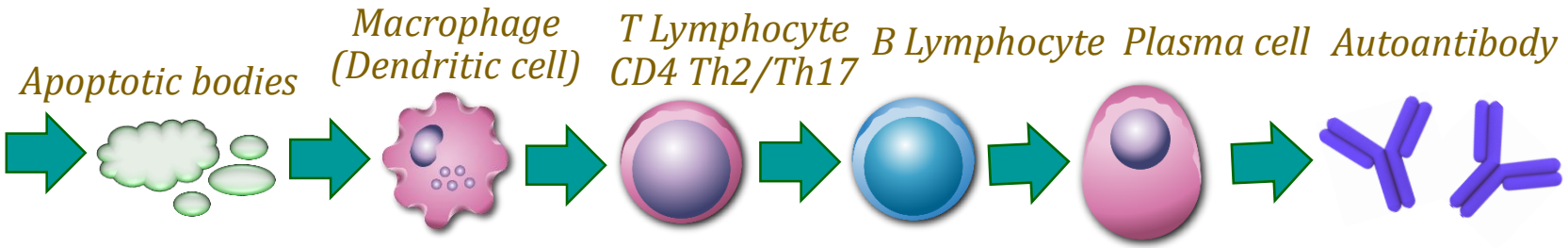
Exclude non-lupus cause

Lupus hepatitis	Autoimmune (lupoid) hepatitis (4.7%)		
Insidious onset of transaminitis AST & ALT elevations <3X	Insidious onset of transaminitis Can be found in SLE, RA, Hashimoto, UC, DM		
Frequently (+) anti-ribosomal P	**Type 1** ANA±anti-SMAs	**Type 2** Anti-LKM1	**Type 3** Anti-SLA/LP
Bx: lymphocytic infiltration of periportal areas w/ isolated areas of necrosis	Bx (type 1): periportal piecemeal necrosis, dense lymphoid infiltrates, prominent plasma cells ↑ANA, ↑globulin (IgG)		

>5-yr: occurs non-concurrent w/other organs

- SMA = **S**mooth **M**uscle **A**ctin
- LKM1 = **L**iver-**K**idney-**M**icrosomal type **1** (Ab against CYP P450 2D6)
- SLA/LP = **S**oluble **L**iver **A**ntigen/**L**iver **P**ancreas

SLE Treatment



Triggers

UVB
Virus
Bacteria
Drugs

Correct

Autoimmunity → Tissue injury ±Damages

Stop immune – mediated tissue inflammation

Prednisolone (5)
3 x 2 pc x 4 wk.
3-0-2 pc 1 wk.
2-0-2 pc 1 wk.
3 x 1 pc 2 wk. → 2½ x 1 2 wk.
2 x 1 2 wk. → 1½ x 1 2 wk.
1 x 1 2 wk. → ½ x 1 2 wk.
½ x 1 AD 2 wk. → off

Induction Px

Minor organ (non life-threatening): Fever, malar rash, arthritis, serositis

: NSAIDS 2 – 4 wks.

: Prednisolone ≤0.5 MKD 2 – 4 wks. → Taper off

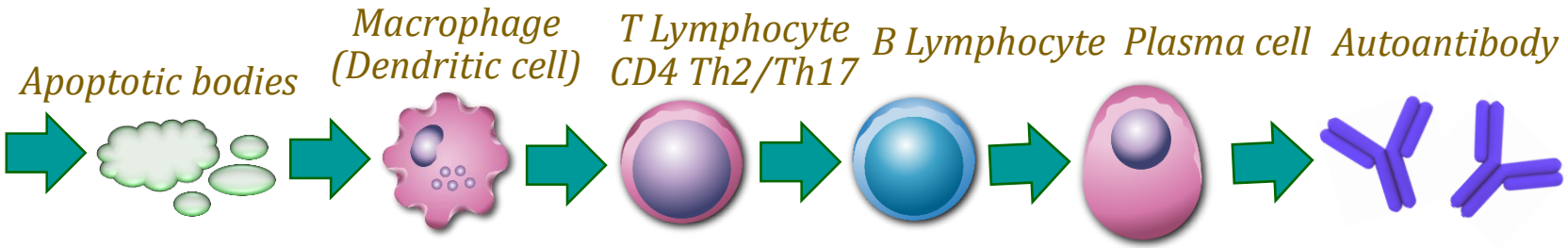
Prevention of (relapse) further damages

Maintenance Px

: Chloroquine 3 MKD [250 mg/tab ½ tab po OD] or Hydroxychloroquine 5 MKD [200 mg/tab OD]
If inadequate control, add Methotrexate (2.5) 2 tab po weekly titrate to (max) 8 tab po weekly [+ folic acid 5 mg/day]
Or Azathioprine 0.5 – 1 MKD Or (add) Leflunomide (20) 1 tab po weekly to 1 x 1
Or (change to) MMF max 3 g/D or Cyclosporine 0.5 – 2.5 MKD

Fanouriakis A, et al. Ann Rheum Dis 2020;79:713–723.

SLE Treatment



Triggers

UVB
Virus
Bacteria
Drugs

Correct

Autoimmunity

Tissue injury ±Damages

Stop immune – mediated tissue inflammation

Prednisolone (5)
↓ 5-10 mg/d q 1–2 wk to 40 mg/d
↓5 mg/d q 1–2 wk to 20 mg/d
↓1 – 2.5 mg/d q 2 wk
To off

Induction Px

Major organ: *AIHA Hb <8 g/dL, ITP <50K, Bleeding, LN type 3, 4, 5, Nervous system*

: Prednisolone 1 MKD 4 - 8 wks. Or Dexamethasone in an equivalent dose Or

: Methylprednisolone 1 g in NSS 100 ml IV drip in 1 hr. 3 – 5 d → Prednisolone 0.5 MKD 4 – 8 wk.
(life-threatening condition: RPGN, DAH, Seizure)

: Cyclophosphamide

NIH regimen: 0.5 – 0.75/BSA (m^2) in NSS 100 mL drip in 1 hr. q 1 month x 6 (total 6 months) [LN W/ AKI, LN 5]

EURO Lupus regimen: 0.5 g in NSS 100 mL drip in 1 hr. q 2 wk. x 6 (total 3 months) [LN 3, 4, ±5 W/O AKI]

: Mycophenolate mofetil 2 – 3 g/day x 6 months [LN 3, 4, 5 W/O AKI]

: MMF 1 – 2 g/day + TAC 2-3 g/day x 6 months [LN V] or TAC 0.08 MKD [LN 5]

Prevention of (relapse) further damages

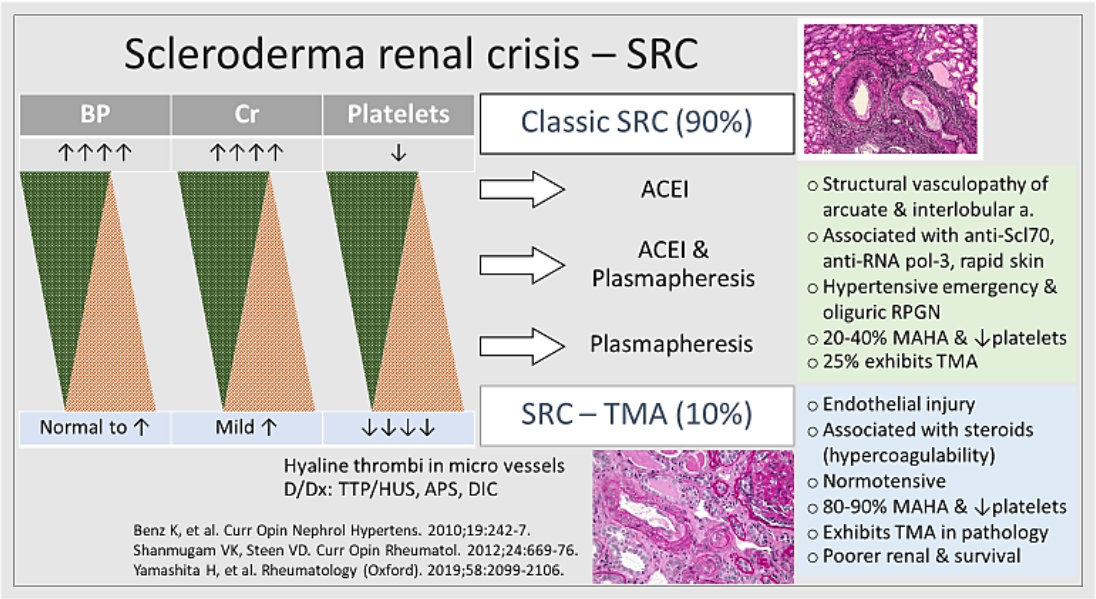
Maintenance Px

: CQ (3 MKD) + Azathioprine 1 – 2 MKD OR Mycophenolate mofetil 1 – 1.5 g/day x 6 months

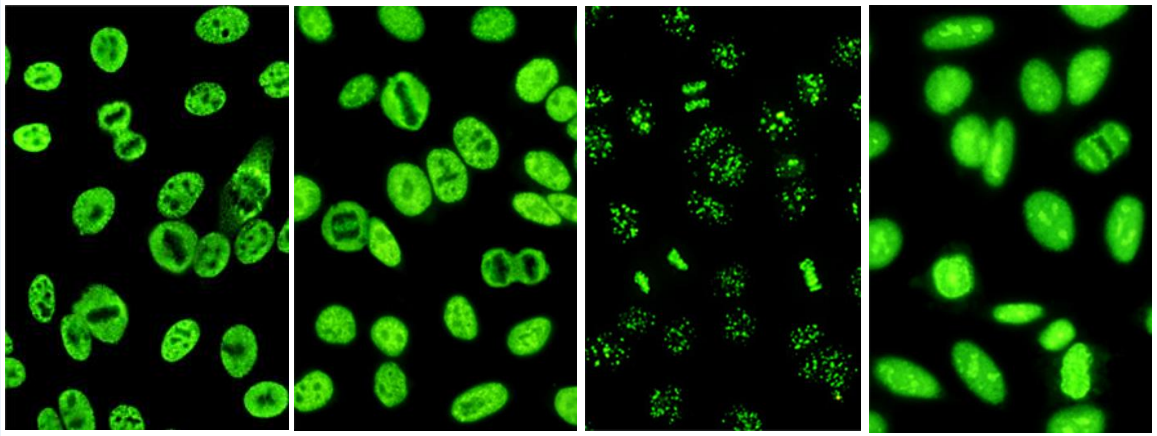
Clinical scenario suspected SSc

A late adult woman presents with

Raynaud, puffy fingers, sclerodactyly,
Scleroderma (skin thickening beyond MCP joint)
Digital ischemic complications, GERD, ILD
AKI, rising Cr in RPGN pattern
Accelerated malignant HT
(within 5-year disease duration)
5% SSc, 15% dcSSc (early)



ANA (Hep2 cell IFA)
Titer ≥1:80 (>1:1,000)
Coarse/Fine/Discrete speckled,
Nucleolar pattern



Anti-Scl70, Anti-centromere

GN occurs in late lcSSc; overlap ANCA GN should be in the differential diagnosis

SSc disease evolution

Matucci-Cerinic M, et al. Ann Rheum Dis. 2009; 68: 1377-80.
Koenig M, et al. Arthritis Rheum. 2008; 58: 3902-12.
Valentini G, et al. Rheumatology 2011; 50: 317-23.
Avouac J, et al. Ann Rheum Dis. 2010; 69: 128.
Sakkas L, et al. Clin Rheumatol. 2015; 34: 1327-31.

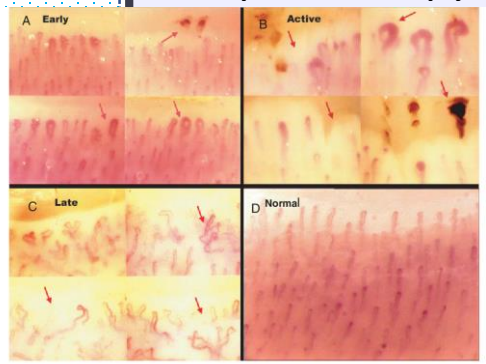
mRSS

*ACR/EULAR 2013

Auto Ab only
1 SSc specific Ab
(Non-disease)

Very early SSc
1 Raynaud
2 SSc specific Ab
3 Capillaroscopy

Early SSc
1 Raynaud
2 SSc specific Ab
3 Capillaroscopy
4 Puffy fingers
5 Arthritis



SSc pattern: B active SSc pattern; C late SSc pattern and D normal pattern (magnification 200×)

การตรวจพบหลัก	การตรวจพบรอง	คะแนนการวินิจฉัย
Proximal scleroderma		9
Sclerodactyly (นับข้อที่มีคะแนนสูงสุด)	1. Puffy fingers 2. Sclerodactyly	2 4
Fingertip lesions (นับข้อที่มีคะแนนสูงสุด)	1. Digital tip ulcers 2. Fingertip pitting scars	2 3
Telangiectasia		2
SSc-pattern nailfold capillaroscopy		2
Pulmonary arterial hypertension and/or interstitial lung disease (คะแนนสูงสุดเท่ากับ 2)	1. Pulmonary arterial hypertension 2. Interstitial lung disease	2 2
Raynaud's phenomenon		3
SSc-related autoantibody (คะแนนสูงสุดเท่ากับ 3)	1. Anti-centromere 2. Anti-topoisomerase-I (Scl-70) 3. Anti RNA polymerase III	3

Digital ulcers
Scleroderma
Interstitial lung
Renal crisis
GERD

PAH

dcSSc

lcSSc

Disease flare

Disease flare

edematous *fibrotic* *atrophic*

Yr.

5 5 5

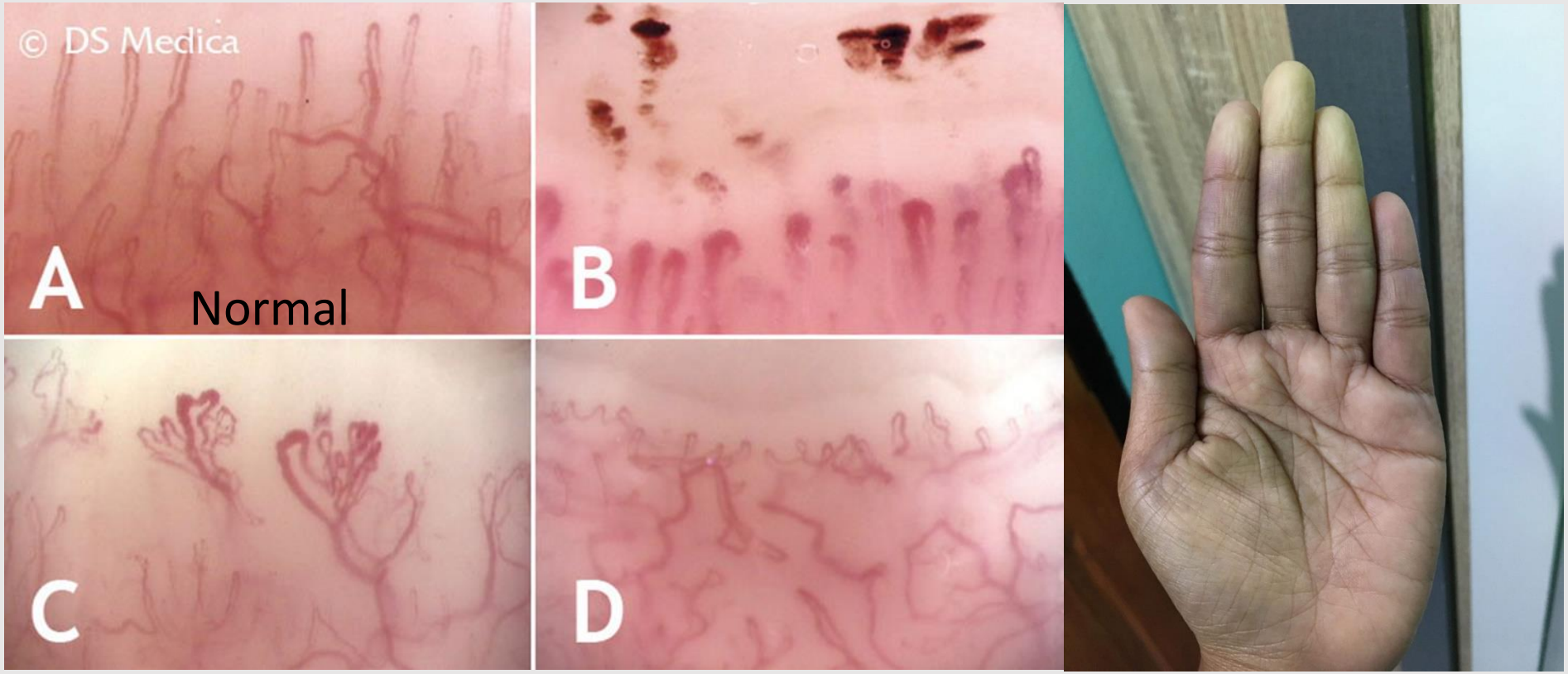
RP symptom

Non RP symptom

Other disease subsets
Sine SSc = RP, DU, PAH, and SSc specific Ab
SSc overlap

Raynaud phenomenon & Digital ischemic complications

Nail fold capillaroscopy



- Endothelial injury is an initiating event in SSc that manifests as RP (95% of SSc)
- D/Dx primary RP VS SSc-RP (secondary RP) is essential

Pic from: http://www.capillaroscopia.it/html/cnt/en/rheumatology.asp

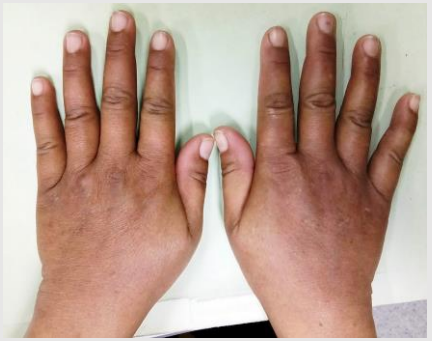
Primary RP (Raynaud disease) VS. SSc-RP

<10% in general population

1º Raynaud	2º Raynaud
Pallor → Cyanosis → Redness	Pallor → Cyanosis
< 40 years; F:M = 3:1	≥ 40 years
No ischemic complications	Ischemic complications

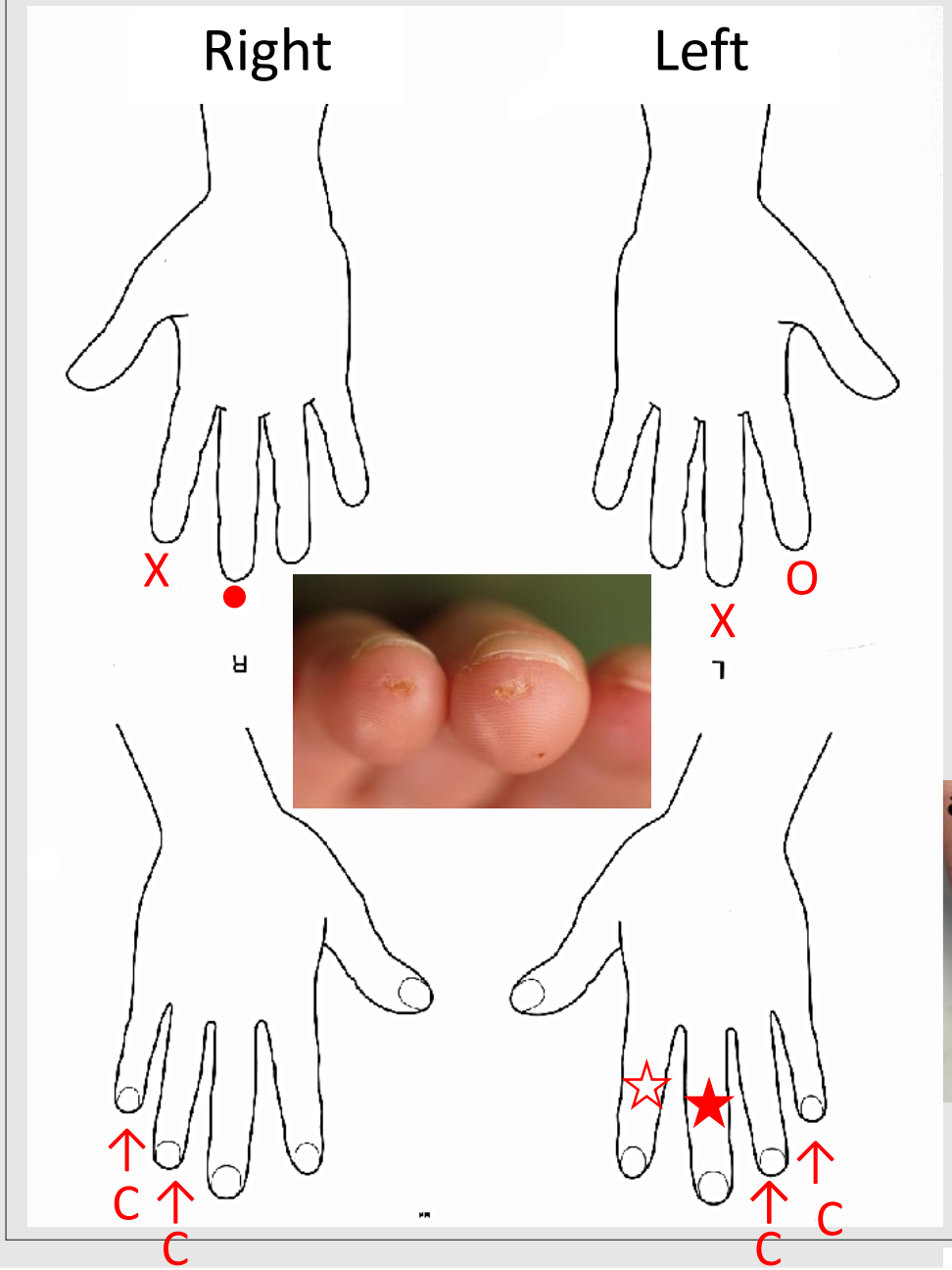
Red flags for SSc – RP
Skin: puffy finger*, sclerodactyly, digital ulcer/pitting scar
GI: GERD*
Serology: +ANA*, SSc specific Ab
* character of early scleroderma

AND



1. +ANA (95%), ATA or ACA → **SSc**
2. +ANA >1:1600, +anti-U1RNP
   anti-dsDNA & anti-Sm neg. → **MCTD**
3. +ANA ≥1:80, +anti-dsDNA or anti-Sm → **SLE**
4. + or – ANA w/o specific antibody → **UCTD**

Pope J, et al. BMJ Clin Evid. 2013; 2013: 1119.
Ann Rheum Dis. 2009; 68:1377-80.
Ann Rheum Dis. Published Online First: 12 Aug 2013 doi: 10.1136/annrheumdis-2013-203716



R: Raynaud (Yes VS No)

P: Puffy finger (Yes VS No)

C: Contracture

↑: digital pulp loss

X : digital pitting scar

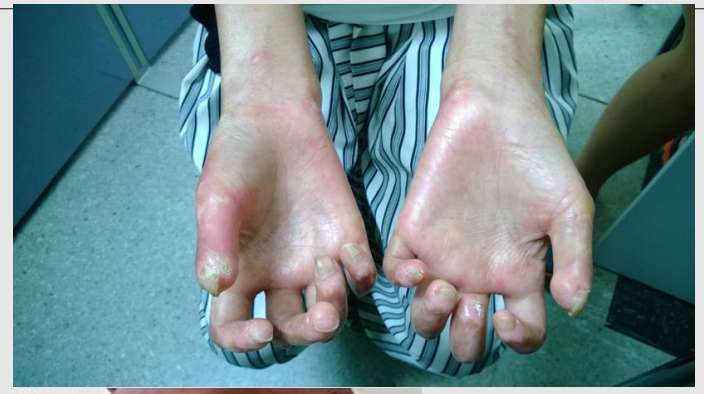
o : digital tip ulcer – active

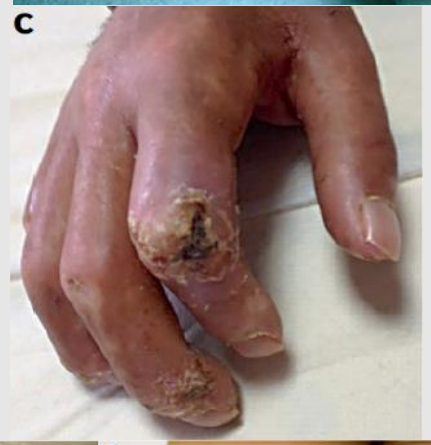
● : digital tip ulcer – heal

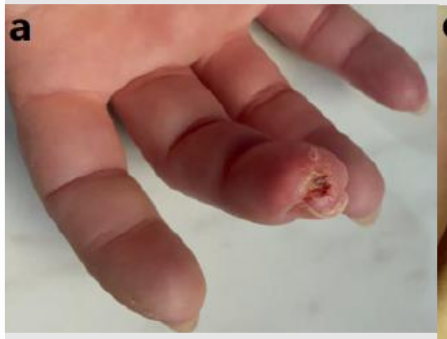
: digital tip gangrene

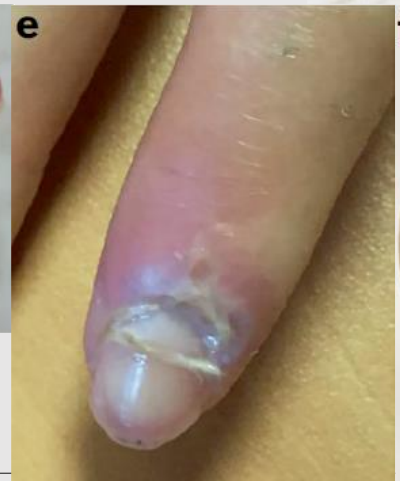
A : digital tip amputation

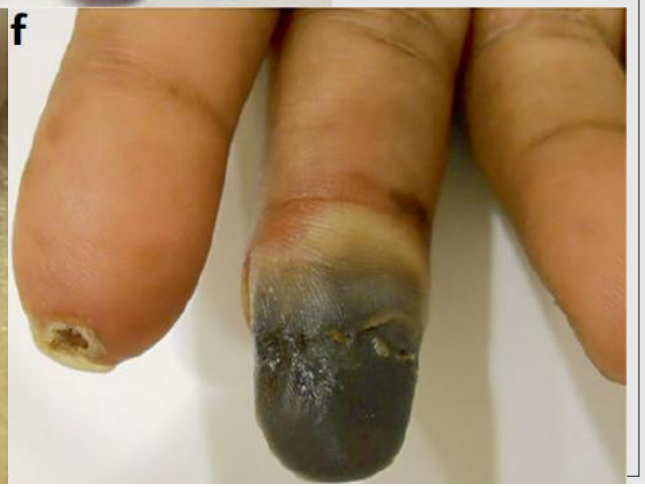
☆ : finger (non-tip) ulcer





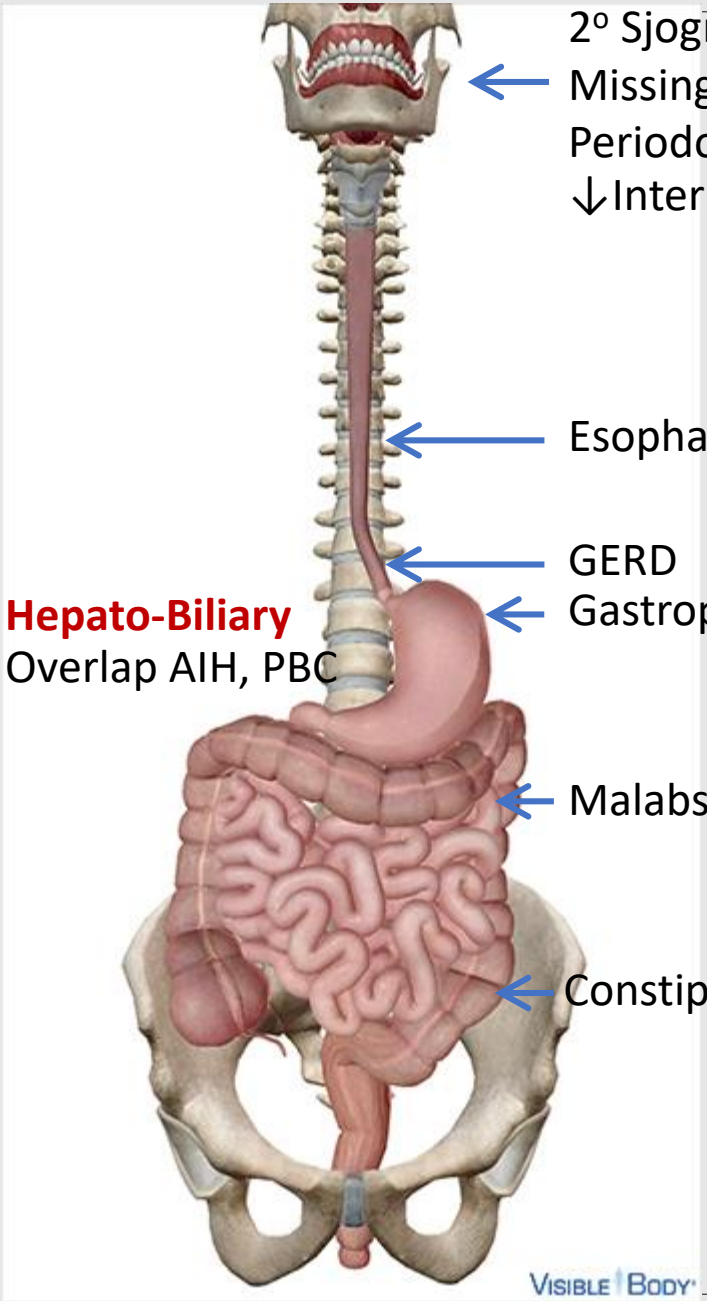






Hughes M, et al. Nat Rev Rheumatol. 2020; 16: 208-221.

Scleroderma GI involvement



1st 5 yr.

Pathophysiology of SSc – GI (4 stages)

1. Vasculopathy → GAVE
2. Neural dysfunction → dysphagia, GERD
3. Smooth muscle atrophy
4. Tissue fibrosis

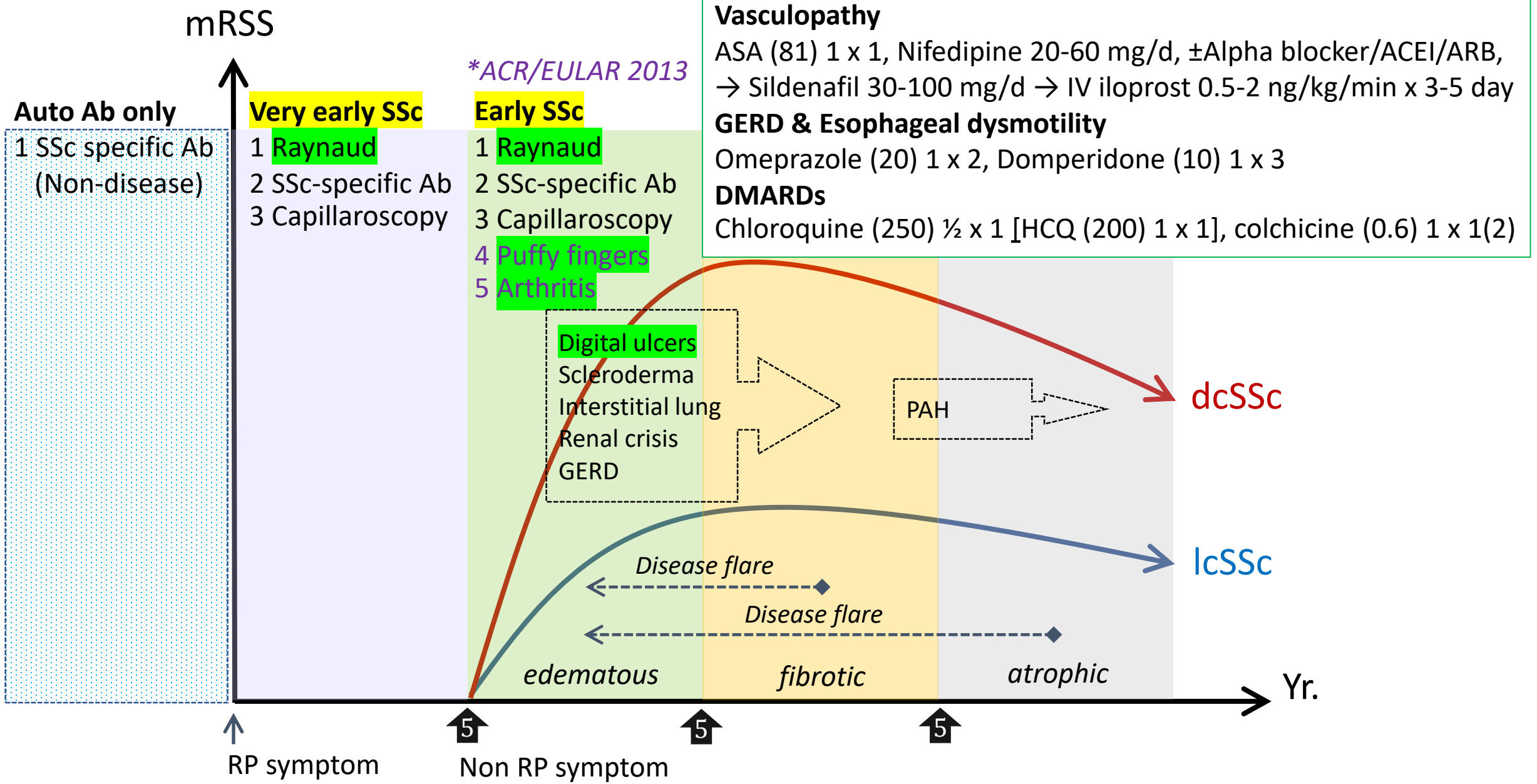
OPD assessment questions

1. Difficulty "retrosternal" swallowing
2. Acid taste in the oro-pharynx
3. Feeling heartburn
4. (postprandial) Regurgitation-supine
5. Early satiety
6. Constipation/ Overflow diarrhea (SIBO)

OPD PE and Lab assessments

- ΔBW (5% -1 Mo; 7.5% -3 Mo; BMI <18.5 kg/m^2)
- Hb (IDA), ↓WBC, ↓albumin <u>(malnutrition)</u>
- AST/ALT <u>(AIH)</u>

SSc Px in very early & early SSc



Vasculopathy
ASA (81) 1 x 1, Nifedipine 20-60 mg/d, ±Alpha blocker/ACEI/ARB, → Sildenafil 30-100 mg/d → IV iloprost 0.5-2 ng/kg/min x 3-5 day

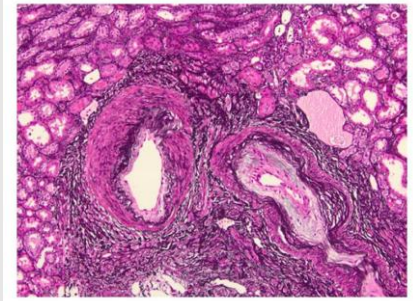
GERD & Esophageal dysmotility
Omeprazole (20) 1 x 2, Domperidone (10) 1 x 3

DMARDs
Chloroquine (250) ½ x 1 [HCQ (200) 1 x 1], colchicine (0.6) 1 x 1(2)

Scleroderma renal crisis – SRC

BP	Cr	Platelets
↑↑↑↑	↑↑↑↑	↓
Normal to ↑	Mild ↑	↓↓↓↓

Classic SRC (90%)



→ ACEI

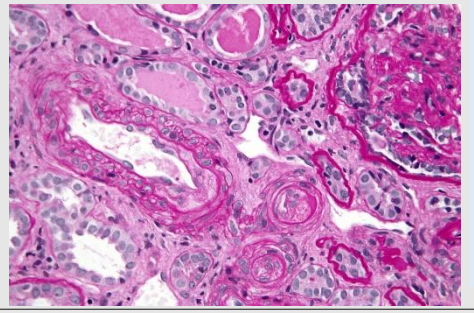
→ ACEI & Plasmapheresis

→ Plasmapheresis

- Structural vasculopathy of arcuate & interlobular a.
- Associated with anti-Scl70, anti-RNA pol-3, rapid skin
- Hypertensive emergency & oliguric RPGN
- 20-40% MAHA & ↓platelets
- 25% exhibits TMA

SRC – TMA (10%)

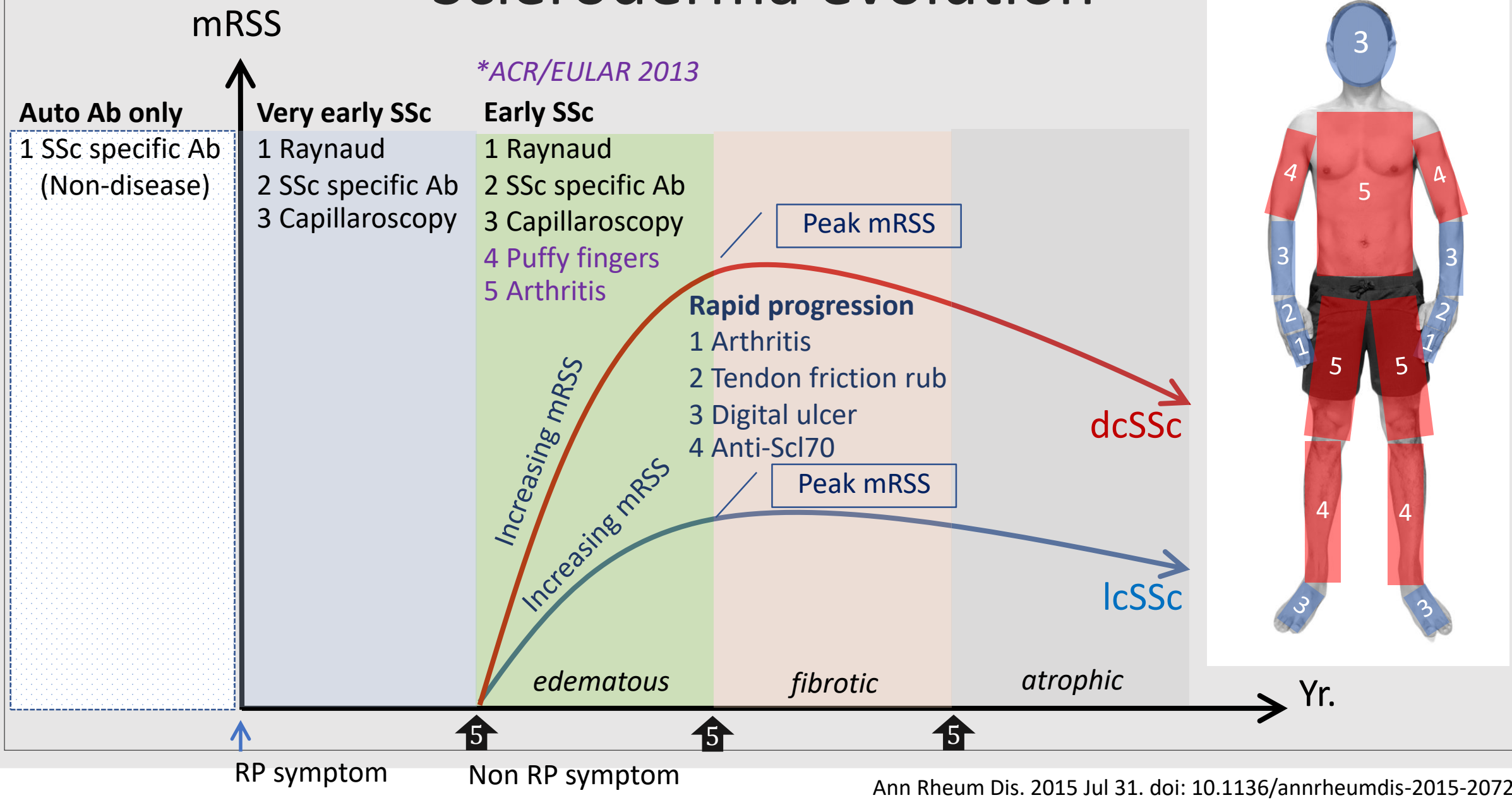
Hyaline thrombi in micro vessels
D/Dx: TTP/HUS, APS, DIC



- Endothelial injury
- Associated with steroids (hypercoagulability)
- Normotensive
- 80-90% MAHA & ↓platelets
- Exhibits TMA in pathology
- Poorer renal & survival

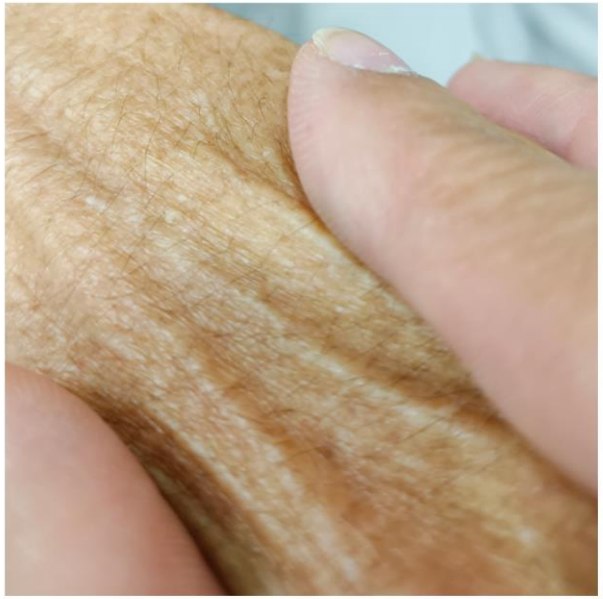
Benz K, et al. Curr Opin Nephrol Hypertens. 2010;19:242-7.
Shanmugam VK, Steen VD. Curr Opin Rheumatol. 2012;24:669-76.
Yamashita H, et al. Rheumatology (Oxford). 2019;58:2099-2106.

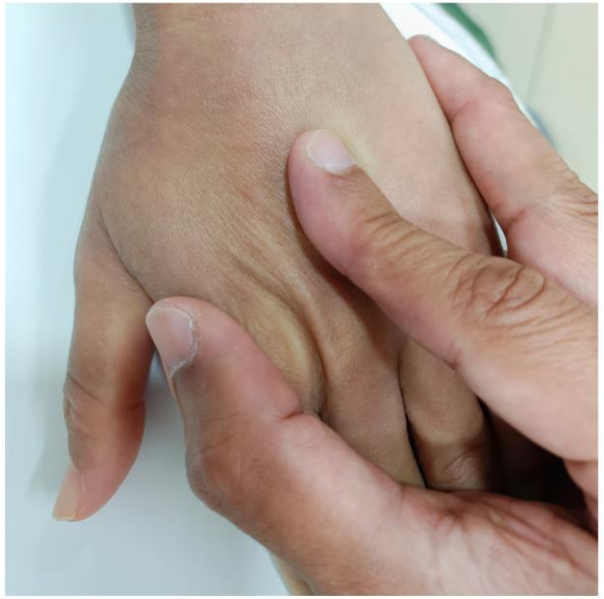
Scleroderma evolution



Ann Rheum Dis. 2015 Jul 31. doi: 10.1136/annrheumdis-2015-207271.

0



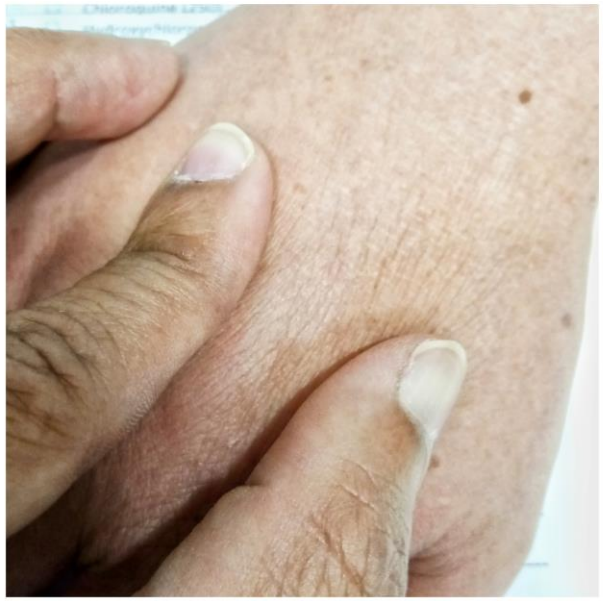


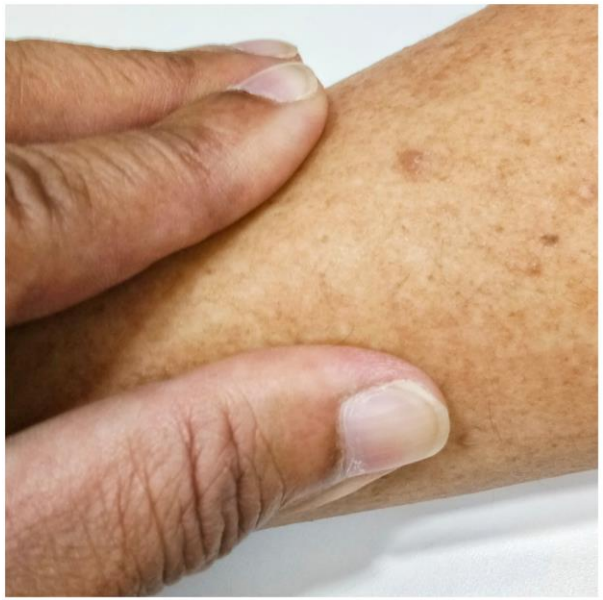
1

Score 0 = Skin fold ปกติ ดัน/ดึงขึ้นได้ skin crease บางละเอียด

Score 1 = Skin fold หนา ดัน/ดึงขึ้นได้ ยังสังเกตพบ skin crease

Score 2 = Skin fold หนา ดัน/ดึงขึ้นได้ยาก skin crease ลดลงมาก





Score 3 = ไม่สามารถดัน/ดึงให้เกิด skin fold ได้ ไม่พบ skin crease

2

3

Khanna D, et al. J Scleroderma Relat Disord. 2017;2:11-18.

17 body areas assessment for **modified Rodnan skin score**

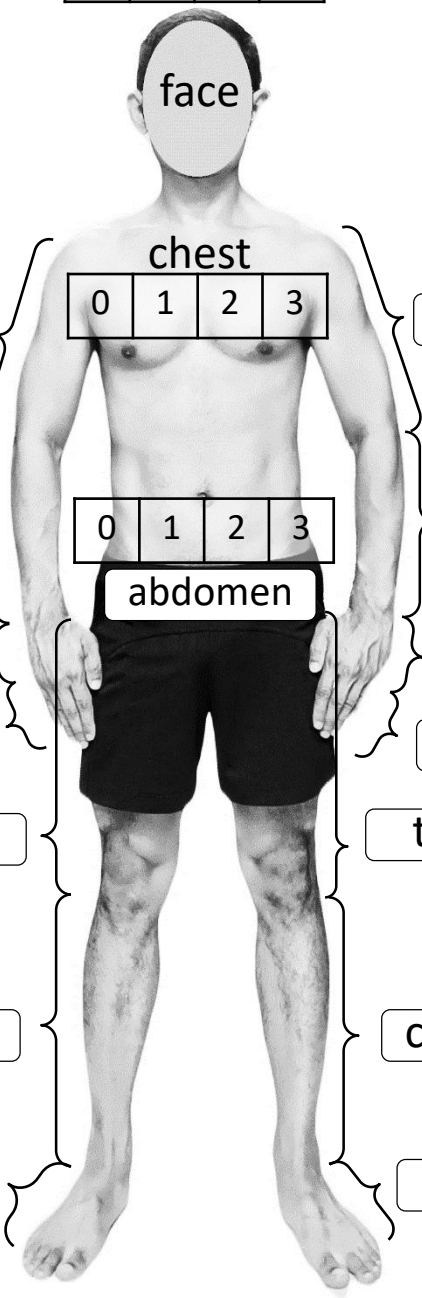
Clinically meaningful changes of mRSS =
5 units or 25% changes

Total score = 51

Score 0 – 10 = mild

Score 11 – 24 = moderate

Score >24 = severe



0 1 2 3 — face

0 1 2 3 — chest

upper arm: 0 1 2 3

upper arm: 0 1 2 3

0 1 2 3 — abdomen

forearm: 0 1 2 3

forearm: 0 1 2 3

hand: 0 1 2 3

hand: 0 1 2 3

fingers: 0 1 2 3

fingers: 0 1 2 3

thigh: 0 1 2 3

thigh: 0 1 2 3

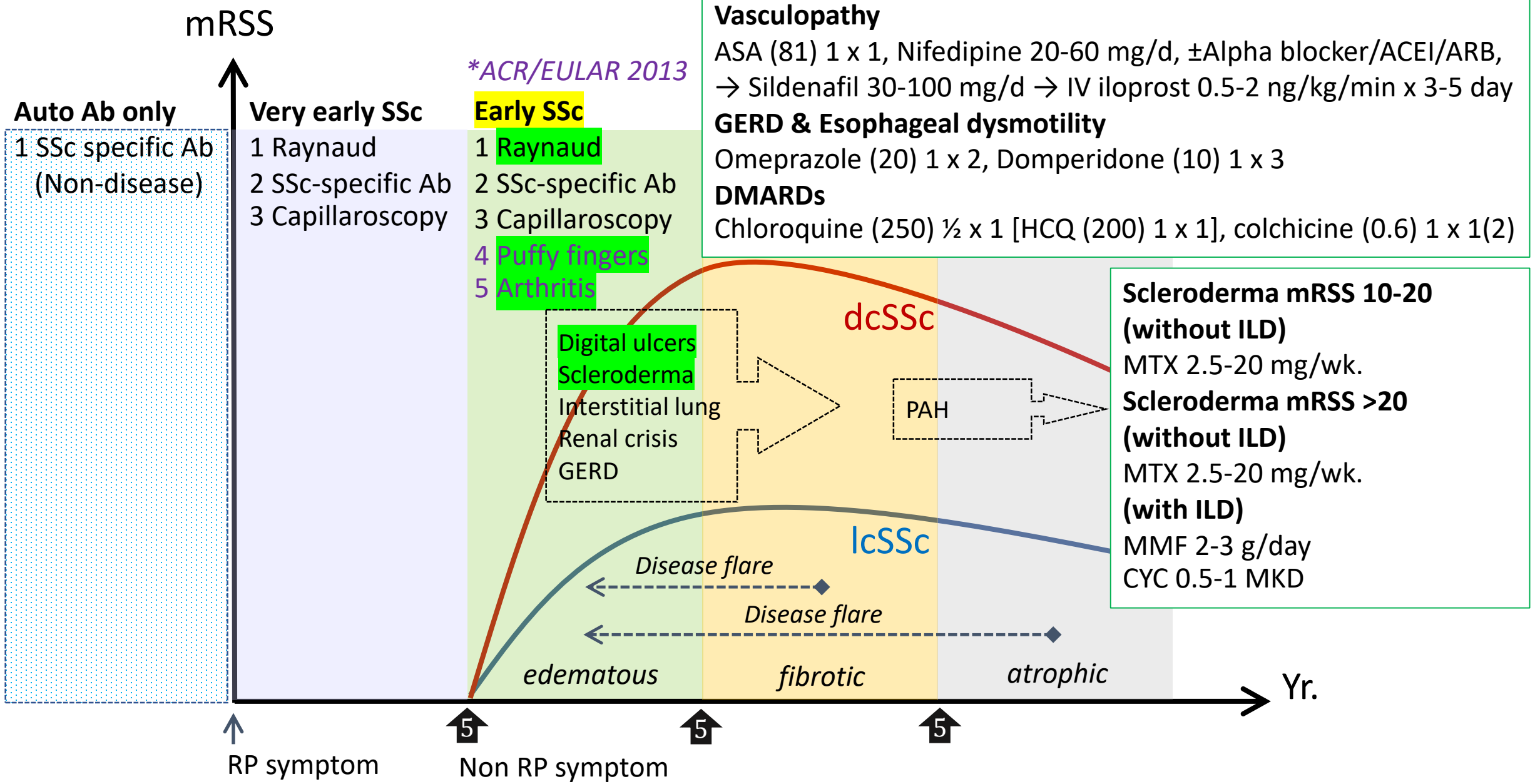
calf: 0 1 2 3

calf: 0 1 2 3

dorsum foot: 0 1 2 3

dorsum foot: 0 1 2 3

SSc Px in early SSc to establish SSc

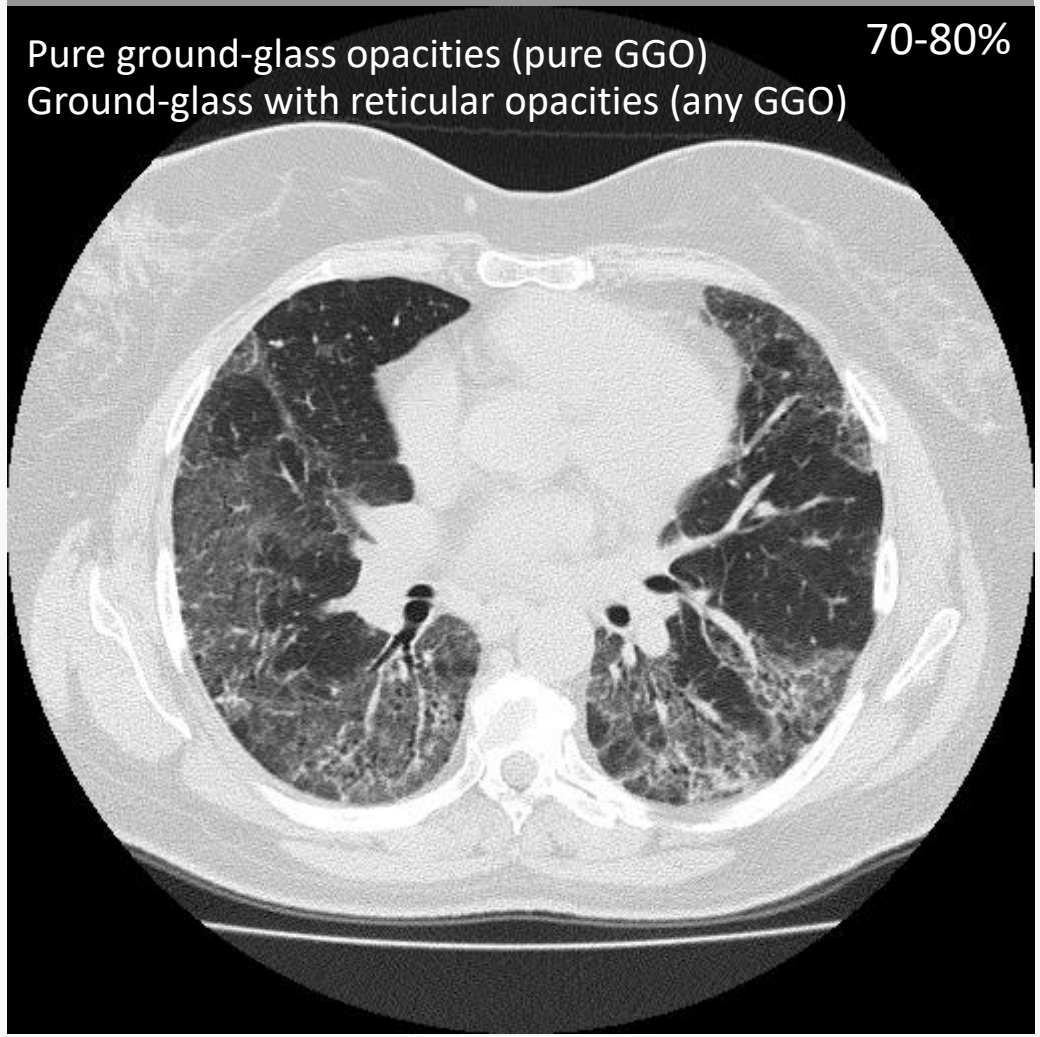


Vasculopathy
ASA (81) 1 x 1, Nifedipine 20-60 mg/d, ±Alpha blocker/ACEI/ARB, → Sildenafil 30-100 mg/d → IV iloprost 0.5-2 ng/kg/min x 3-5 day
GERD & Esophageal dysmotility
Omeprazole (20) 1 x 2, Domperidone (10) 1 x 3
DMARDs
Chloroquine (250) ½ x 1 [HCQ (200) 1 x 1], colchicine (0.6) 1 x 1(2)

Scleroderma mRSS 10-20 (without ILD)
MTX 2.5-20 mg/wk.
Scleroderma mRSS >20 (without ILD)
MTX 2.5-20 mg/wk.
(with ILD)
MMF 2-3 g/day
CYC 0.5-1 MKD

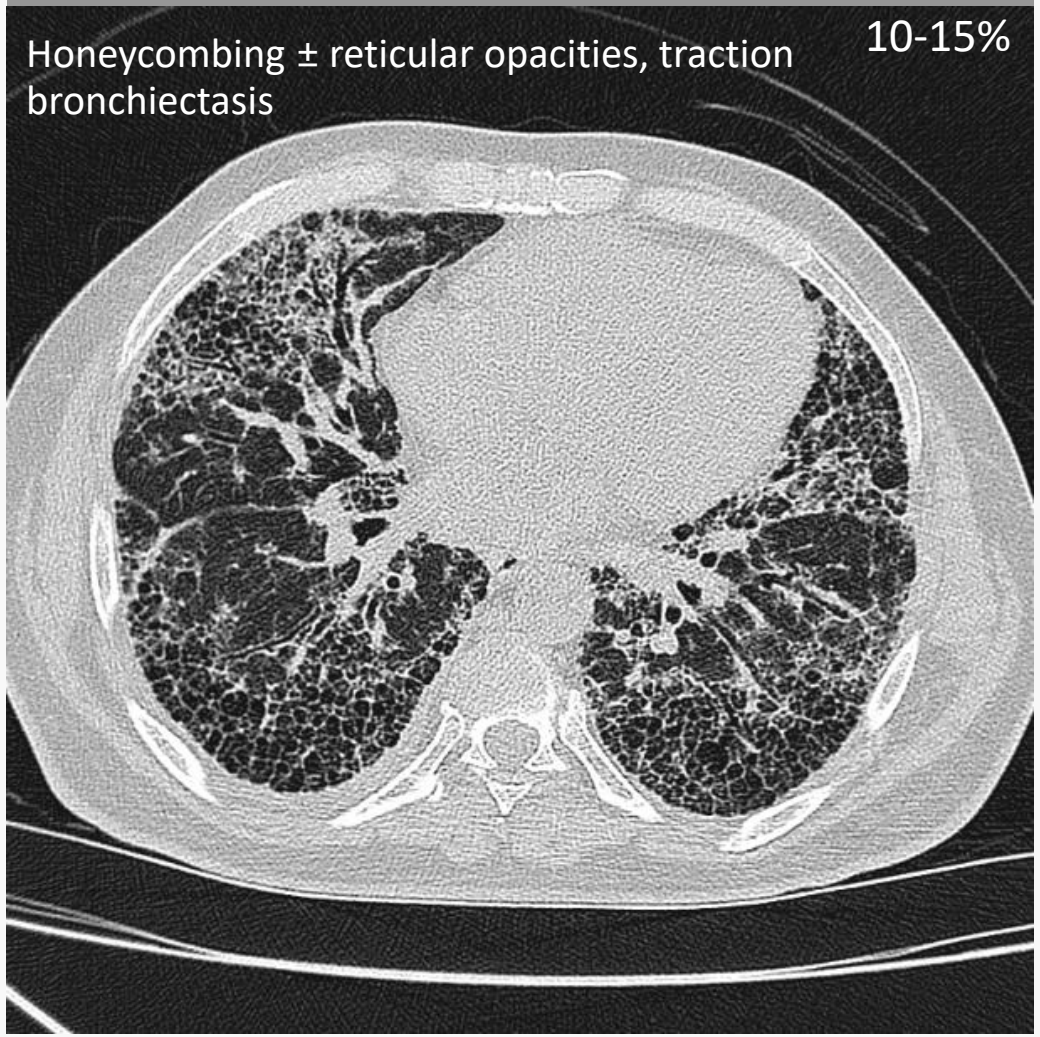
Systemic sclerosis associated Interstitial lung disease

Nonspecific interstitial pneumonia



Case courtesy of Rogério Augusto Lima Guarneri, Radiopaedia.org, rID: 31651

Usual interstitial pneumonia



Case courtesy of Dr David Cuete, Radiopaedia.org, rID: 27858

SSc – ILD: HRCT-chest Pathology & PFT correlation

Nonspecific interstitial pneumonia

Pure GGO

Only ground-glass opacities

PFT %predicted	Result
FVC	≥ 80
TLC	≥ 80
DLCO	< 80

Note: rule out PAH

Any GGO

Ground-glass opacities with Reticular opacities

PFT % predicted	Result
FVC	< 80
TLC	< 80
DLCO	< 80

Usual interstitial pneumonia

10-15%

Honeycombing ±

Reticular opacities, Traction bronchiectasis

PFT %predicted	Result
FVC	< 80
TLC	< 80
DLCO	< 80

Note: FVC/DLCO ratio ≤1.6 (normal = 1.1)

"Pulmonary Restriction"

Definition = Normal FEV1/FVC and at least 1 of the following:
FVC <80 or TCL <80 or DLCO <70

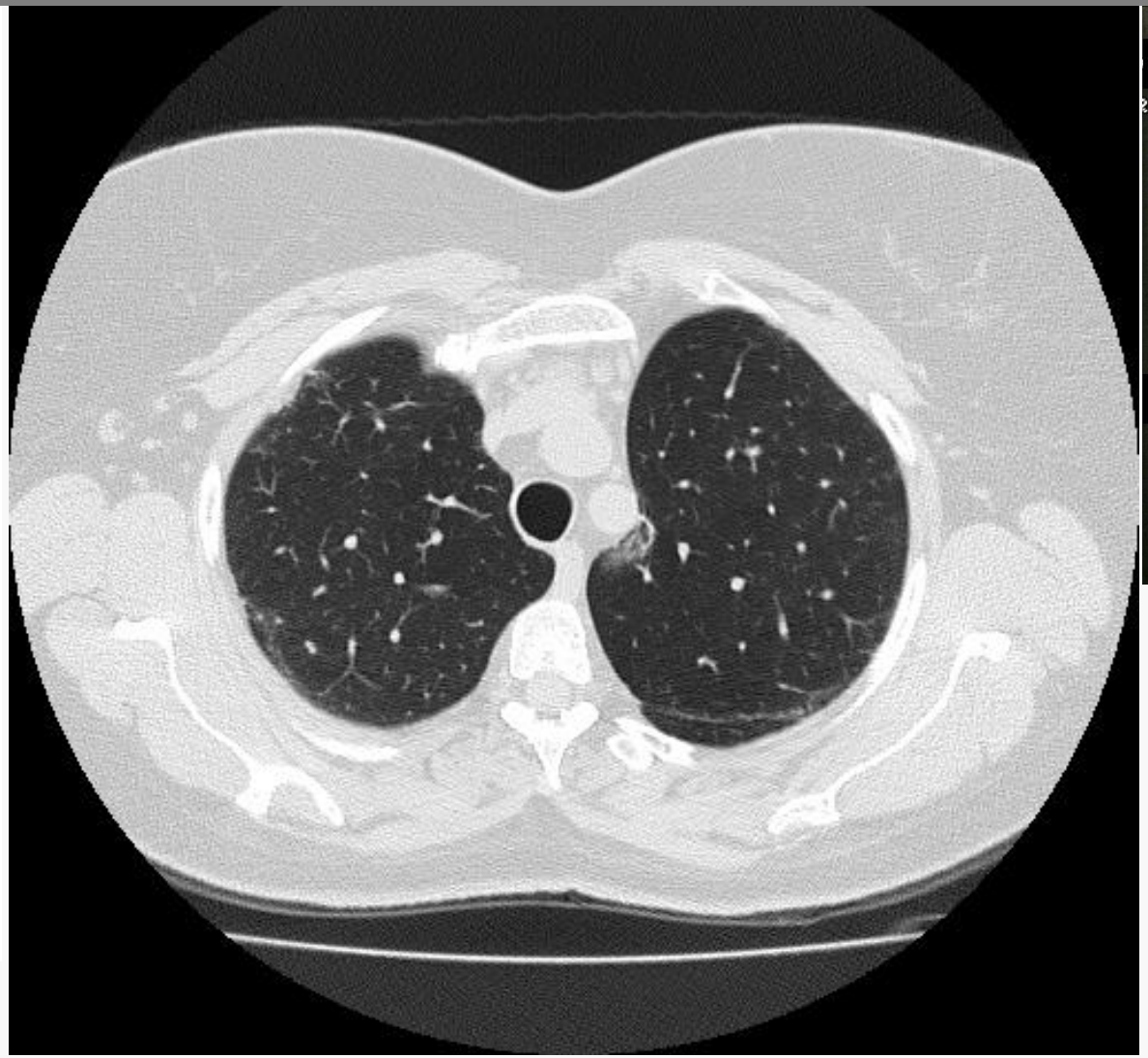
Villalba WO, et al. Chest 2007;131:217–22.

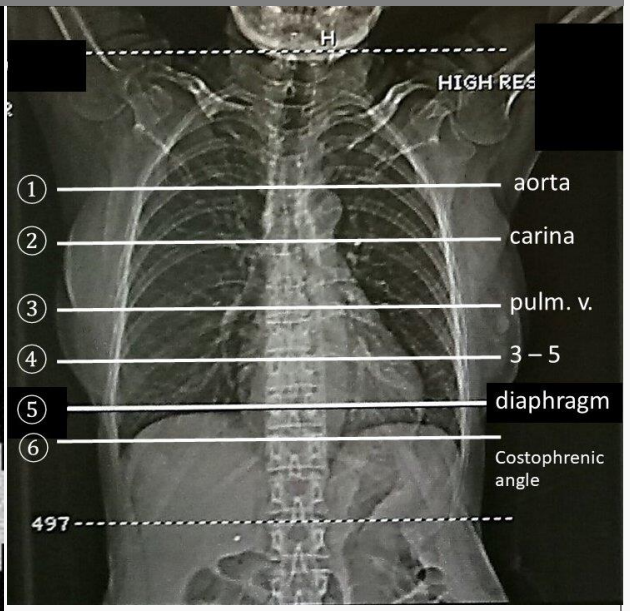
Goh & Wells unadjusted stratification
The Royal college of radiologists of Thailand

Extent of ILD

1. Origin of aorta
   = 0%
2. Carina
   =
3. Pulm. veins
   =
4. Between 3&5
   =
5. 1cm above diaphragm
   =
6. Costophrenic angle
   =

(1 + 2 + 3 + 4 + 5 + 6)/6
=





Case courtesy of Rogério Augusto Lima Guarneri, Radiopaedia.org, rID: 31651

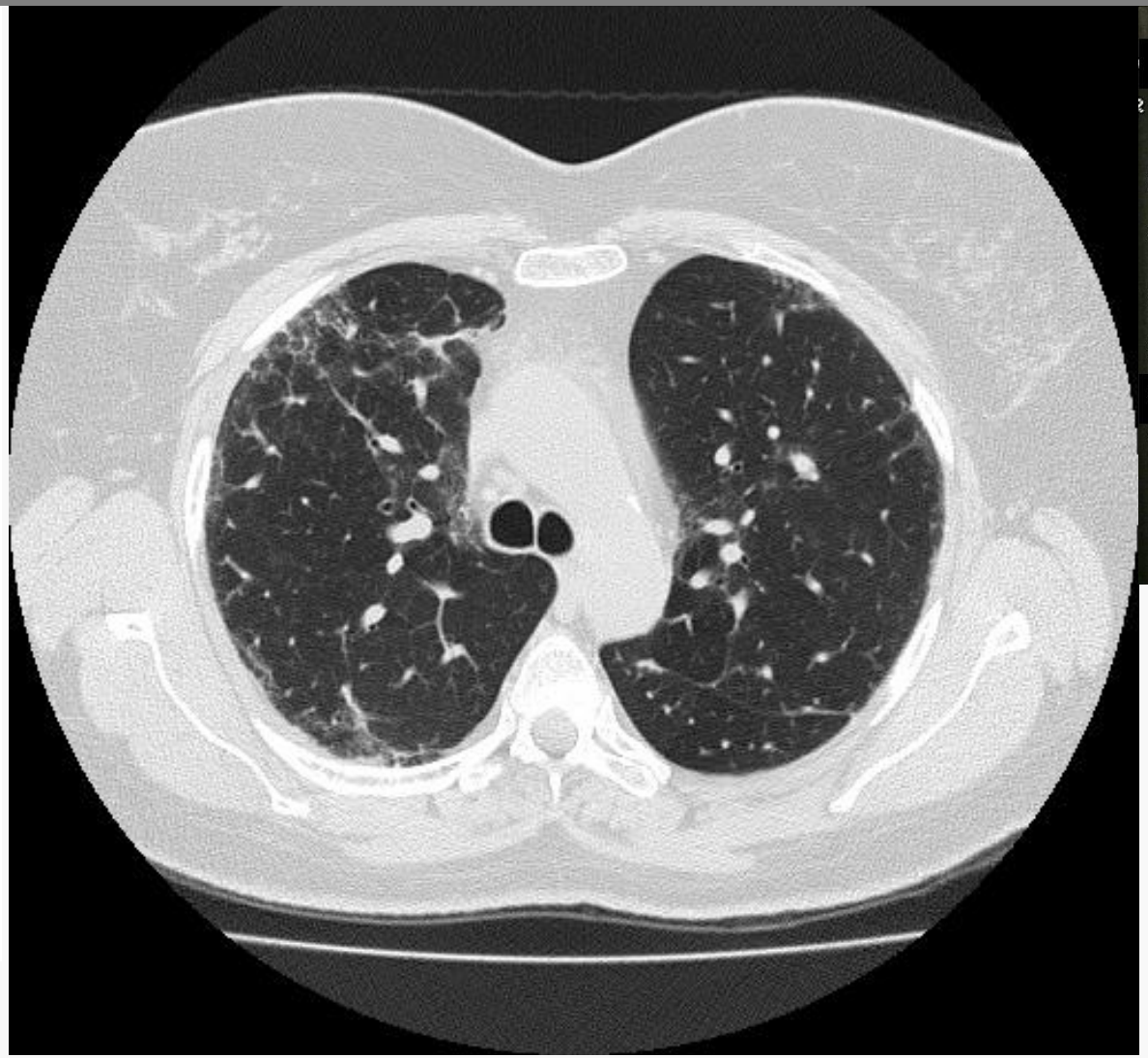
Goh N et al. Am J Respir Crit Care Med. 2008;177:1248–54.

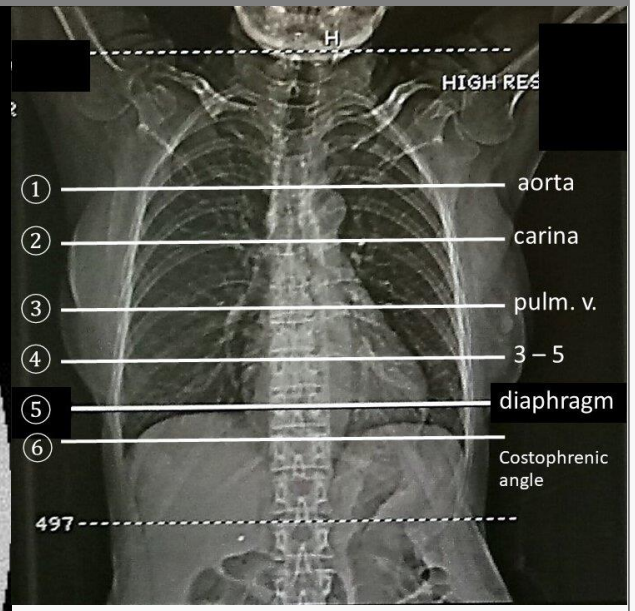
Goh & Wells unadjusted stratification
The Royal college of radiologists of Thailand

Extent of ILD

1. Origin of aorta
   = 0%
2. Carina
   = 5%
3. Pulm. veins
   =
4. Between 3&5
   =
5. 1cm above diaphragm
   =
6. Costophrenic angle
   =

(1 + 2 + 3 + 4 + 5 + 6)/6
=





Case courtesy of Rogério Augusto Lima Guarneri, Radiopaedia.org, rID: 31651

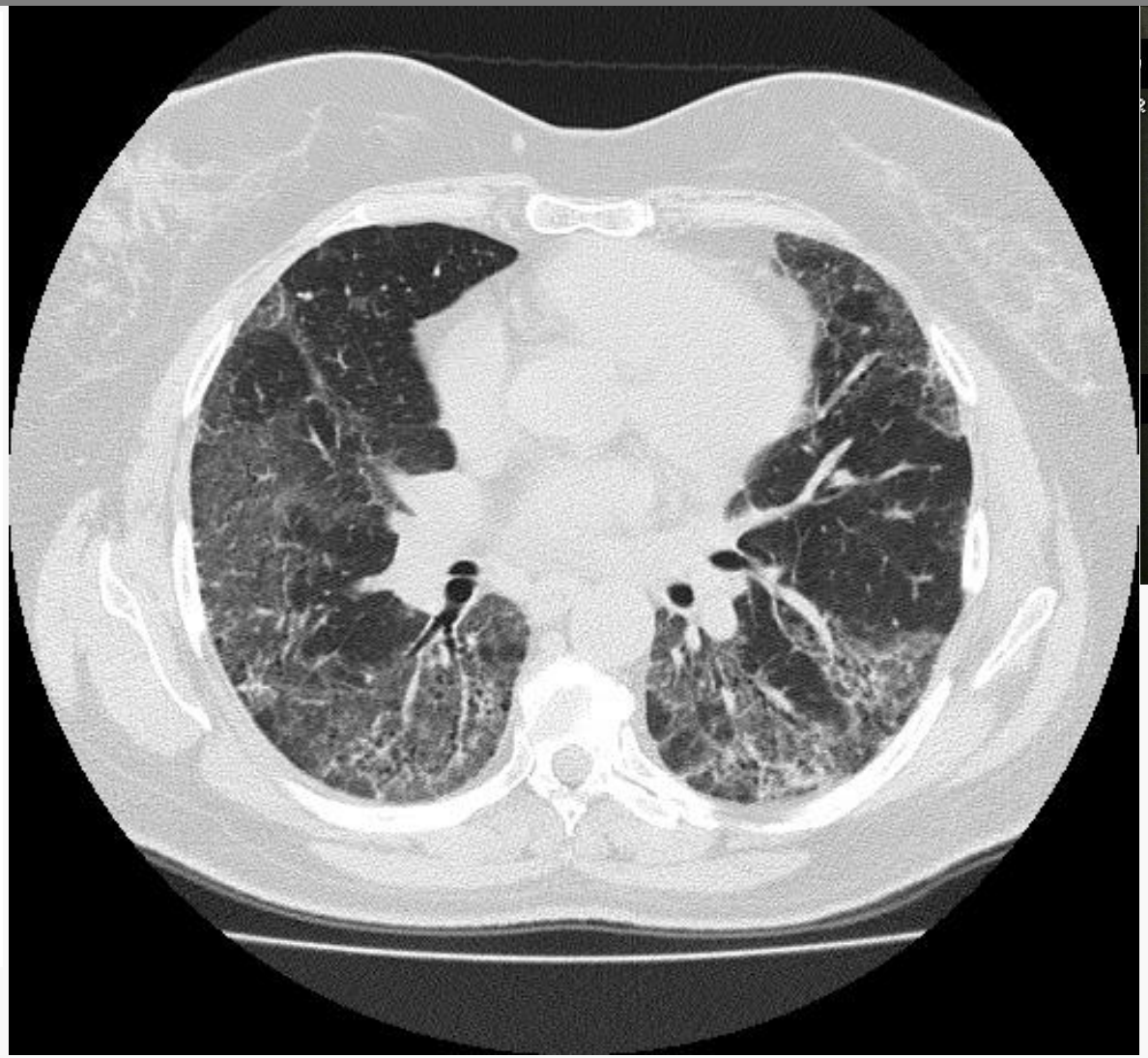
Goh N et al. Am J Respir Crit Care Med. 2008;177:1248–54.

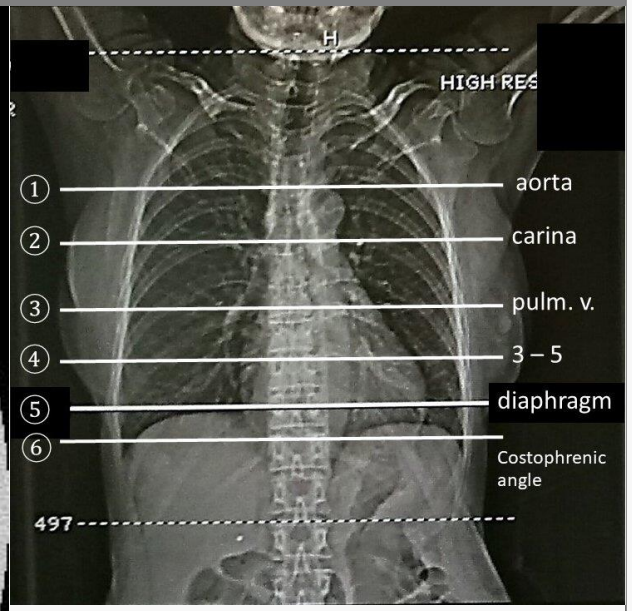
Goh & Wells unadjusted stratification
The Royal college of radiologists of Thailand

Extent of ILD

1. Origin of aorta
   = 0%
2. Carina
   = 5%
3. Pulm. veins
   = 45%
4. Between 3&5
   =
5. 1cm above diaphragm
   =
6. Costophrenic angle
   =

(1 + 2 + 3 + 4 + 5 + 6)/6
=





Case courtesy of Rogério Augusto Lima Guarneri, Radiopaedia.org, rID: 31651

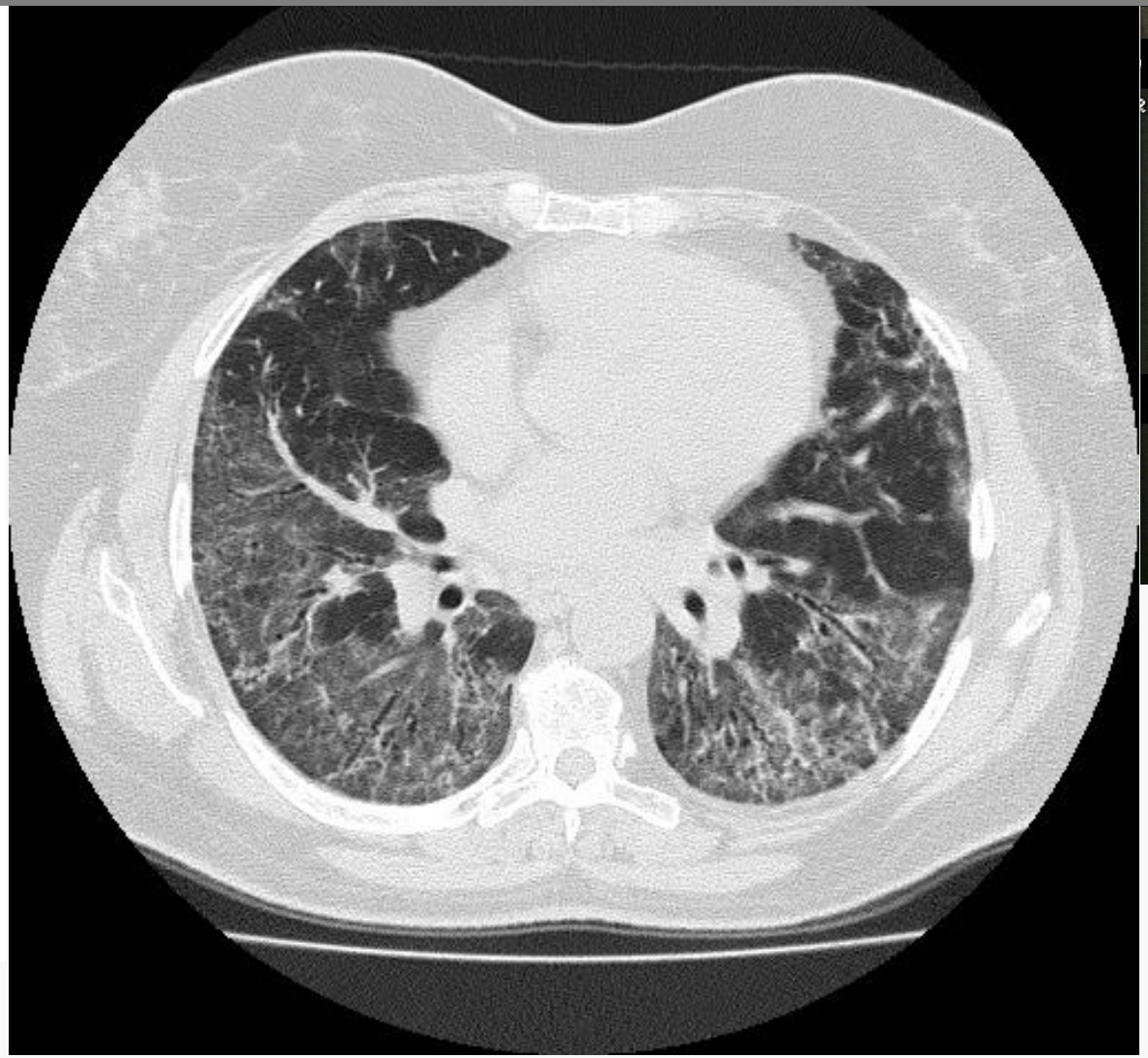
Goh N et al. Am J Respir Crit Care Med. 2008;177:1248–54.

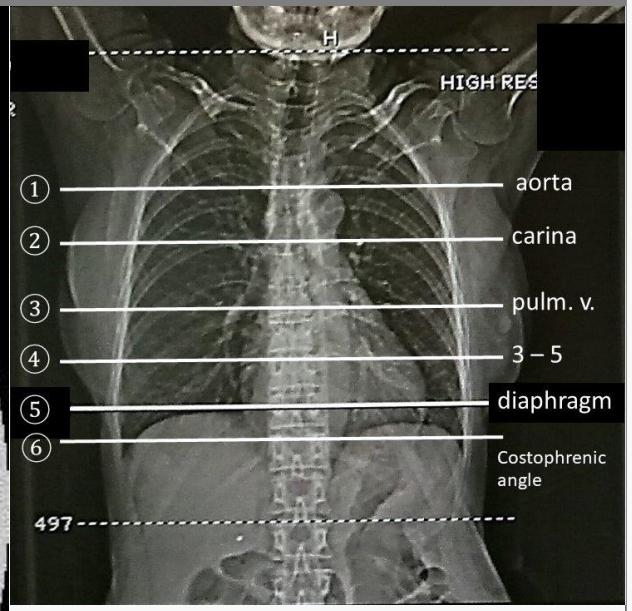
Goh & Wells unadjusted stratification
The Royal college of radiologists of Thailand

Extent of ILD

1. Origin of aorta
   = 0%
2. Carina
   = 5%
3. Pulm. veins
   = 45%
4. Between 3&5
   = 50%
5. 1cm above diaphragm
   =
6. Costophrenic angle
   =

(1 + 2 + 3 + 4 + 5 + 6)/6
=





Case courtesy of Rogério Augusto Lima Guarneri, Radiopaedia.org, rID: 31651

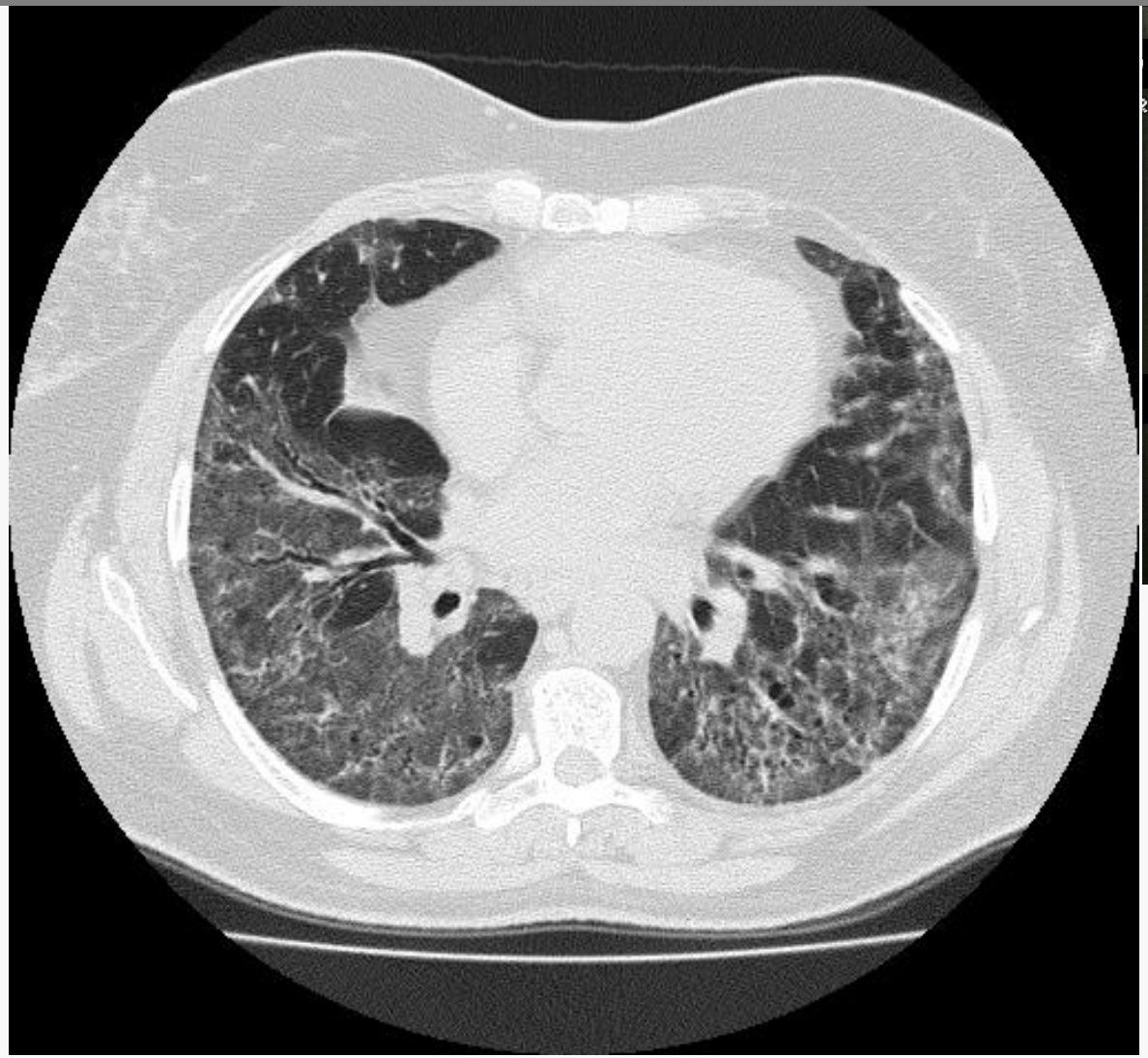
Goh N et al. Am J Respir Crit Care Med. 2008;177:1248–54.

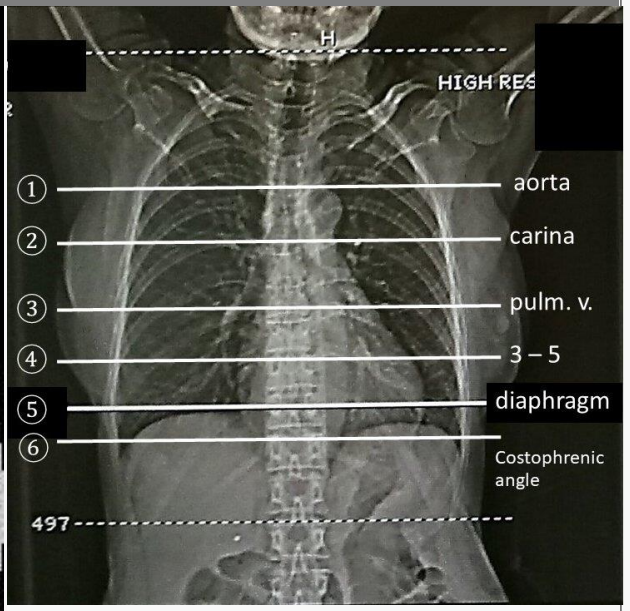
Goh & Wells unadjusted stratification
The Royal college of radiologists of Thailand

Extent of ILD

1. Origin of aorta
   = 0%
2. Carina
   = 5%
3. Pulm. veins
   = 45%
4. Between 3&5
   = 50%
5. 1cm above diaphragm
   = 60%
6. Costophrenic angle
   =

(1 + 2 + 3 + 4 + 5 + 6)/6
   =





Case courtesy of Rogério Augusto Lima Guarneri, Radiopaedia.org, rID: 31651

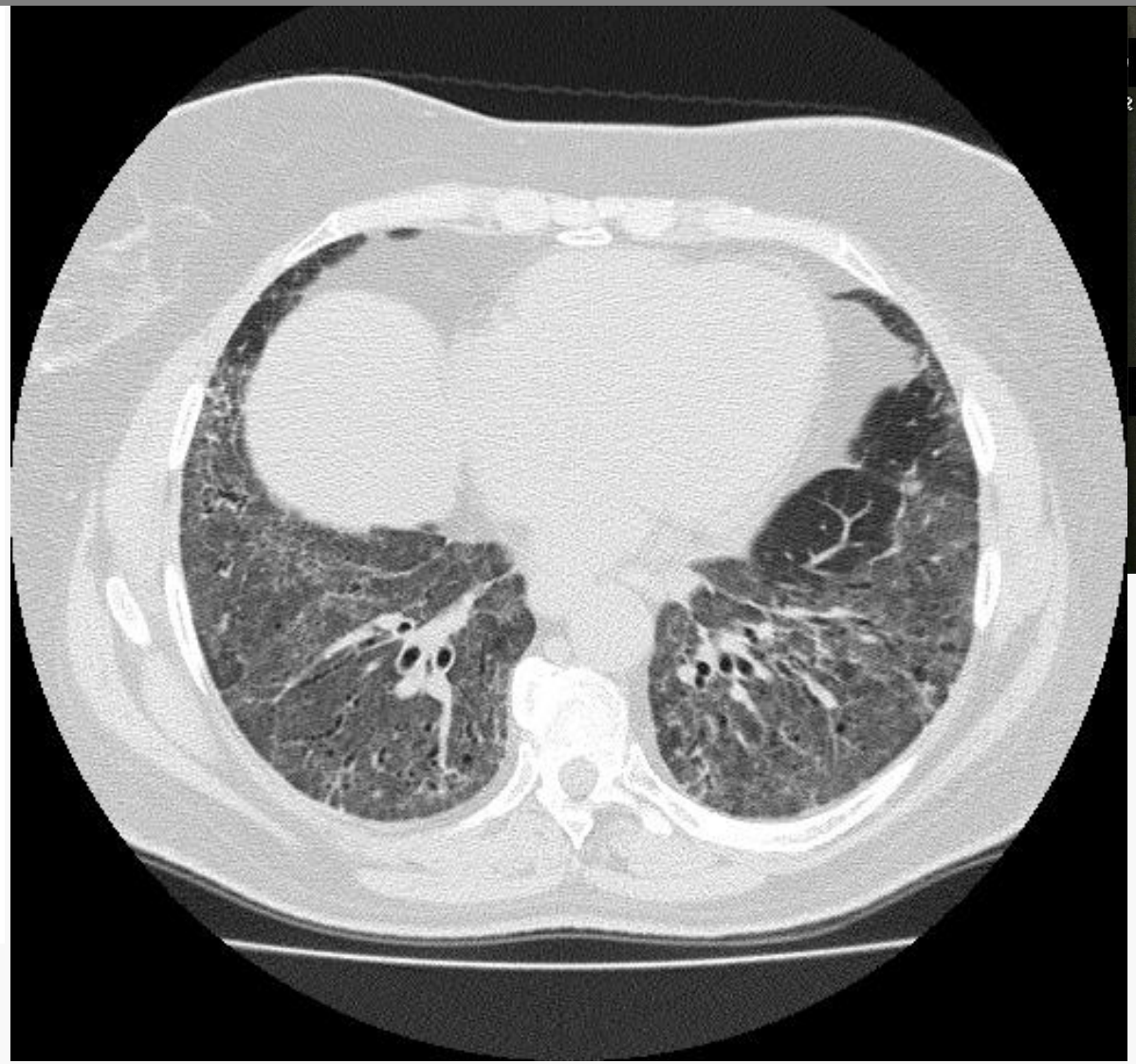
Goh N et al. Am J Respir Crit Care Med. 2008;177:1248–54.

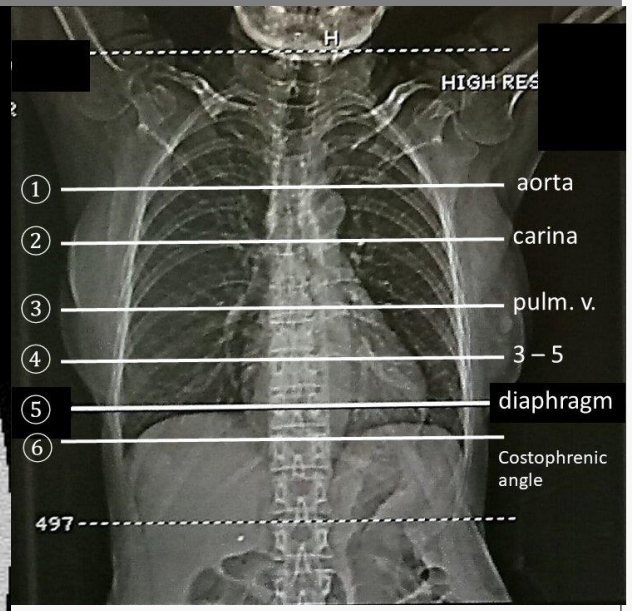
Goh & Wells unadjusted stratification
The Royal college of radiologists of Thailand

Extent of ILD

1. Origin of aorta
   = 0%
2. Carina
   = 5%
3. Pulm. veins
   = 45%
4. Between 3&5
   = 50%
5. 1cm above diaphragm
   = 60%
6. Costophrenic angle
   = 85%

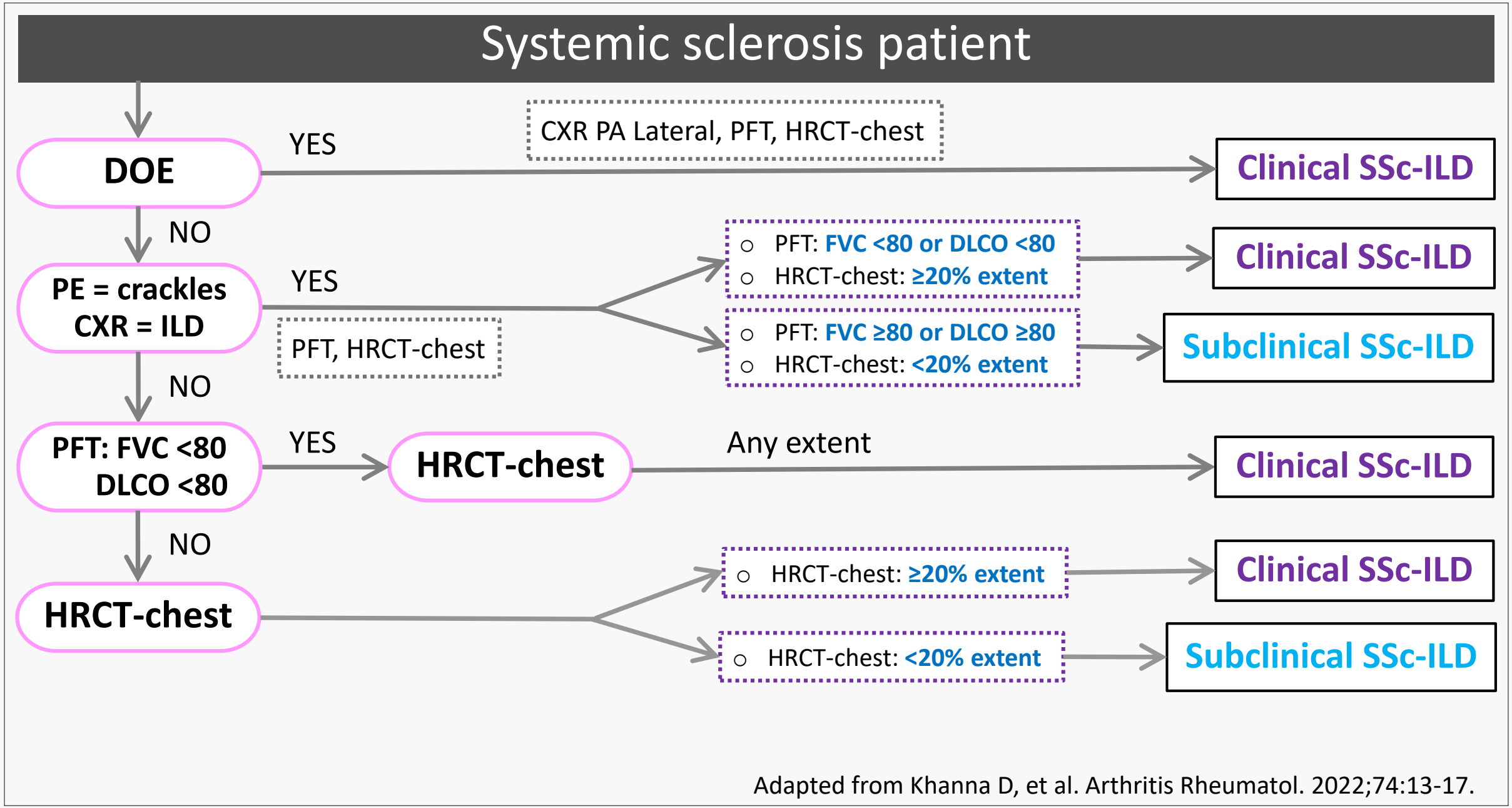
(1 + 2 + 3 + 4 + 5 + 6)/6
   = 40.8%





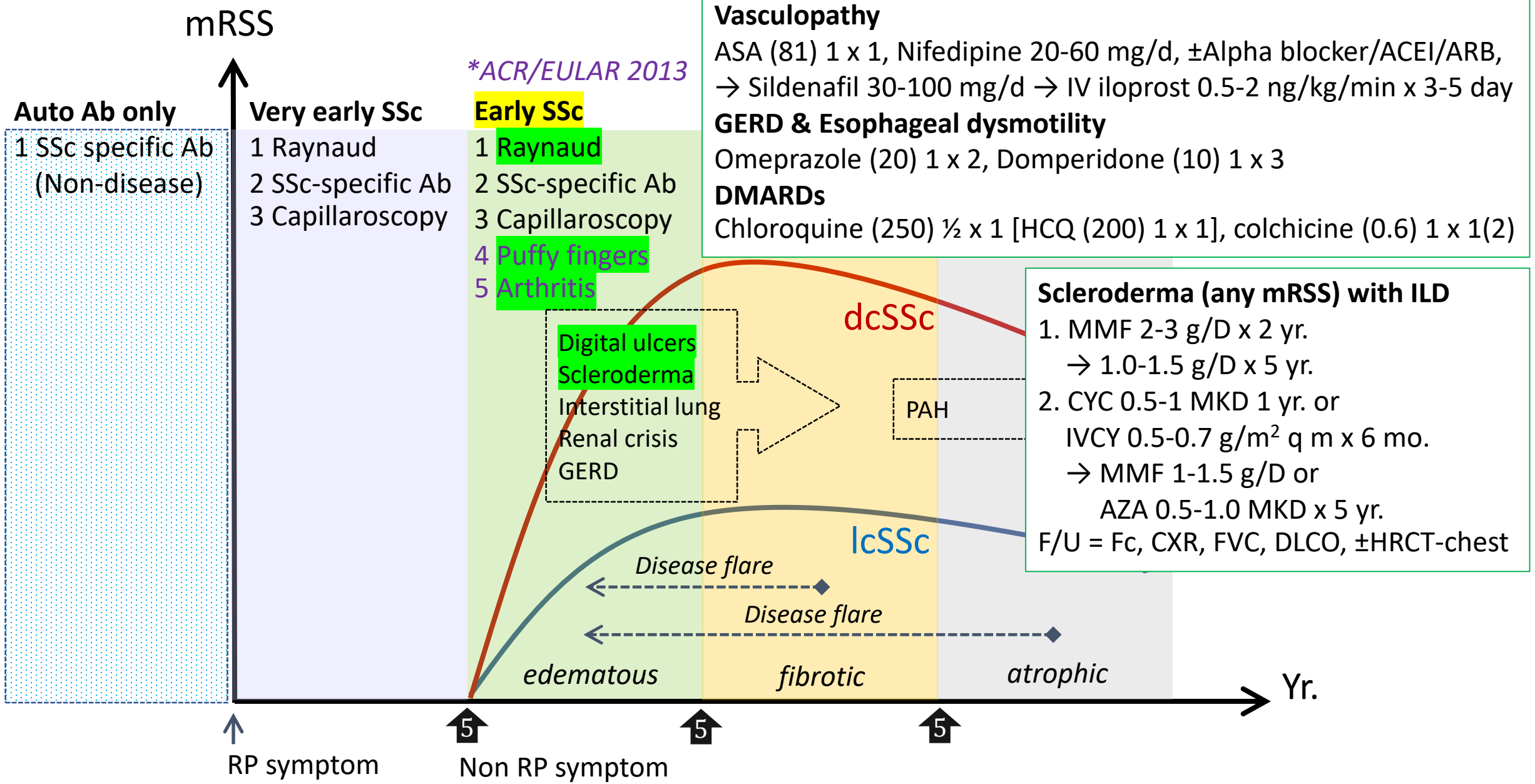
Case courtesy of Rogério Augusto Lima Guarneri, Radiopaedia.org, rID: 31651

Goh N et al. Am J Respir Crit Care Med. 2008;177:1248–54.



Adapted from Khanna D, et al. Arthritis Rheumatol. 2022;74:13-17.

SSc Px in early SSc to establish SSc



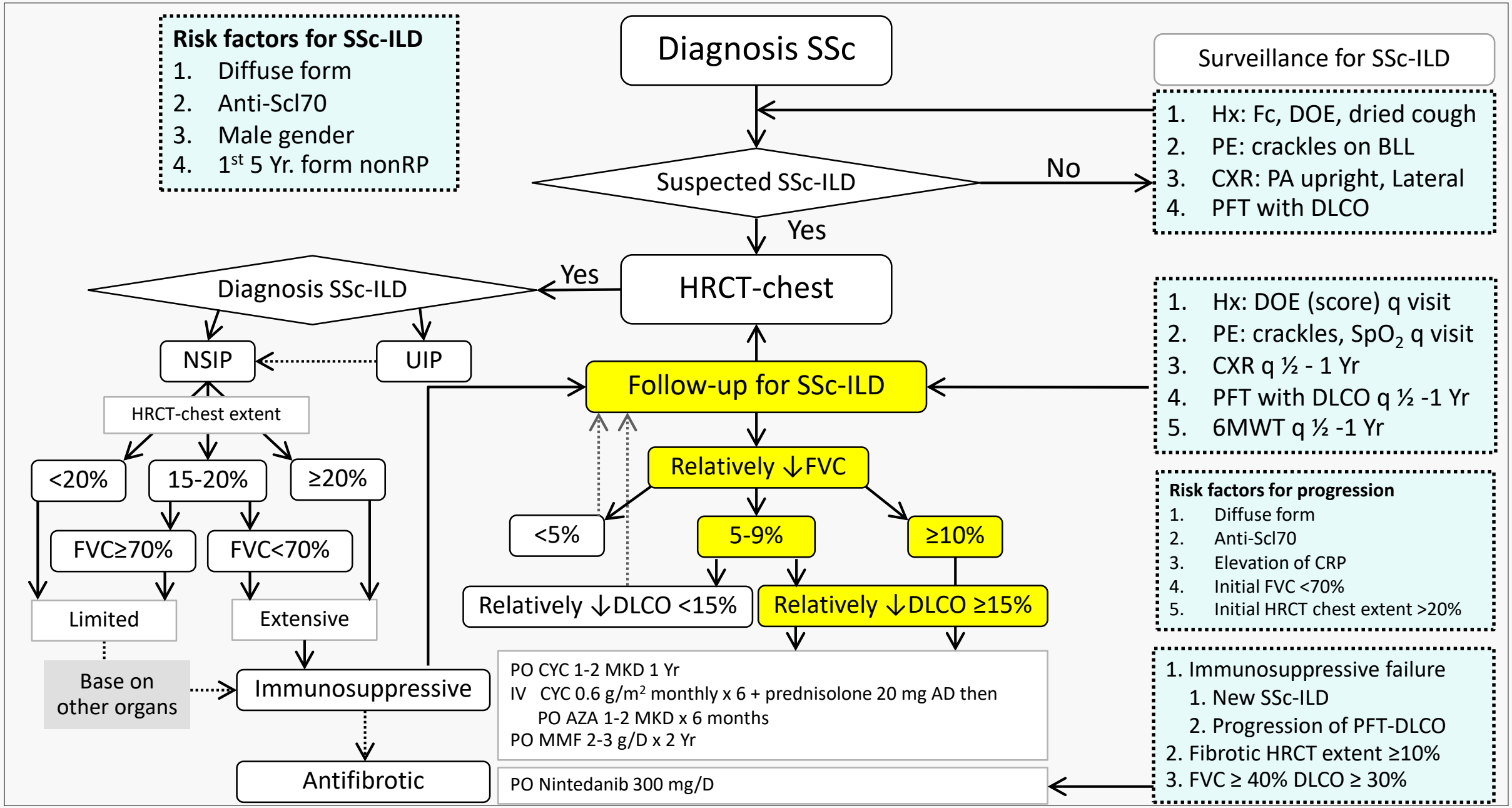
Vasculopathy
ASA (81) 1 x 1, Nifedipine 20-60 mg/d, ±Alpha blocker/ACEI/ARB,
→ Sildenafil 30-100 mg/d → IV iloprost 0.5-2 ng/kg/min x 3-5 day

GERD & Esophageal dysmotility
Omeprazole (20) 1 x 2, Domperidone (10) 1 x 3

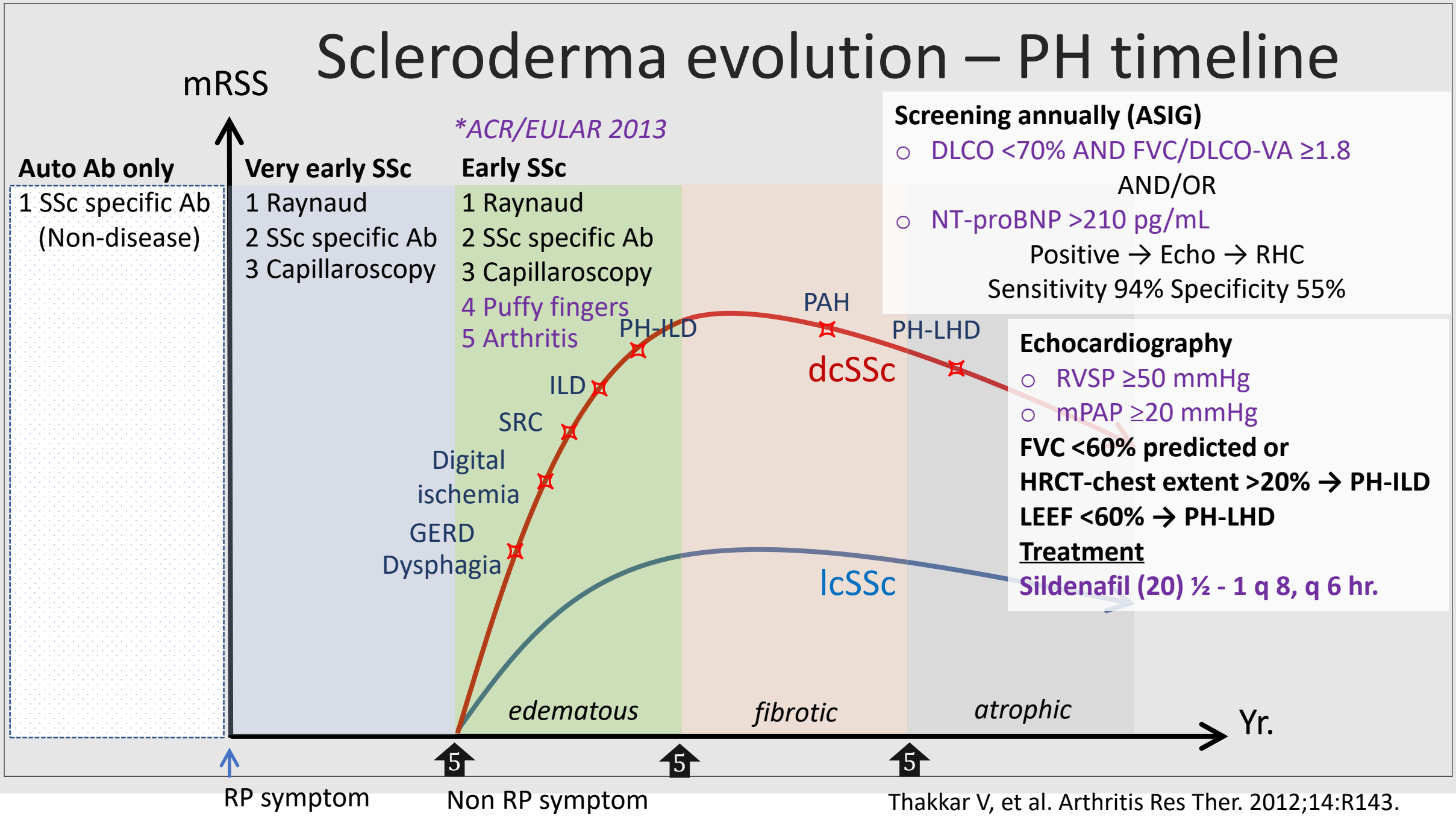
DMARDs
Chloroquine (250) ½ x 1 [HCQ (200) 1 x 1], colchicine (0.6) 1 x 1(2)

Scleroderma (any mRSS) with ILD
1. MMF 2-3 g/D x 2 yr.
   → 1.0-1.5 g/D x 5 yr.
2. CYC 0.5-1 MKD 1 yr. or
   IVCY 0.5-0.7 g/m^2 q m x 6 mo.
   → MMF 1-1.5 g/D or
   AZA 0.5-1.0 MKD x 5 yr.

F/U = Fc, CXR, FVC, DLCO, ±HRCT-chest


Risk factors for SSc-ILD
1. Diffuse form
2. Anti-Scl70
3. Male gender
4. 1st 5 Yr. form nonRP
Diagnosis SSc
Surveillance for SSc-ILD
1. Hx: Fc, DOE, dried cough
2. PE: crackles on BLL
3. CXR: PA upright, Lateral
4. PFT with DLCO
Suspected SSc-ILD
No
Yes
HRCT-chest
Yes
Diagnosis SSc-ILD
NSIP
UIP
HRCT-chest extent
<20%
15-20%
≥20%
FVC≥70%
FVC<70%
Limited
Extensive
Base on other organs
Immunosuppressive
Antifibrotic
Follow-up for SSc-ILD
1. Hx: DOE (score) q visit
2. PE: crackles, SpO2 q visit
3. CXR q ½ - 1 Yr
4. PFT with DLCO q ½ -1 Yr
5. 6MWT q ½ -1 Yr
Relatively ↓FVC
<5%
5-9%
≥10%
Relatively ↓DLCO <15%
Relatively ↓DLCO ≥15%
Risk factors for progression
1. Diffuse form
2. Anti-Scl70
3. Elevation of CRP
4. Initial FVC <70%
5. Initial HRCT chest extent >20%
PO CYC 1-2 MKD 1 Yr
IV CYC 0.6 g/m2 monthly x 6 + prednisolone 20 mg AD then
PO AZA 1-2 MKD x 6 months
PO MMF 2-3 g/D x 2 Yr
PO Nintedanib 300 mg/D
1. Immunosuppressive failure
1. New SSc-ILD
2. Progression of PFT-DLCO
2. Fibrotic HRCT extent ≥10%
3. FVC ≥ 40% DLCO ≥ 30%

Scleroderma evolution – PH timeline



Screening annually (ASIG)

- DLCO <70% AND FVC/DLCO-VA ≥1.8

AND/OR

- NT-proBNP >210 pg/mL

Positive → Echo → RHC

Sensitivity 94% Specificity 55%

Echocardiography

- RVSP ≥50 mmHg
- mPAP ≥20 mmHg

FVC <60% predicted or
HRCT-chest extent >20% → PH-ILD
LEEF <60% → PH-LHD

<u>Treatment</u>

Sildenafil (20) ½ - 1 q 8, q 6 hr.

Thakkar V, et al. Arthritis Res Ther. 2012;14:R143.

Diagnosis SSc

RP, GERD, SRC, NSIP, early DIC, overlap RA/PM — **UIP, PH-ILD** — **PAH, late DIC** — **PH – LHD, malabsorption**

Edematous | Fibrotic | Atrophic

Inflammation → mRSS → Fibrosis

Skin: tightening? (VAS), itching PE: ΔmRSS, finger-to-palm distance Tendon friction rub	Px: moisturizer, sunscreen, anti-histamine, ROM exercise CQ (250) ½ x 1 or HCQ (200) 1 x 1, colchicine (0.6) 1 x 2 (3) → maintenance mRSS >10 → MTX 2.5 mg/wk. → 20 mg/wk. (Target mRSS = 0)
Lung: DOE? (VAS), Functional class PE: Crackles Ix: (annually) CXR-PA/Lat, PFT/DLCO (suspected ILD) HRCT (extent?)	Subclinical NSIP + mRSS >10 Px: MMF 2 – 3 g/d x 2 yr. (induction) → 1 – 1.5 g/d x 5 yr. (maintenance) Clinical NSIP (+any mRSS) Px: MMF 2 – 3 g/d x 2 yr. (induction) → 1 – 1.5 g/d x 5 yr. (maintenance) CYC 1 MKD x 1 yr. (induction) CYC 0.5 – 0.7 g/m^2 IV q M. x 6 (induction) } → MMF 1-1.5 g/d x 5 yr. or AZA 1 MKD x 5 yr. (maintenance)
Vessels: RP attack? (VAS), new DIC PE: Ischemic complications Tip & Fingers & Body	Px: keep warm, early ulcer recognition/wound care ±antibiotics ASA (81) 1 x 1 + Nifedipine SR 20 – 60 mg/d ±alpha blocker/ARB/ACEI → Sildenafil 60-100 mg/d (EMS → IV iloprost 0.5-2 ng/kg/min 3-5D)
GI: 6 questions PE: ΔBW, Inter-incisor, salivary pool Ix: serum albumin	Px: Acid: Omeprazole (20) 1 x 2, alum milk, sucralfate Motility: Domperidone (10) 1 x 3 → Gasmotin (5) 1 x 3 Constipation: senokot, MOM → Prucalopride (2) 1 x 1; BO → antibiotics
CVS: DOE? (VAS), Functional class PE: loud P2, RV heaving, TR murmur Ix: (annually) ECG, Echo, NT-proBNP	Px: PAH: Sildenafil (20) 1 q 8, q 6 hr.

Muscle weakness

Proximal m. weakness suspected Idiopathic inflammatory myopathy excluding IBM

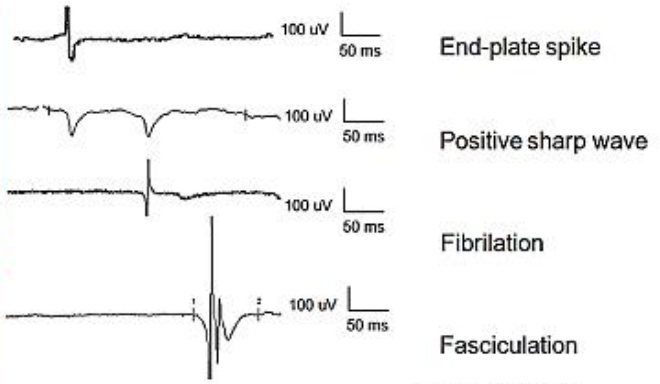
- Painless proximal m. weakness of
  - The hip → shoulder → neck →
  - Trunk → heart → diaphragm
  - ≈ 3-6 months
- HyperCKemia ≈ 3000 ± 1000 U/L
- Skin lesions?
- EMG/NCV
- Muscle Bx
- Compatible with IIM
- Classification

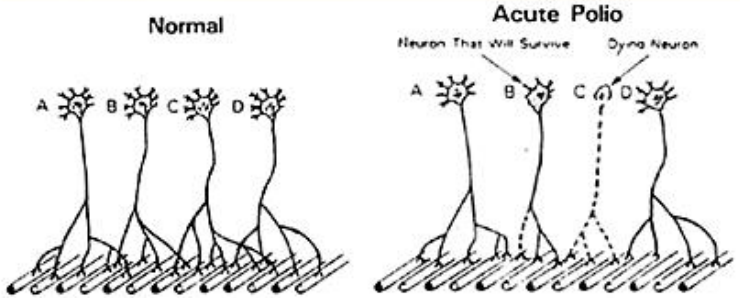
EMG: Resting state: abnormal spontaneous activity (muscle membrane irritability)

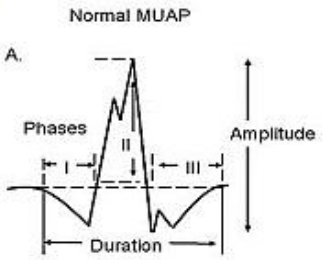
1. increased insertional activity
2. positive sharp wave
3. fibrillation, fasciculation

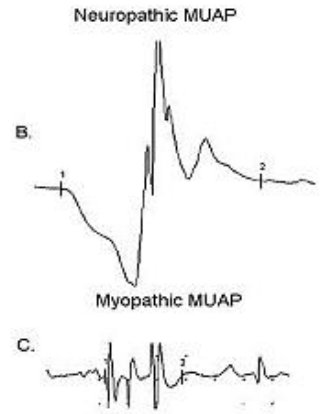
Activating state EMG: MUAP

Myopathic MUAP	Neuropathic MUAP
Short duration	**Long** duration
Small amplitude	**High** amplitude
Polyphasic	Polyphasic
Early recruitment	**Late** recruitment



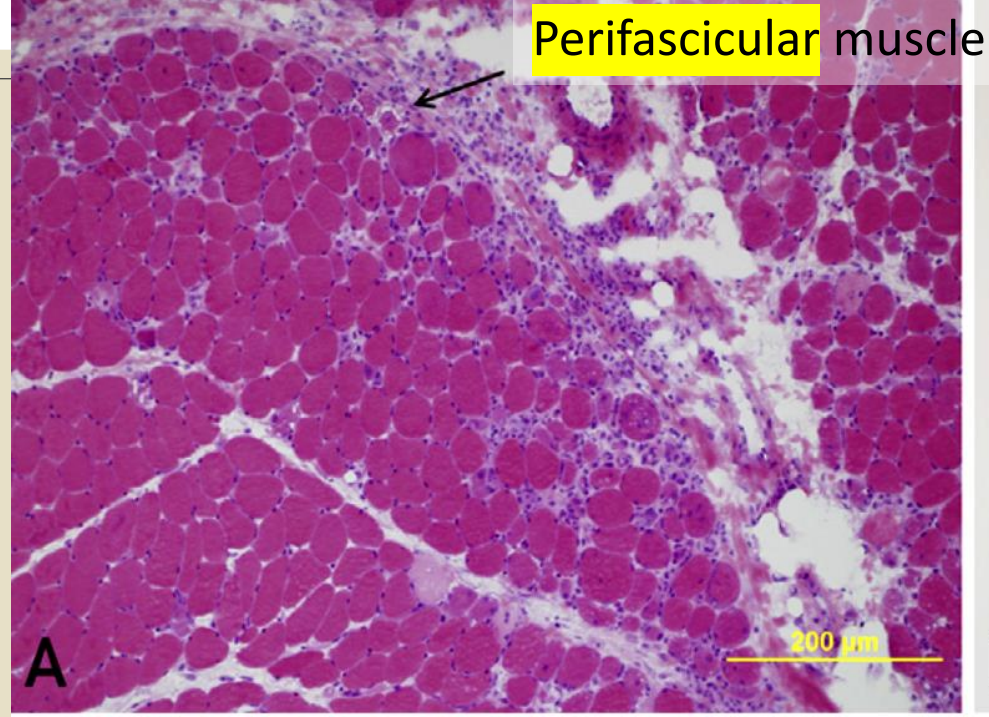


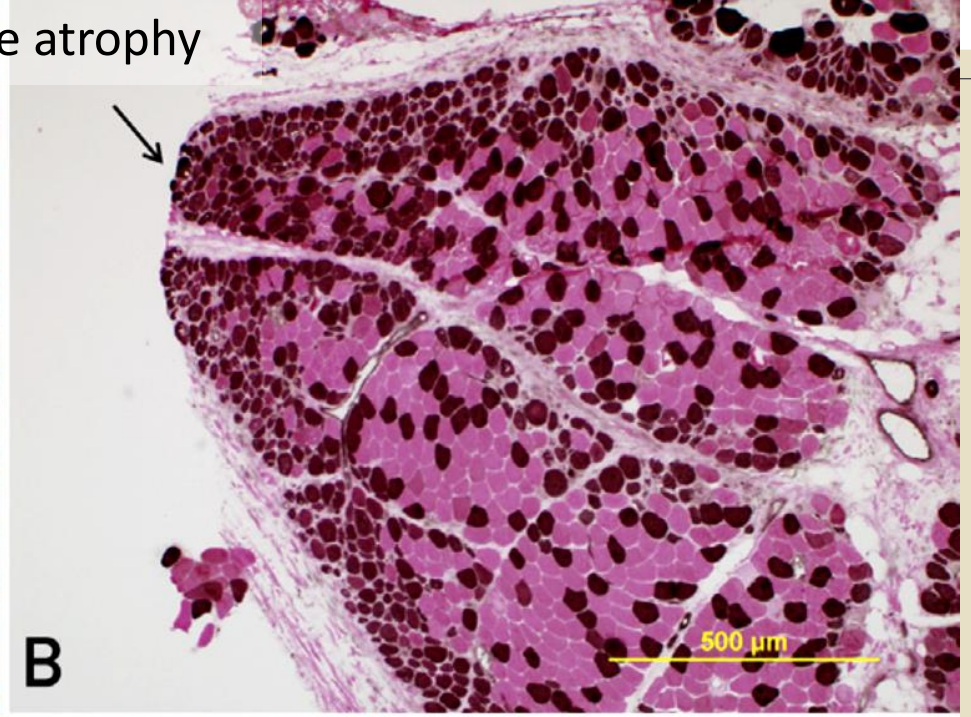


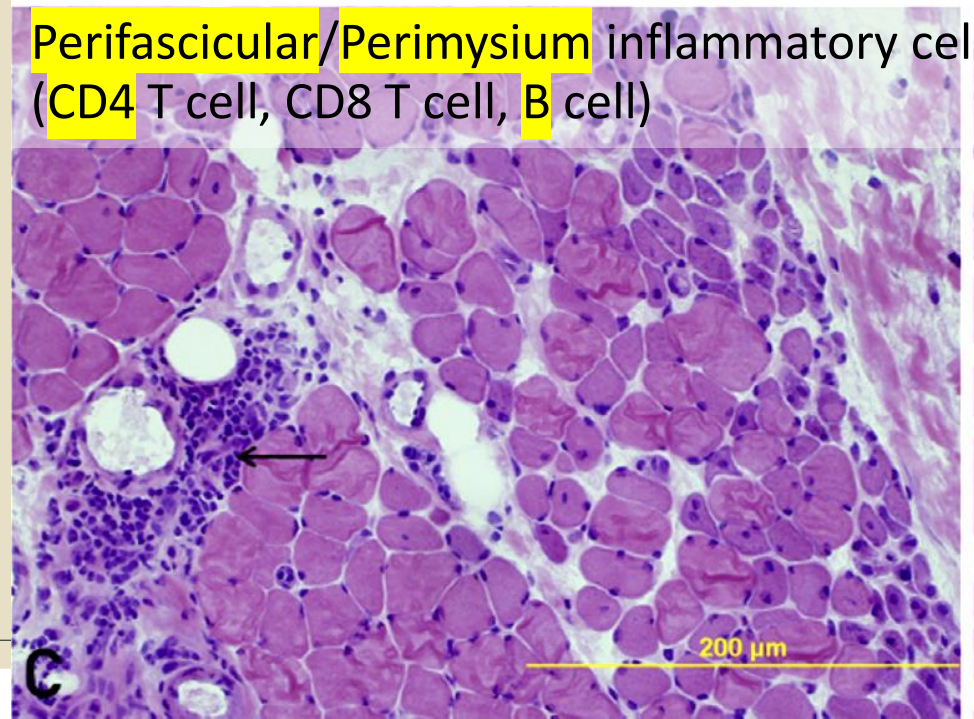


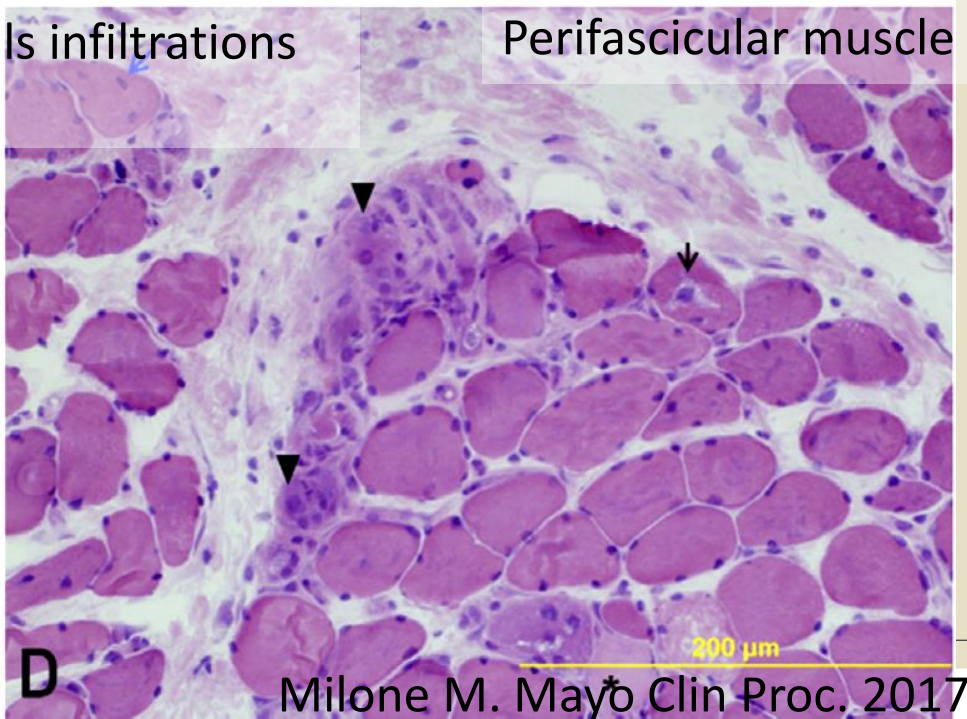
http://www.intechopen.com/books/electrodiagnosis-in-new-frontiers-of-clinical-research/overview-of-the-application-of-emg-recording-in-the-diagnosis-and-approach-of-neurological-disorders

DM



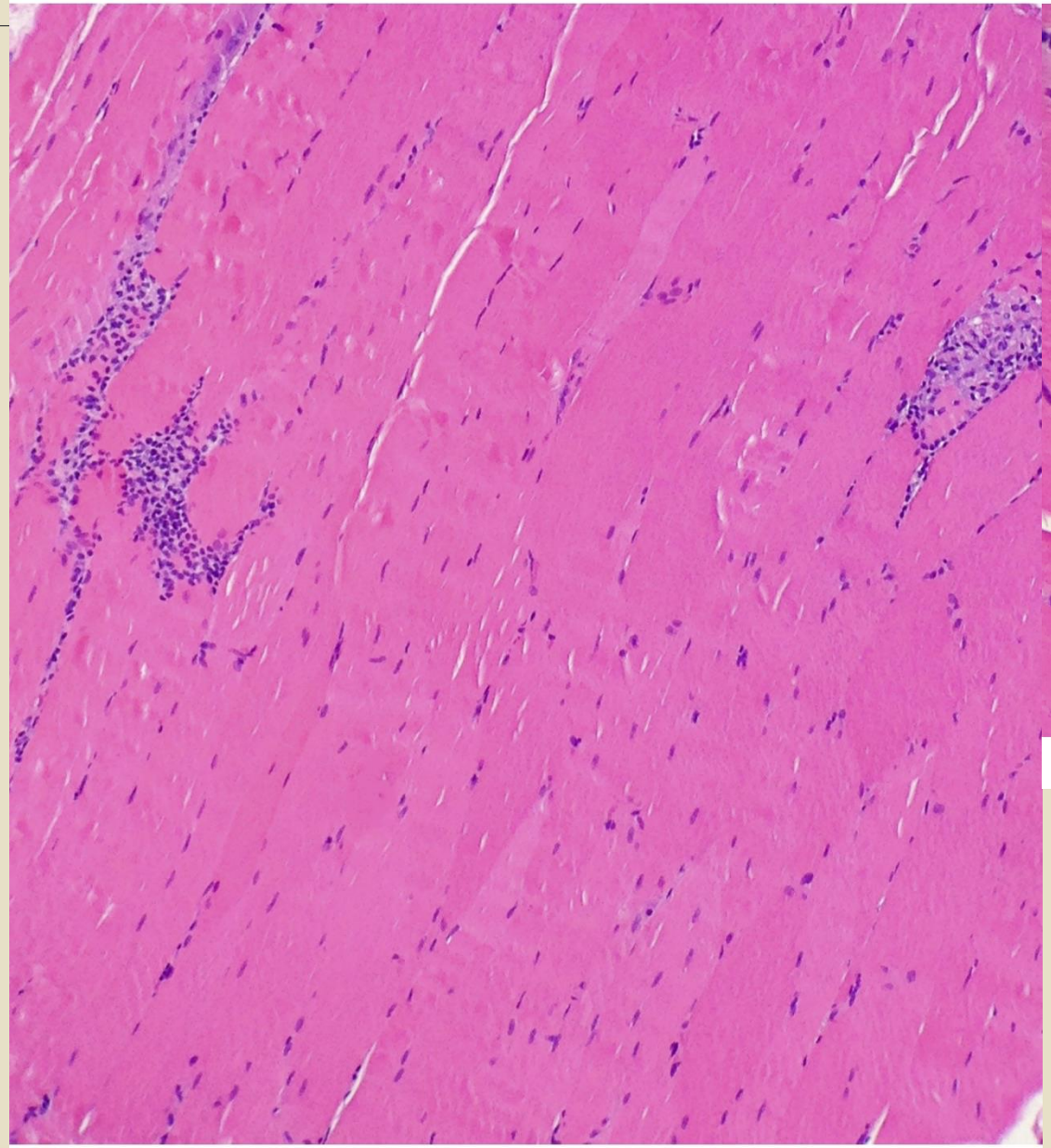




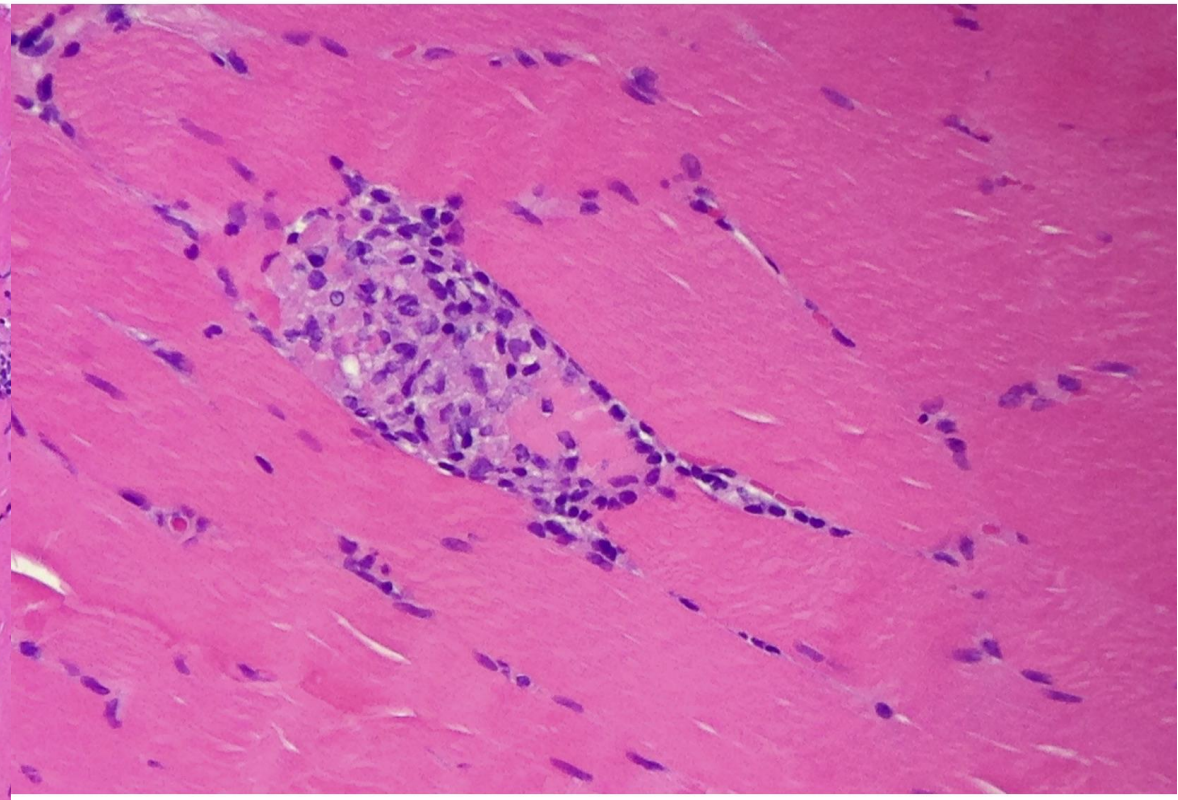


Milone M. Mayo Clin Proc. 2017;92:826-837.

PM



H&E sections of the muscle showing infiltration of lymphocytes; muscle shows myopathic features including occasional smaller myofibers which are rounded and have increased internal nuclei

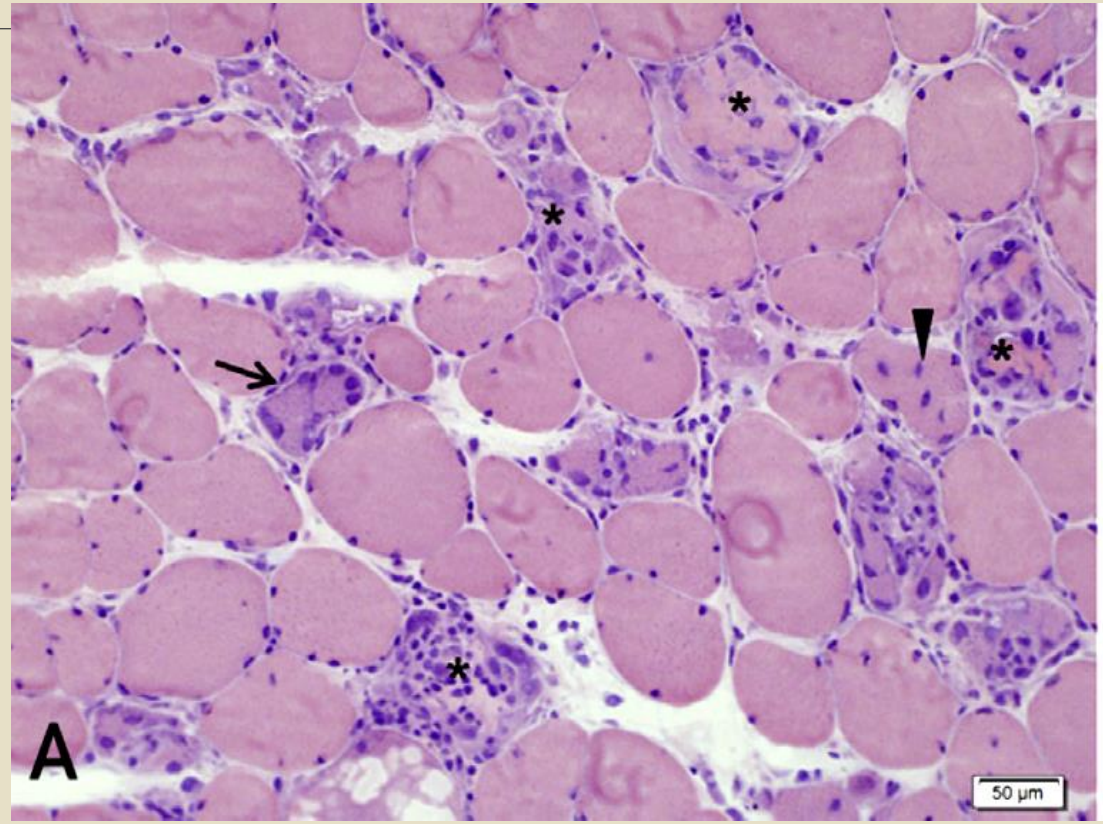


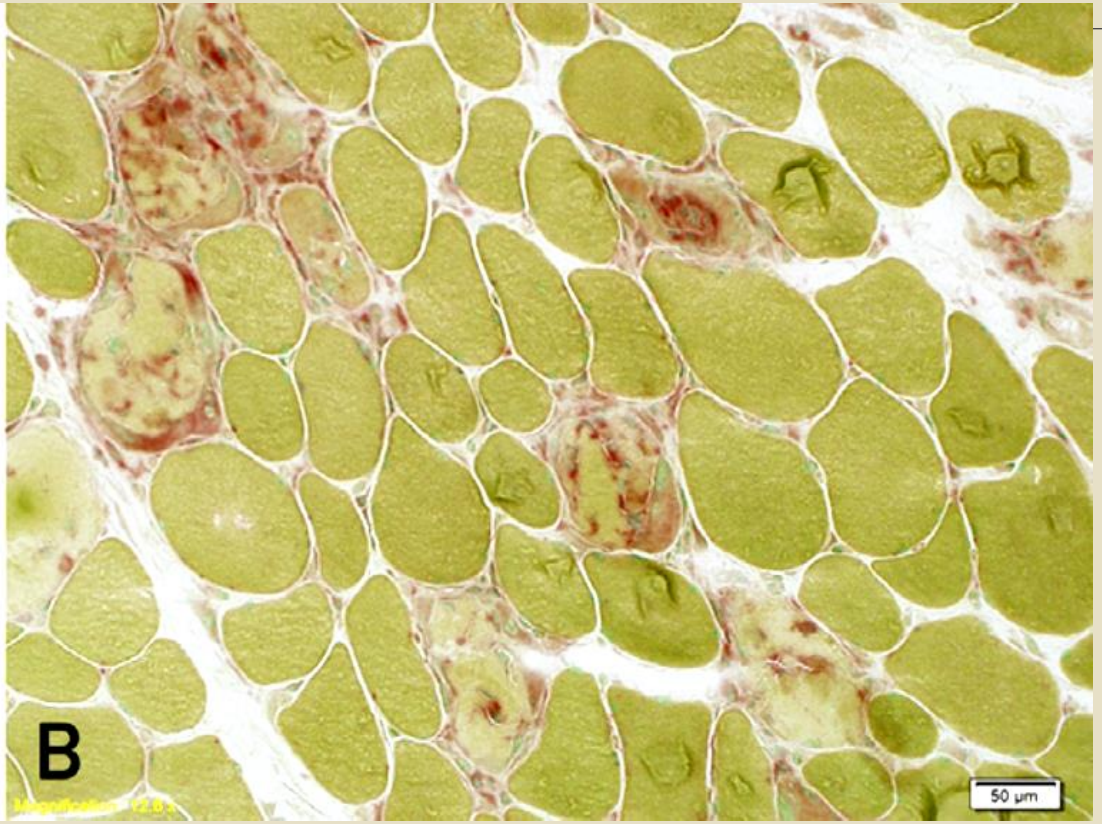
On routine histology, a degenerating muscle fiber being cleared by macrophages

Presence of nonnecrotic muscle fibers being invaded by CD8 T lymphocytes and macrophages (endomysial infiltrations), upregulated HLA class I

Courtesy of Meggen Walsh, D.O., M.S.-P.A.

http://www.pathologyoutlines.com/topic/musclepolymyositis.html





NAM

* Scattered necrotic muscle fibers
↓Fewer regenerating fibers
▼Muscle fibers with internalized nuclei
(B) Macrophages invading muscle fibers appeared red on acid phosphatase stain/ upregulated HLA class I

Anti-HMGCR + NAM → no inflammatory cell infiltrate
Anti-SRP + NAM → CD8 T cell endomysial infiltrate

Milone M. Mayo Clin Proc. 2017;92:826-837.

Bohan A & Peter JB 1975 criteria

1. **Symmetric proximal muscle weakness**
2. **Muscle biopsy evidence of myositis**
3. **Increase in serum skeletal muscle enzymes**
4. **Characteristic electromyographic pattern**
5. **Typical rash of dermatomyositis**

	PM	DM
Definite	All of 1-4	5 + any 3 of 1-4
Probable	Any 3 of 1-4	5 + any 2 of 1-4
Possible	Any 2 of 1-4	5 + any 1 of 1-4

Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med. 1975;292:403-7.
Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292:344-7.

ACR/EULAR criteria for IIM 2017

Variable	No Bx	Bx
Age of onset ≥18 & <40	1.3	1.5
Age of onset ≥40	2.1	2.2
Progressive proximal UE weakness	0.7	0.7
Progressive proximal LE weakness	0.8	0.5
Neck flexors weaker than extensors	1.9	1.6
LE: Proximal M. weaker than Distal M.	0.9	1.2
Heliotrope rash	3.1	3.2
Gottron's papules	2.1	2.7
Gottron's sign	3.3	3.7
Esophageal dysphagia	0.7	0.6

Variable	No Bx	Bx
Anti-Jo-1	3.9	3.8
M. Enzyme: CPK, LDH, AST, ALT	1.3	1.4
Endomysial infiltration		1.7
Perimysial ± perivascular infiltration		1.2
Perifascicular atrophy		1.9
Rimed vacuoles		3.1

Diagnosis	No Bx	Bx
Definite IIM	≥7.5	≥8.7
Probable IIM	≥5.5 & <7.5	≥6.7 & <8.7
Possible IIM	≥5.3 & <5.5	≥6.5 & <6.7

Overlap Myositis & Pure Classic Dermatomyositis

Characteristic	Overlap Myositis (OM) – PM & DM phenotypes				Pure Classic Dermatomyositis
	Anti-synthetase	Anti-MDA-5	OM with ANAs	OM with DM rash	
Frequency, %	50				30 - 35
Myositis	Classic VS Amyopathic	Mild → Amyopathic	Less severe	Classic VS Amyopathic	With Oropharyngeal dysphagia; Amyopathic
DM Rashes	Mechanic's hands (PM > DM phenotype)	Classic rashes[3] (DM phenotype)	None (PM phenotype)	Heliotrope/ Gottron's[3] (DM phenotype)	Classic extensive Chronic refractory
Overlap	RP, Arthritis, ILD	ILD, Arthritis	RA, SLE, SSc, MCTD	RA, SLE, SSc, MCTD	None
Presentation	- As syndrome[1] - As Amyopathic DM	Rapidly progressive ILD	As overlap syndrome[4]	- Weakness → Rashes - Adermatoathic DM (Mechanic's hand)	- Rashes → Weakness
Cancer	≤ 5%			None	Up to 50%
Auto Ab	Jo-1 VS Non-Jo-1[2]	Anti-MDA-5	ANA panels[5]	As other OMs	Anti-Mi-2 Anti-TIF-1γ Anti-NXP-2

1 = RP, RA-liked arthritis, Puffy hands, ILD, Fever, Mechanic's hands
2 = Anti-PL7, Anti- PL12, Anti- OJ, Anti- EJ, Anti- KS, Anti- ZO
3 = Palmar papules, cutaneous ulceration, digital ischemia
4 = Erosive arthritis, SLE features, SSc features, Trigeminal neuropathy
5 = Anti-U1/ U3/ U5/ U11-12 RNP, Anti-Pm-Scl, Anti-KU, Anti-nucleoporins, Anti-CENP-B, Anti-Th/To, Anti-RuvB-like 1/2, Anti-Scl-70, Anti-RNA polymerase III

Senécal JL, et al. Editorial: A New Classification of Adult Autoimmune Myositis. Arthritis Rheumatol. 2017;69(5):878-884.

Polymyositis phenotype and Inclusion body myositis

Characteristic	Polymyositis phenotype				Inclusion body myositis (IBM)
	Necrotizing autoimmune myositis (NAM)			Pure Polymyositis	
	Anti-HMGCR[1]	Anti-SRP	Seronegative		
Frequency, %	10 - 15			≤5	≤5
Myositis	Classic; Late-onset; Less severe	Classic & Severe	Classic	Classic & Subacute LE → UE → Neck→ Trunk → Myocardium → Diaphragm	finger flexor → wrist flexor/extensor → quadriceps
DM Rashes	No	No	No	No	No
Overlap	No	No	No	No	No
Presentation	Proximal muscle weakness	Proximal muscle weakness		Proximal muscle weakness	Distal UE → Proximal LE
Cancer	Yes in statin naïve	No	Yes	No	No
Auto Ab	Anti-HMGCR	Anti-SRP	None	Undefined	Anti-5'-nucleotidase 1A

1 = 2/3 associated with statin use; 1/3 do not

Senécal JL, et al. Editorial: A New Classification of Adult Autoimmune Myositis. Arthritis Rheumatol. 2017;69(5):878-884.

Treatment for DM/PM

- DM/PM without severe organ manifestation i.e. ILD
- **Induction**: prednisolone 0.75-1 MKD for 4 – 12 weeks with

DMARDs choices for maintenance of remission	Dose
Methotrexate (2.5 mg tablet)	15 – 25 mg / week
Azathioprine (50 mg tablet)	1 – 2 MKD in bid. dose
Mycophenolate mofetil (250, 500 mg)	Increment to 2 – 3 g/day

- Assessment @4^{th} – 6^{th} week
  - Improved → taper prednisolone every 2 wk. until completed/ ↓DMARDs to maintenance
  - Not improved → ↑ DMARDs dose or switch to another

mg/day	60	40	30	25	20	15	10	7.5	5	2.5
	6 x 2	4 x 2	6 x 2	3-0-2	2 x 2	3 x 1	2 x 1	2 x 1 AD	1 x 1	1 x 1 AD

Treatment for DM/PM

- Refractory to conventional therapy OR Severe organ-threatening manifestation e.g.
- ILD, Dysphagia with weight loss, Severe weakness, Cardiomyopathy

Prednisolone 0.75 – 1 mg/kg/day OR Methylprednisolone 0.5 – 1 g/day IV for 1 – 3 day(s) then
Cyclophosphamide 0.6-1.0 g/m^2 IV q 4 week for 3-12 month
Cyclophosphamide 1-2 MKD oral for 3-12 month
Cyclosporine A (25, 100 mg/cap) 3.0-3.5 MKD, starting with 1.25-2.5 MKD in divided dose
Tacrolimus 0.075 mg/kg/day in bid dose
IVIG 1 g/kg divided over 1-2 day q month x 1-6 month
Rituximab 1 g IV D1 & D15

- Improved → ↓prednisolone & maintenance DMARDs

F/U lab:
CBC, ESR, CRP, Creatinine
SGOT, SGPT, CPK, LDH
Albumin, Globulin

Clinical scenario suspected MCTD

A late adult woman presents with

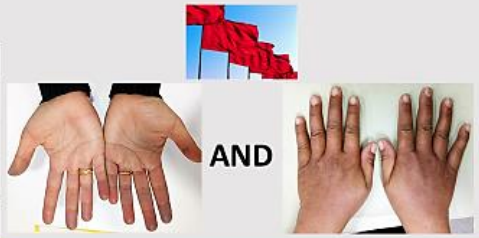
Raynaud, puffy fingers, sclerodactyly,
RA-liked arthritis, Esophageal dysmotility, GERD
Pulmonary vasculitis (HT)
Immune-complexes mediated glomerulonephritis
Podocytopathy

Primary RP (Raynaud disease) VS. SSc-RP

<10% in general population

1° Raynaud	2° Raynaud
Pallor → Cyanosis → Redness	Pallor → Cyanosis
< 40 years; F:M = 3:1	≥ 40 years
No ischemic complications	Ischemic complications

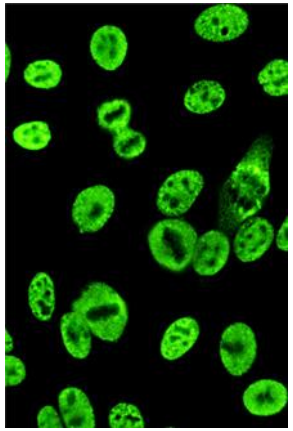
Red flags for SSc – RP
Skin: puffy finger*, sclerodactyly, digital ulcer/pitting scar
GI: GERD*
Serology: +ANA*, SSc specific Ab
* character of early scleroderma



1. +ANA (95%), ATA or ACA → **SSc**
2. +ANA >1:1600, +anti-U1RNP
   anti-dsDNA & anti-Sm neg. → **MCTD**
3. +ANA ≥1:80, +anti-dsDNA or anti-Sm → **SLE**
4. + or – ANA w/o specific antibody → **UCTD**

Pope J, et al. BMJ Clin Evid. 2013; 2013: 1119.
Ann Rheum Dis. 2009; 68:1377-80.
Ann Rheum Dis. Published Online First: 12 Aug 2013 doi: 10.1136/annrheumdis-2013-203716

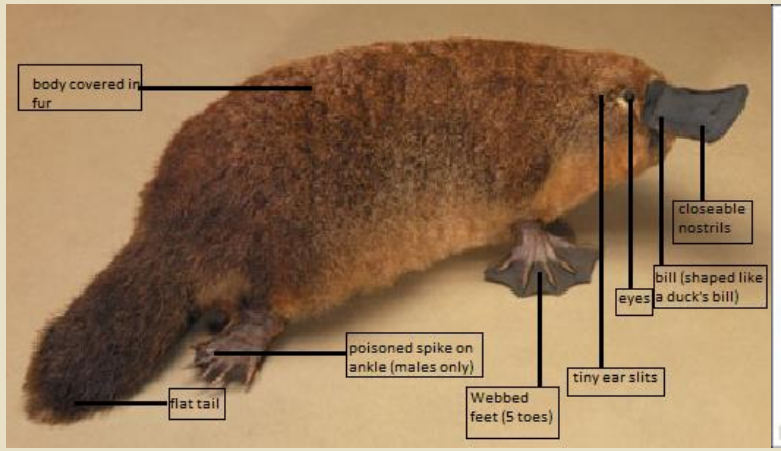
ANA (Hep2 cell IFA)
Titer >1:1,6000 (>1:1,000)
Coarse speckled pattern



Anti-dsDNA, Anti-Sm
Anti-U1RNP

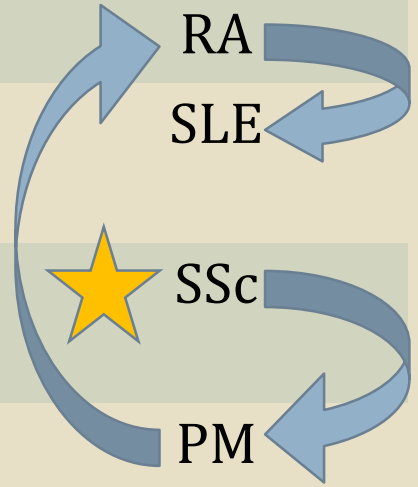
To Dx, MCTD ANA has to be positive with a very high titer, i.e.,>1:1,600, negative anti-dsDNA and anti-Sm, and positive anti-U1RNP.

MCTD liken to hybrids of RA, SLE, SSc, and PM



With serologic study
- ANA > 1:1,600
- (+) anti uRNP
- (-) anti Sm
- (-) anti dsDNA

Clinical Manifestations	Resemble
Erosive RA-liked arthritis	RA
Photosensitivity, Oral ulcer, Jaccoud's arthropathy ↓**WC**, ↓**Plt.**, Serositis, PH-arterial vasculitis	SLE
RP, **Sclerodactyly**, Scleroderma (lcSSc), Telangiectasia, Salt-Pepper skin Esophageal dysmotility	SSc
Proximal muscle weakness with **HyperCKemia**	PM



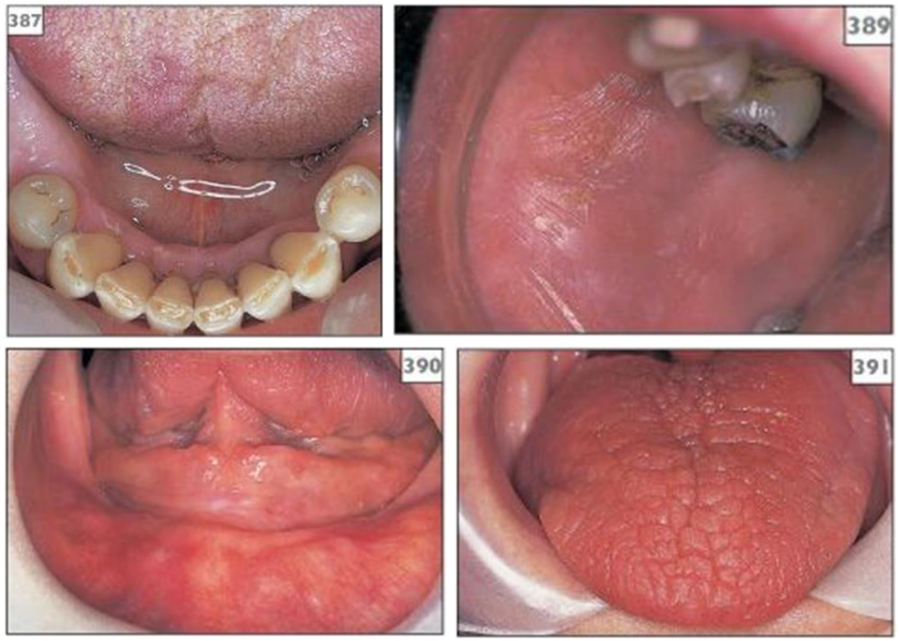
- **Typical initial manifestation**
  - Puffy hands + Raynaud's phenomenon + RA-liked arthritis
- **The Alarcón- Segovia 1987 Classification Criteria**
  1. **Serologic criteria**
     - Anti-U1 snRNP at a hemagglutination titer of ≥ 1:1,600
  2. **Clinical criteria**
     1. **M**yositis
     2. **R**aynaud's phenomenon
     3. **S**ynovitis (i.e. arthritis)
     4. **A**crosclerosis (i.e. sclerodactyly)
     5. **P**uffy hands

Treatment for MCTD

Clinical Manifestations	Resemble	Treatment
○ Erosive RA-liked arthritis	RA	NSAIDs, CQ, DMARDs
○ Photosensitivity, Oral ulcer ○ Jaccoud's arthropathy ○ ↓WC, ↓Plt., ○ Serositis ○ PH-arterial vasculitis	SLE	○ Sunscreen, topical steroids ○ AROM exercise ○ CQ ○ CQ, NSAIDs ○ Prednisolone ≥ 0.5 MKD
○ Raynaud's phenomenon ○ Puffy hands, Sclerodactyly, Scleroderma ○ Esophageal dysmotility, GERD	SSc	○ Vasodilators ○ CQ, colchicine, sunscreen ○ PPI + prokinetics
○ Proximal muscle weakness with ↑CPK	PM	○ Prednisolone ≥ 0.5 MKD
○ Trigeminal neuropathy, SNHL	Itself	○ Prednisolone ≥ 0.5 MKD

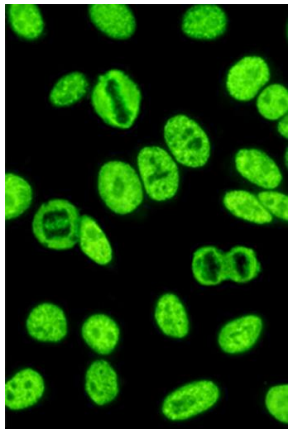
Clinical scenario suspected Sjogren syndrome

A 50-60 YO woman (F: M = 9:) presents with
Xerostomia & Xeropthalmia (40%)
Parotid gland enlargement bilaterally
RA-liked arthritis (70%), Raynaud (30%)
ILD (20% before, 60% concurrently, 20% after)
Leucopenia, Lymphopenia, ITP
TIN with tubular acidosis OR MPGN



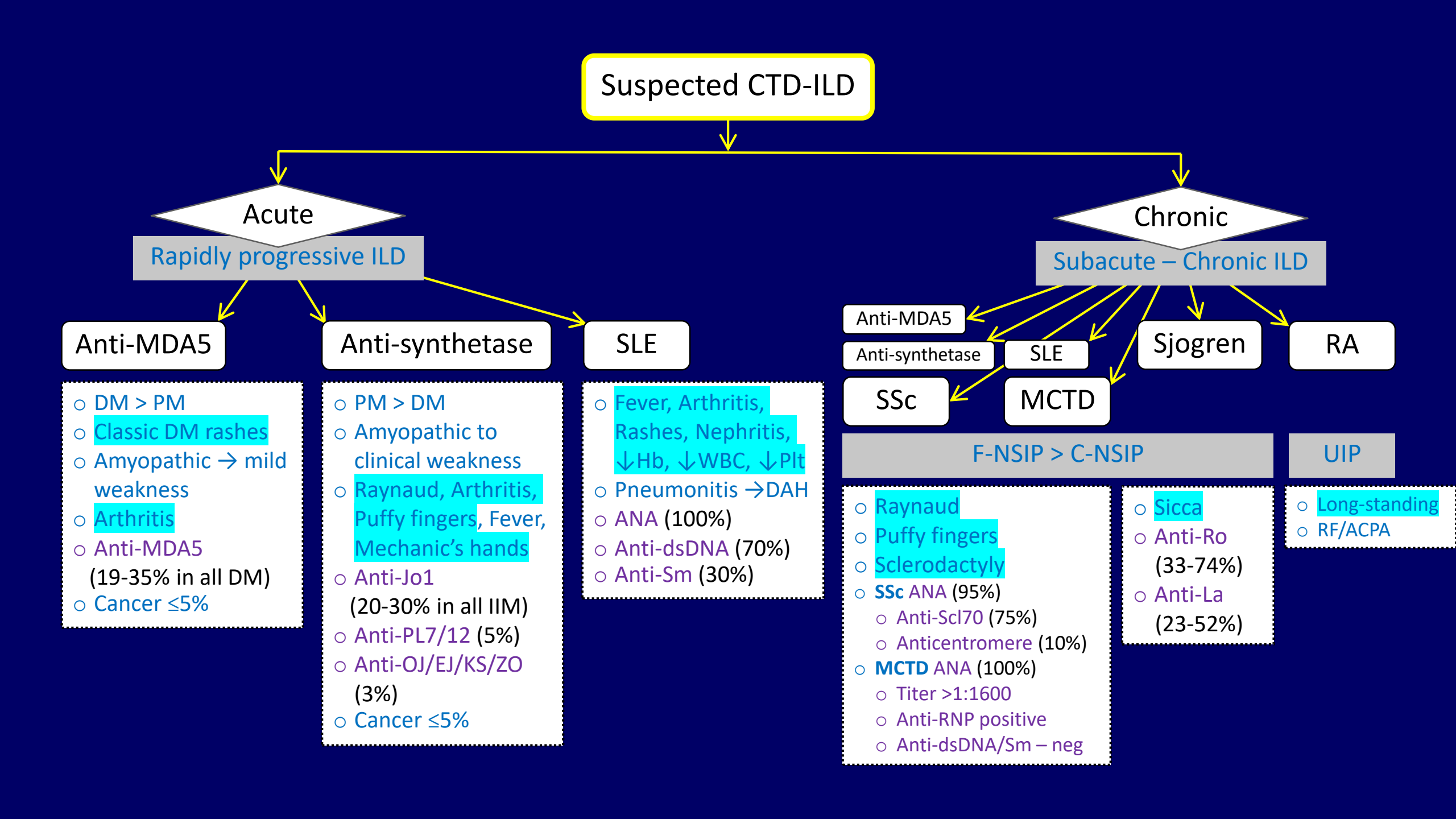
https://pocketdentistry.com/

ANA (Hep2 cell IFA)
Titer >1:320 (80%)
Fine speckled pattern



RF 40% (>20 IU/mL)
Anti-Ro52 or Anti-Ro60/SSA (50%)
Anti-La/SSB (15-20%)
Anti-centromere (20%)

Lin W, et al. BMC Pulm Med. 2022 Feb 27;22(1):73.
Luppi F, et al. Clin Exp Rheumatol. 2020 Jul-Aug;38 Suppl 126(4):291-300.


Suspected CTD-ILD
Acute
Rapidly progressive ILD
Chronic
Subacute – Chronic ILD
Anti-MDA5
Anti-synthetase
SLE
Anti-MDA5
Anti-synthetase
SLE
Sjogren
RA
SSc
MCTD
F-NSIP > C-NSIP
UIP
○ DM > PM
○ Classic DM rashes
○ Amyopathic → mild weakness
○ Arthritis
○ Anti-MDA5 (19-35% in all DM)
○ Cancer ≤5%
○ PM > DM
○ Amyopathic to clinical weakness
○ Raynaud, Arthritis, Puffy fingers, Fever, Mechanic's hands
○ Anti-Jo1 (20-30% in all IIM)
○ Anti-PL7/12 (5%)
○ Anti-OJ/EJ/KS/ZO (3%)
○ Cancer ≤5%
○ Fever, Arthritis, Rashes, Nephritis, ↓Hb, ↓WBC, ↓Plt
○ Pneumonitis →DAH
○ ANA (100%)
○ Anti-dsDNA (70%)
○ Anti-Sm (30%)
○ Raynaud
○ Puffy fingers
○ Sclerodactyly
○ SSc ANA (95%)
○ Anti-Scl70 (75%)
○ Anticentromere (10%)
○ MCTD ANA (100%)
○ Titer >1:1600
○ Anti-RNP positive
○ Anti-dsDNA/Sm – neg
○ Sicca
○ Anti-Ro (33-74%)
○ Anti-La (23-52%)
○ Long-standing
○ RF/ACPA

The Emerald Lake @Alberta Canada Photo by Chayawee

The End
Thank You for
Your Attention