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Myositis 101

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Division of Rheumatology

Mayo Clinic

Myositis Association Annual Conference

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Disclosures

- **Financial:**
  - **Dynavax**
  - **Pfizer**
  - **Mallinckrodt**
  - **American Board of Internal Medicine**
- **Off-label use:**
  - **Nothing is FDA approved other than steroids**

Topics

- Myositis – definition, recognition
- Defining individual diseases
- Epidemiology
- Autoantibodies
- Treatment

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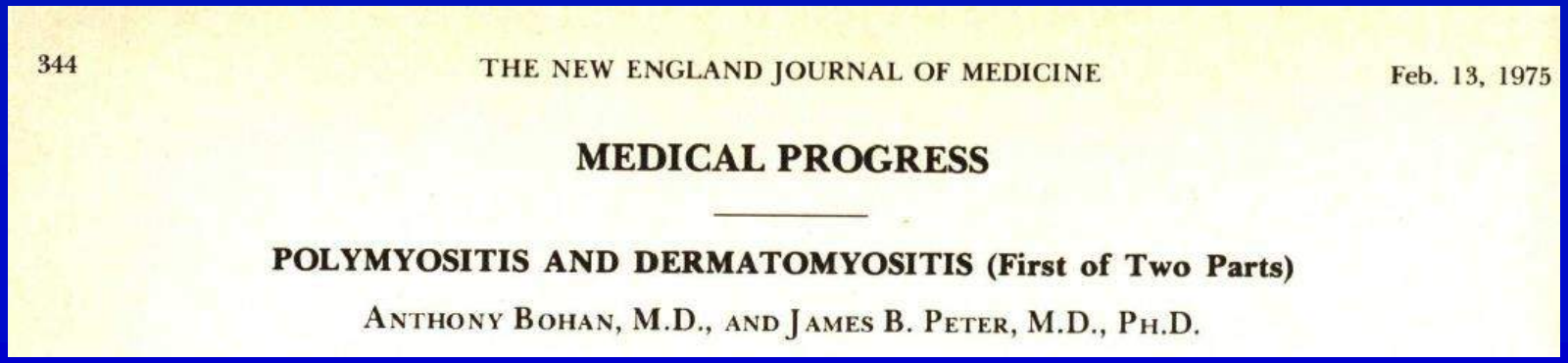
Idiopathic Inflammatory Myopathies

- Polymyositis (PM)
- Dermatomyositis (DM)

- Isolated, adult
- Juvenile
- Malignancy
- Overlap



344 THE NEW ENGLAND JOURNAL OF MEDICINE Feb. 13, 1975

MEDICAL PROGRESS

POLYMYOSITIS AND DERMATOMYOSITIS (First of Two Parts)

ANTHONY BOHAN, M.D., AND JAMES B. PETER, M.D., PH.D.

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Bohan & Peter, N Engl J Med 292: 344, 405, 1975
Bohan et al., Medicine 56: 255, 1977

Idiopathic Inflammatory Myopathies

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- Dermatomyositis (DM)
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  - Juvenile
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- Inclusion body myositis (IBM)
- Antisynthetase syndrome
- Immune-mediated necrotizing myopathy (IMNM)

PM/DM Classification Criteria

- Proximal muscle weakness
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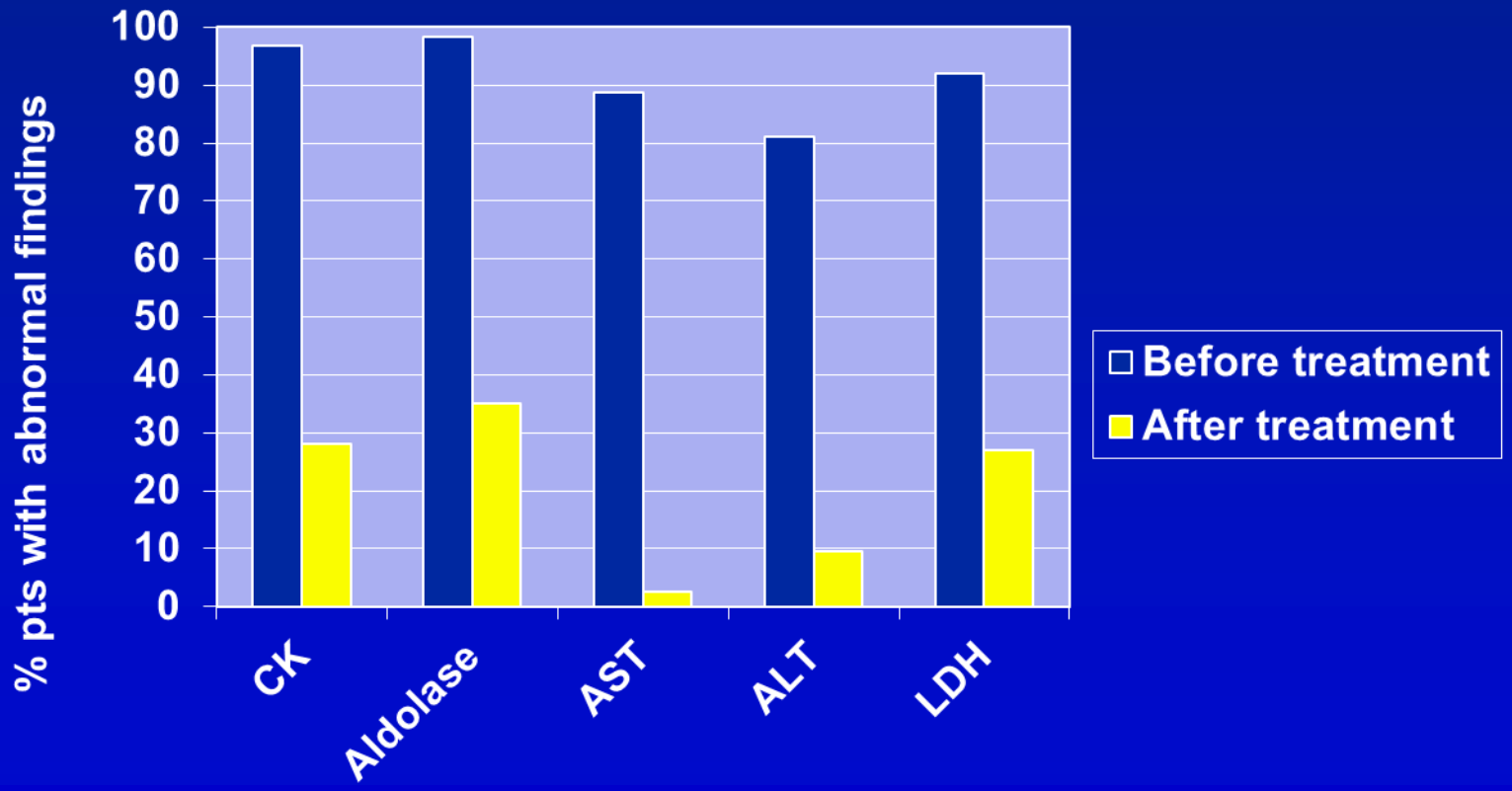
Assessment of Muscle Weakness

- Manual muscle strength testing
- Physiologic testing
- Functional tests
  - Timed stands
  - 6 minute walk
  - Functional Index-2

Evaluation of Muscle Disease: Laboratory Tests

- CK – Creatine kinase (CPK)
- Aldolase
- LDH – Lactate dehydrogenase
- AST – aspartate aminotransferase
- ALT – alanine aminotransferase

Effects of Treatment on Muscle Enzymes



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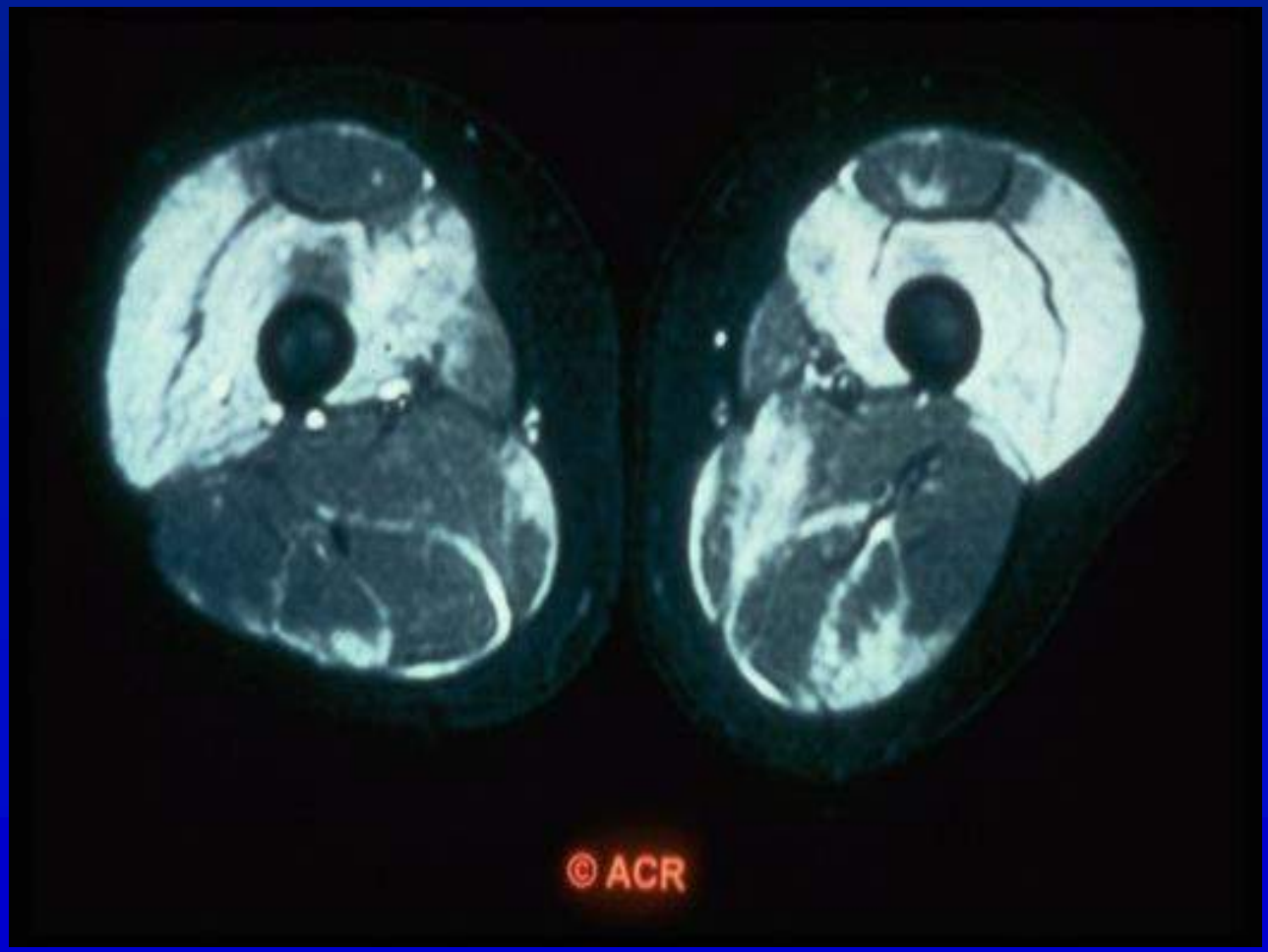
Bohan et al., Medicine 56: 255, 1977

Muscle MRI



EMG Findings in IIM

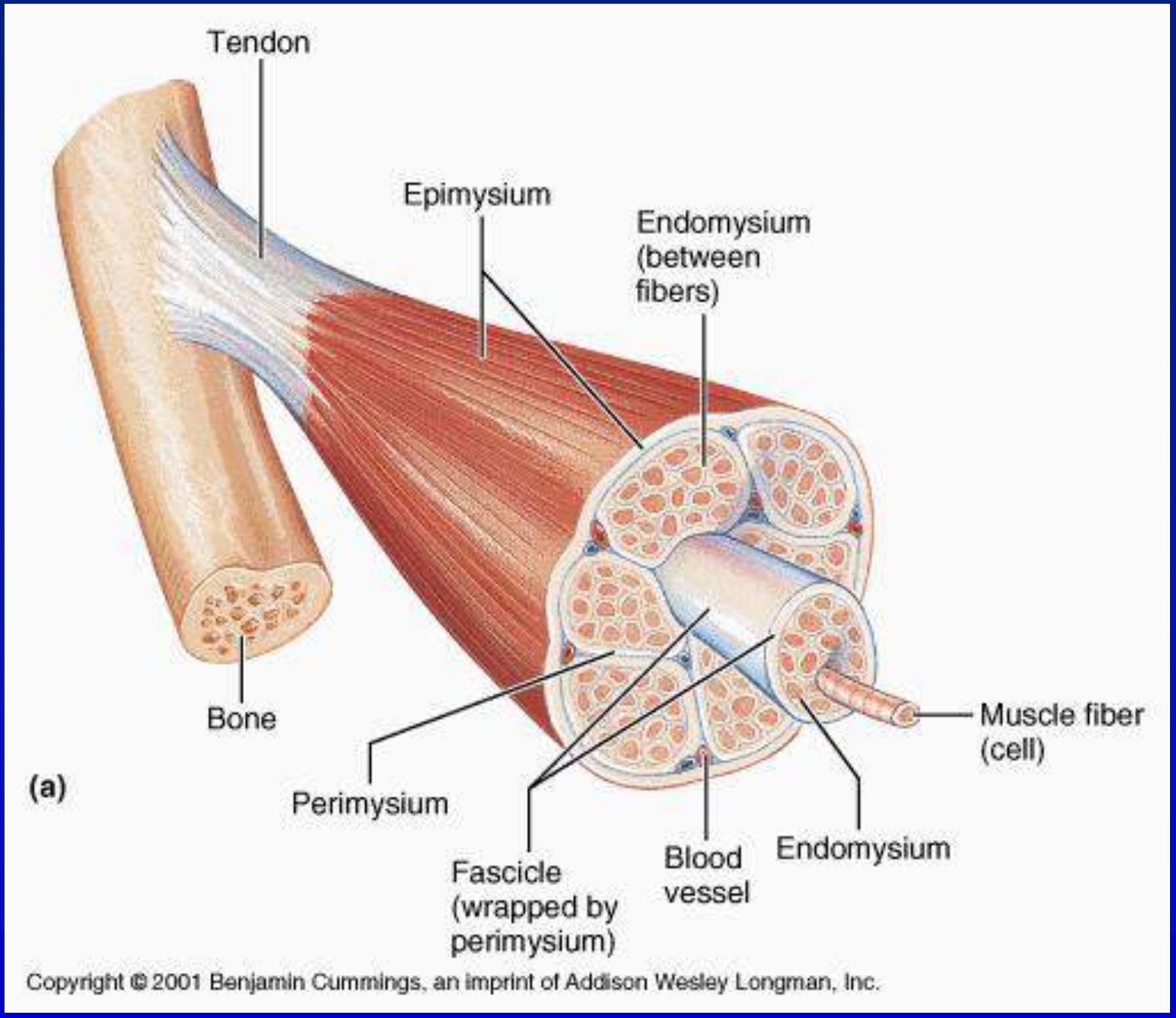
- Irritability on needle insertion and at rest
  - Fibrillations
  - Complex repetitive discharges
  - Positive sharp waves
- Abnormal MUAPs on contraction
  - Short duration
  - Low amplitude
  - Polyphasic

EMG – Polymyositis

INTERPRETATION: The findings are consisent with a myopathy most prominently affecting leg muscles. There could be necrosis, fiber splitting or vacuolization.

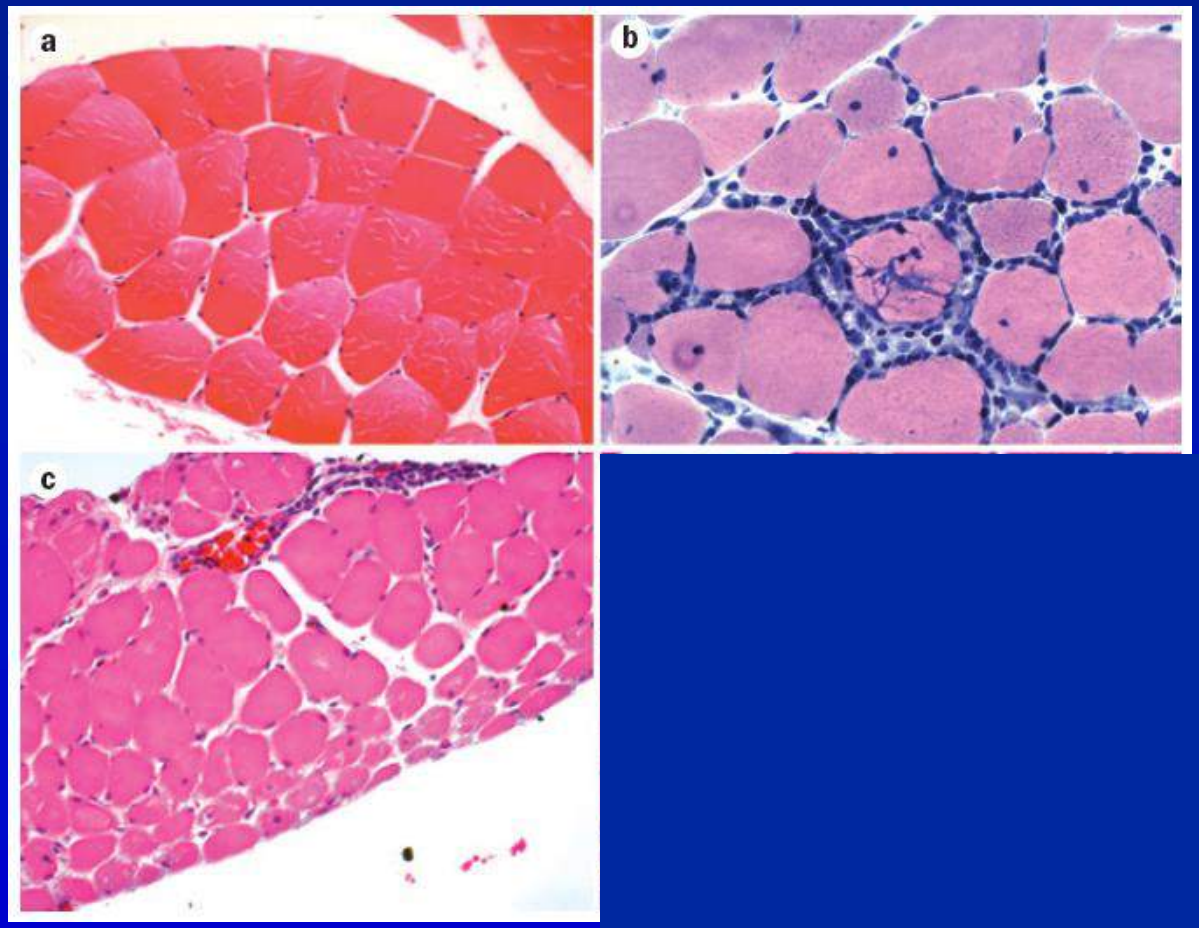
VOLUNTARY MOTOR UNIT POTENTIALS

MUSCLE	INSERT. ACTIVITY	SPONTANEOUS Fib.	SPONTANEOUS Fasc.	MUP NORMAL	RECRUITMENT Act.	RECRUITMENT Reduced	RECRUITMENT Rapid	DURATION LONG	DURATION SHORT	AMPLITUDE HIGH	AMPLITUDE LOW	PHASES %	PHASES TURNS
L. Biceps brachii	Increased	+/-	0						+		+		
L. Deltoid	Normal	0	0						+/-				
L. Triceps brachii	Normal	0	0	Normal					+/-				
L. Medial gastroc.	Increased	++	0						++		+++	25%	
L. Tensor fasciae latae	Normal	0	0						+		+		
L. Tibialis anterior	Increased	+	0									25%	
	Comment: Occasional slow fibs												
L. Vastus lateralis	Increased	+	0						+		+	25%	
L. T10 paraspinal	Increased	0	0	Normal					+/-				



http://www.nooruse.ee/e-ope/opiobjektid/lihasfysioloogia/lihasfsioloogia_alused.html

Muscle histopathology



a) Normal muscle
b) PM – endomysial inflammation
c) DM – perifascicular atrophy

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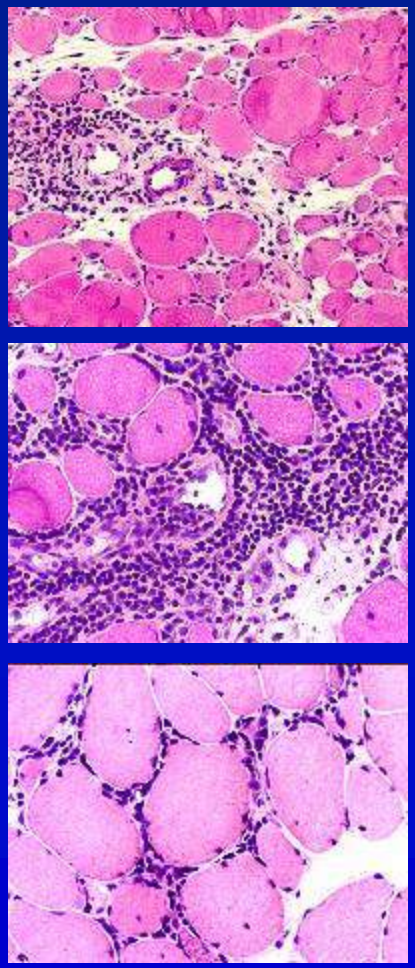
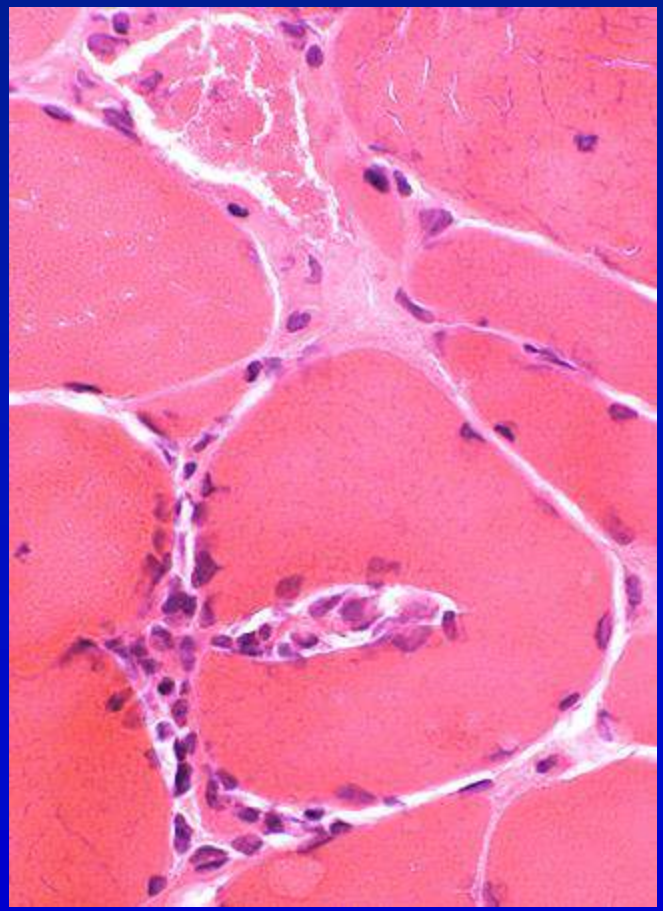
Mammen, Nat Rev Neurol 2011; 7:343-54

Inflammation in IIM





http://www.neuro.wustl.edu/neuromuscular/pathol/inflammation.htm

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Bohan et al., Medicine 56: 255, 1977

Other Features/ Organ System Problems

- **Lung** – interstitial lung disease
- **Gastrointestinal** – dysphagia, anorexia, reflux
- **Heart** – inflammation, fibrosis, rhythm
- **Joints** – arthritis, arthralgia, morning stiffness
- **Raynaud's phenomenon**
- **Constitutional** – fatigue, fever

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- Defining individual diseases
- Epidemiology
- Autoantibodies
- Treatment

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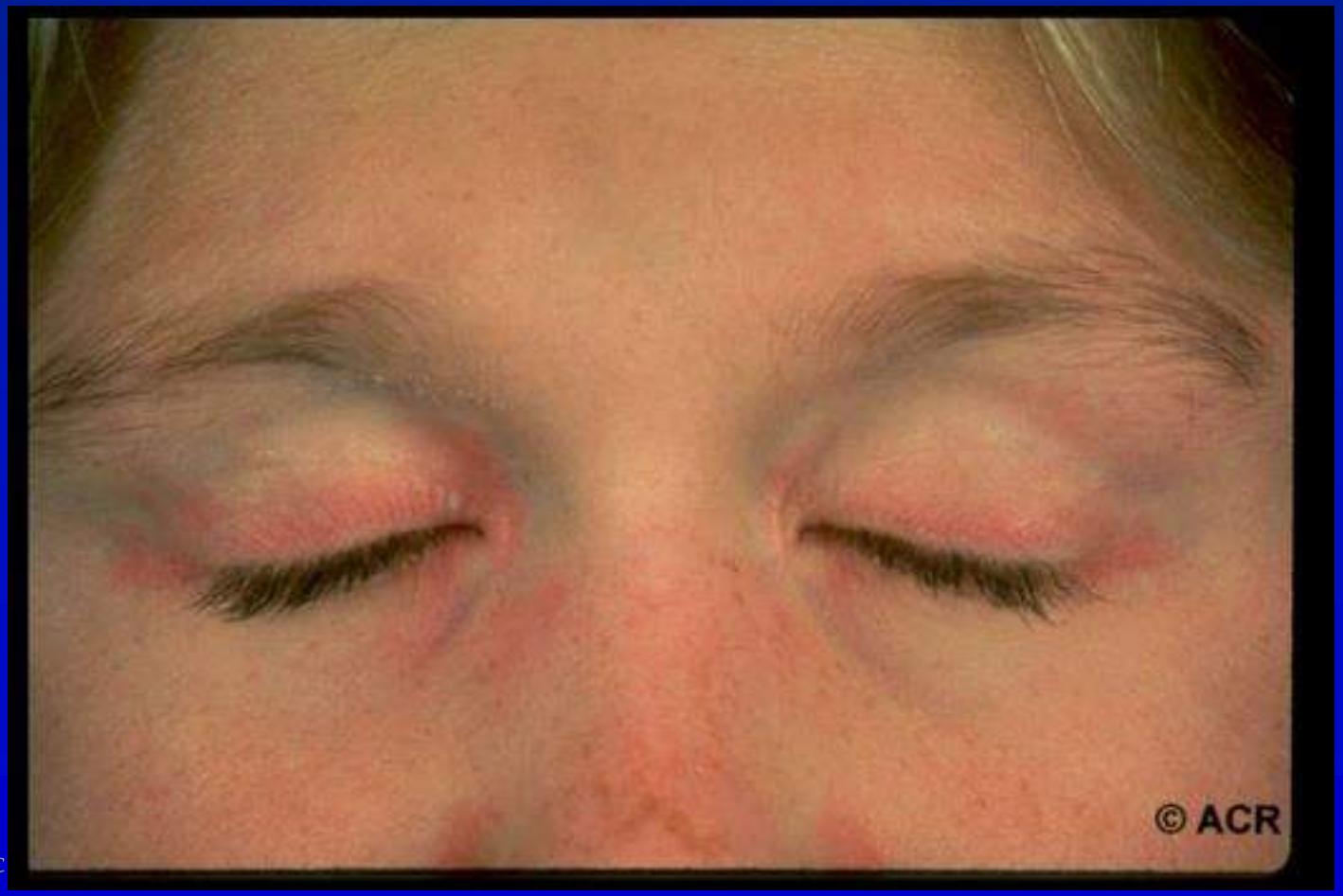
Dermatomyositis

- Skin changes define the disorder, more than muscle involvement

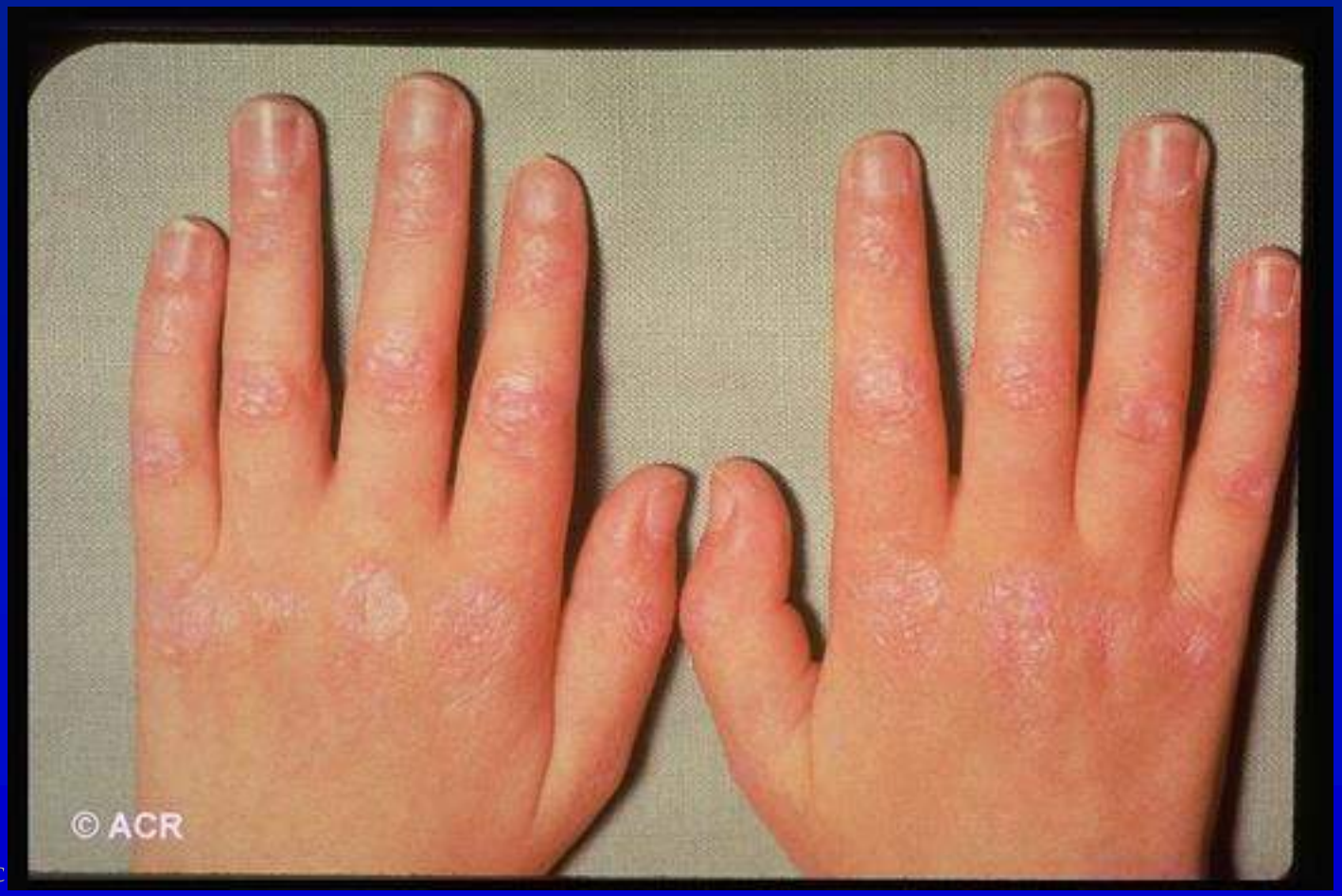
Rashes of Dermatomyositis

- Heliotrope
- Gottron's papules
- Shawl sign & others
- Calcinosis cutis

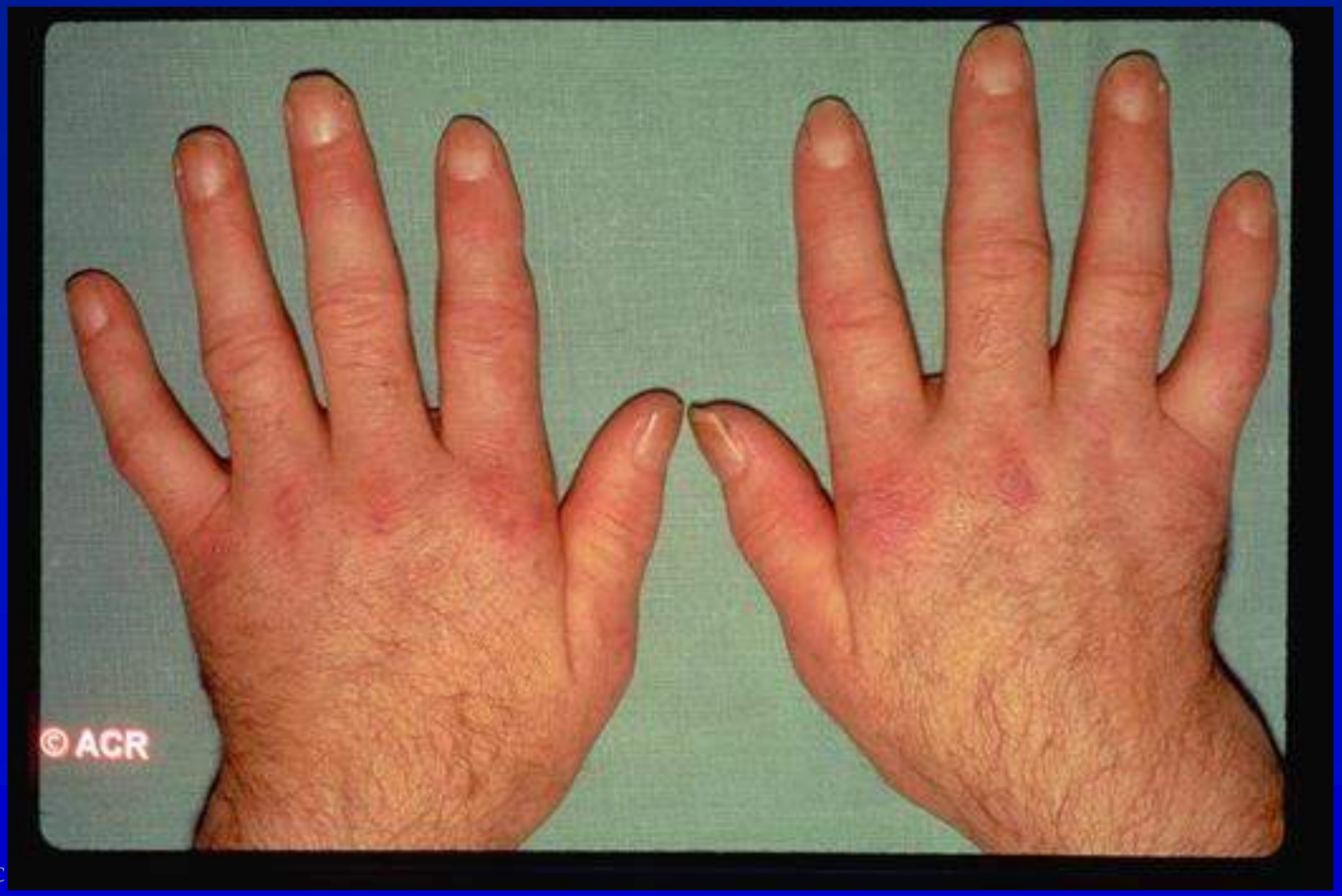
Heliotrope



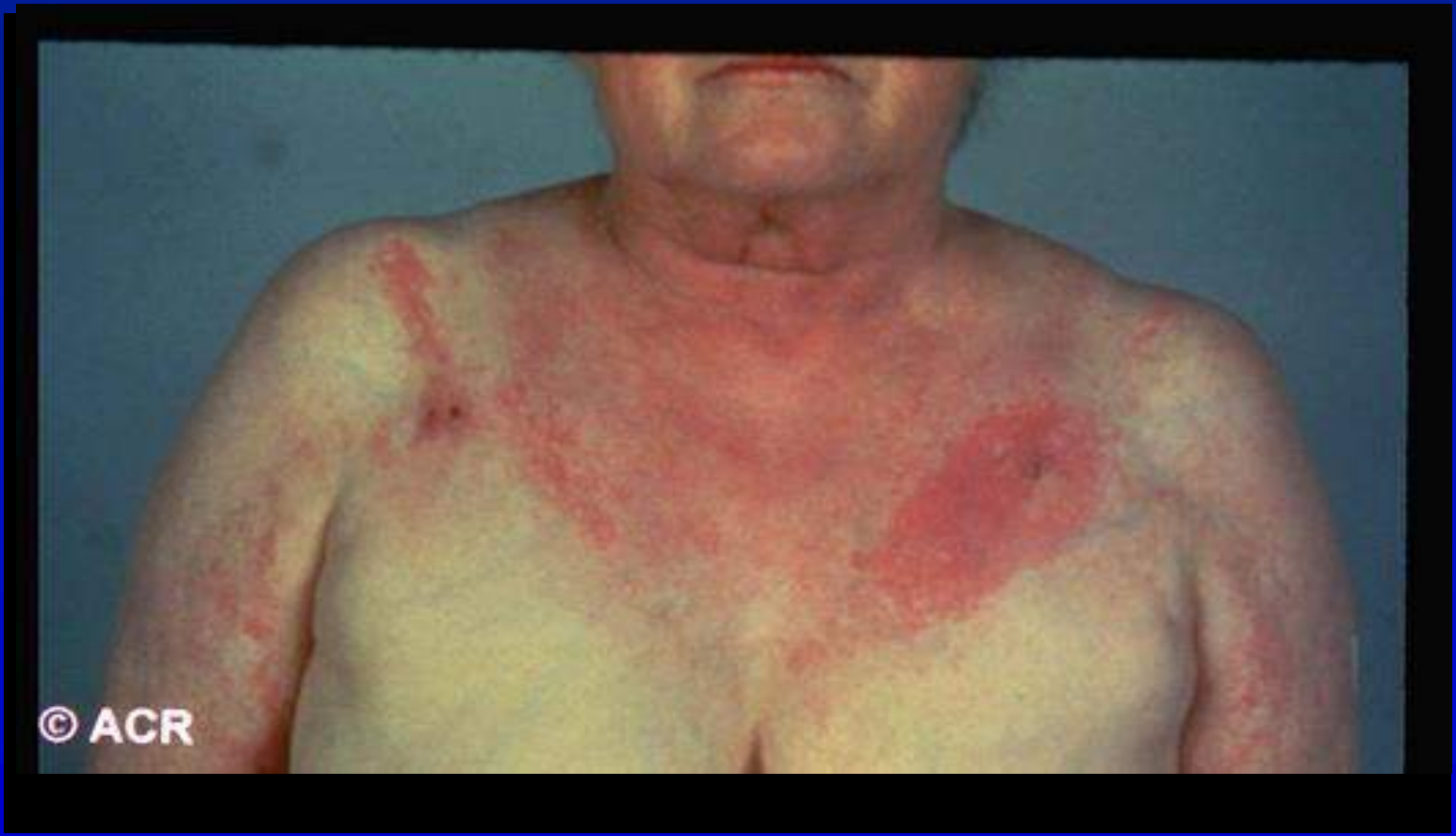
Gottron's papules



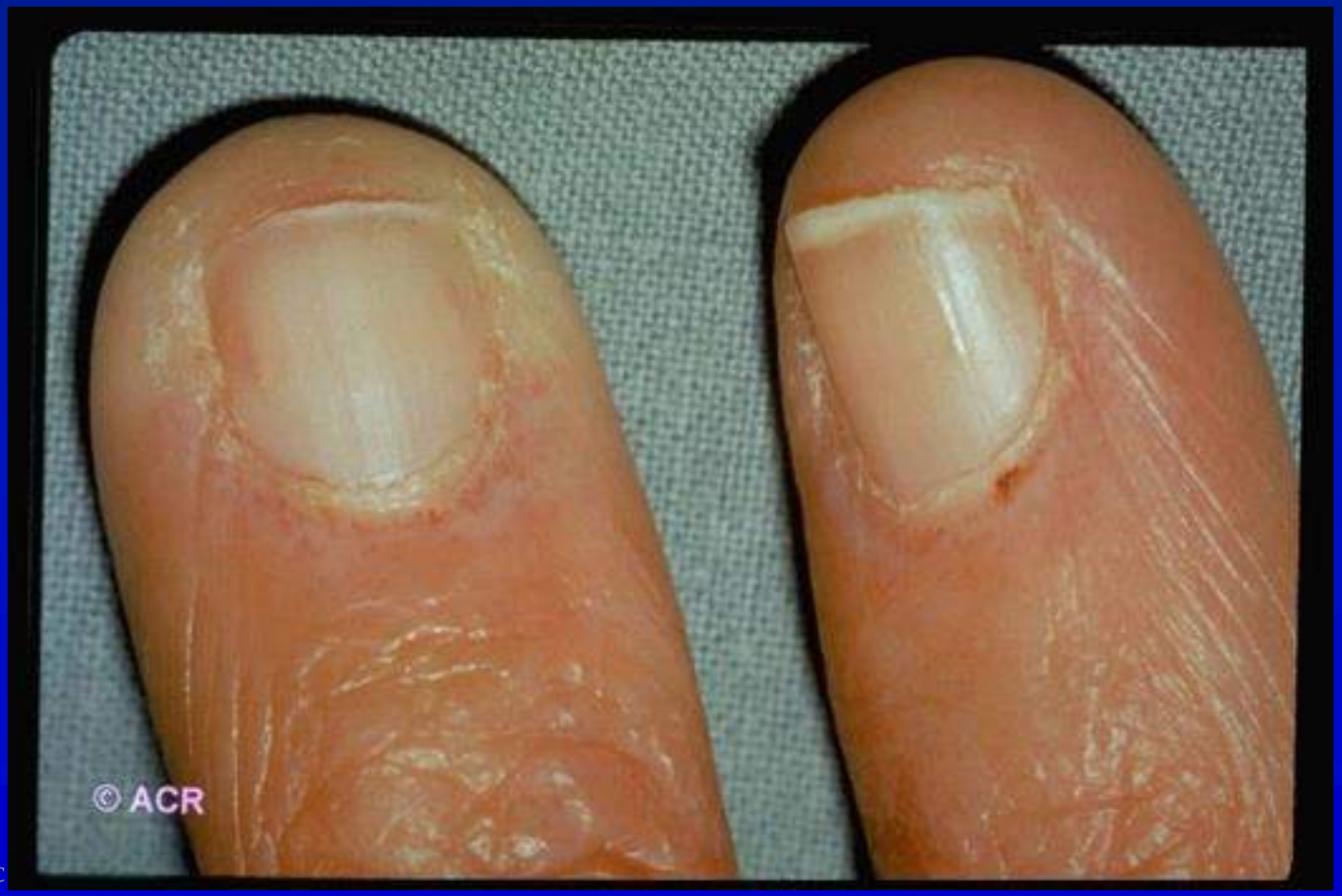
Gottron's sign



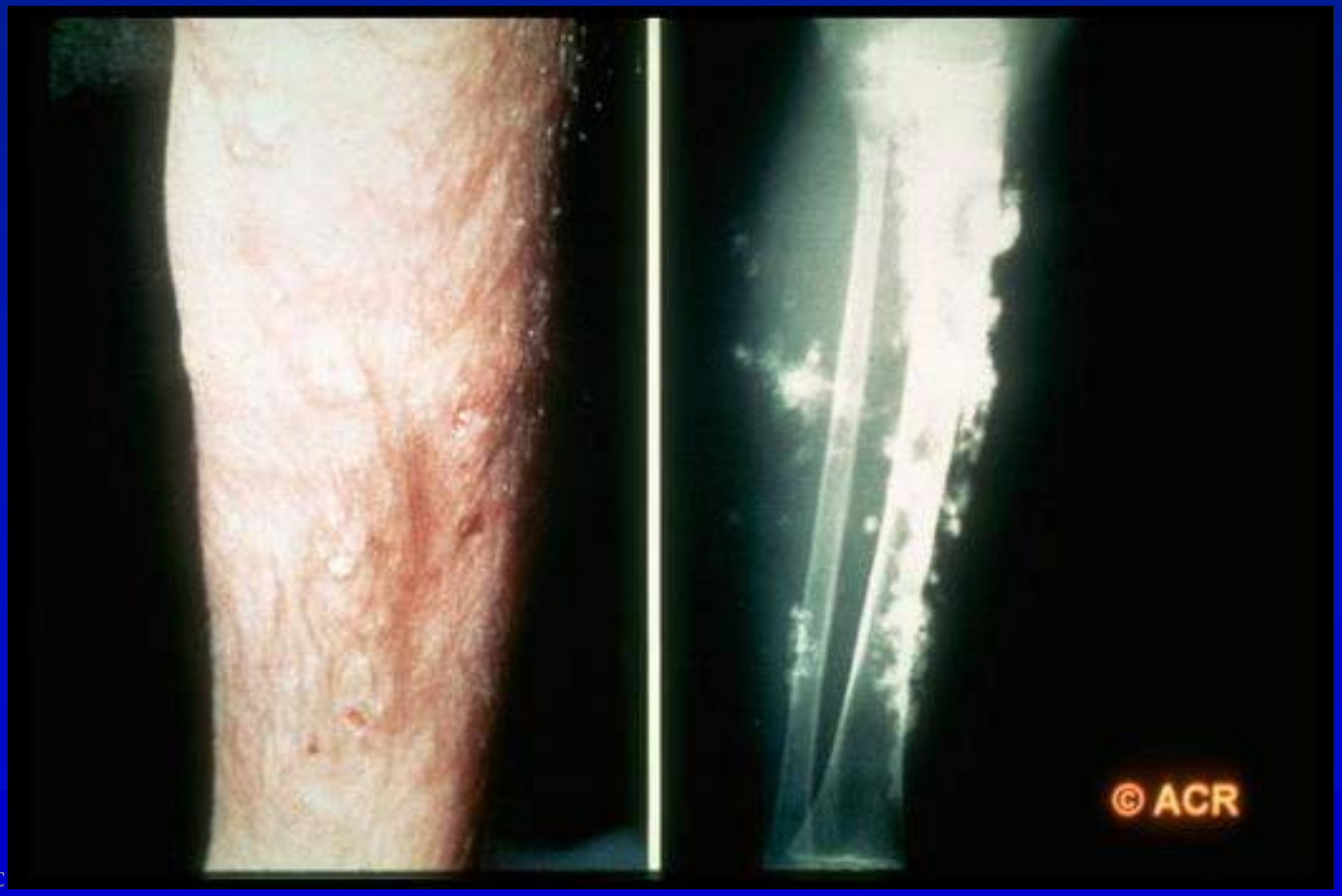
Shawl sign



Periungual erythema



Calcinosis cutis



Amyopathic Dermatomyositis (Dermatomyositis siné myositis)

- Cutaneous features of DM
- No muscle weakness
  - Maybe elevated muscle enzymes or EMG, but not weak

Gerami et al., J Am Acad Dermatol 54:597-613, 2006

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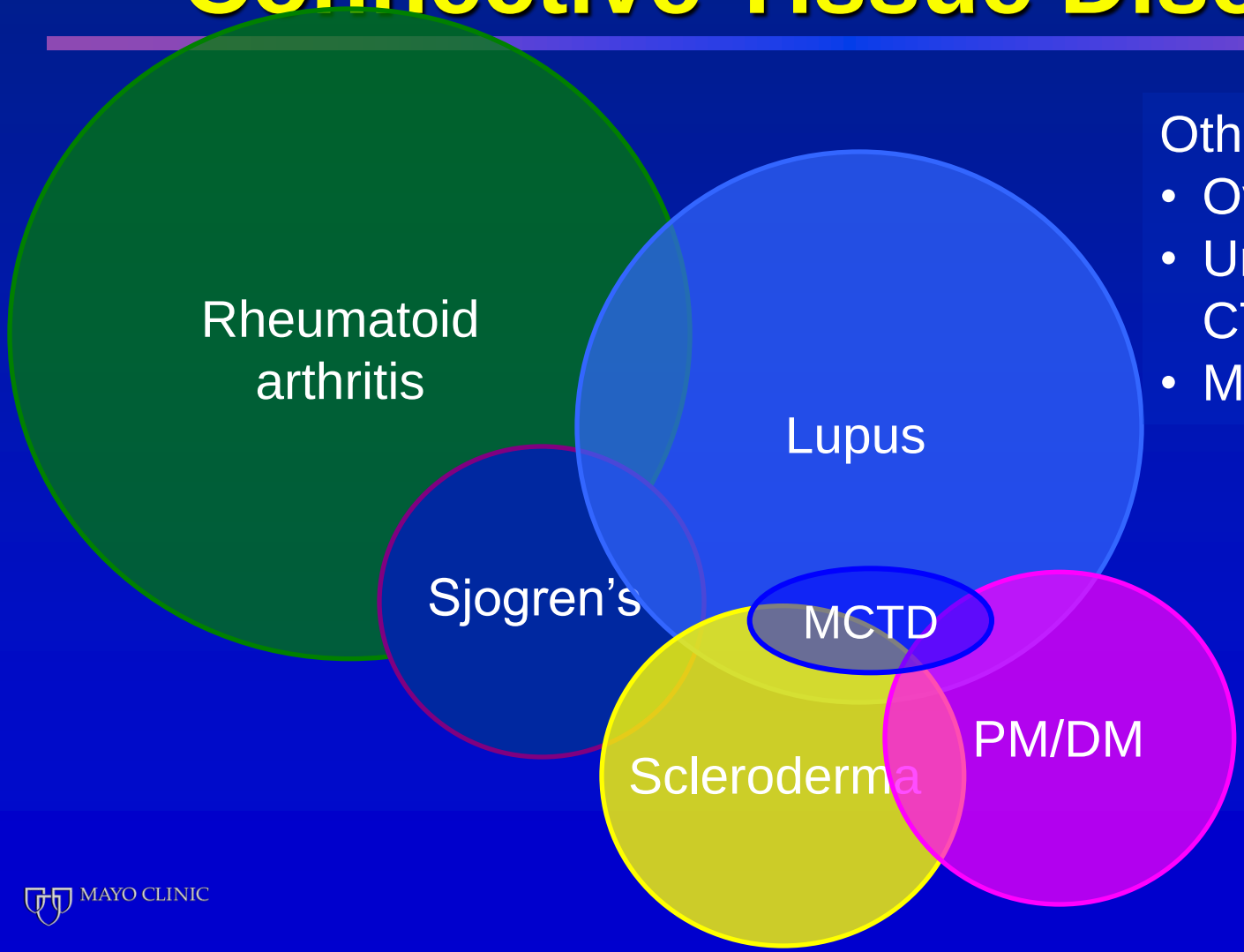
Autoimmune Connective Tissue Diseases



Other terms:

- Overlap CTD
- Undifferentiated CTD
- Mixed CTD

Inclusion body myositis

- Muscle biopsy findings define the disorder

Myxovirus-Like Structures

in a Case of Human Chronic Polymyositis

Abstract. *Intranuclear and intracytoplasmic aggregates of filaments with tubular structures and transverse striations occurred in muscle tissues biopsied from a patient with chronic polymyositis. The filamentous tubules bear a close resemblance to the incomplete form of myxovirus in which the envelope is missing. Three biopsies from the same patient, taken during a period of 1½ years, all revealed these structures. This finding provides presumptive evidence that a chronic persistent viral infection may be involved in the pathogenesis of chronic polymyositis.*

SHI-MING CHOU

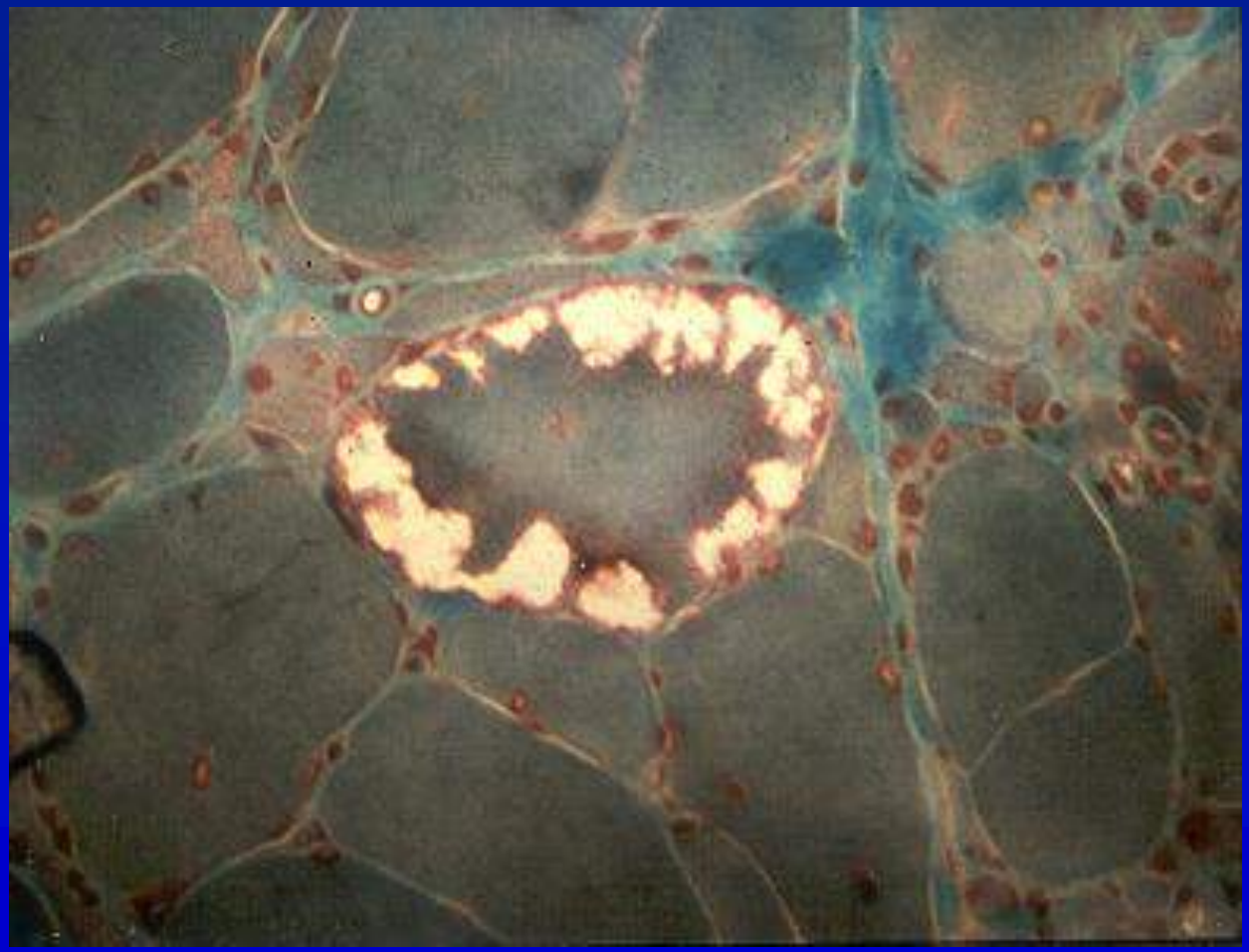
Department of Pathology and
Regional Primate Research Center,
University of Wisconsin
Medical School, Madison

15 DECEMBER 1967

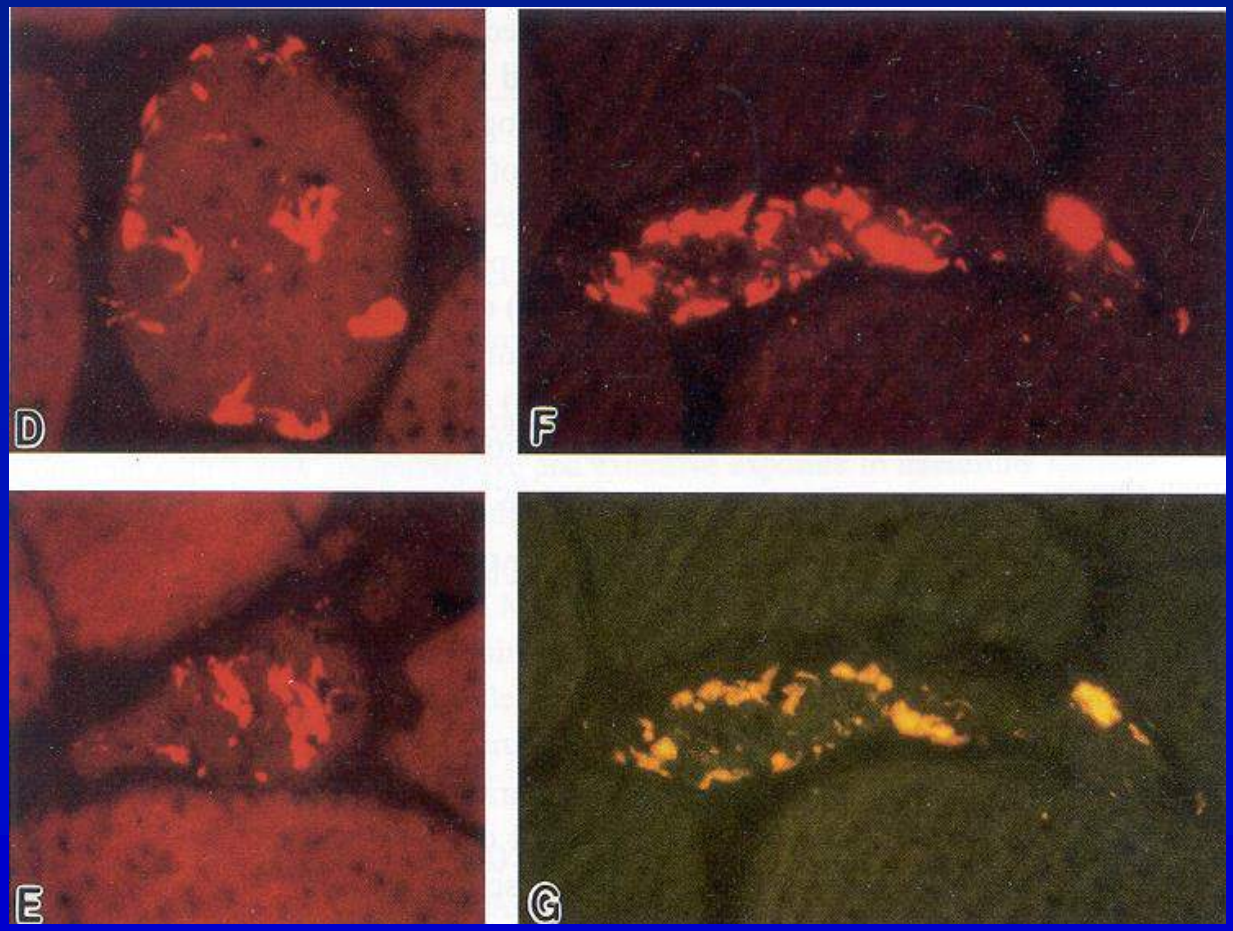
Inclusion Body Myositis

- First description 1967
- "IBM" term coined 1971
- Sporadic form (s-IBM)
- Several hereditary forms (h-IBM)
- Clinically similar:
  - Weakness: insidious, distal, atrophy
  - CK minimally to moderately elevated
  - EMG: myopathic +/- neurogenic
- Hereditary: younger; no inflammation

IBM: Vacuoles



IBM: Congo Red Staining



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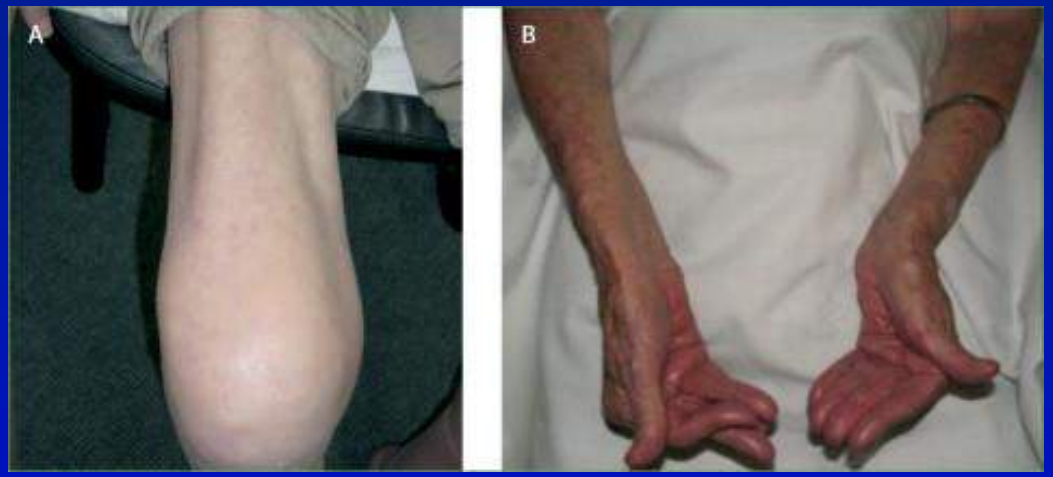
Askansas & Engel, J Neuropathol Exp Neurol 60:1, 2001

Clinical Features of sIBM

- Insidious onset
- ~6 years to diagnosis
- Weakness generalized or localized to limbs; may be asymmetric
- Reflexes normal initially, eventually diminished in 40%
- Dysphagia in 2/3 – late
- Myalgia uncommon but aching in thighs and knees in some



Typical involvement:
- Finger flexors
- Wrist flexors
- Knee extensors
- Ankle dorsiflexors

Needham & Mastaglia, Lancet Neurol 6: 620-31, 2007

Autoantibodies in IBM

Anti-cytoplasmic 5'-nucleotidase 1A

- Initially detected as 43 kd autoantibody
  - 13/25 (52%) IBM + vs 0/40 controls

Salajegheh, et al., PLoS One 2011; 6(5): e20266

- Antigen identified as cN1A
  - Most abundant in skeletal muscle
  - Catalyzes nucleotide hydrolysis to nucleosides
  - Perinuclear and vacuole accumulation of cN1A

Larman, et al., Ann Neruol 2013; 73: 408-18

Anti-cN1A Verification

Table 1 Sensitivity and specificity of anti-cN-1A autoantibodies

Sera	Number	Anti-cN-1A reactivity* n	Per cent
Inclusion body myositis	238	88	37
Polymyositis/dermatomyositis	185	8	4
Polymyositis/scleroderma overlap	12	0	0
Neuromuscular diseases	93	4	4
Sjögren's syndrome	22	8	36
Systemic lupus erythematosus	44	9	20
Scleroderma	44	1	2
Rheumatoid arthritis	44	1	2
Multiple sclerosis	40	2	5
Type 1 diabetes	40	0	0
Disease controls†	*458*	*16*	*3*

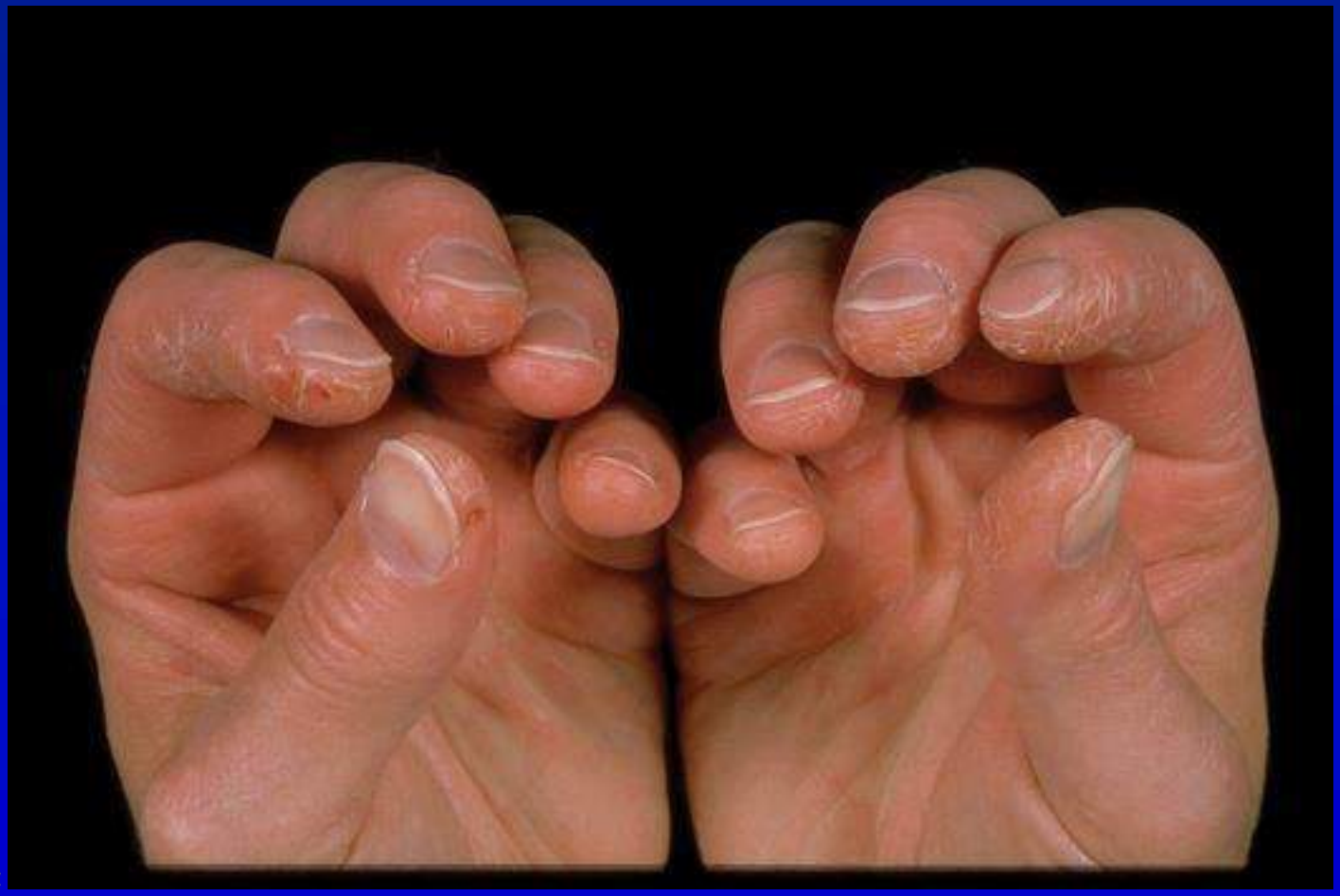
*Reactivity with at least one of the three cN-1A peptides higher than cut-off.
†Disease controls: total of all disease control groups except IBM, SLE and SjS.
cN-1A, cytosolic 5′-nucleotidase 1A; IBM, inclusion body myositis; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus.

Herbert, et al., Ann Rheum Dis 2016; 75:696-701

Anti-synthetase Syndrome

- Anti-synthetase antibody – Jo-1, etc
- PM/DM
- Interstitial lung disease
- Inflammatory arthritis
- Raynaud's phenomenon
- Mechanic's hands
- Fever

Mechanic's hands

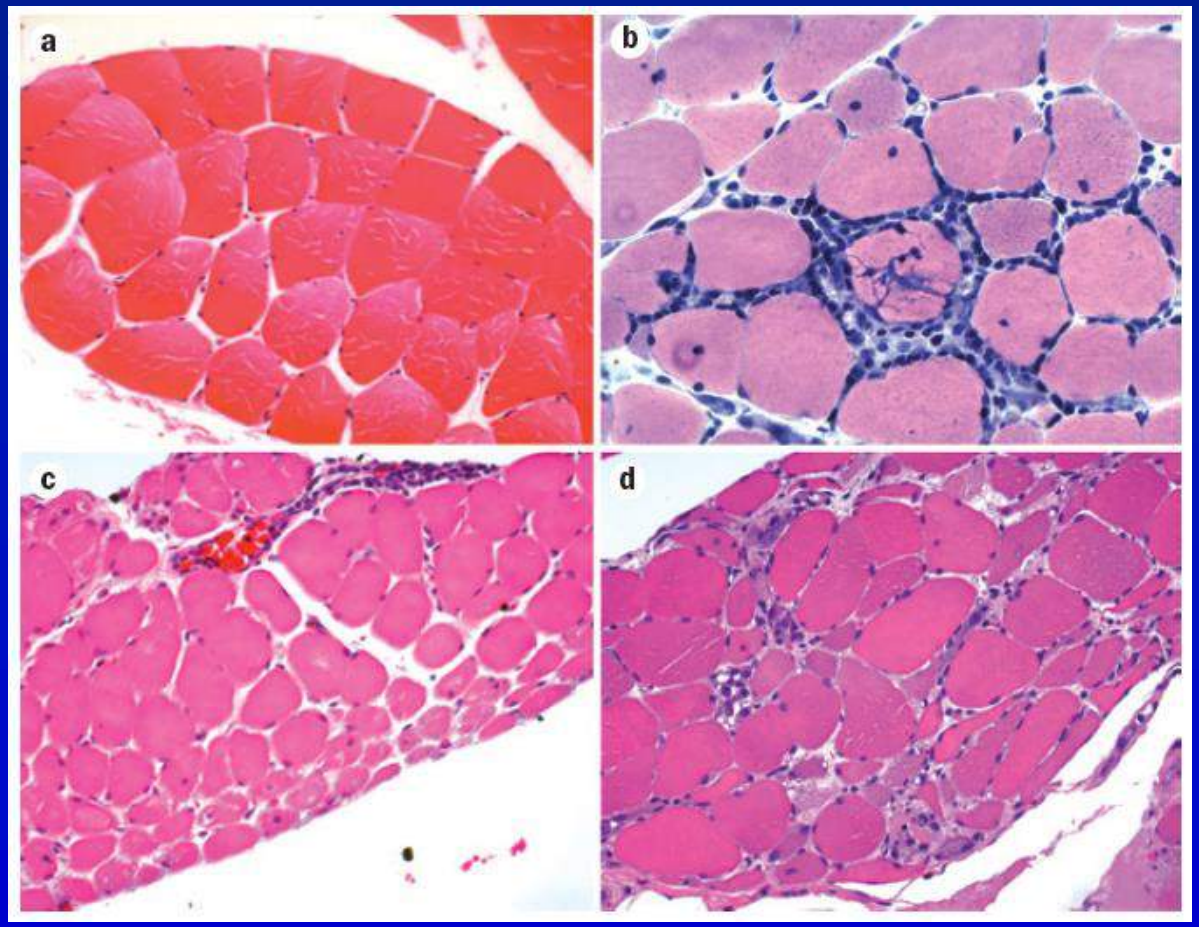


Immune-mediated Necrotizing Myopathy

- Characterized by muscle biopsy with necrotic muscle fibers without inflammation
- Specific autoantibodies
  - Anti-SRP
  - Anti-HMGCR
    - Often associated with statin use

Christopher-Stine, et al. Arthritis Rheum 2010; 62: 2757-66
Mammen, et al. Arthritis Rheum 2011; 63: 713-21

Muscle histopathology



a) Normal muscle
b) PM – endomysial inflammation
c) DM – perifascicular atrophy
d) Necrotizing myopathy

Mammen, Nat Rev Neurol 2011; 7:343-54

Idiopathic Inflammatory Myopathies

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- Autoantibodies
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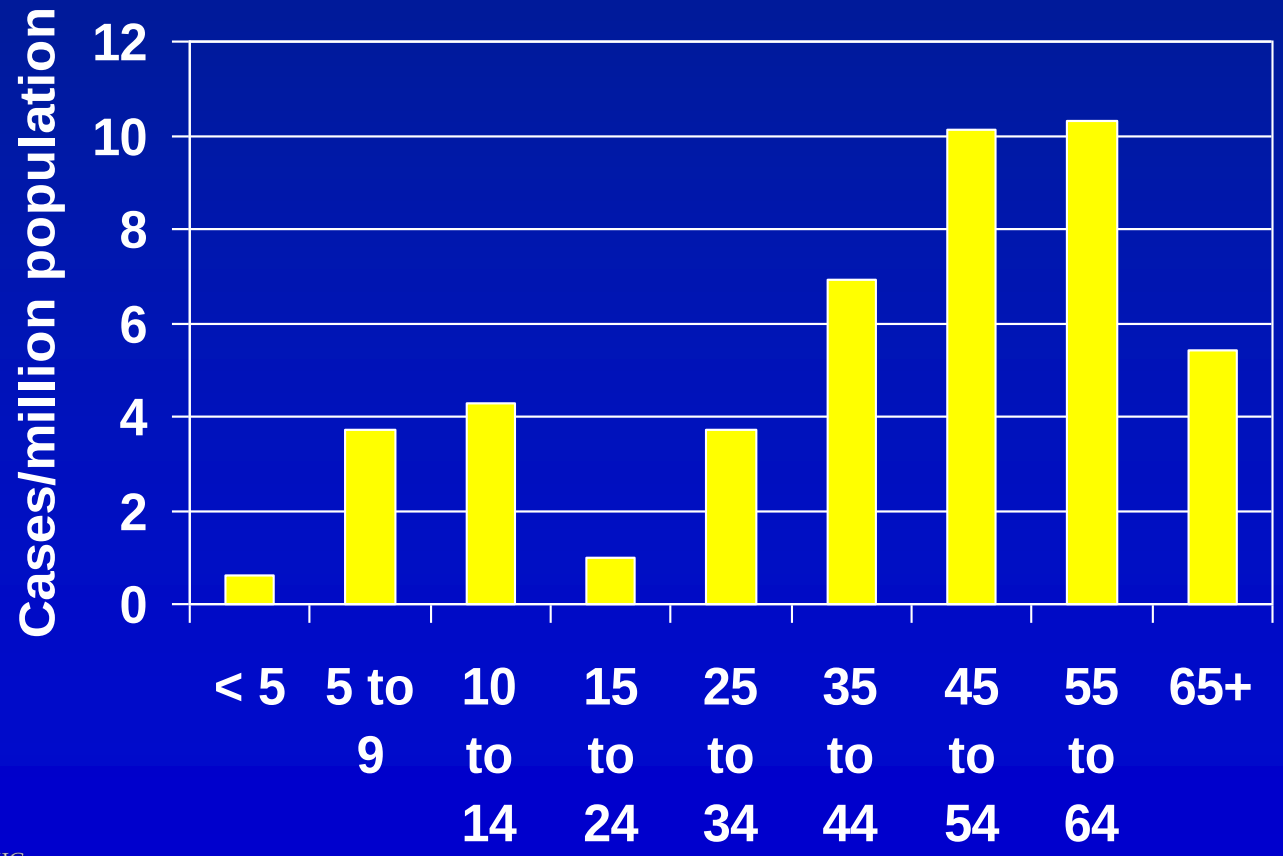
IIM: Epidemiology

Incidence - 0.5 to 8/million

	Polymyositis/ Dermatomyositis	Inclusion Body Myositis
Age	Bimodal, 10-15 in kids 45-60 in adults	>50
Female:male	2:1	1:2

Epidemiology of PM



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Medsger et al., Am J Med 48: 715, 1970

Epidemiology of IBM and PM Olmsted County, 1981-2000*

	IBM	PM
Incidence	0.79 (0.24-1.35)	0.41 (0.08-0.73)
Prevalence	7.06 (0.87-13.24)	3.45 (0.00-7.35)

**Age- and sex-adjusted rates per 100,000 population; (95% CI)*

Wilson et al., J Rheumatol 2008; 35:445-7

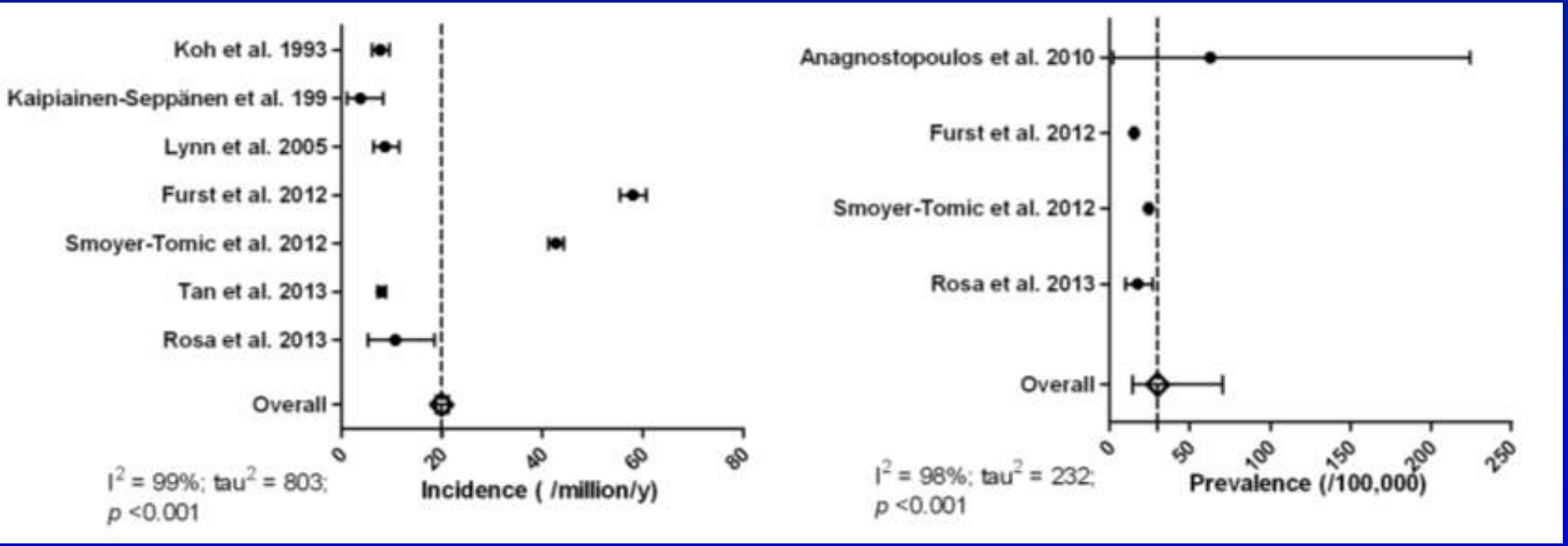
Epidemiology of DM Olmsted County, 1976-2007*

	DM	CADM
Incidence	0.96 (0.61-1.32)	0.21 (0.04-0.38)
Prevalence	2.14 (1.31-2.98)	

**Age- and sex-adjusted rates per 100,000 population; (95% CI)*

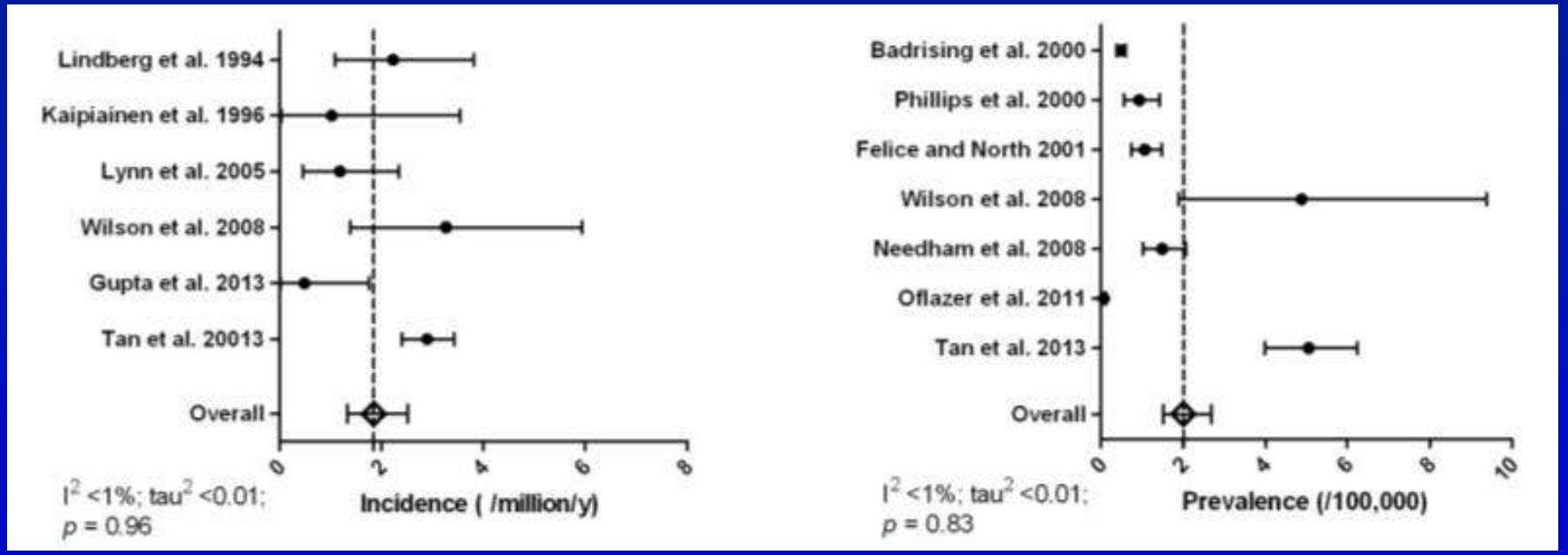
Bendewald et al., Arch Dermatol 2010; 146: 26-30

Systematic Review: Adult IIM



Meyer et al., Rheumatology 2015; 54: 50-63

Systematic Review: sIBM



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Antibodies

- Immunoglobulin
- Produced by plasma cells in the immune system
- Identify and neutralize viruses and bacteria
- Each recognizes a unique protein (antigen)

Autoantibodies

- Antibodies directed toward an individual's normal proteins
- Autoantibodies may:
  - Cause disease
  - Simply be markers of disease

Autoantibody	Target	Disorder
Antinuclear antibodies (ANA)	Contents of cell nuclei	Lupus and related conditions
Rheumatoid factor (RF)	IgG	Rheumatoid arthritis
Anti-Jo-1	Histidyl tRNA synthetase	Polymyositis with ILD
Anti-PR-3 (c-ANCA)	Neutrophil proteinase-3	Granulomatosis with polyangiitis
Anti-thyroid antibodies	TPO Thyroglobulin	Hashimoto's thyroiditis
Anti-AChR	Acetylcholine receptor on muscle	Myasthenia gravis
Anti-TTG	Tissue transglutaminase	Celiac disease

Non-specific Autoantibodies in Myositis

Percent of Patients with Various Autoantibodies

Antibody	All (n=212)	PM (n=58)	DM (n=79)	CTM (n=36)	CAM (n=13)	IBM (n=26)
ANA	52	40	62	77	31	23
ds-DNA	5	3	3	11	8	4
SSA/Ro	12	12	11	17	0	12
SSB/La	8	5	6	19	8	8
Sm	3	0	1	17	0	0
U1RNP	11	7	13	25	0	0
PM/Scl	2	0	4	3	0	0
RF	6	5	8	8	0	4

Love et al, Medicine 1991; 70: 360-74

Myositis-Specific Antibodies

Feature	Synthetase	SRP	Mi-2
Clinical	Arthritis, ILD fever, Raynaud's	Cardiac myalgias; black women	Classic DM
Rate	Acute	Very acute	Acute
Severity	Severe	Very severe	Mild
Season	Spring	Fall	Unknown
Response	Moderate	Poor	Good
Prognosis	Poor (70%)	Terrible (25%)	Good (~100%)
Frequency	20-25%	<5%	5-10%

Antisynthetase antibodies

		Frequency (%)		
Antigen	tRNA synthetase	JDM*	ADM*	Non-white
Any		1-5	30	AA 29
Jo1	Histidyl-	2-5	25-30	AA13
PL12	Alanyl-	1-3	<5	
PL7	Threonyl-	<1	<5	Japanese 17
EJ	Glycyl-	<1	<5	
OJ	Isoleucyl-	<1	<5	
KS	Asparagynyl-	NA	<1	
HA	Tyrosyl-	NA	<1	
ZA	Phenylalanyl-	NA	<1	

*Caucasian

Robinson & Reed, Nat Rev Rheumatol 2011; 7: 664-75

Serologic Subgroups in IIM 2

- **Anti-TIF-1γ (anti-transcription intermediary factor 1γ; anti-p155):** DM, including JDM, malignancy
  Targoff et al., Arthritis Rheum 2006; 54: 3682-3689
  Trallero-Araguas et al., Medicine 2010; 89: 47-52

- **Anti-MDA-5 (anti-melanoma differentiation-associated protein 5; anti-CADM):** CADM, rapidly progressive ILD
  Sato et al., Arthritis Rheum 2005; 52:1571-6
- **Anti-NXP2 (anti-nuclear matrix protein 2; anti-MJ):** JDM, especially with calcinosis, malignancy
  •Gunawardena et al., Arthritis Rheum 2009; 60: 1807-14

Gunawardena et al., Rheumatology 48: 607-12, 2009

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Approach to Treatment of Myositis

Immune suppressing agents

Steroids

Approach to Management

- Start with high-dose prednisone (e.g., 1 mg/kg/day)
  - Consider IV to begin
  - Consider split daily dose
- Continue about 1 month with slow taper
- Use an immunosuppressive agent
- Attention to side effects of therapy (e.g., osteoporosis, infection)

My Approach to Prednisone

- Begin 1 mg/kg/d (usually max 80 mg/d)
- Continue 1 month
- 2 weeks each:
  - 40 mg/d
  - 30 mg/d
  - 25 mg/d
  - 20 mg/d
  - 17.5 mg/d
  - 15 mg/d
  - 12.5 mg/d
- 10 mg/d and then decide what next

My Approach to Immunosuppressives

First-line agents
- Methotrexate
- Azathioprine (Imuran)
- Mycophenolate mofetil (CellCept)

Second-line agents
- IVIg
- Rituximab (Rituxan)
- Tacrolimus (Prograf)
- Cyclosporine A (Neoral, Sandimmune)
- Leflunomide (Arava)

Severe disease
- Cyclophosphamide (Cytoxan)

Studies
- Abatacept (Orencia)
- Tocilizumab (Actemra)
- Belimumab (Benlysta)

Never used
- ACTHAR gel

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Questions?