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Myositis and Cancer

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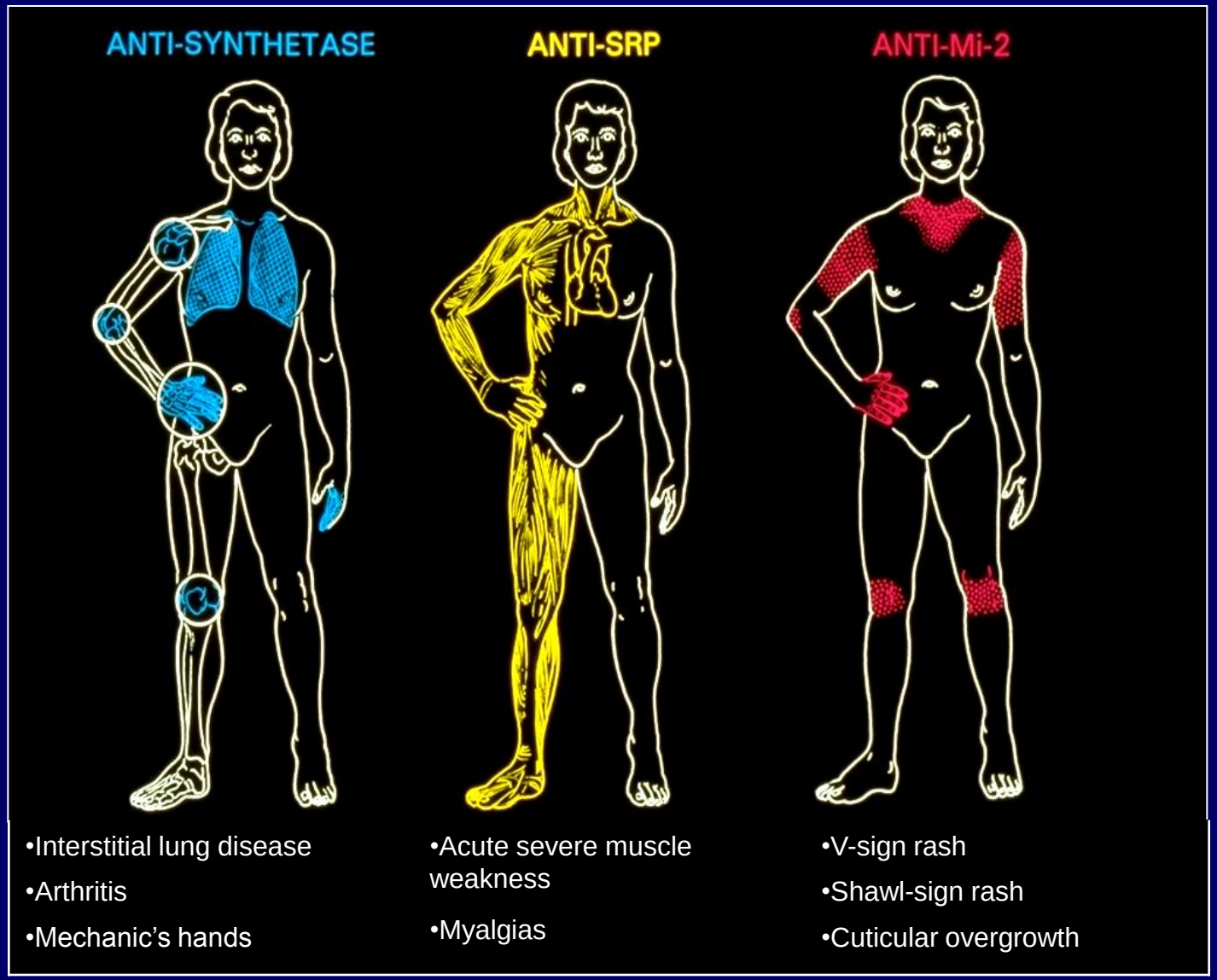
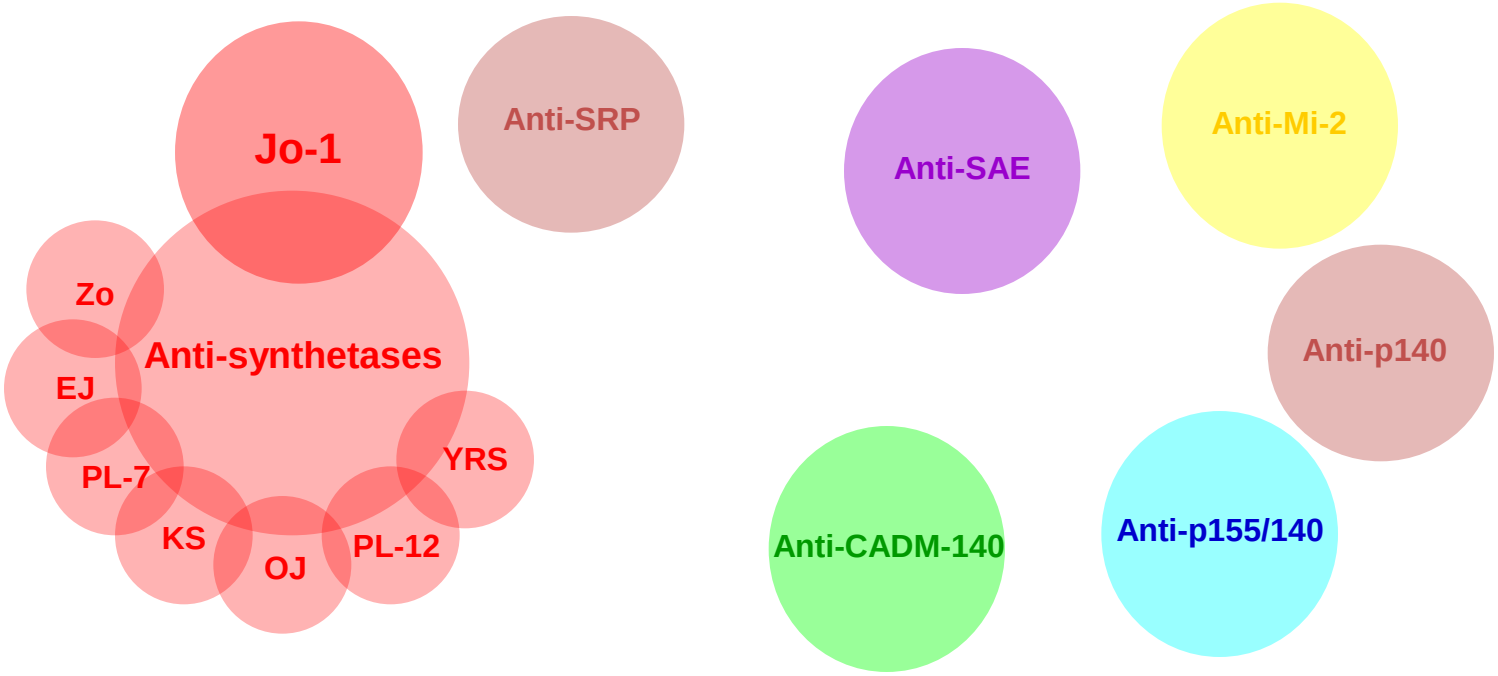
? Classification of myositis according to Abs

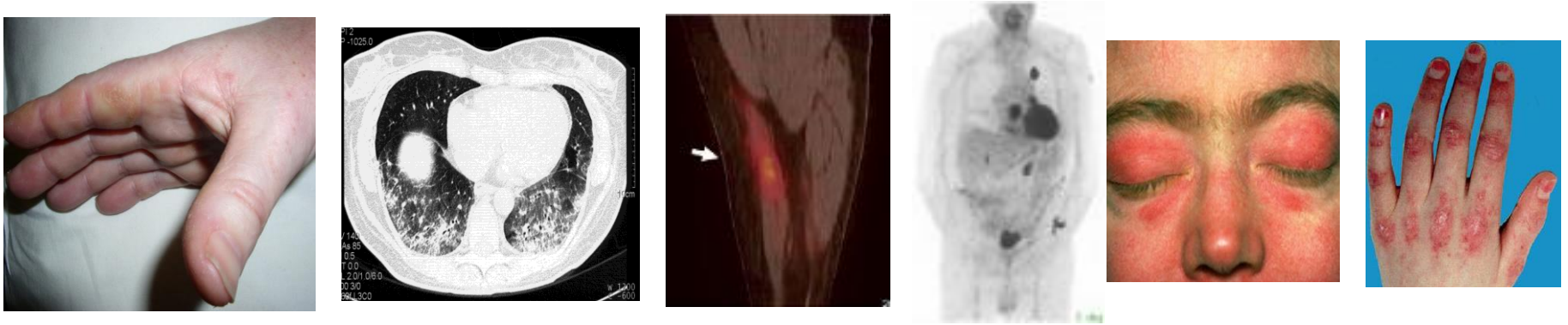


Courtesy of Prof FW Miller -1999

Myositis-specific autoantibodies

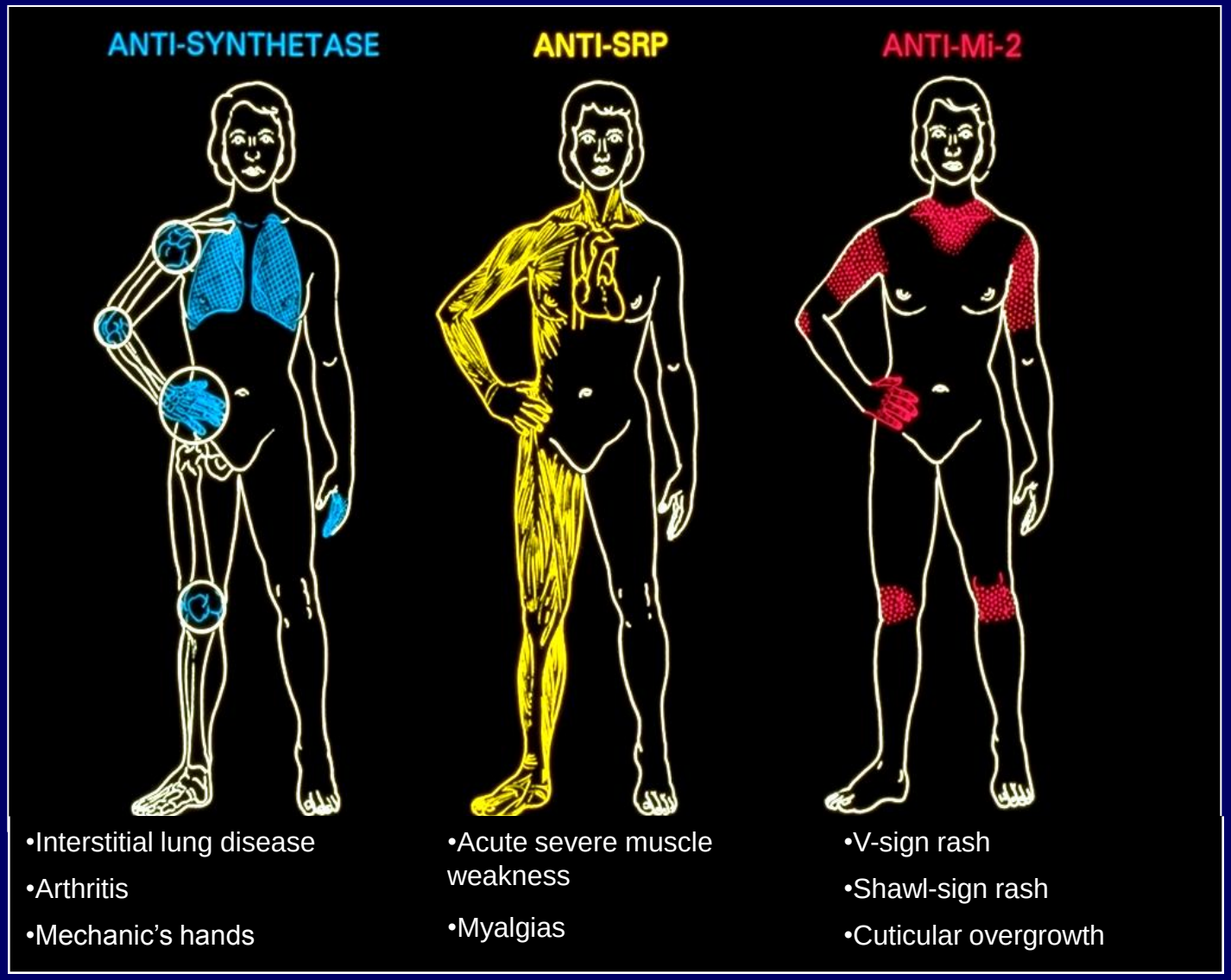


Myositis specific autoantibodies → Clinical phenotypes in adults and children



Slide Courtesy of Dr H Gunawardena

Myositis classification according to Abs



155/140

PM-Scl

140

SAE

etc

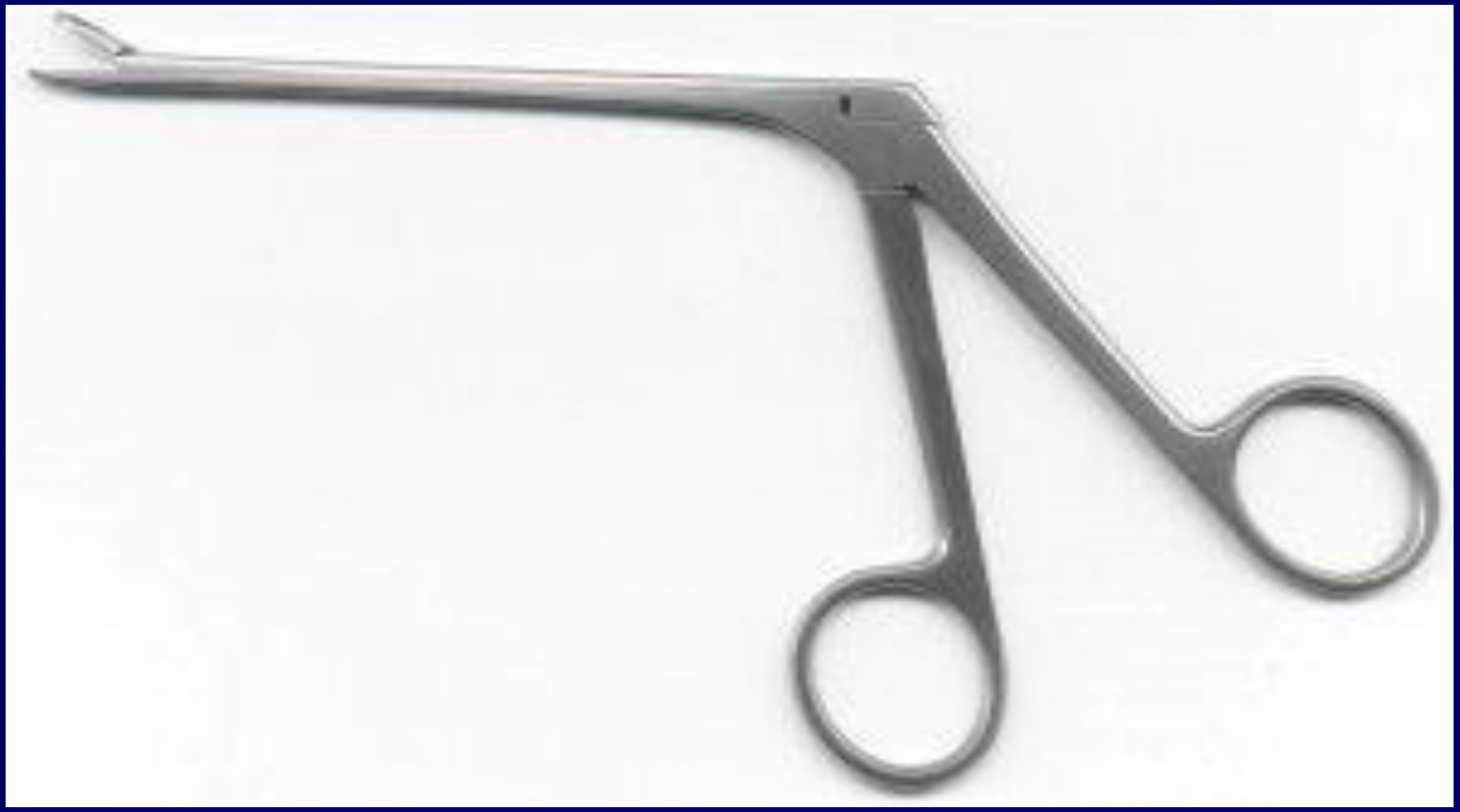
Courtesy of Fred Miller, many other contributors - 2008

Diagnostic Criteria

Bohan & Peter Diagnostic Criteria (N Engl J Med - 1975, 292: 344 & 403)

- Proximal muscle weakness
- Elevated CPK (or other muscle-specific enzymes)
- Characteristic needle EMG findings
- Characteristic muscle histology
  - *Diagnosis of myositis "probable or definite" if 3 or 4 of items respectively are +ve (with characteristic skin changes in DM). Main aim of criteria is to exclude from research studies patients do not have myositis.*

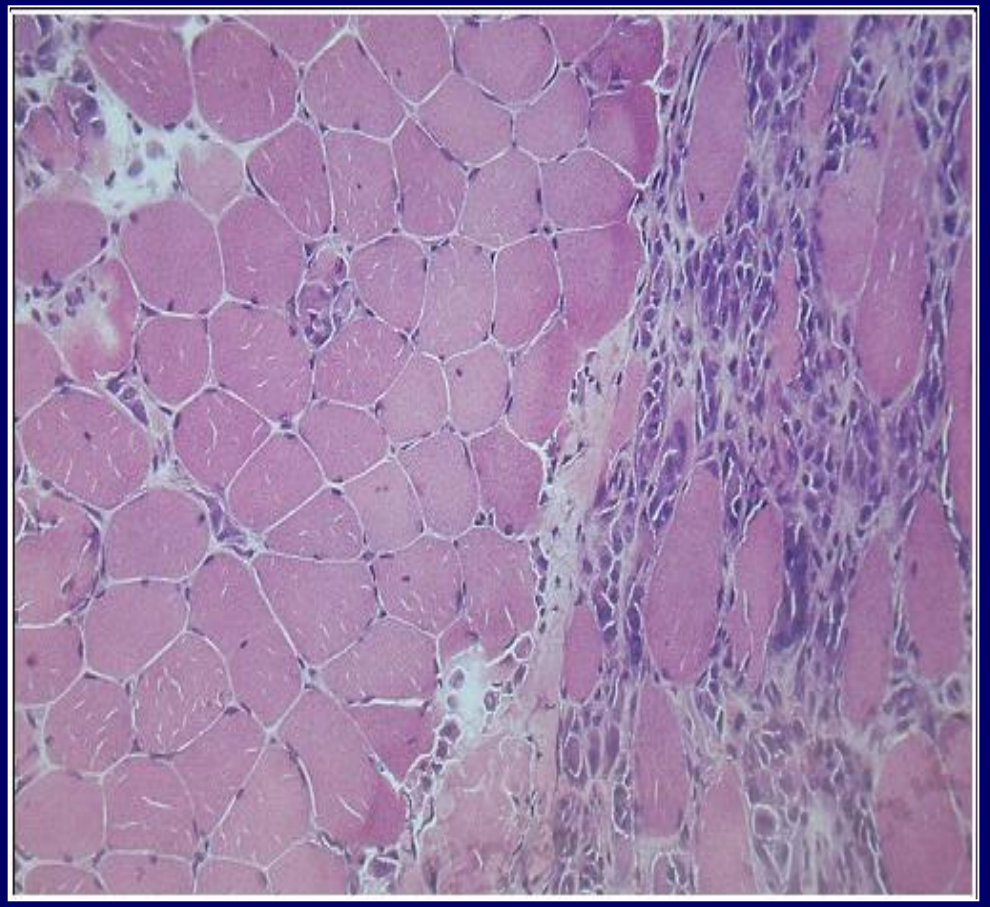
Percutaneous Muscle Biopsy Forceps (Conchotome-type)



Characteristic Muscle Histology

- CD4+ perivascular T cells in DM
- CD8+ endomyseal T cells in PM
- CD68+ macrophages in both
- Up regulation of surface MHC

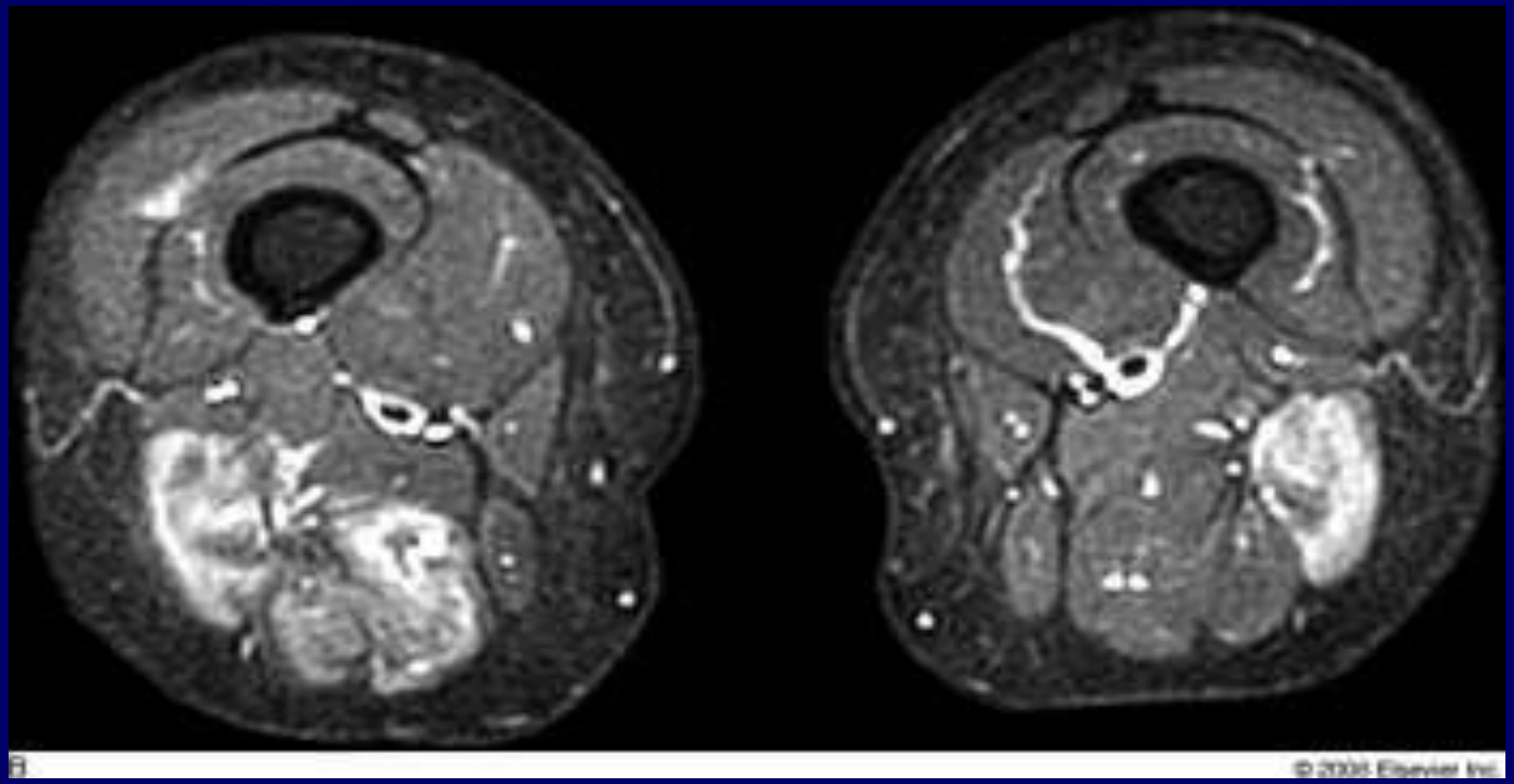
- <u>Problems with histology:</u>
  - Unreliable as disease often patchy
  - Limited availability of full immuno-histochemistry etc
  - **Poor correlation between inflammatory load and weakness**



MRI for Monitoring

- T1-weighted images sensitive at detecting changes in muscle fat content, therefore good at detecting atrophy and fatty replacement.

- STIR images very sensitive to changes in muscle water content, therefore good at detecting oedema, but latter not specific for myositis.

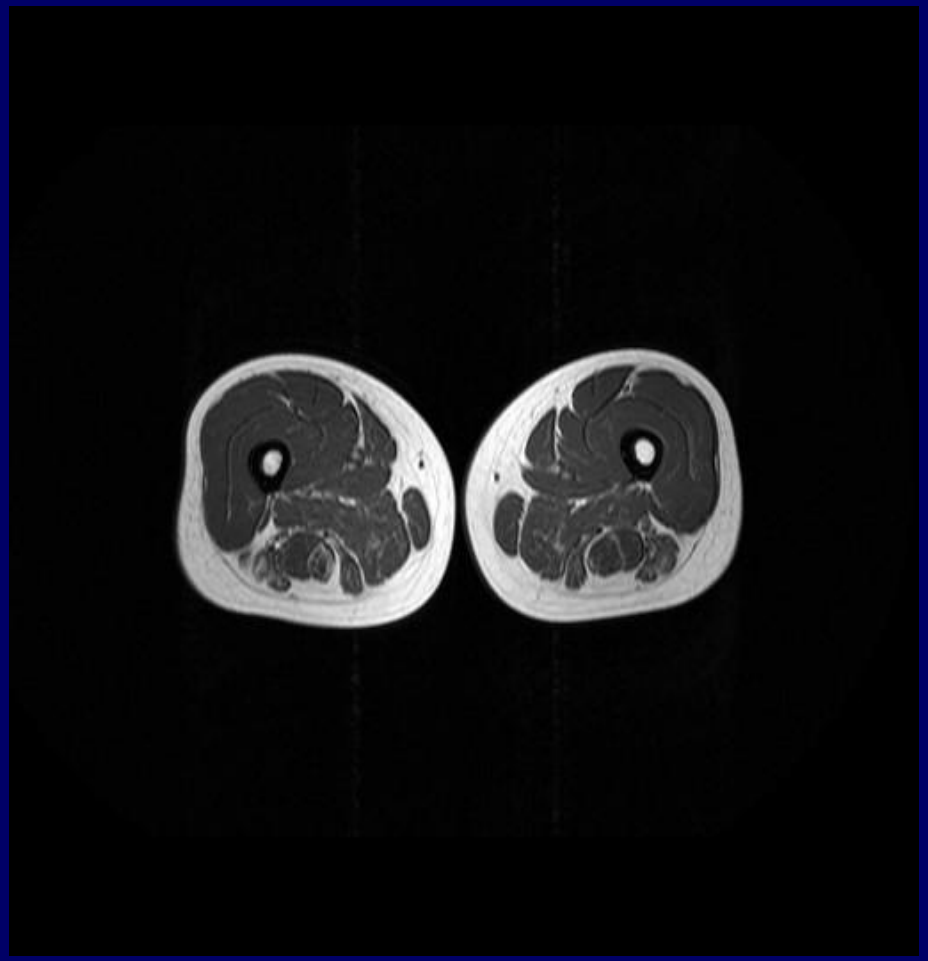


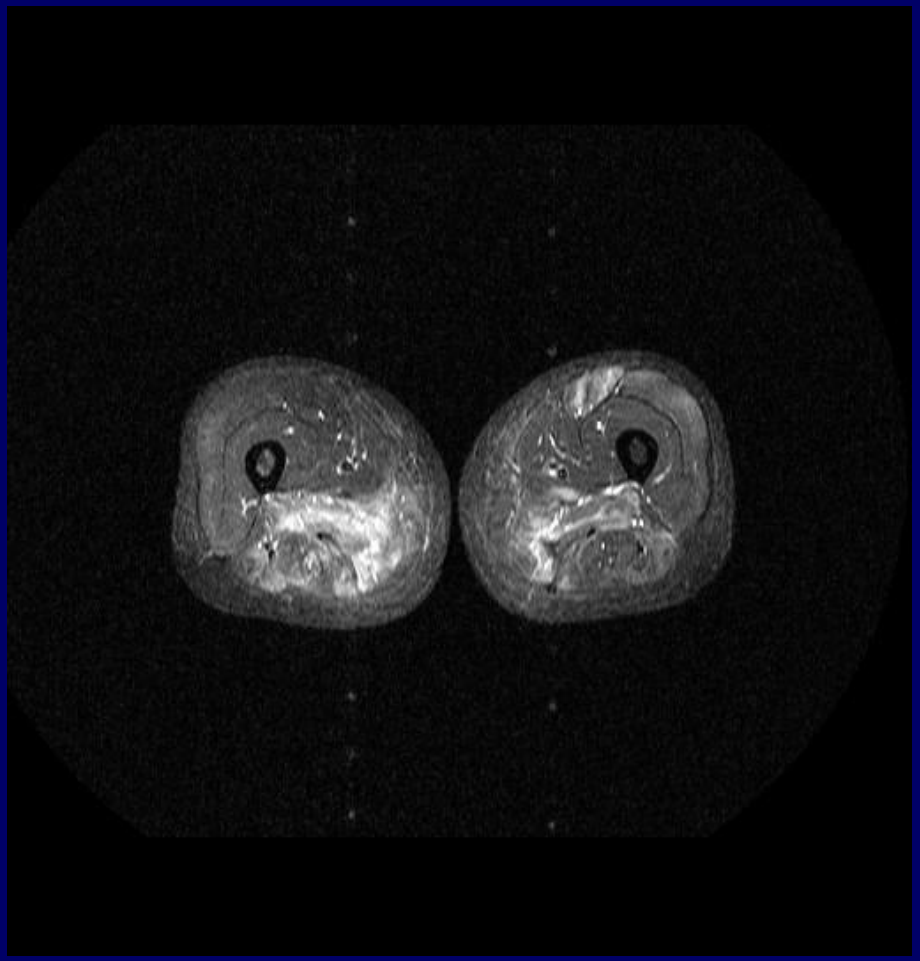
Poor Response to Treatment

CK remains high and/or patient remains weak, despite high dose steroids & multiple DMARDS:

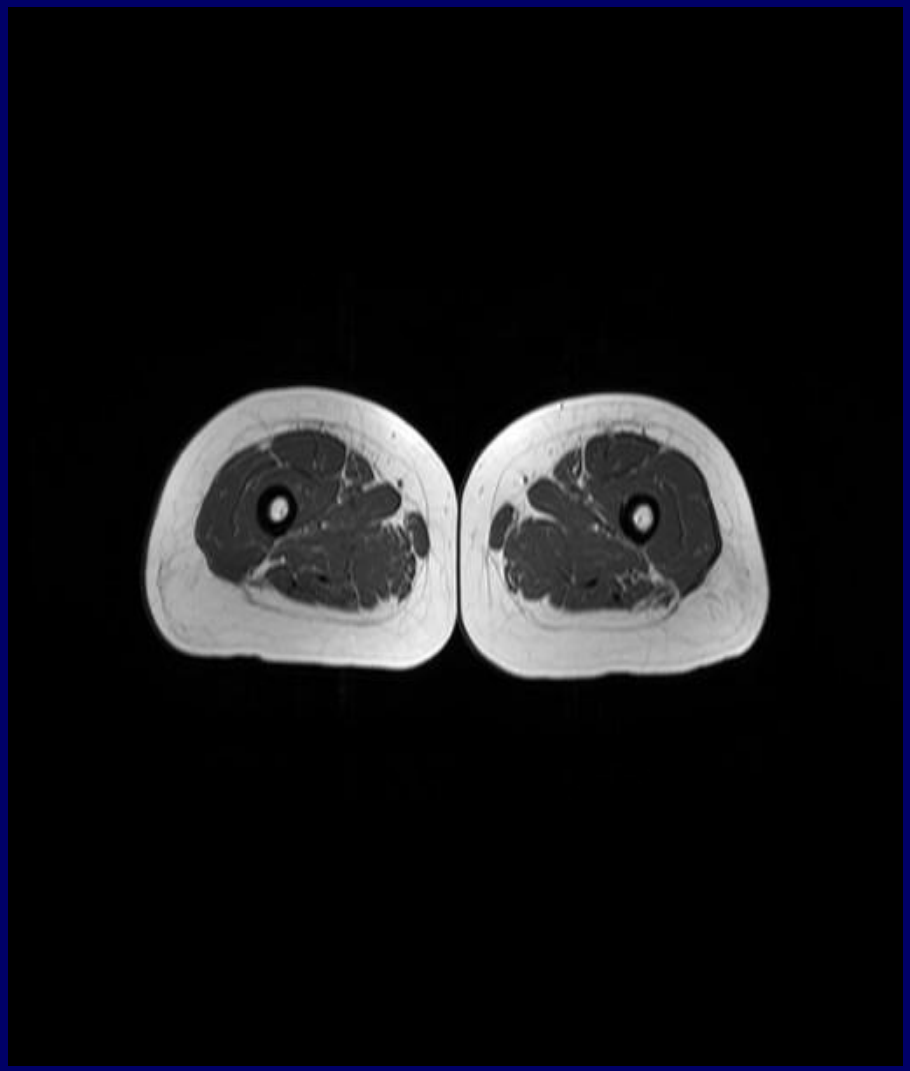
- Myositis truly drug-resistant
- Myositis misdiagnosed
- Myositis fully suppressed, but muscles remain weak
- Myositis cancer-associated

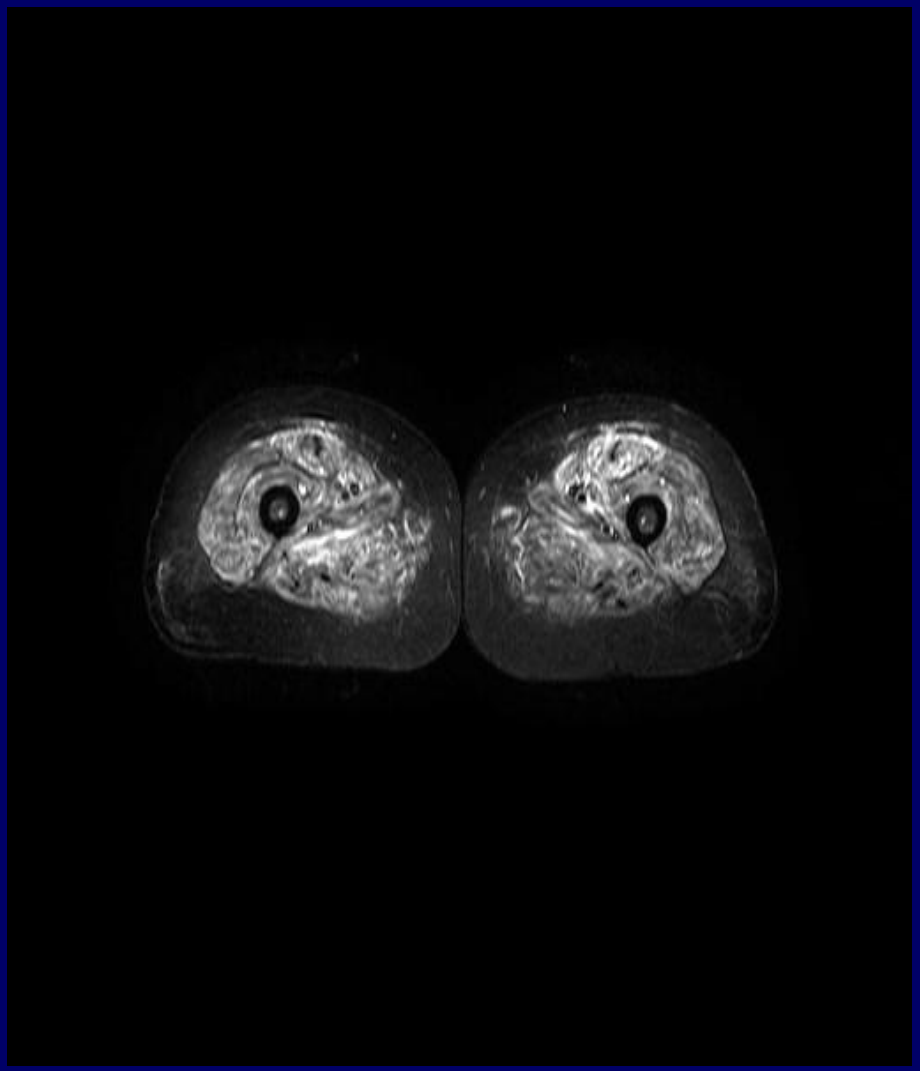
Miss SB (36 year old DM, anti-SRP +ve, CK>3000 for 12 months)





Mrs SF (34 year old DM, anti-140 +ve, CK <150, no response to Rx to date)





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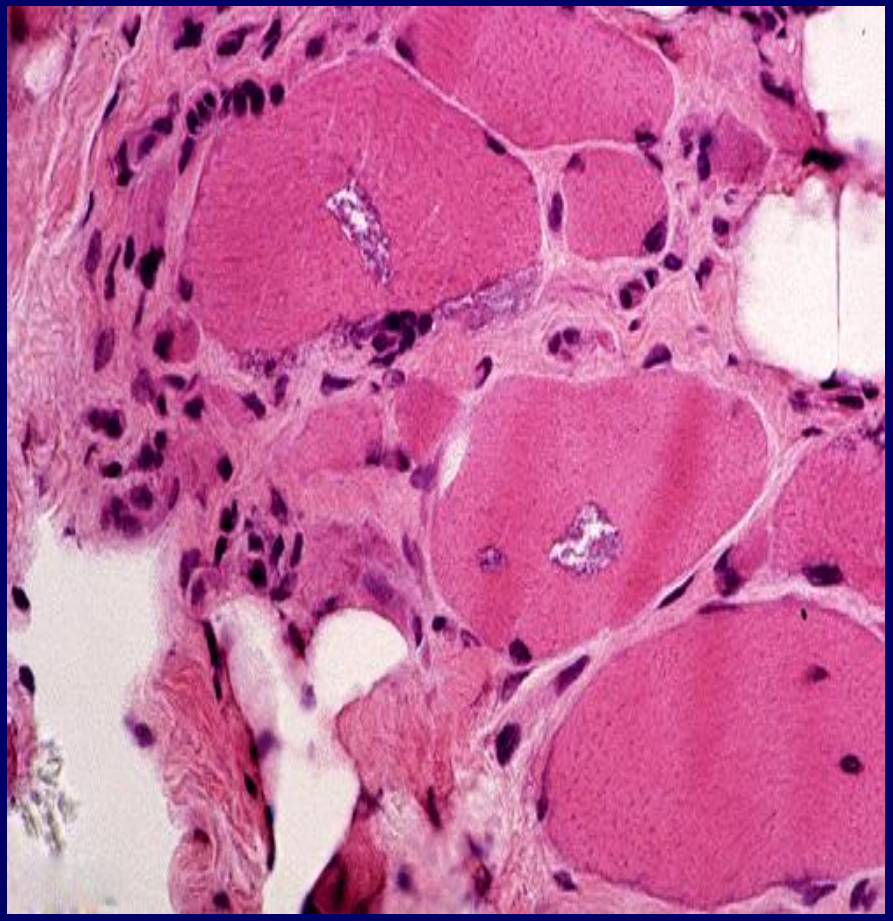
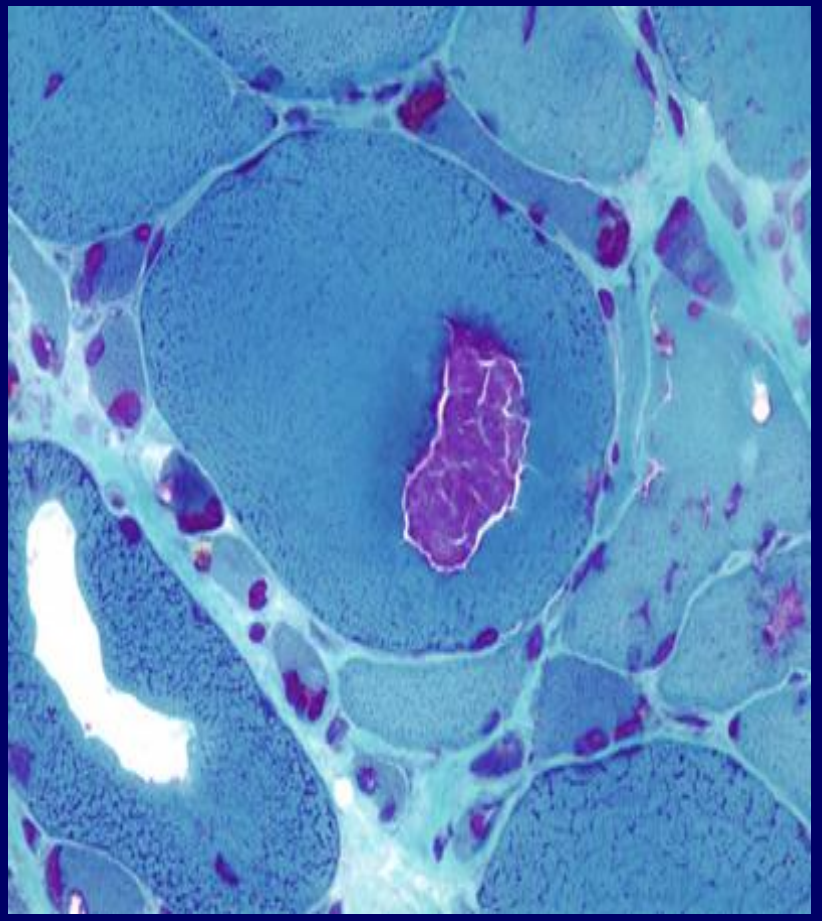
Poor Response to Treatment Should always Prompt a Critical Review of Original Diagnosis



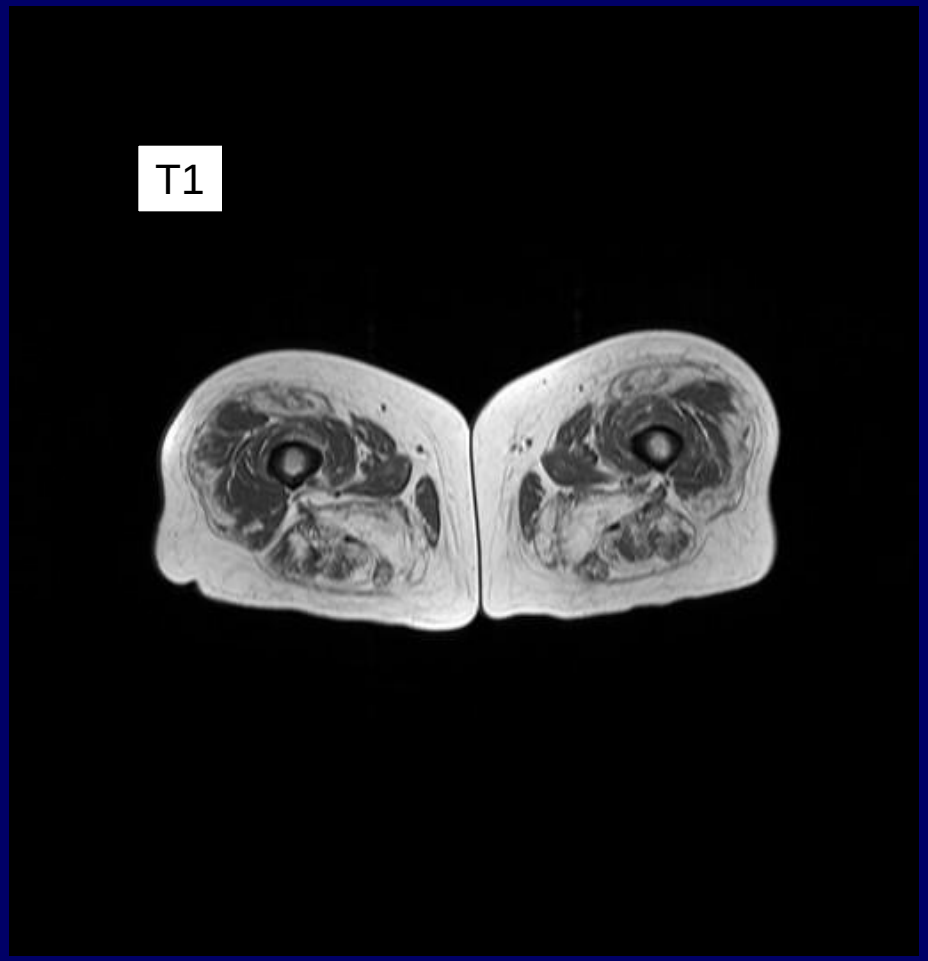


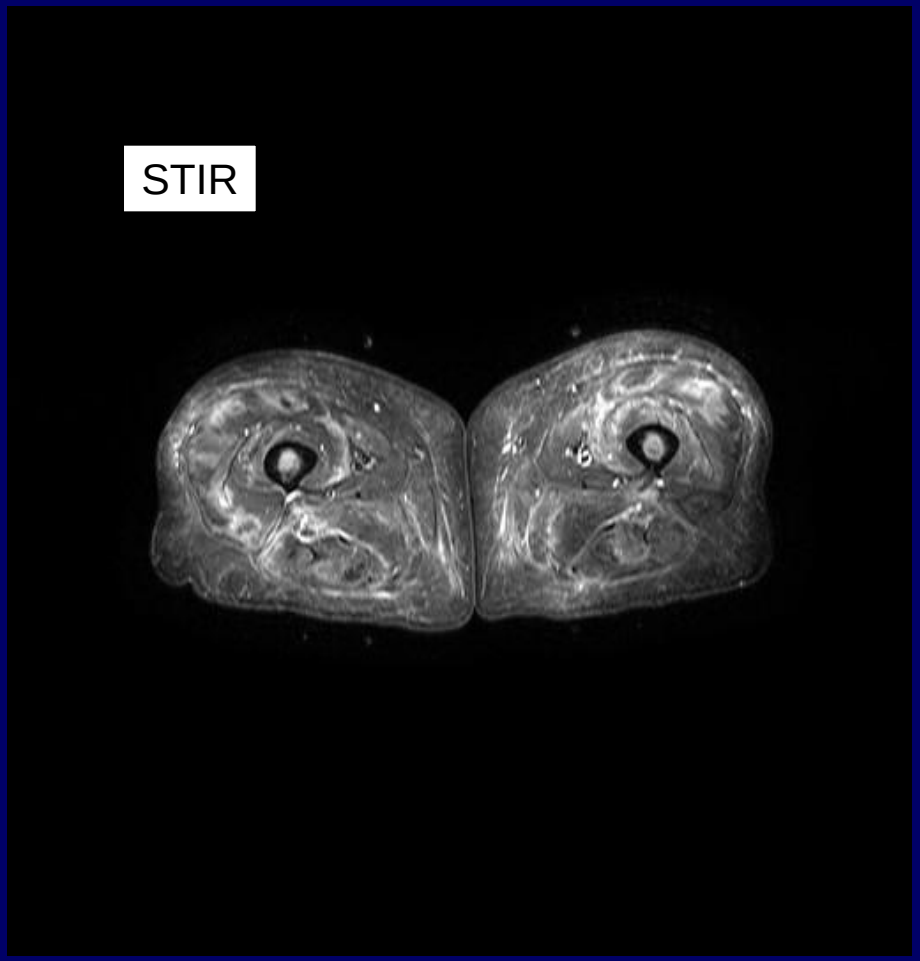
Poor Response to Treatment

CK remains high and/or patient remains weak, despite high dose steroids & multiple DMARDS ± IVIGs:

- Myositis truly drug resistant
- Myositis misdiagnosed
- Myositis suppressed, but muscles remain atrophic and weak
- Myositis cancer-associated

Mrs CH (Anti-Jo-1 +ve PM, CK <150 for years, remains weak)





Poor Response to Treatment

CK remains high and/or patient remains weak, despite high dose steroids & multiple DMARDS ± IVIGs:

- Myositis truly drug resistant
- Myositis misdiagnosed
- Myositis fully suppressed, but muscles remain weak
- Myositis is cancer-associated

Mr ME

- 2003, 63 yr old retired boiler-maker with known pleural plaques developed erythematous rash over scalp, myalgias and weakness.
- S/B local rheumatologist, “atypical” DM, proximal weakness, CK 2000, EMG +ve, Bx NAD, muscle MRI NAD. Bohan & Peter probable, therefore onto pred 60 mg/day (HRCT chest, abdo USS, PSA, clinical exam all –ve for malignancy).
- 2003-5, no response to pred at 45-60 mg/day, therefore AZA 150 mg/day added.
- June 2005, referred to RGC as drug-resistant DM. O/E no rash, obvious proximal weakness (3+). Differential: ?drug resistant myositis, ?IBM, ?other. Admitted to Hope Hospital for investigation.

Mr ME

- Results: CK 408 U/L (N<195), proximal weakness 3+, EMG +ve, Bx +ve (CD4 and CD8+ve cells seen, MHC staining on surface of majority of muscle cells, *no inclusions*), thus Bohan & Peter definite and active myositis. Ciclosporin 150 mg/day added to regime.

- "Progress": By Sept '05 (i.e 4 months of triple Rx, with pred at 25 mg) no improvement at all. RGC asked local rheumatologist to give x3 IVIGs.

- Jan '06 Hope review: IVIGs gave transient improvements in general well being, but not in weakness, ciclosporin and pred therefore increased.

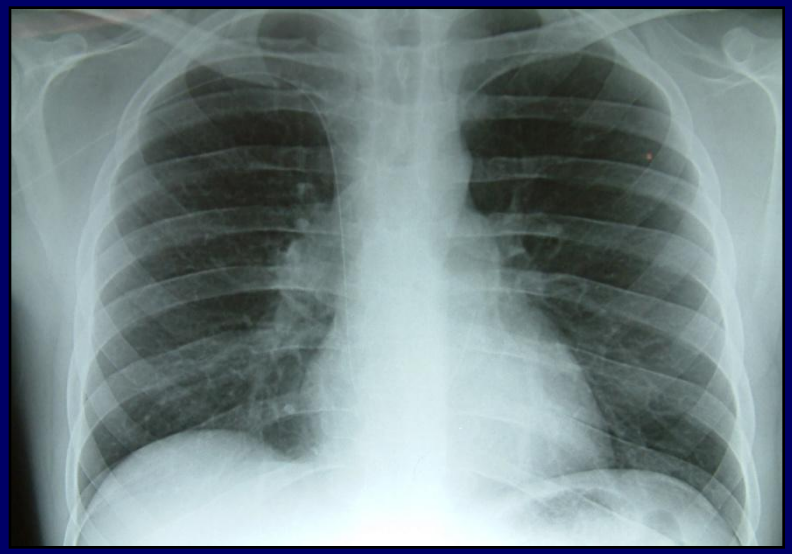
- Feb '06: Admitted breathless to local hospital, CXR now showed new mass lesion, USS showed hepatic mets.
  - Lack of therapeutic response due to malignancy (i.e CAM)

Definition of cancer-associated myositis (CAM)

- Malignancy occurring 3 years either side of and in association with a myositis onset and if malignancy successfully treated, myositis should also get better.

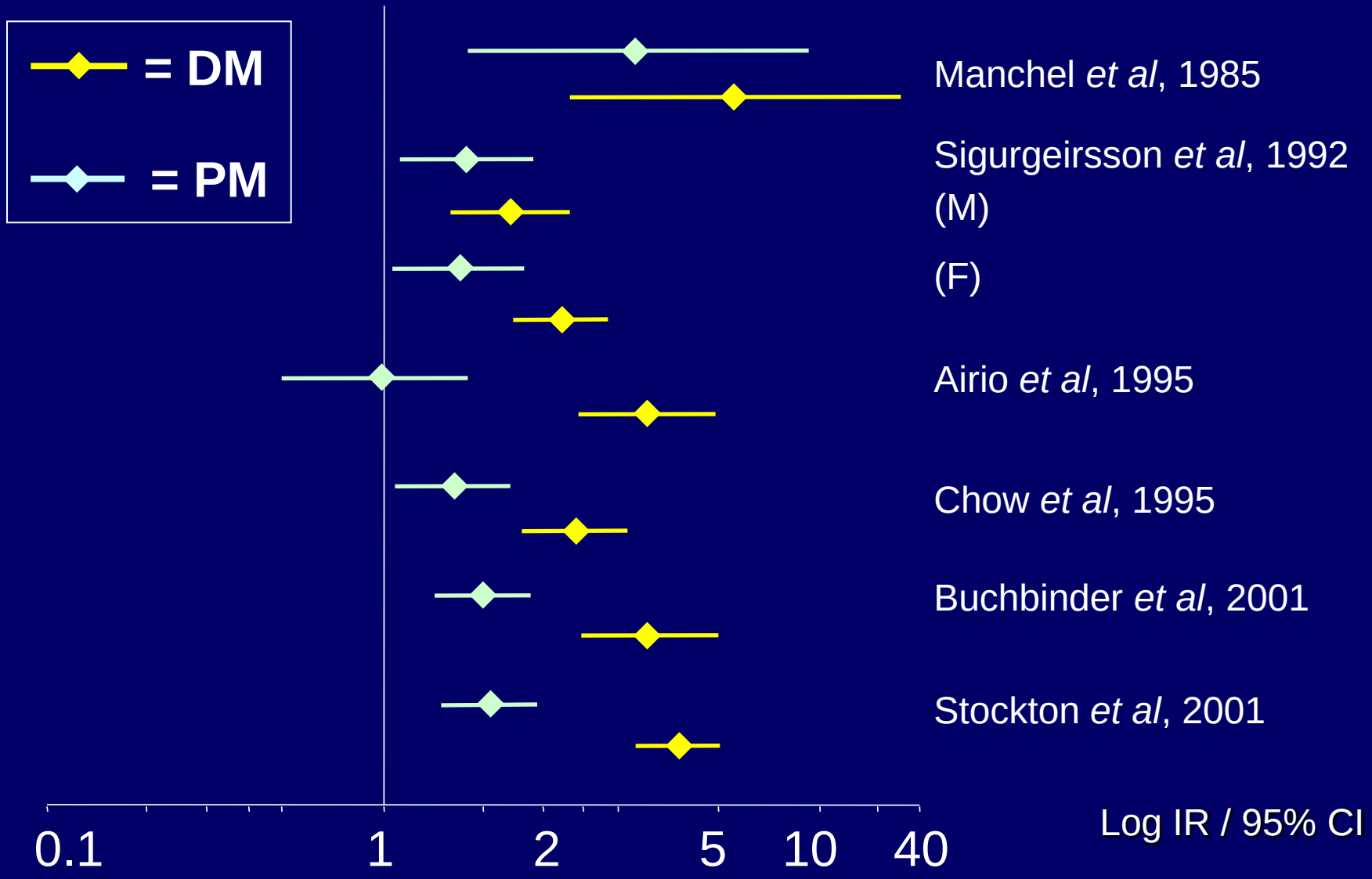
Bohan and Peter 1975

Association of cancer with myositis

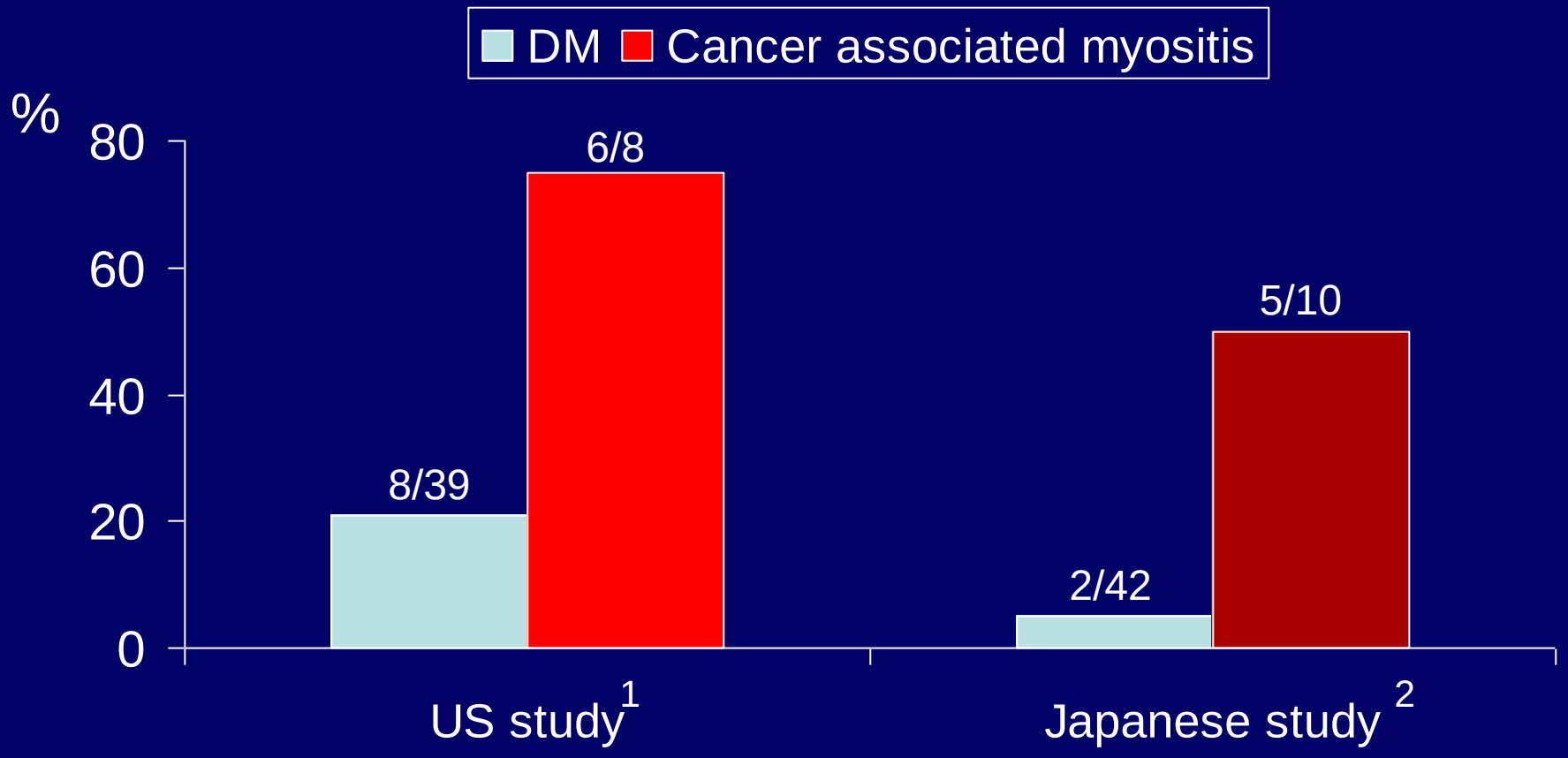


Photos courtesy of Dr I Bruce

Risk of malignancy: comparison of myositis *vs.* general population



Anti-155/140 antibody



[1]Targoff et al. 2006; [2]Kaji et al 2007

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The diagnostic utility of serology for predicting the risk of cancer-associated myositis in adults.

Chinoy et al

arc Clinical Research Fellow / SpR Rheumatology

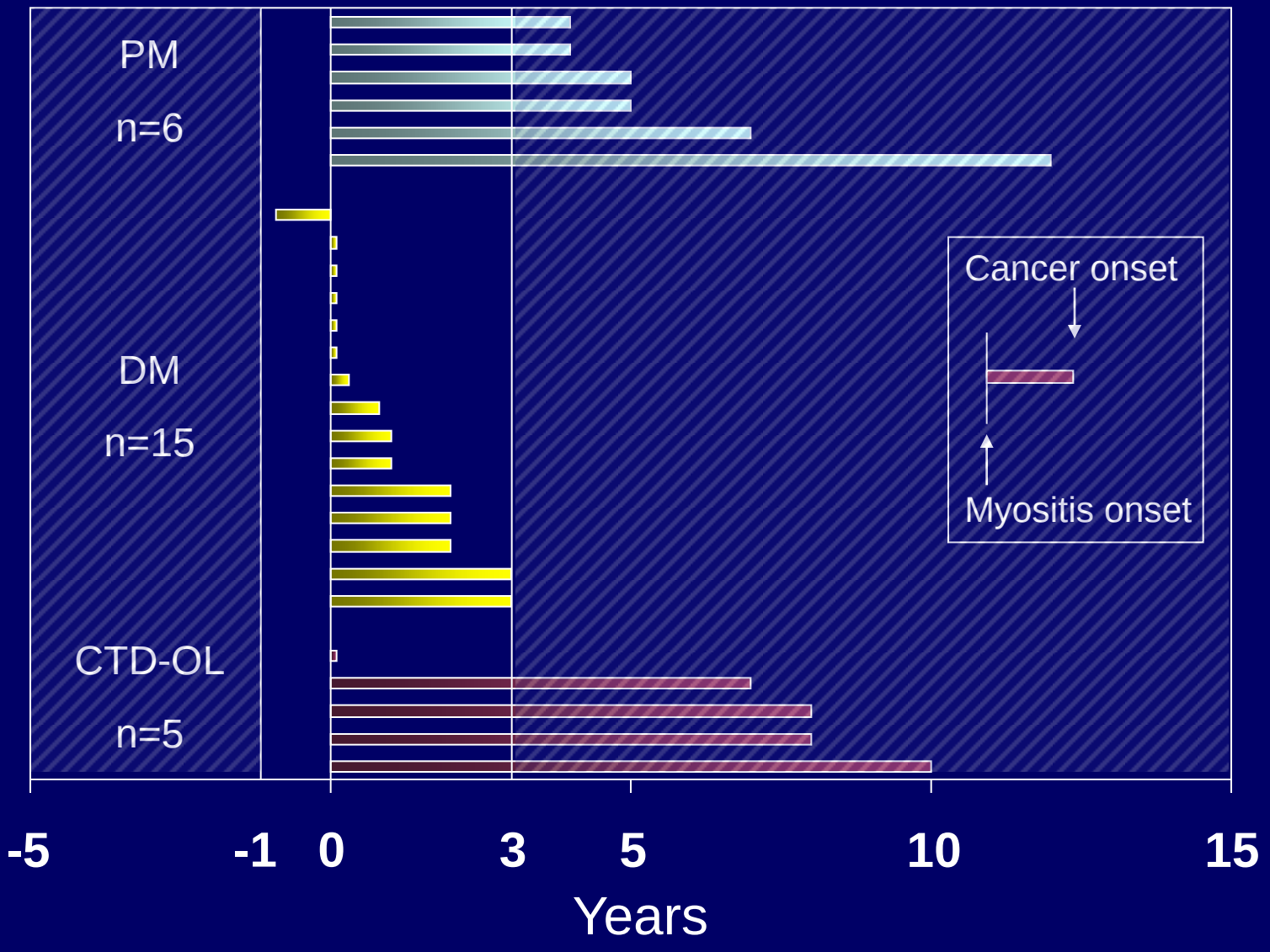
The University of Manchester / Salford Royal Hospitals NHS Trust

Methods

- Cross-sectional design
- AOMIC cohort
- Myositis probable/definite according to Bohan & Peter[1]
- CAM according to modified Bohan & Peter[2]
- PM (n=109)
- DM (n=103)
- CTD-overlap (n=70)

[1]Bohan & Peter, 1975; [2]Troyanov et al, 2005

Relationship between myositis and cancer onset in 282 cases



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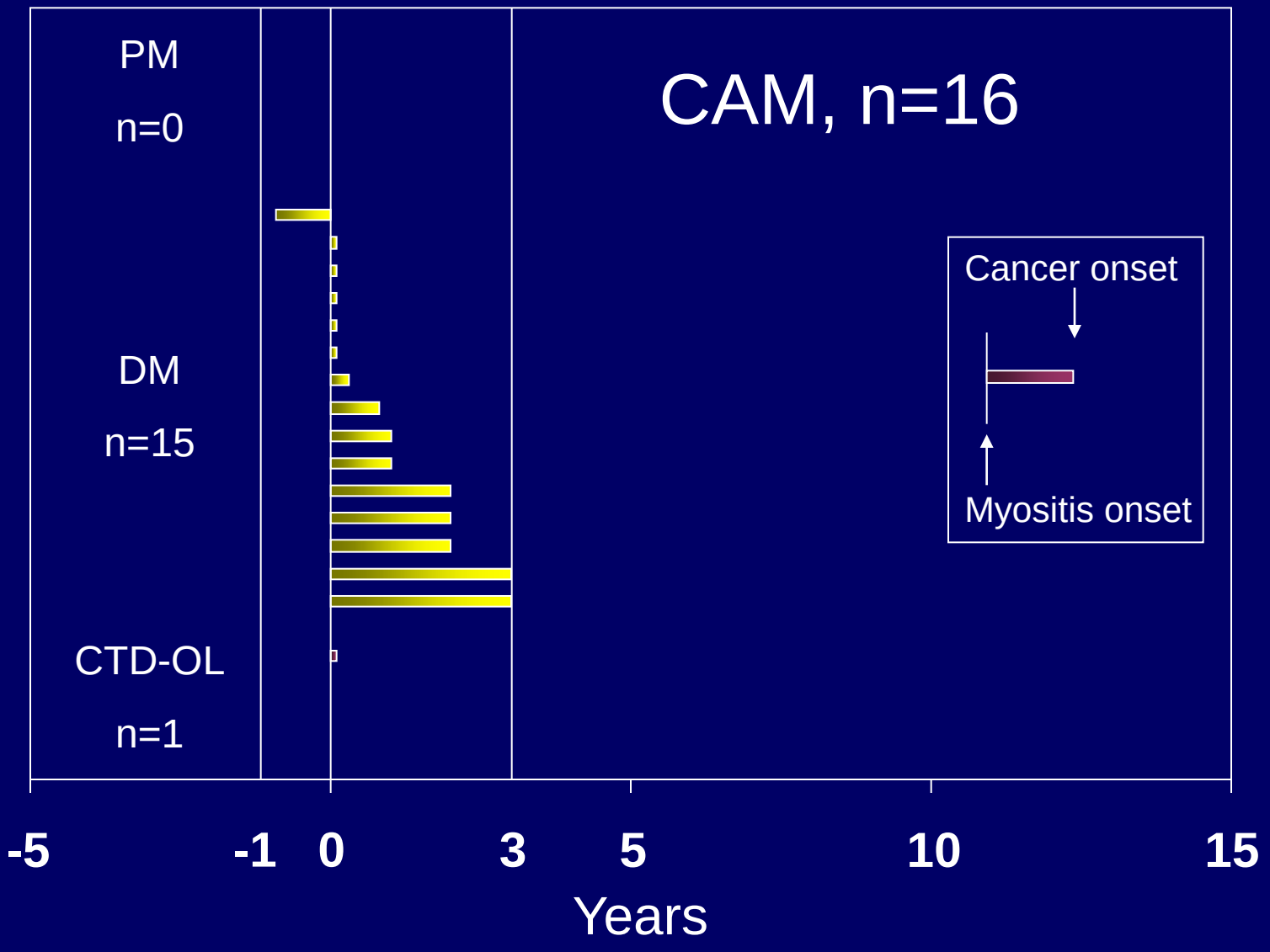
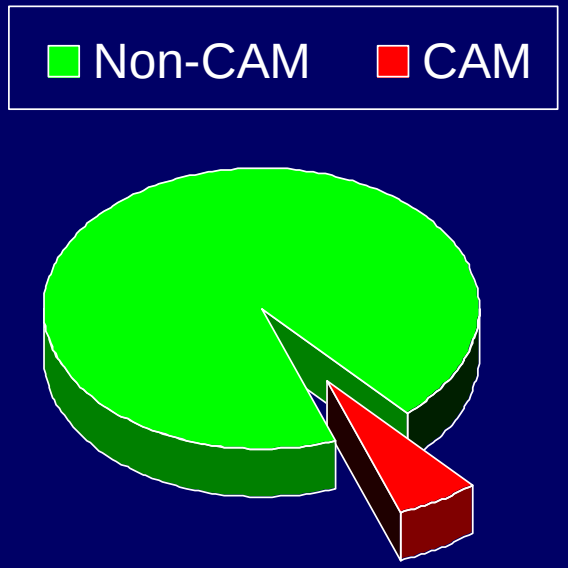


Serological typing

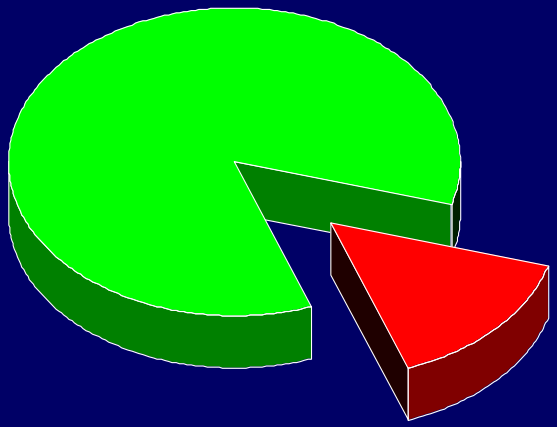
- Performed in University of Pittsburgh, PA
- Anti-aminoacyl tRNA synthetases
  - Jo-1, PL-7, PL-12, EJ, OJ, KS
- Other MSAs/MAAs
  - PM-Scl, Ku, U1-RNP, U3-RNP, Mi-2, SRP
  - 155/140

CAM frequency in 282 cases

Total

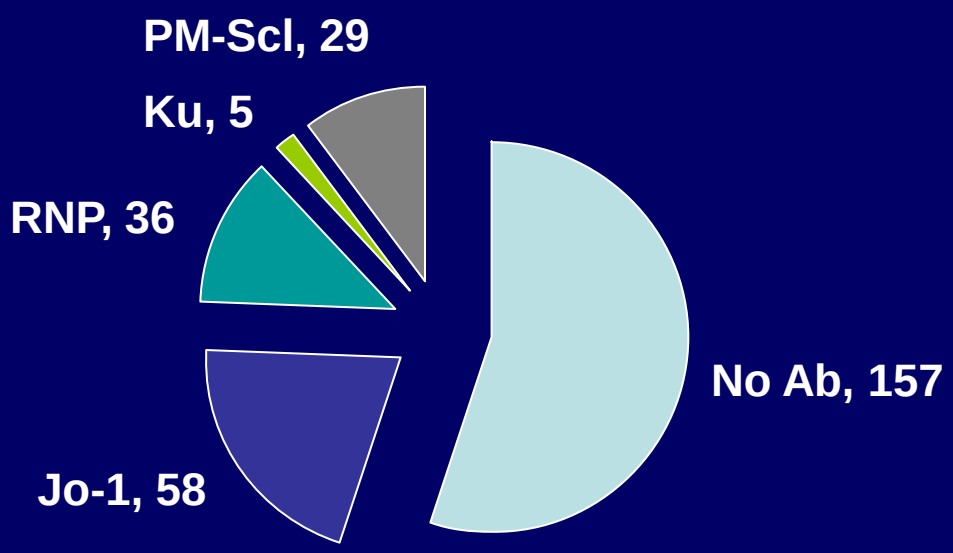


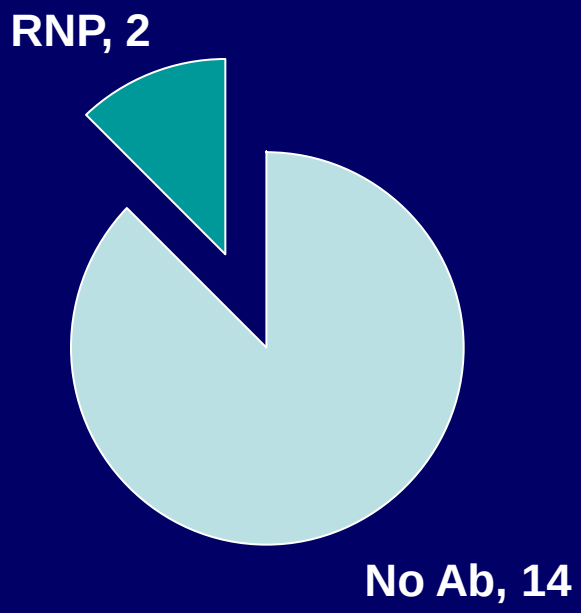
DM



- Total : n = 282
- CAM : n = 16 (6%)
- CAM (DM) : n = 15 (15%)

Antibody frequencies in CAM/non-CAM groups using routine hospital-based immunology





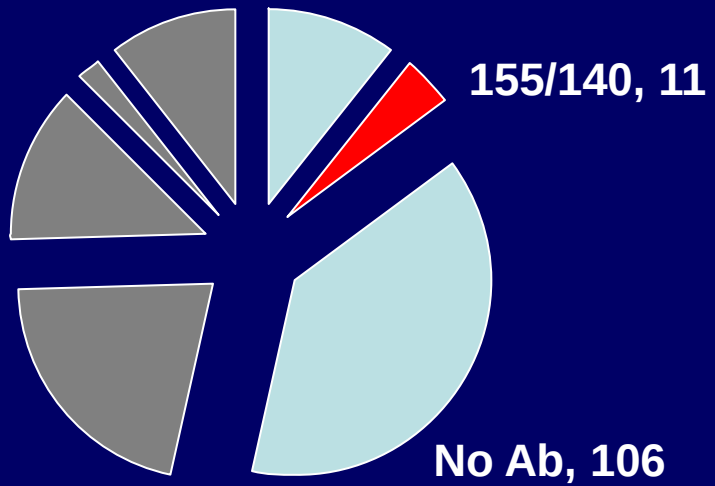
Non-CAM

n=266

CAM

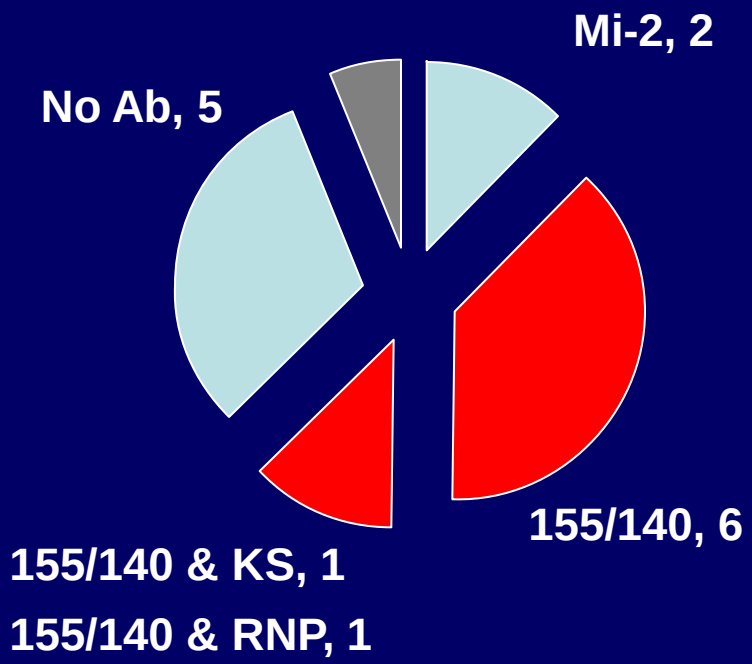
n=16

Antibody frequencies in CAM/non-CAM groups using research laboratory immunology



Non-CAM

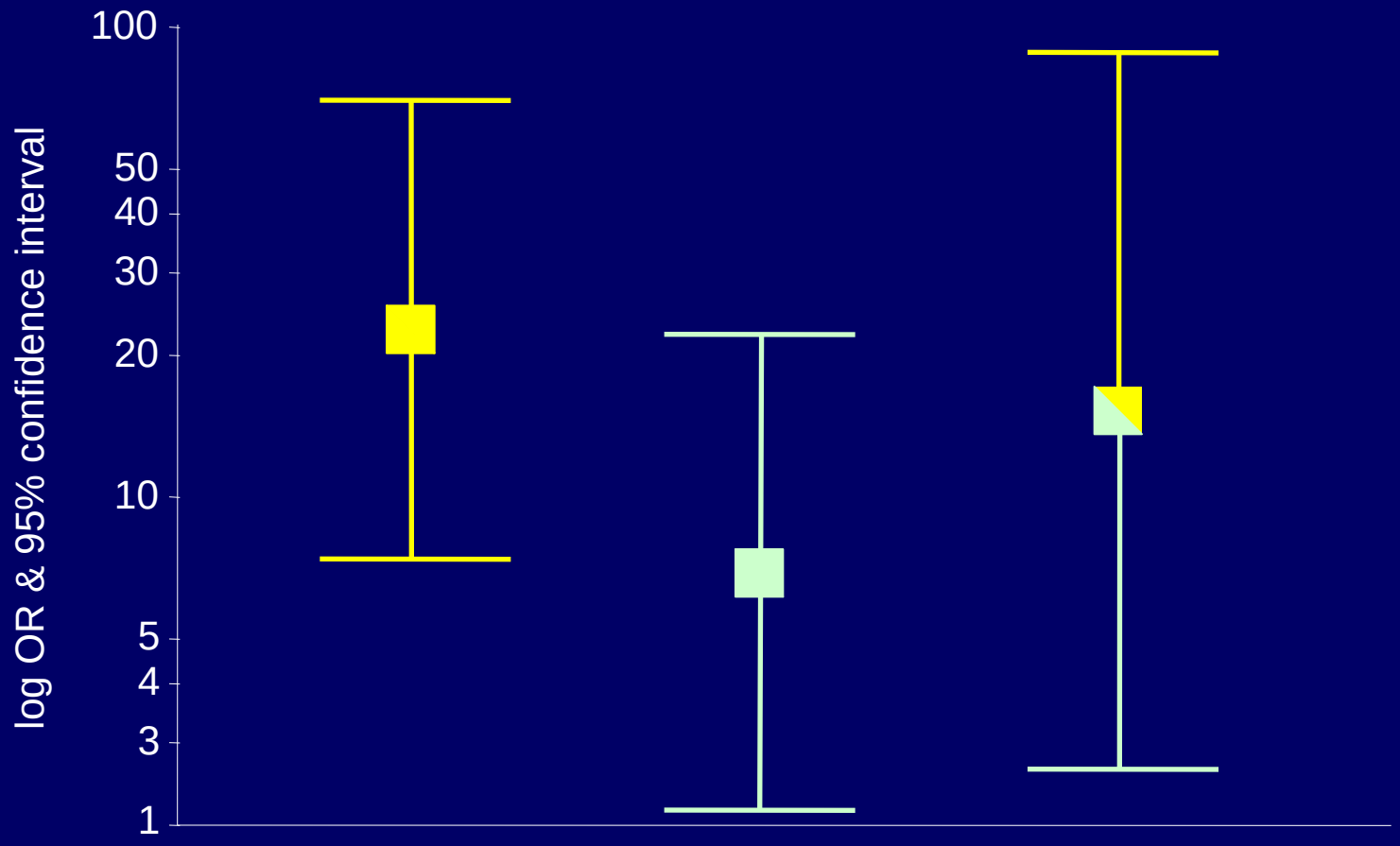
n=266



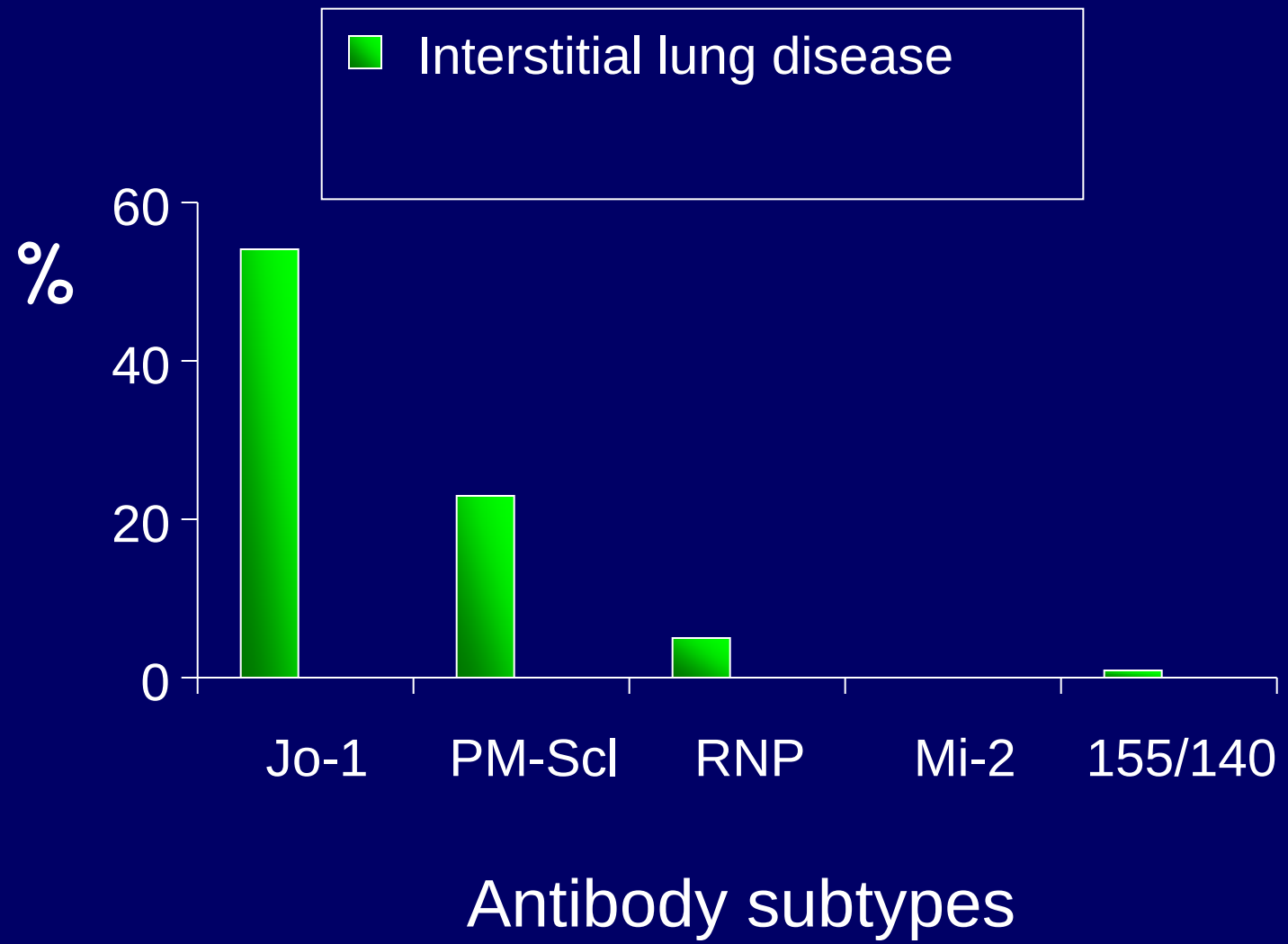
CAM

n=16

Associations with CAM



Frequency of clinical phenotypes by myositis Ab status



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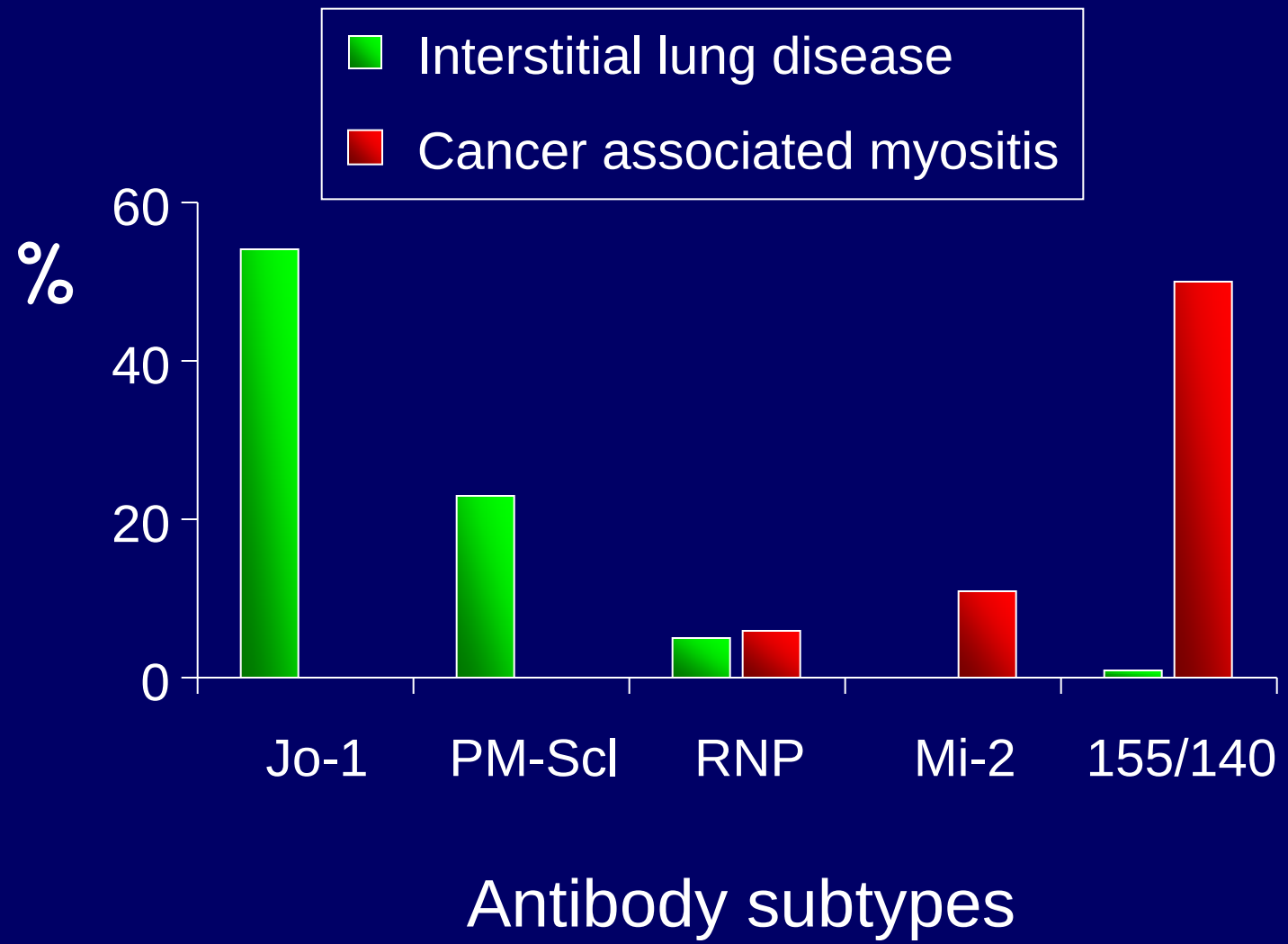
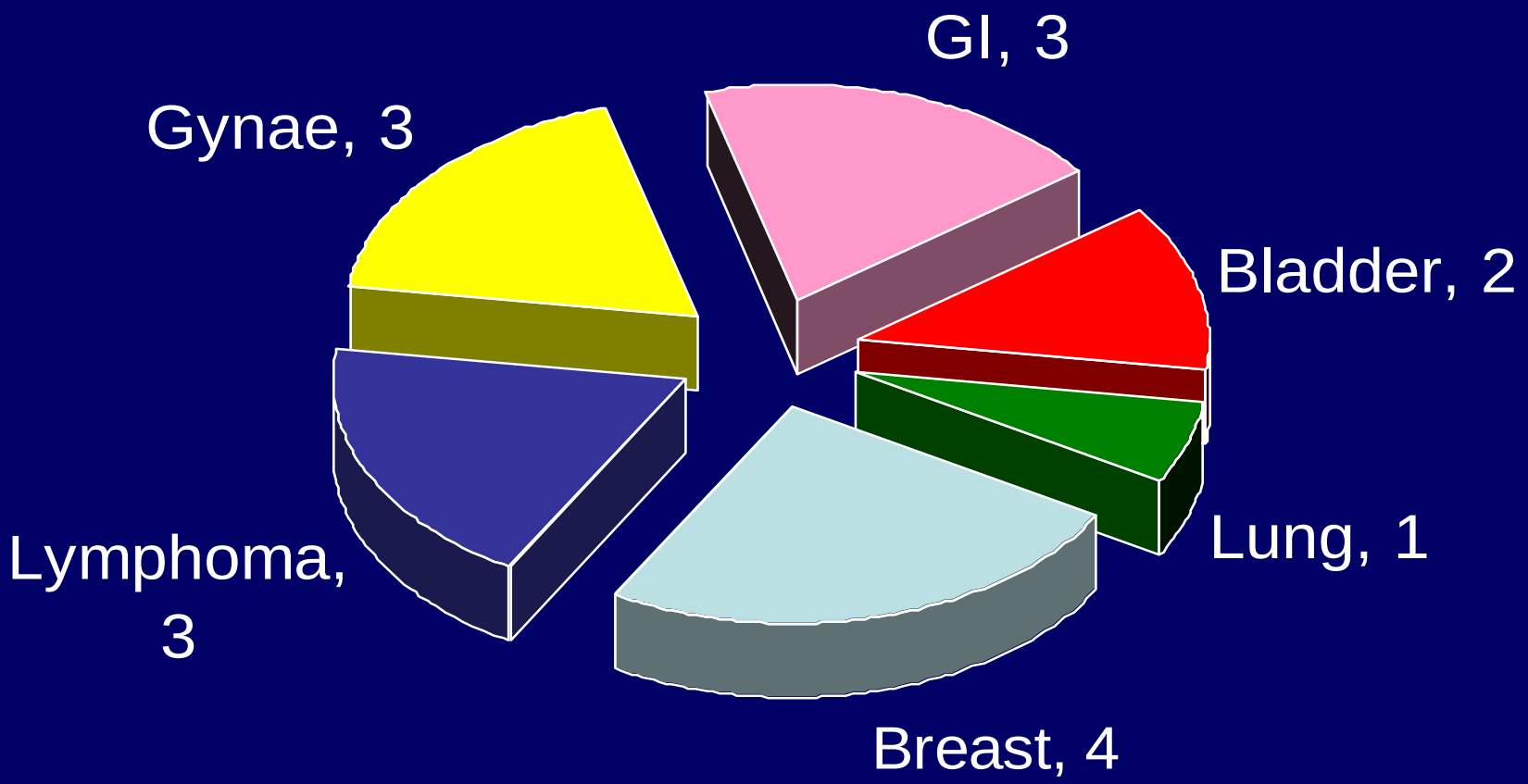


Breakdown of individual malignancies in CAM

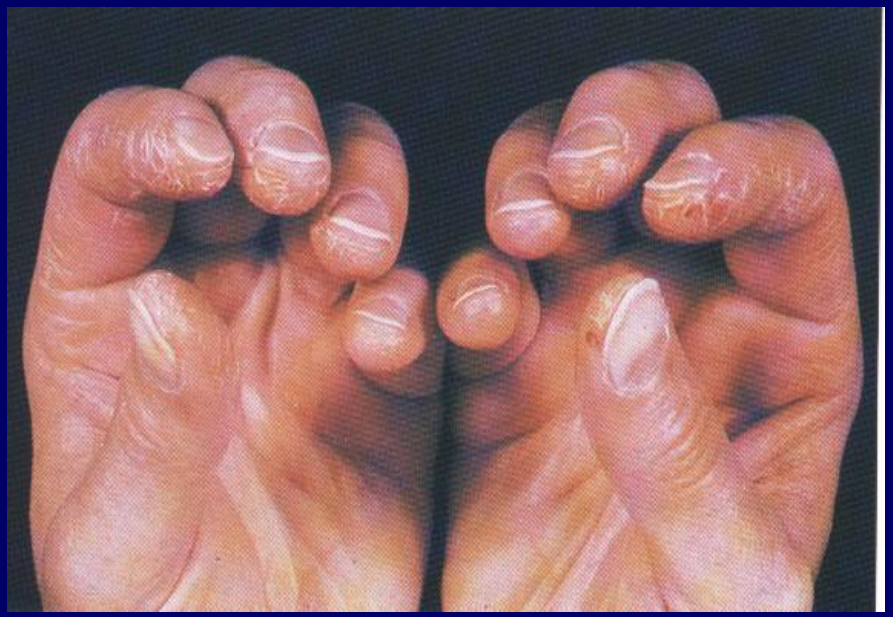


Conclusions

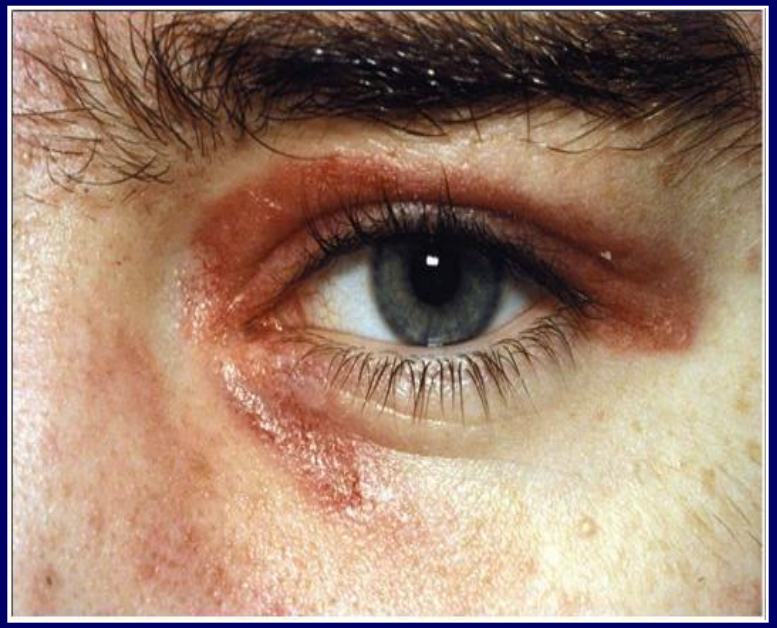
- An absence of MSA/MAAs on routine myositis Ab testing should arouse suspicion of the presence or future development of CAM.
- Anti-155/140 Ab testing defines CAM as a new sero-phenotype.

"Traditional" myositis clinical subtypes

Polymyositis



Dermatomyositis



Commoner Modes of Death in Myositis

- Right heart failure due to ILD.
- Malignancy-related, in cancer-associated myositis (CAM).
- Iatragenic problems – GIT bleeds, ? increased cardiovascular risks and ? increased malignancy risks due to long-term immunosuppression.
- Ventilator-related deaths.