Masterclass in Myositis - Cases

Diagnostic, therapeutic difficulties and prediction of complications

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TEXTBOOK CLINICAL FEATURES BASED ON CRITERIA..

Features

- 1. Symmetrical proximal muscle weakness
- 2. Muscle biopsy evidence of myositis
- 3. Elevation in serum skeletal muscle enzymes
- 4. Characteristic electromyogram pattern of myositis
- 5. Typical rash of dermatomyositis

Polymyositis

- Definite: all of 1–4
- Probable: any 3 of 1–4
- Possible: any 2 of 1–4

Dermatomyositis

- Definite: 5 plus any 3 of 1–4
- Probable: 5 plus any 2 of 1–4
- Possible: 5 plus any 1 of 1–4

I DON'T DIAGNOSE PATIENTS WITH PURELY DM OR PM

YOU WILL MISS CASES JUST LOOKING AT MUSCLE

YOU MAY OVER-DIAGNOSE CASES JUST LOOKING AT MUSCLE

University of BRISTOL North Bristol NHS NHS Trust

AUTOIMMUNE OVERLAP MYOSITIS

WE NOW RECOGNISE THERE ARE DIFFERENT CLINICAL PHENOTYPES / SUBTYPES

1. **PM and DM has a wide spectrum of disease**

2. **Shared features:**
   - Muscle inflammation and weakness
   - Skin rashes, fever, fatigue

3. **But different clinical phenotypes**
   - Some have severe muscle disease at onset
   - Some more at risk of lung disease
   - Some have more skin disease but not much myositis
   - Some more at risk of skin complications – ulceration or calcinosis
   - Some have more arthritis

Case Presentations

Diagnostic, therapeutic difficulties and prediction of complications:

PART (I)

Interstitial pneumonia - anti-synthetase syndrome + other lung syndromes

Case 1

- 38 year old lady (Breast cancer aged 30 – fully treated)
  - Presents to Resp. Clinic – 4 month history dry cough, SOB, fever (repeated Abx in community)
  - Subtle fine basal crackles
  - CXR – normal
  - Normal bloods except ALT 272

  - Other symptoms – Raynaud's, small joint arthritis
  - Swollen 'puffy' fingers

Combined CTD Lung clinic

  - Mechanic's hands, nailfold abnormalities
  - Proximal myopathy – 4+/5
  - CK 3392
  - ANA Hep-2 negative (cytoplasmic stain – anti-Jo1 +ve)

Case 1

- 38 year old lady – anti-Jo1-synthetase syndrome
  - Myositis and arthritis
  - Skin changes
  - Mild lung disease (<20% lung disease on HRCT + FVC > 70%)

1. Prednisolone ~0.5mg/kg (40mg) (+/- induction IV MPRED 500mg x2-3)

2. Early introduction immunoRx (options):

- Azathioprine 2-2.5mg/kg
- MMF 1-1.5g BD

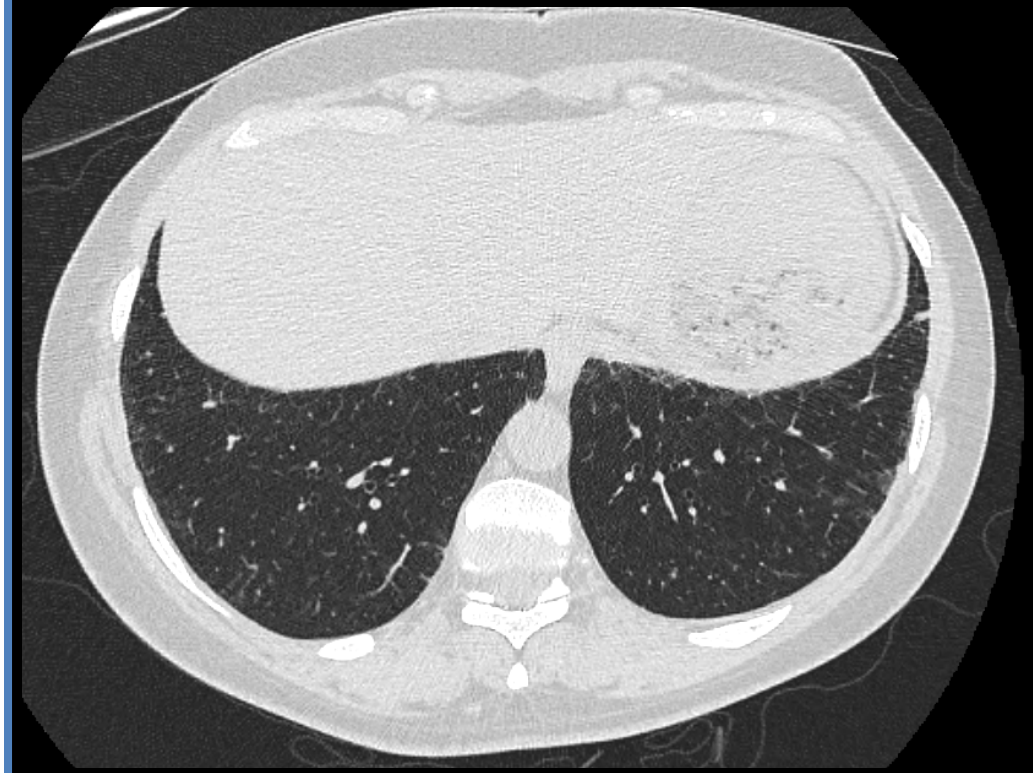
Good response

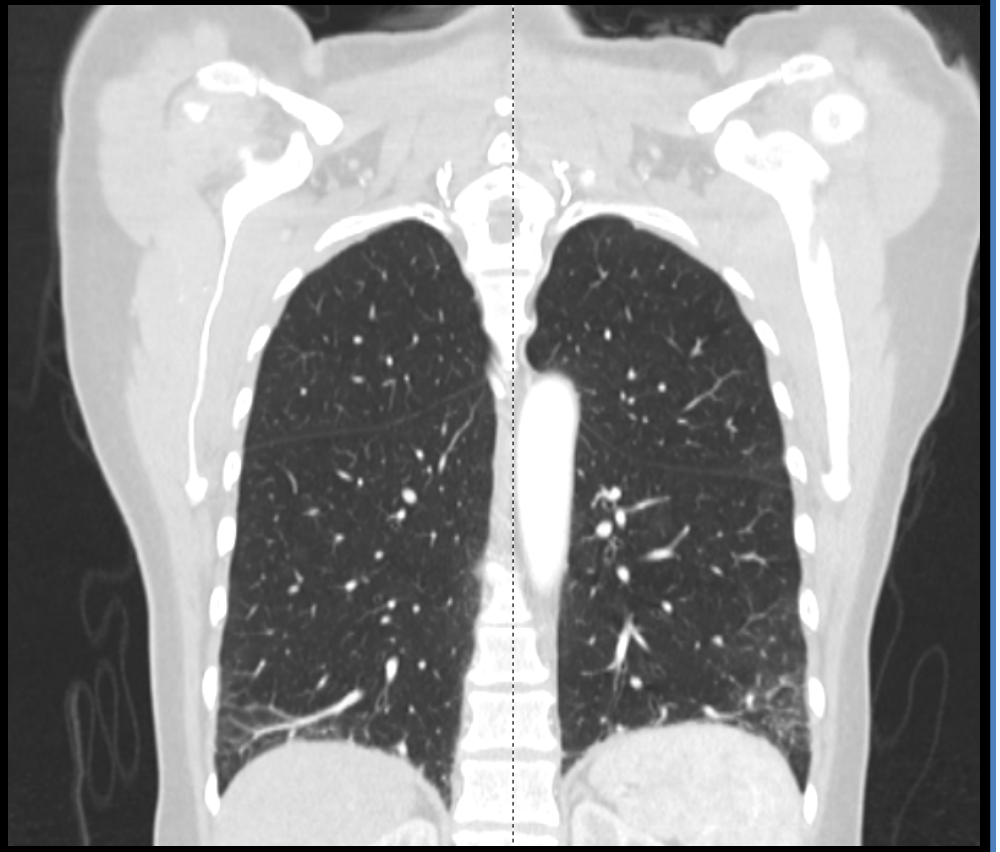
- Resolution of extra-pulmonary disease
- Improvement in serial CTs and FVC / TLco 77%

Case 1

PFTs – FVC 80% + TLco 65%

HRCT





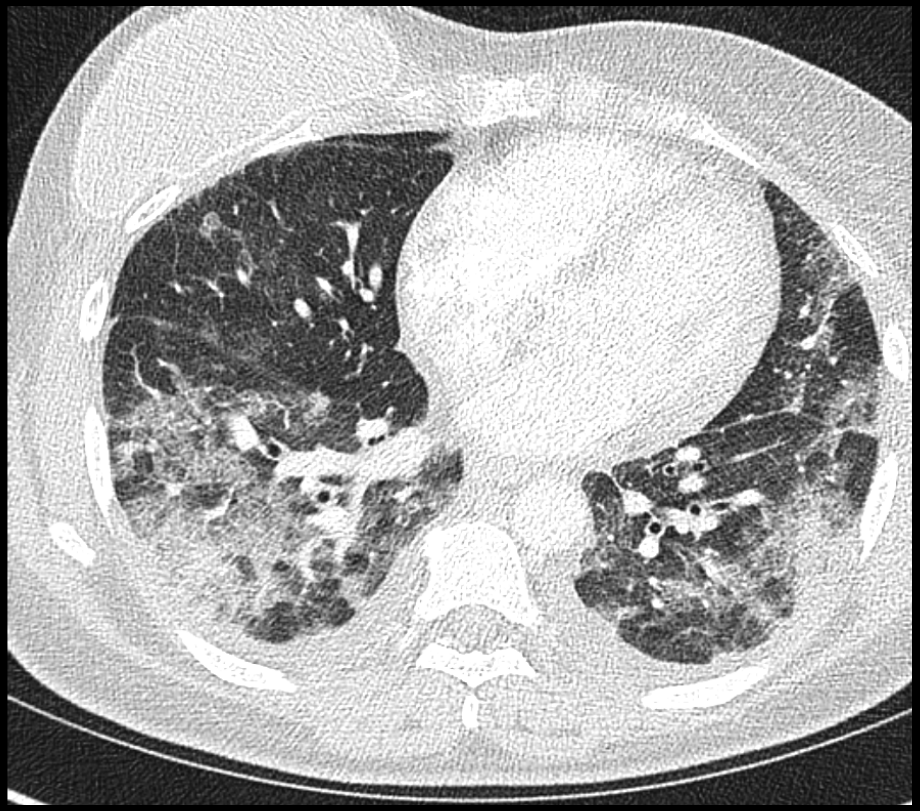
Case 1

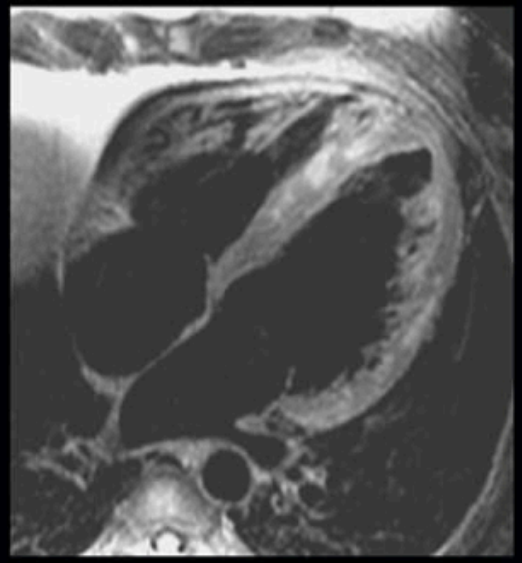
- 38 year old lady – anti-Jo1-synthetase syndrome
  - >2 years after presentation of ASS (now in remission)
  - Breast cancer recurrence
  - Stop MMF
  - Surgery + 6 cycles of adjuvant chemotherapy (Cyclophosphamide 600mgs/m^2 and Docetaxel 75mgs/m^2)
  - Additional Trastuzumab (Herceptin) SC injections every 3 weeks (7 injections)
  - Emergency admission – fever, SOB (FVC 60% + TLco 26%), neutropenia
  - Broad spectrum Abx – no response
  - Continued deterioration – ITU
  - CK 1935, Troponin-T 135, boderline NTproBNP

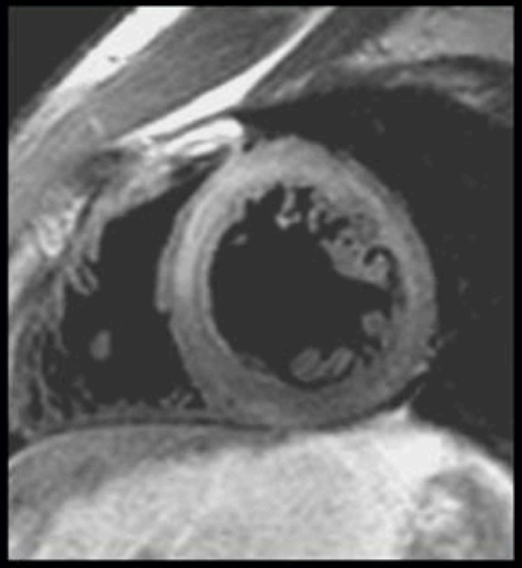
Case 1

HRCT and cMRI

BAL – lymphocytosis +++







Case 1

- 38 year old lady – anti-Jo1-synthetase syndrome

  - ASS flare
    - IV MPRED
    - Restart steroids
    - Abx cover
    - But flare (following adjuvant chemo. inc. 'ASS Rx dose' IV CYCLO).

    Why?

    Treatment options?

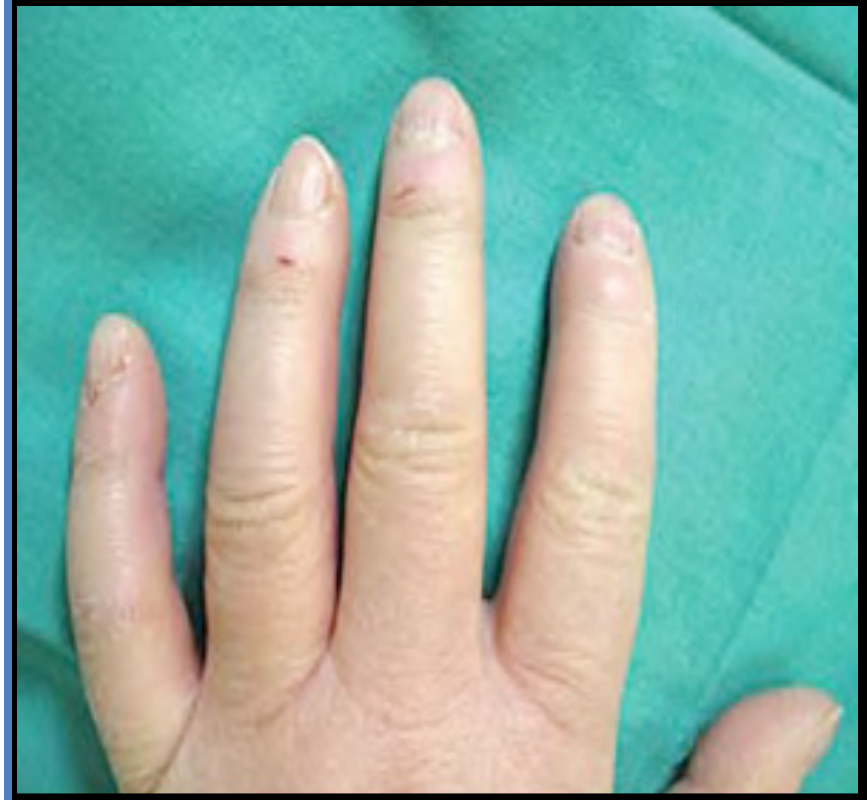
Trastuzumab (Herceptin) induced flare?

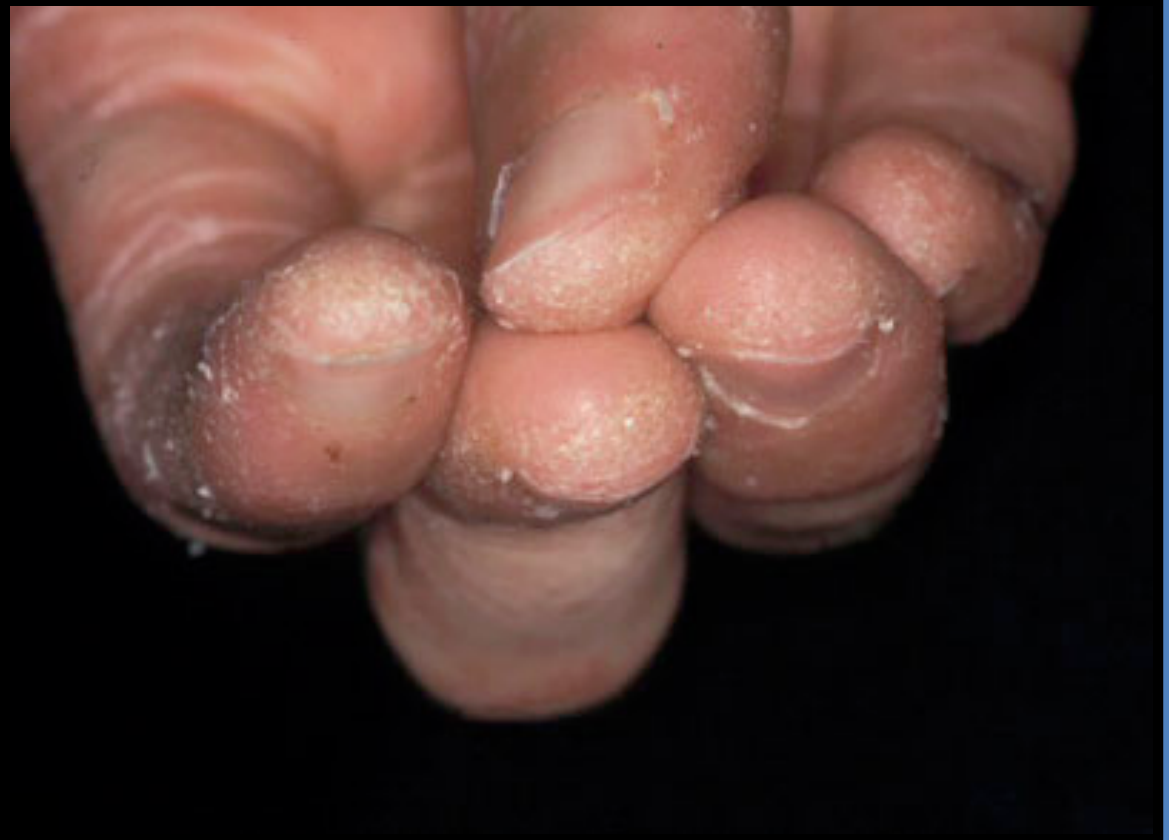
- **Myocarditis, organising pneumonia, myositis**

1. **IV IG 2gram/kg divided doses**
2. **Rituximab 1gram x 2**

Case 2 – other syndromes

- 54 year old
  - 6 months dry cough and limited exercise tolerance
  - Presents with:
    - Raynaud's
    - Puffy tight skin - fingers
    - Mechanics hands
    - Myalgia but not weak
    - CK 1532
    - Significant respiratory decline
    - ANA +ve (nucleolar) – anti-PM-Scl
  - Muscle biopsy not done
  - Organising pneumonia +/- NSIP
  - Treatment approach influenced by degree of lung disease

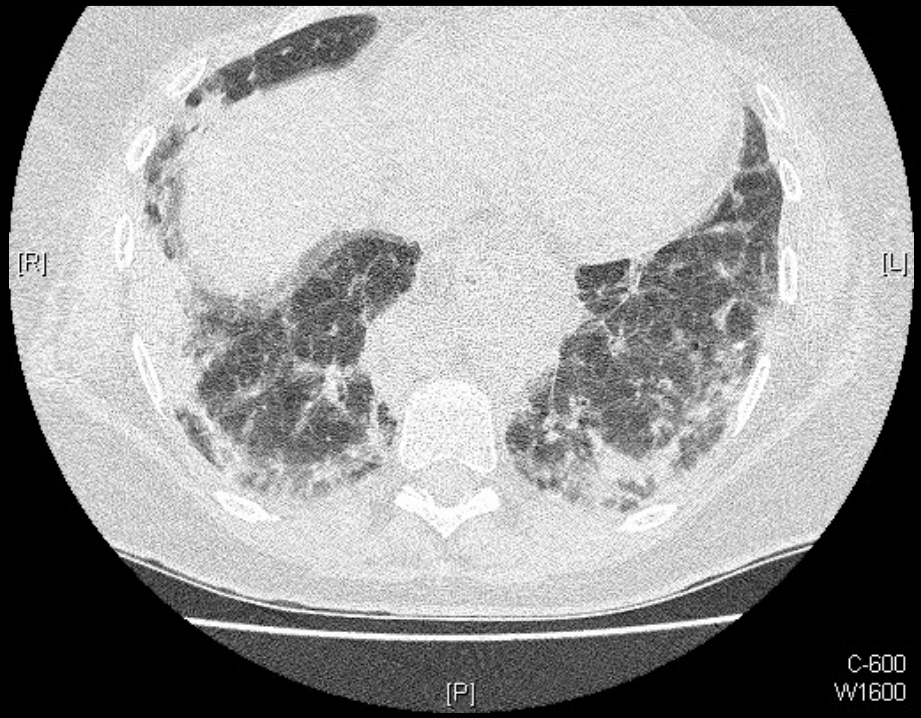


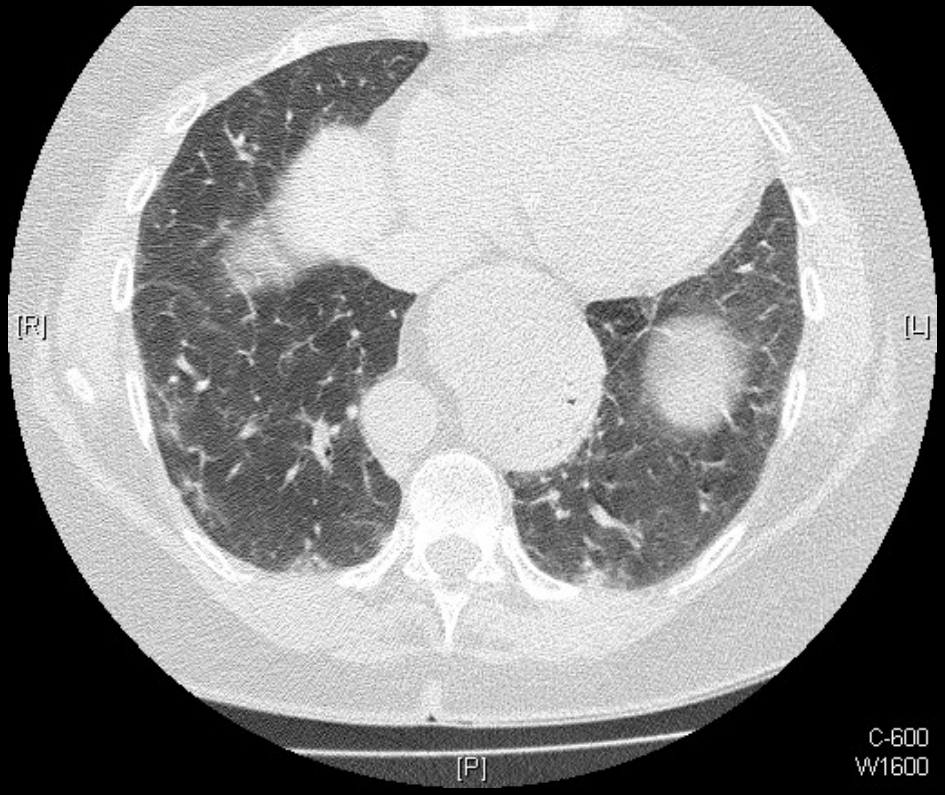


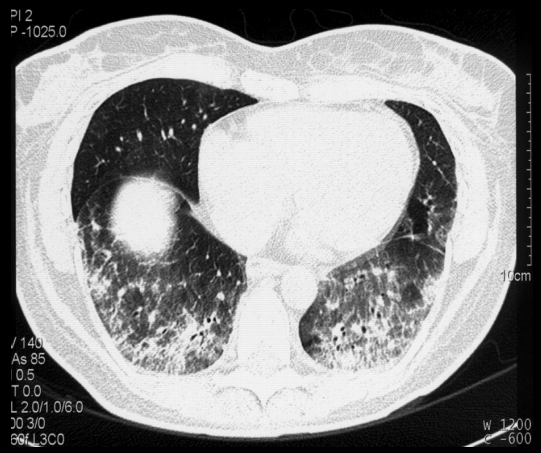
FEV1/FVC 60%
DLCO 52%

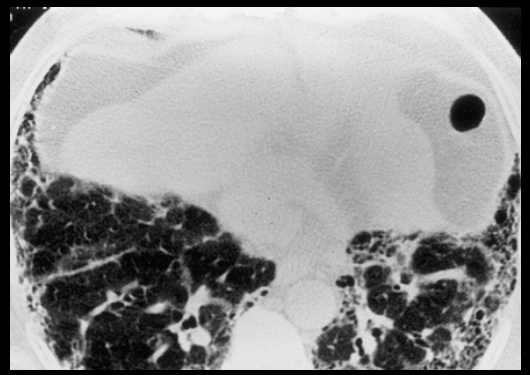
IV CYCLO + steroid induction

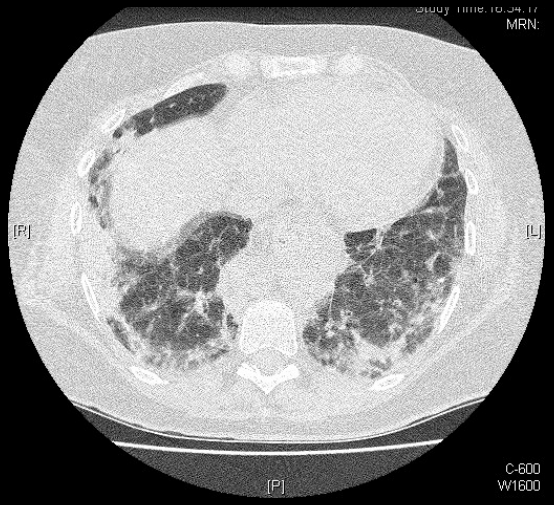
Post treatment scan
Improvement in FVC – 76%
DLco 75%











Jo1

Ha

Zo

EJ

OJ

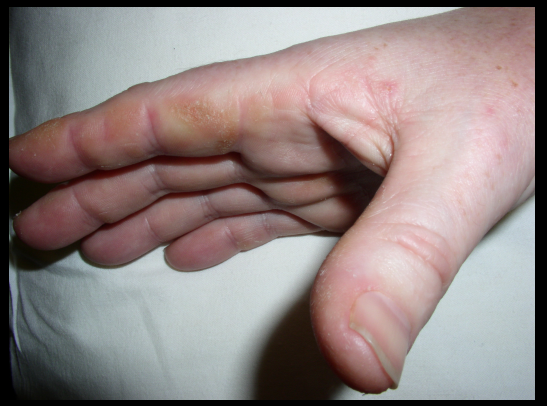
PL7

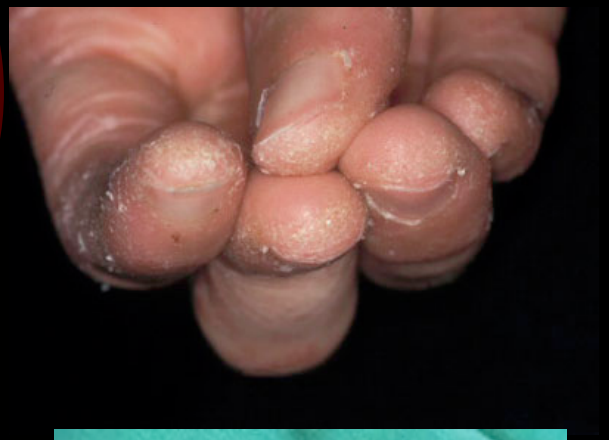
KS

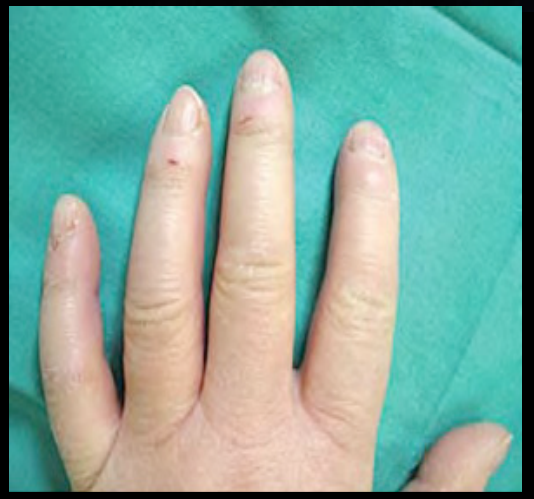
PL12

Anti-synthetase autoantibodies

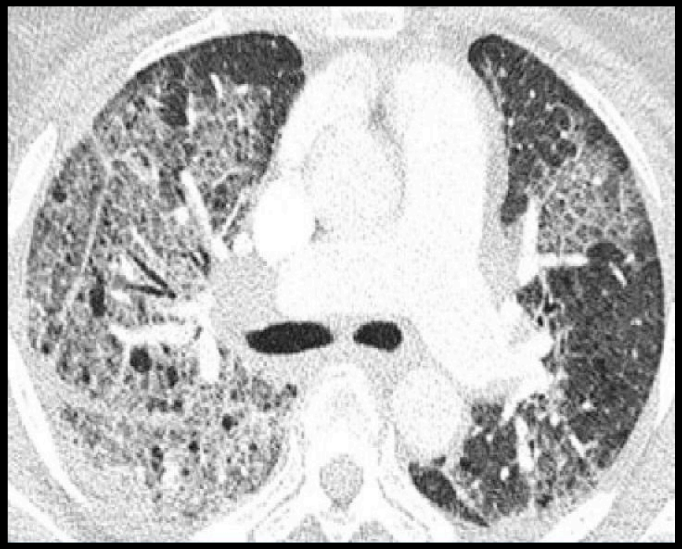
Anti-PMScl







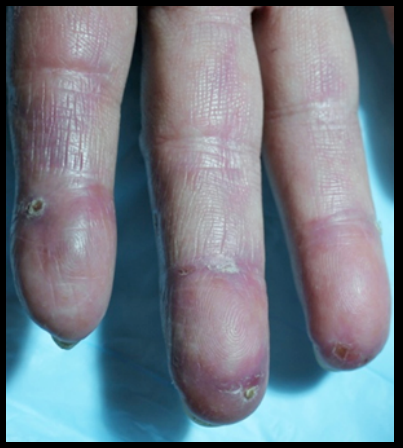
Photos courtesy of Dr David Fiorentino: J Am Acad Dermatol. 2011

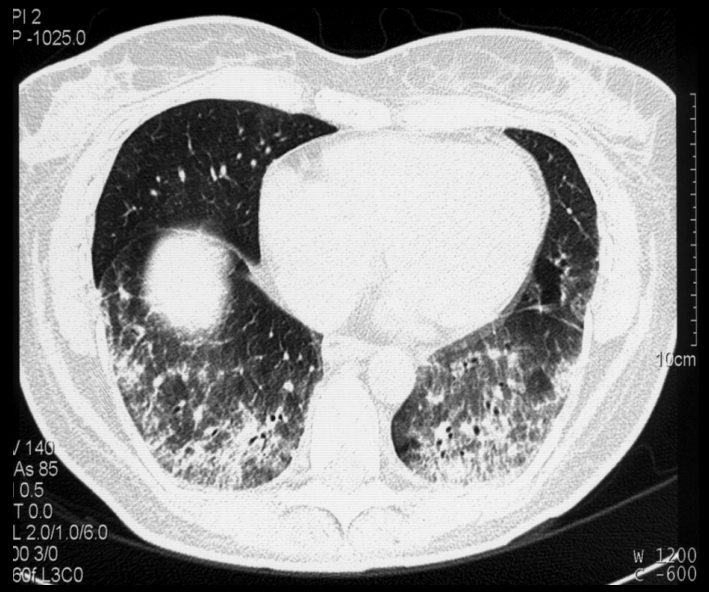


Amyopathic DM patients

Different types of interstitial pneumonia (depending on ethnicity)

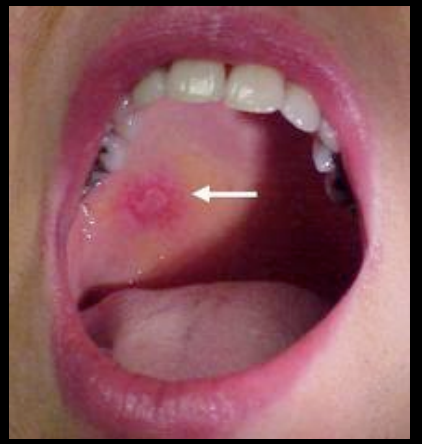
Skin and mucocutaneous vasculopathy





Anti-MDA5

1. Ethnicity
2. Amyopathic DM
3. Skin ulceration
4. Fever



Anti-ARS*	Anti-MDA5	Anti-PM-Scl	Anti-U3RNP	Anti-RuvBL1/2

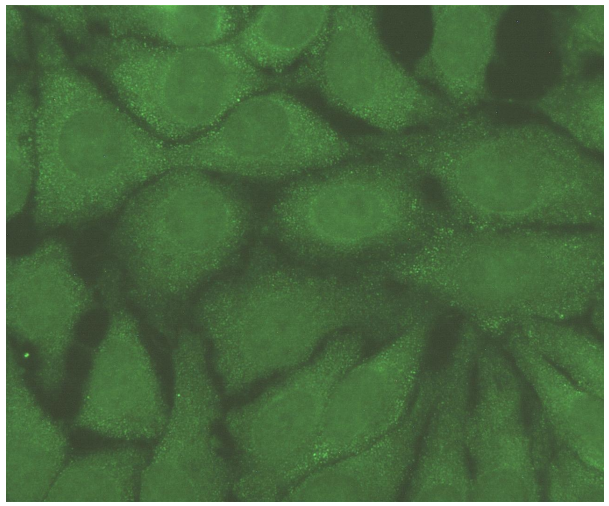
Myopathy-pulmonary spectrum

ASS	Dermatopulmonary	Overlap CTD-SSc-myopathy
ILD: NSIP +/- OP or UIP or AIP (RP-ILD)		ILD
CADM		Diffuse skin disease
Mechanic's hands		PAH
Gottron's lesions		Gastro-intestinal
Raynaud's phenomenon		
Inflammatory arthritis		
Mucocutaneous ulcers		
Palmar papules		
Anti-Jo1 titres	Anti-MDA5 titres	
	Ferritin	
	IL18	

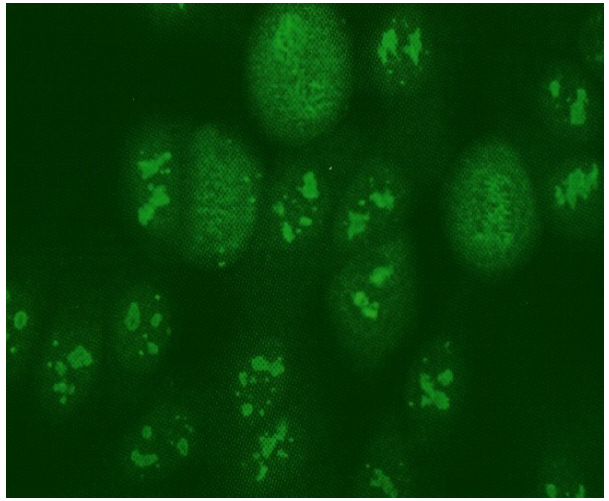
Related to subtype of ILD (non-anti-Jo1 ASS and anti-MDA5 RP-ILD) – worse

Cellular NSIP and OP – better

Cytoplasmic



Nucleolar



Predictors of lung disease

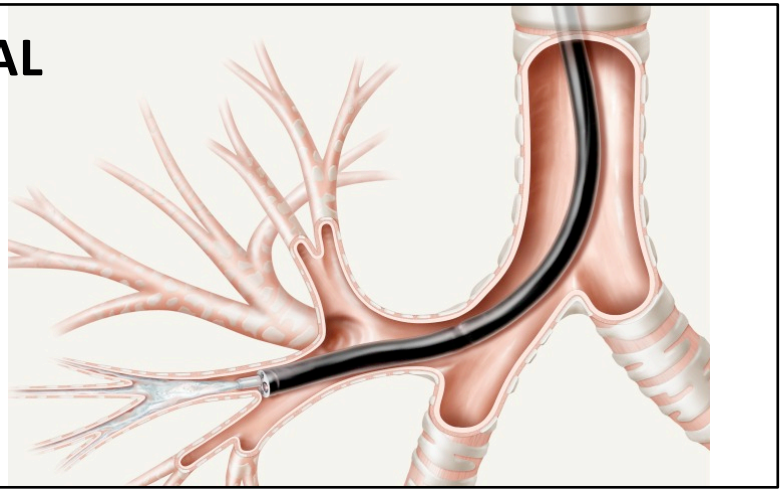
1. **Ethnicity – Asian (Japan, China, Korea)**
2. Overlap syndrome (not 'pure' polymyositis)
3. Skin ulceration and other 'classic' cutaneous features - significant predictive and prognostic factor
4. Fever
5. **Hyperferritinaemia**
6. Normal CPK (amyopathic disease – CADM)
7. **Acute/subacute form - low FVC% and TLco% at presentation AND/OR HRCT > 20% disease**
8. Lymphocytosis vs. neutrophilia on BAL

Serological markers

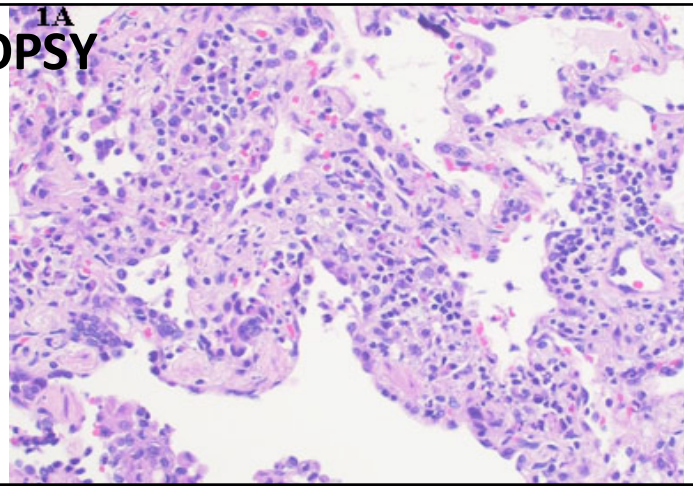
- **Anti-synthetase antibodies (Non-Jo1** > anti-Jo1)
- **Anti-MDA5**
- Anti-PM-Scl

The role of bronchoalveolar lavage and VATS biopsy?

BAL



BIOPSY



Role?

- Infection?
- Inflammatory component?
- Is this fine fibrosis?

Role?

- Diagnostic uncertainty – gold standard for IP subtype
- Inflammatory component?
- Is this fine fibrosis?

Am J Respir Crit Care Med Vol 185, Iss. 9, pp 1004–1014 (2012)

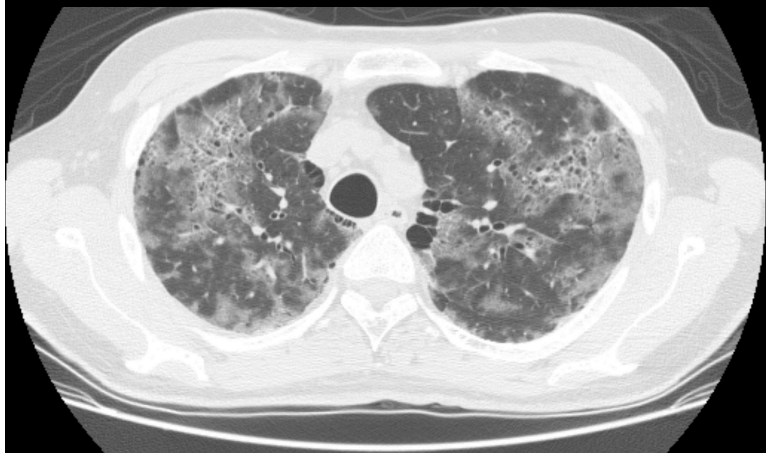
Don’t forget infection

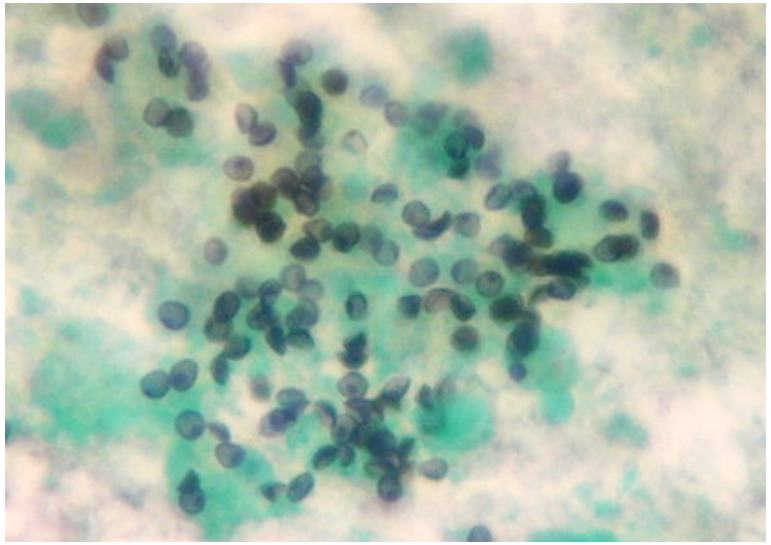
PCP

Perihilar / midzone ground glass

Crazy paving pattern

Reticular opacities





Aspiration + Infection

Respiratory muscle weakness

Deterioration in immunosuppressed patients

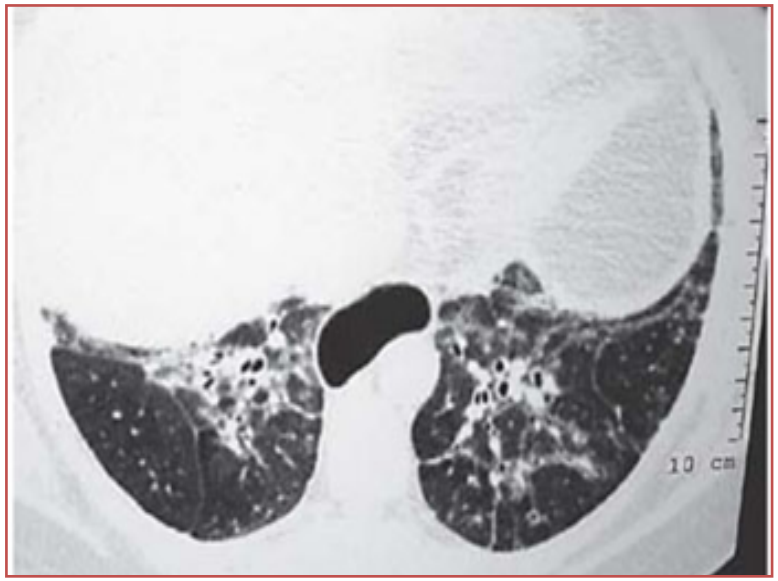
Ethnic risk factors / recent travel

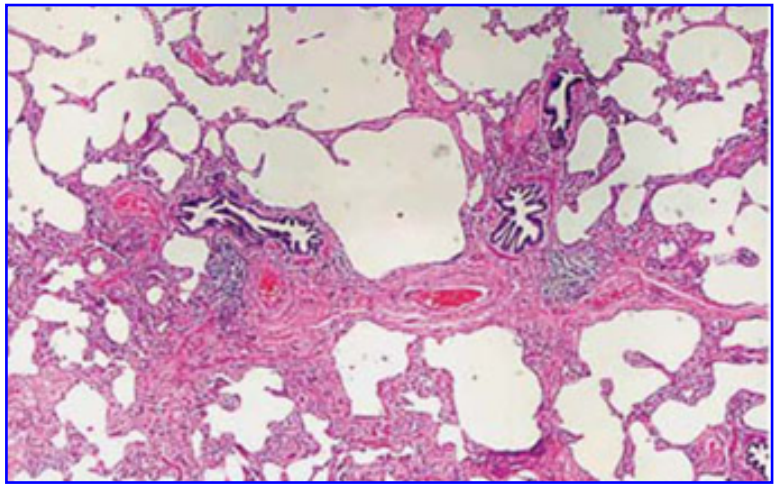
Atypical HRCT appearances

Approach to management:

- Appropriate cultures
- Low threshold for BAL
- Treat early

Don’t forget co-existent reflux





(Bile salts / acid may trigger epithelial injury)

ON HRCT:

1. **Look for dilated patulous oesophagus**
2. **Fibrosis - patchy centrilobular lung injury around small airways**

Approach to management:

- High dose PPI (e.g. Omeprazole 40mg BD)
- Ranitidine 300mg OD (evening)
- Pro-kinetic (e.g. Metoclopramide 10mg TDS)

Treatments

- CYCLO regimes based on SSc data (SLS and FAST study).

  Tashkin et al NEJM 2006 & Tashkin et al Am J Respir Crit Care Med 2007
  Hoyles et al Arthritis Rheum 2006

- *Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease.

  Fischer et al 2013

- Effectiveness and Safety of MMF in treatment of SSc-ILD

  Cuomo et al 2009

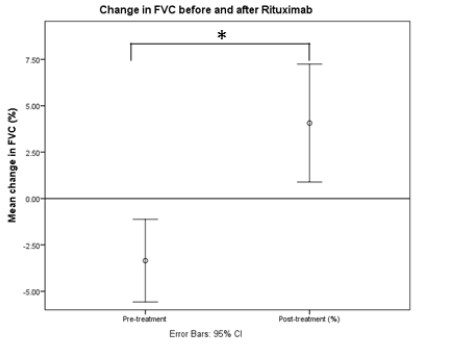
- Small retrospective cases series in SSc and IIM improvements in:
  - Stability in PFTs
  - Improved survival
  - Lower rate of decline in FVC and survival cf. other agents
  - *Be aware of risk of hypogammaglobulinaemia + functional bronchiectasis / recurrent infections

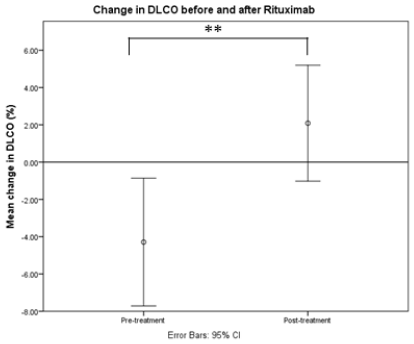
- Tacrolimus and Ciclosporin
  - A number of studies suggest efficacy first line and rescue in ASS and amyopathic DM RP-ILD (AIP)
  - Combination therapy with cyclosporine and cyclophosphamide

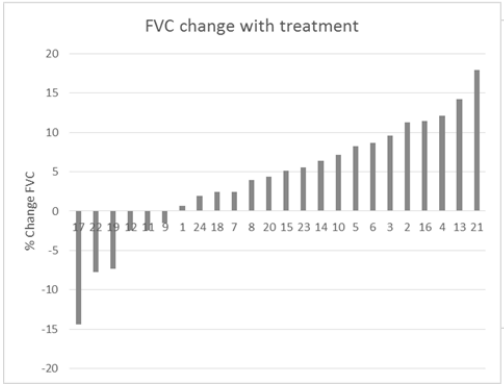
Rituximab

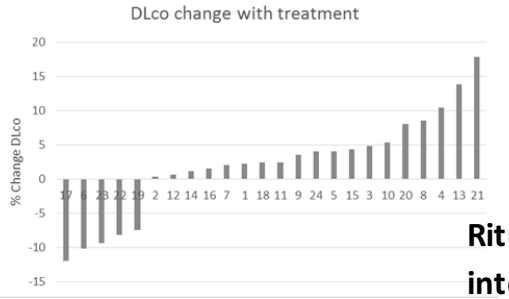
- ✓ **Case reports and series.**
- ✓ Arthritis Rheum. 2013;65:314-24. **Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial.**
- No significant differences in the 2 treatment arms for the primary and secondary end points
- 83% of adult and juvenile myositis patients with refractory disease met the DOI
- **SUBANALYSIS – ANTI-SYNTHETASE PATIENTS RESPOND BETTER**

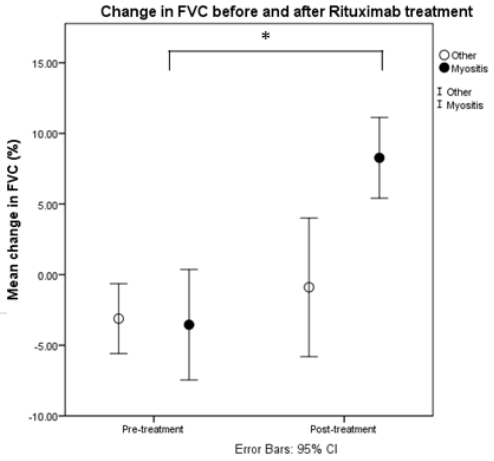
North Bristol – 24 patients (13 CTD – myositis overlap / ASS)

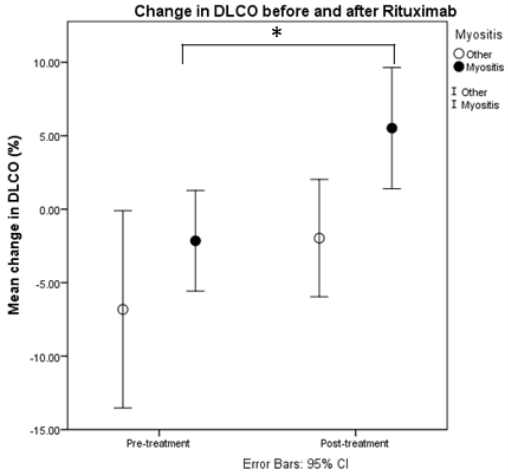












Rituximab in autoimmune connective tissue disease-associated interstitial lung disease

C Sharp, M McCabe, N Dodds, A Edey, L Mahers, H Adamali, AB Millar, H Gunawardena – *paper submitted.*

Interstitial pneumonia in overlap myositis

University of BRISTOL | North Bristol NHS NHS Trust

REFERRAL TO ILD CTD SPECIALIST TEAM

- VALUE OF CTD-ILD MDT
  - ILD + RHEUM
  - ILD RADIOLOGISTS
  - HISTOPATHOLOGISTS
  - ACCESS TO SPECIALIST IMMUNOLOGY
  - ACCESS TO TREAMENT PATHWAYS INC. BIOLOGICS / TRIALS

- **My approach**

1. Induction IV CYCLO 10-15mg/kg every 3 weeks (min: 6 pulses, then reassess)
2. IV MPRED 500mg – maintenance oral Pred 0.5mg/kg + reduce
3. Maintenance or mild disease at onset – MMF 2-3grams/day or AZA
4. Refractory / progressive disease

- Rituximab
- Tacrolimus

Treatment 'response' in some defined as stability

Certain phenotypes 'respond' better than others

Case Presentations

Diagnostic, therapeutic difficulties and prediction of complications:

PART (II)

- ✓ Autoimmune necrotising myopathy
- ✓ Cutaneous disease and calcinosis
- ✓ Cancer-associated myositis

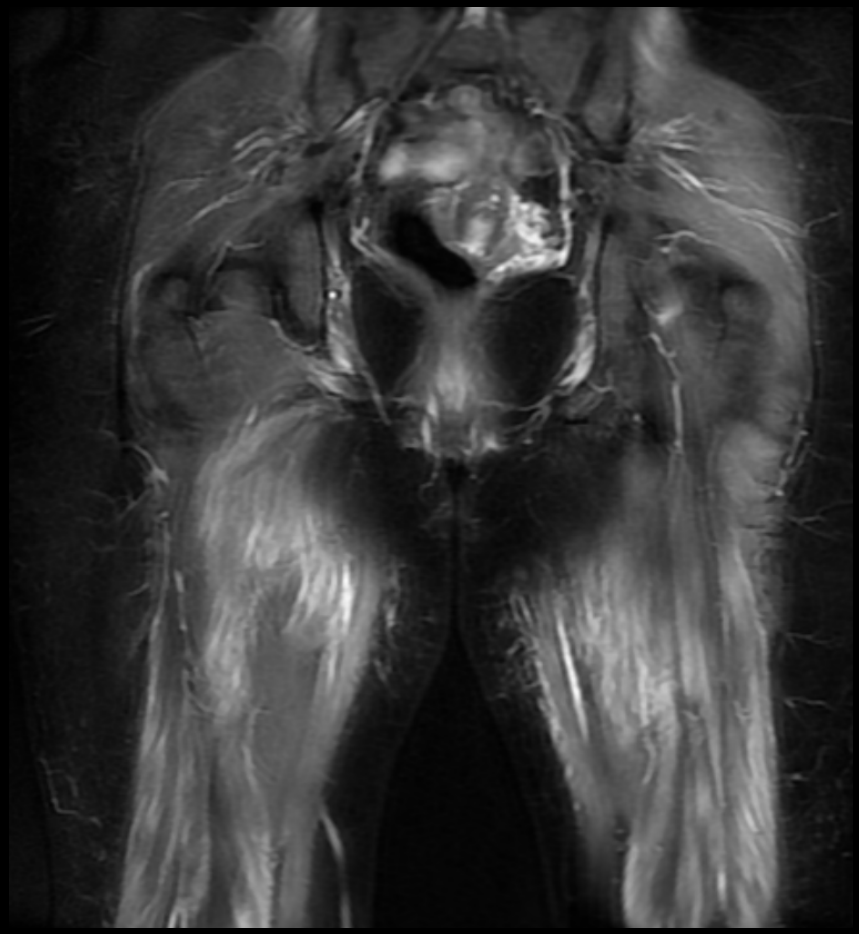
Autoimmune necrotising myopathy

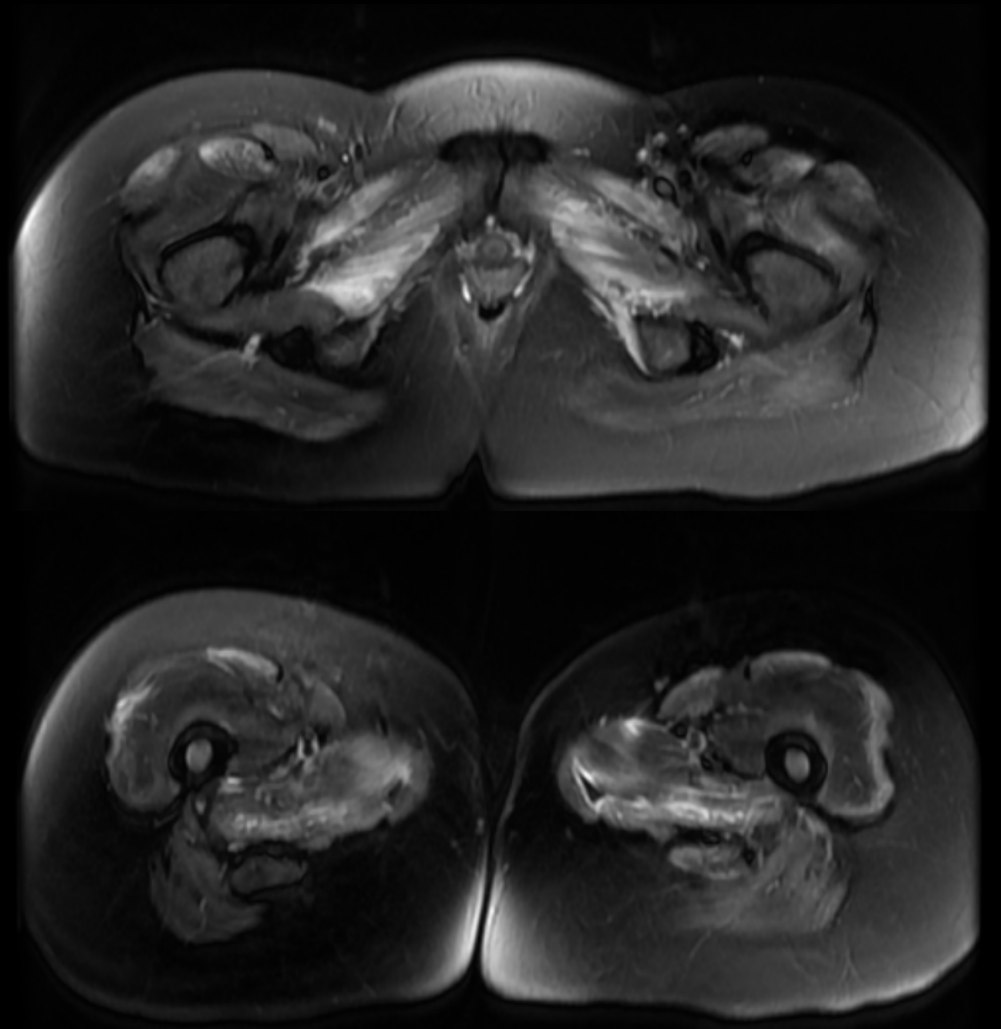
Case 2

- 49 year old lady
  - Unwell for 4 weeks
  - Malaise, fatigue, acute muscle weakness
  - Episodes of chest pain + palpitations
  - No other overlap features
  - Weak: MRC 3/5 – difficulty standing unaided from chair
  - CK 6875
  - Troponin-T 1479
  - Abnormal ECG – runs of bigeminy / tacycardia
  - Normal cMRI

- MRI and EMG consistent with myositis

- Muscle biopsy
  - Necrotic fibres, scanty endomysial + perivascular lymphocytic infiltrate
  - Focal endomysial fibrosis





Case 2

- 49 year old lady
  - ANA negative (cytoplasmic stain on HEp-2)
    - Anti-signal recognition particle +ve

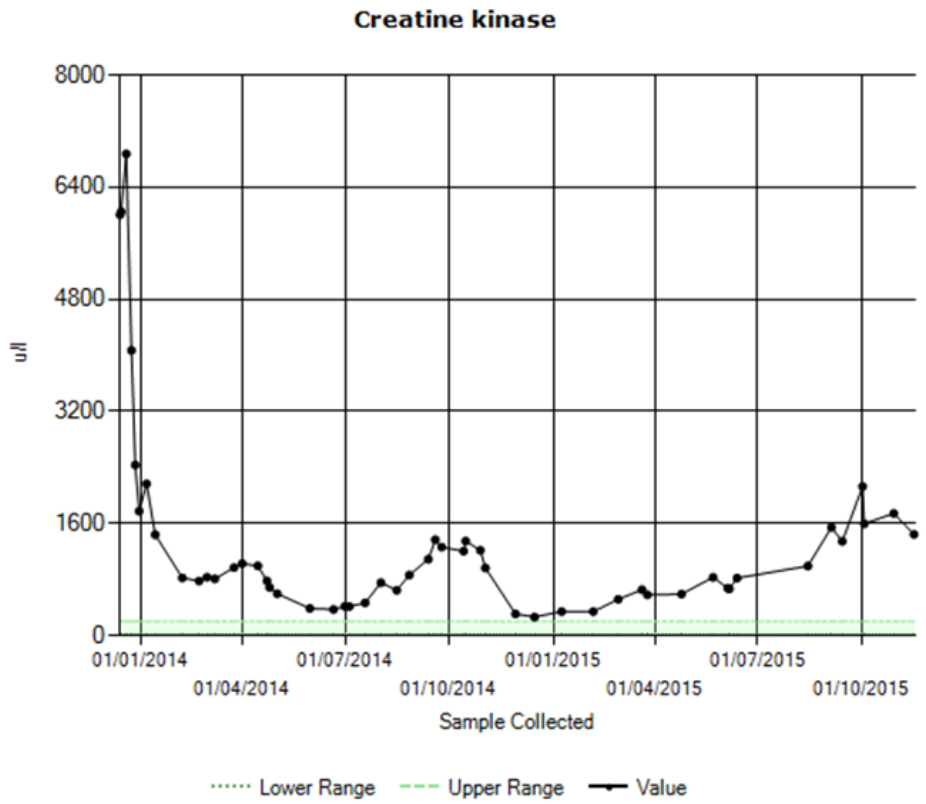
1. Steroid induction – MPRED pulses 500mg (x2-3), then 0.5mg/kg Pred + reduce

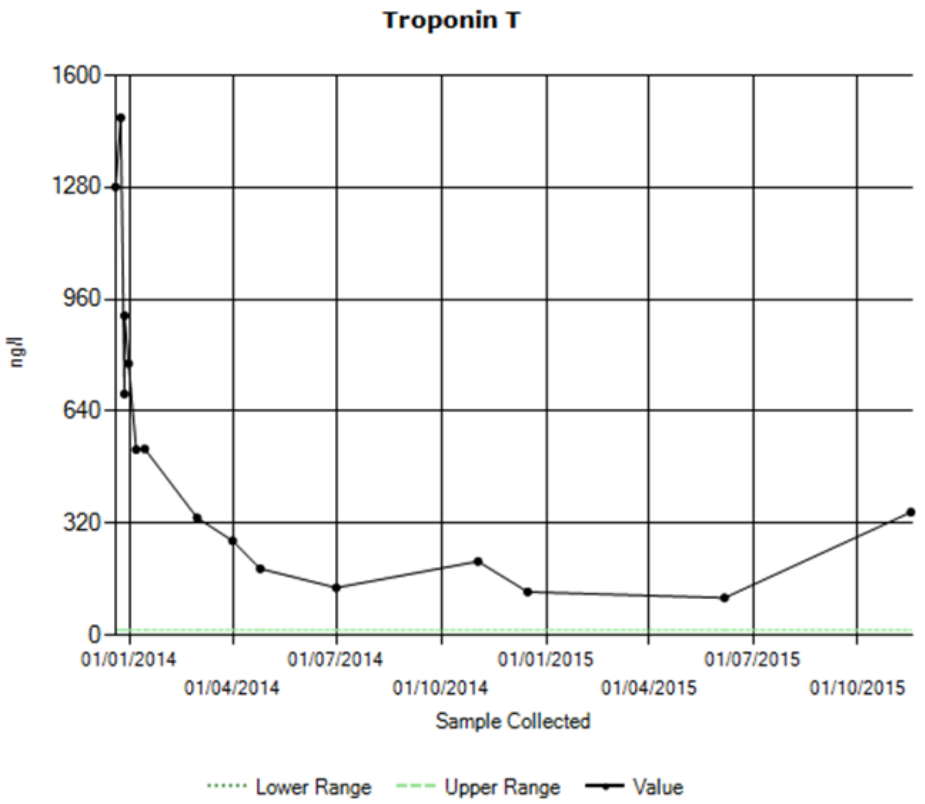
2. Limited evidence base – 'best clinical practice'

- IV IG induction 2gram/kg
- + maintenance (MTX 20-25mg or AZA 2-2.5mg/kg)
- Other options inc. MMF

- Challenge – no optimal Rx strategies in refractory disease?
  - Maintenance IV IG
  - CYCLO induction
  - Rituximab
  - Case reports – Alemtuzumab +/- autologous stem cell transplant

Case 2

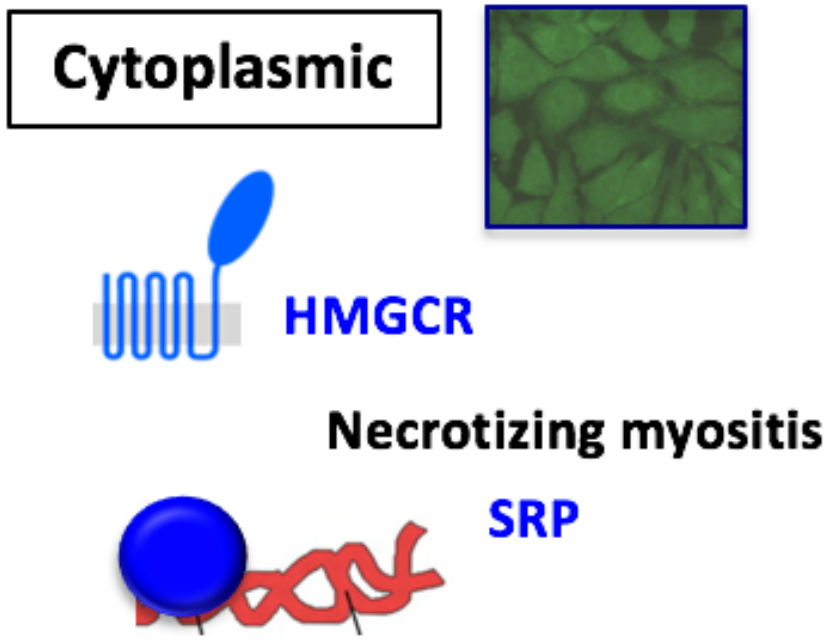




1. CK + TN-T may *not* correlate with disease activity / weakness over time
2. CK + TN-T may *not* normalise / may plateau
3. Interval MRI helpful – muscle oedema vs. atrophy
4. Often refractory – requiring multiple treatments

Immune mediated necrotising myopathy

- Seropositive AIMN is a distinct entity to what we would have previously termed classic PM.
- Anti-SRP and anti-HMGCR syndromes
  - Acute severe muscle disease, mirrored by CK levels
  - Little overlap features
  - Relative absence of inflammatory infiltrate
  - In some - anti-HMG-CoA discontinuation of statins does not result in clinical improvement

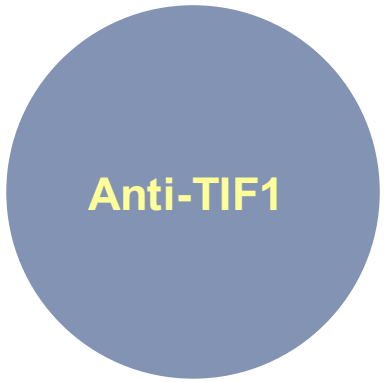


Cancer-associated myositis

Dermatomyositis

Case 3

- 70 year - proximal myopathy over 3 months
- Skin changes
- Dysphagia and weight loss
- Weight 40kg at presentation
- CK 1567 with mild weakness



- EMG – myopathic
- Skin Bx – interface dermatitis consistent with DM

- Endoscopy and biopsy – oesophageal carcinoma

- Standard ANA and ENA –ve
- ANA IIF HEp-2 – weak positive

1. Supportive Care

2. At risk of respiratory failure from resp. muscle weakness

3. At risk of secondary infection

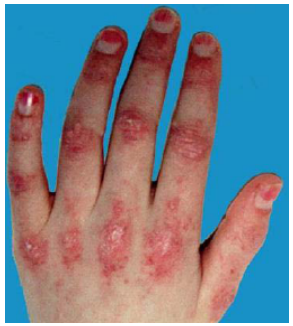
4. Target underlying cancer – chemoRx

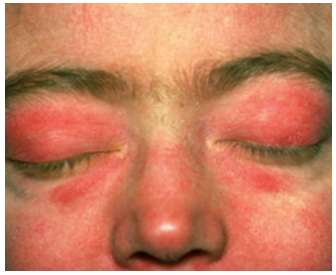
5. Adjuvant Rx:

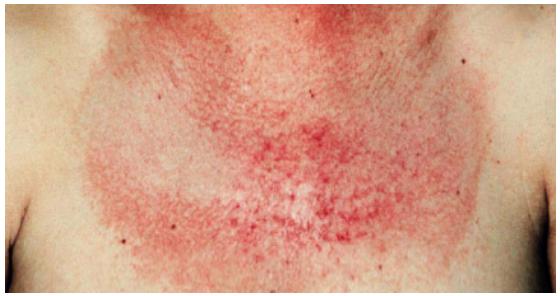
    - Steroids
    - IV IG
    - MTX, HCL, chemo may include CYCLO

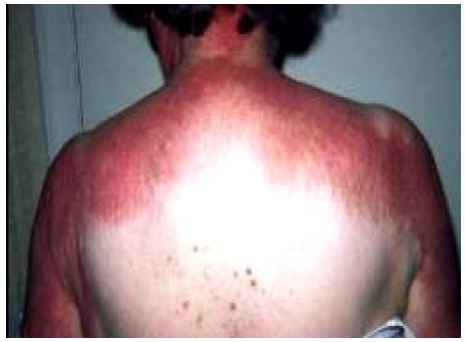
Pooled data for predicting malignancy in adult DM

- Negative predictive value = 93% and odds ratio ≈ 20-25



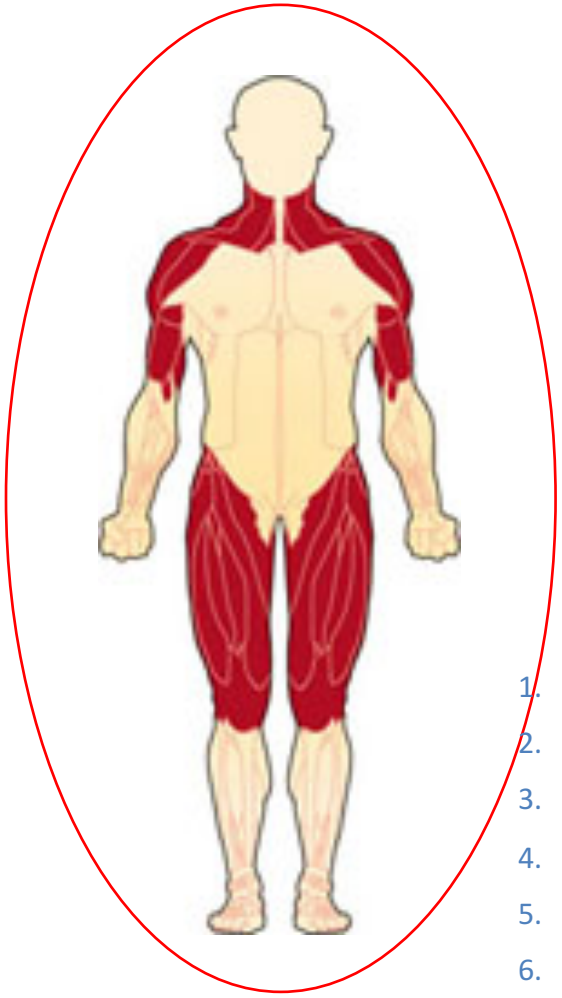


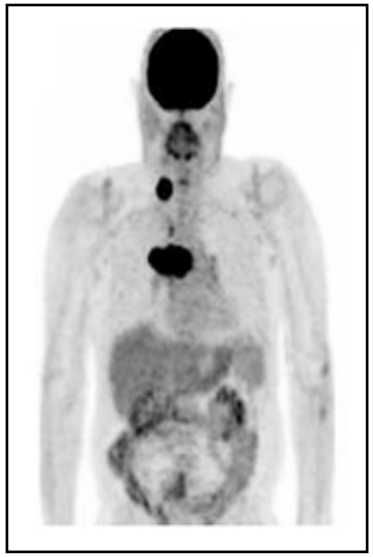




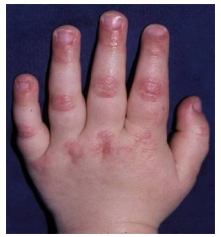
Not associated with ILD

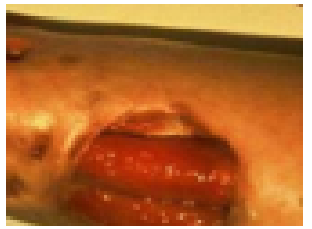
Older adults (men)
Systemic features
Severe DM rash
>50% anti-TIF1 - cancer





Adults Malignancy





JDM
No Malignancy
Skin ++
Ulceration
Vasculitis

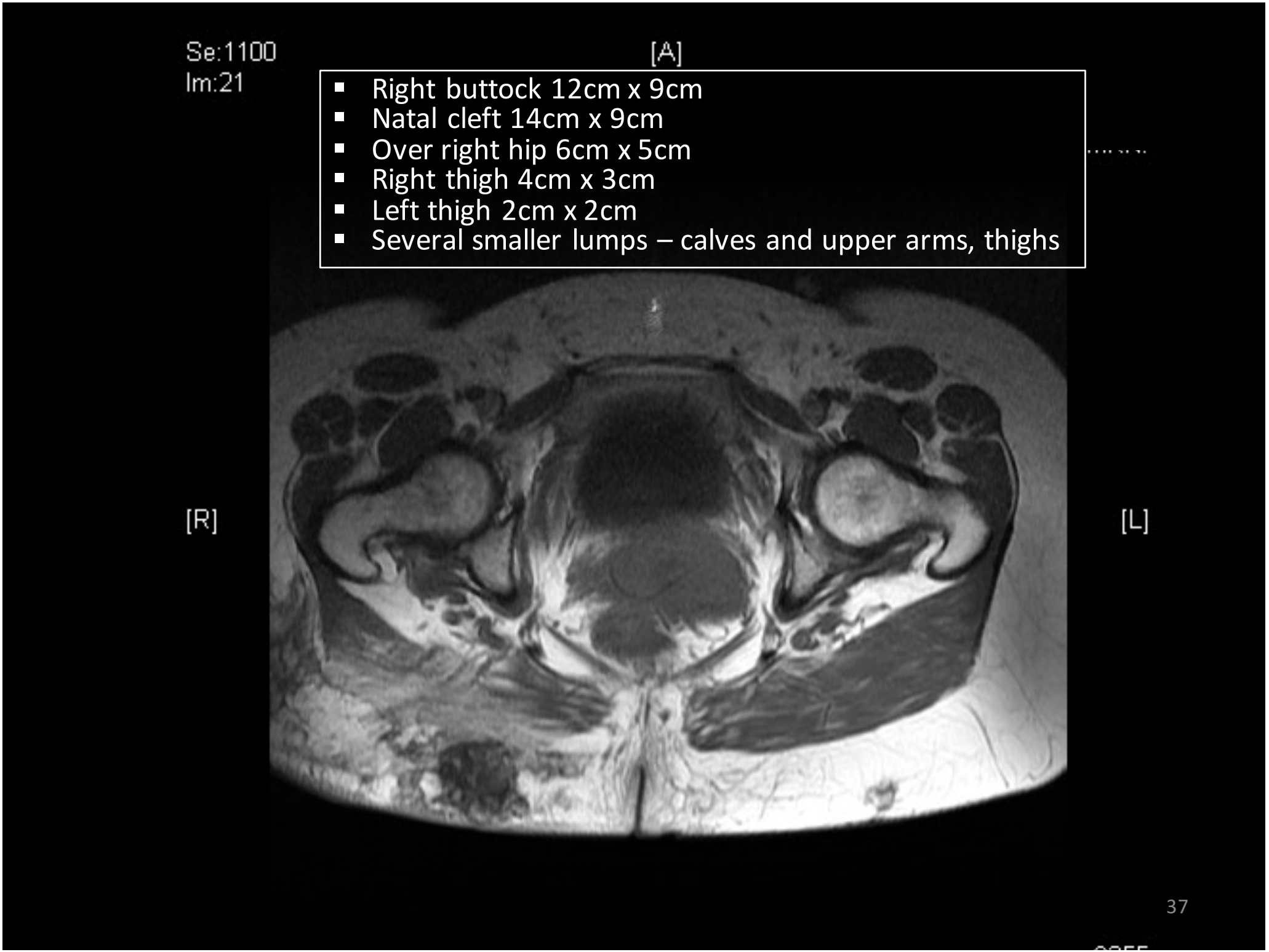
1. Targoff IN *et al.* Arthritis Rheum 2006;54:3682-3689.
2. Kaji K *et al.* Rheumatology 2007;46:25-28.
3. Gunawardena H *et al.* Ann Rheum Dis 2007, 66:S68.
4. Chinoy H *et al.* Ann Rheum Dis 2007;66:1345-1349.
5. Fujikawa K *et* al. Scan J Rheumatol 2009;38:263–267.
6. Trallero-Aragua´s E *at al.* Medicine (Baltimore) 2010;89:47–5
7. Fujimoto M *et al.* Arthritis Rheum 2012;64:513-522.

Skin disease + calcinosis

Case 4

46 year old lady

- Dermatomyositis presented in 2000
- Proximal myopathy, pharyngeal dysfunction, cutaneous manifestations and CK over 15,000
    - Steroids, AZA, MTX
    - Monthly IV IG at diagnosis, further course from 2005 – 2008
    - Surgery for calcinosis
- Moved to Bristol 2007
- Under my care since 2009
    - Low grade disease activity despite Pred 8mg/d and MMF 2g/d
    - MRC muscle strength 4+/5
    - Progressive severe calcinosis and ulceration
    - ANA negative
    - **Further testing – anti-NXP2**



- Right buttock 12cm x 9cm
- Natal cleft 14cm x 9cm
- Over right hip 6cm x 5cm
- Right thigh 4cm x 3cm
- Left thigh 2cm x 2cm
- Several smaller lumps – calves and upper arms, thighs

Case 4

- 46 year old lady
  - Pulsed IV Cyclophosphamide – poorly tolerated / limited response
  - Rituximab 1gram x2* - some response in terms of improvement of myositis, no response in terms of calcinosis progression - given in 2010
  - Continued on Mycophenolate 2011, but progressive disease
  - Late 2011 to Feb 2012 – 4 further doses of IV IG given monthly, again a degree of stability, but limited response
  - Trial of Tacrolimus - limited
- <u>What next?</u>

Case 4

- Infliximab 5mg/kg
- Doses at week 0, 2, 6, then every 8 weeks
- 6 + 12 months – MRI
  - No active disease
  - Calcinosis – unchanged but no progression / no new lesions

- Continued treatment
- 3-monthly disease measures
- Yearly MRI

- Adjuvant Rx:
  1. Correct Vitamin D (marked Vitamin D deficiency may add to calcinosis?)
  2. Bisphosphonates (IV Zoledronate)
  3. Minocycline 100mg / daily (6-12 weeks courses)

Case (anti-NXP2 DM with calcinosis)

Calcinosis - no good evidence-base for treatment (SSc + DM literature)

- Management should include advice on wound-care and avoidance
- Some anecdotal and case-series evidence for:
  - Vasodilators e.g. diltiazem
  - Warfarin
  - Colchicine
  - Probenecid
  - **Minocycline**
  - **IV IG**
  - **Sodium Thiosulphate**
  - Ablative laser therapy (carbon dioxide laser – disrupt epidermis to allow extrusion of calcific deposits)
  - Surgical debridement

Case (calcinosis)

CONCISE REPORT

Treatment of cutaneous calcinosis in limited systemic sclerosis with minocycline

L P Robertson, R W Marshall, P Hickling

Ann Rheum Dis 2003;62:267–269

Intravenous immunoglobulin for treatment of dermatomyositis-associated dystrophic calcinosis
Galimberti et al. JAAD 2015:73(1);174–176

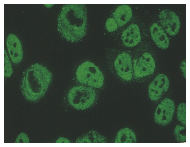
Sodium Thiosulphate

Intravenous Sodium Thiosulfate for Treatment of Refractory Calcinosis in Rheumatic Disease. Ross Thibodaux, Bahnsen Miller and Stephen Lindsey. Louisiana State University Health Science Center, Baton Rouge, LA.

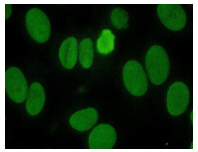
Pleiotropic actions

Calcium chelating agent
Antioxidant
Endothelium protection
Vasodilator
Anti-thrombotic
Anti-MMPs
Increases endogenous calcification inhibiting proteins

CTD-myositis overlap – clinicoserological phenotypes

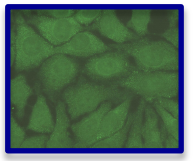


Nuclear



Target autoantigens

Cytoplasmic



Mi2

HMGCR

Skin lesions

SAE

Gastrointestinal

Necrotizing myositis

SRP

Calcinosis

NXP2

Ulceration

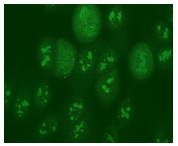
Amino acid

Aminoacyl tRNA Synthetases*

Cancer (adults)

TIF1 family

ILD (only?)



Nucleolar

Anti-RuvBL1 / 2

ILD

RP-ILD

Polyarthritis
Mechanics hands
Raynaud's

Anti-U3RNP

MDA5

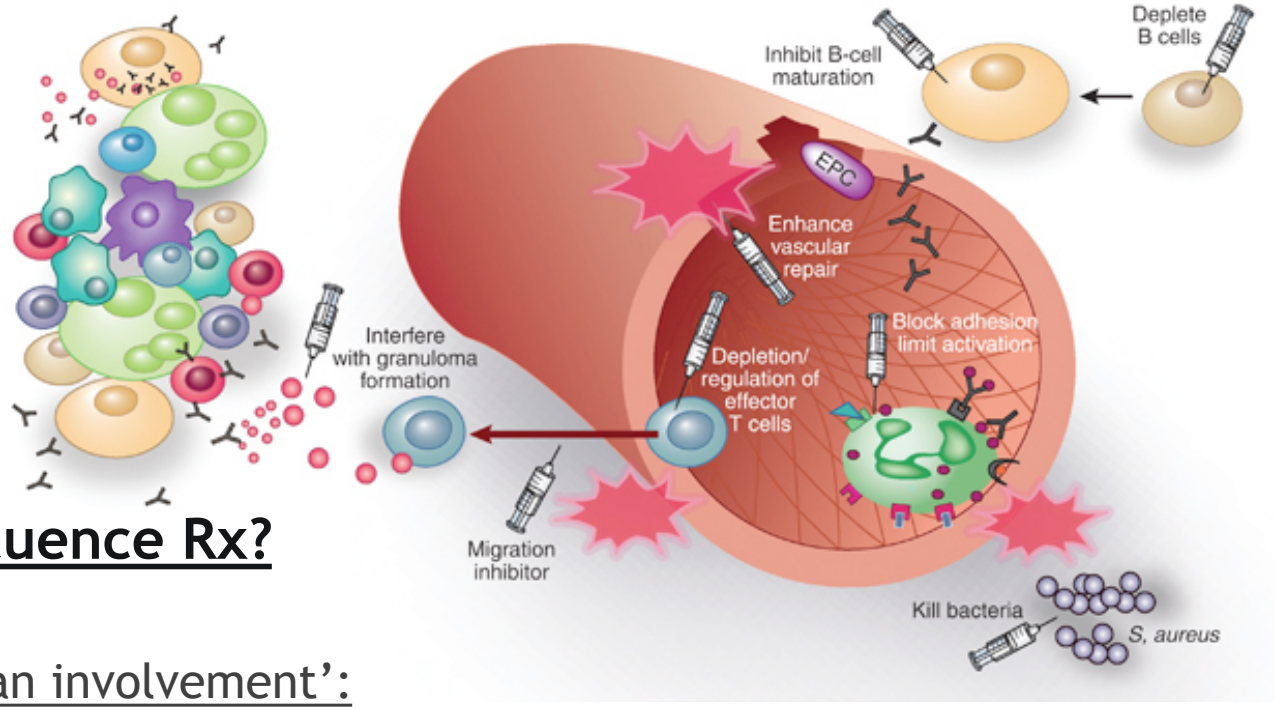
Overlap SSc
Arthritis

Anti-PM-Scl syndrome

Amyopathic disease
Skin lesions
Mucocutaneous lesions

ILD

Treatment approaches



Do clinical phenotypes influence Rx?

1. INDUCTION – 'significant organ involvement':
   - Steroids (0.5mg/kg)
   - Immunomodulatory regime – usually Cyclophosphamide or MMF
   - IV IG
   - Tacrolimus

   (Milder disease – MTX or AZA and/or HCL)

2. MAINTENANCE
   - Reduce steroids
   - Immunomodulatory regime – usually MMF or MTX or AZA or Tacrolimus

3. REFRACTORY disease – CYCLO, Rituximab, Infliximab

Summary

*Clinical case studies to highlight:

Recognise the 'types' of CTD myositis overlap

- Review extra-muscular manifestations in myositis
- Recognise amyopathic disease and associated complications
- Refractory myositis
- **Early intervention is essential – otherwise poor outcomes**
- **Minimise steroid / maximise other treatments**

*Clinical practice
Limited evidence base