Myositis and Cancer

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Classification of myositis according to Abs

- Interstitial lung disease
- Arthritis
- Mechanic’s hands

- Acute severe muscle weakness
- Myalgias

- V-sign rash
- Shawl-sign rash
- Cuticular overgrowth

Courtesy of Prof FW Miller -1999
Myositis-specific autoantibodies

Anti-synthetases
- Jo-1
- Zo
- EJ
- PL-7
- KS
- OJ
- PL-12
- YRS

Anti-SRP

Anti-SAE

Anti-Mi-2

Anti-p140

Anti-CADM-140

Anti-p155/140

Myositis specific autoantibodies → Clinical phenotypes in adults and children

Slide Courtesy of Dr H Gunawardena
Myositis classification according to Abs

- Interstitial lung disease
- Arthritis
- Mechanic’s hands
- Acute severe muscle weakness
- Myalgias
- V-sign rash
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Courtesy of Fred Miller, many other contributors - 2008
Diagnostic Criteria


- 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

Problems with histology:
- 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)
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 cancer-associated
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.

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

Manchel et al, 1985
Sigurgeirsson et al, 1992 (M)
(Airio et al, 1995)
Chow et al, 1995
Buchbinder et al, 2001
Stockton et al, 2001

Log IR / 95% CI
Anti-155/140 antibody

US study \(^1\)  
- DM: 8/39
- Cancer associated myositis: 6/8

Japanese study \(^2\)  
- DM: 2/42
- Cancer associated myositis: 5/10

\(^1\) Targoff et al. 2006; \(^2\) Kaji et al. 2007
The diagnostic utility of serology for predicting the risk of cancer-associated myositis in adults.

Chinoy et al

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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

- PM, n=6
- DM, n=15
- CTD-OL, n=5

Years
-5  -1  0  3  5  10  15

Cancer onset
Myositis onset
Relationship between myositis and cancer onset

- PM, n=0
- DM, n=15
- CTD-OL, n=1

Years

CAM, n=16

Cancer onset
Myositis onset
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** : 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**
- Jo-1, 58
- PM-Scl, 29
- Ku, 5

- RNP, 36
- No Ab, 157

**CAM**
- RNP, 2
- No Ab, 14

**n=266**

**n=16**
Antibody frequencies in CAM/non-CAM groups using research laboratory immunology

Non-CAM
n=266

CAM
n=16
Associations with CAM

Strategy:

- Anti-155/140 Ab
- Negative Ab result on routine Ab testing
- 1 & 2
Frequency of clinical phenotypes by myositis Ab status

Interstitial lung disease

Antibody subtypes:
- Jo-1
- PM-Scl
- RNP
- Mi-2
- 155/140

Jo-1: 60%
PM-Scl: 20%
RNP: 5%
Mi-2: 1%
155/140: 1%
Frequency of clinical phenotypes by myositis Ab status

- Jo-1
- PM-Scl
- RNP
- Mi-2
- 155/140

**Interstitial lung disease**

**Cancer associated myositis**

Antibody subtypes

%
Breakdown of individual malignancies in CAM

Gynae, 3
GI, 3
Bladder, 2
Lymphoma, 3
Breast, 4
Lung, 1
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).

• Iatrogenic problems – GIT bleeds, ? increased cardiovascular risks and ? increased malignancy risks due to long-term immunosuppression.

• Ventilator-related deaths.