IDIOPATHIC INFLAMMATORY MYOPATHIES AND RELATED DISORDERS

Franclo Henning
Division of Neurology
Tygerberg Hospital

Classification systems

- **Clinical (Bohan and Peter)**
- **Clinico-pathological (Dalakas & others)**
- **Pathological (Pestronk)**
- **Clinicoserologic (Troyanov)**

Bohan and Peter Criteria for Diagnosis of PM and DM

- **Primary polymyositis**
- **Primary dermatomyositis**
- **Myositis with another connective tissue disease**
- **Myositis associated with cancer**

Bohan and Peter Criteria for Diagnosis of PM and DM

- Proximal muscle weakness, usually symmetrical
- Elevated serum muscle enzymes (CK, aldolase)
- Electromyographic abnormalities
  - Common – myopathic potential (low amplitude, short duration and polyphasic action potentials)
  - Characteristic triad – myopathic potentials, spontaneous activity, complex repetitive discharges
- Muscle biopsy findings typical of PM or DM – necrosis, phagocytosis, regeneration, inflammation
- Dermatological features of DM, Gottron's sign or papules, or heliotrope rash

Definite diagnosis requires 3 criteria with rash for DM and 4 without rash for PM

Probable diagnosis requires 2 criteria with rash for DM and 3 without rash for PM

Possible diagnosis requires 1 criterion with rash for DM and 2 without rash for PM

Pathological classification (Pestronk)

Classification	Myopathologic features	Clinical and laboratory associations
Immune myopathy with perimysial pathology (IMPP)	Perimysium: fragmentation; histiocytes; Myofibers: necrosis; regeneration Stains: Esterase and AcP: perimysial cell + Alkaline phosphatase: perimysium + MHC class I: perifascicular myofibers	Clinical syndromes: dermatomyositis; polymyositis; interstitial lung disease; fasciitis Antibody: antisynthetase (Jo-1 and other) Aldolase: selectively high
Myovasculopathy	Inflammation: perivascular; B cell Vessels: damage, intermediate and capillary Myofibers: perifascic atrophy and COX reduced Stains: $C_{5b\text{-}9}$: capillaries +; CD20: B-cell foci; COX: reduced regionally UEA1: loss of capillary endothelium	Dermatomyositis (DM-VP): childhood and some adult
Immune polymyopathy	Myofibers: necrosis; regeneration No mononuclear cell foci; MHC class I: myofibers may be normal	Weakness: proximal; severe Antibodies: SRP and HMG-CoAR CK: very high Paraneoplastic
IIM with endomysial pathology (IIM-EP)	Stains: glycoprotein Δ: endomysium $C_{5b\text{-}9}$: endomysium +	Brachio-cervical inflammatory myopathy (BCIM)
Histiocytic inflammatory myopathy	Cells: histiocytic foci Stains: esterase and AcP: cell foci +	Sarcoid; immunizations; Serum CK: often normal
Inflammatory myopathy with vacuoles, aggregates and mitochondrial pathology (IM-VAMP)	Inflammation: endomysial; mononuclear Myofibers: VAMP pathology; Focal invasion by cells (CD4 and CD8+) Stains SMI31: aggregates; Congo red: vacuoles and aggregates; COX: reduced in scattered fibers; MHC class I: diffuse on myofibers	Weakness: quadriceps and forearm flexor; 'inclusion body myositis' Poor response to immunomodulating treatments

Pestronk, Curr Opin Rheumatol, 2011

Clinicoserologic classification

- **Pure polymyositis (PM)**
- **Pure dermatomyositis (DM)**
- **Overlap myositis (OM): myositis with at least 1 clinical overlap feature and/or an overlap antibody**
- **Cancer-associated myositis (CAM): with clinical paraneoplastic features and without an overlap autoantibody or anti-Mi-2**

Troyanov, Medicine, 2005

Relative frequencies (%) in 100 patients

	Bohan & Peter	Clinicoserologic
PM	33	9
DM	30	19
CTM / OM	31	68
CAM	6	4

Troyanov, Medicine, 2005

Relative frequencies (%)

	Bohan & Peter	Clinicoserologic
PM	33	9
DM	30	19
CTM / OM	31	68
CAM	6	4

Best predictor of treatment response

- 50% of PM
- 85-90% of DM & OM

Polyarthritis, Raynaud phenomenon, sclerodactyly, scleroderma proximal to MCP joints, typical SSc-type calcinosis in the fingers, lower esophageal or small-bowel hypomotility, DLCO lower than 70% of the normal predicted value, interstitial lung disease on chest radiogram or CT scan, discoid lupus, anti-native DNA antibodies plus hypocomplementemia, 4 or more of 11 ACR SLE criteria, antiphospholipid syndrome.

- **Overlap myositis: myositis with at least 1 clinical overlap feature** and/or an **overlap antibody**
- **Cancer-associated myositis: with**

Antisynthethases (Jo-1, PL-7, PL-12, OJ, EJ, KS), SSc-associated autoantibodies (SSc-specific antibodies: centromeres, topo I, RNA-polymerases I or III, Th; and antibodies associated with SSc in overlap: U1RNP, U2RNP, U3RNP, U5RNP, Pm-Scl, Ku), and other autoantibodies (SRP, nucleoporins).

Classification systems

- Clinical (Bohan and Peter)
- **Clinico-pathological (Dalakas & others)**
- Pathological (Pestronk)
- Clinicoserologic (Troyanov)

IIMs

- **Polymyositis (PM)**
- **Dermatomyositis (DM)**
- **Inclusion body myositis (IBM)**
- **Necrotizing autoimmune myopathy (NAM)**
- **Myositis in overlap syndromes**
- **Non-specific myositis / Inflammatory myopathy NOS**

IIMs - Intro

- Weakness may develop
  - Acutely (days - weeks) in NAM
  - Sub-acutely (weeks – months) in PM & DM
  - Insidiously (years) in IBM
- Weakness = proximal except IBM – early distal weakness
- Facial muscles affected mostly in IBM, rarely in others
- Pharyngeal muscles often involved in IBM, sometimes in DM and PM
- Respiratory muscles may be affected in PM/DM/NAM
- Wasting of muscles in severe disease
- Tendon reflexes usually preserved but may be absent in very weak, atrophic muscles (especially in IBM)

IIMs - Intro

- All forms more frequent in patients with other autoimmune / connective tissue diseases
- Up to 10% of patients have ILD and anti-Jo-1 Ab's (discussed later)
- ↑Incidence of malignancies in DM (≥15%) & NAM, not PM (but conflicting literature) & IBM

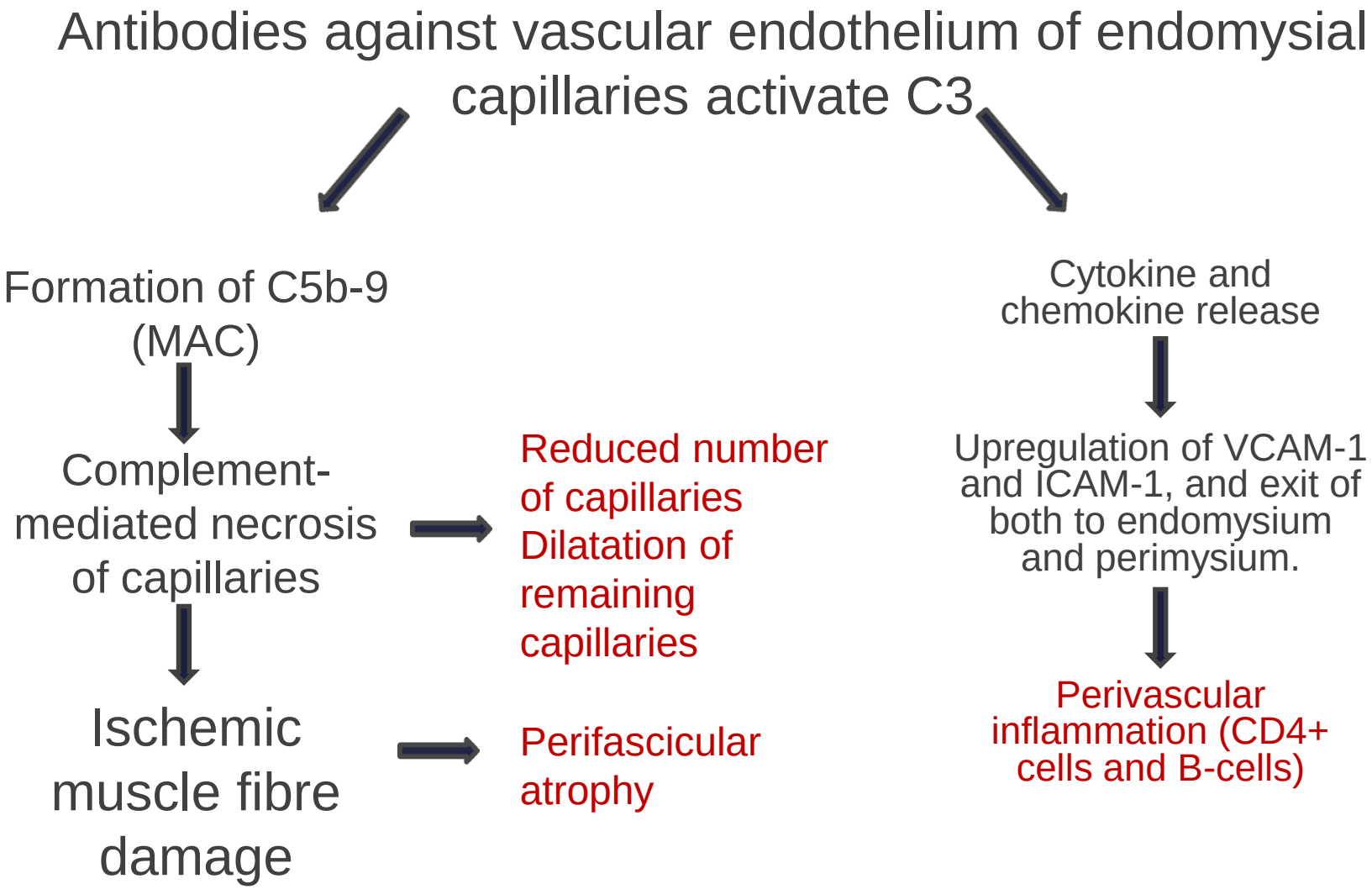
IIMs - Diagnosis

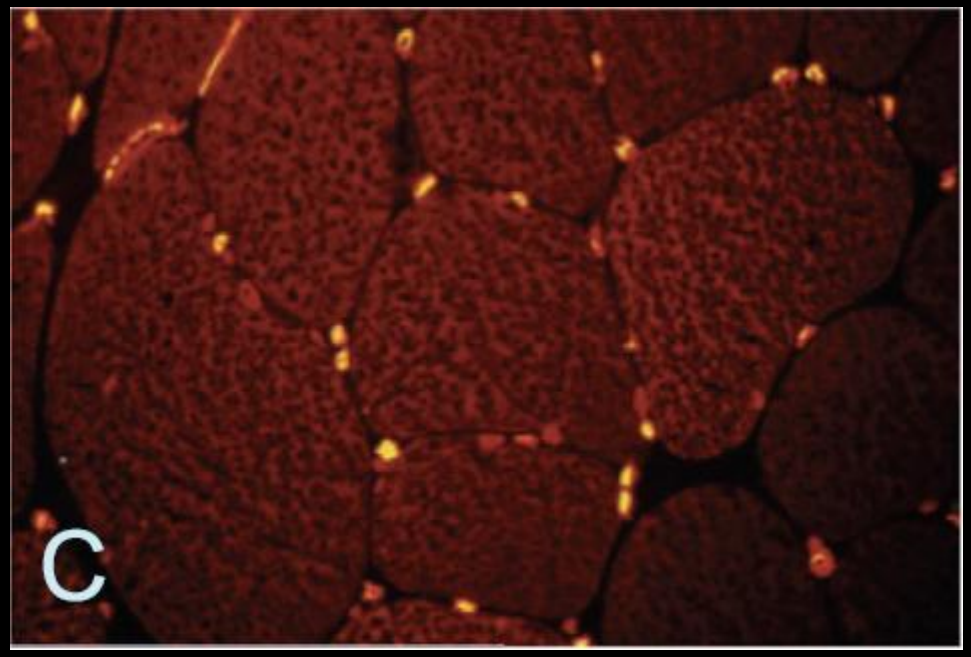
- DM: relatively easy when typical rash present
- CK often normal / slightly elevated in IBM
  - May sometimes be N in DM & PM (even active disease)
  - Very high in NAM
- Needle EMG
  - Myopathic in all forms
  - Mixed myopathic / neurogenic in IBM
  - Spontaneous activity often correlates with CK (feature of muscle fibre necrosis)

IIMs – Muscle biopsy

- Choice of muscle:
  - Ideal: MRI
  - Realistic: moderately weak muscle

Pathogenesis of DM

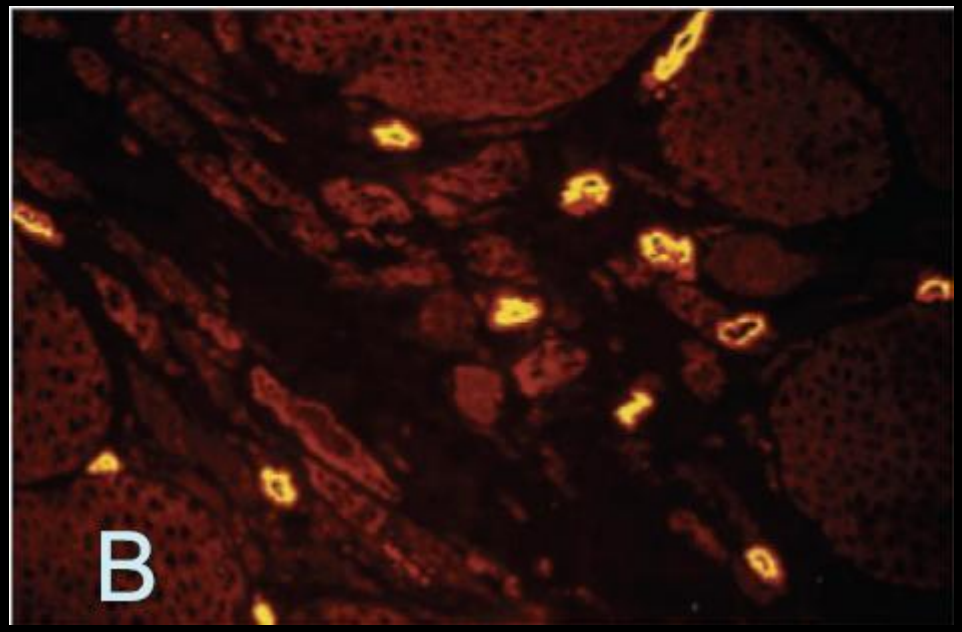




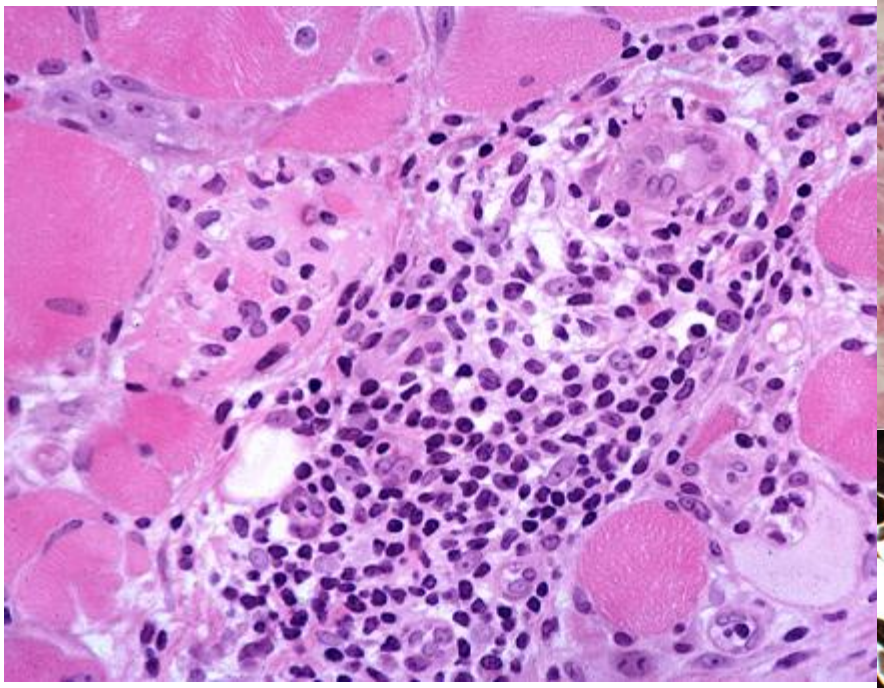
Ulex Europoeaus stain

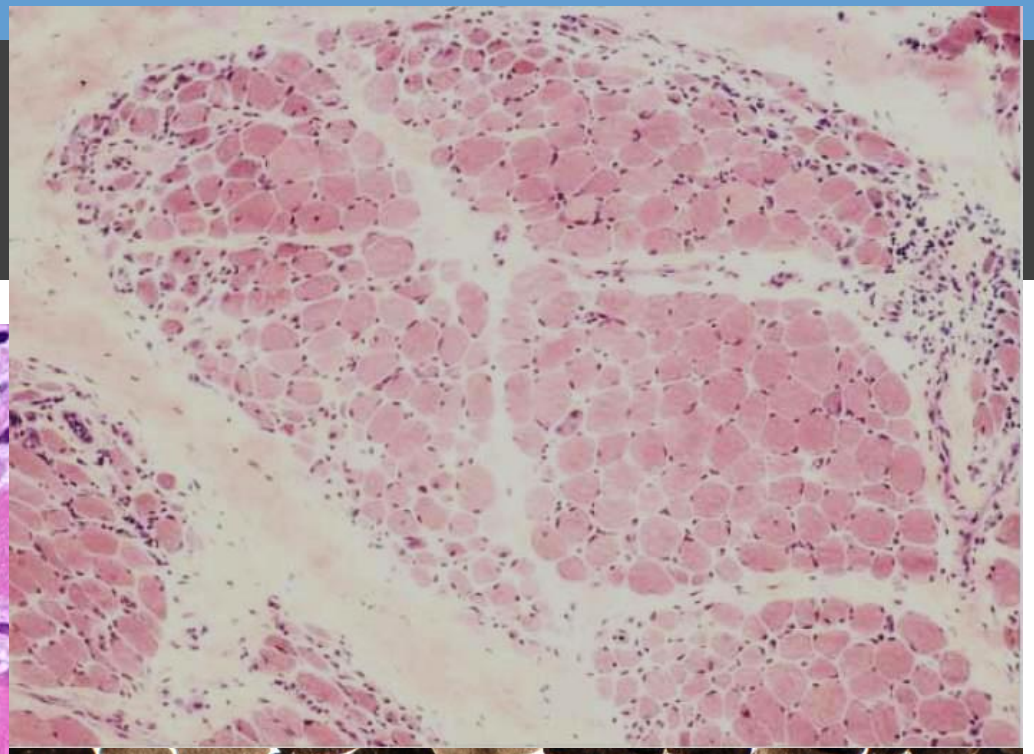
Control

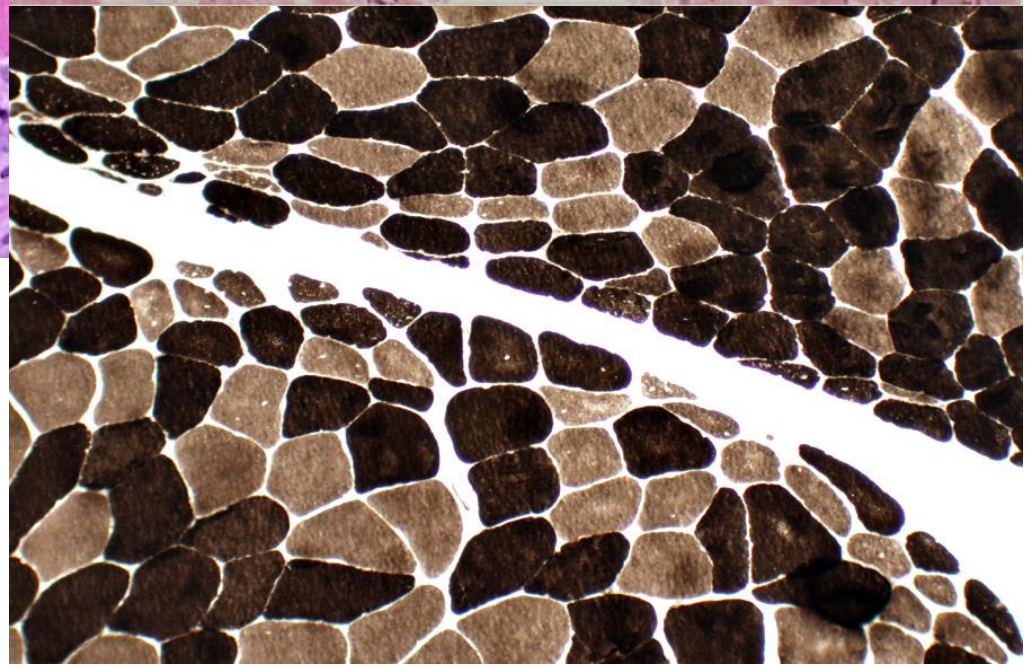
DM



DM – Histology







Pathogenesis of PM

Immunopathology

Overexpression of MHC-1 on muscle fibres

↓

CD8+ cells activated and surround healthy, MHC-1 expressing fibres

↓

Cytotoxic destruction of muscle fibres via *perforin* pathway

↓

Pathogenesis of IBM

Immunopathology

Overexpression of MHC-1 on muscle fibres

↓

CD8+ cells activated and surround healthy, MHC-1 expressing fibres

↓

Cytotoxic destruction of muscle fibres via *perforin* pathway

Degenerative mechanisms

Dysfunctional ubiquitin / proteasome system

OR

Generation of free radicals e.g. NO

OR

Defective autophagy of APP / β-amyloid

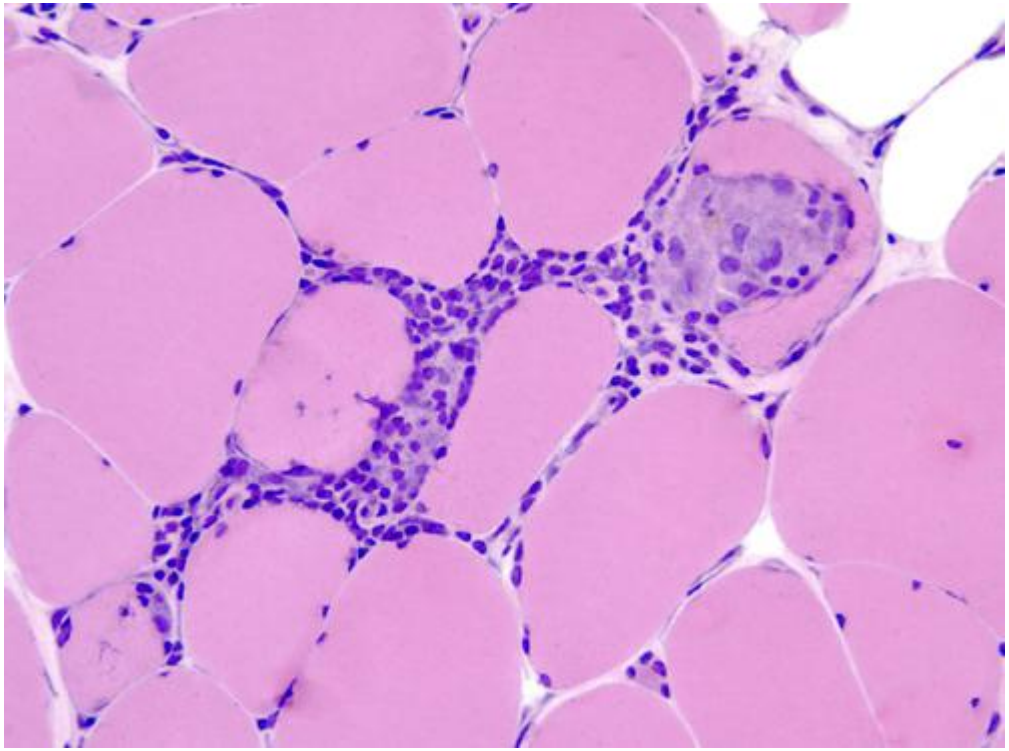
↓

Rimmed vacuoles and intracellular deposition of β-amyloid and related molecules

Pathogenesis of IBM

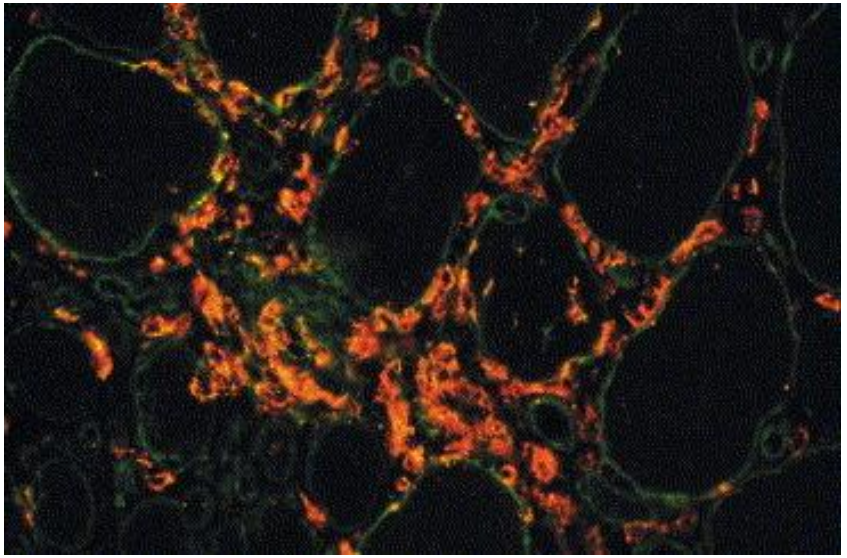
- Possibly “cross-talk” between inflammatory and degenerative processes
  - continuous stimulation of muscle cells by inflammatory cytokines enhances the expression and accumulation of amyloid and misfolded proteins

PM – Histology

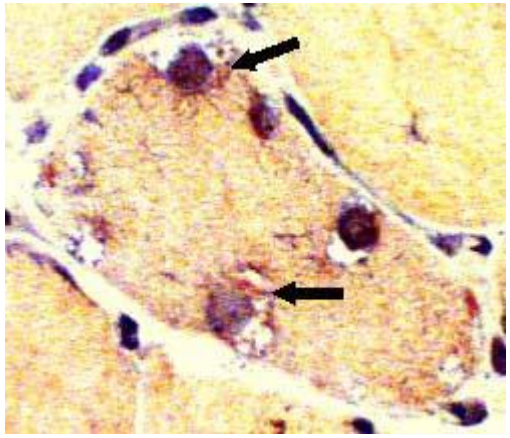


H&E

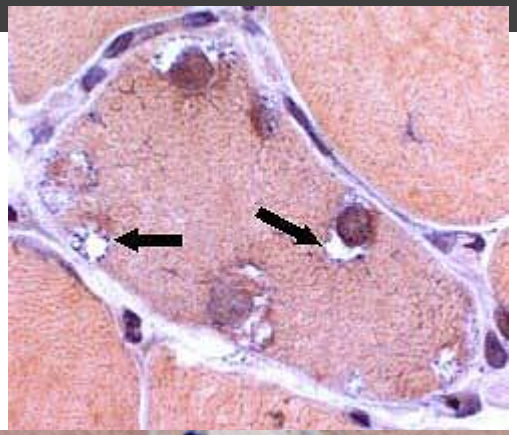
MHC-1 and CD8 dual stain



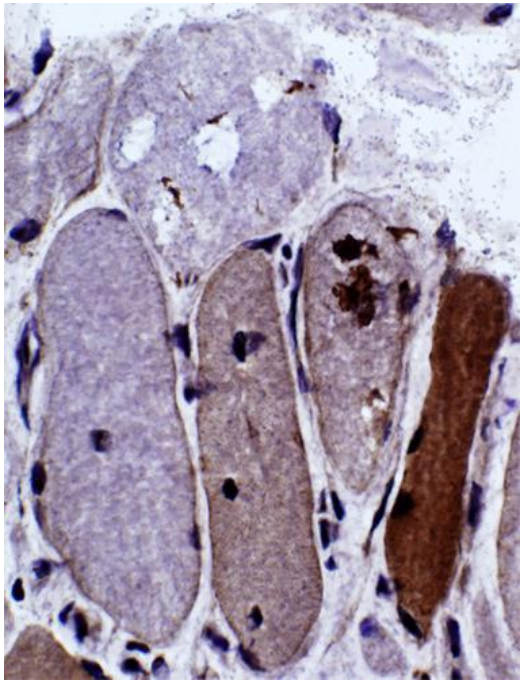
IBM – Histology



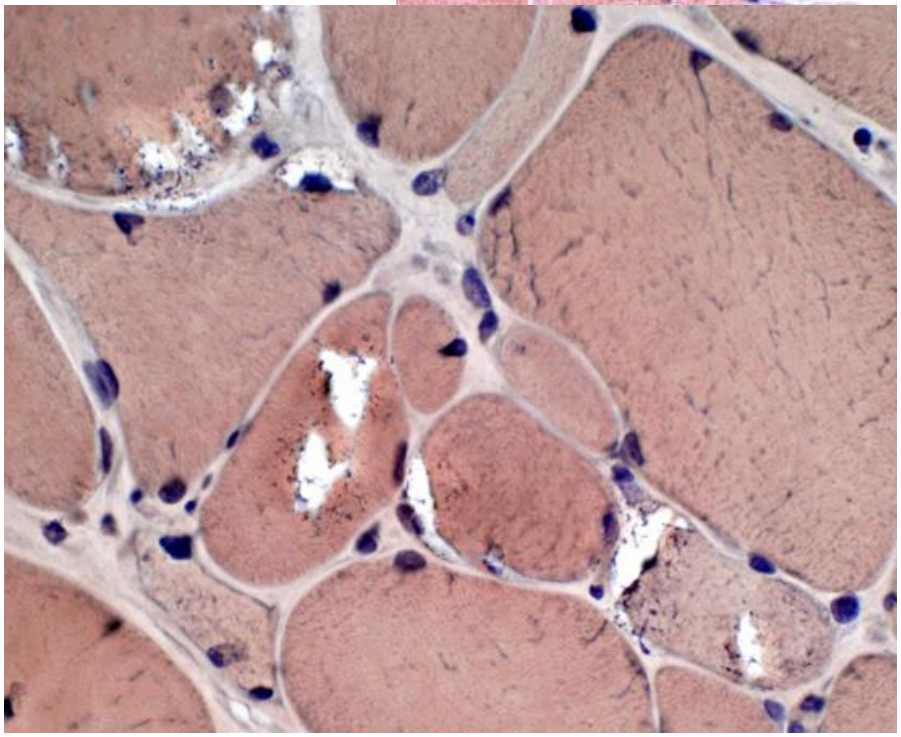
Amyloid (Congo red stain)



Rimmed vacuoles



SMI-31 +ve phosphorylated tau.

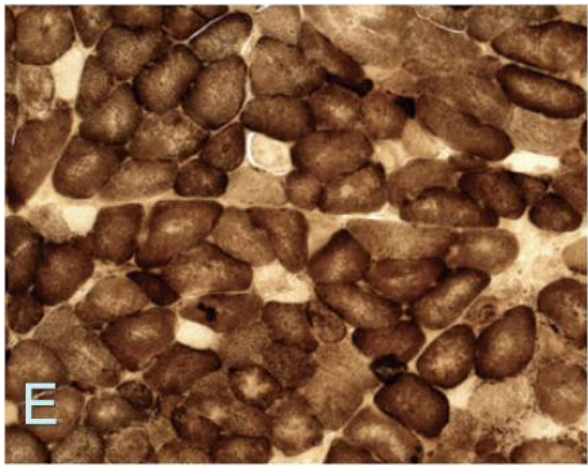


Dilemmas in histo diagnosis of PM & DM

- Clinical features of IBM, but no vacuoles and IB's on histology (thus ?PM)
  - Up to 15% of IBM cases
  - Look for
    - ↑% of COX –ve fibres
    - Signs of chronicity (fibre splitting, large fibres, ↑ connective tissue)
  - NOTE:
    - vacuoles and IB's not required for diagnosis of probable IBM
    - VERY important to distinguish IBM from PM – will guide treatment decisions

Dilemmas in histo diagnosis of PM & DM

- Vacuoles and/or IB's on histology, but clinical features not typical:
  - Consider:
    - Myofibrillar myopathy
      - Inclusions
    - hIBM (GNE mutation)
      - Also rimmed vacuoles, amyloid accumulation, ↑connective tissue
      - BUT no / minimal inflammatory infiltrate and MHC-1 expression.
  - Note: scattered vacuoles may be seen in DM [Limaye, Muscle & Nerve, 2010]



MYOSITIS-SPECIFIC AUTOANTIBODIES (MSA)

Myositis-specific autoantibodies (MSA)

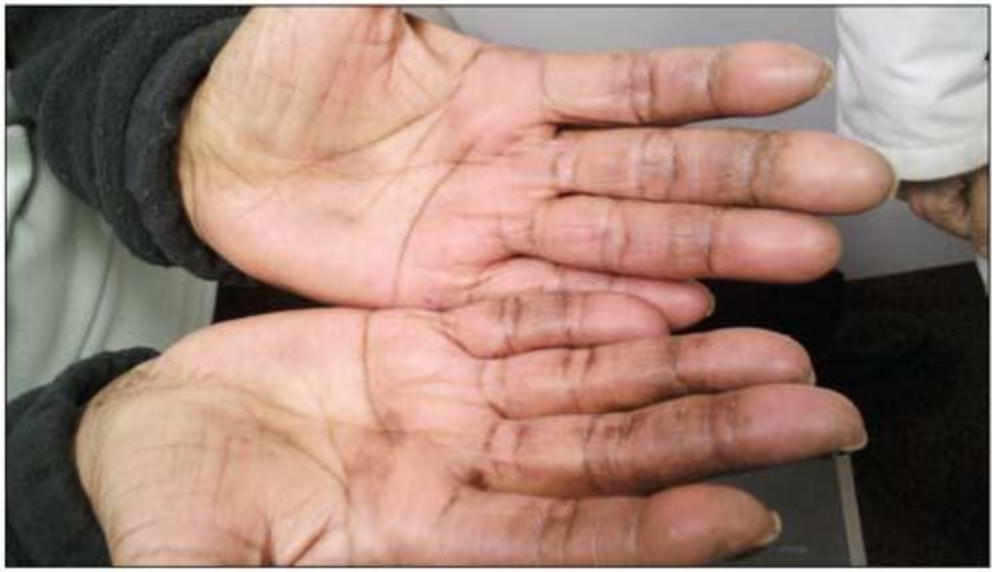
- Antibodies found predominantly in the serum of patients with PM, DM or NAM
  - Ab's to aminoacyl-tRNA synthetases - aaRS (e.g. anti-Jo-1)
  - Anti-Mi2 (15-20% of DM patients)
  - Anti-SRP
- Note: Myositis-associated autoantibodies (MAA) = sometimes found in myositis, primary association with other conditions, e.g. anti-Ro, anti-PM-Scl

Myositis-specific autoantibodies (MSA)

- aaRS
  - Commonest MSA in myositis
    - 27/105 with PM (24 = anti-Jo-1)
    - 25/101 with DM (22 = anti-Jo-1) [Chinoy, *Arthritis Res Ther* 2006]
  - 42 – 89% develop ILD

Myositis-specific autoantibodies (MSA)

- aaRS
  - Anti-synthetase syndrome
    - Myositis
    - ILD
    - Arthritis
    - Raynaud's phenomen
    - Mechanic's hands



Myositis-specific autoantibodies (MSA)

- Newly identified Ab’s
  - Anti-CADM-140: Amyopathic DM
  - Anti-p155: DM

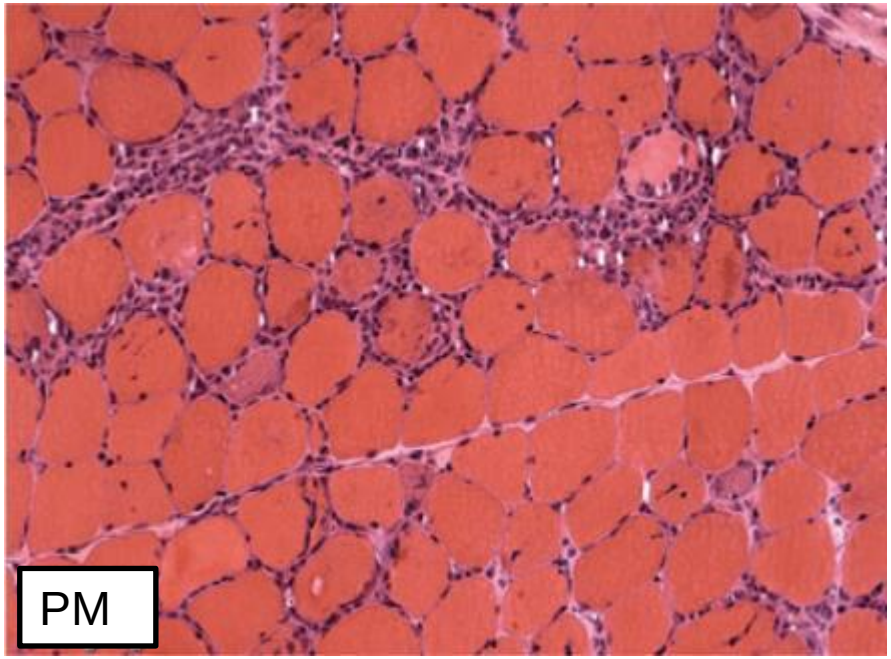
NECROTIZING AUTOIMMUNE MYOPATHY

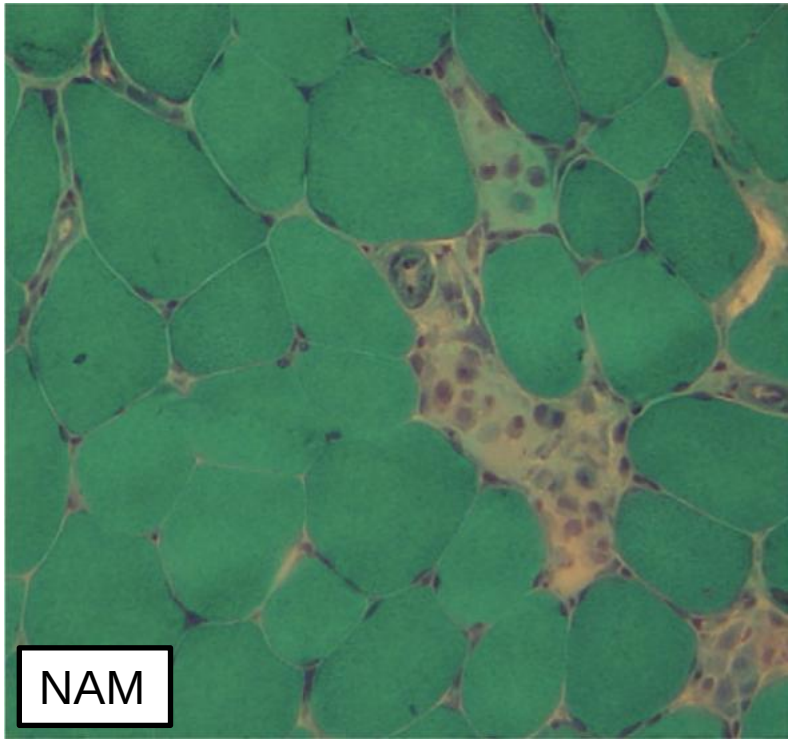
Diff Dx of myofibre necrosis without inflammation

- Toxins & drugs
- Muscular dystrophies
- Rhabdomyolysis due to e.g. metabolic myopathy
- **Necrotizing autoimmune myopathy**

NAM

- Myofibre necrosis without significant inflammation
- Relatively newly recognized subgroup of IIMs

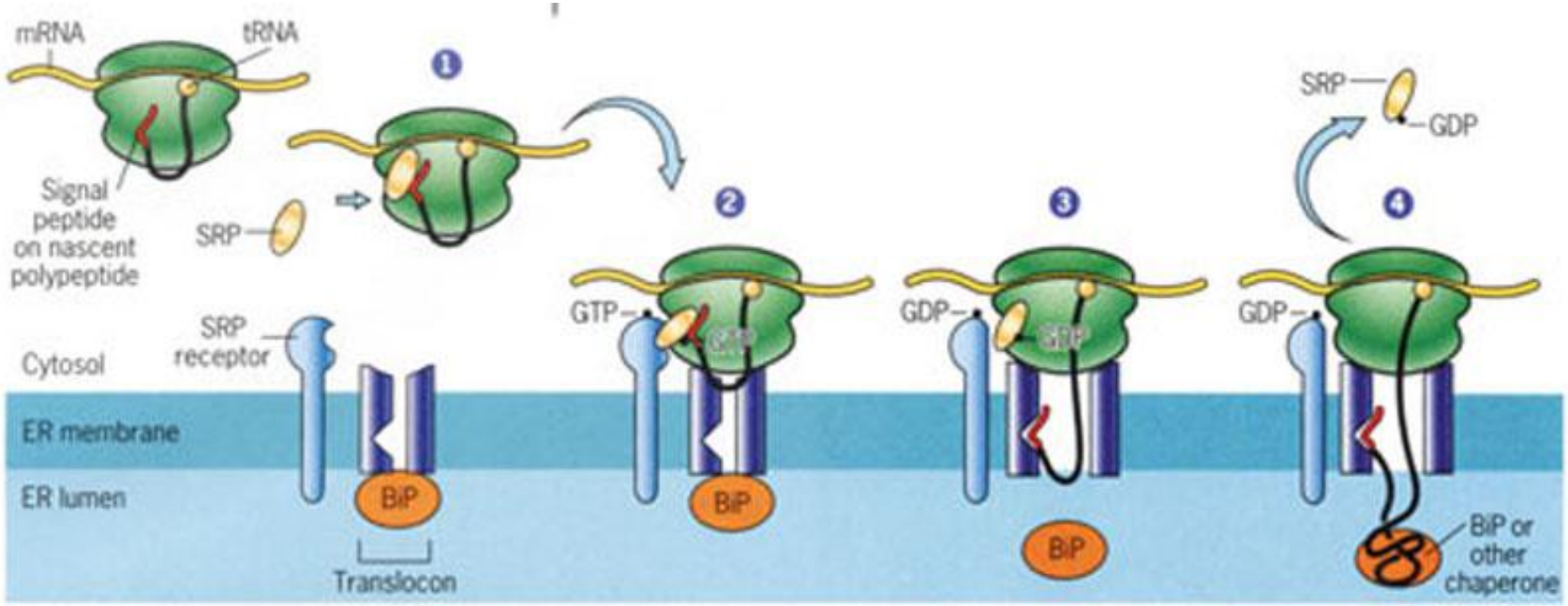




NAM

- Found in association with:
  - **Anti-SRP (signal recognition particle) antibodies**
  - Connective tissue disorders
  - Viral infections (HIV)
  - Malignancy
  - **Statins**
- Lack of MHC-1 staining (in most biopsies) and lack of lymphocytic infiltrate argue against cell-mediated destruction of lymphocytes
  - Probably Ab-dependent, complement-mediated lysis with macrophage as effector cell.

1. Anti-SRP-related NAM



- Guide newly translated polypeptides into ER

2. Statin-triggered NAM

- Statin myopathy usually
  - Toxic effect of statin
  - Recovers within weeks of stopping statin

IMMUNE-MEDIATED NECROTIZING MYOPATHY ASSOCIATED WITH STATINS

PHYLLIS GRABLE-ESPOSITO, MD,[1] HANS D. KATZBERG, MD,[2] STEVEN A. GREENBERG, MD,[1] JAYASHRI SRINIVASAN, MD, PhD,[3,4] JONATHAN KATZ, MD,[5] and ANTHONY A. AMATO, MD[1]

[1] Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[2] Department of Neurology, Stanford University Medical Center, Stanford, California, USA
[3] Department of Neurology, Lahey Clinic, Burlington, Massachusetts, USA
[4] Department of Neurology, Tufts Medical School, Boston, Massachusetts, USA
[5] Department of Neurology, California Pacific Medical Center, San Francisco, California, USA

Accepted 19 June 2009

ABSTRACT: We report patients from two neuromuscular centers who were evaluated between the years 2000 and 2008 and met the following criteria: (1) proximal muscle weakness occurring during or after treatment with statins; (2) elevated serum creatine kinase (CK); (3) persistence of weakness and elevated CK despite discontinuation of the statin; (4) improvement with immunosuppressive agents; and (5) muscle biopsy showing necrotizing myopathy without significant inflammation. Twenty-five patients fulfilled our inclusion criteria. Twenty-four patients required multiple immunosuppressive agents. Fifteen patients relapsed after being tapered off immunosuppressive therapy. Exposure to statins prior to onset was significantly higher in patients with necrotizing myopathy (82%) as compared to those with dermatomyositis (18%), polymyositis (24%), and inclusion-body myositis (38%) seen in the same time period. The lack of improvement following discontinuation of statins, the need for immunosuppressive therapy, and frequent relapse when treatment was tapered suggest an immune-mediated etiology for this rare, statin-associated necrotizing myopathy.

Muscle Nerve **41:** 185–190, 2010

the statin. The majority of cases have been described in reports of individual patients with typical dermatomyositis or polymyositis, with histological features that included robust inflammatory cellular infiltrates.[7–15] In contrast, one recent study suggested that statins may be associated with a distinct myopathy that persists after withdrawal of the drug and can respond to immunosuppressive therapy.[16] Among 8 cases, 6 were notable for the absence of significant inflammation on muscle biopsy. Herein, we describe 25 additional patients who developed a necrotizing myopathy in the setting of statin treatment. These patients had proximal muscle weakness and elevated CK that persisted or worsened despite discontinuation of the

A Novel Autoantibody Recognizing 200 and 100 kDa Proteins is Associated with an Immune-Mediated Necrotizing Myopathy

Lisa Christopher-Stine, MD, MPH, Livia A. Casciola-Rosen, PhD, Grace Hong, BA, Tae Chung, MD, Andrea M. Corse, MD, and **Andrew L. Mammen, MD, PhD**
Johns Hopkins University School of Medicine, Baltimore, MD

Abstract

Objective—Myofiber necrosis without prominent inflammation is a non-specific finding seen in patients with dystrophies and toxic or immune-mediated myopathies. However, the etiology of a necrotizing myopathy is often obscure and which patients would benefit from immunosuppression remains uncertain. We sought to identify novel autoantibodies in necrotizing myopathy patients.

Methods—Muscle biopsy and serum were available for 225 myopathy patients. Antibody specificities were determined by performing immunoprecipitations from ^{35}S-methionine-labeled HeLa cell lysates. Selected biopsies were stained for membrane attack complex (MAC), major histocompatability complex I (MHC I), and endothelial cell marker CD31.

Results—38 of 225 patients had predominant myofiber necrosis on muscle biopsy. 12 of these had a known autoantibody association or other etiology for their myopathy. 16 of the remaining 26 sera immunoprecipitated 200 and 100 kDa proteins; this specificity was found in only 1/187 patients without necrotizing myopathy. Patients with anti-200/100 specificity had proximal weakness (100%), high creatine kinase (CK) levels (mean 10,333 IU/L), and an irritable myopathy on electromyography (EMG) (88%). 63% had exposure to statins prior to the onset of weakness. All patients responded to immunosuppressive therapy and many relapsed with medication tapering. Immunohistochemical studies showed MAC on small blood vessels in 6/8 and on the surface of non-necrotic myofibers in 4/8. 5/8 had abnormal capillary morphology and 4/8 expressed MHC I on the surface of non-necrotic myofibers.

Conclusion—An anti-200/100 kDa specificity defines a subgroup of necrotizing myopathy patients previously considered to be "autoantibody negative." We propose that these patients have an immune-mediated myopathy which is frequently associated with prior statin use and should be treated with immunosuppressive therapy.

Arthritis Rheum 2010

Autoantibodies against 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase (HMGCR) in Patients with Statin-Associated Autoimmune Myopathy

Andrew L. Mammen, MD, PhD, **Tae Chung, MD**, **Lisa Christopher-Stine, MD, MPH**, **Paul Rosen**, **Antony Rosen, MD**, and **Livia A. Casciola-Rosen, PhD**
Johns Hopkins University School of Medicine, Baltimore, MD

Abstract

Objective—In addition to inducing a self-limited myopathy, statin use is associated with an immune-mediated necrotizing (IMNM) myopathy with autoantibodies recognizing ~ 200 and ~100 kDa autoantigens. Identifying these molecules will clarify disease mechanism and facilitate diagnosis.

Methods—The effect of statin treatment on autoantigen expression was addressed by immunoprecipitation using patient sera. The identity of the ~100 kDa autoantigen was confirmed by immunoprecipitating *in vitro*-translated HMGCR protein. HMGCR expression in muscle was analyzed by immunofluorescence. A cohort of myopathy patients was screened for anti-HMGCR autoantibodies by ELISA and genotyped for the rs4149056 C allele, a predictor of self-limited statin myopathy.

Results—Statin exposure induced expression of the ~200/~100 kDa autoantigens in cultured cells. HMGCR was identified as the ~100 kDa autoantigen. Competition experiments demonstrated no distinct autoantibodies recognizing the ~200 kDa protein. In muscle biopsies from anti-HMGCR positive patients, HMGCR expression was up-regulated in cells expressing NCAM, a marker of muscle regeneration. Anti-HMGCR autoantibodies were found in 45 of 750 patients presenting to the Johns Hopkins Myositis Center (6%). Among patients age 50 or older, 92% were exposed to statins. The prevalence of the rs4149056 C allele was not increased in anti-HMGCR subjects.

Conclusion—Statins up-regulate expression of HMGCR, the major target of autoantibodies in statin-associated IMNM. Regenerating muscle cells express high levels of HMGCR, which may sustain the immune response even after statins are discontinued. These studies demonstrate a mechanistic link between an environmental trigger and the development of sustained autoimmunity. Detection of anti-HMGCR autoantibodies may facilitate diagnosis and direct therapy.

Arthritis Rheum 2011

2. Statin-triggered NAM

- Immune-mediated
- Onset average 3 years after starting statin (or even after stopping)
- Persists or even worsens after stopping statin
- Associated with anti-HMGCR Ab's in some patients
  - Note: these antibodies are also present in NAM without statin use
- Clinical:
  - Prox weakness
  - High CK (1000's)
  - Irritable myopathy on needle EMG
  - Necrosis with no/minimal inflammation on biopsy
- Most respond to immunosuppression, relapses when treatment stopped.

Table 1 Characteristics of different necrotizing autoimmune myopathy s with pooled data

Inciting conditions	Anti-SRP antibody-related NAM	Statin-induced immune NAM	Paraneoplastic NAM
Age of onset: mean (range)	**39.9 (2–72)** N = 24 Ref: [3,16,31,32•] Female preponderance [33]	**63.5 (44–89)** N = 56 Ref: [2•,24,25••]	**70.8 (38–87)** N = 13 Ref: [6,11,12,21,28•,29,34]
Clinical – all- subacute onset symm-etrical proximal weakness	Dysphagia [32•,33] Severe muscle atrophy [33] Onset in autumn-winter Weight-loss [3] Cardiac complications [16] Interstitial lung disease [33]	Myalgia [24] Dysphagia [22•]	Dysphagia Facial weakness [21,29] Respiratory involvement [28•] Rash [29] Myopathy not always parallel tumor progression
Creatine kinase: mean (range)	**16167 IU/L** (3064–28000) N = 15 Ref: [3,32•]	**8280 IU/L** (958–24714) N = 56 Ref: [2•,24,5]	**8562 IU/L** (1700–24640) N = 13 Ref: [6,1,21,28•,29,34]
Microscopy/immuno-histochemical finding on muscle biopsy	Variation of muscle fibre size ↓endomysial capillary density MAC on endomysium/ capillaries Alkaline phosphatase staining on perimysial connective tissue [3]	Variable upregulation of MHC-1 on nonnecrotic fibres (multifocal or diffusely) [22•,24]	Higher % of necrotic fibres MAC in necrotic myofibrils [21,29] ''pipestem' capillaries with MAC [12] Alkaline phosphatise staining in regenerating fibres/ perimysial connective tissue [21]
Response to immune-therapy	Variable from steroid alone [3,16]; to refractory requiring rituximab [31,32•]	Steroid + methotrexate resulted in full or partial response [2•,24] Rituximab or IVIG required in some cases [2•]	Resection, steroids, [6,12,28•] IVIG, [29] chemotherapy and cetuximab [34] all been used with response
Main differential diagnoses	Dermatomyositis, other muscle-specific autoantibodies related syndrome, paraneoplastic NAM	Static-induced toxic myopathy	Dermatomyositis, anti-SRP antibody-related NAM

N, number of patients where pooled data was taken from; Ref, references from which data deduced; anti-SRP, antisignal recognition particle; IVIG, intravenous immunoglobulin; NAM, necrotizing autoimmune myopathy; MAC, membrane attack complex. Only cases where muscle biopsy findings were identifiable as consistent with NAM were included.

Liang & Needham, Curr Op Rheuma, 2011

PARANEOPLASTIC MYOPATHY

Paraneoplastic myopathy

- Risk of cancer with DM high (≥15%), no/mild increase with PM
- Most cancers 2 years before to 3 years after myopathy (but up to 5 years)
- Most common cancers with DM = adeno CA: ovary, cervical, stomach, pancreas, colorectal, lymphoma
- Most common cancer with PM = lymphoma
- Protective features: arthritis, Raynaud's, ILD, aaRS antibodies (i.e. anti-synthetase syndrome)

TREATMENT OF INFLAMMATORY MYOPATHIES

Treatment of DM / PM

- 1st line therapy:
  - Corticosteroids
    - Pulse dexamethasone (e.g. 40mg/d x 4/7, every 4 wks x 4 cycles) may be associated with fewer SE's than daily prednisone (1mg/kg x 1/12 , slow taper) but earlier relapse [van de Vlekkert, Neuromuscul Disorders, 2010]
  - Steroid-sparing agents in steroid-responsive patients
    - NB : NO RCTs, thus preference empirical
    - Azathioprine, methotrexate, MMF, cyclosporine

Treatment of DM / PM

- 2nd line therapy: Intravenous immunoglobulin
  - Use if:
    - corticosteroids fail
      - DM: RCT [Dalakas, NEJM, 1993]
      - PM & NAM: open label studies
    - disease is rapidly progressive
    - Resistant pharyngeal weakness
      - Marie et al, Arthritis Care Res, 2010:
        - 118 PM/DM patients with oesophageal weakness
        - 73 steroid-refractory
        - Treated with monthly IVIg (2g/kg)
        - 60/73 (82%) returned to normal oral feeds, 4 (5.5%) improved

Treatment of DM / PM

- 3rd line therapy: Inadequate response to corticosteroids and IVIg
  - Cyclophosphamide
  - Tacrolimus (calcineurin phosphatase inhibtor)
  - Rituximab (CD20 monoclonal antibody)
    - May be more effective in patients with auto-Ab's (e.g. ant-Jo1, anti-SRP)
  - Anti-TNFα agents: etanercept, infiximab
  - Alemtuzumab (CD52 monoclonal antibody)
    - Possibly effective in IBM (single small study with 13 patients)
  - Fingolimod (anti-T-cell migration agent)
  - Natalizumab (anti-adhesion molecule)

Treatment of IBM

- No effective treatment
- Up to 30% of patients may initially respond to corticosteroids / immunosuppressives / IVIg to a certain degree and for a short period
- Alemtuzumab? (see previous slide)
- early therapy may arrest the development of the clinical phenotype
  - Early therapy in “histological IBM” (not yet developed IBM phenotype) can lead to complete remission

Treatment of anti-synthetase syndrome

- Treatment (anecdotal / open label):
  - Corticosteroids frequently inadequate
  - Cyclophosphamide effective, but toxicity concern
  - Cyclosporin and Tacrolimus possibly effective in resistant cases
  - Rituximab [Sem, Rheumatology, 2009]

Conclusions

- Classification of IIMs becoming increasingly complex
- Exact “syndromic” classification may predict treatment response
- Muscle biopsy important for treatment strategy, especially if first line fails