Myositis 101: *Clinical Features, Diagnosis and Management*

Namita Goyal, MD
Associate Professor of Neurology
Director, Neuromuscular Medicine Fellowship
Director, Neuromuscular Diagnostic Laboratory
Associate Director, Neuromuscular Center
UC Irvine

TMA San Diego
September 7, 2017

UC Irvine Health
School of Medicine

Overview of Myositis

- Clinical features of Inflammatory myopathies
- Diagnosis
  - Muscle biopsy features
  - New antibodies & Muscle imaging
    - May improve diagnostic challenges
- Management: Immunotherapy or not?

Inflammatory Myopathies:

Autoimmune Myopathies

- Polymyositis (PM)
- Dermatomyositis (DM)
- Immune-mediated necrotizing myopathy (IMNM)
- Inclusion body myositis (sIBM)
  - A degenerative disease of muscle?
    Abnormal cytoplasmic aggregates (e.g., TDP-43)
  - Partially autoimmune?

Clinical Features

Clinical Features of PM, DM, IMNM

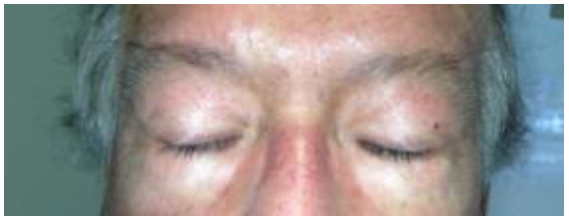
- Weakness of Proximal muscles
  - Symmetric
  - Shoulder girdle and hip girdle muscles
  - Difficulty with “Chairs, Stairs, Hair”
- Females > Males
- Onset: Subacute
- Responsive to immunotherapy

Dermatomyositis

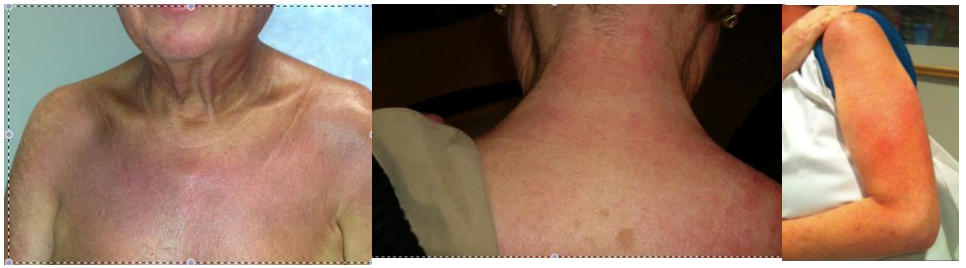
- Distinct Skin rash (hallmark) may precede weakness by weeks to months
- Some may never develop weakness (amyopathic DM)
- Associated with Extramuscular manifestations: pulmonary, cardiac, gastrointestinal, & joints

Dermatomyositis: Skin manifestations

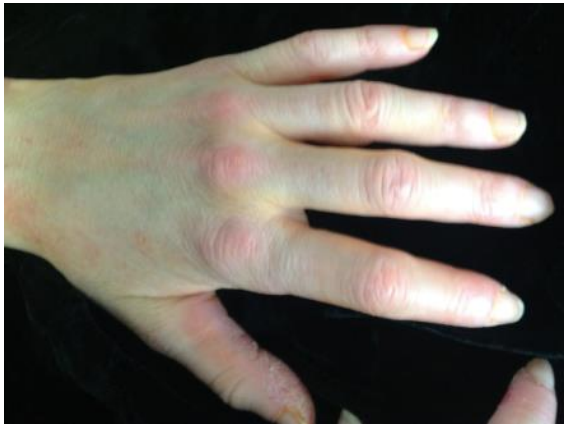
Heliotrope rash



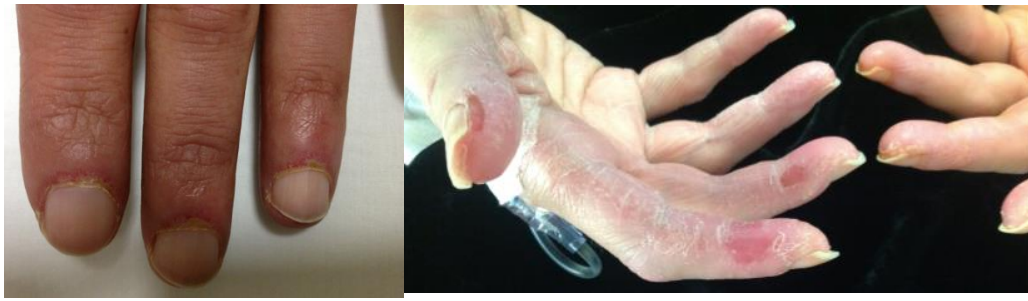
Rash over face, neck, anterior chest (V-sign) and upper back (shawl sign), extensor surfaces



Gottron papules



Nail beds with capillary telangiectasias, mechanic hands

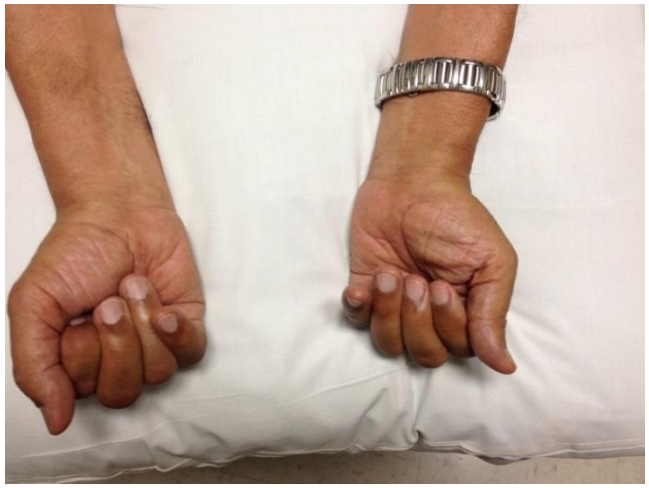


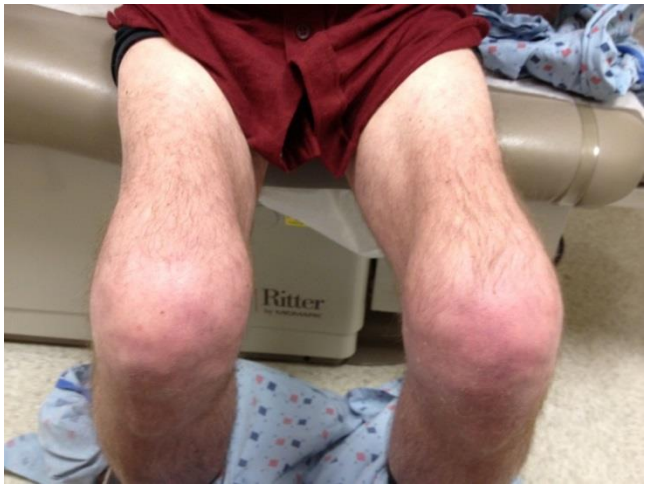
Subcutaneous calcifications

Clinical Features of:

Sporadic Inclusion Body Myositis (sIBM)

- Most common acquired myopathy > age of 50 years
- Slow progressive muscle disease
- Atrophy and asymmetric, predominantly affecting finger flexors, hip flexors, and knee extensors
- Males > Females





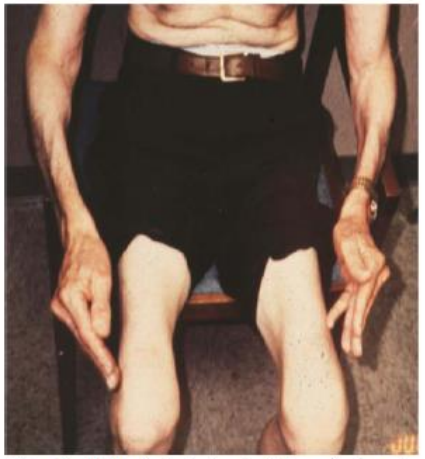


Figure 1. s-IBM patient who has typical prominent weakness and atrophy

Inclusion-body myositis

Clinical, diagnostic, and pathologic aspects

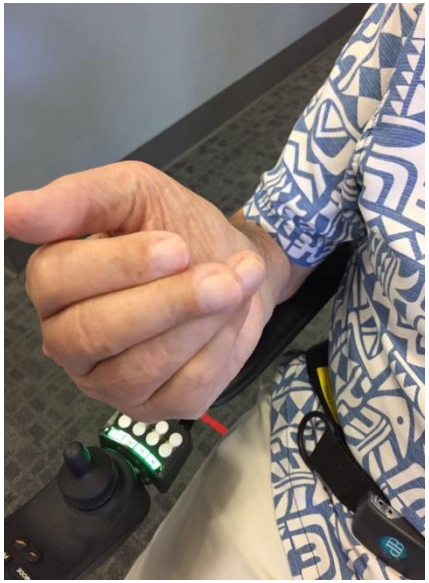
W. King Engel, MD; and Valerie Askanas, MD, PhD

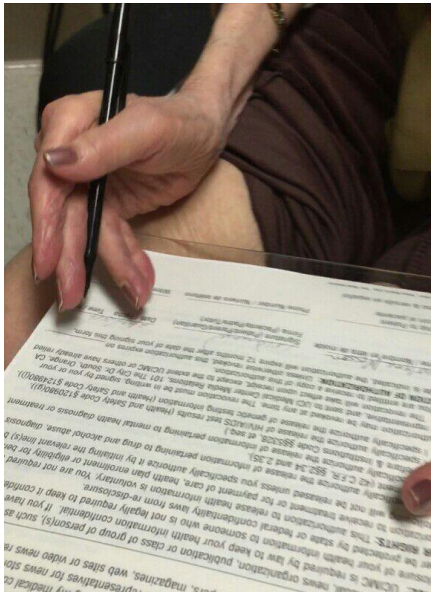
Leg Weakness: Slow progressive in IBM

- Falls
- Gait difficulty
- Arising from low seated position
- Difficulty climbing stairs
- Foot drop (dorsiflexion weakness)
- Knee buckling (quadriceps)

Grip weakness in IBM

- Grip difficulty
- Opening jars
- Manipulating keys
- Writing
- Carrying objects
- Upper arm weakness over time





Swallowing difficulty in IBM

- Frequent, embarrassing and potentially dangerous
- Initially, describe a “stuck” sensation when swallowing
- Unintended weight loss
- Higher incidence of Aspiration pneumonia
- Prevalence ranging from 40-80%

Evaluation

Diagnostic studies

- Muscle Enzymes (Creatine Kinase)
- Nerve conduction/Needle EMG studies
- Muscle biopsy
- Antibodies
- Muscle MRI

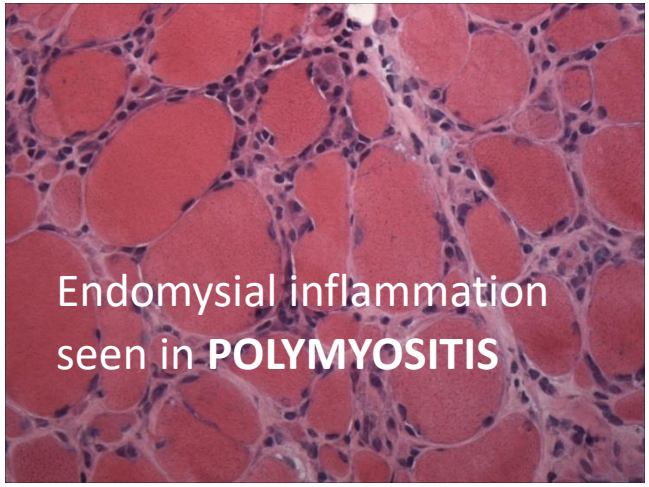
Histological differences

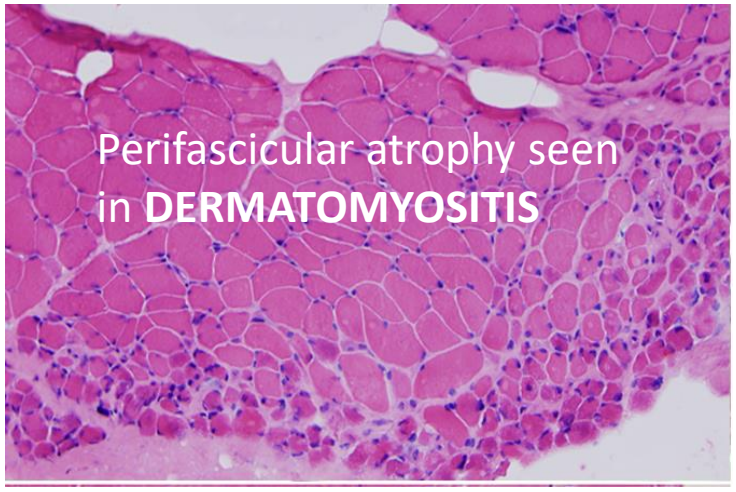
Pathologic hallmarks

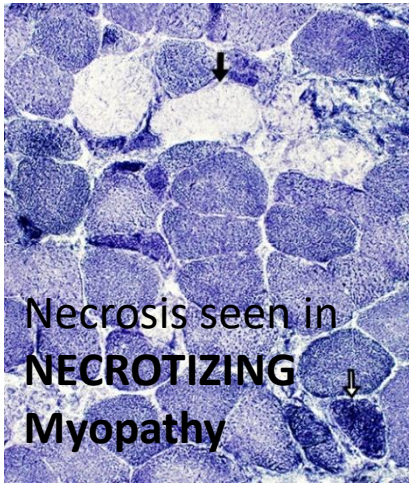
- Dermatomyositis: Perifascicular atrophy
- Polymyositis: Primary inflammation, Nonnecrotic muscle fiber, surrounded and invaded by CD8+ T cells
- Immune-mediated necrotizing myopathy: Degeneration and regeneration, necrotic fibers, with a paucity of inflammation
- Inclusion body myositis: Rimmed vacuoles, inflammation

Muscle biopsy: Key features

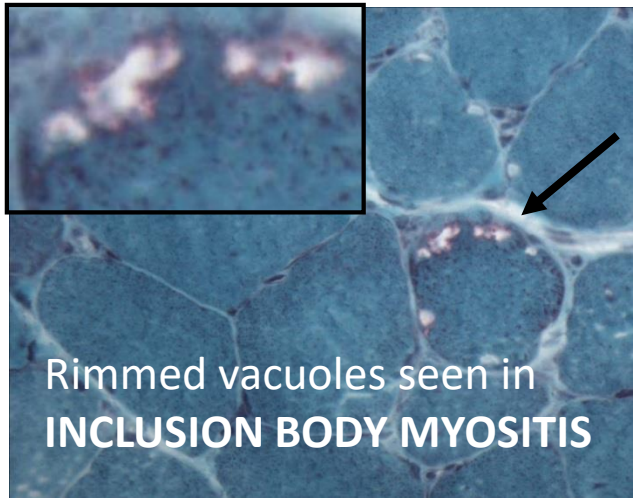
Treatable conditions:

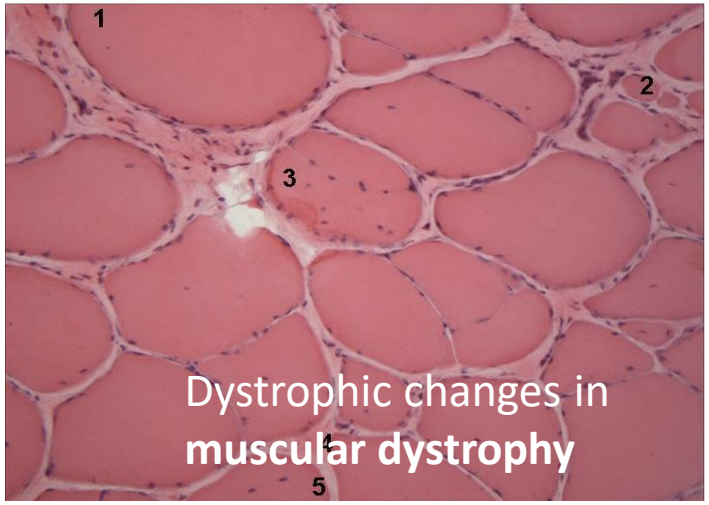


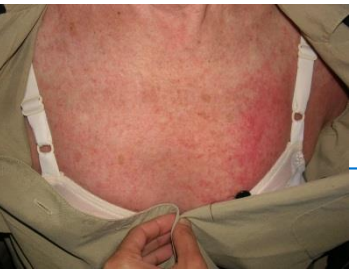




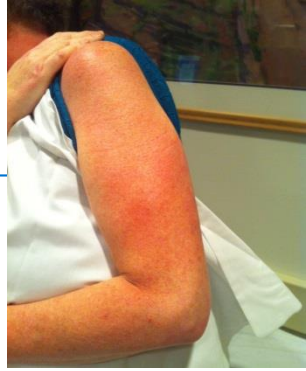
No response to immunotherapy: IBM or Dystrophies- don't respond to immunotherapy







Muscle Histopathology in Dermatomyositis



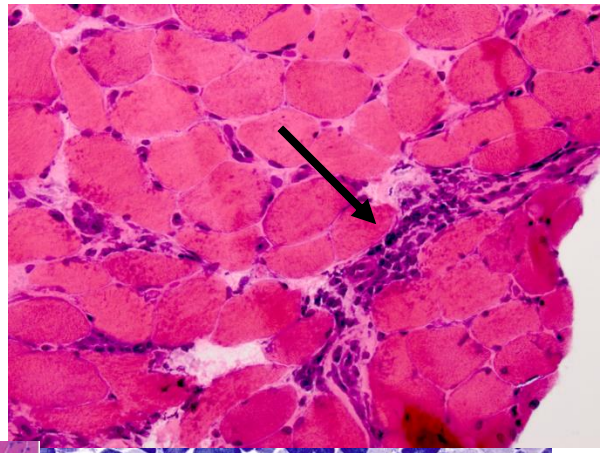
Perivascular, perimysial inflammation

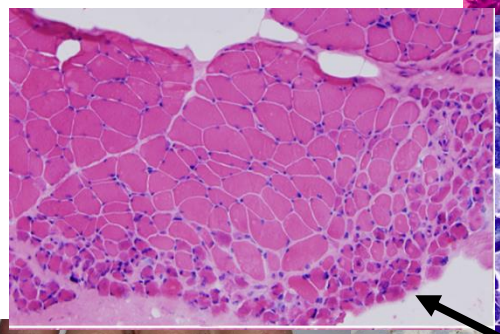
Perifascicular atrophy

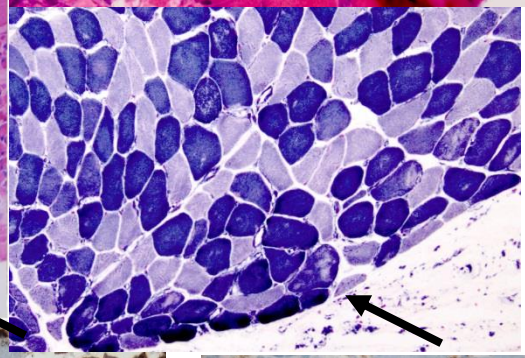
MAC deposition on blood vessels

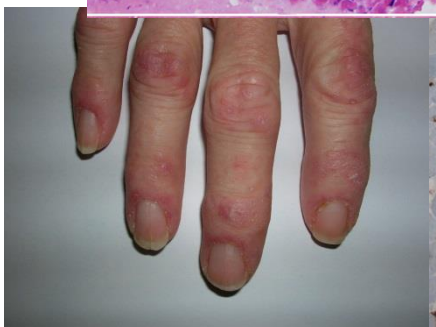
Reduced capillary density (immune mediated microangiopathy)

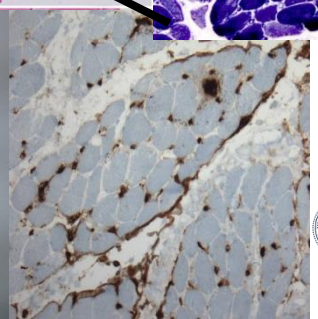
Tubuloreticular inclusions on endothelial walls on EM

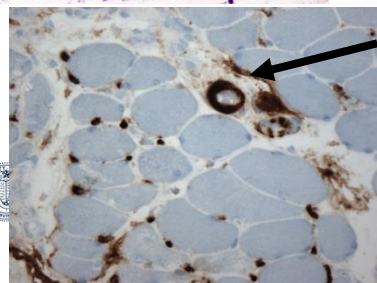






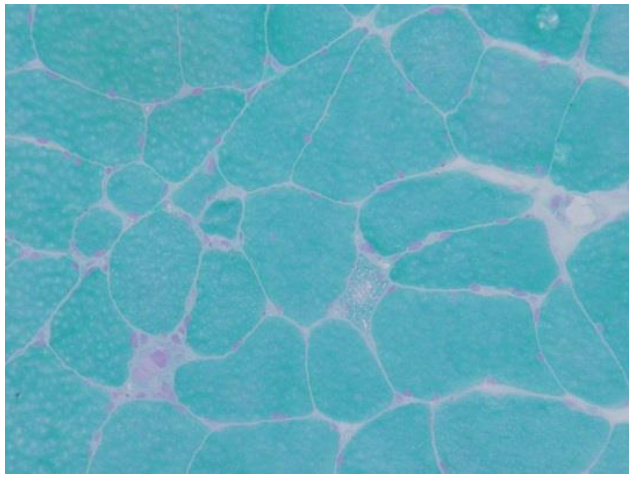


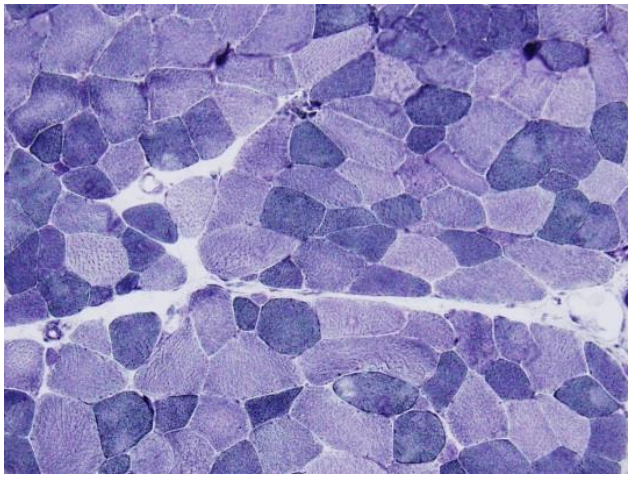




Muscle biopsy in Necrotizing Myopathy:

Paucity or lack of inflammation, yet necrotic fibers





Muscle Histopathology in IBM

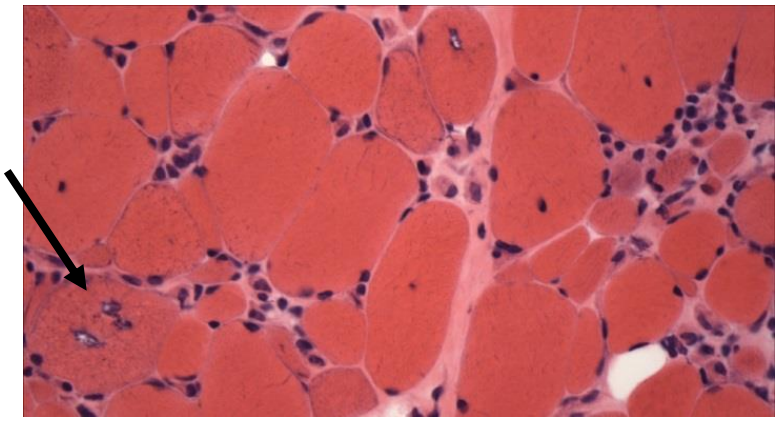
Karpati made most definitive description:
Neurology 1978 28(1): 8-17

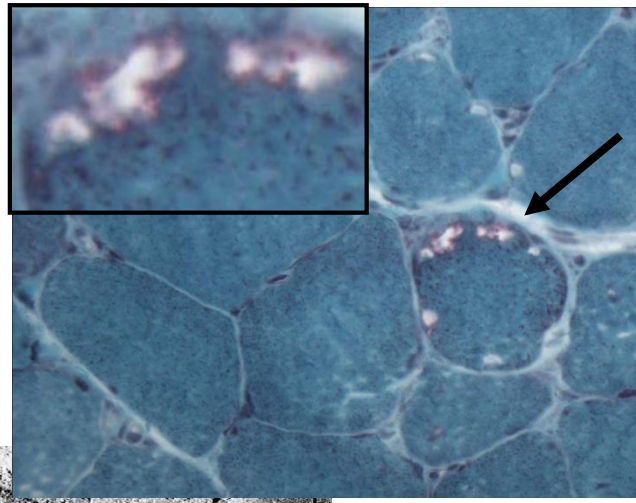
Endomysial inflammation, inflammatory cells surrounding myofibers, invasion of non-necrotic muscle fibers

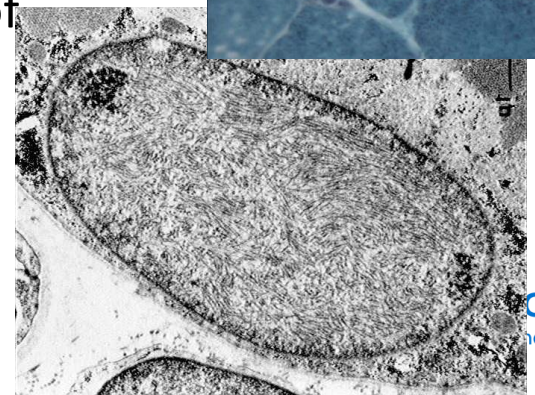
Variation in fiber size, angular fibers (neurogenic atrophy), fibrosis (chronicity)

Rimmed vacuoles in some fibers- commonly visible on Gomori trichrome- vacuoles contain degraded nuclei and membranous material

Tubulofilamentous inclusions on EM- within nuclei or in clumps in sarcoplasm suggestive of former nuclei devoid of nuclear membrane







Myositis Specific Autoantibodies

Myositis Specific Antibodies

In

PM and DM

Table 2 Myositis-specific antibodies: target antigens and clinical associations in adult myositis patients

Autoantibody	Immune target	Function of autoantigen	Clinical associations
Anti-ARS (Jo-1, PL-7, PL-12, EJ, OJ, KS, Ha, Zo)	tRNA synthetases	Aminoacylation of tRNAs	PM Anti-synthetase syndrome
Anti-Mi-2	NuRD subunit	Gene transcription Nucleosome remodeling	"Classic DM" Mild disease
Anti-TIF1-γ	Transcriptional intermediary factor 1γ	Ubiquitination Gene transcription	Severe DM Cancer-associated DM
Anti-NXP-2	Nuclear matrix protein 2	Gene transcription	Severe DM Cancer-associated DM
Anti-MDA5	Melanoma differentiation-associated protein 5	Innate antiviral response	Amyopathic DM ILD Poor prognosis
Anti-SAE	SUMO-1 activating enzyme	Protein sumoylation Gene transcription	DM Initially amyopathic DM

School of Medicine
Autoimmun Highlights (2014) 5:69–75

Dermatomyositis Autoantibodies may help diagnostic yield and predict prognosis

Table 2 Myositis-specific antibodies: target antigens and clinical associations in adult myositis patients

Autoantibody	Immune target	Function of autoantigen	Clinical associations
Anti-ARS (Jo-1, PL-7, PL-12, EJ, OJ, KS, Ha, Zo)	tRNA synthetases	Aminoacylation of tRNAs	PM Anti-synthetase syndrome
Anti-Mi-2	NuRD subunit	Gene transcription Nucleosome remodeling	"Classic DM" Mild disease
Anti-TIF1-γ	Transcriptional intermediary factor 1γ	Ubiquitination Gene transcription	Severe DM Cancer-associated DM
Anti-NXP-2	Nuclear matrix protein 2	Gene transcription	Severe DM Cancer-associated DM
Anti-MDA5	Melanoma differentiation-associated protein 5	Innate antiviral response	Amyopathic DM ILD Poor prognosis
Anti-SAE	SUMO-1 activating enzyme	Protein sumoylation Gene transcription	DM Initially amyopathic DM

Autoimmun Highlights (2014) 5:69–75

Increased Cancer Risk in DM, but not PM or IBM

Greatest risks for:

- Ovarian
- Lung
- Gastric
- Colorectal
- Pancreatic
- Lymphomas

Cancer type (ICD-7 code)	Dermatomyositis (n=618)	
	Number	SIR (95% CI)
All (140–205)	115	3·0 (2·5–3·6)
Oesophagus (150)	1	2·9 (0·4–20·8)
Stomach (151)	7	3·5 (1·7–7·3)
Colorectal (153, 154)	12	2·5 (1·4–4·4)
Pancreas (157)	5	3·8 (1·6–9·0)
Lung, trachea, and bronchus (162)	19	5·9 (3·7–9·2)
Breast (170)	12	2·2 (1·2–3·9)
Cervix (171)	2	2·7 (0·7–10·8)
Ovary (175)	13	10·5 (6·1–18·1)
Prostate (177)	5	1·8 (0·8–4·4)
Kidney (180)	2	1·7 (0·4–6·7)
Bladder (181)	3	1·8 (0·6–5·6)
Non-Hodgkin lymphoma (200)	3	3·6 (1·2–11·1)
Hodgkin's lymphoma (201)	1	5·9 (0·8–42·0)
Myeloma (203)	1	1·5 (0·2–10·5)
Leukaemia (204)	2	2·6 (0·7–10·5)

Table 1: **Standardised incidence ratios (SIR) a cancer after diagnosis of dermatomyositis or**

Hill et al., Lancet 2001

Recommend extensive cancer screening in high risk DM patients

Cancer Screening Recommendations?

- A single PET/CT may be as good as intensive screening

Conventional Cancer Screening versus PET/CT in Dermatomyositis/Polymyositis

Albert Selva-O'Callaghan, MD, PhD,[a]* Josep M. Grau, MD, PhD,[b]* Cristina Gámez-Cenzano, MD, PhD,[c] Antonio Vidaller-Palacín, MD, PhD,[d] Xavier Martínez-Gómez, MD,[e] Ernesto Trallero-Araguás, MD,[a] Eduard Andía-Navarro, MD,[c] Miquel Vilardell-Tarrés, MD, PhD[a]

Am J. Med 2010

- Conventional screen: physical exam + labs + chest/abdomen CT + mammography + gyn exam (including U/S), tumor markers (CA125, CA 19-9, CEA, PSA)
  - PPV= 78%, NPV = 96%
- Whole-body FDG-PET/CT
  - PPV= 86%, NPV = 94%

Immune-Mediated Necrotizing Myopathy

Myositis Antibodies Associated with Necrotizing myopathies

Table 2 Myositis-specific antibodies: target antigens and clinical associations in adult myositis patients

Autoantibody	Immune target	Function of autoantigen	Clinical associations
Anti-SRP	Signal recognition particle	Protein translocation across the ER	Necrotizing myopathy
Anti-HMGCR	3-Hydroxy-3-methylglutaryl-CoA reductase	Cholesterol biosynthesis	Necrotizing myopathy Prior statin use

UC Irvine Health
School of Medicine

Autoimmun Highlights (2014) 5:69–75

NT5C1A Antibody in IBM

- In 2013, Cytosolic 5’-Nucleotidase 1A (NT5C1A) Antibody
- May be involved in DNA repair metabolism
- NT5C1A in sporadic Inclusion Body Myositis patients
  - 60-70% Sensitivity
  - 83-92% Specific

1. Larman HB, *et al*. Cytosolic 5’-nucleotidase 1A autoimmunity in sporadic inclusion body myositis. *Ann Neurol*. 2013 Mar;73(3):408-18.
2. Pluk H, *et al*. Autoantibodies to cytosolic 5’-nucleotidase 1A in inclusion body myositis. *Ann Neurol*. 2013 Mar;73(3):397-407.

NT5C1A Antibody in IBM vs. Autoimmune diseases

Cytosolic 5′-Nucleotidase 1A As a Target of Circulating Autoantibodies in Autoimmune Diseases

THOMAS E. LLOYD, MD, PhD[1], LISA CHRISTOPHER-STINE, MD, MPH[1], IAGO PINAL-FERNANDEZ, MD, PhD[2], ELENI TINIAKOU, MD[1], MICHELLE PETRI, MD, MPH[1], ALAN BAER, MD[1], SONYE K. DANOFF, MD, PhD[1], KATHERINE PAK, MD[3], LIVIA A. CASCIOLA-ROSEN, PhD[1], and ANDREW L. MAMMEN, MD, PhD[4]

Arthritis Care Res (Hoboken). 2016 January

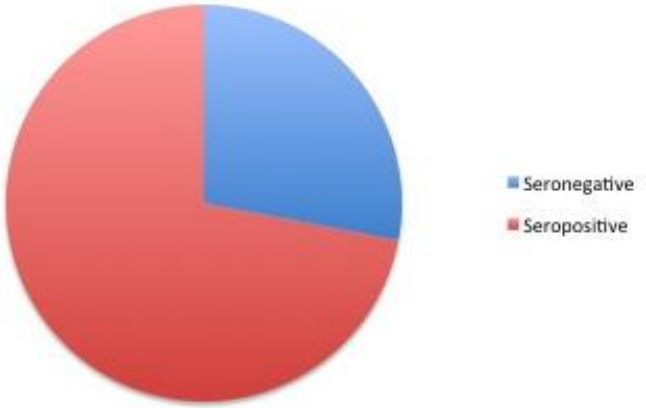
- Detected in 61% of 117 patients with IBM
- 5% with PM
- In Sjogrens (23%) & SLE (14%)- but no muscle weakness
- NT5C1A Ab may be helpful in differentiating IBM from PM

Seropositivity for NT5c1A antibody in sporadic inclusion body myositis predicts more severe motor, bulbar and respiratory involvement

N A Goyal,[1] T M Cash,[1] U Alam,[1] S Enam,[1] P Tierney,[1] N Araujo,[1] F H Mozaffar,[1] A Pestronk,[2,3] T Mozaffar[1,4]

J Neurol Neurosurg Psychiatry 2015;**0**:1–6. doi:10.1136/jnnp-2014-310008

- 25 sIBM patients enrolled in the study
- NT5C1A antibodies detected in 18/25 subjects (72%)
- May predict more severe phenotype
  - Greater motor deficits (assistive devices)
  - Dysphagia
  - Respiratory insufficiency



Muscle Imaging

Muscle Imaging (MRI)

- Easy technique to visualize affected muscles and pattern of muscle involvement
- Detect subclinical changes (prior to detectable weakness on exam)
- May help measure disease progression/activity

Muscle Imaging (MRI)

- Edema
- Atrophy
- Fatty replacement
- Fascial edema

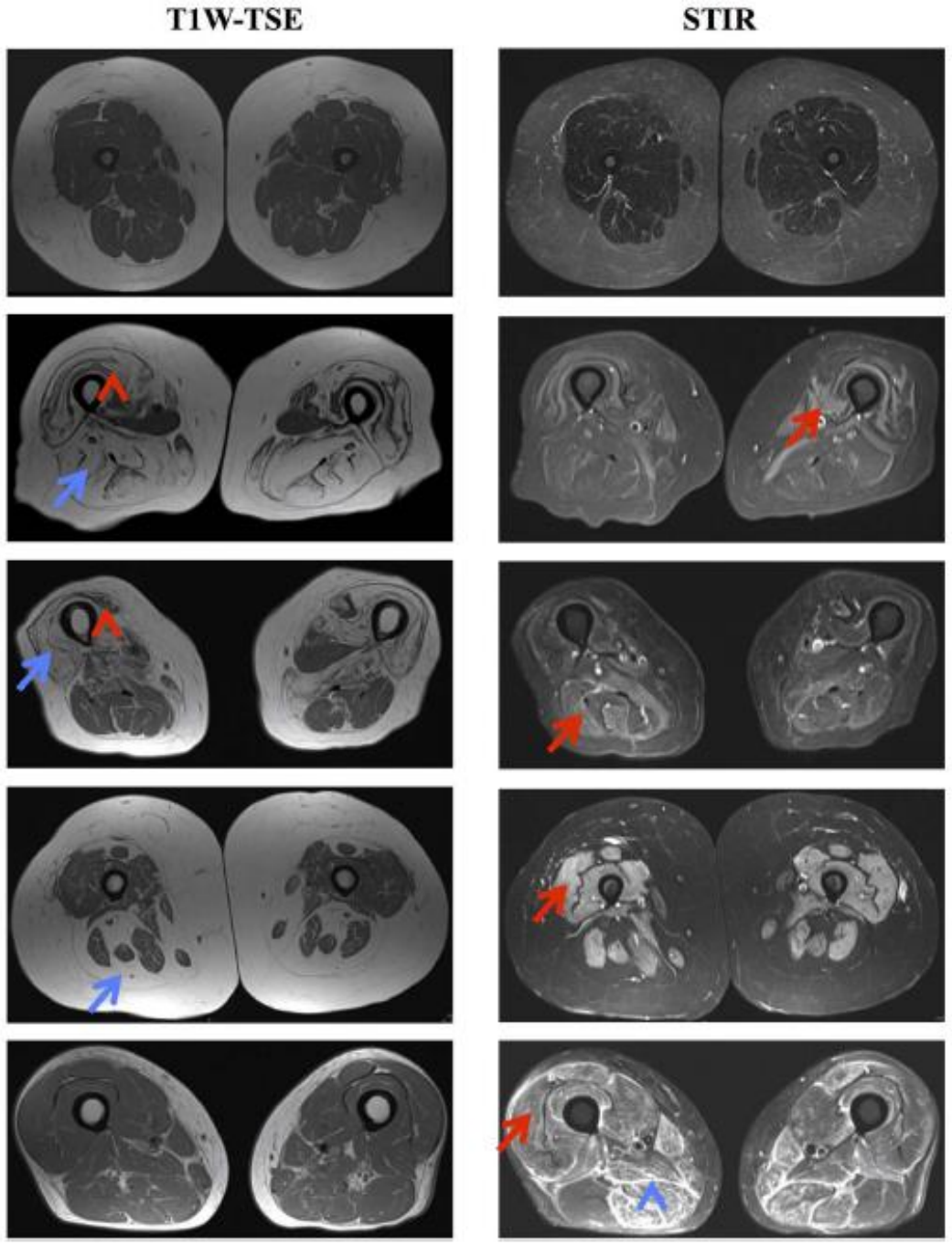


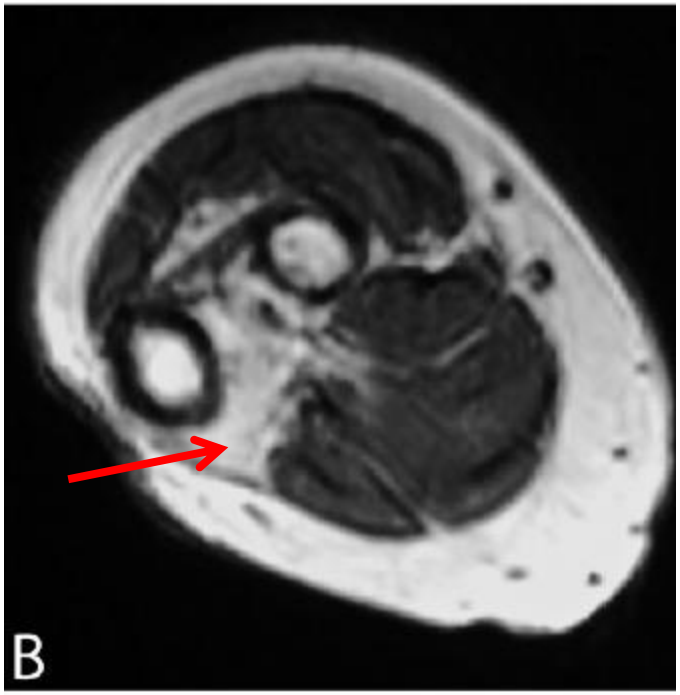
Figure 1 Examples of T1-weighted (T1W) turbo spin echo (TSE) and short-tau inversion recovery (STIR) sequences showing oedema (red arrows), atrophy (red arrow heads), fatty replacement (blue arrows) and fascial oedema (blue arrow heads) in patients with immune-mediated necrotising myopathy (IMNM), inclusion body myositis (IBM), polymyositis (PM) and dermatomyositis (DM).

Pinal-Fernandez et al., Ann Rheum Dis 2016

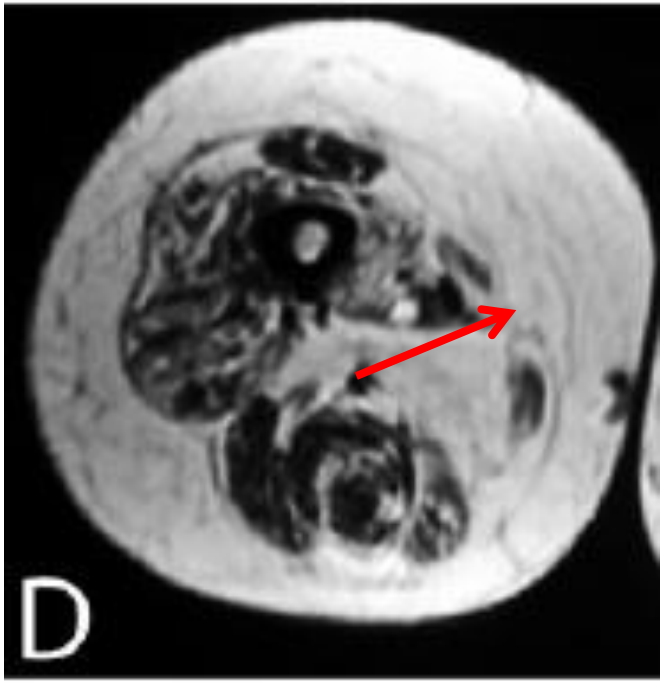
Magnetic resonance imaging of skeletal muscles in sporadic inclusion body myositis

Fieke M. Cox[1], Monique Reijnierse[2], Carla S. P. van Rijswijk[2], Axel R. Wintzen[1], Jan J. Verschuuren[1] and Umesh A. Badrising[1]

Rheumatology 2011;50:1153-1161
doi:10.1093/rheumatology/ker001



MRI forearm:
Severe fatty infiltration of Flexor digitorum profundus (FDP)

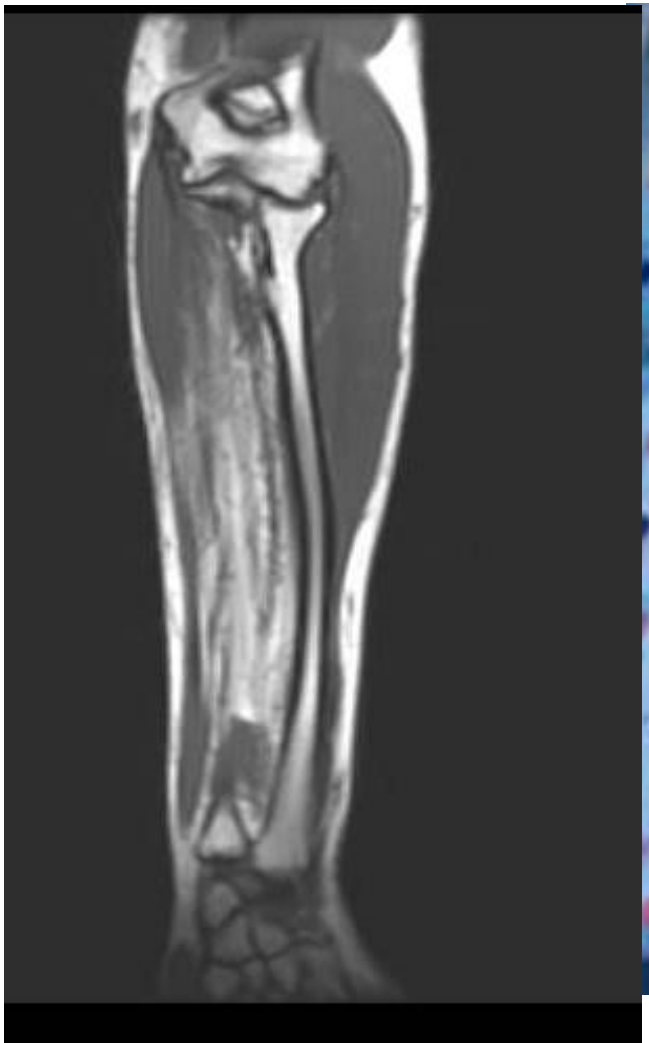


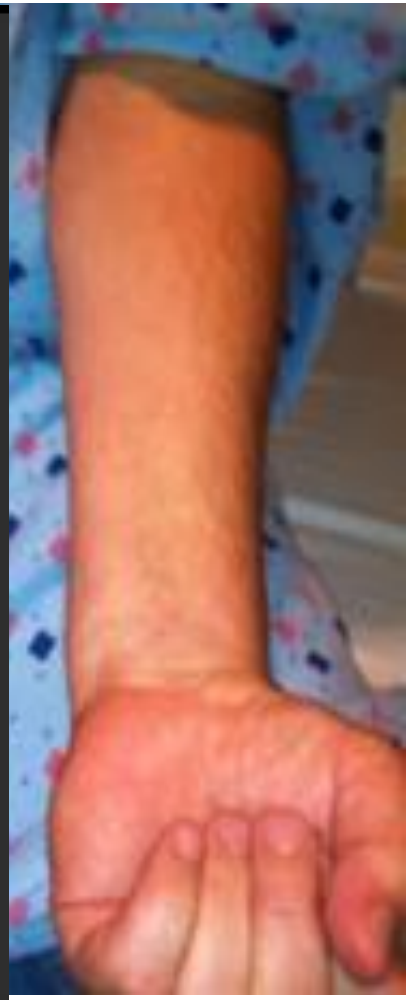
MRI Upper thigh:
Severe fatty infiltration of Vastus lateralis, relative sparing of rectus femoris and hamstrings

Muscle Imaging MRI- in sIBM

especially helpful if mild finger flexor weakness and want to confirm muscle involvement

"Increased T2 signal in medial forearm flexor compartment muscles"





Treatment/Management in DM, PM and Necrotizing myopathy

Treatment: in DM and PM

- Generally good response to therapy
- Understanding of therapeutics: based on small clinical trials, expert experience, and retrospective case series
- Currently, no single correct treatment approach
- Most experts agree that first-line therapy is corticosteroids
- Equipoise on when to begin other therapies

Treatment: DM and PM

- 1st line agent: steroids
- 2nd line agents: Methotrexate, Azathioprine, other immunosuppressive agents (mycophenolate mofetil)
- IVIg shown to be quite effective
- Rituximab for refractory disease
- 3rd line agents (options, less evidence): cyclosporine, tacrolimus, cyclophosphamide

Corticosteroids: Starting treatment

- Considered first-line therapy in DM and PM
- Generally initiated with prednisone at a dose of 0.75-1mg/kg/day, not exceeding 60-80mg daily
- In severe weakness or multisystem involvement (severe rash, dysphagia, interstitial lung disease), short course of IV methylprednisone (1g/d x 3-5 days), followed by high dose oral prednisone
- High dose steroids should be maintained until strength normalizes or improvement plateaus
- Maintained on high dose *2-4 months

Corticosteroids: Tapering

- After improvement in strength (may be 2-4 months)
- Taper methods vary:
  - When high dose, (taper by 20%) or by 10mg/day *every 4 weeks
  - When at 20mg/day, taper by 5mg *every 4 weeks
  - When at 10mg/day, taper by 1-2.5mg/day *every 4 weeks or even every 6-12 months
- Goal: reduce dose to lowest effective dose (maintaining disease control and balancing with prednisone side effects)
- Rapid taper may result in “back-and-forth” of dose and exacerbations of disease

Concurrent Management: Side effects of Steroids

- Monitor: Glucose, potassium levels, blood pressure, eye exam
- Risk of osteoporosis with steroid use
- Baseline and annual DEXA (duel-energy Xray)
- Vitamin D (2000IU/d) and Calcium (1g/d)
- Bisphosphonates if higher risk of osteoporosis
- Dietician to prevent weight gain (low sodium, low carb, high protein diet)

When to Consider Starting a Second-line Agent?

Addition of another immunosuppressive drug:

- Moderate to Severe weakness (at onset)
- Refractory disease (persistent weakness)
- Repeated disease flares
- To allow reduction of dose and duration of glucocorticoid therapy and associated side effects

Treatment options:
Second-line Agents
Generally start with:
Methotrexate or Azathioprine

Methotrexate

- Binds to and inhibits dihydrofolate reductase, resulting in inhibition of DNA synthesis, repair and replication
- Oral or subcutaneous, titrated dose to 15-25mg/wk
- Several case series and expert consensus on efficacy
- Folate 1mg daily
- Monitor: Blood counts, liver and renal indices
- Risk of Pulmonary fibrosis: Avoid in ILD or Jo-1 Ab

Azathioprine

- Inhibits purine metabolism, interfering with cellular replication
- Started at 50mg twice daily, then increase by 50mg every 2-4 weeks, up to 2-2.5mg/kg/day
- Some studies show similar efficacy to MTX, but may take up to 6 months (rather than 2-3 months)
- 10% of patients reaction: fever, abdominal pain, nausea, vomiting, pancreatitis or rash- STOP drug
- Monitor: blood counts (bone marrow suppression), liver and kidney

Treatment options: Second-line Agents Other Options

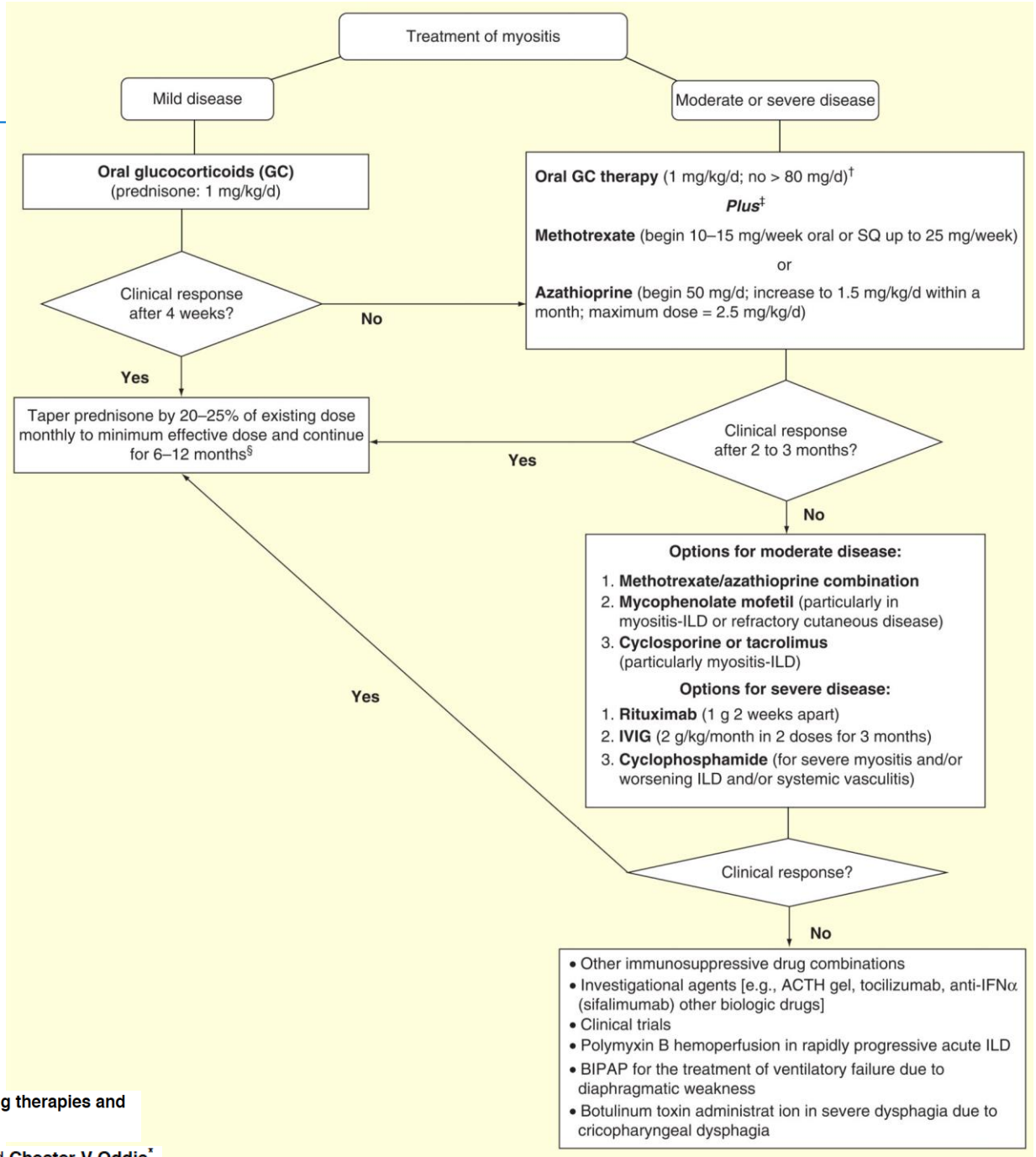
Intravenous Immunoglobulin (IVIg)

- Immunomodulatory agent thought to suppress inflammatory/immune-mediated process
- Several studies show efficacy
- Used in: refractory to prednisone taper, flare on prednisone, refractory to other 2nd line agents
- *Or* in: Severe myositis, start IVIg with steroids and then add 2nd-line agent
- Dose: 2g/kg over 2-5 days, maintained at 1g/kg/month for a few months, then taper pending response
- Well tolerated, S/E: flu-like symptoms, headache

Rituximab

- Monoclonal Ab directed against CD20 antigen on B-lymphocytes
- Several small case reports note benefit in refractory DM and PM
- Use in patients refractory to prednisone and failed one second-line agent
- Dose: 750mg/m^2 (up to 1g) IV, repeated in 2 weeks (consider repeating every 6-18 months)
- Risk of acute of infusion reaction and long-term immunosuppression

Treatment Algorithm



Treatment of inflammatory myopathy: emerging therapies and therapeutic targets

Siamak Moghadam-Kia, **Rohit Aggarwal**, and **Chester V Oddis***

Expert Rev Clin Immunol. 2015 ; 11(11): 1265–1275.

Treatment of anti-HMGR Ab Immune-Mediated Necrotizing Myopathy

- Reports suggest multiple immunosuppressive agents to treat effectively
- Over half published cases = Steroids + 2 agents
- IVIg was often 3rd agent added to achieve remission
- *Also screen for supplements or foods hiding statins (mushrooms, red rice yeast)!*

Mammen and Tiniakou, NEJM, 2015

Treatment of anti-HMGR Ab Immune-Mediated Necrotizing Myopathy

- Reports suggest multiple immunosuppressive agents to treat effectively
- Over half published cases = Steroids + 2 agents
- IVIg was often 3rd agent added to achieve remission
- *Also screen for supplements or foods hiding statins (mushrooms, red rice yeast)!*

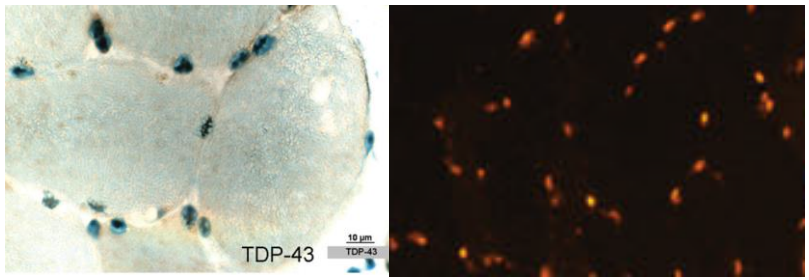
Mammen and Tiniakou, NEJM, 2015

Treatment/Management in Inclusion body Myositis

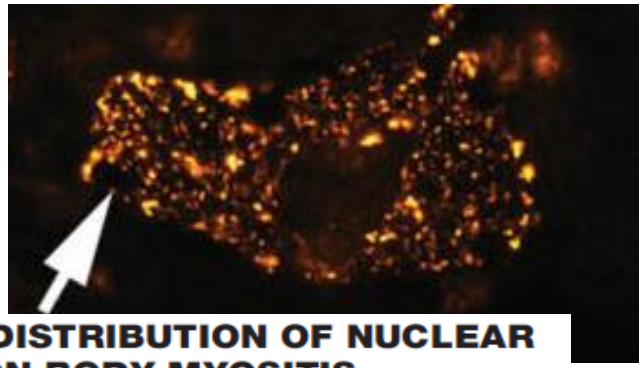
Pathogenesis in IBM? – still Unclear

Unclear if primary inflammatory myopathy or primary degenerative myopathy with secondary inflammatory response

- Immune injury of IBM myofibers due to cytotoxic T cells? – but no response to immunotherapy
- Degenerative disorder with abnormal depositions of amyloid, ubiquitin, tau?
- Rimmed vacuoles lined with nuclear membrane proteins, suggesting derived from myonuclear breakdown
- Discovery of TDP-43 nucleic acid binding protein nonnuclear sarcoplasmic accumulation – toxic to cells



Normal muscle



SARCOPLASMIC REDISTRIBUTION OF NUCLEAR TDP-43 IN INCLUSION BODY MYOSITIS

Muscle Nerve **40:** 19–31, 2009

Immunosuppression in sIBM

Inclusion body myositis : Explanation for poor response to immunosuppressive therapy
R. J. Barohn, A. A. Amato, Z. Sahenk, et al.
Neurology 1995;45;1302

Literature and anecdotal reports

Refractory to immunosuppressive treatment:

- Steroids (uncontrolled trials – stabilization or temporary improvement, prospective trial up to 12 months showed fall in CK level yet deterioration in muscle strength)
- Methotrexate (some trials with apparent stabilization over short period, largest trial of 12 months in 44 patients- MTX did not slow progression of disease)
- Azathioprine
- Cyclophosphamide

IVIg in sIBM

Retrospective study in 16 IBM patients suggested short term benefit in leg muscle strength and dysphagia (benefit was only temporary and limited to a small proportion of patients) Clin Exp Rheumatol 2012; 30:838-842

CONSENSUS STATEMENT: THE USE OF INTRAVENOUS IMMUNOGLOBULIN IN THE TREATMENT OF NEUROMUSCULAR CONDITIONS REPORT OF THE AANEM AD HOC COMMITTEE

Muscle Nerve **40:** 890–900, 2009

Case series or Controlled studies

- None which show complete responses or major benefit
- 3 double blind studies with IVIG – "no statistically significant improvement in muscle strength"

Does Treatment with Immunotherapy make sIBM worse in the long run?

Table 5 Comparison of treated and untreated patients with sporadic IBM

Characteristics of patients	Untreated ($n = 65$)	Treated ($n = 71$)	P
Gender, male ($n = 136$)	40 (61.5)	38 (53.5)	0.39
Age at first symptoms, years ($n = 136$)	63 (57–72)	60 (53–65)	0.02
First symptoms ($n = 136$)			
Muscle weakness and swallowing difficulties	4 (6.1)	7 (10.0)	0.57
Muscle weakness only	59 (90.8)	60 (84.5)	
Swallowing troubles only	2 (3.1)	4 (5.6)	
Previous diagnosis ($n = 136$)			
None	53 (81.5)	41 (57.7)	0.002
Polymyositis	4 (6.1)	19 (26.8)	
Other	8 (12.3)	11 (15.5)	
Delay between first symptoms and sporadic IBM diagnosis, months ($n = 136$)	59 (33–86)	58 (25–98)	0.71
Status at the last visit			
Time since sporadic IBM diagnosis, months ($n = 136$)	18 (3–46)	50 (13–87)	0.001
Age, years ($n = 136$)	73 (66–79)	71 (65–76)	0.21
Muscle weakness ($n = 136$)	65 (100)	71 (100)	1.0
Severe proximal weakness[a] ($n = 136$)	28 (43.1)	36 (52.2)	0.40
Severe distal weakness[a] ($n = 136$)	25 (38.5)	28 (39.4)	1.0
Swallowing troubles ($n = 136$)	29 (44.6)	33 (46.5)	0.86
Creatine kinase, IU/l ($n = 87$)	367 (219–649)	209 (117–559)	0.11
Grip strength kgN ($n = 76$)	13.4 (11.0–17.2)	13.5 (9.0–18.0)	0.84
Walton ($n = 113$)	4 (3–6)	6 (3–6)	0.007
RMI ($n = 88$)	11 (9–13)	10 (4–11)	0.004
IWCI ($n = 71$)	50 (30–65)	40 (25–50)	0.04
Current handicap for walking ($n = 136$)			
None	20 (30.8)	13 (18.3)	0.10
One or two canes	26 (40.0)	26 (36.6)	
Wheelchair	19 (29.2)	32 (45.1)	

Treated group:
Less independent mobility,
Increased use of wheelchair

Brain 2011: 134; 3176–3184

Therapeutic Agents Investigated in sIBM

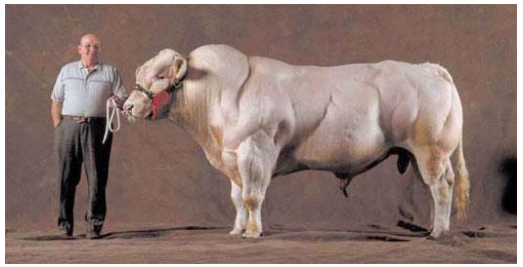
- Arimoclomol
  - May upregulate the cytoprotective heat shock response (HSR) by amplifying heat shock protein expression and potentially dampen the detrimental aspects of inflammation and degeneration
  - Placebo controlled trial (16 active, 8 placebo) –well tolerated, demonstrated proof of concept and supporting further research
    Ann Rheum Dis 2013

- Etanercept (Tumor necrosis factor antagonist)
  - Pilot trial (Neurology 2006) no significant benefit in hand grip at 6 months, but improvement in hand grip at 12 months
  - Placebo-controlled 30 patient study completed

- Alemtuzumab (CAMPATH)
  - Monoclonal Ab, causes depletion of blood lymphocytes
  - Proof of principle study in 13 patients (Brain 2009) reported slowing of disease progression up to 6 months, improvement in strength in some, and reduced endomysial inflammation

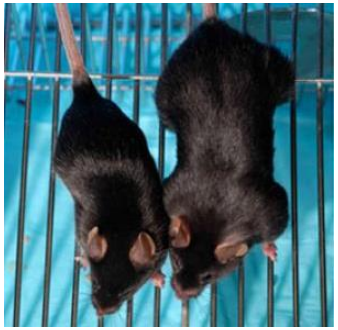
Newer Agents: Myostatin Antagonists in sIBM

- Myostatin negatively regulates skeletal muscle growth
- Inhibition of myostatin results in **hypertrophy** of skeletal muscles (increased muscle mass and strength)
- Myostatin pathway under investigation using 2 agents
  - Follistatin gene transfer (antagonist of myostatin)
  - BYM338 (monoclonal Ab that binds competitively to activin receptor type IIB with greater affinity than myostatin)



Yann Arthus-Bertrand/Corbis

Lee SJ PLoS One 2007

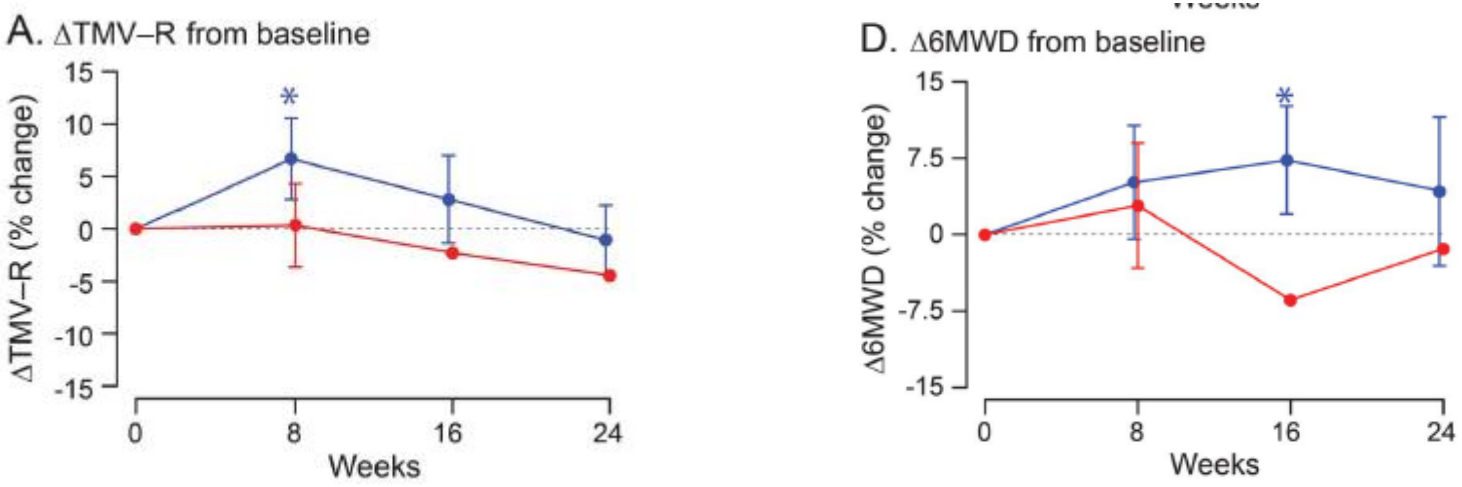


- BYM338 given to two atrophy mouse models- steroid myopathy and disuse – recovery of muscle loss

Treatment of sporadic inclusion body myositis with bimagrumab

Amato A, Sivakumar K, Goyal N et al. Neurology 2014

Figure 3 Effect of bimagrumab compared with placebo on primary and secondary study endpoints over 24 weeks



14 sIBM patients (11 active, 3 placebo):

- Increased thigh muscle volume in treated patients 8 weeks after dosing
- Improved 6 minute walk distance in treated patients 16 weeks after dosing

Management: Multidisciplinary Care

- Mobility
  - Assistive devices (AFOs, cane, braces, walker, wheelchair)
  - Risk of falls
- Dysphagia
  - Diet modification
  - Dilation, botulinum toxin, cricopharyngectomy
  - Gastrostomy tube
  - Risk of aspiration pneumonia
- Respiratory insufficiency: Noninvasive ventilation (BiPAP)
- Adaptive Equipment
  - Shower chair, stair lift, safety rails, hospital bed
  - Home safety evaluations and bathroom modifications
- Role of Exercise: May slow progression

Take Home Points

- Myositis cases diagnostically challenging
- Careful attention to clinical exam for clues to correct diagnosis
- Diagnostic process (in addition to muscle biopsy):
  - Antibodies (Myositis Panel, HMGCR, NT5C1A Ab): quite helpful for establishing diagnosis and predicting treatment response
  - Muscle imaging:
    - Detecting subclinical muscle involvement
    - Pattern of muscle involvement
    - Disease activity
- Establishing diagnosis, before embarking on immunosuppression
- DM, PM, IMNM- treatable! Immunotherapy options!

Thank you

Myositis Specific Antibodies

TIF1-γ Positive

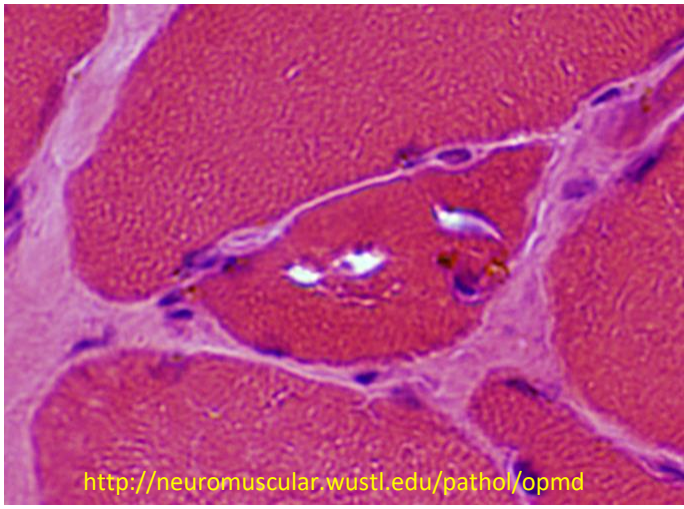
Table 2 Myositis-specific antibodies: target antigens and clinical associations in adult myositis patients

Autoantibody	Immune target	Function of autoantigen	Clinical associations
Anti-ARS (Jo-1, PL-7, PL-12, EJ, OJ, KS, Ha, Zo)	tRNA synthetases	Aminoacylation of tRNAs	PM Anti-synthetase syndrome
Anti-Mi-2	NuRD subunit	Gene transcription Nucleosome remodeling	"Classic DM" Mild disease
Anti-TIF1-γ	Transcriptional intermediary factor 1γ	Ubiquitination Gene transcription	Severe DM Cancer-associated DM
Anti-NXP-2	Nuclear matrix protein 2	Gene transcription	Severe DM Cancer-associated DM
Anti-MDA5	Melanoma differentiation-associated protein 5	Innate antiviral response	Amyopathic DM ILD Poor prognosis
Anti-SAE	SUMO-1 activating enzyme	Protein sumoylation Gene transcription	DM Initially amyopathic DM
Anti-SRP	Signal recognition particle	Protein translocation across the ER	Necrotizing myopathy
Anti-HMGCR	3-Hydroxy-3-methylglutaryl-CoA reductase	Cholesterol biosynthesis	Necrotizing myopathy Prior statin use

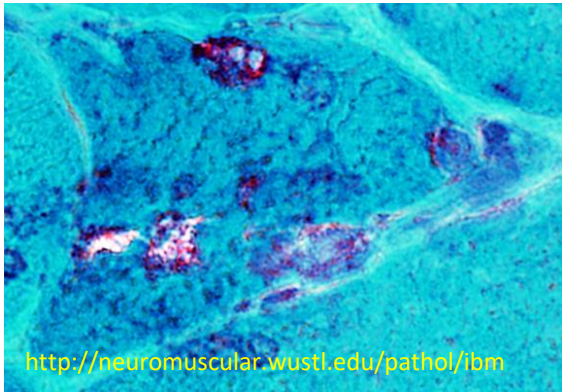
Autoimmun Highlights (2014) 5:69–75

Differential Diagnosis: Pathological

- Endomysial inflammation:
  - Polymyositis
  - Muscular dystrophies



- Vacuoles +/- Rims or Aggregates
  - Oculopharyngeal muscular dystrophy
  - Distal myopathies
    (Welander, Finish-Markesbery, Distal dystrophy, Oculopharyngeal distal)
  - Toxic drug induced: chloroquine or colchicine myopathy
  - Hereditary Inclusion body myopathies
    - HIBM (GNE/Nonaka)
    - Myopathy + Paget's and Frontotemporal Dementia (IBMPFD)
  - LGMD 1A, 1D, 1G, 2G
  - Glycogen storage
  - Myofibrillar myopathy
  - Periodic paralysis



Neurologists are from Mars. Rheumatologists are from Venus: differences in approach to classifying the idiopathic inflammatory myopathies

Lisa Christopher-Stine

Johns Hopkins University, Baltimore, Maryland, USA

Correspondence to Lisa Christopher-Stine, MD, MPH, Johns Hopkins Bayview Medical Center, Johns Hopkins Myositis Center, Mason F. Lord Building Center Tower, Suite 4100, Baltimore, MD 21224, USA
Tel: +1 410 550 6962; fax: +1 410 550 3542; e-mail: lcs@jhmi.edu

Current Opinion in Rheumatology 2010, 22:623–626

Purpose of review

Inflammatory myopathy (IIM) classification criteria have been the source of considerable debate. In the three decades since Bohan and Peter published their criteria which have long stood as the gold standard for diagnosis in clinical practice as well as inclusion into clinical trials, more sophisticated understanding of immunopathogenesis, histology, and specific autoantibody associations has broadened our understanding of these diseases. This editorial review examines the diverse approaches between different subspecialists in deriving appropriate IIM classification utilizing this updated knowledge.

Differences in classifications and approaches

With antibodies and muscle imaging, those differences have been narrowing!

NEUROLOGY 2003;61:288–290

Editorial

Unicorns, dragons, polymyositis, and other mythological beasts

Anthony A. Amato, MD; and Robert C. Griggs, MD

Unicorns, Dragons, Polymyositis, and other Mythological Beasts:

The truth about polymyositis

So how rare is polymyositis?

Are there pathological differentiators?

What about other antibodies?

So is PM nothing more than sIBM or necrotizing immune myopathy (NAM)?

Rheumatol Int
DOI 10.1007/s00296-014-3198-5

Polymyositis, a very uncommon isolated disease: clinical and histological re-evaluation after long-term follow-up

Veronica Silva Vilela · Sergio Prieto-González · José C. Milisenda · Albert Selva-O´Callaghan · Josep M. Grau

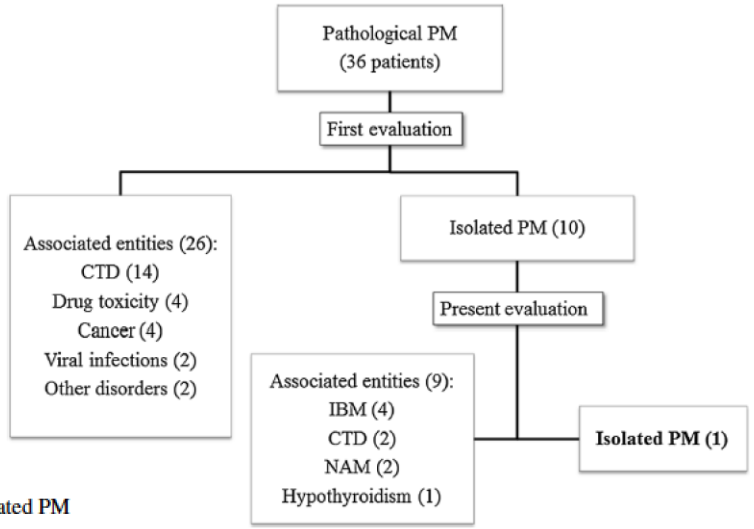
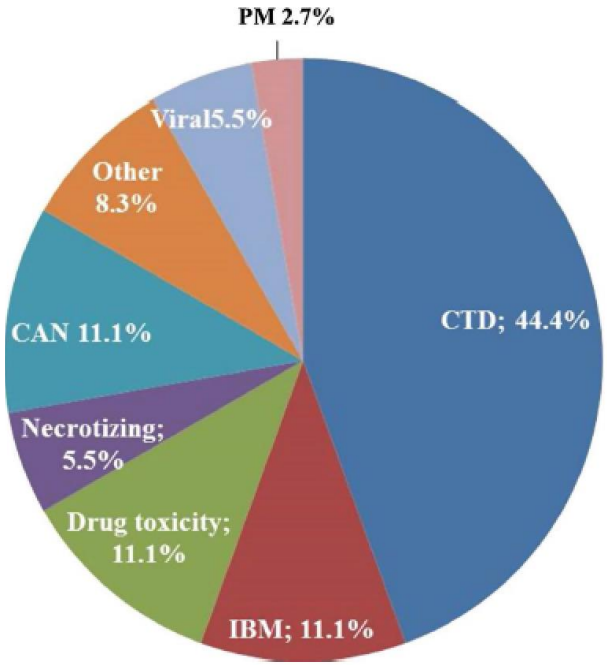


Table 1 Clinical, laboratorial and pathologic features, evolution and final diagnosis of the ten patients initially diagnosed as isolated PM

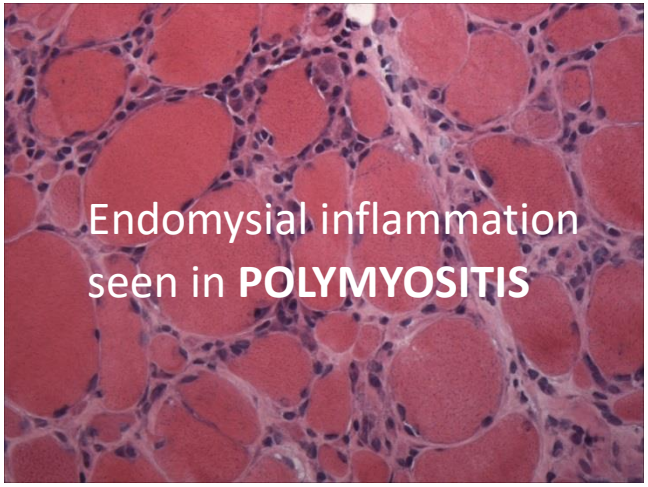
Patient	Initial clinical features (y)	CK (mg/dl)	Biopsy findings (first evaluation)	Clinical follow-up	Biopsy findings (re-evaluation)	Final diagnosis
1	F, 73 Proximal weakness	390	PM	Disabled	Red ragged cell	Definite IBM
2	F, 39 Myalgia and mild weakness	460	PM	RA after 8 years of follow-up	No changes	Rheumatoid arthritis
3	F, 59 Proximal weakness	3,000	PM	Remission with GC	No changes	Isolated PM
4	F, 56 Proximal weakness	7,160	PM	Partial improvement with ciclosporine	Severe necrosis.	NAM
5	F, 51 Proximal with neck weakness	273	PM	Died	Vacuoles	Definite IBM
6	F, 48 Proximal weakness	13,000	PM	Stable with GC and IVIG	Mitochondrial changes	Probable IBM
7	M, 77 Proximal with neck weakness	2,537	PM	Disabled	Ragged red cell	Probable IBM
8	M, 56 Proximal weakness	3,000	PM	Improvement with GC SSc after 10 of follow-up	No changes	SSc
9	F, 29 Asymptomatic (CK rising)	Not available	PM	Improvement with levo-thyroxine	No changes	Hypothyroidism
10	M, 39 Severe proximal weakness	CK 2,600	PM	Anti-SRP Improvement with GC and IVIG	Severe necrosis	NAM

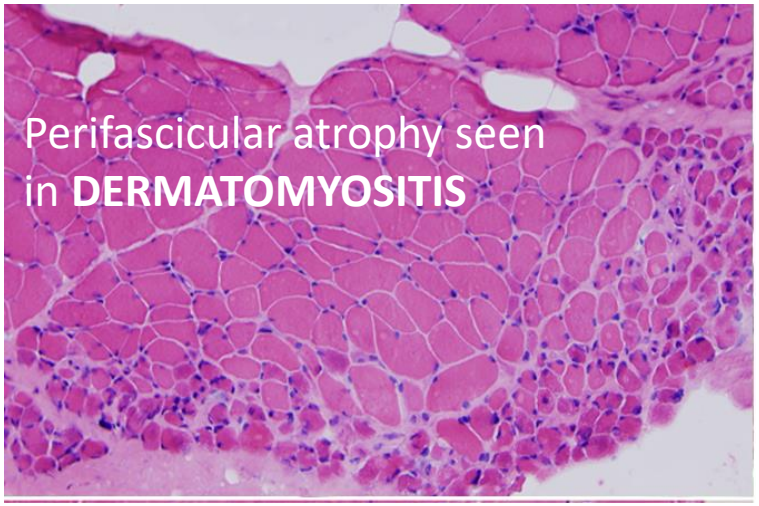
F female, *M* male, *y* years, *CK* creatine kinase, *Anti-SRP Ab* anti-signal recognition particle antibody, *GC* glucocorticoids, *IVIG* intravenous immunoglobulin, *PM* polymyositis, and *SSc* systemic sclerosis



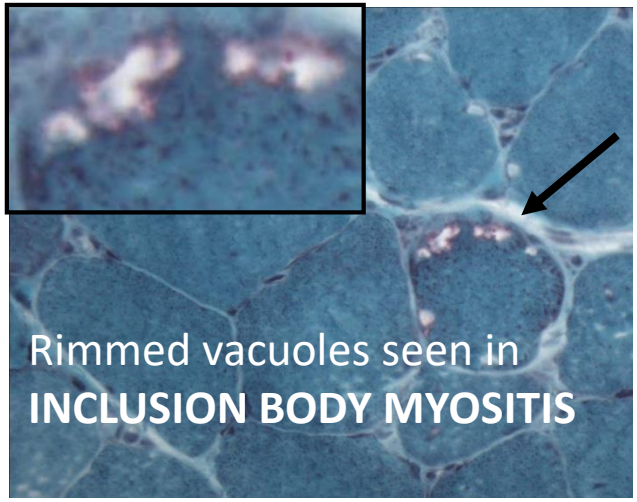
Muscle biopsy

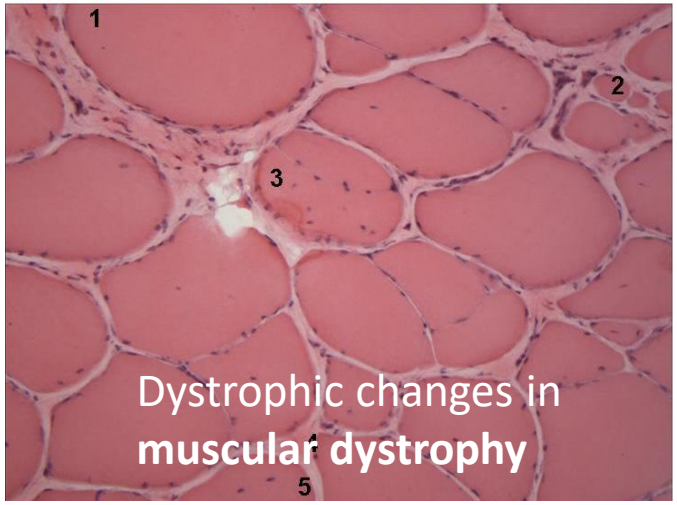
Treatable conditions:



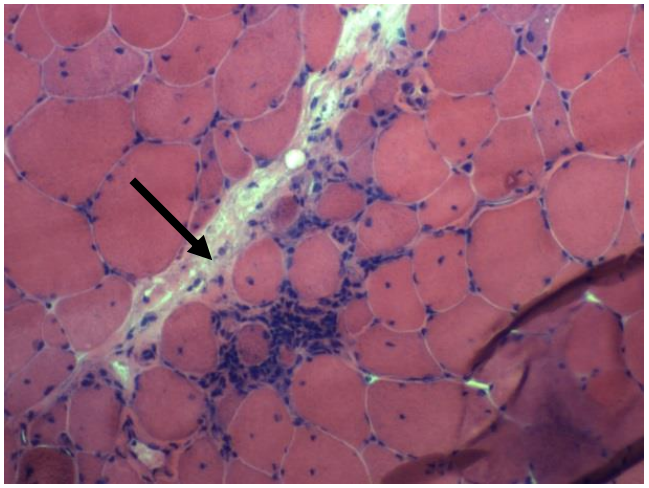


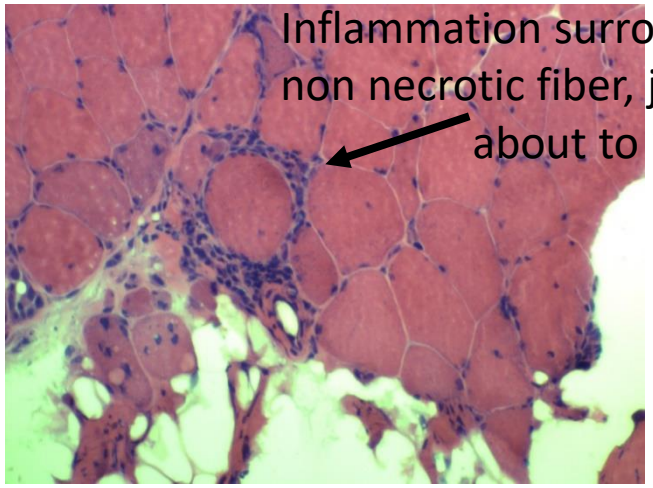
No response to immunotherapy: IBM or Dystrophies- don't respond to immunotherapy

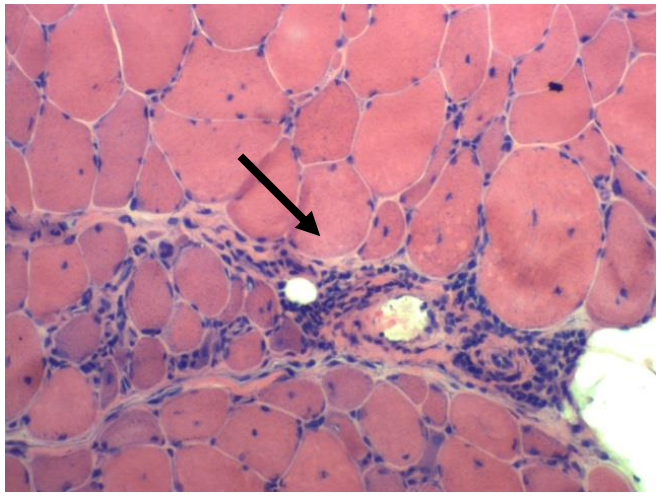


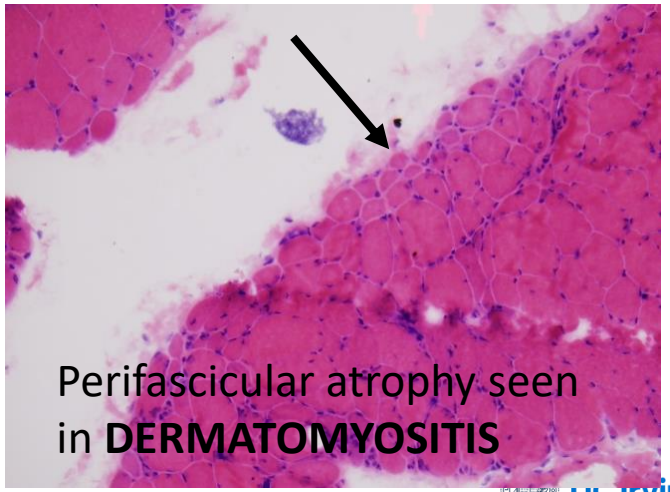


Patient's Muscle Biopsy & Diagnosis: Dermatomyositis



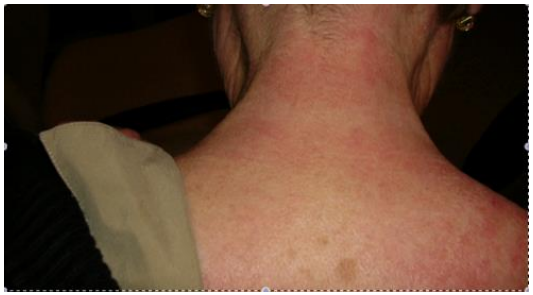




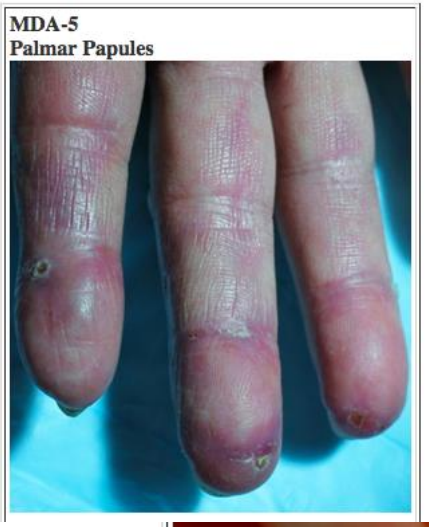


DM Antibodies associated with unique dermatologic features

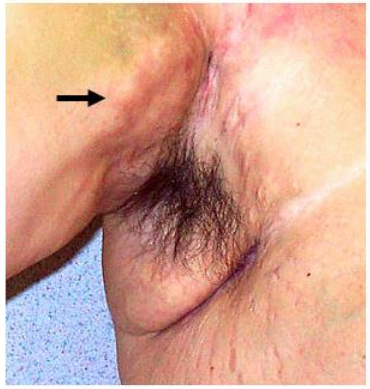
Mi-2: Severe Shawl sign



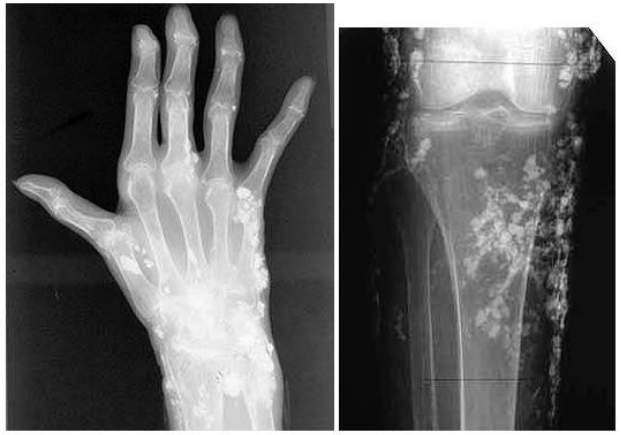
MDA5: Palmar papules,ulcerations



NXP2: Calcinosis



Axillary calcifications



From Drs. Mina Edelman & Franklin Marden

Subcutaneous calcifications in hand and leg

http://neuromuscular.wustl.edu

Presence of Histopathologic Features versus Antibodies in DM

Table 2. Muscle biopsy features, treatments, and duration of disease at biopsy according to autoantibody subsets in patients with dermatomyositis (DM).

	All DM, n = 91	All Jo1, n = 13; 14%	Jo1 with Ro52, n = 9; 10%	Jo1 without Ro52, n = 4; 4%	Anti–TIF1-γ, n = 25; 27%	NXP2, n = 17; 19%	Mi-2, n = 12; 13%	MDA5, n = 5; 5%	PM-Scl, n = 9; 10%	Ro52, n = 22; 24%	No Antibody, n = 15; 16%
Perivascular inflammation	56 (62%)	9 (69%)	8 (89%)	1 (25%)	16 (64%)	11 (65%)	10 (83%)	1 (20%)	7 (78%)	15 (68%)	6 (40%)
Perifascicular atrophy	46 (51%)	8 (62%)	7 (78%)	1 (25%)	16 (64%)	9 (53%)	8 (67%)	2 (40%)	3 (33%)	12 (55%)	4 (27%)
Primary inflammation	21 (23%)	4 (31%)	4 (44%)	0 (0%)	3 (12%)	0 (0%)	6 (50%)	0 (0%)	6 (67%)	6 (27%)	3 (20%)
Mitochondrial dysfunction*	14 (28%)	2 (25%)	2 (29%)	0 (0%)	7 (47%)	2 (25%)	2 (29%)	1 (50%)	0 (0%)	4 (29%)	1 (14%)
Necrotizing myopathy	15 (16%)	2 (15%)	0 (0%)	2 (50%)	2 (8%)	3 (18%)	1 (8%)	0 (0%)	2 (22%)	4 (18%)	4 (27%)
Immunosuppressant prior to biopsy**	55 (61%)	8 (62%)	6 (67%)	2 (50%)	17 (71%)	7 (44%)	7 (58%)	5 (100%)	5 (56%)	15 (68%)	9 (60%)
Taking immunosuppressant during biopsy†	49 (56%)	6 (55%)	5 (63%)	1 (33%)	16 (67%)	7 (44%)	6 (50%)	4 (100%)	4 (44%)	17 (81%)	6 (40%)
Corticosteroids during biopsy**	42 (47%)	4 (31%)	3 (33%)	1 (25%)	14 (58%)	6 (38%)	6 (50%)	4 (80%)	3 (33%)	14 (64%)	5 (33%)
Days from the onset of symptoms to the biopsy, median Q1–Q3	290 (117–615)	721 (531–874)	721 (599–1022)	654 (275–802)	270 (92–561)	125 (66–293)	163 (58–402)	403 (296–637)	232 (114–1880)	497 (291–874)	435 (289–919)

- Perivascular Inflammation (62%)
- Perifascicular atrophy (51%)
- Primary inflammation (23%)

vs. Presence of Ab 84%

Pinal-Fernandez et al., , J. Rheum, 2015

Statin Associated Immune-Mediated Necrotizing Myopathy

IMMUNE-MEDIATED NECROTIZING MYOPATHY ASSOCIATED WITH STATINS

MUSCLE & NERVE February 2010

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]

And anti-HMGCR Antibodies

A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy

Lisa Christopher-Stine, Livia A. Casciola-Rosen, Grace Hong, Tae Chung, Andrea M. Corse, Andrew L. Mammen

A & R 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

A & R 2011

UC Irvine Health
School of Medicine

Anti-HMGCR Ab specific to autoimmune myopathy patients

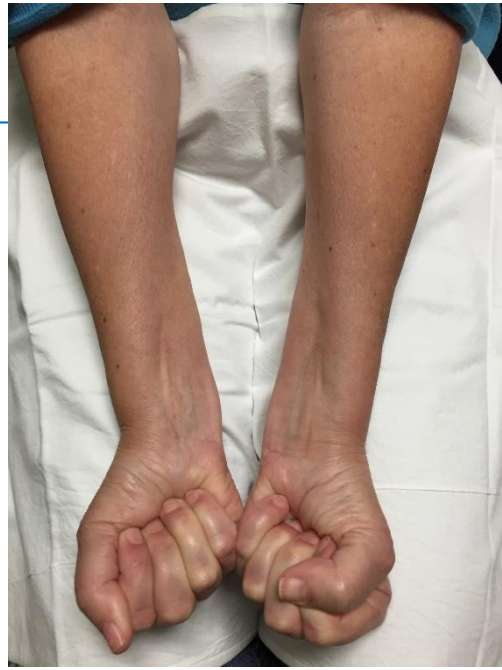
- Not present in 1966 subjects *without* myopathy
  - 763 current statin users
  - 322 former statin uses
  - 881 statin naïve subjects

- Not present in 51 patients with self-limited statin intolerance

Mammen et al., 2012

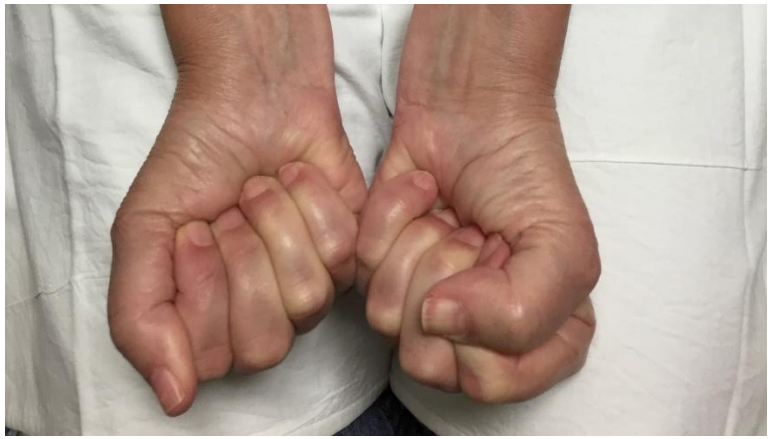
Inclusion Body Myositis

60-year-old with > 10 years of "Refractory Polymyositis"



On exam:

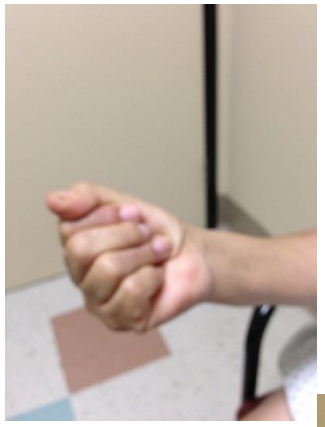
- Facial weakness with eye closure
- Prominent atrophy in forearm muscle compartment (right > left) and both quadriceps (left > right)
- Asymmetric, diffuse limb weakness, worse in:
  deep finger flexors > deltoids
  quadriceps > hip flexors



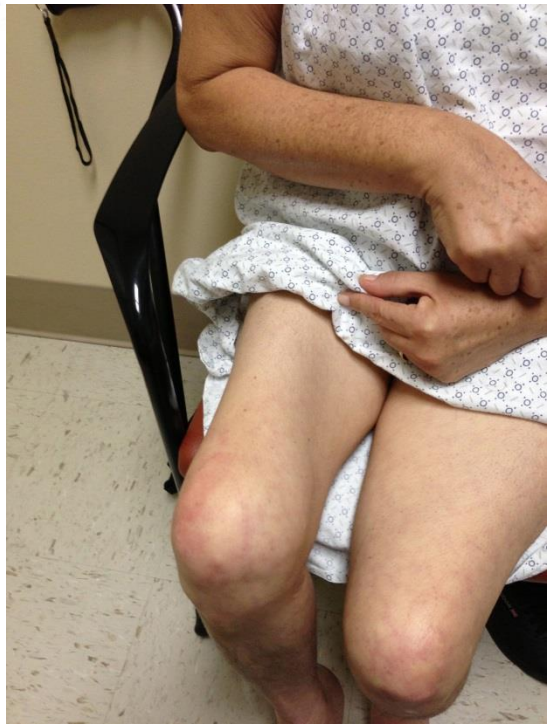
Why is sIBM Commonly Misdiagnosed?

Leading to a delay in diagnosis

Differential: Clinical mimickers



- Polymyositis (Most common)
- Neuropathy (CIDP)
- Muscular dystrophies:
  - Myotonic dystrophy
  - Facioscapulohumeral muscular dystrophy
- Amyotrophic lateral sclerosis (ALS)
- Hereditary inclusion body myopathy
- Distal myopathies
- Weakness attributed to aging?



Evaluation can be misleading at times

Electrodiagnostic studies

- Irritable myopathy
- Confusion: myopathic and neuropathic motor unit action potentials seen
- Up to 1/3 of patients: mild distal sensory axonal peripheral neuropathy

Creatine Kinase levels

- Normal to Moderate Elevation in many
- If Normal
  - May not think of a myopathic process
- Markedly elevated in some (>1000 U/L)
  - May think of polymyositis or a muscular dystrophy

Table 7 Retrospective studies on the natural history of sporadic IBM

Reference	*n*	Male (%)	Age at onset (years)	Age at diagnosis (years)	Creatine kinase level (IU/l)	Patients receiving immunosuppressors (%)	Progression despite therapy (%)
Ringel *et al.*, 1987	19	79	57.8	62.9			
Lotz *et al.*, 1989	40	72.5	56.1	62.4	197	72.5	80.2
Sayers *et al.*, 1992	32	62.5	58	61	1145	87.5	46.4
Beyenburg *et al.*, 1993	36	58.3	47	53.1	279	44.4	93.75
Lindberg *et al.*, 1994	18	55.5	60.4	62.7		88.8	75
Amato *et al.*, 1996	15	86.6	58	64	698	73.3	100
Peng *et al.*, 2000	78	78.2	56.5				
Felice and North, 2001	35	65.7	64.3	70	444	49	100
Badrising *et al.*, 2005	64	67.2	57.6		417	35.9	82.6
Present study 2011	136	57.3	61	66	267	52.2	100

Brain 2011: 134; 3176–3184

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders ■■ (2015) ■■–■■

www.elsevier.com/locate/nmd

Myositis with endomysial cell invasion indicates inclusion body myositis even if other criteria are not fulfilled

J. van de Vlekkert [a,*,1], J.E. Hoogendijk [b], M. de Visser [a]

[a] *Department of Neurology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands*
[b] *Rudolf Magnus Institute for Neuroscience, Department of Neurology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands*

Investigated the disease course in patients with endomysial mononuclear cell infiltrates with invasion of non-necrotic fibers

Hypothesis: disease course in these patients will be in keeping with IBM and not PM, even if they did not fulfill histopathological or clinical criteria for IBM at onset

Table 1
Classification at baseline and at follow up in 81 patients with endomysial mononuclear cell infiltrates with invasion of non-necrotic muscle fibers.

	RVs present	Clinical IBM	Unclassified
At presentation N (%)	49 (60.5)	14 (17.3)	18 (22.2)
At follow up N (%)	ND	29 (36)	3 (4)

RV: rimmed vacuoles; clinical IBM: rimmed vacuoles absent, but fulfilling clinical criteria for IBM; unclassified: fulfilling neither pathological nor clinical criteria for IBM; ND: not determined.

Why Misdiagnosed as Polymyositis?

- CK level: markedly elevated, misleading?
- Muscle biopsy:
  - Report “Inflammation consistent with polymyositis”
  - Comment on “few rimmed vacuoles and differential includes sIBM” overlooked
- Detailed clinical exam missed finger flexor involvement
- Other factors that should have raised suspicion for sIBM
  - Age of 50 years
  - Lack of response to immunosuppression

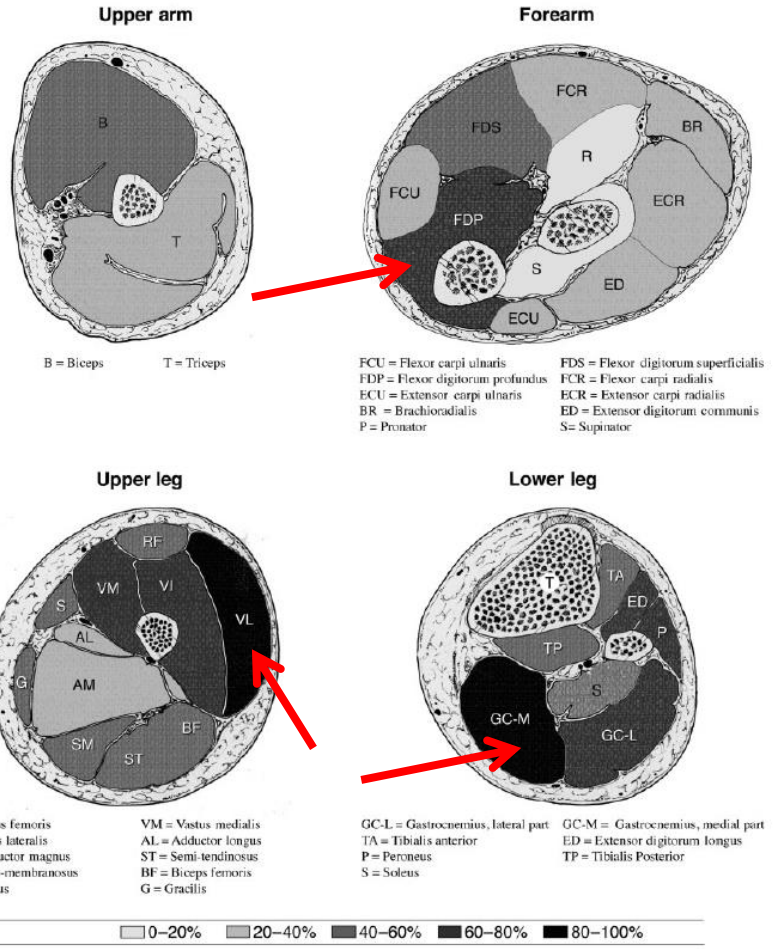
Magnetic resonance imaging of skeletal muscles in sporadic inclusion body myositis

Fieke M. Cox[1], Monique Reijnierse[2], Carla S. P. van Rijswijk[2], Axel R. Wintzen[1], Jan J. Verschuuren[1] and Umesh A. Badrising[1]

Rheumatology 2011;50:1153-1161
doi:10.1093/rheumatology/ker001

Body region	Fatty infiltration, %	Severe fatty infiltration, %
Shoulder	36	12
Arm	44	15
Upper	42	15
Lower	44	15
Pelvis	33	15
Leg	81	42
Upper	76	38
Anterior part	84	50
Posterior part	58	26
Lower	87	44

FIG. 5 Frequency of muscles in the different extremities being infiltrated with fat by >30%.



sIBM pattern helps differentiate from other myopathies:

-Marked FDP involvement

-Fatty infiltration up to 87%

-Sparing of rectus femoris and adductor muscles

-Asymmetry

How to Monitor Disease Control?

- Regardless of choice of initial therapy, early treatment associated with less muscle damage

Indicators of treatment response:

- Objective changes in muscle strength on clinical exam (Mainstay for determining dose adjustment of immunotherapy)
- CK muscle enzyme levels (not as reliable), but rises in levels associated with weakness suggest relapse
- Muscle MRI: new marker to assess disease activity

Corticosteroids: Incomplete response?

- In up to 50%, response may be incomplete on steroids alone, patients may require small dose of prednisone or other second-line agents for long-term control (Troyanov et al 2005)

- If High-dose steroids ineffective, clinicians should reconsider the diagnosis (Mimickers!)
  - IBM
  - Muscular dystrophy or Hereditary myopathy
  - Or Underlying malignancy

Life Expectancy in sIBM: Normal

Survival seems to be <u>similar</u> to the general population

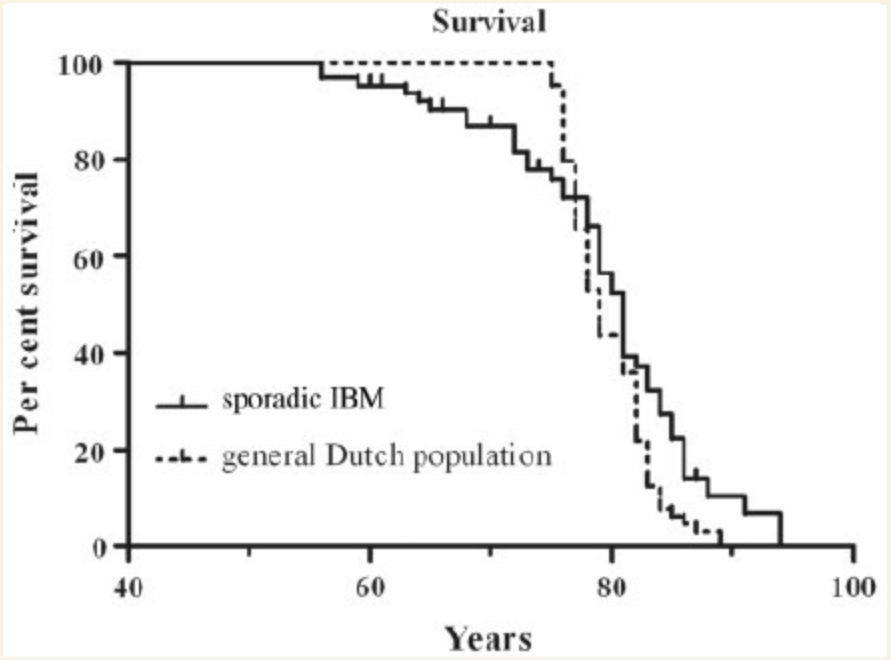


Figure 3 Kaplan-Meier curve showing a comparable survival between sIBM patients and an age- and sex-matched Dutch general population. The curve for the general Dutch population is adjusted for life expectancy for each individual sIBM patient based on the age of onset and gender.

During a 12 year follow up study:
46 of 64 patients died during follow up period
Median age at death = 81 years
In Netherlands, life expectancy 79 years

Cox et al. Brain 2011

Morbidity & Mortality in sIBM

Late Stage disease can cause very significant morbidity

Leading causes of Death:

- Respiratory (pneumonia)
- Cachexia (severe wasting with loss of weight and muscle mass)

Table 2 Causes of death in the Dutch population in the age category 80–85 years and the sporadic IBM cohort

	Dutch population age category 80–84 years (%)	Patients with sporadic IBM (%)	*P*-value	Corrected *P*-value†
Infectious diseases	1.4	2.2	0.66	NS
Neoplasms	23.8	4.3	0.002	0.03*
Diseases of blood/blood-forming organs	0.4	0	0.67	NS
Endocrine/metabolic diseases	3.6	0	0.19	NS
Mental and behavioural disorders	5.6	0	0.10	NS
Diseases of the nervous system	2.8	2.2	0.80	NS
Diseases of the circulatory system (myocardial infarction)	37.7 (7.8)	19.6 (4.3)	0.01	0.16
Diseases of the respiratory system (pneumonia)	11.5 (4.4)	41.3 (28.3)	0.0001*	0.001*
Diseases of the digestive system	4.2	0	0.16	NS
Diseases of the skin	0.3	0	0.71	NS
Diseases of the bone/connective tissue	0.7	0	0.57	NS
Diseases of the genitourinary system	2.8	0	0.25	NS
Cachexia	0.1	6.5	0.0001*	0.001*
External causes of injury and poisoning	2.1	6.5	0.04	0.51
Other/uncertain	3.0	17.4		

†Corrected *P*-value is calculated with a Bonferroni correction of 14. *Significant value.

UC Irvine Health
School of Medicine

Cox et al. Brain 2011