An overview of muscle histopathology in myositis: differentiating subtypes of myositis

Professor Janice Holton
Professor in Neuropathology
UCL Institute of Neurology
Queen Square
London

British Society for Rheumatology
Myositis Masterclass
4th December 2015
Manchester

Overview

- Biopsy features
- Muscle biopsy analysis: classical features
- Autoantibodies
- Evolving story of subtypes

Inflammatory myopathies

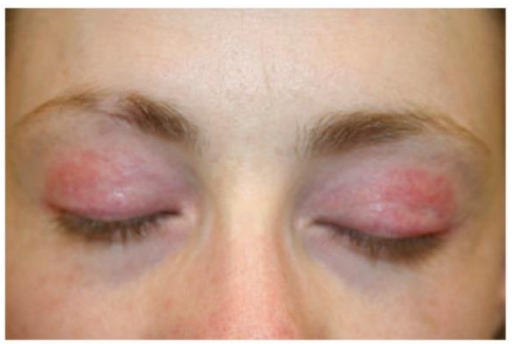
- Idiopathic inflammatory myopathies
  - **Polymyositis**
  - **Inclusion body myositis**
  - **Dermatomyositis/juvenile dermatomyositis**
- Other inflammatory conditions
  - **Anti-synthetase syndrome**
  - **Immune-mediated necrotising myopathies**
  - Vasculitis
  - Sarcoid myopathy
  - Infectious
- Differential diagnosis
  - Dystrophies
  - Myofibrillar and hereditary inclusion body myopathies

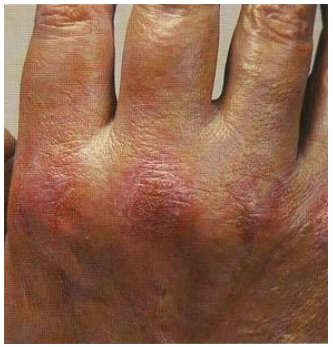
Why classify inflammatory myopathies?

Clinical feature	Polymyositis	Dermatomyositis	Juvenile dermatomyositis	Inclusion body myositis
Age at onset	> 20 years	Peak 30-50 years	Mean 7 years	> 30 years
Male: female	1:2	1:2	1:2.3	3:1
Skin involvement	No	Yes (amyopathic, dermatomyositis sine dermatitis)	Yes	No
Subcutaneous calcinosis	No	Yes	Yes	No
Pattern of weakness	Proximal, symmetrical	Proximal, symmetrical	Proximal, symmetrical	Quadriceps, distal including long finger flexors, often asymmetrical
Myalgia	Uncommon	Generalised	Generalised	Uncommom
Response to immunosuppression	Yes	Yes	Yes	No
Cardiac involvement	Rare	Rare	Rare	Rare
Association with malignancy	No	Yes (20%)	No	No
Other associated conditions	Interstitial lung disease Connective tissue disease	Interstitial lung disease Connective tissue disease	Vasculitis & intestinal infarction, arthritis, fever, abdominal pain	Connective tissue disease
Creatine kinase	Up to 50x normal	Normal - 50x normal	Normal - 50x normal	Normal - 12x normal

Diagnostic criteria: Bohan & Peter 1975

- Definition
  - Polymyositis is an inflammatory myopathy of unknown cause to which the term dermatomyositis is applied in the presence of the characteristic skin rash.
- Pathological criteria
  - Necrosis and phagocytosis
  - Regeneration
  - Atrophy – especially perifascicular
  - Internal nuclei
  - Vacuolation of fibres
  - Variation in fibre diameter
  - Mononuclear inflammatory infiltrate (perivascular most prominent)
  - Increased perimysial and endomysial connective tissue



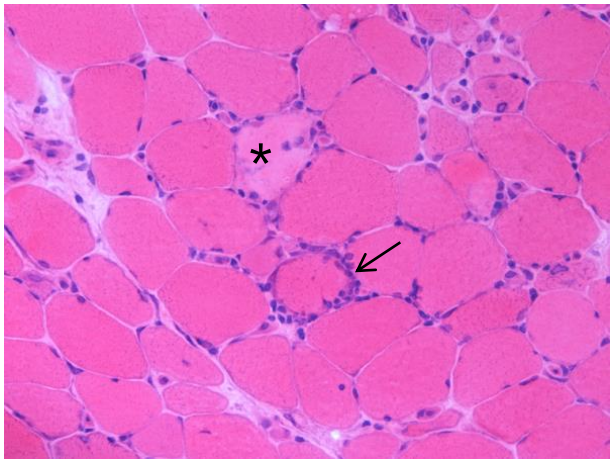


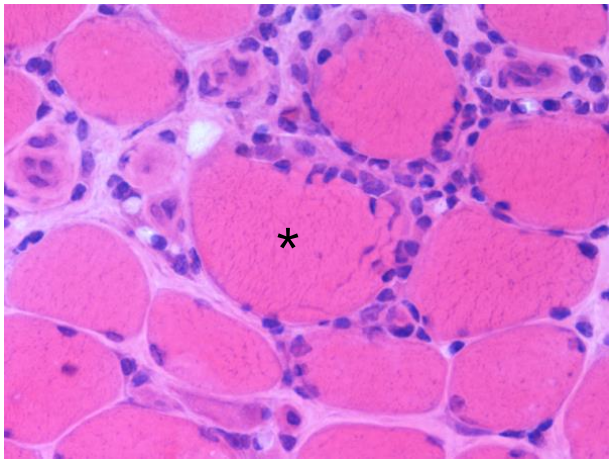
- Muscle biopsy normal in 10-15%
- Criteria do not distinguish IBM, toxic, necrotising or dystrophies with inflammation

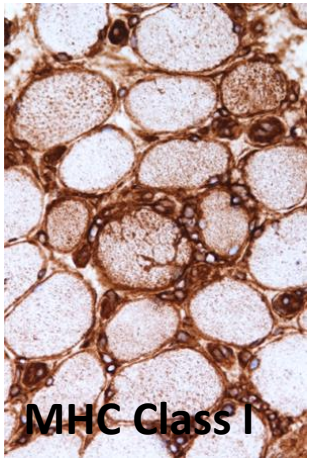
New England Journal of Medicine 1975

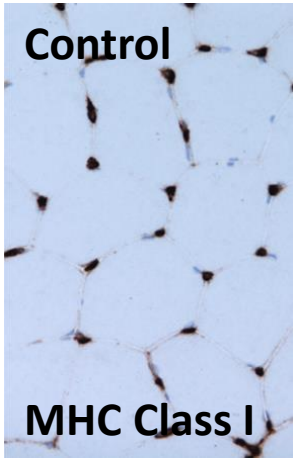
Polymyositis

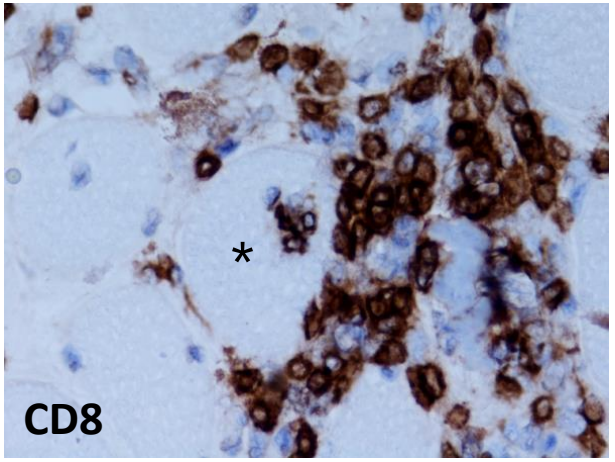
- Necrosis
- Regeneration
- Endomysial inflammation
- Invasion of intact myofibres
- CD8 positive T cells
- Up-regulation of MHC Class I
- Myeloid dendritic cells – antigen presenting
- Plasma cells











NEUROLOGY 2003;61:316–321

Polymyositis

An overdiagnosed entity

M.F.G. van der Meulen, MD; I.M. Bronner, MD; J.E. Hoogendijk, MD, PhD; H. Burger, MD, PhD; W.J. van Venrooij, PhD; A.E. Voskuyl, MD, PhD; H.J. Dinant, MD, PhD; W.H.J.P. Linssen, MD, PhD; J.H.J. Wokke, MD, PhD; and M. de Visser, MD, PhD

NEUROLOGY 2003;61:288–290

Editorial

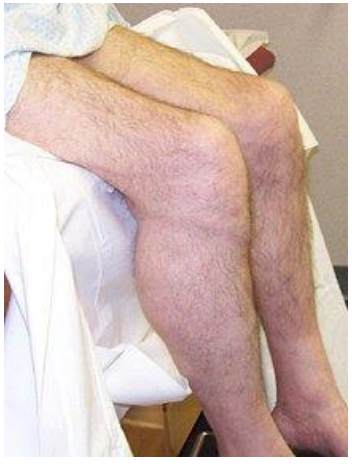
Unicorns, dragons, polymyositis, and other mythological beasts

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

- True PM is rare and the least common IIM
- Consider:
  - DM without rash
  - IBM (look for COX neg fibres and protein aggregates)
  - Immune-mediated necrotising myopathies
  - Dystrophy (FSHD, dysferlin)

Sporadic inclusion body myositis

- Most common acquired myopathy in patients over 50 years
- M:F = 3:2
- Whites > other groups
- Insidious onset
- Classically distinctive clinical pattern
  - Quads – early falls, knees buckle
  - Deep finger flexors – grip
  - Mild facial weakness, dysphagia
  - Asymmetrical involvement
- **<u>Unresponsive to immunosupression</u>**

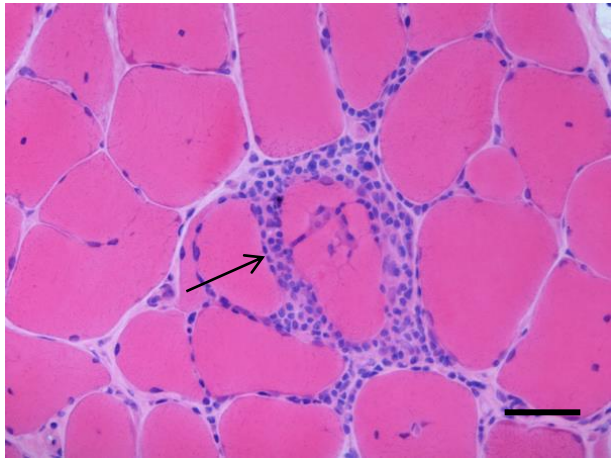


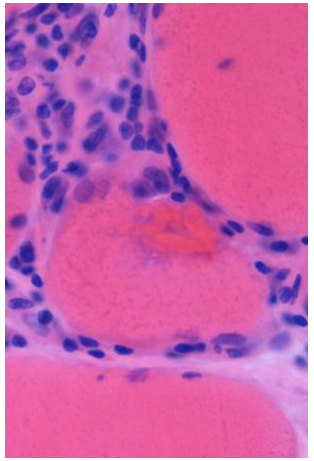
Griggs diagnostic criteria 1995:

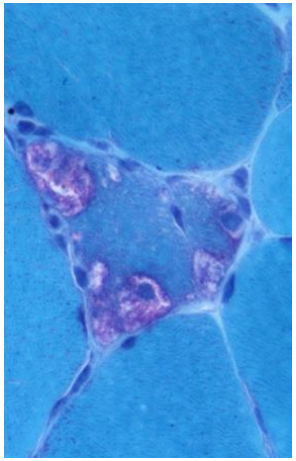
- Definite IBM
  - Invasion of non-necrotic fibres by mononuclear cells
  - Rimmed vacuoles
  - Intracellular amyloid deposits or 15-18nm tubulofilaments
  - Other clinical/ features not required if biopsy features are diagnostic
- Possible IBM
  - Invasion of non-necrotic fibres by mononuclear cells without other features AND characteristic clinical or laboratory features

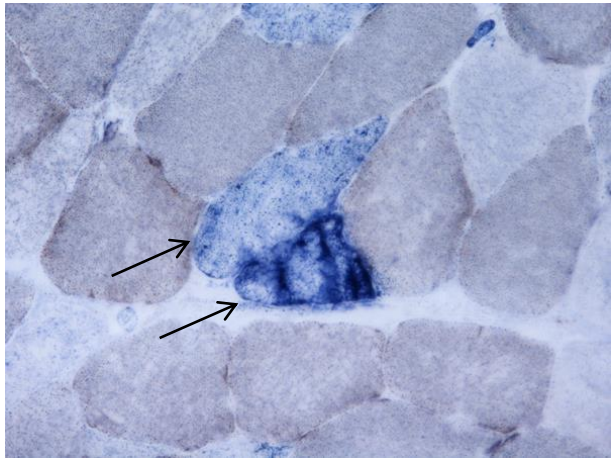
Inclusion body myositis

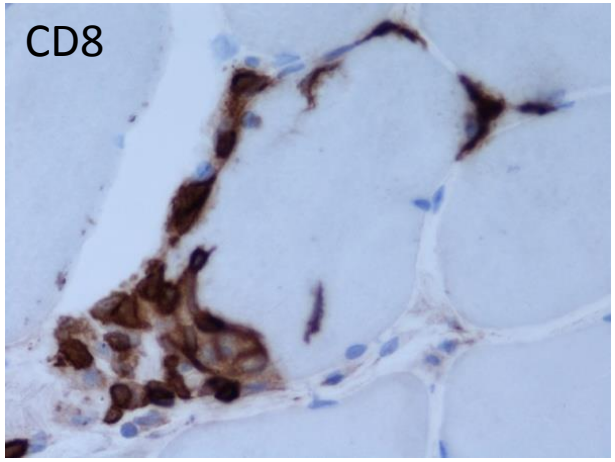
- Endomysial inflammation
- Invasion of intact myofibres
- Rimmed vacuoles
- Necrosis
- Regeneration
- Cox deficient/ragged red fibres
- T cells – CD8
- Macrophages
- Myeloid dendritic cells (antigen presenting)
- Plasma cells
- Up-regulation of MHC Class I





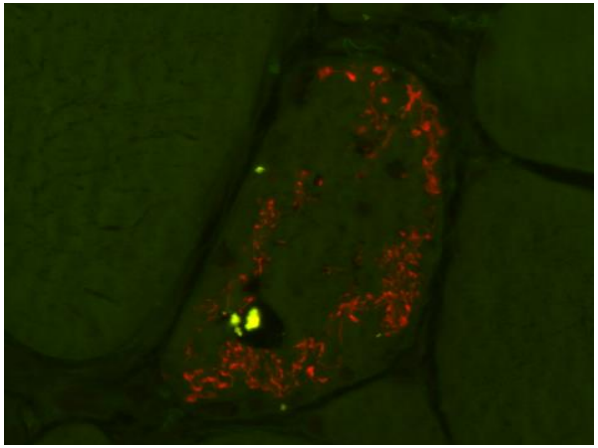


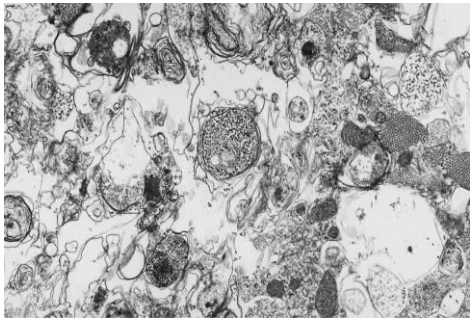


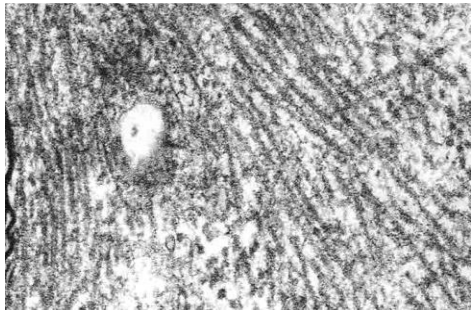


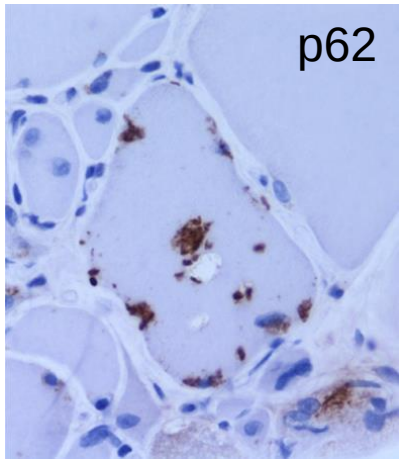
Inclusion body myositis

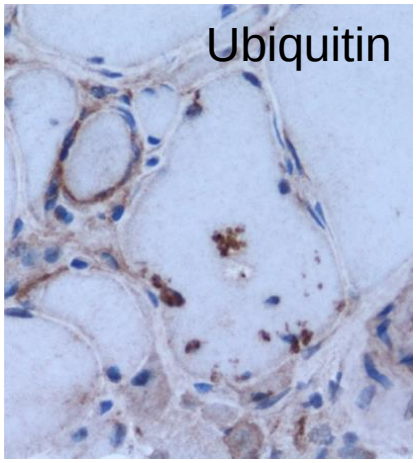
- Amyloid deposition
- Protein aggregation
  - Tau
  - Ubiquitin
  - p62
  - TDP-43
  - etc.

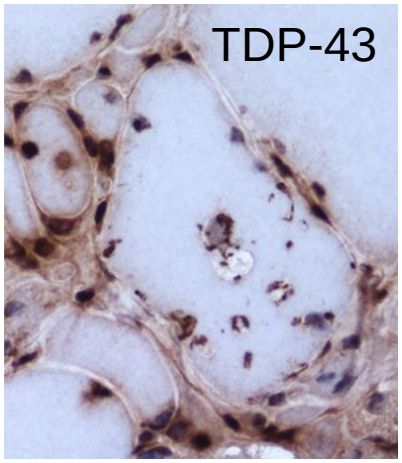












Ultrastructure:

–whorled membranous debris

–Tubulofilamentous inclusions

Pathogenesis remains uncertain: immune mediated or degenerative?

ELSEVIER
CrossMark
Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders 23 (2013) 1044–1055
NMD
www.elsevier.com/locate/nmd

Workshop report

188th ENMC International Workshop: Inclusion Body Myositis, 2–4 December 2011, Naarden, The Netherlands

M.R. Rose *, and ENMC IBM Working Group [1]

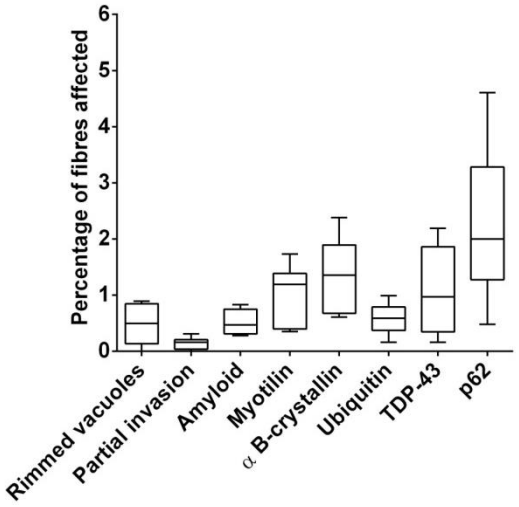
Clinical features	Classification	Pathological features
Duration of weakness >12 months	Clinicopathologically defined IBM	All of the following:
Creatine kinase ≤15× ULN		Endomysial inflammatory infiltrate
Age at onset >45 years		Rimmed vacuoles
Finger flexion weakness > shoulder abduction weakness		Protein accumulation[a] or 15–18 nm filaments
AND/OR		
Knee extension weakness ≥ hip flexor weakness		
Duration of weakness >12 months	Clinically defined IBM	One or more, but not all, of:
Creatine kinase ≤15× ULN		Endomysial inflammatory infiltrate
Age at onset >45 years		Upregulation of MHC Class I
Finger flexion weakness > shoulder abduction weakness		Rimmed vacuoles
AND		Protein accumulation[a] or 15–18 nm filaments
Knee extension weakness ≥ hip flexor weakness		
Duration of weakness >12 months	Probable IBM	One or more, but not all, of:
Creatine kinase ≤15 ULN		Endomysial inflammatory infiltrate
Age at onset >45 years		Upregulation of MHC Class I
Finger flexion weakness > shoulder abduction weakness		Rimmed vacuoles
OR		Protein accumulation[a] or 15–18 nm filaments
Knee extension weakness ≥ hip flexor weakness		

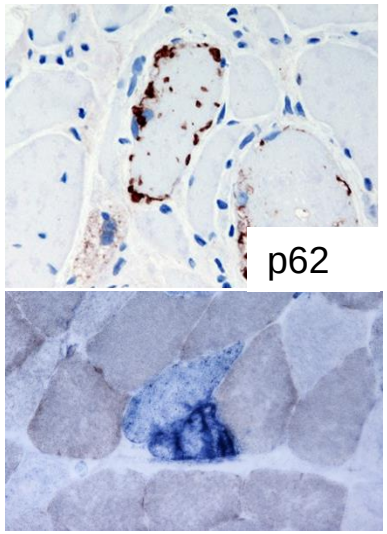
[a]Demonstration of amyloid or other protein accumulation by established methods (e.g. for amyloid Congo red, crystal violet, thioflavin T/S, for other proteins p62, SMI-31, TDP-43). Current evidence favours p62 in terms of sensitivity and specificity, but the literature is limited and further work is required. MHC Class I, Major histocompatibility complex class I; ULN, Upper limit of normal.

BMJ Open A retrospective cohort study identifying the principal pathological features useful in the diagnosis of inclusion body myositis

Stefen Brady,[1] Waney Squier,[2] Caroline Sewry,[3,4] Michael Hanna,[1] David Hilton-Jones,[5] Janice L Holton[6]

Six cases Griggs definite IBM, six normal controls





COX-/SDH+ fibres in all cases

Clinically-typical IBM with (n=15) and without (n=9) RV

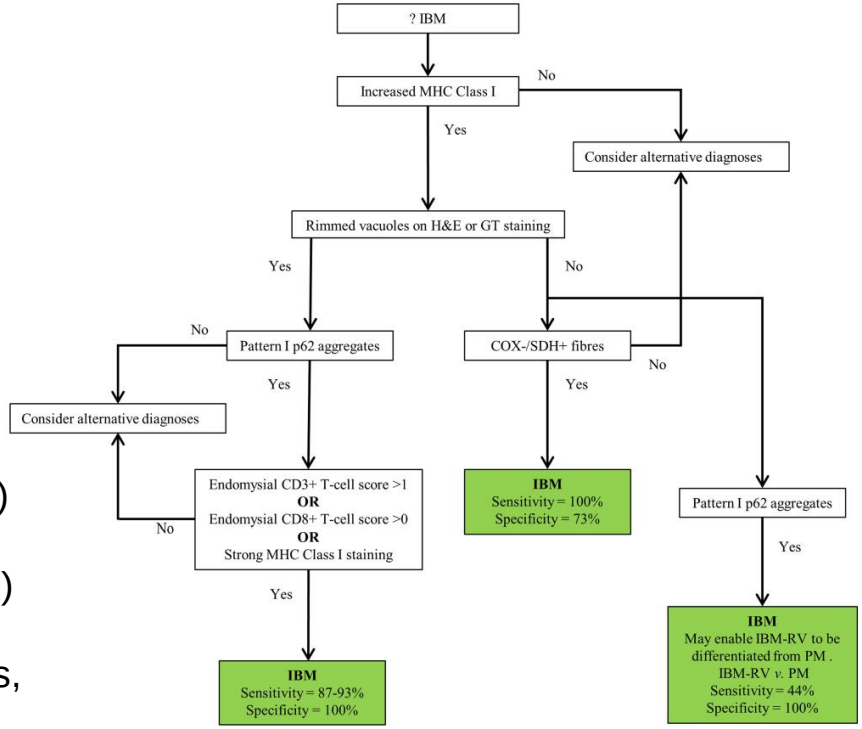
Steroid-responsive inflammatory myopathies (PM&DM; n=11)

Protein accumulation myopathies with rimmed vacuoles (n=7)

Analysed: protein aggregates (CR, IHC), COX negative fibres, MHC Class I upregulation, inflammatory infiltrate

Conclusions

- p62, TDP-43, myotilin, αBCrystallin, ubiquitin positive aggregates in IBM
- COX-/SDH+ fibres in all cases
- MHC class I is upregulated in IBM
- No pathological feature in isolation is diagnostic for IBM
- p62, MHC Class I and COX/SDH are helpful in making a diagnosis of IBM



Autoantibodies against a 43 KDa Muscle Protein in Inclusion Body Myositis

May 2011 | Volume 6 | Issue 5 | e20266
PLoS one

Mohammad Salajegheh[1,2,3]*, Theresa Lam[2], Steven A. Greenberg[1,2,3]

Methodology/Principal Findings: Plasma autoantibodies from 65 people, including 25 with IBM, were analyzed by immunoblots against normal human muscle. Thirteen of 25 (52%) IBM patient samples recognized an approximately 43 kDa muscle protein. No other disease (N = 25) or healthy volunteer (N = 15) samples recognized this protein.

Conclusions: Circulating antibodies against a 43-kDa muscle autoantigen may lead to the discovery of a novel biomarker for IBM. Its high specificity for IBM among patients with autoimmune myopathies furthermore suggests a relationship to disease pathogenesis.

Autoantibodies to Cytosolic 5′-Nucleotidase IA in Inclusion Body Myositis

ANN NEUROL 2012;00:000–000

Helma Pluk, PhD,[1]* Bas J. A. van Hoeve, MD,[2]* Sander H. J. van Dooren, PhD,[1]*
Judith Stammen-Vogelzangs,[1] Annemarie van der Heijden,[1]
Helenius J. Schelhaas, MD, PhD,[2] Marcel M. Verbeek, PhD,[2] Umesh A. Badrising, MD, PhD,[3]
Snjolaug Arnardottir, MD, PhD,[4] Karina Gheorghe,[5] Ingrid E. Lundberg, PhD,[5]
Wilbert C. Boelens, PhD,[1] Baziel G. van Engelen, MD, PhD,[2] and Ger J. M. Pruijn, PhD[1]

- Autoantibody recognising 44kDa peptide (Mup44) high titre in 33% of IBM sera (<5% in PM, DM and other controls) using immunoprecipitation assay.
- The target is cytosolic 5'-nucleotidase IA (role: metabolic regulation and cell replication)
- **May provide the first serological marker for IBM**

Brief Report

Arthritis Care & Research
DOI 10.1002/acr.22600

Article

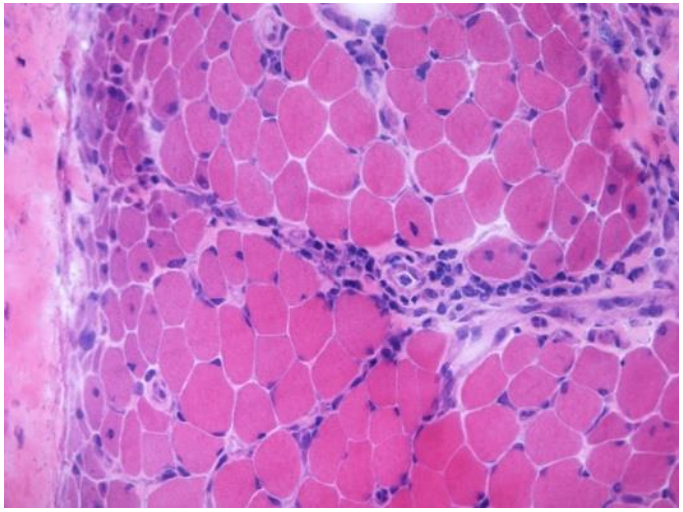
Cytosolic 5'-nucleotidase 1A is a common target of circulating autoantibodies in several autoimmune diseases

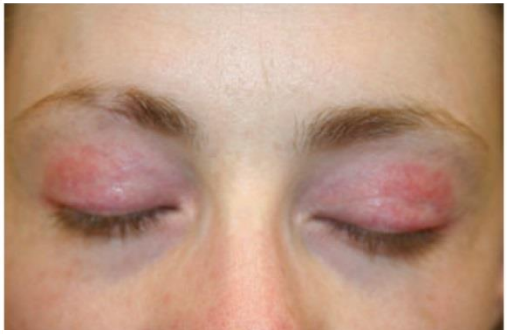
Thomas E. Lloyd*, Lisa Christopher-Stine*, Iago Pinal-Fernandez, Eleni Tiniakou, Michelle Petri, Alan Baer, Sonye Danoff, Katherine Pak, Livia Casciola-Rosen, and Andrew L. Mammen

- 61% IBM
- 5% PM
- 5% controls
- 15% DM
- 23% Sjorgren's
- 14% SLE
- Not associated with muscle disease in SLE and Sjorgren's

Dermatomyositis

- Occurs in adults and children
- May be associated with neoplasia in adults
- Juvenile dermatomyositis
  - Commonest childhood IIM
  - Onset before age 16 years
  - Incidence 2-3/million/year
  - Bohan and Peter diagnostic criteria





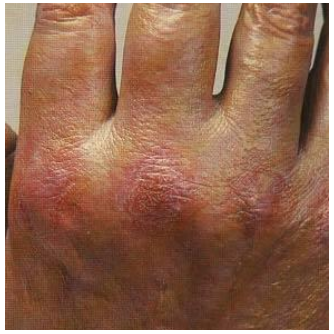
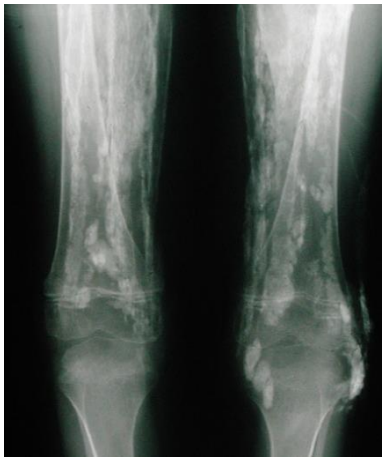
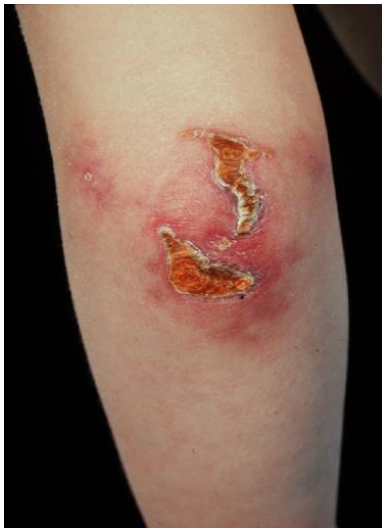


Table 1 | Clinical characteristics and mortality associated with juvenile and adult DM

Disease features	Juvenile DM	Adult DM
Peak age of onset	7 years[6,10–12]	30–50 years[13]
Proportion of IMM cases	80–95%[19,127,128]	35–50%[129]
Proximal weakness	85–95%[10,12]	88%[130]
Characteristic rash	Gotton papule: 73–91%[7,131] Heliotrope rash: 62–83%[7,131] Malar rash: 42–57%[7,131] Abnormal nailfold capillaries: 80%[131]	Gottron papule: 54%[130] Heliotrope rash: 74%[130] Malar rash: data not available Abnormal nailfold capillaries: 43%[132]
Calcinosis or ulceration	26–40%[19,131,133]	2–16%[19,133]
Refractory or chronic disease	59–63%[12,134]	63%[133]
Malignancy	1%[12,133]	15–24%[41,133]
Myositis-specific antibodies	2–40%[19,59]	48–70%[38,59]
Interstitial lung disease	7–19%[29]	35–40%[30]
Gastrointestinal disease	2–3%[4,19]	1%[19]
Raynaud disease	10%[135]	11%[136]
Mortality	<5%[12,13,133]	21%[133]

Abbreviations: DM, dermatomyositis; IMM, inflammatory myopathic myositis.



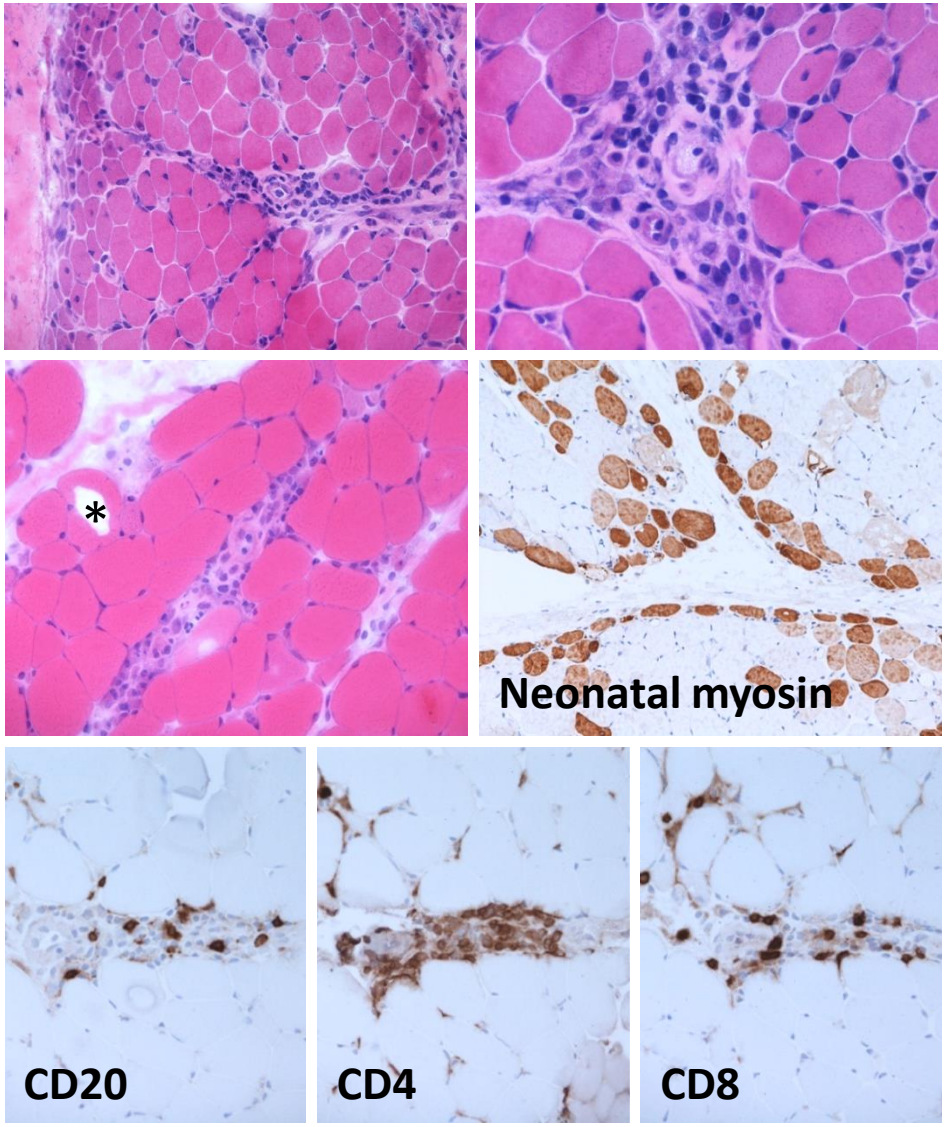


Vascular pathology more prominent in JDM than in adults

Robinson and Reed Nat Rev Rheumatol. 2011; 7(11):664-75..

Dermatomyositis: biopsy features

- Perimysial and perivascular inflammation
- Perifascicular atrophy
- Fibre necrosis
- Fibre regeneration
- Vacuolation
- B Cells
- T cells (CD4>CD8)
- Macrophages
- Plasmacytoid dendritic cells
- Vascular abnormalities
- C5b9 capillary deposition (early event)
- MHC class I expression
- Infarction
- Calcinosis



Dermatomyositis: biopsy features

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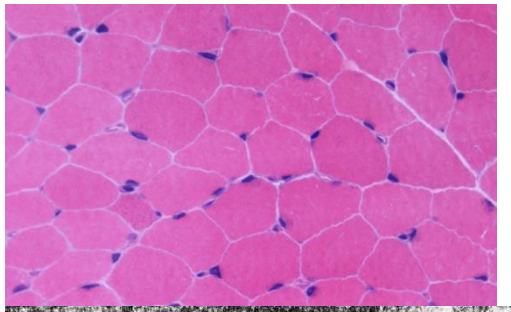

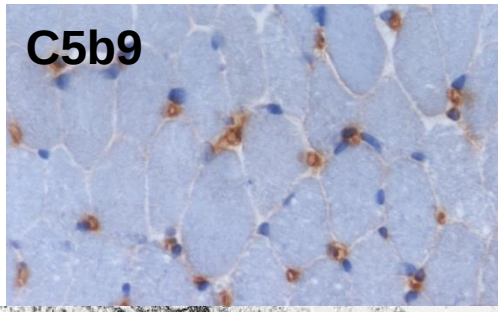

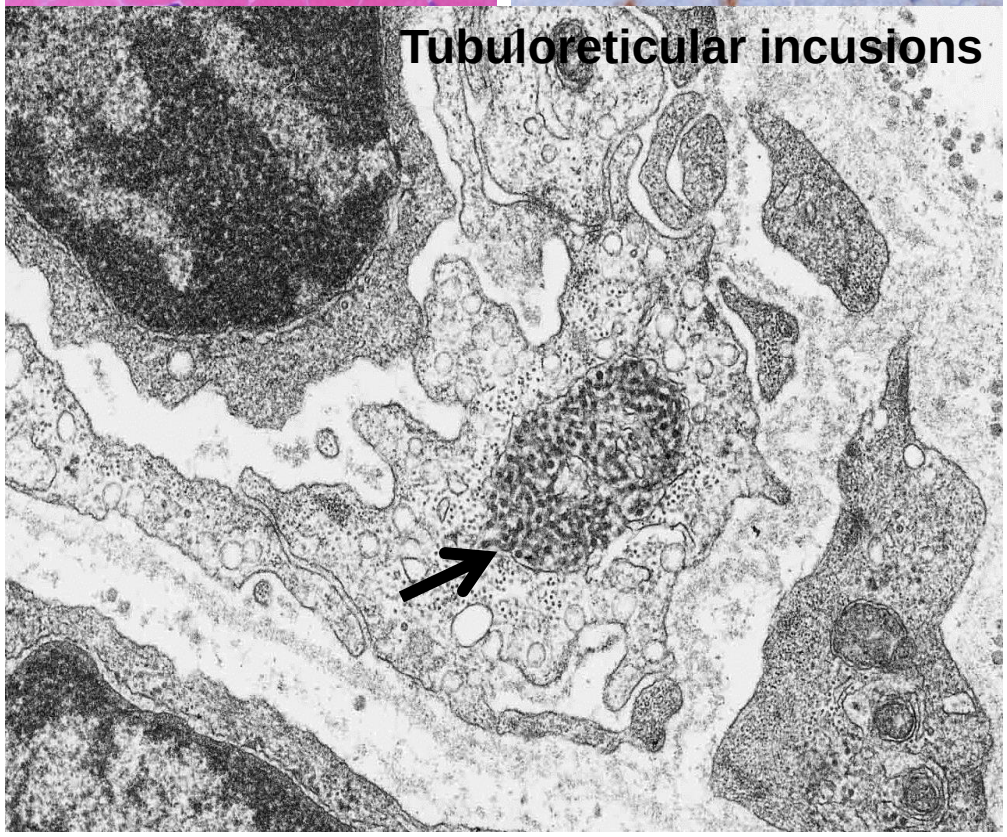

Validation of a score tool for measurement of histological severity in juvenile dermatomyositis and association with clinical severity of disease

Hemlata Varsani,[1] Susan C Charman,[2] Charles K Li,[1] Suely K N Marie,[3] Anthony A Amato,[4] Brenda Banwell,[5] Kevin E Bove,[6] Andrea M Corse,[7] Alison M Emslie-Smith,[8] Thomas S Jacques,[9] Ingrid E Lundberg,[10] Carlo Minetti,[11] Inger Nennesmo,[12] Elisabeth J Rushing,[13] Adriana M E Sallum,[14] Caroline Sewry,[15] Clarissa A Pilkington,[16] Janice L Holton,[17] Lucy R Wedderburn,[1] the UK Juvenile Dermatomyositis Research Group

Ann Rheum Dis. 2013 Epub

- Devise a reliable method to measure 'severity' of pathological change in JDM (not diagnostic tool)
- Test whether severity on biopsy correlates with clinical severity of disease
- Ultimately: improve management of JDM

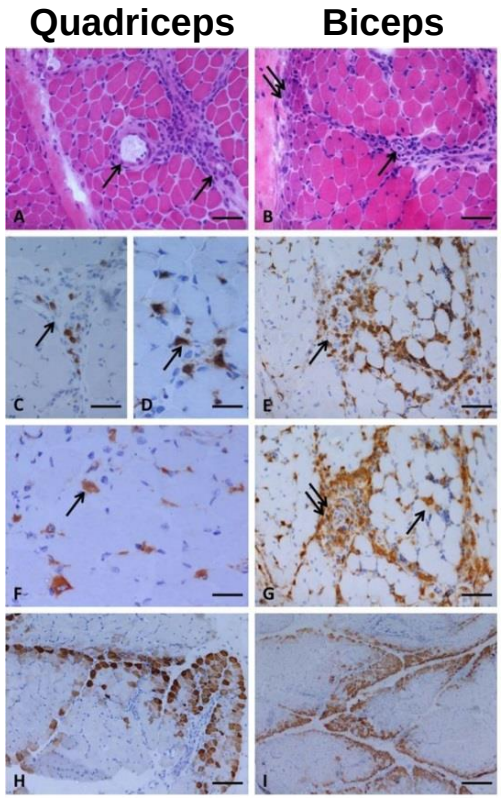

Table 4 Associations between manual muscle testing (MMT) and items of the modified score tool for the combined cohort (London and Brazil)

Domain and item	Knee extensor MMT r*	Knee extensor MMT p Value†	Elbow flexion MMT r*	Elbow flexion MMT p Value†
Inflammatory domain				
CD3+ endomysial infiltration	−0.40	0.006	−0.44	0.003
CD3+ perimysial infiltration	−0.40	0.007	−0.41	0.006
CD68+ endomysial infiltration	−0.53	0.002	−0.62	<0.001
Inflammatory domain total (modified)	−0.56	0.001	−0.59	<0.0001
Muscle fibre domain				
Perifascicular atrophy	−0.30	0.040	−0.40	0.006
Neonatal myosin	−0.57	0.001	−0.57	<0.001
Regeneration/degeneration/necrosis: perifascicular	−0.38	0.009	−0.53	0.002
Muscle fibre domain total (modified)	−0.45	0.002	−0.60	<0.0001
Histopathologists' Visual Analogue Score for severity	−0.45	0.002	−0.62	<0.0001

*Spearman's rank correlation coefficient.
†For test of independence.

- **Biopsy features correlate with measures of muscle strength in JDM**

Myositis specific antibodies

Antibody	Target antigen	Clinical association	Frequency in IIM patients
Antibodies associated with anti-synthetase syndrome			
Anti-amino-acyl-tRNA synthetase (8 identified)	Amino-acyl-tRNA synthetase	Myositis, interstitial lung disease, Raynaud's phenomenon, arthritis. mechanic's hands, fever, ±DM skin rash	Overall: 30-40% (JDM: 1-3%)
-Jo-1	-Histidyl	Myositis, interstitial lung disease	Jo-1: 15-20%
Others: PL7 etc	-Threonyl etc		Others in <5% of cases
Antibodies associated with dermatomyositis			
Anti-Mi-2	NuRD	Decreased risk of malignancy, more severe rash, response to steroids,	<10% (JDM: 4-10%)
Anti-p155/140	TIF1 family	Children: ulceration Adults: malignancy	13-21% (JDM: 22-29%)
Anti-p140	NXP2	Children: calcinosis Adults: interstitial lung disease	<5% (JDM: 23%)
Anti-SAE	SAE	Rash precedes myositis	<5% (JDM: <1%)
Anti-CADM-140	MDA-5	Clinically amyopathic DM, interstitial lung disease	50-73% (JDM: not known)

Tansley *et al. Arthritis Research & Therapy* 2014, **16**:R138
http://arthritis-research.com/content/16/4/R138

arthritis research&therapy

RESEARCH ARTICLE Open Access

Anti-MDA5 autoantibodies in juvenile dermatomyositis identify a distinct clinical phenotype: a prospective cohort study

Sarah L Tansley[1], Zoe E Betteridge[2], Harsha Gunawardena[3], Thomas S Jacques[4], Catherine M Owens[5], Clarissa Pilkington[6], Katie Arnold[7], Shireena Yasin[7], Elena Moraitis[6], Lucy R Wedderburn[8], and Neil J McHugh[9*] on behalf of UK Juvenile Dermatomyositis Research Group

- Anti-melanoma differentiation associated gene 5
- East Asia adults: 19-35% DM, amyopathic, rapidly progressive ILD
- Caucasian adults: little myositis, ILD (no rapid progression), skin ulceration, painful palmar papules
- To determine the clinical phenotype and pathological features in caucasian JDM

Table 1 Demographic characteristics of the 285 patients in this study

	All JDM patients, n = 285	Anti-MDA5-positive patients, n = 21
Female, number (%)	206 (72)	15 (71)
Caucasian, number (%)	220 (78)	16 (76)[b]
Diagnosis, number (%)[a]		
Dermatomyositis	242 (85)	21 (100)
Polymyositis	1 (0.4)	0
Overlap	33 (12)	0
Age at disease onset, years, median (IQR)	6.3 (IQR 4 to 10)	6.6 (IQR 4 to 10)
Length of follow up, years, median (IQR)	9 (IQR 5 to 12)	8 (IQR 5 to 11)
Highest ever CK, u/l, median (IQR)	220 (IQR 111 to 1132)	129 (88 to 157)

Arthritis Research & Therapy 2014, **16**:R138

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- 7.4% of JDM patients
- Associated with:
  - Skin ulceration (P=0.03)
  - Oral ulceration (P=0.01)
  - Arthritis (P<0.01)
  - Clinically milder (CMAS score) (P=0.03)
  - 4/21 had ILD (not rapidly progressive)
  - Histologically less severe – often very subtle changes (JDM biopsy score, P<0.01)

Screening for MDA5 antibodies helpful to identify the group with milder clinical phenotype, possible ILD and who may have only subtle histological features

Autoantibody status may relate to clinical phenotype, biopsy features and treatment response – ongoing area of research

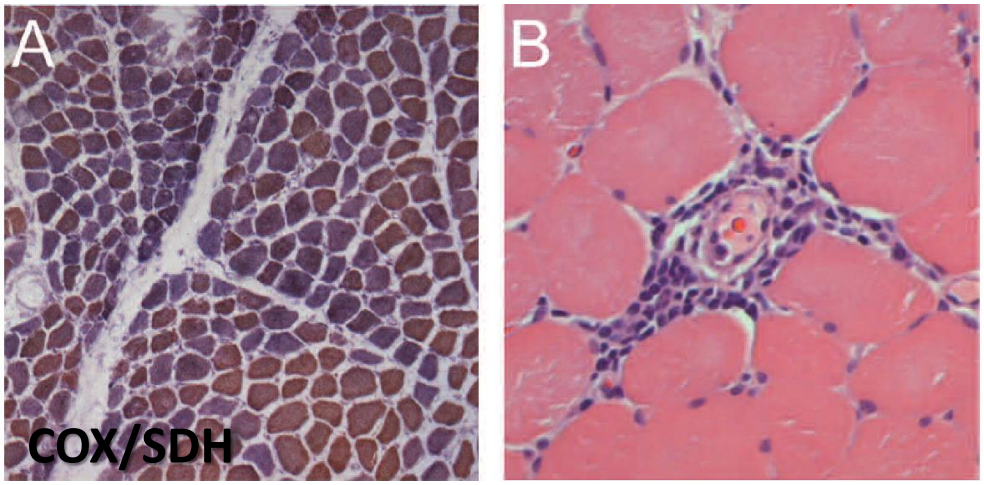
The Prevalence of Individual Histopathologic Features Varies according to Autoantibody Status in Muscle Biopsies from Patients with Dermatomyositis

Iago Pinal-Fernandez, Livia A. Casciola-Rosen, Lisa Christopher-Stine, Andrea M. Corse, and Andrew L. Mammen

J Rheumatol 2015;42:1448–54

- 91 DM
- TIF1γ: mitochondrial dysfunction
- NXP2: less primary inflammation
- Mi-2: more primary inflammation
- PM-scl: more primary inflammation

TIF1γ



Mitochondrial dysfunction
Perifascicular atrophy
Perivascular inflammation

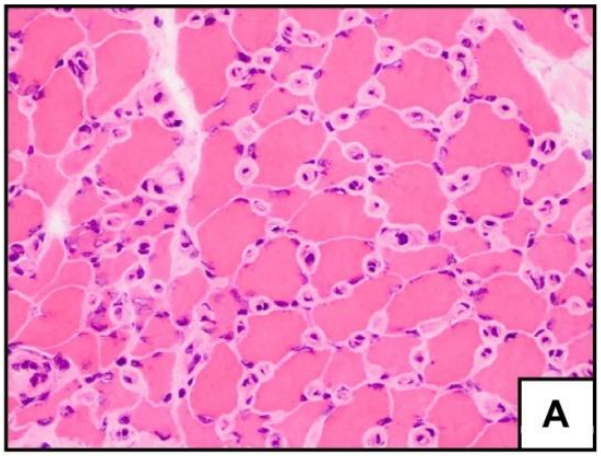
- Considerable variability within each group: histology does not clearly predict antibody status

Immune-mediated necrotising myopathies

- Important group to recognise
- May respond to immunosupression
- May be associated with neoplasia

Immune-mediated necrotising myopathies

- Necrotising myopathies associated with
  - Signal recognition particle antibodies (SRP)
  - 3-hydroxy-3-methylglutaryl-CoA reductase antibodies (HMGCR). Usually related to statin therapy (60-70%)
  - Paraneoplasia
  - Anti-synthetase syndrome (? separate group)
  - Pipestem capillaries
- Histological features:
  - Many necrotic fibres
    - scattered (perifascicular or regional?)
  - Sparse lymphocytic inflammation
  - C5b9 capillary deposition may occur
  - Pipestem capillaries may be seen
- Differential diagnosis
  - Other IIMs
  - Dystrophies such as FSHD and dysferlinopathy



Pipestem capillaries

Immune-mediated necrotising myopathies

	SRP antibodies	HMGCR antibodies	Antisynthetase syndrome	Pipestem capillaries	Paraneoplastic
Auto-antibody	Signal recognition peptide	3-hydroxy-3-methylglutaryl-CoA reductase	Jo-1 (histidyl tRNA synthetase) commonest, PL-7 etc	Not described (6 cases only in literature)	Usually negative
CK	2,000 – 30,000	1,000 -25,000	2,000 – 20,000	600 – 2,000	1,700 – 25,000
Type of myopathy	Necrotising	Necrotising	Necrotising (perifascicular)	Necrotising	Necrotising (regional?)
Cellular infiltrate: Distribution	Endo- and perimysial	Endo- and perimysial	Perimysial predominant	Endo- and perimysial	Endo- and perimysial
Cellular infiltrate: Cell type	Macrophage with myophagocytosis	Macrophage with myophagocytosis	Macrophage with myophagocytosis	Macrophage with myophagocytosis	Macrophage with myophagocytosis
MHC class I	Variable (may be absent)	In 50%	Strong ubiquitous	In some	In some
MAC	Variable capillary (may be absent)	Variable capillary (may be absent)	Capillaries and sarcolemma (perifascicular)	Strong capillary	Strong capillary
Perimysial alkaline phosphatase	Negative	Negative	Positive	Negative	Positive

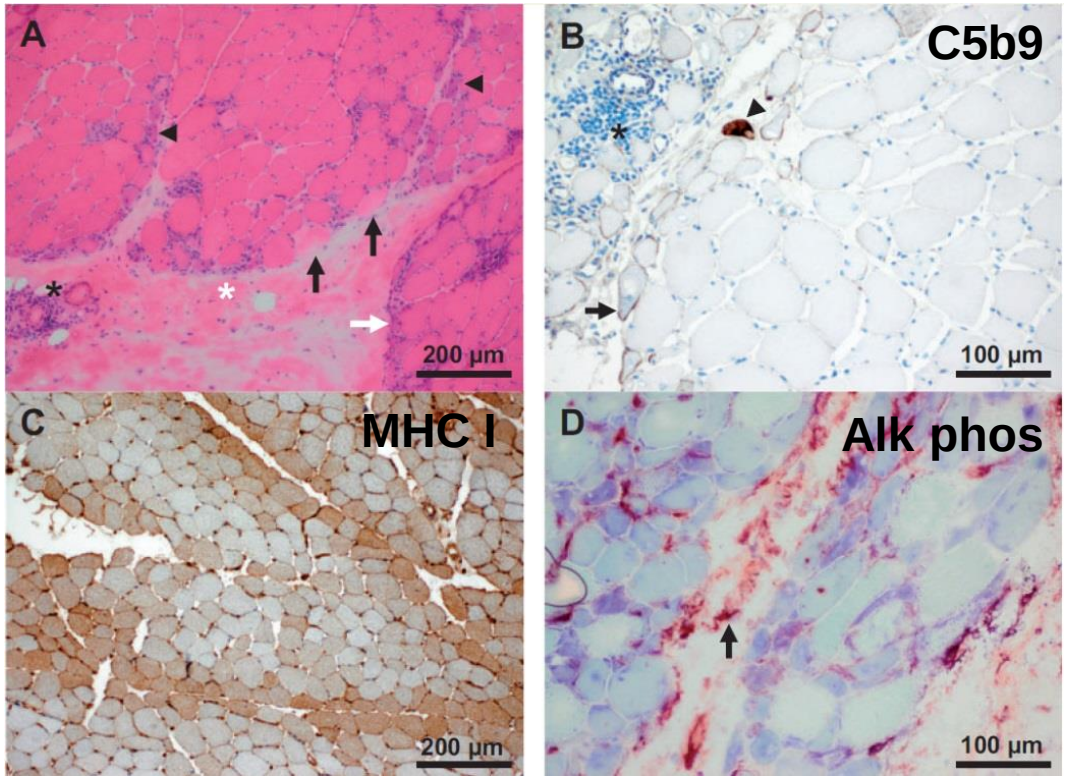
Adapted from: Stenzel W et al NAN (2012) ***38:*** *632-646*

REPORT BRAIN 2015: 138; 2485–2492 | 2485

Anti-Jo-1 antibody-positive patients show a characteristic necrotizing perifascicular myositis

Lénaig Mescam-Mancini,[1,*] Yves Allenbach,[2,3,*] Baptiste Hervier,[2,4,*] Hervé Devilliers,[5] Kuberaka Mariampillay,[2] Odile Dubourg,[6] Thierry Maisonobe,[6] Romain Gherardi,[7] Paulette Mezin,[1] Corinna Preusse,[3] Werner Stenzel[3] and Olivier Benveniste[2]

- 53 Jo-1: biopsy features analysed
- Compared with:
  - 19 Jo-1
  - DM 20
  - IMNM 21
  - sIBM 22



REPORT
BRAIN 2015: 138; 2485–2492 | 2485

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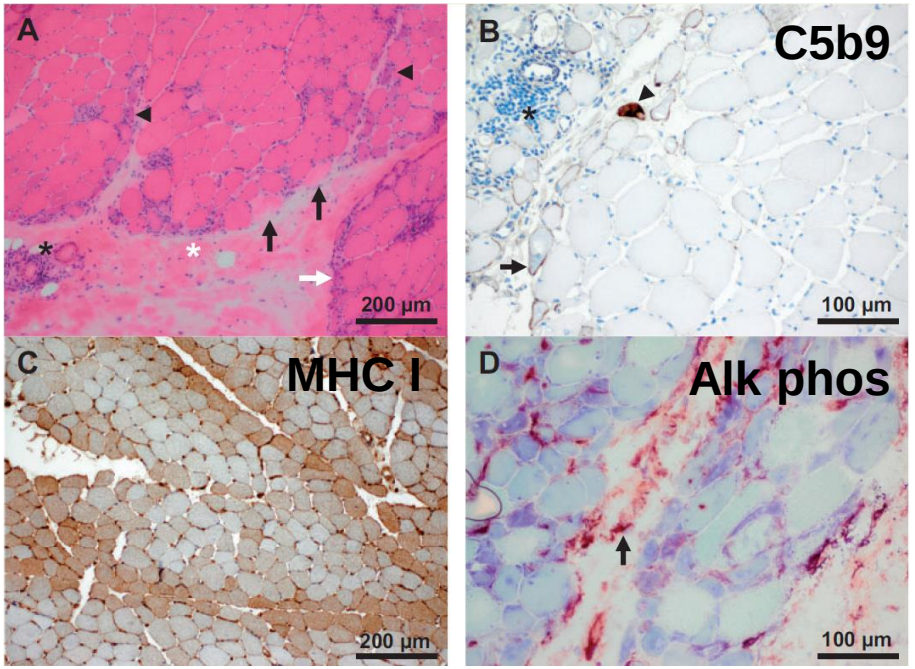
Table 2 Perifascicular pattern in Jo-1 and DM patients

Pathologic features	DM ($n = 20$)	Jo-1 ($n = 19$)
Myofibre necrosis in perifascicular regions	7 (35%)	15 (79%)**
Myofibre atrophy in perifascicular regions	17 (85%)*	12 (63%)
Perimysial fragmentation	9 (45%)	14 (74%)
Perimysial inflammatory infiltrates	20 (100%)	19 (100%)
HLA enhancement in perifascicular regions	17 (85%)	15 (79%)
Sarcolemmal positivity for C5b-9 in perifascicular regions	10 (50%)	14 (74%)

*$P < 0.05$; **$P < 0.01$ calculated after multivariate analysis.



Jo-1 characterised by: necrotising perifasicular myositis

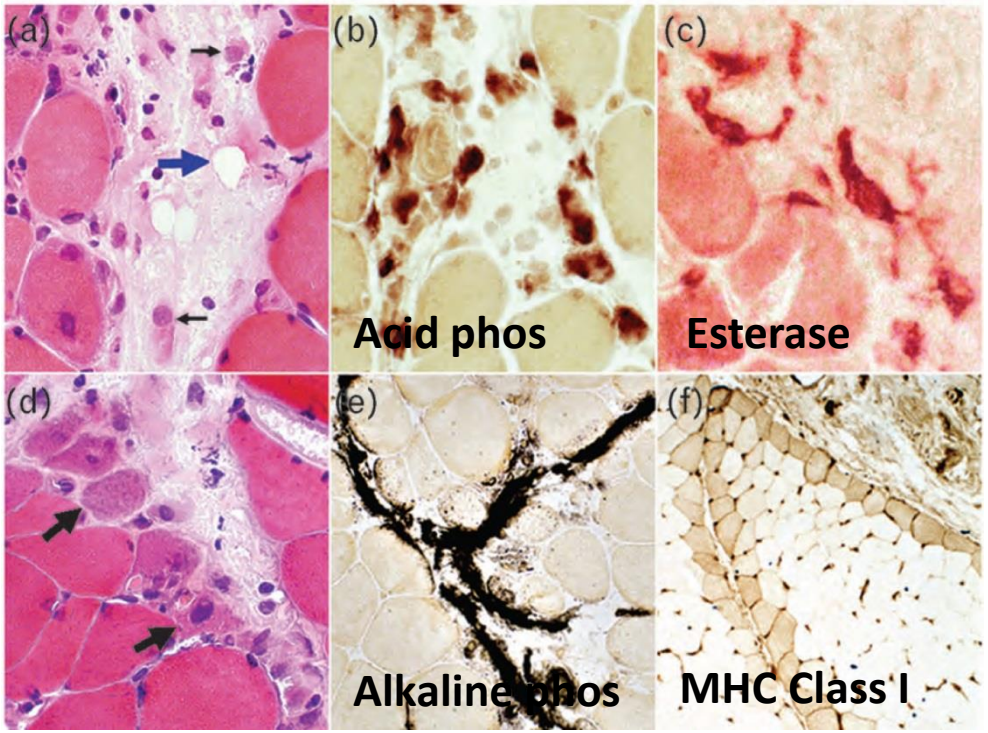
Anti-synthetase syndrome

	Antisynthetase syndrome
Auto-antibody	Jo-1 (histidyl tRNA synthetase) commonest
CK	2,000 – 20,000
Type of myopathy	Necrotising (perifascicular)
Cellular infiltrate: Distribution	Perimysial predominant
Cellular infiltrate: Cell type	Macrophage with myophagocytosis
MHC class I	Strong ubiquitous
MAC	Capillaries and sarcolemma (perifascicular)
Perimysial alkaline phosphatase	Positive
Perimysial disruption	Yes

Acquired immune and inflammatory myopathies: pathologic classification

Alan Pestronk[a,b,c]

Current Opinion in Rheumatology 2011, 23:595–604



Immune myopathy with perimysial pathology (IMPP)

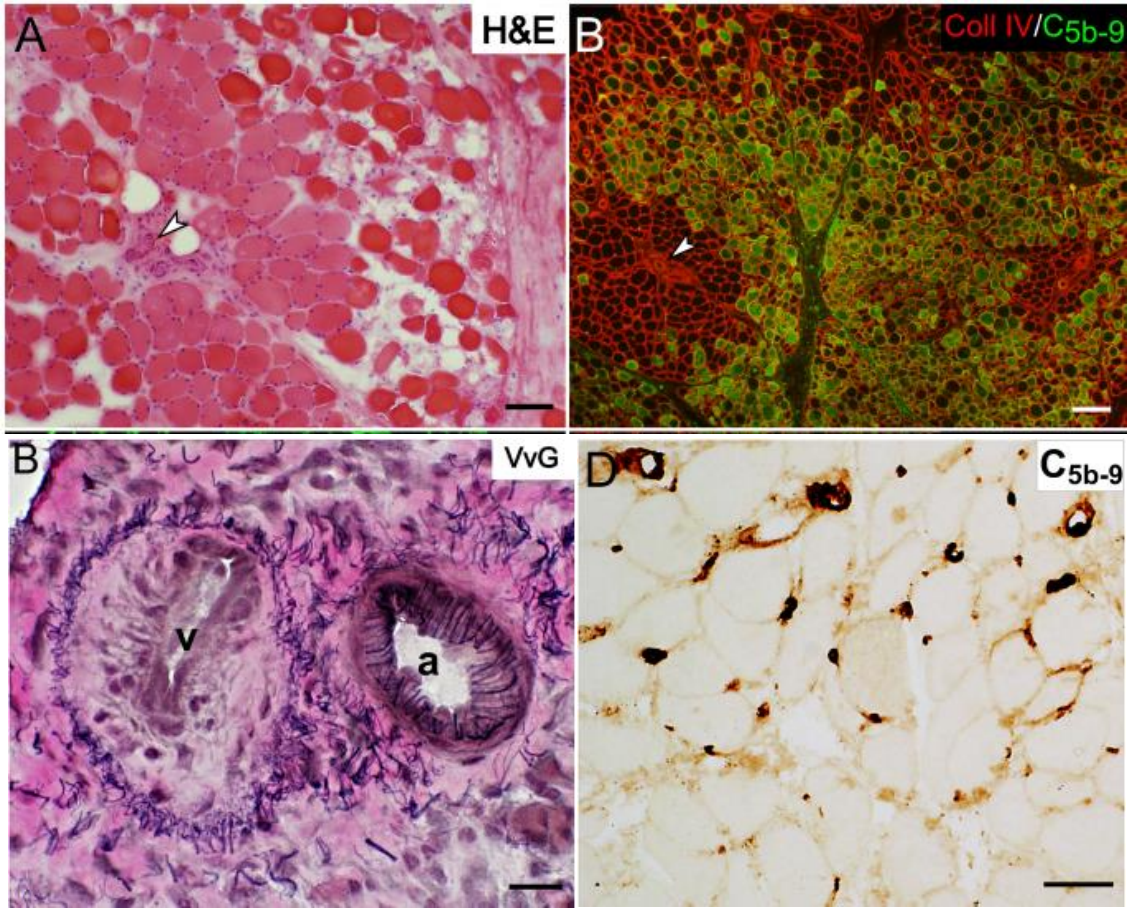
Associated with anti-synthetase antibodies

Regional Ischemic Immune Myopathy: A Paraneoplastic Dermatomyopathy

Chunyu Cai, MD, PhD, Ali Alshehri, MD, Rati Choksi, MS, and Alan Pestronk, MD

J Neuropathol Exp Neurol 2014, 73 1126-1133

- 7 patients (5 F)
- Onset 41-92 years
- Proximal weakness
- Rapid progression (up to 6 weeks)
- Rash 2/7 (face, chest, dorsal arms and hands
- Myalgia
- Neoplasm 5/7
- CK 145 – 217,000



Regional ischaemic damage

Regional Ischemic Immune Myopathy: A Paraneoplastic Dermatomyopathy

Chunyu Cai, MD, PhD, Ali Alshehri, MD, Rati Choksi, MS, and Alan Pestronk, MD

J Neuropathol Exp Neurol 2014, 73 1126-1133

	Dermatomyositis Classical	Anti-synthetase syndrome	Neoplasia associated	MDA5 Antibody
Muscle fibers				
Pathology	Atrophy COX stain reduced Caveolin-3 aggregates	Necrosis	Necrosis	NA
Pathology distribution	Perifascicular Near avascular perimysium	Near perimysium	Regional clusters Border zones	NA
Inflammation	Location: Perivascular Type: Lymphocytes B and T cells	Location: Perimysial Type: Histiocytes	Location: Veins Type: Leukocytes	NA
Vessel pathology				
Intermediate-sized			Leukocytes in wall	
Perimysial connective tissue	Normal	Fragmented histiocytic cells	Normal	NA
Clinical associations	Onset age: Child and adult Skin: Heliotrope rash Extensor limb surface Weakness Calcinosis Serum CK: Normal or Mildly high	Onset age: Adult > child Skin: Mechanic's hands Lungs: Interstitial fibrosis Weakness Neoplasm: Rare Antibodies: tRNA synthetase Aldolase: May be selectively high	Onset age: Late adult Skin: Rash on face, trunk, and limbs Weakness Neoplasm: Often Serum CK: Often high	Onset age: Adult Skin: Ulcers Palmar papules Alopecia Lungs: Interstitial fibrosis Strength: Normal Neoplasm: No Aldolase: May be selectively high
References	(1, 10)	(3)	Current series	(19)

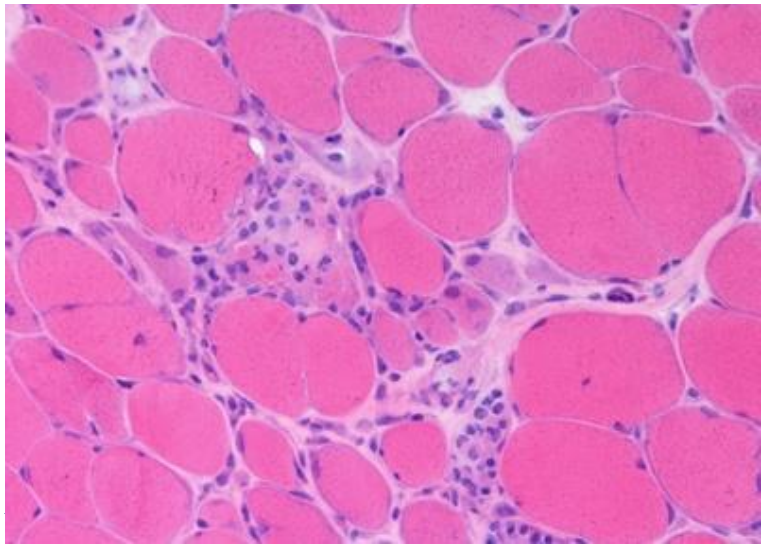
Others?

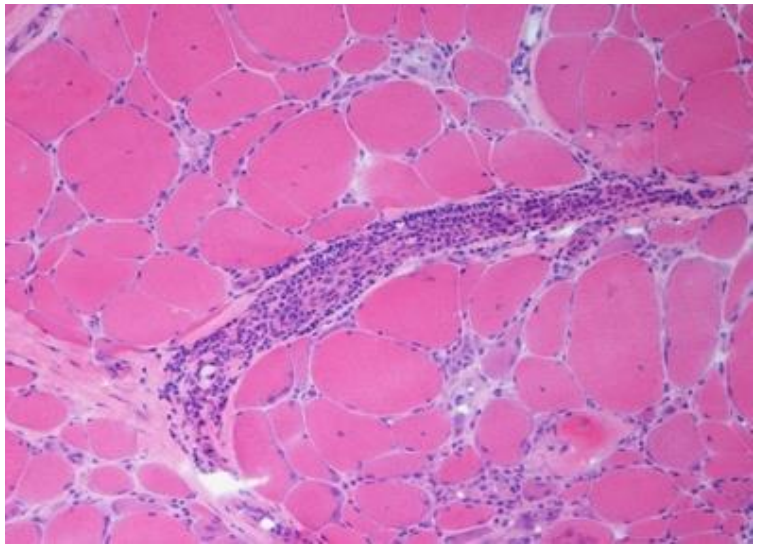
CK, creatine kinase; COX, cytochrome oxidase; DM-VP, dermatomyositis with vasculopathy; IMPP, immune myopathy with perimysial pathology; NA, not applicable; RIIM, regional ischemic immune myopathy.

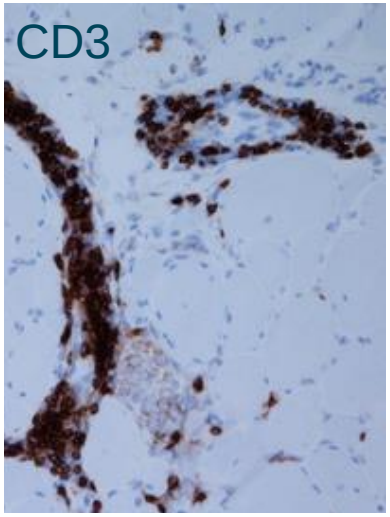
Differential diagnosis of idiopathic inflammatory myopathies

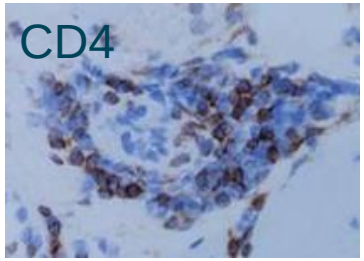
- Dystrophies
  - Facioscapulohumeral muscular dystrophy
  - Dysferlinopathy
- Myofibrillar myopathies and hereditary inclusion body myopathies

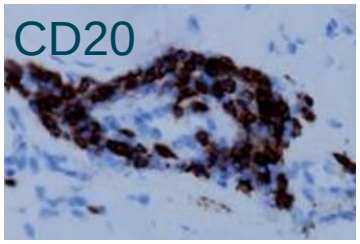
Dysferlinopathy (LGMD 2B/Miyoshi myopathy)

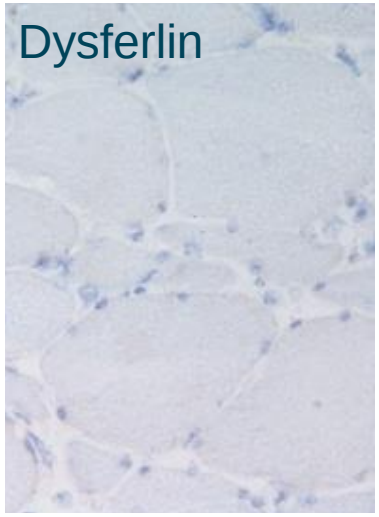


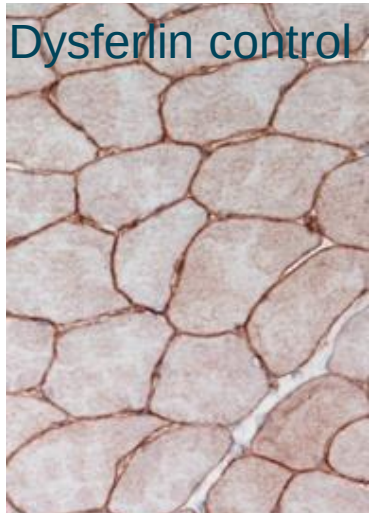








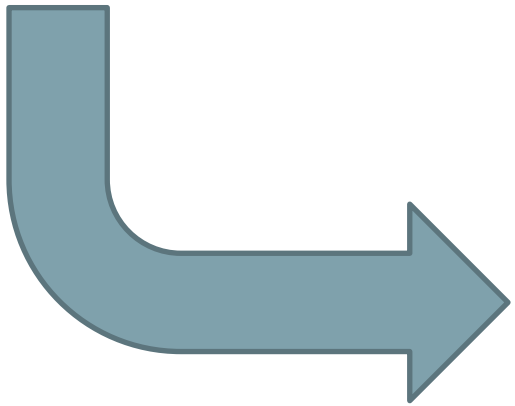




Homozygous for *DYSF* sequence variant c.4200dupC (p.Ile1401HisfsX7) exon 39

Classification of inflammatory myopathies: an evolving field

- Polymyositis
- Inclusion body myositis
- Dermatomyositis



- Polymyositis
- Inclusion body myositis
- Dermatomyositis
  - Antibody specific variants
    - MDA5
    - Others?
- Antisynthetase syndrome
- Immune mediated necrotising myopathies
  - Anti-SRP
  - Anti-HMGCoAR
  - Pipestem capillaries
  - Neoplasia?
- Regional ischaemic immune myopathy
  - Neoplasia?

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