# Update on idiopathic inflammatory myopathies

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# Learning objectives

At the end of this lecture

- the learner is able to diagnose an idiopathic inflammatory myopathy (IIM)
- the learner is able to distinguish the treatable IIMs from inclusion body myositis (IBM)
- the learner is able to treat IIMs

# Disclosures

- Participation in Advisory Board meetings with Medimmune, Neuraltus.
- Member of the DMC of a Lilly study.
- PI Novartis study on IBM

# Outline of the presentation

- Classification
- Diagnosis
- Therapy
- Prognosis

# Diagnostic criteria
# Polymyositis and Dermatomyositis

Bohan and Peter - NEJM 1975;292:344

- Progressive (over weeks to months) symmetrical limb-girdle and neck flexor muscle weakness
- Muscle biopsy evidence of necrosis, phagocytosis, regeneration, perifascicular atrophy, and an inflammatory exsudate, often perivascular
- Increased serum CK activity
- EMG abnormalities: short-duration, low-voltage MUAPs and spontaneous activity
- Dermatological features: lilac discoloration eyelids, Gottron's sign, and erythematous dermatitis of knees, elbows, upper part torso, face, and neck.

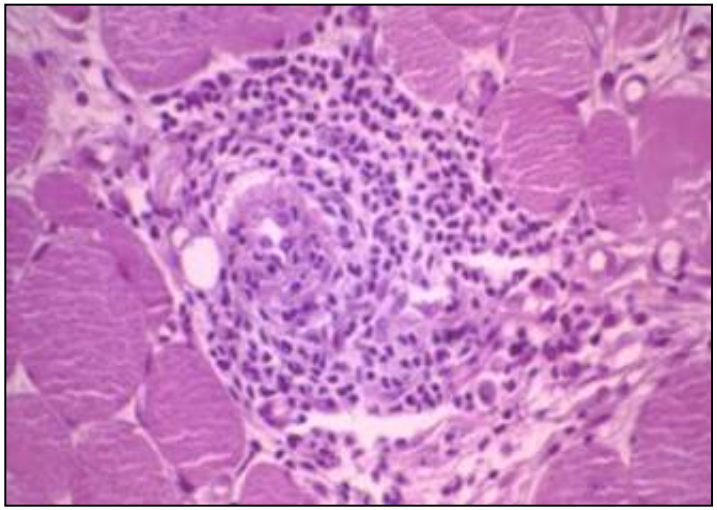
# Bohan and Peter
# PM/DM Criteria - Limitations

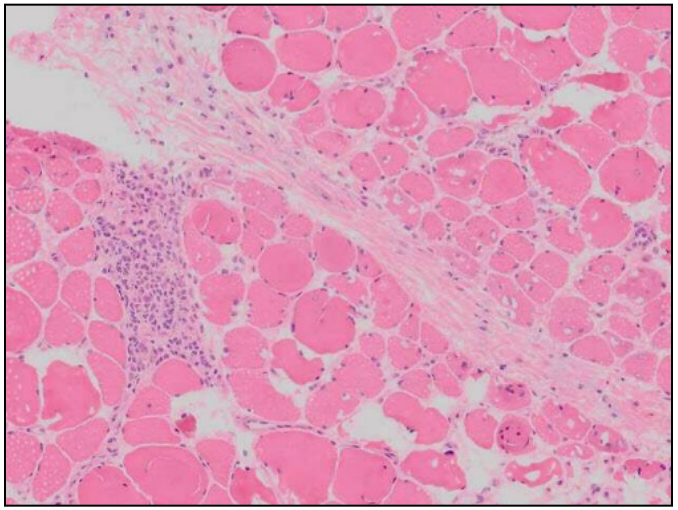
- Case series and data developed from a single institution and based on clinical observations
- No clear instructions as to how to rule out all other forms of myopathy, like sIBM and some muscular dystrophies.
- Most criteria non-specific

# Alternative classification based on histopathology

Engel and Arahata, Ann Neurol 1984

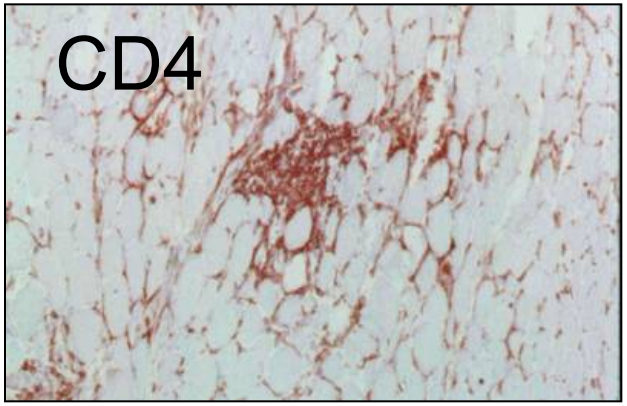
## Dermatomyositis

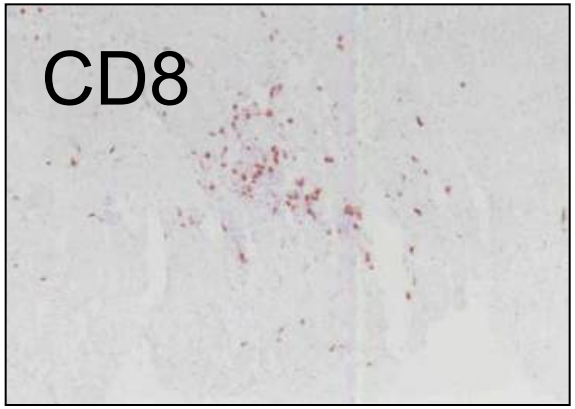




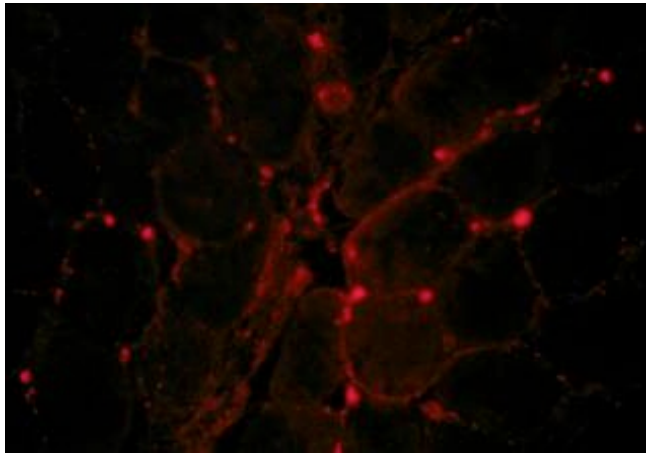
Cell infiltrate usually at perivascular and perimysial sites, note perifascicular atrophy

# Dermatomyositis



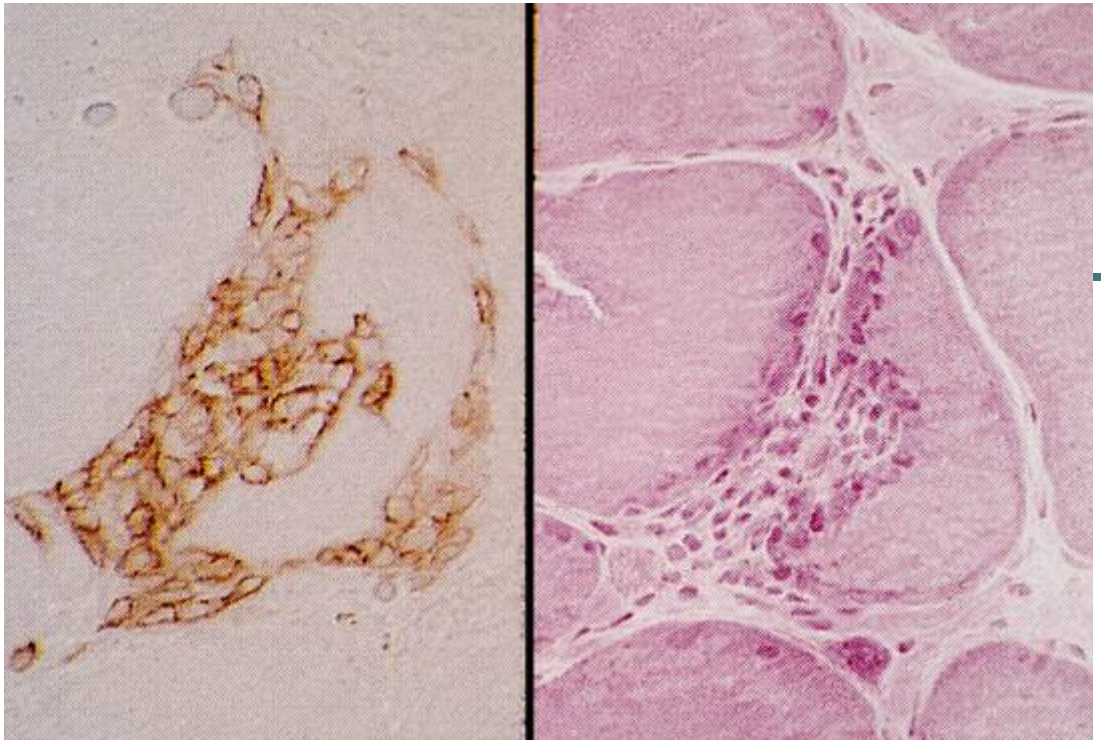



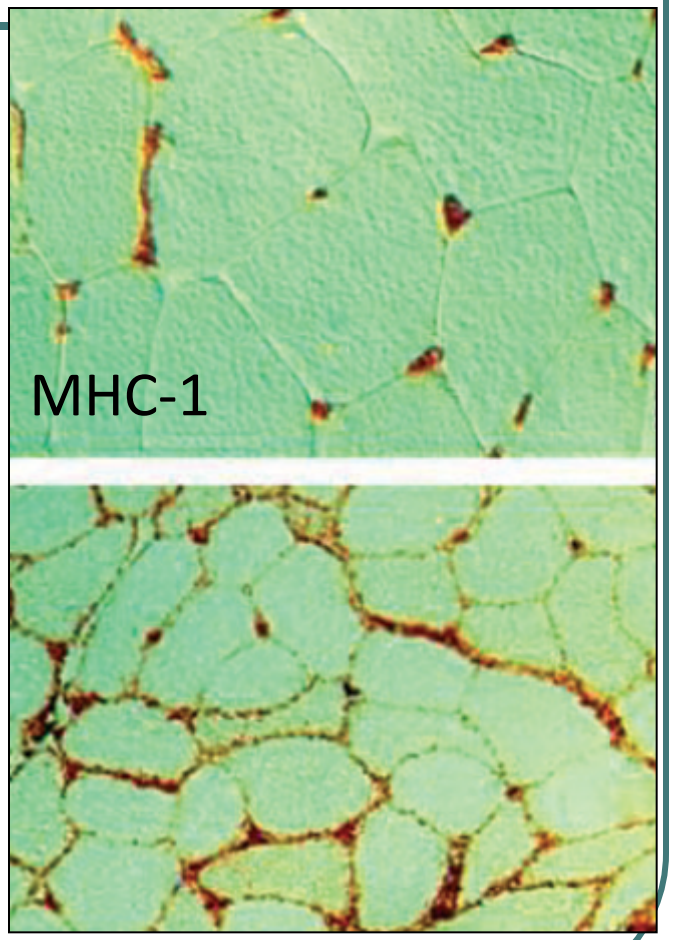

Cell infiltrate includes CD4+ T-cells, macrophages, plasmacytoid dendritic cells and B-cells



The deposition of the C5b-9 complement membrane attack complex (MAC) on small blood vessels precedes inflammation.

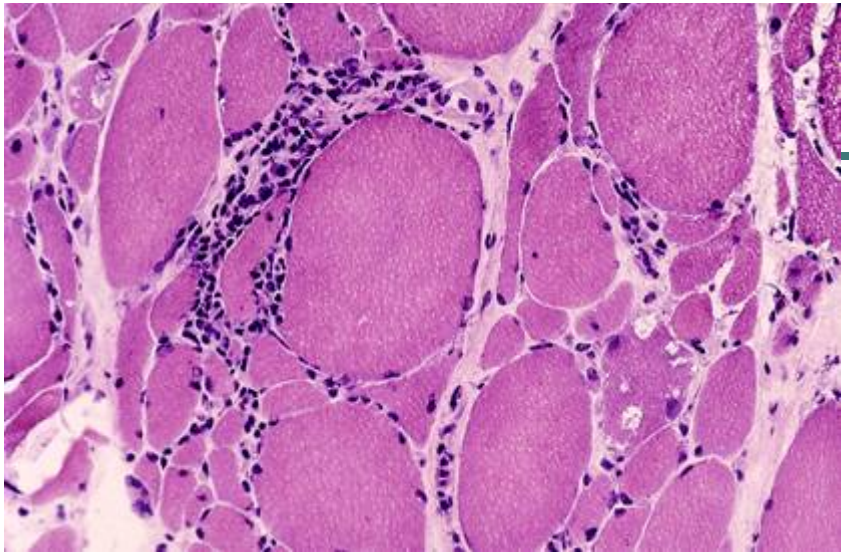
# Polymyositis

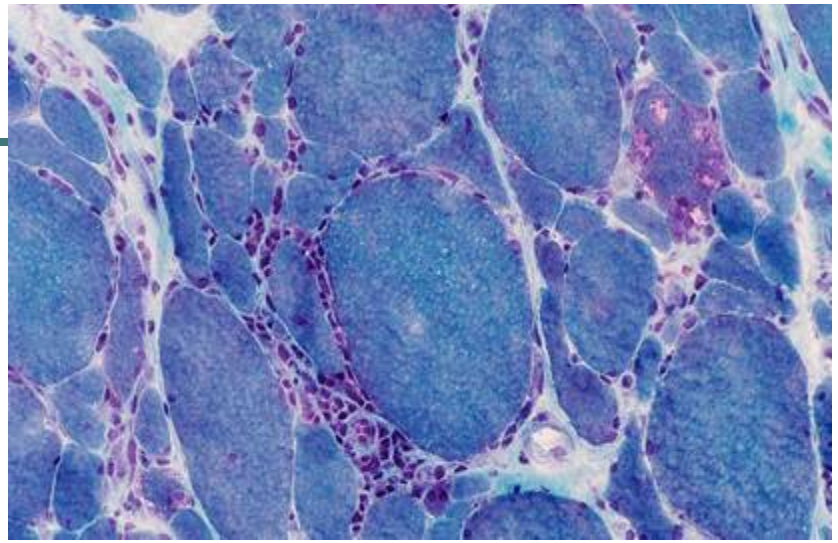




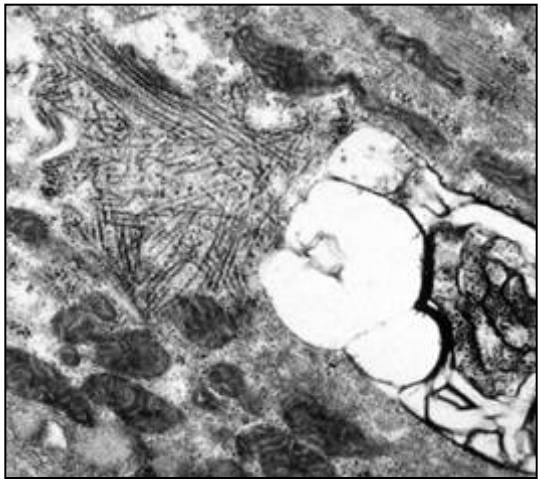

Endomysial cell infiltrates (CD8+ T-cells. plasma cells, myeloid dendritic cells and macrophages) surrounding and invading non-necrotic muscle fibers.
(Engel and Arahata. Ann Neurol 1984)

# Sporadic inclusion body myositis





Endomysial cell infiltrates composed of macrophages and CD8+ T-cells surrounding non-necrotizing myofibres, and rimmed vacuoles
(Engel and Arahata 1984)



CME

# 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

4/165 patients had polymyositis

# Novel Classification of Idiopathic Inflammatory Myopathies Based on Overlap Syndrome Features and Autoantibodies

## *Analysis of 100 French Canadian Patients*

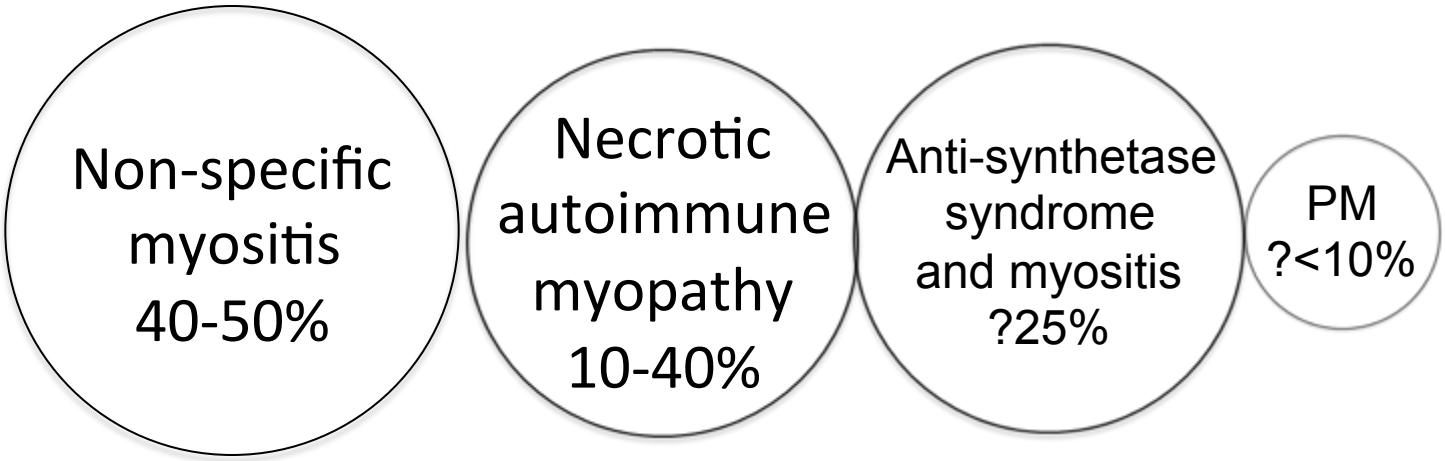
*Yves Troyanov, MD, Ira N. Targoff, MD, Jean-Luc Tremblay, MD, Jean-Richard Goulet, MD, Yves Raymond, PhD, and Jean-Luc Senécal, MD*

Medicine 2005;84:231–249

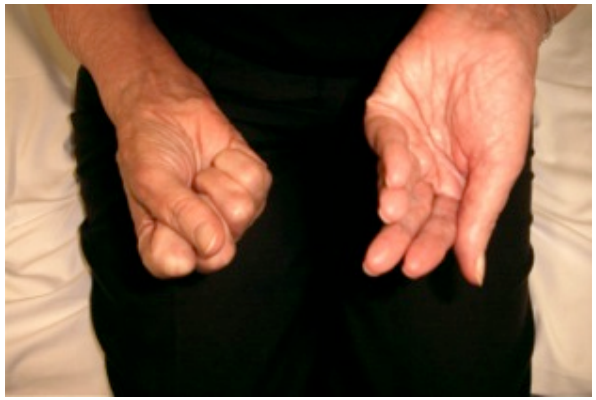
Frequency of PM dropped from 45% to 9%

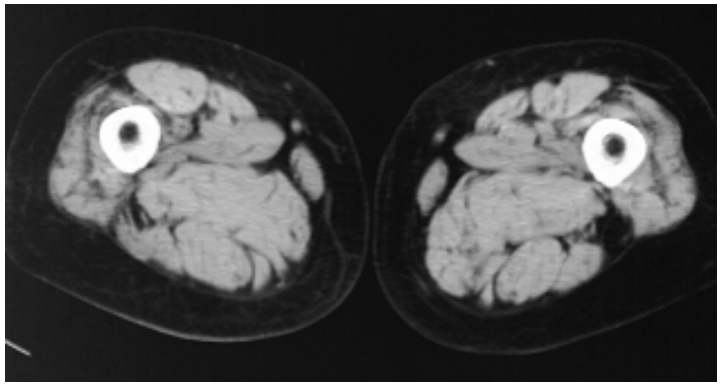
Vilela et al. Rheumat Int 2015: From 1.290 muscle biopsies performed, 36 with PM were identified. After re-evaluation and clinical follow-up, only one patient remained with this diagnosis.

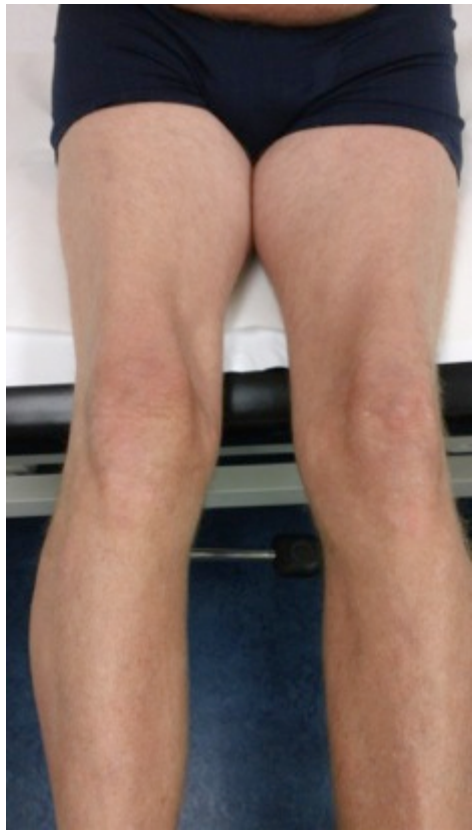
# ‘Polymyositis phenotype’

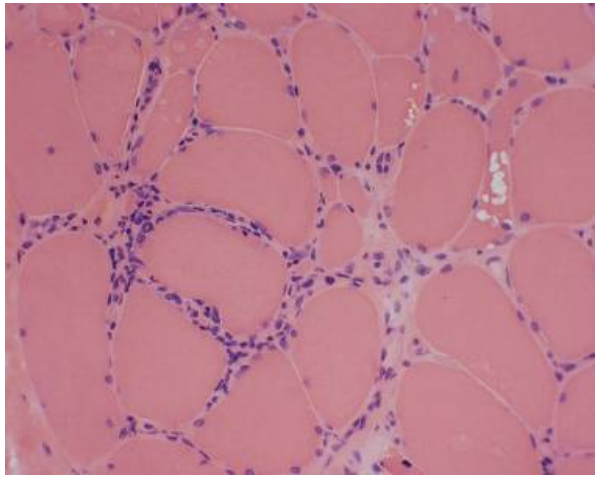


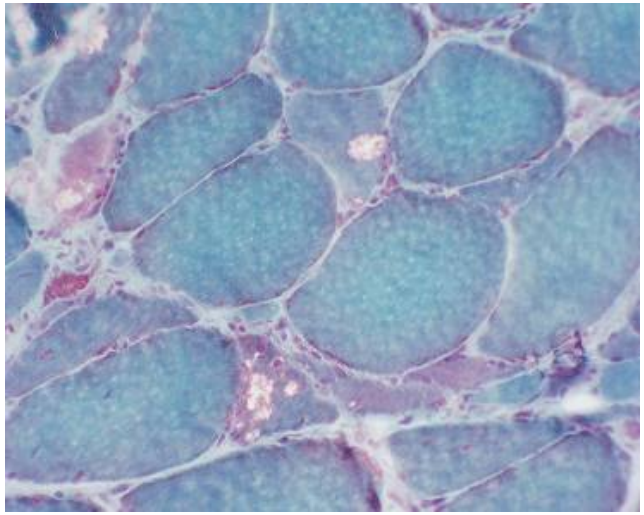
# Inclusion body myositis



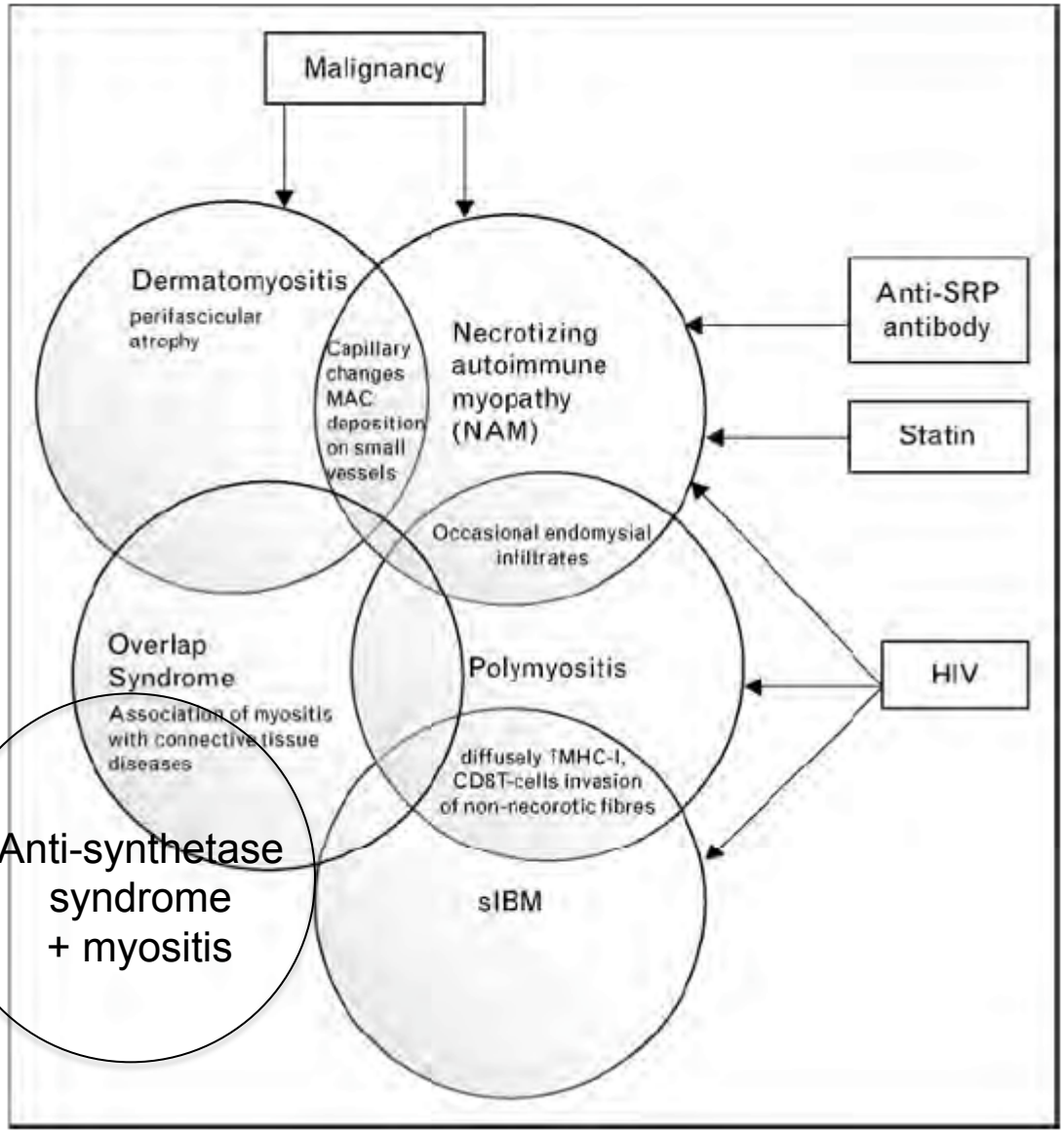








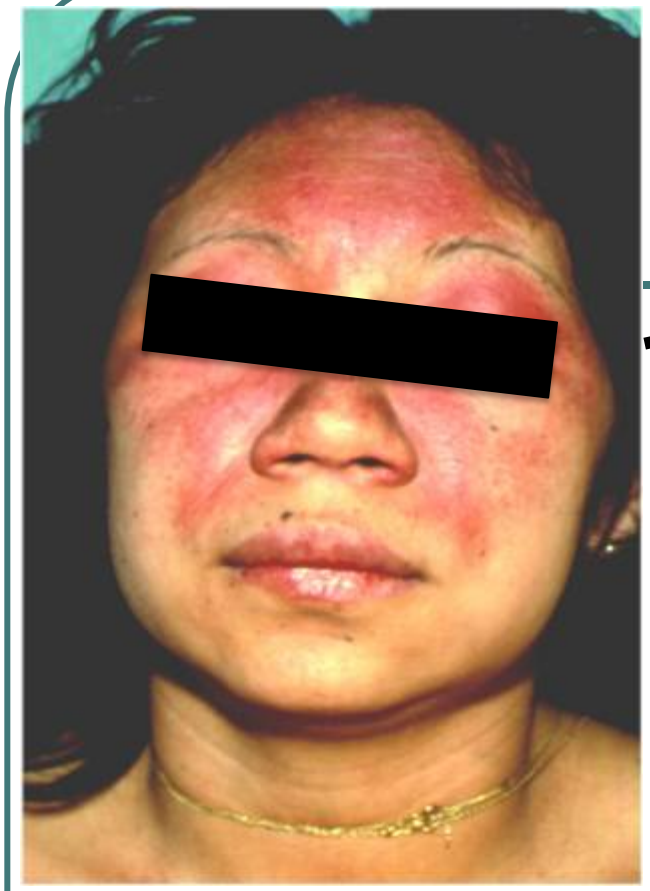
Most frequent myopathy > 50 years.
Dysphaga frequently encountered (40%)
Progressive disease: wheelchair dependency after ~ 15 years
Common cause of death: (aspiration)pneumonia

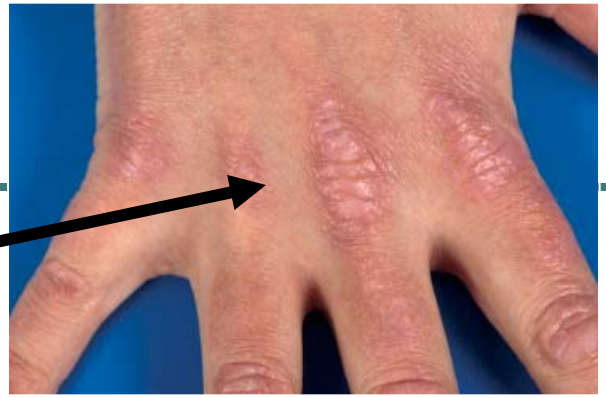



Liang and Needham. Current Opinion in Rheumatology 2011,23:612–619

# Dermatomyositis

- Incidence: 1,5 tot 4 x $10^{-6}$
- Juvenile DM occurs 2 x more frequently in girls as compared to boys
- In adults, DM is associated with cancer: relative risk of cancer for males and females with DM increased: 2.4 – 3.4
- Markedly increased risk at developing ovary, lung, breast and GI cancer.
- Increased risk at developing cancer < 3 jaar after onset of DM (Hill et al. Lancet 2001;357:96)

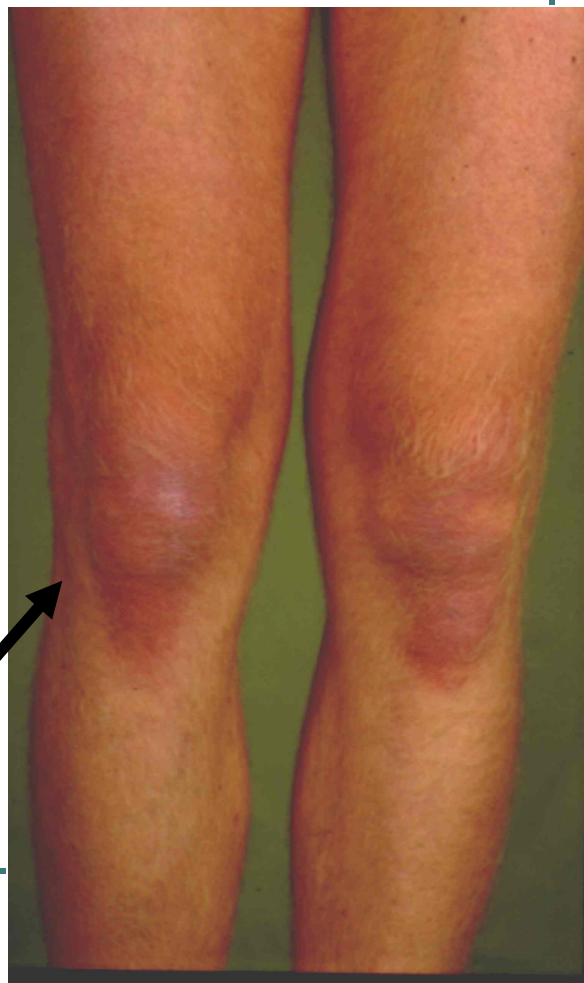




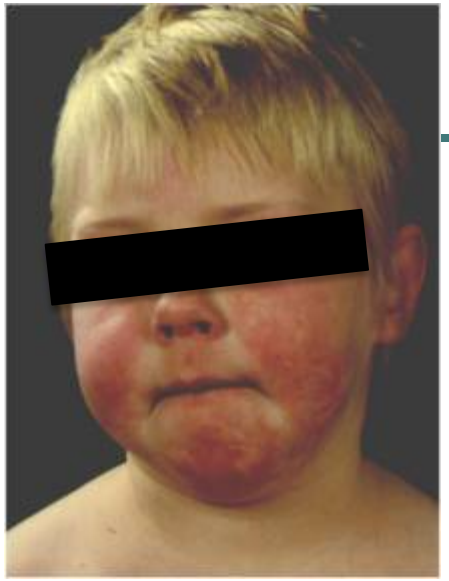
Gottron's papules

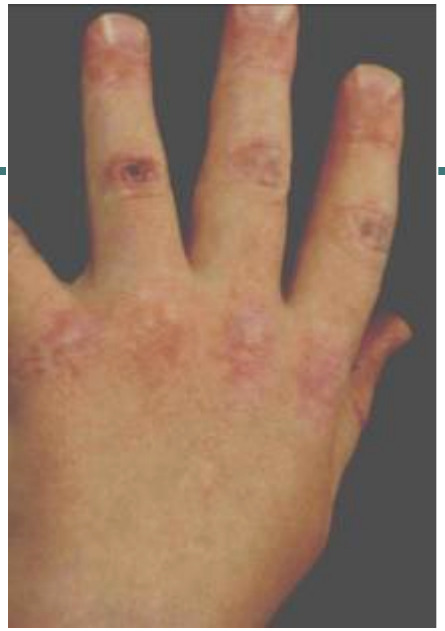
Dermato-myositis

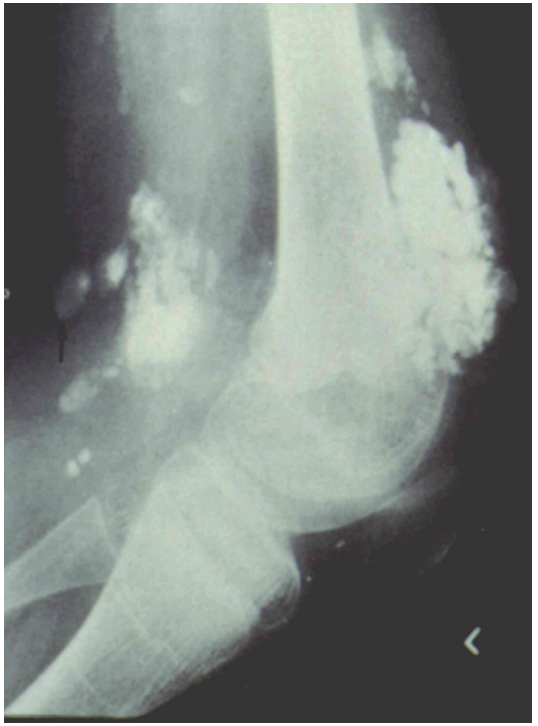
Gottron's sign



# Juvenile dermatomyositis







# Differences between Juvenile and adult onset DM

Adults:

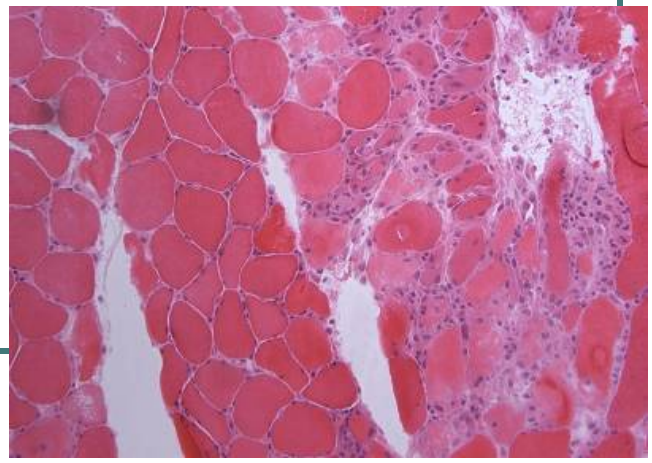
- association with cancer (RR: 2.4-3.4)

Children:

- calcifications
- intestinal vasculitis

# Necrotizing autoimmune myopathy (NAM)

- Immune-mediated necrotizing myopathy (IMNM)
- Presumed immune-mediated nature
  - subacute onset
  - clinical response to immunotherapy
  - serum autoantibody profile



# NAM may be associated with ....

- connective tissue disorders, e.g., MCTD, scleroderma, Sjögren syndrome
- certain medications (a.o. statins)
- malignancy
- viral (HIV) infections

# Clinical features of NAM

- subacute onset
  - In some acute (< 4 weeks) or slowly progressive (9-14 months, even up to > 10 years!)
- also pediatric anti-SRP and anti-HMGCR cases
- progressive proximal limb weakness.
- if weakness is severe, distal and neck extensor (dropped head) muscles may also be involved
- scapular winging in chronic forms
- dysphagia (also as initial symptom) and dysarthria
- severe weight loss
- respiratory insufficiency is rare at onset, but occurs in 30% in the course of the disease
- ? Cardiac changes (conduction abnormalities)

Suzuki et al. Orphanet J Rare Dis 2015; Allenbach et al. Medicine 2014.

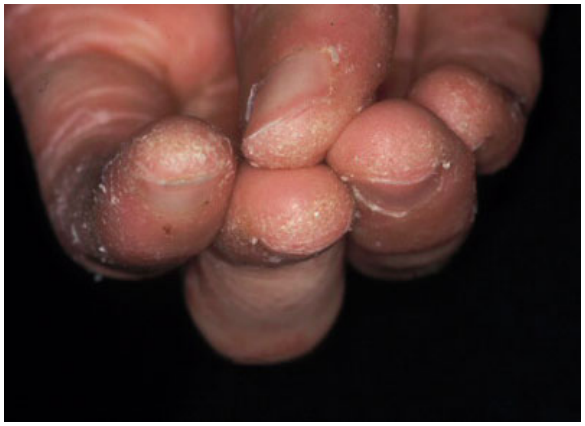
# Non specific myositis

- Associated with CTD (MCTD, SS, RA, Sjögren syndrome) in 20-40%
- Associated with MSAs or MAAs in ~40-70%

Van der Meulen et al. 2003; Troyanov et al. 2005; Váncsa A et al. 2010; Van de Vlekkert et al. 2014

# Antisynthetase syndrome associated (ASS) with myositis

- characterized by
  - myositis
  - Raynaud's phenomenon
  - fever
  - interstitial lung disease
  - mechanic's hands
  - and arthropathy
  - associated with the presence of antibodies against tRNA synthetase, especially anti-Jo-1



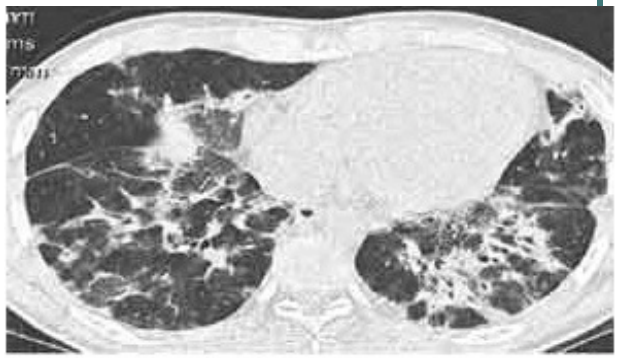


**Figure 2:** CT scan of the lung showing multifocal areas of ground-glass and reticular opacities.

# ILD in steroid-resistent myositis

- Interstitial lung disease (ILD) occurs in nearly 40% of myositis patients.
- Estimated mortality around 30%.
- Prognostic factors associated with poor outcomes include:
  - acute onset,
  - steroid-refractoriness
- Treatment largely based on case reports and small case series

# Diagnosis

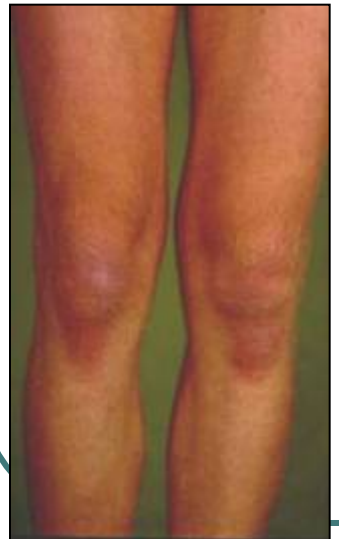
Diagnostic value of disease symptoms in DM

A diagnosis of DM can be established in the presence of:

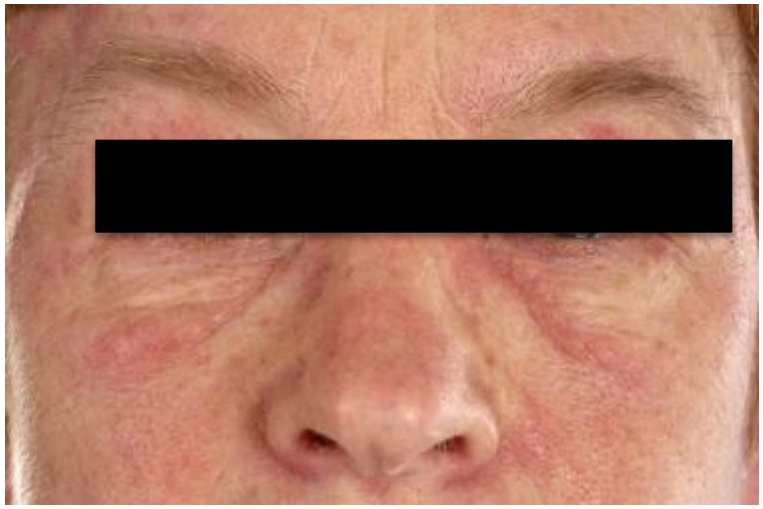
(a) Gottron's papulae/sign in combination with heliotrope erythema

(b) Gottron's papulae/sign or heliotrope erythema in combination with erythema at specific sites of the body (specificity 90.7-99.6% and sensitivity 62-74.2%)

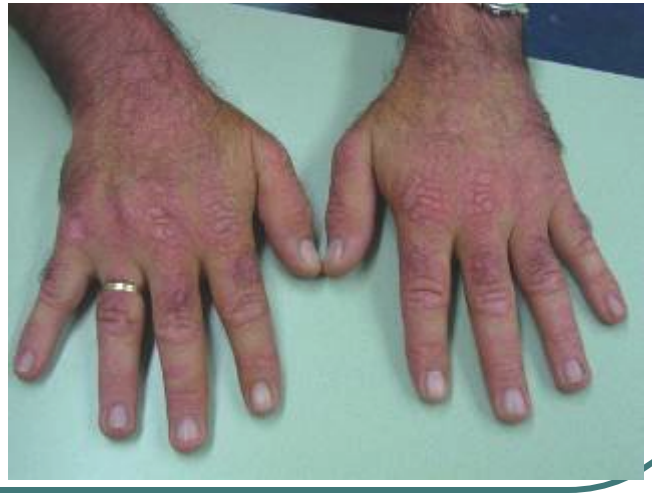
(Tanimoto et al. Classification criteria for polymyositis and dermatomyositis. J Rheumatol 1995;22:668-74)



Gottron's sign



heliotrope erythema



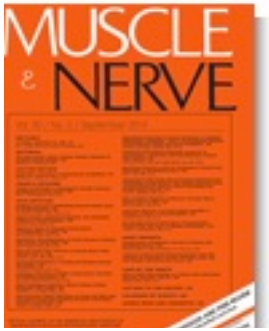
Gottron's papules

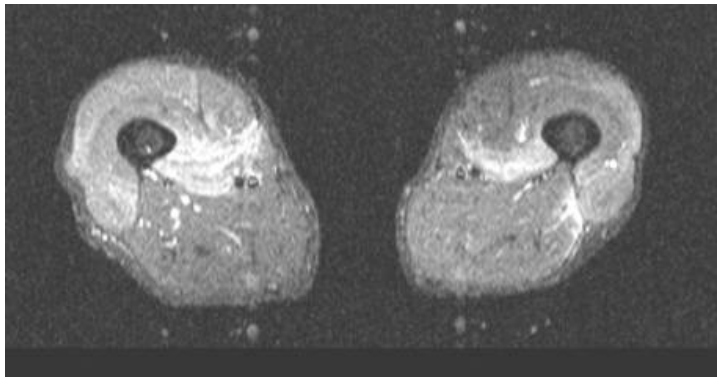
# Ancillary findings

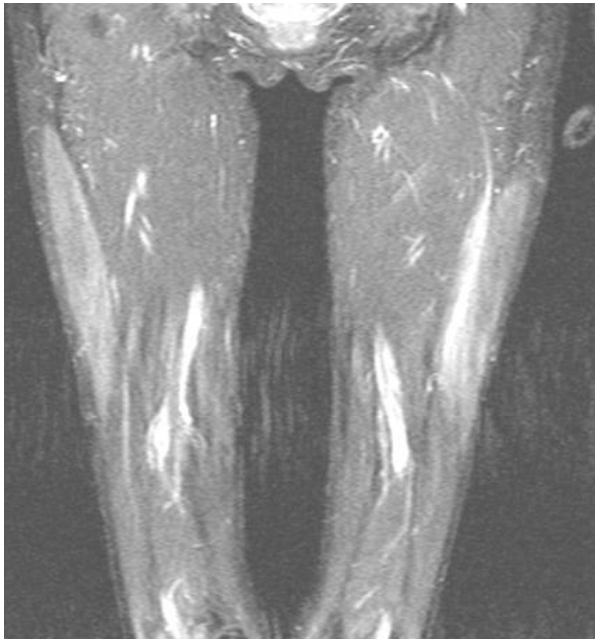
- CK markedly elevated in NAM, can be normal in DM
- EMG is not helpful
- Some myositis specific antibodies are subtype-specific
- In NSM, NAM, ASS and IBM a muscle biopsy is required for diagnosis

# Diagnosis in myositis: MRI can be used to select the most suitable site for a muscle biopsy

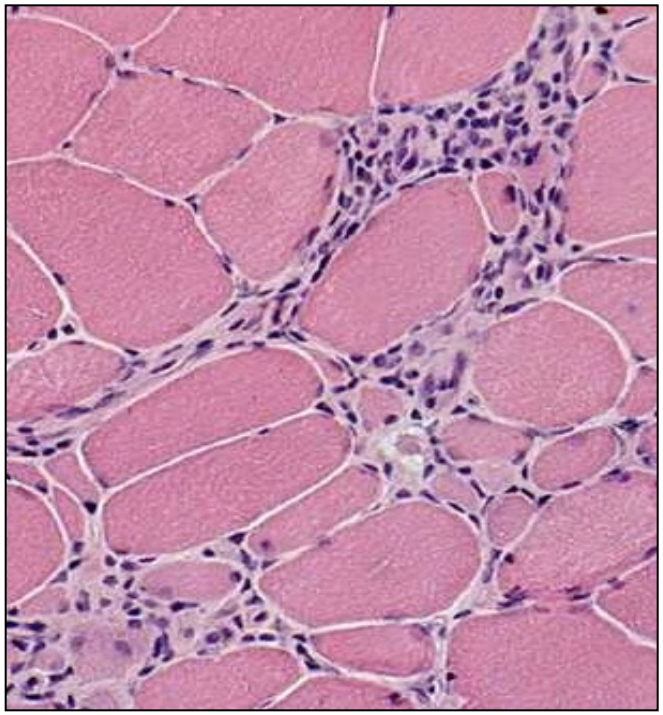
Juni 2014



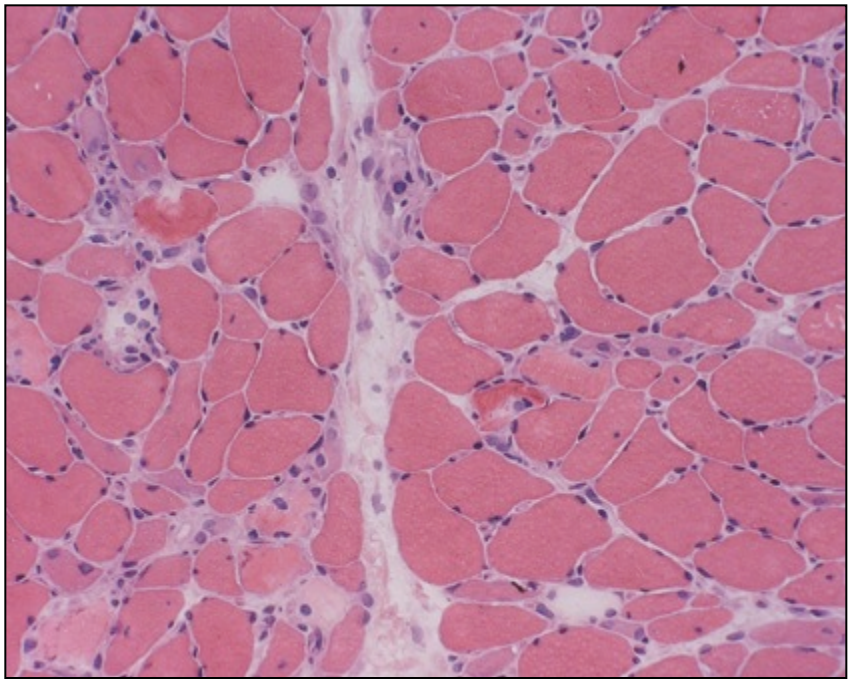





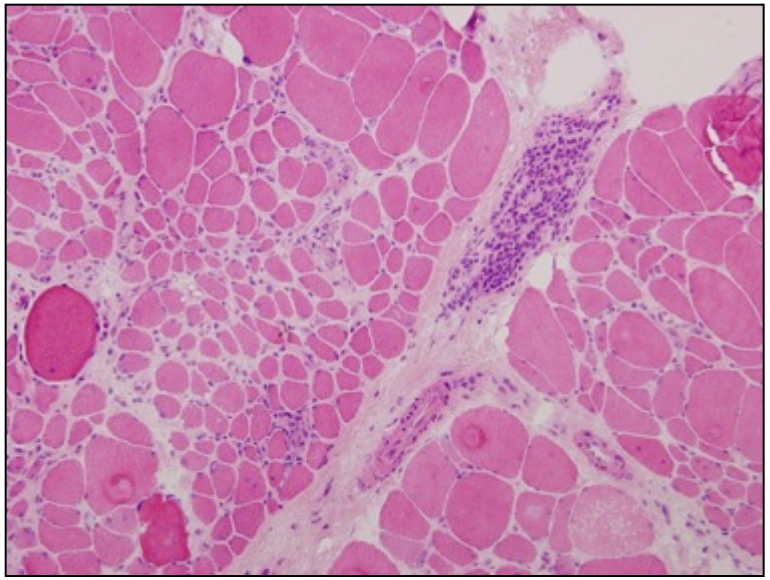
Combining MRI and muscle biopsy improves diagnostic accuracy in subacute-onset idiopathic inflammatory myopathy.
Van de Vlekkert J, Maas M, Hoogendijk JE, de Visser M, van Schaik IN.



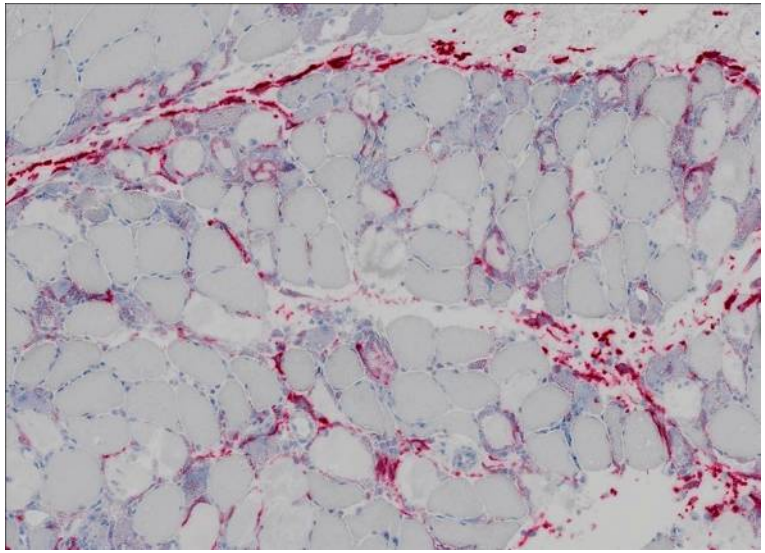
Polymyositis



Necrotizing autoimmune myopathy



Non-specific myositis



Antisynthetase syndrome with myositis

# Myositis specific/associated antibodies

| DM | ASS | NAM | NSM | IBM |
|---|---|---|---|---|
| Mi-2 | Jo-1 | SRP | Jo-1 | anti-cN1A |
| TIF-1γ | PI-7 | HMGCR | RNP | |
| MDA5 | PL-12 | | SS-A | |
| SAE | …… | | ……. | |
| NXP2 | …… | | ……. | |
| | | | | |

Myositis antibodies and clinical phenotypes
Ghirardello et al.
Autoimmune Higlights 2014

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

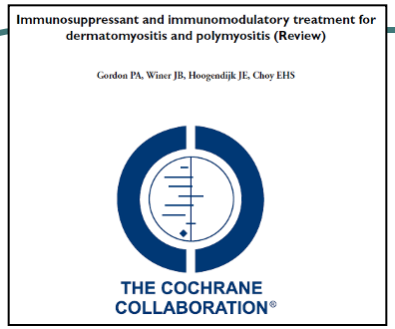
| Autoantibody | Immune target | Function of autoantigen | Clinical associations |
|---|---|---|---|
| Anti-ARS (Jo-1, PL-7, PL-12, EJ, OJ, KS, Ha, Zo) | tRNA synthetases | Aminoacylation of tRNAs | PM<br>Anti-synthetase syndrome |
| Anti-Mi-2 | NuRD subunit | Gene transcription<br>Nucleosome remodeling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

# Treatment of myositis is a challenge

- High dose corticosteroids first line treatment.
- Steroid monotherapy leads to treatment failure or serious side effects necessitating discontinuation of medication in 55% of cases of IIMs (Van de Vlekkert et al. 2014).

# Therapy (expert opinion)

- Treatment of first choice: prednisone 1-1,5 mg/kg/d.
  Slow tapering in 1-2 years, high risk of side effects
- Study on treatment-naive patients: RCT comparing dexamethasone pulse therapy with daily prednisone: equal efficacy and less side-effects (Van de Vlekkert et al. Neuromuscul Disord. 2010;20:382-9).
- In patients with rapidly worsening disease administer i.v. methylprednisolon (1000 mg per day for 3 to 5 days) before starting treatment with oral glucocorticoids.
- Many other therapeutic interventions (e.g., MTX, azathioprine, mycophenolate mofetil). Most of these studied in refractory myositis.




Gordon et al. Cochrane Database Syst Rev 2012

'….insufficient evidence from available RCTs to confirm the value of immunosuppressants in myositis.'

Amongst the six studies comparing immunosuppressant or immunomodulating interventions with placebo, one study, investigating intravenous immunoglobulin (IVIg) in refractory DM, showed statistically significant improvement in scores of muscle strength in the IVIg group over three months (Dalakas et al. NEJM 1993).

In a 42-week pilot study investigating etanercept in adult DM 5/11 patients in the etanercept group were successfully weaned off prednisone in contrast to the 5 placebo-treated Patients (Muscle Study Group. Ann Neurol 2011).

# Therapy (continued)

- Prednisone monotherapy insufficient to control disease in most NAM patients.
- More than half of NAM patients receiving aggressive immunotherapy recover markedly or improve to normal.
- A minority (~10%) shows progressive muscle weakness. Their response to immunotherapy was minimal.
- The relapse rate is high (in 55% of cases) during medication taper or treatment discontinuation.
- Combination of oral corticosteroids and iv immunoglobulin reported to be effective as first-line therapy.

# Rituximab study

ARTHRITIS & RHEUMATISM
Vol. 65, No. 2, February 2013, pp 314–324
DOI 10.1002/art.37754


Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis

A Randomized, Placebo-Phase Trial

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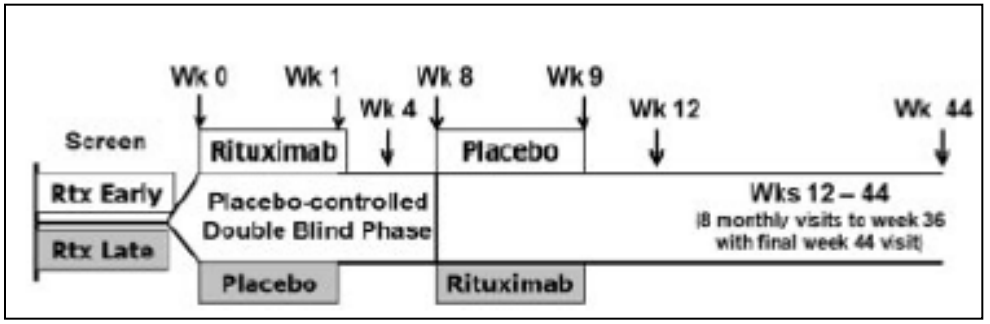


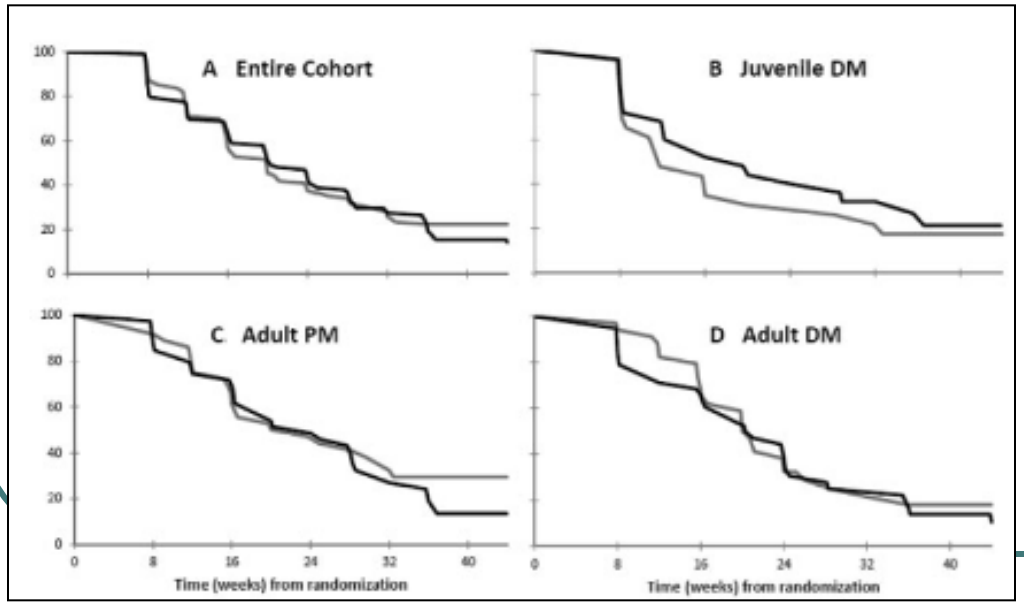


Primary endpoint: time to DOI between the 'rituximab early' and 'rituximab late' groups.

Primary and secondary endpoints were not met.

# Myositis has a great impact on functional ability and quality of life in the medium and long term – Ponyi et al. Rheumatology 2005

- only 17.5% of the patients had no disability and 12.5% were severely disabled.
- majority of patients (70%) mildly to moderately disabled
- only 13% of the patients had active disease at the time of the study.

# Long-term follow-up of 62 patients with myositis – van de Vlekkert et al. J Neurol 2014

- Mortality (10-15%), mostly cancer-related
- Approximately 70% of the patients have a chronic or polyphasic disease course.
- At follow-up, 68 % still perceived disabilities.
- After follow-up (~ 3 years) thirty-four (38 %) dependent on help from others for their activities of daily living (Rankin 3–5).
- Improvement occurred in the first 18 months. After that, the Rankin score and SF-36 remained stable.