



The many faces of myositis



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Outline of the presentation

- Classification
- Diagnosis
- Therapy
- Prognosis





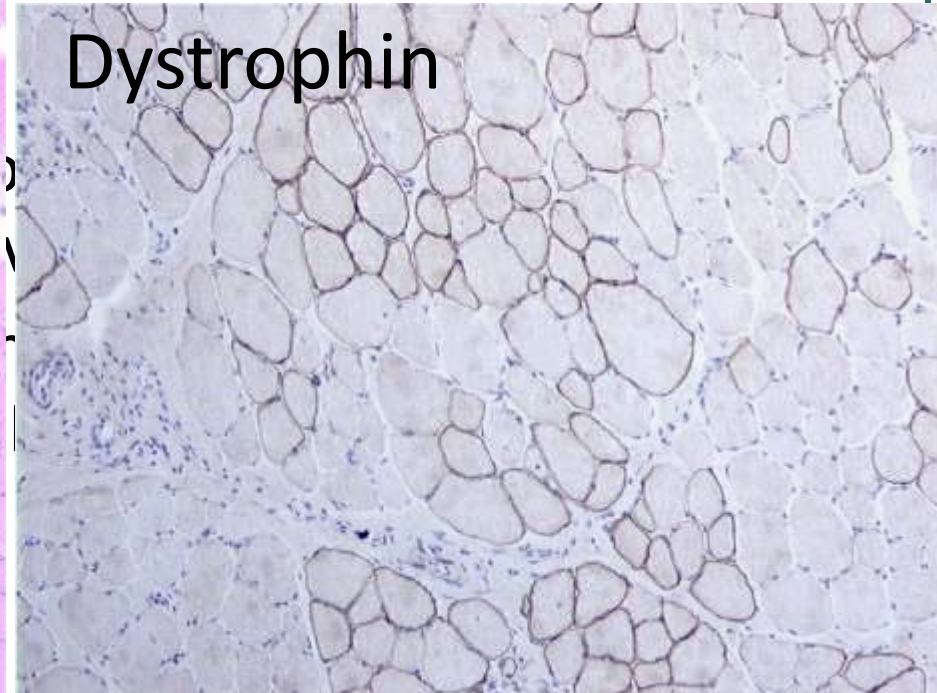
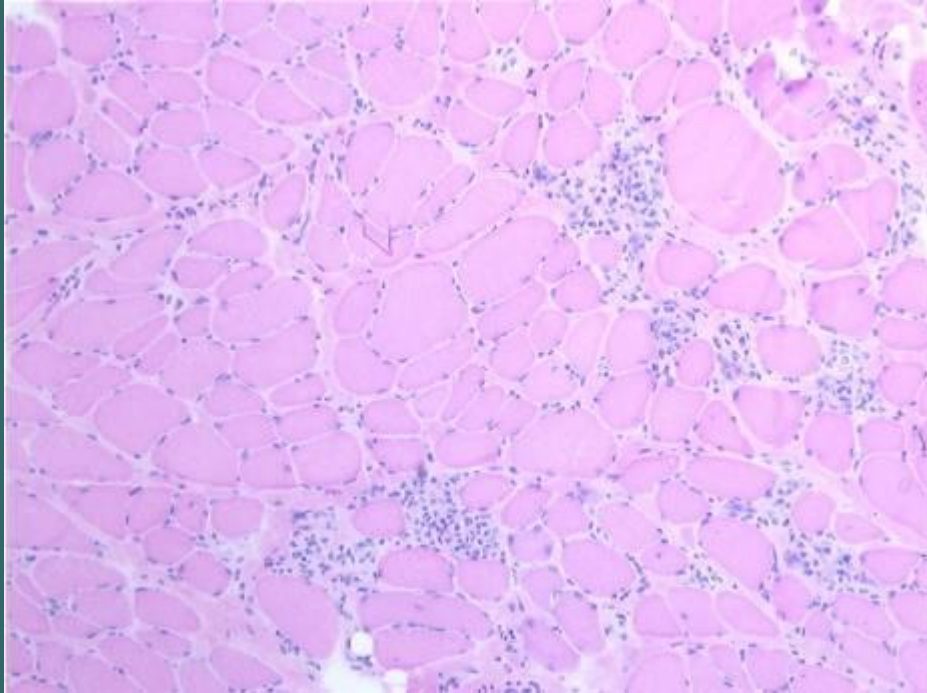
Diagnostic criteria

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



So this patient does not have a myositis but a hereditary muscular dystrophy with a mutation in the dystrophin gene

Dermatomyositis



Facial rash in the shape of a butterfly on the cheeks, nose and chin

Gottron's papules

Gottron's sign



Juvenile DM

Same rash as in adult DM

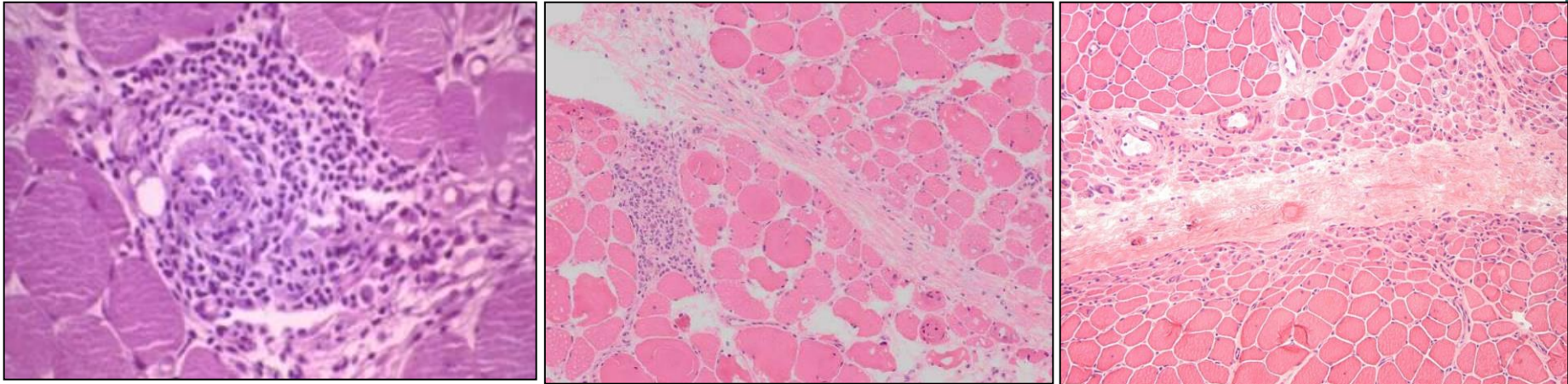




Classification based on muscle biopsy

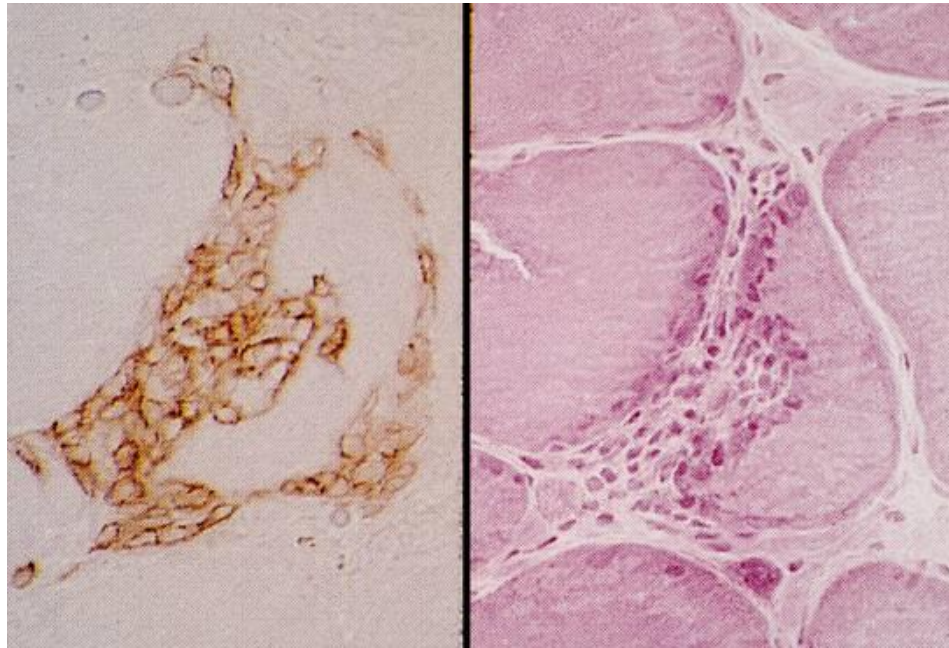
Engel and Arahata, Ann Neurol 1984

Dermatomyositis



Inflammatory cells usually around blood vessel between fascicles. Note small muscle cells at the border of the muscle bundle.

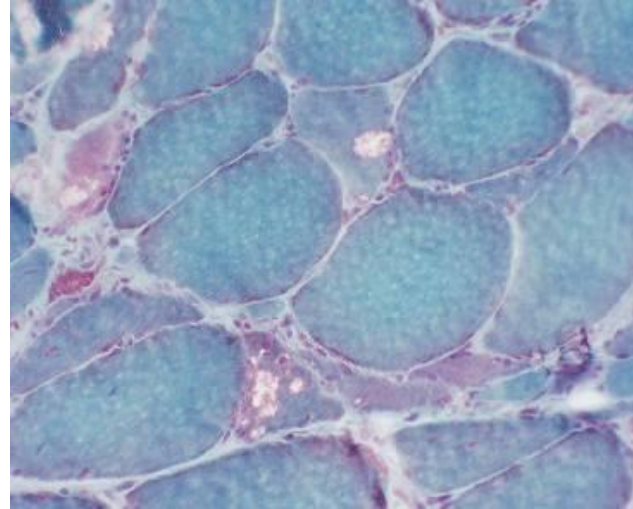
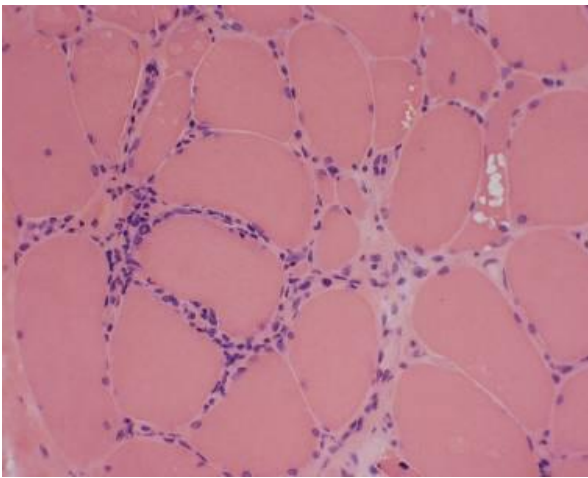
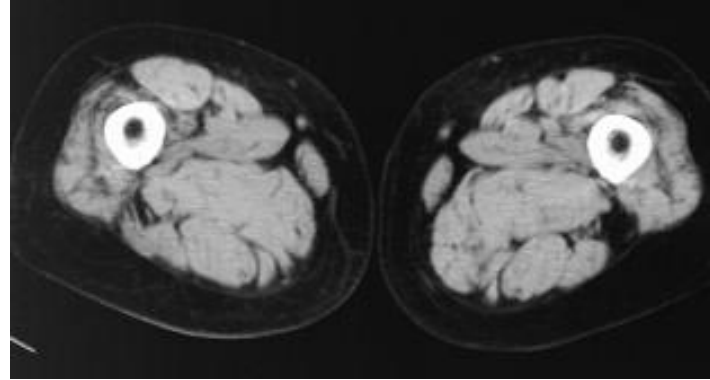
Polymyositis



Inflammatory cells between individual muscle fibers and sometimes invading normal looking muscle fibers

(Engel and Arahata. Ann Neurol 1984)

Inclusion body myositis



Most frequent myopathy > 50 years.

Swallowing difficulty frequently encountered (40%)

Progressive disease: wheelchair dependency after ~ 15 years

Common cause of death: (aspiration)pneumonia



'Polymyositis is a melting pot'



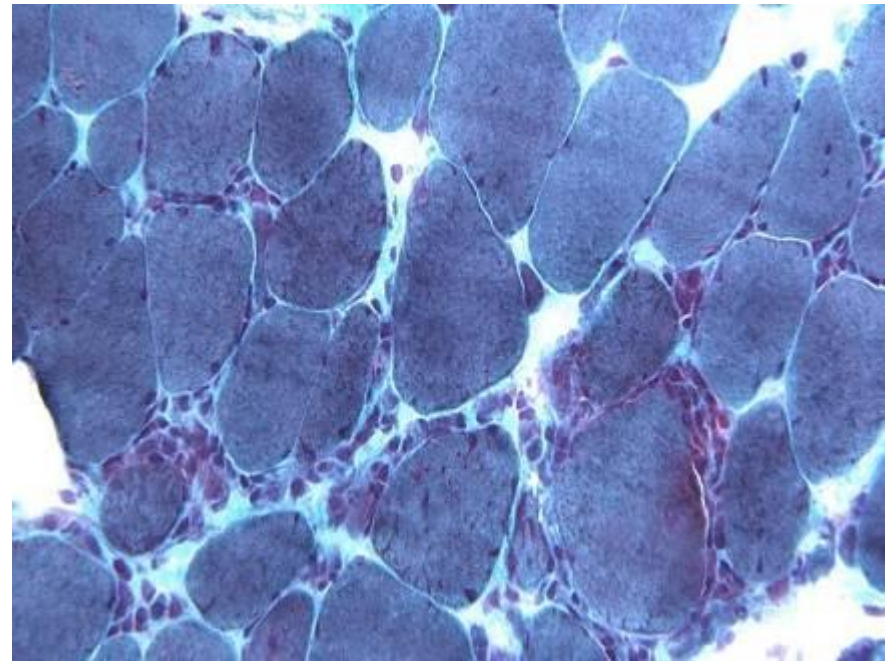
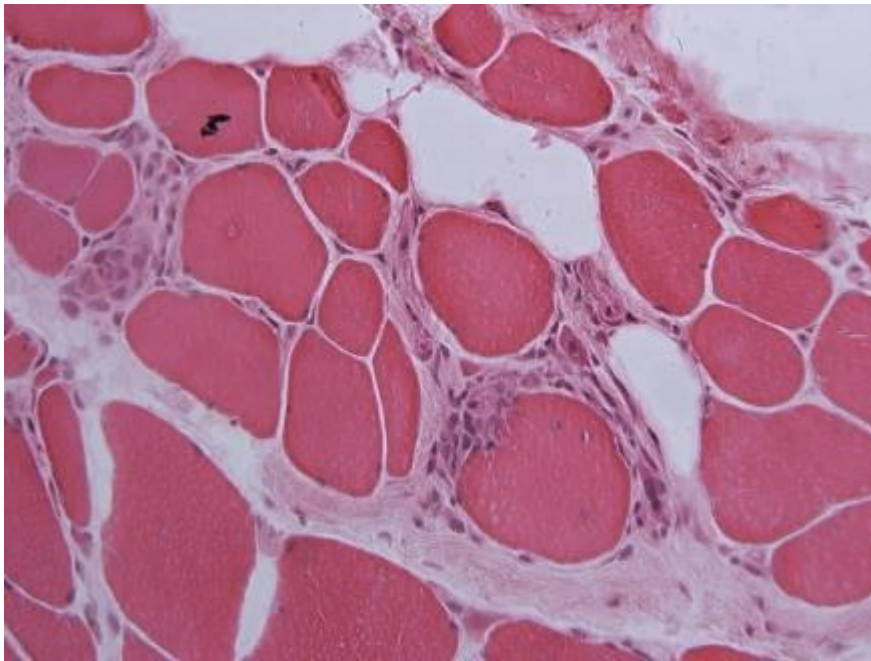
Overlap
myositis
40-50%

Necrotic
autoimmune
myopathy
10-40%

Anti-
synthetase
syndrome
?25%

PM
<10%

Diagnosis IBM also possible without the vacuoles if clinical picture characteristic





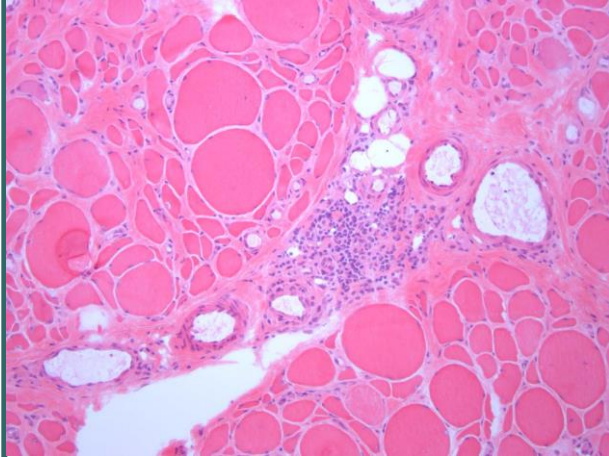
Overlap myositis

Hx/ 29-year-old man with a history of myalgia, stiffness and muscle weakness of arms and legs since 6 months. He also complained about pain at the joints and Raynaud phenomenon and was later diagnosed with rheumatoid arthritis.

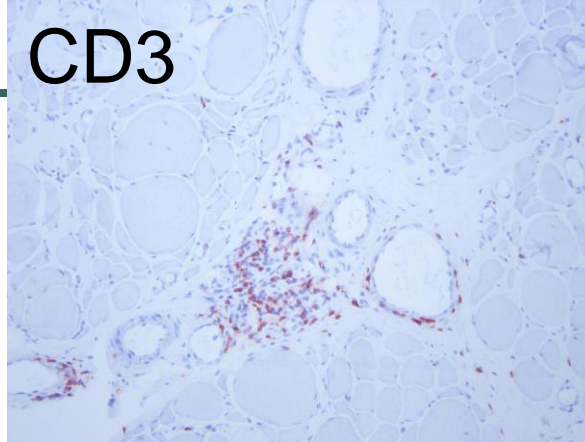
Ex/ Moderate muscle weakness of proximal muscles, legs > arms.

CK: 1409 IU/L

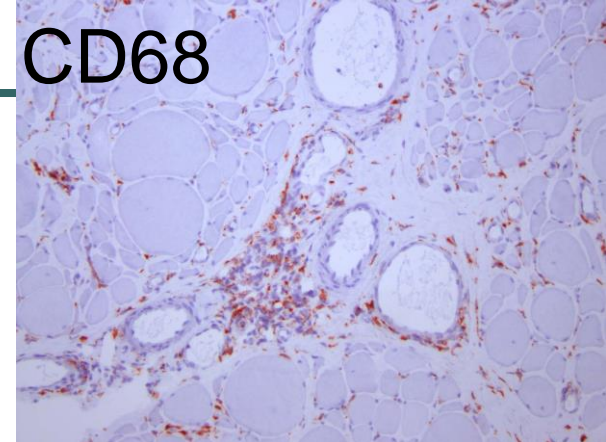
Muscle biopsy



CD3



CD68



He was treated with dexamethasone 40 mg for 4 consecutive days in monthly cycles for 6 months and recovered completely.



Overlap myositis

- Associated with CTD (MCTD (mixed connective tissue disease), Sjögren syndrome, rheumatoid arthritis, scleroderma) in 20-40%
- Associated with myositis associated antibodies in ~40-70%

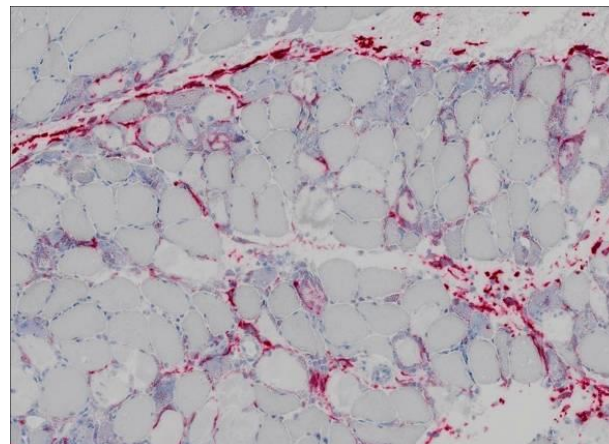
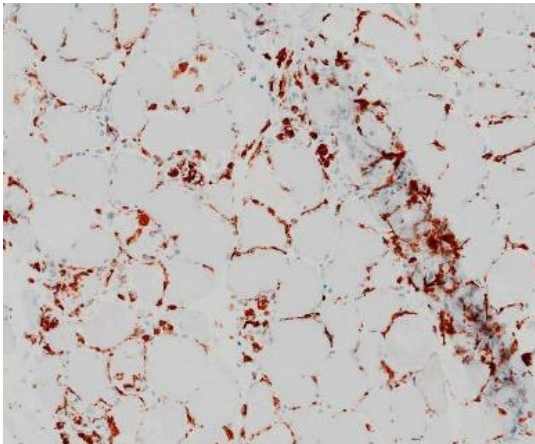
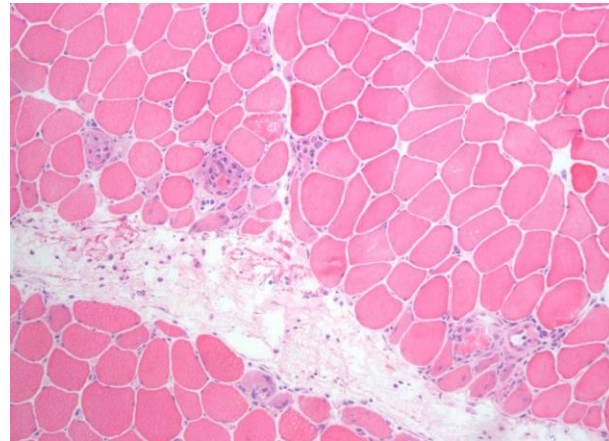
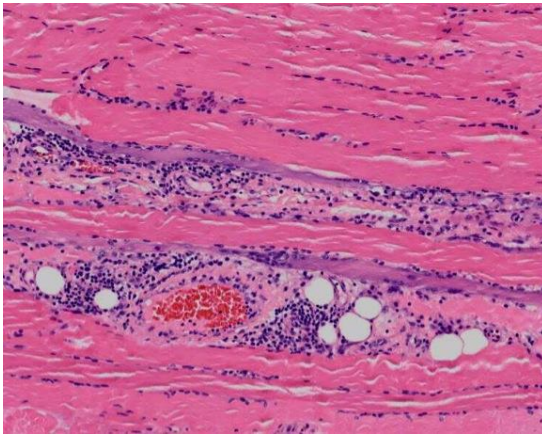
Van der Meulen et al. 2003; Troyanov et al. 2005; Váncsa A et al. 2010; Van de Vlekkert et al. 2014



Antisynthetase syndrome

- Hx/ 37-year-old man who was referred in December 2004 because of fatigue, muscle pain and shortness of breath since a few weeks.
- Ex/ Muscle weakness proximal more than distal, arms (severe) more than legs (moderate).
- sCK 16864 IU/l; positive anti-Jo1 antibodies
- CT chest consistent with interstitial lung disease.

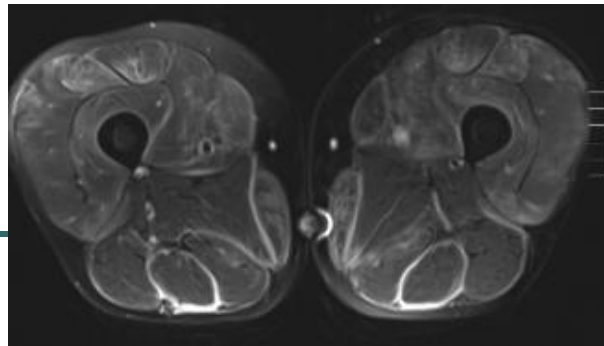
Muscle biopsy



Course of the disease

He was treated with daily high-dose prednisone and muscle weakness resolved. In June 2005 he relapsed, the prednisone dosage had to be increased and again he came in remission. He relapsed in 2007 and was treated with prednisone 30 mg and azathioprine 200 mg. Since then he had several relapses for which he was treated with pulse methylprednisolon i.v. on top of a maintenance dose of prednisone, rituximab, MTX.

MRI 2009



Clinical manifestations of Antisynthetase syndrome

Clinical manifestations	Prevalence (%)
Myositis	>90
Interstitial lung disease	60
Arthritis	50
Raynaud's phenomenon	40
Fever	20
Mechanic's hands	30



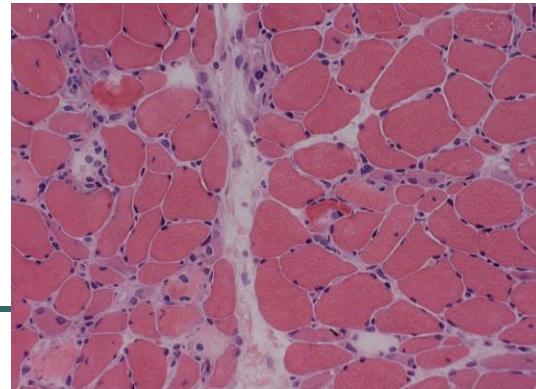
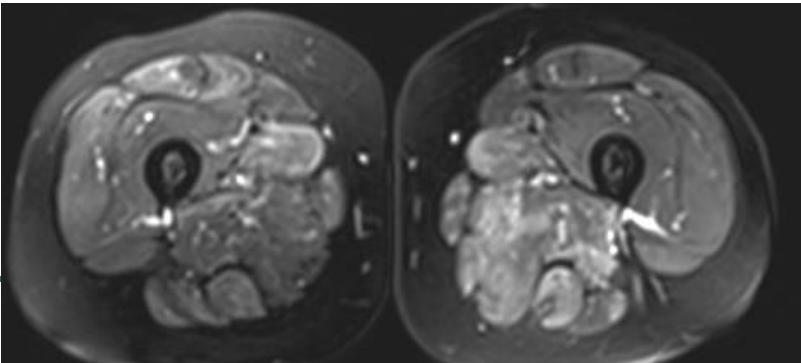
Necrotizing autoimmune myopathy

Hx/ 61-year-old woman complained about progressive muscle weakness in arms and legs since ~4 months and about difficulty with swallowing solid food. She had had exposure to statins some three years ago.

Ex/ Weakness m. deltoideus, m. triceps brachii, m. iliopsoas and neck flexors (MRC grade 4).

Ancillary investigations: sCK 9982 IU/L

Antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) were positive.





Course of the disease

She was treated with pulsed high dose dexamethasone (6 months, one cycle/month) and muscle weakness resolved. However she relapsed 7 months after the last cycle (mild muscle weakness and sCK 12,000IU/L).

Again she was started on dexamethasone and responded well.

After a second flare daily Prednisone 20 mg was added.



NAM may be associated with

- connective tissue disorders, e.g., MCTD, scleroderma, Sjögren syndrome
- ILD in 20% of the cases
- certain medications (a.o. statins)
- ?cancer

Clinical manifestations

- subacute onset, i.e. < 1 year
 - In some acute and progressive (9-14 months, even)
- children can also have
- if weakness is proximal and lower leg muscles and pelvic girdle leading to a dropped may
- rarely scapular winging (arms)
- swallowing difficulties (symptom)
- severe weight loss
- respiratory insufficiency is rare at onset, but occurs in 30% in the course of the disease
- ? cardiac changes



Diagnosis



**"I already diagnosed myself on the Internet.
I'm only here for a second opinion."**

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 a rash above the eyes
- (b) Gottron's papulae/sign or heliotrope erythema in combination with a rash at specific sites of the body



Facial rash and discoloration of the skin above the eyes which is called heliotrope erythema



Gottron's sign

Gottron's papules



61-year-old man

Hx/ Referred because of muscle pain, reddish discoloration of the face, oedematous bags under his eyes, decrease in muscle strength of the legs while cycling, and swallowing difficulty since 2 months.

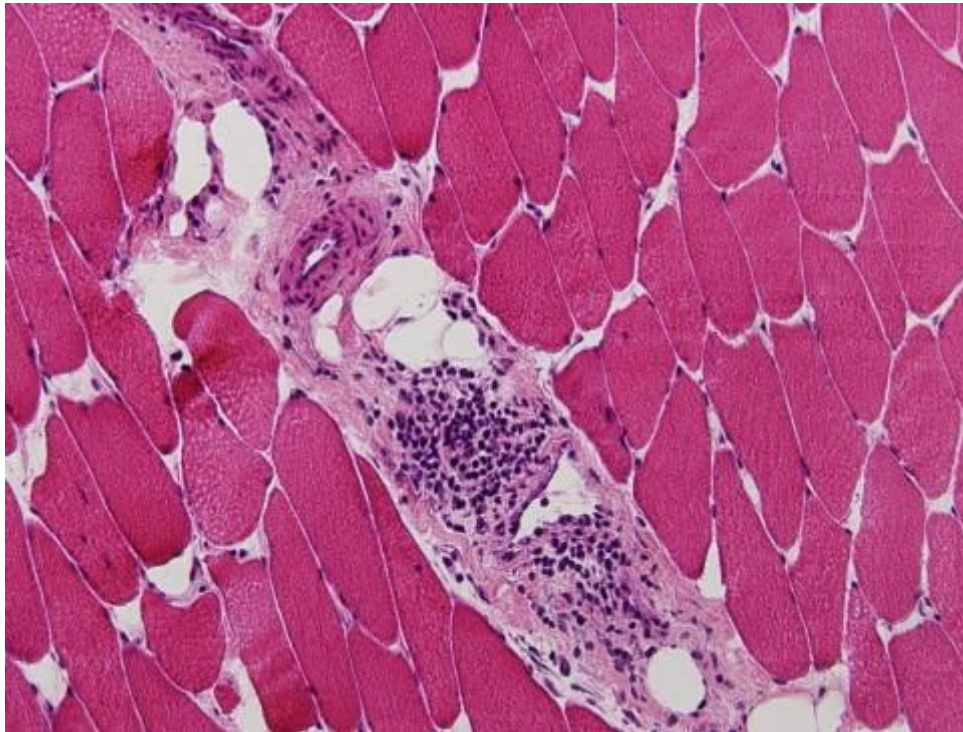
Ex/ facial skin abnormalities, mild weakness of neck flexors, deltoids and iliopsoas muscles.

Dx: Probable DM and therefore we did a muscle biopsy to be sure that the diagnosis was right.



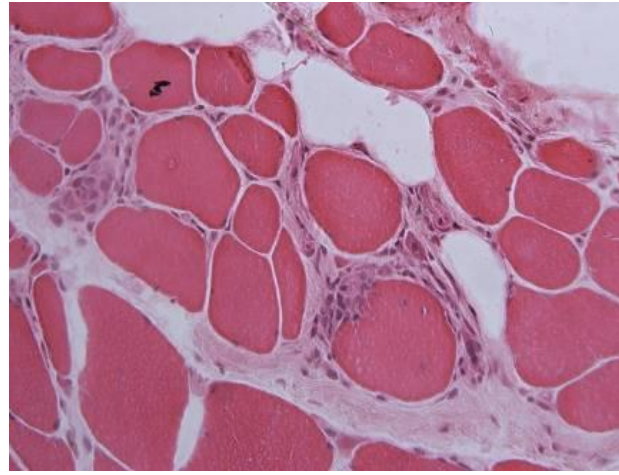
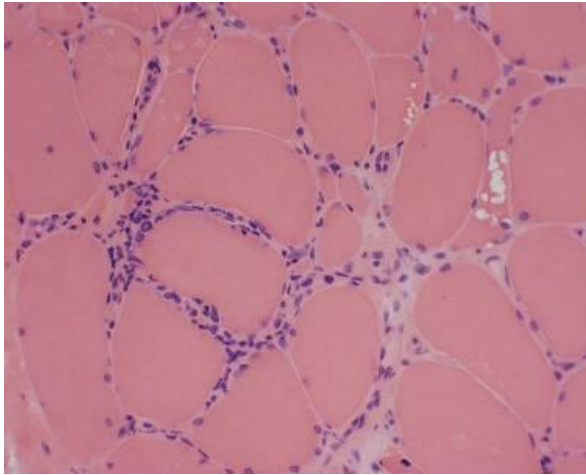
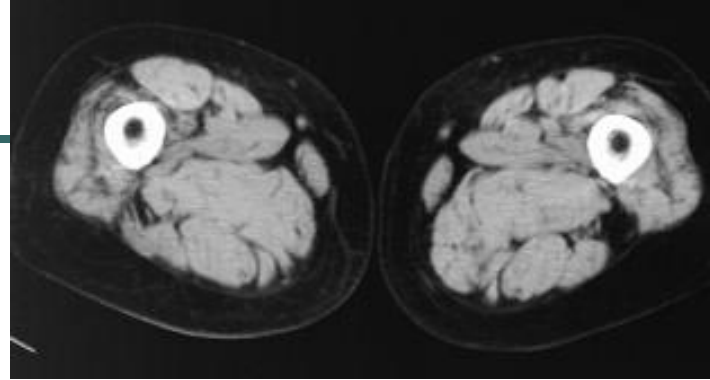
CK 241 (N < 190 IU/L)

Muscle bx showed inflammatory cells around blood vessels.





Inclusion body myositis



Most frequent myopathy > 50 years.

Swallowing difficulty frequently encountered (40%)

Progressive disease: wheelchair dependency after ~ 15 years

Common cause of death: (aspiration)pneumonia



Ancillary findings

- Blood tests: creatine kinase (CK) indicating leakage from the muscle cells is markedly elevated in NAM, but can be normal in DM
- EMG is usually not very helpful
- In Overlap Myositis, Necrotizing Autoimmune Myopathy, Anti-synthetase syndrome and IBM a muscle biopsy is required for diagnosis
- Some myositis specific antibodies are specific to a subtype



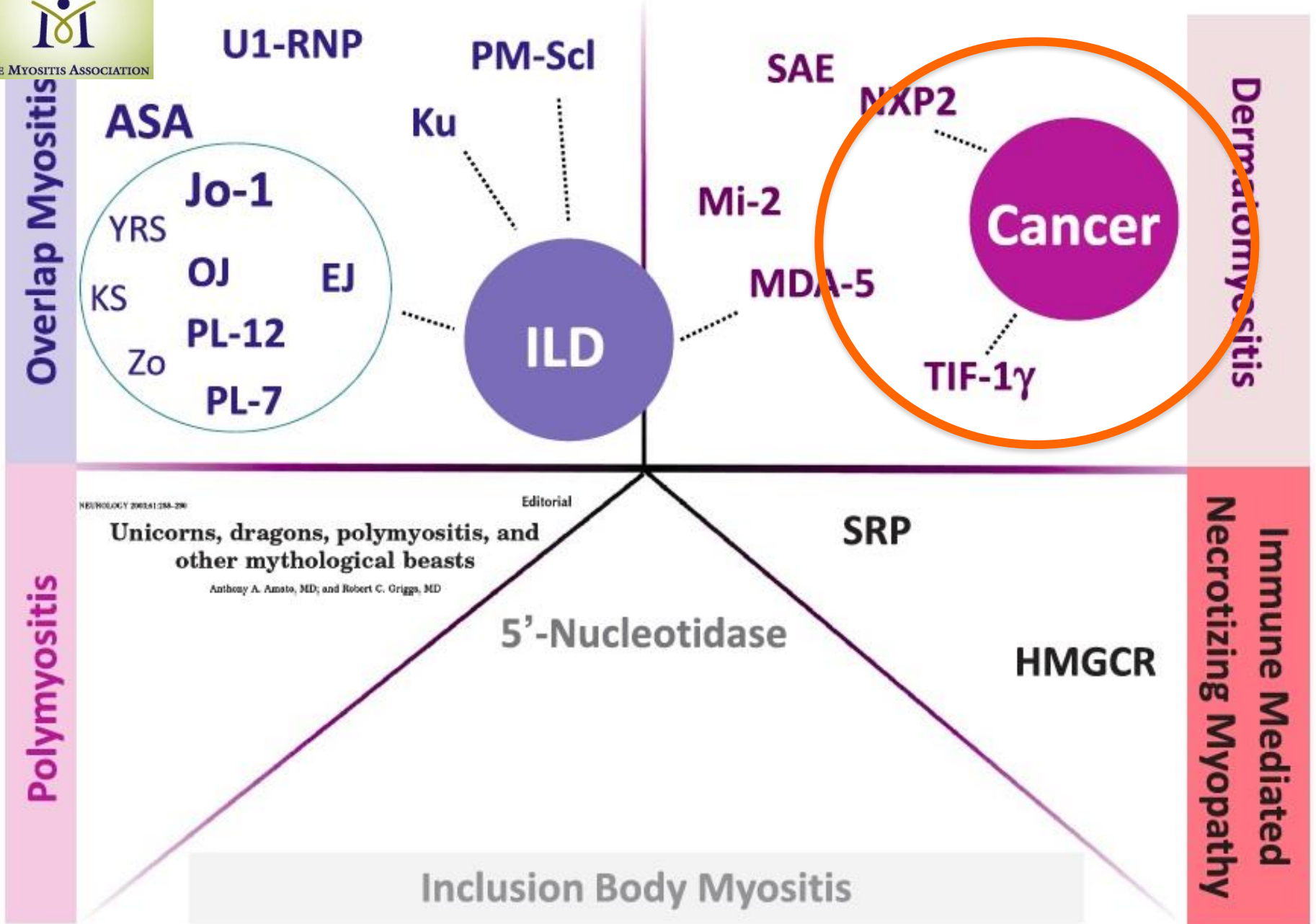
Myositis specific/associated antibodies

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



Diagnostic Utility of Auto-Antibodies in myositis



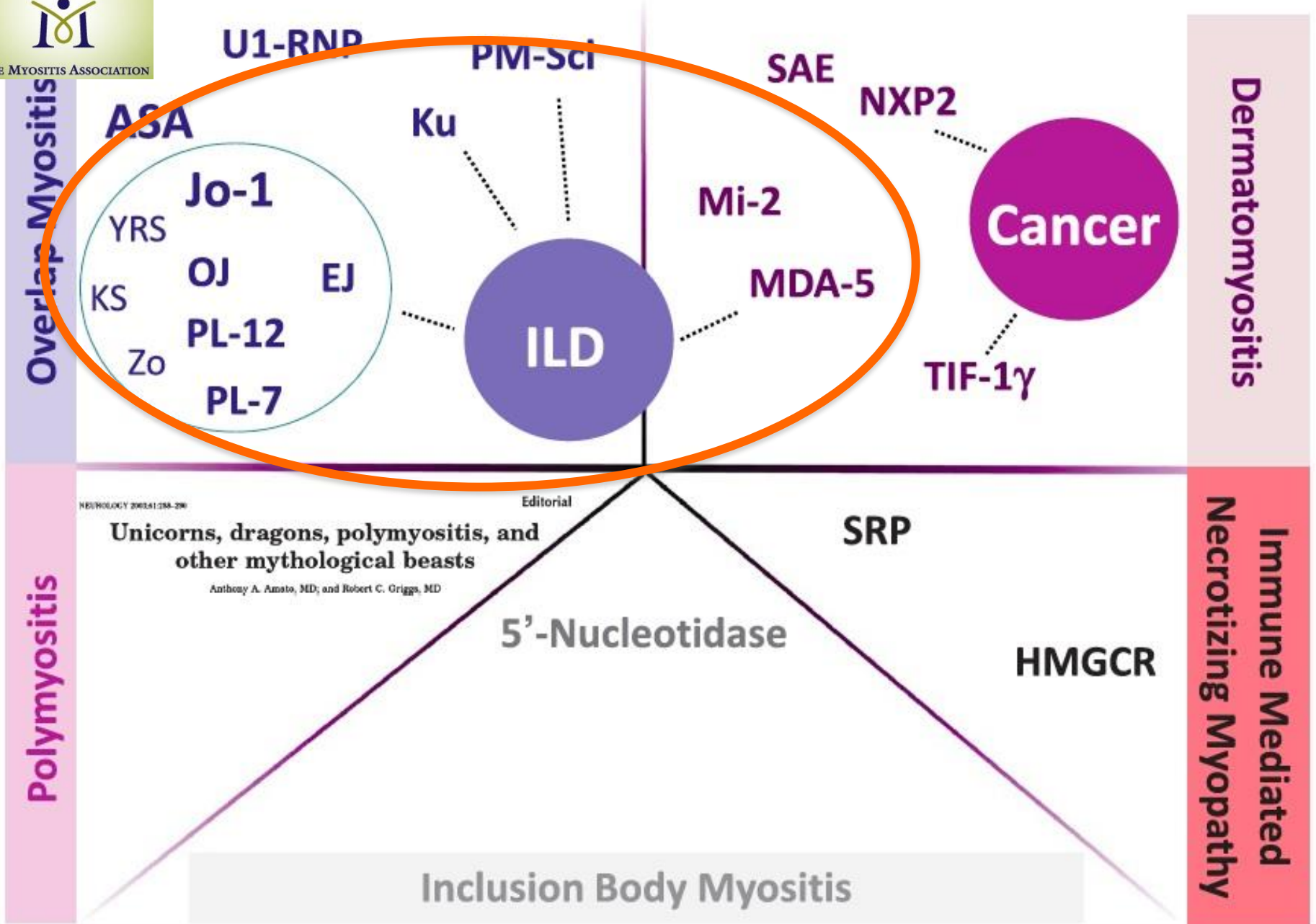


NEUROLOGY 2005;61:294-296
 Editorial
Unicorns, dragons, polymyositis, and other mythological beasts
 Anthony A. Amato, MD; and Robert C. Griggs, MD



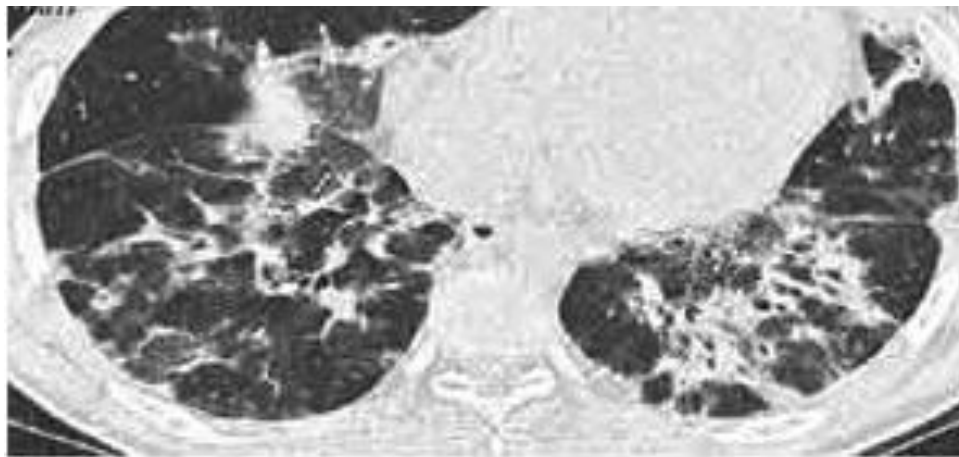
Association with cancer

- In 20-30% of adults and not in children, DM is associated with cancer.
- Association with autoantibodies TIF1- γ , NPX-2.
- Increased risk at developing cancer < 3 jaar after onset of DM
- ?Association with cancer in HMGCR-related NAM



Association with Interstitial Lung Disease

- Antisynthetase syndrome (anti-Jo1)(70-90%)
- DM with anti-MDA5 antibody (> 80%)



Association with skin lesions



DM + Anti-MDA5



DM + Anti-NXP2



Anti-Jo1



Anti-Mi-2

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 (Van de Vlekkert et al. 2014).

THERAPY IS REALLY SIMPLE. JUST LET ME LICK YOU, WAG MY TAIL AND YOU'LL FEEL MUCH BETTER!





Therapy (expert opinion)

- Treatment of first choice: prednisone 1-1,5 mg/kg/d.
Slow reducing the dose over 1-2 years, high risk of side effects
- Study on treatment-naive patients: RCT comparing dexamethasone pulse therapy with daily prednisone: equally effective 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, rituximab). Most of these studied in refractory myositis.

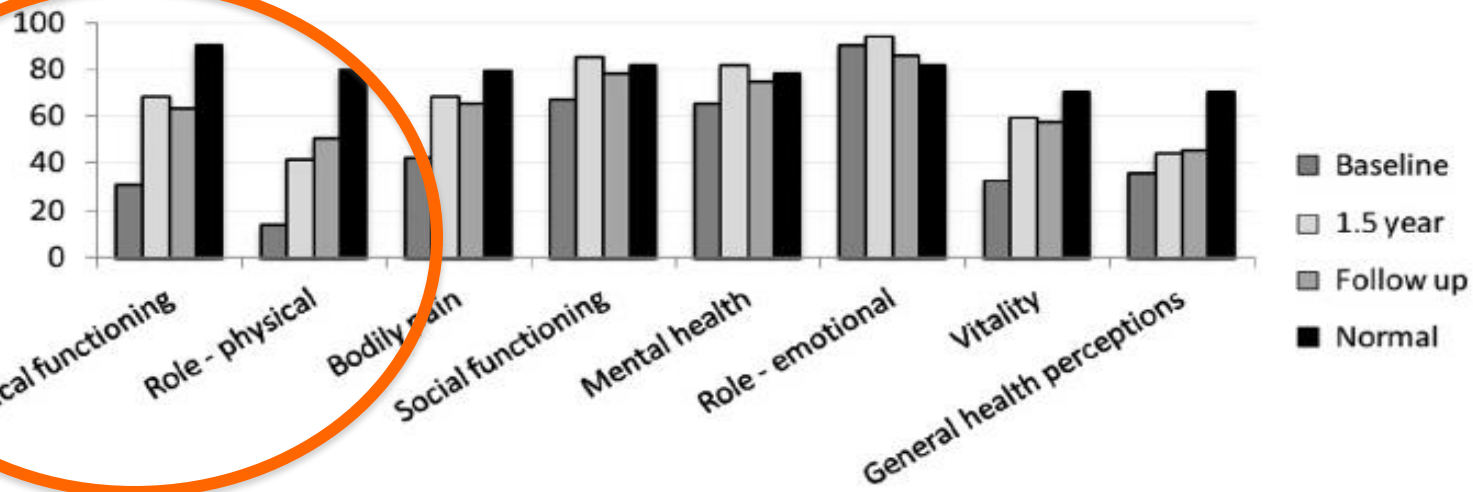


Therapy (continued)

- Prednisone monotherapy insufficient to control disease in most Necrotizing Autoimmune Myopathy patients.
- The relapse rate is high (in 55% of cases) during reduction of the medication or treatment discontinuation.
- Combination of oral corticosteroids and iv immunoglobulin reported to be effective as first-line therapy.
- More than half of NAM patients receiving aggressive immunotherapy recover markedly or improve to normal.

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

- Mortality 17% (10-15%), mostly cancer-related
- Approximately 70% of the patients have a chronic or polyphasic disease course.
- At follow-up (1.5 years), 68 % still perceived disabilities.
- After follow-up (~ 3 years) thirty-four (38 %) dependent on help from others for their activities of daily living.
- Improvement occurred in the first 18 months. After that, the disability score and quality of life score remained stable.





2001;70:569
M. Dalakas

Journal of
neurology
neurosurgery
& **psychiatry**

EDITORIAL

Progress in inflammatory myopathies: good but not good enough



We need more effective therapy and therapy with less side effects. The hemorrhages on the legs of this patient are caused by prednisone.