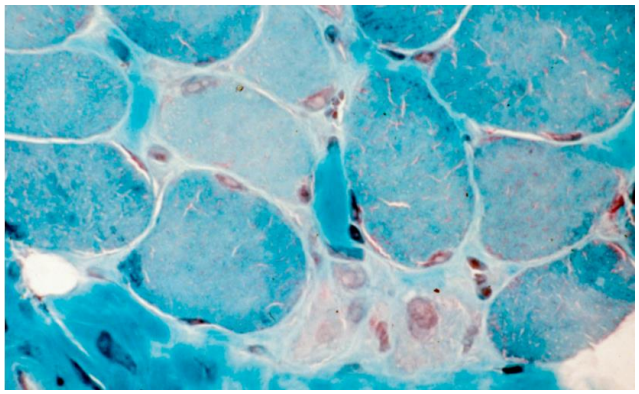
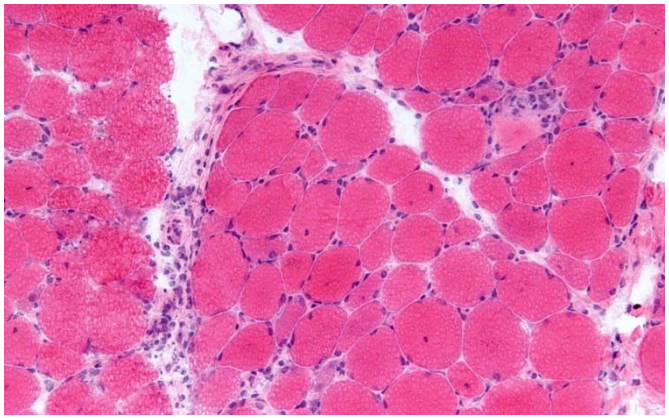
2nd SEMINARY OF LAREDIAB
8th CONGRESS OF AMIWIT
9 and 10 june 2021

# Inflammatory myopathy

Dr Bensefia Amel
Pr A.Lounici
Service de médecine interne
CHU Tlemcen





# Definition

- Heterogeneous group of rares diseases : Chronic inflammation in skeletal muscle.
- Large spectrum of clinical phenotypes
- Systemic disease : joint , skin , lungs , gastrointestinal tract , heart.
- Differents subgroups identified: *Dermatomyositis, Immune Mediated Necrotizing Myopathy , inclusion body myositis, Overlap myositis (including ASS), Polymyositis.*
- *Treatment response and prognosis vary within the subgroups.*

# First description

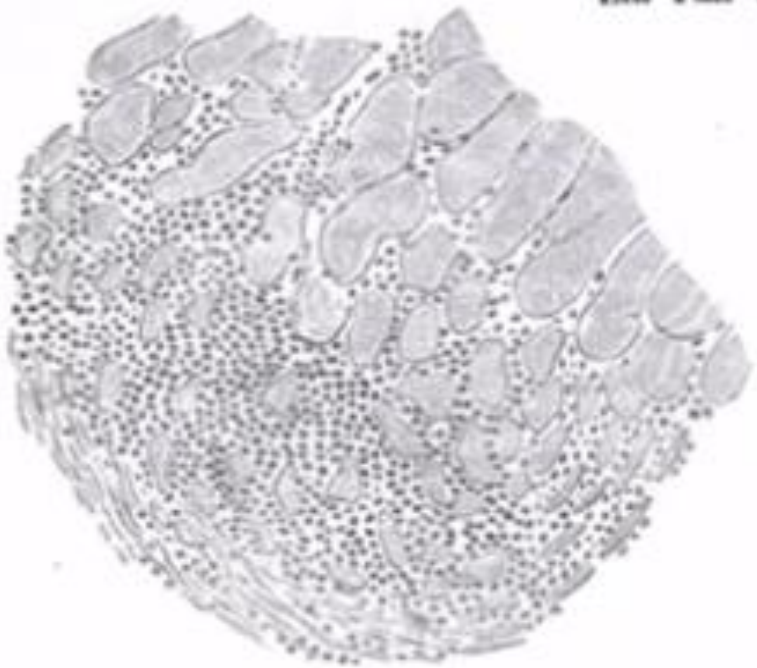
1885

XIV.

Ein Fall von acuter Polymyositis.

Von

E. Wagner.



# Classification

- *Dermatomyositis*
- *Immune mediated necroziting myopathy*
- *Inclusion body myositis*
- *Overlap Myositis*
- *Polymyositis*

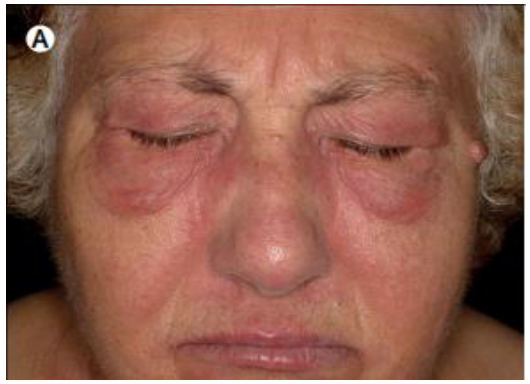
# Dermatomyositis

- Proximal Muscle weakness ( excepting amyopathic DM )
- Pathognomonic Skin features
- Elevated muscle enzymes
- EMG: myopatic pattern
- MRI: intramuscular T2 hyper intensities (inflammation or necrosis). T2 hyperintensities around individual muscles (fascial involvement)
- Muscle Biopsy :

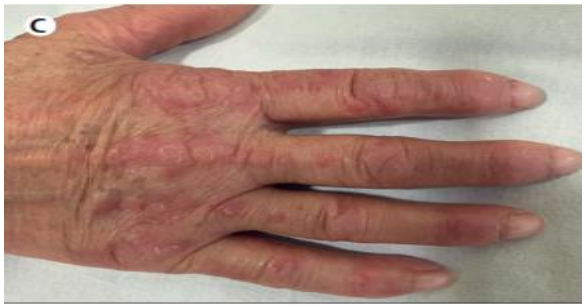
Perifascicular atrophy (specificity >90%)

cellular infiltrates : predominance of plasmacytoid dendritic cells, B cells, CD4 T cells, and macrophages. These cells often surround medium sized blood vessels and invade the perimysium.

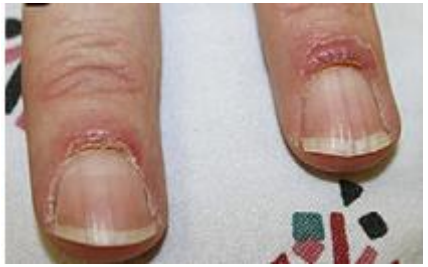
Deposition of membrane attack complex prominent in perifascicular regions.



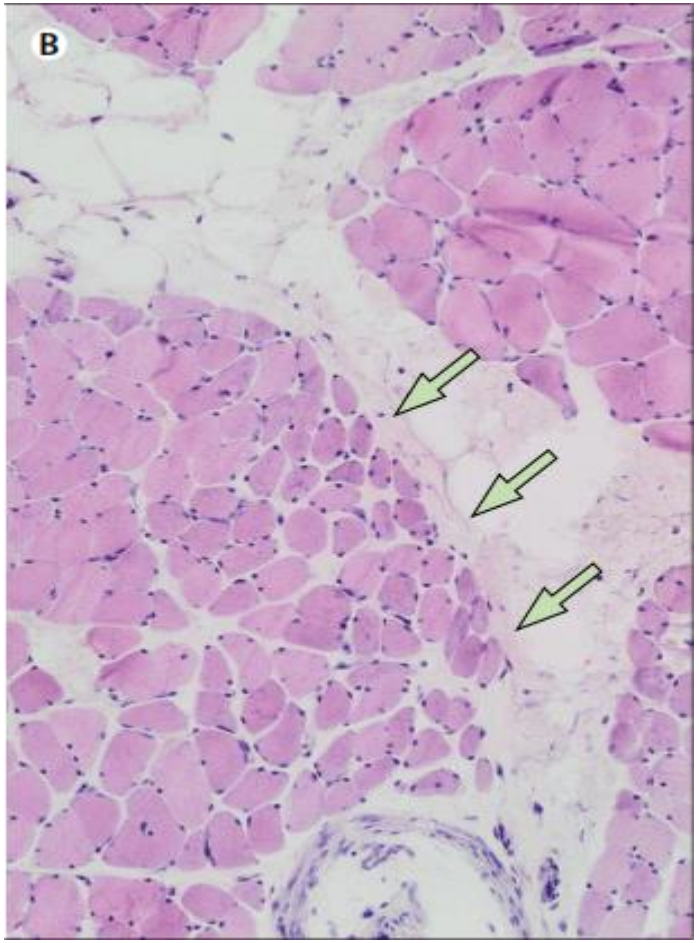

Heliotrope rash



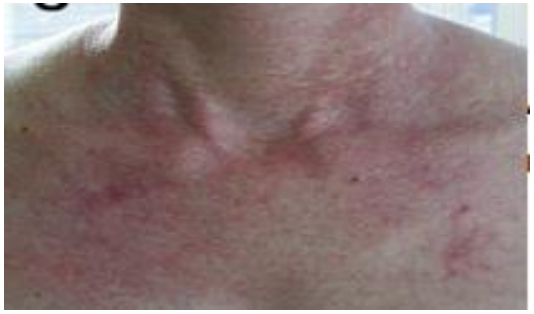

Gottron’s papules



Manucure sign




Peri fascicular atrophy



Neck erythema

| | Clinical features | Type of organ involvement and severity | | |
|---|---|---|---|---|
| | | Muscle | Lung | Skin |
| Dermatomyositis | | | | |
| Anti-Mi2 autoantibodies[12] | Mild-to-moderate muscle involvement with classical skin rash | Moderate | None | Moderate |
| Anti-NXP2 autoantibodies[13,14] | Mild-to-moderate muscle involvement with myalgia, classical skin rash, calcinosis, distal extensor weakness and oedema, and dysphagia; increased risk of cancer | Moderate | None | Moderate |
| Anti-TIF1 autoantibodies[14,15] | Strong association with cancer; mild muscle involvement with marked skin involvement, occasionally this type of myositis can present as clinically amyopathic dermatomyositis | Mild | None | Moderate |
| Anti-SAE autoantibodies[16] | Mild-to-moderate muscle involvement with classical skin rash | Mild | None | Moderate |
| Anti-MDA5 autoantibodies[17–19] | Severe skin rash with no muscle involvement (hypomyopathic or amyopathic dermatomyositis) and occasionally highly lethal forms of rapidly progressive interstitial lung disease | None or mild | Severe | Severe |
| Antibody-negative dermatomyositis[20] | Mild-to-moderate muscle involvement with classical skin rash | Mild | Unknown | Moderate |

NXP2=nuclear matrix protein 2. TIF1=transcription intermediary factor 1. SAE=small ubiquitin-like modifier activating enzyme. MDA5=melanoma differentiation-associated gene 5.

**Clinical characteristics of the main clinical and phenotype-specific autoantibody groups in inflammatory myopathies.** ***The Lancet Neurol 2018; 17: 816–28***

# Immune-mediated necrotising myositis

- Distinct type of inflammatory myopathy
- Severe Proximal muscle weakness
- Exceptionally high muscle enzyme concentrations.
- Myopathic EMG findings.

- Muscle biopsies :

  -**Necrosis or regeneration** with no or minimal lymphocytic infiltrates.

  -Classe1 major histocompatibility complex **upregulation,** M2 macrophage infiltration, and membrane attack complex (C5b_9)deposition on non-necrotic fibres.

- Extramuscular manifestations : Rare and Mild.

| | Clinical features | Type of organ involvement and severity | | |
|---|---|---|---|---|
| | | Muscle | Lung | Skin |
| Immune-mediated necrotising myopathy | | | | |
| Anti-SRP autoantibodies[21-23] | Severe muscle involvement, dysphagia, and 20% of patients with lung involvement with no skin lesions | Severe | Mild | None |
| Anti-HMGCR autoantibodies[24-26] | Exclusive severe muscle involvement; statin-exposed patients | Severe | None | None |
| Antibody-negative immune-mediated necrotising myopathy | Strong association with cancer | Unknown | Unknown | None |

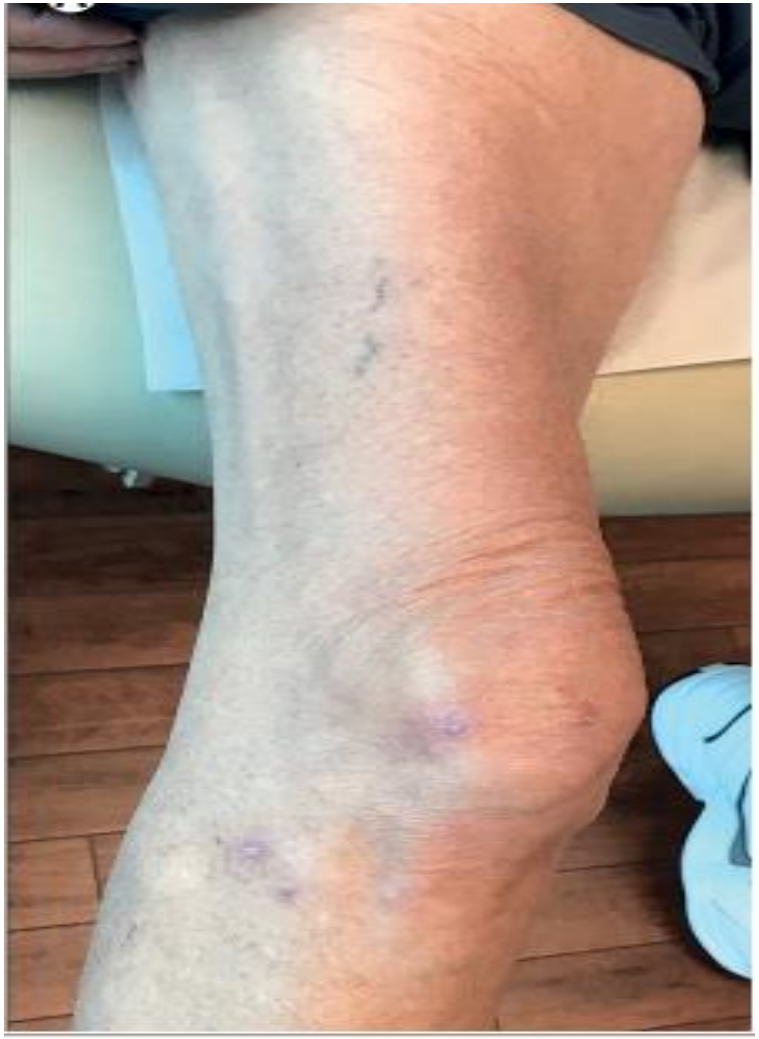
SRP=signal recognition particle. HMGCR=3-hydroxy 3-methylglutaryl coenzyme A reductase. J

**Clinical characteristics of the main clinical and phenotype-specific autoantibody groups in inflammatory myopathies.** ***The Lancet Neurol 2018; 17: 816–28***

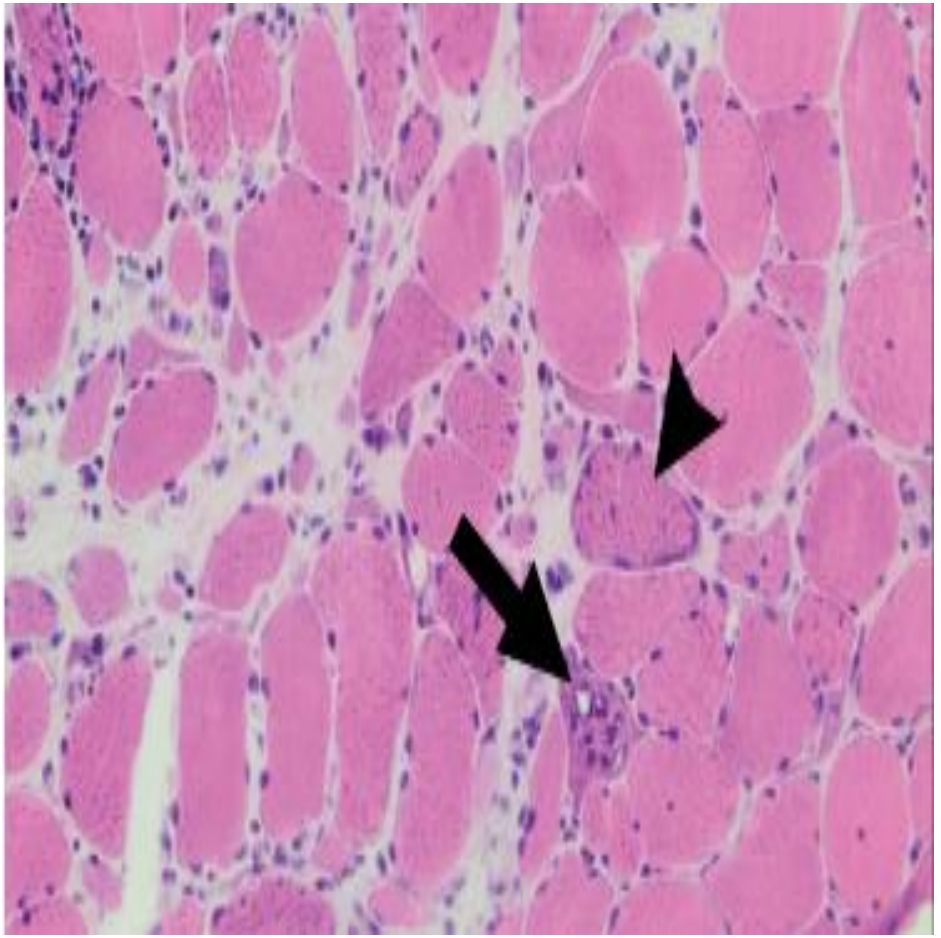
# Inclusion-body myositis

- Patients >50years.  Man=woman
- Distal muscle weakness , slowly progressive.
- asymmetric pattern of muscle weakness.
- ↑creatine kinase
- Myopathic EMG features.
- Prominent knee extensor weakness, distal weakness,

  deep finger flexors, wrist flexors, and ankle dorsiflexors; arm abductors.
- Progressive dysphagia  which can lead to broncho aspiration
- Muscle biopsies histologically unique : coexisting inflammation, mitochondrial  dysfunction, and abnormal protein aggregation.
- cN1A antibody in 30-60%.



Quadriceps Atrophy



Muscular Fibres with rimmed vacuoles

*Quadriceps image courtesy of Dr Tom Lloyd (Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA).*

# Overlap Myositis

- Autoimmune myopathy associated with other connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis).
- Antisynthetase Syndrom:

  Inflammatory myopathy

  Interstitial lung disease

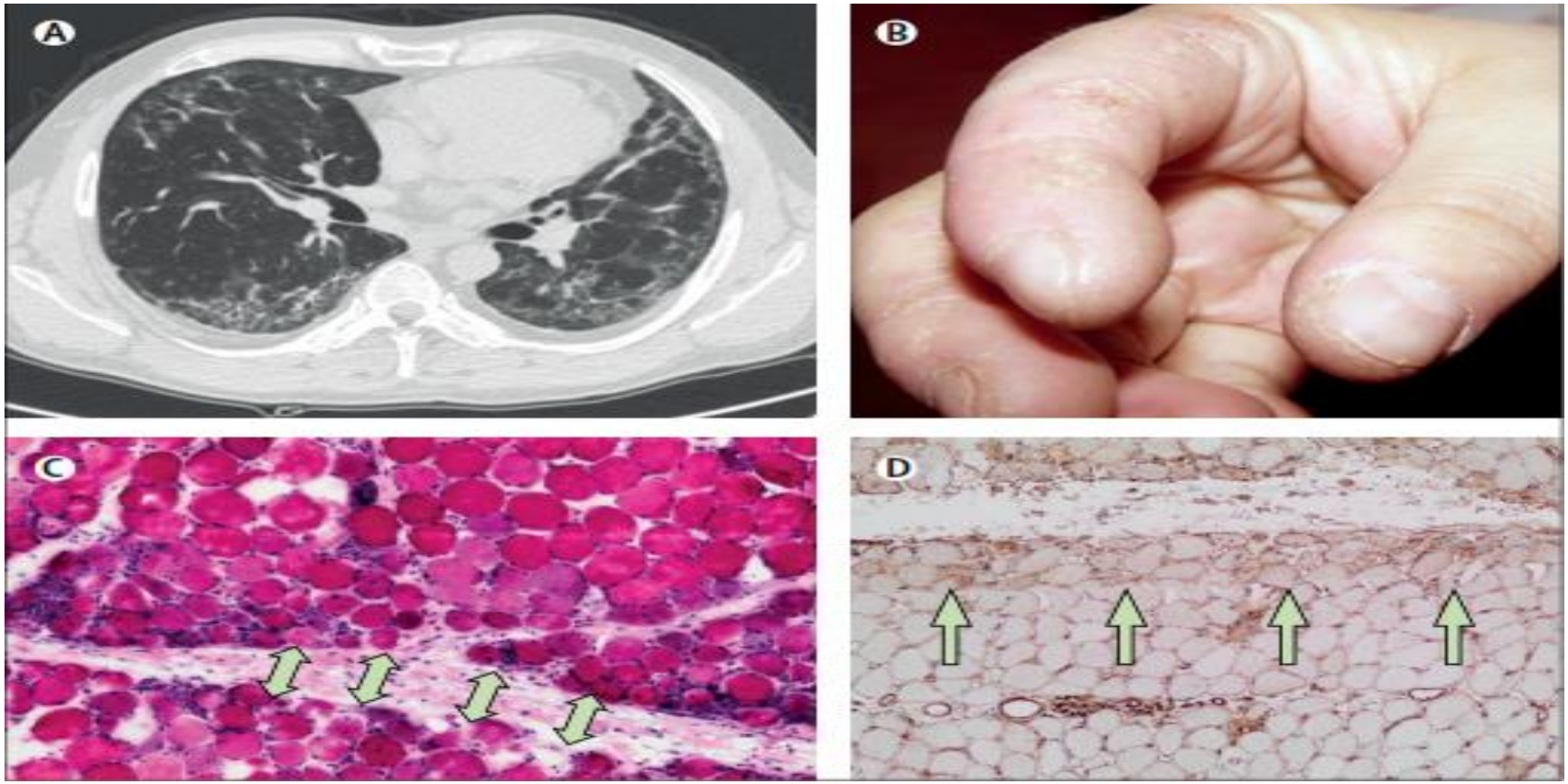
  Arthritis

  Raynaud syndrome, fever

  Hyperkeratotic radial-finger lesions =''mechanic's hands''

  anti- JO1

# Antisynthetase Syndrom




A woman aged 45 years presented with muscle weakness and dyspnoea. (A) A high-resolution chest CT scan showed interstitial lung disease. She had crackles in both lung bases and (B) mechanic's hands. Muscle biopsy showed (C) necrotic and regenerating muscle fibres in the perifascicular area (arrows) and (D) prominent class-1 major histocompatibility complex positivity predominantly in the perifascicular area (arrows). Serum was positive for anti-Jo1 antibodies. Jo1=histidyl tRNA synthetase.

*Dalakas MC. Inflammatory muscle diseases. N Engl J Med 2015;* ***373: 393–94.***

| | Clinical features | Type of organ involvement and severity | | |
|---|---|---|---|---|
| | | Muscle | Lung | Skin |
| Overlap myositis | | | | |
| Antisynthetase syndrome | | | | |
| Anti-Jo1 autoantibodies[28,29] | Mild-to-moderate muscle involvement with progressive lung involvement and possible mild dermatomyositis skin rash (~50% of patients); other characteristic cutaneous features (eg, mechanic's hands and Raynaud syndrome) | Moderate | Moderate | Mild |
| Anti-PL7 autoantibodies[28] | Symptoms are similar to those of anti-Jo1 autoantibody-positive myositis with more severe lung involvement | Moderate | Severe | Mild |
| Anti-PL12 autoantibodies[28] | Severe lung involvement with mild muscle weakness | Mild | Severe | Mild |
| Anti-Pm/Scl autoantibodies[30] | Mild myositis and scleroderma features with muscle weakness, interstitial lung disease, and skin involvement | Mild | Mild | Mild |
| Anti-Ku autoantibodies[31] | Mild muscle involvement and interstitial lung disease | Mild | Mild | Mild |
| Anti-U1RNP autoantibodies[32] | Myositis, scleroderma, and systemic lupus erythematosus features; glomerulonephritis and pulmonary hypertension are possible | Mild | Mild | Mild |

Jo1=histidyl tRNA synthetase. PL7=threonyl tRNA synthetase. PL12=alanyl tRNA synthetase. Pm/Scl=anti-polymyositis-scleromyositis, EXOSC9 and EXOSC10 antigens. U1RNP=U1 ribonucleoprotein.

**Clinical characteristics of the main clinical and phenotype-specific autoantibody groups in inflammatory myopathies.** ***The Lancet Neurol 2018; 17: 816–28***

# Polymyositis

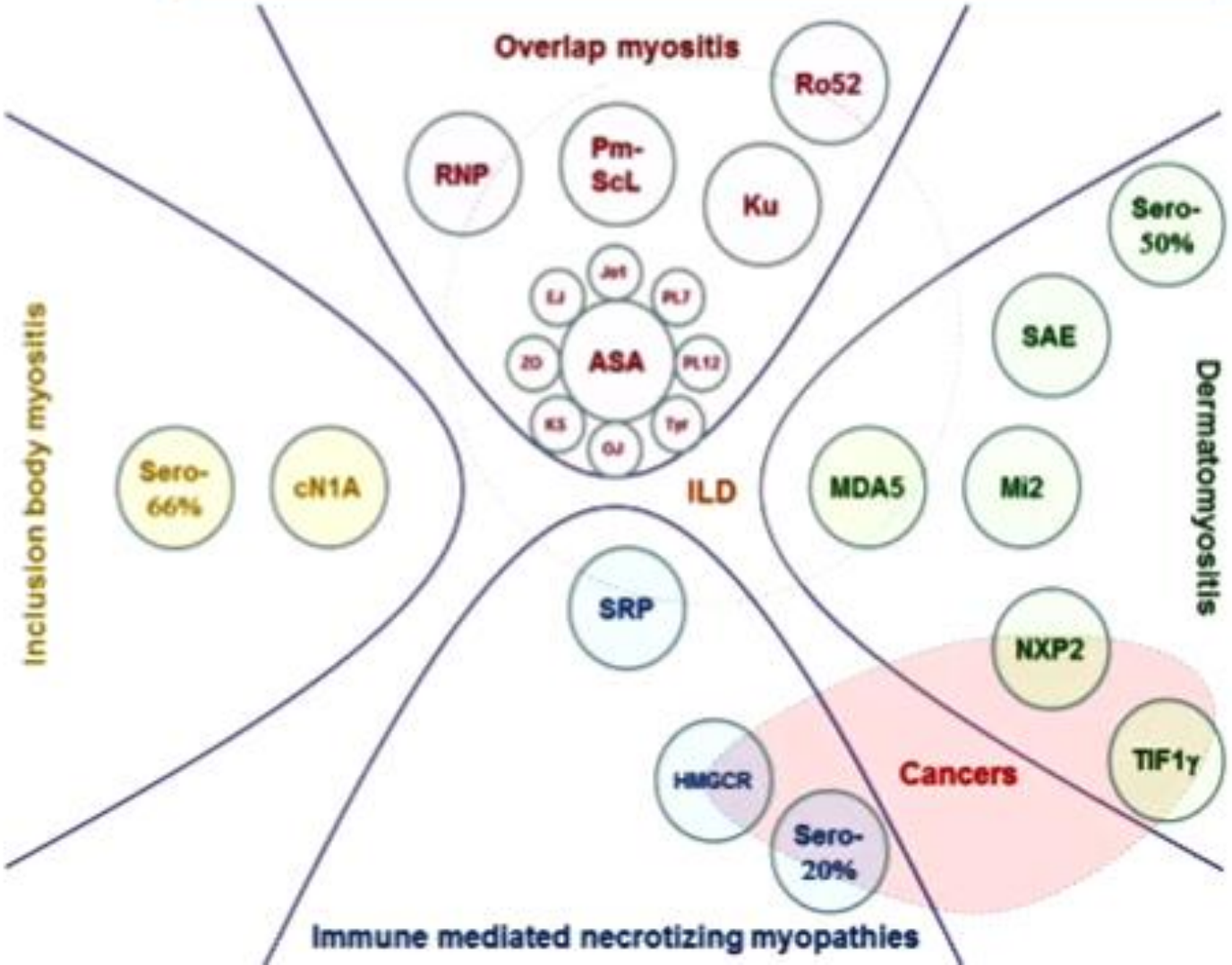
- Muscle weakness, elevated creatine phosphokinase concentrations, myopathic EMG features, and inflammatoryCD8 T-cell infiltrates on muscle biopsy
- None of the characteristic Accompanying features of the other above mentioned groups.
- Diagnosis of exclusion.
- patients should be closely monitored for new clinical features suggesting alternative diagnoses.

CURRENT OPINION

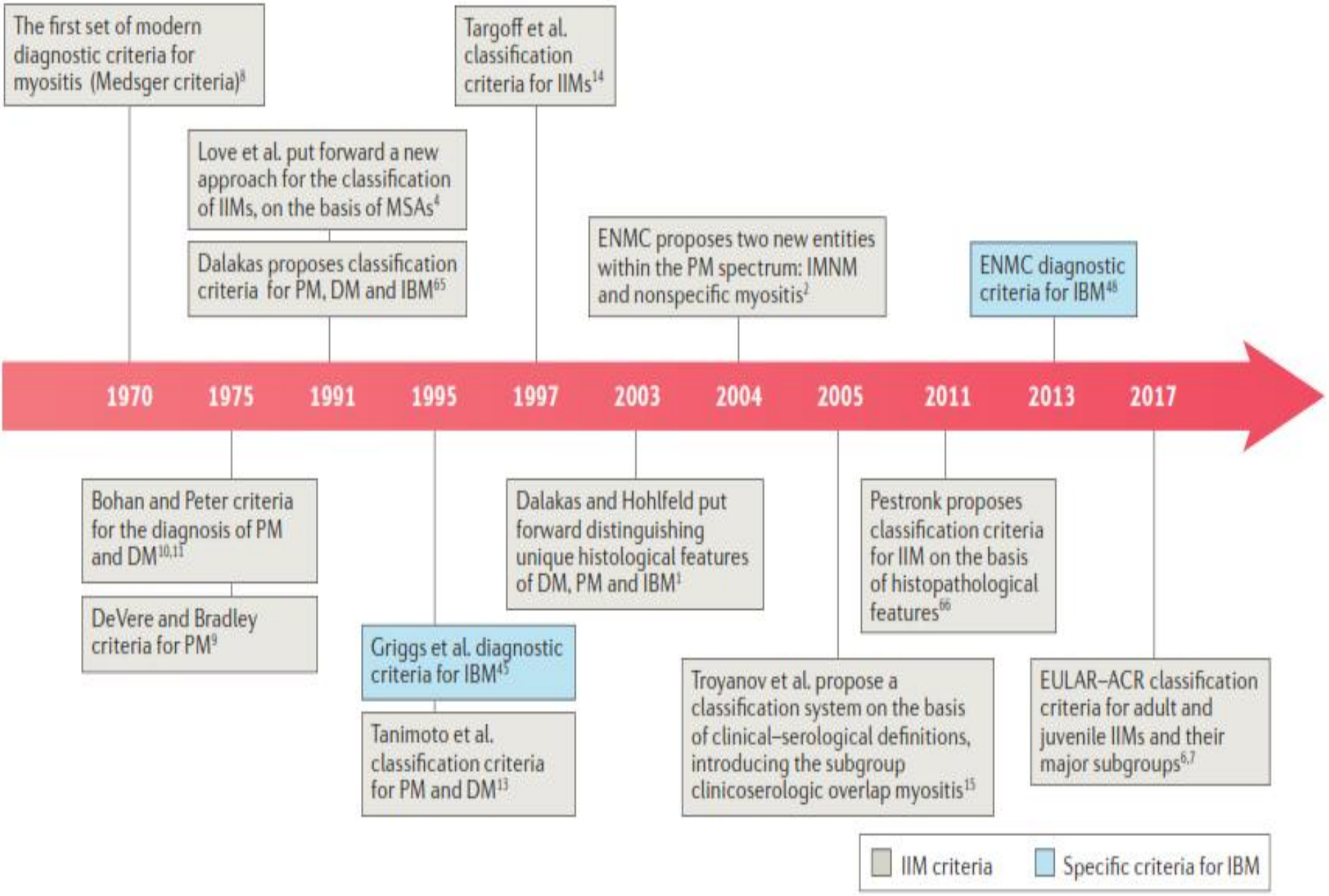
# Advances in serological diagnostics of inflammatory myopathies

Volume 29 • Number 5 • October 2016

Olivier Benveniste[a,b], Werner Stenzel[c], and Yves Allenbach[a,b]



# Classification criteria




**Developpement of diagnostic and classification criteria for inflammatory idiopathic myopathy over time**

## The Bohan and Peter criteria for DM and PM

First, rule out all other forms of myopathies

1. Symmetrical weakness, usually progressive, of the limb-girdle muscles with or without dysphagia and respiratory muscle weakness
2. Muscle biopsy evidence of myositis

   Necrosis of type I and type II muscle fibers; phagocytosis, degeneration, and regeneration of myofibers with variation in myofiber size; endomysial, perimysial, perivascular, or interstitial mononuclear cells.
3. Elevation of serum levels of muscle-associated enzymes (CK, LDH, transaminases, aldolase)
4. EMG triad of myopathy
   a. Short, small, low-amplitude polyphasic motor unit potentials
   b. Fibrillation potentials, even at rest
   c. Bizarre, high-frequency repetitive discharges
5. Characteristic rashes of dermatomyositis

Definite PM: all first four elements, probable PM: 3 of first 4, possible PM: 2 of first 4.
Definite DM: rash *plus* 3 others, probable DM: rash *plus* 2 others, possible DM: rash *plus* 1 other

CK, creatinine kinase; LDH, lactate dehydrogenase; EMG, electromyography; PM, polymyositis; DM, dermatomyositis

Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med. 1975;292(8):403–7.

Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292(7):344–7.

# The EULAR/ACR classification

Box 1 | **The EULAR–ACR classification criteria for adult and juvenile IIMs and their major subgroups**[6,7]

**Muscle biopsy available**

- Probable idiopathic inflammatory myopathies (IIMs): aggregated score (probability ≥55% and <90%) ≥6.7 and <8.7
- Definite IIMs: aggregated score (probability ≥90%) ≥8.7

**Muscle biopsy not available**

- Probable IIMs: aggregated score (probability ≥55% and <90%) ≥5.5 and <7.5
- Definite IIMs: aggregated score (≥90% probability) ≥7

| Variable | Score | |
|---|---|---|
| | Without muscle biopsy | With muscle biopsy |
| Age of onset of first symptom assumed to be related to the disease ≥18 years and <40 years | 1.3 | 1.5 |
| Age of onset of first symptom assumed to be related to the disease ≥40 years | 2.1 | 2.2 |
| ***Muscle weakness*** | | |
| Objective symmetrical weakness, usually progressive, of the proximal upper extremities | 0.7 | 0.7 |
| Objective symmetrical weakness, usually progressive, of the proximal lower extremities | 0.8 | 0.5 |
| Neck flexors are relatively weaker than neck extensors | 1.9 | 1.6 |
| In the legs, proximal muscles are relatively weaker than distal muscles | 0.9 | 1.2 |
| ***Skin manifestations*** | | |
| Heliotrope rash | 3.1 | 3.2 |
| Gottron papules | 2.1 | 2.7 |
| Gottron sign | 3.3 | 3.7 |

| | | |
|---|---|---|
| ***Other clinical manifestations*** | | |
| Dysphagia or oesophageal dysmotility | 0.7 | 0.6 |
| ***Laboratory measurements*** | | |
| Anti-histidyl-transfer RNA synthetase (Jo1) autoantibody present | 3.9 | 3.8 |
| Elevated serum levels of one of the following enzymes[a]: creatine kinase, lactate dehydrogenase, aspartate aminotransferase or alanine aminotransferase | 1.3 | 1.4 |
| ***Muscle biopsy features — presence of*** | | |
| Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibres | – | 1.7 |
| Perimysial and/or perivascular infiltration of mononuclear cells | – | 1.2 |
| Perifascicular atrophy | – | 1.9 |
| Rimmed vacuoles | – | 3.1 |

Table adapted from Lundberg, I. E. et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann. Rheum. Dis.* **76**, 1955–1964 (2017) (REF. 6) and with permission from REF. 7, Wiley. [a]Serum levels above the upper limit of normal.

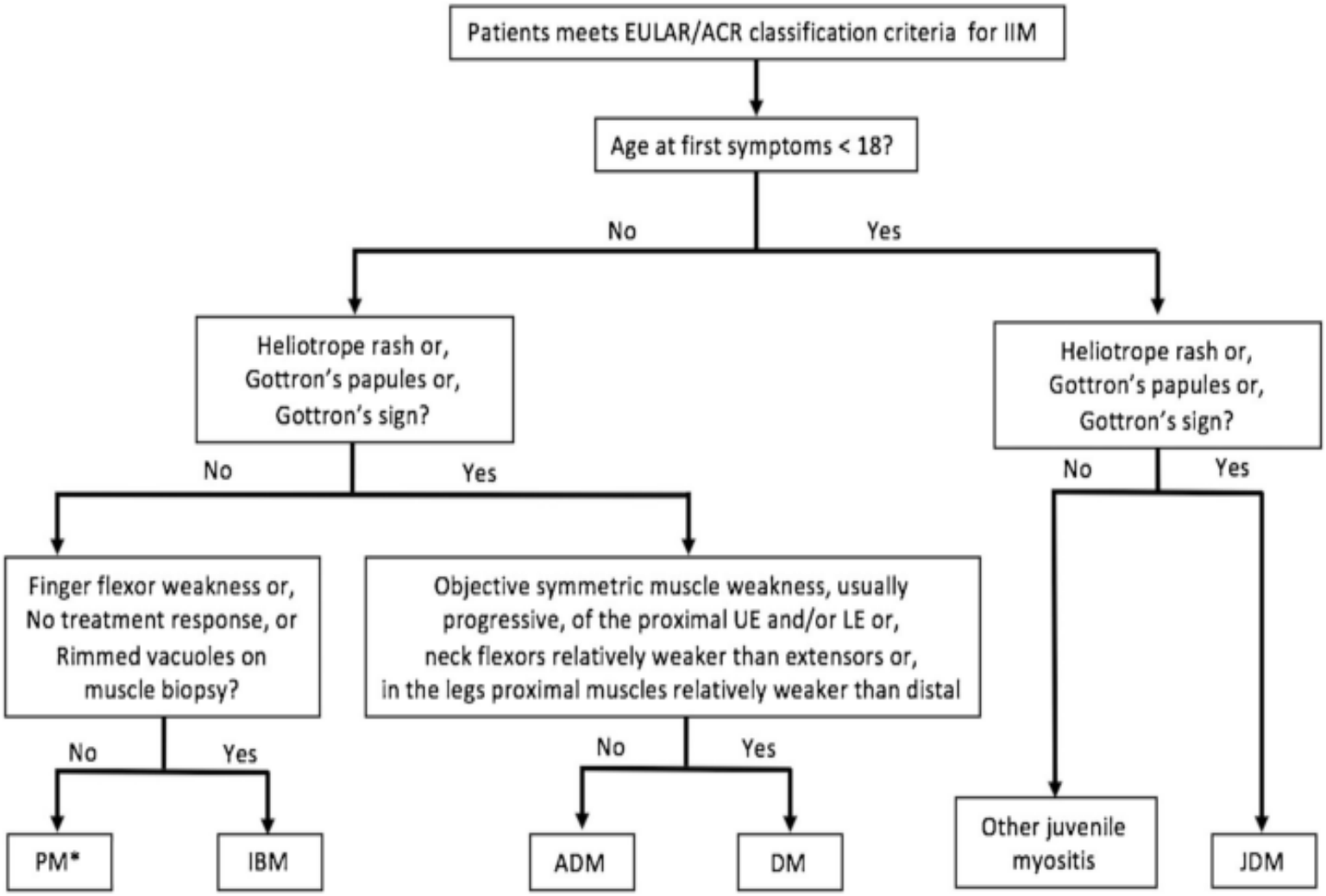



**Fig. 1** Subgroups of IIM according to the 2017 EULAR/ACR classification criteria [7]. *The PM subset includes immune-mediated necrotizing myopathies (IMNM). PM, polymyositis; IBM, inclusion body myositis; ADM, amyopathic dermatomyositis; DM, dermatomyositis; JDM, juvenile dermatomyositis

Lundberg IE, Tjarnlund A, Bottai M, Werth VP, Pilkington C, Visser M, et al. European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Ann Rheum Dis. 2017;76(12):1955–64

Comparison of various classification and diagnostic criteria sets

| | Type of criteria | SN[a] | SP[a] | Type of classification | | | | IIM subtypes proposed |
|---|---|---|---|---|---|---|---|---|
| | | | | EMG | BX | MSA | MRI | |
| Bohan and Peter [1, 2] | Diagnostic/classification | 94–98% | 29–55% | X | X | | | DM, PM<br>Childhood DM/PM with vasculitis<br>DM/PM with neoplasia or CTD. |
| Tanimoto [17] | Classification | 89–96% | 29–31% | X | X | X | | DM, PM |
| Targoff [10] | Diagnostic/classification | 97–93% | 29–89% | X | X | X | X | DM, PM<br>Childhood DM/PM with vasculitis<br>DM/PM with neoplasia or CTD<br>IBM |
| Dalakas [21] | Diagnostic | 6–77% | 99% | X | X | | | DM, PM, ADM |
| ENMC [27] | Classification | 52–71% | 82–97% | X | X | X | X | DM, PM, ADM<br>DM sine dermatitis<br>Non-specific myositis<br>IMNM<br>IBM |
| EULAR/ACR [7] | Classification | No biopsy 87%<br>Biopsy 93% | 82%<br>88% | | X[b] | X | | DM, PM, ADM<br>JDM<br>IBM |

SN, sensitivity; SP, specificity; EMG, electromyography; BX, muscle biopsy; MSA, myositis-specific autoantibodies; MRI, magnetic resonance imaging; DM, dermatomyositis; PM, polymyositis; ADM, amyopathic dermatomyositis; CTD, connective tissue disease; IBM, sporadic inclusion body myositis; IMNM, immune-mediated necrotizing myopathy; JDM, juvenile dermatomyositis

[a] "Definite" and "probable" diagnoses were considered positive cases, and "possible" diagnoses, negative cases. Specialist diagnosis represented the gold standard [7, 41]

[b] The EULAR/ACR classification can be used with or without muscle biopsy results

Leclair, V., Lundberg, I.E. New Myositis Classification Criteria—What We Have Learned Since Bohan and Peter. *Curr Rheumatol Rep* **20,** 18 (2018)

# Management

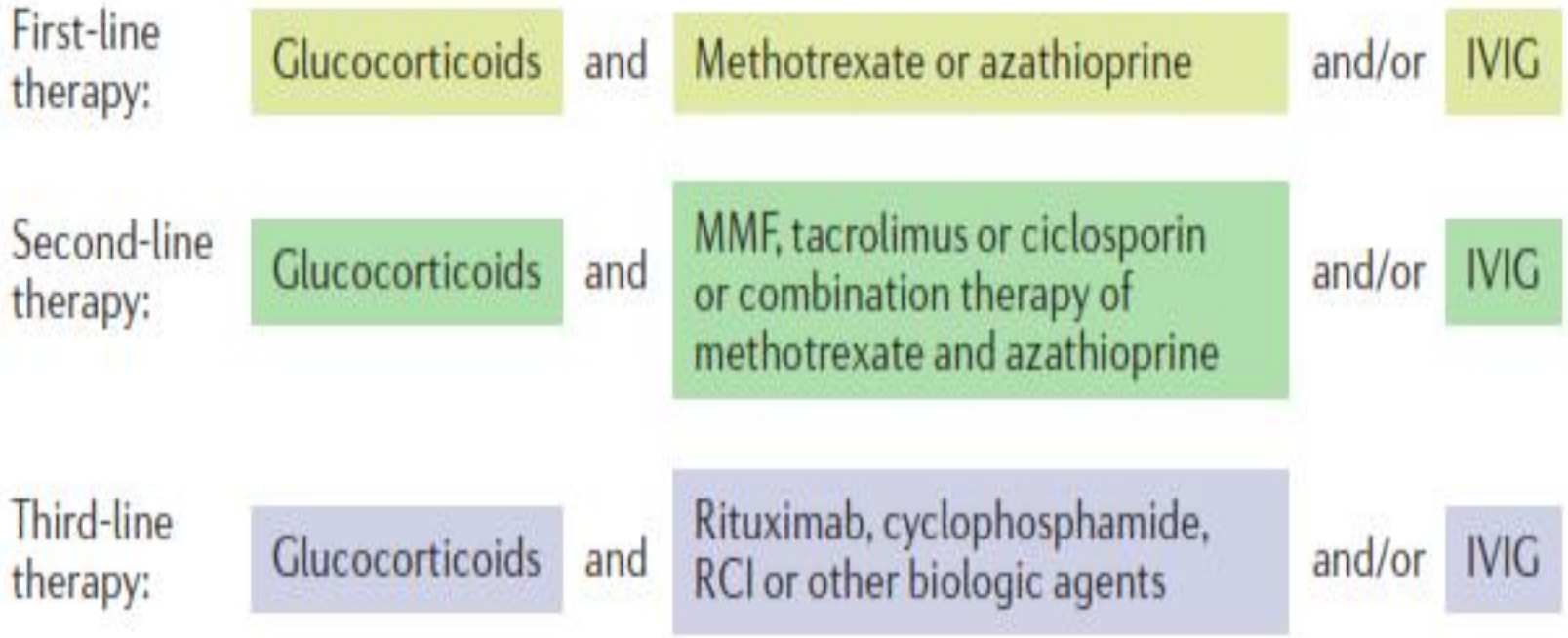
## Non inclusion body myopathies

| | Doses and treatment suggestions | Treatment for | Side-effects |
|---|---|---|---|
| Immunosuppressive or immunomodulatory drugs | | | |
| Corticosteroids[3] | Prednisone 0·5–1 mg/kg per day. Consider adding 500 mg to 1 g intravenous methylprednisolone pulses once per day for 3 days for severe cases | All patients and all manifestations | Hypertension, hyperglycaemia, hyperlipidaemia, osteoporosis, infections, and cataracts |
| Azathioprine[3] | 2–3 mg/kg per day | Predominantly myositis | Gastrointestinal symptoms, myelosuppression, leukaemia pancreatitis, infections, and liver toxicity |
| Methotrexate[3,77] | Up to 25 mg per week | Arthritis; use with caution in interstitial lung disease | Stomatitis, gastrointestinal symptoms, leucopoenia, liver toxicity, infections, and lung toxicity |
| Ciclosporin[78] | Up to 5 mg/kg per day | Skin involvement (panniculitis and dermatomyositis skin rashes) and interstitial lung disease | Renal insufficiency, anaemia, infections, and hypertension |
| Tacrolimus[79] | 0·06 mg/kg per day | Interstitial lung disease | Hypertension, renal insufficiency, gastrointestinal symptoms, infections, and tremor |
| Mycophenolate mofetil[80] | 2–3 g per day | Interstitial lung disease | Gastrointestinal symptoms, myelosuppression, infections, and hypertension |
| Cyclophosphamide[81] | Intravenous 0·5–1 g/m$^2$ per month or 10–15 mg/kg per month for 6–12 months | Interstitial lung disease | Myelosuppression, myeloproliferative disorders, haemorrhagic cystitis, bladder cancer, infections, and infertility |
| Intravenous immunoglobulins[82,83] | 2 g per kg every 4–6 weeks | Dysphagia and severe disease refractory to other treatments | Hypotension, anaphylaxis, headache, aseptic meningitis, blood clots, infections, and renal toxicity |

| | Doses and treatment suggestions | Treatment for | Side-effects |
|---|---|---|---|
| Biological agents | | | |
| Rituximab[21,40,84,85] | 1 g given twice within a 2-week interval; maintenance with either one or two doses of 0·5–1 g rituximab on the basis of the patient's clinical situation and their CD19 and CD20 counts (usually given every 6–9 months) | Rapidly progressive interstitial lung disease and severe cases of inflammatory myopathies | Infusion-related reaction, infections, and progressive multifocal leukoencephalopathy |
| Abatacept[86] | 750 mg intravenously every 4 weeks (if patient's weight <60 kg, 500 mg; if patient's weight >100 kg, 1000 mg) | Consider for refractory disease | Infusion reactions and infections |
| Tocilizumab[87] | 8 mg per kg intravenously every 4 weeks or 162 mg per week subcutaneously | Consider for refractory disease | Liver toxicity, neutropaenia, thrombocytopaenia, infections, hyperlipidaemia, and intestinal perforation |
| Physical exercise[73,74] | Aerobic and resistance-tailored programmes (about 4 weeks after starting medical treatment or as soon as the patient can cope with exercise) | All patients, as a coadjuvant therapy | Not described |

*Treatment options for inflammatory myopathies other than inclusion –body myositis .* ***The Lancet Neurology september 2018***

- Some cases habe reported the efficacity of anakinra (antiinterleukin1), alemtuzumab (anti-CD52), Tofacinib and ruxolitinib (janus-kinase inhibitors) in inflammatory myopathies, but confirmatory studies are required for these treatments to be widely used in clinical practice.




**Oddis, C., Aggarwal, R. Treatment in myositis. *Nature Reviews Rheumatology* 14, 279–289 (2018)**

## *Panel:* Sequential treatment approach and treatment of severe manifestations of the disease

### Inflammatory myopathies

*Initial treatment*

- Corticosteroids and physical exercise with the addition of a corticosteroid-sparing agent (azathioprine, methotrexate, ciclosporin, tacrolimus, or mycophenolate mofetil) in all patients to minimise the toxicity of corticosteroids[3,73,74,76]

*Treatment for severe or refractory cases of disease*

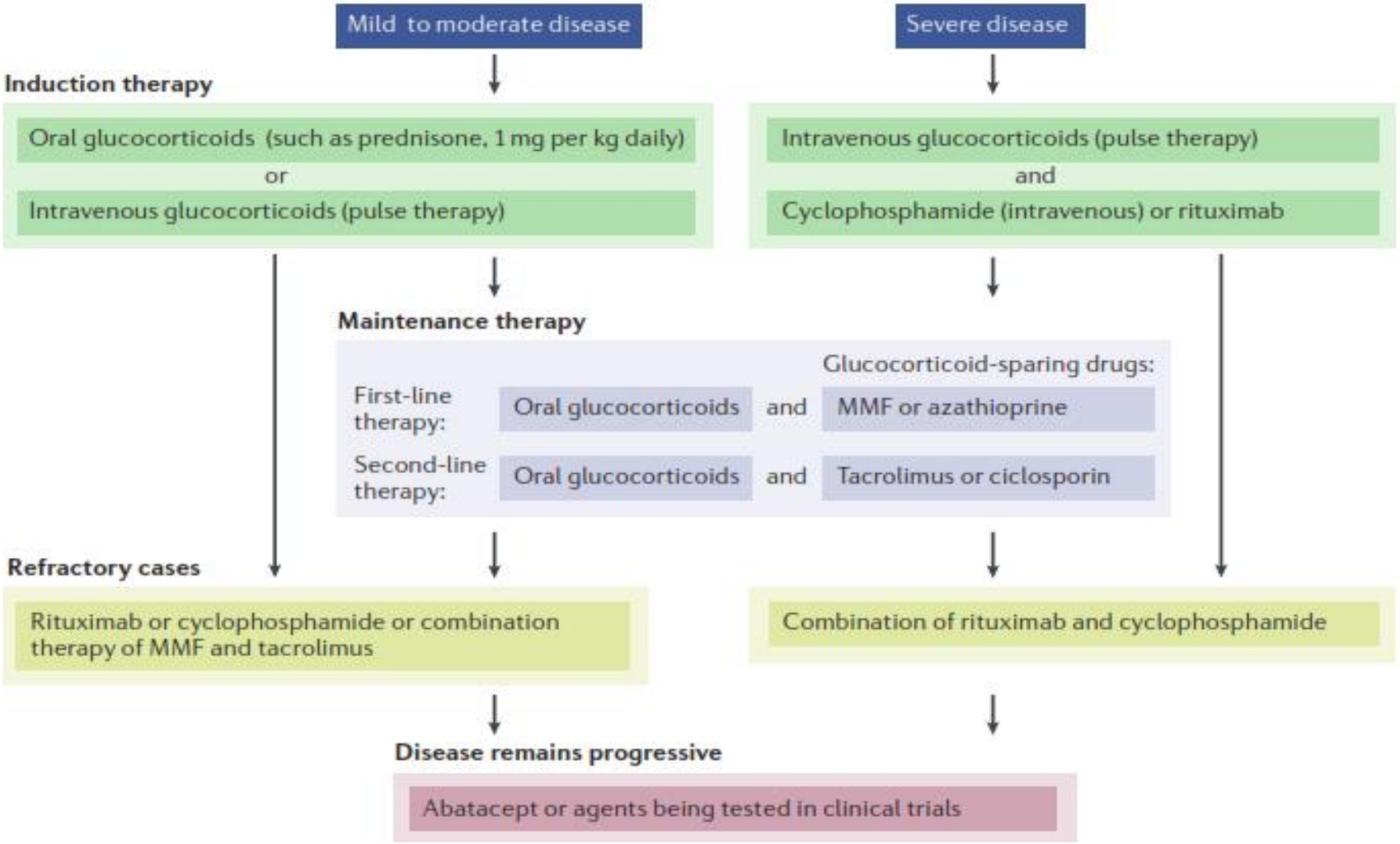
- Corticosteroids and physical exercise with the addition of intravenous immunoglobulins, rituximab, or both agents; in patients with refractory disease, other biological agents, such as abatacept and tocilizumab, can be used[86,87]

### Dysphagia

- Corticosteroids, a second-line treatment agent, and intravenous immunoglobulin; in selected patients, local therapies including cricopharyngeal myotomy, pharyngo-oesophageal balloon dilatation, or injection of botulinum toxin into the upper oesophageal sphincter can be used[107–109]

### Rapidly progressive interstitial lung disease

- Pulses of methylprednisolone followed by systemic corticosteroids along with a second-line treatment agent (eg, tacrolimus, mycophenolate mofetil, cyclophosphamide, or rituximab). Additionally, the following treatments should be considered: two sessions of polymyxin in 24 h, daily plasmapheresis over the course of 3 days and on alternate days thereafter until the completion of seven sessions, and 400 mg intravenous immunoglobulin per kg after each plasmapheresis session




**Proposed approach to treating myositis-associated interstitial lung disease.**

*Chester V. Oddis*. Rohit Aggarwal. Treatement in Myositis. Nature Review Rhumatology. April2018.*

# Management

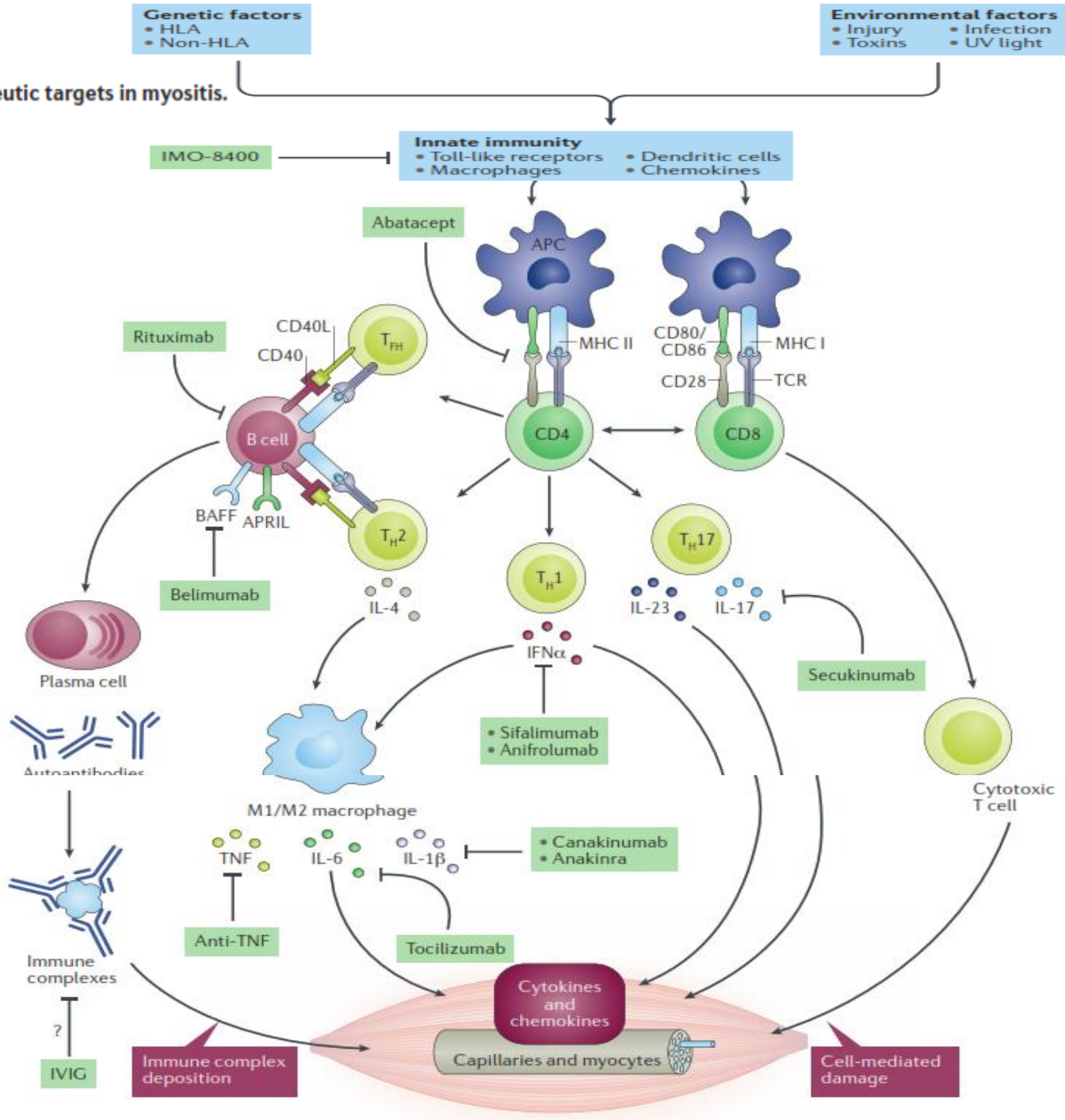
## inclusion body myositis

# Inclusion body myositis

- No pharmacological therapy has been shown to be effective in IBM.
- Treatment remains largely suggestive supportive.
- Immunosuppressive drugs such a corticosteroids, azathioprine, methotrexate,Etanercept, Anakinra, or Interferonß are **not effective** in inclusion-body myositis.

- **Alemtuzumab** : anti-T-cell agent
- **Bimagrumab** a human monoclonal antibody that blocks the myostatin pathway.
- **Sirolimus**: inhibitor of myostatinl ocally delivered using an adenovirus.
- **Arimoclomol** : ongoing trial (NCT02753530) (a drug that prevents aberrant protein–protein interaction and promotes adequate protein folding
- **Natalizumab** Ongoing trial (NCT02483845) investigating is ongoing.
- Other drugs with alternative mechanisms of action
- have been investigated: **Oxandrolone,** an anabolic steroid, and **simvastatin**, a cholesterol-lowering agent, were not shown to be effective in small clinical trials.

**Immune-related potential therapeutic targets in myositis.**



# Références


- O'Callaghan.A .Classification and management of adult inflammatory myopathies. The Lancet Neurology volume 17,Issue9, 816-828.
- *I.E. Lundberg. Classification of myositis. Nature Review Rhumatology.Volume14.May2018*
- Leclair V. Lundberg, I.E. New Myositis Classification Criteria—What We Have Learned Since Bohan and Peter. *Curr Rheumatol Rep* **20,** 18 (2018)
- Lundberg IE, Tjarnlund A, Bottai M, Werth VP, Pilkington C, Visser M, et al. European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Ann Rheum Dis. 2017;76(12):1955–64
- *Chester V. Oddis*. Rohit Aggarwal. Treatement in Myositis. Nature Review Rhumatology. April2018.*

Merci de votre attention