# II Simposio Multidisciplinar

# Enfermedades Autoinmunes Sistémicas

#multiEAS

## Madrid

**20-21 enero 2023**

NH COLLECTION EUROBUILDING

AEDV Academia Española de Dermatología y Venereología

SEMI Sociedad Española de Medicina Interna

SEI Sociedad Española de Inmunología

Sociedad Española de Nefrología

Sociedad Española de Neumología y Cirugía Torácica SEPAR

Sociedad Española de Reumatología

SEPD Sociedad Española de Patología Digestiva

# Relación entre HISTOLOGÍA y TERAPÉUTICA en las MIOPATÍAS INFLAMATORIAS

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21 de enero de 2023

# Hoja de ruta

① Introducción

② Entidades: histología + autoanticuerpos

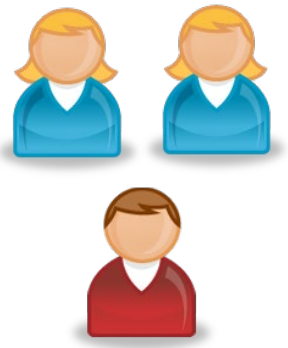
③ Tratamiento: músculo +/- otras manifestaciones

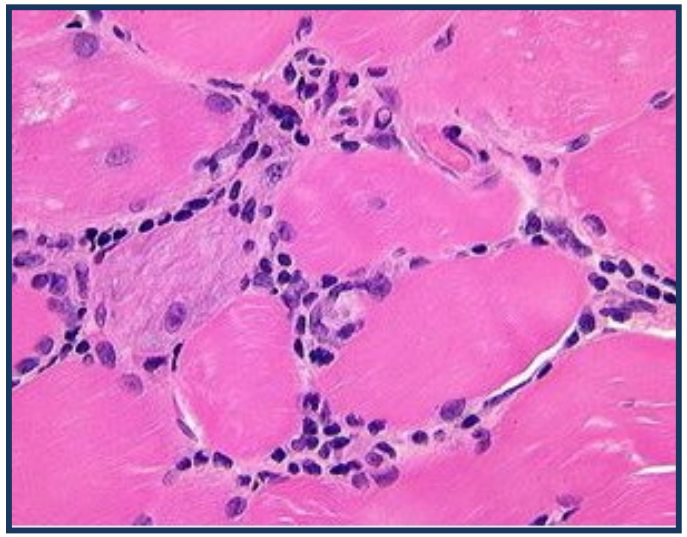
④ Situaciones especiales

⑤ Conclusiones

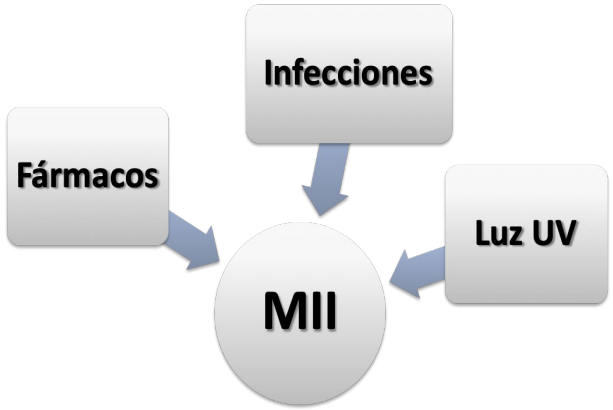
# Introducción

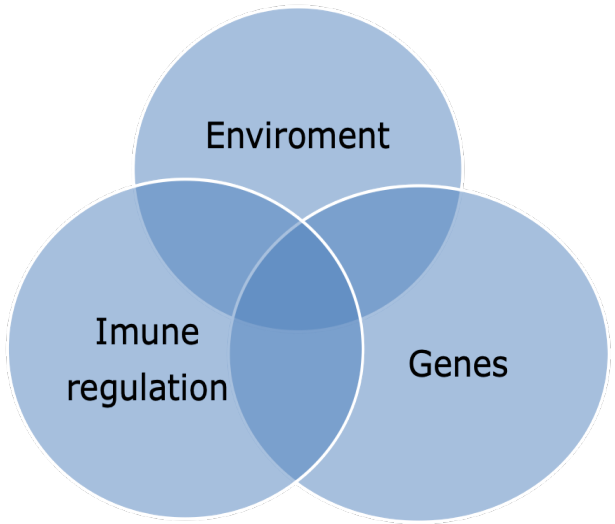
- Grupo heterogéneo de entidades
- Causa desconocida
- 40-50 años





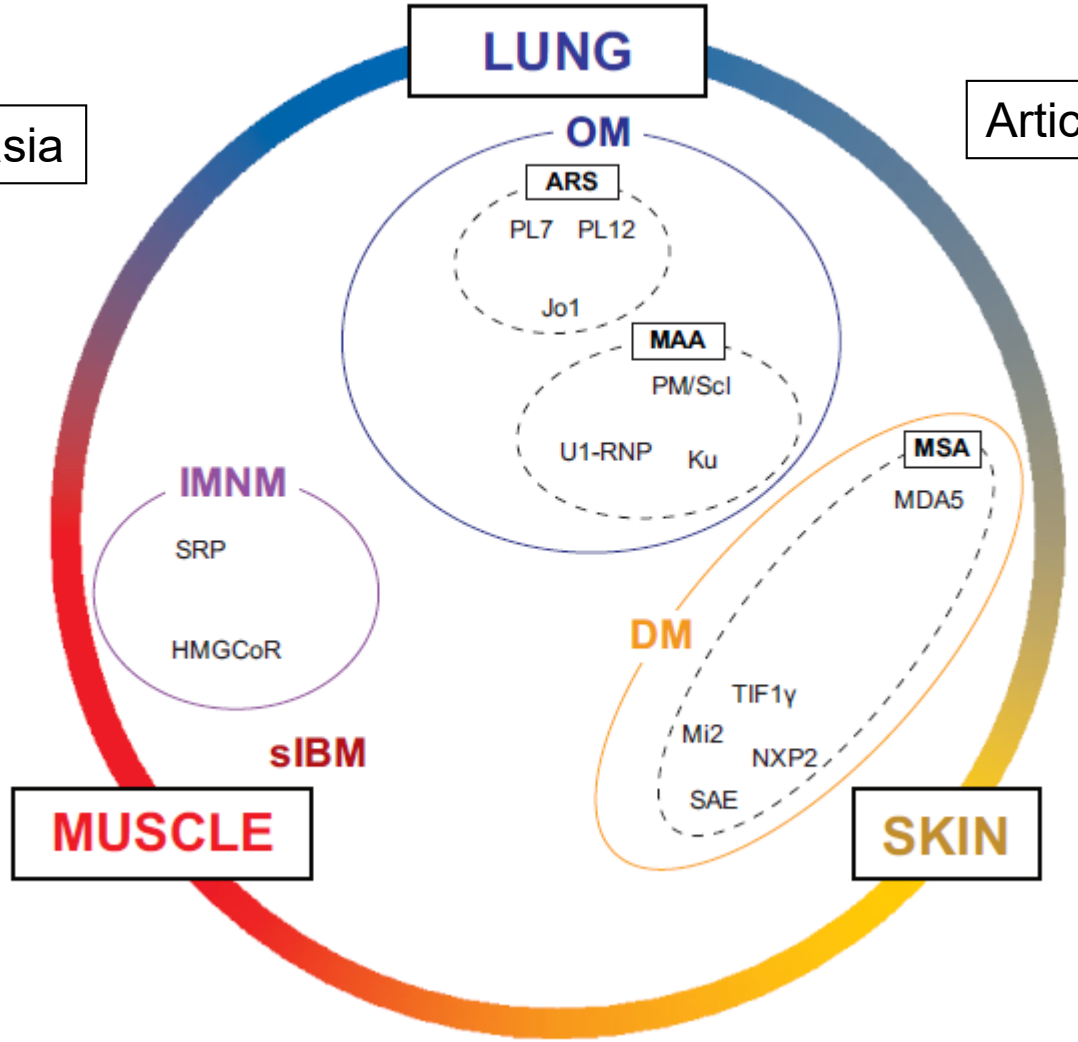
*Dalakas M. Lancet 2003*
*Vincze M. Best Pract Clin Rheumatol 2012*




Neoplasia

Articulación




*Prieto S, Grau JM. Autoimmun Rev 2010*

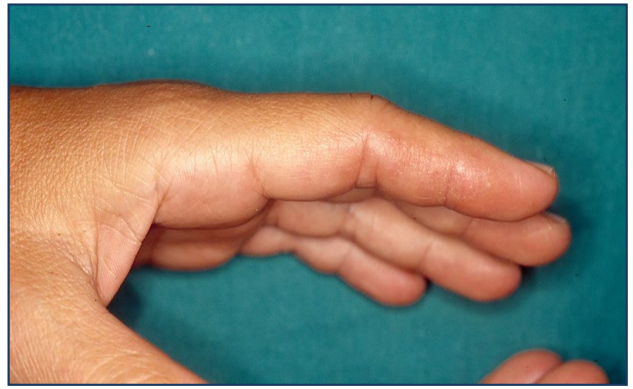
*Barba T et al. Semin Respir Crit Care Med 2019*

# Entidades

① Dermatomiositis

② Polimiositis

**Inflamación muscular**
**+/-**
**Lesiones cutáneas**



*Bohan & Peter. N Engl J Med 1975*

# Entidades

① Dermatomiositis

② Polimiositis

③ Miositis con cuerpos de inclusión

**Criterios histológicos**

*Dalakas MC. N Engl J Med 1991*

# Entidades

① Dermatomiositis → Anticuerpos: **MDA5, TIF1g, SAE, Mi2, NXP2**

② Polimiositis

③ Miositis con cuerpos de inclusión

④ Miopatía necrosante inmunomediada → Anticuerpos: **HMGCAR, SRP**

**Criterios histológicos**

*Hoogendijk JE et al. Neuromuscul Disord 2004*

# Entidades

- Síndrome antisintetasa → ¿Histología?
- Asociada a otras EAS (*overlap*)
- DM (CADM) asociada a MDA5
- Miositis asociada a cáncer

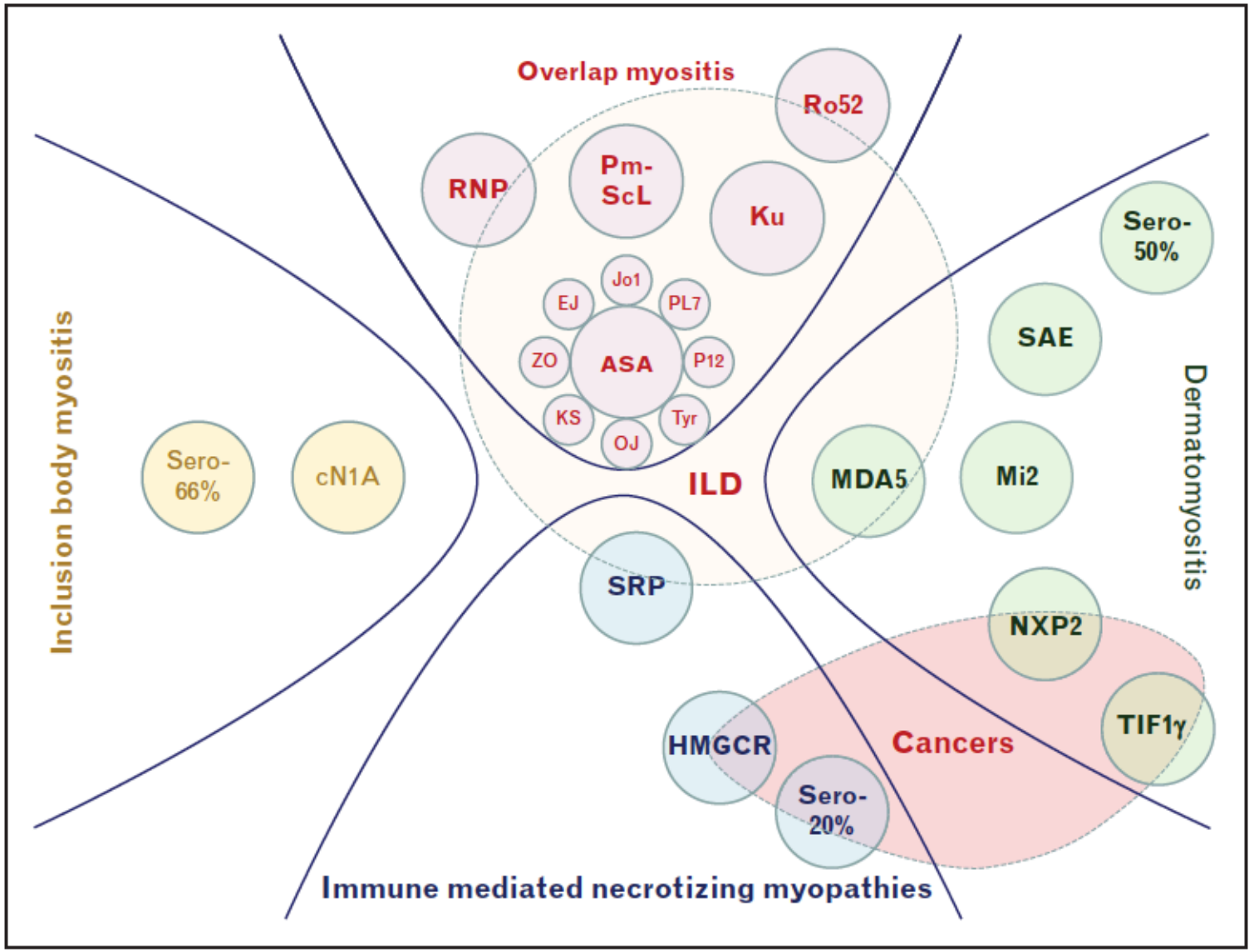
**Autoanticuerpos**

*Rider LG and Miller FW. Lancet 2011*

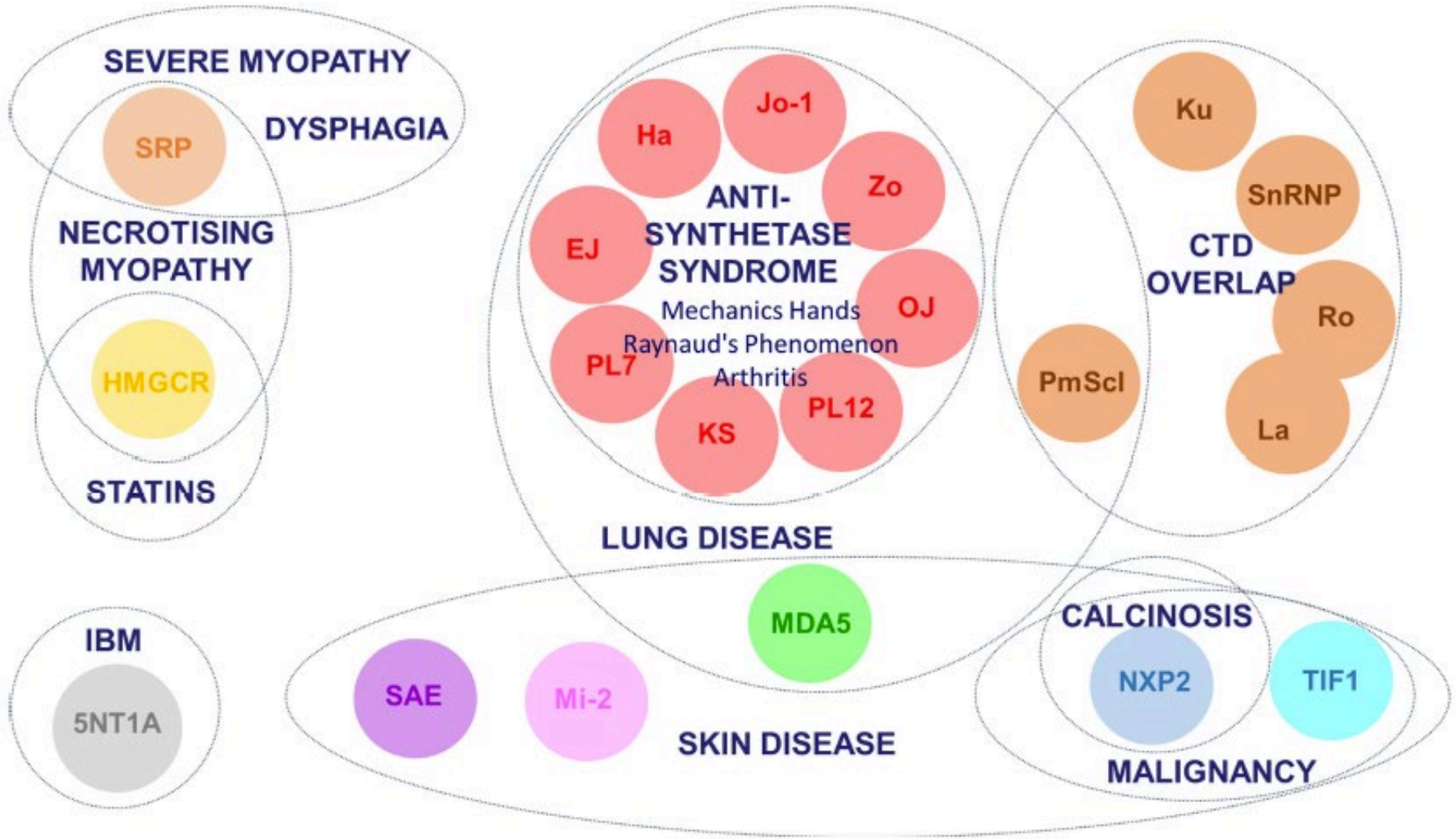
Table MSAs in autoimmune compared to genetic muscle disease

| Autoantibody | Genetic muscle disease, n = 47 | Dermatomyositis, n = 91 | Specificity (95% CI) | Sensitivity (95% CI) | PPV | NPV |
|---|---|---|---|---|---|---|
| Anti-TIF1g | 0 | 25 | 100 (91-100) | 27 (19-38) | 100 (83-100) | 42 (33-51) |
| Anti-NXP2 | 0 | 17 | 100 (91-100) | 19 (12-29) | 100 (77-100) | 39 (30-48) |
| Anti-Mi2 | 1 | 12 | 98 (87-100) | 13 (7-22) | 92 (62-100) | 37 (28-46) |
| Anti-MDA5 | 0 | 5 | 100 (91-100) | 5 (2-13) | 100 (46-100) | 35 (27-44) |
| Anti-Jo1 | 1 | 13 | 98 (87-100) | 14 (8-24) | 93 (64-100) | 37 (29-46) |
| DM MSAs + Anti-Jo1 | 2 | 61[a] | 96 (84-99) | 67 (56-76) | 97 (88-99) | 60 (48-71) |

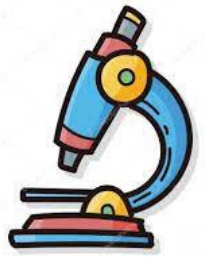
*Mammen AL et al. Neurology 2015*




*Benveniste O et al. Curr Opin Neurol 2016*




*Betteridge and McHugh. J Intern Med 2016*

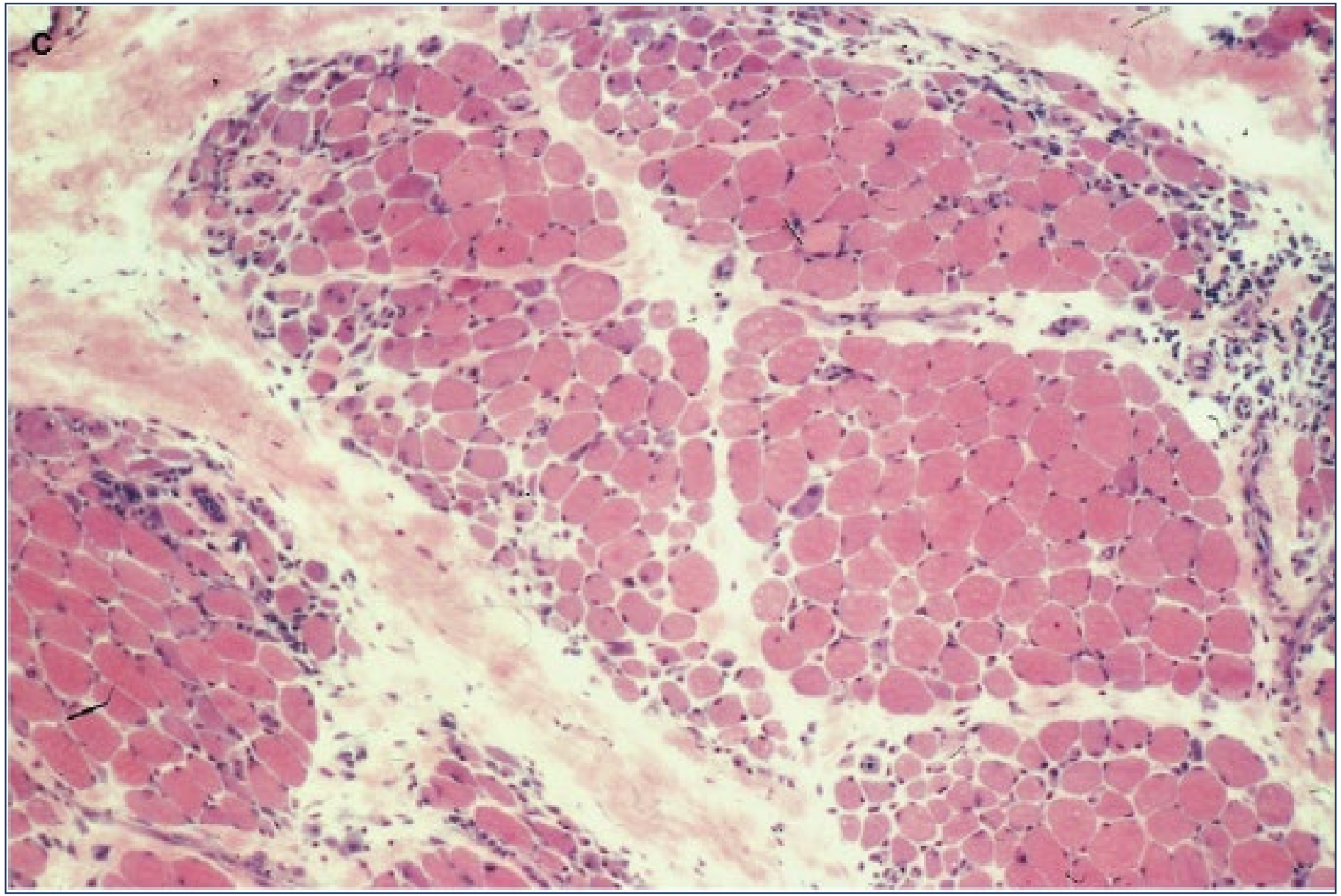


# Histología

## DERMATOMIOSITIS

- Infiltrado mononuclear perimisial y perivascular (LB y LT CD4+)
- Depósito vascular Igs y C5b9
- Deplección capilar
- Necrosis (subletal) y regeneración fibras
- Microinfartos
- Atrofia perifascicular
- Ags MHC I (perifascicular)

*Dalakas MC. N Engl Med J 1991*
*Dalakas MC. Lancet 2003*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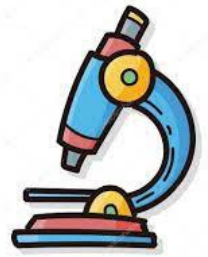
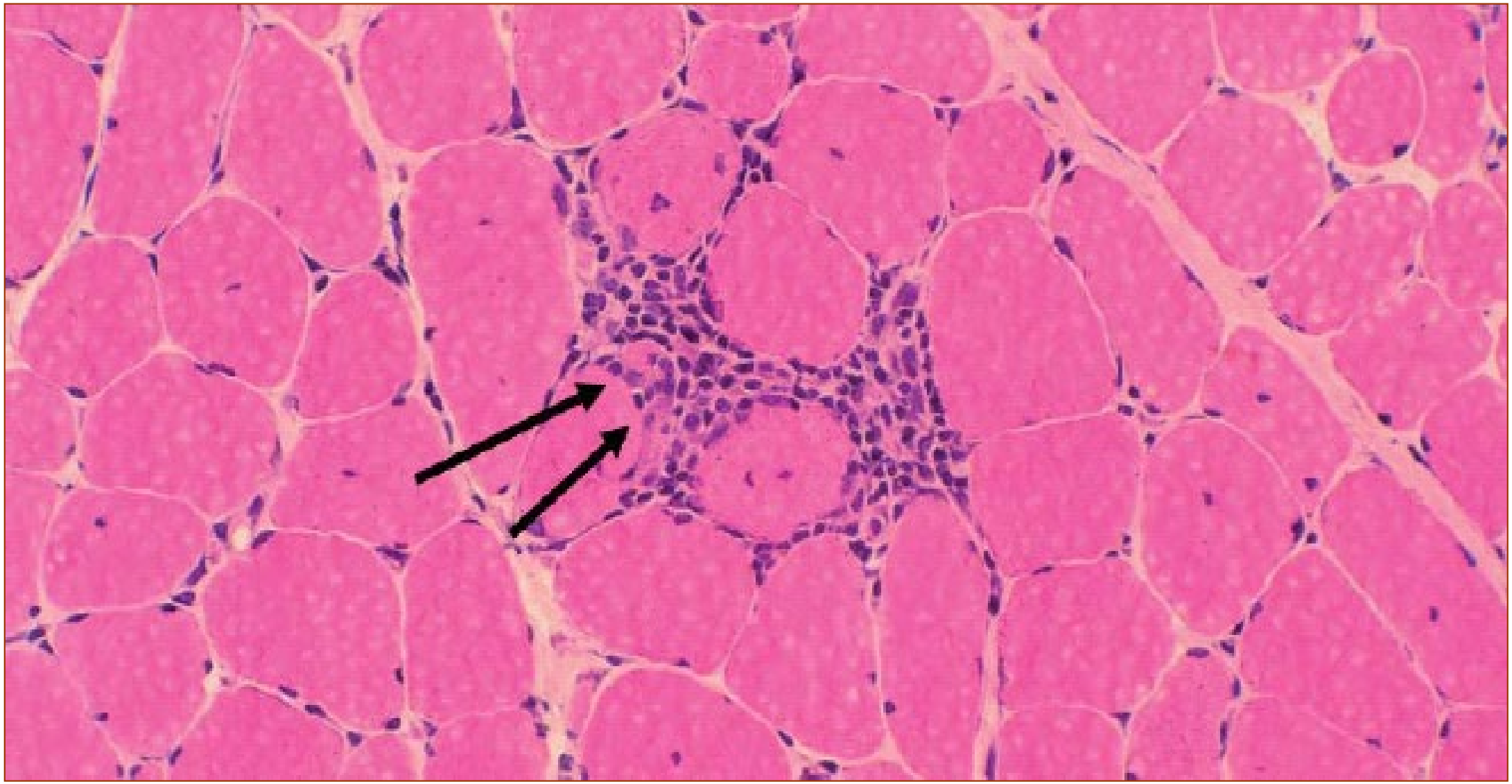


# Histología

## POLIMIOSITIS

- Infiltrado mononuclear endomisial (LT CD8+)
- Invasión celular parcial (macrófagos y LT) de células no necróticas
- Necrosis y regeneración de fibras
- Ags de MHC I

*Dalakas MC. N Engl Med J 1991*
*Dalakas MC. Lancet 2003*

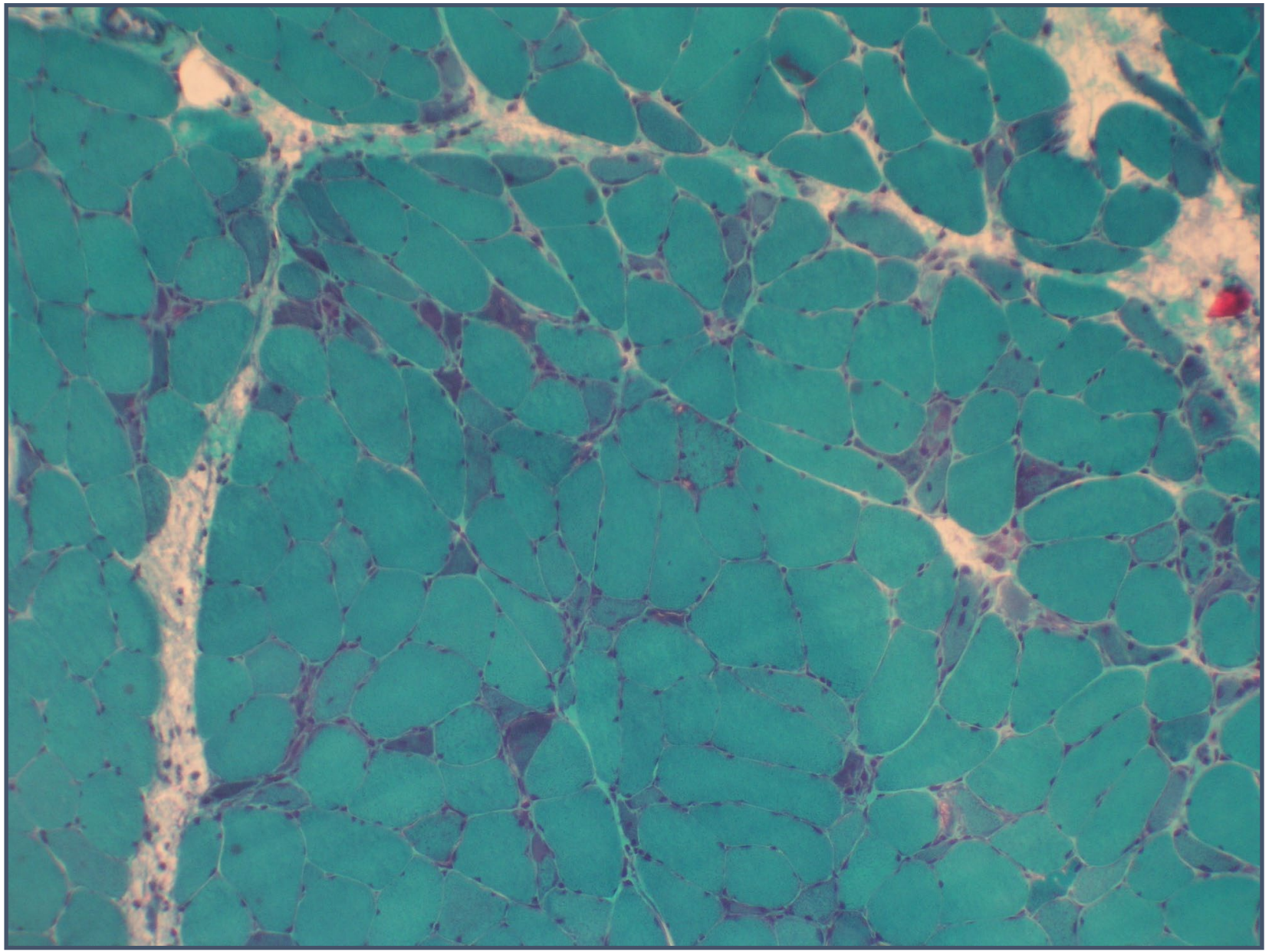


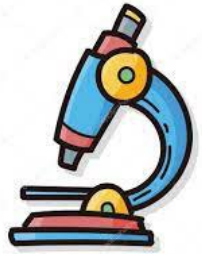
# Histología

## MIOPATÍA NECROSANTE INMUNOMEDIADA

- Necrosis y regeneración de fibras
- Infiltrado mononuclear endomisial leve (macrófagos)
- Invasión celular parcial de células no necróticas
- Ags de MHC I

*Dalakas MC. N Engl Med J 1991*
*Dalakas MC. Lancet 2003*



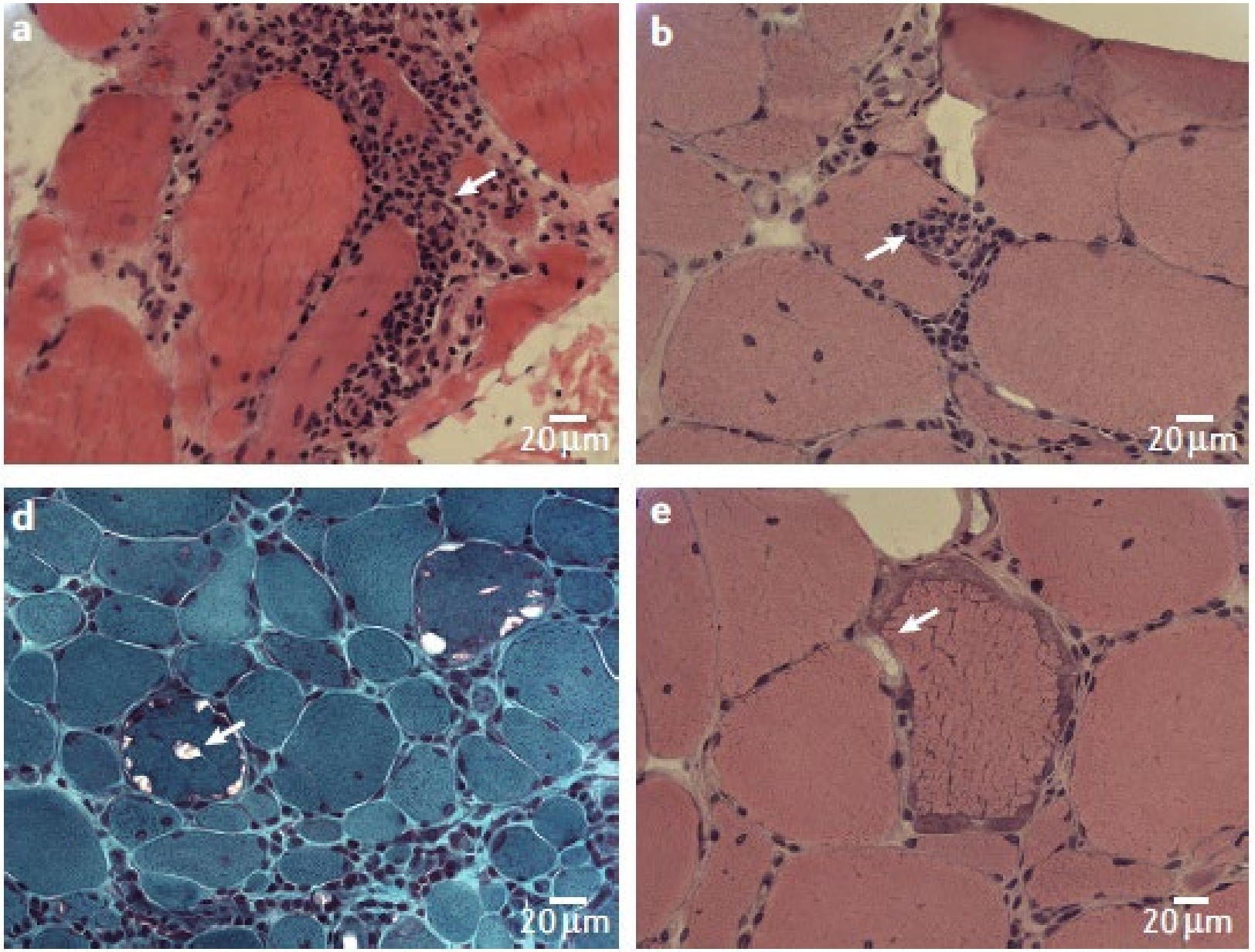


# Histología

## MIOSITIS CON CUERPOS DE INCLUSIÓN

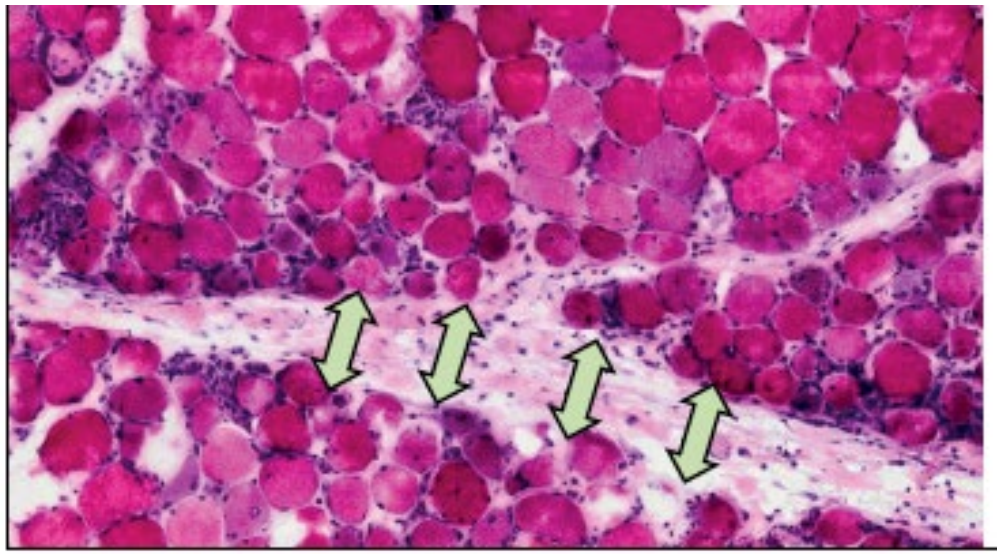
- Infiltrado mononuclear endomisial (LT CD8+)
- Invasión celular parcial (macrófagos y LT) de células no necróticas
- Vacuolas ribeteadas
- Cambios mitocondriales (*ragged red myofibres*)

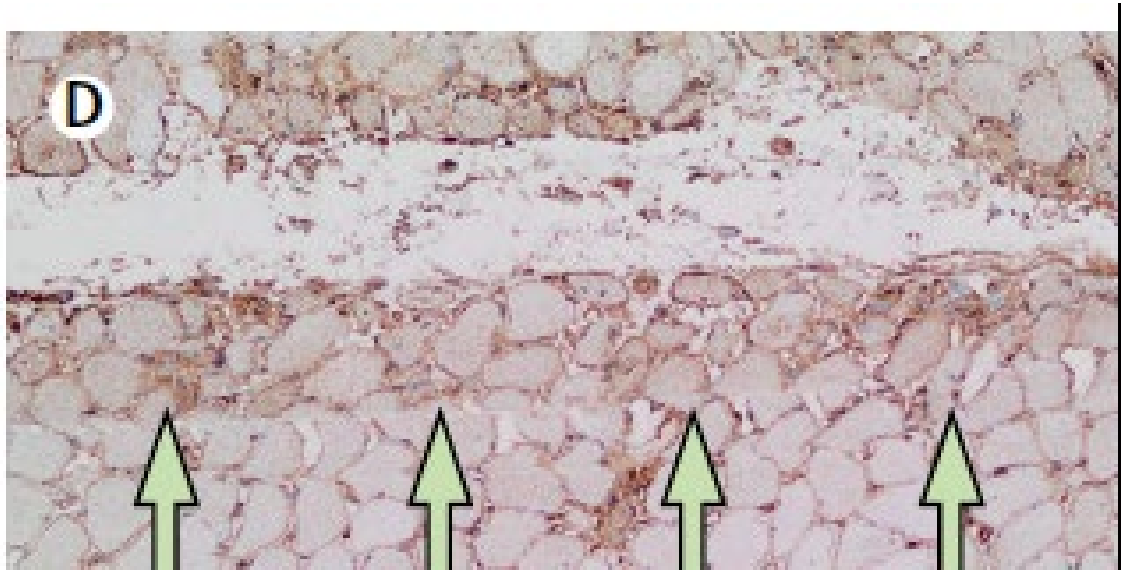
*Greenberg SA. Nat Rev Rheumatol 2019*


a
20 µm
b
20 µm
d
20 µm
e
20 µm

# Histología

## SÍNDROME ANTISINTETASA

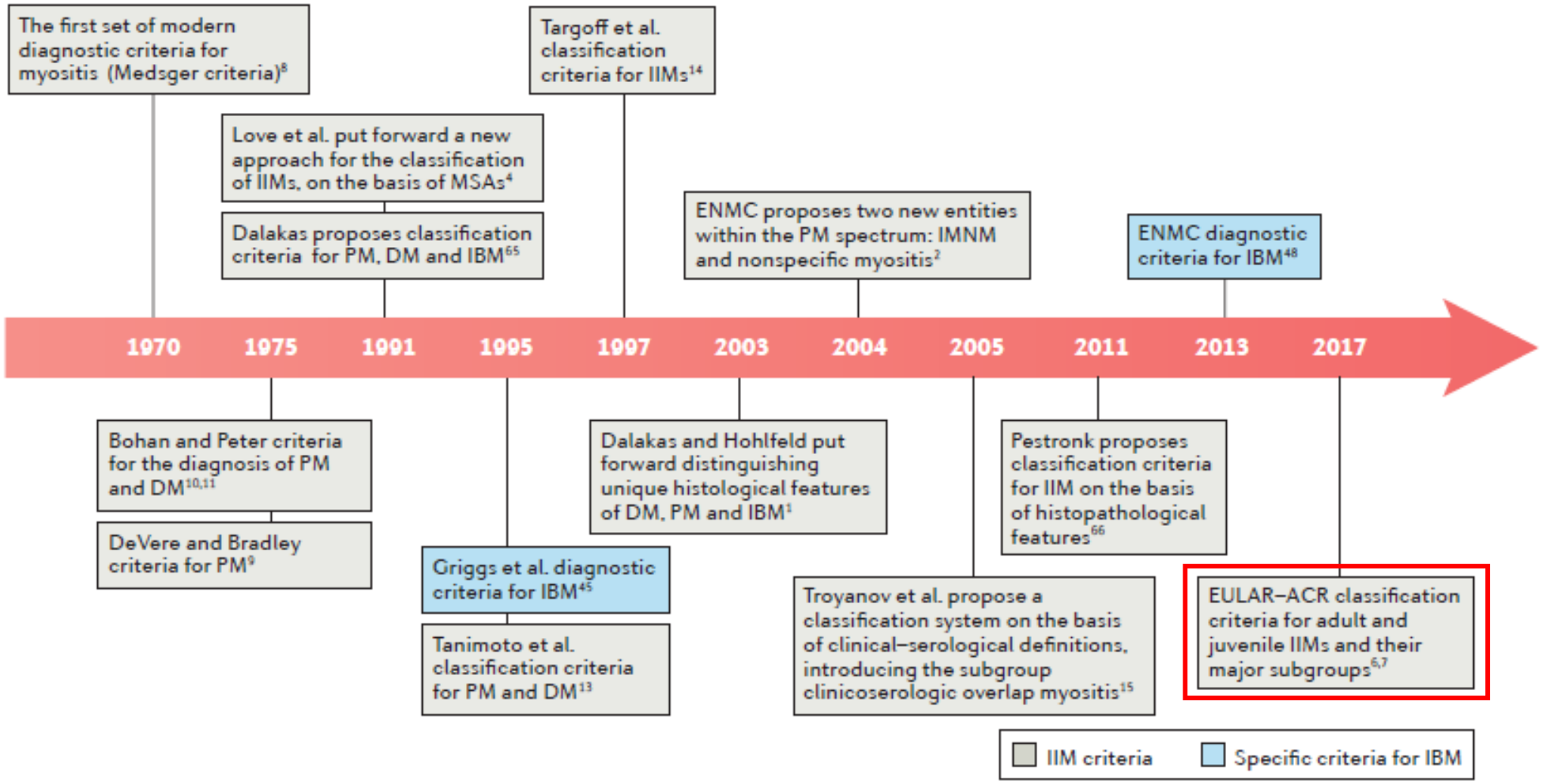





*Selva-O'Callaghan A, et al. Lancet Neurol 2018*

# Tratamiento

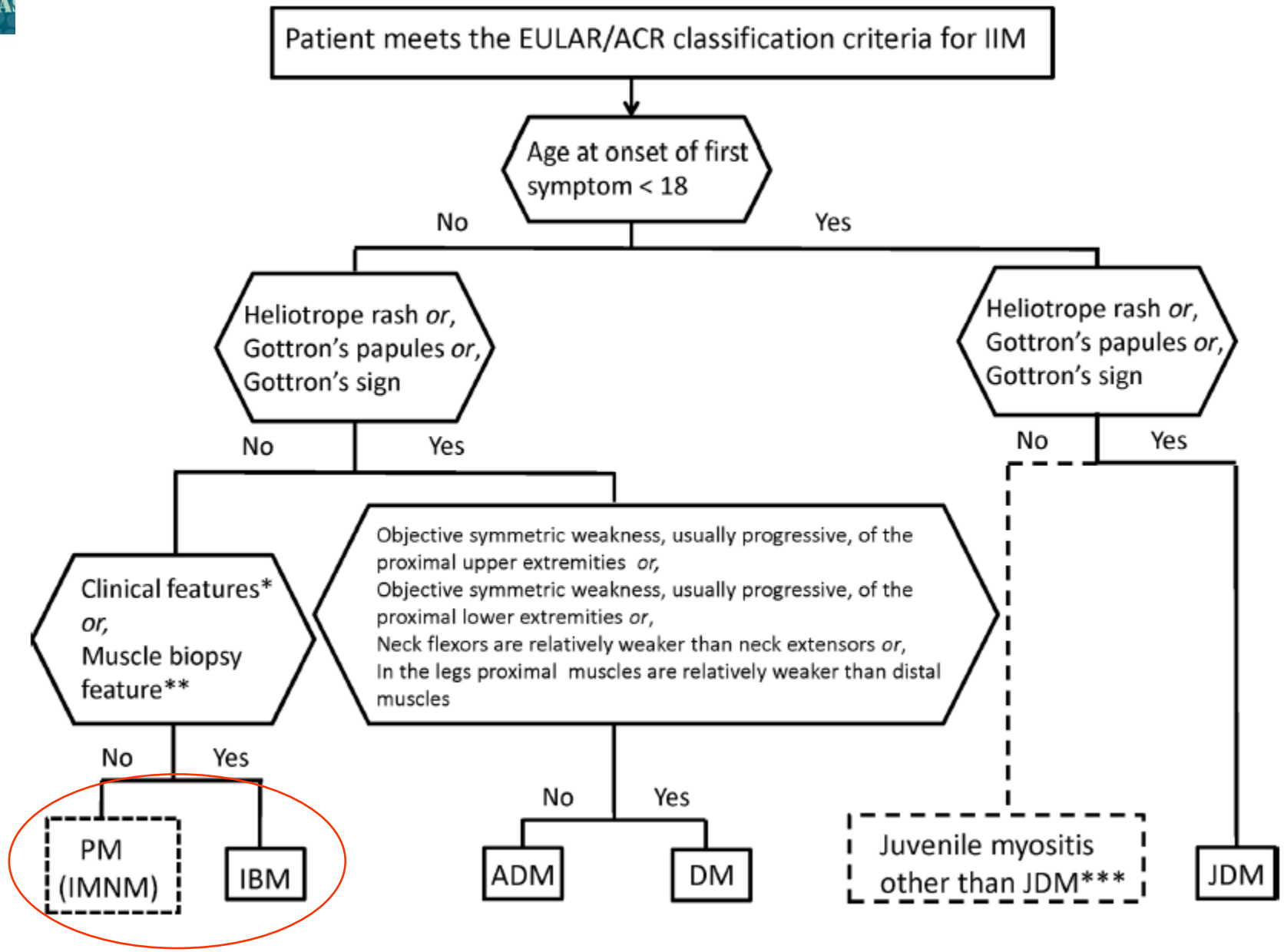
- Subtipo histológico: muestra idónea




*Lundberg IE et al. Nat Rev Rheumatol 2018*

| 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*: 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 |

*Lundberg IE et al. Ann Rheum Dis 2017*




DM *sine*

*Lundberg IE et al. Ann Rheum Dis 2017*

# Tratamiento

- Subtipo histológico: muestra idónea, *timing*
- Asegurar el diagnóstico (especialmente en refractariedad)
- Factores externos: fármacos, infecciones, cáncer, etc

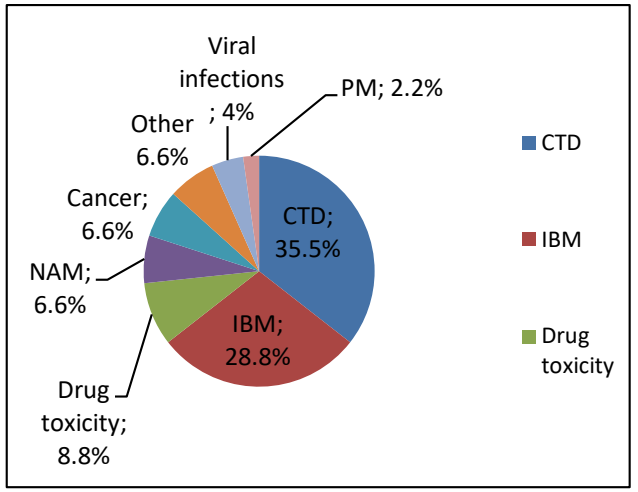
# Polymyositis, a very uncommon isolated disease: clinical and histological re-evaluation after long-term follow-up

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

Patrón histológico

- ***Overlap*** (otras EAS)
- MCI o MNIM
- Fármacos, infecciones, cáncer, etc

¡DIAGNÓSTICO DE EXCLUSIÓN!




*Rheumatol Int 2015*

# Tratamiento

- Subtipo histológico: muestra idónea, *timing*
- Asegurar el diagnóstico (especialmente en refractariedad)
- Factores externos: fármacos, infecciones, cáncer, etc
- Manifestaciones orgánicas
- Autoanticuerpos

| AutoAc | Piel | Músculo | Pulmón |
|---|---|---|---|
| Mi-2 | | | |
| MDA5 | | | |
| TIF1g | | | |
| NXP-2 | | | |
| AAS | | | |
| SRP | | | |
| HMGCR | | | |
| Jo-1 + Ro-52 | | | |

| Diseases | Autoantibodies | Prevalence of the ILD |
|---|---|---|
| | **Myositis-specific autoantibodies** | |
| Dermatomyositis | MDA-5 | 90% |
| Antisynthetase syndrome | All ARS | 80% |
| | Jo-1 | 70% |
| | Non-Jo-1 | 85% |
| | **Myositis-associated autoantibodies** | |
| Overlap myositis | RNP | 50% |
| | PM-Scl | 25% |
| | Ku | 35% |

| | MSAs | Prevalence (95% CI) |
|---|---|---|
| | Jo-1 | 0.77 (0.60, 0.93) |
| * | EJ | 0.91 (0.77, 1.04) |
| | PL-7 | 0.62 (0.31, 0.93) |
| | PL-12 | 0.85 (0.65, 1.05) |
| | MDA-5 | 0.88 (0.81, 0.95) |
| * | Mi-2 | 0.16 (−0.16, 0.48) |
| | SAE | 0.5 (0.06, 0.94) |
| | SRP | 0.26 (0, 0.52) |
| | TIF1-$\gamma$ | 0.22 (0.05, 0.39) |

*Sun KY et al. Semin Arthritis Rheum 2021*
*Hervier B et al. Front Med (Lausanne) 2020*

# Tratamiento

- **Subtipo histológico**: muestra idónea, *timing*
- Asegurar el diagnóstico (especialmente en refractariedad)
- Factores externos: fármacos, infecciones, cáncer, etc
- **Manifestaciones orgánicas**
- **Autoanticuerpos**

# Miositis con cuerpos de inclusión

- *Primum non nocere* (múltiples ECR)
- Manejo multidisciplinar: rehabilitación, nutrición (PEG), VNI
- **Fármacos**: inicio agudo +/- inflamación histológica +/- asociación con EAS
- GC + IGIVI +/- IS

*Connolly CM, et al. Best Pract Res Clin Rheumatol 2022*

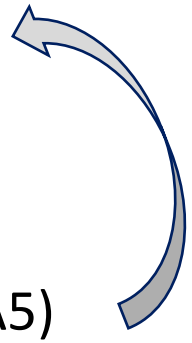
# Miopatía necrosante inmunomediada

- Ausencia de ECR
- GC + IS:
  - HMGCoAR: MTX
  - SRP: RTX
- IGIV: debut grave (disfagia) o refractariedad
- Descartar neoplasia en seronegativos y refractarios

*Connolly CM, et al. Best Pract Res Clin Rheumatol 2022*

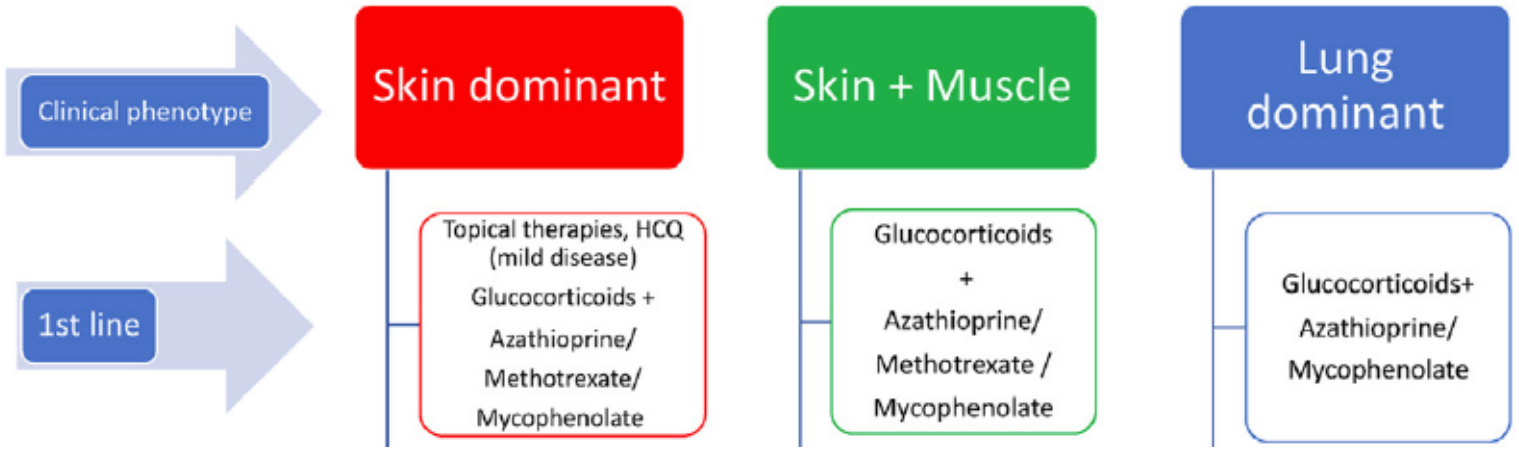
# Dermatomiositis

- Compromiso orgánico/sistémico
- Gravedad
- Autoanticuerpos: subtipos clínicos (SAS, MDA5)
- Neoplasia

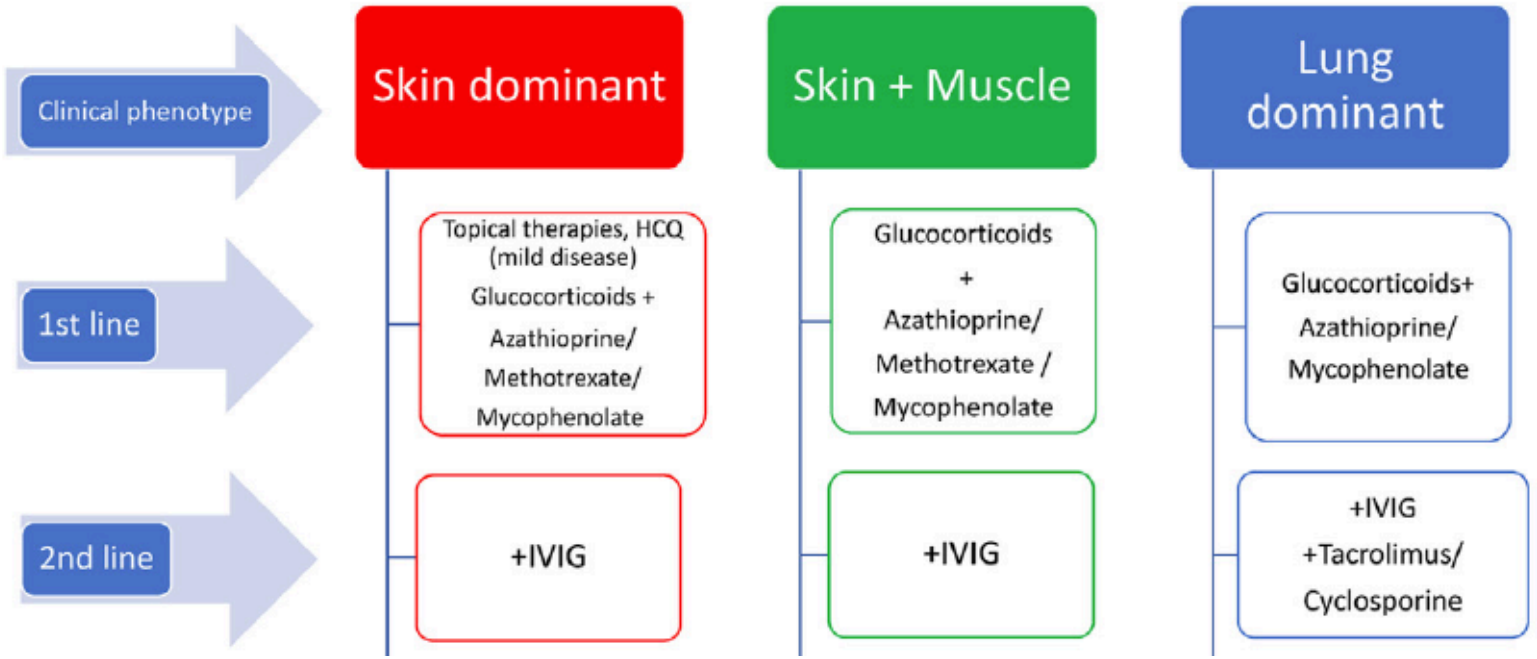


*Connolly CM, et al. Best Pract Res Clin Rheumatol 2022*

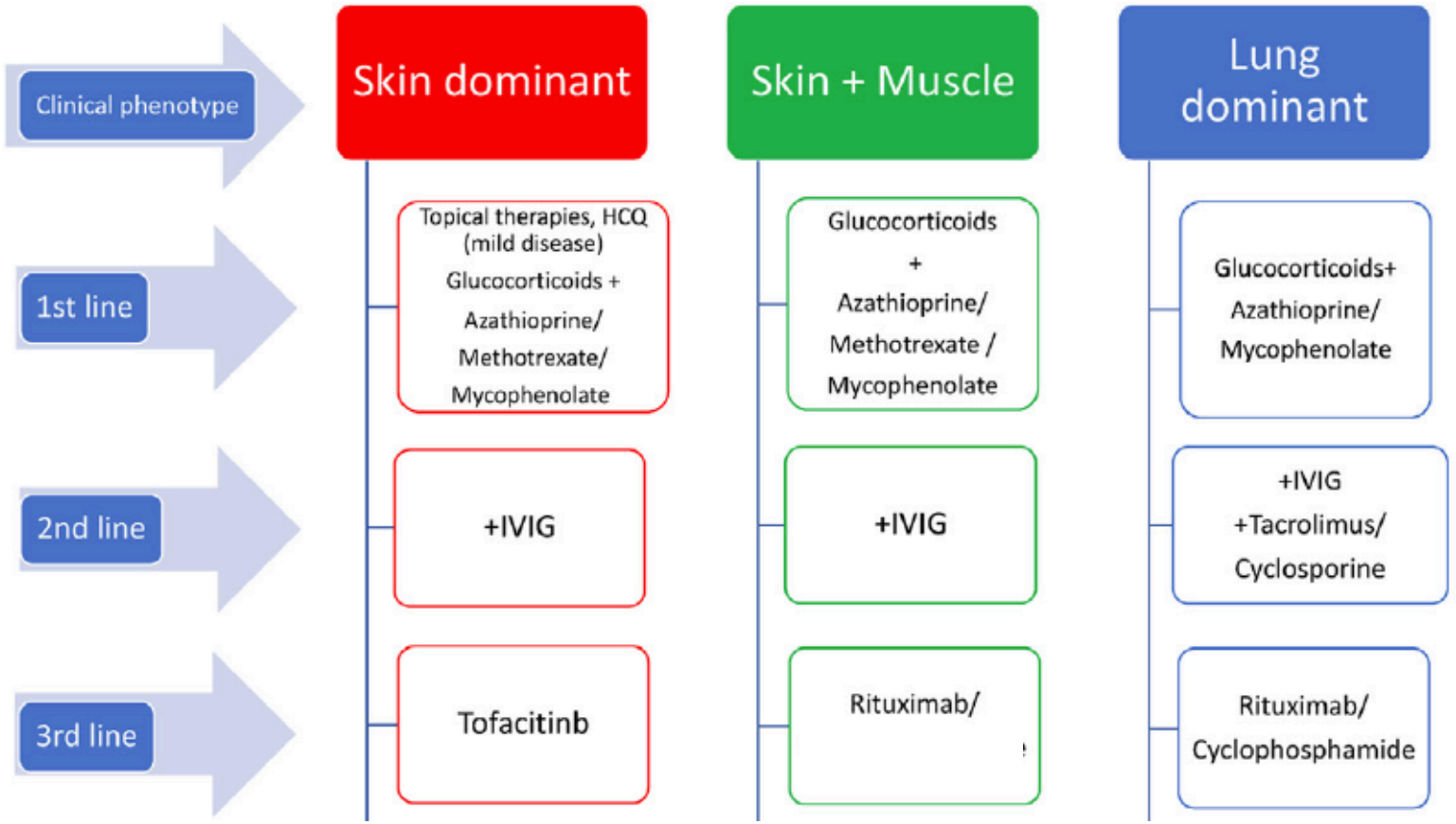
*Connolly CM, et al. Best Pract Res Clin Rheumatol 2022*



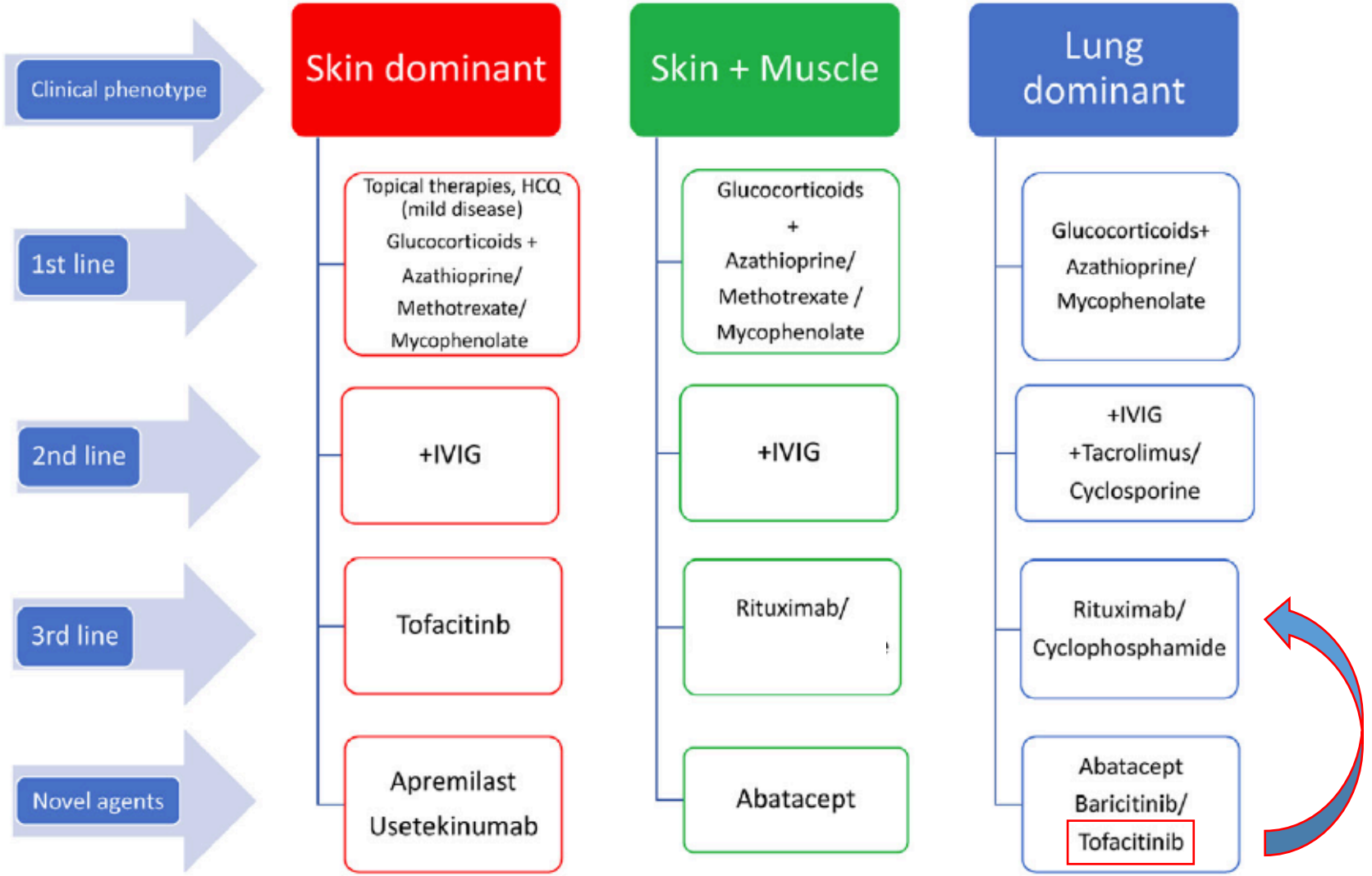

*Connolly CM, et al. Best Pract Res Clin Rheumatol 2022*



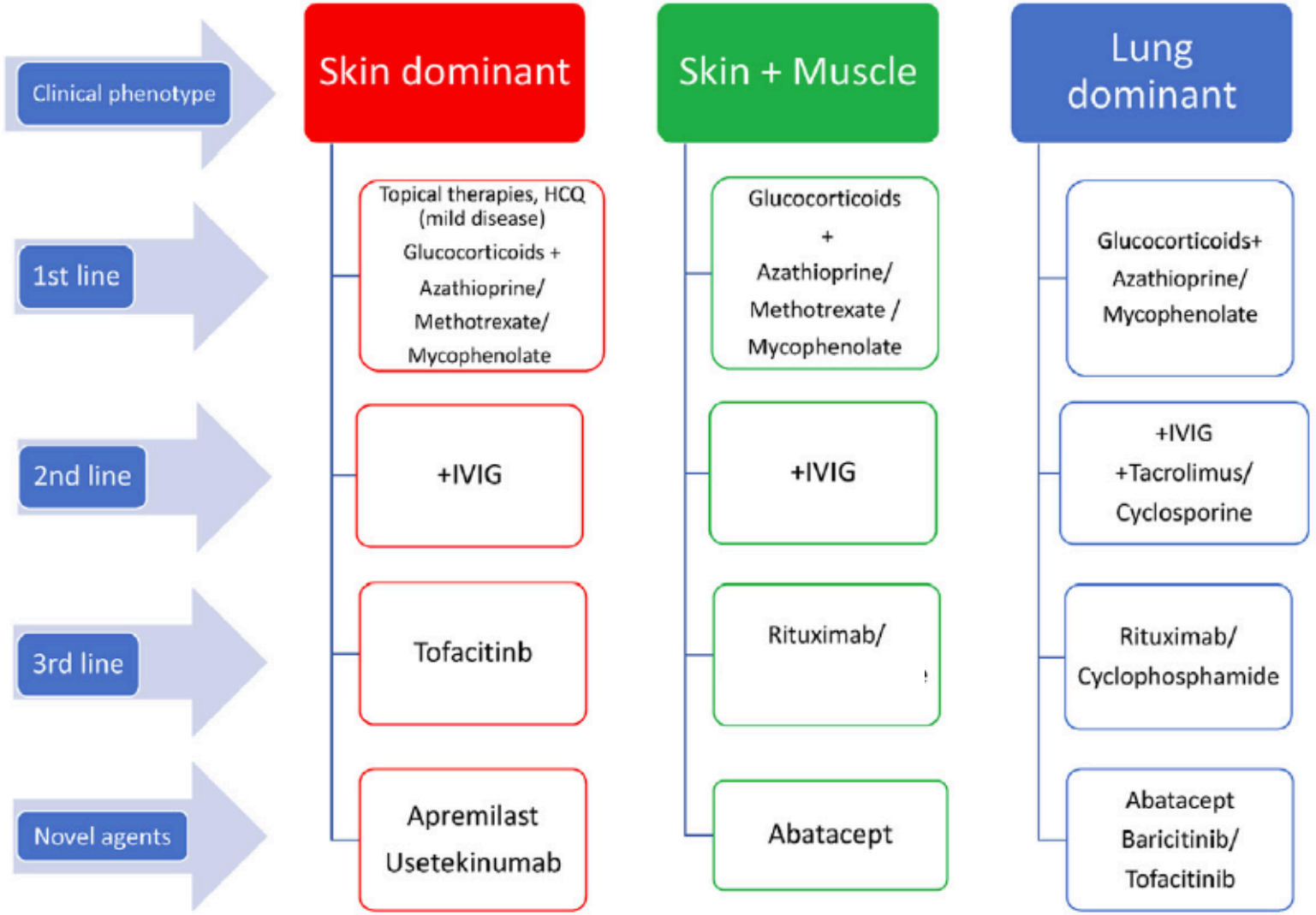

*Connolly CM, et al. Best Pract Res Clin Rheumatol 2022*




*Connolly CM, et al. Best Pract Res Clin Rheumatol 2022*




*Connolly CM, et al. Best Pract Res Clin Rheumatol 2022*




**¿ANTIFIBRÓTICOS?**

*Connolly CM, et al. Best Pract Res Clin Rheumatol 2022*

Pirfenidona y Nintedanib

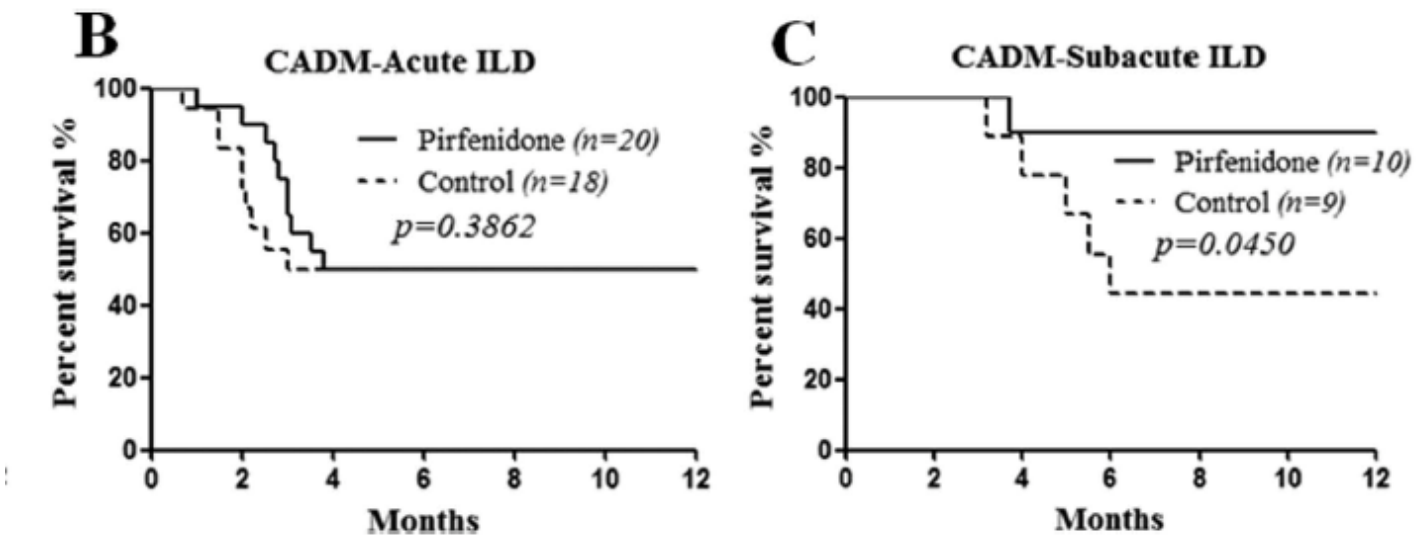
- EC SENSIS: EPID en SSc
- EC INBUILD: EPI fibrosante progresiva (no FPI)
- EC RELIEF: EPI fibrosante progresiva (no FPI)

**MII**: estudio abierto y retrospectivo; RCT ongoing

*Wilfong EM, Aggarwal R.Ther Adv Musculoskelet Dis. 2021*

# Pirfenidone in patients with rapidly progressive interstitial lung disease associated with clinically amyopathic dermatomyositis

30 pacientes prospectivos vs 27 cohorte histórica



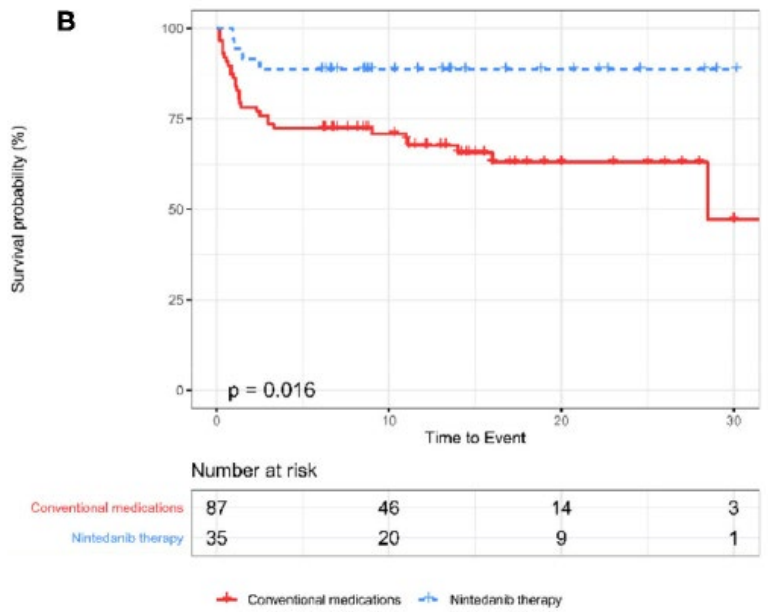

*Li T et al. Sci Rep 2016*

# Efficacy and Tolerability of Nintedanib in Idiopathic-Inflammatory-Myopathy-Related Interstitial Lung Disease: A Pilot Study

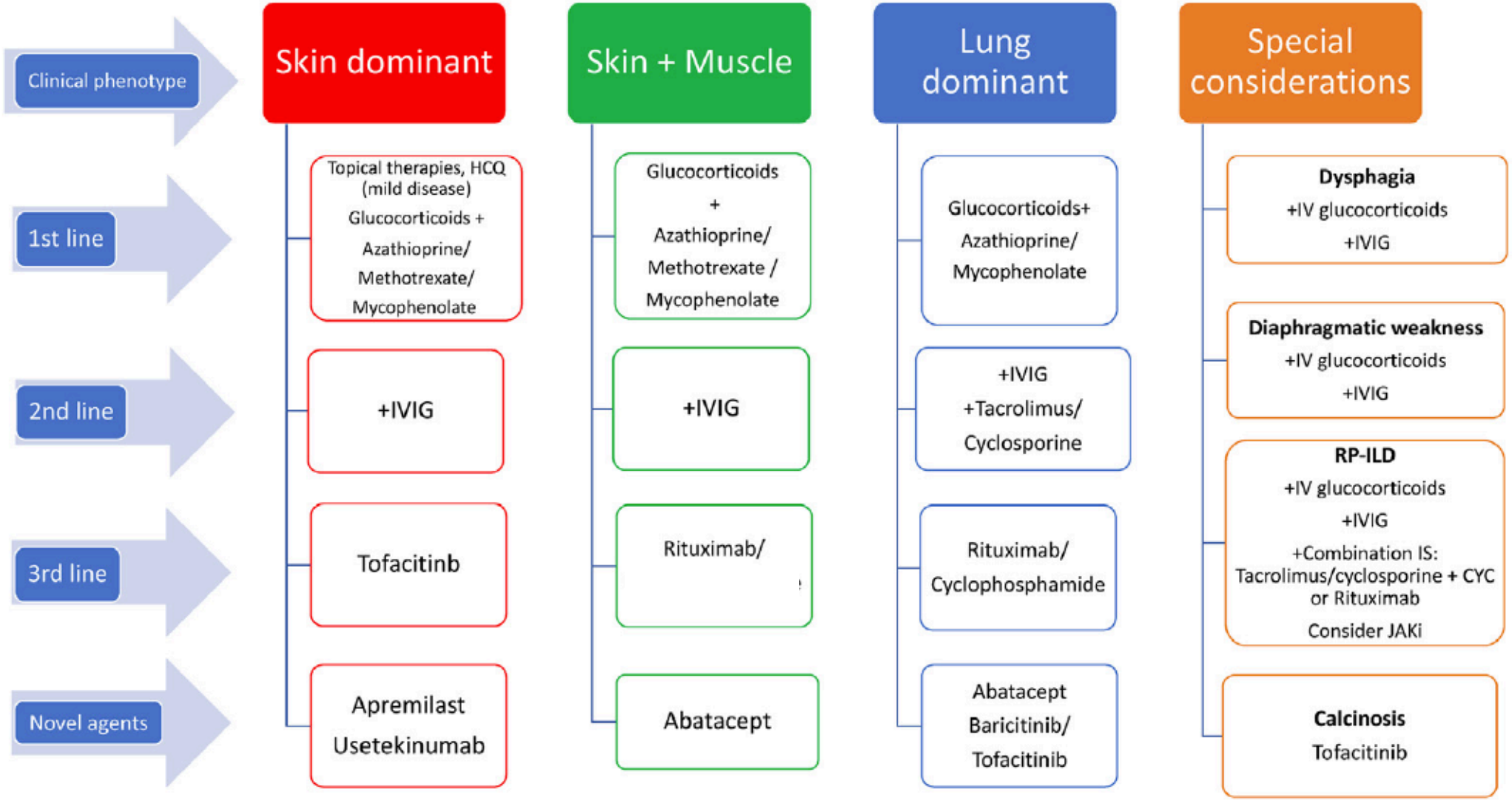
Pacientes retrospectivos (151) en 2 años

36 nintedanib vs 87 (PM)

| Multivariate analysis | | | |
|---|---|---|---|
| MYOACT score | <0.001 | 1.214 | 1.110~1.328 |
| Anti-MDA5 | <0.001 | 3.300 | 1.714~6.357 |
| Nintedanib | 0.013 | 0.268 | 0.096~0.754 |




*Liang j et al. Front Med (Lausanne) 2021*




IA / RP

*Connolly CM, et al. Best Pract Res Clin Rheumatol 2022*

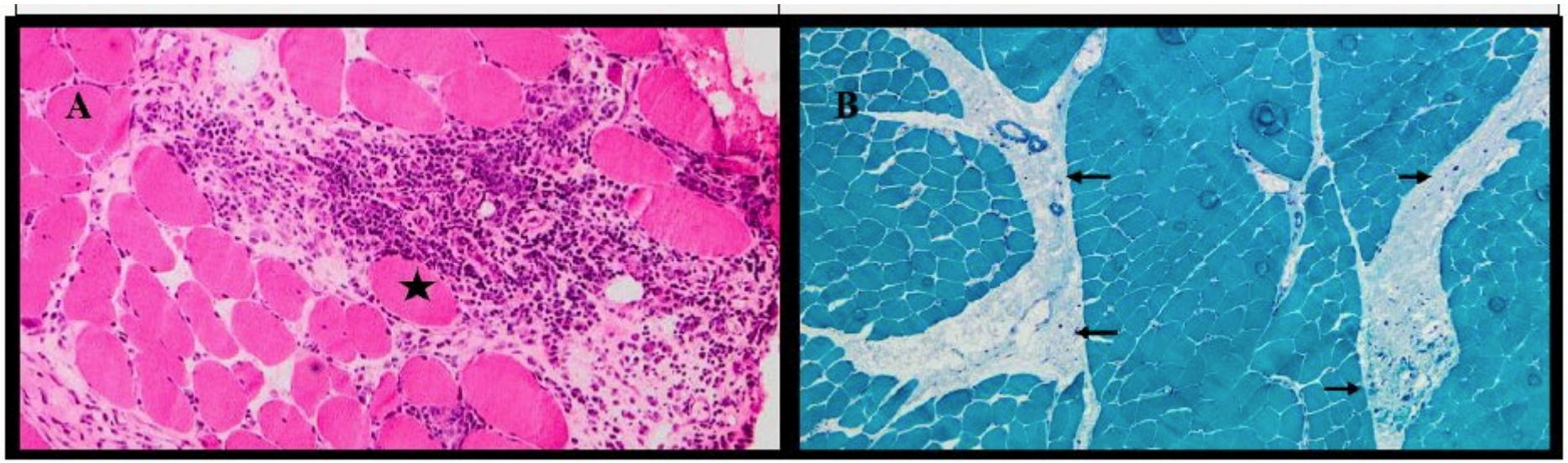
# Situaciones especiales

- Miopatía en la esclerosis sistémica

- Miositis asociada a la inmunoterapia (*immune checkpoint inhibitors*)

# Clinico–pathological phenotypes of systemic sclerosis–associated myopathy: analysis of a large multicentre cohort

Ana Matas-García [1,*], Alfredo Guillén-Del-Castillo[2,*], Boris Kisluk[3], Albert Selva-O'Callaghan [2], Gerard Espinosa [4], Sergio Prieto-González [1], Pedro Moreno Lozano[1], Glòria Garrabou[1], Josep María Grau-Junyent[1], Carmen Pilar Simeon-Aznar[2,*] and José C. Milisenda[1,*]




*Matas-García A, et al. Rheumatology (Oxford) 2022*

| Inflammatory pattern | Fibrosing pattern |
|---|---|
| • Major weakness at diagnosis, but achieve greater improvement<br>• Active DM skin lesions<br>• Elevation of muscle biomarkers<br>• Anti-PM/Scl<br>• Adequate response to immunosuppressants | • Mild disease, but less improvement<br>• Ischemic heart disease/arrhythmias<br>• Elevation of acute phase reactant proteins<br>• Anti-topo I<br>• Poor prognosis, higher mortality |

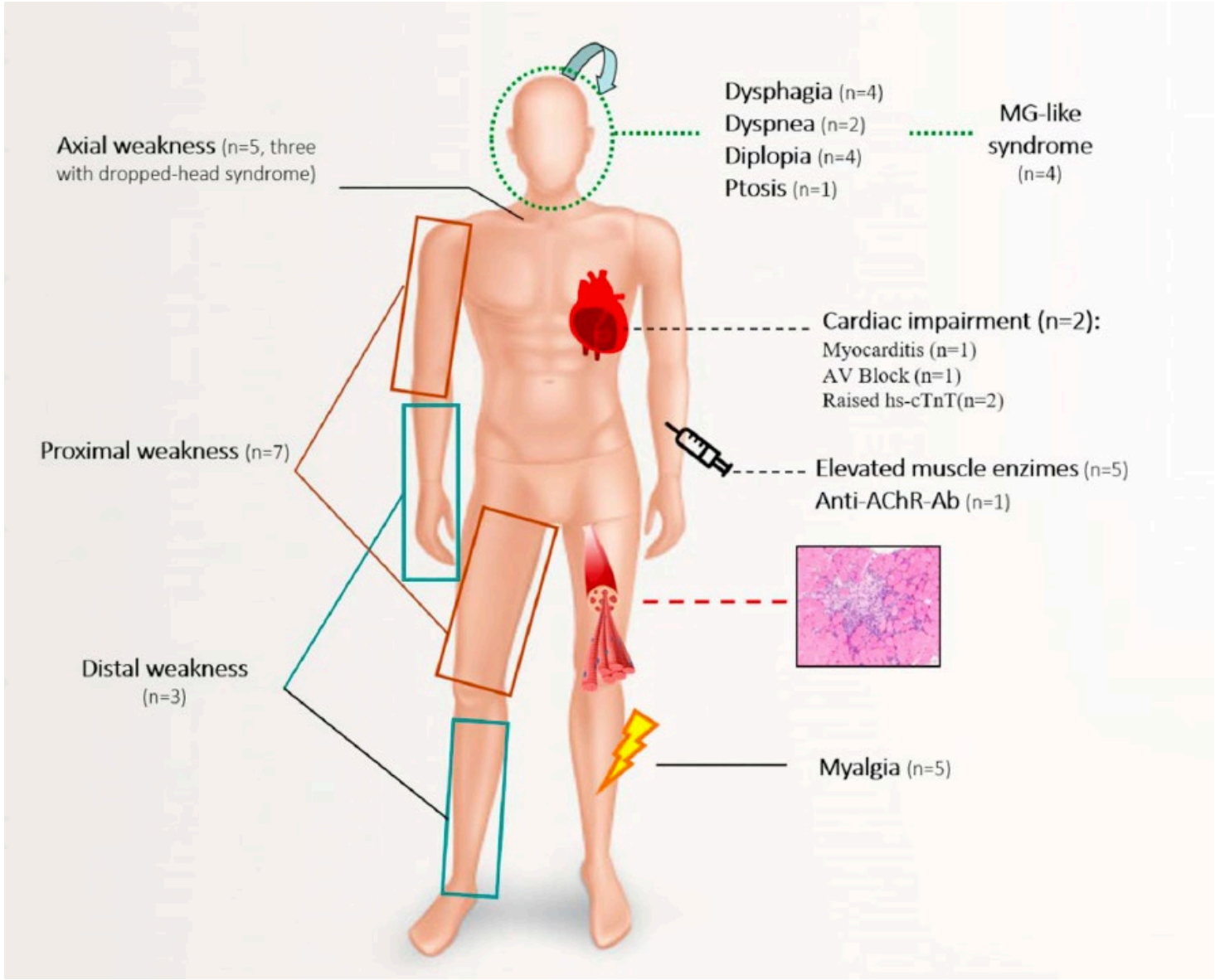
Manejo terapéutico y pronóstico

*Matas-García A, et al. Rheumatology (Oxford) 2022*

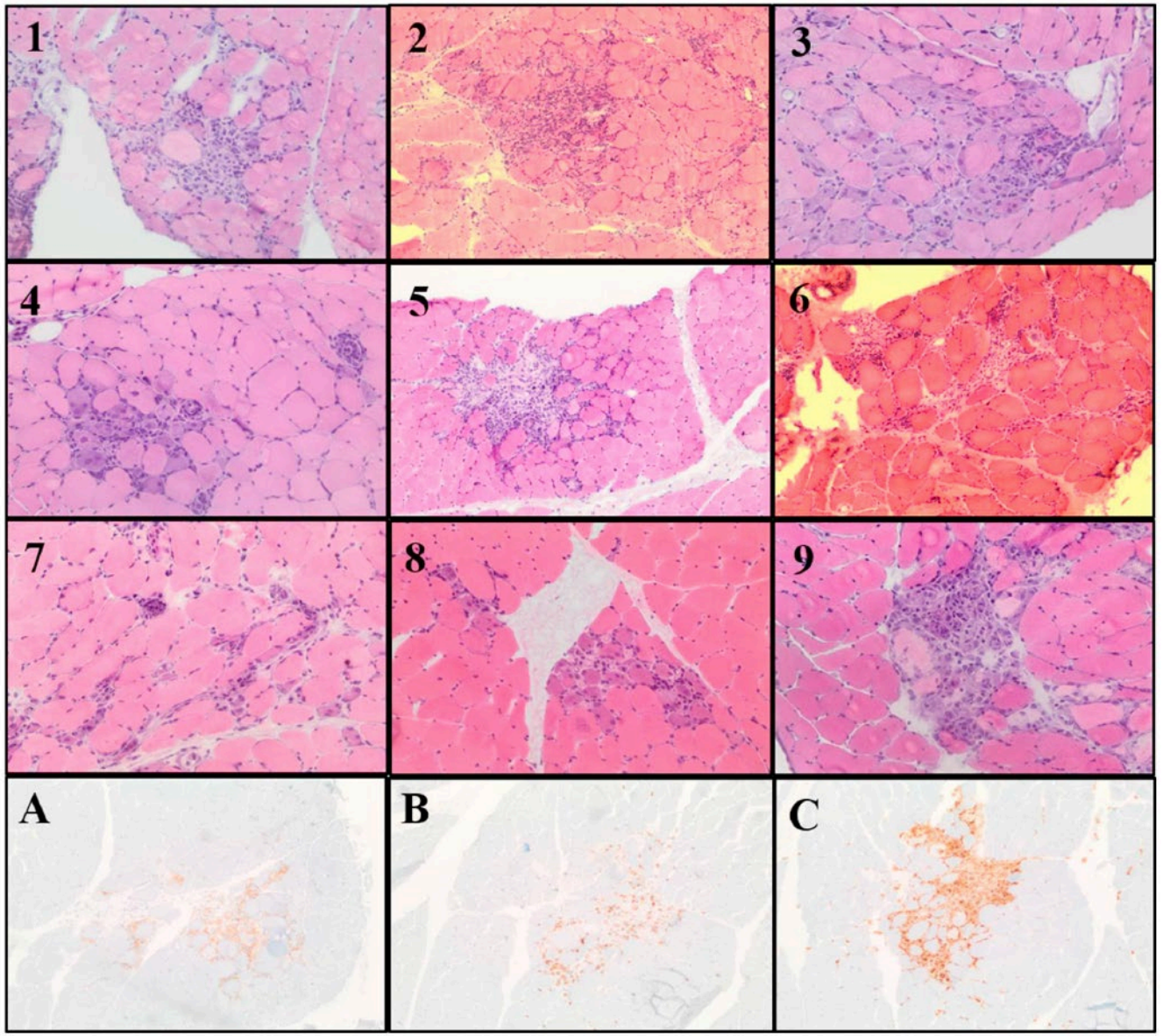
# Emerging PD-1 and PD-1L inhibitors-associated myopathy with a characteristic histopathological pattern

Ana Matas-García[a,1], José C. Milisenda[a,*,1], Albert Selva-O'Callaghan[b], Sergio Prieto-González[c], Joan Padrosa[a], Carlos Cabrera[d], Noemi Reguart[d], Natalia Castrejón[e], Manel Solé[e], Javier Ros[f], Ernesto Trallero-Araguas[g], Maria Noelia Antoniol[h], Gemma Vila-Pijoan[i], Josep María Grau[a]

*Matas-García A, et al. Autoimmun Rev 2020*




*Matas-García A, et al. Autoimmun Rev 2020*

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# Emerging PD-1 and PD-1L inhibitors-associated myopathy with a characteristic histopathological pattern

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- Patrón clínico: miositis/miastenia +/- miocarditis
- Histología muy característica
- Potencial gravedad: disfagia/miocarditis
- **Tratamiento**: retirada de ICPI + intensivo precoz

*Matas-García A, et al. Autoimmun Rev 2020*

# Conclusiones

- Entidades muy heterogéneas
- Frecuente afectación sistémica (manejo multidisciplinar)
- Importancia del diagnóstico histológico (correcto)
- Utilidad de los autoAc asociados a miositis (fenotipos)
- Tratamiento individualizado y estratificado

¡Gracias!

@sergioprietoglz