# MIOPATÍAS INFLAMATORIAS

***Sesión grupo ENA 12/12/2017***

Yolanda Pamblanco Bataller
Hospital Francesc de Borja. Gandía.

# Introducción

344 THE NEW ENGLAND JOURNAL OF MEDICINE Feb. 13, 1975

**MEDICAL PROGRESS**

**POLYMYOSITIS AND DERMATOMYOSITIS (First of Two Parts)**

ANTHONY BOHAN, M.D., AND JAMES B. PETER, M.D., PH.D.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Inflammatory Muscle Diseases

Marinos C. Dalakas, M.D.

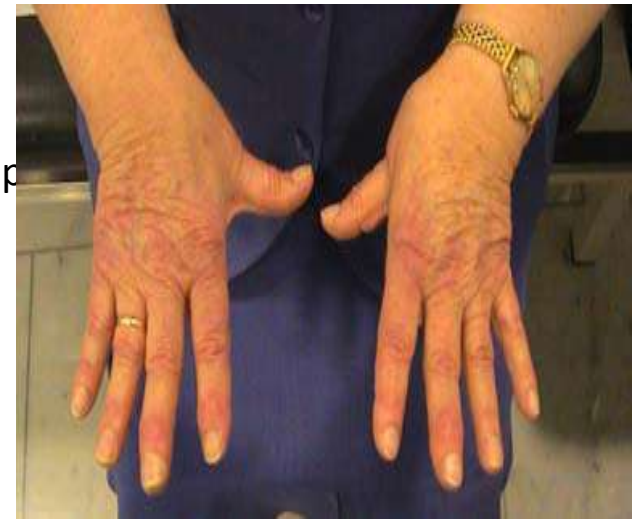
2015

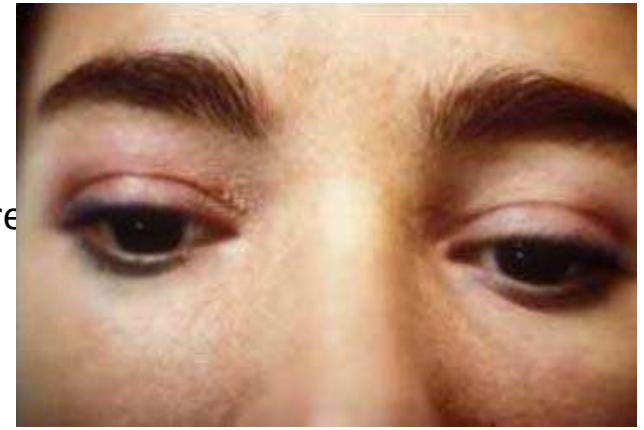
- Grupo heterogéneo de enfermedades disinmunes.
- Morbi-mortalidad significativa.
- Incidencia 4.27-7.89 casos/100,000 individuos/año.

- Clasificación 1975: Bohan and Peter: DM/PM.

# Dermatomiositis

- Niños y adultos. + frec. Mujeres.
- *Rash cutáneo, debilidad muscular*
- Clínica dermatológica:
  - Eritema heliotropo: eritema violáceo (párpado sup
    espalda), rash descamativo (codos, rodillas, orejas)
  - Eritema de Gottron (manos, nudillos)
  - Afectación ungueal, piel engrosada pulpejos
  - Suele preceder a la debilidad
- Debilidad muscular
  - Proximal
  - Evolución aguda o subaguda
  - +/- afectación bulbar
- Neoplasia asociada
  - Mujer: ovario
  - Hombre: estómago
  - Pulmón, mama, linfoma no Hodgkin, colorectal, páncre
  - Búsqueda de tumor 3-5 años

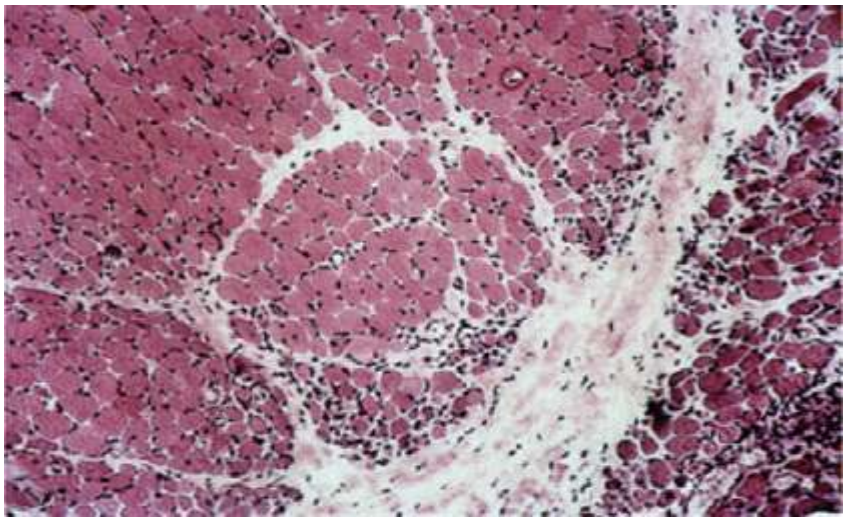




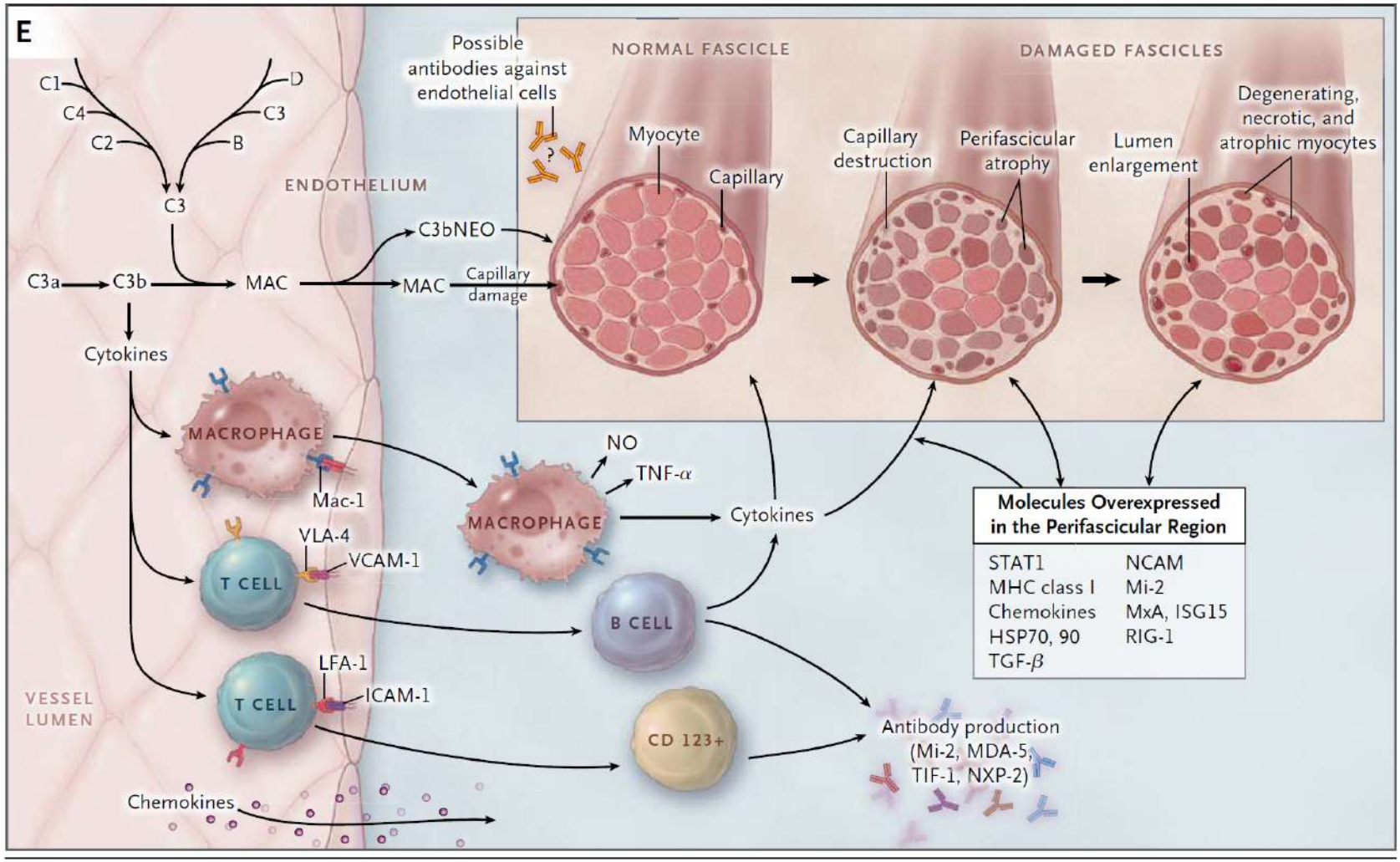
# Dermatomiositis

- **Biopsia muscular:**
  - Depósitos de complemento en las fibras musculares y en los capilares endomisiales
  - Infiltrados inflamatorios (linfocitos T CD4 y B) en zonas perimisiales y perivasculares, septo interfascicular/periferia fascículos
  - Fagocitosis de fibras musculares por macrófagos
  - Atrofia perifascicular (microinfartos e hipoperfusión).
  - Expresión MHC-I

  (fibras perifasciculares)



# Fisiopatología DM



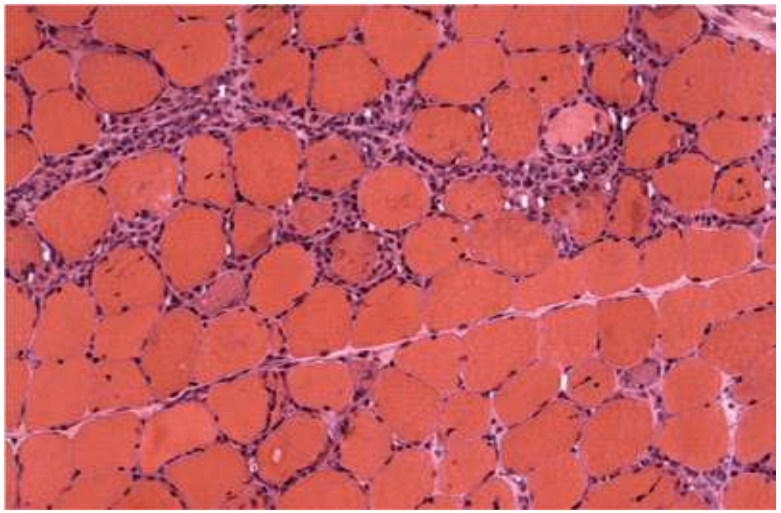

Tomado de: Dalakas, M.C. Inflammatory muscle disease. N. Engl. J. Med.2015,372,1734-1747.

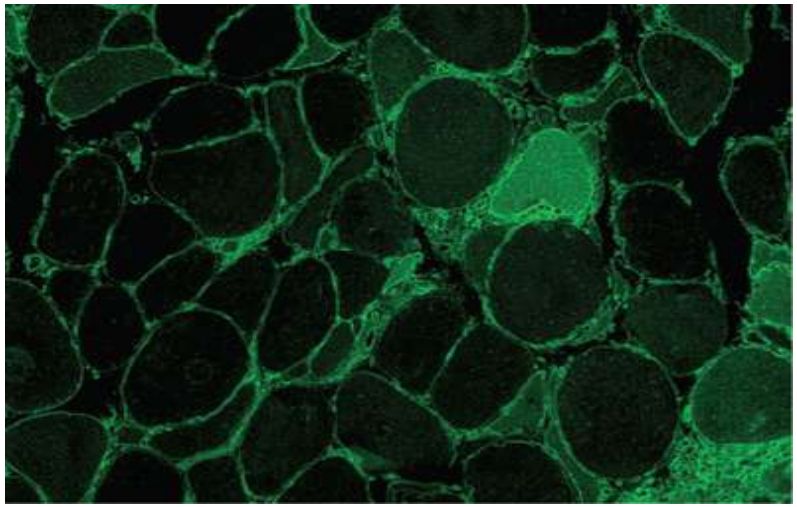
# Polimiositis

- Edad adulta, + frecuente mujeres
- Debilidad proximal simétrica aguda o subaguda
- Afectación bulbar y del cuello
- Menor asociación a neoplasias malignas
- Puede asociarse conectivopatías (LES, esclerodermia), infecciones (VIH, Lyme)
- Predomina respuesta de la inmunidad celular
- Linfocitos T CD 8 invaden y destruyen fibras musculares
- Expresión difusa de MHC-I, a diferencia de las distrofias musculares (sólo expresan MHC-I las fibras enfermas) en PM e IBM se expresa también en fibras sanas.

# Polimiositis

- **Biopsia muscular:**
  - Expresión aumentada MHC-I
  - Infiltrados inflamatorios linf T CD8, macrófagos: nivel perivascular y endomisial.
  - Complejo MHC-CD8.
  - Fibras sanas fagocitadas.



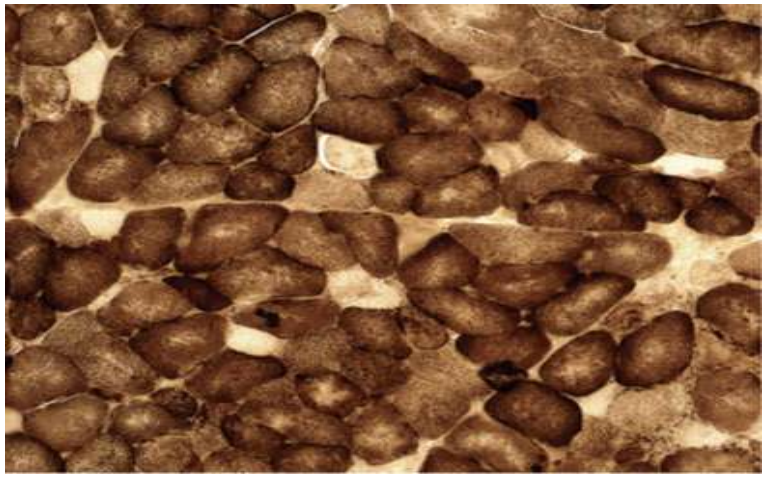


# IBM

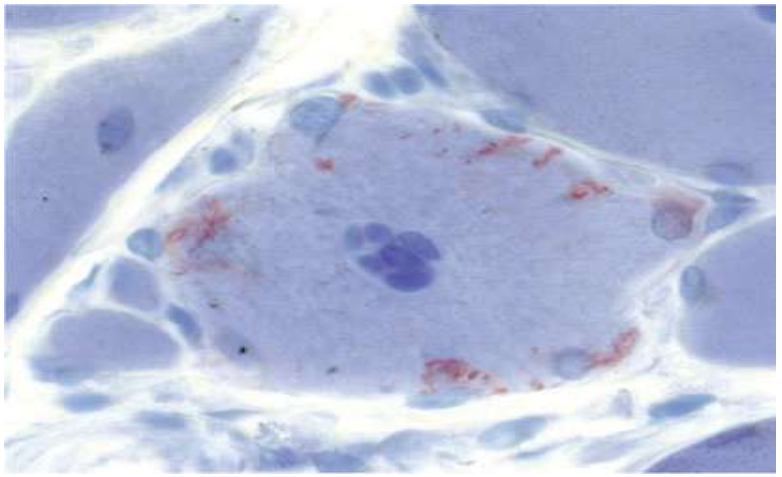
- + frecuente en hombres
- = o > 50 años (MI más frecuente)
- Prevalencia variable (4.9-51 a 70 casos/millón)
- Curso lentamente progresivo (años)
- DD distrofias musculares de inicio tardío/EMN
- Distribución asimétrica: músculos flexores dedos de las manos, cuádriceps, musculatura distal anterior piernas, extensores pies (afectación temprana)→ caídas
- Disfagia (en > 50%), debilidad facial, debilidad flexores cuello
- Musculatura axial puede afectarse→ camptocormia.

# IBM

- **Biopsia muscular:**
  - **Patología mixta: autoinmune, degenerativa**
  - Expresión difusa de MHC-I
  - Infiltrados inflamatorios (linf T-CD8, macrófagos, fagocitosis)
  - Complejo MHC-CD8
  - Cambios miopáticos: variabilidad tamaño ff, aumento del tejido conectivo, ff atróficas/hipertróficas, vacuolas autofágicas; fibras RR y COX negativas, depósitos de amiloide.

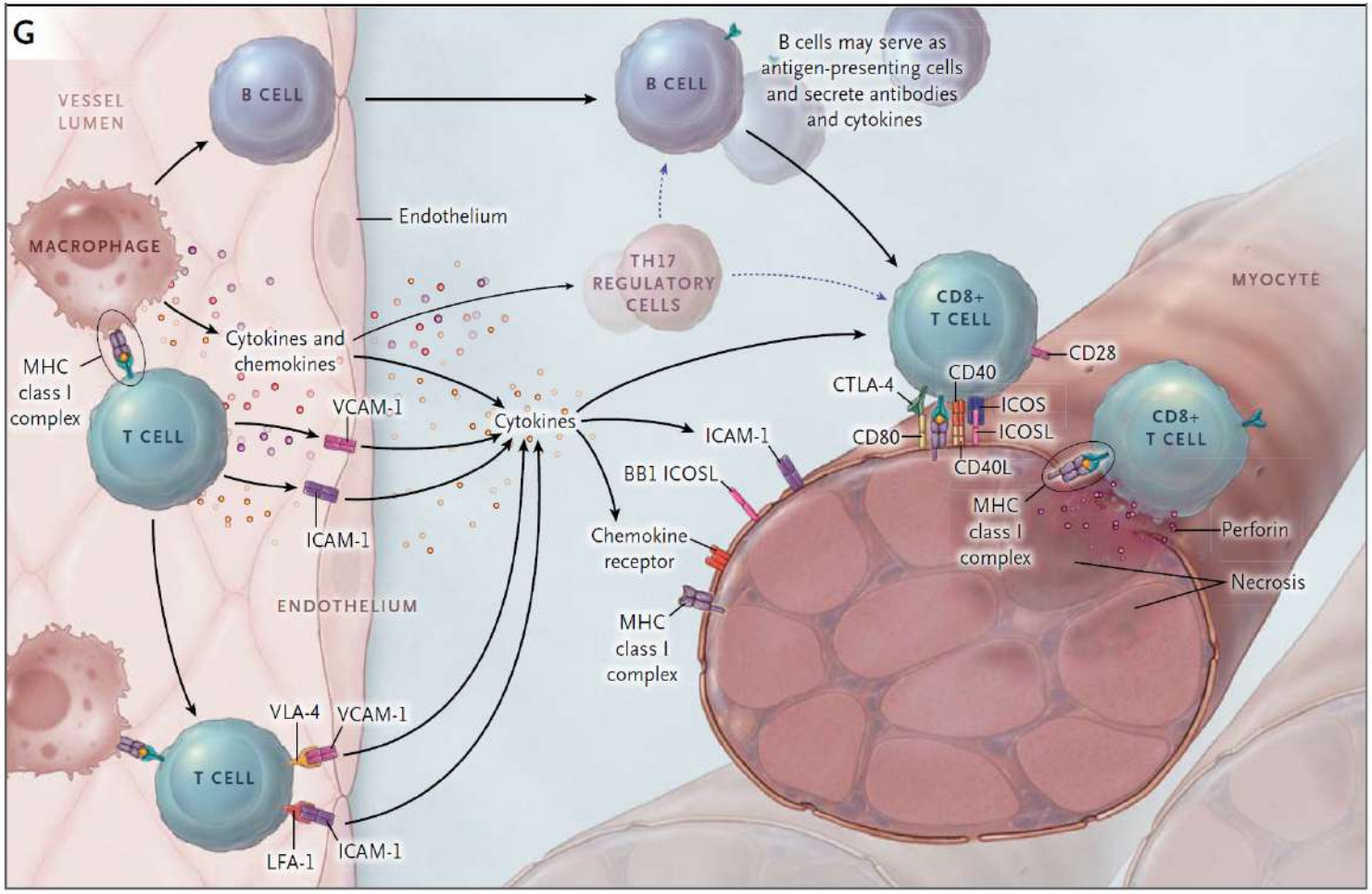


Fibras COX negativas



Vacuolas/amiloide

# Fisiopatología PM e IBM

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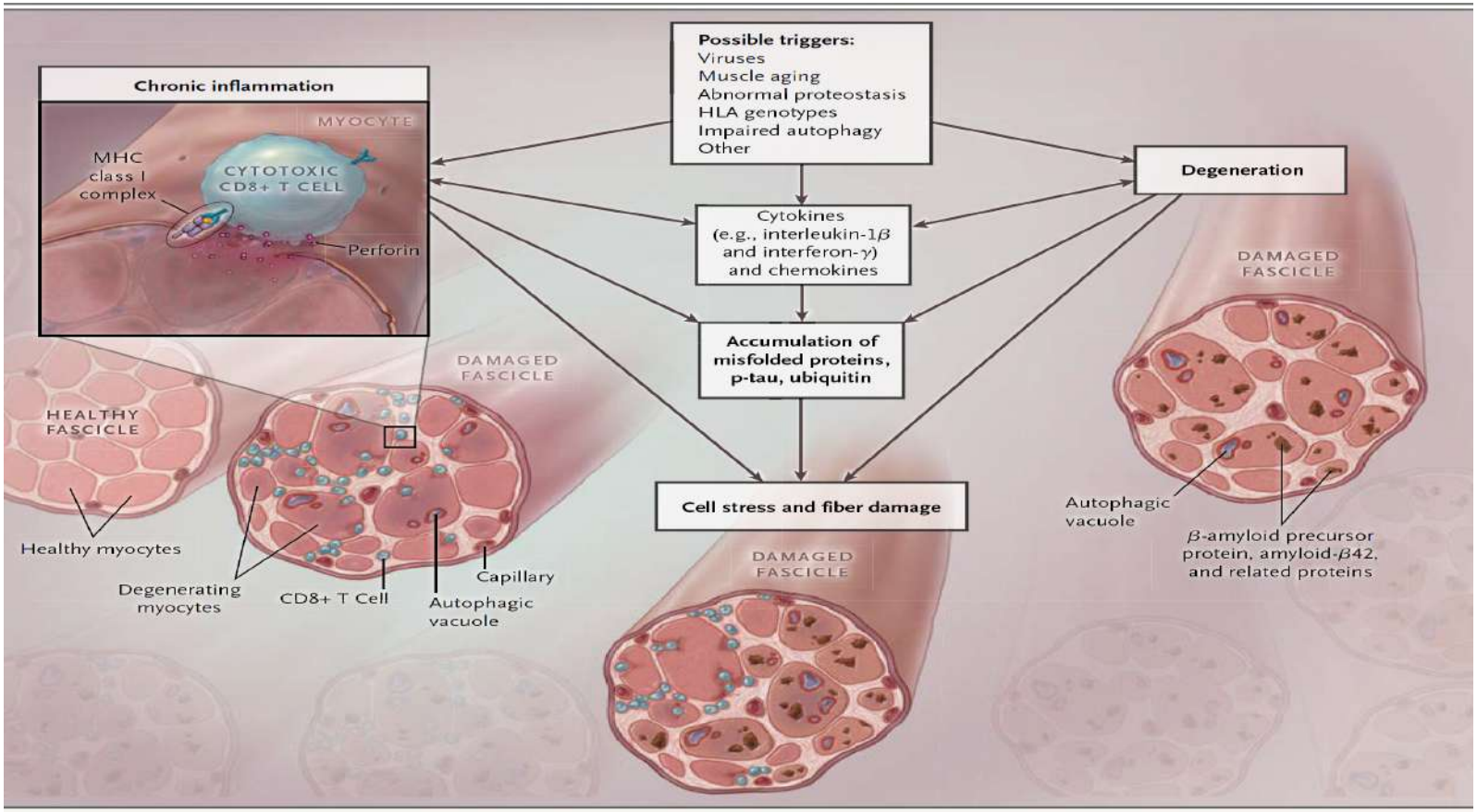


**Figure 3. Proposed Mechanisms in Inclusion-Body Myositis.**

Shown is a hypothetical schematic diagram of the pathogenesis of inclusion-body myositis, highlighting the interaction between the long-standing chronic inflammatory process and degeneration, which leads to cell stress and deposits of β-amyloid precursor protein, amyloid-β42, and misfolded proteins similar to the ones seen in neuroinflammatory disorders such as Alzheimer's disease. Therefore, inclusion-body myositis can be considered to be a peripheral model of neuroinflammation. The factors that trigger the disease are unclear, but viruses, muscle aging, protein misregulation (such as abnormal proteostasis), impaired autophagy, and HLA genotypes may play a role, either alone or in combination. Whether the primary event is inflammatory or degenerative is highly debated and remains unclear.

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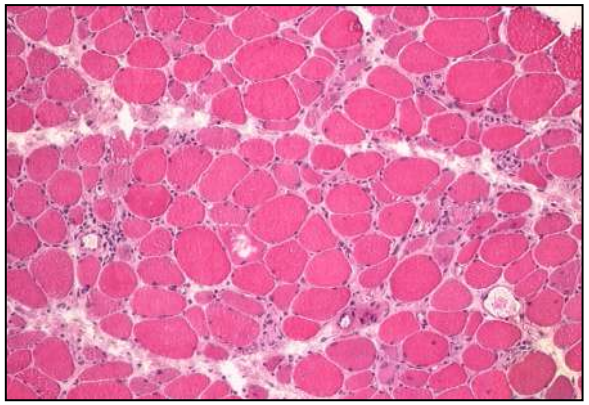
# Miopatía necrotizante inmunomediada

- Entidad clinicopatológica diferenciada
- Más frecuente que PM (20% de todas la MI)
- Cualquier edad, principalmente en adultos
- Inicio agudo (pico días o semanas) o subagudo
- Debilidad proximal severa
- Niveles muy elevados de CK
- Puede ocurrir:
  - De forma aislada
  - Después de infecciones virales
  - En asociación con cáncer/ conectivopatías (esclerodermia)
  - Estatinas
- Acs asociados: anti-HMGCR y anti-SRP.

# Miopatía necrotizante inmunomediada

- **Biopsia muscular:**
  - Abundantes fibras necróticas invadidas o rodeadas por macrófagos.
  - Infiltrados linfocitarios escasos.
  - Expresión de MHC clase I.
  - Frecuentemente depósitos de complemento.



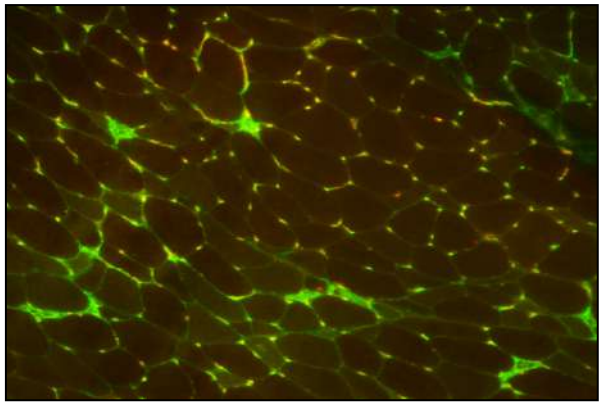


**Table 1.** Idiopathic inflammatory myopathies subcategories and classical muscle biopsy pathology findings [1,4]. The presence of vacuoles are pathognomonic for inclusion body myositis [1,4]. Idiopathic inflammatory myositis (IIM); Major histocompatibility complex (MHC).

| IIMs Sub-Category | Muscle Pathology | Vacuole Formation |
|---|---|---|
| Polymyositis | $CD8^+$ T-cells; MHC-1 antigen expression | No |
| Dermatomyositis | Perivascular; perimysial; perifascicular inflammation; +/− necrotic fibers; perifascicular atrophy and decreased capillaries; macrophages, B-cells and $CD4^+$ T-cells | No |
| Autoimmune necrotizing myositis | Necrotic fibers with macrophages; absence of $CD8^+$ T-cells; complement deposition may be present | No |
| Sporadic inclusion body myositis | $CD8^+$ T-cells; cytochrome-oxidase negative; congophilic amyloid deposits | Yes |

Tomado de: Int. J. Mol. Sci. 2017, 18, 1084; doi:10.3390/ijms18051084

# ¿ Qué hay de nuevo?

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

## Inflammatory Muscle Diseases

Marinos C. Dalakas, M.D.

frontiers in Immunology

MINI REVIEW
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## Autoimmune Myopathies: Where Do We Stand?

*Jean-Philippe Simon[1,2], Isabelle Marie[2], Fabienne Jouen[2], Olivier Boyer[2,*] and Jérémie Martinet[2]*

*[1] Laboratory of Neuropathology, CHU Caen, Normandie University, UNICAEN, Caen, France, [2] Normandie University, UNIROUEN, Pathophysiology and Biotherapy of Inflammatory and Autoimmune Diseases, INSERM, CHU Rouen, Rouen, France*

International Journal of *Molecular Sciences*

MDPI

*Review*

## Idiopathic Inflammatory Myopathies: A Review of the Classification and Impact of Pathogenesis

**Dana E. Mandel *, Charles J. Malemud and Ali D. Askari**

Department of Medicine, Division of Rheumatic Diseases, Case Western Reserve University School of Medicine and University Hospitals Cleveland Medical Center, Cleveland, OH 44106-5076, USA; cjm4@cwru.edu (C.J.M.); ali.askari@uhhospitals.org (A.D.A.)

* Correspondence: dana.mandel@uhhospitals.org; Tel.: +1-216-844-2289; Fax: +1-216-844-2288

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# Autoanticuerpos

- Acs dirigidos contra el RNA nuclear o contra antígenos del citoplasma se detectan en torno al 60% de los pacientes con miopatías inflamatorias.

- El papel patogénico de los anticuerpos es desconocido.

- Parecen específicos para distintos fenotipos clínicos y genotipos HLA-DR.

# Autoanticuerpos

- Acs contra aminoacyl tRNA synthetases (ARSs) detectados en el 20-30% de los pacientes.
- Anti-Jo 1 es el más frecuente (75%) en pacientes con **síndrome antisintetasa:**

  - Miositis con patología perimisial y perifascicular
  - Enfermedad pulmonar intersticial (70%)
  - Artritis, fenómeno de Raynaud
  - Fiebre
  - Manos de mecánico.

# Autoanticuerpos

- Miopatía necrotizante inmunomediada:
  - Anti-SRP (against the translational transport protein)
  - Anti-HMGCR (enzima 3-hidroxi-3-metilglutaril-coenzima A reductasa)

- Dermatomiositis:
  - Anti-Mi-2: asociado a lesiones dérmicas típicas
  - Anti-MDA-5: DM amiopática/enfermedad pulmonar intersticial
  - Anti-TIF-1ɣ (anti-transcriptional intermediary factor 1ɣ)
  - Anti-NXP-2 (anti-nuclear matrix protein 2)

  } DM asociada a cáncer en el adulto

- Miopatía por cuerpos de inclusión:
  - Anti-cN1A (anti-cytosolic 5'-nucleotidasa 1 A): 60-70%

# Autoanticuerpos

**Table 2.** Myositis specific antibodies and disease associations [2,4,8]. The specificity of autoantibodies on the associated disease processes is unknown as is their role in the pathogenicity of IIMs.

| Myositis-Specific Auto-Antibodies | Disease Association(s) |
|---|---|
| Anti-Aminoacyl-tRNA (e.g., Anti-Jo1, Anti-PL-7, Anti-PL-12 (anti-alanyl-tRNA synthase)) | Anti-Synthetase syndrome; ILD; gastrointestinal complications |
| Anti-HMGCR (3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Antibodies) | Necrotizing Autoimmune Myositis |
| Anti-Signal Recognition Particle (SRP) | Necrotizing Autoimmune Myositis/Polymyositis |
| Anti-Melanoma Differentiation-Associated Protein-5 (MDA-5) | Amyopathic Dermatomyositis; rapidly progressive ILD |
| Anti-Mi-2 (chromodomain-helicase-DNA binding protein 4) | Dermatomyositis with typical skin lesions |
| Anti-Cytosolic 5′-Nucleotidase 1A (cN1A) | Inclusion Body Myositis |
| Anti-Transcriptional Intermediary Factor 1-γ (TIF-1-γ/α) | Malignancy-associated Dermatomyositis |
| Anti-Nuclear Matrix Protein-2 (NXP-2) | Malignancy-associated Dermatomyositis; Juvenile-Dermatomyositis with calcinosis |
| Anti-Four & a Half Limb Domain-1 (FHL-1) | Myositis with severe muscle atrophy and dysphagia but without lung or joint involvement |

Tomado de: Int. J. Mol. Sci. 2017, 18, 1084; doi:10.3390/ijms18051084

# Diagnóstico

- Combinación de:
  - Historia clínica
  - Curso/progresión de la enfermedad
  - Patrón de afectación muscular
  - Niveles de CK: indicador más sensible
  - Autoanticuerpos
  - RM muscular: de utilidad para identificar edema, miofascitis y patrón de atrofia muscular (útil en IBM)
  - EMG: miopático con actividad espontánea
  - **Biopsia muscular**

# Diagnóstico

- RM muscular:
  - Edema: brillo en STIR
  - Infiltración grasa
  - Atrofia o fibrosis

- Utilidad:
  - Selección músculo para la biopsia.
  - Definir patrón/extensión afectación muscular (sbt en IBM)
  - Actividad de la enfermedad.

**Table 1. Criteria Supporting the Diagnosis of Inflammatory Myopathies.**

| Criterion | Dermatomyositis | Polymyositis | Necrotizing Autoimmune Myositis | Inclusion-Body Myositis |
|---|---|---|---|---|
| Pattern of muscle weakness | Subacute onset of proximal symmetric weakness with characteristic skin rash in patients of any age | Subacute onset of proximal symmetric weakness in adults (diagnosis is made when other causes have been ruled out)* | Acute or subacute onset of proximal, often severe weakness in adults | Slow onset of proximal and distal weakness; atrophy of quadriceps and forearms; frequent falls; mild facial muscle weakness in people older than 50 years of age |
| Creatine kinase level | High, up to 50 times the upper limit of normal; can at times be normal | High, up to 50 times the upper limit of normal in early active disease; may linger at up to 10 times the upper limit of normal | Very high; more than 50 times the upper limit of normal in early active disease | Up to 10 times the upper limit of normal; can be normal or slightly elevated |
| Electromyography | Myopathic units (active and chronic) | Myopathic units (active and chronic) | Active myopathic units | Myopathic units (active and chronic) with some mixed large-size potentials |
| Muscle biopsy | Perivascular, perimysial, and perifascicular inflammation; necrotic fibers in "wedge-like" infarcts; perifascicular atrophy; reduced capillaries† | CD8+ cells invading healthy fibers; widespread expression of MHC class I antigen; no vacuoles; ruling out of inflammatory dystrophies | Scattered necrotic fibers with macrophages; no CD8+ cells or vacuoles; deposits of complement on capillaries‡ | CD8+ cells invading healthy fibers; widespread expression of MHC class I antigen; autophagic vacuoles,§ ragged-red or ragged-blue fibers; congophilic amyloid deposits¶ |
| Autoantibodies | Anti-MDA-5, anti-Mi-2; anti-TIF-1 and anti-NXP-2 (implicated in cancer-associated dermatomyositis) | Antisynthetase antibodies (often seen in overlap myositis) associated with interstitial lung disease, arthritis, fever, and "mechanic's hands" | Anti-SRP and anti-HMGCR, specific for necrotizing autoimmune myositis | Anti-cN1A (of uncertain pathologic significance) |
| Magnetic resonance imaging | May show active inflammation | May show active inflammation; could guide biopsy site | May show active inflammation; could guide biopsy site | Shows selective muscle involvement, but might be difficult to distinguish atrophy from chronic inflammation |

* Drug-induced myopathies (e.g., penicillamine, statins, or antiretrovirals), inflammatory dystrophies (such as those due to mutations in the genes encoding dysferlin, calpain, or anoctamin; Becker's muscular dystrophy; facioscapulohumeral muscular dystrophy; or myofibrillar myopathies), inclusion-body myositis, necrotizing autoimmune myositis, metabolic myopathies, and fasciitis or fibromyalgia need to be ruled out.

† Similar pathologic changes in the perifascicular, perimysial, and interfascicular areas (to a lesser degree of severity) can be seen in overlap myositis (without skin lesions) or the antisynthetase syndrome.

‡ Metabolic muscle diseases presenting as myoglobinuria and toxic or drug-induced myopathies need to be ruled out.

§ In clinical inclusion-body myositis, when patients have the typical inclusion-body myositis phenotype, vacuoles are absent; such patients are erroneously thought to have polymyositis because of polymyositis-like inflammation; ragged-red fibers or cytochrome oxidase–negative fibers are frequently present and are helpful in diagnosis.

¶ TDP43 and p62 deposits, detected with the use of immunostaining, have been proposed as tissue biomarkers.

Tomado de: Dalakas, M.C. Inflammatory muscle disease. N. Engl. J. Med.2015,372,1734-1747.

# Tratamiento

**Table 2. Treatment of Inflammatory Myopathies: A Step-by-Step Approach.**

| Scenario | Treatment for Dermatomyositis, Polymyositis, and Necrotizing Autoimmune Myositis | Treatment for Inclusion-Body Myositis |
|---|---|---|
| Initiation of therapy | | |
| New-onset disease | Prednisone (1 mg per kilogram, up to 100 mg per day) for 4–6 weeks; taper to alternate days | Physical therapy; participation in research trial |
| When weakness at onset is severe or rapidly worsening | Intravenous glucocorticoids (1000 mg per day) for 3 to 5 days, then switch to oral regimen | Not applicable |
| For glucocorticoid sparing, if the patient's condition responds to glucocorticoids | Azathioprine, methotrexate, mycophenolate, cyclosporine* | Not applicable† |
| If response to glucocorticoids is insufficient | Intravenous immune globulin (2 g per kilogram in divided doses over a period of 2 to 5 consecutive days) | Not applicable‡ |
| If response to glucocorticoids and intravenous immune globulin is insufficient | Reevaluate and reconsider diagnosis; initiate treatment with rituximab§ if diagnosis is reconfirmed, recommend participation in a research trial¶ if disease does not respond to rituximab | Participation in research trial |

* The use of these agents is based on experience but not on controlled studies. Azathioprine can be given at a dose of up to 3 mg per kilogram, methotrexate at a dose of up to 20 mg per week, mycophenolate at a dose of 2000 to 3000 mg per day, and cyclosporine at a dose of up to 300 mg daily. Intravenous cyclophosphamide (0.8 to 1 g per square meter of body surface area) and oral tacrolimus (4–8 mg per day) may help patients with interstitial lung disease.
† All glucocorticoid-sparing agents are ineffective, either alone or in combination.
‡ In some patients, the dysphagia responds to intravenous immune globulin.
§ Efficacy has not been established with a controlled study, but the evidence of efficacy is compelling.
¶ Candidate agents include eculizumab, alemtuzumab, tocilizumab (anti–interleukin-6), anti–interleukin-17, and anti–interleukin-1$\beta$.

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# Conclusiones

- Cinco subcategorías de MI: DM, PM, IBM, MNI, sd. antisintetasa.
- A tener en cuenta la presencia de anticuerpos y la RM muscular.
- La principal herramienta diagnóstica es la biopsia muscular, siempre interpretada en el contexto clínico del paciente.
- En un futuro, relevancia de los tratamientos biológicos.