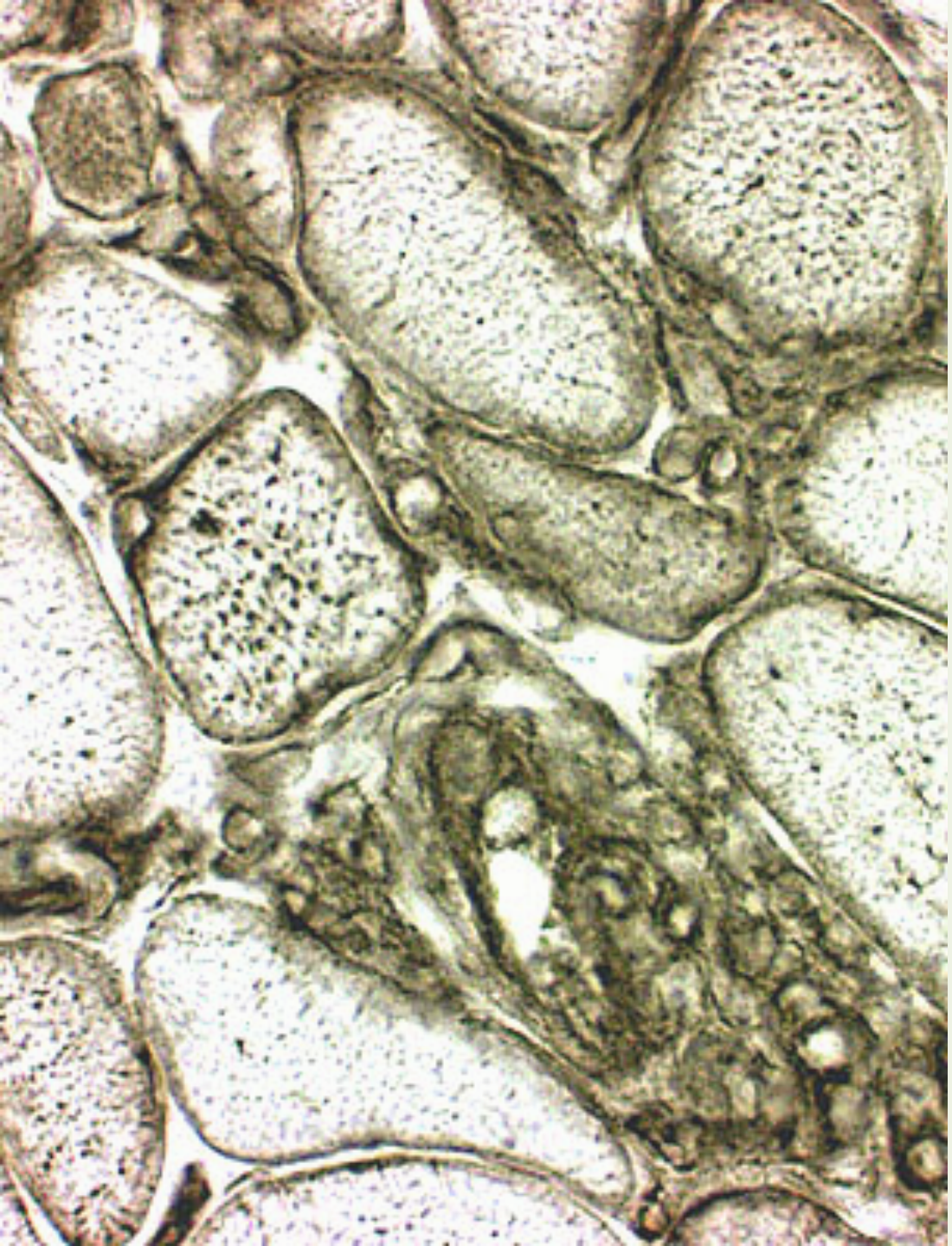


Abordatge Clínico-Analític

MIOSITIS

Dra Teresa Clavaguera
Reumatòloga
Hospital de Palamós
27 de setembre de 2014
Acadèmia de Ciències Mèdiques
Barcelona

Fig: Miositis per cossos inclusió

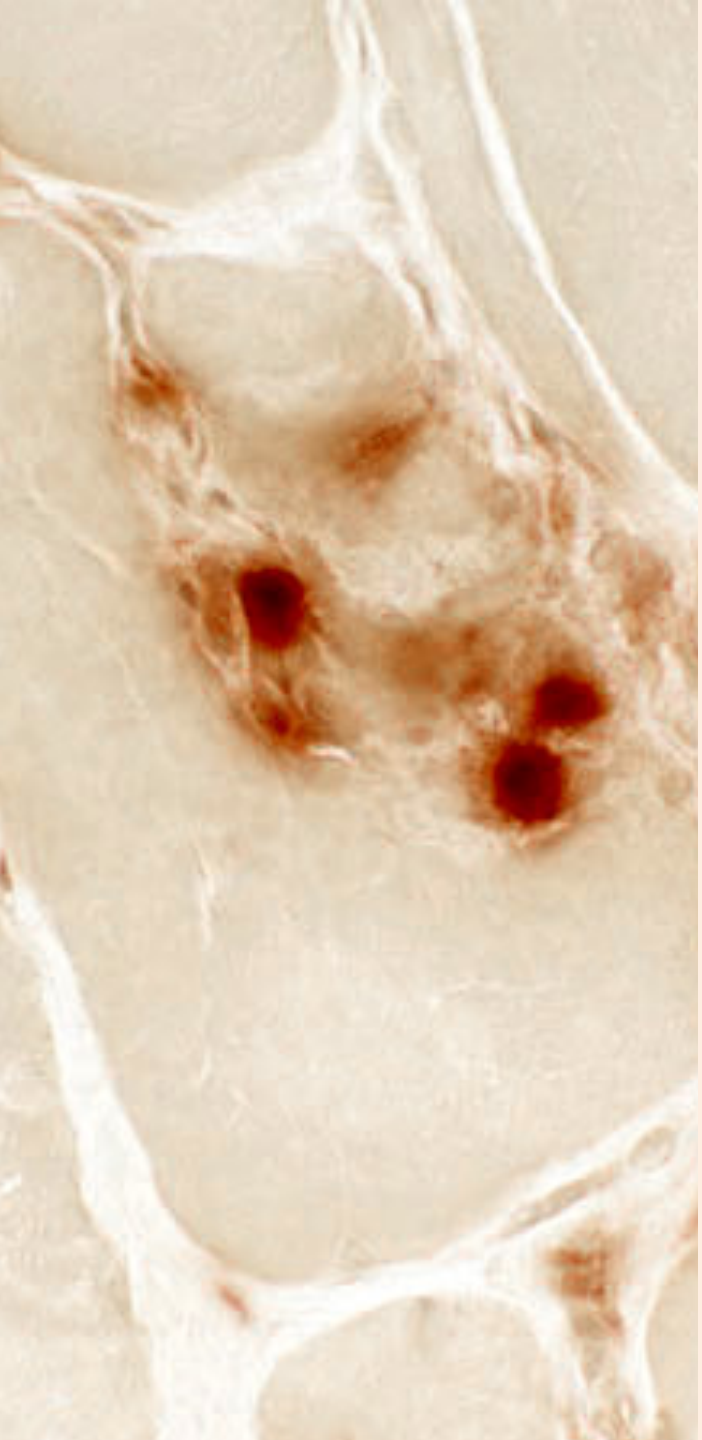
Introducció

Nous Criteris Diagnòstics

Anticossos

Consideracions finals

Fig: Tinció components del complement C5b-9 (Complexe d'Atac de Membrana)



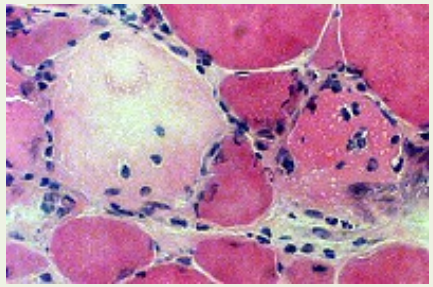
DEFINICIÓ:

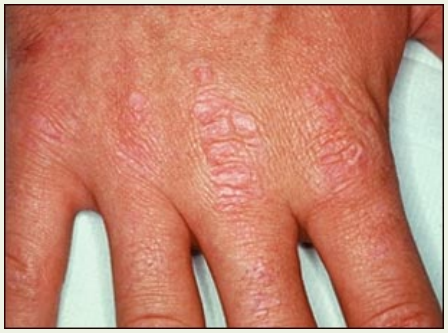
Debilitat muscular proximal simètrica

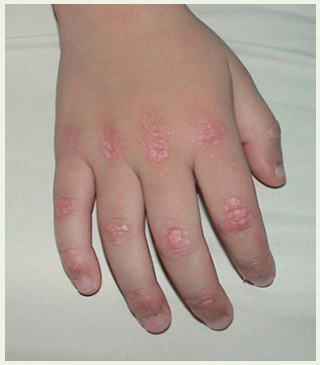
Biòpsia: inflamació i/o necrosi

Si DM: lesions cutànies

Fig: Progressiva invasió local de fibres musculars (tinció Fosfatassa Àcida)







NECROTITZANTS

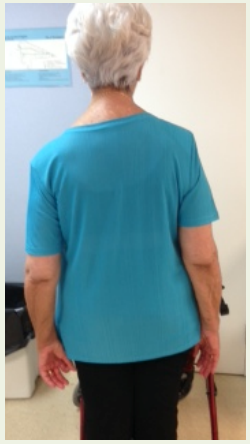
JUVENIL

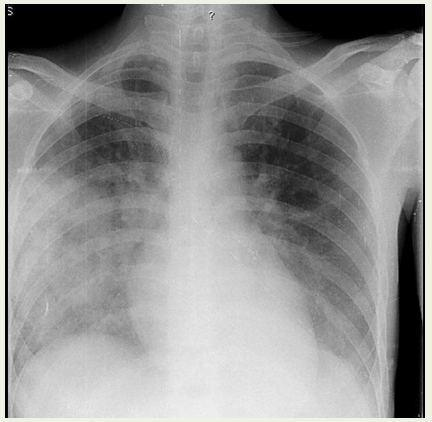
MII

DM

PM

MII-MTC





CLASSIFICACIÓ DE LES MIOSITIS EN PRÀCTICA CLÍNICA

EPIDEMIOLOGIA

Incidència: 1,16 a 19 /milió/any

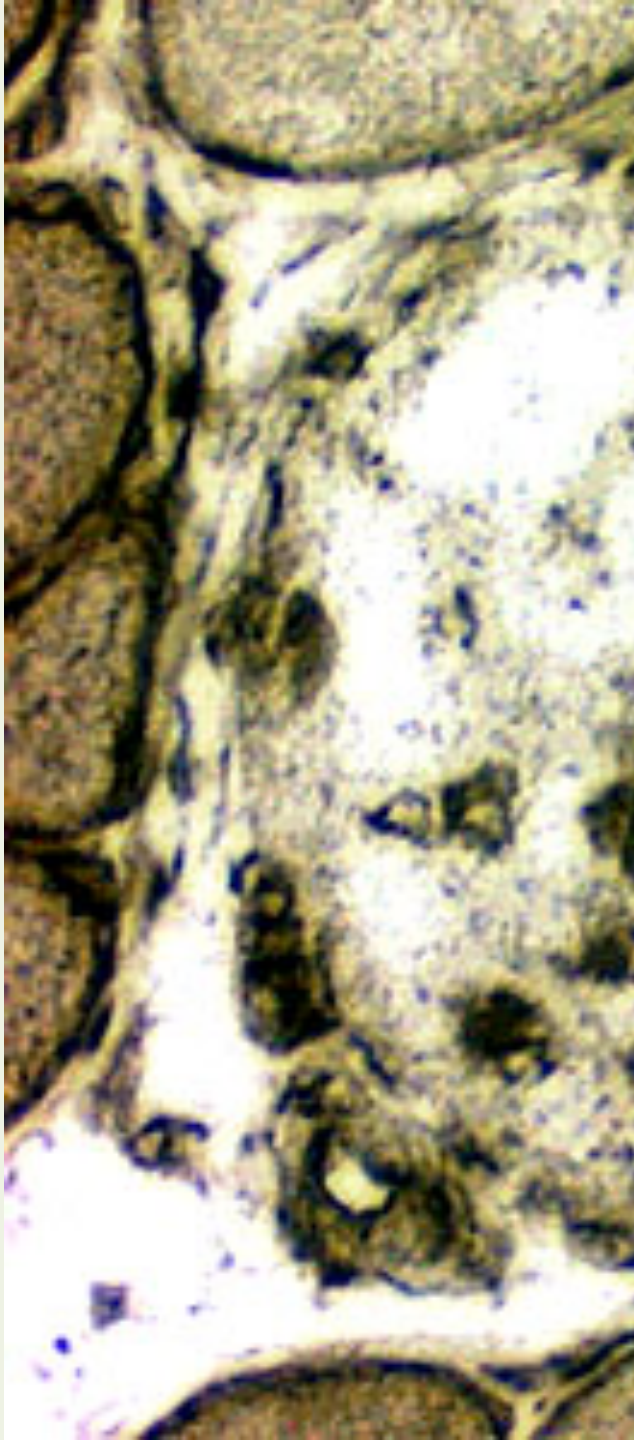
Prevalença: 2,4-33,8 / 100.000 hab

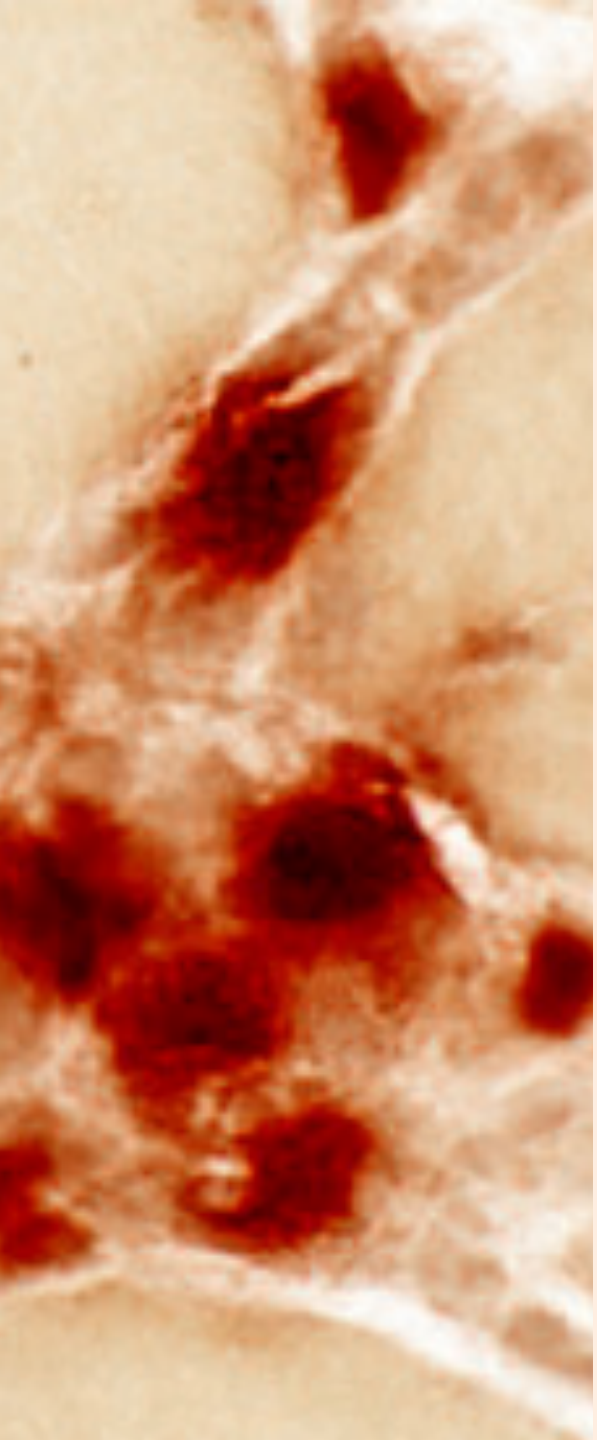
2 pics d'edat:
- 5-15 anys en nens
- 30-50 anys en adults

Sexe: 3:1 dones, excepte en la MCI

Ref: Meyer A, Meyer N, Schaeffer M, Gottenberg JE, Geny B, Sibilia J
Incidence and prevalence of inflammatory myopathies: a systematic review.
Rheumatology (Oxford). 2014 Jul 26.[Epub ahead of print]

Fig: presència de necrosi en cèl·lules de la fibra muscular





MOTIU DE CONSULTA

Elevació d'enzims musculars

Debilitat muscular

Miàlgies

Fenomen de Raynaud

Derivació d'una DM

Diagnòstic diferencial "AR seronegativa"

ARTRITIS a les MIOSITIS

53% artritis durant de la malaltia

37% una artritis d'inici

22% artritis abans de debilitat

27/29 Ac Jo-1 + tenien artritis.

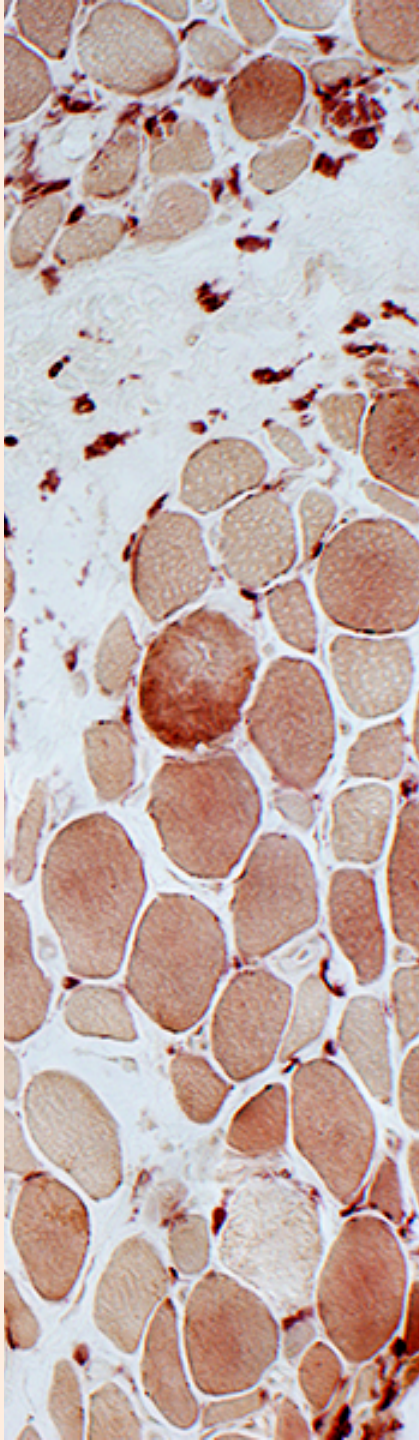
Ref: Klein M, Mann H, Plestilova L et al . Arthritis in idiopathic inflammatory myopathy: clinical features and autoantibody associations. J Rheumatol. 2014 Jun;41(6):1133-9..


KEEP
CALM
AND MAKE
DIFFERENTIA
DIAGNOSIS

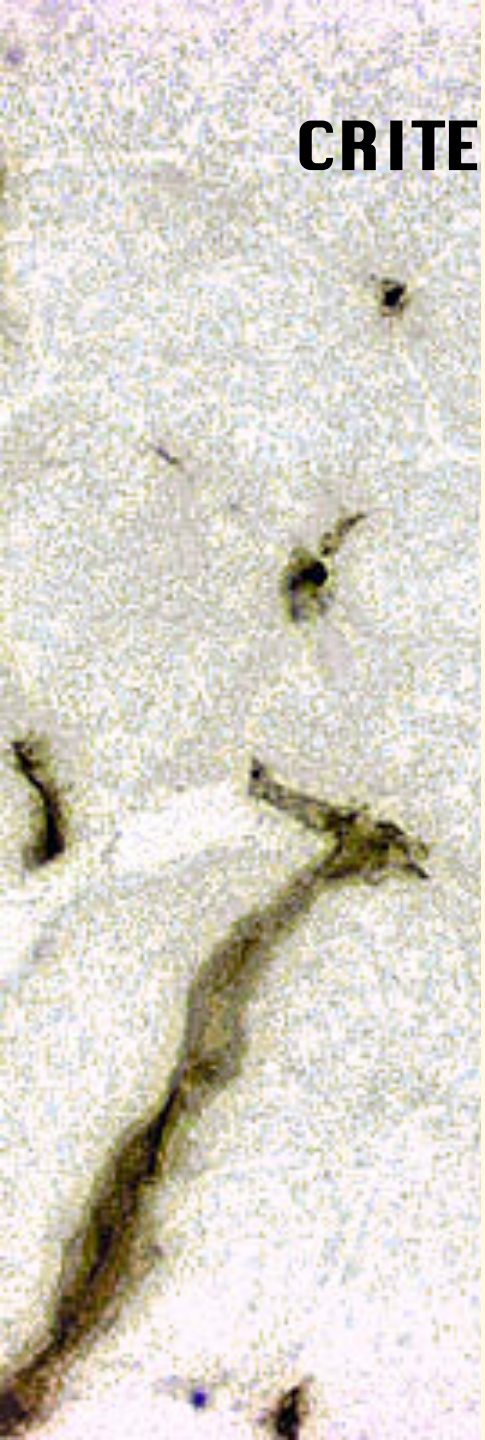
Malalties neuromusculars
Fàrmacs miotòxics:
- D-penicilamina
- Zidovudina
- Estatines

Malalties Endocrines:
- Hipo i hiperT
- HipoparaT
- Hipercortisolisme

Malalties neurogèniques
Distròfies musculars i miopaties metabòliques
Miositis per cossos inclusió
Infeccions:
- Víriques: HIV, VHC, HTLV-1
- Paràsits: Trichina, sarcocystis



Milisenda JC et al. J Autoimm. 2014; 48-49: 118-121.
Lazarou I and Guerne PA. J Rheumatol. 2013; 40(5) 550-551.



CRITERIS DIAGNÒSTICS: BOHAN I PETERS (1975)

TABLE 139. 1 BOHAN AND PETER CRITERIA FOR DIAGNOSIS OF POLYMYOSITIS AND DERMATOMYOSITIS

Individual criteria

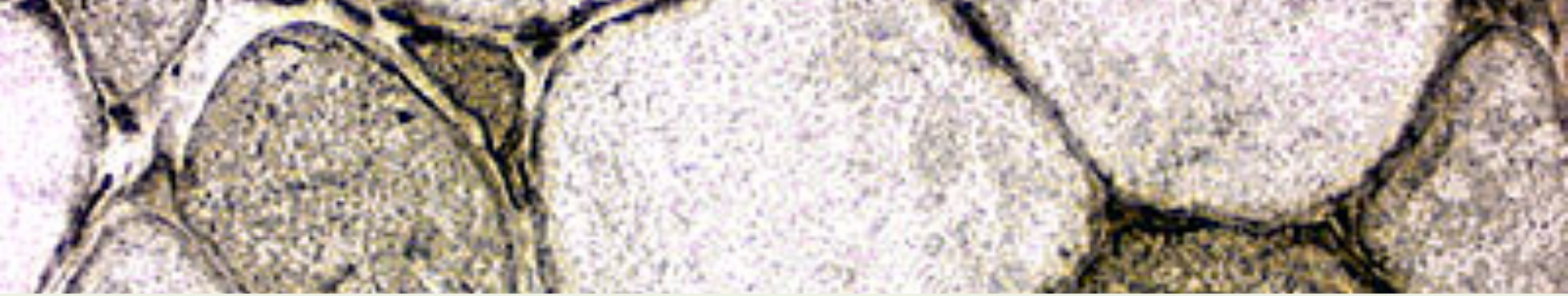
1. Symmetric proximal muscle weakness
2. Muscle biopsy evidence of myositis
3. Increase in serum skeletal muscle enzymes
4. Characteristic electromyographic pattern
5. Typical rash of dermatomyositis

Diagnostic criteria

Polymyositis:	
Definite:	all of 1–4
Probable:	any 3 of 1–4
Possible:	any 2 of 1–4
Dermatomyositis:	
Definite:	5 plus any 3 of 1–4
Probable:	5 plus any 2 of 1–4
Possible:	5 plus any 1 of 1–4

(Modified with permission from Bohan and Peter[12].)

Fig. Fibra muscular normal. Expressió de MCH-I a vasos no a fibres musculars.



CRITERIS DIAGNÒSTICS: DALAKAS

Criterion	Polymyositis		Myopathic dermatomyositis		Amyopathic dermatomyositis
	Definite	Probable	Definite	Probable	Definite
Myopathic muscle weakness	Yes*	Yes*	Yes*	Yes*	No†
Electromyographic findings	Myopathic	Myopathic	Myopathic	Myopathic	Myopathic or non-specific
Muscle enzymes	High (up to 50 times normal)	High (up to 50 times normal)	High (up to 50 times normal) or normal	High	High (up to 10 times normal) or normal
Muscle-biopsy findings	Primary inflammation, with the CD8/MHC-1 complex and no vacuoles	Ubiquitous MHC-I expression, but no CD8-positive infiltrates or vacuoles‡	Perifascicular, perimysial or perivascular infiltrates; perifascicular atrophy	Perifascicular, perimysial or perivascular infiltrates; perifascicular atrophy	Non-specific or diagnostic for dermatomyositis (subclinical myopathy)
Rash or calcinosis	Absent	Absent	Present	Not detected	Present

*Myopathic muscle weakness, affecting proximal muscles more than distal ones and sparing eye and facial muscles, is characterised by a subacute onset (weeks to months) and rapid progression in patients who have no family history of neuromuscular disease, no exposure to myotoxic drugs or toxins, and no signs of biochemical muscle disease. The myopathic weakness has a pattern distinct from that seen in inclusion-body myositis (table 1). †Although strength is apparently normal, many patients have new onset of easy fatigue, myalgia, and reduced endurance. Careful muscle testing may reveal mild muscle weakness. ‡If such a patient has the clinical phenotype of sporadic inclusion-body myositis, the diagnosis will be probable inclusion-body myositis; a repeat biopsy is indicated.

Table 2: **Diagnostic criteria for inflammatory myopathies**

Ref: Dalakas M, Hohlfeld H. Polymyositis and dermatomyositis. *Lancet.* 2003; **362**: 971-982.

Fig: MCI tinció MHC-I que tenyeix cèl·lules mononuclears.

MYO NET

GLOBAL MYOSITIS NETWORK

Interdisciplinary Research Project on Inflammatory Myopathies, Myositis.

HOME | ABOUT US | MYOSITIS | ACTIVITIES | RESEARCH AREAS | PUBLICATIONS | NEWS | CONTACT

International collaboration

research and treatment

registry for myositis specialists

READ

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. S3, March 2014, pp S70–S71
DOI 10.1002/art.38463

A47: Progress Report on the Development of New Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies

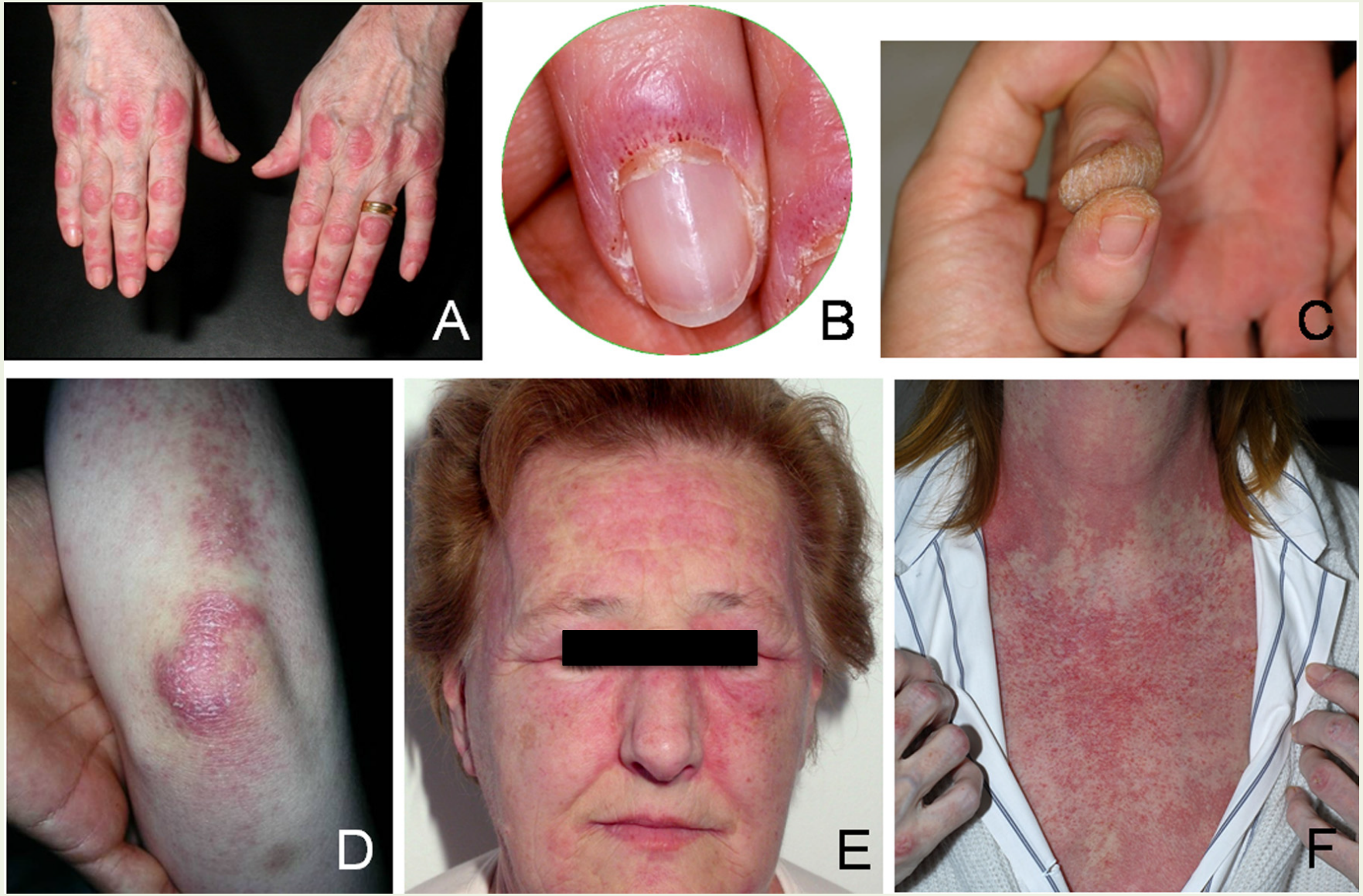
Clarissa Pilkington,[1] Anna Tjärnlund,[2] Matteo Bottai,[3] Lisa G Rider,[4] Victoria P Werth,[5] Marianne de Visser,[6] Lars Alfredsson,[3] Anthony A Amato,[7] Richard J Barohn,[8] Matthew H Liang,[9] Jasvinder A Singh,[10] Frederick W Miller,[11] Ingrid E. Lundberg,[12] and On behalf of the members of the IMCCP International Myositis Classification Criteria Project[2]

Table 2. New model for classification criteria for IIM and performance of criteria

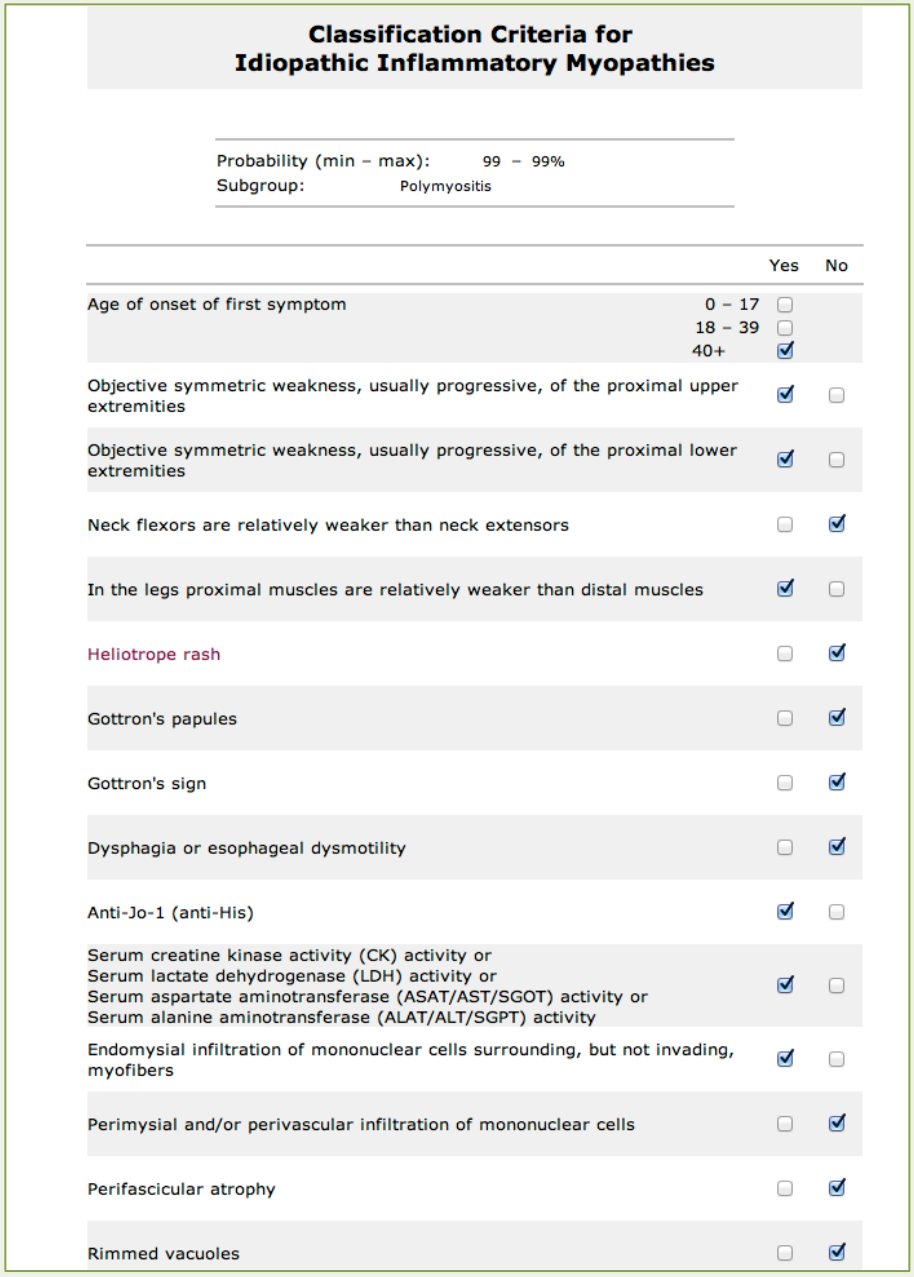
Probability model	
Variable	**Score points**
18 ≤ Age of onset of first symptom < 40	1.6
Age of onset of first symptom ≥ 40	2.3
Clinical Muscle Variables	
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.6
Neck flexors are relatively weaker than neck extensors	1.6
In the legs proximal muscles are relatively weaker than distal muscles	1.5
Skin Variables	
Heliotrope rash	3.3
Gottronxs papules	2.3
Gottron's sign	3.4
Other Clinical Variables	
Dysphagia or esophageal dysmotility	0.7
Laboratory Variables	
Serum creatine kinase activity (CK) activity	1.2
Serum lactate dehydrogenase (LDH) activity or Serum aspartate aminotransferase (ASAT/AST/SGOT) activity or Serum alanine aminotransferase (ALAT/ALT/SGPT) activity	
Anti-Jo-1 (anti-His) antibody positivity	4.2
Score-sum from above items[a]	0.9
Muscle Biopsy Variables	
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers	1.4
Perimysial and/or perivascular infiltration of mononuclear cells	1.2
Perifascicular atrophy	1.6
Rimmed vacoules	2.2

[a] When muscle biopsies are available, multiply the score-sum of all other variables by 0.9 and then add the scores of the positive biopsies. Probability of disease can be obtained using the web calculator: www.imm.ki.se/biostatistics/calculators/iim

Pilkington C1, Tjärnlund A, Bottai M, Rider LG, Werth VP, Visser Md, Alfredsson L, Amato AA, Barohn RJ, Liang MH, Singh JA, Miller FW, Lundberg IE; members of the IMCCP International Myositis Classification Criteria Project. A47: Progress report on the development of new classification criteria for adult and juvenile idiopathic inflammatory myopathies. Arthritis Rheumatol. 2014 Mar;66 Suppl 11:S70-1.



Iaccarino L et al. J Autoimmun. 2014 Feb-Mar;48-49:122-7



Classification Criteria for Idiopathic Inflammatory Myopathies

Probability (min – max): 99 – 99%
Subgroup: Polymyositis

		Yes	No
Age of onset of first symptom	0 – 17	☐	
	18 – 39	☐	
	40+	☑	
Objective symmetric weakness, usually progressive, of the proximal upper extremities		☑	☐
Objective symmetric weakness, usually progressive, of the proximal lower extremities		☑	☐
Neck flexors are relatively weaker than neck extensors		☐	☑
In the legs proximal muscles are relatively weaker than distal muscles		☑	☐
Heliotrope rash		☐	☑
Gottron's papules		☐	☑
Gottron's sign		☐	☑
Dysphagia or esophageal dysmotility		☐	☑
Anti-Jo-1 (anti-His)		☑	☐
Serum creatine kinase activity (CK) activity or Serum lactate dehydrogenase (LDH) activity or Serum aspartate aminotransferase (ASAT/AST/SGOT) activity or Serum alanine aminotransferase (ALAT/ALT/SGPT) activity		☑	☐
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		☑	☐
Perimysial and/or perivascular infiltration of mononuclear cells		☐	☑
Perifascicular atrophy		☐	☑
Rimmed vacuoles		☐	☑

http://www.imm.ki.se/biostatistics/calculators/iim/

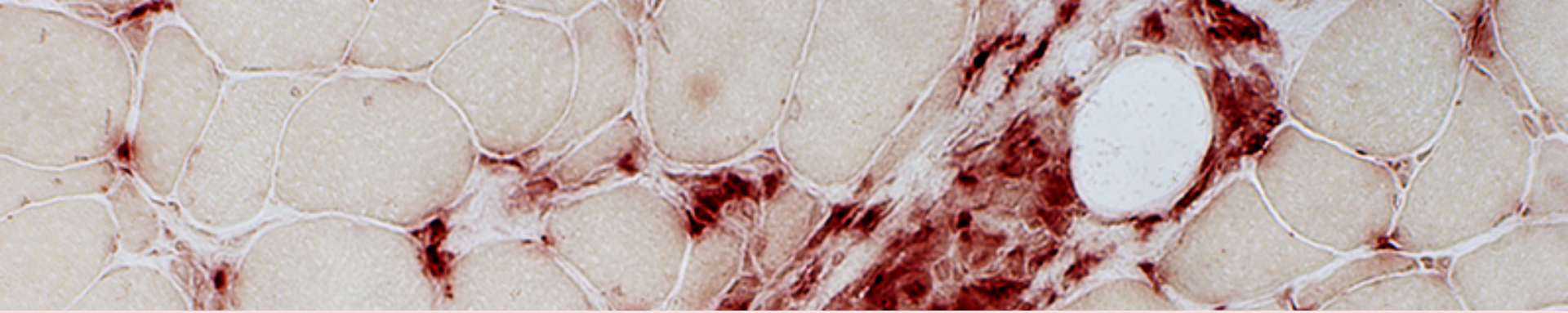


Table 1. PERFORMANCE OF NEW AND EXISITING CLASSIFICATION/DIAGNOSTIC CRITERIA FOR IIM

Probability model[a]								
Performance(%)	Without muscle biopsy data(Model 1)	With muscle biopsy data (Model 2)	Classification Tree	Peter & Bohan [1][b]	Tanimoto et al. [2]	Targoff et al. [3][b]	Dalakas & Hohlfeld [4][b]	Hoogendijk et al.[5][b]
Sensitivity	87	88	88	98	96	93	6	51
Specificity	88	89	72	55	31	88	99	96
Correctly classified	87	88	84	86	79	91	45	70

[a] Cut point for probability: 55%

[b] Definite and probable polymyositis and dermatomyositis

Pilkington C1, Tjärnlund A, Bottai M, Rider LG, Werth VP, Visser Md, Alfredsson L, Amato AA, Barohn RJ, Liang MH, Singh JA, Miller FW, Lundberg IE; members of the IMCCP International Myositis Classification Criteria Project. A47: Progress report on the development of new classification criteria for adult and juvenile idiopathic inflammatory myopathies. Arthritis Rheumatol. 2014 Mar;66 Suppl 11:S70-1.


AC ASSOCIATS MII (AAMS)
AC ESPECÍFICS MII (AEMS)

Ac ASSOCIATS A MII

Pacients amb MII associats a altres MTC

Són ANA (excep Ro52)

Solen existir des de l'inici de la malaltia

No canvien durant el curs de la mateixa

No es modifiquen amb el tractament

No serveix la seva titulació

Mètode convencional: IFI (més sensible)

Anti- Pm-Scl

Anti- Ku

Anti-U1 RNP

Anti-Ro60

Anti-Ro52

ANTICOSSOS ESPECÍFICS MII

Són Ac que no apareixen en altres MTC

Elevat cost (Immunoblot)

Orienten a fenotips determinats de la malaltia

Aporten valor pronòstic i terapèutic.

DL 1530-1601 G	Myositis Profile (Mi-2, Ku, PM-Scl, Jo-1, PL-7, PL-12, Ro-52 separately)	IgG	membrane strip with antigens (EUROLINE)		16 x 01
DL 1530-1601-3 G	Myositis Profile 3 (Mi-2, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52 separately)	IgG	membrane strip with antigens (EUROLINE)		16 x 01
DL 1530-1601-4 G	Autoimmune Inflammatory Myopathies 15 Ag (Mi-2 alpha, Mi-2 beta, TIF1g, MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ separately)	IgG	membrane strip with antigens (EUROLINE)		16 x 01

ANTICOSSOS ESPECÍFICS DE LES MII (MSAs)

Sd antisintetasa
Febre
F Raynaud
Artritis
Mans mecànic
Miositis
Fibrosi pulmonar

Miositis Necrotizant

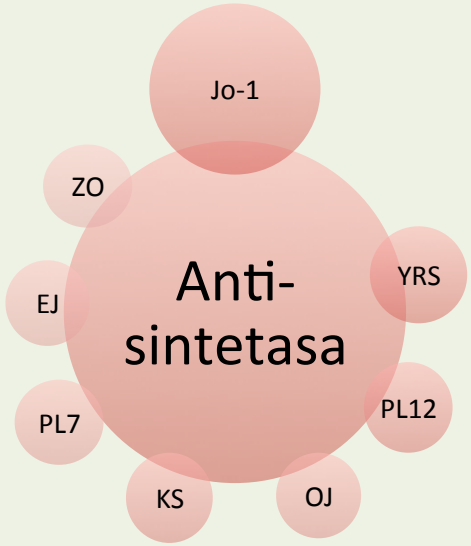
↑↑ CK

DM Amiopàtica

Rash sine miositis
Hipomiopàtica
Rash previ miositis

DM

Rash
Malignitat
Calcinosi/ vasculitis (nens)



Anti-SRP

Anti-HMGCR

Anti-SAE

Anti-MDA-5

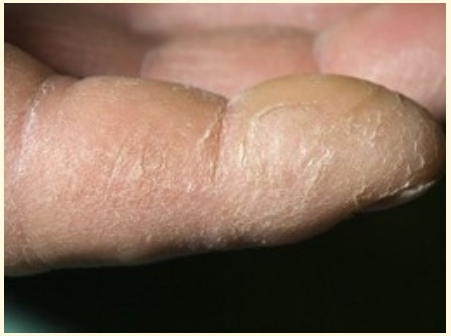
Anti-NPX-2

Anti-Tifγ

Anti-Mi2

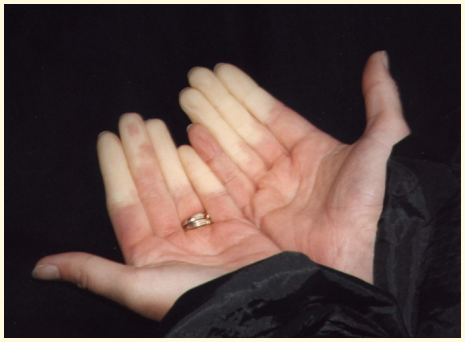
Diapositiva H. Chinoy adaptada de Gunawardena H. Eular 2014.

SÍNDROME ANTISINTETASA (SAS)



No tothom té un quadre complert.

- Afectació pulmonar predominant.
- Discreta afecció cutània i la miositis (inici)



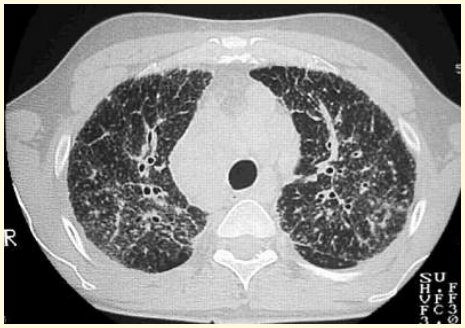
Jo-1+: > freq de miositis i artritis.

Jo-1-: > freq de FR a l'inici.

Prevalença Ac SAS: 60% Jo-1+[1]

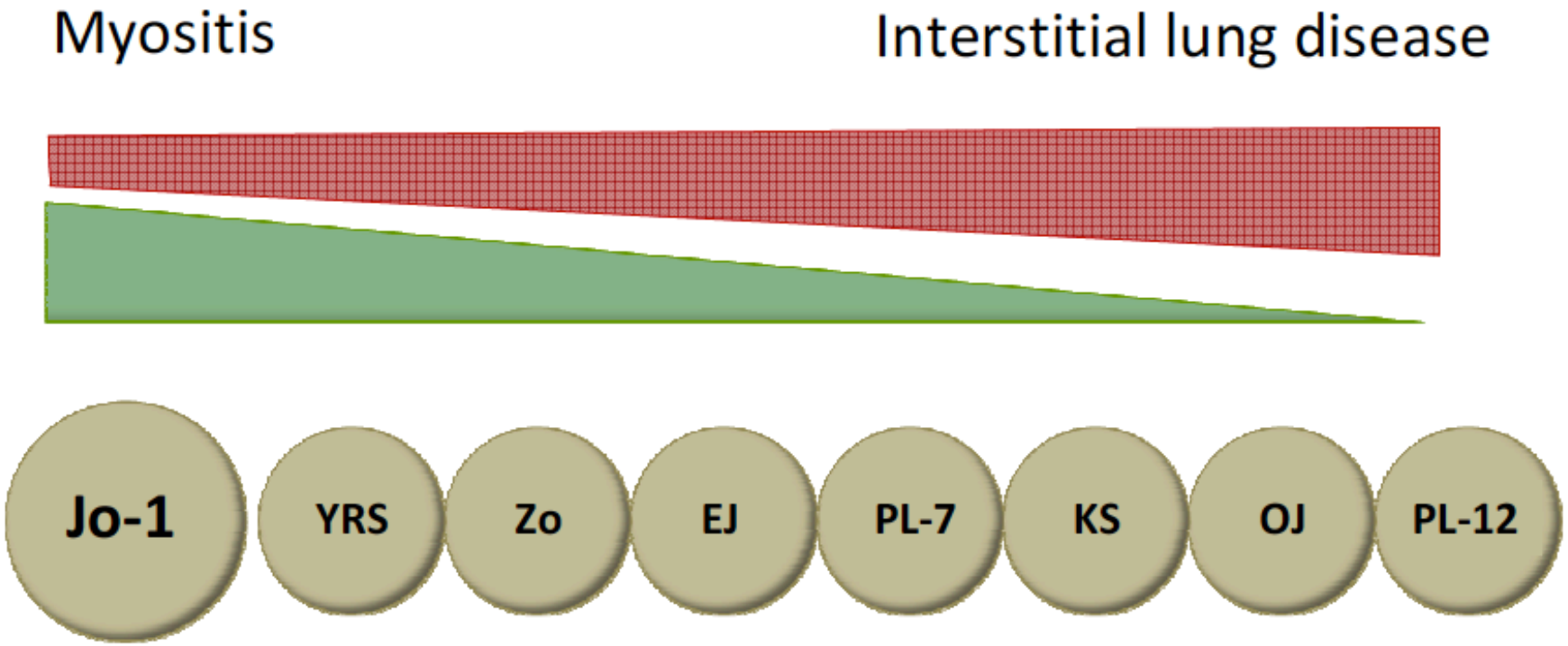
Millor supervivència els Jo1+[2]

Causa de mort: fibrosi pulmonar (49%).

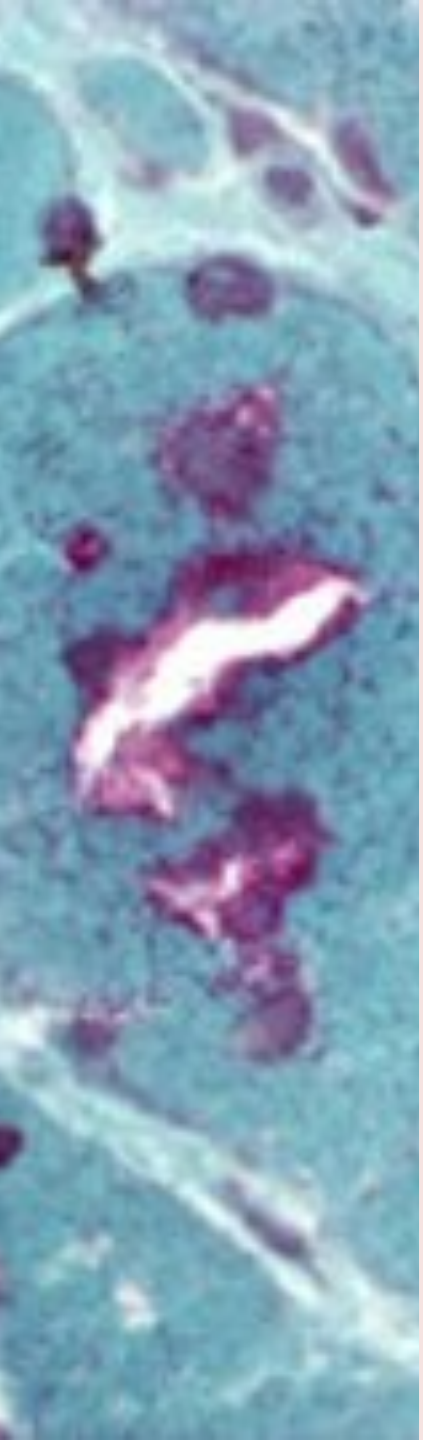


[1] ***Oddis Ch,*** cohort de Pittsburg. EULAR 2014
[2]***Aggarwal R et al.,*** Ann Rheum Dis. 2014 Jan;73(1):227-32.

Antisynthetase syndrome and ARS antibodies



From Jiří Vencovský. Prague Institut.



MIOSITIS NECROTIZANT: Anti-HMGCR

Exposició estatines:

- 67% global
- 92% en població > 50 anys

Debilitat muscular predomini proximal (96%)

CK molt important (mitjana: 9.718)

EMG + (73%)

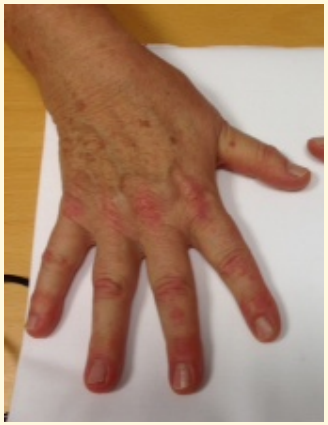
Bx: necrosi (100%) amb un lleu infiltrat inflamatori (20%)

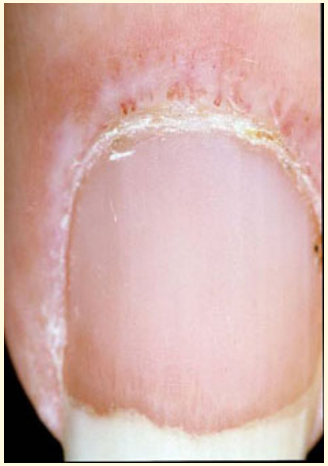
(fig)

Nivell d'Ac correlació amb grau activitat de la malaltia

Mammen AL et al. Arthritis Rheum. 2011 Mar;63(3):713-21.
Mammen AL et al. Arthritis Care Res (Hoboken). 2012 Feb;64(2):269-72.
[1]*Alabayda L et Mammen AL 2014.* Curr Rheumatol Rep. 2014 Aug;16(8):433.

DM AMIOPÀTICA: ANTI-SAE





DM

Amiopàtica o hipomiopàtica

Compromís sistèmic (disfàgia/ GI)

Poca associació a neoplàsia

No associada a MIP.

2-10% de les DM de l'adult.

<1% de les DM juvenils.

Fig: Tinció citocrom oxidasa en una DM: fibres musculars a vora d'un perimisi avascular.

DM AMIOPÀTICA: ANTI-MDA5 (CADM-140)

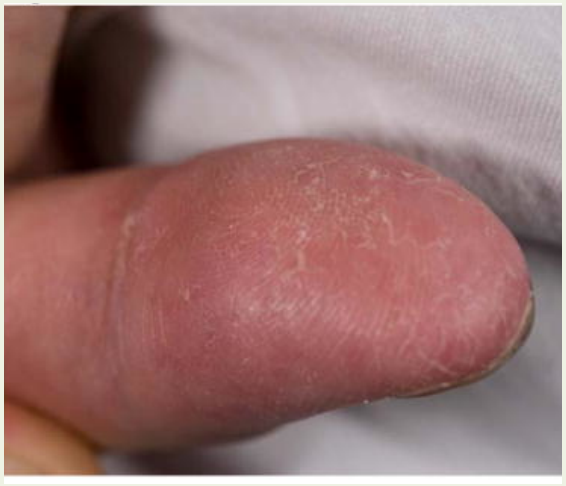
Clàssicament associada a DM sine miositis
Freqüència:

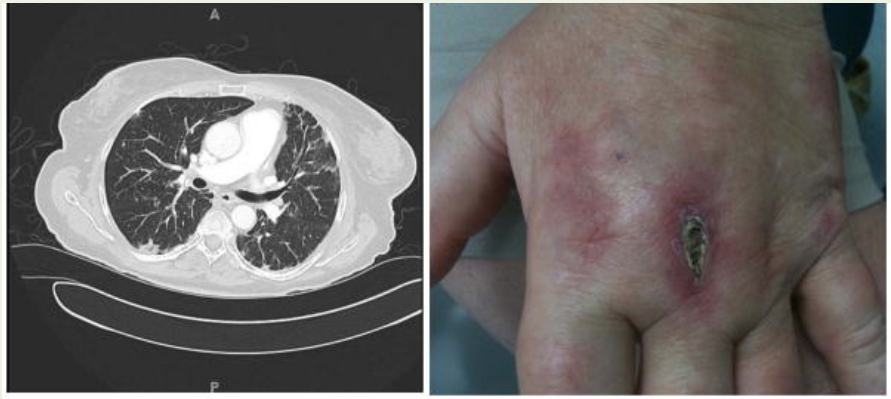
- 19-35% DM
- 53-65% DMAM
- 38% DMJ

Associació a MIP (67-100%)
Adults afectació cutània:

- Ulceracions a pell i boca
- Edema de mans
- Paniculitis
- Alopècia
- Mans mecànic
- Artritis
- Afectació periungueal
- Pàpules palmars

Associació neoplàsia ≈ DM (14/15%)





Chaison MF et al. Medicine (Baltimore). 2012 Jul;91(4):220-8.

DM: ANTI- Tif-1γ (p155)

Adults DM (20%) i Juvenils (36%)

Adults associació a

- Úlceres i vasculitis
- Neoplasia (VPP 58%; VPN 95%)[1,2]
- Major titulació major risc (≥ 50).

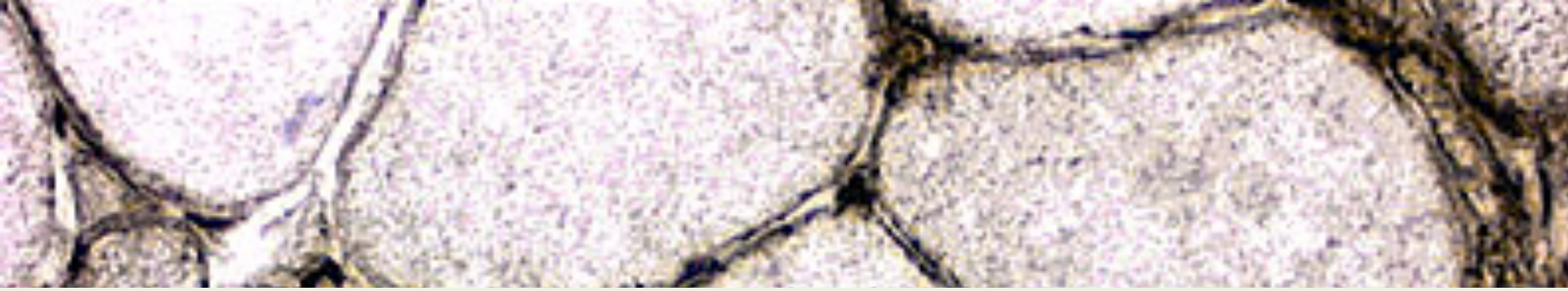
Nens associació:

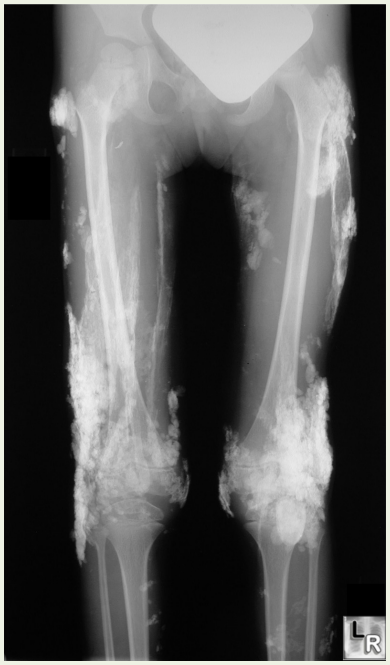
- Úlceres, calcinosi severes
- No neoplàsia

No s'observa en PM ni Miositis associades a MTC.

ELISA o Immunoblot

[1] *Labrador-Horrillo M, et al. Ann Rheum Dis. 2012*
[2] *Chinoy H, Ann Rheum Dis 2007*
[3] *Aggarwal et al, ACR 2012*





DM: ANTI-NPX-2

36% de la JDM, poc freqüent a adults

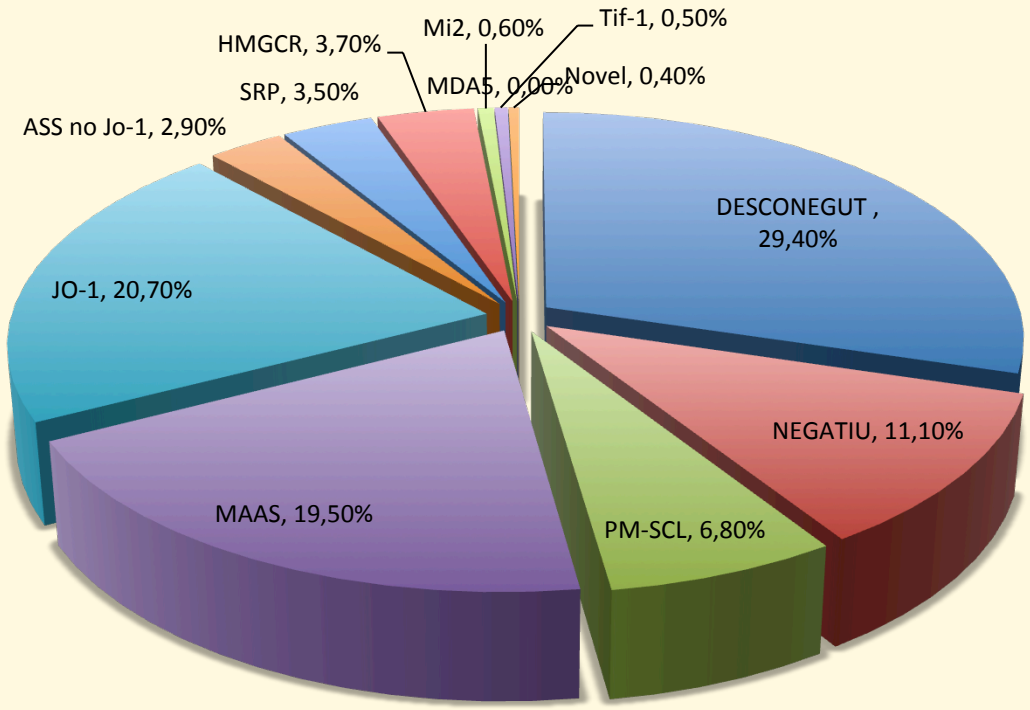
Associació a:

- Calcinosi (predictor)
- Contractures
- Atròfies

Fig: MCI, tinció CMH-I a la superfície de moltes fibres

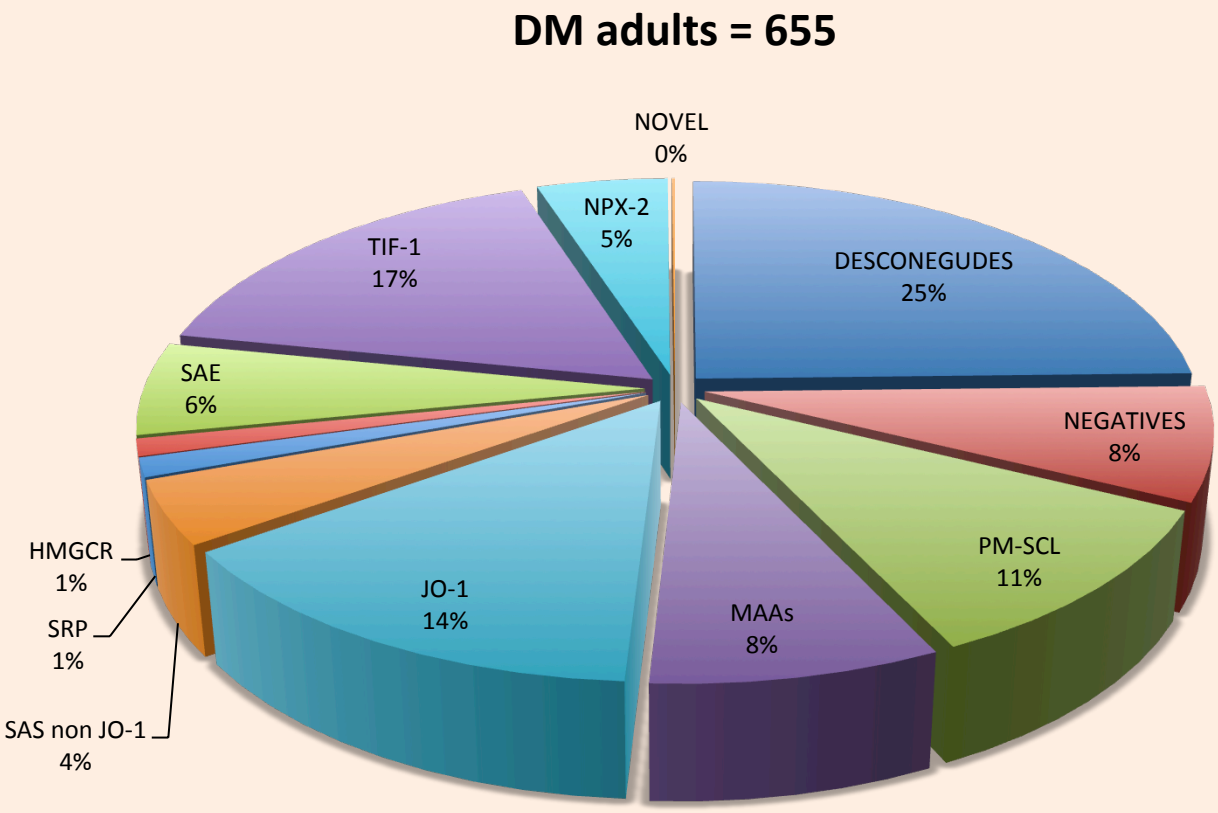
FREQÜÈNCIA D'AC A PM (EUMYONET)

PM adultes n= 842



Diapositiva adaptada de H Chinoy / Dr Betteritge. EULAR 2014.

FREQÜÈNCIA D'AC A DM (EUMYONET)



Diapositiva adaptada de H Chinoy / Dr Betteritge. EULAR 2014.

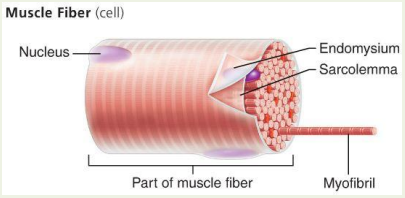
CONSIDERACIONS FINALS

CLASSIFICACIÓ DE LES MII

PM ≠ DM

Invasió de cèl.lules T CD8+
a fibres musculars

Diana: fibra muscular



PM
- PMi
- PM-MTC **(MAAs)**
- PM-neos

PM necrotitzants

II de c. B i C5-C9 (CAM) perivascular
Atròfia fascicular
Cél.lules T CD4+ endomisials

Diana: Vas

DM
- DMi
- DM-neos
- DM-MTC **(MAAs)**

DM amiopàtiques

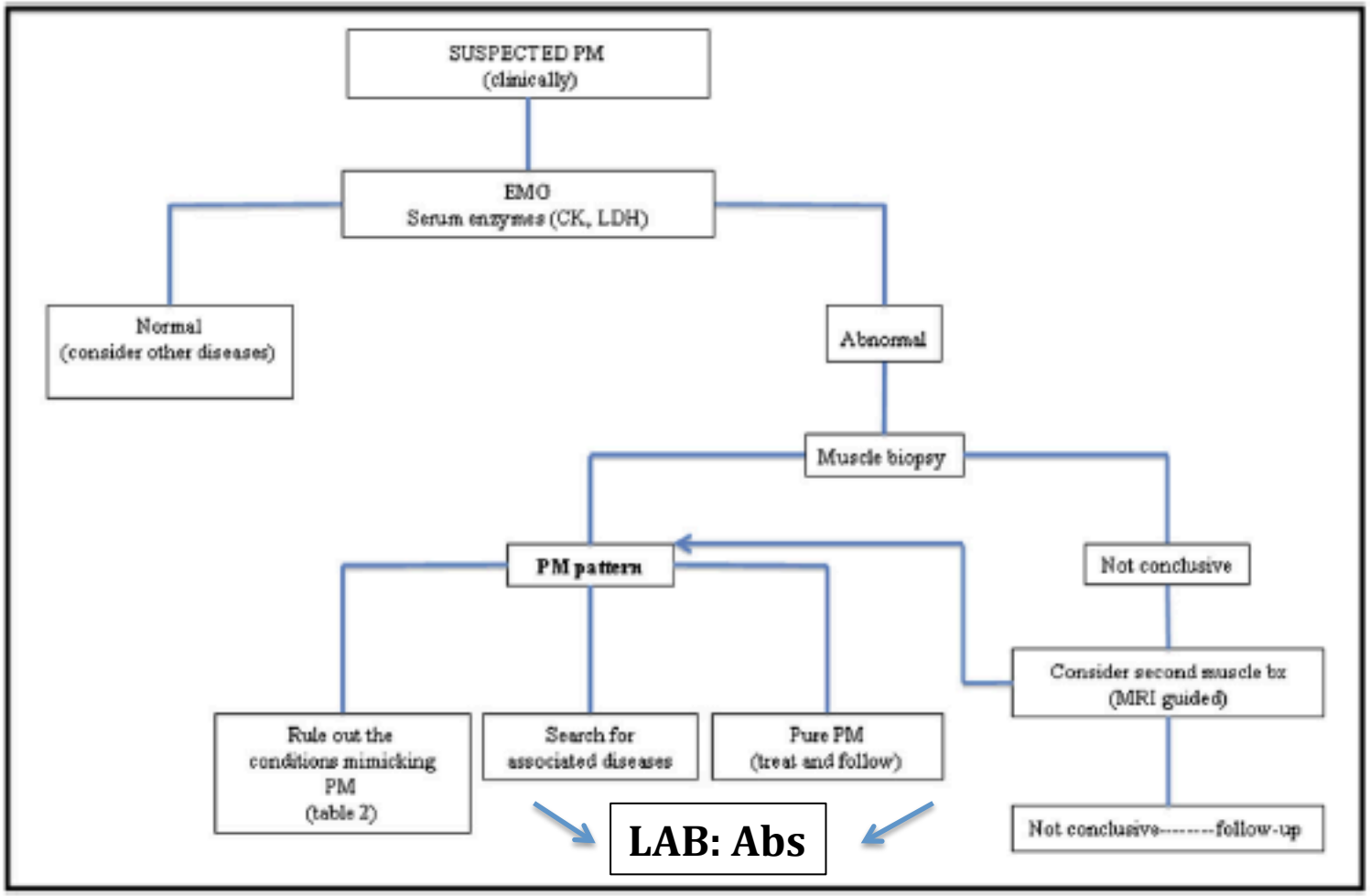
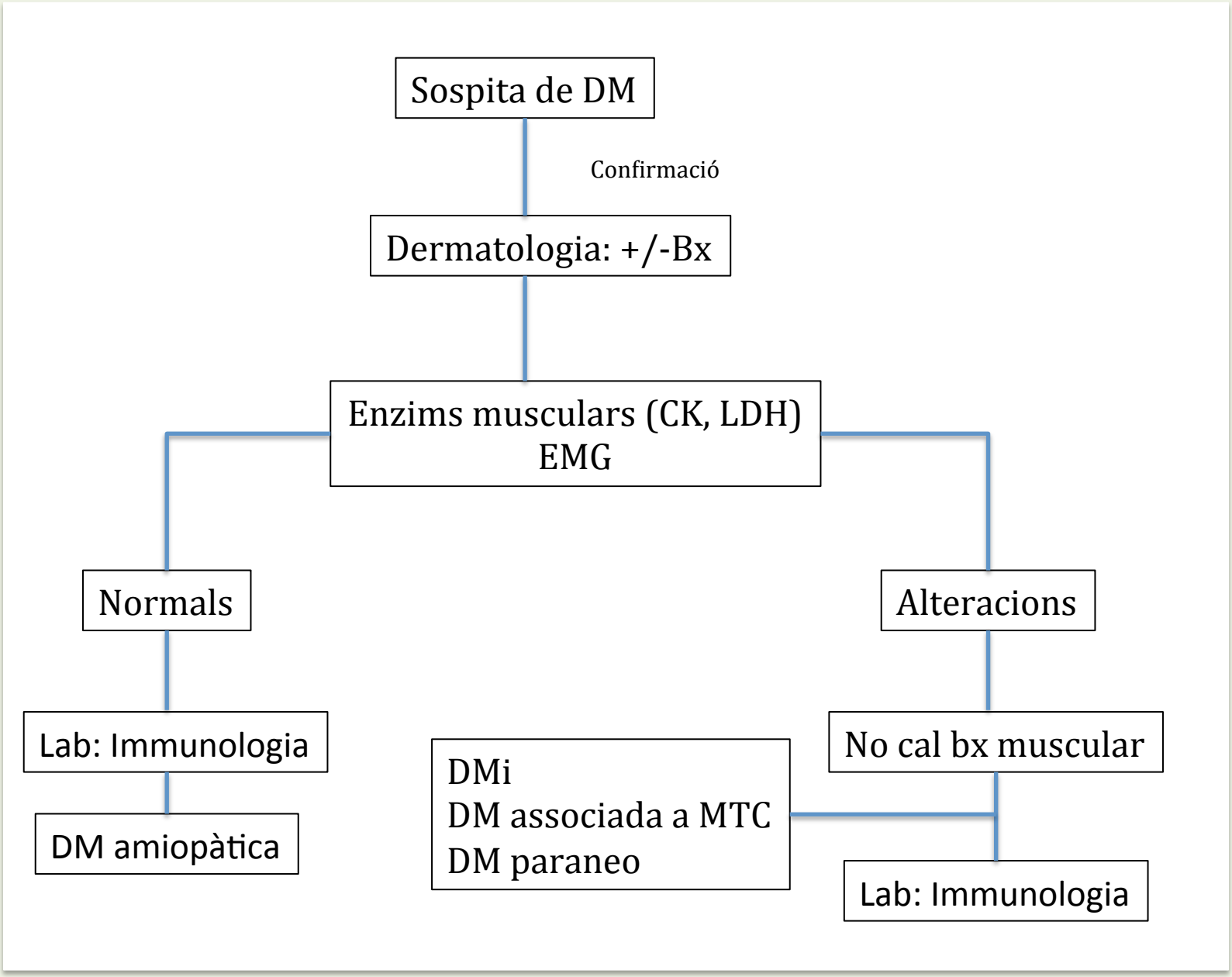


Fig. 2. Diagnostic algorithm for PM.

Ref: Milisenda JC, Selva A, Grau JM. The diagnosis and Classification of Polymyositis. J Autoimm. 2014; 48-49: 118-121.


Sospita de DM
Confirmació
Dermatologia: +/-Bx
Enzims musculars (CK, LDH)
EMG
Normals
Alteracions
Lab: Immunologia
DM amiopàtica
DMi
DM associada a MTC
DM paraneo
No cal bx muscular
Lab: Immunologia


COLLABO
-RATION