Inflammatory myopathies(autoimmune myositis): challenges in the diagnosis and management

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Learning objectives

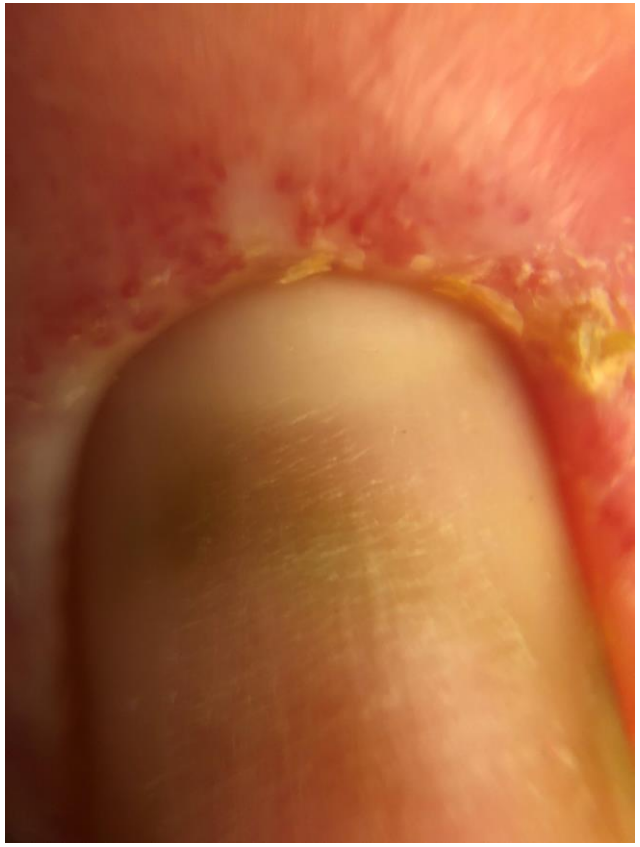
- Understand the clinical manifestations of different subtypes on IM
- Describe the auto-antibodies associated with IM
- Become familiar with the management options and the prognosis

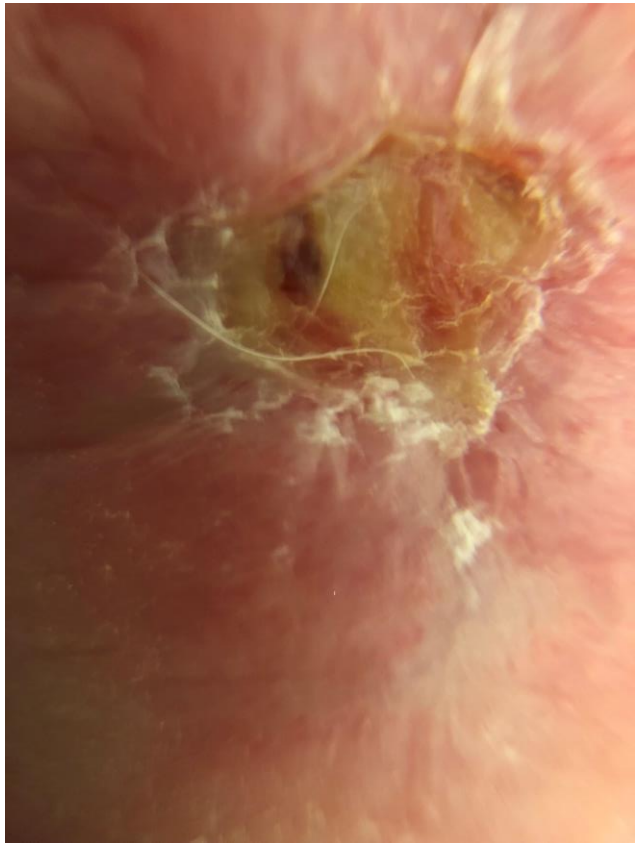
Case 1

- 59 y/o female p/w worsening productive cough(white sputum), low grade of fever+ rash+ mild SOB, began 2 months ago.
- 8/4: admitted
- PMHX: HTN, hysterectomy
- ROS: Raynaud’s and polyarthralgias and photosensivity
- Weight loss, fatigue
- No dysphagia

PE (+ve)

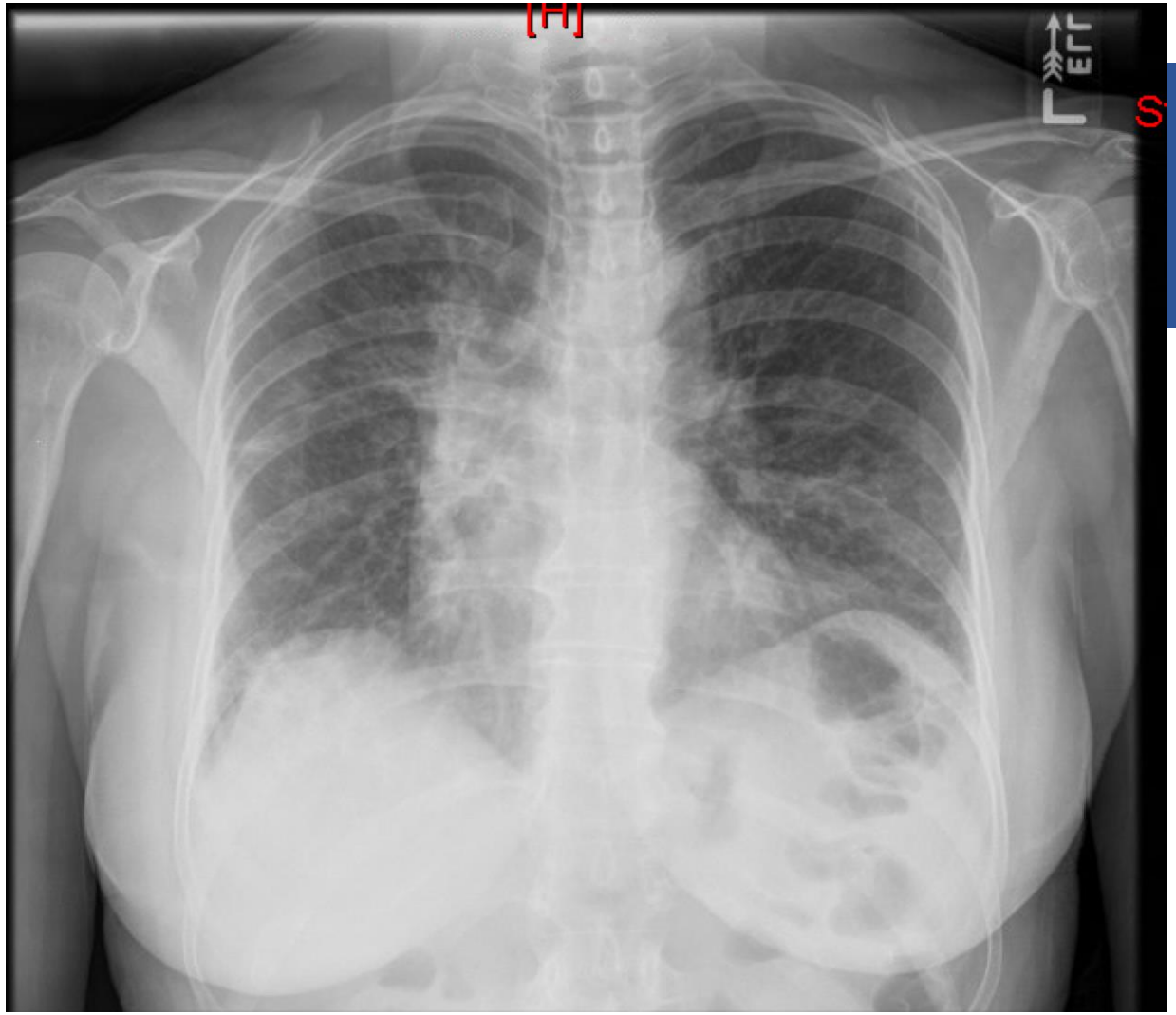
- Left upper eyelid edema and violaceous color
- Chest with V-neck distributed erythema
- +red papules on the MCP region
- + dilated loops of capillaries nailfold telangiectasia with ulcers DIPs/PIPs
- + apthae on the left upper palate
- Elbows and knees with erythema and scaling
- Palmar hands with violaceous patches distal tip to DIP region
- +4/5 bilateral strength upper and lower extremities



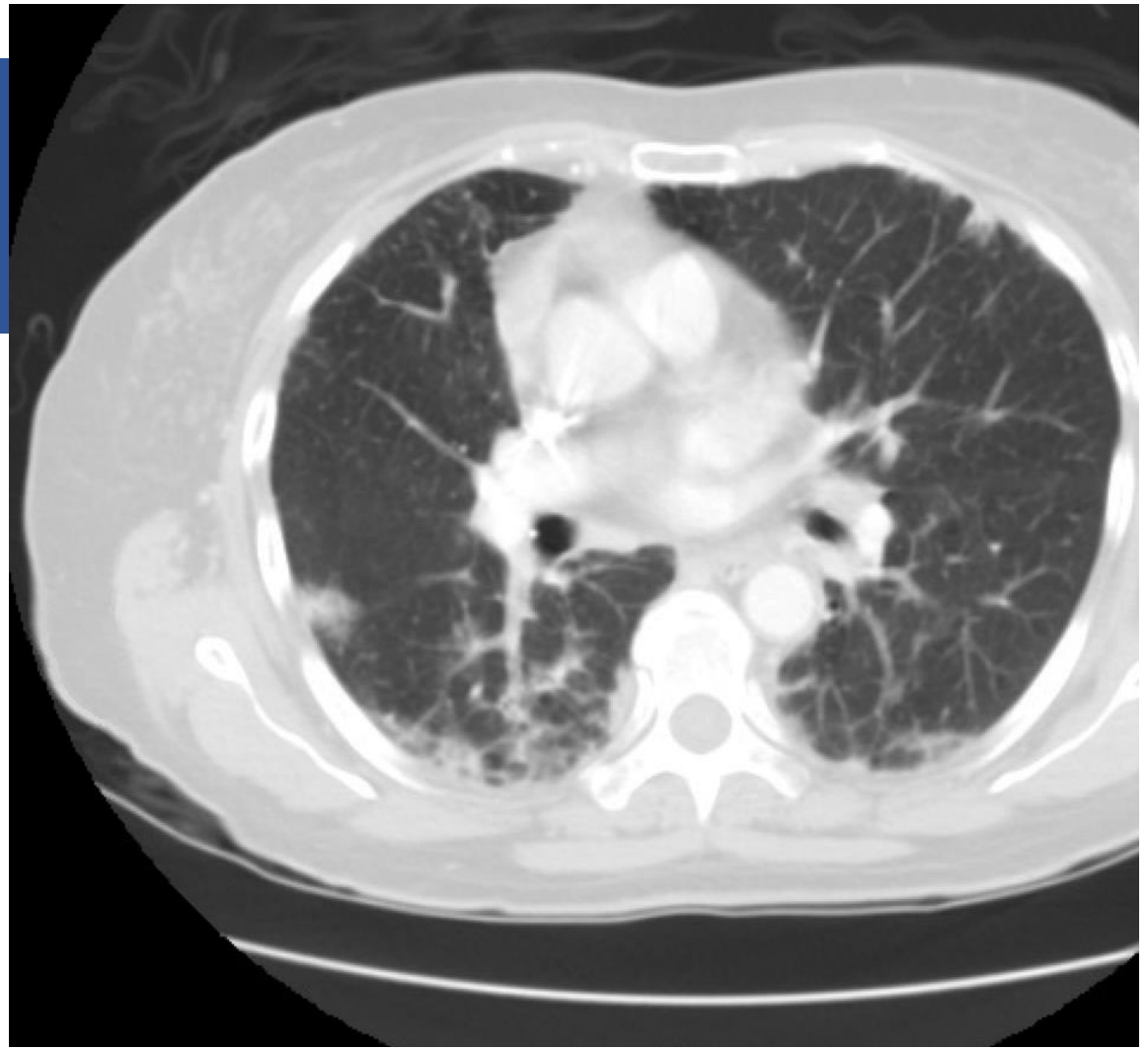


Lab work

- Wbc 4.8(Lymphopenia : 0.7)
- ESR 45, CRP 14
- AST 70
- Normal CK, Aldolase
- Neg ANA, ENA, C3, C4, UA, MPO, PR3, APL panel



Coarse interstitial markings with loss of distinction of the lateral aspect of the right hemidiaphragm and focal opacity of the lingula.



Multifocal patchy peripheral ground-glass opacities in a predominantly subpleural distribution are again noted.

- April 10th: bronchoscopy with BAL- neg cultures
- Endobronchial biopsies: patchy fibrinous acute injury with reactive changes in lung parenchyma with early neutrophilic infiltrate
- Pan-cultures:neg
- Cont to worsened

Skin biopsy: interface dermatitis

Diagnosis:

Review of Outside Microscopic Slides:

A. Skin, right upper arm (SP-14-2239, A; 04/09/2014): Suggestive of interface dermatitis.

B. Skin, right dorsal hand (SP-14-2239, B; 04/09/2014): Suggestive of interface dermatitis.

Microscopic Description:
A. In the reviewed H&E sections, there is a punch biopsy specimen extending through the dermis. Keratinocytes of the epidermal basal layer have a suggestion of vacuolization. Rare apoptotic keratinocytes are identified at the basement membrane zone. In the superficial dermis, there is a mild perivascular inflammatory infiltrate composed mostly of lymphocytes. The GMS stain, which was submitted with the case, is negative for fungal organisms.

B. In the reviewed H&E sections, there is a shave biopsy specimen extending through the superficial dermis. The epidermis is hyperkeratotic. Keratinocytes of the epidermal basal layer are focally vacuolated. Within the superficial dermis, there is a sparse perivascular lymphocytic inflammatory infiltrate. The GMS stain, which was submitted with the case, is negative for fungal organisms.

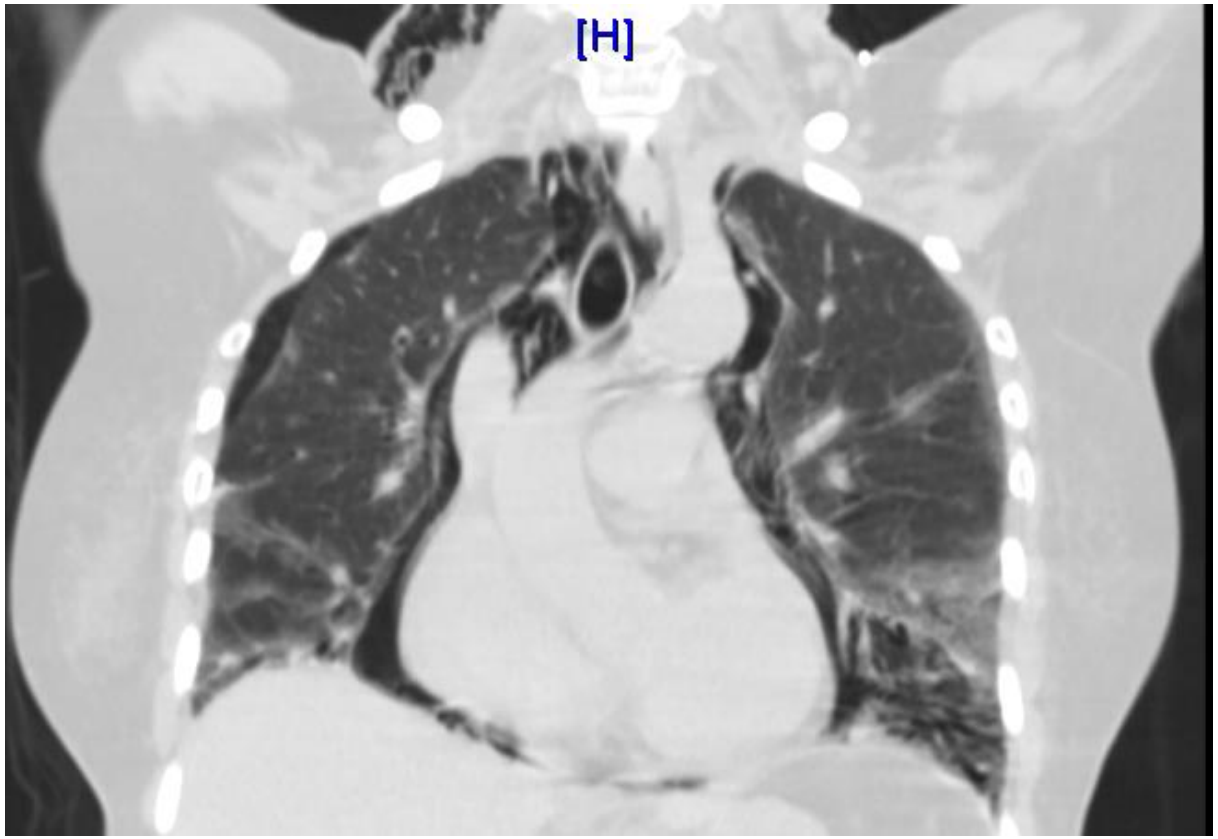
Diagnosis Comment:
The histopathologic findings are subtle but suggest a differential diagnosis of lupus erythematosus, dermatomyositis, or an allergic drug reaction. Clinical correlation is recommended.

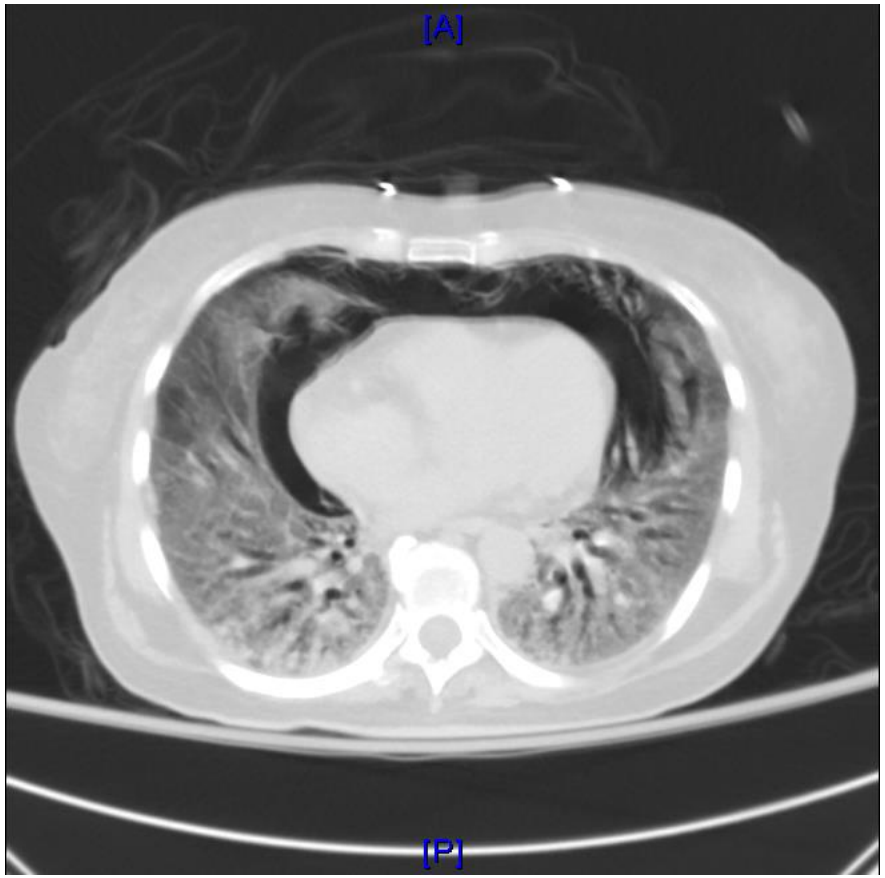
Interpretation:
Direct Immunofluorescence, Biopsy:
IgG: Negative
IgM: Discontinuous weak granular basement membrane zone
IgA: Negative
C3: Discontinuous weak granular to linear basement membrane zone
Fibrinogen: Patchy staining of connective tissue fibers

- Suspicion for ILD induced by DM
- Pulse steroids 1 gm daily x 3 says, PJP prophylaxis
- And IVIG 1gm/kg for 2 days
- No improvement with steroids
- Cytoxan 1.2 gm once
- No s/s of improvement
- Rituxan 1 gm once IV

Workup

- Flow cytometry peripheral blood unremarkable
- SPEP: polyclonal hypergamma
- Echo: wnl
- Colonoscopy and EGD: wnl
- CT abdomen/pelvis: wnl


[H]


[A]
[P]

Cause of death(April 25th)

- CTD-ILD/Dermatomyositis, amyopathic with acute hypoxic respiratory failure, pneumothoraces, pneumomediastinum
- Antibody positive MDA5

Panel

OMRF Myositis Laboratory (allow 6-8 weeks for results)

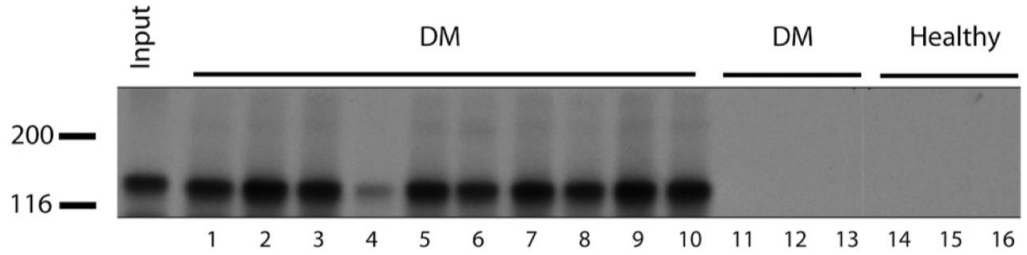
❑	Traditional Myositis Autoantibody Profile Jo-1, PL7, PL12, EJ, OJ, SRP, Mi-2, PMScl, Ku, Ro60, U1RNP, U2RNP	$350.00
❑	Comprehensive Myositis Autoantibody Profile Jo-1, PL7, PL12, EJ, OJ, SRP, Mi-2, PMScl, Ku, Ro60, U1RNP, U2RNP, p155/140 (TIF1g), MJ (NXP2), caDM140 (MDA5)	$490.00
❑	Scleroderma Autoantibody Profile anti-Centromere by IFA, anti-SCL-70 by Immunodiffusion, IPP for anti-RNA Polymerase, U3RNP, PM-SCL, U1RNP, KU, TH/TO	$280.00
	Individual Autoantibody Testing by Immunoprecipitation-blotting ❑ p155/140 (TIF1g) ❑ MJ (NXP2) ❑ caDM140 (MDA5)	$200.00/ea

Antibody-Antigen discovery

RNA Helicase Encoded by Melanoma Differentiation–Associated Gene 5 Is a Major Autoantigen in Patients With Clinically Amyopathic Dermatomyositis

Association With Rapidly Progressive Interstitial Lung Disease

Shinji Sato,[1] Kana Hoshino,[1] Takashi Satoh,[1] Tomonobu Fujita,[1] Yutaka Kawakami,[1] Takashi Fujita,[2] and Masataka Kuwana[1]



- Observation: Asian pt with CADM+RP-ILD
- RP-ILD: worsening radiologic interstitial change with progressive dyspnea/hypoxemia within 1 month
- CADM-140 antigen is a cytoplasmic protein of 140 kd
- Authors identified an RNA helicase encoded by melanoma differentiation–associated gene 5 (MDA-5)as the CADM-140 antigen
- Series of molecular and immunologic techniques.

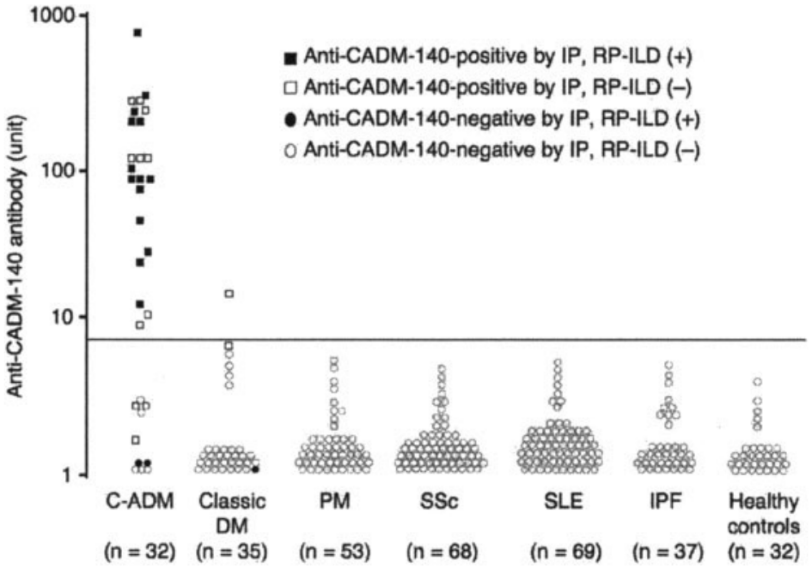
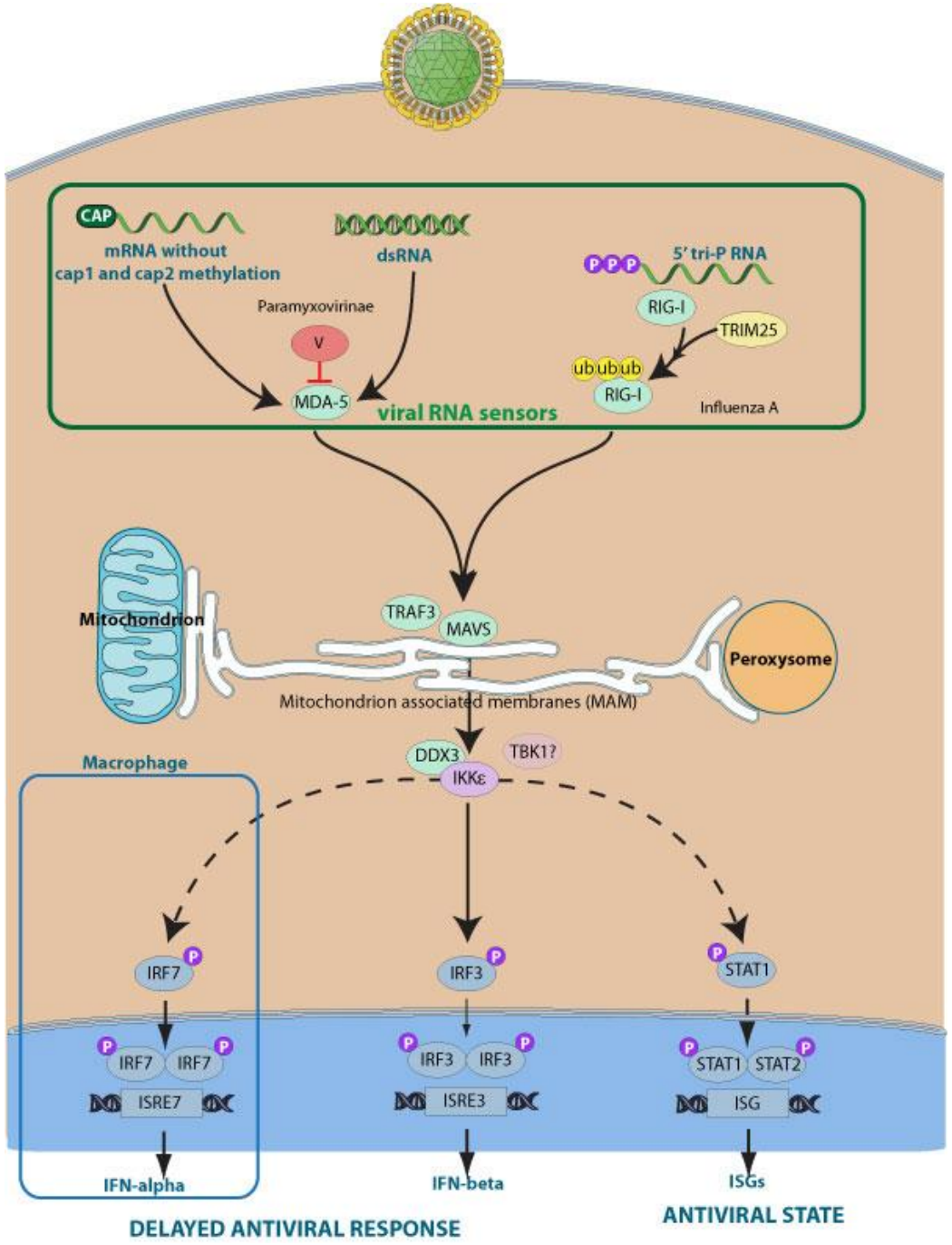


Figure 4. Measurement of anti–CADM-140 antibody in 326 serum samples from patients with various connective tissue diseases, patients with idiopathic pulmonary fibrosis (IPF), or healthy control subjects, by enzyme-linked immunosorbent assay. All samples were classified as positive or negative for anti–CADM-140 antibody, as determined by immunoprecipitation (IP) assay. The antibody units were calculated from the optical density at 450 nm values, using a standard curve obtained from serial concentrations of a serum containing a high titer of the anti–CADM-140 antibody. The cutoff value (8.0 units) is indicated by a horizontal line. RP-ILD = rapidly progressive interstitial lung disease; C-ADM = clinically amyopathic dermatomyositis; DM = dermatomyositis; PM = polymyositis; SSc = systemic sclerosis; SLE = systemic lupus erythematosus.

Sato et al. A&R, 2009

MDA-5

- Involved in innate immune defense against viruses, cellular growth suppression, and apoptosis
- Viral induced?
- Upregulation of MDA-5
- Apoptosis of infected cells (Cytotoxicity)
- Release of proteolytic fragments of MDA-5
- Autoimmunity

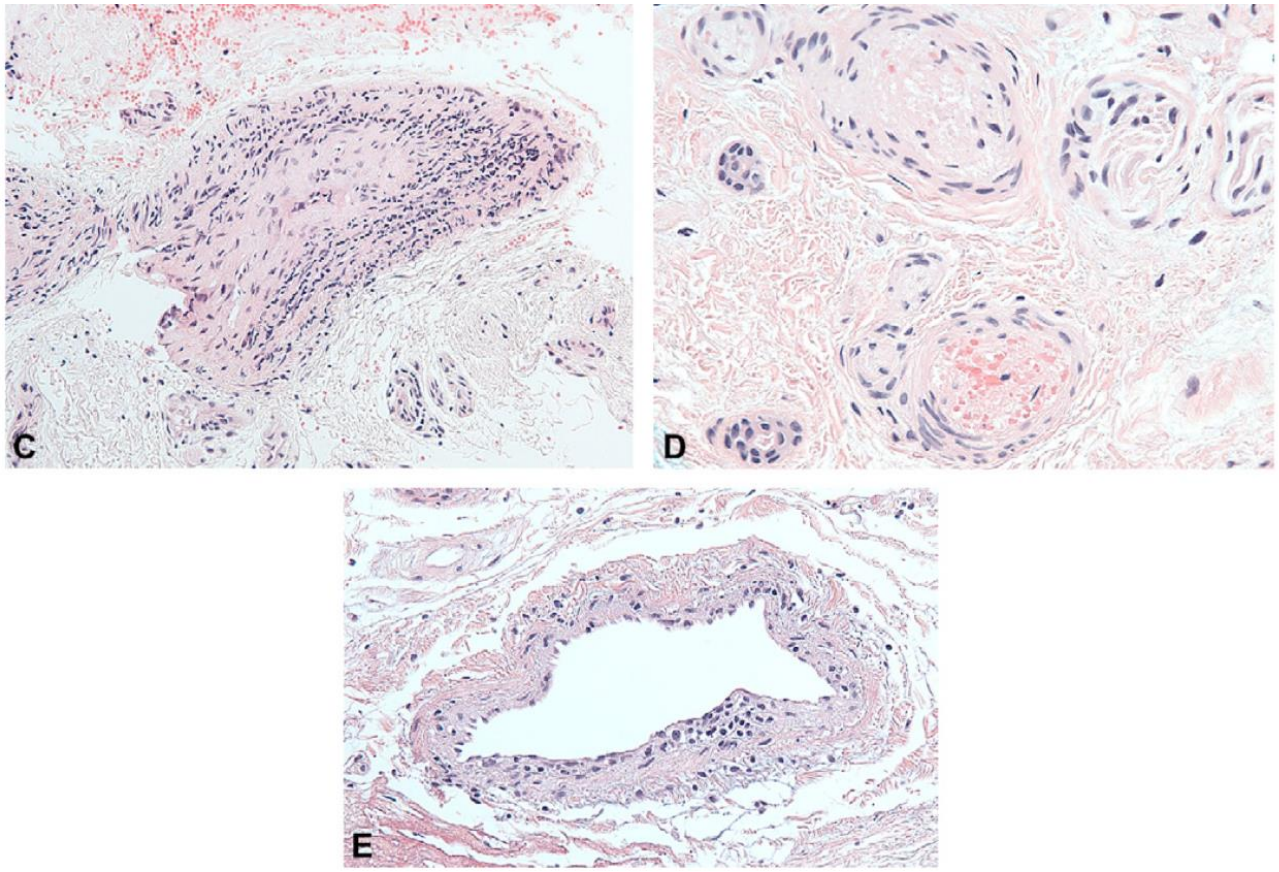


The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): a retrospective study.

Table II. Clinical findings of antimelanoma differentiation-associated gene 5 patients

	Total (N = 77), N (%)	anti-MDA5-positive (N = 10), N (%)	anti-MDA5-negative (N = 67), N (%)	*P* value
Age onset, y ± SD	48.2 ±16	51.5 ± 8.8	47.7 ± 16.8	.50
Female	51 (65)	7 (87.5)	44 (63.8)	.25
Cancer	12 (15.6)	0 (0)	12 (17.9)	.347
Tobacco use	19 (26)	1 (10)	18 (29)	.438
Raynaud	13 (25)	3 (38)	10 (22)	.389
Interstitial lung disease	**16 (25)**	**6 (67)**	**10 (18)**	**.005**
Rapidly progressive lung disease	5 (6.6)	2 (22.2)	3 (4.5)	.104
Hand swelling	**9 (13.8)**	**4 (40)**	**5 (9.1)**	**.026**
Arthritis/arthralgia	**20 (31.2)**	**7 (70)**	**13 (24)**	**.0076**
Amyopathic	10 (13)	3 (30)	7 (10)	.117
Clinically amyopathic	**13 (16.9)**	**5 (50)**	**8 (11.9)**	**.010**
Skin ulceration (any)	**20 (26.0)**	**8 (80)**	**12 (18)**	**.0002**
Ulceration (Gottron)	**5 (6.5)**	**3 (30)**	**2 (3)**	**.0142**
Ulceration (digit pulp/periungual)	**11 (14.3)**	**8 (80)**	**3 (4.5)**	**<.0001**
Ulceration (elbow)	**4 (5.2)**	**3 (30)**	**1 (1.5)**	**.0061**
Ulceration (chest/arms)	6 (7.8)	0 (0)	6 (9)	1.000
Palmar papules	**7 (9.6)**	**6 (60)**	**1 (1.6)**	**<.0001**
Mechanic hands	**15 (22.4)**	**6 (67)**	**9 (15.5)**	**.0028**
Panniculitis	**2 (3.1)**	**2 (20)**	**0 (0)**	**.0216**
Calcinosis cutis	3 (4.8)	1 (11.1)	2 (3.7)	.375
Alopecia	**22 (34)**	**7 (78)**	**15 (27)**	**.0053**
Heliotrope rash	42 (60)	7 (70)	35 (58)	.729
Gottron papules	38 (53.5)	7 (70)	31 (51)	.32
Violaceous erythema				
Scalp	42 (62.7)	6 (67)	36 (62)	1.00
Face	57 (80.3)	10 (100)	47 (77)	.193
V area of the chest-neck	54 (79.4)	8 (89)	46 (78)	.673
Elbow/knee	**48 (69.6)**	**10 (100)**	**46 (78)**	**.0259**
Periungual telangiectasia	50 (73.6)	9 (90)	41 (71)	.27
Pruritus	44 (68.8)	6 (67)	38 (69)	1.00
Oral pain/ulcers	**9 (13.9)**	**5 (50)**	**4 (7.3)**	**.0029**

Fiorentino, et al. JAAD, 2011



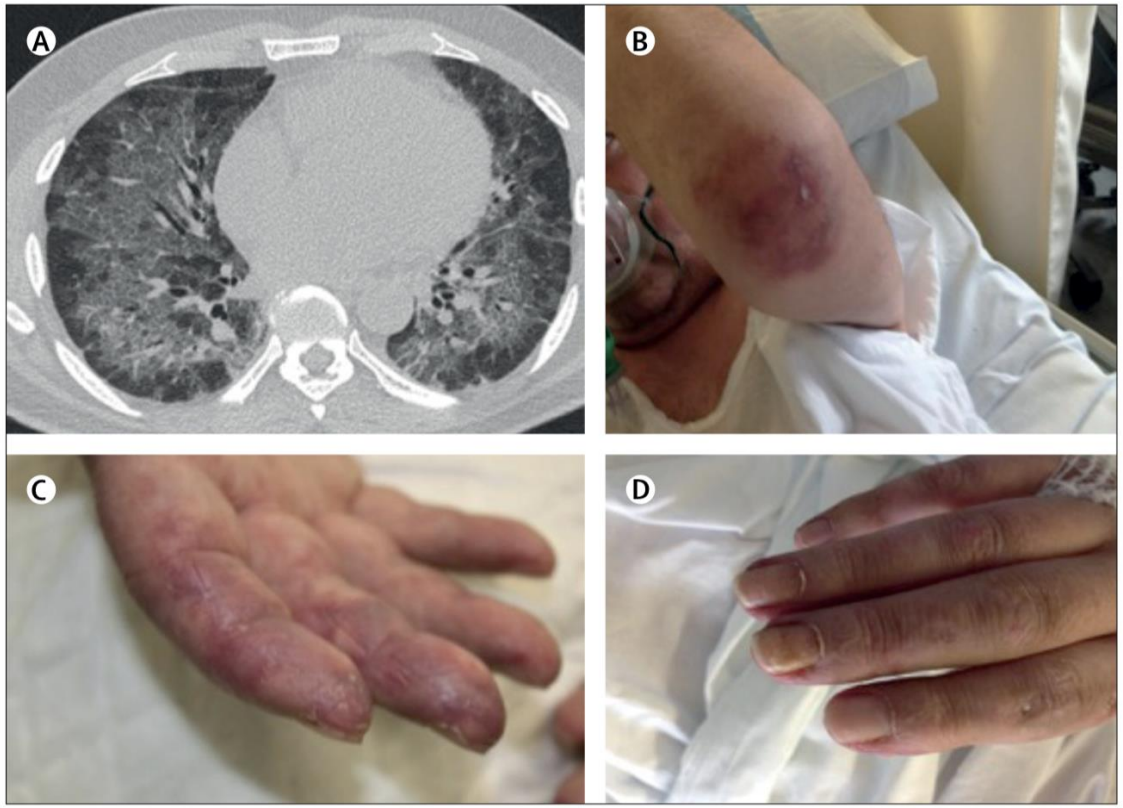


Figure 2: Clinical features and radiological findings of anti-melanoma differentiation-associated gene 5 syndrome

Vasculopathy

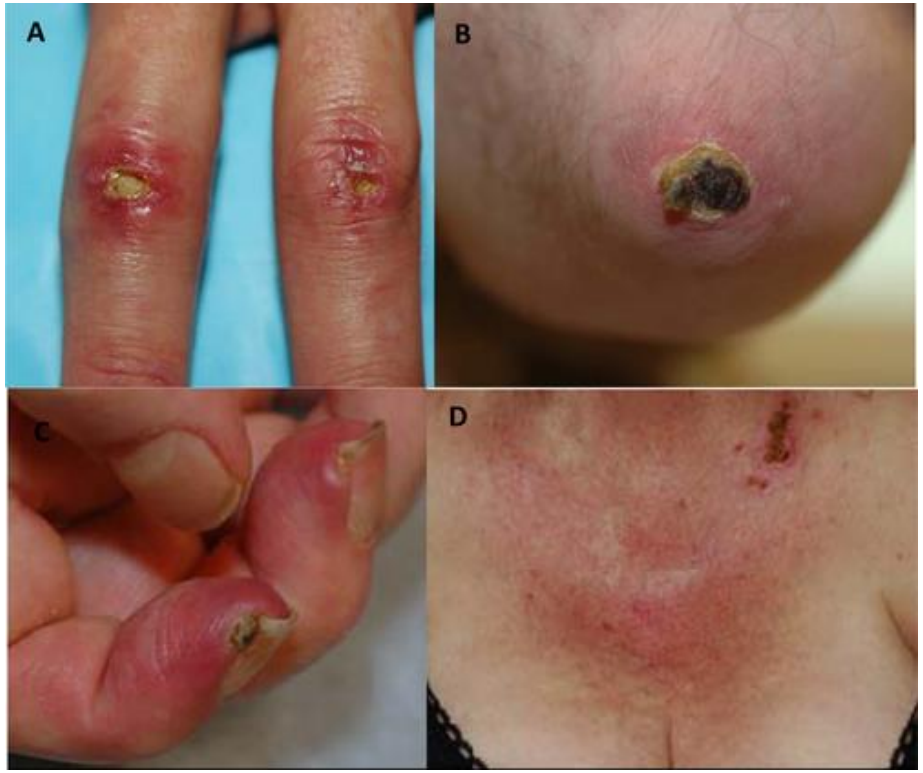
Selva-O'Callaghan,et al. Lancet Neurology. 2018

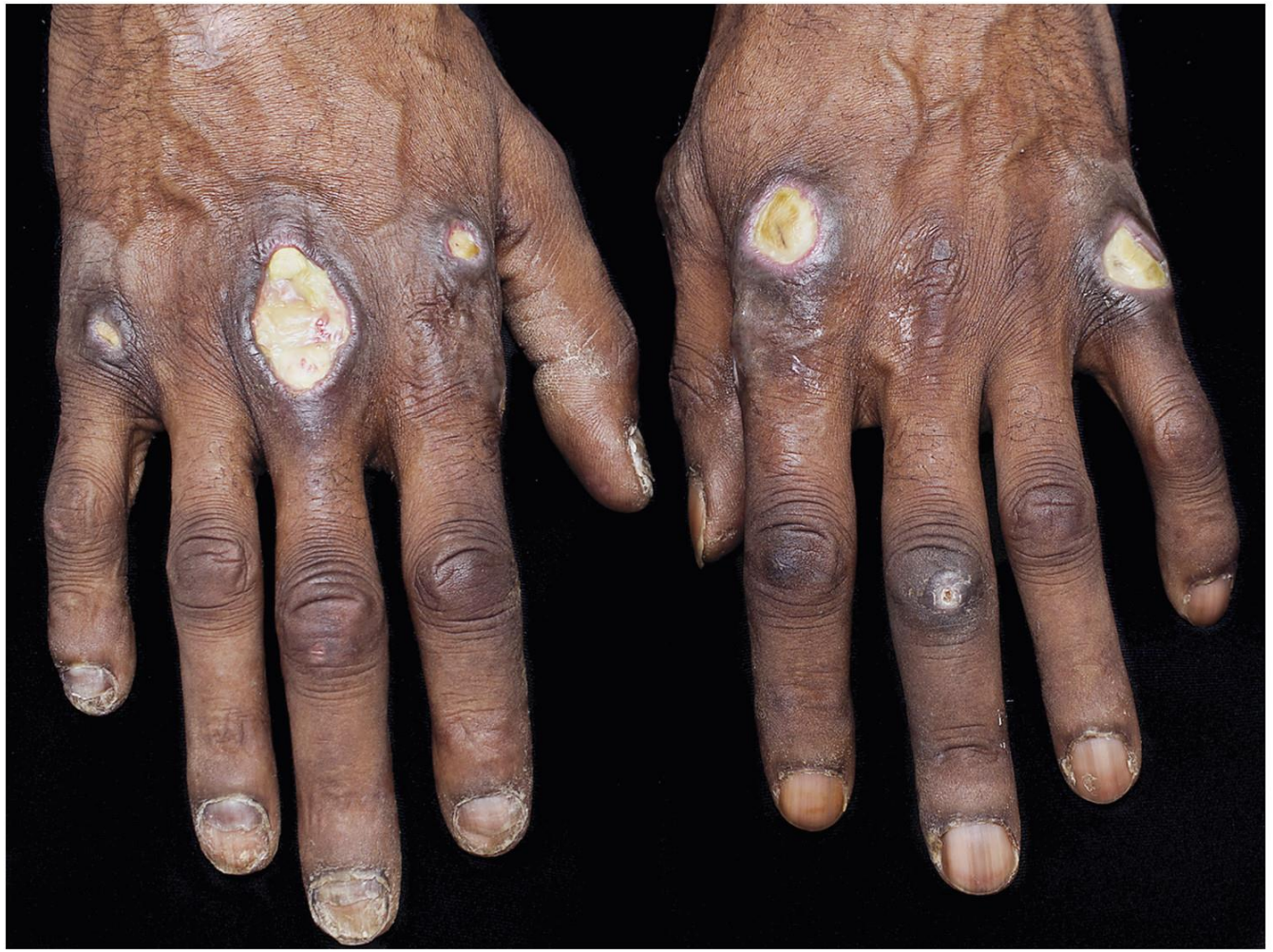
Cutaneous Ulceration in Dermatomyositis: Association With Anti–Melanoma Differentiation–Associated Gene 5 Antibodies and Interstitial Lung Disease

Table 3. Multivariate model for predictors of cutaneous ulcers in dermatomyositis patients[a]

	OR	95% CI	*P*
Asian	2.58	0.72–9.17	0.14
Hispanic	0.29	0.03–2.55	0.26
NXP2 positive	0.38	0.07–1.98	0.25
MDA5 positive	10.14	1.95–52.78	0.0059
Ro52 positive	2.52	0.83–7.69	0.10
Mi-2	0.65	0.12–3.43	0.61

[a] OR = odds ratio; 95% CI = 95% confidence interval; NXP2 = nuclear matrix protein 2; MDA5 = melanoma differentiation gene 5.





A Charrow, RA Vleugels. N Engl J Med 2019;381:465-465.

Arthritis Care & Research
Vol. 65, No. 8, August 2013, pp 1307–1315
DOI 10.1002/acr.21992

ORIGINAL ARTICLE

Anti–Melanoma Differentiation–Associated Protein 5–Associated Dermatomyositis: Expanding the Clinical Spectrum

JOHN C. HALL, LIVIA CASCIOLA-ROSEN, LESLY-ANN SAMEDY, JESSIE WERNER, KRISTIE OWOYEMI, SONYE K. DANOFF, AND LISA CHRISTOPHER-STINE

- Autoantibodies against (MDA-5) have been described in several Asian dermatomyositis (DM) cohorts
- Associated with amyopathic DM+ RP-ILD
- US (Baltimore), 160 pts DM
- screened for MDA-5 autoantibodies by immunoprecipitation and antibody titers
- Conclusion: Jo-1 Like less RL-ILD

Table 3. Demographics and clinical characteristics of anti–MDA-5–positive and anti–MDA-5–negative dermatomyositis patients*

	Anti–MDA-5 positive (n = 11)	Anti–MDA-5 negative (n = 149)	*P*
Demographics			
Sex			0.94
Male	3 (27.3)	39 (26.2)	
Female	8 (72.7)	110 (73.8)	
Race			0.24
White	8 (72.7)	124 (83.2)	
African American	2 (18.2)	17 (11.4)	
Asian	0 (0)	6 (4.0)	
Other	1 (9.1)	2 (1.3)	
Age at diagnosis, mean years	41.4	44.9	0.48
Disease duration, median months	24.5	26.3	0.9
Clinical features			
Gottron's papules/sign	11 (100)	111 (75)†	0.055
Heliotrope rash	9 (81.8)	71 (48.0)†	0.03
Weakness	6 (54.5)	138 (93.2)†	< 0.001
Fever	5 (45.5)	24 (16.4)‡	0.017
Inflammatory arthropathy	9 (81.8)	39 (26.7)‡	< 0.001
Raynaud's phenomenon	5 (45.5)	44 (30.3)§	0.3
Mechanics hands	9 (81.8)	28 (19.0)¶	< 0.001
Interstitial lung disease	8 (72.7)	17 (11.4)	< 0.001
Calcinosis	3 (27.3)	18 (12.1)	0.15

Hall at al. Arth Care Res, 2013

Arthritis Care & Research
Vol. 68, No. 5, May 2016, pp 689–694
DOI 10.1002/acr.22728

ORIGINAL ARTICLE

Anti–Melanoma Differentiation–Associated Gene 5 Is Associated With Rapidly Progressive Lung Disease and Poor Survival in US Patients With Amyopathic and Myopathic Dermatomyositis

SIAMAK MOGHADAM-KIA,[1] CHESTER V. ODDIS,[1] SHINJI SATO,[2] MASATAKA KUWANA,[3] AND ROHIT AGGARWAL[1]

Table 1. Frequency of anti–MDA-5 antibody, ILD, and RPILD in CADM compared to classic DM*

	CADM (n = 61)	Classic DM (n = 61)	*P*
Anti–MDA-5	8 (13.1)	8 (13.1)	1
ILD	19 (31.1)	16 (26.2)	0.55
RPILD	5 (8.2)	3 (5)	0.46

* Values are the number (percentage). Anti–MDA-5 = anti–melanoma differentiation–associated gene 5; ILD = interstitial lung disease; RPILD = rapidly progressive ILD; CADM = clinically amyopathic dermatomyositis; DM = dermatomyositis.

- Pittsburgh, 61 CADM vs 61 classic DM
- MDA5 +ve total 16: 8+8
- Anti–MDA-5 +ve is significantly associated with ILD, RPILD, worse pulmonary outcome, and survival in US classic DM and CADM patients

Table 2. Frequency of ILD and RPILD in anti–MDA-5–positive and anti–MDA-5–negative DM patients*

	Anti–MDA-5 positive (n = 16)	Anti–MDA-5 negative (n = 106)	*P*
ILD	8 (50)	27 (25.5)	0.043
RPILD	7 (87.5)	1 (3.7)	< 0.001

* Values are the number (percentage) of the total clinically amyopathic dermatomyositis (DM) and DM patients (n = 122). ILD = interstitial lung disease; RPILD = rapidly progressive ILD; anti–MDA-5 = anti–melanoma differentiation–associated gene 5.

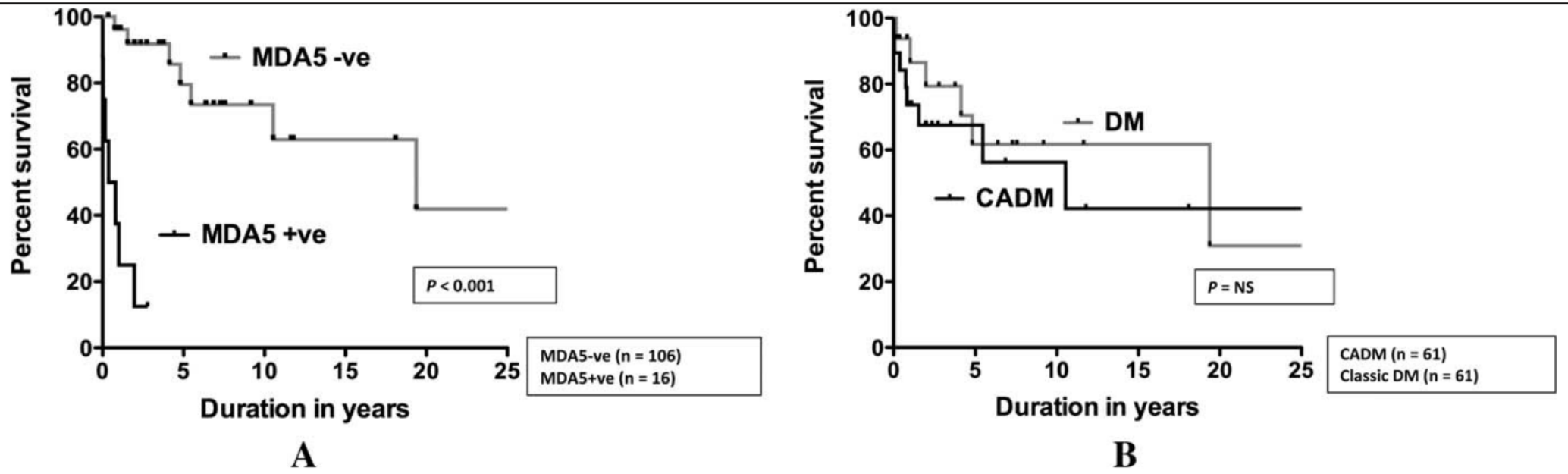
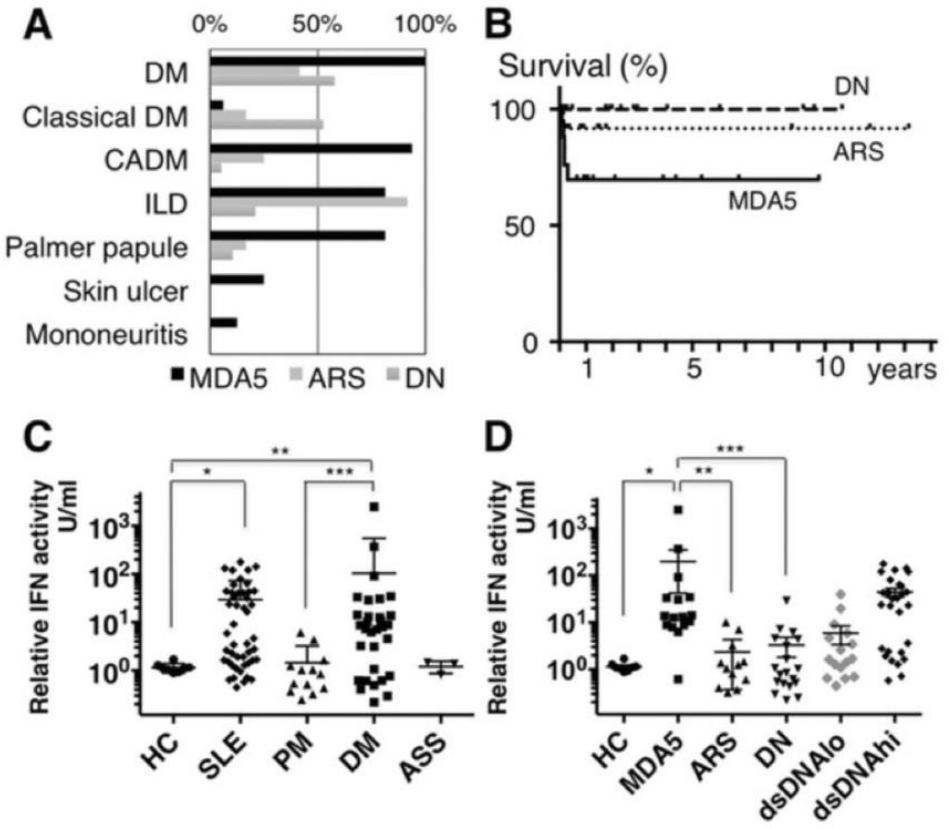


Figure 2. Kaplan-Meier pulmonary outcome curves for interstitial lung disease patients with **A,** melanoma differentiation–associated gene 5 (MDA-5) positive versus MDA-5 negative, and **B,** clinically amyopathic dermatomyositis (CADM) versus classic dermatomyositis (DM). Anti–MDA-5 positivity was significantly associated with poor pulmonary outcome. CADM was not predictive of poor pulmonary outcome. NS = not significant.

The relationship between type 1 IFN and vasculopathy in anti-MDA5 antibody-positive dermatomyositis patients

FIG. 1 The comparisons of clinical phenotypes and T1-IFN signatures among the MDA5, ARS and DN groups



- 47 pts
- MDA- 5 (16)
- anti-aminoacyl- tRNA synthetase patients (12),
- Double- negative patients (19)

Ono et al, Rheumatology, 2018

Management strategies

Clinical Rheumatology (2018) 37:1983–1989
https://doi.org/10.1007/s10067-018-4122-2

BRIEF REPORT

CrossMark

Rituximab for refractory rapidly progressive interstitial lung disease related to anti-MDA5 antibody-positive amyopathic dermatomyositis

Ho So[1] · Victor Tak Lung Wong[2] · Virginia Weng Nga Lao[1] · Hin Ting Pang[1] · Ronald Man Lung Yip[2]

- 4 patients
- Failed GC, Cytoxan, Tacro, IVIG, MMF

RHEUMATOLOGY

doi:10.1093/rheumatology/key188
Advance Access publication 27 July 2018

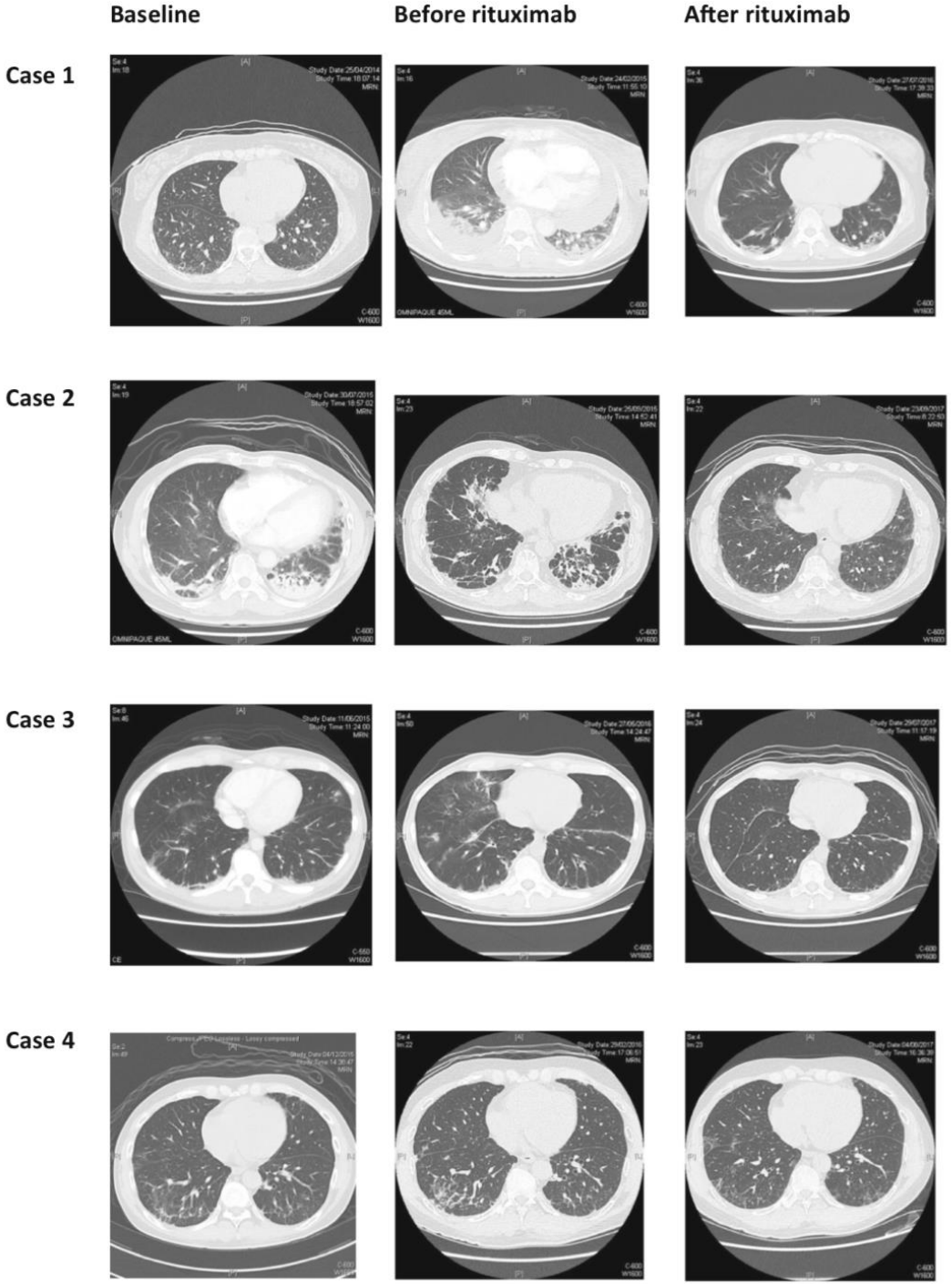
Concise report

Tofacitinib for refractory interstitial lung diseases in anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis

- Case series
- 5 patients(3 survived)

Mycophenolate mofetil for the patients with interstitial lung diseases in amyopathic dermatomyositis with anti-MDA-5 antibodies

Masachika Hayashi[1] · Toshiaki Kikuchi[1] · Toshinori Takada[1,2]



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

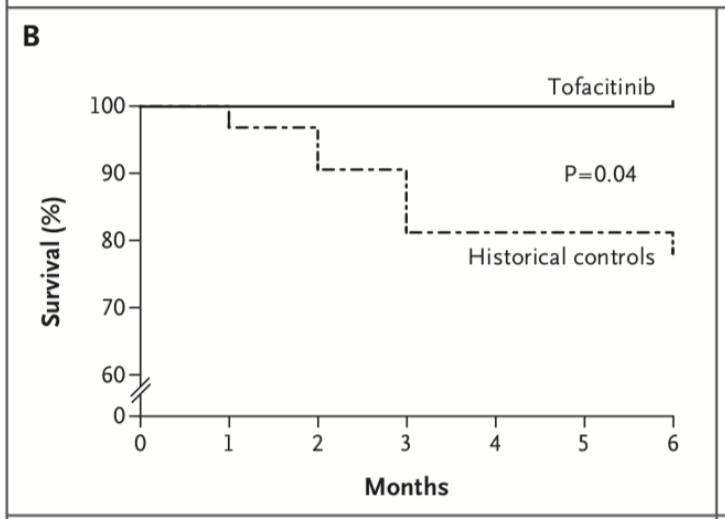
Tofacitinib in Amyopathic Dermatomyositis–Associated Interstitial Lung Disease

- Tofa vs historical control
- Survival 6 months higher in tofa > control after the onset of ILD w(18/ 18, 100%) vs(25/32, 78%) (P=0.04)

Chen et al, NEJM, July 2019

A

	Tofacitinib (N=18)	Historical Controls (N=32)	P Value
Age — yr	47.6±13.8	52.5±10.6	0.16
Female sex — no. (%)	11 (61)	25 (78)	0.33
History of smoking — no. (%)	2 (11)	2 (6)	0.61
Duration of ILD — mo	1.4±0.7	1.7±1.3	0.45
FVC — % of predicted value	73.4±15.2	71.9±15.3	0.76
SB DLCO — %	44.8±12.8	47.3±16.1	0.59
High-resolution CT score	118.2±13.2	127.2±24.8	0.16
Ferritin level — ng/ml	936.9±798.1	737.8±631.6	0.34
Creatine kinase level — U/ml	86.7±98.2	50.6±43.5	0.09
Albumin level— g/liter	33.5±5.3	31.8±3.3	0.18
Lactate dehydrogenase level — IU/liter	362.8±294.4	317.5±149.0	0.49
ESR — mm/hr	31.0±19.0	29.9±21.1	0.85
Maximum dosage of glucocorticoid — mg/day	78.0±54.4	87.9±81.8	0.65
Exposure to immunosuppressant — no. (%)			
Cyclosporine	2 (11)	19 (59)	
Mycophenolate mofetil	1 (6)	6 (19)	
Cyclophosphamide	0	2 (6)	
Azathioprine	0	1 (3)	
Exposure to pirfenidone — no. (%)	1 (6)	12 (38)	0.02



Management of MDA5

Basiliximab may improve the survival rate of rapidly progressive interstitial pneumonia in patients with clinically amyopathic dermatomyositis with anti-MDA5 antibody

- 4 patients with RPILD
- 1 died
- A chimeric mouse-human monoclonal antibody to the α chain (CD25) of the IL-2 receptor of T cells.

Zhou et al. ARD, 2014

Table 1 The clinical data of patients

	Case 1	Case 2	Case 3	Case 4
Clinical data of patients before pred+CsA treatment				
Age at diagnosis (years)	54	46	54	51
Sex	Female	Female	Female	Male
Disease duration of IP (weeks)	3	2	2	3
Cutaneous manifestation				
Heliotrope rash	Positive	Positive	Positive	Positive
Gottron's papule	Positive	Positive	Positive	Positive
Skin ulceration	Negative	Negative	Negative	Negative
Electromyography (EMG)	Negative	Negative	Negative	Negative
Peripheral blood				
WBC (/μl)	6600	9200	7400	6890
Creatine (mg/dl)	38.7	57.4	33.0	38.6
ALT (U/l)	118	45	372	26
LDH (U/l)	273	253	637	338
CRP (mg/dl)	0.17	3.30	3.45	5.2
CK (U/l)	59	116	288	63
ANA antibody (≥1:80)	1:80	Negative	Negative	Negative
Anti-Jo-1 antibody	Negative	Negative	Negative	Negative
Anti-MDA5 antibody	Positive	Positive	Positive	Positive
Ferritin (mg/dl)	634	1780	1920	2217
Arterial blood gas				
PH	7.39	7.441	7.478	7.43
P/F ratio	357	387	376	404
PCO_2 (mm Hg)	38.7	41.6	30.6	35.2
HCO_3- (mEq/l)	24.1	23.6	22.8	23.4
mMRC	2	2	3	2
HRCT score	110.8	156.7	185.8	143.3
Pulmonary function				
FVC	64	63	59	58
TLC	67	58	57	53
DLCO	55	45	44	39
Basic treatment				
Pred (mg)	80	80	100	100
CsA (mg)	150	175	180	150
Response to pred+CsA				
Progressed time after pred +CsA treatment	5th week	9th week	2nd week	4th week
Time of IVIg treatment	5th week	9th week	/	/
Time of basiliximab treatment	6th week	10th week	2nd week	4th week
Cumulative dose of basiliximab	40	40	20	40

Case 2

- 62 y/o m here for necrotizing myositis
- PMHx of remote h/o ETOH abuse in the past, HTN, DM type 2, CAD, MI, s/p CABG, HLD, rx with atorvastatin for the past 10 years, presents for myositis
- Presented to OSH with gradually worsening muscle weakness, started 3 months before, associated with difficulty getting up from a chair, extending his knees, dysphagia and found to have elevated CK.
- P/E : 3/5 proximal muscle weakness
- No rash

- Meds
- Atorvastatin
- Metoprolol
- Lisinopril
- ASA/Plavix
- Metformin, glipizide
- Nitro prn

Workup(+ve)

- CK was 19972, ESR 53 and CRP 60
- TSH: wnl.
- Workup with CTA chest/Abd/pelvis was unremarkable.
- EGD and colonoscopy wnl

Muscle biopsy

Addenda Findings

ADDENDUM MICROSCOPIC DESCRIPTION:

Stains reviewed include frozen section H&E, trichrome NADH-TR, succinate dehydrogenase, cytochrome oxidase, acid phosphatase, alkaline phosphatase, ATP'ase pH 9.4 and 4.6, nonspecific esterase, oil red O, and PAS with and without diastase. Sections demonstrate excessive variation in fiber size with scattered mildly atrophic fibers of various shapes. No angulated nonspecific esterase positive fibers are seen. Fiber type distribution is normal without grouping. Scattered degenerating/regenerating fibers are seen. Scattered frankly necrotic fibers are seen. Rare fibers undergoing phagocytosis are present. Oxidative enzyme stains are unremarkable. No abnormal glycogen or lipid storage is seen. No myofibrillary structural abnormalities or inclusions are seen. The percentage of fibers with internal nuclei is modestly increased. Blood vessels and connective tissue are unremarkable. There is no primary inflammation.

ADDENDUM DIAGNOSIS:

Skeletal muscle biopsy:

- Consistent with noninflammatory necrotizing myopathy

- Rx with prednisone 60 mg daily but developed elevated BG, polyuria, tremor
- Prednisone taper to 5 mg in 4 weeks
- IVIG was added 1 gm/kg every 2 weeks
- CK normalized, symptoms improved after 3 months
- Off treatment with no new symptoms
- 6 months later doing very well

Lab result

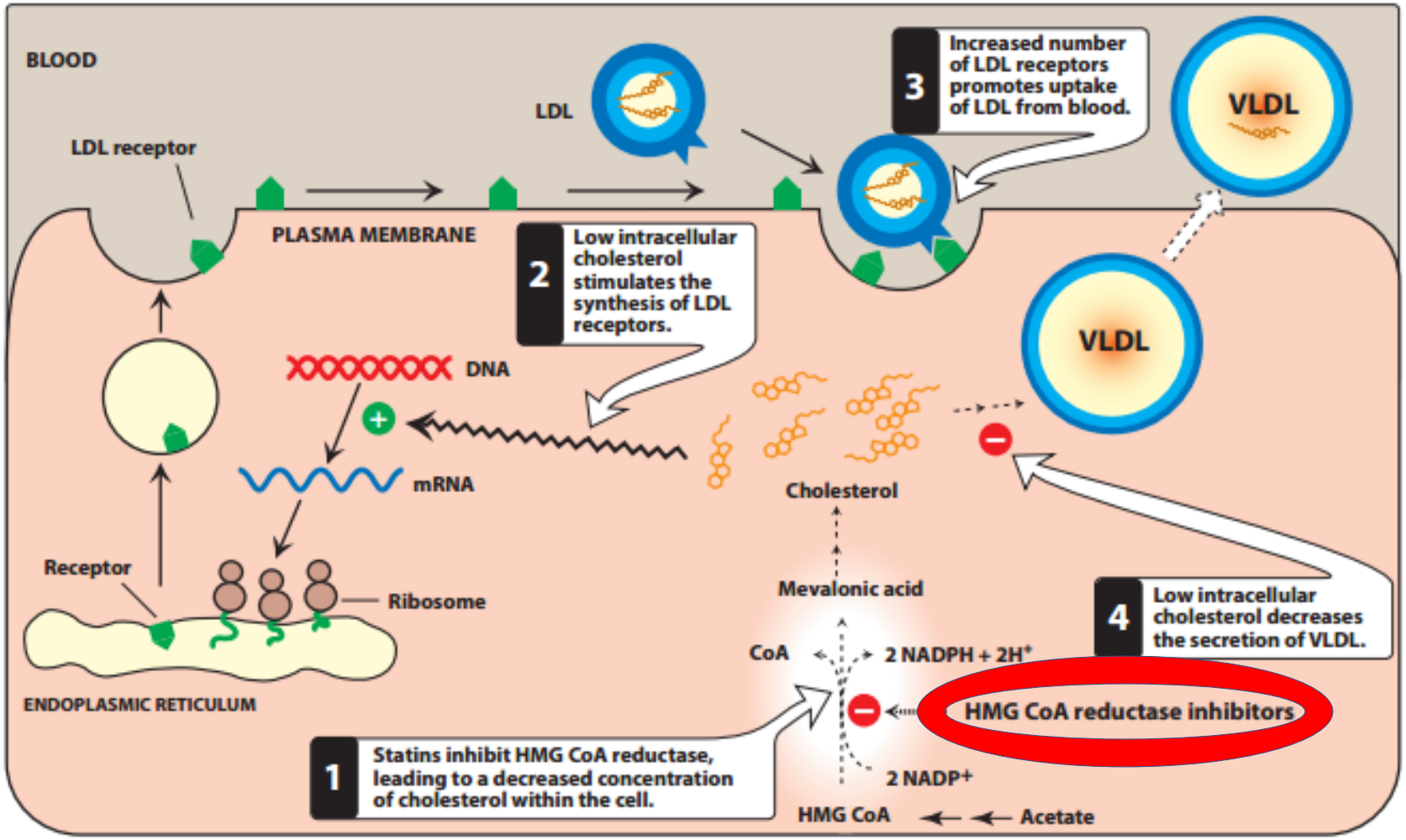
3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase (HMGCR) Antibody, IgG

~~ARUP test code 2013101~~

HMGCR Antibody, IgG	55 Units	H	(Ref Interval: 0-19)

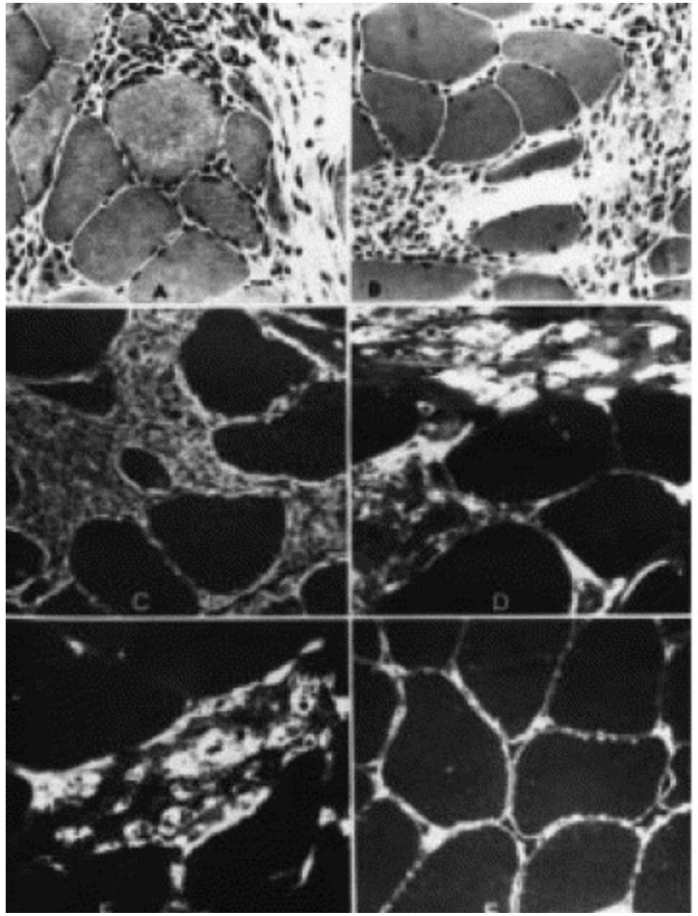
ANA, ENA, MYOSITIS PANEL: Neg

STATIN MECHANISM OF ACTION



Polymyositis associated with simvastatin

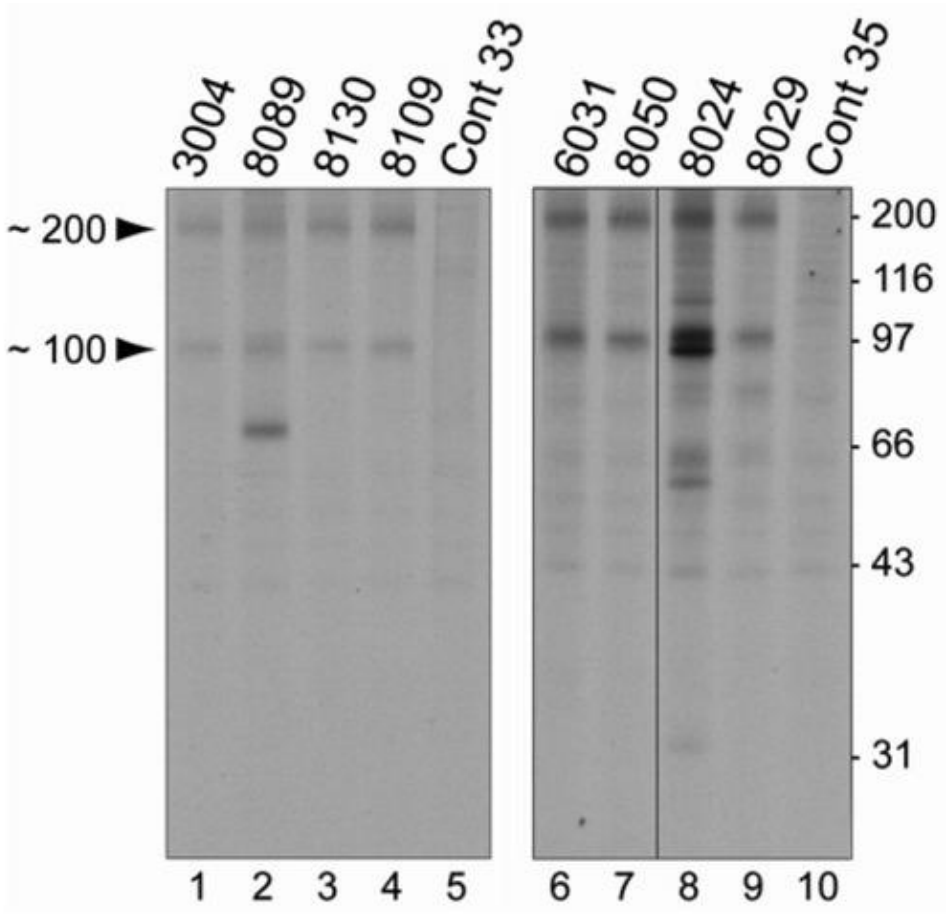
- 42 y/o male
- Biopsy: necrotizing myositis
- Successfully treated with GC
- Conclusion: “Our case suggests that simvastatin myopathy is not spontaneously reversible and the histopathological findings suggest that the myopathy is caused not only by an increase in muscle “membrane fluidity”but also by immunological mechanisms”



Giordano, et al. Lancet, 1997

A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy

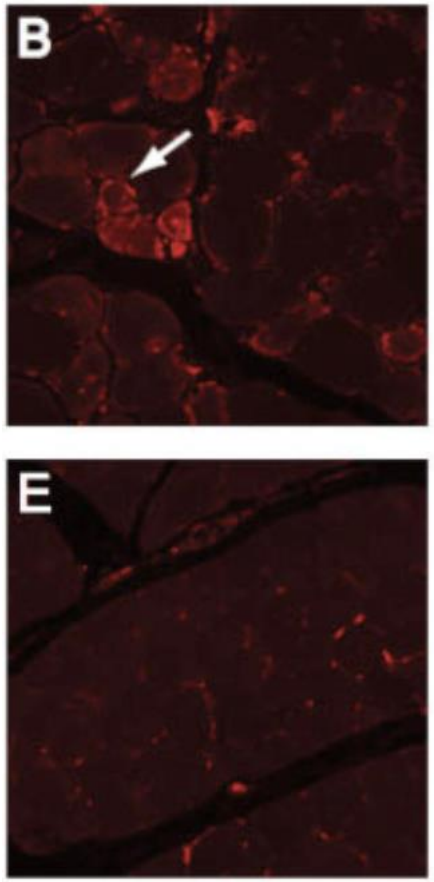
- 16/26 pts with unknown NM had muscle biopsy specimens and serum samples
- Found to have anti–200/100-kd autoantibodies
- 63% exposed to statin
- CK mean 8702 IU/liter
- Responded to immunosuppression
- Among the 187 pts who did not have NM , the serum from only 1pt (0.5%) immunoprecipitated the 200-kd and 100-kd proteins



Christopher-Stine et al, A&R, 2010

Autoantibodies against 3-Hydroxy-3-Methylglutaryl-Coenzyme A(HMG-CoA) Reductase in Pts with Statin-Associated Autoimmune Myopathy

- anti–200/100-kd autoantibodies=HMG-CoA reductase auto-abs
- 45/750(6%) JH myositis cohort
- Regenerating muscle cells express high levels of HMGCR(even after discontinuation)
- 94-95% sensitive and 99 -100% specific



Mammen, et al. A&R, 2011

Hypothesis

- Expression of HMG-CoA reductase is low in most tissues, but it is markedly ⬆ when muscle/other cells are exposed to statins
- Regenerating muscle cells express ⬆ levels of HMG-CoA reductase-required for normal muscle-cell differentiation

Morikawa et al, J Atheroscler Thromb 2005
Mammen et al, A&R, 2011

Statin exposure

	Statin use	No use
All patients (n=45)	30(66%)	15(33%)
Age >50(n=26)	24(92%)	2(8%)

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

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

Statin-Associated Autoimmune Myopathy

Andrew L. Mammen, M.D., Ph.D.

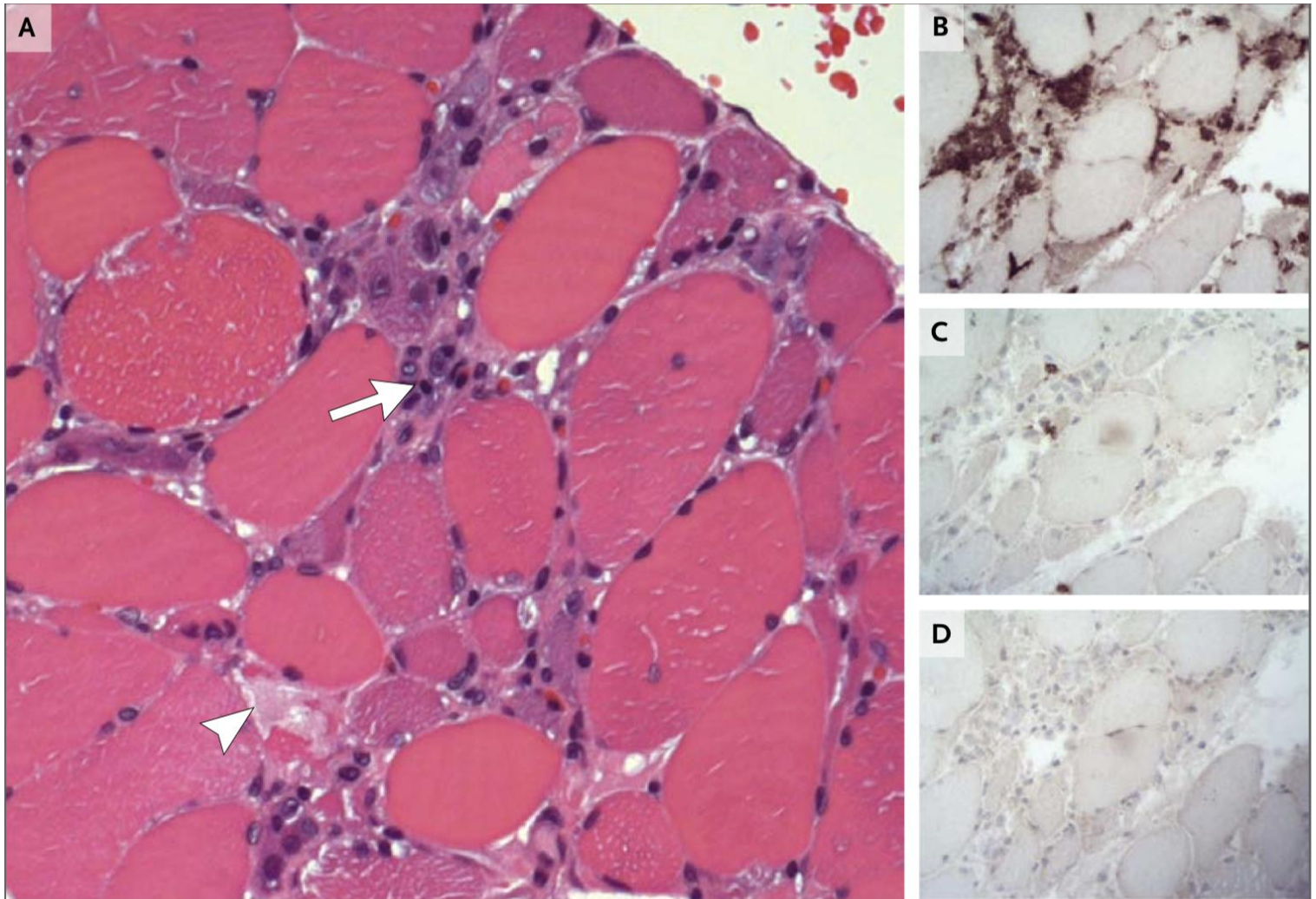


Figure 1. Muscle-Cell Necrosis and Macrophage Infiltration in Statin-Associated Autoimmune Myopathy.

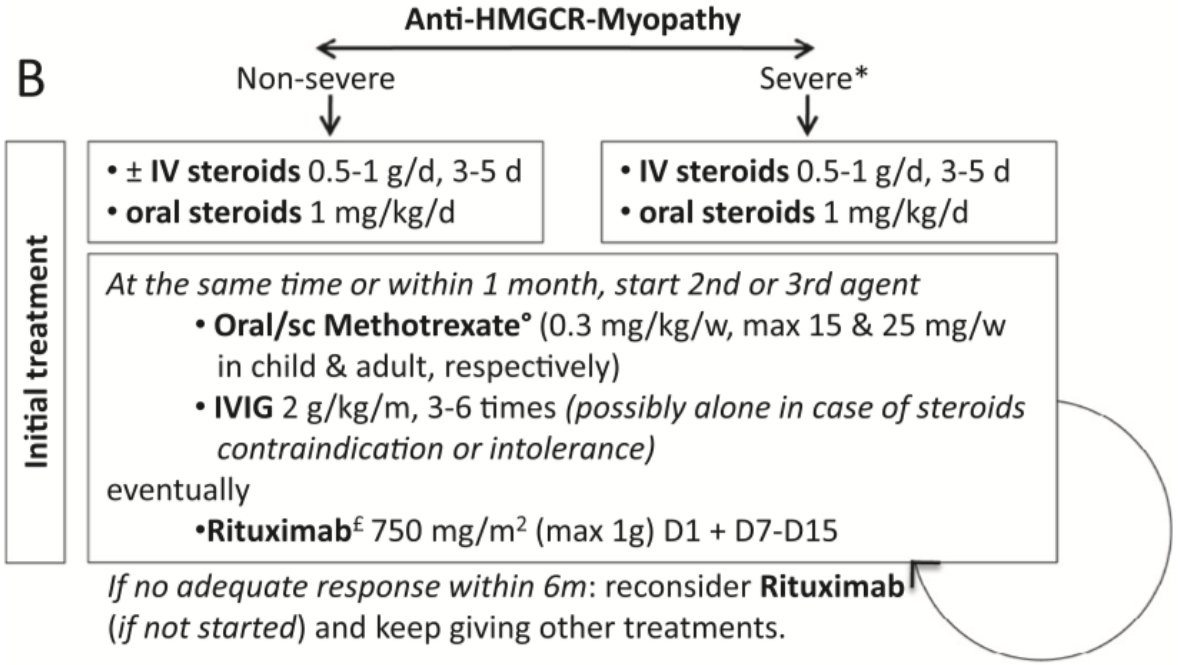
Muscle-cell necrosis and infiltration of macrophages are characteristic features of muscle-biopsy specimens from patients with statin-associated autoimmune myopathy. Hematoxylin and eosin staining of a paraffin-embedded specimen reveals muscle-fiber necrosis (arrowhead) and myophagocytosis (arrow) in a patient with the condition who is positive for anti–3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase autoantibodies (Panel A). Serial frozen sections from the same patient were immunostained with antibody against CD68 (a macrophage marker) (Panel B), CD8 (a cytotoxic T-cell marker) (Panel C), and CD20 (a B-cell marker) (Panel D); antibody-positive cells are stained brown. Macrophages are the predominant type of infiltrating cell. Panels B, C, and D are reproduced, with permission, from Chung et al.[19]

Management

IVIG(monotherapy)	2/3 patients(declined steroids due to DM) had excellent response	Mammen, Tiniakou, NEJM, 2017
Rituximab	3/9 patients demonstrated stable or improved muscle strength ± decline in creatine kinase levels	Landon-Cardinal et al, J Rheum, 2019

Workshop report

224th ENMC International Workshop:
Clinico-sero-pathological classification of immune-mediated necrotizing myopathies
Zandvoort, The Netherlands, 14–16 October 2016



More severe disease and slower recovery in younger patients with HMG-CoA reductase-associated autoimmune myopathy

- 22/50(44%) pts followed for >2 years, reached full strength with Rx
- 56% continued to have CK levels > 500 IU/l and only 3 tapered off Rx
- older at disease onset were stronger at all time points ($P < 0.001$) and improved faster ($P < 0.008$) than younger patients
- H/o statin exposure was not independently associated with improvement
- Younger patients were more likely to have refractory disease ($P=0.02$)
- 8 refractory pts whole exome sequencing did not reveal pathogenic mutations in dystrophy genes.
- The risk of cancer was not increased compared with the gen population

Tiniakou et al, Rheumatology 2017

THANK YOU!!