# MDA5 Associated Clinically Amyopathic Dermatomyositis with Interstitial Lung Disease

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# Clinical Case

- 43 y/o Hispanic male with history of atrial fibrillation s/p multiple ablations and OSA on CPAP that presented to combined rheumatology and dermatology clinic on 7/2015 for persistent rash.
- Initially following with dermatology for rash involving his face, scalp, neck that was diagnosed as sebopsoriasis with irritant dermatitis from CPAP mask.
- The rash was accompanied by joint pain without swelling involving his b/l wrists, MCP, PIP, knees, and MTP joints.
- Skin biopsy obtained from upper back on 6/2015 consistent with focal interface dermatitis concerning for lupus.
- July rheumatology/dermatology clinic complaining of worsening rash now involving torso, fatigue, 10 pound weight loss, dysphagia, and hoarseness.
- Denied any recent exposures to chemicals, recent travel but did start several new supplements from GNC but unsure of the names.
- Review of systems negative for oral or nasal ulcers, alopecia, dry eyes or mouth, chest pain, shortness of breath, weakness, paresthesia, or Raynaud's.

**Past Medical History:**

Persistent Atrial Fibrillation

Obstructive Sleep Apnea on CPAP

**Past Surgical History:**

Cardiac ablation 7/2014 and 4/2015 and multiple cardioversions

**Family History:**

Adopted, unknown

**Social History:**

Tobacco: previous smoker, 1 ppd x 15 years  quit in 2004

Etoh: Occasional, beer

Illicit: Denies

**Medications**:

Diltiazem 120 mg SR BID
Rivaroxaban 20 mg daily
Ketoconazole 2% shampoo
Mometasone 0.1% ointment
Triamcinolone 0.1% ointment
Bioflavonoid Products 1 tab BID
Various multivitamins from GNC

**Had previously been on amiodarone (last 8/2014) and flecainide (last 1/2015) but discontinued due to treatment failure and self-discontinued dabigatraban 6/2015 due to rash and joint pain.

# Physical Exam

Clinic Visit 7/2015:

BP 120/82, T 97.9 F, Wt 106.9 kg

General: NAD, speaking full sentences

HEENT: EOMI b/l, no redness or discharge, MMM without oral ulcers, normal salivary pooling

Lungs: crackles in bases b/l

CV: RRR without murmur

Abdomen: soft, +bowel sounds

Msk: Full ROM shoulder, wrists, DIP, hips, knees and ankles. Unable to fully extend left elbow with mild synovitis and mild synovitis of scattered PIP joints

Neuro: CN 2-12 intact grossly, 5/5 proximal and distal upper and lower muscle strength, 5/5 grip b/l

Skin:

- medial cheeks and glabella with violaceous-erythematous to hyperpigmented geometric plaque
- scalp with diffuse violaceous erythema with mild scale and excoriated papules
- temples, central forehead and pre-auricular cheeks, chin with hyperpigmented to violaceous reticulated patches
- helices with few hyperpigmented macules
- proximal arms and legs as well as abdomen with multiple flagellate pink papules and plaques
- periungual telangiectasia with some swelling of the proximal nailfolds
- few calluses on the finger tips
- back w flagellate hyperpigmentation

# Labs

| Lab | Value | Normal Range |
|---|---|---|
| WBC | 7.4 K/UL | 3.5-10.5 K/UL |
| Hgb | 14.6 GM/DL | 13-17.5 GM/DL |
| Platelets | 246 K/UL | 150-400 K/UL |
| BUN | 8 MG/DL | 7-22 MG/DL |
| Creatinine | 0.74 MG/DL | 0.6-1.4 MG/DL |
| ESR | 48 MM/HR | 0-20 MM/HR |
| CRP | 0.5 MG/DL | <0.8 MG/DL |
| Albumin | 2.8 GM/DL | 3.6-5 GM/DL |
| AST | 57 IU/L | 15-45 IU/L |
| LDH | 557 IU/L | 98-192 IU/L |
| Creatinine Kinase | 195 IU/L | 50-320 IU/L |
| Aldolase | 4.8 U/L | 1.2-7.6 U/L |
| ANA | 1:40 Speckled Pattern | Negative |
| ENA panel | Negative | Negative |
| Double Stranded DNA | <10 IU/ML | <30 IU/ML |
| Complement C3 | 144 MG/DL | 79-152 MG/DL |
| Complement C4 | 45 MG/DL | 16-38 MG/DL |
| ANCA | Negative | Negative |
| Myomarker 3 Panel | +MDA-5 25 U otherwise negative | MDA-5 <20 U negative |
| Urinalysis | 5 RBC otherwise no proteinuria | Negative |

ENA panel includes: SSA, SSB, Scl-70, Smith, RNP and Myomarker 3 panel includes: Anti-JO, PL7, PL12, EJ, OJ, SRP, MI-2, TIF1 Gamma (P155/140), MDA-5, NXP-2, Anti-PM/Scl Ab, Fibrillarin (U3 RNP), U2 snRNP, Anti-U1-RNP Ab, KU, Anti-SSA.

# Imaging

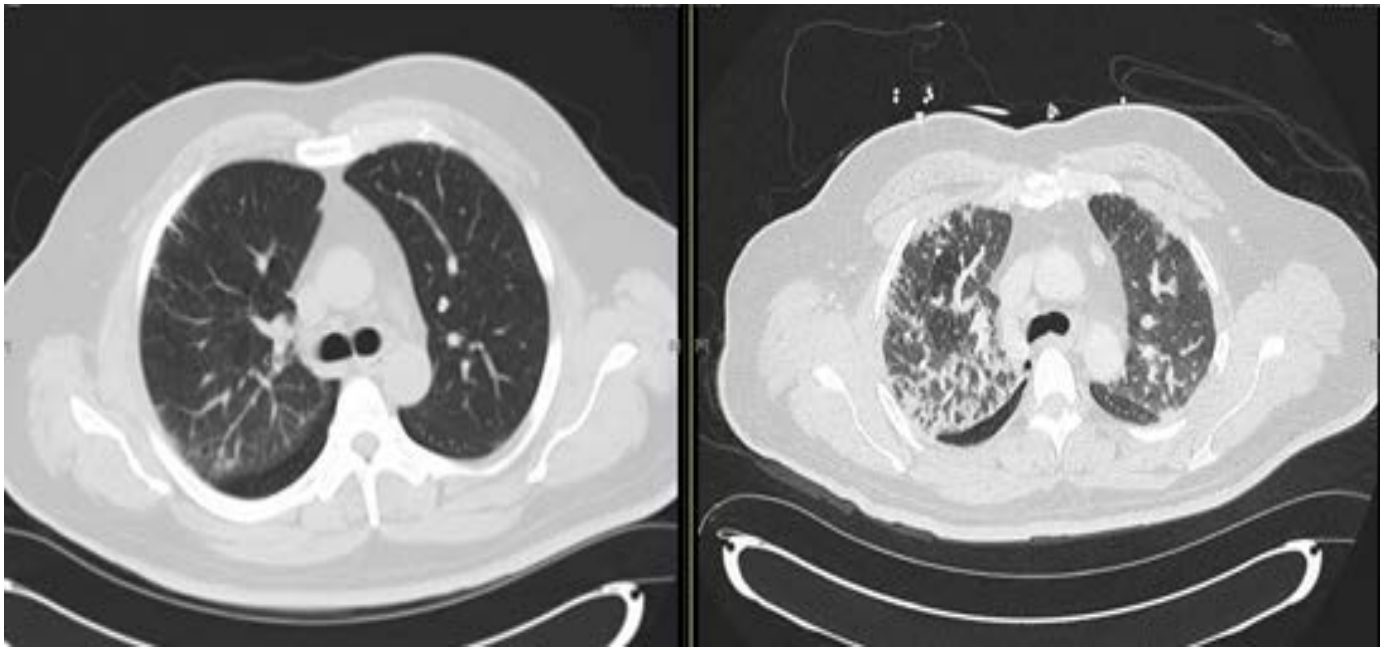
- **5/15/15 CXR:** Congestive changes with mild cardiomegaly since the prior exam, pulmonary venous hypertension and interstitial edema.

- **7/14/15 CXR:** Increased nonspecific linear, predominantly interstitial opacities in the left lower lung. Question infectious process versus inflammatory process versus less likely edema. Mild interstitial opacities in the right lower lung appear grossly similar to prior.

- **7/14 CT Chest without contrast:** Prominent reticular opacities with lower lobe predominance (exclusion of early honeycombing is not entirely possible) with scattered bilateral groundglass opacities.

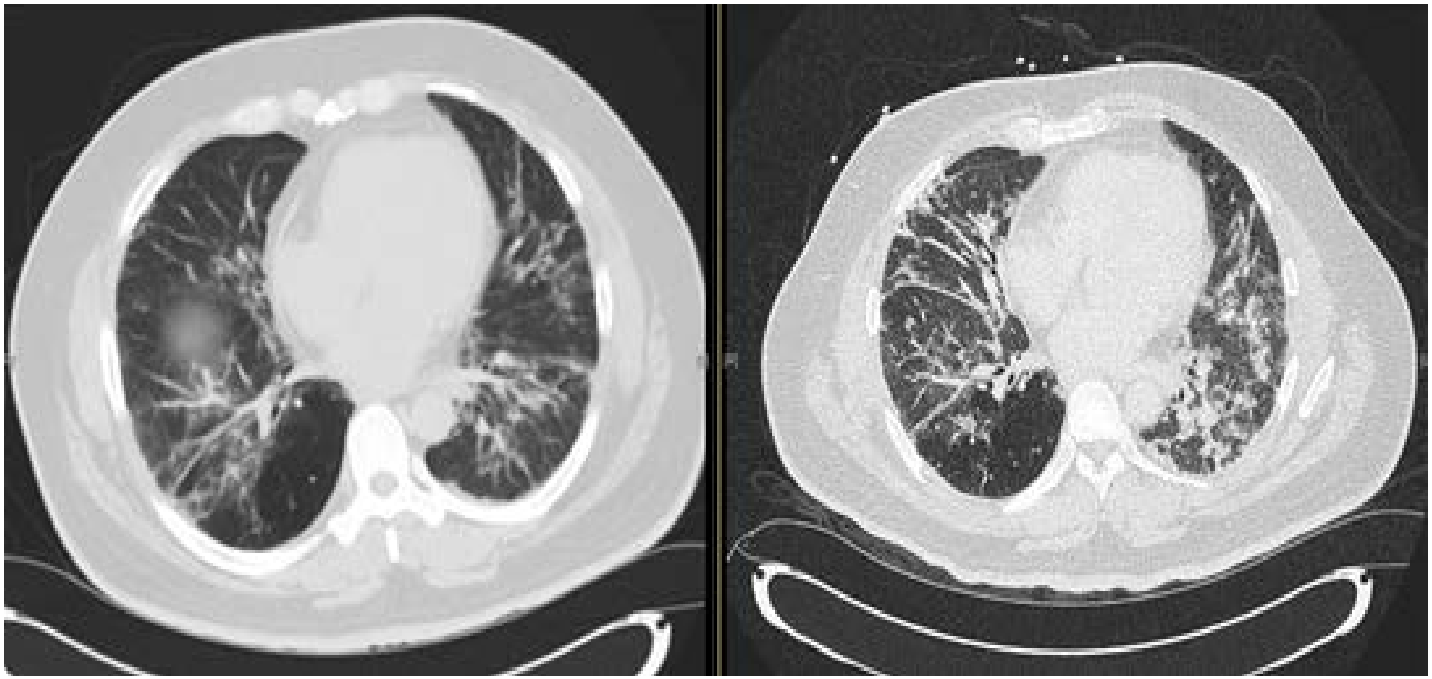
- **9/4/15 High Resolution CT Chest:** Nonspecific multifocal septal thickening with superimposed groundglass and consolidative opacities and early fibrotic changes consistent with interstitial lung disease.

# Imaging



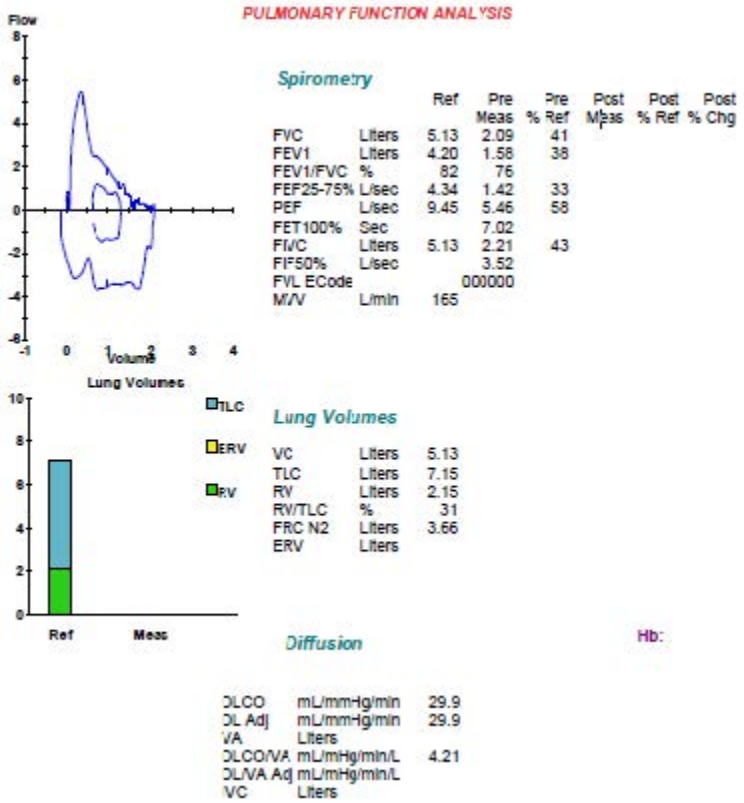
CT Chest 7/2015 and 9/2015 at the level of the carina

# Imaging



CT Chest 7/2015 and 9/2015 at the basilar lung

# Imaging Continued



PULMONARY FUNCTION ANALYSIS

Flow

Volume

Lung Volumes

TLC
ERV
RV

Ref
Meas

**Spirometry**

| | | Ref | Pre Meas | Pre % Ref | Post Meas | Post % Ref | Post % Chg |
|---|---|---|---|---|---|---|---|
| FVC | Liters | 5.13 | 2.09 | 41 | | | |
| FEV1 | Liters | 4.20 | 1.58 | 38 | | | |
| FEV1/FVC | % | 82 | 76 | | | | |
| FEF25-75% | L/sec | 4.34 | 1.42 | 33 | | | |
| PEF | L/sec | 9.45 | 5.46 | 58 | | | |
| FET100% | Sec | | 7.02 | | | | |
| FIVC | Liters | 5.13 | 2.21 | 43 | | | |
| FIF50% | L/sec | | 3.52 | | | | |
| FVL ECode | | | 000000 | | | | |
| MVV | L/min | 165 | | | | | |

**Lung Volumes**

| | | |
|---|---|---|
| VC | Liters | 5.13 |
| TLC | Liters | 7.15 |
| RV | Liters | 2.15 |
| RV/TLC | % | 31 |
| FRC N2 | Liters | 3.66 |
| ERV | Liters | |

**Diffusion**

Hb:

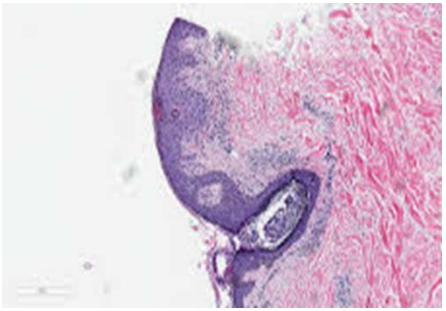
| | | |
|---|---|---|
| DLCO | mL/mmHg/min | 29.9 |
| DL Adj | mL/mmHg/min | 29.9 |
| VA | Liters | |
| DLCO/VA | mL/mHg/min/L | 4.21 |
| DL/VA Adj | mL/mHg/min/L | |
| VC | Liters | |

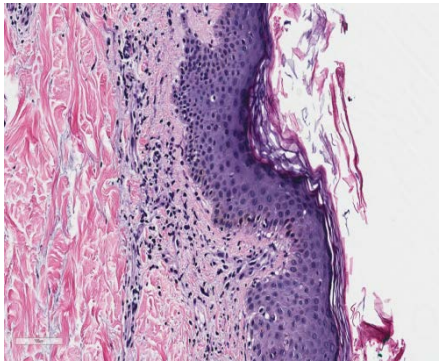
FINDINGS:
Spirometry reveals FVC is severely reduced, FEV-1 is severely reduced and the FEV-1/FVC is normal.

IMPRESSION:
There is severe restriction on this exam.

Echocardiogram 9/2015: Normal

Skin biopsy 6/2015:





Focal interface dermatitis and follicular plug with underlying superficial and deep mild perivascular and interstitial predominately lymphocytic inflammation

# Clinical Course

- **7/2015**
  - Started on prednisone 60 mg daily with taper without improvement of symptoms of rash and joint pain
- **8/2015**
  - He felt his symptoms were secondary to dabigatraban so self-discontinued his cardiac medications which included diltiazem & dabigatraban with reported improvement of rash. Also had previously been on amiodarone (discontinued 8/2014) and flecainide (discontinued 1/2015) due to treatment failure
  - Seen by outpatient by ENT for hoarseness and found to have bilateral vocal cord thickening with plaques concerning for inflammatory process
  - Went into atrial fibrillation after discontinuing medications; had outpatient cardioversion and started on flecainide 150 mg BID, metoprolol XL 25 mg BID, and apixaban
- **9/2015**
  - Admitted with worsening dyspnea, repeat CT chest showed rapidly progressive ILD compared to CT chest 7/2015 and PFTs revealed severe restriction
  - Flecainide discontinued due to concern for possible drug toxicity causing fibrosis
  - Clinical picture, laboratory testing and skin biopsy results concerning for MDA-5 associated clinically amyopathic dermatomyositis
  - Started on methylprednisolone 125 mg IV q6h for 3 days with improvement of dyspnea and rash however requiring 2L supplemental oxygen on discharge
  - Discharged on prednisone 60 mg daily with taper and plan for outpatient biopsy of vocal cord

# Physical Exam

Patient presented to ED due to worsening dyspnea 10/2015 after discontinuing prednisone due to psychosis

**Exam:**

BP 107/68, P 128, RR 31, O2 sat 87% on RA and 100% on NRB

General: Unable to speak in full sentences, use of accessory muscles

HEENT: No oral ulcers

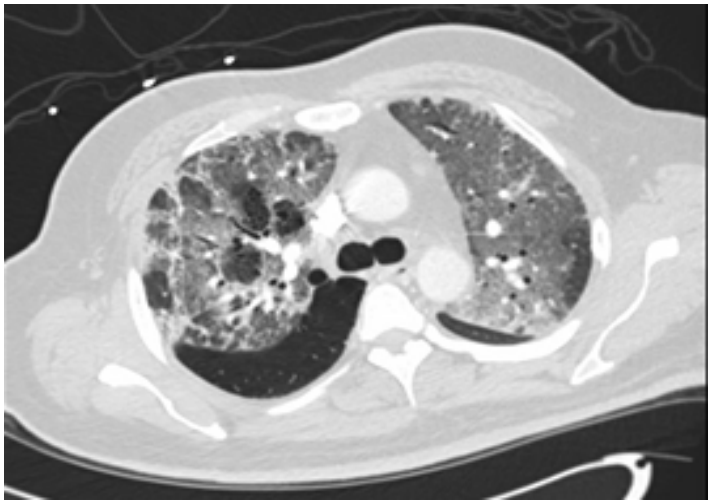
CV: RRR without murmur

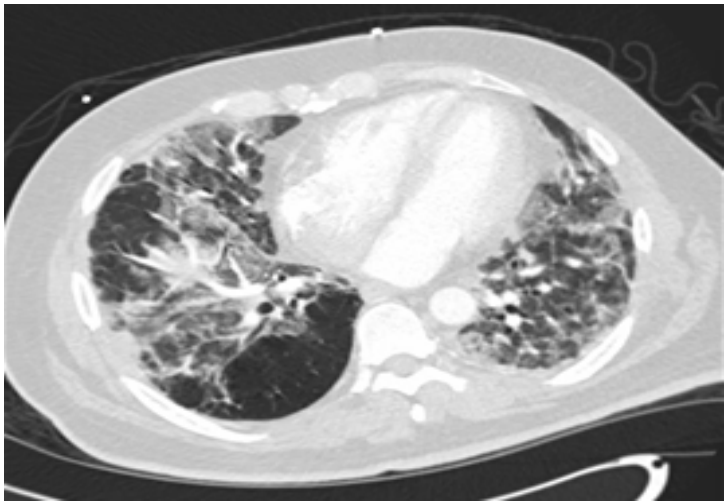
Lungs: Crackles to mid-lung fields b/l

Msk: No synovitis.

Skin: Hyperpigmentation in areas of prior skin lesions, no new rashes or ulceration

# Imaging





CT Chest with contrast at the level of the carina and basilar lung 10/2015

**10/6/15 CT PE:** Motion artifact renders evaluation of the distal pulmonary arteries suboptimal. Within these confines there no pulmonary emboli in the main, lobar, or proximal segmental pulmonary arteries. Diffuse groundglass and scattered solid opacities in the bilateral lungs have markedly progressed since prior exam. Mild diffuse bronchiectasis and septal thickening with air trapping in the right middle lobe are also noted. Findings compatible with worsening of chronic interstitial lung disease, however superimposed infectious process cannot be excluded. Prominent and enlarged mediastinal and hilar lymph nodes have mildly increased in size, likely reactive.

# Clinical Course

- **10/2015**
  - Unable to tolerate steroids due to psychosis and admitted after self-discontinuing prednisone, now with acute hypoxic respiratory failure and worsening CT chest with concern for multifocal pneumonia superimposed on ILD vs progression of ILD
  - Required intubation c/b right sided spontaneous pneumothorax s/p chest tube placement
  - Bronchoscopy was grossly normal and BAL was negative for bacterial, fungal, or viral process
  - Remained on broad spectrum antibiotics for pneumonia
  - Started methylprednisolone 40 mg IV BID and tacrolimus 1 gram BID for treatment of autoimmune associated ILD (Rituximab and Cyclophosphamide considered however due to possible infection withheld)
  - Patient family withdrew care and patient expired

# Background

- Idiopathic inflammatory dermatomyopathies have been described by various clinical and pathologic criteria and include conventional dermatomyositis, polymyositis, clinically amyopathic dermatomyositis, and inclusion body myositis.
- Clinical manifestations represent a disease spectrum of varying degrees of muscle, skin, lung involvement, and malignant disease.
- "Dermatomyositis-like skin syndrome" is used to describe patients with distinctive or predominantly cutaneous manifestations of DM without clinical evidence of myositis.
  - These patients are at higher risk for developing acute and rapidly progressive interstitial lung disease, malignancy, and delayed onset of myositis.
  - Variable presentation of cutaneous lesions from rash to ulcerations, have even been described to present after the development of ILD.
  - Associated with negative anti-Jo-1 antibodies with the clinical behavior similar to anti-synthetase syndrome, with mild or absent myopathy.

Chaisson N, Paik J, Orbai AM, et al. A novel dermato-pulmonary syndrome associated with MDA-5 antibodies: Report of 2 cases and review of the literature. Medicine (Baltimore) NIH Public Access. 2012; 91 (4): 220-228

# MDA5

- MDA5, or CADM-140, was identified by Sato et al. and published in Arthritis and Rheumatism in 2009 as a major autoantigen associated with clinically amyopathic dermatomyositis and the development of rapidly progressive interstitial lung disease
  - Association most prevalent in Asian populations, original studies and case reports from Japan and China
- Melanoma differentiation-associated gene 5
- Protein that plays a role in the innate immune response, triggers production of type I interferons, which further up-regulate MDA5 to suppress viral replication and modulate subsequent adaptive immunity
- Acts against the retinoic acid-inducible gene receptors involved in recognizing viral proteins
  - Specifically RNA viruses including picornaviruses (polio, coxsackie, and rhinovirus), flavaviruses (Dengue and West Nile), and vaccinia (DNA virus)
- Often appears in isolation and not associated with other myositis-specific antibodies and patients typically ANA negative
- Titers have been shown to correlate with severity and decrease and even become negative with treatment

Sato S, Hoshino K, Satoh T et al. 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. Arthritis Rheum 2009; 60;2193-200.

# Presentation

- Initial patients reported in literature were of Asian heritage and had variable clinical findings.
- The cutaneous findings were not well reported in the original Japanese cohorts
- As of 2013, there were only small numbers of case reports of Caucasian patients with positive MDA5 antibodies and rapidly progressive ILD
- Literature review at that time demonstrated the most common clinical presentations of patients with MDA5 antibodies:
  - Ground-glass attenuation in random distribution or present focally in lower lobes
  - Skin ulcerations, symmetric inflammatory arthritis (non-erosive), mechanic's hands, palmar papules, helitrope rash, Gottron's papules, periungual erythema, periungual telangiectasia, tender gums and oral lesions, and fever

Chaisson N, Paik J, Orbai AM, et al. A novel dermato-pulmonary syndrome associated with MDA-5 antibodies: Report of 2 cases and review of the literature. Medicine (Baltimore) NIH Public Access. 2012; 91 (4): 220-228

# Clinical Association

- Cao et al. collected serum from 140 Chinese adult patients with CTDs or idiopathic IPF from 2009-2011, including 12 healthy controls.
  - 32 patients with classic DM, 32 with CADM, 15 with PM, 18 with SLE, 14 with systemic sclerosis, 15 with Sjogren's, 9 with MCTD, and 5 with IPF
- In 64 samples from DM/CADM patients, 15 were positive for anti-MDA5 antibody (12/32 CADM and 3/32 DM, p=0.016)
  - MDA-5 antibodies were not found in the serum of PM, SLE, SS, SSc, MCTD, IPF, or healthy controls
- Incidence of skin ulcerations was higher in MDA5 positive patients (12/15 vs 4/49 in MDA-negative patients, p<0.001) and antibody titer appeared to be related to the severity of skin lesions
  - 8 patients with anti-MDA-5 antibody levels <500 units/ml had solitary or superficial skin ulcerations without necrosis
- The presence of ILD was significantly more in MDA5 positive patients as well (15/15 vs 31/49, p= 0.003) and anti-MDA antibody levels in patients with acute/subacute ILD were higher than in those with chronic ILD (p=0.012)
- 4 patients with MDA5 antibody levels >500 units/ml exhibited rapid progression of ILD and developed uncontrolled respiratory failure.
  - 3 were treated with steroids (>2 mg/kg/day) combined with cyclophosphamide and/or IVIG and 1 was treated with steroids 1 mg/kg/day combined with cyclophosphamide.
  - All 4 patients died within 1-2 months after onset if disease
- 11 patients with MDA5 antibody levels <500 units/ml with ILD were treated with steroids (<0.5-1 mg/kg/day) alone or steroids with cyclophosphamide or cyclosporine A
  - Respiratory and skin symptoms improved and 5/11 patients had reduction in MDA5 antibody levels

Cao H, Pan M, Kang Y, Xia Q, et al. Clinical manifestations of dermatomyosistis and clinically amyopathic dermatomyositis patients with positive expression of anti-melanoma differentiation-associated gene antibody. Arthritis care and Research. 2012, 64(10):1602-1610.

**Table 1. Comparison of clinical data between MDA-5–positive and MDA-5–negative patients upon admission***

| | Anti–MDA-5 antibodies | | |
|---|---|---|---|
| | Positive (n = 15) | Negative (n = 49) | *P*† |
| Age at onset, mean ± SD years | 46.2 ± 9.6 | 49.0 ± 14.0 | 0.466 |
| Sex, male:female | 6:9 | 10:39 | 0.173 |
| Diagnosis | | | |
| DM | 3 (20.0) | 29 (59.2) | 0.016 |
| CADM | 12 (80.0) | 20 (40.8) | 0.016 |
| Skin eruption | | | |
| Heliotrope rash | 14 (93.3) | 43 (87.8) | 1.000 |
| Gottron's rash | 14 (93.3) | 45 (91.8) | 1.000 |
| Skin ulceration | 12 (80.0) | 4 (8.2) | < 0.001 |
| Clinical features | | | |
| Hoarseness and bucking | 7 (46.7) | 4 (8.2) | 0.002 |
| Internal malignancy | 1 (6.7) | 7 (14.3) | 0.668 |
| Myalgia | 4 (26.7) | 30 (61.2) | 0.036 |
| ILD | 15 (100.0) | 31 (63.3) | 0.003 |
| Acute/subacute IP | 9 (60.0) | 1 (2.0) | < 0.001 |
| Death | 4 (26.7) | 1 (2.0) | 0.009 |
| Laboratory findings, mean ± SD | | | |
| CK level, IU/liter | 145.3 ± 231.3 | 1,877 ± 3,352 | 0.038 |
| LDH level, IU/liter | 357.1 ± 164.5 | 293.3 ± 214.9 | 0.033 |
| Albumin level, gm | 29.1 ± 6.8 | 33.0 ± 5.6 | 0.034 |

* Values are the number (percentage) unless otherwise indicated. MDA-5 = melanoma differentiation–associated gene 5; DM = dermatomyositis; CADM = clinically amyopathic DM; ILD = interstitial lung disease; IP = interstitial pneumonia; CK = creatine kinase; LDH = lactate dehydrogenase.
† Obtained with Fisher's exact test for the comparison of frequencies and the *t*-test for the comparisons of mean values.

Cao H, Pan M, Kang Y, Xia Q, et al. Clinical manifestations of dermatomyosistis and clinically amyopathic dermatomyositis patients with positive expression of anti-melanoma differentiation-associated gene antibody. Arthritis care and Research. 2012, 64(10):1602-1610.

# Therapy

- Retrospective analysis of 114 patients diagnosed with PM/DM/CADM-ILD by Fujisawa et al
- 30 PM-associated ILD, 41 DM-associated ILD, and 43 CDM-associated ILD cases
- Clinical presentation of ILD was acute or subacute in 59 patients (51.8%) and chronic in 55 patients (48.2%)
- Patients with acute/subacute ILD had much lower survival rates than chronic ILD ($p<0.001$) and patients with CADM-ILD had a lower survival rate than those with PM-ILD ($p=0.034$)
- Treatment in 23 patients included corticosteroids alone (PO prednisone 40-60 mg/day), IV methylprednisolone pulse therapy (1 g/day for 3 days).
- In 88 patients, cyclosporine, cyclophosphamide, and/or azathioprine were administered in addition to steroids
- IVIG was administered to 11 patients who did not respond to corticosteroids plus immunosuppressive agents
- MDA5 unfortunately was not measured though discussed as an association with rapidly progressive ILD and poor outcome

Fujisawa T, Hozumi H, Kono M, Enomoto N, Hashimoto D, et al. (2014). Prognostic factors for myositis-assiciated interstitial lung disease. PLoS ONE 9(6); e98824

**Table 6.** Treatment and outcome in myositis-associated ILD.

| Treatment | Total | PM-ILD | DM-ILD | CADM-ILD |
|---|---|---|---|---|
| Number of patients | 114 | 30 | 41 | 43 |
| Corticosteroids alone | 23 | 9 | 7 | 7 |
| Corticosteroids + immunosuppressive agents | 88 | 21 | 33 | 34 |
| Cyclosporine | 75 | 12 | 31 | 32 |
| Cyclophosphamide | 22 | 5 | 7 | 10 |
| Azathioprine | 13 | 8 | 3 | 2 |
| Intravenous Igs | 11 | 1 | 5 | 5 |
| Mortality (%) | 31 (27.2) | 5 (16.7) | 10 (24.4) | 16 (37.2) |

Data are presented as the n (%).
ILD: interstitial lung disease; Ig: immunoglobulin.
doi:10.1371/journal.pone.0098824.t006

Fujisawa T, Hozumi H, Kono M, Enomoto N, Hashimoto D, et al. (2014). Prognostic factors for myositis-assiciated interstitial lung disease. PLoS ONE 9(6); e98824.

# Therapy

- Ge et al conducted a systematic review of 12 articles that collectively involved 178 patients with idiopathic inflammatory myopathy (IIM) and IIM-related ILD (IIM-ILD) who were treated with cyclophosphamide between 1975 and 2014
  - MDA-5 antibody measurements not included, frequency of Jo-1 positive patients with ILD was 55.4% (107/193 patients)
- Doses ranged from 0.3-1.5 g/m2 or 10-15 mg/kg given at weekly to monthly intervals for 6-12 months
  - Cumulative doses ranged from 5-15 g
- Typically supplemented with corticosteroids and 5 studies included cyclosporine, methotrexate, IVIG, azathioprine, mycophenolate, and tacrolimus in combination with steroids
- Three studies reported survival rates of patients with acute/subacute IL after cyclophosphamide treatment, total of 43 patients received treatment and 58.1% (25/43) survived

Ge Y, Peng Q, Zhang S, Zhou H et al. Cyclophosphamide treatment for idiopathic inflammatory myopathies and related interstitial lung disease: a systematic review. Clinical Rheumatol (2015) 34:99-105.

# Therapy

- Yamasaki et al conducted an open-label study of 17 patients with DM/CADM treated with cyclophosphamide and prednisolone
  - 11/17 patients had improvement in dyspnea and 8/17 patients had a 10% improvement in vital capacity and regression in lung fibrosis on high-resolution CT chest
- Levine et al published a study in which 6 patients with DM received 4 weekly infusions of 375 mg/m2 rituximab and demonstrated improvement in muscle strength, reduction of CK levels and improved cutaneous and pulmonary disease after 12 weeks
- MDA5 antibodies were not reported in either of these studies

Ernste F, Reed AM. Idiopathic inflammatory myopathies: current trends in pathogenesis, clinical features, and up-to-date treatment recommendations. Mayo Clin Proc, 2012: 88(1):83-105

# Therapy

- Kurita et al published a report regarding the use of calcineurin inhibitors for the treatment of interstitial lung disease in patients with polymyositis/dermatomyositis
- Cyclosporine and tacrolimus have shown efficacy in the treatment of PM/DM-associated ILD and small studies have been published
  - Tacrolimus was shown to have improved survival in patients with ILD in a small study (n=5) published by Takada et al. where all 5 patients demonstrated clinical improvement after treatment with tacrolimus and corticosteroids
  - The 5 patients had been treated with cyclosporine and corticosteroids and reported to have refractory disease
- Triple combination therapy with corticosteroids, calcineurin inhibitors and cyclophosphamide have shown promising results in a small study of 10 patients with PM/DM-associated ILD (MDA5 data not available)
  - Pulse steroids, 10-30 mg/kg/day of cyclophosphamide every 3-4 weeks and 2-4 mg/kg/day of cyclosporine

Kameda H, Nagasawa H, Ogawa H et al. Combination therapy with corticosteroids, cyclosporin A, and intravenous pulse cyclophosphamide for acute/subacute interstitial pneumonia in patients with dermatomyositis. J Rheumatolo 2005; 32:1719-1726
Kurita T, Yasuda S, Amengual O, Atsumi T. The efficacy of calcineurin inhibitors for the treatement of interstitial lung disease associated with dermatomyositis/polymyositis. Lupus 2015; 24: 3-9
Takada K, Nagasaka K, Miyasaka N et al. Polymyositis/dermatomyositis and interstitial lung disease: a new therapeutic approach with T-cell specific immunosuppressants. Autoimmunity 2005; 38:383-392

# Conclusions

- There are no current established treatments for DM/CADM patients with anti-MDA5 antibodies
- Corticosteroids, immunosuppressive agents, and IVIG are regarded as effective treatments, the therapeutic response is often disappointing
- There are not conventional doses or combination regimens that have proven to be more effective than steroids alone
- Treatment course is often complicated by the subsequent development of infection and unpredictable nature of interstitial lung disease progression
- There are not yet established guidelines for testing of MDA5 and current data consists of small retrospective review studies and extrapolation from small populations, with only 1 reported US study

# References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