Skin Manifestations of Dermatomyositis

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Overview

- **Pathogenesis: Inflammatory cells in the skin, Interferon, medications (TNF inhibitors, statins), autoantibodies**
- **Clinical: Amyopathic vs Classical DM**
- **Lung Disease in DM**
- **Quality of Life in DM**
- **Evaluation and Treatment**

Antibodies in Pathogenesis of DM

- **140-kDa [RNA helicase, melanoma differentiation-associated gene 5 (MDA-5); IFN induced with helicase C domain protein 1 (IFIH1)]**
- **155/140-kDa (transcriptional intermediary factor 1-γ, TIF1-γ)**
- **May help increase understanding about antigens triggering immune reactions**

(Sato S et al, Arthritis Rheum 60:2193, 2009; Hoshino K et al, Rheumatol 49:1726, 2010)

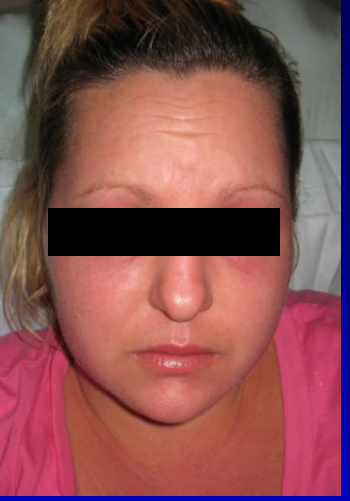
Antibodies in Pathogenesis of DM

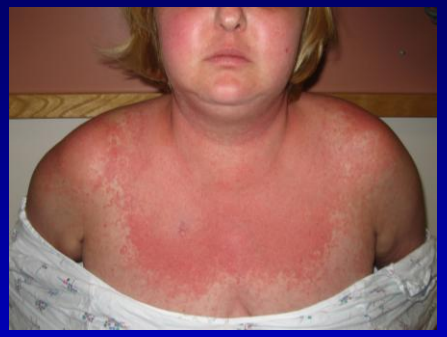
- **p155/p140: present in sera of 23-29% Juvenile DM cases and associated with more severe skin involvement and generalized lipodystrophy**

Targoff IN et al, Arthr Rheum 54:3689, 2006;
Bingham A et al, Medicine 87:70, 2008

TNF inhibition and DM

- **Nineteen different medications have been implicated,**
  - **Hydroxyurea (36 cases)**
  - **Penicillamine (10 cases)**
  - **HMG-CoA reductase inhibitors (6 cases)**
- **Association with tumor necrosis factor (TNF) inhibitors** ***(Dastmalchi M, Ann Rheum Dis 67: 1760, 2008)***





TNF inhibition and DM

Four additional cases

- **One with severe flare within days of one injection of etanercept for a flare of arthralgias, mild rash**
- **Within days she developed very severe myalgias, arthralgias, exacerbation of her rash, shortness of breath, and fevers to 104.5 °F**
- **Aldolase was elevated (18 U/L; reference range 1.2-7.6 U/L**
- **Pulmonary function tests (PFTs) showed mild restrictive lung disease with decreased carbon monoxide diffusing capacity (DLCO)**

Klein R et al, Arch Dermatol, 146:780, 2010

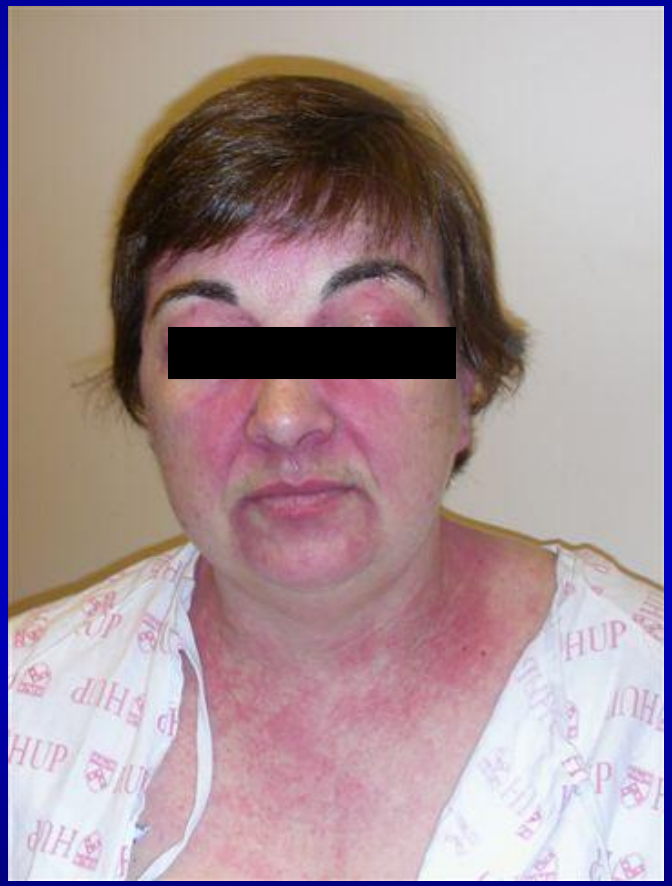
TNF inhibition and DM

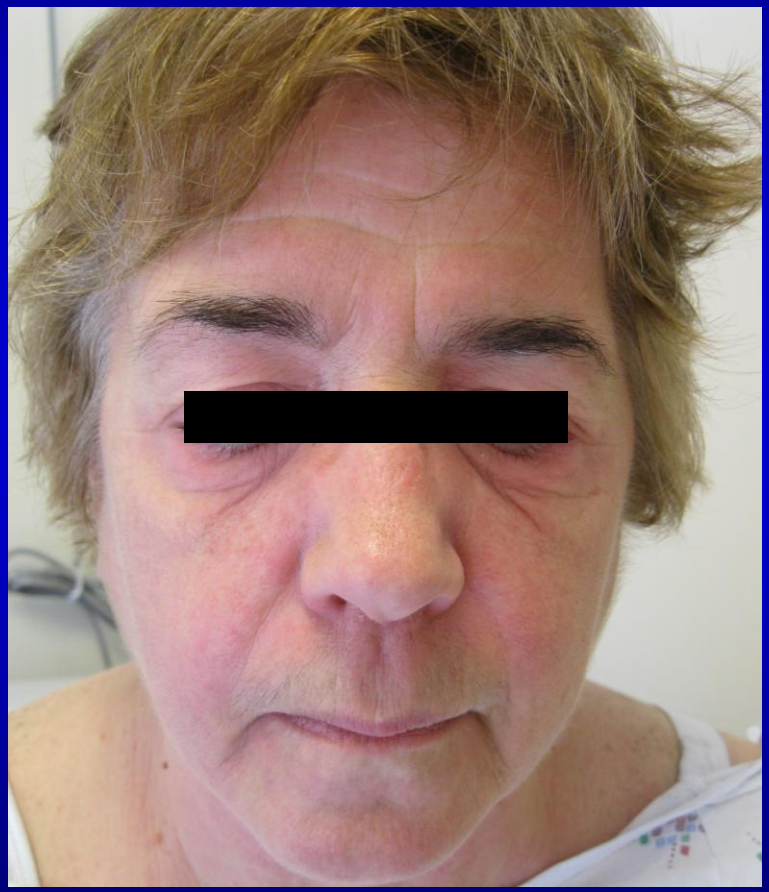
- **The cytokine-shift hypothesis**
  - **Inhibition of TNF-α promotes the expression of type I interferon (IFN) by altering the balance between Th1 and Th2 cytokine *production (Palucka AK et al, PNAS 102:3372, 2005)***
- **This increase in type I IFN may contribute to the exacerbation of symptoms**

Overview

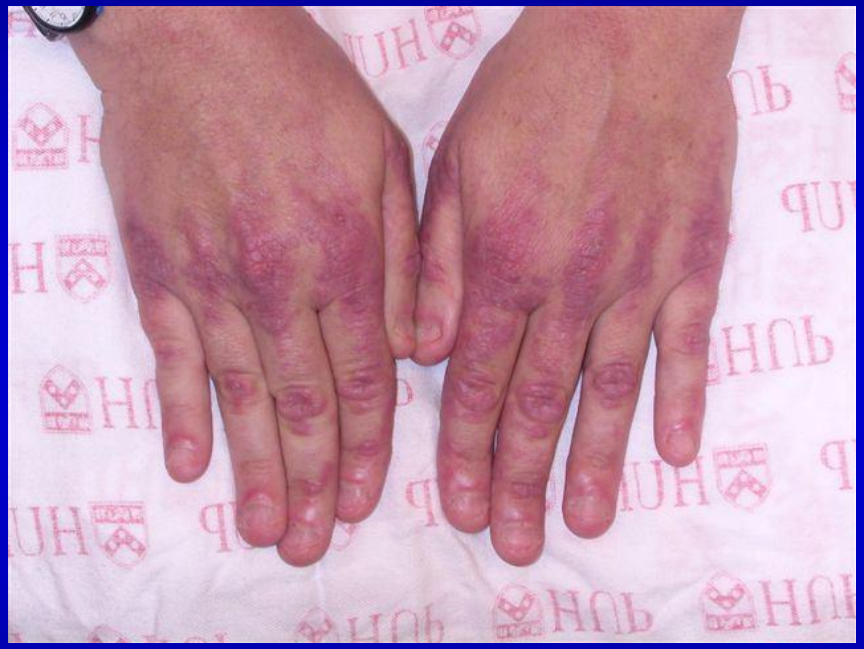
- Pathogenesis: Lichenoid tissue reactions, IFN, meds (TNF inhibitors), antibodies.
- Clinical Findings
- Lung Disease in DM
- Quality of Life in DM
- Treatment

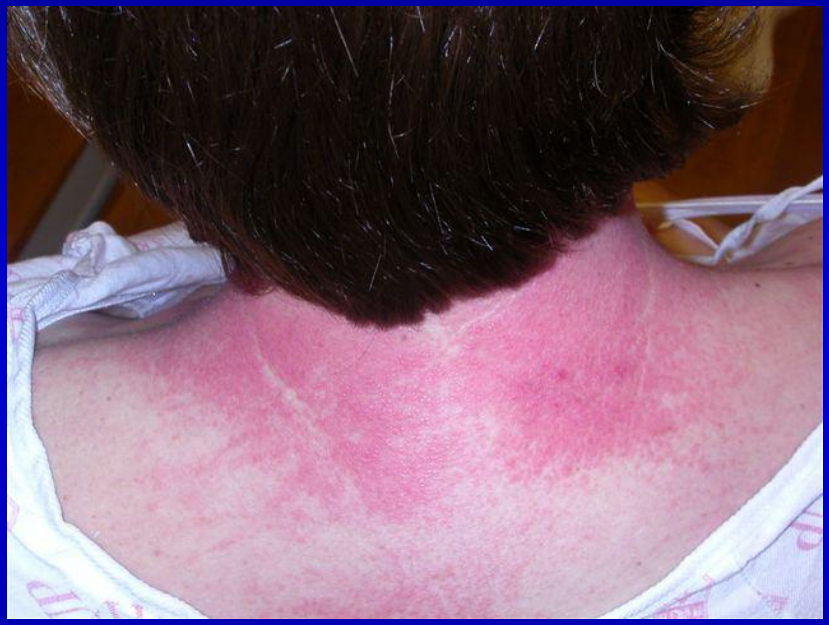
Dermatomyositis



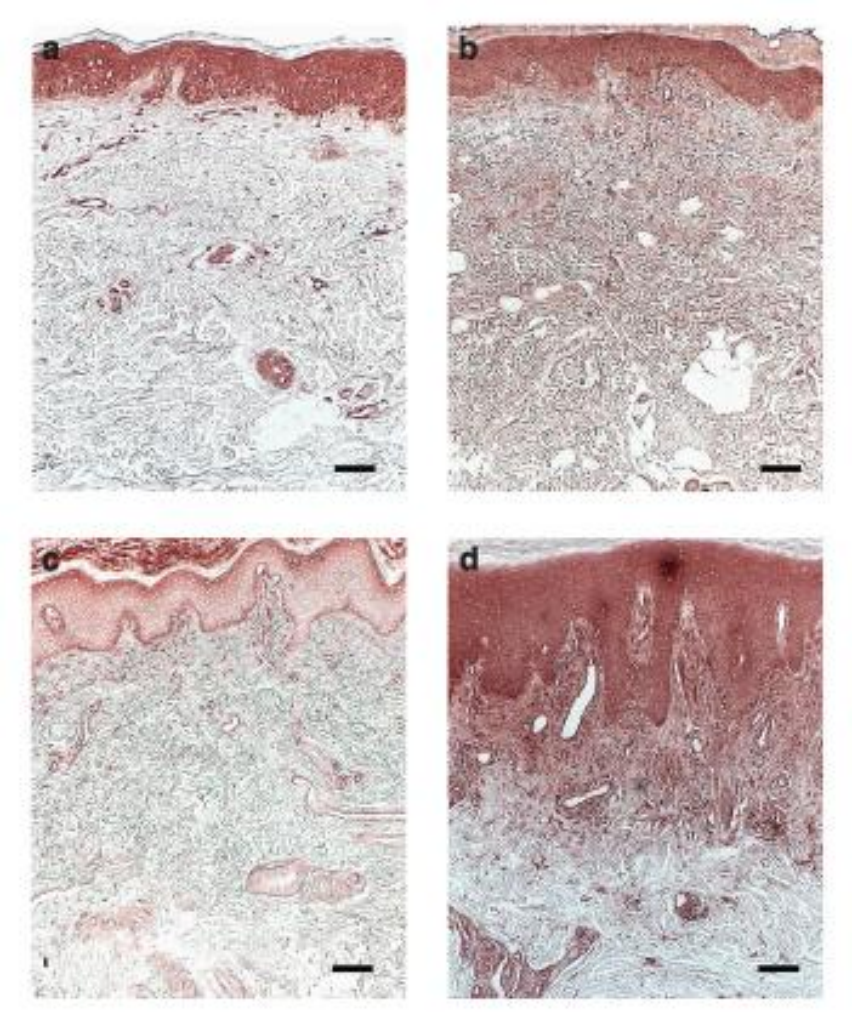


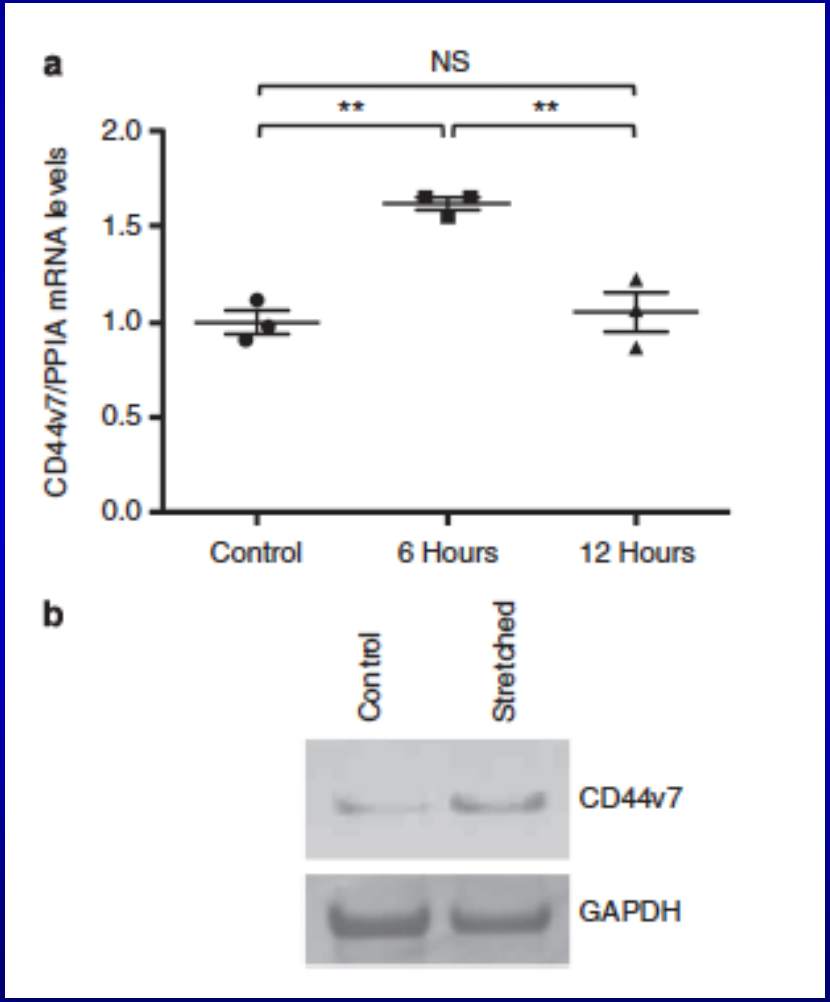
Dermatomyositis





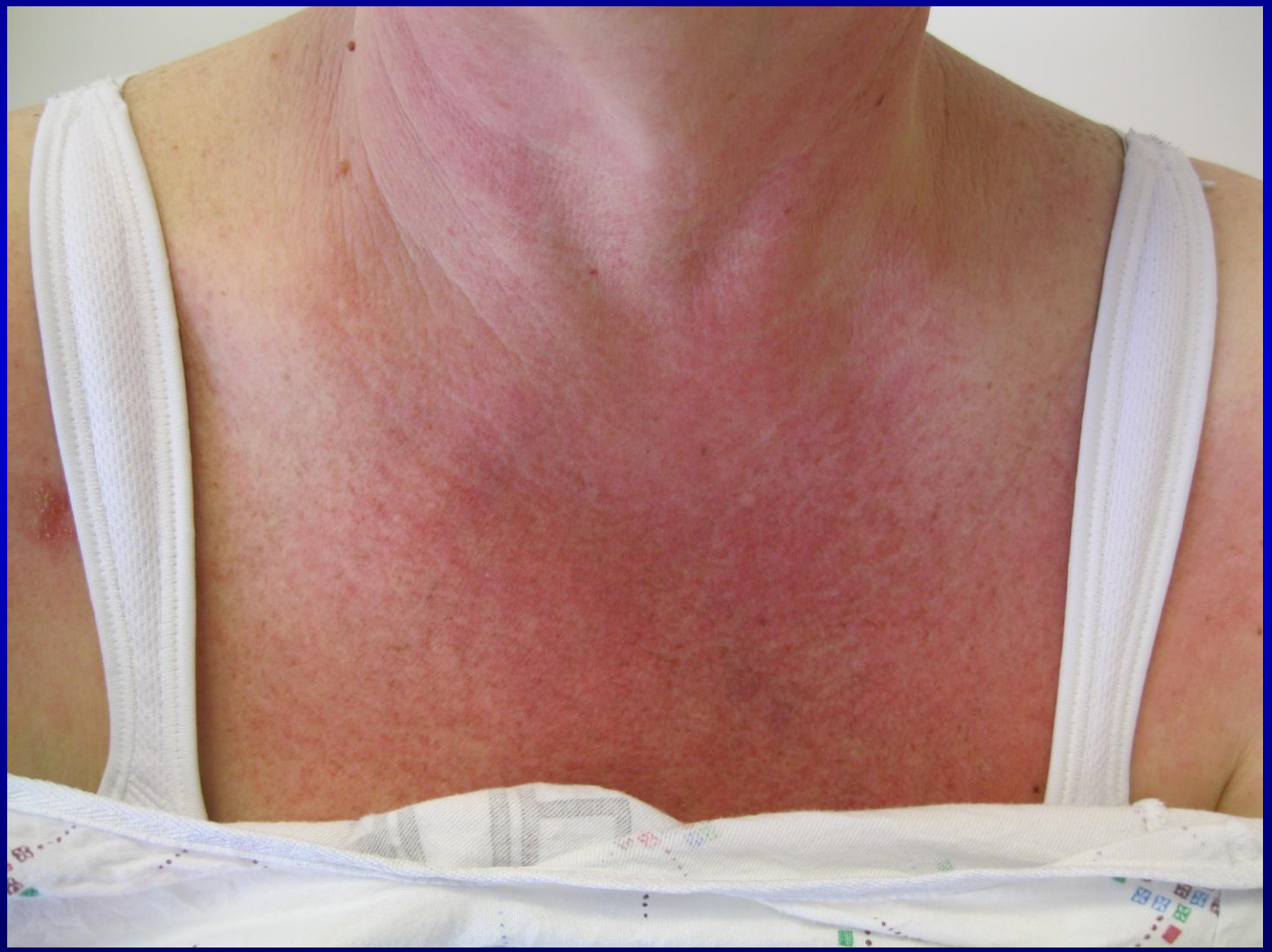
Dermatomyositis: Inflammation related to increased glycoprotein + binding partner



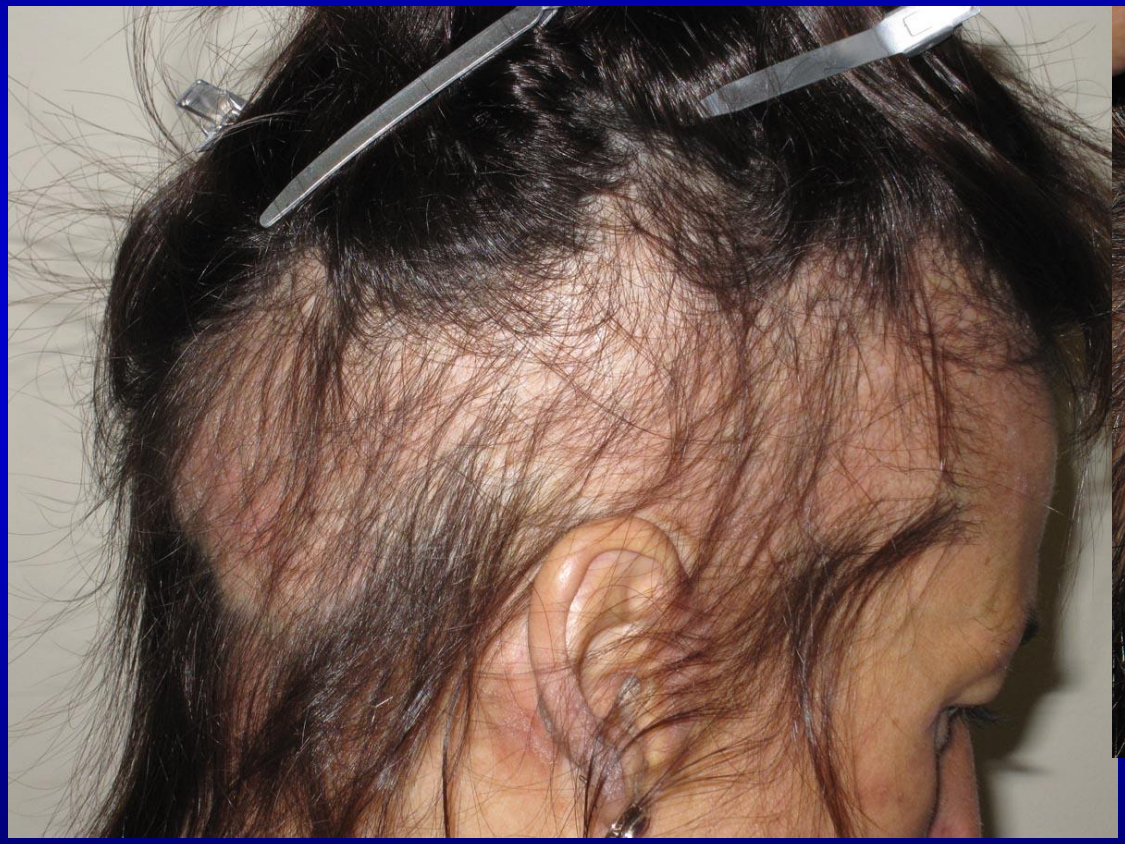


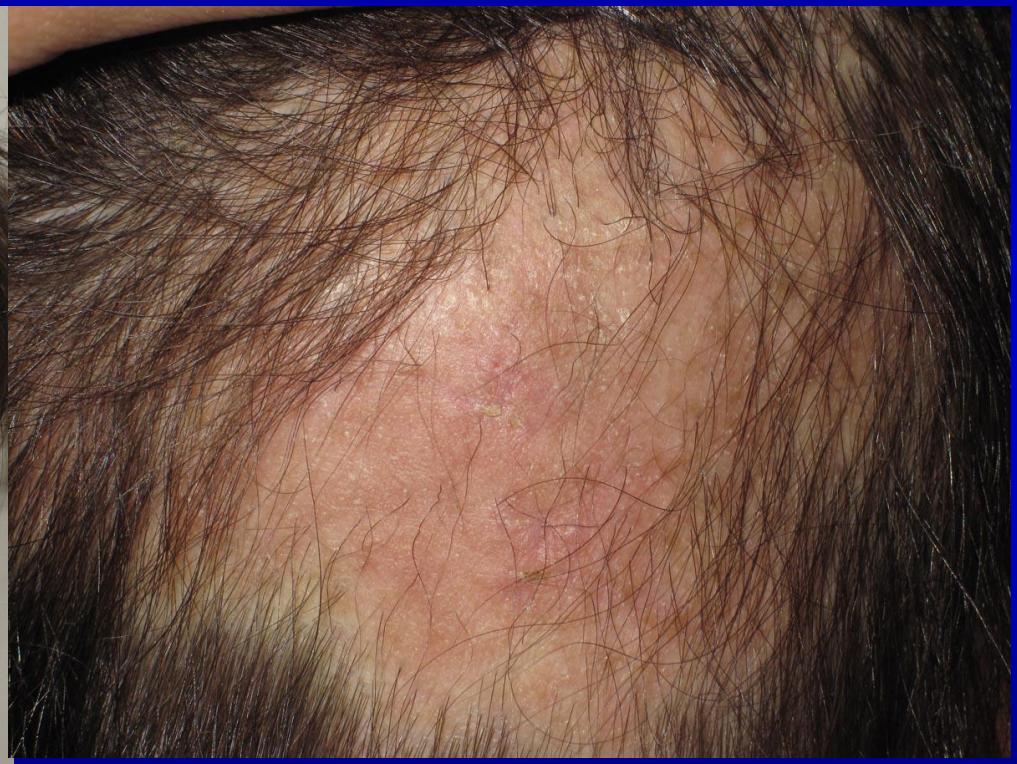
Kim and Werth J Invest Dermatol 132:1825, 2012

Dermatomyositis

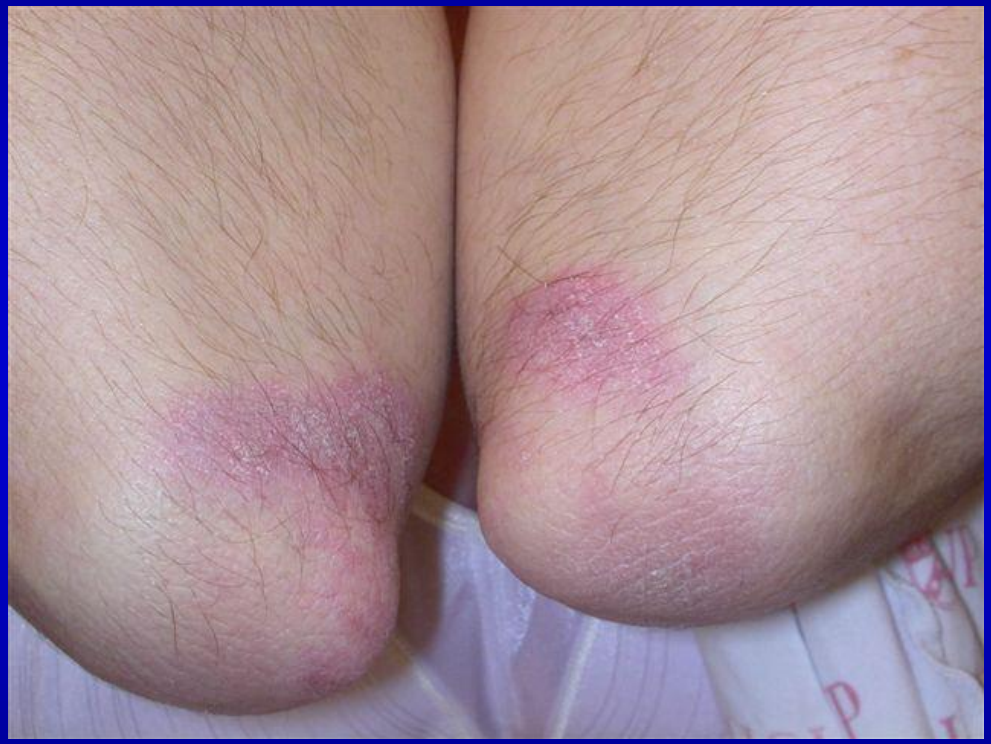


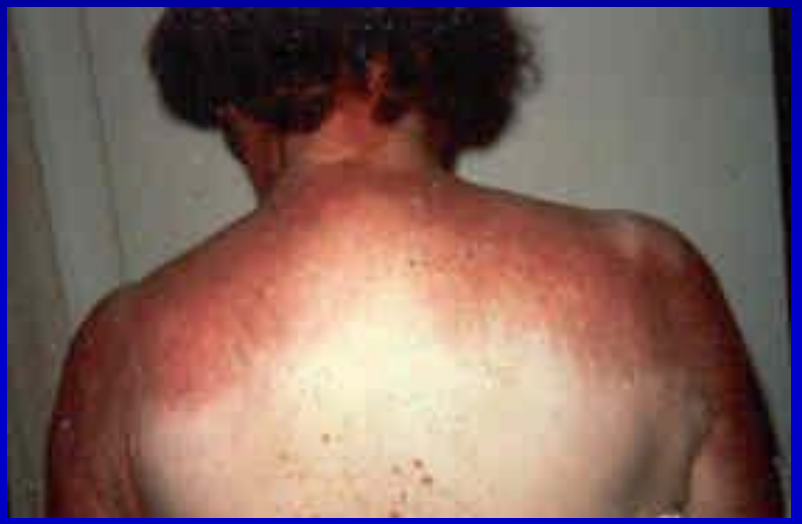
Dermatomyositis



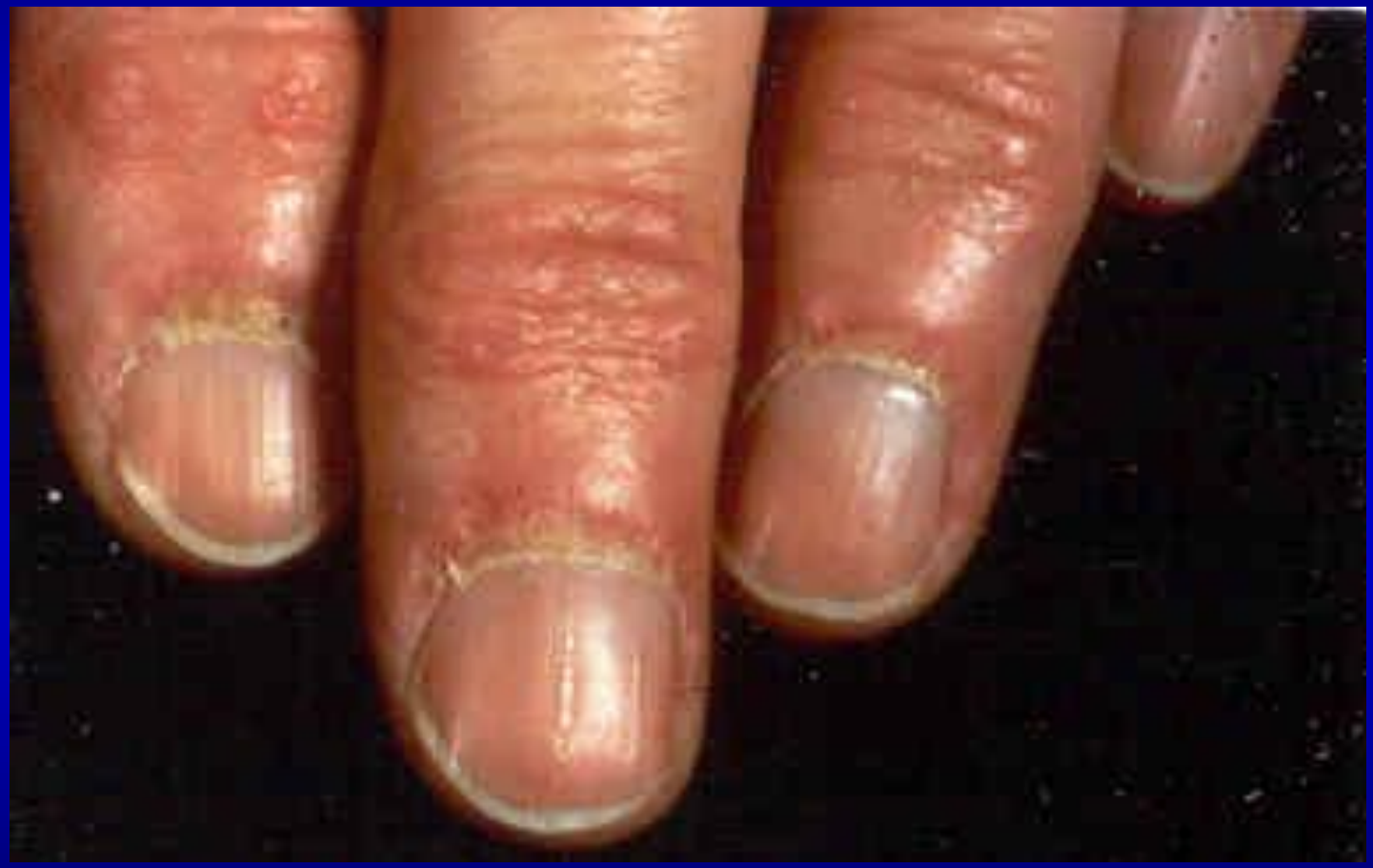


Dermatomyositis

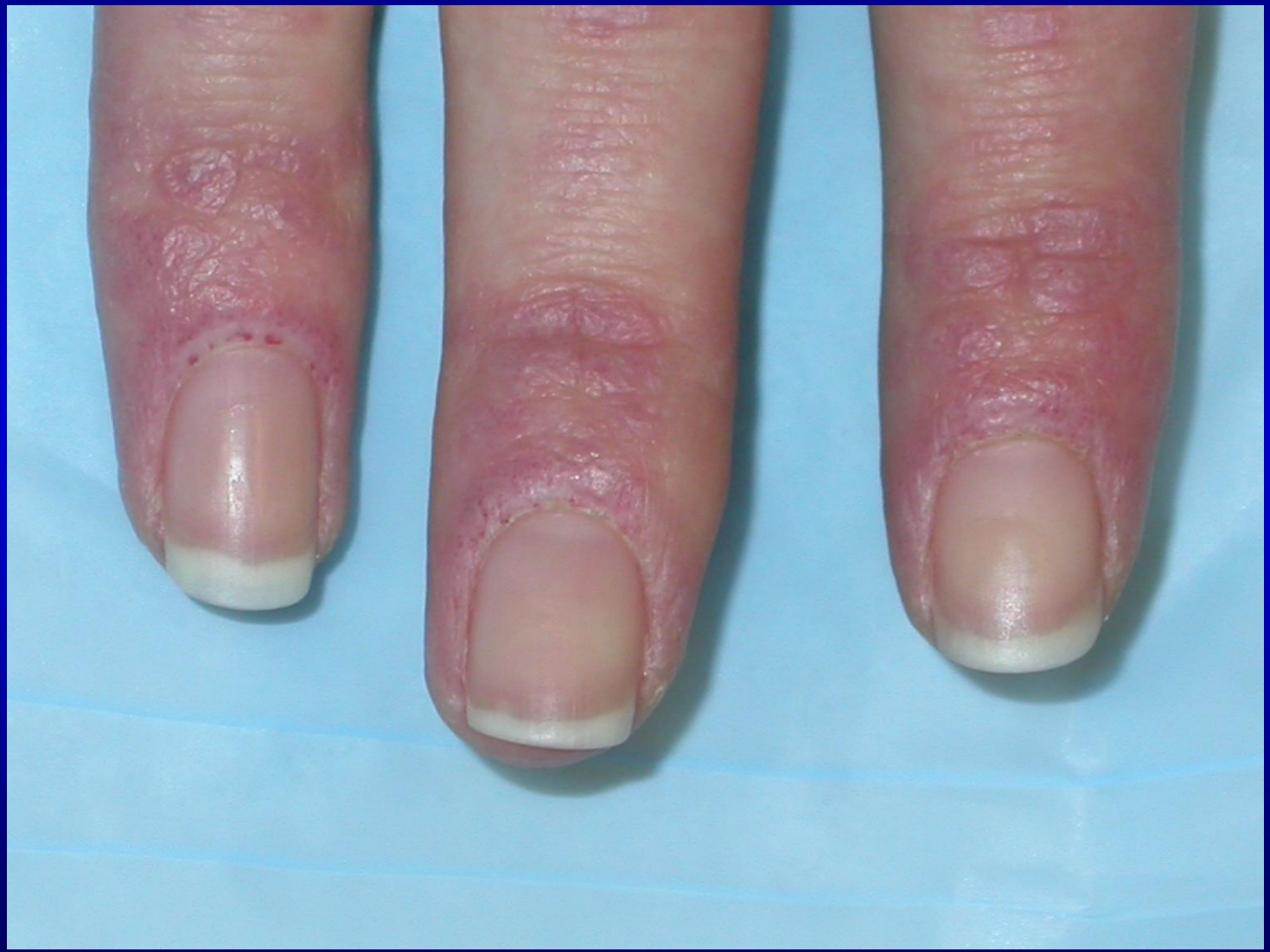




Dermatomyositis



Dermatomyositis

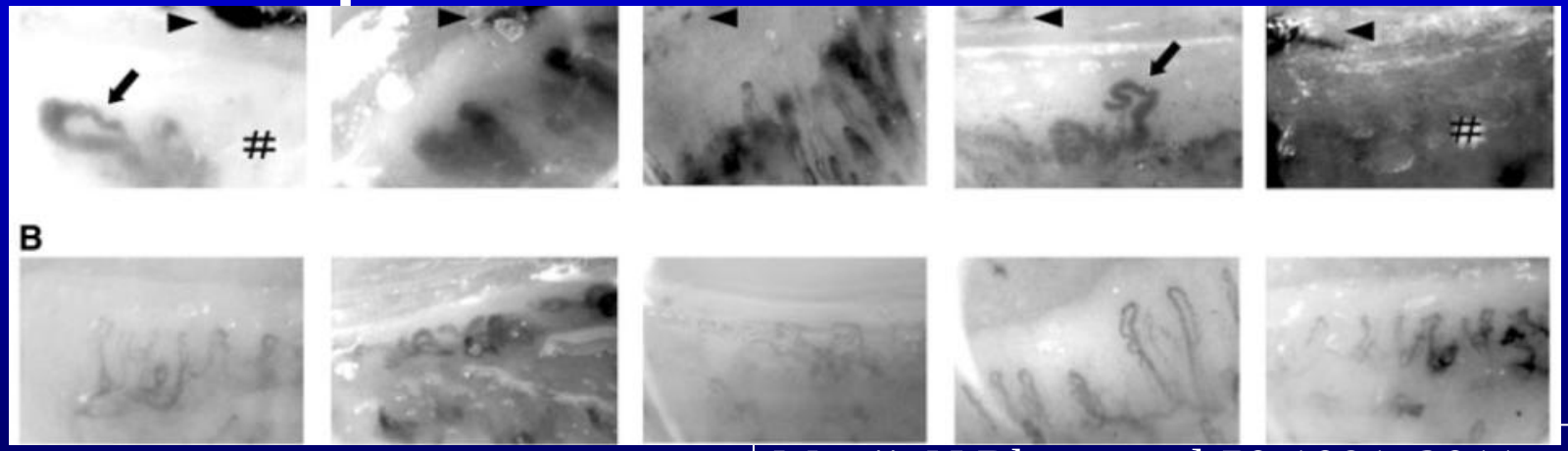


Nailfolds in Dermatomyositis

- **Loss of nailfold capillary loops has strong association with cutaneous disease activity**
  - **Hemorrhages**
  - **Irregularly enlarged capillaries**
  - **Loss of capillaries**

Before Treatment

After



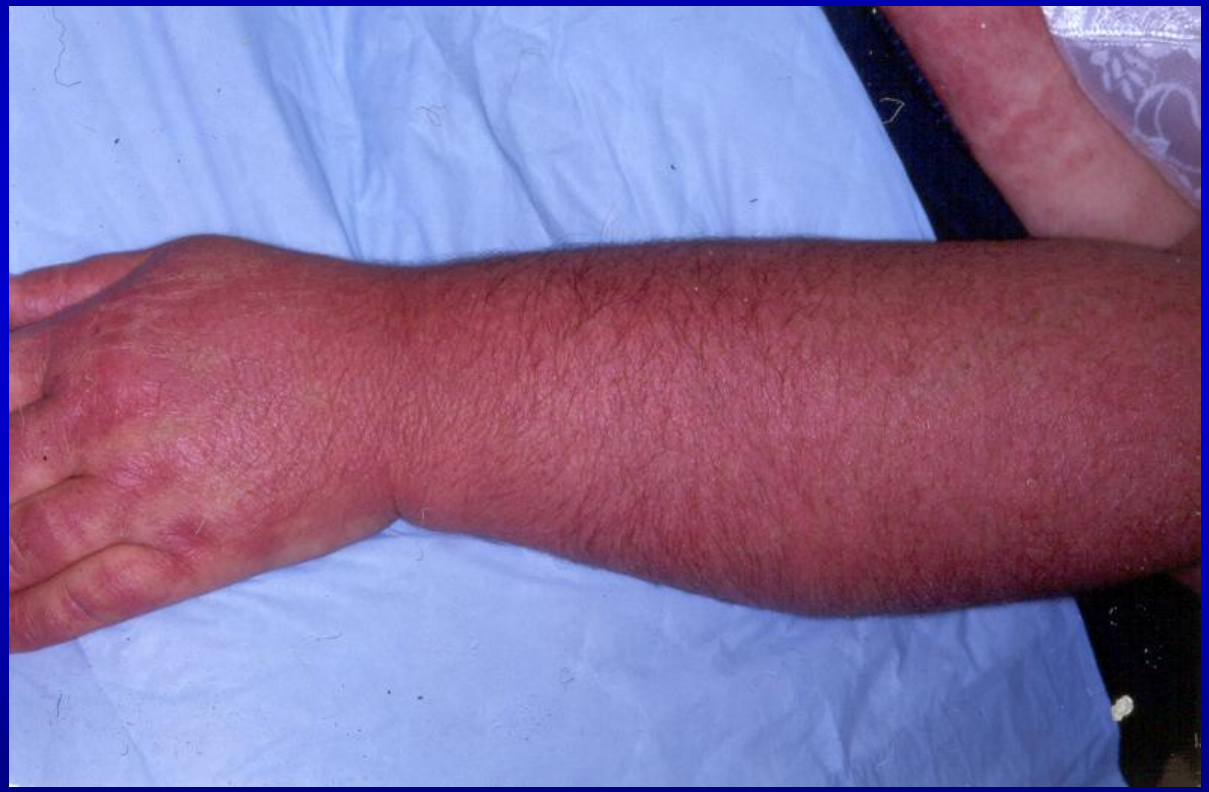
Mugii, N Rheumatol 50:1091, 2011
Schmeling H et al, Rheumatology 50:885, 2011

Antip 155/140 Antibody

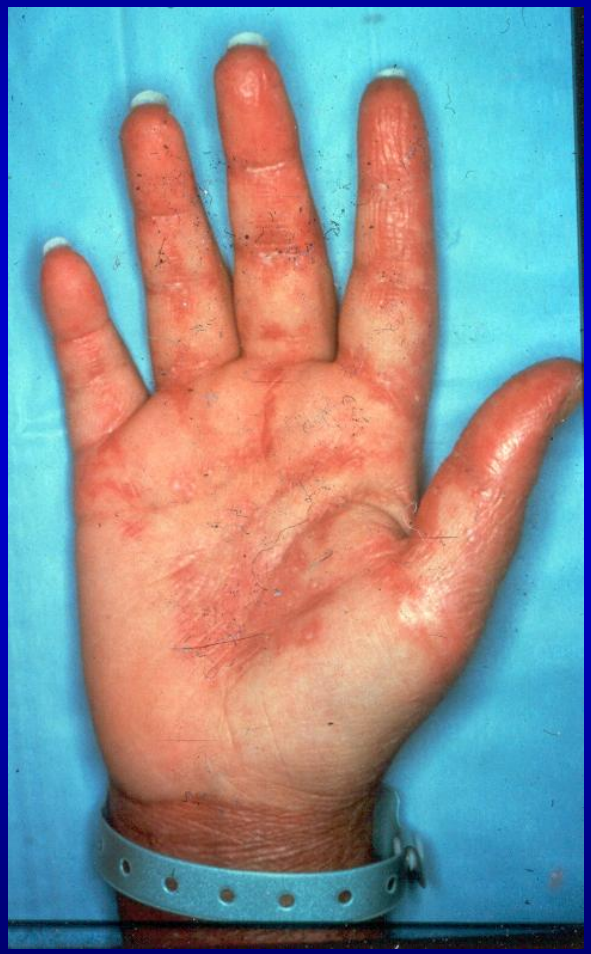
- **Poikiloderma**
- **Flagellate erythema**
- **Bullae formation**

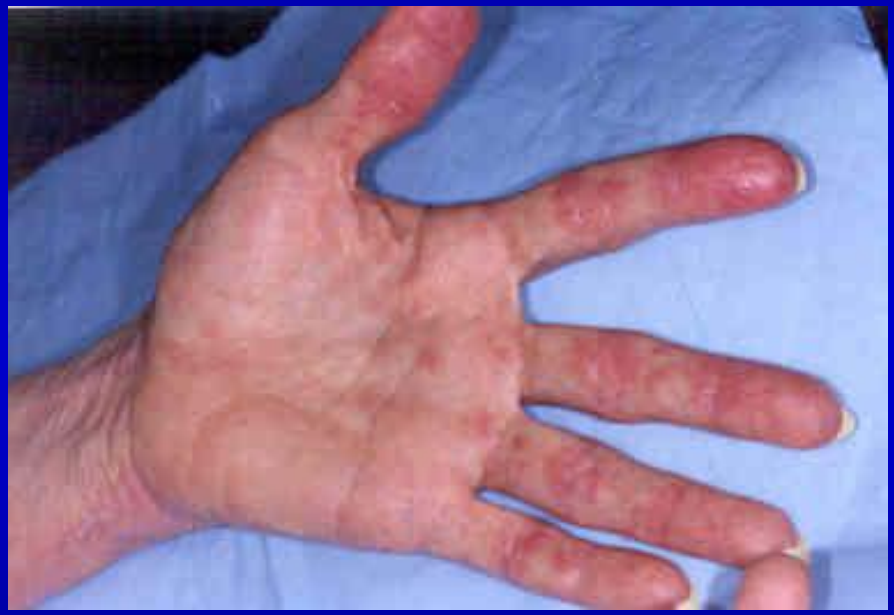
Ikeda N et al. J Dermatol 38:973, 2011

Dermatomyositis

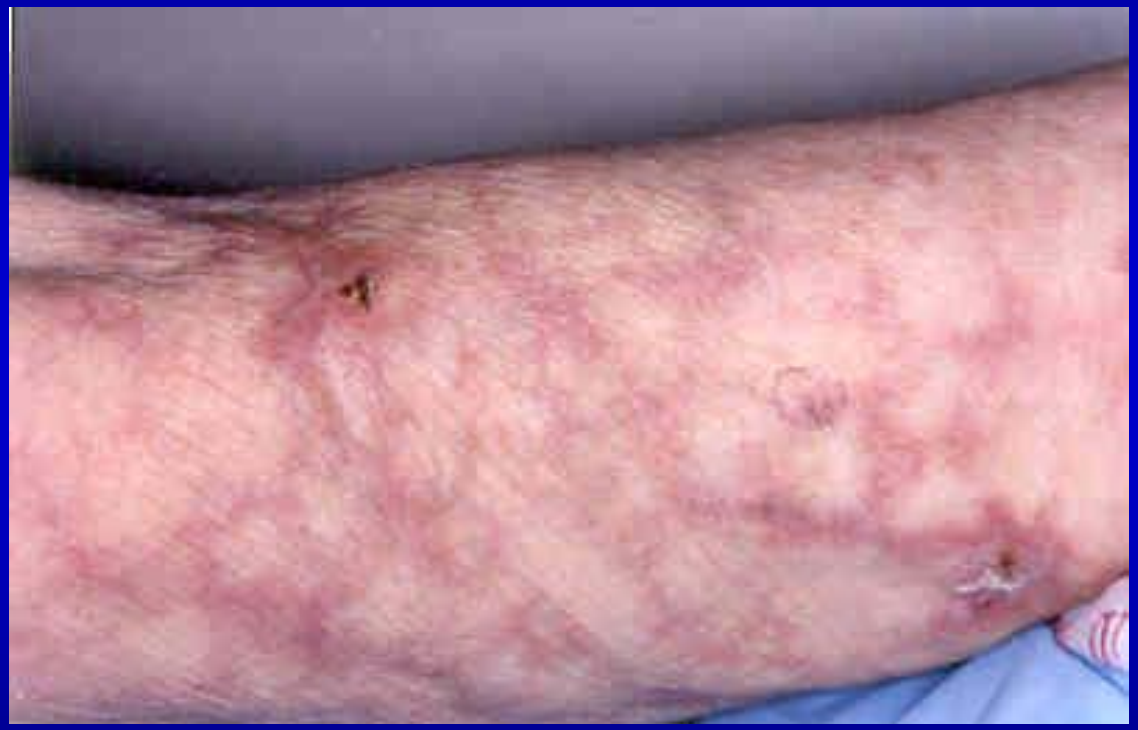


Mechanic's Hands

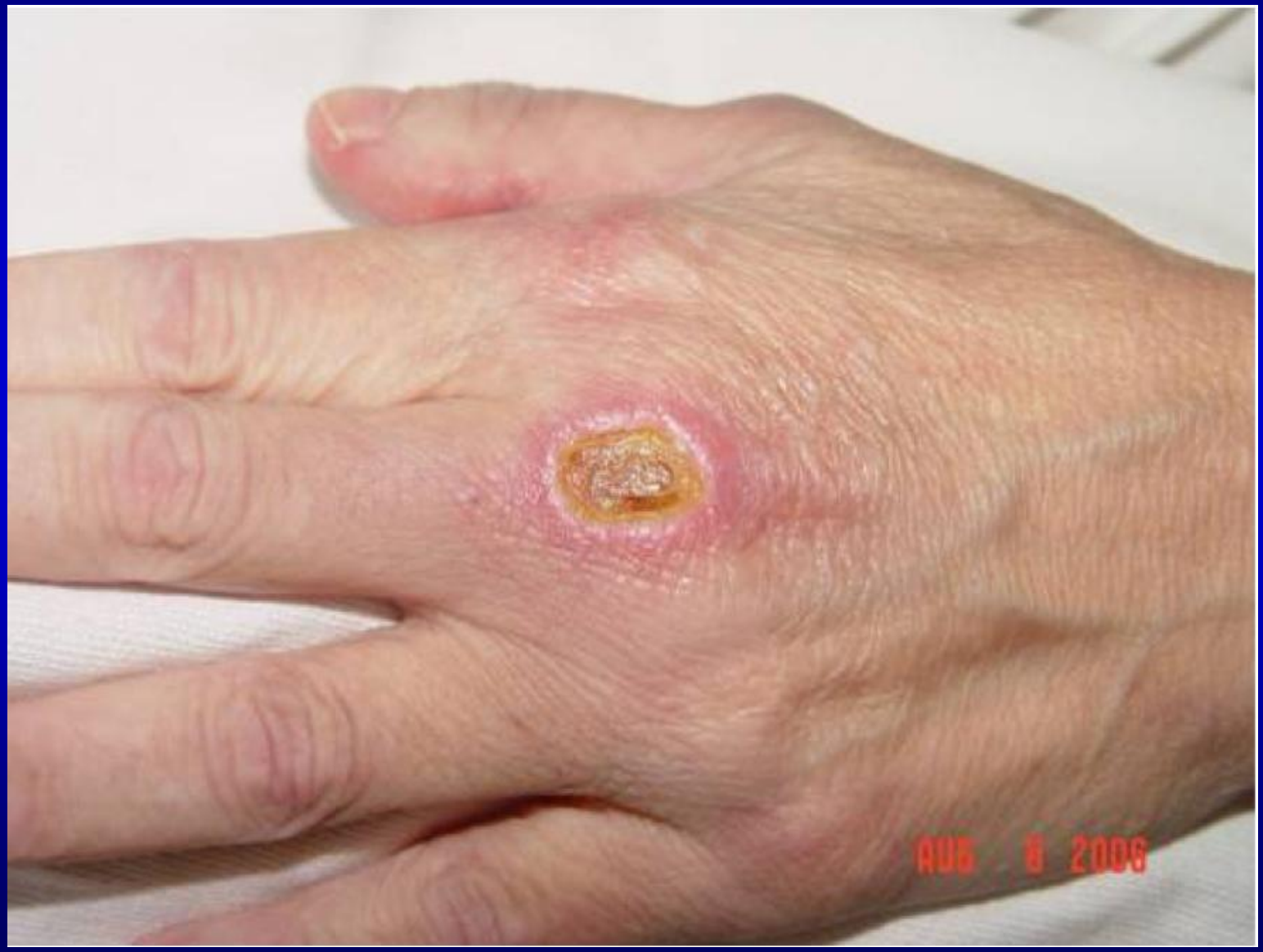




Vasculopathy



Ulcers



Classification of DM

- I. Adult Polymyositis
- II. Adult Dermatomyositis
- III. DM/PM with malignancy
- IV. Childhood DM/PM
- V. DM/PM associated with other connective tissue disease (Overlap)
- VI. Amyopathic Dermatomyositis
- VII. Inclusion Body Myositis

Diagnostic Criteria for DM (Bohan and Peter's)

- Symmetric proximal weakness with or without dysphagia or respiratory muscle involvement
- Abnormal muscle biopsy specimen
- Elevation of skeletal muscle-derived enzymes
- Abnormal electromyogram
- Typical skin rash
  - Definite DM: rash and 3 or 4 criteria
  - Probable DM: rash and 2 criteria
  - Possible DM: rash and 1 criterion

Diagnosis of DM

- Skin biopsy
- EMG or MRI
- Muscle biopsy
- Examples of myositis autoantibodies:
  - Anti-Jo-1
  - Anti-PM-1
  - Anti-Mi-2
  - CADM140
  - CADM140/155

Diagnosis of Amyopathic DM

- Typical skin changes of DM
- Lack of muscle weakness for 2 years or longer
- Normal serum muscle enzymes
- Normal electromyogram studies
- Normal MRI, P-31 magnetic resonance spectroscopy

Diagnosis of Amyopathic DM

- Problems in getting a diagnosis
- Often misdiagnosed with SLE
- SLE criteria often positive (malar rash, photosensitivity, +ANA, oral ulcers)
- Skin biopsy indistinguishable between DLE and DM
- Redoing criteria

Hypomyopathic DM

- Patients with DM-specific skin disease and no clinical evidence of muscle disease
- Subclinical evidence of myositis on laboratory, electrophysiologic, and/or radiologic evaluation

Clinically Amyopathic DM

- **Amyopathic DM and hypomyopathic DM.**
- **This designation has been coined to emphasize the fact that their predominant clinical problem is skin disease.**

Clinically Amyopathic DM

- **A population-based retrospective study of dermatomyositis**
- **Rochester Epidemiology database**
- **29 patients (1976-2007)**
- **Overall age-adjusted and sex-adjusted incidence of CADM was 2.08 per 1 million persons**
- **CADM 21% of dermatomyositis**

Bendewald, MJ et al, Arch Dermatol 146:26, 2010

Presentation of DM at University of Pennsylvania (3 years)

	Dermatology # patients	Rheumatology # patients
Classic DM	27 (32.5%)	24 (88.9%)
Amyopathic DM	33 (39.8%)	1 (3.7%)
Hypomyopathic DM	23 (27.7%)	2 (7.4%)

Quain and Werth, JAAD, 57:937, 2007

Overview

- Pathogenesis: Lichenoid tissue reactions, IFN, meds (TNF inhibitors), antibodies.
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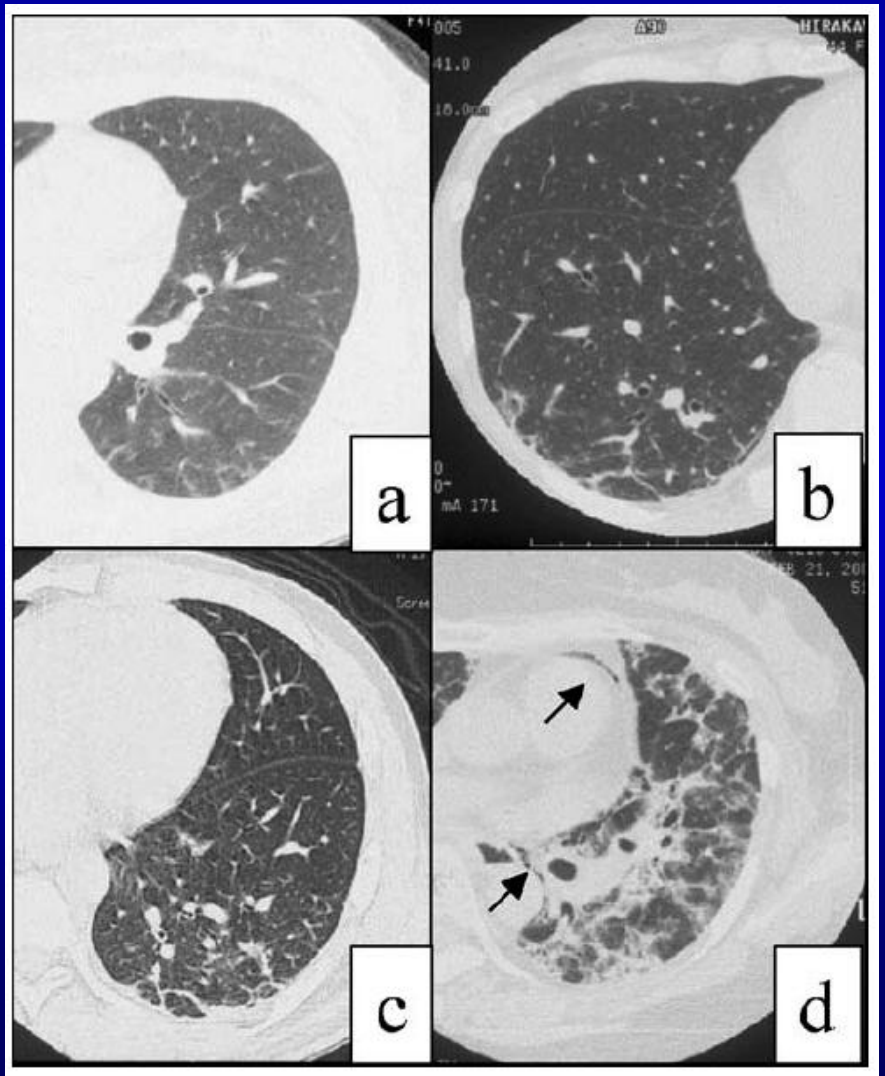
Interstitial Lung Disease with DM



Interstitial lung disease in DM

- **Prevalence of pulmonary involvement as high as 46% in PM/DM**
- **Pulmonary disorders a common cause of morbidity in PM/DM**
- **ILD may lead to life-threatening complications, i.e., ventilatory failure, secondary pulmonary arterial hypertension, or cor pulmonale**

Chen et al, Clin Rheumatol 28:639, 2009
Connors, et al. Chest 138:1464, 2010
Fathi et al, Ann Rhem Dis 63;297, 2004

Interstitial lung disease in DM

- **ILD can occur prior to, at time of onset of initial PM/DM clinical manifestations, or after onset.**
- **Subset with rapidly progressive disease associated with high mortality**
- **Others with indolent or slowly progressive course**
- **Can regress with treatment (steroids, immunosuppressives)**

Predictors of poor outcome of ILD in DM

- Worse PFTs initially and at follow-up
- Symptomatic: cough, dyspnea
- UIP pattern
- Steroid-refractory

ILD in CADM (11) vs Classic DM (13) in Japan

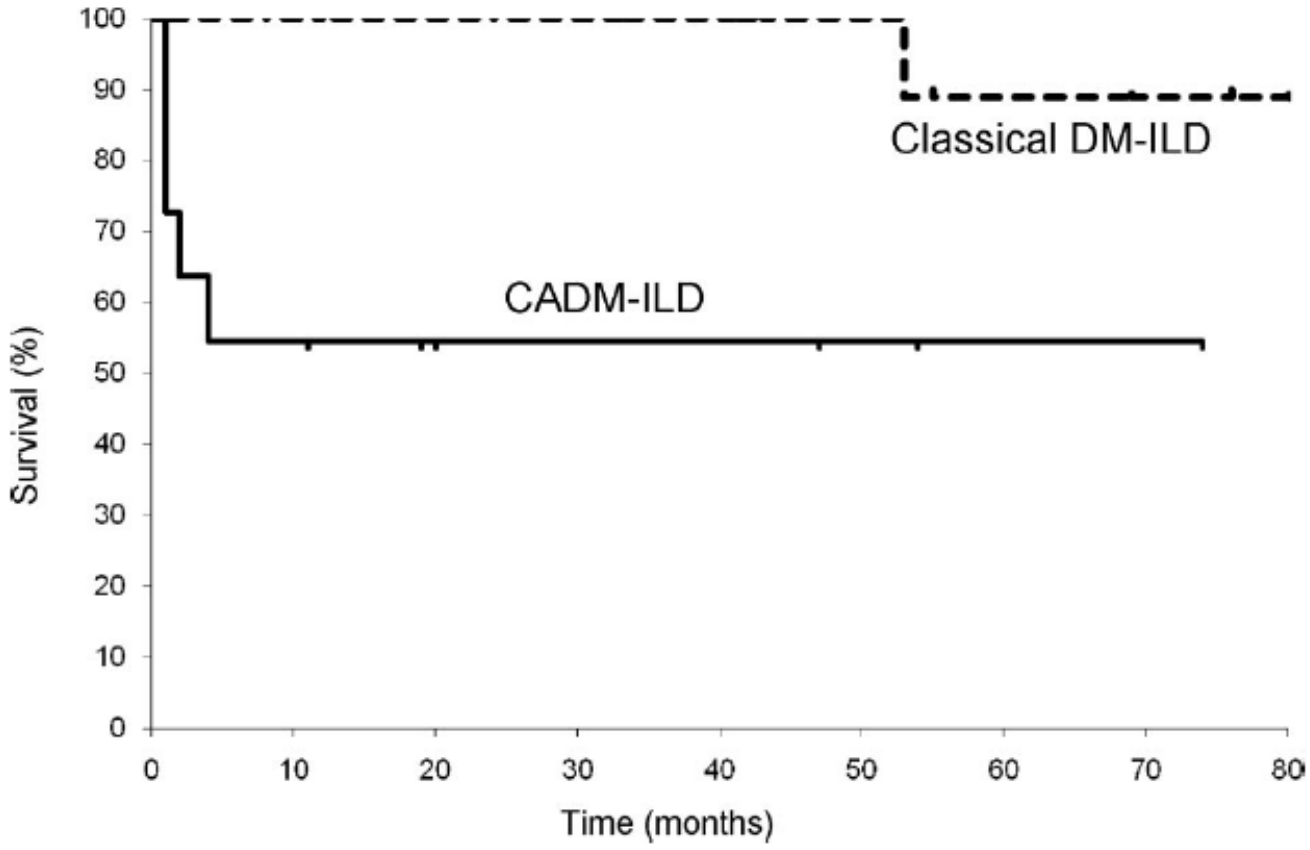


FIGURE 3. Overall survival curves of patients with CADM-ILD and classic DM-ILD. Time indicates the number of months since the onset of respiratory or skin symptoms.

Mukae H et al, Chest 136:1341, 2009)

CADM-140 Antibodies DM

- **140-kDa [RNA helicase, melanoma differentiation-associated gene 5 (MDA-5); IFN induced with helicase C domain protein 1 (IFIH1)]**
- **Anti-CADM-140 autoantibodies significantly associated with CADM**

Sato S et al, Arthritis Rheum 60:2193, 2009
Hamaguchi Y et al, Arch Dermatol 147:391, 2011

CADM-140 Antibodies DM

- **More rapidly progressive interstitial lung disease (ILD) when compared with patients without anti-CADM-140 autoantibodies (50% versus 6%; P = 0.008)**

Sato S et al, Arthritis Rheum 60:2193, 2009
Hamaguchi Y et al, Arch Dermatol 147:391, 2011

ILD in DM at University of Pennsylvania (3 years)

ILD	Classic DM	Amyopathic DM	Hypomyopathic DM
Present	23 (40%)	9 (26%)	11 (44%)
Absent	35 (60%)	26 (74%)	14 (56%)

P=0.27

Quain and Werth, JAAD, 57:937, 2007

ILD in DM

- **Patients with lower initial DLCO values have a higher prevalence of ILD**
- **Patients with normal initial DLCO may have a decrease in DLCO over time and may develop interstitial lung disease**
- **All patients should be screened with serial DLCO**
- **Other testing (HRCT, echocardiography) and need for pulmonary referral may be based on DLCO result**

Morganroth et al, Arch Derm 146:729, 2010

Overview

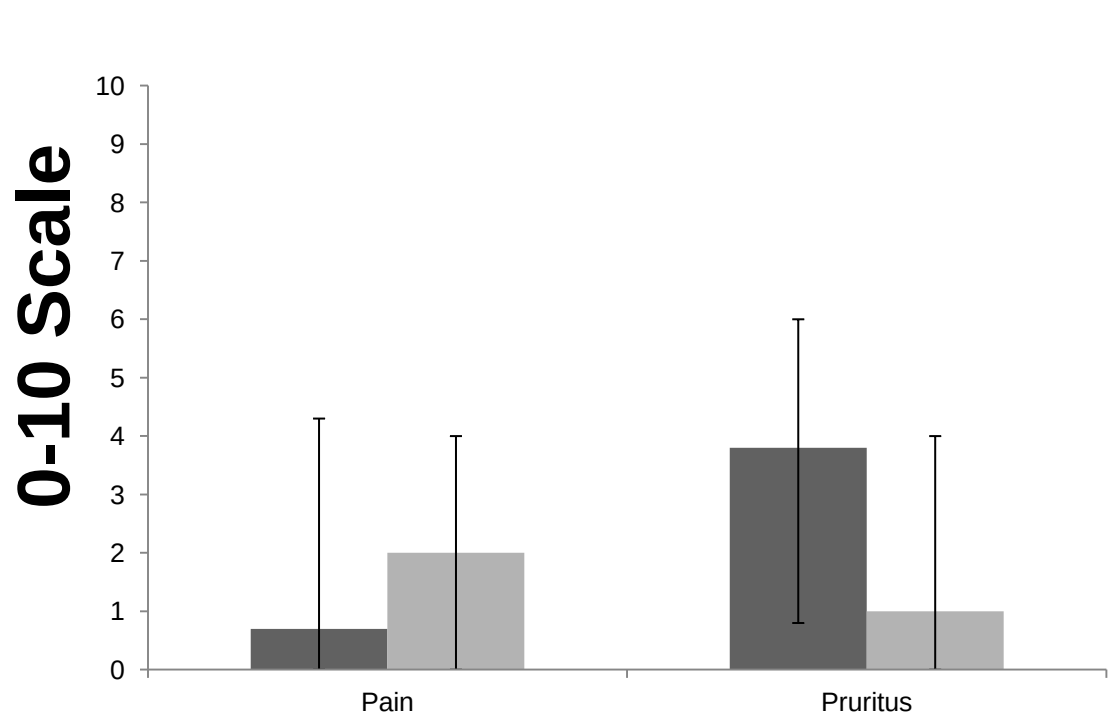
- Pathogenesis: Lichenoid tissue reactions, IFN, meds (TNF inhibitors), antibodies.
- Clinical Findings
- Lung Disease in DM
- Quality of Life in DM
- Treatment

QoL DM (SF-36)

- **QoL in DM worse than other diseases (Recent MI, HTN, type II diabetes)**
- **Particularly true in the emotional realm (vitality, social functioning, role-emotional, mental health)**

Goreshi et al, J Am Acad Dermatol 65:1107, 2011

Median Pain and Pruritus Scores in DM and CLE



Pruritus: p<0.0001

Pain: p=0.9743

Goreshi et al, J Am Acad Dermatol 65:1107-1116, 2011

Overview

- **Pathogenesis: Lichenoid tissue reactions, IFN, meds (TNF inhibitors), antibodies.**
- **Clinical Findings**
- **Lung Disease in DM**
- **Quality of Life in DM**
- **Work-up and Treatment**

Relationship of DM to malignancy

- **Population-based retrospective study of 537 patients with biopsy-positive idiopathic inflammatory myopathy**
- **Childhood myositis (4%)**
- **Polymyositis [18%, SIR 2.0 (CI 1.4-2.7)]**
- **Dermatomyositis [(42%, SIR 6.2 (CI 3.9-10)]**

Buchbinder et al, Ann Int Med 134:1087,2001

Relationship of DM to malignancy

- **Adjusted relative risk for malignant disease was higher in the first 3 years after dagnosis of myositis than at any later time**
- **Risk still increased 5 years after diagnosis [1.2 (0.5-2.5]**
- **Relative risk for malignant disease in DM 2.4 (CI 1.3-4.2) relative to polymyositis**

Buchbinder et al, Ann Int Med 134:1087,2001

Relationship of DM to malignancy

- **Lung (SIR 5.9, 3.7-9.2)**
- **Ovary (SIR 10.5, 6.1-18.1)**
- **Pancreatic (SIR 3.8, 1.6-9.0)**
- **Stomach (3.5,1.7-7.3)**
- **Colorectal (2.5, 1.4-4.4)**
- **Non-Hodgkin lymphoma (3.7, 1.7-8.2)**

Hill et al, Lancet 357:96, 2001

Work-up and Follow-up of DM

- Screen for malignancies where early detection and treatment improve patient outcome
- Occult blood in stool
- Tumor markers?
- Mammography
- Chest x-ray
- Pap smear

Work-up and Follow-up of DM

- High resolution Chest CT
- Abdominal ultrasound or CT
- Pelvic CT or ultrasound

- Maintain vigilance since risk remains high for years
- Re-evaluate for internal malignancy every 6-12 months after diagnosis for 2-5 years

Evidence for Systemic therapy

- Almost no prospective double-blinded randomized controlled trials
- Evidence poor for use of therapies
  - Expert opinion
  - Case series, usually retrospective
- Partially validated outcome measure should advance level of evidence

CDASI

- Klein RQ, Br J Dermatol. 2008;159:887-94.
- Yassaee M, Br J Dermatol. 2010;162:669-73.
- Goreshi R, et al. J Invest Dermatol. 2011.

Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) *ver02*

Select the score in each anatomical location that describes the most severely affected dermatomyositis-associated skin lesion

activity ⟵ | damage ⟶

Extent

Anatomical Location	Erythema	Scale	Excoriation/Ulceration	Poikiloderma (Dyspigmentation or Telangiectasia)	Calcinosis	Anatomical Location
	0-absent 1-pink, faint erythema 2-red 3-dark red	0-absent 1-scale 2-crust, hyperkeratosis	0-absent 1-present	0-absent 1-present	0-absent 1-present	
Scalp						Scalp
Malar, Nose						Malar, Nose
Periorbital						Periorbital
Rest of the face						Rest of the face
V-area neck (Frontal)						V-area neck (Frontal)
Posterior Neck						Posterior Neck
Upper Back & Shoulders						Upper Back & Shoulders
Rest of Back & Buttocks						Rest of Back & Buttocks
Abdomen						Abdomen
Lateral Upper Thigh						Lateral Upper Thigh
Rest of Leg & Feet						Rest of Leg & Feet
Arm						Arm
Mechanic's Hand						Mechanic's Hand
Dorsum of Hands (not over joints)						Dorsum of Hands (not over joints)
Gottron's – Not on Hands						Gottron's – Not on Hands

Gottron's – Hands

Examine patient's hands and double score if papules are present		Ulceration	Examine patient's hands and score if damage is present	
0-absent 1-pink, faint erythema 2-red erythema 3-dark red			0-absent 1-dyspigmentation 2-scarring	

Periungual

Periungual changes (examine)			
0-absent 1-pink/red erythematous microscopic telangiectasias 2-visible telangiectasias			

Alopecia

Recent Hair loss (within last 90 days as reported by patient)			
0-absent 1-present			

Total Activity Score
(For the activity score, please add up the scores of the left side, i.e. Erythema, Scale, Excoriation, Ulceration, Gottron's, Periungual, Alopecia)

Total Damage Score
(For the damage score, add up the scores of the right side, i.e. Poikiloderma, Calcinosis)

Dermatomyositis

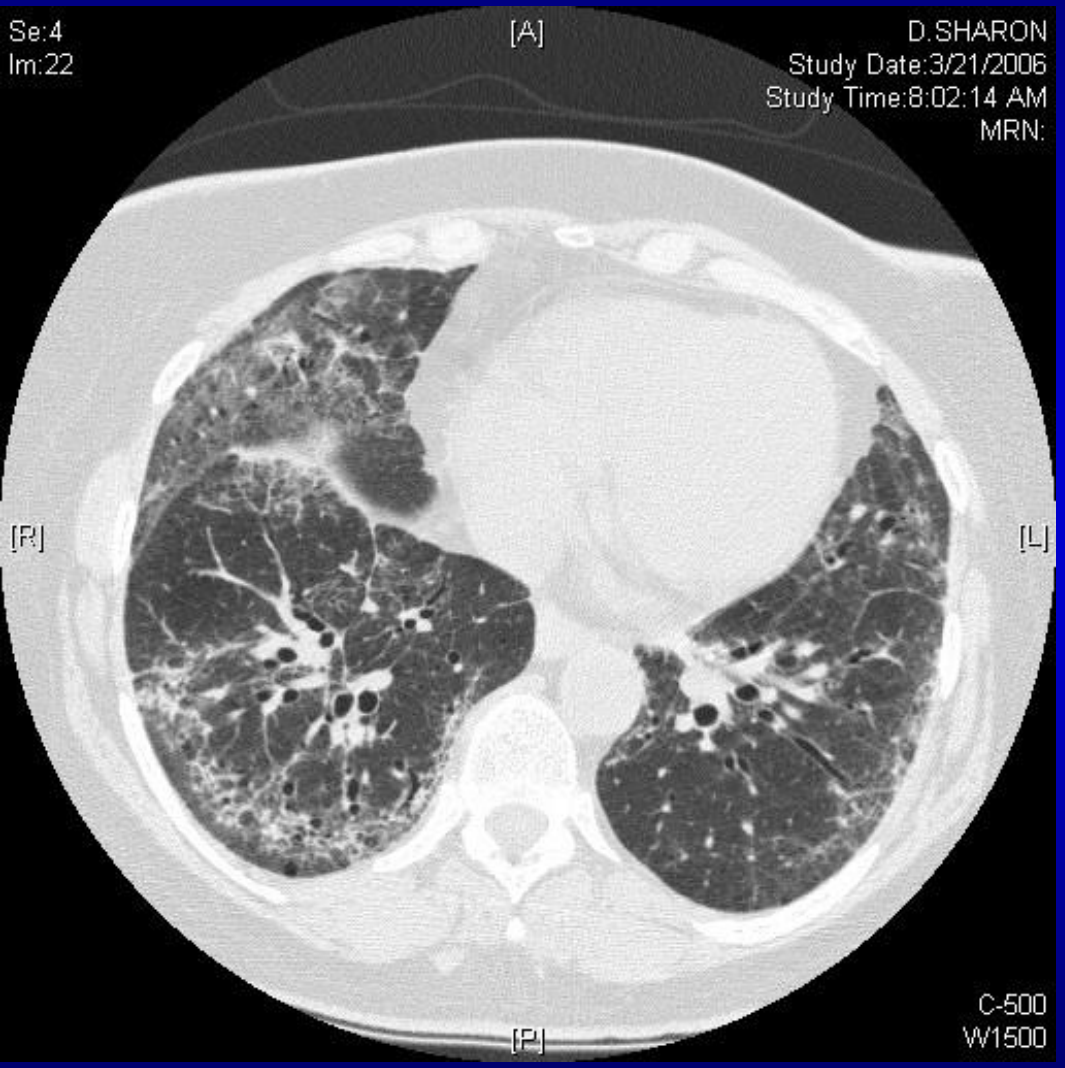
- Therapy determined by whether there is underlying muscle or pulmonary disease
- Interstititial lung disease in 25% of patients with amyopathic dermatomyositis (steroids ± Mycophenolate mofetil or Cyclophosphamide)
- Muscle disease must be treated differently (steroids, immunosuppressives, IVIG, ?Rituximab)
- "More research is needed to investigate the efficacy of immunosuppressant and immunomodulatory agents in DM" *(Choy et al, Cochrane Rev, 2007)*

Outcome of ILD

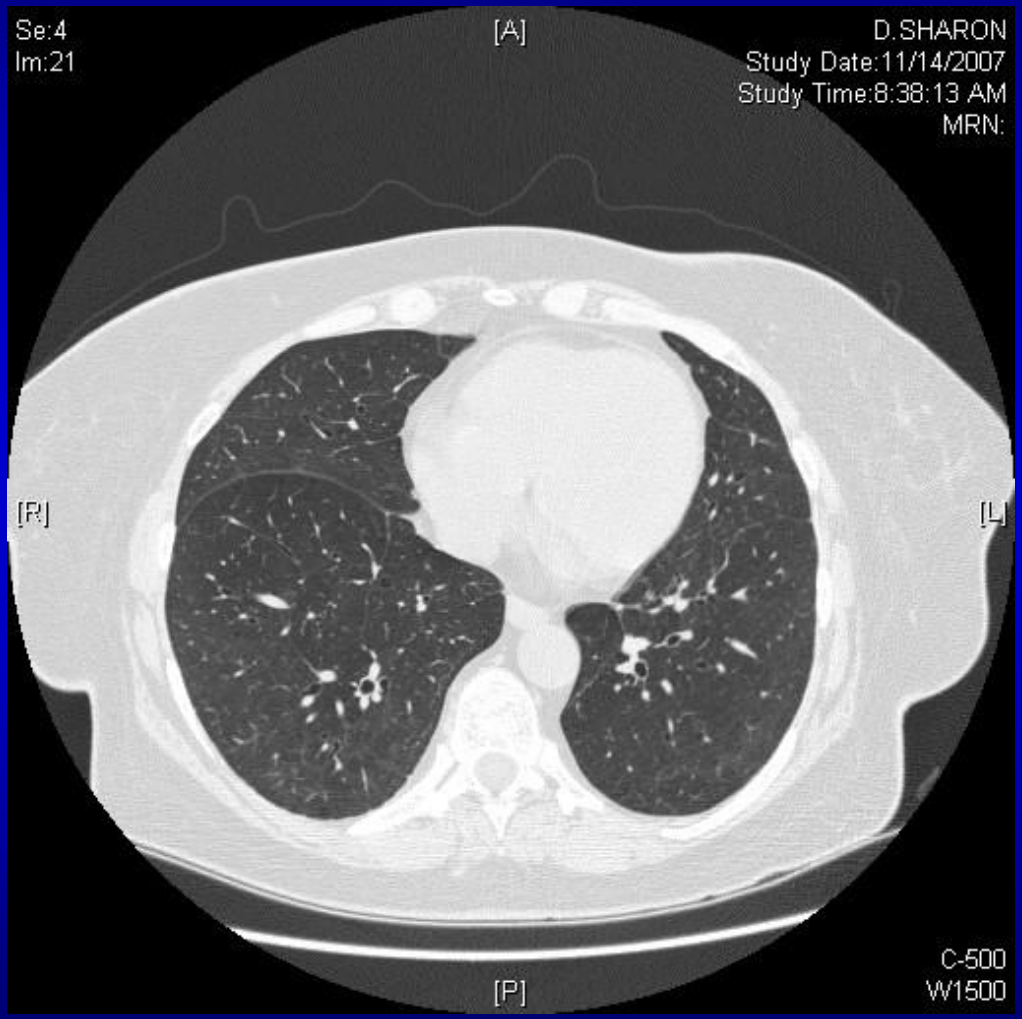
- 16 DM patients with ILD in 3 years
- 4 treated with Mycophenolate mofetil and had PFT data available
- 3 f/u for at least 1 year
- All 3 with normalization of PFTs and resolution of dyspnea
- Patient with pre- and post-treatment high resolution CTs had total resolution of interstitial opacities

Morganroth et al, Arthritis Care & Res, in press

ILD



Before CellCept



After CellCept

Treatment of amyopathic DM

- **First Line Therapies**
  - **Sunscreens**
  - **Topical Steroids**
  - **Intralesional Steroids**
  - **Elidil or Protopic**
  - **Antimalarials (Hydroxychloroquine, Quinacrine, Chloroquine)**

Sunscreens and Dermatomyositis

- Sunscreens
  - UVB #30 or greater
  - Mexoryl
  - Helioplex
  - Physical Blockers (Titanium, Zn Oxide)

Dermatomyositis: Skin

- Second-line therapies
  - Immunosuppressives (Methotrexate, Mycophenolate mofetil, Azathioprine, Cyclosporine, Tacrolimus)
  - Gluocorticoids
  - Thalidomide
  - IVIG

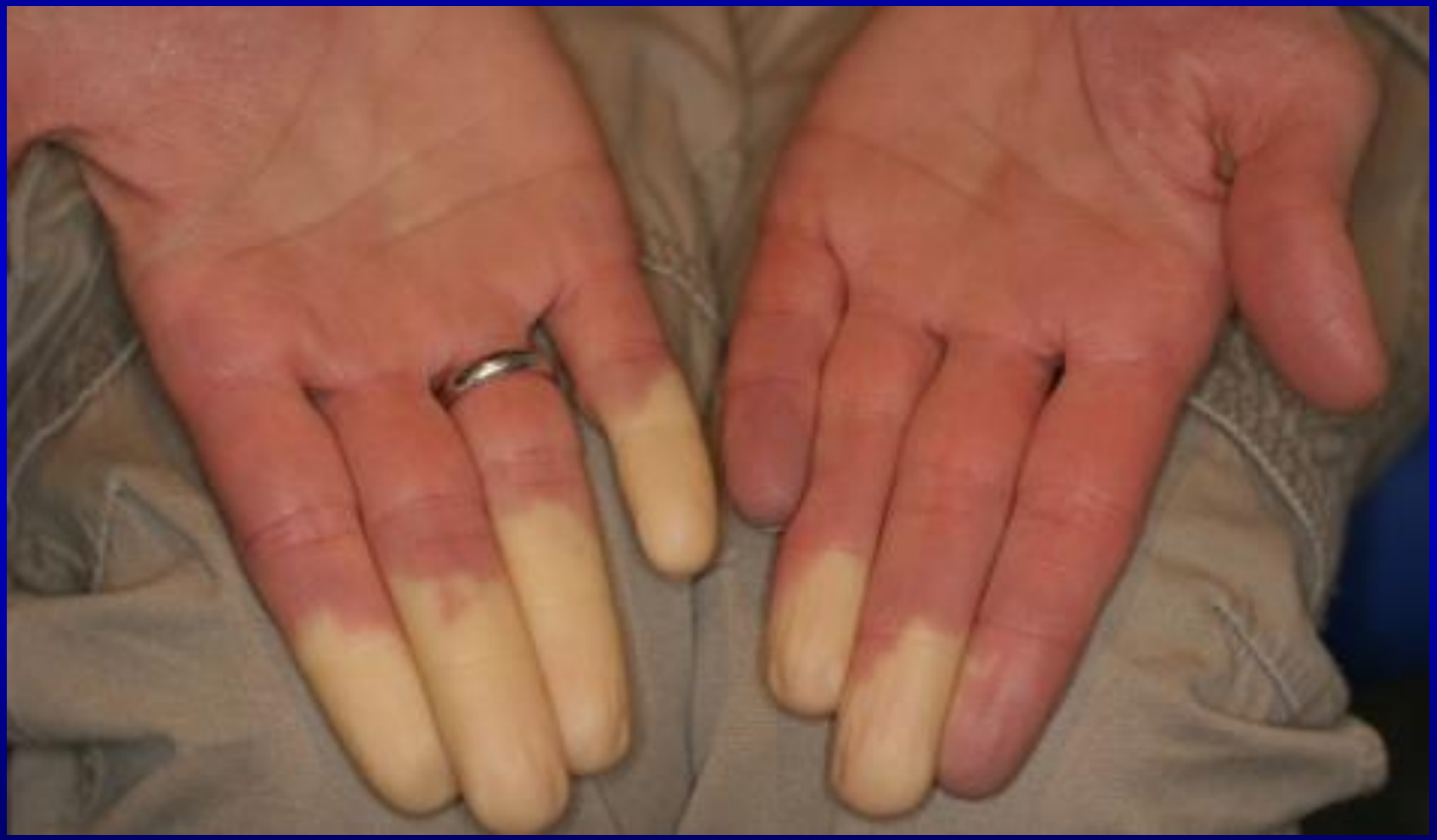
Side Effects of Plaquenil/Chloroquine

- Retinopathy
- Cardiomyopathy (CHF, heart block, restrictive cardiomyopathy)
- Myopathy-proximal muscle weakness
- Nausea, diarrhea
- Psychosis
- Hypo- and Hyperpigmentation
- Exanthem, hives

Experimental Therapies in Dermatomyositis

- **B cell directed therapy**
  - **Anti-CD20 (Some evidence that may help muscle, not skin)** *(Dinh et al, JAAD 56:148, 2007; Chung et al, Arch Dermatol 143:763, 2007)*
- **Cytokine inhibitors**
  - **Anti-TNFα: May actually induce/exacerbate DM** *(Hengstman et al, Eur Neurol 50:10, 2003; Efthimiou et al, Ann Rheum Dis, 2006)*
  - **Anti-interferon-α**

Raynaud's Phenomenon



Raynaud's Phenomenon

- Digital pain
- sequential pallor, cyanosis, rubor
- Acral ulceration less common

- Primary
- Secondary: underlying disease process, such as scleroderma, lupus, or dermatomyositis

Raynaud's Phenomenon

- Endothelial dysfunction and vascular remodelling
  - Tissue ischemia
  - Digital ulcers
- Can occur in dermatomyositis, but more common in Systemic sclerosis
- Spasm of vessels intermittently
- Can cause ulcers, infection, ischemia or gangrene

Raynaud's Phenomenon

- **Nailfold capillaroscopy: dilated proximal nailfold in Raynaud's associated with autoimmune disease**

Treatment of Raynaud's Phenomenon

- Calcium Channel blockers
  - Nifedipine 10-30 mg tid or 30-90 mg/ day in SR
  - Amlodipine 5-10 mg a day
  - Diltiazem 30-120 mg tid
- Angiotensin II Receptor Blockers
  - Losartan 50 mg/day
- ACE inhibitors
  - Captopril 6.5-25 mg tid
- Alpha-adrenergic blocker
  - Prazosin 1-5 mg bid

Treatment of Raynaud's Phenomenon

- Topical nitrates
- Prostacyclin and prostacyclin analogs (intravenously)
  - Variable effectiveness
  - Significant adverse effects
- Sildenafil and other phosphodiesterase type V inhibitors [1]
- Endothelin Receptor antagonists
  - Bosentan 62.5-125 mg bid

[1] Herrick AL et al, Arthritis.Rheum 63:775, 2011

Treatment of Raynaud's Phenomenon

- Anti-platelet agents: aspirin, clopidrogel
- Low molecular weight heparin and tissue plasminogen acivator
- Pentoxyfilline
- Local anaesthetic blocks and digital sympathectomy

Treatment of Raynaud's Phenomenon with Botulinum Toxin

- **Blocks vascular smooth muscle depolarization and vasoconstriction**
- **Blockade of central nervous stimuli for vasoconstriction**

Treatment of Raynaud's Phenomenon with Botulinum Toxin

- Blocks trasmission of norepinephrine vesicle, prevention sympathetic vasconstriction of the vascular smooth muscle
- Blocks recruitment of specific alpha 2c-adrenoreceptor, which decreases the activity of chronically upregulated C-fiber nociceptors
- Subsequent reduction in cold-induced vascular smooth muscle constriction and pain

Iorio ML et al, Botulinum Toxin A treatment of raynaud's phenomenon. Semin Arthritis Rheum 41:599-603, 2012

Treatment of Raynaud's Phenomenon with Botulinum Toxin

- 10 units botulinum toxin A on each neurovascar bundle at the level of the MCP flexion crease
- 33 patients
- 28/33 with reduced pain
- Tissue perfusion changes 48% -317 %, using laser Doppler perfusion

Neumeister MW. J Hand Surg Am 35:2085, 2010