Dermatomyositis

Advice from Experts: Improving Your Medical Dermatology Diagnostic and Management Skills

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University of Louisville
Learning Objectives

• Following this lecture, the attendee will be able to:
  – Diagnose dermatomyositis and differentiate it from lupus erythematosus
  – Construct an evaluation for the patient with dermatomyositis
  – Manage cutaneous dermatomyositis more effectively
Introduction

- Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM)
- Bohan & Peter* suggested 5 criteria:
  - Progressive, proximal, symmetrical weakness
  - Elevated muscle enzymes
  - Abnormal EMG
  - Abnormal Muscle biopsy
  - Compatible skin disease
- DM and PM are probably different diseases

Relationship between the skin & systemic disease

• ADM – patients with typical lesions of DM that are not weak and have normal muscle enzymes for at least 2 years in the absence of therapy
• With MR, ultrasound, EMG, or biopsy some of these patients do have definable muscle disease (?hypomyopathic DM)
• Some patients have DM and with treatment their myositis is controlled, and their skin disease remains active
Diagnosis of Amyopathic DM

• Required
  – Typical skin lesions of DM
  – Lack of muscle weakness for 2 years or longer
  – Normal serum muscle enzymes

• Possibly required in the future
  – Normal EMG
  – Normal MRI, P-31 MRS
Exclusion criteria for ADM

- Treatment with systemic immunosuppressives for 2 consecutive months or longer with the first 6 months after onset of the skin disease
- Use of drugs known to be capable of producing DM-like lesions
  - Hydroxyurea
  - Lipid lowering agents
  - TNF antagonists
Dermatomyositis

Infections
- Trypanosoma cruzi
- Coxsackie
- Parvovirus B19
- Echo
- Influenza
- HIV
- HTLV-I

Environmental factors
- UV

Medications
- Cimetidine
- Chloroquine
- Colchicine
- Statins
- Steroids
- Fibrates
- Nicotinic acid

Genetic factors
- HLA DRB1*0301
- DQA1*0501
- DRB1*07 or DQA*0201
- Tyrosine phosphatase gene
- PTPN22
- IL1-RN A1 in juvenile DM
- Non-HLA: 308 TNFα genotype

Conclusion. Serum sPD-L1 levels increased significantly in sDM, and markedly high sPD-L1 levels could be a diagnostic indicator for malignancies in patients with DM, especially in those with anti-TIF1-γ antibodies. (First Release February 1 2018; J Rheumatol 2018;45:835–40; doi:10.3899/jrheum.170544)

- **Implications:**
  - Therapy with agents affecting PD-L1 might benefit patients with cutaneous dermatomyositis
  - Measurement of PD-L1 might predict the risk of cancer-associated disease in patients with DM
UV and DM

- The action spectrum is not known, but the disease appears to be photo-exacerbated.
- UV intensity correlates with incidence of DM in women (Caucasian) and the presence of Mi-2 antibodies.
  - *Arthritis Rheum.* 2009; 60: 2499-2504
- UV light stimulates Mi-2 expression *in vitro*.
- Ultraviolet radiation exposure is associated with clinical and autoantibody phenotypes in juvenile myositis.
UV and DM - Continued

• Genetic background may contribute to the latitude-dependent prevalence of dermatomyositis and anti-TIF1-γ autoantibodies in adult patients with myositis
  – These authors found a correlation of DM with latitude, no relation with Mi-2 presence, and a reverse correlation with anti-TIF1-γ
  – They also found that HLA alleles associated with these antibodies were negatively correlated with latitude
  – They concluded that a genetic background, in addition to UV light, contributes to the prevalence of DM

DM is a Systemic Disease

- Arthritis
- Esophageal disease – distal v. proximal
- Pulmonary disease
  - Interstitial pneumonitis – correlates with anti-Jo-1, and is perhaps more frequent in PM
  - Aspiration – correlates with esophageal disease
Systemic Disease in DM - 2

• Pulmonary disease (continued) –
  – Hypoventilation due to weakness suggests grave prognosis
  – Drug-induced hypersensitivity
  – Infectious complication in the immunosuppressed patient

• Cardiac disease
  – When clinically symptomatic, associated with a poor prognosis
Myositis and Malignancy

- Population-based studies generally reveal that about 20-25% of DM patients have or will develop a cancer
  - Hill et al, Lancet 2001;357: 96-100
- ADM patients may also have cancer
- PM patients generally have lower rates and subsequent malignancy is much closer to that of the general population, suggesting that the presence of the association is due to a ‘diagnostic suspicion bias’
### Risk of Malignancy in Dermatomyositis and Polymyositis: A Systematic Review and Meta-Analysis

#### Risk of Malignancy in DM

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|                  |            |             |             |         |
|                  | Rate ratio | 4.39        | 3.22        | 9.37    |

**Decreased risk**  **Increased risk**
ADULT DERMATOMYOSITIS & MALIGNANCY
Myositis and Malignancy-II

• Gynecologic malignancy may be more common, in particular ovarian cancer
• In Southeast Asia – Nasopharyngeal cancer is overrepresented
• None of the population-based studies have linked therapy to a risk of malignancy
Purpose of Evaluation

• Exclude other causes of myopathy or skin disease
• Assess the presence of systemic involvement
• Assess the severity of the condition
• Exclude a potential associated malignancy
How should DM patients be evaluated for cancer?

Conventional Cancer Screening versus PET/CT in Dermatomyositis/Polymyositis

Albert Selva-O’Callaghan, MD, PhD,a Josep M. Grau, MD, PhD,a Cristina Gámez-Cenzano, MD, PhD,b Antonio Vidal-Puebla, MD, PhD,c Xavier Martínez-Gómez, MD,a Ernesto Trallero-Araguás, MD,a Eduard Andia-Navarro, MD,c Miguel Vilardell-Tarrés, MD, PhDa

METHODS: We prospectively studied 55 consecutive patients with a recent diagnosis of myositis in 3 teaching hospitals over a 3-year period by whole-body FDG-PET/CT and compared the results with those of conventional cancer screening, which included thoracoabdominal CT, mammography, gynecologic examination, ultrasonography, and tumor marker analysis. Comparisons were made using predictive values and their 95% confidence intervals.

CONCLUSION: The performance of FDG-PET/CT, a single imaging study, for diagnosing occult malignant disease in patients with myositis was comparable to that of broad conventional screening, which includes multiple tests.

Retrospective analysis of 400 patients
48 patients (12%) had malignancies (53 total)
21 cancers (40%) were diagnosed within 1-year of DM diagnosis
Both classic DM and ADM were associated with cancer
27 (6.8%) patients had a cancer at the time of diagnosis
59% of the cancers were asymptomatic and were discovered with CT scans, suggesting that “blind” screening is effective in identifying cancers in DM patients

My Evaluation

- Barium swallow, PFTs, EKG
- Malignancy evaluation
  - Chest X-ray, CT of Chest and abdomen, stool hematest – all patients
  - Mammogram, pelvic ultrasound and or CT of the pelvis in women
  - Age, race or ethnicity related testing
- Annual evaluation x 3 years, and careful assessment of any ‘new’ symptom
Obtain baseline spirometry, lung volumes, and **diffusing capacity** in all dermatomyositis patients.

**MANAGE BASED ON DIFFUSING CAPACITY***

- **NORMAL**
  - (>79% predicted)
  - REPEAT PFTs IN 12 MONTHS

- **BORDERLINE LOW**
  - (76-79% predicted)
  - REPEAT PFTs IN 6 MONTHS

- **MILD DECREASE**
  - (61-75% predicted)
  - OBTAIN HRCT

- **MODERATE/SEVERE DECREASE**
  - (60% predicted or less)
  - OBTAIN HRCT AND REFER TO PULMONARY

  - **POSITIVE FOR ILD**
    - REFER TO PULMONARY

  - **NEGATIVE FOR ILD**
    - OBTAIN ECHOCARDIOGRAM TO R/O PULMONARY HTN AND CBC TO R/O ANEMIA AND REPEAT PFTs IN 6 MONTHS
Myositis specific and associated antibodies

- Anti-synthetase ab, including Jo-1: generally associated with PM and interstitial fibrosis
- Anti-Mi2 – DM, but only 25% +
- Anti-MDA5 (melanoma differentiation-associated protein 5) – 10-20% of DM patients, but particularly CADM and ILD, particularly in Asian populations
- Anti-NXP (nuclear matrix protein) – 1.6-30% of DM patients, possibly associated with calcinosis
- Anti- TIF-1γ - transcription intermediary factor 1γ – unknown percentage, but associated with cancer in adults and extensive disease and/or ulcerations in children
ORIGINAL ARTICLE

Distinctive cutaneous and systemic features associated with specific antimyositis antibodies in adults with dermatomyositis: a prospective multicentric study of 117 patients

M. Best,1 M. Jachiet,2 N. Molinari,3,4 F. Manna,3 C. Girard,1 V. Pallure,5 A. Cosnes,6 D. Lipsker,7 T. Hubiche,8 J.-L. Schmutz,9 Y. Le Corre,10 N. Cordel,11 M. Dandurand,12 O. Dereure,1,13 B. Guillot,1,13 A. Du-Thanh,1,13 C. Bulai Livideanu,14 F. Chasset,15 J.-D. Bouaziz,2 C. Francès,15 D. Bengoufa,16 T. Vincent,17 D. Bessis,1,13,* and on behalf of the Study Group of Systemic Diseases in Dermatology (EMSED: Étude des Maladies Systémiques en Dermatologie)

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<tr>
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<td>Calcinosis</td>
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<td>Mechanic’s hands</td>
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<td>Raynaud’s phenomenon</td>
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<td>CPK elevation</td>
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<td>Poikilodermia</td>
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# Results

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<th>Antibody</th>
<th>Associations</th>
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<td>TIF-1γ</td>
<td>Poikiloderma</td>
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<tr>
<td>NXP-2</td>
<td>Calcinosis</td>
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</table>
Comment – Contrasting/New Data

• Unable to associate presence of necrosis with increase risk of ILD
• Failed to show association with TIF-1γ and cancer, unlike most prior studies
  – Low number of patients with this antibody
• Failed to show association with ARS antibodies (Jo1) and ILD, unlike most prior studies
  – Initial recruitment based on cutaneous findings only
• Limitations:
  – Exclusively dermatologic recruitment
  – Limited to 2 year follow up in most patients
  – Use of dot immunoassay rather than immunoprecipitation, which is the gold standard for detection of MSAs
Most Patients With Cancer-Associated Dermatomyositis Have Antibodies to NXP-2 or TIF-1γ

- Study of 213 patients from Stanford & Johns Hopkins
- 29 (13.6%) had cancer (CAM)
- 17% and 38% had anti-NXP-2 and TIF-1γ, respectively.
- Reactivity against either NXP-2 or TIF-1γ identified 83% of patients with CAM.
- In addition to older age and male sex, cancer was associated with antibodies to NXP-2 or TIF-1 on multivariate analysis (OR = 3.78 [95% CI 1.33–10.8]).
- Stratification by sex revealed that anti–NXP-2 was specifically associated with cancer in males (OR = 5.78 [95% CI 1.35–24.7]).

Therapy of Cutaneous DM

• Sun-protective measures – behavior, sunscreens, protective clothing
  – Assess Vitamin D levels and/or supplement
• Topical emollients, corticosteroids, calcineurin inhibitors
• Antimalarials
• Methotrexate
• Mycophenolate mofetil
• IVIG
• Other agents – dapsone, thalidomide, leflunomide, sirolimus, chlorambucil, etanercept, infliximab, rituximab (?), apremilast, tofacitinib
Antimalarial therapy of DM

• Open-label studies or small case series only
• Hydroxychloroquine or chloroquine, with or without quinacrine
• No beneficial effects on myopathy, possible toxic effect
• Possible increase risk of drug eruption
Hydroxychloroquine Therapy
Drug Eruption following Hydroxychloroquine Administration
Hydroxychloroquine eruption – 3 days after initiation of therapy for DM
Antimalarials – Is there an increased risk of cutaneous drug reactions?

- Pelle & Callen studied 68 patients with DM (8 possible ADM)
  - 42 had taken hydroxychloroquine and all but 3 children were age, sex and race matched with a patient with cutaneous LE who had taken this drug
  - 12/39 v. 1/39 had a drug reaction (1/3 of JDMS) (p = 0.0032)
  - 11 reactions were morbilliform, 1 was Stevens-Johnson like syndrome (see also Clin Exp Dermatol 2001; 26: 457)
  - All began within 3 weeks of therapy and were often intensely pruritic.
Antimalarials – Is there an increased risk of cutaneous drug reactions?

• Treatment - discontinuation of the drug and corticosteroids
• Chloroquine therapy was used in 3 patients – 1 developed a morbilliform eruption
• Conclusions: Antimalarials are associated with a high frequency of non-life-threatening drug eruptions. There may be cross-reactivity between hydroxychloroquine and chloroquine.
  » Arch Dermatol 2002; 138: 1231-3
Methotrexate therapy of DM
Mycophenolate Mofetil for DM

- In a cohort of 42 patients with various dermatomyositis subtypes, 83% showed improvement in refractory cutaneous dermatomyositis and also other refractory symptoms with IVIG treatment.
- Most patients (80%) were able to decrease/discontinue glucocorticoids and occasionally decrease steroid-sparing immunosuppressive medications.
- IVIG can effectively treat refractory cutaneous dermatomyositis regardless of dermatomyositis subtype.
DM Before & After IVIG
Tofacitinib Citrate for Refractory Cutaneous Dermatomyositis: An Alternative Treatment

- Mean decrease in CDASI: 12
- Decreased pruritus
Sirolimus Therapy of Dermatomyositis

Open-label study of 11 patients with refractory disease defined as failing glucocorticoid and/or ≥1 immunosuppressive agent, as well as active disease defined as significant muscle weakness & >2 additional abnormal core set measures (CSMs) or a cutaneous 10 cm Visual Analogue Scale score of ≥3 cm and at least three other abnormal CSMs

All patients received RCI of 80 units subcutaneously twice weekly for 24 weeks.
Results

- Ten of the 11 enrolled subjects (6 D M, 4 PM) completed the study.
- 7/10 met the primary end point of efficacy at a median of 8 weeks.
- There was a significant decrease in prednisone dose from baseline to conclusion (18.5 (15.7) vs 2.3 (3.2); P<0.01).
- Two of 3 patients with severe cutaneous disease improved.
- No patient developed significant weight gain or an increase of haemoglobin A1c or cushingoid features.
Results - continued

Figure 2  Cutaneous rash improvement in a patient with dermatomyositis before and after repository corticotropin injection (RCI).

Figure 4  Changes in prednisone dose at baseline and 6 months last follow-up.

Comment

- The effects are not explained by increased cortisol levels
- The authors postulate that the MOA is direct effect on melanocortin receptors which have been demonstrated to be on immune cells
- Limitations:
  - Open label
  - Small sample size
  - Did not use a validated skin score (e.g. CDASI)
  - Cost of the medication (one 5 mL vial [10 doses] costs $40,840.00)
Efficacy and safety of leflunomide as an adjuvant drug in refractory dermatomyositis with primarily cutaneous activity

R.C. de Souza, F.H.C. de Souza, R. Miossi, S.K. Shinjo
Methods

• Retrospective, single center
• N-18, 2001-2016, 6 month follow up
• Classical or clinically amyopathic DM
• All patients were glucocorticoid dependent and had inadequate response (min 3 months at full dose) to at least 2 immunosuppressives or contraindication/adverse event to rituximab.
• Patients were continued on prednisone, one immunosuppresive and leflunomide was added
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Statistical data are expressed as mean ± standard deviation, median (interquartile 25th–75th). AM: antimalarial; Aza: azathioprine; CP: cyclosporine; CPK: creatinine phosphokinase; Cut: cutaneous; IVIg: human intravenous immunoglobulin pulse therapy; F: female; M: male; mm: muscular; MMF: mycophenolate mofetil; MP: methylprednisolone pulse therapy; MTX: methotrexate; Pred: prednisone. *Suspended.
Results and Comment

• 12/18 had improvement and total control of cutaneous activity and also had improvement of strength
• 6/18 stopped leflunomide after 6 mo f/u due to a lack of response or side effects
• Median prednisone dose was tapered from 17.5 to 6.0mg (p=.008)
• Leflunomide is an option for refractory DM.
• Limitations: single center, small sample size, short follow up, monotherapy was not investigated
Itch in dermatomyositis: the role of increased skin interleukin-31

H.J. Kim, M. Zeidi, D. Bonciani, S.M. Pena, J. Tiao, S. Sahu and V.P. Werth

What’s already known about this topic?

- Interleukin (IL)-31 has been implicated in pruritus associated with various pruritic skin diseases, including atopic dermatitis and cutaneous T-cell lymphoma.
- Pruritus is a prominent feature in dermatomyositis (DM).

What does this study add?

- The severity of itch correlates with the disease activity of DM.
- Skin IL-31 is significantly upregulated in DM, and CD4+ T cells are the most common cell type to produce IL-31.
- Flow cytometry indicates that not only CD4+ T cells, but also other cell types expressing CD8, CD68, CD11b or CD11c, secrete IL-31 in DM.
What is the translational message?

- This study suggests that IL-31 may play a role in the pathogenesis of DM-related pruritus.
- Lenabasum, a new emerging treatment for DM, significantly downregulated IL-31, as well as IL-4, from CpG-stimulated peripheral blood mononuclear cells.
- Ongoing trials will evaluate the effects of systemic treatment on IL-31 and itch in DM.
Therapy of Cutaneous DM

- Sun-protective measures – behavior, sunscreens, protective clothing
  - Assess Vitamin D levels and/or supplement
- Topical emollients, corticosteroids, calcineurin inhibitors
- Antimalarials
- Methotrexate
- Mycophenolate mofetil
- IVIG
- Other agents – dapsone, thalidomide, leflunomide, sirolimus, chlorambucil, etanercept, infliximab, rituximab (?), apremilast, tofacitinib, lenabasum (JBT-101) a cannabinoid that is anti-itch (anti-IL-31)*

* FDA recently granted orphan drug approval
Future Therapies
(source ClinicTrials.gov – accessed 7-6-18)

• Study of Tofacitinib in Refractory Dermatomyositis - NCT03002649
• Safety, Tolerability, and Efficacy of JBT-101 in Subjects With Dermatomyositis (nonpsychoactive cannabinoid derivative) - NCT02466243
• Subcutaneous Immunoglobulin (Hizentra) in Patients with Dermatomyositis - NCT02271165
• Trial of IMO-8400 in Adult Patients With Dermatomyositis - NCT02612857
• Efficacy and Safety of H.P. Acthar Gel for the Treatment of Refractory Cutaneous Manifestations of Dermatomyositis - NCT02245841
Some of the Unresolved Questions

1. What is the cause of DM-associated skin disease?
2. Is there a specific test to differentiate DM from LE?
3. Are serologic tests useful in DM patients?
4. Should patients be serially assessed with PFTs?
5. What is the appropriate malignancy evaluation? When should it be repeated?
6. What is the best therapy for skin disease?
7. Do patients on methotrexate need liver biopsies?
Conclusions

- Dermatomyositis is a multisystem disorder with primary manifestations in the skin and muscles
- Adults with DM should be assessed for malignancy
- Successful management is possible